Supporting Information for

Enantioselective Total Synthesis of Aspidophytine

Shinjiro Sumi,¹ Koji Matsumoto,¹ Hidetoshi Tokuyama,^{1,2} and Tohru Fukuyama*¹

¹Graduate School of Pharmaceutical Sciences, The University of Tokyo, ²PRESTO, The Japan Science and Technology Corporation, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-0033, Japan

General: All reactions sensitive to oxygen and moisture were carried out in oven-dried glassware under a slight positive pressure of argon unless otherwise noted. Melting points (mp), determined on a Yanako MP-500V melting point apparatus, are uncorrected. ¹H-NMR (400 Hz), and ¹³C-NMR (100 Hz) spectra were determined on a JEOL JNM-AL400 or JEOL JNM-LA400 instrument. Chemical shifts for ¹H-NMR were reported in parts per million (ppm) downfield from tetramethylsilane as the internal standard and coupling constants are in Hertz (Hz). The following abbreviations are used for spin multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, and br = broad. Chemical shifts for ¹³C-NMR were reported in ppm relative to the central line of a triplet at 77.0 ppm for deuteriochloroform. Infrared (IR) spectra were recorded on a JASCO FT/IR-410 Fourier Transform Infrared Spectrophotometer and are reported in wave numbers (cm⁻¹). Mass spectra (MS) were obtained on a JEOL JMS-700 or a JEOL JMS-GCmate at 70 eV, using direct probe insertion at temperatures of 70 to 350 °C. High resolution mass spectra were obtained under similar conditions. Optical rotations were measured on a JASCO DIP-1000 Digital Polarimeter at room temperature, using the sodium D line. Analytical thin layer chromatography (TLC) was performed on Merck precoated analytical plates, 0.25 mm thick, silica gel 60 F₂₄₅. Preparations TLC separations were performed on 6.7 x 20 cm Merck precoated analytical plates, 0.50 mm thick, silica gel 60 F₂₄₅. Compounds were eluted from the absorbent with 20% methanol in dichloromethane. Flash column chromatography was performed on Merck Kieselgel 60 (230-400 mesh) or KANTO CHEMICAL Silica Gel (spherical 40-100 μm). Reagents and solvents were commercial grades and were used as supplied. Dichloromethane, dimethyl sulfoxide, benzene, toluene were distilled from calcium hydride and stored over molecular sieves 4Å. THF, *N,N*-dimethylformamide, methanol, ethanol, diethyl ether, and acetonitrile were purchased anhydrous and stored over molecular sieves 4Å under argon. Methanol was purchased anhydrous and stored over molecular sieves 3Å. Triethylamine was distilled from calcium hydride and stored over potassium hydroxide pellets.

3-[(Triisopropyl-silanyl)-ethynyl]-cyclopent-2-enol (**4**)

To a THF (6 mL) solution of ethynyl-triisopropyl-silane (1.61 mL, 7.16 mmol) was added *n*-BuLi (4.36 mL, 5.97 mmol, 1.37 M in hexane) dropwise at -78°C over 5 minutes. After stirring for 30 minutes, anhydrous CeCl_3 (7.16 mmol, 0.24 M in THF) was added to the mixture over 5 minutes, and the resulting yellow suspension was stirred at -78°C for 30 minutes. To the mixture was added cyclopentenone (**3**) (0.500 mL, 5.97 mmol) dropwise, and the mixture was stirred for 10 minutes, at which time the reaction temperature was allowed to raise to room temperature. The reaction was quenched by addition of saturated NH_4Cl . The reaction mixture was diluted with Et_2O , filtered, and concentrated. The residue was dissolved in EtOAc and washed with saturated NH_4Cl . The aqueous layer was back-extracted with EtOAc twice. The combined organic extracts were washed with brine, dried over MgSO_4 , filtered, and concentrated to obtain crude product. The crude material was passed through a silica gel short column (elution with 10 to 30% EtOAc in hexane) and used for the next step without further purification. To a THF (14 mL) solution of the crude material was added 3% H_2SO_4 (6 mL) and the solution was stirred at room temperature for 6.5 hours. The reaction mixture was partitioned between EtOAc and saturated NaHCO_3 . The aqueous layer was back-extracted with EtOAc twice. The combined organic extracts were washed with brine, dried over MgSO_4 , filtered, and concentrated to give a crude product. Purification by column chromatography on silica gel (elution with 10% EtOAc in hexane) gave the desired product **4** (1.48 g, 94% in two steps); IR (film, cm^{-1}) 3308, 2943, 2892, 2866, 2147, 1609, 1463, 1038, 883; ^1H -NMR (400 MHz, CDCl_3) δ 6.09 (d, 1H, $J = 2.0$ Hz), 4.90 (br s, 1H), 2.68-2.62 (m, 1H), 2.42-2.29 (m, 2H), 1.79-1.71 (m, 1H); ^{13}C -NMR (100 MHz, CDCl_3) δ 138.6, 129.0, 103.2, 94.7, 77.6, 35.1, 33.6, 18.6, 11.2; HR-MS (FAB) calcd for $\text{C}_{16}\text{H}_{28}\text{OSi}$ [M^+] 264.1909, found 264.1921.

(2S)-3-[(Triisopropyl-silanyl)-ethynyl]-cyclopent-2-enol (**5**)

A white suspension of 3-[(Triisopropyl-silanyl)-ethynyl]-cyclopent-2-enol (**4**) (10.7 g, 40.5 mmol), vinyl acetate (7.46 mL, 80.9 mmol) and lipase PS (2.14 g, Amano enzymes) in *t*-BuOMe (135 mL) was stirred at 48 - 50°C for 20 hours. The suspension was filtered through a

pad of Celite and concentrated. The residual material was purified by column chromatography on silica gel (elution with 5 to 20% EtOAc in hexane) to give the desired (*S*)-alcohol (**5**) (5.11 g, 48%) and (*R*)-acetate (6.00 g, 48%). The optical purity of the alcohol was determined by NMR analysis after conversion to MTPA ester to be >99% ee; $[\alpha]_D^{24} -27.7$ (*c* 1.01, methanol). The absolute configuration of the recovered alcohol **5** was determined according to Kusumi-Kakisawa method.¹ The alcohol **5** was converted to (*S*)-MTPA ester and (*R*)-MTPA ester using (*R*)- α -methyl- α -(trifluoromethyl) phenylacetic acid chloride ((*R*)-MTPACl) and (*S*)- α -methyl- α -(trifluoromethyl) phenylacetic acid chloride ((*S*)-MTPACl), respectively. (*S*)-MTPA ester of **5**; ¹H-NMR (400 MHz, CDCl₃) δ 7.51 (t, 2H, *J* = 3.9 Hz), 7.40 (dd, 3H, *J* = 3.9, 5.8 Hz), 6.11 (d, 1H, *J* = 2.0 Hz), 5.95 (dd, 1H, *J* = 2.9, 6.8 Hz), 3.56 (s, 3H), 2.68-2.61 (m, 1H), 2.49-2.34 (m, 2H), 1.91-1.85 (m, 1H), 1.08 (s, 21H); (*R*)-MTPA ester of **5**; ¹H-NMR (400 MHz, CDCl₃) δ 7.51 (t, 2H, *J* = 3.9 Hz), 7.41 (dd, 3H, *J* = 3.9, 5.9 Hz), 6.05 (d, 1H, *J* = 4.9 Hz), 5.94 (dd, 1H, *J* = 2.0, 5.9 Hz), 3.55 (s, 3H), 2.69-2.61 (m, 1H), 2.50-2.39 (m, 2H), 2.03-1.95 (m, 1H), 1.08 (s, 21H).

(1*R*)-(1-Ethynyl-cyclopent-2-enyl)-acetic acid ethyl ester (6)

A mixture of cyclopentenol **5** (5.00 g, 18.9 mmol), triethyl orthoacetate (34.7 mL, 189 mmol), and pivalic acid (38.6 mg, 0.378 mmol) in xylene (190 mL) was heated at reflux. Ethanol was gradually removed through Dean-Stark trap. Additional amount of pivalic acid (231.6 mg, 2.27 mmol), and triethyl orthoacetate (27.7 mL, 151 mmol) were added in several portions over 8 hours and the solution was stirred at reflux for 2 hours. To the reaction mixture was added 1 N HCl, and the resulting reaction mixture was stirred for 20 minutes at room temperature. The organic phase was diluted with EtOAc, washed with saturated NaHCO₃ and brine, dried over MgSO₄, filtered, and concentrated. The residue was passed through a silica gel short pass to obtain a crude product. The crude material was used in the next step without further purification. To a THF (30 mL) of the oily crude material was added tetra-*n*-butylammonium fluoride (1.0 M in THF, 22.9 mL, 22.9 mmol), and the resulting mixture was stirred at 50 °C for 45 minutes. The reaction mixture was partitioned between EtOAc and saturated ammonium chloride. The aqueous layer was back-extracted with EtOAc. The combined organic extracts were dried over MgSO₄, filtered, and concentrated. The residue was passed through a silica gel short-pass to give a crude product as a mixture of the desired terminal acetylene **6** and inseparable compounds (5.3 g). Spectral data of **6** were determined after a careful purification of the small portion of the crude material; IR (film, cm⁻¹) 3291,

2980, 2938, 2109, 1737; $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 5.83 (dt, 1 H, $J = 2.9, 5.9$ Hz), 5.79 (dt, 1 H, $J = 2.0, 5.9$ Hz), 4.17 (q, 2 H, $J = 6.8$ Hz), 2.57 (dd, 2 H, $J = 14.4, 15.6$ Hz), 2.46-2.51 (m, 1 H), 2.50 (s, 1 H), 2.25-2.42 (m, 2 H), 2.09-2.16 (m, 1 H), 1.27 (t, 2 H, $J = 6.8$ Hz); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 170.6, 134.8, 132.0, 88.1, 79.1, 69.5, 60.4, 44.9, 38.1, 31.2, 14.3; HR-MS (FAB) calcd for $\text{C}_{11}\text{H}_{14}\text{O}_2$ [M^+] 178.0994, found 178.0990.

(3R)-3-(3-Hydroxy-propyl)-3-hydroxymethyl-pent-4-ynoic acid ethyl ester (7)

To a crude product containing ethynyl cyclopentene **6** (5.3 g) in acetone (40 mL) were added *N*-methylmorpholine *N*-oxide (3.58 g, 30.4 mmol), water (10 mL), and OsO_4 (1% w/v solution in *t*-BuOH, 3.88 mL, 0.15 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 80 minutes. The mixture was partitioned between EtOAc and saturated $\text{Na}_2\text{S}_2\text{O}_3$. The aqueous layer was back-extracted with EtOAc three times. The combined organic extracts were washed with brine, dried over Na_2SO_4 , filtered and concentrated to give a crude material. Purification by passing the oily material through a silica gel short pass (neutral silica gel, 20 to 100% EtOAc in hexane) afforded a diastereomeric mixture of 1,2-diol (2.10 g). A mixture of the 1,2-diol was oxidatively cleaved with NaIO_4 . To a solution of 1,2-diol (2.10 g) in 5:1 mixture of THF and water (30 mL) was added NaIO_4 (3.17 g, 14.8 mmol) at 0 °C, and the resulting mixture was stirred at 0 °C for 25 minutes. The reaction mixture was diluted with EtOAc, and washed with water. The aqueous layer was back-extracted with EtOAc four times. The combined organic extracts were washed with brine, dried over MgSO_4 , and concentrated to obtain a crude material (2.30 g), which was used for the next step without purification. To the crude product dissolved in ethanol (30 mL) was added NaBH_4 (0.749 g, 19.8 mmol) at -20 °C and the mixture was stirred for 15 minutes at this temperature. The reaction mixture was then terminated by addition of saturated ammonium chloride and diluted with EtOAc. The aqueous layer was washed extracted with EtOAc four times. The combined organic extracts were washed with brine, dried over Na_2SO_4 , filtered, and concentrated to a crude material. Purification by column chromatography on silica gel (elution with 50 to 80% EtOAc in hexane) gave the desired diol **7** (1.49 g, 38% in 5 steps); $[\alpha]_D^{25} -1.7$ (*c* 0.57, methanol); IR (film, cm^{-1}) 3376, 3291, 2944, 2876, 2110, 1729, 1372, 1187, 1056; $^1\text{H-NMR}$ δ 4.17 (q, 2H, $J = 6.8$ Hz), 3.74-3.65 (m, 4H), 2.63 (d, 1H, $J = 14.6$ Hz), 2.58 (d, 1H, $J = 14.6$ Hz), 2.50 (t, 1H, $J = 6.8$ Hz), 2.26 (s, 1H), 1.79-1.73 (m, 2H), 1.70-1.66 (m, 2H), 1.42 (br s, 1H), 1.28 (t, 3H, $J = 6.8$ Hz); $^{13}\text{C-NMR}$ δ 171.2, 85.4, 72.3,

67.0, 62.7, 60.8, 40.6, 39.8, 31.7, 27.5, 14.2; HR-MS (FAB) calcd for $C_{11}H_{19}O_4$ $[(M+H)^+]$ 215.1283, found 215.1275.

(3R)-3-[3-(*tert*-Butyl-diphenyl-silanyloxy)-propyl]-3-hydroxymethyl-pent-4-ynoic acid ethyl ester

To the diol **7** (1.44 g, 6.72 mmol) in CH_2Cl_2 (23 mL) was added *t*-butylchlorodiphenylsilane (2.10 mL, 8.06 mmol), Et_3N (1.87 mL, 13.4 mmol), and 4-dimethylaminopyridine (246 mg, 2.02 mmol) at $-20\text{ }^\circ\text{C}$. The reaction mixture was stirred for 45 minutes as the temperature was raised to $-10\text{ }^\circ\text{C}$. The reaction was terminated by addition of ammonium chloride, and diluted with EtOAc. The aqueous layer was extracted with EtOAc, and the combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated. Purification by column chromatography on silica gel (elution with 15 to 20% EtOAc in hexane) gave the desired mono-protected compound (2.88 g, 95%); $[\alpha]_D^{26} -2.1$ (c 0.63, methanol); IR (film, cm^{-1}) 3461, 3304, 2956, 2932, 2858, 1732, 1428, 1188, 1112; 1H -NMR (400 MHz, $CDCl_3$) δ 7.66 (d, 4H, $J = 6.8$ Hz), 7.44-7.35 (m, 6H), 4.15 (dq, 2H, $J = 2.0, 6.8$ Hz), 3.70-3.62 (m, 4H), 2.60 (d, 1H, $J = 14.8$ Hz), 2.55 (d, 1H, $J = 14.8$ Hz), 2.41 (t, 1H, $J = 6.8$ Hz), 2.23 (s, 1H), 1.76-1.69 (m, 2H), 1.67-1.62 (m, 2H), 1.26 (t, 3H, $J = 6.8$ Hz), 1.05 (s, 9H); ^{13}C -NMR (100 MHz, $CDCl_3$) δ 171.2, 135.6, 133.9, 129.6, 127.6, 85.5, 72.2, 67.6, 63.9, 60.7, 40.6, 40.0, 32.2, 27.6, 26.8, 19.2, 14.2; HR-MS (FAB) calcd for $C_{27}H_{37}O_4Si$ $[(M+H)^+]$ 453.2461, found 453.2456.

(3R)-3-[3-(*tert*-Butyl-diphenyl-silanyloxy)-propyl]-3-dimethoxymethyl-pent-4-ynoic acid ethyl ester (8**)**

To a CH_2Cl_2 (5 mL) solution of DMSO (1.35 mL, 19.1 mmol) was added $(COCl)_2$ (1.11 mL, 12.7 mmol) at $-78\text{ }^\circ\text{C}$ over 5 minutes. After stirring for 30 minutes at this temperature, CH_2Cl_2 solution of alcohol (2.88 g, 6.36 mmol) was added over 10 minutes. After the reaction mixture was stirred for 30 minutes, Et_3N (3.55 mL, 25.4 mmol) was added and the reaction temperature was allowed to warm to room temperature. The reaction mixture was partitioned between EtOAc and saturated $NaHCO_3$. The aqueous layer was extracted with EtOAc, and the combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and

concentrated to give a crude material, which was used for the next acetal formation without purification. To the crude product in a 1:1 mixture of MeOH and trimethyl orthoformate (20 mL) was added camphorsulfonic acid (444 mg, 1.91 mmol). The reaction mixture was stirred at room temperature for 30 minutes. The reaction was terminated by addition of excess Et₃N, and the resulting mixture was concentrated in vacuo. The residue was purified by column chromatography on silica gel (elution with 5 to 10% EtOAc in hexane) afforded the desired dimethyl acetal **8** (2.35 g, 74% in 2 steps); [α]_D²⁶ +2.4 (*c* 0.85, methanol); IR (film, cm⁻¹) 3286, 2956, 2932, 2858, 1735, 1428, 1189, 1111, 1082; ¹H-NMR (400 MHz, CDCl₃) δ 7.66 (d, 4H, *J* = 7.8 Hz), 7.43-7.35 (m, 6H), 4.49 (s, 1H), 4.13 (q, 2H, *J* = 6.8 Hz), 3.67 (t, 2H, *J* = 5.9 Hz), 3.55 (s, 3H), 3.54 (s, 3H), 2.61 (s, 2H), 2.23 (s, 1H), 1.79-1.70 (m, 4H), 1.25 (t, 3H, *J* = 6.8 Hz), 1.05 (s, 9H); ¹³C-NMR (100 MHz, CDCl₃) δ 170.9, 135.5, 133.9, 129.5, 127.5, 108.3, 84.9, 71.8, 64.1, 60.2, 58.5, 58.2, 43.3, 38.8, 30.1, 27.7, 26.8, 19.2, 14.2; HR-MS (FAB) calcd for C₂₉H₄₀O₅Si [M⁺] 496.2645, found 496.2636.

3-(3,4-Dimethoxy-2-nitro-phenyl)-acrylic acid ethyl ester (**10**)

To a two-phase mixture of *n*-Bu₄NI (1.75 g, 4.7 mmol) in NaOH (50% in water, 105 mL) and CH₂Cl₂ (105 mL) was added CH₂Cl₂ (70 mL) solution of 2-nitroveratraldehyde (**9**) (37.0 g, 175 mmol) and triethyl phosphonoacetate (43.2 g, 193 mmol) dropwise at 5 °C over 25 minutes. The organic phase was separated and evaporated under reduced pressure to give a yellow solid (44.5 g). This solid was purified by crystallization from EtOAc to afford **10** (36.4 g, 74.1%) as yellow needles. The second crop was recovered from the mother to obtain additional **10** (3.2 g, 6.4%); Mp: (EtOAc-hexane, 2:1) 136.3-139.7 °C; IR (film, cm⁻¹) 3020, 2985, 2956, 1704, 1638, 1604, 1536, 1510, 1374, 1230; ¹H-NMR (400 MHz, CDCl₃) δ 7.44 (d, 1H, *J* = 15.6 Hz), 7.38 (d, 1H, *J* = 8.8 Hz), 7.04 (d, 1H, *J* = 8.8 Hz), 6.34 (dd, 1H, *J* = 15.9, 1.7 Hz), 4.25 (q, 2H, *J* = 7.0 Hz), 3.96 (s, 3H), 3.94 (s, 3H), 1.32 (t, 3H, *J* = 7.0 Hz); ¹³C-NMR (100 MHz, CDCl₃) δ 165.7, 154.4, 145.8, 140.7, 135.9, 122.6, 121.0, 119.2, 113.7, 62.1, 60.7, 56.4, 19.7; HR-MS (FAB) calcd for C₁₃H₁₆NO₆ [(M+H)⁺] 282.0977, found 282.0977.

3-(2-Formylamino-3,4-dimethoxy-phenyl)-acrylic acid ethyl ester

To a suspension of **10** (40.5 g, 144 mmol) and Zn powder in CH_2Cl_2 (200 mL) was added AcOH (70 mL) dropwise at 10 °C over an hour, and the resulting mixture was stirred for an additional 30 minutes at room temperature. The reaction mixture was filtered through a pad of Celite and washed with CH_2Cl_2 (400 mL). To the combined filtrates was added water (200 mL) and solid NaHCO_3 until pH reached to 8.0 (67 g). The resulting mixture was separated, and aqueous phase was extracted with CH_2Cl_2 (30 mL). The combined organic extracts were washed with brine (100 mL), dried over MgSO_4 , filtered, and evaporated under reduced pressure to give yellow oil. A mixture of HCO_2H (16.3 mL, 432 mmol) and Ac_2O (40.8 mL, 432 mmol) was stirred at 55 °C for 30 minutes and cooled to 5 °C, to which was added a CH_2Cl_2 (80 mL) solution of the above crude product at 5 °C. After stirring for 10 minutes, the reaction mixture was poured into a mixture of CH_2Cl_2 (300 mL) and water (200 mL), and solid NaHCO_3 was added until pH reached to 7 (100 g). The resulting two-phase mixture was separated, and the aqueous phase was extracted with CH_2Cl_2 (40 mL). The combined extracts were washed with brine (100 mL), dried over MgSO_4 , filtered, and evaporated under reduced pressure to dryness to afford the titled formanilide as white needles (40.6 g, quantitative in 2 steps), which was pure enough for next step. This material was obtained as a mixture of rotational isomers; Mp: (EtOAc-hexane, 1:4) 147.6-149.5 °C; IR (film, cm^{-1}) 3259, 2982, 1703, 1634, 1596, 1490, 1300, 1267, 1182; ^1H -NMR (400 MHz, CDCl_3) δ 8.49 (s, 0.4H), 8.33 (s, 0.3H), 8.30 (s, 0.3H), 7.76 (d, 0.4H, $J = 15.9$ Hz), 7.68 (d, 0.3H, $J = 15.9$ Hz), 7.66 (d, 0.3H, $J = 15.9$ Hz), 7.42 (d, 0.4H, $J = 8.7$ Hz), 7.36 (d, 0.6H, $J = 8.7$ Hz), 6.89 (d, 0.4H, $J = 8.7$ Hz), 6.34 (d, 1H, $J = 15.9$ Hz), 4.24 (q, 2H, $J = 7.1$ Hz), 3.93 (s, 1.8H), 3.90 (s, 1.2H), 3.83 (s, 1.2H), 3.82 (s, 1.8H), 1.32 (t, 3H, $J = 7.1$ Hz); ^{13}C -NMR (100 MHz, CDCl_3) δ 166.9, 166.4, 164.8, 160.3, 154.3, 154.1, 143.5, 142.5, 140.1, 138.9, 129.4, 128.7, 124.5, 123.1, 122.2, 119.1, 117.4, 111.1, 110.4, 60.8, 60.6, 60.5, 60.4, 56.0, 55.9, 14.3; HR-MS (FAB) calcd for $\text{C}_{14}\text{H}_{18}\text{NO}_5$ [(M+H) $^+$] 280.1185, found 280.1188.

3-(3,4-dimethoxy-2-isocyano-phenyl)-acrylic acid ethyl ester (11)

To a solution of the formanilide (39.3 g, 141 mmol) and pyridine (87 mL) in CH_2Cl_2 (160 mL)

was added phosphorus oxychloride (22 mL, 233 mmol) dropwise over 20 minutes at 5 °C. After stirring for 50 minutes, the reaction mixture was slowly poured into a mixture of CH₂Cl₂ (80 mL) and saturated NaHCO₃, and separated. The organic phase was washed with saturated NaHCO₃ (100 mL), brine (100 mL), dried over MgSO₄, filtered, and evaporated under reduced pressure. Purification by flash column chromatography on silica gel (CH₂Cl₂) afforded **11** (23.3 g, 63.3%) as white needles; Mp (EtOAc-Hexane, 1:4) 96.6-97.4 °C; IR (film, cm⁻¹) 2988, 2122, 1714, 1638, 1593, 1499, 1259, 1184, 1075; ¹H-NMR (400 MHz, CDCl₃) δ 7.86 (d, 1H, *J* = 15.9 Hz), 7.36 (d, 1H, *J* = 8.8 Hz), 6.97 (d, 1H, *J* = 8.8 Hz), 6.43 (d, 1H, *J* = 15.9 Hz), 4.28 (q, 2H, *J* = 7.1 Hz), 3.97 (s, 3H), 3.93 (s, 3H), 1.35 (t, 3H, *J* = 7.1 Hz); ¹³C-NMR (100 MHz, CDCl₃) δ 172.3, 166.1, 154.2, 145.6, 137.6, 123.7, 122.1, 120.0, 113.0, 61.1, 60.7, 56.2, 14.3; HR-MS (FAB) calcd for C₁₄H₁₅NO₄ [M⁺] 261.1001, found 261.0994.

(2-Iodo-6,7-dimethoxy-1*H*-indol-3-yl)-acetic acid ethyl ester (12**)**

A mixture of **11** (20.1 g, 77 mmol), AIBN (0.63 g, 3.9 mmol), and Bu₃SnH (24 mL, 85 mmol) in CH₃CN (400 mL) was heated at reflux for 1.5 hours and then cooled to room temperature. To this solution was added I₂ (19.5 g, 77.0 mmol). After stirring for an hour, the reaction mixture was washed with hexane (100 mL x 3), and the combined hexane layer was extracted with CH₃CN (20 mL). The combined CH₃CN layers were evaporated under reduced pressure. Purification by flash column chromatography on silica gel (EtOAc-hexane, 1:4) afforded **12** (29.1 g, 84.6%) as pale yellow oil; IR (film, cm⁻¹) 3325, 2980, 2934, 1728, 1512, 1426, 1346, 1288, 1250; ¹H-NMR (400 MHz, CDCl₃) δ 8.18 (br s, 1H), 7.19 (d, 1H, *J* = 8.8 Hz), 6.84 (d, 1H, *J* = 8.8 Hz), 4.16 (q, 2H, *J* = 7.1 Hz), 3.98 (s, 3H), 3.91 (s, 3H), 3.67 (d, 1H, *J* = 8.8 Hz), 3.65 (d, 1H, *J* = 8.8 Hz), 1.26 (t, 3H, *J* = 7.1 Hz); ¹³C-NMR (100 MHz, CDCl₃) δ 170.8, 147.1, 133.4, 133.0, 123.9, 115.4, 113.1, 108.4, 77.9, 60.8, 57.2, 33.2, 14.2. Anal. Calcd for C₁₄H₁₆INO₄. C, 43.21; H, 4.14. Found. C, 43.02; H, 4.32.

Acetic acid 2-(2-iodo-6,7-dimethoxy-1*H*-indol-3-yl)-ethyl ester **13**

To a solution of **12** (14.3 g, 37.7 mmol) in toluene (225 mL) was added DIBAL (1.0 M in toluene, 84 mL, 84 mmol) slowly at 5 °C. After stirring for 50 minutes at this temperature, the

reaction was quenched by addition of MeOH (59 mL). The mixture was diluted with EtOAc (155 mL) and washed with potassium sodium tartrate (30% solution in water, 100 mL x 1, 45 mL x 2), and aqueous phase was back-extracted with EtOAc (25 mL). The combined organic extracts were washed with brine (100 mL), dried over MgSO₄, filtered, and evaporated under reduced pressure to yield crystalline solid (12.5 g). This solid was dissolved in pyridine (56 mL), to which was added Ac₂O (27 mL) slowly. After stirring for 30 minutes, the reaction mixture was diluted with EtOAc (150 mL) and water (100 mL), and solid NaHCO₃ was added until pH reached to 7 (ca. 38 g). The resulting mixture was separated and the organic phase was washed with 4 N HCl (80 mL), saturated NaHCO₃ (80 mL), and brine (80 mL), and dried over MgSO₄, filtered, and evaporated under reduced pressure. Purification by flash column chromatography on silica gel (EtOAc-hexane, 1:4) afforded **13** (12.2 g, 85.3%) as pale brown plates; Mp: (EtOAc-hexane, 1:4) 85.2-86.8 °C; IR (film, cm⁻¹) 3322, 2955, 2934, 2834, 1732, 1510, 1425, 1249; ¹H-NMR (400 MHz, CDCl₃) δ 8.24 (br s, 1H), 7.20 (d, 1H, *J* = 8.5 Hz), 6.82 (d, 1H, *J* = 8.5 Hz), 4.19 (t, 2H, *J* = 7.1 Hz), 3.98 (s, 3H), 3.91 (s, 3H), 2.99 (t, 2H, *J* = 7.1 Hz); ¹³C-NMR (100 MHz, CDCl₃) δ 170.9, 147.0, 133.5, 133.1, 124.1, 118.1, 112.7, 108.2, 76.9, 63.8, 60.8, 57.2, 26.5, 21.1; HR-MS (FAB) calcd for C₁₄H₁₆INO₄ [M⁺] 389.0124, found 389.0128.

(3R)-(5-[3-(2-Acetoxy-ethyl)-6,7-dimethoxy-1H-indol-2-yl]-3-[3-(*tert*-butyl-diphenyl-silanyloxy)-propyl]-3-dimethoxymethyl-pent-4-ynoic acid ethyl ester (14**)**

To a solution of indole **8** (1.25 g, 3.20 mmol) and acetylene **13** (1.59 g, 3.20 mmol) in Et₃N (30 mL) were added Pd(PPh₃)₄ (74 mg, 0.06 mmol) and CuI (24 mg, 0.13 mmol) under Ar. This solution was stirred at 70 °C for 2 hours. The resulting mixture was cooled to room temperature, diluted with EtOAc (90 mL), and washed with 10% NH₄Cl (30 mL). The aqueous phase was extracted with EtOAc (20 mL). The combined organic extracts were washed with brine (30 mL x 2), dried over MgSO₄, filtered, and evaporated under reduced pressure. Flash column chromatography on silica gel (EtOAc-hexane, 1:5) afforded **14** (1.89 g, 78.0%) as pale yellow oil; [α]_D²⁵ +7.6 (*c* 0.25, CH₃Cl); IR (film, cm⁻¹) 3338, 2934, 2858, 1737, 1515, 1459, 1365, 1242, 1111, 1094; ¹H-NMR (400 MHz, CDCl₃) δ 8.14 (s, 1H), 7.67 (d, 4H, *J* = 7.3 Hz), 7.37 (m, 6H), 7.23 (d, 1H, *J* = 8.8 Hz), 6.84 (d, 1H, *J* = 8.8 Hz), 4.28 (t, 2H, *J* = 7.1 Hz), 4.14 (q, 2H, *J* = 7.1 Hz), 3.96 (s, 3H), 3.92 (s, 3H), 3.70 (m, 2H), 3.58 (s, 3H), 3.57 (s,

3H), 2.73 (d, 1H, $J = 14.9$ Hz), 2.67 (d, 1H, $J = 14.9$ Hz), 1.90-1.78 (m, 4H), 1.25 (t, 3H, $J = 7.1$ Hz), 1.05 (s, 9H); ^{13}C -NMR (100 MHz, CDCl_3) δ 170.8, 170.7, 147.8, 135.4, 133.7, 133.6, 130.0, 129.4, 127.4, 123.7, 117.5, 116.9, 113.9, 108.2, 108.1, 96.5, 75.4, 64.1, 64.0, 60.8, 60.3, 58.4, 58.2, 57.1, 44.3, 39.0, 30.3, 28.0, 26.8, 24.7, 21.0, 19.2, 14.2; HR-MS (FAB) calcd for $\text{C}_{43}\text{H}_{55}\text{NO}_9\text{Si}$ [M^+] 757.3643, found 757.3646.

(3'R)-3-(2-Acetoxy-ethyl)-2-[6-(*tert*-butyl-diphenyl-silanyloxy)-3-dimethoxymethyl-3-ethoxycarbonylmethyl-hex-1-ynyl]-6,7-dimethoxy-indole-1-carboxylic acid *tert*-butyl ester

To a solution of **14** (4.40 g, 3.22 mmol) in CH_3CN (37 mL) were added Boc_2O (0.94 g, 4.31 mmol) and DMAP (40 mg, 0.33 mmol) at room temperature. After being stirred for 15 minutes, the reaction mixture was evaporated under reduced pressure to dryness. Flash column chromatography on silica gel (EtOAc-hexane, 1:6) afforded Boc-protected **14** (2.61 g, 94.3%) as colorless oil; $[\alpha]_{\text{D}}^{25} +5.4$ (c 0.33, CHCl_3); IR (film, cm^{-1}) 2934, 2857, 1741, 1505, 1428, 1368, 1348, 1242, 1152, 1112; ^1H -NMR (400 MHz, CDCl_3) δ 7.66 (m, 4H), 7.41-7.33 (m, 6H), 7.21 (d, 1H, $J = 8.6$ Hz), 6.92(d, 1H, $J = 8.6$ Hz), 4.61(s, 1H), 4.26 (t, 2H, $J = 7.1$ Hz), 4.13 (q, 2H, $J = 7.1$ Hz), 3.92 (s, 3H), 3.85 (s, 3H), 3.69 (m, 2H), 3.57 (s, 3H), 3.56 (s, 3H), 3.07 (t, 2H, $J = 7.1$ Hz), 2.73 (s, 2H), 1.99 (s, 3H), 1.86 (m, 4H), 1.61 (s, 9H), 1.23 (t, 3H, $J = 7.1$ Hz), 1.04 (s, 9H); ^{13}C -NMR (100 MHz, CDCl_3) δ 170.8, 170.6, 150.2, 149.7, 136.2, 135.4, 133.8, 129.3, 129.0, 127.4, 124.9, 121.6, 119.1, 113.8, 109.7, 108.1, 99.7, 83.8, 74.1, 64.2, 63.7, 60.4, 60.2, 58.2, 57.9, 57.0, 44.4, 38.9, 30.4, 27.9, 27.6, 26.8, 24.6, 21.0, 19.2, 14.2; HR-MS (FAB) calcd for $\text{C}_{48}\text{H}_{63}\text{NO}_{11}\text{Si}$ [M^+] 857.4170, found 857.4174.

(1Z)-(3R)-3-(2-Acetoxy-ethyl)-2-[6-(*tert*-butyl-diphenyl-silanyloxy)-3-dimethoxymethyl-3-ethoxycarbonylmethyl-hex-1-enyl]-6,7-dimethoxy-indole-1-carboxylic acid *tert*-butyl ester (15**)**

To a solution of the Boc-protected **14** (2.57 g, 3.00 mmol) in EtOH (39mL) was added 10% Pd on carbon (50.9% H₂O, 1.2 g). The reaction mixture was stirred at room temperature under H₂ (1 atm) for 3.5 hours. The resulting suspension was filtered through a pad of Celite. The filtrate was evaporated under reduced pressure to dryness to afford **15** (2.56 g, 97.0%) as colorless oil, which was pure enough for the next step; $[\alpha]_D^{25} -12.5$ (*c* 0.35, CHCl₃); IR (film, cm⁻¹) 2935, 2902, 2858, 1739, 1502, 1429, 1369, 1344, 1241, 1152, 1111; ¹H-NMR (400 MHz, C₆D₆, 60 °C) δ 7.77 (br s, 4H), 7.27-7.18 (m, 7H), 6.73 (d, 1H, *J* = 8.5 Hz), 6.48 (br d, 1H, *J* = 12.7 Hz), 6.11 (br d, 1H, *J* = 12.7 Hz), 4.63 (br s, 1H), 4.41-3.80 (m, 2H), 3.88 (s, 3H), 3.78 (q, 2H, *J* = 7.1 Hz), 3.71 (m, 2H), 3.53 (s, 3H), 3.38 (s, 3H), 3.32 (m, 1H), 3.26 (s, 3H), 3.16 (br s, 1H), 2.78 (br d, 1H, *J* = 14.9 Hz), 2.65 (br d, 1H, *J* = 14.9 Hz), 1.95 (m, 4H), 1.67 (s, 3H), 1.51 (s, 9H), 1.17 (s, 9H), 0.83 (t, 3H, *J* = 7.1 Hz); ¹³C-NMR (100 MHz, C₆D₆, 60 °C) δ 171.6, 170.0, 150.9, 150.5, 140.8, 138.4, 136.1, 134.9, 133.6, 130.5, 129.9, 128.6, 128.5, 128.2, 127.7, 126.9, 119.9, 114.0, 111.4, 83.4, 65.5, 63.9, 60.5, 59.9, 58.4, 58.2, 57.6, 49.9, 31.8, 28.5, 27.5, 25.5, 20.8, 19.8, 14.3; HR-MS (FAB) calcd for C₄₈H₆₅NO₁₁Si [M⁺] 859.4327, found 859.4329.

(1*Z*)-(3*R*)-2-[6-(*tert*-Butyl-diphenyl-silanyloxy)-3-dimethoxymethyl-3-ethoxycarbonylmethyl-hex-1-enyl]-3-(2-hydroxy-ethyl)-6,7-dimethoxy-indole-1-carboxylic acid *tert*-butyl ester

To a solution of **15** (2.47 g, 2.87 mmol) in MeOH (120 mL) was added aqueous K₂CO₃ (0.5 M, 27 mL) at room temperature, which was then stirred for an hour. The reaction mixture was concentrated under reduced pressure to remove MeOH, diluted with CH₂Cl₂ (50 mL), and separated. The aqueous phase was extracted with CH₂Cl₂. The combined organic extracts were washed with brine, dried over MgSO₄, filtered, and evaporated under reduced pressure. Flash column chromatography on silica gel (EtOAc-hexane, 1:3-2:3) afforded an 3-indolylethanol derivative (2.28 g, 96.2%) as pale yellow oil; $[\alpha]_D^{25} -10.1$ (*c* 0.43, CHCl₃); IR (film, cm⁻¹) 3482, 2933, 2858, 1499, 1429, 1369, 1344, 1256, 1152, 1112; ¹H-NMR (400 MHz, C₆D₆, 60 °C) δ 7.78 (m, 4H), 7.24 (m, 6H), 7.11 (d, 1H, *J* = 8.5 Hz), 6.74 (d, 1H, *J* = 8.5 Hz), 6.50 (d, 1H, *J* = 13.0 Hz), 6.10 (d, 1H, *J* = 13.0 Hz), 4.64 (s, 1H), 3.90 (3, 3H), 3.80 (q, 2H, *J* = 7.1 Hz), 3.76 (m, 4H), 3.55 (s, 3H), 3.34 (s, 3H), 3.26 (s, 3H), 2.95-3.10 (m, 1H), 2.80 (d,

1H, $J = 15.0$ Hz), 2.67 (d, 1H, $J = 15.0$ Hz), 1.95 (m, 4H), 1.52 (s, 9H), 1.17 (s, 9H), 0.83 (t, 3H, $J = 7.1$ Hz); ^{13}C -NMR (100 MHz, C_6D_6 , 60 °C) δ 171.6, 150.4, 138.4, 136.0, 134.8, 133.5, 130.4, 129.7, 128.5, 128.1, 127.9, 127.0, 120.1, 114.1, 111.3, 111.2, 83.2, 65.4, 62.4, 60.4, 59.8, 58.3, 58.2, 57.5, 49.7, 31.6, 29.5, 28.4, 27.4, 19.7, 14.2; HR-MS (FAB) calcd for $\text{C}_{46}\text{H}_{63}\text{NO}_{10}\text{Si}$ [M^+] 817.4221, found 817.4218.

(1Z)-(3R)-2-[6-(*tert*-Butyl-diphenyl-silanyloxy)-3-dimethoxymethyl-3-ethoxycarbonylmethyl-hex-1-enyl]-6,7-dimethoxy-3-[2-(2-nitro-benzenesulfonylamino)-ethyl]-indole-1-carboxylic acid *tert*-butyl ester

To a solution of the 3-indolyethanol derivative (2.21 g, 2.71 mmol) in benzene (60 mL) were added PPh_3 (0.99 g, 3.79 mmol), 2-nitrobenzenesulfonamide (*o*-NsNH₂) (0.77 g, 3.79 mmol), and DEAD (40% solution in toluene, 1.71 mL, 3.79 mmol) at room temperature under Ar. After being stirred for 5 minutes, the reaction mixture was cooled in an ice-bath to precipitate triphenylphosphine oxide, filtered, and evaporated under reduced pressure. Flash column chromatography on silica gel (CH_2Cl_2 -hexane, 3:1) afforded a Ns-amide (2.51 g, 92.7%) as yellow oil; $[\alpha]_{\text{D}}^{25} -1.9$ (c 0.31, CHCl_3); IR (film, cm^{-1}) 3322, 2935, 2900, 2859, 1732, 1541, 1501, 1428, 1367, 1258, 1170, 1111; ^1H -NMR (400 MHz, C_6D_6 , 60 °C) δ 7.77 (dt, 4H, $J = 7.3$, 2.2 Hz), 7.69 (d, 1H, $J = 8.5$ Hz), 7.25 (m, 6H), 7.08 (d, 1H, $J = 8.5$ Hz), 6.84 (d, 1H, $J = 8.5$ Hz), 6.68 (td, 1H, $J = 7.6$, 2.0 Hz), 6.63 (td, 1H, $J = 7.6$, 2.0 Hz), 6.38 (d, 1H, $J = 12.9$ Hz), 6.30 (d, 1 H, $J = 12.9$ Hz), 5.24 (br s, 1H), 4.53 (s, 1H), 3.86 (s, 3H), 3.78 (m, 2H), 3.65 (br s, 2H), 3.50 (s, 3H), 3.32 (m, 3H), 3.29 (s, 3H), 3.24 (s, 3H), 3.16 (br s, 1H), 2.63 (d, 1H, $J = 14.7$ Hz), 2.52 (d, 1H, $J = 14.7$ Hz), 1.85 (m, 4H), 1.54 (s, 9H), 1.16 (s, 9H), 0.82 (t, 3H, $J = 7.1$ Hz); ^{13}C -NMR (100 MHz, C_6D_6 , 60 °C) δ 171.4, 150.3, 148.0, 141.0, 138.0, 136.0, 134.7, 134.3, 133.9, 132.4, 131.7, 130.5, 130.1, 129.8, 128.4, 128.1, 127.9, 125.8, 125.0, 119.5, 113.4, 111.2, 110.9, 83.6, 65.3, 60.3, 59.9, 58.5, 58.1, 57.3, 49.6, 43.7, 28.2, 28.0, 27.4, 25.8, 19.7, 14.2; HR-MS (FAB) calcd for $\text{C}_{52}\text{H}_{67}\text{NO}_{13}\text{SSi}$ [M^+] 1001.4164, found 1001.4169.

(1Z)-(3R)-2-(3-Dimethoxymethyl-3-ethoxycarbonylmethyl-6-hydroxy-hex-1-enyl)-6,7-dimethoxy-3-[2-(2-nitro-benzenesulfonylamino)-ethyl]-indole-1-carboxylic acid *tert*-butyl ester (16)

To a solution of the Ns-amide (2.48 g, 2.47mmol) in THF (50 mL) was added TBAF (1 M solution in THF, 5.0 mL, 5.0 mmol) at room temperature. After being stirred for an hour, the reaction mixture was diluted with CH₂Cl₂ (30 mL) and washed with brine (20 mL x 2). The aqueous phase was extracted with CH₂Cl₂ (10 mL). The combined organic extract was dried over MgSO₄, filtered, and evaporated under reduced pressure. Flash column chromatography on silica gel (EtOAc-hexane, 1:1-2:1 gradient) afforded **16** (1.76 g, 93.0%) as a yellow oil; $[\alpha]_D^{25}$ -10.8 (*c* 0.30, CHCl₃); IR (film, cm⁻¹) 3568, 3316, 2980, 2938, 1732, 1542, 1501, 1444, 1368, 1344, 1258, 1164, 1089, 1072; ¹H-NMR (400 MHz, C₆D₆, 60 °C) δ 7.73 (d, 1H, *J* = 7.8 Hz), 7.08 (d, 1H, *J* = 7.8 Hz), 6.91 (d, 1H, *J* = 7.8 Hz), 6.72 (t, 1H, *J* = 7.8 Hz), 6.66 (t, 1H, *J* = 7.8 Hz), 6.61 (d, 1H, *J* = 7.8 Hz), 6.38 (d, 1H, *J* = 12.7 Hz), 6.02 (d, 1H, *J* = 12.7 Hz), 4.50 (s, 1H), 3.90 (s, 3H), 3.50 (s, 3H), 3.32 (m, 3H), 3.28 (s, 3H), 3.22 (s, 3H), 2.95 (m, 1H), 2.61 (d, 1H, *J* = 15.6 Hz), 2.53 (d, 1H, *J* = 15.6 Hz), 1.82-1.61 (m, 4H), 1.55 (s, 9H), 0.86 (t, 3H, *J* = 6.8 Hz); ¹³C-NMR (100 MHz, C₆D₆, 60 °C) δ 171.8, 150.9, 150.7, 148.4, 141.2, 138.2, 134.7, 134.0, 132.8, 132.0, 130.7, 130.4, 128.1, 126.1, 125.2, 119.7, 113.7, 111.5, 111.2, 83.9, 63.6, 60.5, 60.1, 58.42, 58.41, 57.4, 49.7, 43.7, 31.3, 28.5, 28.1, 26.1, 14.3; HR-MS (FAB) calcd for C₃₆H₄₉NO₁₃S [M⁺] 763.2986, found 763.2978.

(11R)-(12Z)-11-Dimethoxymethyl-11-ethoxycarbonylmethyl-1,2-dimethoxy-7-(2-nitro-benzenesulfonyl)-6,7,8,9,10,11-hexahydro-5H-7,14-diaza-cycloundeca[*a*]indene-14-carboxylic acid *tert*-butyl ester (17)

To a solution of **16** (1.72g, 2.25 mmol) in benzene (60 mL) were added PPh₃ (0.76 g, 2.91 mmol), and DEAD (40% solution in toluene, 1.32 mL, 2.91 mmol) at room temperature under

Ar. After being stirred for 5 minutes, the reaction mixture was evaporated under reduced pressure. The residue was slurried in EtOAc-hexane (1:1) to precipitate triphenylphosphine oxide, filtered, and evaporated under reduced pressure. Flash column chromatography on silica gel (CHCl₃-MeOH, 150:1) afforded **17** (0.55 g, 92.4%) as yellow foam; $[\alpha]_D^{25} +14.3$ (*c* 0.33, CHCl₃); IR (film, cm⁻¹) 2981, 2939, 2834, 1732, 1544, 1503, 1371, 1348, 1257, 1153, 1073; ¹H-NMR (400 MHz, C₆D₆, 60 °C) δ 7.52 (d, 1H, *J* = 8.5 Hz), 7.21 (d, 1H, *J* = 8.5 Hz), 6.78 (m, 2H), 6.76 (d, 1H, *J* = 8.5 Hz), 6.60 (br t, 1H, *J* = 7.8 Hz), 6.29 (d, 1H, *J* = 24.9 Hz), 6.26 (d, 1H, *J* = 24.9 Hz), 4.63 (s, 1H), 3.96 (dd, 1H, *J* = 7.1, 2.4 Hz), 3.94 (dd, 1H, *J* = 7.1, 2.4 Hz), 3.91 (s, 3H), 3.78 (m, 2H), 3.51 (s, 3H), 3.30 (s, 3H), 3.28 (s, 3H), 3.11-3.24 (m, 2H), 2.95 (d, 1H, *J* = 16.0 Hz), 2.86 (dd, 2H, *J* = 12.0, 6.0 Hz), 2.60 (d, 1H, *J* = 16.0 Hz), 2.02 (m, 1H), 1.94 (m, 1H), 1.84 (m, 2H), 1.48 (s, 9H), 0.98 (t, 3H, *J* = 7.1 Hz); ¹³C-NMR (100 MHz, C₆D₆, 60 °C) δ 171.7, 151.1, 150.4, 149.1, 141.9, 138.0, 133.7, 133.3, 132.7, 131.3, 130.7, 127.8, 126.5, 123.8, 120.8, 115.2, 111.6, 111.1, 83.5, 60.6, 60.0, 58.5, 58.0, 57.3, 50.4, 49.3, 41.2, 32.3, 28.1, 27.6, 26.1, 14.5; HR-MS (FAB) calcd for C₃₆H₄₇N₃O₁₂S [M⁺] 745.2880, found 745.2871.

(11R)-(12Z)-11-Ethoxycarbonylmethyl-11-formyl-1,2-dimethoxy-7-(2-nitro-benzenesulfonyl)-6,7,8,9,10,11-hexahydro-5H-7,14-diaza-cycloundeca[*a*]indene-14-carboxylic acid *tert*-butyl ester

To a solution of **17** (1.46 g, 1.95 mmol) in CH₂Cl₂ (45 mL) was added TMSBr (0.34 mL, 2.54 mmol) at -70 °C under Ar. After being stirred for 15 minutes, the reaction mixture was diluted with THF (15 mL), poured into the mixture of phosphate buffer (0.2 M, pH 7.0, 45 mL) and THF (9 mL) with vigorous stirring, and separated. The aqueous phase was extracted with CH₂Cl₂ (15 mL). The combined organic extracts were dried over MgSO₄, filtered, and evaporated under reduced pressure. Since compound **17** was regenerated during post-treatment, the residue was dissolved in CH₂Cl₂ (45 mL), and TMSBr (0.15 mL, 1.17 mmol) was added at -70 °C under Ar. After being stirred for 15 minutes, the same post-treatment was performed. The residue was purified by flash column chromatography on silica gel (EtOAc-hexane, 1:3-1:2 gradient) to afford an aldehyde (1.26 g, 91.9%) as yellow foam; $[\alpha]_D^{25} -18.6$ (*c* 0.31, CHCl₃); IR (film, cm⁻¹) 2981, 2938, 2837, 1732, 1543, 1504, 1372, 1348, 1257, 1152,

1070; ^1H -NMR (400 MHz, DMSO, 100 °C) δ 9.52 (s, 1H), 7.88-7.76 (m, 4H), 7.26 (d, 1H, J = 8.8 Hz), 6.97 (d, 1H, J = 7.8 Hz), 6.50 (d, 1H, J = 11.7 Hz), 6.19 (d, 1H, J = 11.7 Hz), 4.05 (q, 2H, J = 6.8 Hz), 3.88 (br s, 5H), 3.83 (s, 3H), 3.26 (m, 2H), 2.99 (br s, 2H), 2.87 (d, 1H, J = 16.6 Hz), 2.70 (d, 1H, J = 16.6 Hz), 1.93-1.63 (m, 4H), 1.52 (s, 9H), 1.18 (t, 3H, J = 6.8 Hz); ^{13}C -NMR (100 MHz, DMSO, 100 °C) δ 200.3, 169.6, 149.6, 148.7, 147.6, 136.6, 133.7, 131.6, 131.1, 130.9, 129.4, 129.0, 124.8, 123.6, 122.5, 114.6, 114.0, 110.3, 83.6, 59.5, 59.4, 56.9, 52.4, 48.6, 48.3, 29.6, 26.8, 26.1, 23.4, 13.3; HR-MS (FAB) calcd for $\text{C}_{34}\text{H}_{41}\text{N}_3\text{O}_{11}\text{S}$ $[\text{M}^+]$ 699.2462, found 699.2469.

Pentacyclic Compound 18

To a solution of **18** (1.14 g, 1.62 mmol) in CH_3CN (20 mL) was added Cs_2CO_3 (1.72 g, 4.87 mmol) and thiophenol (0.39 mL, 3.73 mmol). After being stirred for 20 minutes at 55 °C, resulting suspension was diluted with CH_2Cl_2 , cooled in an ice-bath, filtered through a pad of Celite, and evaporated under reduced pressure. The residue was dissolved in CH_2Cl_2 (20 mL), and Me_2S (6 mL) and TFA (5 mL) were added sequentially at room temperature. After being stirred for 5 minutes, the reaction mixture was evaporated under reduced pressure and dissolved in EtOAc (30 mL). Phosphate buffer (0.2 M, pH 7.8, 120 mL) was added to the solution, stirred for 30 minutes at 5 °C, and separated. The aqueous phase was extracted with EtOAc (20 mL x 1, 10 mL x 1). The combined organic extracts were washed with brine, dried over MgSO_4 , filtered, and evaporated under reduced pressure. Flash column chromatography on silica gel (EtOAc-hexane, 1:1-2:1) afforded **18** (0.36 g, 56.4%) as yellowish brown oil; $[\alpha]_{\text{D}}^{25}$ +417.7 (c 0.15, CHCl_3); IR (film, cm^{-1}) 2937, 2776, 1731, 1429, 1256, 1174, 1080; ^1H -NMR (400 MHz, CDCl_3) δ 6.94 (d, 1H, J = 7.8 Hz), 6.84 (d, 1H, J = 10.0 Hz), 6.72 (d, 1H, J = 7.8 Hz), 6.54 (dd, 1H, J = 10.0, 2.0 Hz), 4.19 (s, 3H), 3.97 (q, 2H, J = 7.1 Hz), 3.89 (s, 3H), 3.16 (br d, 1H, J = 11.0 Hz), 3.09 (t, 1H, J = 7.0 Hz), 2.67 (m, 2H), 2.42 (br t, 1H, J = 10.5 Hz), 2.32 (br d, 1H, J = 13.7 Hz), 2.21 (td, 1H, J = 10.5, 7.0 Hz), 1.81 (d, 1H, J = 15.5 Hz), 1.72 (d, 1H, J = 15.5 Hz), 1.69 (br s, 2H), 1.36 (td, 1H, J = 13.7, 5.3 Hz), 1.14 (t, 3H, J = 7.1 Hz); ^{13}C -NMR (CDCl_3) δ 182.9, 170.1, 151.7, 149.1, 145.2, 141.6, 139.1, 123.9, 113.9, 109.1, 68.9, 62.2, 61.8, 60.2, 56.3, 52.5, 50.6, 45.3, 39.7, 38.0, 33.9, 22.8, 14.0; HR-MS (FAB) calcd for $\text{C}_{23}\text{H}_{29}\text{N}_2\text{O}_4$ $[(\text{M}+\text{H})^+]$ 397.2127, found 397.2124.

Methylamine **19**

To a solution of **18** (333 mg, 0.84 mmol) in MeOH (20 mL) was added HCHO (37% in water, 1.3 mL 16.8 mmol), phosphate buffer (0.2 M, pH 7.0, 5 mL), and then NaBH₃CN (317 mg, 5.04 mmol) at -70 °C. The reaction mixture was stirred at -70 °C for additional 30 minutes and warmed to room temperature over a period of 2 hours. To the reaction mixture were added EtOAc (20 mL) and brine (15 mL), and separated. The aqueous phase was extracted with EtOAc (15 mL). The combined organic extracts were washed with brine, dried over MgSO₄, filtered, and evaporated under reduced pressure. Flash column chromatography on silica gel (5% MeOH in CHCl₃-hexane 1:1) afforded a methylamine **19** (231 mg, 66.7%) as yellowish brown oil; $[\alpha]_D^{25} +65.3$ (*c* 0.19, CHCl₃); IR (film, cm⁻¹) 2933, 2782, 1732, 1611, 1475, 1266, 1175, 1070; ¹H-NMR (400 MHz, CDCl₃) δ 6.73 (d, 1H, *J* = 8.1 Hz), 6.24 (d, 1H, *J* = 8.1 Hz), 6.12 (dd, 1H, *J* = 9.3, 5.0 Hz), 5.97 (d, 1H, *J* = 9.3 Hz), 4.03-3.92 (m, 2H), 3.81 (s, 3H), 3.71 (s, 3H), 3.63 (d, 1H, *J* = 5.0 Hz), 3.12 (d, 1H, *J* = 9.8 Hz), 3.08 (s, 3H), 3.05 (d, 1H, *J* = 8.6 Hz), 2.39 (d, 1H, *J* = 15.1 Hz), 2.32 (q, 1H, *J* = 8.6 Hz), 2.22 (br s, 1H), 2.12 (d, 1H, *J* = 13.2 Hz), 2.04 (m, 2H), 1.99 (d, 1H, *J* = 15.1 Hz), 1.94 (d, 1H, *J* = 13.2 Hz), 1.60 (br s, 2H), 1.41 (br t, 1H, *J* = 13.2 Hz), 1.15 (t, 3H, *J* = 7.1 Hz); ¹³C-NMR (100 MHz, CDCl₃) δ 171.4, 153.2, 143.2, 137.7, 133.4, 130.8, 125.2, 118.1, 101.6, 75.9, 72.8, 60.4, 59.7, 55.8, 53.1, 52.4, 51.6, 45.0, 37.7, 36.2, 34.8, 22.8, 14.1; HR-MS (FAB) calcd for C₂₄H₃₂N₂O₄ [M⁺] 412.2362, found 412.2358.

(-)-Aspidophytine (**2**)

To a solution of **19** (181 mg) in EtOH (12 mL) was added NaOH (1 M, 4 mL) at 70 °C under Ar. After being stirred for 2.5 hours, the reaction mixture was cooled to 5 °C, and concd HCl was added dropwise until pH reached to 8.0. The resulting mixture was evaporated under reduced pressure to dryness. The residue was dissolved *t*-BuOH-H₂O (1:2) at 5 °C under Ar, and solid NaHCO₃ (0.55 g, 6.59 mmol) was added followed by solid K₃Fe(CN)₆ (1.08 g, 3.29 mmol) and warmed to room temperature immediately. After stirring an hour, the reaction

mixture was cooled at 5 °C, and additional NaHCO₃ (100 mg, 1.20 mmol) and K₃Fe(CN)₆ (200 mg, 0.61 mmol) were added. The reaction mixture was stirred at room temperature for additional 15 min, and diluted with water (10 ml), extracted with CH₂Cl₂ (15 mL x 1, 5 mL x 2). The combined organic extracts were washed with sat NaHCO₃ (10 mL). The aqueous layer was back-extracted with CH₂Cl₂ (5 mL). The combined extracts were washed with brine, dried over MgSO₄, filtered, and evaporated under reduced pressure. Flash column chromatography on silica gel (5% MeOH in CHCl₃-hexane 1:1) afforded aspidophytine (**2**) (66 mg, 39.4%) as white needles; $[\alpha]_D^{25}$ -122.0 (*c* 0.16, CHCl₃) (Lit.² -118.4); Mp (CH₂Cl₂-MeOH, 1:2) 198.6-201.9 °C (Lit. 196-198 °C); IR (film, cm⁻¹) 2944, 2851, 1750, 1608, 1493, 1466, 1446, 1417, 1267, 1222, 1133, 1069; ¹H-NMR (400 MHz, CDCl₃) δ 6.96 (d, 1H, *J* = 8.3 Hz), 6.19 (d, 1H, *J* = 8.3 Hz), 5.84 (dd, 1H, *J* = 10.2, 2.2 Hz), 5.52 (dd, 1H, *J* = 10.2, 1.3 Hz), 3.78 (s, 3H), 3.75 (s, 3H), 3.67 (t, 1H, *J* = 1.8 Hz), 3.19 (q, 1H, *J* = 8.3 Hz), 3.15 (s, 3H), 3.07 (m, 1H), 2.90 (m, 1H), 2.73 (br d, 1H, *J* = 11.5 Hz), 2.36 (d, 1H, *J* = 16.4 Hz), 2.30 (ddd, *J* = 12.9, 8.6, 3.5 Hz), 2.23 (d, 1H, *J* = 16.4 Hz), 2.07 (ddd, 1H, *J* = 12.9, 10.5, 6.8 Hz), 1.71 (br d, 1H, *J* = 12.7 Hz), 1.64-1.51 (m, 3H); ¹³C-NMR (100 MHz, CDCl₃) δ 175.7, 153.6, 143.4, 133.4, 130.3, 128.9, 125.3, 125.2, 119.9, 107.0, 101.8, 96.0, 71.6, 61.1, 56.9, 55.6, 53.4, 47.7, 47.2, 43.2, 41.3, 35.2, 35.1, 34.4, 21.4; HR-MS (FAB) calcd for C₂₂H₂₆N₂O₄ [M⁺] 382.1963, found 382.1963.

References

- (1) Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092.
- (2) He, F.; Bo, Y.; Altom, J. D.; Corey, E. J. *J. Am. Chem. Soc.* **1999**, *121*, 6771.