Enantioselective Total Synthesis of (–)-Dehydrobatzelladine C

Shawn K. Collins[†], Andrew I. McDonald,^{††} Larry E. Overman* and Young Ho Rhee

Department of Chemistry, 516 Rowland Hall, University of California at Irvine, Irvine, California, 96697-2025.

Supporting Information (9 pages)

Experimental procedures and characterization data for 2,2,5,7,8-pentamethylchroman-6-sulfonamide, *S,S*-dimethyl *N*-(2,2,5,7,8-pentamethylchroman-6-sulfonyl)carbonimido-dithioate (**8**), and new compounds reported in Schemes 1–3; ¹H and ¹³C NMR spectra of synthetic (–)-dehydrobatzelladine C (**6**).

2,2,5,7,8-Pentamethylchroman-6-sulfonamide. Following a general procedure,¹ a solution of ClSO₃H (46.3 mL, 227 mmol) and CH₂Cl₂ (290 mL) was added dropwise to a solution of 2,2,5,7,8-pentamethylchroman (47.1 g, 231 mmol) and CH₂Cl₂ (1.5 L) at 0 °C. Upon complete addition, the reaction mixture was allowed to warm to rt over 3.5 h. The reaction mixture was then quenched by pouring into saturated aqueous NaHCO₃ (1.5 L). The layers were separated and the organic layer was washed with H₂O (3 × 1.5 L) and brine (0.5 L), then dried (MgSO₄), filtered through a plug of silica and the filtrate was used directly in the following reaction.

Ammonia was bubbled through the above solution of crude 2,2,5,7,8-pentamethylchroman-6-sulfonyl chloride at 0 °C for 3 h. The reaction mixture then was filtered through a plug of silica gel, which was rinsed with EtOAc. The combined eluents were concentrated and the resulting crude solid was triturated with hexanes to yield 28.1 g (43%) of 2,2,5,7,8-pentamethylchroman-6-sulfonamide: mp 159–161 °C; ¹H NMR (400 MHz, CDCl₃) δ 4.83 (s, 2 H), 2.65 (t, *J* = 6.9 Hz, 2 H), 2.56 (s, 3 H), 2.55 (s, 3 H), 2.13 (s, 3 H), 1.83 (t, *J* = 6.9 Hz, 2 H), 1.32 (s, 6 H); ¹³C NMR (100 MHz, CDCl₃) 154.4, 135.5, 135.2, 131.2, 124.7, 118.4, 74.0, 32.6, 26.7, 21.4, 18.5, 17.4, 12.1; IR (KBr) 3424, 3286, 2974, 2933, 1560, 1459, 1320, 1146, 873 cm^{–1}. Anal. Calcd for C₁₄H₂₁NO₃S: C, 59.34; H, 7.47; N, 4.94. Found: C, 59.43; H, 7.46; N, 4.85.

¹Heizmann, G.; Felder, E. R. *Peptide Res.* **1994**, 7, 328.

***S,S*,-Dimethyl *N*-(2,2,5,7,8-pentamethylchroman-6-sulfonyl)carbo-nimidodithioate (8):** A solution of 2,2,5,7,8-pentamethylchroman-6-sulfonamide (13.1 g, 46.2 mmol) and DMF (300 mL) was added to NaH (5.5 g, 138 mmol, washed 3 □ with hexanes) at 0 °C. The reaction was stirred vigorously for 15 min, warmed to rt for 15 min, then re-cooled to 0 °C before CS₂ (8.3 mL, 138 mmol) was added. After another 15 min, MeI (8.6 mL, 137 mmol) was added. After another 15 min, the reaction was poured into 50% aqueous NH₄Cl (500 mL) and Et₂O (500 mL). The layers were separated and the organic layer was washed with brine (3 □ 200 mL), dried (MgSO₄), filtered through a plug of silica gel and concentrated. The resulting residue was purified on silica gel (4:1 hexanes-EtOAc) to yield 17.3 g (97%) of **8** as a colorless solid: mp 133–135 °C; ¹H NMR (500 MHz, CDCl₃) □ 2.63 (t, *J* = 6.8 Hz, 2 H), 2.56 (s, 3 H), 2.55 (s, 3 H), 2.50 (s, 6 H), 2.11 (s, 3 H), 1.81 (t, *J* = 6.8 Hz, 2 H), 1.30 (s, 6 H); ¹³C NMR (125 MHz, CDCl₃) 181.6, 154.5, 136.5, 136.6, 130.2, 124.3, 118.1, 73.9, 32.5, 26.6, 21.2, 18.4, 17.3, 16.3, 12.0; IR (KBr) 2970, 2930, 1552, 1472, 1307, 1144, 925, 802, 621, 542 cm⁻¹. Anal. Calcd for C₁₇H₂₅NO₃S₃: C, 52.68; H, 6.50; N, 3.61. Found: C, 52.75; H, 6.47; N, 3.57.

(*S*)-*N*-[(Aminomethylene)-2,2,5,7,8-pentamethylchroman-6-sulfonamide]-3-amino-7-methyl-6-octenol (9): A solution of (*S*)-3-amino-7-methyl-6-octenol² (3.12 g, 19.8 mmol) *S,S*-dimethyl *N*-(2,2,5,7,8-pentamethylchroman-6-sulfonyl)carbonimidodithioate (**8**, 5.13 g, 13.2 mmol), and benzene (15 mL) was maintained at reflux for 4 h. The reaction was then concentrated and the resulting residue was purified on silica gel (2:1 hexanes-EtOAc) to yield 4.54 g (71%) of (*S*)-*N*-[(methylthiomethylene)-2,2,5,7,8-pentamethylchroman-6-sulfonamide]-3-amino-7-methyl-6-octenol as a slightly yellow oil: [α]_D²⁵ -10.8, [α]_D²⁵ -10.9, [α]_D²⁵ -12.2, [α]_D²⁵ -21.7, [α]_D²⁵ -25.5, (*c* 1.2, CHCl₃); ¹H NMR (500 MHz, CDCl₃) □ 7.76 (d, *J* = 9.8 Hz, 1 H), 5.00–5.03 (m, 1 H),

²Franklin, A. S.; Ly, S. K.; Mackin, G. H.; Overman, L. E.; Shaka, A. J. *J. Org. Chem.* **1999**, *64*, 1512.

3.73–3.77 (m, 1 H), 3.62–3.65 (m, 2 H), 2.62 (t, $J = 6.8$ Hz, 2 H), 2.57 (s, 3 H), 2.55 (s, 3 H), 2.33 (s, 3 H), 2.09 (s, 3 H), 1.90–1.95 (m, 2 H), 1.77–1.85 (m, 3 H), 1.66 (s, 3 H), 1.56–1.63 (m, 2 H), 1.53 (s, 3 H), 1.46–1.50 (m, 1 H), 1.29 (s, 6 H), the OH signal was too broad to observe; ^{13}C NMR (125 MHz, CDCl_3) 167.0, 153.9, 135.8, 135.2, 132.6, 132.1, 124.1, 122.8, 117.9, 73.7, 58.6, 52.1, 37.7, 35.4, 32.6, 26.6, 25.6, 24.1, 21.2, 18.5, 17.6, 17.4, 14.1, 12.0 ppm; IR (film) 3492, 3289, 2930, 1732, 1574, 1446, 1296, 1119, 842 cm^{-1} . Anal. Calcd for $\text{C}_{25}\text{H}_{40}\text{N}_2\text{O}_4\text{S}_2$: C, 60.45; H, 8.12; N, 5.64. Found: C, 60.45; H, 8.17; N, 5.65.

Silver nitrate (66 mL, 0.2 M in MeCN) was added rapidly via cannula to a 0 °C solution of this pseudothiurea (4.54 g, 4.85 mmol) and MeCN (175 mL) which had been previously saturated with NH_3 . The reaction mixture was allowed to warm to rt and, after 3 h, EtOAc (200 mL) was added and the resulting mixture was filtered through a plug of silica gel. The eluent was concentrated and the resulting residue was purified on silica gel (1:2 hexanes-EtOAc) to yield 3.45 g (81%) of **9** as a colorless solid: mp 54–57 °C; $[\alpha]_D^{25} -15.0$, $[\alpha]_{577}^{25} -14.1$, $[\alpha]_{546}^{25} -15.6$, $[\alpha]_{435}^{25} -17.8$, $[\alpha]_{405}^{25} -16.2$, (c 1.3, CHCl_3); ^1H NMR (500 MHz, DMSO, 80 °C) δ 6.38 (m, 3 H), 4.98–5.01 (m, 1 H), 4.17 (s, 1 H), 3.65 (s, 1 H), 3.39–3.43 (m, 2 H), 2.59 (t, $J = 6.8$ Hz, 2 H), 2.51 (s, 3 H), 2.50 (s, 3 H), 2.03 (s, 3 H), 1.85–1.86 (m, 2 H), 1.76 (t, $J = 6.8$ Hz, 2 H), 1.58 (m, 4 H), 1.48 (m, 4 H), 1.32–1.45 (m, 2 H), 1.26 (s, 6 H); ^{13}C NMR (125 MHz, DMSO, 80 °C) 155.6, 152.1, 134.5, 134.2, 133.6, 130.5, 123.5, 122.3, 117.4, 73.0, 57.4, 47.5, 37.3, 34.4, 32.1, 26.1, 26.1, 24.8, 23.5, 20.4, 17.5, 16.9, 16.5, 11.3; IR (film) 3445, 3330, 2933, 1622, 1538, 1454, 1385, 1265, 1111 cm^{-1} . Anal. Calcd for $\text{C}_{24}\text{H}_{39}\text{N}_3\text{O}_4\text{S}$: C, 61.91; H, 8.44; N, 9.02. Found: C, 62.04; H, 8.48; N, 8.96.

(4a*R*,7*S*)-4-(Allyloxycarbonyl)-3-[(4*S*)-4-(*tert*-butyldimethylsiloxy)pentyl]-7-(2-hydroxyethyl)-1-(2,2,5,7,8-pentamethylchroman-6-sulfonylimino)-1,2,4a,5,6,7-hexahydropyrrolo[1,2-*c*]pyrimidine (12**).** Osmium tetroxide (1.0 mL, 0.1 M in *tert*-BuOH) was added to a solution of **9** (468 mg, 1.01 mmol), *N*-methylmorpholine-*N*-oxide (590 mg, 5.02 mmol), pyridine (30 μL , 0.4 mmol) and 10:1 THF– H_2O (10 mL). After 30 min, Florisil (1 g), NaHSO_3 (1 g) and EtOAc (20 mL) were added and the resulting mixture was stirred. After 30 min, the reaction mixture was filtered and the filtrate was concentrated to provide the corresponding 1,2-diol as a colorless oil, which was used without further purification.

A solution of this crude diol, $\text{Pb}(\text{OAc})_4$ (535 mg, 1.21 mmol) and CH_2Cl_2 (15 mL) was maintained for 30 min at rt. The reaction mixture was then filtered through a plug of Celite, and the filtrate was concentrated to provide the crude aminal as a slightly yellow oil.

A solution of this crude aminal, α -keto ester **11**³ (495 mg, 1.51 mmol), morpholinium acetate (222 mg, 1.51 mmol), AcOH (30 μ L, 0.3 mmol), and 2,2,2-trifluoroethanol (2.51 mL) was maintained at 100 °C for 8.5 h. After cooling to rt, the reaction was quenched by addition of Et₂O (50 mL) and 50% aqueous NH₄Cl (5 mL). The layers were separated, the organic layer was dried (MgSO₄), filtered and the filtrate was concentrated. The resulting oil was purified on silica gel (2:1 hexanes–EtOAc) to provide a 430 mg (58%) of **12** as a slightly yellow oil along with 60 mg (8%) of a minor isomer. **12**: ¹H NMR (500 MHz, CDCl₃) δ 9.43 (s, 1 H), 5.88–5.96 (m, 1H), 4.61 (dt, *J* = 13.1, 6.0 Hz, 2 H), 4.17 (dd, *J* = 10.9, 4.9 Hz, 1 H), 4.08 (dd, *J* = 13.5, 7.5 Hz, 1 H), 3.81 (sextet, *J* = 6.0 Hz, 1 H), 3.46–3.52 (m, 2 H), 2.66 (m, 1 H), 2.62 (t, *J* = 6.8 Hz, 2 H), 2.56 (s, 3 H), 2.55 (s, 3 H), 2.47–2.53 (m, 1 H), 2.32 (br s, 1 H), 2.09 (s, 3 H), 1.96–2.02 (m, 1 H), 1.81–1.88 (m, 2 H), 1.79 (t, *J* = 6.5 Hz, 2 H), 1.39–1.70 (m, 6 H), 1.29 (s, 6 H), 1.12 (d, *J* = 6.0, 3 H), 0.09 (s, 9 H), 0.04 (s, 6 H); ¹³C NMR (100 MHz, CDCl₃) 164.5, 153.9, 149.6, 149.2, 135.5, 135.2, 132.5, 132.0, 124.1, 118.8, 118.0, 104.0, 73.7, 68.1, 65.1, 59.4, 57.2, 54.5, 38.9, 38.1, 32.6, 31.2, 29.8, 29.7, 26.7, 25.8, 24.0, 23.5, 21.3, 18.5, 18.0, 17.4, 12.0, –4.5, –4.8; IR (film) 3480, 3292, 2930, 2857, 1703, 1614, 1552, 1470, 1298, 1258, 1109 cm^{–1}. Anal. Calcd for C₃₈H₆₁N₃O₇SSi: C, 62.35; H, 8.40; N, 5.74. Found: C, 62.27; H, 8.47; N, 5.65.

(4*R*,7*S*)-3-[4-(*tert*-Butyldimethylsiloxy)pentyl]-7-(2-hydroxyethyl)-1-(2,2,5,7,8-pentamethylchroman-6-sulfonylimino)-1,5,6,7-tetrahydropyrrolo[1,2-*c*]pyrimidine-4-carboxylic acid allyl ester (14**).** Benzoyl peroxide (4 mg, 0.16 mmol) was added to a solution of **12** (16 mg, 0.021 mmol) and THF (2 mL) under an atmosphere of O₂ (1 atm). The solution was warmed to 60 °C and stirred for 4 h until TLC analysis showed complete consumption of **12**. The reaction mixture was concentrated and the residue purified by chromatography (10:1 hexanes:EtOAc) to afford 10 mg (65 %) of **14**: [α]_D²⁷₅₈₉ –10.0, [α]_D²⁷₅₇₇ –9.8, [α]_D²⁷₅₄₆ –11.9, [α]_D²⁷₄₃₅ –30.0, [α]_D²⁷₄₀₅ –42.2 (c 2.3, MeOH); ¹H NMR (500 MHz, CDCl₃) δ 6.03–5.94 (m, 1 H), 5.40 (dd, *J* = 18.4, 1.3 Hz, 1 H), 5.34 (dd, *J* = 10.3, 1.3 Hz, 1 H), 5.14–5.10 (m, 1 H), 4.78–4.71 (m, 2 H), 3.98–3.93 (m, 1 H), 3.85–3.80 (m, 1 H), 3.74–3.70 (m, 1 H), 3.52–3.39 (m, 3 H), 2.81–2.75 (m, 2 H), 2.72 (s, 3 H), 2.68 (s, 3 H), 2.65 (t, *J* = 6.7 Hz, 2 H), 2.45–2.32 (m, 3 H), 2.14 (s, 3 H), 1.92–1.90 (m, 1 H), 1.82 (t, *J* = 6.7 Hz, 2 H), 1.54–1.48 (m, 1 H), 1.38–1.28 (m, 9 H), 1.08 (d, *J* = 6.1 Hz, 3 H), 0.90 (s, 9 H), 0.06 (s, 3 H), 0.04 (s, 3 H); ¹³C NMR (125 MHz, CDCl₃) δ 177.0, 165.7, 163.6, 153.5, 151.6, 136.3, 135.5, 132.5, 131.2, 123.5, 120.0, 117.5, 108.4, 73.4, 68.2, 66.2, 62.7, 59.0, 39.5, 37.8, 34.0, 33.0, 32.8, 29.6, 26.7, 26.6, 26.3, 25.8, 25.2, 23.4, 21.4, 18.5, 18.0, 17.5, 12.1, –4.5, –4.8; IR (thin film) 3402, 2927, 1717, 1598, 1279,

³Coffey, D. S.; McDonald, A. I.; Overman, L. E.; Rabinowitz, M. H.; Renhowe, P. A. *J. Am. Chem. Soc.* **2000**, *122*, 4893.

1117, 1009, 835 cm^{-1} ; HRMS (ESI⁺) m/z 730.3904 (730.3922 calcd for $\text{C}_{38}\text{H}_{60}\text{O}_7\text{N}_3\text{SSi}$ $[\text{M}+\text{H}]^+$).

3-Oxo-octanoic acid 4-*tert*-butoxycarbonylaminobutyl ester (16). DMAP (29 mg, 0.24 mmol) was added to a solution of *N*-(*tert*-butoxycarbonyl)-4-aminobutanol (400 mg, 2.12 mmol), **15** (1.09 g, 6.35 mmol) and toluene (12 mL) and heated to 100 °C for 18 h. The reaction mixture was concentrated and the residue purified by chromatography (10:1 hexanes:EtOAc) to afford 541 mg (78%) of **16** as a clear oil: ¹H NMR (500 MHz, CDCl_3) δ 4.75 (br s, 1 H), 4.12 (t, J = 6.5 Hz, 2 H), 3.43 (s, 2 H), 3.15–3.10 (m, 2 H), 2.51 (t, J = 7.4 Hz, 2 H), 1.68–1.63 (m, 2 H), 1.59–1.52 (m, 4 H), 1.42 (s, 9 H), 1.32–1.24 (m, 4 H), 0.87 (t, J = 6.8 Hz, 3 H); ¹³C NMR (125 MHz, CDCl_3) 202.8, 167.1, 155.8, 88.7, 78.9, 64.7, 49.0, 42.9, 31.0, 28.2, 26.4, 25.7, 22.9, 22.2, 13.8; IR (thin film) 3500, 2966, 1699, 1522, 1398, 1251, 1166, 919, 733 cm^{-1} ; HRMS (CI⁺) m/z 330.2285 (330.2280 calcd for $\text{C}_{17}\text{H}_{32}\text{O}_5\text{N}$ $[\text{M}+\text{H}]^+$).

(2a*S*,7*S*)-7-Heptyl-4-pentyl-1,2,6,7,8,8a-tetrahydro-5,6,8b-triazaacenaphthalene-3-carboxylic acid 4-(*tert*-butoxycarbonyl)aminobutyl ester (19) β -Ketoester **16** (173 mg, 0.527 mmol) was added to a solution of hemiaminal **17**² (61 mg, 0.195 mmol), morpholine (20 μL , 0.20 mmol), AcOH (13 μL , 0.20 mmol) and Na_2SO_4 (110 mg, 0.78 mmol) in TFE (390 μL , 0.55 M). The reaction mixture was heated to 65–70 °C and stirred for 72 h. The reaction mixture was cooled, filtered and concentrated. The residual oil was purified by preparative HPLC (Phenomenex C-18, 16 mL/min, 210 nm, 10 % MeCN:0.1 % TFA in H_2O to 90% MeCN: 0.1 % TFA in H_2O over 20 min) to give pure **18** (67 mg, 48% yield) and 25 mg of a mixture of **16** and **18** (1:2 mixture determined by ¹H NMR) as a colorless oil that was used directly in the next step

Purification of a comparable sample (20 mg) by preparative HPLC (Phenomenex C-18, 16 mL/min, 210 nm, 10 % MeCN:0.1 % TFA in H_2O to 90% MeCN: 0.1 % TFA in H_2O) gave 14 mg of pure **18**: $[\alpha]_{589}^{27} -90.3$, $[\alpha]_{577}^{27} -98.2$, $[\alpha]_{546}^{27} -115$, $[\alpha]_{435}^{27} -198$,

$[\alpha]_D^{27} -212$ (c 1.5, MeOH); ^1H NMR (500 MHz, CDCl_3) δ 12.3 (br s, 1 H), 10.7 (br s, 1 H), 4.55 (br s, 1 H), 4.44 (m, 1 H), 4.16 (t, $J = 6.5$ Hz, 2 H), 3.68 (m, 1 H), 3.42 (m, 1 H), 3.16 (m, 2 H), 2.66-2.72 (m, 2 H), 2.53 (m, 1 H), 2.38 (m, 1 H), 2.15 (m, 1 H), 1.30-1.80 (m, 25 H), 1.45 (s, 9 H), 0.88-0.92 (m, 6 H); ^{13}C NMR (125 MHz, CDCl_3) 165.1, 156.0, 149.3, 146.8, 100.0, 64.0, 57.1, 55.8, 50.2, 40.2, 33.5, 33.3, 33.2, 31.7, 31.5, 30.7, 29.2, 29.1, 28.4, 28.2, 27.0, 26.9, 26.1, 25.3, 22.6, 22.3, 14.0, 13.9; IR (thin film) 3404, 2923, 2858, 1721, 1636, 1594, 1316, 1258, 1167 cm^{-1} ; HRMS (ESI) m/z 547.4206 (547.4223 calculated for $\text{C}_{31}\text{H}_{55}\text{N}_4\text{O}_4$ $[\text{M}^+]$).

Ceric ammonium nitrate (65 mg, 0.12 mmol) was added to a solution of crude **18** (approximately 78 mg, 0.12 mmol) and MeCN (3 mL) and stirred for 30 min. The reaction mixture was filtered and purified by preparative HPLC (Phenomenex C-18, 16 mL/min, 254 nm, 85 % MeCN: 0.1% HCl in H_2O) to afford **19** (38 mg, 33%) as a pale yellow oil: $[\alpha]_D^{27} -55.5$, $[\alpha]_D^{27} -58.0$, $[\alpha]_D^{27} -61.9$, $[\alpha]_D^{27} -86.3$, $[\alpha]_D^{27} -95.8$ (c 0.5, MeOH); ^1H NMR (500 MHz, CD_3OD) δ 4.58-4.54 (m, 1 H), 4.37 (t, $J = 6.5$ Hz, 2 H), 3.82-3.78 (m, 1 H), 3.65-3.52 (m, 2 H), 3.46-3.42 (m, 2 H), 3.09 (t, $J = 8.8$ Hz, 2 H), 3.05-2.96 (m, 2 H), 2.59-2.54 (m, 2 H), 2.03-1.98 (m, 1 H), 1.85-1.55 (m, 9 H), 1.54-1.35 (m, 20 H), 0.92-0.88 (m, 6 H); ^{13}C NMR (125 MHz, CD_3OD) δ 181.4, 167.0, 164.7, 158.7, 152.3, 112.6, 67.0, 66.1, 63.1, 53.2, 40.4, 38.5, 35.1, 34.5, 32.9, 32.7, 31.0, 30.6, 30.3, 30.2, 29.0, 27.0, 26.7, 26.0, 25.4, 23.7, 23.5, 14.4, 14.3; IR (thin film) 3404, 2923, 2858, 1721, 1636, 1594, 1316, 1258, 1167 cm^{-1} ; HRMS (ESI) m/z 545.4067 (545.4067 calcd for $\text{C}_{31}\text{H}_{53}\text{O}_4\text{N}_4$ $[\text{M}^+]$). Also isolated was 11 mg (12%) of the corresponding primary amine **20**.

(-)-Dehydrobatzelladine C (6). To a stirred solution of **19** (21 mg, 0.036 mmol) and CHCl_3 was added trifluoroacetic acid (0.5 mL) and the resulting solution was maintained at rt for 1.5 h. The solution was concentrated in vacuo and azeotroped with heptane (2 $\times$ 10 mL) to remove excess trifluoroacetic acid. Crude **20** was used in the next reaction without further purification: ^1H NMR (500 MHz, CD_3OD) δ 4.56 (m, 1 H), 4.38 (t, $J = 6.5$ Hz, 2 H), 3.82-3.78 (m, 1 H), 3.62-3.58 (m, 1 H), 3.46-3.42 (m, 1 H), 3.12 (t, $J = 7.0$ Hz, 2 H), 3.02 (t, $J = 7.2$ Hz, 2 H), 2.64-2.61 (m, 1 H), 2.60-2.56 (m, 1 H), 2.02-1.98 (m, 1 H), 1.29-1.87 (m, 26 H), 0.92 (m, 6 H).

This sample of amine **20** was dissolved in dry DMF (1 mL) and the solution was cooled to 0°C . Di-Boc-thiourea (9.8 mg, 0.036 mmol), triethylamine (12.4 μL , 0.089 mmol), and mercuric chloride (17 mg, 0.036 mmol) were added sequentially in that order. The yellow solution gradually became opaque and the reaction was completed after 15 min. The reaction mixture was filtered and the filtrate was purified by preparative HPLC (Phenomenex C-18, 16 mL/min, 210 nm, 10 % MeCN: 0.1 % TFA in H_2O to 90 % MeCN: 0.1% TFA in H_2O over 20 min) to yield 27 mg (92%) of the guanylated product as a colorless oil: ^1H NMR (500 MHz, CD_3OD) δ 4.60 (m, 1 H), 4.43 (t, $J = 6.5$ Hz, 2 H), 3.82-3.86 (m, 1 H), 3.59-3.63 (m, 3H), 3.41-3.46 (m, 1 H), 3.12 (t, J

= 7.0 Hz, 2 H), 2.66-2.70 (m, 1 H), 2.57-2.61 (m, 1 H), 2.00-2.02 (m, 1 H), 1.63 (s, 9 H), 1.61 (s, 9 H), 1.35-1.95 (m, 26 H), 0.92-0.95 (m, 6 H).

A portion of this material (22mg, 0.027mmol) was dissolved in CHCl_3 (1 mL) and TFA (1 mL) was added. This solution was maintained at rt for 16 h. The reaction mixture was concentrated and the residue was purified by preparative HPLC (Phenomenex C-18, 16 mL/min, 210 nm, 10 % MeCN: 0.1% TFA in H_2O to 90 % MeCN: 0.1 % TFA in H_2O over 20 min) to give **6** (15 mg, 98%) as a clear oil: $[\alpha]_D^{27} -87.8$, $[\alpha]_D^{27} -89.1$, $[\alpha]_D^{27} -105$, $[\alpha]_D^{27} -251$, (*c* 0.23, MeOH); ^1H NMR (500 MHz, CD_3OD) δ 4.58-4.54 (m, 1 H), 4.37 (t, *J* = 6.5Hz, 2 H), 3.82-3.78 (m, 1 H), 3.60-3.56 (m, 1 H), 3.46-3.42 (m, 1 H), 3.25 (t, *J* = 7.0 Hz, 2 H), 3.09 (t, *J* = 7.2 Hz, 2 H), 2.67-2.63 (m, 1 H), 2.60-2.56 (m, 1 H), 2.02-1.99 (m, 1 H), 1.86-1.83 (m, 3 H), 1.75-1.68 (m, 4 H), 1.69-1.58 (m, 1 H), 1.48-1.46 (m, 2 H), 1.40-1.27 (m, 12 H), 0.9 2(t, *J* = 6.9 Hz, 3 H), 0.91 (t, *J* = 7.0 Hz, 3 H). A sample of **6** (12 mg, 0.022 mmol) was purified again by preparative HPLC (Phenomenex C-18, 16 mL/min, 210 nm, 10 % MeCN: 0.1 % acetic acid in H_2O to 90 % MeCN: 0.1 % acetic acid in H_2O) to give the acetate salt of **6** (14 mg) as a clear oil. ^{13}C NMR (125MHz, CD_3OD) δ 181.3, 166.9, 164.7, 158.7, 152.4, 112.7, 66.5, 63.1, 53.3, 42.1, 38.6, 35.1, 32.9, 32.7, 31.0, 30.6, 30.3, 30.2, 29.0, 26.9, 26.7, 26.0, 23.7, 23.5, 14.4, 14.3; IR (thin film) 3357, 2929, 2858, 1719, 1636, 1542, 1256, 1125 cm^{-1} ; HRMS (ESI) *m/z* 487.3755 (487.370 calcd for $\text{C}_{27}\text{H}_{47}\text{O}_2\text{N}_6$ [M^+]).

¹H spectrum

Chemical structure of the compound, showing a complex molecule with a central ring system, a side chain, and a terminal group. The structure is labeled with "2 Cl⁻".

ppm

[illegible]