Supporting Information

Total Synthesis of [Ψ[C(=S)NH]Tpg^4]Vancomycin Aglycon, [Ψ[C(=NH)NH]Tpg^4]Vancomycin Aglycon, and Related Key Compounds: Reengineering Vancomycin for Dual D-Ala-D-Ala and D-Ala-D-Lac Binding

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Improved protocol for the macrocyclization of **9**.

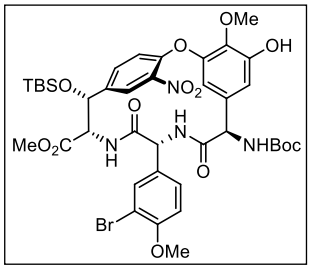


Table S1. Selected cyclization conditions examined.

Entry	Base 1	Additive	Solvent	Temperature (ºC)	Time (h)	Conversion (%)	Yield (%), *M*-**10** : *P*-**10**
1	K_2CO_3 20 eq.	$CaCO_3$ 20 eq.	DMF	45 ºC	18	100	60-68%, 1.1:1
2	Li_2CO_3 5 eq.	$CaCO_3$ 10 eq.	DMF	45 ºC	14	66	51%, 1:1.5
3	Li_2CO_3 40 eq.	$CaCO_3$ 10 eq.	DMF	45 ºC	20	50	47%, 1.2:1
4	Li_2CO_3 20 eq.	$CaCO_3$ 10 eq.	DMF	75 ºC	20	98	65%, 1.2:1
5	Rb_2CO_3 5 eq.	$CaCO_3$ 10 eq.	DMF	45 ºC	14	84	37%, 1:1.5
6	Cs_2CO_3 5 eq.	$CaCO_3$ 10 eq.	DMF	45 ºC	14	86	37%, 1:3.0
7	K_2CO_3 20 eq.	$CaCO_3$ 20 eq.	THF	45 ºC	40	25	18%, 1.8:1
8	K_2CO_3 20 eq.	$CaCO_3$ 20 eq.	THF	75 ºC	40	100	43%, 1.8:1
9	Li_2CO_3 20 eq.	$CaCO_3$ 10 eq.	DMSO	45 ºC	20	100	63%, 1.2:1
10	Li_2CO_3 20 eq.	$CaCO_3$ 20 eq.	DMSO	25 ºC	20	<5	--
11	K_2CO_3 20 eq.	$CaCO_3$ 20 eq.	DMSO	25 ºC	4-8	100	75-85%, 1:1.2

Compound 10. Method A: A vial containing K_2CO_3 (3.03 g, 22 mmol, 20 equiv), $CaCO_3$ (2.22 g, 22 mmol, 20 equiv), 4Å molecular sieves (2 g, 2 w/w equiv) under Ar was treated with anhydrous DMSO (220 mL) followed by **9** (1.00 g, 11 mmol). The reaction mixture was stirred at 25 ºC for 4 h. The reaction mixture was filtered through a plug of Celite, and quenched with cold saturated aqueous NH_4Cl (400 mL). The aqueous phase was extracted with cold EtOAc (3 × 100 mL) and saturated aqueous NaCl (100 mL), dried (Na_2SO_4) and the solvent removed under reduced pressure. Chromatography (SiO_2, 50% EtOAc–hexane to 40% acetone-hexane gradient elution) afforded (*P*)-**10** (natural atropisomer, 410 mg, 42%) as a foam followed by (*M*)-**10** (unnatural atropisomer, 415 mg, 43%) as a foam identical in all respects with material previously disclosed.[17] For (*P*)-**10**: mp 42 ºC (dec); $[\alpha]^{25}_{D}$ –35 (*c* 0.1, $CHCl_3$); ^{1}H NMR (acetone-d_6, 400 MHz) δ 8.32 (s, 1H), 8.16 (d, *J* = 2.1 Hz, 1H), 7.68–7.62 (m, 1H), 7.58–7.48 (m, 2H), 7.37 (d, *J* = 8.6 Hz, 1H), 7.37–7.32 (m, 1H), 7.18 (d, *J* = 8.4 Hz, 1H), 6.76 (d, *J* = 2.2 Hz, 1H), 6.68 (d, *J* = 2.2 Hz, 1H), 6.35–6.25 (m, 1H), 5.90 (d, *J* = 8.5 Hz, 1H), 5.62 (s, 1H), 5.49 (d, *J* = 7.4 Hz, 1H), 5.19–5.10 (m, 1H), 4.56 (d, *J* = 8.5 Hz, 1H), 3.944 (s, 3H), 3.936 (s, 3H), 3.78 (s, 3H), 1.39 (s, 9H), 0.79 (s, 9H), 0.02 (s, 3H), –0.11 (s, 3H); ^{13}C NMR (acetone-d_6, 125 MHz) δ 169.8, 169.1, 168.5, 157.1, 152.8, 151.7, 151.4, 143.5, 138.7, 138.6, 133.6, 132.4, 130.3, 129.8, 124.60, 124.57, 122.9, 113.3, 113.2, 112.6, 109.9, 79.4, 74.2, 61.5, 61.3, 60.9, 58.2, 57.6, 53.0, 28.5 (3C), 25.9 (3C), 18.3, –4.3, –5.7; IR (film) ν_{max} 3408, 2956, 1742, 1709, 1677, 1582, 1530, 1495, 1343, 1252, 1166, 110 cm^{-1}; ESI-TOF HRMS *m/z* 1021.1332 (M^+ + Na, $C_{39}H_{49}N_4O_{13}BrSi$ requires 1021.1303).

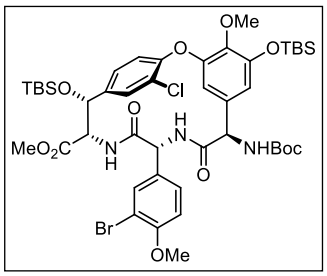
Method B: A round-bottom flask containing K_2CO_3 (6.06 g, 44.0 mmol) and 4Å molecular sieves (4.00 g, powdered) in anhydrous DMSO (400 mL) was treated with *nano*-$CaCO_3$ (8.88 mL of 0.5 g/1 mL suspension, 340 nm particle size, 44.0 mmol)[S1] and **9** (2.00 g, 2.20 mmol) in anhydrous DMSO (40 mL). The reaction mixture was stirred at room temperature for 6 h, then filtered through Celite. The filtrate was added to saturated aqueous NH_4Cl (80 mL) and extracted with EtOAc. The organic layer was washed with H_2O and saturated aqueous NaCl, and dried (Na_2SO_4). The solvent was removed under reduced pressure and the residue was purified by flash chromatography (SiO_2, 50% EtOAc–hexane) to provide (*P*)-**10** (581 mg, 30%) as a yellow foam, followed by (*M*)-**10** (917 mg, 46%) as an orange foam. Typical conversions on this scale were 75–85% using this procedure. The spectroscopic and analytical data for each were in accordance with that reported for authentic samples.[17]

Method C: A round-bottom flask containing K_2CO_3 (7.60 g, 55.0 mmol), $CaCO_3$ (5.50 g, 55.0 mmol) and 4Å molecular sieves (7.50 g, powdered) was purged with argon and flame-dried under high vacuum for 1 min. The flask was cooled to room temperature and anhydrous DMSO (500 mL) and **9** (2.50 g, 2.75 mmol) were added. The resulting mixture was stirred at room temperature for 10 h, then filtered through a plug of Celite. The filtrate was added to saturated aqueous NH_4Cl (100 mL) and extracted with EtOAc. The organic layer was washed with H_2O and saturated aqueous NaCl, and dried (Na_2SO_4). The solvent was removed under reduced pressure and the residue was purified by flash chromatography (SiO_2, 50% EtOAc–hexane) to provide (*P*)-**10** (734 mg, 30%) as a yellow foam, followed by (*M*)-**10** (943 mg, 38%) as an orange foam. The spectroscopic and analytical data for each were in accordance with that reported for authentic samples.

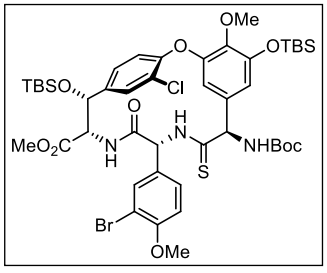
Improved procedure for unnatural (*M*)-10 to natural (*P*)-10 atropisomer equilibration. A microwave vial containing (*M*)-**10** (100 mg, 0.113 mmol) under Ar was treated with *o*-dichlorobenzene (purified by basic AlO_3 plug, storage over 4Å molecular sieves, and

[S1] Prepared by milling $CaCO_3$ with HD ZrO (1:6, $CaCO_3$ to beads) over 7 days.

degassed with Ar). The vial was sealed and heated by means of microwave irradiation (210 ˚C, 2 x 6 min, high absorbance). The reaction mixture was cooled and loaded onto a SiO_2 column (1 x 12 cm, 100% hexanes until *o*-dichlorobenzene eluted, then 50% EtOAc–hexanes until (*P*)-**10** eluted, followed by 40% acetone hexanes) to afford (*P*)-**10** (45 mg, 45%) and (*M*)-**10** (44 mg, 44%) as tan films.

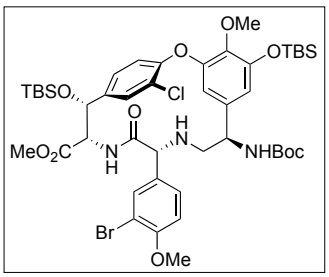


Compound 12. A solution of **11** (615 mg, 0.700 mmol) and imidazole (238 mg, 3.50 mmol) in anhydrous CH_2Cl_2 (12 mL) was treated with *tert*-butylchlorodimethylsilane (316 mg, 2.10 mmol) at 0 °C and the mixture was stirred for 45 min. The solvent was removed under reduced pressure and the residue was purified by flash chromatography (SiO_2, 5–12% acetone–CH_2Cl_2 gradient) to afford **12** (700 mg, quant.) as a colorless solid: m.p. 166–168 °C; $[\alpha]^{25}_D$ –39 (*c* 0.22, MeOH); ^{1}H NMR (CD_3OD, 600 MHz, rotamers (10:1), major given) δ 7.55 (s, 1H), 7.51 (br s, 1H), 7.40 (dd, *J* = 1.5, 8.4 Hz, 1H), 7.21 (br s, 1H), 7.20 (s, 1H), 7.13 (d, *J* = 8.6 Hz, 1H), 6.70 (d, *J* = 1.4 Hz, 1H), 6.54 (d, *J* = 1.4 Hz, 1H), 5.45 (d, *J* = 1.4 Hz, 1H), 5.37 (s, 1H), 5.20 (br s, 1H), 4.66 (s, 1H), 3.96 (s, 3H), 3.93 (s, 3H), 3.77 (s, 3H), 1.44 (s, 9H), 1.05 (s, 9H), 0.80 (s, 9H), 0.25 (s, 3H), 0.24 (s, 3H), 0.01 (s, 3H), –0.10 (s, 3H); ^{13}C NMR (CD_3OD, 150 MHz, rotamers (10:1), major given) δ 171.4, 170.6, 169.9, 158.2, 158.1, 154.5, 153.4, 151.3, 142.1, 139.8, 135.2, 134.4, 130.7, 130.4, 129.1, 128.5, 127.3, 124.0, 116.9, 113.6, 113.4, 110.1, 81.0, 74.9, 61.7, 61.5, 58.9, 58.6, 57.0, 53.4, 28.9, 26.4, 26.4, 19.4, 18.9, –4.1, –4.15, –4.21, –5.4; IR (film) ν_{max} 3420, 3307, 2953, 2931, 2895, 2857, 1705, 1658, 1603, 1580, 1495, 1472, 1433, 1392, 1364, 1333, 1284, 1253, 1163, 1096, 1064, 1007 cm^{-1}; ESI-TOF HRMS *m/z* 992.2956 (M^+ + H, $C_{45}H_{63}BrClN_3O_{11}Si_2$ requires 992.2946).

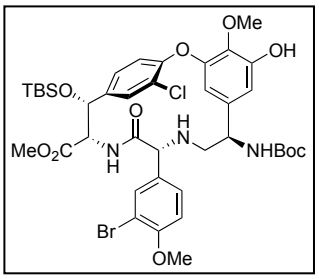


Compound 13. A solution of **12** (700 mg, 0.700 mmol) in anhydrous toluene (12 mL) was treated with Lawesson's reagent (recryst. from toluene, 311 mg, 0.770 mmol) at room temperature and the mixture was warmed at 60 °C for 3 h. The reaction mixture was cooled to 25 °C and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (SiO_2, 25% EtOAc–hexane) followed by PTLC (SiO_2, 1.5% acetone–CH_2Cl_2) to afford **13** (619 mg, 88%) as a colorless solid: m.p. 172–175 °C; $[\alpha]^{25}_D$ –44 (*c* 0.40, MeOH); ^{1}H NMR [$CDCl_3$, 600 MHz, rotamers (1:1)] δ 7.56 (d, *J* = 1.8 Hz, 0.5H), 7.45 (s, 0.5H), 7.37 (d, *J* = 1.8 Hz, 0.5H), 7.35 (s, 0.5H), 7.24 (d, *J* = 8.4 Hz, 0.5H), 7.09 (d, *J* = 8.4 Hz, 0.5H), 7.04 (d, *J* = 8.4 Hz, 0.5H), 6.88 (d, *J* = 8.4 Hz, 0.5H), 6.80 (d, *J* = 8.4 Hz, 0.5H), 6.72 (br s, 1H), 6.63 (br s,

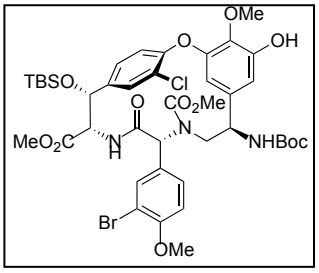
1H), 6.22 (s, 0.5H), 5.93 (d, J = 9.9 Hz, 0.5H), 5.77 (d, J = 9.1 Hz, 0.5H), 5.43 (s, 0.5H), 5.29 (s, 0.5H), 5.23 (d, J = 5.7 Hz, 1H), 5.20 (s, 1H), 4.92 (d, J = 9.6 Hz, 0.5H), 4.34 (d, J = 11.8 Hz, 0.5H), 4.00 (s, 1.5H), 3.94 (s, 1.5H), 3.87 (s, 1.5H), 3.84 (s, 1.5H), 3.77 (s, 1.5H), 3.67 (s, 1.5H), 1.41 (s, 9H), 1.02 (s, 4.5H), 1.00 (s, 4.5H), 0.86 (s, 4.5H), 0.70 (s, 4.5H), 0.23 (s, 3H), 0.20 (s, 1.5H), 0.19 (s, 1.5H), 0.00 (s, 1.5H), –0.07 (s, 1.5H), –0.07 (s, 1.5H), –0.24 (s, 1.5H); ^{13}C NMR [$CDCl_3$, 150 MHz, rotamers (1:1)] δ 202.6, 199.7, 170.0, 168.9, 168.3, 167.8, 156.2, 155.4, 155.2, 154.3, 154.0, 152.6, 151.7, 150.3, 150.2, 142.8, 139.5, 138.5, 137.0, 135.4, 133.2, 133.1, 132.5, 129.0, 128.7, 128.6, 128.4, 128.1, 127.8, 127.7, 127.4, 127.3, 127.2, 127.1, 126.1, 125.2, 123.0, 117.9, 113.1, 112.4, 112.2, 111.8, 108.5, 105.8, 80.1, 74.5, 73.2, 62.7, 61.6, 61.4, 60.8, 59.8, 57.4, 56.5, 56.3, 53.0, 52.9, 28.6, 28.4, 25.9, 25.8, 25.6, 18.52, 18.46, 18.3, 17.8, –4.25, –4.29, –4.32, –4.38, –4.42, –5.3, –5.6; IR (film) ν_{max} 3389, 3251, 2952, 2931, 2895, 2857, 1706, 1668, 1602, 1581, 1493, 1416, 1365, 1329, 1286, 1253, 1160, 1097, 1053, 1006 cm^{-1}; ESI-TOF HRMS m/z 1008.2727 (M^+ + H, $C_{45}H_{63}BrClN_3O_{10}SSi_2$ requires 1008.2717).



Compound 15. A solution of **13** (40.0 mg, 39.6 μmol) in CH_3OH was treated with excess Raney nickel (~200 mg) and formamidine acetate (20.0 mg) at –20 °C and warmed to 0 °C. The resulting mixture was stirred under an atmosphere of H_2 at 0 °C for 3 h. After this time, the reaction mixture was filtered through a plug of Celite (eluted with CH_3OH) and concentrated under reduced pressure. The residue was purified by PTLC (SiO_2, 20% EtOAc–hexane) to afford **15** (22.7 mg, 59%) as a white film: $[\alpha]^{25}_D$ +15 (*c* 0.4, CH_3OH); ^{1}H NMR (CD_3OD, 400 MHz) δ 7.52 (d, J = 1.6 Hz, 1H), 7.29 (d, J = 2.0 Hz, 1H), 7.24 (dd, J = 2.0, 8.4 Hz, 1H), 7.21–7.16 (m, 2H), 7.12 (d, J = 8.4 Hz, 1H), 6.65 (br s, 1H), 6.61 (d, J = 1.6 Hz, 1H), 5.52 (d, J = 2.4 Hz, 1H), 4.78 (d, J = 2.4 Hz, 1H), 4.55–4.49 (br m, 1H), 4.20 (s, 1H), 4.01 (s, 3H), 3.93 (s, 3H), 3.77 (s, 3H), 3.03 (dd, J = 5.6, 8.0 Hz, 1H), 2.64 (dd, J = 3.2, 8.0 Hz, 1H), 1.44 (s, 9H), 1.08 (s, 9H), 0.77 (s, 9H), 0.29 (s, 3H), 0.28 (s, 3H), 0.02 (s, 3H), –0.10 (s, 3H); ^{13}C NMR (CD_3OD, 150 MHz) δ 173.1, 169.9, 157.1, 153.9, 150.0, 141.7, 138.4, 133.2, 130.5, 129.6, 128.3, 127.4, 123.5, 117.0, 112.9, 112.6, 73.4, 65.9, 61.1, 59.8, 56.2, 52.5, 52.1, 28.2, 25.7, 25.6, 18.7, 18.1, –4.8, –4.9, –6.2; IR (film) ν_{max} 3321, 2931, 1682, 1494, 1431, 1062 cm^{-1}; ESI-TOF HRMS m/z 978.3149 (M + H^+, $C_{45}H_{65}BrClN_3O_{10}Si_2$ requires 978.3153).

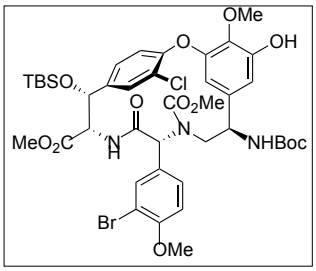


Compound 16. A solution of **15** (4.3 mg, 4.4 μmol) in anhydrous THF (400 μL) and acetic acid (2 μL, 21.95 μmol) was treated with Bu_4NF (1.0 M in THF, 4.39 μL, 4.39 μmol) at room temperature for 0.5 h. The mixture was purified by PTLC (SiO_2, 40% EtOAc–hexane) to provide **16** (3.6 mg, 96%) as a white film: $[\alpha]^{25}_D$ –18 (*c* 0.96, $CHCl_3$); ^{1}H NMR (acetone-d_6, 400 MHz) δ 8.10 (s, 1H), 7.59 (d, *J* = 2.0 Hz, 1H), 7.42 (d, *J* = 2.1 Hz, 1H), 7.31 (d, *J* = 8.4 Hz, 1H), 7.31 (dd, *J* = 8.4, 2.1 Hz, 1H), 7.22 (dd, *J* = 8.5, 2.5 Hz, 1H), 7.15 (d, *J* = 8.5 Hz, 1H), 6.63 (br s, 1H), 6.56 (s, 2H), 5.58 (d, *J* = 9.3 Hz, 1H), 5.50 (d, *J* = 2.2 Hz, 1H), 4.70 (dd, *J* = 9.7, 2.2 Hz, 1H), 4.55 (br s, 1H), 4.15 (s, 1H), 3.99 (s, 3H), 3.92 (s, 3H), 3.74 (s, 3H), 3.16 (dd, *J* = 11.8, 6.1 Hz, 1H), 2.70 (br d, *J* = 9.0 Hz, 1H), 1.37 (s, 9H), 0.75 (s, 9H), 0.00 (s, 3H), –0.13 (s, 3H); ^{13}C NMR (acetone-d_6, 150 MHz) δ 170.4, 169.6, 161.3, 157.8, 155.1, 154.1, 153.7, 152.0, 146.6, 139.5, 137.9, 136.7, 135.6, 135.1, 133.3, 129.5, 129.3, 127.8, 127.6, 127.1, 118.8, 79.5, 74.4, 73.9, 65.4, 61.8, 61.4, 60.9, 59.6, 57.3, 56.2, 52.9, 50.9, 28.5, 26.1, 18.6, 18.5, 1.4, –4.3, –5.5; IR (film) ν_{max} 2911, 1669, 1492, 1094, 832 cm^{-1}; ESI-TOF HRMS *m/z* 864.2275 (M^+ + H, $C_{39}H_{52}BrClN_3O_{10}Si$ requires 864.2288).

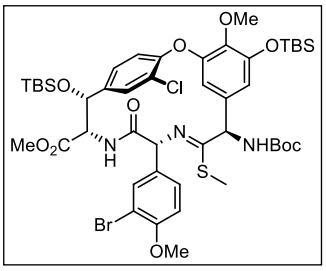


Compound 17. A solution of **15** (4.2 mg, 4.3 μmol) in THF (430 μL) was treated with dimethyldicarbonate (458 μL, 4.3 mmol) and 4 N aqueous NaOH (215 μL) at 25 °C and the mixture was stirred for 0.5 h. After this time, the reaction mixture was quenched with the addition of saturated aqueous NH_4Cl (2 mL) and extracted with EtOAc. The organic layer was washed with H_2O and saturated aqueous NaCl, and dried (Na_2SO_4). The solvent was removed under reduced pressure and the residue was purified by PTLC (SiO_2, 25% EtOAc–hexane) to provide **17** (4.0 mg, 91%) as a white film: $[\alpha]^{25}_D$ –104 (*c* 0.4, CH_3OH); ^{1}H NMR (CD_3OD, 400 MHz) mixture of two rotamers (rotamer A:B = 3:1) δ (for rotamer A) 7.78–7.73 (m, 1H), 7.60 (d, *J* = 8.4 Hz, 1H), 7.52 (s, 1H), 7.36 (d, *J* = 8.4 Hz, 1H), 7.30–7.23 (m, 1H), 7.16 (d, *J* = 8.4 Hz, 1H), 6.55 (s, 1H), 6.49–6.42 (m, 1H), 6.17 (br s, 1H), 5.64–5.57 (m, 1H), 5.61 (s, 1H), 5.05 (d, *J* = 9.2 Hz, 1H), 4.75–4.68 (m, 1H), 3.98 (s, 3H), 3.92 (s, 3H), 3.83 (s, 3H), 3.72–3.66 (m, 1H), 3.63 (s, 3H), 3.21–3.13 (m, 1H), 2.70–2.50 (br m, 1H), 1.37 (s, 9H), 1.06 (s, 9H), 0.79 (s, 9H), 0.27 (s, 3H), 0.24 (s, 3H), 0.03 (s, 3H), –0.04 (s, 3H); ^{13}C NMR (CD_3OD, 150 MHz) mixture of two rotamers (rotamer A:B = 3:1) δ (for rotamer A) 170.9, 170.3, 158.4, 157.6, 156.9, 155.4, 152.6, 149.6, 140.1, 139.4, 134.3, 131.0, 129.8, 129.6, 129.5, 129.3, 127.2, 124.4, 79.6, 74.2, 61.4, 60.9, 56.3, 53.3, 52.9, 51.8, 28.2, 25.6, 18.7, 18.2, –4.8, –4.9, –5.0, –6.1; IR (film) ν_{max}

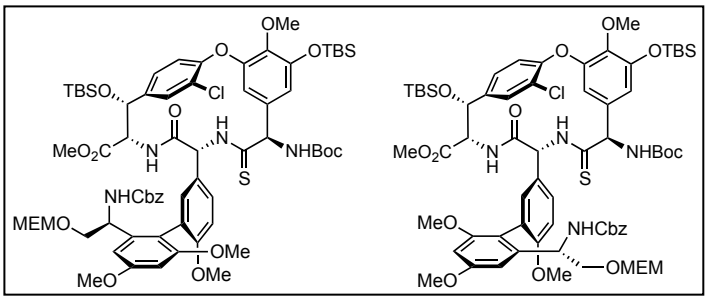
3310, 2944, 2832, 1664, 1449, 1117, 1019 cm^{-1}; ESI-TOF HRMS *m/z* 1036.3193 ($M + H^+$, $C_{45}H_{67}BrClN_3O_{12}Si_2$ requires 1036.3208).



Compound 18. A solution of **17** (1.9 mg, 1.8 μmol) in anhydrous THF (180 μL) was treated with Bu_4NF (3.6 μL of 1.0 M in THF, 3.6 μmol) and HOAc (3.6 μL, 9.0 μmol) at 25 °C. The reaction mixture was stirred for 1 h. After this time, the reaction mixture was quenched with the addition of saturated aqueous $NaHCO_3$ (1 mL) and extracted with EtOAc. The organic layer was washed with H_2O and saturated aqueous NaCl, and dried (Na_2SO_4). The solvent was removed under reduced pressure and the residue was purified by PTLC (SiO_2, 50% EtOAc–hexane) to afford **18** (1.6 mg, 95%) as a white solid identical in all respects with authentic material (^1H NMR, $CDCl_3$).[23]



Compound 20. A solution of **13** (1.06 g, 1.05 mmol) and K_2CO_3 (580 mg, 4.20 mmol) in acetone (30 mL) was treated with iodomethane (131 mL, 2.10 mmol) at room temperature and the mixture was stirred for 3 h. The solvent was removed under reduced pressure and the residue was purified by flash chromatography (SiO_2, 25–33% EtOAc–hexane gradient) followed by flash chromatography (SiO_2, 5% acetone–CH_2Cl_2) to provide **20** (787 mg, 73%; typically 73–94%) as a colorless solid: m.p. 138–142 °C; $[\alpha]^{25}_D$ +60 (*c* 0.41, MeOH); ^1H NMR (CD_3OD, 600 MHz) δ 8.11 (d, *J* = 9.4 Hz, 1H), 7.47 (d, *J* = 1.9 Hz, 1H), 7.18 (dd, *J* = 1.9, 8.5 Hz, 1H), 7.06 (d, *J* = 8.4 Hz, 1H), 7.01–7.00 (m, 2H), 6.94 (dd, *J* = 1.6, 8.4 Hz, 1H), 6.66 (dd, *J* = 1.9, 5.2 Hz, 2H), 5.90 (d, *J* = 9.7 Hz, 1H), 5.49 (d, *J* = 1.9 Hz, 1H), 5.43–5.42 (m, 1H), 5.09 (s, 1H), 4.82 (dd, *J* = 2.2, 7.8 Hz, 1H), 3.99 (s, 3H), 3.88 (s, 3H), 3.77 (s, 3H), 2.48 (s, 3H), 1.41 (s, 9H), 1.06 (s, 9H), 0.72 (s, 9H), 0.28 (s, 3H), 0.25 (s, 3H), –0.01 (s, 3H), –0.18 (s, 3H); ^{13}C NMR (CD_3OD, 150 MHz) δ 173.0, 170.6, 169.3, 157.8, 157.2, 156.2, 155.0, 149.7, 143.4, 138.4, 136.8, 134.2, 130.6, 130.5, 128.5, 128.4, 127.8, 123.9, 118.9, 116.9, 113.3, 113.2, 80.8, 74.1, 68.7, 61.9, 60.9, 57.8, 56.9, 53.3, 49.7, 28.8, 26.4, 26.2, 19.4, 18.7, 14.8, –4.0, –4.2, –4.3, –5.5; IR (film) ν_{max} 3424, 2953, 2929, 2891, 2856, 1754, 1671, 1602, 1580, 1494, 1434, 1392, 1364, 1332, 1284, 1238, 1166, 1095, 1056, 1006 cm^{-1}; ESI-TOF HRMS *m/z* 1022.2878 ($M^+ + H$, $C_{46}H_{65}BrClN_3O_{10}SSi_2$ requires 1022.2874).



Compound 22. A solution of **20** (580 mg, 0.567 mmol), **19** (406 mg, 0.876 mmol) and 1 M aqueous $NaHCO_3$ (0.690 mL, 0.690 mmol) in toluene (3.48 mL) and CH_3OH (1.16 mL) was treated with $Pd_2(dba)_3$ (174 mg, 0.189 mmol), and (*o*-tolyl)$_3$P (290 mg, 0.951 mmol) at room temperature and the solution was stirred at 80 °C for 40 min. The reaction mixture was cooled to 25 °C, and directly purified by flash chromatography (SiO_2, 25% EtOAc–hexane followed by 100% EtOAc–hexane) to afford **21** (typically 65–80%) as an atropisomeric mixture. This mixture of atropisomers was separable, however overall conversions were higher if this intermediate was used directly in the next step.

A mixture of the crude residue and collidine (85.0 μL, 1.14 mmol) in CH_3OH (40 mL) was stirred at room temperature under an atmosphere of H_2S for 2 h. The solvent was removed under reduced pressure and the residue was purified by flash chromatography (SiO_2, 6% acetone–CH_2Cl_2) to afford **22** (499 mg, 65%, 2 steps) as a mixture of atropisomers (1:1.1 (*P*)-**22** : (*M*)-**22**). The atropisomers were separated by flash chromatography (SiO_2, 50% EtOAc–hexane) followed by PTLC (SiO_2, 4% acetone–CH_2Cl_2 for (*P*)-**22**) and (SiO_2, 3% CH_3OH–CH_2Cl_2 for (*M*)-**22**) to provide (*P*)-**22** and (*M*)-**22** as colorless foams.

In the course of the studies, pure samples of (*P*)-**21** and (*M*)-**21** were isolated and characterized. (*P*)-**21**: $[\alpha]^{25}_D$ +65 (*c* 0.21, $CHCl_3$); ^{1}H NMR (acetone-d_6, 600 MHz) δ 7.44 (s, 3H), 7.36 (s, 2H), 7.31 (d, *J* = 5.4 Hz, 1H), 7.22 (d, *J* = 6.8 Hz, 1H), 7.11 (s, 1H), 7.10 (s, 1H), 6.97 (d, *J* = 7.7 Hz, 1H), 6.91 (s, 1H), 6.87 (d, *J* = 6.8 Hz, 1H), 6.75 (s, 2H), 6.71 (s, 1H), 6.62 (d, *J* = 6.8 Hz, 1H), 6.46 (s, 1H), 6.24 (s, 1H), 5.76 (d, *J* = 7.3 Hz, 1H), 5.51 (d, *J* = 2.9 Hz, 1H), 5.32–5.29 (m, 2H), 5.11 (d, *J* = 11.3 Hz, 1H), 4.68 (br s, 2H), 4.40–4.32 (m, 2H), 3.82 (s, 6H), 3.76 (s, 3H), 3.75 (s, 3H), 3.61 (s, 3H), 3.46–3.36 (m, 6H), 3.27 (s, 3H), 2.29 (s, 3H), 1.36 (s, 9H), 1.00 (s, 9H), 0.86 (s, 9H), 0.15 (s, 3H), 0.14 (s, 3H), 0.09 (s, 3H), –0.09 (s, 3H); ^{13}C NMR (acetone-d_6, 150 MHz) δ 170.4, 169.4, 167.3, 161.1, 159.1, 158.7, 156.6, 156.2, 154.5, 153.5, 149.4, 141.9, 141.6, 138.5, 138.3, 136.2, 132.2, 129.4, 129.2, 129.1, 128.7, 128.64, 128.61, 128.4, 126.6, 126.5, 124.0, 119.8, 117.1, 114.1, 111.9, 104.3, 97.9, 95.7, 79.5, 73.7, 72.6, 70.7, 69.1, 67.5, 66.8, 61.3, 60.6, 59.6, 58.8, 56.1, 55.8, 55.6, 53.7, 52.8, 28.6, 26.2, 19.0, 18.6, 14.8, –4.27, –4.31, –4.4, –5.3; IR (film) ν_{max} 3417, 2931, 2887, 2856, 1714, 1682, 1605, 1582, 1496, 1469, 1434, 1393, 1363, 1322, 1237, 1201, 1156, 1094, 1046 cm^{-1}; ESI-TOF HRMS *m/z* 1361.5517 (M^+ + H, $C_{68}H_{93}ClN_4O_{17}SSi_2$ requires 1361.5556).

For (*M*)-**21**: $[\alpha]^{25}_D$ +92 (*c* 0.21, $CHCl_3$); ^{1}H NMR (acetone-d_6, 600 MHz) δ 7.53 (s, 1H), 7.39–7.25 (m, 7H), 7.05 (br s, 3H), 6.80 (s, 1H), 6.75 (s, 1H), 6.64 (d, *J* = 8.3 Hz, 1H), 6.59 (d, *J* = 6.7 Hz, 1H), 6.54 (s, 1H), 6.45 (s, 1H), 6.23 (d, *J* = 6.7 Hz, 1H), 5.57 (s, 2H), 5.07 (s, 1H), 5.02 (s, 2H), 4.82 (d, *J* = 6.9 Hz, 1H), 4.75 (d, *J* = 6.9 Hz, 1H), 4.40 (s, 2H), 3.97 (s, 3H), 3.82 (s, 3H), 3.78 (s, 3H), 3.73 (s, 3H), 3.65 (s, 3H), 3.50 (br s, 1H), 3.43 (s, 3H), 3.37 (s, 2H), 3.25 (s, 3H), 2.37 (s, 3H), 1.38 (s, 9H), 1.05 (s, 9H), 0.82 (s, 9H), 0.27 (s, 3H), 0.25 (s, 3H), 0.07 (s, 3H), –0.08 (s, 3H); ^{13}C NMR (acetone-d_6, 150 MHz) δ 177.6, 170.6, 170.3, 167.3, 161.3, 159.3, 158.2, 156.4, 155.7, 154.2, 149.6, 142.1, 141.7, 138.9, 138.6, 136.2, 134.9, 129.2, 129.0, 128.7, 128.6,

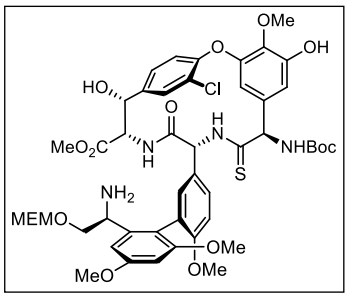
127.1, 126.0, 124.2, 119.7, 117.0, 113.4, 112.0, 104.0, 98.4, 95.9, 79.7, 73.8, 72.5, 71.4, 70.4, 67.4, 66.4, 61.3, 59.7, 59.2, 58.8, 56.4, 55.7, 55.6, 53.1, 52.7, 28.6, 26.2, 19.0, 18.6, 15.0, –4.2, –4.32, –4.35, –5.2; IR (film) ν_{max} 3413, 2931, 2890, 2857, 1712, 1681, 1605, 1582, 1495, 1469, 1433, 1393, 1363, 1321, 1237, 1201, 1157, 1095, 1060, 1045 cm^{-1}; ESI-TOF HRMS *m/z* 1361.5531 ($M^+ + H$, $C_{68}H_{93}ClN_4O_{17}SSi_2$ requires 1361.5556).

For (*P*)-**22**: $[\alpha]^{25}_D$ –92 (*c* 0.23, $CHCl_3$); ^1H NMR [acetone-d_6, 600 MHz, rotamers (2:1)] δ 9.91 (br s, 0.33H), 9.50 (d, *J* = 8.0 Hz, 0.66H), 7.89 (s, 0.33H), 7.77 (s, 0.33H), 7.58–6.93 (m, 11.33H), 6.82, 6.76, 6.70, 6.66, 6.64 and 6.57 (six s, 4H), 6.49–6.46 (m, 1H), 8.37 (d, *J* = 8.2 Hz, 0.66H), 6.08 (br s, 0.33H), 6.01 (d, *J* = 8.4 Hz, 0.33H), 5.71 (d, *J* = 8.4 Hz, 0.66H), 5.64 (s, 0.33H), 5.60 (s, 0.66H), 5.42 (s, 1H), 5.35 (d, *J* = 5.6 Hz, 0.33H), 5.32 (d, *J* = 12.2 Hz, 0.33H), 5.23 (d, *J* = 12.2 Hz, 0.33H), 4.92 (d, *J* = 12.0 Hz, 0.33H), 4.88–4.84 (m, 0.66H), 4.71–4.69 (m, 0.33H), 4.65 (*J* = 11.9 Hz, 0.5H), 4.59 (*J* = 11.9 Hz, 0.5H), 4.48 (d, *J* = 6.5 Hz, 0.66H), 4.41–4.38 (m, 1H), 4.28–4.25 (m, 1H), 3.92, 3.82, 3.81, 3.79, 3.75, 3.74, 3.71, 3.71, 3.69 and 3.60 (ten s, 15H), 3.48–3.29 (m, 6H), 3.24 and 3.21 (two s, 3H), 1.43 (s, 9H), 1.00 and 0.98 (two s, 9H), 0.89 and 0.79 (two s, 9H), 0.19, 0.12, 0.05, 0.00 and 0.13 (five s, 12H); ^{13}C NMR [acetone-d_6, 150 MHz, rotamers (2:1)] δ 202.2, 201.8, 171.3, 169.7, 169.1, 166.9, 161.6, 161.3, 160.1, 159.52, 159.47, 159.3, 157.8, 157.2, 155.8, 155.7, 153.33, 153.25, 152.3, 151.5, 150.5, 142.3, 141.5, 140.6, 140.4, 140.0, 139.8, 138.2, 138.0, 137.5, 137.1, 136.1, 132.7, 131.7, 130.6, 130.1, 129.4, 129.3, 129.2, 129.0, 128.8, 128.6, 127.8, 127.2, 126.9, 126.7, 125.42, 125.36, 124.2, 120.3, 119.8, 113.9, 112.9, 112.0, 107.9, 107.7, 104.3, 104.2, 98.8, 98.5, 95.5, 95.3, 79.9, 79.8, 75.5, 75.3, 72.54, 72.50, 67.6, 67.5, 67.3, 63.5, 62.2, 61.4, 61.0, 60.94, 60.86, 59.1, 58.8, 56.6, 56.4, 56.1, 55.9, 55.7, 55.6, 55.0, 53.3, 53.2, 52.8, 28.8, 28.7, 26.24, 26.18, 26.12, 26.07, 19.0, 18.9, 18.8, 18.7, –4.0, –4.21, –4.25, –4.27, –4.33, –5.0, –5.2; IR (film) ν_{max} 3398, 3249, 2931, 2889, 2857, 1700, 1666, 1605, 1581, 1488, 1416, 1364, 1323, 1250, 1201, 1158, 1095, 1061, 1049, 1025 cm^{-1}; ESI-TOF HRMS *m/z* 1347.5397 ($M^+ + H$, $C_{67}H_{91}ClN_4O_{17}SSi_2$ requires 1347.5399).

For (*M*)-**22**: $[\alpha]^{25}_D$ –32 (*c* 0.26, $CHCl_3$); ^1H NMR [acetone-d_6, 600 MHz, rotamers (1:1)] δ 9.05 (d, *J* = 6.5 Hz, 0.5H), 7.85 (s, 0.5H), 7.61–7.19 (m, 11H), 6.81–6.64 (m, 4.5H), 6.55 (s, 0.5H), 6.51 (s, 0.5H), 6.42 (br s, 0.5H), 6.27 (d, *J* = 8.1 Hz, 0.5H), 6.09 (br s, 0.5H), 6.03 (d, *J* = 8.0 Hz, 0.5H), 5.69 (s, 0.5H), 5.57 (d, *J* = 8.0 Hz, 0.5H), 5.51 (s, 0.5H), 5.46–5.41 (m, 1H), 5.02–4.97 (m, 2H), 4.80 (d, *J* = 11.9 Hz, 0.5H), 4.71–4.70 (m, 0.5H), 4.65–4.62 (m, 1H), 4.49–4.48 (m, 0.5H), 4.39 (s, 1.5H), 3.97, 3.95, 3.82, 3.80, 3.74, 3.73, 3.71, 3.64 and 3.61 (nine s, 15H), 3.58–3.39 (m, 5.5H), 3.27 (s, 1.5H), 3.22 (s, 0.5H), 3.15 (s, 1.5H), 1.47 and 1.42 (two s, 9H), 1.05 and 1.03 (two s, 9H), 0.89 and 0.87 (two s, 9H), 0.26, 0.25 and 0.23 (three s, 6H), 0.07 and 0.05 (two s, 3H), –0.02 and –0.03 (two s, 3H); ^{13}C NMR [acetone-d_6, 150 MHz, rotamers (1:1)] δ 202.2, 201.8, 171.4, 169.8, 168.8, 167.2, 161.5, 161.1, 159.3, 159.2, 159.1, 158.3, 156.5, 156.2, 156.1, 156.0, 153.8, 153.7, 152.8, 152.1, 150.6, 150.4, 142.6, 142.3, 141.3, 140.2, 140.1, 139.6, 138.7, 138.6, 137.7, 137.0, 135.4, 133.9, 130.3, 129.9, 129.5, 129.4, 129.2, 128.78, 128.72, 128.6, 127.4, 127.3, 127.1, 126.7, 126.1, 125.2, 123.6, 119.8, 119.6, 115.9, 113.4, 112.5, 112.0, 109.3, 107.2, 104.7, 103.9, 98.48, 98.44, 96.7, 96.1, 80.2, 79.7, 75.7, 74.8, 72.9, 72.6, 71.6, 67.6, 67.1, 66.4, 66.3, 63.7, 62.7, 62.1, 61.2, 61.1, 61.0, 58.9, 58.9, 58.8, 56.5, 56.3, 56.0, 55.7, 55.6, 53.7, 53.3, 53.0, 52.8, 28.8, 28.7, 26.35, 26.29, 26.23, 26.21, 19.0, 19.0, 18.9, 18.7, –4.1, –4.2, –4.2, –4.3, –4.8, –5.3; IR (film) ν_{max} 3249, 2930, 2887, 2857, 1700, 1665, 1604, 1580, 1490, 1415, 1365, 1321, 1236, 1200, 1158, 1095, 1063, 1048, 1025 cm^{-1}; ESI-TOF HRMS *m/z* 1347.5381 ($M^+ + H$, $C_{67}H_{91}ClN_4O_{17}SSi_2$ requires 1347.5399).

Thermal Equilibration of (*M*)-22

A solution of (*M*)-**22** (345 mg, 0.256 mmol) in *o*-dichlorobenzene (2.5 mL, filtered through basic Al_2O_3) under Ar was placed into a 20 mL microwave reactor vial. The vial was loaded into a microwave reactor (Biotage Initiator) and warmed at 160 °C for 30 min. The mixture was cooled and the compounds were purified by flash chromatography (SiO_2, 50% EtOAc–hexane) followed by PTLC (SiO_2, 4% acetone–CH_2Cl_2 for (*P*)-**22**) and (SiO_2, 3% CH_3OH–CH_2Cl_2 for (*M*)-**22**) to provide (*P*)-**22** (181 mg, 53%) and (*M*)-**22** (138 mg, 40%) as colorless foams.

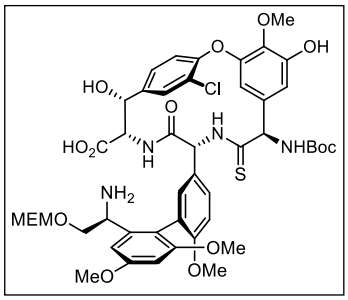


Compound 24. A solution of $Pd(OAc)_2$ (9.6 mg, 0.045 mmol) and *N*-methylmorpholine (distilled, 14.4 μL, 0.131 mmol) in CH_2Cl_2 (480 μL, distilled over P_2O_5) was treated with Et_3SiH (144 μL, 0.902 mmol) at 25 °C. The mixture was stirred for 15 min and then added to a solution of (*P*)-**22** (118 mg, 0.088 mmol) in CH_2Cl_2 (360 μL). This protocol was repeated for a second 118 mg of (*P*)-**22** and the batches were later combined for work-up. The reaction mixtures were vigorously stirred at room temperature for 24 h, at which point the solution was diluted with CH_2Cl_2 and filtered through Celite. The filtrate was added to saturated aqueous NH_4Cl (2 mL), stirred for 2 h and extracted with CH_2Cl_2. The organic layer was washed with H_2O and saturated aqueous NaCl, and dried (Na_2SO_4). The solvent was removed under reduced pressure and the residue was purified by flash chromatography (SiO_2, 5% acetone–CH_2Cl_2, then 10% CH_3OH–CH_2Cl_2) to provide **23** (*ca*. 205 mg) as a colorless solid. A solution of **23** in anhydrous THF (2 mL) and acetic acid (76.5 μL, 1.34 mmol, 8.0 equiv) was treated with Bu_4NF (1.0 M in THF, 1.03 mL, 1.03 mmol) at room temperature for 3 h. The reaction mixture was quenched with the addition of saturated aqueous $NaHCO_3$ and extracted with EtOAc. The organic layer was washed with H_2O, saturated aqueous NaCl, and dried (Na_2SO_4). The solvent was removed under reduced pressure and the residue was purified by flash chromatography (SiO_2, 5–15% *i*-PrOH–CH_2Cl_2 gradient) followed by PTLC (SiO_2, 8% CH_3OH–CH_2Cl_2) to afford **24** (129 mg, 75%, 2 steps; typically 75–88%) as a colorless solid.

For **23**: $[\alpha]^{25}_D$ +18 (*c* 0.39, $CHCl_3$); ^{1}H NMR (CD_3OD, 600 MHz, rotamers (4:1), major given) δ 7.50 (d, *J* = 1.5 Hz, 1H), 7.47 (dd, *J* = 2.1, 8.4 Hz, 1H), 7.13 (d, *J* = 8.4 Hz, 1H), 6.90 (br s, 1H), 6.74 (d, *J* = 2.0 Hz, 1H), 6.70 (d, *J* = 2.0 Hz, 1H), 6.66 (br s, 1H), 6.48 (d, *J* = 2.0 Hz, 1H), 6.28 (d, *J* = 1.9 Hz, 1H), 6.22 (br s, 1H), 5.67 (br s, 1H), 5.48 (d, *J* = 2.0 Hz, 1H), 5.22 (s, 1H), 4.89 (s, 1H), 4.46 (*J* = 6.7 Hz, 1H), 4.38 (*J* = 6.7 Hz, 1H), 3.95–3.93 (m, 1H), 3.84 (s, 3H), 3.82 (s, 3H), 3.75 (s, 3H), 3.62 (s, 3H), 3.61 (s, 3H), 3.50–3.41 (m, 5H), 3.32 (s, 3H), 3.19–3.16 (m, 1H), 1.42 (s, 9H), 1.06 (s, 9H), 0.87 (s, 9H), 0.23 (s, 3H), 0.20 (s, 3H), 0.06 (s, 3H), –0.12 (s, 3H); ^{13}C NMR (CD_3OD, 150 MHz, rotamers (4:1), major given) δ 201.8, 170.7, 170.1, 162.2, 159.8, 159.8, 157.7, 154.8, 154.0, 150.8, 143.0, 140.5, 139.3, 135.1, 132.9, 129.8, 129.7, 128.6, 128.1, 127.2, 126.2, 124.6, 119.9, 117.2, 112.6, 110.5, 103.9, 98.6, 96.3, 81.6, 74.6, 73.0, 73.0, 67.8, 62.7, 61.7, 61.3, 59.2, 56.6, 56.1, 56.0, 53.4, 52.4, 49.5, 28.8, 26.6, 26.4, 19.4, 19.0, –3.8, –4.2, –4.3, –5.3; IR (film) ν_{max} 3246, 2930, 2889, 2856, 1700, 1667, 1604, 1581, 1489, 1463, 1417, 1365, 1324,

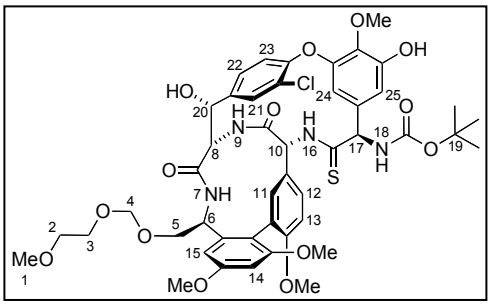
1250, 1239, 1203, 1158, 1096, 1061, 1048, 1009 cm^{-1}; ESI-TOF HRMS *m/z* 1213.5011 (M^+ + H, $C_{59}H_{85}ClN_4O_{15}SSi_2$ requires 1213.5032).

For **24**: m.p. 172 °C (decomposition); $[\alpha]^{25}_D$ +87 (*c* 0.21, $CHCl_3$); ^1H NMR (CD_3OD, 600 MHz) δ 7.45 (d, *J* = 2.0 Hz, 1H), 7.38 (dd, *J* = 2.3, 8.5 Hz, 1H), 7.27 (d, *J* = 7.9 Hz, 1H), 7.06 (d, *J* = 8.5 Hz, 1H), 6.72 (d, *J* = 2.2 Hz, 1H), 6.61 (d, *J* = 2.0 Hz, 1H), 6.50 (d, *J* = 2.3 Hz, 1H), 6.49 (br s, 1H), 6.35 (br s, 1H), 5.75 (s, 1H), 6.65 (br s, 1H), 5.39 (d, *J* = 3.5 Hz, 1H), 5.22 (s, 1H), 5.02 (d, *J* = 3.5 Hz, 1H), 4.46 (*J* = 6.7 Hz, 1H), 4.40 (d, *J* = 6.7 Hz, 1H), 3.87 (dd, *J* = 3.3, 9.0 Hz, 1H), 3.85 (s, 3H), 3.79 (s, 3H), 3.78 (s, 3H), 3.74 (s, 3H), 3.65 (s, 3H), 3.51–3.43 (m, 4H), 3.38 (dd, *J* = 10.2, 3.3 Hz, 1H), 3.20–3.17 (m, 1H), 1.42 (s, 9H); ^{13}C NMR (CD_3OD, 150 MHz) δ 202.4, 171.3, 171.0, 162.3, 159.8, 159.6, 157.6, 154.6, 153.1, 152.6, 142.2, 140.5, 138.9, 135.2, 131.8, 130.4, 129.5, 128.6, 128.0, 127.0, 126.9, 124.9, 120.3, 112.3, 111.7, 106.5, 103.6, 98.4, 96.2, 81.5, 73.0, 72.8, 72.7, 67.9, 63.1, 61.7, 60.7, 59.2, 56.24, 56.15, 56.0, 53.2, 52.8, 49.7, 28.8; IR (film) ν_{max} 3257, 2934, 2838, 1698, 1671, 1603, 1585, 1489, 1455, 1430, 1366, 1324, 1235, 1201, 1156, 1057, 1029 cm^{-1}; ESI-TOF HRMS *m/z* 985.3294 (M^+ + H, $C_{47}H_{57}ClN_4O_{15}S$ requires 985.3302).



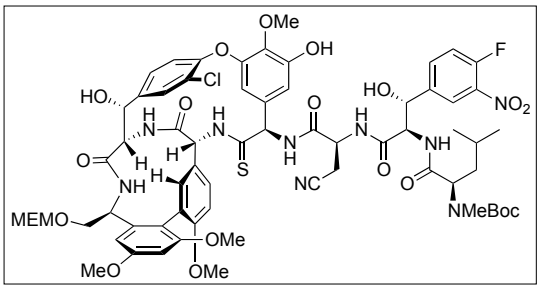
Compound 25. A solution of **24** (150 mg, 0.152 mmol) in *t*-BuOH (3.6 mL) and H_2O (1.8 mL) was treated with LiOH–H_2O (13.8 mg, 0.329 mmol) at 0 °C and stirred at 0 °C for 2 h. The reaction mixture was quenched with the addition of saturated aqueous NH_4Cl (2 mL) and extracted with EtOAc. The organic layer was washed with H_2O and saturated aqueous NaCl, and dried (Na_2SO_4). The solvent was removed under reduced pressure and the residue was purified by PTLC (SiO_2, 7% CH_3OH–CH_2Cl_2) to afford **25** (129 mg, 87%; typically 87–95%) as a colorless solid: m.p. 165 °C (decomposition); $[\alpha]^{25}_D$ +42 (*c* 0.12, $CHCl_3$); ^1H NMR (CD_3OD, 600 MHz, rotamers (1:1)) δ 7.57 (br s, 0.5H), 7.54 (s, 0.5H), 7.44 (d, *J* = 8.3 Hz, 0.5 Hz), 7.41 (s, 0.5H), 7.37 (br s), 7.30 (d, *J* = 8.3 Hz, 0.5H), 7.23 (d, *J* = 8.0 Hz, 0.5H), 7.18 (s, 0.5H), 7.05 (d, *J* = 6.8 Hz, 0.5H), 7.00 (d, *J* = 8.5 Hz, 0.5H), 6.96 (d, *J* = 8.7 Hz, 0.5H), 6.80 (d, *J* = 2.0 Hz, 0.5H), 6.78 (d, *J* = 2.0 Hz, 0.5H), 6.66 (br s, 1.5H), 6.62 (d, *J* = 2.1 Hz, 0.5H), 6.43 (d, *J* = 9.7 Hz, 0.5H), 6.40 (s, 0.5H), 6.18 (br s, 0.5H), 5.73 (br s, 0.5H), 5.69 (br s, 0.5H), 5.42 (d, *J* = 4.1 Hz, 0.5H), 5.40 (s, 0.5H), 5.32 (s, 0.5H), 5.19 (s, 0.5H), 4.70 (*J* = 7.0 Hz, 0.5H), 4.69 (*J* = 7.0 Hz, 0.5H), 4.60 (*J* = 6.6 Hz, 0.5H), 4.57 (*J* = 6.6 Hz, 0.5H), 4.43 (d, *J* = 4.2 Hz, 0.5H), 4.22 (s, 0.5H), 4.20–4.18 (m, 0.5H), 4.05–4.03 (m, 0.5H), 3.99 (s, 1.5H), 3.98 (s, 1.5H), 3.88 (s, 1.5H), 3.86 (s, 1.5H), 3.82–3.79 (m, 1H), 3.72 (s, 1.5H), 3.70 (s, 1H), 3.67 (s, 1.5H), 3.66 (s, 1.5H), 3.65–3.42 (m, 5H), 3.35 (s, 1.5H), 3.33 (s, 1.5H), 1.49 (s, 4.5H), 1.48 (s, 4.5H); ^{13}C NMR (CD_3OD, 150 MHz, rotamers (1:1)) δ 205.7, 203.8, 175.7, 174.7, 172.1, 170.5, 162.5, 160.4, 160.2, 159.2, 158.7, 157.7, 157.4, 157.3, 154.4, 153.7, 152.4, 152.3, 151.4, 143.1, 142.4, 137.9, 137.8, 137.5, 136.7, 136.2, 136.00, 135.97, 135.4, 132.9, 130.0, 129.6, 129.1, 129.0, 128.6, 128.4, 128.3, 127.6, 127.5, 127.2, 126.3, 125.2, 125.1, 124.9, 121.3, 112.8, 112.0, 108.9, 108.8, 105.7, 105.1, 104.0, 103.7, 100.5, 100.0, 96.8, 96.5, 81.3, 81.2, 74.5, 74.3, 73.01, 72.99, 72.8, 70.0, 69.6, 68.5, 68.4, 66.0,

63.6, 63.4, 63.1, 62.4, 62.3, 61.6, 61.5, 59.7, 59.29, 59.27, 56.7, 56.4, 56.25, 56.21, 56.18, 56.16, 53.2, 53.1, 50.0, 49.7, 29.0, 28.9; IR (film) ν_{max} 3246, 2927, 2889, 2832, 1699, 1655, 1603, 1583, 1488, 1458, 1424, 1366, 1325, 1288, 1234, 1201, 1157, 1057, 1030 cm^{-1}; ESI-TOF HRMS *m/z* 971.3157 ($M^+ + H$, $C_{46}H_{55}ClN_4O_{15}S$ requires 971.3146).



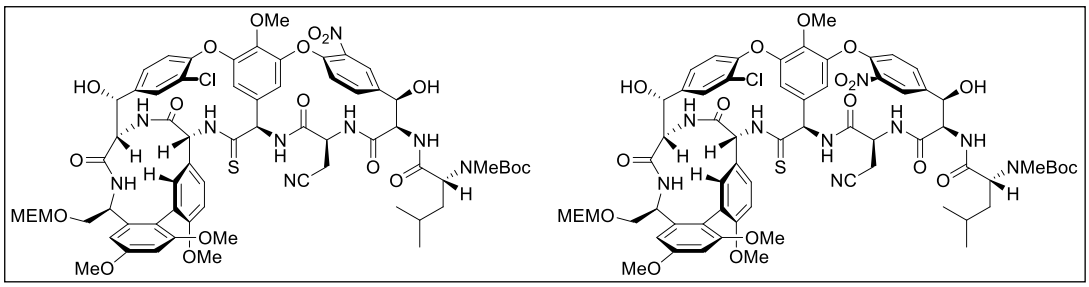
Compound 26. A solution of **25** (43 mg, 0.107 mmol) and *N*-methylmorpholine (57 μL, 0.535 mmol, 5 equiv) in THF (20 mL) was treated with DEPBT (157 mg, 0.535 mmol, 5 equiv) at 0 °C. The reaction mixture was allowed to warm to room temprature and stirred for 17 h. The solvent was removed under reduced pressure and the residue was purified by flash chromatography (SiO_2, 2–10% MeOH–CH_2Cl_2 gradient) followed by PTLC (SiO_2, 100% EtOAc) to afford **25** (32 mg, 76%) as a colorless solid: m.p. 195 °C (decomposition); $[\alpha]^{25}_D$ –30 (*c* 0.22, $CHCl_3$); ^1H NMR (CD_2Cl_2, 600 MHz) δ 7.34 (dd, *J* = 1.6, 8.3 Hz, C_{22}–H); 7.31 (s, C_{21}–H), 7.23 (dd, *J* = 2.1, 8.6 Hz, C_{12}–H), 7.20 (br s, N_9–H), 7.05 (s, C_{13}–H), 7.03 (dd, *J* = 2.2, 2.2 Hz, C_{11}–H), 6.81–6.80 (m, C_{25}–H), 6.74 (d, *J* = 2.0 Hz, C_{15}–H), 6.59 (d, *J* = 2.0 Hz, C_{14}–H), 6.40 (br s, C_{17}–H), 6.20 (d, *J* = 7.0 Hz, N_7–H), 6.09 (s, N_{16}–H), 5.90 (d, *J* = 9.8 Hz, N_{18}–H), 5.76 (br s, C_{23}–H), 5.59 (s, C_{20}–H), 5.29 (d, *J* = 6.2 Hz, C_{10}–H), 5.09 (s, C_{24}–H), 4.75 (d, *J* = 6.8 Hz, C_4–H_a), 4.68 (d, *J* = 6.8 Hz, C_4–H_b), 4.43 (dd, *J* = 8.6, 8.6 Hz, C_5–H_a), 4.26 (br s, OH), 4.08 (s, OMe), 4.05–4.03 (m, C_5–H_b, C_8–H), 4.00–3.97 (m, C_6–H), 3.89 (s, OMe), 3.77 (s, OMe), 3.74 (s, OMe), 3.71–3.67 (m, C_3–H_a), 3.62–3.56 (m, C_3–H_b, C_2–H_a, C_2–H_b), 3.37 (s, OMe), 1.49 (s, *t*Bu); ^{13}C NMR (CD_2Cl_2, 150 MHz) δ 203.8 (s, C=S), 173.3 (s), 166.3 (s), 160.7 (s), 158.8 (s), 157.9 (s), 156.3 (s), 152.0 (s), 150.8 (s), 150.0 (s), 141.0 (s), 138.4 (s), 137.4 (s), 136.0 (d, C_{11}), 135.1 (s), 128.1 (s), 127.7 (d, C_{21}), 127.2 (d, C_{22}), 126.8 (s), 126.8 (d, C_{12}), 125.6 (s), 124.5 (d, C_{23}), 120.8 (s), 113.4 (d, C_{13}), 106.8 (d, C_{25}), 106.6 (d, C_{15}), 103.4 (d, C_{24}), 98.0 (d, C_{14}), 95.9 (t, C_{14}), 81.1 (s, C_{19}), 72.3 (t, C_2), 71.8 (d, C_{20}), 67.6 (t, C_5), 67.4 (t, C_3), 66.4 (d, C_8), 61.8 (q, OMe), 61.4 (d, C_{17}), 59.6 (q, OMe), 59.6 (d, C_{10}), 56.7, 56.4, and 56.0 (three q, three OMe), 53.6 (d, C_6), 28.7 (q, *t*Bu); IR (film) ν_{max} 3247, 2975, 2933, 2837, 1667, 1604, 1582, 1503, 1486, 1425, 1367, 1320, 1234, 1199, 1158, 1084, 1059, 1024 cm^{-1}; ESI-TOF HRMS *m/z* 953.3030 ($M^+ + H$, $C_{46}H_{53}ClN_4O_{14}S$ requires 953.3046). The 2D ^1H-^1H ROESY spectrum (CD_2Cl_2, 600 MHz) displayed the following diagnostic NOE crosspeaks: C_8–H/C_{10}–H, C_8–H/C_{11}–H, C_{11}–H/C_8–H, C_{21}–H/C_{20}–H, C_{21}–H/C_8–H, C_{15}–H/C_5–H_a, N_7–H/C_6–H, C_{15}–H/C_8–H, C_8–H/C_5–H_b, N_{18}–H/C_{25}–H, C_3–H_a/C_2–H_b.

The single crystal x-ray structure of **26** (CDCC 837960) was solved using a parallelepiped-shaped crystal grown from acetone and hexanes confirming its structure, stereochemistry, and conformation.



Compound 29. A solution of **26** (16.5 mg, 0.017 mmol) in anhydrous CH_2Cl_2 (0.2 mL) was treated with HCO_2H (99+%, 0.2 mL) and stirred at 25 ºC for 12 h. The reaction mixture was diluted with CH_2Cl_2 (2 mL) and the solvent was removed under a stream of N_2. The residue was dissolved in EtOAc (2 mL) and treated with saturated aqueous $NaHCO_3$. The layers were separated and the aqueous phase was extracted with EtOAc (2 × 3 mL). The combined organic phases were washed with saturated aqueous NaCl (1 × 2 mL), dried (Na_2SO_4), and the solvent was removed under reduced pressure to give the crude free amine **27** (14.5 mg, 98%) that was carried forward without purification.

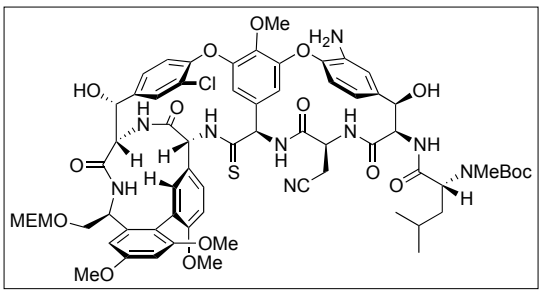
A solution of **27** (14.5 mg, 0.017 mmol) and **28** (12.5 mg, 0.022 mmol, 1.3 equiv) in anhydrous THF (50 μL) at 0 °C was treated sequentially with *i*-Pr_2NEt (12 μL, 0.069 mmol, 4.0 equiv) and a solution of T3P (25.5 mg, 50% in EtOAc, 0.040 mmol, 2.4 equiv) in THF (50 μL), and the reaction mixture was stirred at 0 °C for 30 min. The reaction was quenched by addition of saturated aqueous NH_4Cl (1 mL) and the aqueous phase was extracted with EtOAc (3 × 1 mL). The combined organic phases were washed with saturated aqueous saturated aqueous NaCl (1 × 2 mL), dried (Na_2SO_4), and the solvent was removed under reduced pressure. PTLC (SiO_2, 10% CH_3OH–CH_2Cl_2) afforded **29** (12.8 mg, 54%; typically 52–56%) as a white solid: $[\alpha]^{25}_D$ +19 (*c* 0.1, $CHCl_3$); ^{1}H NMR (CD_3OD, 600 MHz) δ 8.10 (dd, *J* = 6.0, 1.9 Hz, 1H), 7.74–7.68 (m, 1H), 7.57 (d, *J* = 1.9 Hz, 1H), 7.42 (dd, *J* = 6.0, 1.9 Hz, 1H), 7.18 (br s, 1H), 7.10 (dd, *J* = 6.0, 2.0 Hz, 1H), 6.98 (d, *J* = 5.9 Hz, 1H), 6.92 (d, *J* = 2.1 Hz, 1H), 6.65 (d, *J* = 1.9 Hz, 1H), 6.61 (d, *J* = 2.0 Hz, 1H), 6.56 (s, 1H), 6.49 (br s, 1H), 5.23 (br s, 1H), 5.22 (s, 1H), 5.16 (s, 1H), 4.97–4.85 (m, 3H), 4.76 (s, 2H), 4.74–4.64 (m, 1H), 4.58–4.43 (m, 2H), 4.37 (dd, *J* = 7.8, 4.3 Hz, 1H), 4.17 (br s, 1H), 4.06 (dd, *J* = 7.8, 4.2 Hz, 1H), 3.89 (s, 3H), 3.70 (s, 3H), 3.66 (br s, 3H), 3.58 (t, *J* = 5.1 Hz, 1H), 3.37 (s, 3H), 3.21–3.13 (m, 1H), 2.98–2.89 (m, 1H), 2.52 (br s, 3H), 1.63–1.35 (m, 3H), 1.43 (s, 9H), 0.90–0.79 (m, 6H); ^{13}C NMR (CD_3OD, 150 MHz) δ 204.0, 173.1, 172.2, 171.8, 169.7, 169.6, 161.7, 160.2, 158.7, 157.0, 155.2, 153.4, 152.4, 151.3, 142.6, 140.0, 139.4, 138.3, 136.9, 135.6, 128.9, 128.7, 128.4, 128.0, 127.2, 125.7, 124.7, 122.8, 119.3, 119.2, 118.5, 113.5, 109.2, 106.8, 104.8, 98.9, 96.8, 82.1, 81.6, 73.2, 72.9, 71.5, 68.5, 68.3, 64.9, 61.4, 61.2, 59.2, 56.7, 56.2, 56.0, 53.1, 51.2, 49.9, 38.0, 30.7, 30.3, 28.6 (3C), 26.9, 26.0, 23.74, 23.73, 21.9, 20.9; ESI-TOF HRMS *m/z* 1402.4750 (M^+ + H, $C_{66}H_{77}ClFN_9O_{20}S$ requires 1402.4751).



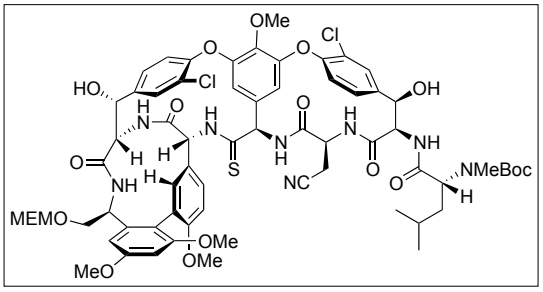
Compound 30. A solution of **29** (12.8 mg, 9.1 μmol) in anhydrous DMSO (1.8 mL) was treated with Cs_2CO_3 (12.1 mg, 37.1 μmol, 4.1 equiv) at 25 °C under Ar and allowed to stir for 12 h. The reaction mixture was cooled to 0 °C and quenched by the addition of 0.2 N HCl (4 mL) and the aqueous phase was extracted with EtOAc (2 × 3 mL). The combined organic phases were washed with saturated aqueous NaCl (5 mL), dried (Na_2SO_4), and the solvent was removed under reduced pressure. PTLC (SiO_2, 7% CH_3OH–EtOAc) afforded (*P*)-**30** (8.3 mg, 66%) as a white solid and its atropisomer (*M*)-**30** (1.1 mg, 9%) as a white solid.

For (*P*)-**30**: $[\alpha]^{25}_D$ +30 (*c* 0.2, $CHCl_3$); ^{1}H NMR (CD_3OD, 600 MHz) δ 8.11 (d, *J* = 8.6 Hz, 1H), 8.00–7.94 (m, 1H), 7.59 (br s, 1H), 7.53 (d, *J* = 7.9 Hz, 1H), 7.42 (d, *J* = 8.5 Hz, 1H), 7.17 (d, *J* = 2.1 Hz, 1H), 7.06–6.98 (m, 1H), 6.96 (d, *J* = 8.6 Hz, 1H), 6.95–6.92 (m, 1H), 6.91 (d, *J* = 2.0 Hz, 1H), 6.64 (d, *J* = 2.1 Hz, 1H), 6.32 (br s, 1H), 5.70 (s, 1H), 5.47 (d, *J* = 6.6 Hz, 1H), 5.34 (s, 1H), 5.23 (s, 1H), 5.17 (s, 1H), 4.90–4.76 (m, 2H, obscured by H_2O), 4.76 (s, 2H), 4.36 (dd, *J* = 7.8, 4.1 Hz, 1H), 4.16 (s, 1H), 4.14 (s, 3H), 4.05 (dd, *J* = 10.2, 10.2 Hz, 1 H), 3.93 (dd, *J* = 10.1, 4.3 Hz, 1 H), 3.89 (s, 3H), 3.77–3.71 (m, 2H), 3.69 (s, 3H), 3.64 (s, 3H), 3.58 (t, *J* = 4.5 Hz, 2H), 3.37 (s, 3H), 2.87–2.84 (m, 1H), 2.83 (br s, 3H), 2.72 (dd, *J* = 16.9, 7.8 Hz, 1H), 1.89–1.81 (m, 1H), 1.67–1.47 (m, 2H), 1.53 (s, 9H), 1.04–0.87 (m, 6H); ^{13}C NMR (CD_3OD, 125 MHz) δ 201.5, 173.1, 170.6, 169.9, 168.5, 168.2, 160.7, 159.2, 157.8, 153.3, 150.0, 148.5, 143.7, 141.8, 139.3, 138.5, 137.4, 137.3, 135.7, 133.1, 127.9, 127.7, 127.1, 126.9, 126.3, 126.0, 124.7, 124.4, 123.9, 121.8, 116.6, 112.7, 106.4, 106.1, 105.8, 98.0, 95.8, 81.1, 72.2, 71.9, 71.0, 67.5, 67.3, 63.9, 61.1, 60.3, 59.9, 58.2, 56.3, 55.6, 55.3, 55.0, 52.1, 51.5, 48.9, 35.9, 31.1, 29.7, 28.6, 27.8 (3C), 24.8, 22.9, 20.8, 20.2; ESI-TOF HRMS *m/z* 1404.4472 (M^+ + Na, $C_{66}H_{76}ClN_9O_{20}SNa$ requires 1404.4508).

For (*M*)-**30**: $[\alpha]^{25}_D$ +38 (*c* 0.22, MeOH); ^{1}H NMR (CD_3OD, 600 MHz) δ 8.42 (s, 1H), 8.30 (br s, 1H), 7.65–7.55 (m, 2H), 7.55–7.31 (m, 1H), 7.19 (s, 1H), 7.10–6.81 (m, 3H), 6.63 (m, 2H), 5.87 (br s, 1H), 5.52 (br s, 1H), 5.38–5.25 (m, 2H), 5.16 (br s, 1H), 4.85–4.78 (m, 2H), 4.77 (s, 2H), 4.37 (br s, 1H), 4.19 (br s, 1H), 4.13 (s, 3H), 4.12–4.06 (m, 1H), 3.95 (br s, 1H), 3.87 (s, 3H), 3.80–3.61 (m, 4H), 3.58 (s, 3H), 3.54 (s, 3H), 3.38 (s, 3H), 2.91–2.85 (m, 1H), 2.84 (br s, 1H), 1.89–1.78 (m, 1H), 1.55 (s, 9H), 1.05–0.85 (m, 6H); ^{13}C NMR (CD_3OD, 125 MHz) δ 201.9, 174.3, 171.1, 170.2, 168.8, 161.4, 159.6, 158.3, 158.2, 156.9, 153.9, 150.2, 147.5, 144.0, 142.5, 140.1, 138.9, 137.8, 137.5, 135.5, 132.8, 128.3, 127.9, 127.7, 127.3, 126.8, 126.4, 126.1, 125.1, 124.2, 123.8, 122.2, 117.1, 114.3, 113.1, 106.3, 106.0, 98.5, 96.3, 81.6, 72.7, 72.4, 67.9, 67.7, 64.3, 61.2, 61.0, 60.8, 58.7, 56.6, 56.2, 55.7, 55.5, 54.3, 52.5, 51.8, 36.2, 30.21, 30.15, 28.3 (3C), 25.3, 23.3, 21.2; ESI-TOF HRMS *m/z* 1382.4681 (M^+ + H, $C_{66}H_{77}ClN_9O_{20}S$ requires 1382.4688).

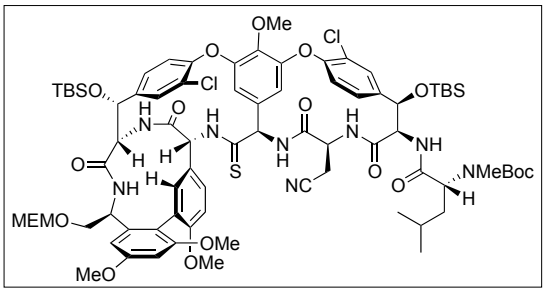


Compound 31. A solution of **30** (36.2 mg, 26.2 μmol) in 500 μL degassed acetone was treated with 100 μL degassed saturated aqueous NH_4Cl and zinc nano particles (68 mg, 1.05 mmol, 40 equiv). The reaction mixture was stirred at 25 °C under Ar for 4 h before the solvent was removed under a stream of N_2. The residue was dissolved in EtOAc and purified by passage through a short plug of silica gel (10% CH_3OH–CH_2Cl_2) to give **31** (32.2 mg, 91%; typically 75–94%) as a white solid that was carried forward to the next step without further purification or characterization.

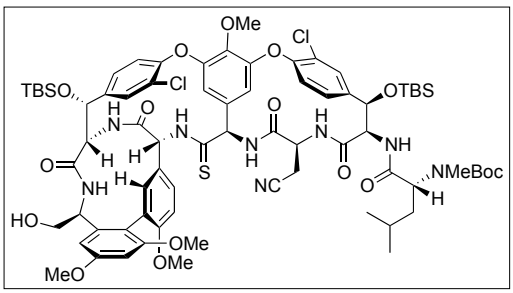


Compound 32. The reaction was performed on scales ranging from 6.5–10.0 mg (47–63%, 3.1–5.1 mg); a representative procedure follows: A solution of **31** (6.9 mg, 5.1 μmol) in CH_3CN (250 μL) was treated with HBF_4 (0.1 mM in CH_3CN, 56 μL, 5.6 μmol) at 0 °C, and the reaction mixture was stirred at 0 °C for 2 min before the dropwise addition of *t*-butylnitrite (0.1 mM in CH_3CN, 56 μL, 5.6 μmol). The resulting mixture was stirred at 0 °C for 2 min and then treated with an aqueous mixture (250 μL) containing CuCl (13 mg, 128 μmol) and $CuCl_2$ (21 mg, 153 μmol) that was cooled to 0 °C. The heterogeneous mixture was allowed to warm to 25 °C and was stirred for 45 min. The reaction was quenched with the addition of saturated aqueous HCO_3NH_4 (4 mL) and extracted with EtOAc (3 × 2 mL). The combined organic layers were washed with saturated aqueous NaCl (4 mL), dried (Na_2SO_4), and the solvent was removed under reduced pressure. PTLC (SiO_2, 7% CH_3OH–CH_2Cl_2) afforded **32** (4.0 mg, 57%; typically 57–63%) as a white solid: $[\alpha]^{25}_D$ +42 (*c* 0.1, MeOH); ^{1}H NMR (CD_3OD, 600 MHz) δ 8.32 (br s, 1H), 7.74 (d, *J* = 8.8 Hz, 1H), 7.52 (br s, 1H), 7.51–7.44 (m, 1H), 7.38–7.30 (m, 2H), 7.17 (s, 1H), 7.06 (d, *J* = 6.6 Hz, 1H), 6.99 (d, *J* = 6.7 Hz, 1H), 6.91 (s, 1H), 6.69 (s, 1H), 6.64 (s, 1H), 6.23 (br s, 1H), 5.72 (s, 1H), 5.40 (d, *J* = 4.6 Hz, 1H), 5.33 (s, 1H), 5.23 (s, 1H), 5.19 (s, 1H), 5.07–5.02 (m, 1H), 4.95–4.80 (m, 2H, obscured by H_2O), 4.77 (s, 2H), 4.37 (m, 1H), 4.18 (s, 3H), 4.16 (s, 1H), 4.09–4.03 (m, 1H), 3.96–3.92 (m, 1H), 3.88 (s, 3H), 3.77–3.71 (m, 2H), 3.69 (s, 3H), 3.65 (s, 3H), 3.59 (t, *J* = 4.4 Hz, 2H), 3.38 (s, 3H), 2.96–2.90 (m, 1H), 2.83 (br s, 3H), 2.66–2.59 (m, 1H), 1.91–1.84 (m, 1H), 1.53 (s, 9H), 0.95 (br d, *J* = 6.4 Hz, 3H), 0.93 (br d, *J* = 6.3 Hz, 3H); ^{13}C NMR (CD_3OD, 150 MHz) δ 202.9, 174.7, 171.8, 171.3, 169.5, 169.3, 161.7, 160.1, 158.8,

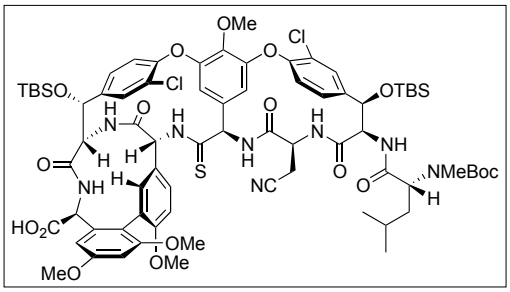
154.5, 153.4, 152.4, 151.2, 142.6, 140.2, 139.5, 138.3, 138.1, 136.8, 130.4, 130.3, 129.1, 128.7, 127.2, 127.1, 125.7, 125.6, 124.7, 122.7, 117.4, 113.6, 106.7, 106.5, 106.4, 98.9, 96.8, 82.3, 73.3, 72.9, 71.9, 71.5, 70.6, 68.5, 68.2, 64.9, 62.0, 61.4, 61.3, 59.2, 57.1, 56.5, 56.3, 56.04, 55.99, 53.0, 52.4, 49.4, 36.5, 32.1, 30.4, 29.5, 28.9 (3C), 25.7, 23.9, 22.3, 21.7; ESI-TOF HRMS *m/z* 1393.4264 (M^+ + Na, $C_{66}H_{76}Cl_2N_8O_{18}SNa$ requires 1393.4267).



Compound 33. The reaction was performed on scales ranging from 4.2–10.0 mg (85–94%, 4.2–9.8 mg); a typical procedure follows: A solution of **32** (4.0 mg, 2.92 μmol) in anhydrous CH_3CN (200 μL) was treated with MTBSTFA (69 μL, 2.92 mmol, 100 equiv). The reaction mixture was warmed at 55 °C under Ar and stirred for 24 h. The reaction mixture was cooled to 25 °C and the solvent was removed under a stream of N_2. The residue was diluted with EtOAc (0.5 mL), 0.1 N HCl (0.5 mL) was added, and the mixture was stirred for 30 min. The layers were separated, and the aqueous layer was extracted with EtOAc (3 × 0.5 mL). The combined organic layers were washed with saturated aqueous NaCl (0.5 mL), dried (Na_2SO_4) and the solvent was removed under reduced pressure. PTLC (SiO_2, 4% CH_3OH–CH_2Cl_2) afforded **33** (4.4 mg, 94%) as a white solid: $[\alpha]^{25}_D$ +17 (*c* 0.1, $CHCl_3$); ^{1}H NMR (CD_3OD, 600 MHz) δ 7.67 (d, *J* = 8.2 Hz, 1H), 7.51 (d, *J* = 8.1 Hz, 1H), 7.42 (br s, 1H), 7.37 (d, *J* = 8.4 Hz, 1H), 7.28 (br s, 1H), 7.19 (br s, 1H), 7.05 (s, 2 H), 6.92 (br s, 1 H), 6.66 (d, *J* = 2.2 Hz, 1H), 5.72–5.68 (m, 1H), 5.57 (d, *J* = 4.2 Hz, 1H), 5.37 (br s, 1H), 5.31 (br s, 1H), 5.27–5.15 (m, 2H), 5.10 (br s, 1H), 4.93–4.84 (m, 2H, obscured by H_2O), 4.78–4.70 (m, 2H), 4.60 (br s, 1H), 4.43–4.38 (m, 1H), 4.21 (s, 3H), 4.16 (d, *J* = 2.1 Hz, 1H), 3.98–3.93 (m, 1H), 3.93–3.90 (m, 1H), 3.89 (s, 3H), 3.75–3.72 (m, 2H), 3.71 (s, 3H), 3.66 (s, 3H), 3.58 (t, *J* = 4.6 Hz, 2H), 3.38 (s, 3H), 3.05–2.98 (m, 1H), 2.89 (s, 3H), 2.83 (s, 2H), 2.68–2.58 (m, 1H), 1.97–1.89 (m, 1H), 1.51 (s, 9H), 1.50–1.43 (m, 2H), 1.04 (s, 9H), 0.97 (d, *J* = 6.4 Hz, 1H), 0.93 (s, 9H), 0.92–0.89 (m, 3H), 0.15 (s, 3H), 0.14 (s, 3H), 0.14 (s, 3H), 0.13 (s, 3H); ^{13}C NMR (acetone-d_6, 150 MHz) δ 202.7, 171.8, 170.6, 169.5, 168.4, 168.3, 167.6, 161.1, 159.7, 158.4, 157.3, 154.4, 152.8, 151.6, 151.0, 141.6, 140.0, 139.4, 138.3, 137.6, 136.1, 130.5, 129.9, 129.6, 129.3, 127.9, 127.8, 127.3, 126.7, 125.5, 125.2, 124.6, 122.6, 116.9, 113.4, 106.5, 106.2, 99.0, 96.4, 80.9, 77.2, 74.6, 73.8, 72.5, 68.0, 67.8, 64.3, 61.6, 60.9, 60.8, 60.3, 60.1, 58.8, 56.6, 56.5, 56.1, 55.8, 52.7, 51.8, 37.0, 30.6, 23.6, 22.6, 19.2, 19.0, 14.3, 1.4, –4.2, –4.6, –4.8, –4.9; ESI-TOF HRMS *m/z* 1621.5940 (M^+ + Na, $C_{78}H_{104}Cl_2N_8O_{18}SSi_2Na$ requires 1621.5997).

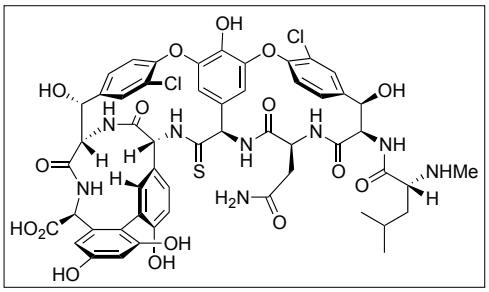


Compound 34. The reaction was performed on scales ranging from 2.4–5.4 mg (50–76%, 1.5–2.9 mg); a typical procedure follows: A solution of **33** (2.4 mg, 1.5 μmol) in anhydrous CH_2Cl_2 (200 μL) at 0 °C was treated with *B*-bromocatecholborane (1.2 mg, 6.0 μmol, 4 equiv) in 50 μL CH_2Cl_2 and stirred at 0 °C under Ar for 2 h. After the reaction was complete, the mixture was treated with *i*-Pr_2NEt (2.6 μL, 15 μmol, 10 equiv) followed by Boc_2O (1.7 μL, 7.5 μmol, 5 equiv). The reaction mixture was stirred at 25 °C for 12 h, concentrated, and the residue purified by PTLC (SiO_2, 6% CH_3OH–CH_2Cl_2) followed by passage through a short silica gel plug (2% CH_3OH–CH_2Cl_2) to afford **34** (1.5 mg, 66%) as a white solid: $[\alpha]^{25}_D$ +11 (*c* 0.1, $CHCl_3$); ^{1}H NMR (acetone-d_6, 600 MHz) δ 7.65–7.47 (m, 3H), 7.39 (br s, 1H), 7.31 (d, *J* = 8.2 Hz, 1H), 7.26 (br s, 1H), 7.14 (br d, *J* = 8.2 Hz, 1H), 7.04 (br d, *J* = 8.4 Hz, 1H), 6.96 (s, 1H), 6.89 (br s, 1H), 6.75 (br s, 1H), 6.66 (d, *J* = 2.2 Hz, 1H), 6.52 (br s, 1H), 6.15–5.95 (br m, 1H), 5.56 (d, *J* = 4.2 Hz, 1H), 5.53 (s, 1H), 5.34 (br s, 1H), 5.32–5.10 (m, 2H), 4.65 (br s, 1H), 4.54–4.46 (m, 1H), 4.32–4.26 (m, 1H), 4.17 (s, 3H), 4.04–3.94 (m, 3H), 3.88 (s, 3H), 3.81 (s, 1H), 3.67 (s, 3H), 3.60 (s, 3H), 2.95–2.87 (m, 1H), 2.86 (br s, 3H), 2.60 (s, 1H), 2.15 (s, 2H), 1.71–1.64 (m, 1H), 1.53 (s, 9H), 1.50–1.43 (br m, 2H), 1.20 (s, 3H), 1.03 (s, 9H), 0.98–0.95 (m, 3H), 0.92 (s, 9H), 0.91–0.84 (m, 3H), 0.18 (s, 3H), 0.17 (s, 3H), 0.15 (s, 3H), 0.12 (s, 3H); ^{13}C NMR (acetone-d_6, 150 MHz) δ 202.9, 171.9, 170.8, 169.7, 168.7, 168.5, 161.3, 159.8, 158.5, 157.4, 154.5, 152.9, 151.8, 151.2, 141.7, 140.1, 139.6, 138.4, 137.7, 136.2, 130.6, 130.0, 129.7, 129.4, 128.1, 127.9, 127.4, 126.9, 125.6, 125.3, 124.7, 122.7, 117.0, 113.5, 106.4, 106.3, 99.1, 81.0, 77.3, 74.7, 73.9, 69.8, 64.3, 63.6, 63.4, 61.7, 61.5, 60.9, 60.4, 60.3, 56.7, 56.6, 56.2, 56.0, 55.8, 55.6, 55.5, 55.4, 51.9, 37.1, 32.1, 28.8, 26.5, 26.4, 25.9, 23.8, 22.7, 19.2, 19.2, –4.2, –4.5, –4.6, –4.9; ESI-TOF HRMS *m/z* 1533.5412 (M^+ + Na, $C_{78}H_{104}Cl_2N_8O_{18}SSi_2Na$ requires 1533.5472).

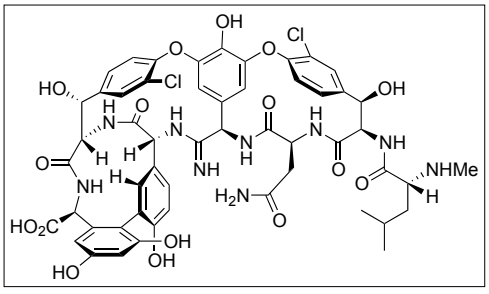


Compound 35. The reaction was performed on scales ranging from 0.5–3.2 mg (typical yield ~50%). A representative procedure follows: A solution of CrO_3 (17.9 mg) in water (340 μL) was treated with 30 μL of conc. H_2SO_4. An aliquot of this stock solution (7.6 μL, 4 equiv of CrO_3) was added into a solution of **34** (1.40 mg, 0.93 μmol) in acetone (100 μL). The reaction

mixture was stirred at 25 °C for 7 h, cooled to 0 °C, and quenched with the addition of isopropanol (200 μL). The mixture was passed through a plug of Celite (acetone wash). The solvent was removed under a stream of N_2. Purification by PTLC (SiO_2, 12% CH_3OH–CH_2Cl_2) gave **35** (0.96 mg, 69%) as a white solid that was typically carried forward without further characterization: ESI-TOF HRMS *m/z* 1525.5470 (M^+ + H, $C_{74}H_{94}Cl_2N_8O_{17}SSi_2$ requires 1525.5446).

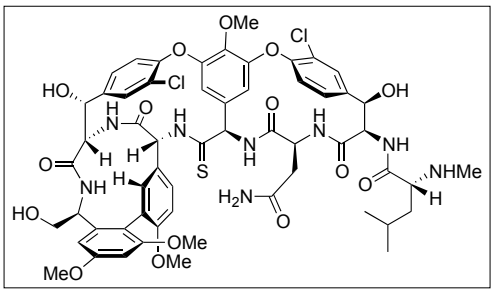


Compound 8. A solution of **35** (0.96 mg, 0.63 μmol) in neat TFA (100 μL) was stirred at 25 ºC for 12 h. The solvent was removed under a stream of N_2 and the residue containing **36** (95%) was treated with $AlBr_3$ (44 mg, 167 μmol, 249 equiv) and EtSH (50 μL). The resulting mixture was stirred at room temperature for 60 h before it was cooled to 0 ºC, and quenched by the addition of CH_3OH (0.2 mL). The solvent was removed under a stream of N_2. The residue was suspended in water (0.5 mL) and purified by short reverse phase silica gel chromatography (C18-SiO_2, 50% CH_3CN–H_2O) and subsequent semi-preparative reverse-phase HPLC (5–20% MeCN/H_2O–0.07% TFA gradient over 10 min then 20% MeCN/H_2O–0.07% TFA isocratic) to afford **8** (0.46 mg, 63%, 2 steps) as a white film: ^{1}H NMR (CD_3OD, 600 MHz) δ 7.65 (br s, 3H), 7.59 (d, *J* = 12 Hz, 1H), 7.37 (br s, 1H), 7.28 (d, *J* = 6.0 Hz, 1H), 7.21 (br s, 1H), 6.75 (d, *J* = 6 Hz, 1H), 6.44 (s, 1H), 6.39 (s, 1H), 6.12 (br s, 1H), 5.82 (br s, 1H), 5.41–5.24 (m, 4H), 4.85–4.70 (m, 3H, obscured by D_2O), 4.42 (d, *J* = 12 Hz, 1H), 4.27 (s, 1H), 4.05–3.97 (m, 1H), 3.03 (d, *J* = 6 Hz, 1H), 2.77 (s, 3H), 2.22–2.17 (m, 1H), 1.91–1.93 (m, 1H), 1.74–1.64 (m, 1H), 1.64–1.56 (m, 1H), 0.99–0.89 (m, 6H); ESI-TOF HRMS *m/z* 1159.2710 (M^+ + H, $C_{53}H_{53}Cl_2N_8O_{16}S$ requires 1159.2672).

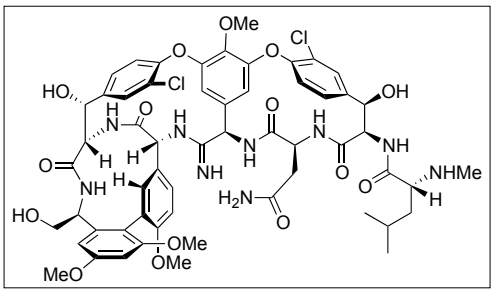


Compound 7. The reaction was performed on scales ranging from 0.3–1.2 mg. A representative procedure follows: A solution of **8** (0.46 mg, 0.40 μmol) in anhydrous saturated NH_3–CH_3OH (0.5 mL) was treated with silver acetate (0.70 mg, 4.2 μmol, 10 equiv). The reaction mixture was stirred at 25 °C for 12 h before the solvent was removed under a stream of N_2. The residue was dissolved in 50% MeOH in H_2O (0.4 mL) and purified by reverse-phase

HPLC (5–20% MeCN/H_2O–0.07% TFA gradient over 10 min then 20% MeCN/H_2O–0.07% TFA isocratic) to afford **7** (50%) as a white film: ^{1}H NMR (CD_3OD, 600 MHz) δ 7.73–7.64 (m, 2H), 7.61–7.52 (br m, 1H), 7.41 (br s, 1H), 7.12 (d, *J* = 6 Hz, 1H), 7.08–7.02 (m, 2H), 6.87 (d, *J* = 12 Hz, 1H), 6.49–6.42 (m, 2H), 6.16–6.04 (br m, 1H), 5.53 (br s, 1H), 5.47–5.29 (m, 4H), 4.75–4.50 (m, 3H, obscured by D_2O), 4.31–4.24 (m, 1H), 4.22–4.12 (m, 1H), 4.11–4.05 (m, 1H), 2.85 (s, 3H), 2.85–2.81 (m, 1H), 2.45–2.37 (m, 1H), 1.85–1.75 (m, 1H), 1.64–1.54 (m, 2H), 0.94–0.79 (m, 6H); MALDI-TOF *m/z* 1142.3 (M^+ + H, $C_{53}H_{54}Cl_2N_9O_{16}$ requires 1142.3); ESI-TOF HRMS *m/z* 1142.3077 (M^+ + H, $C_{53}H_{54}Cl_2N_9O_{16}$ requires 1142.3066).
Prior to biological evaluation, the compound was purified by semi-preparative reverse-phase HPLC (5–20% MeCN/H_2O–0.07% TFA gradient over 10 min then 20% MeCN/H_2O–0.07% TFA isocratic).

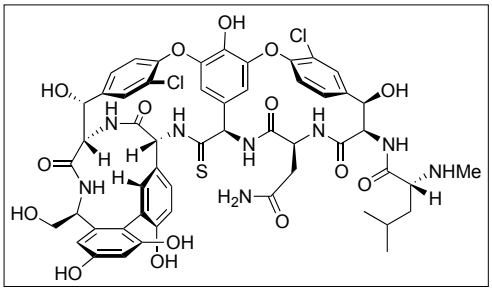


Compound 42. A solution of **32** (2.05 mg, 1.49 μmol) in neat TFA (0.5 mL) was stirred at 25 ºC for 12 h. The solvent was removed under a stream of N_2, the crude residue was dissolved in MeOH and the solution was stirred for 18 h before the solvent was removed under a stream of N_2. The residue was dissolved in 1:1 MeOH:H_2O (0.5 mL) and purified by semi-preparative reverse-phase HPLC (10–50% MeCN/H_2O–0.07% TFA) to afford **42** (1.24 mg, 69%) as a white film: ^{1}H NMR (CD_3OD, 600 MHz) δ 7.67–7.63 (m, 2H), 7.58 (dd, *J* = 12.2, 2.2 Hz, 1H), 7.51 (br s, 1H), 7.38 (d, *J* = 12.1 Hz, 1H), 7.33 (d, *J* = 12.2 Hz, 1H), 7.30 (dd, *J* = 14.5, 4.4 Hz, 1H), 7.03 (d, *J* = 12.2 Hz, 1H), 6.85 (d, *J* = 2.1 Hz, 1H), 6.58 (d, *J* = 2.2 Hz, 1H), 6.53 (d, *J* = 2.3 Hz, 1H), 6.26 (d, *J* = 2.2 Hz, 1H), 6.04 (d, *J* = 2.2 Hz, 1H), 5.49 (d, *J* = 4.6 Hz, 1H), 5.32 (d, *J* = 4.5 Hz, 1H), 5.21 (t, *J* = 4.6 Hz, 1H), 5.16 (s, 1H), 4.22–4.14 (m, 1 H), 4.17 (s, 3H), 4.01–3.94 (m, 2H), 3.93–3.87 (m, 1H), 3.86 (s, 3H), 3.75 (s, 1H), 3.74–3.71 (m, 2H), 3.69 (s, 3H), 3.64 (s, 3H), 2.83 (s, 3H), 2.78 (dd, *J* = 12.4, 4.6 Hz, 1H), 2.56 (dd, *J* = 12.1, 4.5 Hz, 1H), 1.90–1.84 (m, 2H), 1.74–1.64 (m, 2H), 0.93 (d, *J* = 6.2 Hz, 3H), 0.90 (d, *J* = 6.2 Hz, 3H); ESI-TOF HRMS *m/z* 1201.2483 (M^+ + H, $C_{57}H_{62}Cl_2N_8O_{15}S$ requires 1201.3505).

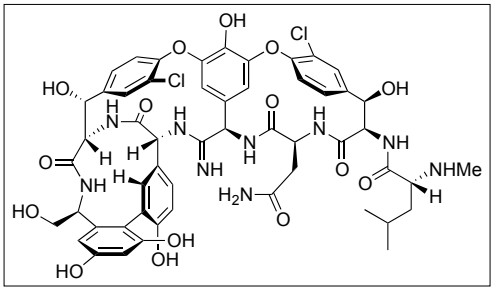


Compound 43. A solution of **42** (1.24 mg, 1.03 μmol) in anhydrous saturated NH_3–CH_3OH (0.5 mL) was treated with silver acetate (1.72 mg, 10.3 μmol, 10 equiv). The

reaction mixture was stirred at room temperature for 24 h before the solvent was removed under a stream of N_2. The residue was dissolved in 40% MeOH–H_2O (0.4 mL + 10 μL TFA) and purified by semi-preparative reverse-phase HPLC (10–50% MeCN/H_2O–0.07% TFA) to afford **43** (0.77 mg, 63%) as a white film. The sample of **43**, even after repeated purification, rapidly (< 1h) equilibrates to three interconverting and easily separable (HPLC) components (1:1:2), all of which display the same mwt (MS): ESI-TOF HRMS *m/z* 1184.3874 (M^+ + H, $C_{57}H_{63}Cl_2N_9O_{15}$ requires 1184.3893).



Compound 44. A solution of **32** (2.20 mg, 1.60 μmol) in neat TFA (0.6 mL) was stirred at 25 ºC for 12 h. The solvent was removed under a stream of N_2 and the residue of **42** was treated with $AlBr_3$ (107 mg, 400 μmol) and EtSH (100 μL). The resulting mixture was stirred at 25 ºC for 60 h before it was diluted with CH_2Cl_2 (0.5 mL), cooled to 0 ºC, and quenched by the addition of CH_3OH (0.2 mL). The solvent was removed under a stream of N_2. The residue was suspended in water (0.5 mL), and purified by short reverse-phase silica gel chromatography (C18-SiO_2, 50% CH_3CN–H_2O) and semi-preparative reverse-phase HPLC (5–20% MeCN/H_2O–0.07% TFA gradient over 10 min then 20% MeCN/H_2O–0.07% TFA isocratic) to afford **44** (1.26 mg, 69%, 2 steps) as a white film: ^{1}H NMR (CD_3OD, 500 MHz) δ 8.34 (br d, *J* = 12.2 Hz, 1H), 8.23 (br s, 1H), 7.70–7.57 (m, 4H), 7.37–7.32 (m, 1H), 7.29 (d, *J* = 12.2 Hz, 1H), 7.19 (d, *J* = 2.2 Hz, 1H), 6.80 (m, 1H), 6.75 (d, *J* = 12.1 Hz, 1H), 6.65 (d, *J* = 2.1 Hz, 1H), 6.42 (d, *J* = 2.2 Hz, 1H), 6.15 (br d, *J* = 2.2 Hz, 1H), 5.82 (br s, 1H), 5.39–5.24 (m, 4H), 4.46 (d, *J* = 12.2 Hz, 1H), 4.28 (d, *J* = 4.6 Hz, 1H), 4.23 (s, 1H), 4.08–3.96 (m, 3H), 3.02 (br d, *J* = 12.2 Hz, 1H), 2.78 (s, 3H), 2.32–2.22 (m, 1H), 1.92–1.83 (m, 1H), 1.78–1.65 (m, 2H), 1.00 (d, *J* = 6.2 Hz, 3H), 0.98 (d, *J* = 6.2 Hz, 3H); ESI-TOF HRMS *m/z* 1145.1974 (M^+ + H, $C_{53}H_{55}Cl_2N_8O_{15}S$ requires 1145.2806).



Compound 45. A solution of **44** (1.12 mg, 0.977 μmol) in anhydrous saturated NH_3–CH_3OH (0.3 mL) was treated with silver acetate (1.63 mg, 9.77 μmol). The reaction mixture was stirred at 25 ºC for 12 h before the solvent was removed under a stream of N_2. The residue was dissolved in 40% MeOH–H_2O (0.4 mL + 10 μL TFA) and purified by short reverse-phase silica gel chromatography (C18-SiO_2, 50% CH_3CN–H_2O) to provide **45** (0.94 mg, 85%) as

an off-white solid that was further purified by semi-preparative reverse-phase HPLC (5–20% MeCN/H_2O–0.07% TFA gradient over 10 min then 20% MeCN/H_2O–0.07% TFA isocratic) prior to biological testing to afford **45** as a white film: ^{1}H NMR (CD_3OD, 600 MHz) δ 7.56 (s, 1H), 7.52–7.46 (m, 2H), 7.34 (s, 1H), 7.21 (d, J = 12.1 Hz, 2H), 6.96–6.90 (m, 2H), 6.73 (d, J = 12.2 Hz, 1H), 6.58 (s, 1H), 6.31 (s, 1H), 5.68 (s, 1H), 5.34 (d, J = 4.4 Hz, 1H), 5.19 (s, 2H), 5.10–4.70 (m, 2H, obstructed by H_2O), 4.52 (br s, 1H), 4.26 (br s, 1H), 4.13–4.04 (m, 1H), 4.01–3.87 (m, 3H), 2.75 (d, J = 12.2 Hz, 1H), 2.35 (dd, J = 16.2, 4.4 Hz, 1H), 2.26 (s, 3H), 1.81–1.71 (m, 1H), 1.60–1.41 (m, 2H), 1.31–1.08 (m, 2H), 0.91–0.80 (m, 6H); ESI-TOF HRMS *m/z* 1128.2276 (M^+ + H, $C_{53}H_{56}Cl_2N_9O_{15}$ requires 1128.3195).

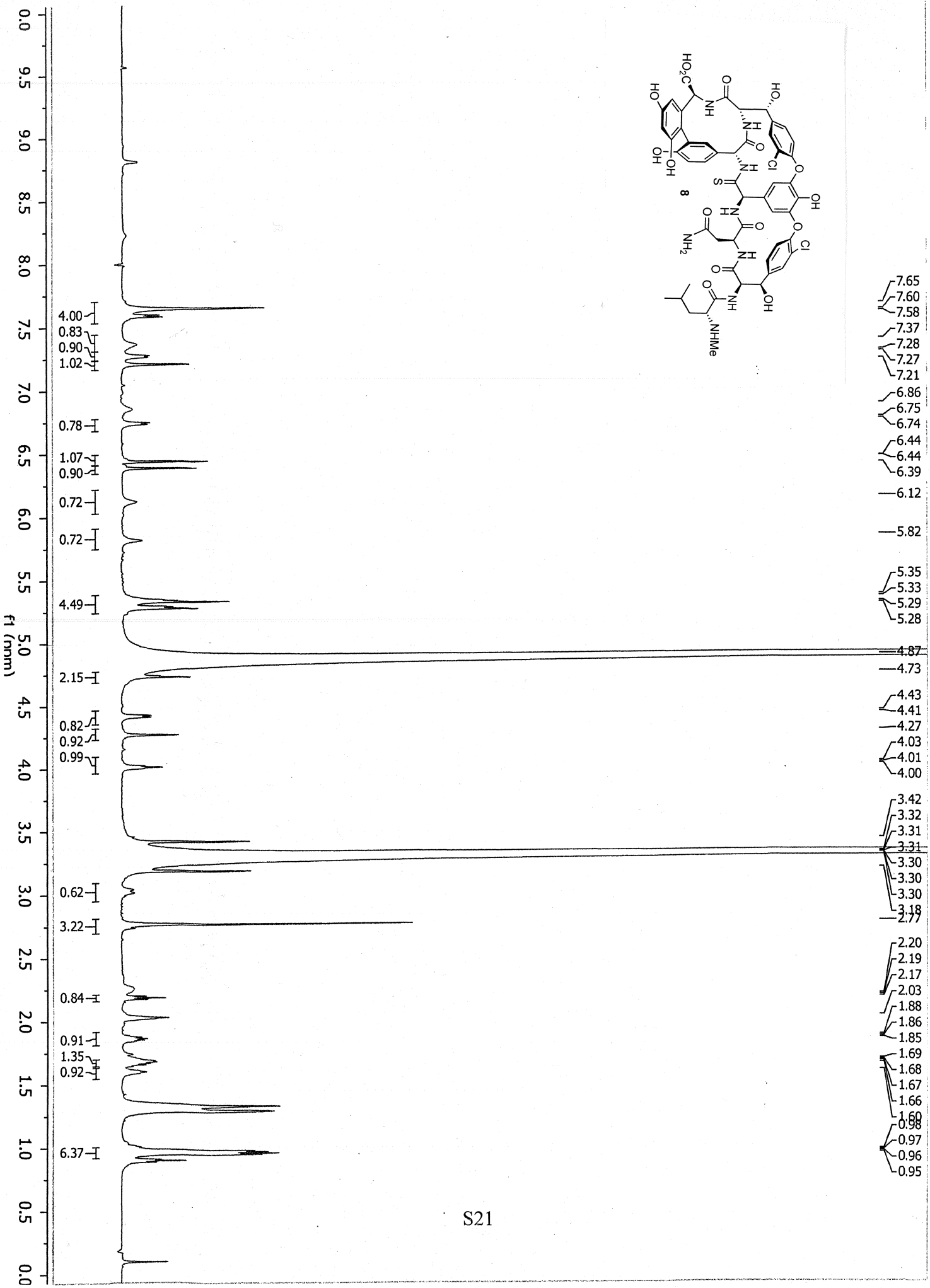
Titration Binding Assays with Model D-Ala-D-Ala and D-Ala-D-Lac Ligands 2 and 4. The binding constants for all compounds for association with the model ligands *N,N'*-Ac_2-Lys-D-Ala-D-Ala (**2**), *N,N'*-Ac_2-Lys-D-Ala-D-Lac (**4**), ketone **3**[12], and **48–50** were determined according to literature protocol.[44] UV difference experiments were carried out on a CARY 3E UV-Vis spectrometer. UV scans were run with a baseline correction that consisted of 0.02 M sodium citrate buffer (pH = 5.1) and covered a range from 200 to 345 nm. A solution of the vancomycin aglycon derivative (7.7×10^{-5} M in 0.02 M sodium citrate buffer) was placed into a quartz UV cuvette (0.1 cm path length) and the UV spectrum recorded versus a reference cell containing 0.02 M sodium citrate buffer. UV spectra were recorded after each addition of a solution of *N,N'*-Ac_2-Lys-D-Ala-D-Ala (**2**), *N,N'*-Ac_2-Lys-D-Ala-D-Lac (**4**), or the related ligands **3** and **48–50** in 0.02 M sodium citrate buffer to each cell from 0.1 to 60.0 equivalents. The absorbance value at the λ_{max} was recorded and the running change in absorbance, $\Delta A_{x\ equiv}$ ($A_{initial} - A_{x\ equiv}$), measured. The number of ligand equivalents was plotted versus ΔA to afford the ligand binding titration curve. The break point of this curve is the saturation point of the system and its xy coordinates were determined by establishing the intersection of the linear fits of the pre and postsaturation curves. $\Delta A_{saturation}$ was calculated and employed to determine the concentration of free ligand in solution at each titration point. ΔA was plotted versus ΔA/free ligand concentration to give a Scatchard plot from which the binding constants were determined.

Antimicrobial Assays. *E. Faecilis* (BM4166) was propagated and MICs were determined in duplicate by the broth microdilution method according to standard microbiological practice.[S2]

S2. Clinical and Laboratory Standards Institute. *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically;* Approved Standard, 7th ed.; CLSI document M07-A8; Clinical and Laboratory Standards Institute: Wayne, PA, 2009.

Full citation for reference 5c: Klevens, R. M.; Morrison, M. A.; Nadle, J.; Petit, S.; Gershman, K.; Ray, S.; Harrison, L. H.; Lynfield, R.; Dumyati, G.; Townes, J. M.; Craig, A. S.; Zell, E. R.; Fosheim, G. E.; McDougal, L. K.; Carey, R. B.; Fridkin, S. K. *J. Am. Med. Assoc.* **2007**, *298*, 1763.

Full citation for reference 26a: Kamenecka, T. M.; Park, Y.-J.; Lin, L. S.; de Laszlo, S.; McCauly, E. D.; Riper, G. V.; Egger, L.; Kidambi, U.; Mumford, R. A.; Tong, S.; Tang, W.; Colletti, A.; Teffera, Y.; Stearns, R.; MacCoss, M.; Schmidt, J. A.; Hagmann, W. K. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 2323.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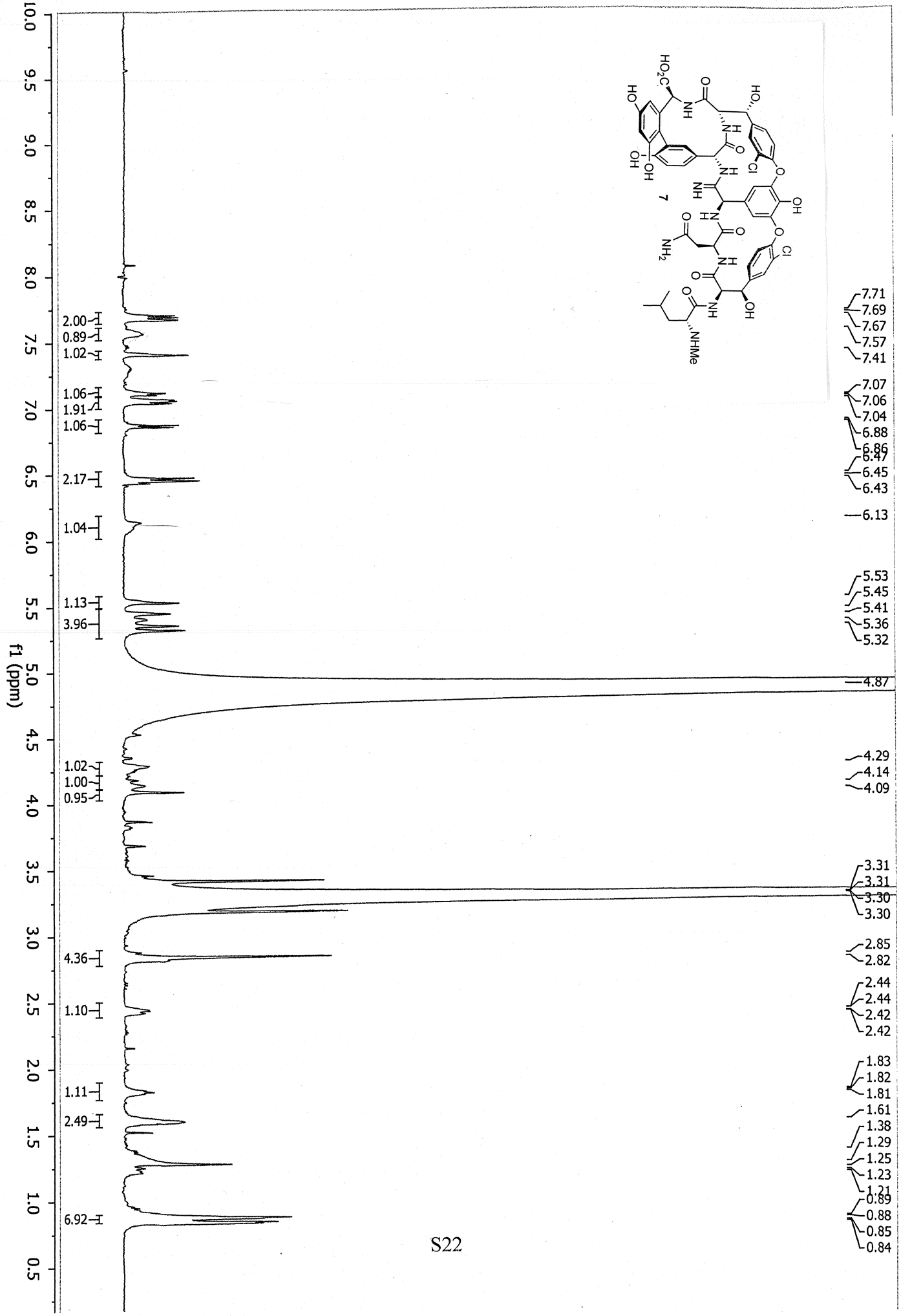
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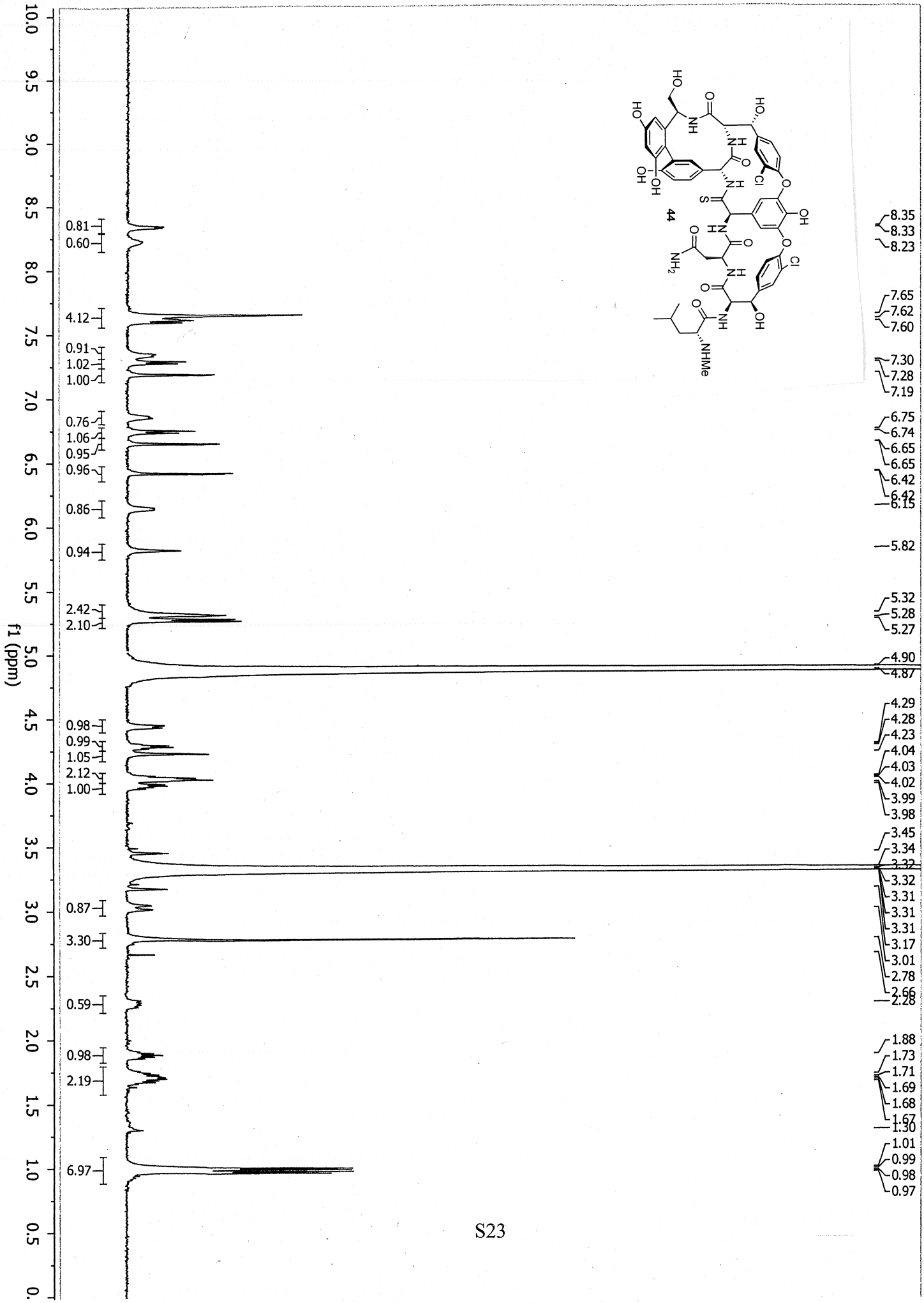
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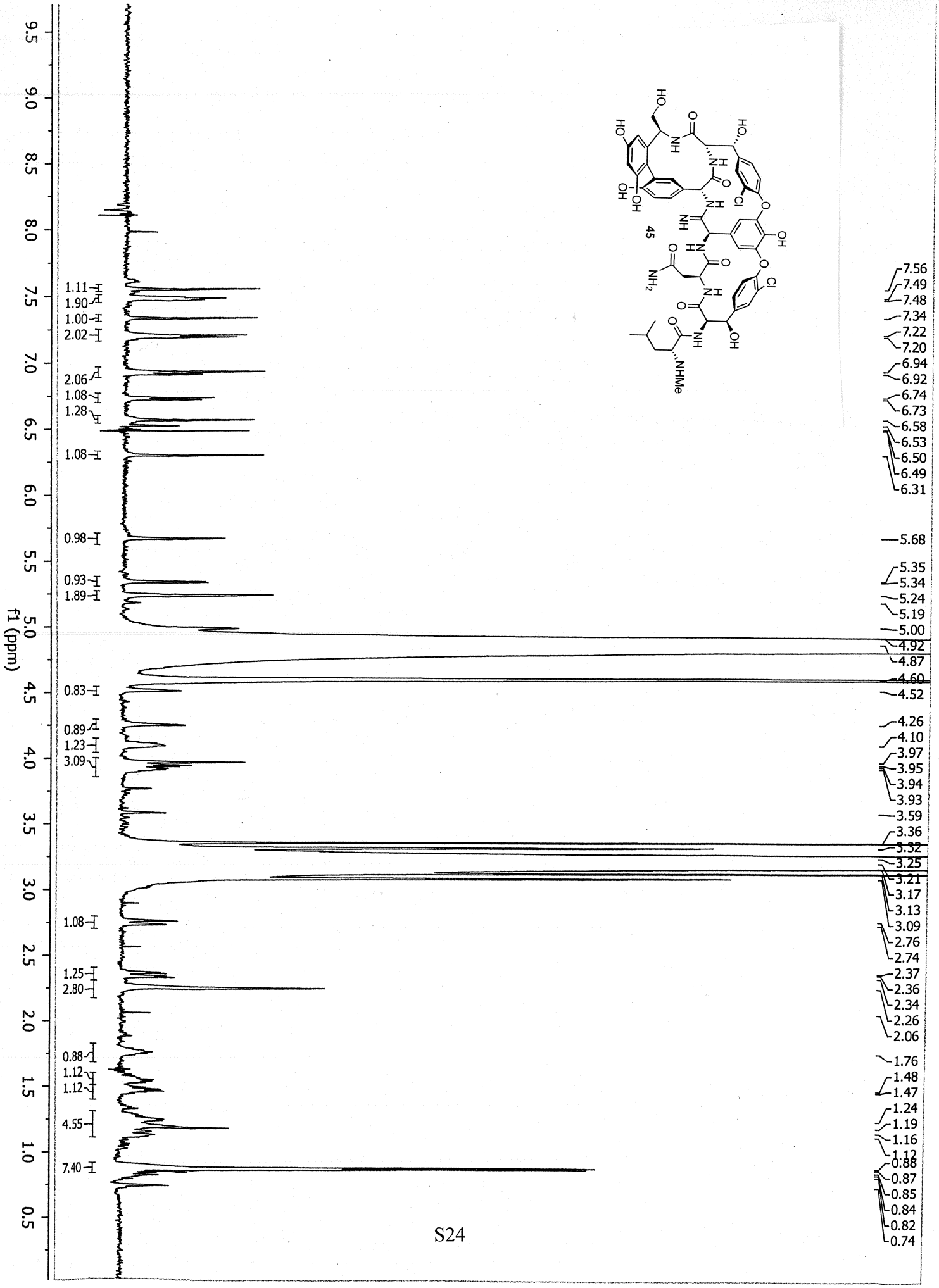
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