SYNTHESIS OF SCEPTRIN ALKALOIDS

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SUPPORTING INFORMATION: Experimental procedures (8 pages), ^1H NMR and ^{13}C NMR spectra (35 pages).

EXPERIMENTAL PART.

General. All reagents were used as received from commercial sources, unless specified otherwise, or prepared as described in the literature. Reactions were monitored by thin layer chromatography (TLC) using EM Science 60F silica gel plates. Flash column chromatography was performed over ICN Ecochrom silica gel (32-63 μm). Reactions requiring anhydrous conditions were performed in vacuum heat-dried glassware under nitrogen atmosphere. Reaction mixtures were stirred magnetically. Tetrahydrofuran and toluene were distilled from sodium and benzophenone immediately before use. Dichloromethane and DMF were distilled from CaH_2 . ^1H NMR and ^{13}C NMR spectra were recorded using a Varian Unity Plus-300 spectrometer (at 300 MHz and 75 MHz, respectively) and a Varian Unity Inova-600 spectrometer (at 600 MHz and 125 MHz, respectively). The chemical shifts are reported as δ values (ppm) relative to TMS. Infrared spectra were recorded on a Perkin-Elmer Spectrum Bx using thin film technique and NaCl plates. Low-resolution electron impact mass spectra (m/z) were recorded on a Finnigan LCQ-Classic Ion-Trap mass spectrometer using electrospray ionization (ESI). High-Resolution mass spectral analyses were performed on a Kratos MS-50TA spectrometer using the fast atom bombardment method (FAB), and Micromass QTOF-Ultima quadrupole-TOF mass spectrometer with electrospray ionization (ESI). Melting points were measured on a Mel-Temp II capillary melting point apparatus and are uncorrected.

3,4-Bis-chloromethyl-cyclobutane-1,2-dicarboxylic acid dimethyl ester (7)

A procedure similar to that reported by Wissner and Meinwald¹¹ was followed, except for the esterification step. A solution of maleic anhydride **6** (1.57 g, 16.0 mmol) and benzophenone (0.728 g, 4.00 mmol) in *trans*-1,4-dichloro-2-butene **5** (20.0 g, 160 mmol) was degassed with N_2 and loaded into 15 NMR tubes. The tubes were arranged around a 450-W Hanovia lamp in a water-cooled Pyrex immersion well and the mixture was irradiated at room temperature for 72 hours. The contents of the tubes were combined; the unreacted **5** was recovered by distillation under reduced pressure and used in subsequent runs without additional purification. The residue was refluxed with 26 mL of methanol in the presence of 3 drops of conc. H_2SO_4 overnight. The methanol was evaporated under reduced pressure and the residue was dissolved in ether (100

mL), which was washed with saturated aqueous NaHCO_3 and brine. The organic phase was dried (Na_2SO_4), and evaporated to dryness. The residue was purified by flash column chromatography with ethyl acetate/hexanes (1/6, v/v) to afford **7** (3.36 g, 78%) as clear oil.

^1H NMR (300 MHz, CDCl_3): δ 3.74-3.78 (m, 1H), 3.68 (s, 3H), 3.65-3.69 (m, 1H), 3.64 (s, 3H), 3.60 (s, 1H), 3.57 (s, 1H), 3.42-3.50 (m, 1H), 3.18 (dd, J = 0.7, 2 Hz, 1H), 3.15 (dd, J = 0.7, 2 Hz, 1H), 2.78-2.89 (m, 1H); **^{13}C NMR** (75 MHz, CDCl_3): δ 171.9, 171.5, 52.0, 51.9, 46.5, 43.3, 42.9, 41.8, 38.4, 38.1; **IR** (neat) 2998, 2953, 2848, 1736, 1436, 1369, 1329, 1252, 1202, 1174, 1112, 1048, 968; **HRMS** (FAB) m/z $[(\text{M}+\text{Li})^+]$ ($\text{C}_{10}\text{H}_{14}\text{Cl}_2\text{O}_4\text{Li}$) calculated 275.0429, found 275.0431.

3,4-Bis-(N-phthalimidomethyl)-cyclobutane-1,2-dicarboxylic acid dimethyl ester (**8**)

A mixture of **7** (6.30 g, 23.4 mmol), potassium phthalimide (17.3 g, 93.7 mmol) and KI (7.80 g, 46.8 mmol) and DMF (78 mL) was stirred at 100 °C overnight. The reaction mixture was poured into water (400 mL), and the aqueous layer was extracted with ethyl acetate. The combined organic extracts were washed with saturated brine, dried (Na_2SO_4), and concentrated to dryness. The residue was purified by flash column chromatography with ethyl acetate/hexanes (1/1, v/v) to afford **8** (5.50 g, 48%) as a white solid, **mp** 81-83 °C.

^1H NMR (300 MHz, CDCl_3): δ 7.76-7.79 (m, 4H), 7.64-7.67 (m, 4H), 3.73-3.87 (m, 4H), 3.38 (s, 6H), 3.08 (A_2B_2 , J = 2.6, 9.3 Hz, 2H), 2.58 - 2.64 (m, 2H); **^{13}C NMR** (75 MHz, CDCl_3): δ 172.0, 168.2, 133.8, 131.9, 123.2, 51.9, 41.1, 40.4, 33.8; **IR** (neat) 3462, 2928, 2853, 1770, 1713, 1613, 1467, 1430, 1395.6, 1360, 1266, 1189, 1066, 1016, 929; **IR** (neat) 3464, 2952, 1771, 1713, 1613, 1467, 1434, 1395, 1367, 1333, 1234, 1189, 1087, 1069, 1033, 998, 920; **HRMS** (ESI) m/z $[(\text{M}+\text{H})^+]$ ($\text{C}_{26}\text{H}_{23}\text{N}_2\text{O}_8$) calculated 491.1454, found 491.1446.

3,4-Bis-[(2-carboxy-benzoylamino)-methyl]-cyclobutane-1,2-dicarboxylic acid (**9**)

A mixture of **8** (100 mg, 0.204 mmol), NaOH (80 mg, 2.0 mmol) H_2O (0.5 mL) and MeOH (5 mL) is stirred at rt for 2 h. The reaction mixture was then adjusted with 2N HCl to pH 4 and evaporated to dryness. The residue was washed with MeOH (0.6 mL, 3 times). The MeOH was removed to give **9** (85 mg, 84%) as a white solid, **mp** 88-90 °C.

^1H NMR (300 MHz, CD_3OD): δ 7.74-7.77 (m, 2H), 7.40-7.53 (m, 6H), 3.67 (dd, J = 6.5, 13.6 Hz, 2H), 3.44 (dd, J = 6.5, 13.6 Hz, 2H), 2.92 (A_2B_2 , J = 2.9, 9.2 Hz, 2H), 2.55 - 2.58 (m, 2H); **^{13}C NMR** (75 MHz, CD_3OD): δ 176.4, 172.9, 170.0, 139.4, 132.8, 131.2, 131.1, 130.6, 128.7, 44.0, 42.3, 41.1; **IR** (neat) 3417 (br), 2626, 2359, 2078, 1704, 1633, 1555, 1488, 1434, 1274,

1143, 1082, 1015; **HRMS** (ESI) m/z $[(M+H)^+]$ ($C_{24}H_{23}N_2O_{10}$) calculated : 499.1353, found 499.1365.

1,2-Bis-bromoacetyl-3,4-bis-(N-phthalimidomethyl)-cyclobutane (**11**)

A mixture of **9** (4.38 g, 8.8 mmol) and $SOCl_2$ (19.3 mL, 264 mmol) was refluxed for 2 h. The excess of $SOCl_2$ was removed under reduced pressure. The residue was co-evaporated with toluene (5 mL) 3 times. The crude acyl chloride was dissolved in CH_2Cl_2 (10 mL) and added dropwise at $-10\text{ }^{\circ}C$ to a solution of CH_2N_2 in CH_2Cl_2 (200 mL) prepared from N-nitroso-N-methylurea (23.7 g, 0.230 mol) and 40% KOH (60 mL) and dried with KOH pellets for 3 h. The reaction mixture was stirred at $0\text{ }^{\circ}C$ for 1 h and concentrated to a volume of about 80 mL. To this solution was added dropwise aqueous conc. HBr (48%, 10 mL, 88 mmol) at $-10\text{ }^{\circ}C$. The reaction mixture was stirred at the same temperature for 10 min, washed with saturated aqueous $NaHCO_3$ and brine. The organic phase was dried (Na_2SO_4), and concentrated to dryness. The residue was purified by flash column chromatography with ethyl acetate/hexanes (1/10, v/v) to afford **11** (1.79 g, 33% overall yield) as a white solid, **mp** 112–115 $^{\circ}C$.

1H NMR (300 MHz, $CDCl_3$): δ 7.78–7.81 (m, 4H), 7.69–7.71 (m, 4H), 4.09 (s, 4H), 3.81–3.84 (m, 4H), 3.32 (A_2B_2 , $J=2.5, 9.7$ Hz, 2H), 2.33–2.53 (m, 2H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 199.4, 168.6, 134.2, 131.7, 123.5, 45.3, 39.3, 38.8, 33.8; **IR** (neat) 3462, 2928, 2853, 1770, 1713, 1613, 1467, 1430, 1395, 1360, 1266, 1189, 1066, 1016, 929; **HRMS** (ESI) m/z $[(M+H)^+]$ ($C_{26}H_{21}Br_2N_2O_6$) calculated 614.9766, found 614.9772.

1,2-Bis-(2-acetylamino-1H-imidazol-4-yl)-3,4-bis-(N-phthalimidomethyl)-cyclobutane (**13**)

A solution of **11** (1.6 g, 2.6 mmol) and N-acetylguanidine **12** (1.6 g, 15.8 mmol) in DMF (8.7 mL) was stirred at rt overnight. The DMF was removed under reduced pressure. The residue was treated with acetone-water (1:1, 10 mL) to give suspension, and the acetone was evaporated. The precipitate was collected by filtration, washed with water (10 mL, 3 times) and ethyl acetate (10 mL, 3 times) to give **13** as a white solid (0.66 g, 41%), **mp** 202–205 $^{\circ}C$ (dec).

1H NMR (600 MHz, $DMSO-d_6$): δ 11.14 (s, 2H), 11.11 (s, 2H), 7.62–7.80 (m, 4H), 7.43–7.56 (m, 4H), 3.43–3.74 (m, 4H), 2.98 (A_2B_2 , $J=1.9, 8.6$ Hz, 2H), 2.48 (m, 2H), 2.00 (s, 6H); **^{13}C NMR** (125 MHz, $DMSO-d_6$): δ 168.1, 167.7, 140.6, 137.3, 134.1, 131.1, 122.5, 108.2, 42.4, 41.2, 40.7, 22.6; **IR** (neat) 3333 (br), 2359, 1769, 1712, 1613, 1467, 1433, 1396, 1188, 1069, 1026, 928; **HRMS** (ESI) m/z $[(M+H)^+]$ ($C_{32}H_{29}N_8O_6$) calculated 621.2210, found 621.2214.

3,4-Bis-azidomethyl-cyclobutane-1,2-dicarboxylic acid dimethyl ester (**14**)

A mixture of **7** (6.35 g, 23.6 mmol), NaN₃ (9.20 g, 142 mmol) and KI (7.84 g, 47.2 mmol) and DMF (78 mL) was stirred at 80 °C overnight. The reaction mixture was poured into water (400 mL), and the aqueous layer was extracted with ethyl acetate. The combined organic extracts were washed with saturated brine, dried (Na₂SO₄), and concentrated to dryness. The residue was purified by flash column chromatography with ethyl acetate/hexanes (1/10, v/v) to afford **14** (5.46 g, 82%) as clear oil.

¹H NMR (300 MHz, CDCl₃): δ 3.68 (s, 3H), 3.64 (s, 3H), 3.43-3.48 (m, 2H), 3.43-3.48 (m, 3H), 3.05 (t, J = 9.8 Hz, 1H), 2.89-2.99 (m, 1H), 2.49-2.61 (m, 1H); ¹³C NMR (75 MHz, CDCl₃): δ 171.9, 171.6, 52.8, 52.0, 51.8, 51.1, 41.5, 40.4, 38.7, 35.6; IR (neat) 2953, 2100, 1731, 1436, 1354, 1204, 1171, 1065, 1020, 924; HRMS (FAB) m/z [(M+Li)⁺] (C₁₀H₁₄N₆O₄Li) calculated 289.1237, found 289.1249.

3,4-Bis-azidomethyl-cyclobutane-1,2-dicarboxylic acid (**15**)

A solution of **14** (5.1 g, 18 mmol) and KOH (10.0 g, 178 mmol) in MeOH (90 mL) was stirred at rt overnight. The MeOH was removed under reduced pressure, and the residue was dissolved in water (100 mL). The aqueous phase was extracted with ethyl acetate which was discarded. The aqueous phase was acidified to pH 4 with conc. HCl and extracted with ethyl acetate. The combined organic extract was washed with saturated brine, dried (Na₂SO₄), and concentrated to give **15** (4.57 g, 100%) as clear oil.

¹H NMR (300 MHz, CD₃OD): δ 3.43-3.56 (m, 4H), 2.95 (A₂B₂, J = 2.2, 9.1 Hz, 2H), 2.39 - 2.42 (m, 2H); ¹³C NMR (75 MHz, CD₃OD): δ 176.6, 54.5, 42.5, 40.0; IR (neat) 2926, 2100, 1708, 1249; HRMS (ESI) m/z [(M+Na)⁺] (C₈H₁₀N₆O₄Na) calculated 277.0661, found 277.0667.

1,2-Bis-bromoacetyl-3,4-bis-azidomethylcyclobutane (**17**)

A mixture of **15** (4.57 g, 18 mmol) and SOCl₂ (39.4 mL, 540 mmol) was refluxed for 2 h. The excess of SOCl₂ was removed under reduced pressure. The residue was coevaporated with toluene (5 mL) 3 times. The crude acyl chloride was dissolved in CH₂Cl₂ (10 mL) and added dropwise at -10 °C to a solution of CH₂N₂ in CH₂Cl₂ (400 mL) prepared from N-Nitroso-N-methylurea (51.5 g, 0.500 mol) and 40% KOH (154 mL) and dried with KOH pellets for 3 h.

The reaction mixture was stirred at 0 °C for 1 h and concentrated to a volume of about 100 mL. To this solution was added dropwise aqueous conc. HBr (48%, 9.23 mL, 90 mmol) at -10 °C. The reaction mixture was stirred at the same temperature for 10 min, washed with saturated aqueous NaHCO₃ and brine. The organic phase was dried (Na₂SO₄), and concentrated to dryness. The residue was purified by flash column chromatography with ethyl acetate/hexanes (1/10, v/v) to afford **17** (5.29 g, 72% overall yield) as clear oil.

¹H NMR (300 MHz, CDCl₃): δ 3.95 (s, 4H), 3.48-3.53 (m, 6H), 2.39 - 2.46 (m, 2H); **¹³C NMR** (75 MHz, CDCl₃): δ 199.5, 53.3, 44.9, 38.1, 32.8; IR (neat) 2931, 2100, 1709, 1386, 1262; **HRMS** (FAB) *m/z* [(M+Li)⁺] (C₁₀H₁₂Br₂N₆O₂Li) calculated 412.9548, found 412.9547.

1,2-Bis-(2-tert-butoxycarbonylamino-1H-imidazol-4-yl)-3,4-bis-azidomethyl-cyclobutane (**19**)

A solution of **17** (3.8 g, 9.3 mmol) and **18**¹⁴ (8.80 g, 55.9 mmol) in DMF (31 mL) was stirred at rt overnight. The DMF was removed under reduced pressure. The residue was treated with ethyl acetate. The precipitate was collected by filtration, washed with ethyl acetate (10 mL, 3 times) to give **19** (1.5 g, 30%) as a white solid, **mp** 192-194 °C (dec).

¹H NMR (300 MHz, CDCl₃ + 1 drop of HOAc): δ 6.51 (s, 2H), 3.48-3.50 (m, 4H), 2.98 (A₂B₂, J = 2.7, 9.1 Hz, 2H), 2.34 - 2.41 (m, 2H), 1.53 (s, 18H); **¹³C NMR** (75 MHz, CDCl₃ + 1 drop of HOAc): δ 151.3, 148.5, 133.5, 106.8, 86.0, 53.8, 41.3, 38.5, 27.7; IR (neat) 3298 (br), 1733, 1630, 1357, 1256, 1157, 1124; **HRMS** (ESI) *m/z* [(M+H)⁺] (C₂₂H₃₃N₁₂O₄) calculated 529.2748, found 529.2737.

1,2-Bis-(2-tert-butoxycarbonylamino-1H-imidazol-4-yl)-3,4-bis-aminomethyl-cyclobutane (**20**)

A mixture of **19** (200 mg, 0.380 mmol) and PPh₃ (398 mg, 1.52 mmol) in THF (4 mL) was refluxed for 30 min, whereupon it became homogeneous. To the reaction mixture was added NH₄OH (20%, 0.5 mL), the reflux was continued for 10 min, and the mixture was concentrated to dryness. The residue was purified by flash column chromatography with CH₂Cl₂/MeOH saturated with NH₃ (1/1, v/v) to afford **20** (169 mg, 93% yield) as a white solid, **mp** 158-160 °C (dec).

¹H NMR (300 MHz, CD₃OD): δ 6.68 (s, 2H), 2.85 (A₂B₂, J = 2.4, 9.0 Hz, 2H), 2.74-2.82 (m, 4H), 2.07 - 2.10 (m, 2H), 1.59 (s, 18H); **¹³C NMR** (75 MHz, CD₃OD): δ 152.4, 150.6, 140.4,

107.6, 86.1, 48.1, 46.6, 41.5, 28.1; **IR** (neat) 3298 (br), 1733, 1630, 1357, 1256, 1157, 1124; **HRMS** (ESI) m/z $[(M+H)^+]$ ($C_{22}H_{37}N_8O_4$) calculated 477.2938, found 477.2945.

1,2-Bis-(2-tert-butoxycarbonylamino-1H-imidazol-4-yl)-3,4-bis-[(4-bromo-1H-pyrrole-2-carbonyl)-amino]-methyl-cyclobutane (21a)

A solution of **20** (150 mg, 0.315 mmol) and 2-trichloroacetyl-4-bromopyrrole¹⁵ (368 mg, 1.26 mmol) in DMF (1 mL) was stirred at rt overnight. The DMF was removed under reduced pressure. The residue was purified by flash column chromatography with CH_2Cl_2 /MeOH saturated with NH_3 (40/1, v/v) to give **21a** (212 mg, 82%) as a white solid, **mp** >196 °C (dec). **¹H NMR** (300 MHz, CD_3OD): δ 6.91 (d, J = 1.6 Hz, 2H), 6.80 (d, J = 1.6 Hz, 2H), 6.61 (s, 2H), 3.43-3.53 (m, 4H), 2.92 (A_2B_2 , J = 2.7, 9.2 Hz, 2H), 2.28 - 2.32 (m, 2H), 1.57 (s, 18H); **¹³C NMR** (75 MHz, CD_3OD): δ 162.7, 152.3, 150.5, 139.6, 127.6, 122.7, 113.3, 107.8, 97.4, 86.1, 43.7, 43.2, 41.5, 28.1; **IR** (neat) 3298, 1736, 1624, 1457, 1371, 1258, 1156, 1126, 921; **HRMS** (ESI) m/z $[(M+H)^+]$ ($C_{32}H_{41}Br_2N_{10}O_6$) calculated 819.1577, found 819.1572.

Sceptrin (2a)

A solution of **21a** (147 mg, 0.179 mmol) in 50% TFA in CH_2Cl_2 (2 mL) was stirred at rt for 1 h. The reaction mixture was concentrated to give sceptrin trifluoroacetate (152 mg, 100%) as a white solid, **mp** 152-154 °C.

¹H NMR (300 MHz, CD_3OD): δ 6.91 (d, 1.4 Hz, 2H), 6.75 (d, 1.4 Hz, 2H), 6.56 (s, 2H), 3.48-3.50 (m, 4H), 2.99 (A_2B_2 , 2.5, 9.5 Hz), 2.34-2.37 (m, 2H); **¹³C NMR** (75 MHz, CD_3OD): δ 163.0, 148.9, 128.7, 127.2, 123.0, 113.4, 110.2, 97.5, 44.2, 42.3, 39.2; **IR** (neat) 3151, 2360, 2341, 1681, 1557, 1435, 1320, 1201, 1137.

The free base of sceptrin was obtained by treatment of sceptrin•2TFA with 3 eq of KOH in MeOH followed by flash column chromatography with CH_2Cl_2 /MeOH saturated with NH_3 (1/1, v/v) as a white solid, **mp** >192 °C (dec).

¹H NMR (300 MHz, CD_3OD): δ 6.91 (d, J = 1.4 Hz, 2H), 6.82 (d, J = 1.4 Hz, 2H), 6.31 (s, 2H), 3.41 - 3.55 (m, 4H), 3.02 (A_2B_2 , J = 2.6, 9.4 Hz, 2H), 2.16 - 2.26 (m, 2H); **¹³C NMR** (75 MHz,

CD₃OD): δ 161.7, 149.5, 133.9, 126.4, 121.5, 112.3, 110.9, 96.3, 43.3, 42.1, 40.6; **IR** (neat) 3287 (br), 2359, 2340, 1622, 1568, 1521, 1455, 1386, 1327, 1129, 921, **HRMS** (ESI) m/z [(**M**+**H**)⁺] (C₂₂H₂₅Br₂N₁₀O₂) calculated 619.0565, found 619.0557.

For comparison with the ¹H NMR spectra of synthetic and natural sceptrin•HCl reported by Baran's group,¹² sceptrin hydrochloride was obtained by addition of 2N HCl in Et₂O to the free base in MeOH followed by evaporation to dryness. White solid, **mp** 216-220 °C (dec).

¹H NMR (300 MHz, D₂O): δ 7.00 (d, *J* = 1.6 Hz, 2H), 6.56 (d, *J* = 1.6 Hz, 2H), 6.53 (s, 2H), 3.40 – 3.52 (m, 4H), 2.98 (A₂B₂, *J* = 2.4, 9.6 Hz, 2H), 2.46 – 2.48 (m, 2H).

1,2-Bis-(2-tert-butoxycarbonylamino-1H-imidazol-4-yl)-3,4-bis-((4,5-dibromo-1H-pyrrole-2-carbonyl)-amino)-methyl-cyclobutane (**21b**)

A solution of **20** (136 mg, 0.286 mmol) and 2-trichloroacetyl-4,5-dibromopyrrole¹⁶ (423 mg, 1.14 mmol) in DMF (1 mL) was stirred at rt for 2 days. The DMF was removed under reduced pressure. The residue was purified by flash column chromatography with CH₂Cl₂/MeOH saturated with NH₃ (40/1, v/v) to give **21b** (137 mg, 49%) as a white solid, **mp** >194 °C (dec).

¹H NMR (300 MHz, CD₃OD): δ 6.78 (s, 2H), 6.56 (s, 2H), 3.40 – 3.44 (m, 4H), 2.88 (A₂B₂, *J* = 2.2, 9.3 Hz, 2H), 2.18 – 2.29 (m, 2H), 1.54 (s, 18H); **¹³C NMR** (75 MHz, CD₃OD): δ 161.9, 152.3, 150.5, 139.8, 128.9, 114.3, 107.8, 105.9, 99.9, 86.1, 43.6, 43.3, 41.6, 28.1; **IR** (neat) 1730, 1621, 1557, 1523, 1416, 1350, 1241, 1154, 1120; **HRMS** (ESI) m/z [(**M**+**H**)⁺] (C₃₂H₃₉Br₄N₁₀O₆) calculated 974.9787, found 974.9760.

Dibromosceptrin (**2b**)

A solution of **21b** (82 mg, 0.084 mmol) in 50% TFA in CH₂Cl₂ (2 mL) was stirred at rt for 1 h. The reaction mixture was concentrated to give dibromosceptrin•2TFA (84 mg, 100%) as a white solid, **mp** 100-102 °C.

¹H NMR (300 MHz, CD₃OD): δ 6.77 (s, 2H), 6.56 (s, 2H), 3.47 – 3.49 (m, 4H), 2.99 (A₂B₂, *J* = 2.6, 9.6 Hz, 2H), 2.34 – 2.37 (m, 2H); **¹³C NMR** (75 MHz, CD₃OD): δ 162.1, 149.0, 128.7,

128.5, 114.4, 110.2, 106.4, 100.1, 44.1, 42.4, 39.2; IR (neat) 3168 (br), 2360, 1681, 1567, 1529, 1417, 1326, 1201, 1141, 1022, 979.

The free base of dibromosceptrin was obtained by treatment of dibromosceptrin•2TFA with 3 eq of KOH in MeOH followed by flash column chromatography with CH₂Cl₂/MeOH saturated with NH₃ (1/3 to 1/1, v/v) as a white solid, **mp** >202 °C (dec).

¹H NMR (300 MHz, CD₃OD): δ 6.81 (s, 2H), 6.28 (s, 2H), 3.38 - 3.49 (m, 4H), 2.89 (A₂B₂, J = 2.9, 9.2 Hz, 2H), 2.20 - 2.23 (m, 2H); **¹³C NMR** (75 MHz, CD₃OD): δ 162.2, 150.7, 135.1, 129.0, 114.5, 112.2, 106.4, 99.7, 44.5, 43.3, 41.7; IR (neat) 3320 (br), 2360, 2340, 1621, 1568, 1418; **HRMS** (ESI) m/z [(M+H)⁺] (C₂₂H₂₃Br₄N₁₀O₂) calculated 774.8739, found 774.8740.

For comparison with the ¹H NMR and ¹³C NMR data of natural dibromosceptrin•2HOAc reported by Keifer's group,⁵ dibromosceptrin•2HOAc in CD₃OD was obtained by titration of the free base in CD₃OD with HOAc in CD₃OD monitored by ¹H NMR.

¹H NMR (300 MHz, CD₃OD): δ 6.81 (s, 2H), 6.51 (s, 2H), 3.48-3.49 (m, 4H), 2.99 (dd, A₂B₂, J = 2.6, 9.5 Hz, 2H), 2.33-2.36 (m, 2H), 1.95 (s, 6H); **¹³C NMR** (75 MHz, CD₃OD): δ 180.1, 162.1, 149.4, 129.7, 128.6, 114.5, 110.1, 106.2, 100.0, 44.2, 42.4, 39.5, 23.9.

Table 1. ¹H NMR ¹³C NMR Data for Synthetic and Natural Dibromosceptrin •2HOAc

Synthetic	6.81 (s, 2H)	6.51 (s, 2H)	3.48-3.49 (m, 4H)	2.99 (dd, 2H)	2.33-2.36 (m, 2H)	1.95 (s, 6H)
Natural	6.81 (s, 2H)	6.52 (s, 2H)	3.48 (br s, 4H)	3.00 (m, 2H)	2.35 (br s, 2H)	1.93 (s, 6H)

Table 2. ¹³C NMR Data for Synthetic and Natural Dibromosceptrin•2HOAc*

Synthetic	180.1	162.1	149.4	129.7	128.6	114.5	110.1	106.2	100.0	44.2	42.4	39.5	23.9
Natural	180.1	162.0	149.2	128.7	128.5	114.7	110.1	106.3	100.1	44.2	42.5	39.1	24.0

* The ¹³C NMR chemical shifts of dibromosceptrin•2HOAc are concentration-dependent, and up to 0.5 ppm differences were observed at different concentrations.

16

J-52 /Oct 21, 2003
Pulse Sequence: zgpg30

16

J-52-C13, Oct 21, 2003

Pulse Sequence: e2pul

17

J-54 / Oct 23, 2003
Pulse Sequence: s2pul

17

J-54-C13, Oct 22, 2003

Pulse Sequence: s2pul

18

J-57 / March 26, 2004

Pulse Sequence: s2pul

18

J-57-C13 / March 26, 2004

Pulse Sequence: s2pul

20

J-72 / Dec 3, 2003

Pulse Sequence: s2pul

20

J-72-C13 / Dec 3, 2003

Pulse Sequence: s2pul

22

22

23

J-65 / Nov 7, 2003
Pulse Sequence: zgpg30

23

J-65-Cl3 / Nov 7, 2003

Pulse Sequence: s2pul

24

J-111 / Jan 27, 2004

Pulse Sequence: s2pul

24

J-111-cl3 / Jan 28, 2004

Pulse Sequence: s2pul

26

J-115 / Jan 29, 2004

Pulse Sequence: s2pul

26

J-115-C13 / Feb 14, 2004

Pulse Sequence: s2pul

28

J-116-CDCl₃-AcOH / Feb 24, 2004

Pulse Sequence: zgpg30

J-116-C13-CDCl3-AcOH / Feb 24, 2004

Pulse Sequence: s2pul

J-117 / March 18, 2004
Pulse Sequence: s2pul

29

J-117-C13 / March 18, 2004

Pulse Sequence: s2pul

30a

J-144 / March 17, 2004

Pulse Sequence: s2pul

30a

J-144-C13 / march 19, 2004

Pulse Sequence: s2pul

3a

Sceptrix-2TFA / March 18, 2004

Pulse Sequence: s2pul

3a

scepterin-TFA-Cl3 / March 18, 2004

Pulse Sequence: s2pul

3a

Scepterin / March 19, 2004

Pulse Sequence: s2pul

3a

Sceptin-Cl3 / March 19, 2004

Pulse Sequence: s2pul

Synthetic ($\pm$)-Sceptrin
Hydrochloride, this study

Natural Sceptrin
Hydrochloride*

Synthetic ($\pm$)-Sceptrin
Hydrochloride by Baran *et al.*^{12*}

* From Supporting Information in Ref. 12.

30b

J-145 / March 23, 2004

Pulse Sequence: #2pul

3b

Dibromoscepterin-TFA / March 23, 2004

Pulse Sequence: s2pul

3b

Dibromosceptin-Cl3 / March 25, 2004

Pulse Sequence: s2pul

3b

Dibromoscepterin / March 24, 2004

Pulse Sequence: s2pul

3b

Dibromoseptin-C13 / March 25, 2004

Pulse Sequence: zgpg30

Dibromocaptin-AcOH / April 14, 2004

Pulse Sequence: s2pul

3b

Dibromosceptrin-AcOH-Cl3 / April 14, 2004

Pulse Sequence: s2pul