Total Synthesis of (±)-Actinophyllic Acid

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Supporting Information
(57 pages)

Part 1. Experimental Procedures

General Experimental Procedures. Reactions were performed in oven-dried glassware under a positive pressure of nitrogen or argon. A 3-way stopcock was used for reactions performed at temperatures below 0 °C. All other reactions employed rubber septa. Dichloromethane, *N*,*N*-dimethylformamide (DMF), methanol (MeOH), benzene (PhH), toluene (PhMe), and acetonitrile (MeCN) were dried by passage through activated alumina. Tetrahydrofuran (THF) was dried and deoxygenated by distillation from sodium/benzophenone ketyl. Diisopropylamine and triethylamine were distilled from calcium hydride. Trifluoroacetic acid (TFA) used as an eluent additive for reverse phase C18 chromatography was purified by distillation. Anhydrous carbon tetrachloride was purchase from Aldrich and used without modification. *N*-Bromosuccinimide (NBS) was recrystallized from water and stored at –20 °C. The oxidant $[Fe(DMF)_3Cl_2][FeCl_4]$ was prepared by the procedure of Tobinaga and Kotani and stored in a desiccator.[1] Anhydrous cerium trichloride was purchased from Strem and stored in an inert atmosphere (N_2) box. All other commercial reagents were used without further purification. *N*-Butyllithium was titrated with diphenylacetic acid. Thin layer chromatography was performed on Merck 60 F_{254} precoated silica gel plates or EM Science RP-18 F_{254}s precoated silica gel plates. TLC plates were visualized by exposure to UV light (254 nm) or stained with *p*-anisaldehyde or ceric ammonium molybdate. Flash column chromatography was performed using normal phase silica gel (60 Å, 230–240 mesh, Merck KGA) or reverse phase C18 silica gel (125 Å, 55–105 mesh, Waters). Neutralized silica gel was prepared by adding 5 wt% of pH 7 phosphate buffer solution to dry silica gel and mixing by rotation in a round-bottom flask. Reverse phase C18 HPLC chromatography was performed using a 250 mm x 21.20 mm Phenomenex Luna 5μm column. All NMR spectra were recorded with Brucker Advanced spectrometers. ^{1}H NMR spectra were recorded at 500 MHz or 600 MHz as indicated. ^{13}C spectra were recorded at 125 MHz and hydrogen multiplicities were determined by HMQC correlation. Infrared spectra were recorded using an ASI ReactIR 1000 or a Varian 800 spectrometer. Mass spectra were obtained with a Micromass LCT spectrometer.

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[1] Tobinaga, S.; Kotani, E. *J. Am. Chem. Soc*. **1972**, *94*, 309–310.

2-[2-(2-Nitrophenyl)acetyl]malonic acid di-*tert*-butyl ester (8). The general procedure of Mahboobi and Bernauer was followed.[2] Thionyl chloride (4.4 mL, 60 mmol) was added to a mixture of 2-(nitrophenyl)acetic acid (10.0 g, 55.2 mmol) and DMF (0.50 mL, 6.5 mmol) in 600 mL of benzene. This suspension was stirred for 20 h at room temperature. During this time, the reaction mixture became homogeneous. This solution was concentrated *in vacuo* to afford a dark red oil. A 300 mL portion of toluene was added to this oil, and the solution was concentrated *in vacuo* once more.

In a separate flask, magnesium turnings (1.5 g, 61 mmol), which were crushed with a mortar and pestle immediately prior to use, were combined with 15 mL of methanol. This mixture was stirred in a room temperature water bath, and a 10 mL portion of MeOH was added to facilitate stirring once the mixture became thick. After 20 h at room temperature, di-*tert*-butyl malonate (17 mL, 61 mmol) was added and the reaction mixture was concentrated *in vacuo*. The colorless solid obtained was dissolved in 20 mL of THF. A solution of the acid chloride described in the preceding paragraph in 15 mL of THF was added by cannula and residue in the transfer vessel was washed into the reaction solution with an additional 5 mL of THF. The reaction solution was maintained at 60 ^{o}C for 3.5 h before it was diluted with 50 mL of 1 N HCl and 50 mL of EtOAc. The layers were separated, and the aqueous layer was extracted with dichloromethane (2 x 50 mL). The combined organic layers were dried with $MgSO_4$ and concentrated *in vacuo* to afford 23.9 g of a red oil. This residue was purified by flash silica gel chromatography (20%→30%→40% Et_2O in hexanes) to afford 16 g (78%) of keto diester **8** as a colorless oil: ^{1}H NMR (600 MHz, $CDCl_3$, two tautomers) δ 13.4 (s, 1H of minor tautomer), 8.12 (d, J = 8.1 Hz, 1H of major tautomer), 8.00 (d, J = 8.1 Hz, 1H of minor tautomer), 7.60 (t, J = 7.0 Hz, 1H of major tautomer) 7.57 (t, J = 7.3 Hz, 1H of minor tautomer), 7.49–7.46 (m, 1H of both tautomers), 7.43 (t, J = 7.4 Hz, 1H of major tautomer), 7.34 (d, J = 7.6 Hz, 1H of minor tautomer), 4.48 (s, 1H of major tautomer), 4.41 (s, 2H of major tautomer), 4.20 (s, 2H of minor tautomer), 1.53 (s, 18 H of major tautomer), 1.50 (s, 18H of minor tautomer); ^{13}C NMR (125 MHz, $CDCl_3$, only signals for the major tautomer are reported) δ 195.8 (C), 171.0 (C), 149.0 (C), 133.8 (CH), 133.8 (CH), 129.6 (C), 128.8 (CH), 125.5 (CH), 83.6 (C), 67.5 (CH), 46.6 (CH_2), 28.1 (CH_3);

[2] Mahboobi, S.; Bernauer, K. *Helv. Chim. Acta* **1988**, *71*, 2034–2041.

IR (thin film) 2981, 2937, 1748, 1717, 1526, 1347, 1306, 1254, 1138 cm^{-1}; HRMS (ESI-TOF) *m/z* calcd for $C_{19}H_{25}NO_7Na$ $(M + Na)^+$ 402.1529, found 402.1532.

2-(1*H*-Indol-2-yl)malonic acid di-*tert*-butyl ester (9). The general procedure of Mahboobi and Bernauer was followed.[2] Pearlman's catalyst (0.6 g, palladium hydroxide, 20 wt% Pd on carbon, wet) was combined with a solution of keto diester **8** (11.9 g, 31.4 mmol) in 150 mL of isopropanol. The reaction mixture was stirred in a pressure vessel under an atmosphere of hydrogen (700 psi) for 72 h at room temperature. The reaction mixture was diluted with 100 mL of EtOAc to dissolve the precipitate that had formed. The resulting solution was filtered through Celite, and the filtrate was concentrated *in vacuo* to afford 10 g of a colorless solid. This residue was crystallized from 45 mL of toluene at 100 °C to afford 6.7 g of colorless crystals. The mother liquor was concentrated, purified by silica gel chromatography (10% Et_2O in hexanes), and crystallized from 5 mL of toluene at 100 °C to afford a second crop of 0.43 g of colorless crystals. The two crops were combined to give 7.1 g (69%) of indole-2-malonate **9**: mp 146–147 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.03 (s, 1H), 7.57 (d, *J* = 7.8 Hz, 1H), 7.37 (d, *J* = 8.1 Hz, 1H), 7.17 (t, *J* = 7.4 Hz, 1H), 7.08 (t, *J* = 7.5 Hz, 1H), 6.45 (s, 1H), 4.72 (s, 1H), 1.48 (s, 18H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.8 (C), 136.6 (C), 129.8 (C), 127.9 (C), 122.2 (CH), 120.6 (CH), 119.9 (CH), 111.4 (CH), 103.0 (CH), 83.1 (C), 53.8 (CH), 28.0 (CH_3); IR (thin film) 3392, 3004, 2983, 1746, 1715, 1291, 1131 cm^{-1}; HRMS (ESI-TOF) *m/z* calcd for $C_{19}H_{25}NO_4Na$ $(M + Na)^+$ 354.1681, found 354.1678.

2-[3-(1-*tert*-Butoxycarbonyl-3-oxopiperidin-2-yl)-1*H*-indol-2-yl] malonic acid di-*tert*-butyl ester (11). *N*-Bromosuccinimide (0.775 g, 4.35 mmol) and azobisisobutyronitrile (1 mg, 0.006 mmol) were added to a solution of 1-(*tert*-butoxycarbonyl)-3-piperidone[3] (0.867 g, 4.35 mmol) in 25 mL of anhydrous CCl_4. The resulting suspension was stirred and heated at reflux for 50 min before it was cooled in an ice bath for 20 min. This suspension was filtered, and the pale yellow filtrate was concentrated *in vacuo* in a foil-wrapped flask to afford crude bromopiperidone **10** as a yellow oil. This oil was used immediately in the subsequent reaction without purification. Diagnostic data: ^{1}H NMR (600 Mz, $CDCl_3$) δ 6.65 (s, 1H), 3.99 (d, *J* = 8.7 Hz, 1H), 3.22

[3] 1-(*tert*-Butoxycarbonyl)-3-piperidone was prepared according to: Kubota, H.; Kakefuda, A.; Watanabe, T.; Taguchi, K.; Ishii, N.; Masuda, N.; Sakamoto, S.; Tsukamoto, S. *Bioorg. Med. Chem. Lett*. **2003**, *13*, 2155–2158.

(br t, *J* = 11.1 Hz, 1H), 3.13 (ddd, *J* = 15.9, 13.1, 6.1 Hz, 1H), 2.46 (dt, *J* = 15.7, 4.1 Hz, 1H), 2.21–2.16 (m, 1H), 1.96–1.88 (m, 1H), 1.53 (s, 9H).

This sample of crude bromopiperidone **10** was dissolved in 4.2 mL of DMF. Indole-2-malonate **9** (0.900 g, 2.72 mmol) was added and the solution was maintained at room temperature for 30 min. The reaction solution was diluted with 5 mL of a saturated aqueous solution of Na_2CO_3 and 10 mL of water, and extracted with EtOAc (2 x 20 mL). The combined organic layers were washed with water (2 x 50 mL), washed with brine (1 x 30 mL), dried with $MgSO_4$, and concentrated *in vacuo* to afford 1.72 g of a brown solid. This residue was purified by flash silica gel chromatography (20%→30% Et_2O in hexanes) to afford 1.2 g (85%) of piperidone-substituted indole derivative **11** as a colorless amorphous solid: ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.25 (s, 1H), 7.37 (t, *J* = 8.7 Hz, 2H), 7.17 (t, *J* = 7.4 Hz, 1H), 7.06 (t, *J* = 7.5 Hz, 1H), 5.93 (s, 1H), 5.15 (s, 1H), 4.02–3.97 (m, 1H), 3.36–3.32 (m, 1H), 2.73 (dt, *J* = 16.2, 7.0 Hz, 1H), 2.61 (dt, *J* = 16.2, 6.9, 1H), 2.17–2.10 (m, 1H), 2.11–2.03 (m, 1H), 1.53 (s, 9H), 1.52 (s, 9H), 1.51 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 207.6 (C), 166.8 (C), 166.8 (C), 154.7 (C), 135.9 (C), 128.7 (C), 125.6 (C), 122.3 (CH), 120.3 (CH), 119.3 (CH), 111.8 (CH), 109.1 (C), 83.4 (C), 83.3 (C), 81.0 (C), 61.2 (CH), 51.5 (CH), 39.9 (CH_2), 37.7 (CH_2), 28.5 (CH_3), 28.1 (CH_3), 28.0 (CH_3), 22.7 (CH_2); IR (thin film) 3436, 2979, 1719, 1686, 1368, 1250, 1156, 1136 cm^{-1}; HRMS (ESI-TOF) *m/z* calcd for $C_{29}H_{40}N_2O_7Na$ $(M + Na)^+$ 511.2733, found 551.2727.

2-(*tert*-butoxycarbonyl)-6,6-(di-*tert*-butoxycarbonyl)-1,2,3,4,5,6-hexahydro-l,5-methanoazocino[4,3-*b*]indole-12-one (12). A 3.2 M solution of *n*-butyllithium (18.8 mL, 60.3 mmol) was slowly added to a –78 °C solution of diisopropylamine (9.0 mL, 64 mmol) in 85 mL of THF. This solution was maintained at –78 °C for 30 min. A –78 °C solution of indole derivative **11** (10.3 g, 19.5 mmol) in 85 mL of THF was added to the LDA solution by cannula, and the residue in the transfer vessel was washed into the reaction solution with an additional 20 mL of THF at –78 °C. The reaction solution was maintained at –78 °C for 15 min before a –78 °C solution of $[Fe(DMF)_3Cl_2][FeCl_4]$ (37 g, 68 mmol) in 85 mL of THF was added by cannula. The resulting dark-blue solution was stirred at –78 °C for 5 min before the solution was allowed to warm to room temperature for 1.5 h. This solution was poured into 500 mL of a 1:1 mixture of water and EtOAc.

The layers were separated and the aqueous layer was extracted with EtOAc (3 x 250 mL). The organic layers were combined, washed with water (2 x 500 mL), dried with $MgSO_4$, and concentrated *in vacuo* to afford 10.2 g of a brown solid. This residue was dissolved in 120 mL of toluene at 100 °C and allowed to crystallize for 48 h at –20 °C to afford 6.5 g (63%) of tetracyclic ketone **12** as colorless crystals: mp 209 °C dec; ^{1}H NMR (500 MHz, $CDCl_3$, two rotamers) δ 8.74 (s, 1H), 8.70 (s, 1H), 7.75 (br s, 1H), 7.62 (br d, *J* = 7.5 Hz, 1H), 7.45–7.40 (m, 1H of both rotamers), 7.28–7.25 (m, 1H of both rotamers), 7.18–7.15 (m, 1H of both rotamers), 5.87 (s, 1H), 5.72 (s, 1H), 3.85 (br d, *J* = 9.0 Hz, 1H), 3.73–3.62 (m, 1H), 3.47 (s, 1H of both rotamers), 3.02–2.82 (m, 1H of both rotamers), 2.32–2.18 (br m, 1H of both rotamers), 2.05–1.95 (m, 1H of both rotamers), 1.60 (s, 9H), 1.56 (s, 9H of both rotamers), 1.41 (s, 9H of both rotamers), 1.41 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$, two rotamers) δ 203.0 (C), 170.1 (C), 166.9 (C), 166.6 (C), 154.4 (C), 154.0 (C), 137.5 (C), 130.5 (C), 130.3 (C), 125.0 (C), 123.8 (CH of both rotamers), 120.5 (CH of both rotamers), 120.5 (CH) 119.4 (CH), 111.7 (CH), 111.4 (CH), 110.2 (C), 109.5 (C), 84.4 (C), 84.0 (C), 83.9 (C), 81.1 (C), 80.5 (C), 62.4 (C), 56.2 (CH), 54.8 (CH), 47.7 (CH), 47.5 (CH), 36.8 (CH_2), 35.3 (CH_2), 31.1 (CH_2), 31.0 (CH_2), 28.7 (CH_3), 28.4 (CH_3), 28.1 (CH_3 of both rotamers), 27.9 (CH_3 of both rotamers); IR (thin film) 3319, 2979, 1733, 1395, 1366, 1154, 1138 cm^{-1}; HRMS (ESI-TOF) *m/z* calcd for $C_{29}H_{38}N_2O_7Na$ $(M + Na)^+$ 549.2577, found 549.2580.

(1*R,5*R**,12*R**)-2-(*tert*-butoxycarbonyl)-6,6-(di-*tert*-butoxycarbonyl)-12-hydroxy-12-vinyl-1,2,3,4,5,6-hexahydro-l,5-methanoazocino[4,3-*b*]indole (13).** A suspension of anhydrous cerium trichloride (1.17 g, 4.75 mmol) in 10 mL of THF was stirred for 20 h at room temperature. This suspension was cooled to –78 °C and drops of a 1.7 M solution of *tert*-butyllithium were added until the slurry became a persistent faint pink color. This suspension was then allowed to warm to room temperature. A solution of tetracyclic ketone **12** (1.0 g, 1.9 mmol) in 10 mL of THF was added by cannula, and the residue in the transfer vessel was washed into the reaction mixture with an additional 5 mL of THF. This suspension was stirred for 2 h at room temperature before it was cooled to –78 °C. A 1.15 M solution of vinylmagnesium bromide[4] (4.1 mL, 4.7 mmol) was

[4] Vinylmagnesium bromide was prepared according to: Scott, W. J.; Crisp, G. T.; Stille, J. K. *Organic Syntheses* **1990**, *68*, 116–129.

slowly added, and the heterogeneous reaction mixture was stirred at –70 °C for 24 h. A solution of 1 mL of acetic acid in 5 mL of THF was added to the –70 °C mixture before it was allowed to warm to room temperature. The reaction mixture was then diluted with 50 mL of Et_2O and 50 mL of H_2O. The layers were separated and the aqueous layer was extracted with Et_2O (2 x 50 mL). The combined organic layers were washed with a saturated aqueous solution of Na_2CO_3 (2 x 25 mL), dried with $MgSO_4$, and concentrated *in vacuo* to afford 1.20 g of an orange solid. This residue was filtered and washed through a plug of silica gel with Et_2O to afford 1.1 g (99%) of a pale yellow amorphous solid: ^{1}H NMR (600 MHz, $CDCl_3$, two rotamers) δ 8.48 (s, 1H of both rotamers), 7.74 (d, *J* = 8.0 Hz, 1H), 7.61 (d, *J* = 7.9 Hz, 1H), 7.40–7.36 (m, 1H of both rotamers), 7.22–7.17 (m, 1H of both rotamers), 7.12–7.7.07 (m, 1H of both rotamers), 6.53–6.46 (m, 1H of both rotamers), 5.67 (m, 1H of both rotamers), 5.59 (s, 1H), 5.42 (s, 1H), 5.39–5.36 (m, 1H of both rotamers), 3.76 (dd, *J* = 13.7, 6.1 Hz, 1H), 3.55 (dd, *J* = 13.0, 5.7 Hz, 1H), 3.16 (s, 1H), 3.13 (s, 1H), 3.08 (br s, 1H), 2.78 (s, 1H), 2.60–2.52 (m, 1H of both rotamers), 2.14–2.05 (m, 1H of both rotamers), 1.60–1.55 (m, 1H of both rotamers), 1.60 (s, 9H), 1.54 (s, 9H of both rotamers), 1.51 (s, 9H of both rotamers), 1.40 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$, two rotamers) δ 169.9 (C), 169.6 (C), 168. 4 (C), 168.3 (C), 154.9 (C), 154.4 (C), 141.7 (CH), 141.7 (CH), 136.9 (C), 136.8 (C), 129.5 (C), 129.2 (C), 125.3 (C), 122.6 (CH), 122.5 (CH), 120.3 (CH), 119.7 (CH), 119.6 (CH), 119.4 (CH), 116.0 (CH2), 115.9 (CH2), 111.2 (CH), 110.9 (CH), 110.6 (C), 110.4 (C), 84.2 (C), 83.9 (C), 83.7 (C), 83.5 (C), 80.2 (C), 79.7 (C), 72.6 (C), 72.5 (C), 60.6 (C), 60.5 (C), 51.7 (CH), 50.4 (CH), 42.4 (CH),. 42.3 (CH), 36.1 (CH_2), 34.7 (CH_2), 28.9 (CH_3), 28.6 (CH_3), 28.1 (CH_3 of both rotamers), 28.0 (CH_3 of both rotamers), 25.4 (CH_2), 25.0 (CH_2); IR (thin film) 3485, 2977, 1717, 1675, 1368, 1156, 1140 cm^{-1}; HRMS (ESI-TOF) *m/z* calcd for $C_{31}H_{42}N_2O_7Na$ $(M + Na)^+$ 577.2890, found 577.2897.

Pentacyclic Diester 14. Trifluoroacetic acid (2.0 mL) was added to a 0 °C solution of allylic alcohol **13** (0.30 g, 0.54 mmol) in 15 mL of dichloromethane. The solution was maintained at 0 °C for 1.25 h, before it was diluted with 20 mL of a saturated aqueous solution of Na_2CO_3. The layers were separated and the aqueous layer was extracted with dichloromethane (4 x 20 mL). The combined organic layers were dried with $MgSO_4$ and concentrated *in vacuo* to afford 0.27 g of the secondary amine as a

pale yellow solid. This material was used in the next step without further purification. Diagnostic data: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.55 (s, 1H), 7.55 (d, *J* = 7.8 Hz, 1H), 7.41 (d, *J* = 8.1 Hz, 1H), 7.20 (t, *J* = 7.1 Hz, 1H), 7.10 (t, *J* = 7.2 Hz, 1H), 6.84 (dd, *J* = 17.4, 10.8 Hz, 1H), 5.66 (d, J = 17.5 Hz, 1H), 5.41 (d, J = 10.9 Hz, 1H), 4.25 (s, 1H), 3.19 (appar s, 1H), 2.76 (appar s, 1H), 2.52 (m, 2H), 2.29 (br s, 1H), 2.17 (s, 1H), 2.17–2.05 (m, 1H), 1.53 (s, 9H), 1.50 (s, 9H).

Camphorsulfonic acid (0.11 g, 0.46 mmol) and paraformaldehyde (16 mg, 0.54 mmol) were added to a solution of the secondary amine described in the preceding paragraph (0.27 g) in 12 mL of benzene. The reaction mixture was stirred at 70 ^{o}C for 16 h, before it was diluted with 20 mL of a 1 N aqueous solution of NaOH. The layers were separated and the aqueous layer was extracted with dichloromethane (3 x 20 mL). The combined organic layers were dried with $MgSO_4$ and concentrated *in vacuo* to afford 0.29 g of a yellow solid. This material was used in the next step without further purification.

An analytical sample of pentacyclic diester **14** was obtained by flash silica gel chromatography (neutralized silica gel, 70:20:10 hexanes:acetone:triethylamine) as a colorless amorphous solid: ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.98 (s, 1H), 7.65 (d, *J* = 7.9 Hz, 1H), 7.39 (d, *J* = 8.1 Hz, 1H), 7.23 (t, *J* = 7.6 Hz, 1H), 7.14 (t, *J* = 7.5 Hz, 1H), 4.53 (d, *J* = 5.2 Hz, 1H), 3.68–3.66 (m, 1H), 3.41–4.36 (m, 1H), 3.26–3.14 (m, 3H), 2.69 (br d, *J* = 15.0 Hz, 1H), 2.50–2.44 (m, 1H), 2.22–2.09 (m, 2H), 2.97–1.92 (m, 1H), 1.54 (s, 9H), 1.46 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 213.2 (C), 167.8 (C), 167.5 (C), 135.7 (C), 130.5 (C), 128.0 (C), 123.2 (CH), 120.0 (CH), 118.6 (CH), 111.1 (CH), 110.7 (C), 84.4 (C), 84.1 (C), 61.9 (C), 57.7 (CH), 57.6 (CH), 55.3 (CH), 51.1 (CH_2), 48.1 (CH_2), 34.1 (CH_2), 28.1 (CH_3), 27.9 (CH_3), 26.6 (CH_2); IR (thin film) 3471, 3440, 3058, 2977, 2933, 2877, 1733, 1702, 1474, 1459, 1395, 1370, 1252, 1156, 1084, 1032, 1015, 919, 897, 839 cm^{-1}; HRMS (ESI-TOF) *m/z* calcd for $C_{27}H_{35}N_2O_5$ $(M + H)^+$ 467.2546, found 467.2545.

Amino Acid Trifluoroacetate Salt 15. Trifluoroacetic acid (6 mL) was added to the unpurified pentacyclic diester **14** (0.29 g) described above. The reaction solution was maintained at room temperature for 4.5 h, before it was concentrated *in vacuo* to afford 0.37 g of a dark brown solid. This residue was purified by reverse phase C18

chromatography (20% MeOH in H_2O with 1% TFA) to afford 0.18 g (76% from **13**) of amino acid trifluoroacetate salt **15** as a colorless amorphous solid: ^{1}H NMR (500 MHz, CD_3OD) δ 7.65 (d, *J* = 7.9 Hz, 1H), 7.38 (d, *J* = 8.1 Hz, 1H), 7.21 (t, *J* = 7.5 Hz, 1H), 7.14 (t, *J* = 7.5 Hz, 1H), 5.60 (d, *J* = 7.0 Hz, 1H), 4.43 (d, *J* = 5.1 Hz, 1H), 3.93 (appar q, *J* = 9.4 Hz, 1H), 3.84 (appar t, *J* = 10.1 Hz, 1H), 3.67 (t, *J* = 13.7 Hz, 1H), 3.59–3.52 (m, 2H), 3.35–3.31 (m, 1H), 2.79 (q, *J* = 11.7 Hz, 1H), 2.64 (t, *J* = 15.6 Hz, 1H), 2.50–2.43 (m, 1H), 2.04 (d, *J* = 16.1 Hz, 1H); ^{13}C NMR (125 MHz, CD_3OD, TFA resonances are omitted) δ 208.9 (C), 173.0 (C), 137.6 (C), 136.8 (C), 128.6 (C), 124.3 (CH), 121.5 (CH), 118.7 (CH), 112.4 (CH), 102.3 (C), 61.2 (CH), 56.1 (CH), 52.0 (CH_2), 50.6 (CH), 48.4 (CH_2), 47.4 (CH), 27.4 (CH_2), 21.9 (CH_2); IR (KBr pellet): 3399, 1711, 1674, 1462, 1200, 1140 cm^{-1}; HRMS (ESI-TOF) *m/z* calcd for $C_{18}H_{19}N_2O_3$ $(M - CF_3CO_2)^+$ 311.1396, found 311.1392.

Pentacyclic Ester Trifluoroacetate Salt 16. Procedure A. A 0.5 M solution of methanolic HCl was prepared by adding thionyl chloride (0.18 mL, 2.5 mmol) to 10 mL of methanol at 0 °C. Amino acid trifluoroacetate salt **15** (25 mg, 0.059 mmol) was added to 5 mL of this 0.5 M solution of HCl in methanol. The reaction solution was maintained at 50 °C for 13 h, before it was concentrated *in vacuo* to afford a yellow solid. This material was dissolved in a solution of 3 mL of water and 2 mL of methanol. The solution was maintained at room temperature for 1 h, before it was concentrated *in vacuo* to afford 25 mg of a yellow solid. This residue was purified by reverse phase C18 chromatography (0%→10%→20%→30%→40% MeOH in H_2O with 1% TFA). The appropriate column fractions were combined and a saturated aqueous solution of Na_2CO_3 was added until the solution of combined fractions became basic (as indicated by pH paper). This solution was extracted with dichloromethane (20 mL x 4), and the combined organic layers were dried with $MgSO_4$. Excess trifluoroacetic acid (~0.03 mL) was added before the solution was concentrated *in vacuo* to afford 24 mg (92%) of **16** (a 2:1 mixture of α and β ester epimers, **16a** and **16b**) as a colorless solid.

Analytical samples of **16a** and **16b** were obtained by reverse phase C18 HPLC (40% MeOH in H_2O with 0.1% TFA) as colorless amorphous solids. **16a:** ^{1}H NMR (500 MHz, CD_3OD) δ 7.66 (d, *J* = 8.0 Hz, 1H), 7.37 (d, *J* = 8.1 Hz, 1H), 7.22 (t, *J* = 7.6 Hz, 1H), 7.15 (t, *J* = 7.5 Hz, 1H), 5.60 (d, *J* = 7.1 Hz, 1H), 4.48 (d, *J* = 5.4 Hz, 1H), 3.97–

3.90 (m, 1H), 3.86 (s, 3H), 3.86–3.80 (m, 1H), 3.63 (td, *J* = 14.2, 2.5 Hz, 1H), 3.57 (appar t, *J* = 8.1 Hz, 1H), 3.49 (appar t, *J* = 3.4 Hz, 1H), 3.33 (m, 1H), 2.78 (qd, *J* = 15.0 Hz, 3.6 Hz, 1H), 2.60 (t, *J* = 15. Hz, 1H), 2.48–2.41 (m, 1H), 1.92 (appar d, 17.1 Hz, 1H); ^{13}C NMR (125 MHz, CD_3CN) δ 208.7 (C), 171.3 (C), 136.8 (C), 135.6 (C), 128.3 (C), 124.1 (CH), 121.2 (CH), 119.3 (CH), 112.2 (CH), 103.5 (C), 59.5 (CH), 55.7 (CH), 53.8 (CH_3), 51.1 (CH_2), 50.4 (CH), 47.4 (CH_2), 46.6 (CH), 27.2 (CH_2), 21.7 (CH_2); IR (thin film): 3396, 2960, 1735, 1717, 1671, 1198, 1175 1133 cm^{-1}; HRMS (ESI-TOF) *m/z* calcd for $C_{19}H_{21}N_2O_3$ $(M - CF_3CO_2)^+$ 325.1552, found 325.1559. **16b:** ^{1}H NMR (600 MHz, CD_3OD) δ 7.65 (d, *J* = 8.0 Hz, 1H), 7.38 (d, *J* = 8.1 Hz, 1H), 7.21 (t, *J* = 7.6 Hz, 1H), 7.14 (t, *J* = 7.2 Hz, 1H), 5.57 (d, *J* = 6.7 Hz, 1H), 4.44 (d, *J* = 2.7 Hz, 1H), 3.91–3.85 (m, 1H), 3.80–3.76 (m, 1H), 3.75 (s, 1H), 3.63–3.59 (m, 1H), 3.47 (m, 1H), 3.29–3.24 (m, 2H), 2.83–2.76 (m, 1H), 2.65–2.58 (m, 1H), 2.41–2.35 (m, 1H), 2.27–2.22 (m, 1H); ^{13}C NMR (125 MHz, CD_3CN, TFA resonances omitted) δ 209.4 (C), 172.7 (C), 137.8 (C), 136.6 (C), 128.5 (C), 124.4 (CH), 121.5 (CH), 118.9 (CH), 112.4 (CH), 102.8 (C), 61.2 (CH), 56.5 (CH), 53.5 (CH_3), 52.8 (CH), 51.1 (CH_2), 48.1 (CH_2), 47.9 (CH), 28.2 (CH_2), 24.3 (CH_2); IR (KBr pellet): 3399, 2957, 1740, 1676, 1202, 1178, 1135 cm^{-1}; HRMS (ESI-TOF) *m/z* calcd for $C_{19}H_{21}N_2O_3$ $(M - CF_3CO_2)^+$ 325.1552, found 325.1555.

Pentacyclic Ester Trifluoroacetate Salt 16. Procedure B. Trifluoroacetic acid (3.5 mL) was added to allylic alcohol **13** (0.15 g, 0.27 mmol). The solution was maintained at room temperature for 4 h, before it was concentrated *in vacuo* to afford 0.17 g of the tetracyclic amino acid trifluoroacetate salt as a brown solid. This material was used in the next step without further purification. Diagnostic data: ^{1}H NMR (500 MHz, CD_3OD) δ 7.62 (d, *J* = 7.8 Hz, 1H), 7.41 (d, *J* = 8.1 Hz, 1H), 7.15 (t, *J* = 7.1 Hz, 1H), 7.09 (t, *J* = 7.0 Hz, 1H), 6.48 (dd, *J* = 17.4, 10.9 Hz, 1H), 5.83 (d, *J* = 17.4 Hz, 1H), 5.62 (d, *J* = 11.0 Hz, 1H), 4.96 (s, 1H), 4.45 (d, *J* = 5.8 Hz, 1H), 2.96–2.86 (m, 2H), 2.79 (appar s, 1H), 2.25–2.15 (m, 1H), 1.89 (appar d, *J* = 15.8 Hz, 1H).

Paraformaldehyde (8 mg, 0.3 mmol) and acetonitrile (3 mL) were added to the tetracyclic amino acid trifluoroacetate salt (0.17 g) described in the preceding paragraph. The mixture was stirred for 3 h at 70 ^{o}C, before it was concentrated *in vacuo* to afford 0.14 g of a 3:2 mixture of amino acid trifluoroacetate salt **15** and its carboxylic acid

epimer ***epi*-15** as a brown solid. This material was used in the next step without further purification.

An analytical sample of ***epi*-15** was obtained by reverse phase C18 chromatography (10%→20%→30%→40% MeOH in H_2O with 1% TFA) as a colorless amorphous solid: ^{1}H NMR (600 MHz, D_2O, MeOH internal reference: 3.34 ppm) δ 7.65 (d, *J* = 8.0 Hz, 1H), 7.50 (d, *J* = 8.2 Hz, 1H), 7.31 (t, *J* = 7.5 Hz, 1H), 7.24 (t, *J* = 7.5 Hz, 1H), 5.55 (d, *J* = 6.7 Hz, 1H), 4.45 (d, *J* = 2.7 Hz, 1H), 3.90 (td, *J* = 12.6, 7.5 Hz, 1H); 3.82–3.76 (m, 1H), 3.68 (appar t, *J* = 8.4 Hz, 1H), 3.58 (br s, 1H), 3.32–3.20 (m, 2H), 2.86–2.78 (m, 1H), 2.66–2.60 (m, 1H), 2.46–2.40 (m, 1H), 2.25 (appar d, *J* = 16.5 Hz, 1H); ^{13}C NMR (125 MHz, D_2O, MeOH internal reference: 49.15 ppm) δ 212.3 (C), 174.8 (C), 163.4 (q, 35.4 Hz, C), 136.1 (C), 135.5 (C), 126.9 (C), 123.7 (CH), 120.9 (CH), 117.9 (CH), 116.7 (q, 290 Hz, CF_3), 111.9 (CH), 101.8 (C), 59.8 (CH), 55.2 (CH), 51.1 (CH), 50.3 (CH_2), 46.9 (CH), 46.9 (CH_2), 26.8 (CH_2), 22.9 (CH_2); IR (KBr pellet): 3390, 2957, 1710, 1675, 1462, 1203, 1136 cm^{-1}; HRMS (ESI-TOF) *m/z* calcd for $C_{18}H_{19}N_2O_3Na$ $(M + Na - CF_3CO_2)^+$ 333.1215, found 333.1212.

A 0.50 M solution of methanolic HCl was prepared by adding thionyl chloride (0.36 mL, 5.0 mmol) to 20 mL of methanol at 0 °C. The mixture of amino acid trifluoroacetate salt **15** and its carboxylic acid epimer ***epi*-15** described above (0.14 g) was added to 18 mL of this 0.5 M solution of HCl in methanol. The reaction solution was maintained at 50 °C for 12 h, before it was concentrated *in vacuo* to afford a yellow solid. This material was dissolved in a solution of 10 mL of water and 10 mL of methanol. The solution was maintained at room temperature for 2 h before it was concentrated *in vacuo* to afford 0.11 g of a brown solid. This residue was purified by reverse phase C18 chromatography (0%→10%→20%→30%→40% MeOH in H_2O with 1% TFA). The appropriate column fractions were combined and a saturated aqueous solution of Na_2CO_3 was added until the solution of combined fractions became basic (as indicated by pH paper). This solution was extracted with dichloromethane (4 x 60 mL), and the combined organic layers were dried with $MgSO_4$. Excess trifluoroacetic acid (~0.1 mL) was added to this solution, before it was concentrated *in vacuo* to afford 87 mg (73% from **13**) of **16**, a 1:1 mixture of ester epimers **16a** and **16b**, as a colorless solid. This material was contaminated with an unidentified impurity and was used in the next step without further

purification. The yield of pure **16** was determined to be 62% (from **13**) by NMR analysis with the use of an internal standard.

(±)-Actinophyllic Acid Hydrochloride (17). A 2.6 M solution of *n*-butyllithium (0.35 mL, 0.91 mmol) was slowly added to a –78 °C solution of diisopropylamine (0.14 mL, 1.0 mmol) in 2.5 mL of THF. The reaction solution was maintained at –78 °C for 35 min. A solution of pentacyclic ester **16** (0.11 g, 0.26 mmol, from procedure B) in 1.5 mL of THF was added by cannula to the LDA solution at –78 °C, and residue in the transfer vessel was washed into the reaction solution with additional THF (2 x 0.5 mL). The reaction solution was maintained at –78 °C for an additional 30 min. A ~0.5 M solution of monomeric formaldehyde[5] in THF (5.2 mL, ~2.6 mmol) was added by syringe, and the reaction mixture was stirred for 5 min at –78 °C. A solution of trifluoroacetic acid (0.077 mL, 1.0 mmol) in 1 mL of THF was then added, and the reaction mixture was allowed to warm to room temperature. The mixture was concentrated *in vacuo* to afford a dark red oil. This residue was purified by reverse phase C18 chromatography (2 column-volumes of H_2O with 1% TFA, then 25% MeOH in H_2O with 1% TFA) to afford 0.10 g of partially purified actinophyllic acid methyl ester trifluoroacetate salt as a colorless solid. This material was used in the next step without further purification.

An analytical sample of actinophyllic acid methyl ester trifluoroacetate salt was obtained by reverse phase C18 HPLC (40% MeOH in H_2O with 0.1% TFA) as a colorless amorphous solid: ^{1}H NMR (500 MHz, CD_3OD) δ 7.62 (d, J = 7.9 Hz, 1H), 7.42 (d, J = 8.1 Hz, 1H), 7.20 (t, J = 7.5 Hz, 1H), 7.13 (t, J = 7.5 Hz, 1H), 5.47 (d, J = 7.4 Hz, 1H), 4.40 (d, J = 8.0 Hz, 1H), 3.91 (s, 3H), 3.77–3.69 (m, 1H), 3.72 (d, J = 7.9 Hz, 1H), 3.61–3.55 (m, 1H), 3.28 (td, J = 14.3, 3.1 Hz, 1H), 3.21 (t, J = 8.9 Hz, 1H), 3.03 (appar d, J = 14.0 Hz, 1H), 2.91 (d, J = 5.5 Hz, 1H), 2.76–2.96 (m, 1H), 2.54–2.45 (m, 1H), 2.40 (appat t, J = 13.6 Hz, 1H), 2.29–2.24 (m, 1H); ^{13}C NMR (125 MHz, CD_3OD, TFA resonances omitted) 171.6 (C), 138.7 (C), 137.7 (C), 128.4 (C), 124.0 (CH), 121.5 (CH), 118.5 (CH), 112.7 (CH), 107.9 (C), 103.7 (C), 75.0 (CH_2), 62.4 (CH), 58.7 (C), 55.9 (CH), 53.7 (CH_3), 53.5 (CH), 50.8 (CH_2), 47.1 (CH_2), 26.2 (CH_2), 19.9 (CH_2); IR (KBr

[5] Monomeric formaldehyde was prepared according to: Schlosser, M.; Jenny, T.; Guggisberg, Y. *Synlett* **1990**, 704.

pellet): 3401, 2960, 1730, 1675, 1203, 1139 cm^{-1}; HRMS (ESI-TOF) *m/z* calcd for $C_{20}H_{22}N_2O_4$ $(M - CF_3CO_2)^+$ 355.1658, found 355.1661.

A solution of 4 M aqueous HCl (17.5 mL) was added to this sample (0.10 g) of actinophyllic acid methyl ester trifluoroacetate salt. The reaction solution was maintained at 70 °C for 13 h, before the solution was concentrated *in vacuo* to afford 98 mg of a pale yellow solid. This residue was purified by reverse phase C18 chromatography (0%→10%→20% MeOH in H_2O) to afford 49 mg (50% from **16**) of (±)-actinophyllic acid hydrochloride (**17**) as a colorless amorphous solid. An analytical sample of actinophyllic acid hydrochloride was prepared for NMR analysis by adding excess HCl to an aqueous solution of the purified material and concentrating *in vacuo*: ^{1}H NMR (500 MHz, D_2O, MeOH internal reference: 3.34 ppm) δ 7.64 (d, *J* = 7.9 Hz, 1H), 7.54 (d, *J* = 8.2 Hz, 1H), 7.32 (t, *J* = 7.6 Hz, 1H), 7.24 (t, J = 7.5 Hz, 1H), 5.53 (d, *J* = 7.6 Hz, 1H), 4.40 (d, *J* = 8.2 Hz, 1H), 3.79 (d, J = 8.4 Hz, 1H), 3.76 (appar t, *J* = 12.2 Hz, 1H), 3.63 (appar td, *J* = 11.4, 4.6 Hz, 1H), 3.30–3.25 (m, 2H), 3.09–3.05 (m, 2H), 2.70–2.63 (m, 1H), 2.63–2.55 (m, 1H), 2.43 (appar t, *J* = 15.1 Hz, 1H), 2.35 (appar d, *J* = 14.6 Hz, 1H); ^{13}C NMR (125 MHz, D_2O, MeOH internal reference: 49.5 ppm) δ 173.3 (C), 137.9 (C), 136.2 (C), 127.2 (C), 123.8 (CH), 121.2 (CH), 117.9 (CH), 112.5 (CH), 107.7 (C), 102.5 (C), 74.4 (CH_2), 61.1 (CH), 57.9 (C), 54.4 (CH), 51.8 (CH), 50.2 (CH_2), 46.2 (CH_2), 25.3 (CH_2), 18.7 (CH_2); IR (KBr pellet): 3384, 2956, 2859, 1719, 1460, 1232 cm^{-1} ; HRMS (ESI-TOF) *m/z* calcd for $C_{19}H_{20}N_2O_4Na$ $(M + Na - HCl)^+$ 363.1321, found 363.1329.

Comparison of the ^{1}H NMR Spectrum of Synthetic Actinophyllic Acid to the Reported ^{1}H NMR Spectrum of Natural Actinophyllic Acid. A 0.2 M solution of sodium methylsulfinylmethylide-d_5 (NaDMSO-d_5) was prepared by adding 7 mg of sodium hydride (free of mineral oil) to 2 mL of DMSO-d_6. The suspension was stirred at 65 °C for 1 h, before it was allowed to cool to room temperature.

An analytical sample of actinophyllic acid hydrochloride (**17**) was prepared by reverse phase C18 HPLC (30% MeOH in H_2O). One drop of conc. aqueous HCl was added to an aqueous solution of 5 mg of this purified material to ensure complete formation of the hydrochloride salt. This solution was concentrated *in vacuo*, and excess water was removed by methanol azeotrope (3 x 5 mL) *in vacuo* to afford a colorless solid. This sample was dissolved in 0.750 mL of DMSO-d_6 for NMR analysis. Spectra

were obtained before NaDMSO-d_5 was added and in succession after 10–15 μL portions of the 0.2 M solution of NaDMSO-d_5 were added (Figure S1). Spectra matching the reported spectrum[6] of actinophyllic acid were obtained when ~1 equivalent of NaDMSO-d_5 was added (Figure S2). The analytical sample precipitated out of solution if NaDMSO-d_5 was added even in slight excess of the amount required to match the spectrum of the natural sample.

[6] Carrol, A. R.; Hyde, E.; Smith, J.; Quinn, R. J.; Guymer, G.; Foster, P. I. *J. Org. Chem.* **2005**, *70*, 1096–1099.

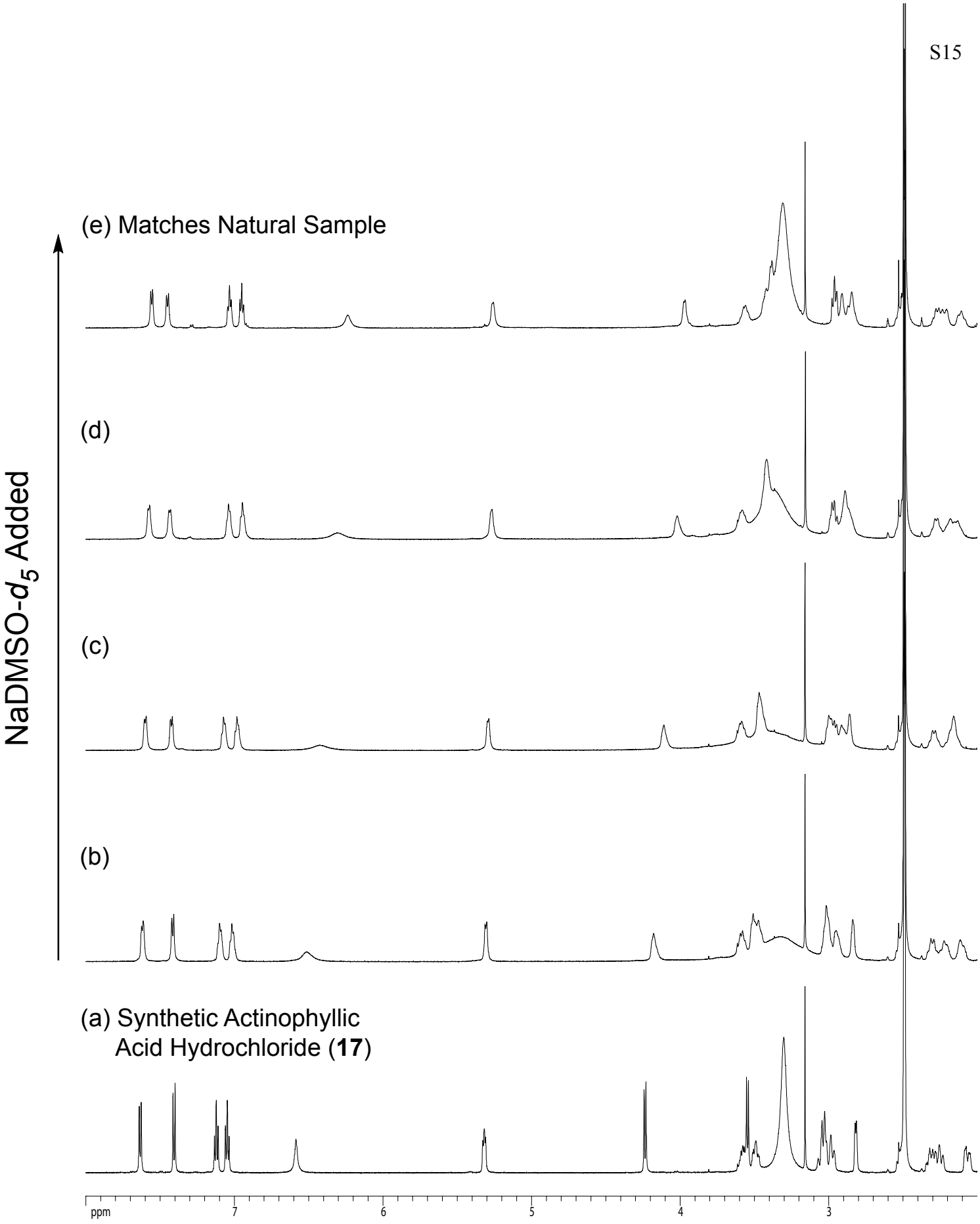

Figure S1. Variation of ^{1}H NMR Resonances of Actinophyllic Acid in DMSO-d_6 with the Amount of NaDMSO-d_5 Added

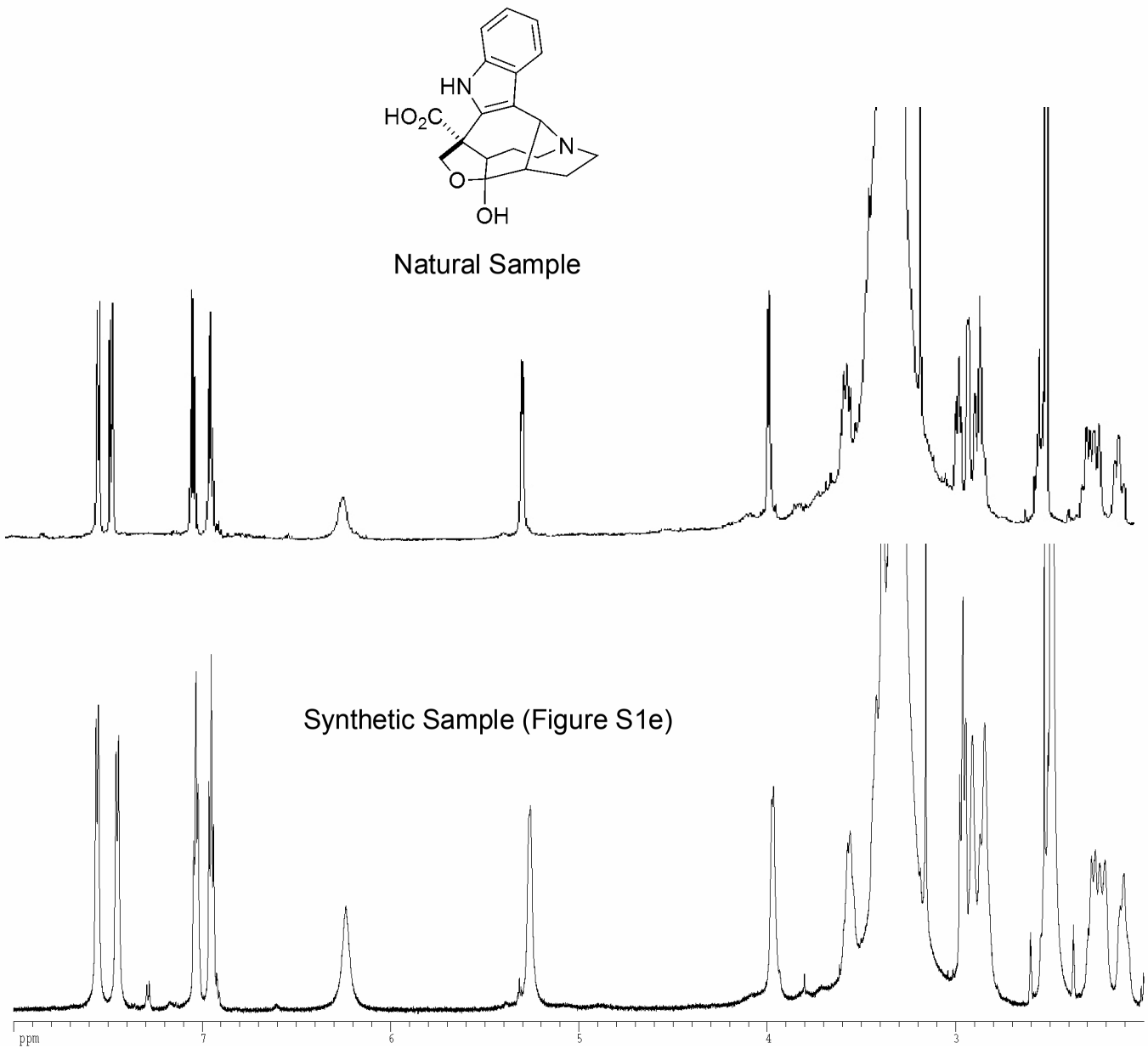

Figure S2. Comparison of ^{1}H NMR Spectra of Natural and Synthetic Actinophyllic Acid