Supporting information

Total Synthesis of Marine Sponge Bis(indole) Alkaloids of Topsentin Class

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General methods

^1H NMR, ^{13}C and DEPT ^{13}C NMR spectra were recorded at 300 and 75.5 MHz respectively. Chemical shifts are given in ppm (δ) and were referenced to the internal solvent signal or to TMS used as an internal standard. Multiplicities are declared as follow: *s* (singlet), *br s* (broad singlet), *d* (doublet), *t* (triplet), *q* (quadruplet), *quint* (quintuplet), *sept* (septet), *dd* (doublet of doublet), *ddd* (doublet of doublet of doublet), *dt* (doublet of triplet), *m* (multiplet). Coupling constants *J* are given in Hz.

Infrared spectra (IR) were obtained either as neat films on sodium chloride discs or in potassium bromide plates. Data are reported in reciprocal centimetres (cm^{-1}).

Melting points were uncorrected.

LRMS mass spectra were recorded using DCI (NH_3 +isobutane) or ESI+ (ion polarity: positive) as ion sources. **HRMS mass spectra** were recorded with ESI+ as ion source.

Reactions were performed using oven dried glasswares under an atmosphere of dry argon. They were monitored by thin layer chromatography (TLC) using commercial aluminium-backed silica gel plates. TLC spots were viewed under ultraviolet light and by heating the plate after treatment with an appropriate revelatory (ninhydrin, KMnO_4 , TTC).

Solvents: Tetrahydrofuran and diethyl ether were refluxed on sodium-benzophenone and then distilled. Dichloromethane and methanol were dried by refluxing on CaH_2 and then distilled. Unless otherwise noted, all reagent-grade chemicals and solvents were obtained from commercial suppliers and were used as received.

1-(indol-3'-yl)-2-(piperidin-1-yl)-2-thioxoethanone (11a). To a solution of 2 g (17.1 mmol) of indole **3a** in anhydrous diethyl ether (35 mL) at 0 °C, oxalyl chloride (1.72 mL, 19.8 mmol) was added dropwise over 30 min. The reaction mixture was stirred at 0 °C for 3 h and then allowed to warm to rt during an additional hour. The resulting yellow crystals were collected by filtration, washed with cold anhydrous diethyl ether and dried under vacuum. The yellow solid **10a** has been used without further purification (1.63 g, 15.7 mmol, 92 %). **10a** (3.07 g, 14.8 mmol) was dissolved into 15 mL of EtOAc at 0 °C. A solution of tributyltin hydride (3.98 mL, 14.82 mmol) in 20 mL of EtOAc was then added. The reaction mixture was stirred at 0 °C for 30 min, warmed to rt and then stirred for an additional night. Hexane was added and the resulting yellow powder was collected by filtration. Washing with a large amount of hexane and drying under vacuum gave the corresponding ketoaldehyde (2.038 g, 11.78 mmol, 79 %) which was used without further purification. The ketoaldehyde (600 mg, 3.49 mmol) was dissolved into 3.5 mL of pyridine. Sulfur was then added (139 mg, 4.36 mmol) followed by piperidine (445 mg, 5.24 mmol). The resulting mixture was warmed to 80 °C during 5 h. It was then poured in water. Aqueous layer was extracted three times by EtOAc. The combined organic layers were washed with brine, dried over anhydrous MgSO₄, filtered and evaporated under vacuum. Pyridine excess was azeotropically evaporated with toluene. The obtained solid was purified by column chromatography on silica gel (Eluent: EtOAc/Pentane, 1:1). The resulting thioamide **11a** was collected as brown solid and recrystallised in methanol to give brown crystals (365 mg, 1.34 mmol, 38 %; 30 % from **10a**). Mp: 158-159 °C. IR (neat): 3269, 2942, 2856, 1601, 1520, 1507, 1438, 1246, 1176, 1131 cm⁻¹. ¹H NMR (CDCl₃, 300 MHz): δ= 1.35-1.85 (m, 6H), 3.53 (t, *J*= 5.1 and 5.6 Hz, 2H), 4.19 (t, *J*= 4.7 and 5.6 Hz, 2H), 7.1-7.3 (m, 2H), 7.39 (dd, *J*= 2.2 and 6.9 Hz, 1H), 7.85 (s, 1H), 8.22 (d, *J*= 6.7 Hz, 1H), 10.16 (s, 1H). ¹³C NMR (CDCl₃, 75.5 MHz): δ= 23.8, 25.3, 26.4, 48.3, 52.9, 112.4, 113.2, 121.5, 122.9, 123.9, 125.2, 135.5, 136.7, 185.6, 195.0. LRMS (DCI,

NH₃+isobutane): $m/z = 273$ [(M+H)⁺]. HRMS (ESI) calcd for C₁₅H₁₇N₂OS: 273.1062. Found: 273.1071 [(M+H)⁺]. Anal. calcd for C₁₅H₁₆N₂OS: C, 66.15; H, 5.92, N, 10.28. Found: C, 66.40, H, 5.95, N, 10.30.

1-[2-(indol-3'-yl)-1-methylsulfanyl-2-oxo-ethylidene]-piperidinium iodide (4a).

Thioamide **11a** (200 mg, 0.735 mmol) was dissolved into 0.95 mL of methyl iodide (20 equiv). The mixture was refluxed during 5 h, cooled at rt and excess of methyl iodide was evaporated under vacuum. The thioimide salt **4a** was obtained as a white unstable solid (295 mg, 0.72 mmol), which was immediately used without further purification. Yield: 98 %. ¹H NMR (CD₃OD, 300 MHz): $\delta = 1.70$ -2.10 (m, 5H), 2.10-2.20 (m, 1H), 2.65 (s, 3H), 3.85-4.00 (m, 1H), 4.00-4.10 (m, 1H), 4.15-4.30 (m, 2H), 7.30-7.45 (m, 2H), 7.55-7.65 (m, 1H), 8.20-8.38 (m, 1H), 8.63 (s, 1H). ¹³C NMR (CD₃OD, 75.5 MHz): $\delta = 16.8, 23.4, 26.8, 28.1, 55.9, 58.7, 114.1, 114.3, 122.6, 125.3, 125.8, 126.5, 139.2, 140.3, 176.8, 186.0$.

1-(6'-bromoindol-3'-yl)-2-(piperidin-1-yl)-2-thioxoethanone (11b). To a solution of 500 mg (2.55 mmol) of 6-bromoindole in anhydrous diethyl ether (5 mL) at 0 °C was added dropwise oxalyl chloride (0.25 mL, 2.93 mmol) over 30 min. The reaction mixture was stirred at 0 °C for 3 h, and then allowed to warm to 23 °C during an additional hour. The resulting yellow crystals were collected by filtration, washed with cold anhydrous diethyl ether and dried under vacuum. The yellow solid **10b** (600 mg, 2.09 mmol, 82 %) has been used without further purification. **10b** (740 mg, 2.58 mmol) was dissolved into 2.6 mL of EtOAc at 0 °C. A solution of tributyltin hydride (0.69 mL, 2.58 mmol) in 3.8 mL of EtOAc was then added. The reaction mixture was stirred at 0 °C for 30 min, warmed to rt and then stirred for an additional night. Hexane was added and the resulting yellow powder was collected by filtration. Washing with a large amount of hexane and drying under vacuum gave the ketoaldehyde (453 mg, 1.79 mmol, 69 %) which was used without further purification. The ketoaldehyde (453 mg, 1.79 mmol) was dissolved into 2 mL of pyridine. Sulfur was then

added (58 mg, 1.79 mmol) followed by piperidine (0.27 mL, 229 mg, 2.69 mmol). The resulting mixture was warmed to 80 °C during 5 h. It was then poured into water. Aqueous layer was extracted three times by EtOAc. Organic layers were washed with brine, dried over anhydrous MgSO_4 and evaporated under vacuum. Excess pyridine was azeotropically evaporated with toluene. The obtained solid was purified by column chromatography on silica gel (Eluent: Et_2O). The product **11b** was then obtained as a yellow solid (280 mg, 0.798 mmol, 45 %; 30 % from **10b**) and recrystallized in methanol. Mp: 242-243 °C. IR (neat): 3160, 2940, 2914, 2856, 1712, 1622, 1512, 1421, 1247, 1176, 1143 cm^{-1} . ^1H NMR (DMSO, 300 MHz): δ = 1.4-1.6 (m, 2H), 1.6-1.8 (m, 4H), 3.55 (t, J = 5.1 et 5.6 Hz, 2H), 4.18 (br s, 2H), 7.38 (dd, J = 1.5 et 8.5 Hz, 1H), 7.72 (d, J = 1.8 Hz, 1H), 8.02 (d, J = 8.5 Hz, 1H), 8.12 (s, 1H). ^{13}C NMR (DMSO, 75.5 MHz): δ = 23.3, 24.9, 26.2, 47.5, 52.3, 112.4, 115.3, 115.8, 122.5, 124.2, 125.2, 136.8, 137.7, 184.2, 193.8. LRMS (DCI, NH_3 +isobutane): m/z = 351 and 353 $[(\text{M}+\text{H})^+]$. HRMS (ESI) Calcd for $\text{C}_{15}\text{H}_{15}^{79}\text{BrN}_2\text{NaOS}$: 372.9986. Found: 372.9988 $[(\text{M}+\text{Na})^+]$. Anal. calcd for $\text{C}_{15}\text{H}_{15}\text{BrN}_2\text{OS}$: C, 51.29; H, 4.30; Br, 22.75; N, 7.97. Found: C, 51.26; H, 4.37; Br, 22.80; N, 7.74.

1-[2-(6'-bromoindol-3'-yl)-1-methylsulfanyl-2-oxo-ethylidene]-piperidinium iodide (4b). The thioamide **11b** (213 mg, 0.605 mmol) was dissolved into 0.77 mL of methyl iodide (20 eq). The mixture was refluxed during 5 h, cooled at rt and methyl iodide was removed under vacuum. The product **4b** was collected as a yellow unstable solid (296 mg, 0.60 mmol) which was immediately used without further purification. Yield: 100%. ^1H NMR (CD_3OD , 300 MHz): δ = 1.65-2.05 (m, 5H), 2.05-2.25 (m, 1H), 2.65 (s, 3H), 3.85-4.00 (m, 1H), 4.0-4.1 (m, 1H), 4.1-4.3 (m, 2H), 7.49 (dd, J = 1.7 and 8.5 Hz, 1H), 7.78 (d, J = 1.4 Hz, 1H), 8.14 (d, J = 8.5 Hz, 1H), 8.68 (s, 1H). DEPT ^{13}C NMR (CD_3OD , 75.5 MHz): δ = 16.9, 23.4, 26.8, 28.1, 56.0, 58.8, 114.2, 117.1, 119.6, 124.0, 124.7, 128.4, 140.0, 141.0, 177.0, 185.7.

1-(6'-methoxyindol-3'-yl)-2-piperidin-1-yl-2-thioxoethanone (11c). To a solution of 250 mg (1.7 mmol) of 6-methoxyindole in anhydrous diethyl ether (2.5 mL) at 0 °C was added dropwise oxalyl chloride (0.17 mL, 2.6 mmol) over 30 min. The reaction mixture was stirred at 0 °C for 3 h, and then allowed to warm to 23 °C during an additional hour. The obtained brown solid **10c** (331 mg, 1.2 mmol, 71 %) has been used without further purification. **10c** (900 mg, 3.79 mmol) was dissolved into 3.8 mL of EtOAc at 0 °C. A solution of tributyltin hydride (10.1 mL, 3.79 mmol) in 5.6 mL of EtOAc was then added. The reaction mixture was stirred at 0 °C for 30 min, warmed to rt and then stirred for an additional night. Hexane was added and the resulting brown powder was collected by filtration. Washing with a large amount of hexane and drying under vacuum gave the ketoaldehyde as a brown solid (780 mg, 3.84 mmol, quant.) which was used without further purification. The ketoaldehyde (780 mg, 3.84 mmol) was dissolved into 4 mL of pyridine. Sulfur was then added (122 mg, 3.84 mmol) followed by piperidine (0.57 mL, 490 mg, 5.76 mmol). The resulting mixture was warmed to 80 °C during 5 h. It was then poured into water. Aqueous layer was extracted three times by EtOAc. Organic layers were washed with brine, dried over anhydrous MgSO₄ and evaporated under vacuum. Excess pyridine was azeotropically evaporated with toluene. The obtained oil was purified by column chromatography on silica gel (Eluent: Et₂O). The product **11c** was then obtained as a brown solid (384 mg, 1.27 mmol, 33 %; 33% from **10c**). Mp: 124-126 °C. IR (KBr): 3268, 2957, 2932, 2854, 1604, 1579, 1517, 1501, 1443, 1248, 1157, 1021 cm⁻¹. ¹H NMR (CD₃OD, 300 MHz): δ= 1.50-1.62 (m, 2H), 1.68-1.85 (m, 4H), 3.58 (t, *J*= 4.6 and 6.0 Hz, 2H), 3.82 (s, 3H), 4.23 (t, *J*= 4.6 and 6.0 Hz, 2H), 6.89 (dd, *J*= 2.3 and 8.7 Hz, 1H), 6.99 (d, *J*= 2.3 Hz, 1H), 7.89 (s, 1H), 8.01 (dd, *J*= 0.4 and 8.7 Hz, 1H). ¹³C NMR (CD₃OD, 75.5 MHz): δ= 25.0, 26.4, 27.6, 49.22, 54.0, 56.0, 96.5, 113.5, 114.4, 120.7, 123.0, 136.6, 139.5, 159.0, 187.6, 196.5. LRMS (ESI): *m/z*= 303 [(M+H)⁺]. HRMS (ESI) Calcd for C₁₆H₁₉N₂O₂S:

303.1167. Found: 303.1168 [(M+H)⁺]. Anal. calcd for C₁₆H₁₈N₂O₂S: C, 63.55; H, 6.00; N, 9.26. Found: C, 63.61; H, 6.14; N, 9.11.

1-[2-(6'-methoxyindol-3'-yl)-1-methylsulfanyl-2-oxo-ethylidene]-piperidinium iodide (4c). The thioamide **11c** (178 mg, 0.59 mmol) was dissolved into 0.75 mL of methyl iodide (20 eq). The mixture was refluxed during 5 h. The crude mixture was then cooled at rt and methyl iodide was removed under vacuum. The product **4c** was obtained as a brown unstable solid (260 mg, 0.59 mmol) which was immediately used without further purification. Yield: 100 %. ¹H NMR (CD₃OD, 300 MHz): δ= 1.7-2.0 (m, 5H), 2.05-2.20 (m, 1H), 2.63 (s, 3H), 3.84 (s, 3H), 3.90-4.10 (m, 2H), 4.20 (t, *J*= 5.7 and 5.5 Hz, 2H), 6.96 (dd, *J*= 2.3 and 8.7 Hz, 1H), 7.13 (d, *J*= 2.3 Hz, 1H), 8.04 (d, *J*= 8.7 Hz, 1H), 8.57 (s, 1H). DEPT ¹³C NMR (CD₃OD, 75.5 MHz): δ= 17.1, 23.3, 26.7, 28.0, 55.8, 56.3, 58.6, 97.2, 114.2, 114.9, 119.2, 123.1, 139.6, 140.1, 159.8, 176.4, 185.8.

Spongotine B (2b). To a stirred solution of indolic diamine dihydrochloride **8a** (50 mg, 0.20 mmol) and thioimide iodide **4b** (100 mg, 0.20 mmol) in distilled methanol (1 mL) was added Amberlyst A21 (200 mg). The resulting mixture was stirred for 60 h at rt. Methanol was then removed under vacuum. To the residue was added water and ethyl acetate. The aqueous layer was extracted three times with EtOAc. The combined organic layers were then washed with brine and dried over anhydrous MgSO₄. After the removal of the solvent, the residue was purified by column chromatography on silica gel (Eluent: EtOAc/pentane, 9:1). Spongotine B **2b** was obtained as a brown solid (38 mg, 0.09 mmol). Yield: 46 %. Mp: 250 °C. IR (KBr): 2850, 1615, 1570, 1518, 1454, 1369, 1253, 1169, 827 cm⁻¹. ¹H NMR (CD₃OD, 300 MHz): 3.90 (dd, *J*= 8.6 and 12.2 Hz, 1H), 4.23 (t, *J*= 11.9 Hz, 1H), 5.45 (dd, *J*= 8.6 and 11.3 Hz, 1H), 7.00 (dt, *J*= 1.0 and 7.2 Hz, 1H), 7.11 (dt, *J*= 1.0 and 7.0 Hz, 1H), 7.25 (s, 1H), 7.32-7.43 (m, 1H), 7.63 (d, *J*= 1.7 Hz, 1H), 7.67 (d, *J*= 1.7 Hz, 1H), 8.00 (s, 1H), 8.09 (d, *J*= 8.6 Hz, 1H), 8.20 (d, *J*= 8.6 Hz, 1H), 8.52 (s, 1H). ¹³C NMR (CD₃OD, 75.5 MHz): δ= 57.5,

59.5, 112.7, 115.7, 116.2, 118.0, 118.2, 119.9, 120.0, 122.7, 123.5, 124.3, 126.3, 126.8, 126.9, 138.8, 139.2, 139.8, 164.3, 182.1. LRMS (DCI, NH₃+isobutane): m/z = 407 and 409 [(M+H)⁺]. HRMS (ESI) calcd for C₂₀H₁₆⁷⁹BrN₄O: 407.0507. Found: 407.0525 [(M+H)⁺].

6'-methoxyindol-3'-yl-[5-(indol-3''-yl)-4,5-dihydroimidazol-2-yl] ketone (2c). To a stirred solution of indolic diamine dihydrochloride **8a** (280 mg, 1.14 mmol) and thioimide iodide **4c** (504 mg, 1.14 mmol) in distilled methanol (4 mL) was added amberlyst A21 (1.1 g). The resulting mixture was stirred for 60 h at rt. Methanol was then removed under vacuum. The resulting residue was purified by column chromatography on silica gel (eluant: EtOAc). The α -ketoimidazoline **2c** was obtained as a yellow solid (256 mg, 0.72 mmol). Yield: 63 %. Mp: 230 °C (dec). IR (KBr): 3399, 3166, 2927, 1634, 1589, 1576, 1525, 1447, 1421, 1201, 1163, 1092 cm⁻¹. ¹H NMR (CD₃COCD₃, 300 MHz): 3.81 (s, 3H), 3.99 (dd, J = 8.8 and 12.1 Hz, 1H), 4.39 (t, J = 12.1 Hz, 1H), 5.58 (dd, J = 8.8 and 11.0 Hz, 1H), 6.90 (dd, J = 2.3 and 8.7 Hz, 1H), 7.01 (t, J = 7.1 and 7.9 Hz, 1H), 7.07-7.17 (m, 2H), 7.39 (d, J = 2.1 Hz, 1H), 7.45 (d, J = 8.1 Hz, 1H), 7.65 (d, J = 7.8 Hz, 1H), 8.19 (d, J = 8.7 Hz, 1H), 8.87 (s, 1H), 10.27 (s, 1H, NH indol.), 11.29 (s, 1H, NH indol.). ¹³C NMR (CD₃COCD₃, 75.5 MHz): δ = 55.8, 57.0, 58.5, 96.4, 112.6, 113.1, 115.2, 117.3, 119.8, 119.9, 121.1, 122.5, 123.4, 123.6, 126.6, 138.2, 138.4, 138.6, 158.4, 163.2, 178.5. LRMS (ESI): m/z = 359 [(M+H)⁺]. HRMS (ESI) calcd for C₂₁H₁₉N₄O₂: 359.1508. Found: 359.1504 [(M+H)⁺].

Isobromodeoxytopsentin (1d). IBX (0.05 mmol, 14 mg) was added to a solution of spongotone B **2b** (18 mg, 0.044 mmol) in 0.2 mL of DMSO. The resulting mixture was stirred at rt during 15 h to completion. It was then quenched by addition of a saturated aqueous solution of Na₂S₂O₃ (0.11 mL) and an equal volume of EtOAc. The mixture was treated with a saturated aqueous solution of NaHCO₃. Aqueous layer was then extracted two times by EtOAc. Combined organic layers were washed with an aqueous saturated solution of NaHCO₃, with brine and then dried over anhydrous MgSO₄. After the removal of the solvent,

the residue was purified by column chromatography on silica gel (Eluent: EtOAc/pentane, 1:1). The isobromodeoxytopsentine **1d** was obtained as a yellow solid (6 mg, 0.015 mmol). Yield: 34 %. Mp: 246 °C (dec). IR (neat): 3431, 3283, 1699, 1596, 1518, 1454, 1240, 859 cm⁻¹. ¹H NMR (CD₃COCD₃, 500 MHz): *isomer a* : δ= 7.10-7.26 (m, 2H), 7.40 (dd, *J*= 1.0 and 8.0 Hz, 1H), 7.47 (d, *J*= 8.0 Hz, 1H), 7.74 (s, 1H), 7.79 (d, *J*= 1.0 Hz, 1H), 7.85 (d, *J*= 2.0 Hz, 1H), 8.22 (d, *J*= 7.5 Hz, 1H), 8.45 (d, *J*= 7.5 Hz, 1H), 9.62 (s, 1H), 10.38 (s, 1H), 11.24 (s, 1H), 12.10 (s, 1H). *isomer b* : δ= 7.10-7.26 (m, 2H), 7.38 (dd, *J*= 1.5 and 8.0 Hz, 1H), 7.52 (d, *J*= 8.0 Hz, 1H), 7.63 (s, 1H), 7.77 (d, *J*= 1.5 Hz, 1H), 7.96 (d, *J*= 7.0 Hz, 1H), 8.08 (d, *J*= 2.0 Hz, 1H), 8.42 (d, *J*= 7.5 Hz, 1H), 9.40 (s, 1H), 10.64 (s, 1H), 11.20 (s, 1H), 12.18 (s, 1H). ¹H NMR (CD₃COCD₃ + TFA-*d* + D₂O, 500 MHz): δ= 7.21 (t, *J*= 7.0 and 8.0 Hz, 1H), 7.26 (t, *J*= 7.0 and 8.0 Hz, 1H), 7.45 (dd, *J*= 1.5 and 8.0 Hz, 1H), 7.56 (d, *J*= 8.0 Hz, 1H), 7.82 (d, *J*= 2.0 Hz, 1H), 7.96 (d, *J*= 7.5 Hz, 1H), 8.07 (s, 1H), 8.12 (s, 1H), 8.26 (d, *J*= 8.0 Hz, 1H), 8.87 (s, 1H). DEPT ¹³C NMR (CD₃COCD₃, 75.5 MHz): *Isomers a and b*: δ= 111.9, 112.4, 112.8, 115.3, 115.7, 115.8, 116.7, 116.8, 120.3, 120.4, 121.1, 121.2, 122.4, 123.1, 123.3, 124.4, 124.4, 124.5, 125.7, 125.8, 126.0, 126.4, 126.5, 127.1, 127.3, 131.3, 132.6, 137.8, 137.58, 137.9, 137.95, 138.2, 138.35, 138.3, 138.7, 140.4, 176.9. DEPT ¹³C NMR (CD₃COCD₃, TFA-*d*, D₂O, 75.5 MHz): δ= 102.9, 113.2, 114.9, 116.5, 118.2, 119.7, 121.8, 123.7, 124.0, 125.4, 125.9, 126.5, 127.1, 132.4, 137.7, 138.7, 138.9, 141.3, 171.7. LRMS (ESI): *m/z*= 405 and 407 [(M+H)⁺]. HRMS (ESI) calcd for C₂₀H₁₄⁷⁹BrN₄O: 405.0351. Found: 405.0345 [(M+H)⁺].

O-methyltopsentin (1e). IBX (0.04 mmol, 12 mg) was added to a solution of 4,5-dihydro-O-methyltopsentin **2c** (13 mg, 0.036 mmol) in 0.2 mL of DMSO. The resulting mixture was stirred at rt during 15 h to completion. It was then quenched by addition of a saturated aqueous solution of Na₂S₂O₃ (0.1 mL) and an equal volume of EtOAc. The mixture was treated with a saturated aqueous solution of NaHCO₃. Aqueous layer was then extracted

two times by EtOAc. Combined organic layers were washed with an aqueous saturated solution of NaHCO₃, with brine and then dried over anhydrous MgSO₄. After the removal of the solvent, the residue was purified by column chromatography on silica gel (Eluent: EtOAc). The *O*-methyltopsentin **1e** was obtained as a yellow solid (13 mg, 0.036 mmol). Yield: 100 %. IR (KBr): 3394, 2956, 2918, 2848, 1733, 1716, 1519, 1456, 1254, 1158 cm⁻¹. ¹H NMR (CD₃COCD₃, 300 MHz): isomer a : δ= 3.85 (s, 3H), 6.87-6.95 (m, 1H), 7.07-7.13 (m, 1H), 7.13-7.30 (m, 2H), 7.45-7.50 (m, 1H), 7.70 (d, *J*= 2.1 Hz, 1H), 7.83 (d, *J*= 2.4 Hz, 1H), 8.20-8.26 (m, 1H), 8.37 (d, *J*= 8.7 Hz, 1H), 9.49 (d, *J*= 3.0 Hz, 1H), 10.35 (s, 1H), 10.90 (s, 1H), 12.05 (s, 1H). isomer b : δ= 3.84 (s, 3H), 6.87-6.95 (m, 1H), 7.07-7.13 (m, 1H), 7.13-7.30 (m, 2H), 7.50-7.55 (m, 1H), 7.60 (s, 1H), 7.93-7.99 (m, 1H), 8.07 (d, *J*= 2.5 Hz, 1H), 8.36 (d, *J*= 8.7 Hz, 1H), 9.27 (d, *J*= 2.8 Hz, 1H), 10.60 (s, 1H), 10.88 (s, 1H), 11.98 (s, 1H). ¹H NMR (CD₃COCD₃ + TFA-*d* + D₂O, 300 MHz): δ= 3.84 (s, 3H), 6.96 (dd, *J*= 2.3 and 8.7 Hz, 1H), 7.16 (d, *J*= 2.1, 1H), 7.20 (dt, *J*= 1.5 and 7.0 Hz, 1H), 7.25 (dt, *J*= 1.7 and 7.0 Hz, 1H), 7.54-7.59 (m, 1H), 7.90-7.96 (m, 1H), 8.05 (s, 1H), 8.11 (s, 1H), 8.17 (dd, *J*= 0.5 and 8.7 Hz, 1H), 8.60 (s, 1H). DEPT ¹³C NMR (CD₃COCD₃, TFA-*d*, D₂O, 75.5 MHz): δ= 55.7, 96.6, 103.5, 113.0, 113.5, 114.9, 116.6, 119.7, 121.5, 121.8, 123.1, 123.4, 125.4, 126.1, 132.5, 137.6, 140.0, 141.9, 158.7, 172.1. LRMS (ESI): *m/z*= 357 [(M+H)⁺]. HRMS (ESI) calcd for C₂₁H₁₆N₄O₂: 367.1352. Found: 367.1365 [(M+H)⁺].

8.6284
8.2607
8.2577
8.2505
8.2394
8.2326
7.6239
7.6179
7.6052
7.5958
7.4141
7.4081
7.4025
7.3932
7.3825
7.3782
7.3727

4.2343
4.2168
4.2100
4.1980
4.1827
4.0709
4.0551
4.0432
4.0291
3.9758
3.9596
3.9485
3.9344
3.9050
3.3100
2.6493
2.1405
1.8636
1.8504
1.8385

¹H NMR, MeOD

186.0352
176.8194

140.3048
139.2457

126.5041
125.7843
125.3441
122.6298

114.2898
114.1064

58.6834
55.8637

28.1201
26.7675
23.4389
16.8457

¹³C NMR, MeOD

2b

¹H NMR, MeOD

¹H NMR, CD₃COCD₃

2c

¹³C NMR, CD₃COCD₃

2c

¹H NMR, CD₃COCD₃

¹H NMR, CD₃COCD₃ + D₂O + TFA

DEPT ¹³C NMR, CD₃COCD₃

— 177.1136

146.5692
140.2002
138.0450
137.8520
137.7923
137.5855
137.3695
137.3144
130.9730
129.5714
128.0458
127.0992
126.4283
125.9826
124.2410
123.8458
123.7631
123.1979
123.0003
122.9635
122.7705
122.6832
122.3753
121.2219
120.9968
120.4315
120.3075
115.3630
115.3033
115.0230
112.7713
112.7437
112.7116
112.3210
111.8798
106.5264

DEPT ¹³C NMR, CD₃COOD₃ + D₂O + TFA

1a
— 171.8667

141.6435
138.3028
137.9860
137.6307

— 132.3267

126.9494
126.3304
125.4128
125.1985
123.9165
123.5538
122.5007
121.8322
121.6491
119.7297
— 118.0356
— 116.4110
114.8616
114.2370
113.4953
113.1308
— 110.4404

— 103.1272

$^1\text{H NMR}$, $\text{CD}_3\text{COCD}_3 + \text{D}_2\text{O} + \text{TFA}$

12.0581
12.0432
12.0163
11.9830

10.9218
10.8821
10.6006
10.3456
9.4998
9.4900
9.2775
9.2682
8.3882
8.3707
8.3592
8.3417
8.2398
8.2159
8.2116
8.0713
8.0628
7.9728
7.9502
7.8354
7.8273
7.7019
7.6951
7.6043
7.5326
7.5266
7.5121
7.5045
7.4865
7.4819
7.4656
7.4588
7.2827
7.2537
7.2315
7.2264
7.2174
7.2093
7.2012
7.1927
7.1871
7.1773
7.1722
7.1581
7.1534
7.1466
7.1329
7.1283
7.1048
7.0967
7.0852
7.0438
7.0148
6.9312
6.9235
6.9150
6.9069
6.9022
6.8941
6.8860
6.8783

¹H NMR, CD₃COOD₃

1e, isomer

1e, isomer

8.5977
8.1839
8.1822
8.1549
8.1532
8.1076
8.0491
7.9442
7.9416
7.9399
7.9348
7.9186
7.9139
7.9114
7.5795
7.5774
7.5727
7.5556
7.5509
7.5492
7.5463
7.2532
7.2481
7.2319
7.2289
7.2255
7.2221
7.2063
7.2016
7.1632
7.1564
6.9730
6.9653
6.9440
6.9363

¹H NMR, CD₃COCD₃ + D₂O + TFA

1e

DEPT ^{13}C NMR, $\text{CD}_3\text{COCD}_3 + \text{D}_2\text{O} + \text{TFA}$

1e

172.0894
141.9434
138.9540
137.5831
132.4709
127.4595
126.0519
125.3779
123.3926
123.0946
121.7742
121.4991
120.7242
119.7476
117.9732
116.6436
114.9242
114.1769
113.4616
113.0444
110.3760
103.4985
96.5798
55.8242