SUPPORTING INFORMATION

Structure Assignment, Total Synthesis and Evaluation of the Phosphatase Modulating Activity of Glucolipsin A

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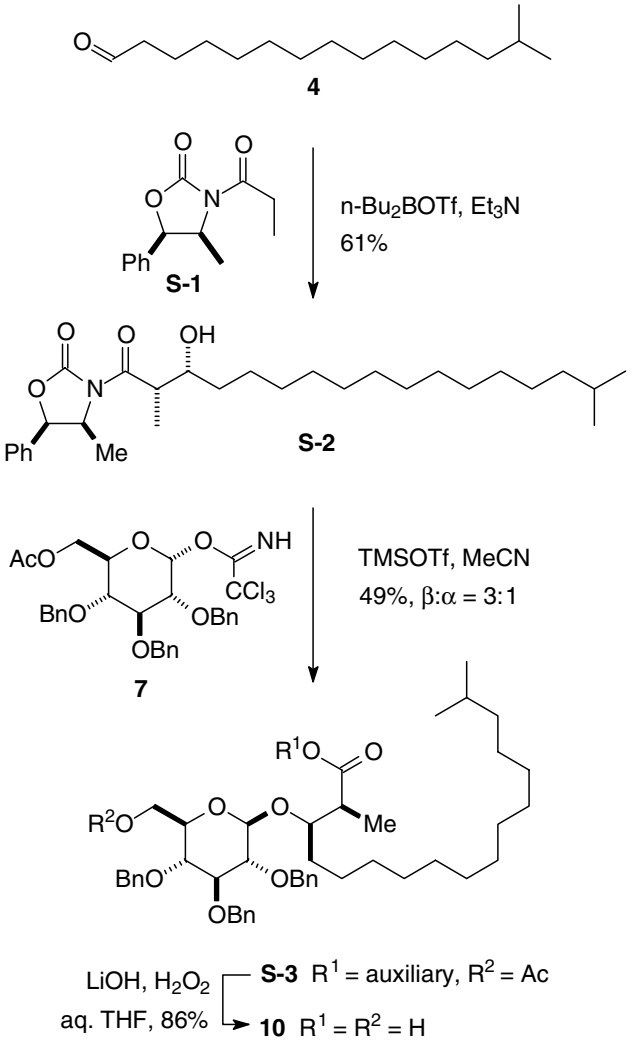
General. All reactions were carried out under Ar. The solvents were purified by distillation over the drying agents indicated and were transferred under Ar: THF, Et_2O, DME (Mg-anthracene), CH_2Cl_2 (P_4O_{10}), MeCN, Et_3N, pyridine, DMF (CaH_2), MeOH (Mg), hexane, toluene (Na/K). Flash chromatography: Merck silica gel 60 (230-400 mesh). Melting points are uncorrected. NMR: chemical shifts (δ) are given in ppm relative to TMS, coupling constants (J) in Hz. IR: wavenumbers in cm^{-1}. All commercially available compounds were used as received.

SYN-ALDOL DERIVATIVES

The synthesis of hydroxy acid **10** is depicted in Scheme S-1 and follows exactly the procedures described in the Experimental Section for the preparation of its diastereomer **9**. The analytical and spectroscopic data of all new compounds are compiled below.

SCHEME S-1. Preparation of the *syn* aldol derivative 10.



Compound S-2. $[\alpha]_D^{20}$ = –12 (*c* 0.87, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 7.45 ~ 7.27 (m, 5H), 5.69 (d, 1H, *J* = 7.3 Hz), 4.80 (quint., 1H, *J* = 6.6 Hz), 3.98 ~ 3.94 (m, 1H), 3.79 (qd,

1H, *J* = 7.0, 2.7 Hz), 3.50 ~ 3.00 (br. s, 1H, -OH), 1.52 (non., 1H, *J* = 6.6 Hz), 1.65 ~ 1.13 (m, 24H), 1.24 (d, 3H, *J* = 7.1 Hz), 0.90 (d, 3H, *J* = 6.6 Hz), 0.87 (d, 6H, *J* = 6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.4, 152.6, 133.2, 128.8, 128.7, 125.6, 78.9, 71.6, 54.7, 42.2, 39.0, 33.9, 29.9, 29.7, 29.6, 27.9, 27.4, 26.0, 22.6, 14.3, 10.2; IR (KBr) 3447, 2920, 2851, 1797, 1688, 766, 698 cm^{-1}; MS (EI) *m/z* (rel. intensity): 455 (4), 367 (67), 323 (4), 322 (5), 311 (5), 279 (7), 233 (38), 178 (5), 134 (26), 118 (17), 116 (9), 112 (18), 107 (44), 95 (16), 88 (37), 82 (24), 79 (14), 70 (40), 67 (14), 57 (100), 55 (37), 44 (14), 41 (28), 39 (4); HRMS (CI-DE) *calcd.* for $C_{29}H_{47}NO_4$ [$(M+H)^+$] 474.358332; *found* 474.358645. Anal. Calcd. for $C_{29}H_{47}NO_4$: C, 73.53; H, 10.00; N, 2.96. Found: C, 73.42; H, 10.11; N, 2.92.

Compound S-3. $[\alpha]_D^{20}$ = + 11 (*c* 0.57, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50 ~ 7.09 (m, 20H), 5.66 (d, 1H, *J* = 7.1 Hz), 4.95 (d, 1H, *J* = 11.0 Hz), 4.95 (d, 1H, *J* = 11.0 Hz), 4.85 (d, 1H, *J* = 11.0 Hz), 4.78 (d, 1H, *J* = 11.0 Hz), 4.71 (d, 1H, *J* = 11.0 Hz), 4.68 (quint., 1H, *J* = 6.7 Hz), 4.57 (d, 1H, *J* = 11.0 Hz), 4.45 (d, 1H, *J* = 7.8 Hz), 4.42 (dd, 1H, *J* = 11.9, 1.8 Hz), 4.12 (dd, 1H, *J* = 11.9, 4.8 Hz), 4.06 (q, 1H, *J* = 6.1 Hz), 3.95 (qd, 1H, *J* = 6.8, 5.2 Hz), 3.66 (t, 1H, *J* = 8.8 Hz), 3.51 (dd, 1H, *J* = 9.8, 8.3 Hz), 3.47 ~ 3.45 (m, 1H), 3.41 (dd, 1H, *J* = 9.1, 7.9 Hz), 1.99 (s, 3H), 1.51 (non., 1H, *J* = 6.6 Hz), 1.75 ~ 1.12 (m, 27H), 0.89 (d, 3H, *J* = 6.6 Hz), 0.86 (d, 6H, *J* = 6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.4, 170.8, 152.9, 138.6, 138.4, 137.9, 133.5, 128.7, 128.4, 128.3, 128.1, 128.0, 127.9, 127.7, 127.6, 125.7, 101.6, 84.8, 82.1, 78.9, 78.3, 77.5, 75.6, 74.9, 72.8, 63.2, 55.2, 42.0, 39.1, 31.9 ~ 29.5 (12C), 28.0, 27.4, 25.3, 22.6, 20.7, 14.3, 11.4; IR (film) 2920, 2851, 1769, 1734, 1698, 1606, 1497, 1453, 1230, 1115, 1091, 732, 697 cm^{-1}; MS (EI) *m/z* (rel. intensity): 618 (2), 474 (2), 456 (62), 412 (7), 400 (6), 277 (4), 253 (21), 240 (19), 193 (5), 181 (10), 178 (5), 160 (8), 134 (12), 118 (4), 97 (3), 91 (100), 81 (3), 43 (5); MS (ESI-pos): 970.65 [$(M+Na)^+$]. Anal. Calcd. for $C_{58}H_{77}NO_{10}$: C, 73.47; H, 8.18; N, 1.48. Found: C, 73.54; H, 8.14; N, 1.52.

Hydroxy Acid 10. $[\alpha]_D^{20}$ = + 7 (*c* 0.86, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 ~ 7.25 (m, 15H), 5.40 ~ 5.00 (br. s, 1H), 4.91 (d, 1H, *J* = 11.0 Hz), 4.90 (d, 1H, *J* = 11.0 Hz), 4.82 (d, 1H, *J* = 11.2 Hz), 4.78 (d, 1H, *J* = 11.2 Hz), 4.71 (d, 1H, *J* = 11.1 Hz), 4.57 (d, 1H, *J* = 11.0 Hz), 4.43 (d, 1H, *J* = 7.7 Hz), 4.15 ~ 4.13 (m, 1H), 3.88 ~ 3.84 (m, 1H), 3.66 ~ 3.59 (m, 2H), 3.40 (dd, 1H, *J* = 9.3, 7.5 Hz), 3.43 ~ 3.33 (m, 2H), 2.60 (qd, 1H, *J* = 7.0, 2.1 Hz), 1.51 (non.,

1H, *J* = 6.6 Hz), 1.72 ~ 1.16 (m, 25H), 1.18 (d, 3H, *J* = 7.1 Hz), 0.86 (d, 6H, *J* = 6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.1, 138.6 ~ 127.5, 103.4, 84.7, 82.2, 81.5, 77.9, 75.6, 75.2, 75.0, 74.9, 62.2, 43.6, 39.1, 34.0, 29.9, 29.7, 29.6, 29.5, 28.0, 27.4, 25.9, 22.6, 9.0; IR (film) 3400-2700, 2918, 2851, 1700, 1605, 1497, 1227, 1090, 737, 695 cm^{-1}; HRMS (ESI-pos): 769.65 [(M + Na)$^+$]. Anal. Calcd. for $C_{46}H_{66}O_8$: C, 73.96; H, 8.91. Found: C, 73.87; H, 8.86.

Compound 15. $[\alpha]_D^{20}$ = + 5 (*c* 1.4, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.91 ~ 3.87 (m, 1H), 3.72 (s, 3H), 2.55 (qd, 1H, *J* = 7.2, 3.5 Hz), 2.50 ~ 2.00 (br. s, 1H, -OH), 1.51 (non., 1H, *J* = 6.6 Hz), 1.48 ~ 1.10 (m, 24H), 1.18 (d, 3H, *J*= 7.2 Hz), 0.87 (d, 6H, *J* = 6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.6, 71.7, 51.8, 44.1, 39.1, 33.8, 29.9, 29.7, 29.6, 29.5, 28.0, 27.4, 26.0, 22.6, 10.6; IR (film) 3460, 2925, 2853, 1739, 1723, 1436, 1199, 722 cm^{-1}; MS (EI) *m/z* (rel. intensity): 310 (3), 117 (22), 97 (3), 88 (100), 85 (6), 57 (16), 56 (6), 55 (7), 41 (5); HRMS: *calcd.* for $C_{20}H_{40}O_3$ [(M + H)$^+$] 329.305570; *found* 329.305990. Anal. Calcd. for $C_{20}H_{40}O_3$: C, 73.12; H, 12.27. Found: C, 73.21; H, 12.22.

Compound 16. Mixture of anomers, β:α = 2.5:1; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37 ~ 7.23 (m, 15H), 4.94 (d, 1H, *J* = 10.9 Hz), 4.92 (d, 1H, *J* = 9.6 Hz), 4.84 (d, 1H, *J* = 10.9 Hz), 4.78 (d, 1H, *J* = 11.0 Hz), 4.69 (d, 1H, *J* = 11.0 Hz), 4.55 (d, 1H, *J* = 10.9 Hz), 4.42 (d, 1H, *J* = 7.8 Hz), 4.29 (dd, 1H, *J* = 11.7, 2.2 Hz), 4.19 (dd, 1H, *J* = 11.7, 4.8 Hz), 3.98 (q, 1H, *J* = 6.0 Hz), 3.66 ~ 3.62 (m, 1H), 3.64 (s, 3H), 3.49 (dd, 1H, *J* = 9.8, 8.5 Hz), 3.47 ~ 3.43 (m, 1H), 3.40 (dd, 1H, *J* = 9.1, 7.9 Hz), 2.65 (qd, 1H, *J* = 7.0, 5.4 Hz), 2.03 (s, 3H), 1.51 (non., 1H, *J* = 6.6 Hz), 1.58 ~ 1.17 (m, 24H), 1.19 (d, 3H, *J* = 7.1 Hz), 0.86 (d, 6H, *J* = 6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.0, 170.6, 138.5 ~ 127.6, 102.1, 84.8, 82.1, 79.6, 77.5, 75.6, 74.9, 74.8, 72.5, 63.1, 51.5, 43.5, 39.1, 32.6, 29.9, 29.7, 29.6, 29.5, 28.0, 27.4, 25.4, 22.7, 20.8, 11.8; IR (film): 2924, 2853, 1744, 1455, 1070, 698 cm^{-1}; MS (EI) *m/z* (rel. intensity): 473 (3), 447 (3), 355 (5), 311 (16), 277 (5), 253 (20), 240 (12), 197 (3), 193 (7), 181 (10), 91 (100), 81 (2), 69 (2), 65 (2), 43 (3); HRMS (ESI-pos) *calcd.* for $C_{49}H_{70}O_9$ [(M + Na)$^+$] 825.491754; *found* 825.49318. Anal. Calcd. for $C_{49}H_{70}O_9$: C, 73.28; H, 8.79. Found: C, 73.22; H, 8.85.

ANTI-ALDOL DERIVATIVES

Compound 18. To a stirred solution of compound **17** (734 mg, 1.53 mmol) and Et_3N (0.52 mL, 3.67 mmol) in CH_2Cl_2 (8 mL) at –78°C was added dropwise a solution of dicyclohexylboron triflate (1.0 M in hexane, 3.4 mL, 3.4 mmol) over 20 min. The resulting mixture was stirred at that temperature for 2h before a solution of aldehyde **4** (442 mg, 1.84 mmol) in CH_2Cl_2 (15 mL) was introduced. Stirring was continued for 1h at –78°C before the mixture was allowed to reach ambient temperature over a period of 2 h. For work-up, the reaction was quenched with pH 7 buffer solution (6 mL), the mixture was diluted with MeOH (31 mL) and 30% hydrogen peroxide (3.1 mL) was added carefully. The mixture was then vigorously stirred overnight before it was concentrated. The residue was partitioned between water and CH_2Cl_2, the combined organic phases were dried over Na_2SO_4 and evaporated, and the residue was purified by flash chromatography (hexane:EtOAc, 30/1 $\rightarrow$ 9/1) to give the compound **18** as a colorless syrup (862 mg, 71%). $[\alpha]_D^{20}$ = + 10 (*c* 1.75, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32 ~ 7.16 (m, 8H), 6.92 ~ 6.86 (m, 4H), 5.84 (d, 1H, *J*= 4.4 Hz), 4.76 (d, 1H, *J* = 6.5 Hz), 4.53 (d, 1H, *J* = 16.5 Hz), 4.13 (qd, 1H, *J* = 7.0, 4.4 Hz), 3.64 ~ 3.61 (m, 1H), 2.48 (s, 6H), 2.45 (quint., 1H, *J* = 7.1 Hz), 2.45 ~ 2.35 (br. s, 1H, -OH), 2.27 (s, 3H), 1.52 (non., 1H, *J* = 6.6 Hz), 1.58 ~ 1.12 (m, 24H), 1.18 (d, 3H, *J* = 6.5 Hz), 1.13 (d, 3H, *J* = 7.2 Hz), 0.86 (d, 6H, *J* = 6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.6, 142.6 ~ 126.0, 78.2, 73.2, 56.8, 48.3, 45.5, 39.1, 34.4, 30.0, 29.7, 29.6, 27.9, 27.4, 25.4, 22.9, 22.7, 20.9, 14.1, 13.6; IR (film) 3535, 2924, 2853, 1741, 1604, 1496, 1455, 1326, 1154, 859, 756, 698, 660 cm^{-1}; MS (EI) *m/z* (rel. intensity): 406 (5), 318 (7), 316 (100), 222 (4), 183 (7), 134 (3), 132 (3), 119 (22), 91 (82), 57 (13), 41 (4). Anal. Calcd. for $C_{44}H_{65}NO_5S$: C, 73.39; H, 9.10; N, 1.17. Found: C 73.34; H, 9.03; N, 1.91.

Compound 19. A mixture of trichloroacetimidate **7** (82 mg, 0.13 mmol), alcohol **18** (46 mg, 0.064 mmol) and molecular sieves 4Å in CH_3CN (6.5 mL) was stirred for 30 min at ambient temperature. The solution was then cooled to –40 °C prior to the addition of TMSOTf (1.2 μL) and stirring was continued for 2h at that temperature. Aq. $NaHCO_3$ was added, the mixture was filtered through a pad of Celite, and the filtrate was purified by flash

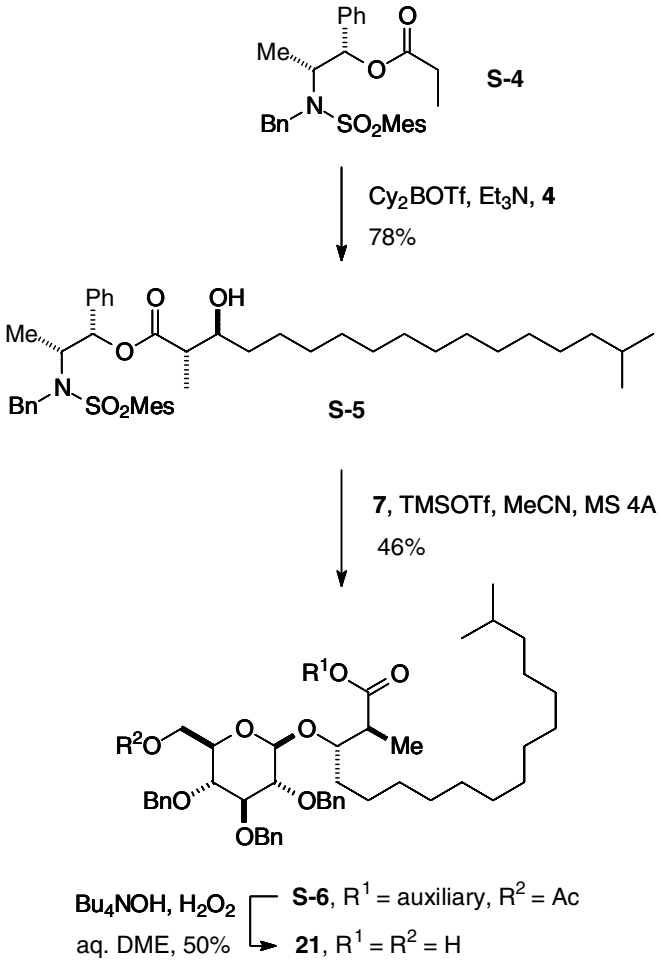
chromatography (hexane:EtOAc, 30/1 → 85/15) to give the compound **19** (47 mg, 62%) as a colorless syrup. $[\alpha]_D^{20}$ = + 11 (*c* 1.76, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51 ~ 7.12 (m, 18H), 6.90 (d, 2H, *J* = 6.9 Hz), 6.83 (s, 2H), 5.80 (d, 1H, *J* = 4.8 Hz), 4.91 (d, 1H, *J* = 11.0 Hz), 4.84 (d, 1H, *J* = 11.0 Hz), 4.82 (d, 1H, *J* = 11.0 Hz), 4.77 (d, 1H, *J* = 11.0 Hz), 4.75 (d, 1H, *J* = 16.4 Hz), 4.59 (d, 1H, *J* = 11.0 Hz), 4.55 (d, 1H, *J* = 11.0 Hz), 4.50 (d, 1H, *J* = 16.4 Hz), 4.41 (d, 1H, *J* = 7.9 Hz), 4.30 (d, 1H, *J* = 10.8 Hz), 4.19 ~ 4.12 (m, 2H), 3.91 (br. quint., 1H, *J* = 4.4 Hz), 3.63 (tm, 1H, *J* = 9.0 Hz), 3.45 ~ 3.43 (m, 2H), 3.31 (dd, 1H, *J* = 9.0, 7.9 Hz), 2.92 (qd, 1H, *J* = 7.1, 4.4 Hz), 2.45 (s, 6H), 2.26 (s, 3H), 1.94 (s, 3H), 1.52 (non., 1H, *J* = 6.6 Hz), 1.48 ~ 1.00 (m, 24H), 1.20 (d, 3H, *J* = 6.9 Hz), 1.14 (d, 3H, *J* = 7.1 Hz), 0.86 (d, 6H, *J* = 6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.2, 170.6, 142.4 ~ 126.0, 103.4, 84.8, 82.2, 81.1, 78.0, 77.7, 75.6, 74.9, 74.8, 72.8, 63.1, 56.8, 48.2, 44.3, 39.1, 30.9, 30.0, 29.9, 29.7, 29.6, 29.4, 28.0, 27.4, 25.7, 22.9, 22.7, 20.8, 20.7, 13.9, 10.95; IR (film) 2925, 2853, 1741, 1695, 1383, 1110, 833, 752, 698 cm^{-1}; MS (ESI-pos): 1217.00 [$(M + Na)^+$]. Anal. Calcd. for $C_{73}H_{95}NO_{11}S$: C, 73.40; H, 8.02; N, 1.17. Found: C, 73.36; H, 7.95; N, 1.22.

Compound 20. To a solution of compound **19** (34mg, 0.029mmol) in DME (0.1mL) was added dropwise H_2O_2 (30% w/w, 0.006mL, 0.057mmol) at 0ºC, followed by *n*-Bu_4NOH (0.037mL, 0.057mmol). After 5h, the reaction was quenched with aq. Na_2SO_3 (1.6M) and stirring was continued for 1h at ambient temperature before the mixture was evaporated. The residue was acidified by addition of aq. HCl (6M) and the aqueous phase was extracted with MTBE. The combined organic layers were dried (Na_2SO_4) and purified by chromatography (hexane:EtOAc:HOAc, 8/2/0.01) to give compound **20** (12mg, 54%) as a white solid. $[\alpha]_D^{20}$ = + 2 (*c* 1.41, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51 ~ 7.22 (m, 15H), 5.30 ~ 5.00 (br. s, 1H), 4.92 (d, 1H, *J* = 11.3 Hz), 4.90 (d, 1H, *J* = 11.3 Hz), 4.82 (d, 1H, *J* = 11.0 Hz), 4.78 (d, 1H, *J* = 11.0 Hz), 4.71 (d, 1H, *J* = 11.1 Hz), 4.59 (d, 1H, *J* = 11.0 Hz), 4.46 (d, 1H, *J* = 7.8 Hz), 3.94 ~ 3.90 (m, 1H), 3.87 (dd, 1H, *J* = 12.2, 2.5 Hz), 3.67 ~ 3.62 (m, 2H), 3.45 (dd, 1H, *J* = 9.6, 8.8 Hz), 3.42 (dd, 1H, *J* = 9.1, 7.8 Hz), 3.68 ~ 3.34 (m, 1H), 2.98 (quint., 1H, *J* = 7.0 Hz), 1.51 (non., 1H, *J* = 6.6 Hz), 1.56 ~ 1.13 (m, 25H), 1.14 (d, 3H, *J* = 7.0 Hz), 0.86 (d, 6H, *J* = 6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 184.7, 138.5 ~ 126.9, 103.1, 84.7, 82.3, 81.6, 78.0, 75.7, 75.1, 74.9, 62.2, 45.2, 39.1, 31.9, 30.0, 29.7, 29.6, 29.5, 28.0, 27.4, 24.4, 22.7,

13.3; IR (film): 3442-2700, 2923, 2853, 1711, 1454, 1071, 734, 696 cm^{-1}; MS (EI) *m/z* (rel. intensity): 459 (2), 433 (2), 432 (2), 341 (7), 316 (4), 253 (19), 240 (10), 235 (3), 197 (3), 193 (4), 181 (7), 163 (4), 92 (9), 91 (100), 69 (3), 57 (4), 55 (3), 43 (5); HRMS: *calcd.* for $C_{46}H_{66}O_8$ [$(M + H)^+$] 747.483595; *found* 747.483382. Anal. Calcd. for $C_{46}H_{66}O_8$: C, 73.96; H, 8.91. Found: C, 74.08; H, 8.96.

The diastereomeric *anti* aldol derivative **21** was prepared analogously as depicted in Scheme S-2. The analytical and spectroscopic data of new products are compiled below:

SCHEME S-2. Preparation of the *anti* aldol derivative 21.



Compound S-5. $[\alpha]_D^{20}$ = −17 (*c* 13.3, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32 ~ 7.08 (m, 8H), 6.92 ~ 6.85 (m, 4H), 5.84 (d, 1H, *J* = 4.4 Hz), 4.76 (d, 1H, *J* = 16.5 Hz), 4.53 (d, 1H, *J* = 16.5 Hz), 4.13 (qd, 1H, *J* = 7.0, 4.4 Hz), 3.64 ~ 3.61 (m, 1H), 2.48 (s, 6H), 2.47 (quint., 1H, *J* = 7.1 Hz), 2.27 (s, 3H), 1.52 (non., 1H, *J* = 6.6 Hz), 1.58 ~ 1.12 (m, 25H), 1.18 (d, 3H, *J* = 7.0 Hz), 1.13 (d, 3H, *J* = 7.2 Hz), 0.86 (d, 6H, *J* = 6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.5, 142.5 ~ 126.0, 78.2, 73.2, 56.7, 48.2, 45.5, 39.1, 34.4, 30.0, 29.7, 29.6, 27.9, 27.4, 25.4, 22.9, 22.6, 20.8, 14.1, 13.5; IR (film) 3530, 2926, 2853, 1739, 1604, 1496, 1382, 1205, 858, 758, 698 cm^{-1}; MS (EI) *m/z* (rel. intensity)*:* 406 (3), 326 (2), 318 (7), 316 (100), 183 (8), 180 (9), 119 (24), 91 (89), 57 (15), 41 (7); HRMS (ESI) *calcd.* for $C_{44}H_{65}NO_5S$ [$(M + NH_4)^+$] 737.49223; found 737.49223. Anal. Calcd. for $C_{44}H_{65}NO_5S$: C, 73.39; H, 9.10; N, 1.17. Found: C, 73.31; H, 9.03; N, 1.91.

Glycoside S-6. $[\alpha]_D^{20}$ = −0.4 (*c* 2.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37 ~ 7.13 (m, 23H) 6.88 (d, 2H, *J* = 7.1 Hz), 6.82 (s, 2H), 5.82 (d, 1H, *J* = 5.1 Hz), 4.91 (d, 1H, *J* = 11.1 Hz), 4.88 (d, 1H, *J* = 11.0 Hz), 4.83 (d, 1H, *J* = 11.0 Hz), 4.78 (d, 1H, *J* = 11.0 Hz), 4.68 (d, 1H, *J* = 10.9 Hz), 4.67 (d, 1H, *J* = 16.4 Hz), 4.54 (d, 1H, *J* = 10.9 Hz), 4.47 (d, 1H, *J* = 16.4 Hz), 4.27 (dd, 1H, *J* = 11.6, 2.1 Hz), 4.25 (d, 1H, *J* = 7.7 Hz), 4.16 ~ 4.12 (m, 2H), 3.90 ~ 3.87 (m, 1H), 3.58 (t, 1H, *J* = 8.8 Hz), 3.45 (dd, 1H, *J* = 9.7, 8.6 Hz), 3.41 ~ 3.33 (m, 1H), 3.35 (dd, 1H, *J* = 9.0, 8.0 Hz), 2.68 (qd, 1H, *J* = 7.1, 4.1 Hz), 2.43 (s, 6H), 2.26 (s, 3H), 1.97 (s, 3H), 1.52 (non., 1H, *J* = 6.6 Hz), 1.55 ~ 1.14 (m, 24H), 1.17 (d, 3H, *J* = 7.0 Hz), 1.09 (d, 3H, *J* = 7.1 Hz), 0.86 (d, 6H, *J* = 6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.1, 170.6, 142.5 ~ 126.4, 101.9, 84.9, 82.0, 79.7, 78.0, 77.7, 75.6, 74.9, 72.5, 63.2, 56.7, 48.1, 42.9, 39.1, 31.0, 30.0, 29.7, 29.5, 28.0, 27.4, 25.5, 22.9, 22.7, 20.8, 20.7, 13.8, 10.6; IR (film): 2924, 2853, 1743, 1604, 1497, 1454, 1327, 1154, 858, 753, 698 cm^{-1}; MS (EI) *m/z* (rel. intensity): 406 (21), 318 (7), 316 (100), 240 (5), 181 (6), 119 (11), 91 (76); HRMS (ESI) *calcd.* for $C_{73}H_{95}NO_{11}S$ [$(M + NH_4)^+$] 1211.696960; found 1211.69657. Anal. Calcd. for $C_{73}H_{95}NO_{11}S$: C, 73.40; H, 8.02; N, 1.17; S, 2.68. Found: C, 73.30; H, 8.08; N, 1.13; S, 2.62.

Hydroxy acid 21. To a solution of compound **S-6** (15 mg, 0.013 mmol) in DME (0.1 mL) was added dropwise H_2O_2 (30% w/w, 2.6 μL, 0.025 mmol) at 0ºC, followed by *n*-Bu_4NOH (0.016 mL, 0.025 mmol). After stirring for 20h, the reaction was quenched with aq. Na_2SO_3

(1.6 M) and the mixture was stirred for 1h at ambient temperature before the solvent was evaporated. The residue was acidified with aq. HCl (6 M) and extracted with MTBE. The combined organic layers were dried (Na_2SO_4) and purified by flash chromatography (hexane:ethyl acetate:acetic acid, 8/2/0.01) it gave compound **21** (4.7 mg, 50%) as a white solid. $[\alpha]_D^{20}$ = + 6 (*c* 4.17, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ9.50 ~ 7.90 (br. s, 1H), 7.37 ~ 7.23 (m, 15H), 4.92 (d, 1H, *J* = 11.2 Hz), 4.89 (d, 1H, *J* = 11.1 Hz), 4.83 (d, 1H, *J* = 11.0 Hz), 4.79 (d, 1H, *J* = 11.0 Hz), 4.71 (d, 1H, *J* = 11.2 Hz), 4.62 (d, 1H, *J* = 11.0 Hz), 4.52 (d, 1H, *J* = 7.8 Hz), 4.03 ~ 3.99 (m, 1H), 3.85 (dd, 1H, *J* = 11.9, 2.8 Hz), 3.69 (dd, 1H, *J* = 11.9, 4.7 Hz), 3.65 (t, 1H, *J* = 9.1 Hz), 3.54 (t, 1H, *J* = 9.1 Hz), 3.39 (dd, 1H, *J* = 9.1, 7.8 Hz), 3.39 ~ 3.35 (m, 1H), 2.84 (qd, 1H, *J* = 7.0, 5.9 Hz), 1.51 (non., 1H, *J* = 6.6 Hz), 1.63 ~ 1.19 (m, 25H), 1.15 (d, 3H, *J* = 7.1 Hz), 0.86 (d, 6H, *J* = 6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ180.0, 138.5 ~ 127.5, 102.1, 84.7, 82.2, 79.9, 77.7, 75.6, 75.0, 74.9, 62.1, 43.1, 39.1, 31.3, 29.9, 29.7, 29.6, 27.9, 27.4, 25.2, 22.6, 11.7; IR (KBr) 3400-2700, 2922, 2851, 1734, 1710, 1465, 1066, 735, 697 cm^{-1}; MS (EI) *m/z* (rel. intensity): 341 (5), 253 (19), 240 (8), 193 (5), 103 (5), 92 (10), 91 (100), 74 (5), 57 (5), 43 (5); HRMS (ESI-pos) *calcd.* for $C_{46}H_{66}O_8$ [(M + $Na)^+$] 769.46554; *found* 769.46715. Anal. Calcd. for $C_{46}H_{66}O_8$: C, 73.96, H, 8.91. Found C, 73.87, H, 8.95.

MACRODIOLIDES AND ADDITIONAL COMPOUNDS FOR BIOLOGICAL TESTING

Macrodiolide 25. $[\alpha]_D^{20}$ = + 6 (*c* 2.7, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38 ~ 7.25 (m, 15H), 4.95 (d, 1H, *J* = 10.9 Hz), 4.94 (d, 1H, *J* = 11.0 Hz), 4.80 (d, 1H, *J* = 10.7 Hz), 4.78 (d, 1H, *J* = 11.0 Hz), 4.71 (d, 1H, *J* = 11.0 Hz), 4.57 (d, 1H, *J* = 10.7 Hz), 4.51 (br. d, 1H, *J* = 11.2 Hz), 4.46 (d, 1H, *J* = 7.7 Hz), 4.04 (q, 1H, *J* = 5.7 Hz), 3.87 (dd, 1H, *J* = 11.2, 5.6 Hz), 3.66 (t, 1H, *J* = 8.9 Hz), 3.45 ~ 3.37 (m, 3H), 2.65 (quint., 1H, *J* = 6.7 Hz), 1.51 (non., 1H, *J* = 6.7 Hz), 1.59 ~ 1.11 (m, 27H), 0.86 (d, 6H, *J* = 6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ174.2, 138.5 ~ 127.6, 101.9, 84.9, 82.5, 78.0, 75.7, 75.1, 74.9, 72.9, 63.8, 44.2, 39.1, 32.7,

30.0, 29.9, 29.8, 29.7, 29.6, 28.0, 27.4, 25.4, 22.7, 12.5. IR (film): 2923, 2853, 1735, 1454, 1362, 1263, 1069, 697 cm^{-1}; HRMS (ESIpos) *calcd.* 1479.92018 [$(M+Na)^+$]; *found* 1479.92004.

Macrodiolide 27. $[\alpha]_D^{20}$ = - 2 (*c* 2.4, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 7.37 ~ 7.23 (m, 15H), 4.95 (d, 2H, *J* = 11.0 Hz), 4.85 (d, 1H, *J* = 10.9 Hz), 4.78 (d, 1H, *J* = 11.0 Hz), 4.71 (d, 1H, *J* = 11.1 Hz), 4.56 (d, 1H, *J* = 11.0 Hz), 4.53 (d, 1H, *J* = 7.9 Hz), 4.22 (dd, 1H, *J* = 11.3, 1.9 Hz), 4.05 (dd, 1H, *J* = 11.3, 10.0 Hz), 3.99 ~ 3.97 (m, 1H), 3.68 (t, 1H, *J* = 9.0 Hz), 3.61 (td, 1H, *J* = 10.0, 1.9 Hz), 3.42 (dd, 1H, *J* = 9.1, 7.9 Hz), 3.28 (dd, 1H, *J* = 9.7, 9.0 Hz), 3.22 (qd, 1H, *J* = 7.0, 4.9 Hz), 1.51 (non., 1H, *J* = 6.6 Hz), 1.54 ~ 1.11 (m, 24H), 1.12 (d, 3H, *J* = 7.0 Hz), 0.86 (d, 6H, *J* = 6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.9, 138.4 ~ 127.6, 105.1, 84.7, 82.3, 82.1, 78.6, 75.7, 75.1, 74.9, 72.6, 64.5, 44.5, 39.1, 30.9, 30.1, 30.0, 29.9, 29.8, 29.7, 29.5, 27.9, 27.4, 26.4, 22.7, 8.96; IR (film): 2923, 2853, 1735, 1455, 1084, 1070, 697 cm^{-1}; MS (EI) *m/z* (rel. intensity): 513 (5), 369 (2), 339 (2), 316 (3), 279 (5), 253 (9), 240 (18), 211 (3), 193 (5), 181 (19), 127 (3), 109 (3), 97 (4), 91 (100), 85 (3), 81 (3), 69 (3), 57 (4), 55 (3), 43 (3); MS (ESI-pos): 1479.00 [$(M + Na)^+$].

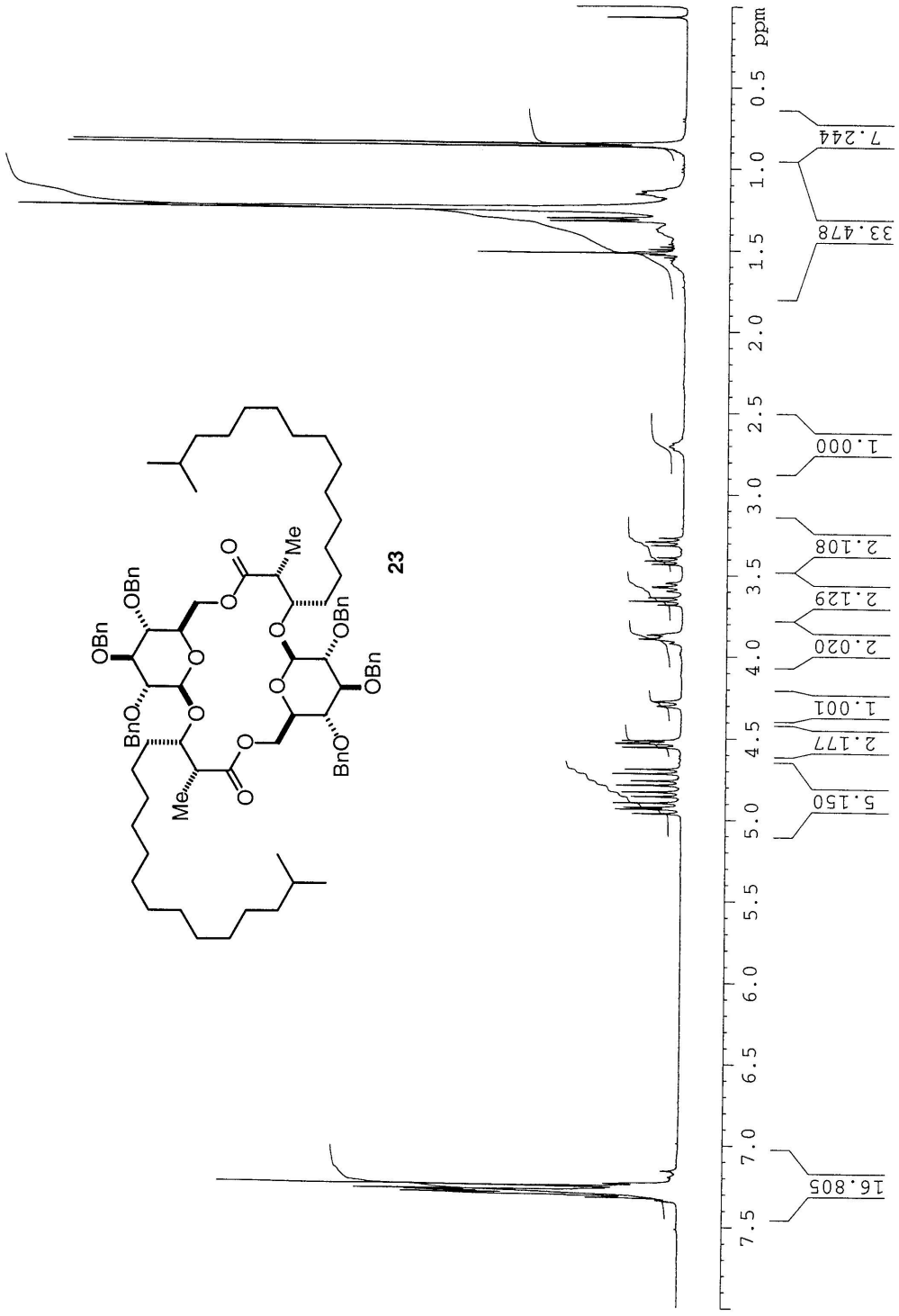
Macrodiolide 29. $[\alpha]_D^{20}$ = + 21 (*c* 2.44, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 7.37 ~ 7.23 (m, 15H), 4.94 (d, 1H, *J* = 11.0 Hz), 4.93 (d, 1H, *J* = 11.0 Hz), 4.85 (d, 1H, *J* = 11.0 Hz), 4.78 (d, 1H, *J* = 11.0 Hz), 4.72 (d, 1H, *J* = 11.0 Hz), 4.56 (d, 1H, *J* = 11.0 Hz), 4.48 (d, 1H, *J* = 7.7 Hz), 4.40 (d, 1H, *J* = 10.4 Hz), 4.24 (m, 1H), 3.85 (dd, 1H, *J* = 11.3, 9.9 Hz), 3.68 (t, 1H, *J* = 9.0 Hz), 3.63 (td, 1H, *J* = 9.7, 0.9 Hz), 3.42 (dd, 1H, *J* = 9.1, 7.8 Hz), 3.29 (dd, 1H, *J* = 9.7, 9.0 Hz), 3.00 (qd, 1H, *J* = 6.9, 4.0 Hz), 1.49 (non., 1H, *J* = 6.6 Hz), 1.52 ~ 1.14 (m, 24H), 1.11 (d, 3H, *J* = 6.9 Hz), 0.86 (d, 6H, *J* = 6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.8, 138.4 ~ 127.6, 98.9, 85.0, 82.1, 78.4, 75.8, 75.7, 75.1, 75.0, 73.1, 65.2, 40.6, 39.1, 30.4, 30.1, 30.0, 29.9, 29.8, 29.6, 28.0, 27.5, 26.0, 22.7, 8.5; IR (film): 2924, 2853, 1738, 1454, 1195, 1071, 751, 698 cm^{-1}.

Hydroxy acid 31. $[\alpha]_D^{20}$ = –17 (*c* 1.37, CH_3OH); ^1H NMR (400 MHz, CD_3OD): δ 4.29 (d, 1H, *J* = 7.7 Hz), 4.02 ~ 4.01 (m, 1H), 3.93 (br. d, 1H, *J* = 11.5 Hz), 3.68 ~ 3.60 (m, 1H), 3.36 ~ 3.33 (m, 1H), 3.22 ~ 3.20 (m, 2H), 3.16 (dd, 1H, *J* = 9.2, 7.7 Hz), 2.40 (quint., 1H, *J* = 6.6 Hz), 1.53 (non., 1H, *J* = 6.6 Hz), 1.64 ~ 1.07 (m, 24H), 1.13 (d, 3H, *J* = 7.0 Hz), 0.87 (d, 6H,

J = 5.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 186.5, 103.3, 81.7, 78.1, 77.9, 75.4, 72.0, 63.2, 48.1, 40.2, 34.5, 31.1, 31.0, 30.8, 29.1, 28.5, 26.5, 23.0, 13.7; IR (film) 3400-2700, 2923, 2853, 1568, 1465, 1384, 1077, 1043 cm^{-1}; MS (EI) *m/z* (rel. intensity): 440 (3), 296 (14), 279 (8), 278 (21), 113 (20), 112 (8), 100 (11), 97 (31), 95 (17), 87 (61), 85 (16), 82 (15), 74 (30), 67 (19), 56 (33), 55 (50), 45 (12), 44 (16), 43 (100), 41 (50), 39 (9), 31 (12); HRMS (ESI-pos) *calcd.* for $C_{25}H_{48}O_8$ [(M + Na)$^+$] 499.324689; *found* 499.32485.

Hydroxy acid 32. $[\alpha]_D^{20}$ = –8 (*c* 0.47, CH_3OH); ^{1}H NMR (400 MHz, CD_3OD): δ 4.37 (d, 1H, J = 7.7 Hz), 3.91 ~ 3.87 (m, 1H), 3.82 (dd, 1H, J = 11.7, 2.5 Hz), 3.68 (dd, 1H, J = 11.7, 5.1 Hz), 3.77 (dd, 1H, J = 9.1, 8.8 Hz), 3.30 ~ 3.23 (m, 2H), 3.16 (dd, 1H, J = 9.1, 7.7 Hz), 2.56 (quint., 1H, J = 7.1 Hz), 1.51 (non., 1H, J = 6.6 Hz), 1.61 ~ 1.14 (m, 24H), 1.06 (d, 3H, J = 7.1 Hz), 0.87 (d, 6H, J = 6.6 Hz); ^{13}C NMR (100 MHz, CD_3OD): δ 183.7, 103.9, 83.5, 78.1, 77.7, 75.7, 71.7, 63.0, 47.5, 40.2, 32.8, 31.0, 30.8, 30.7, 29.1, 28.5, 25.7, 23.0, 14.0; IR (KBr) 3400-2700, 2924, 2853, 1571, 1466, 1413, 1367, 1075, 1020 cm^{-1}; MS (EI) *m/z* (rel. intensity) 296 (5), 278 (7), 113 (9), 112 (6), 100 (5), 97 (19), 95 (11), 87 (33), 82 (13), 74 (19), 72 (6), 67 (14), 56 (26), 45 (14), 43 (100), 41 (44), 39 (9), 31 (21); HRMS (ESI-pos) *calcd.* for $C_{25}H_{48}O_8$ [(M + Na)$^+$] 499.324689; *found* 499.32505.

Hydroxy acid 34. $[\alpha]_D^{20}$ = –20 (*c* 0.76, CH_3OH); ^{1}H NMR (400 MHz, CD_3OD): δ 4.34 (d, 1H, J = 7.7 Hz), 4.00 ~ 3.96 (m, 1H), 3.82 (d, 1H, J = 11.9 Hz), 3.62 ~ 3.36 (m, 1H), 3.36 ~ 3.22 (m, 3H), 3.17 (dd, 1H, J = 9.3, 7.7 Hz), 2.65 (quint., 1H, J = 7.1 Hz), 1.51 (non., 1H, J = 6.6 Hz), 1.58 ~ 1.12 (m, 24H), 1.04 (d, 3H, J = 7.1 Hz), 0.87 (d, 6H, J= 6.6 Hz); ^{13}C NMR (100 MHz, CD_3OD): δ 183.9, 103.3, 82.1, 78.0, 77.9, 75.3, 71.8, 62.9, 48.4, 40.2, 31.4, 31.1, 31.0, 30.8, 29.1, 28.5, 25.8, 23.0, 13.8; IR (KBr) 3400-2700, 2925, 2853, 1576, 1467, 1414, 1367, 1078, 1022 cm^{-1}; MS (EI) *m/z* (rel. intensity): 323 (3), 322 (3), 279 (9), 278 (9), 223 (3), 222 (2), 113 (8), 97 (18), 95 (10), 87 (38), 82 (11), 74 (19), 72 (6), 67 (11), 56 (24), 44 (29), 43 (100), 41 (36), 31 (24), 26 (3); HRMS (ESI-pos) *calcd.* for $C_{25}H_{48}O_8$ [(M + Na)$^+$] 499.324689; *found* 499.32442.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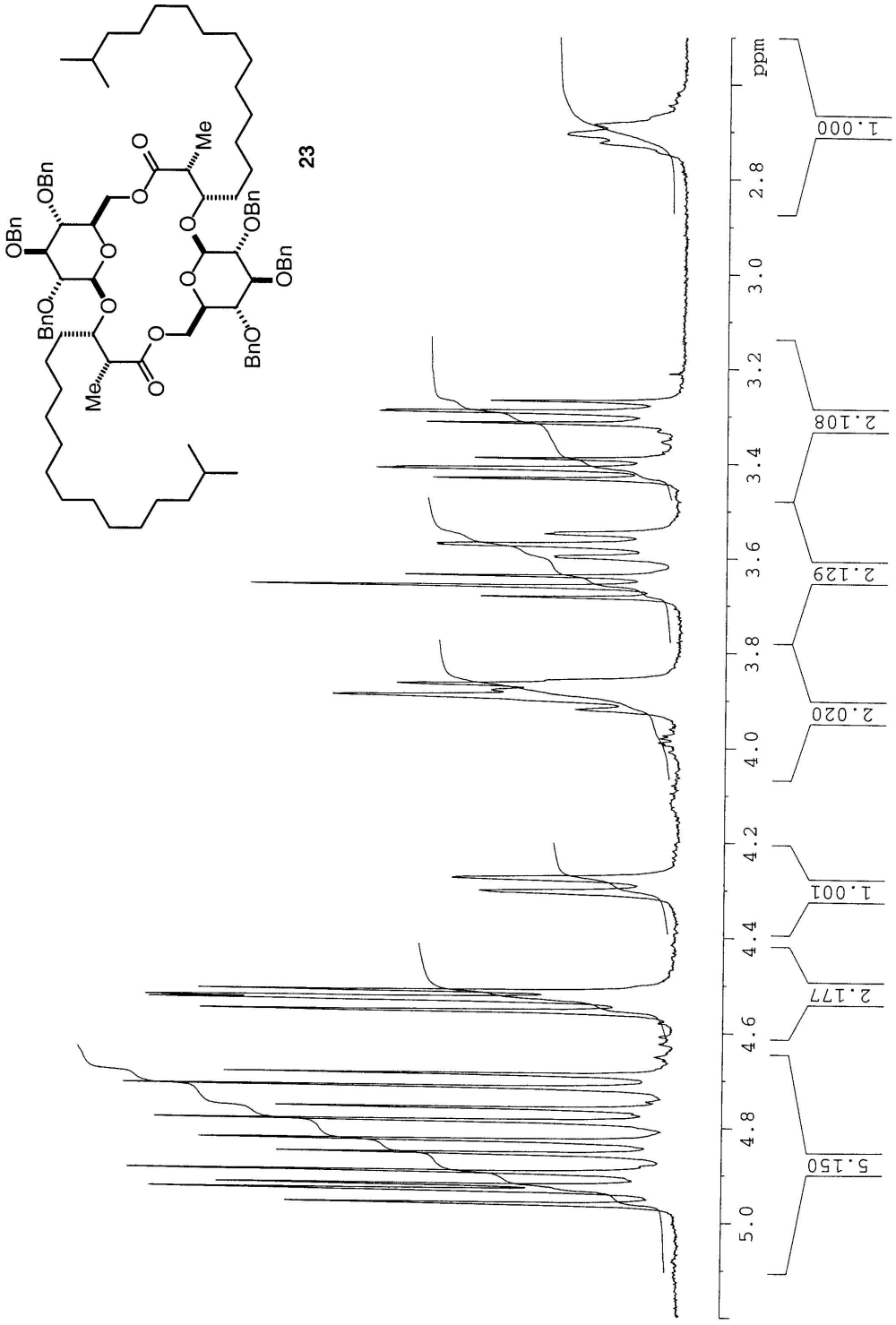
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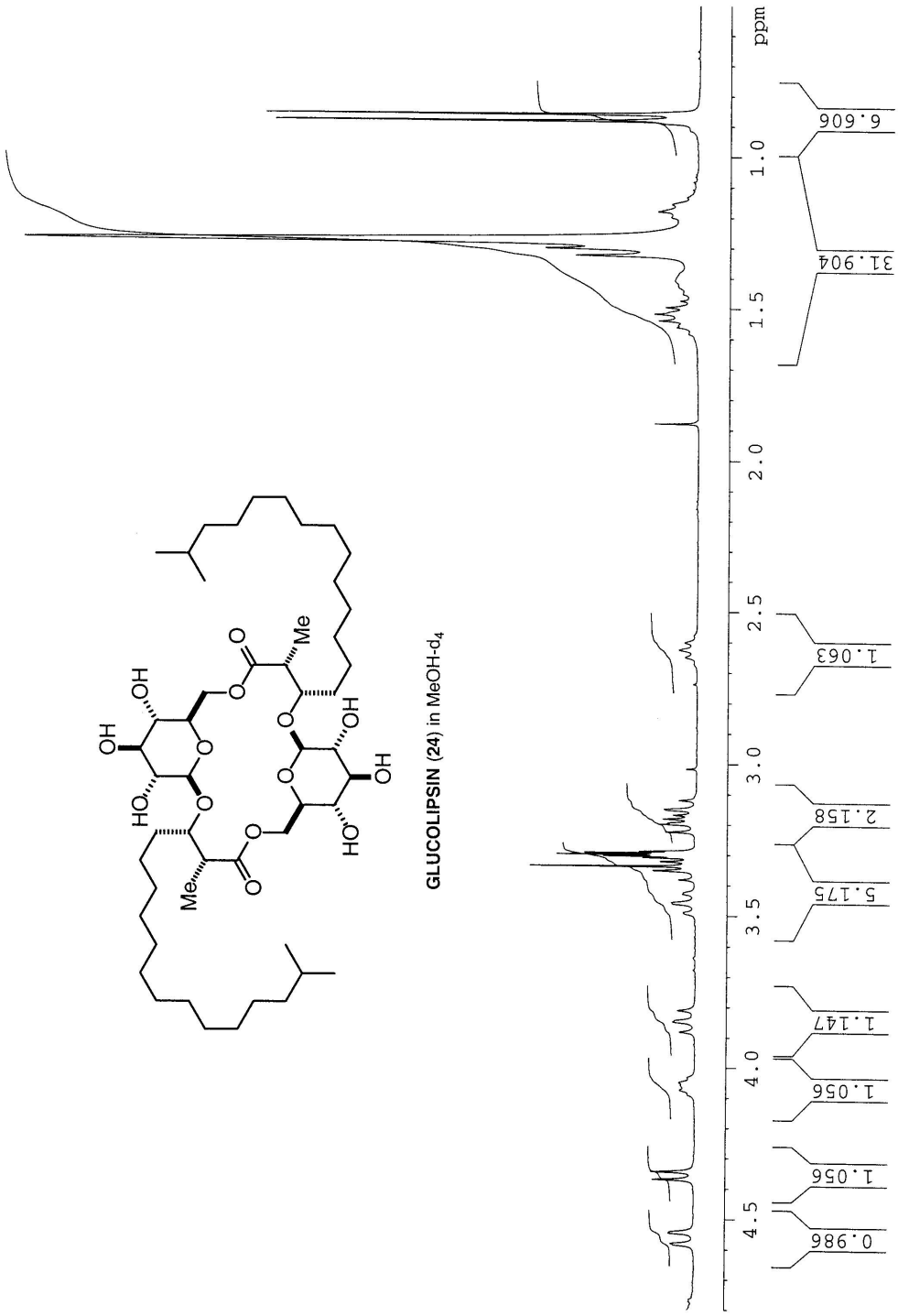
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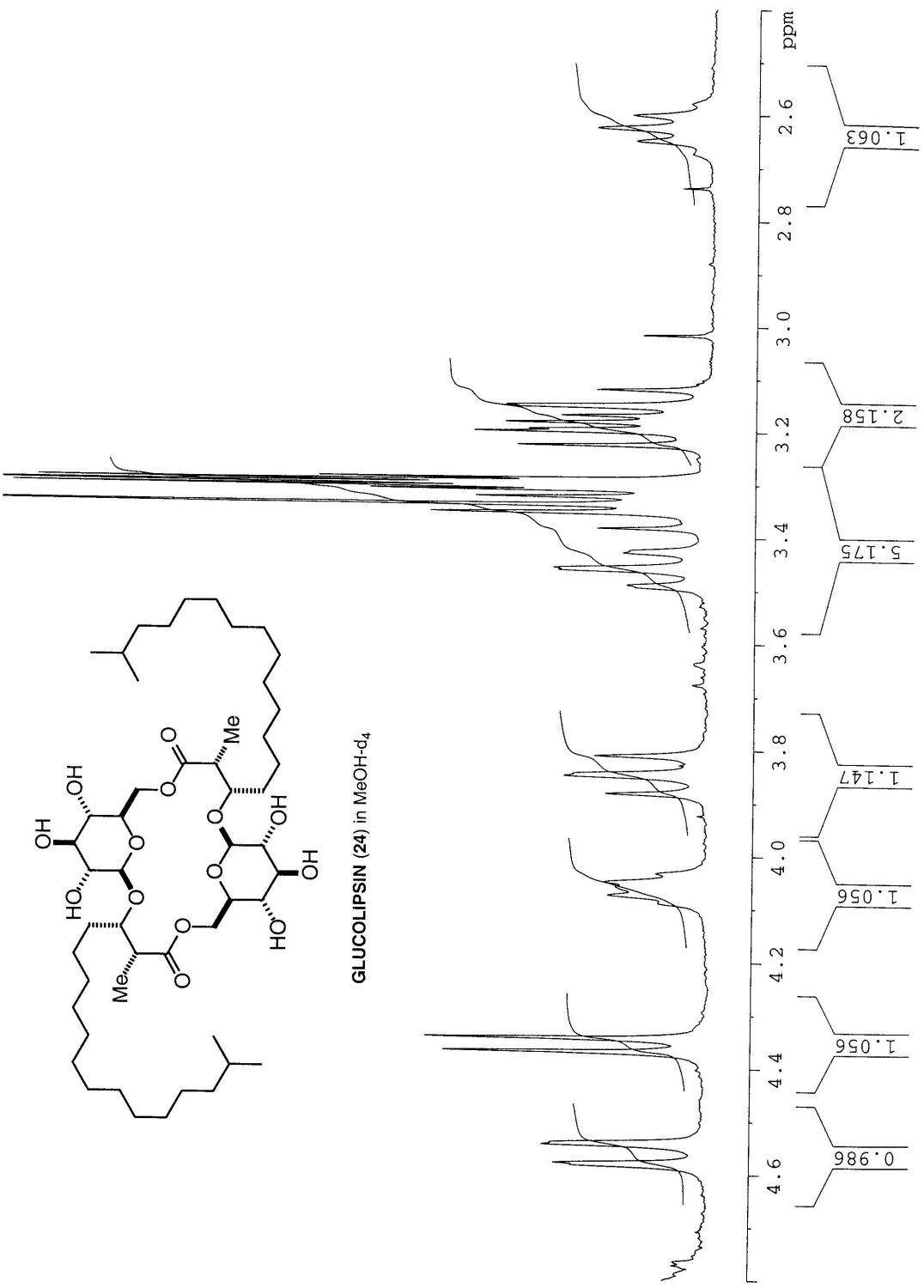

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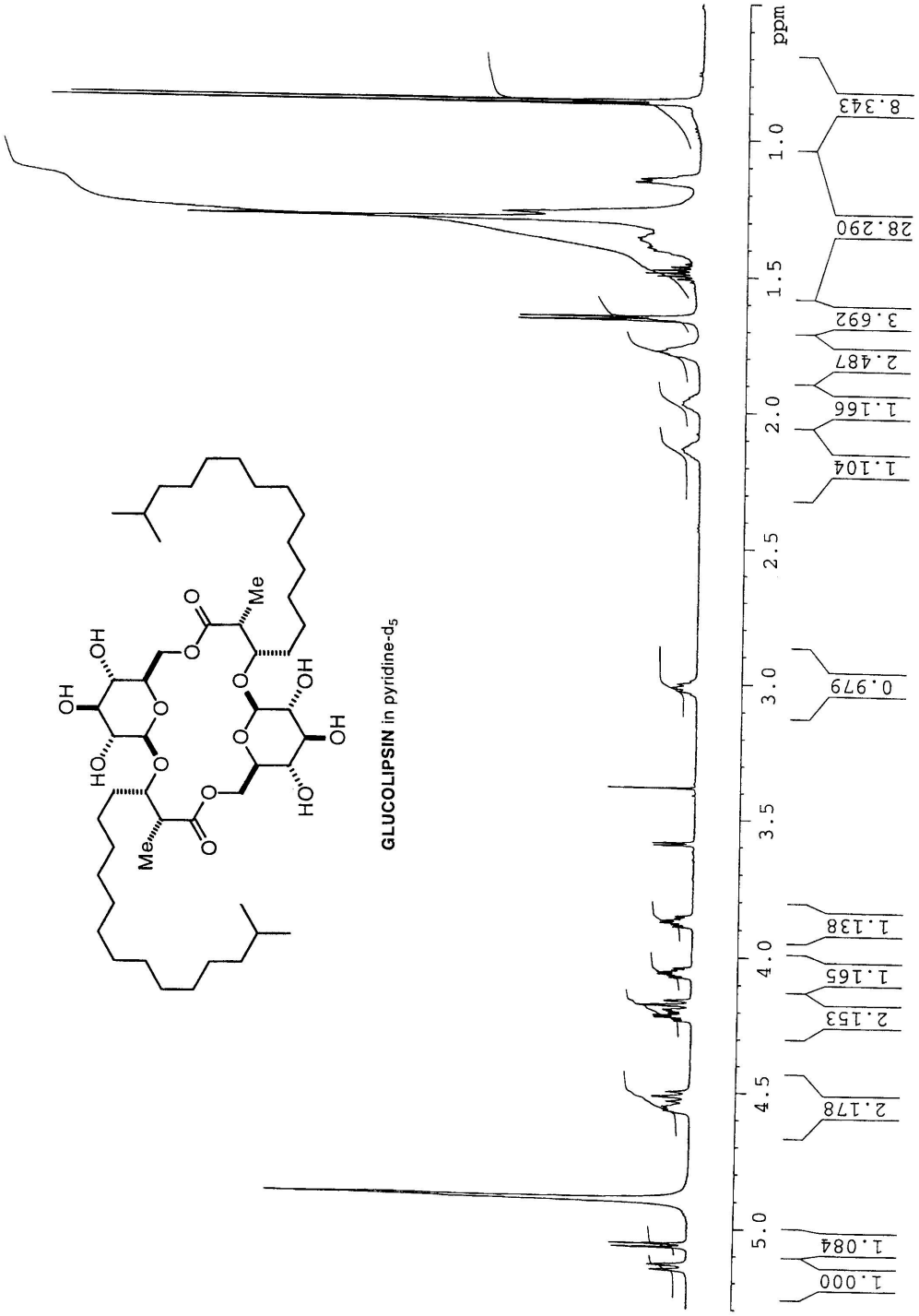
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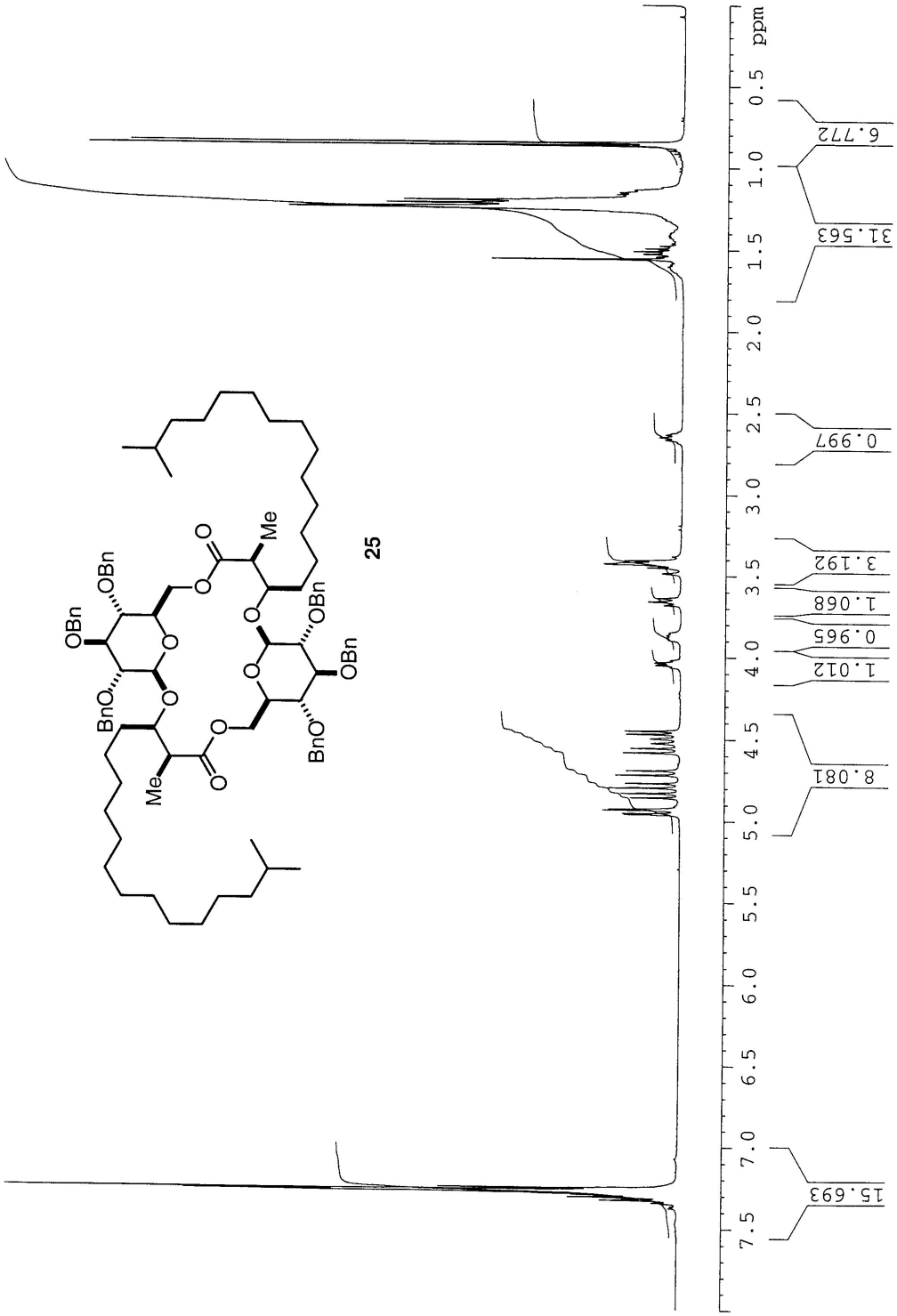
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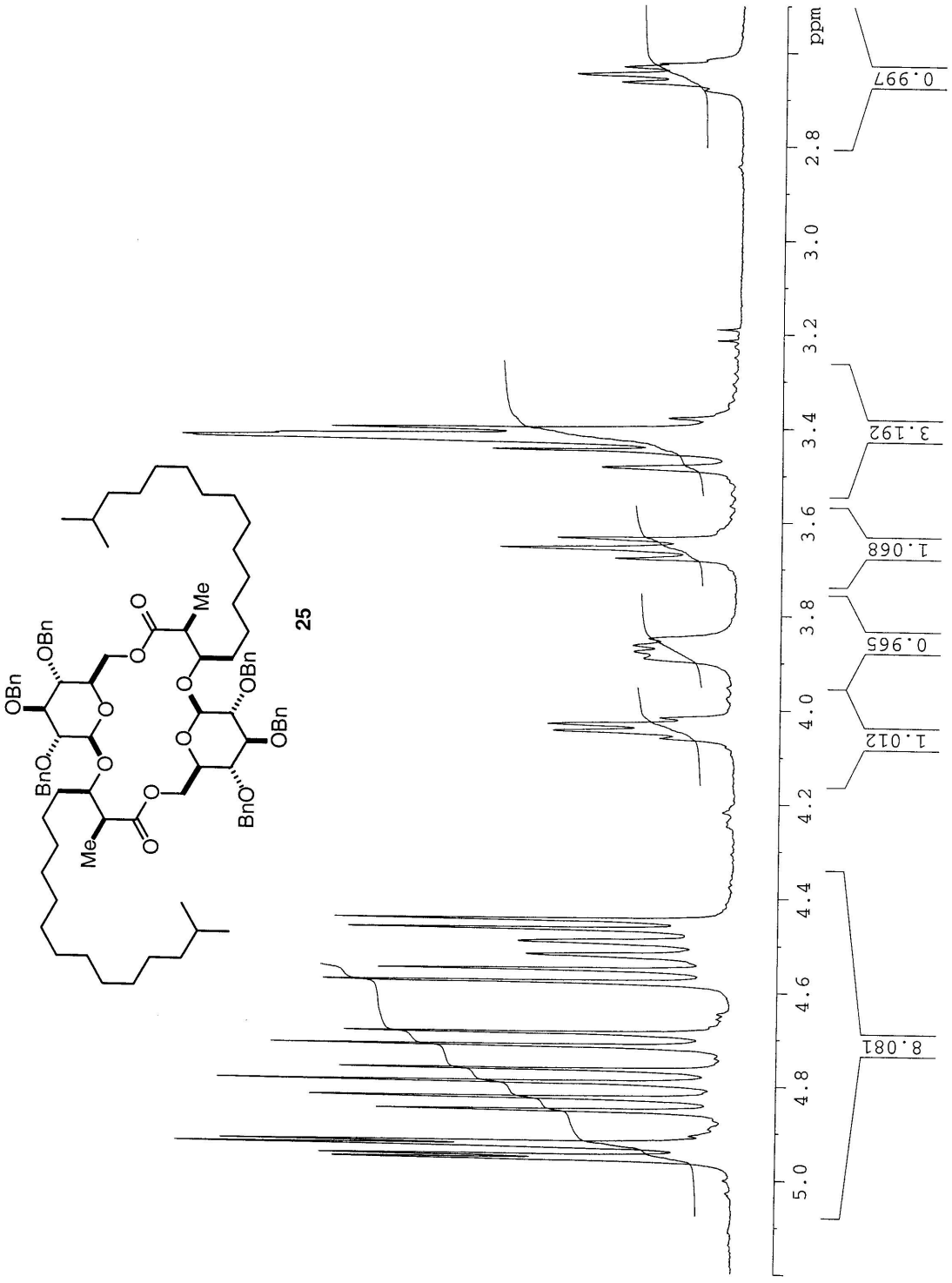
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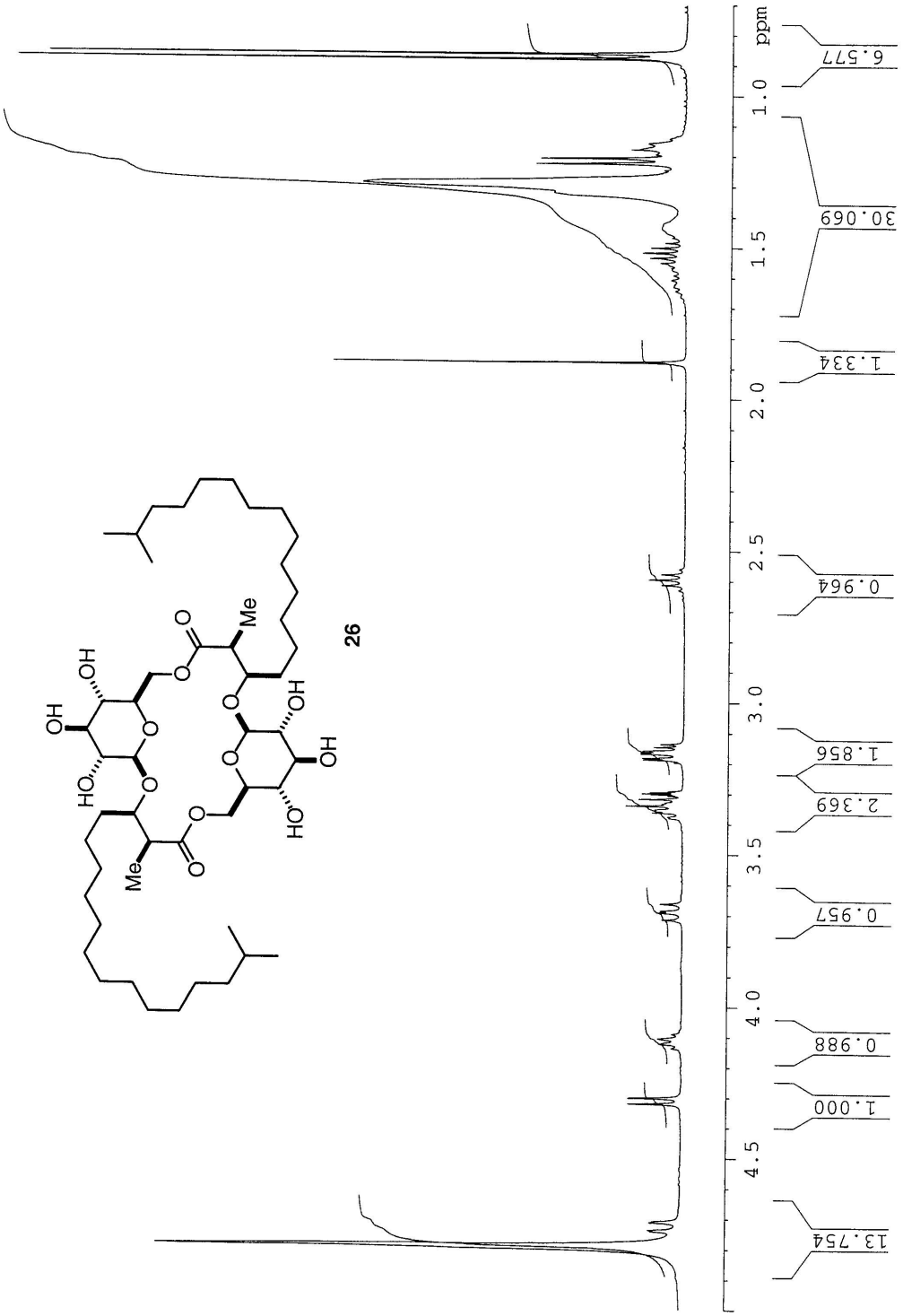
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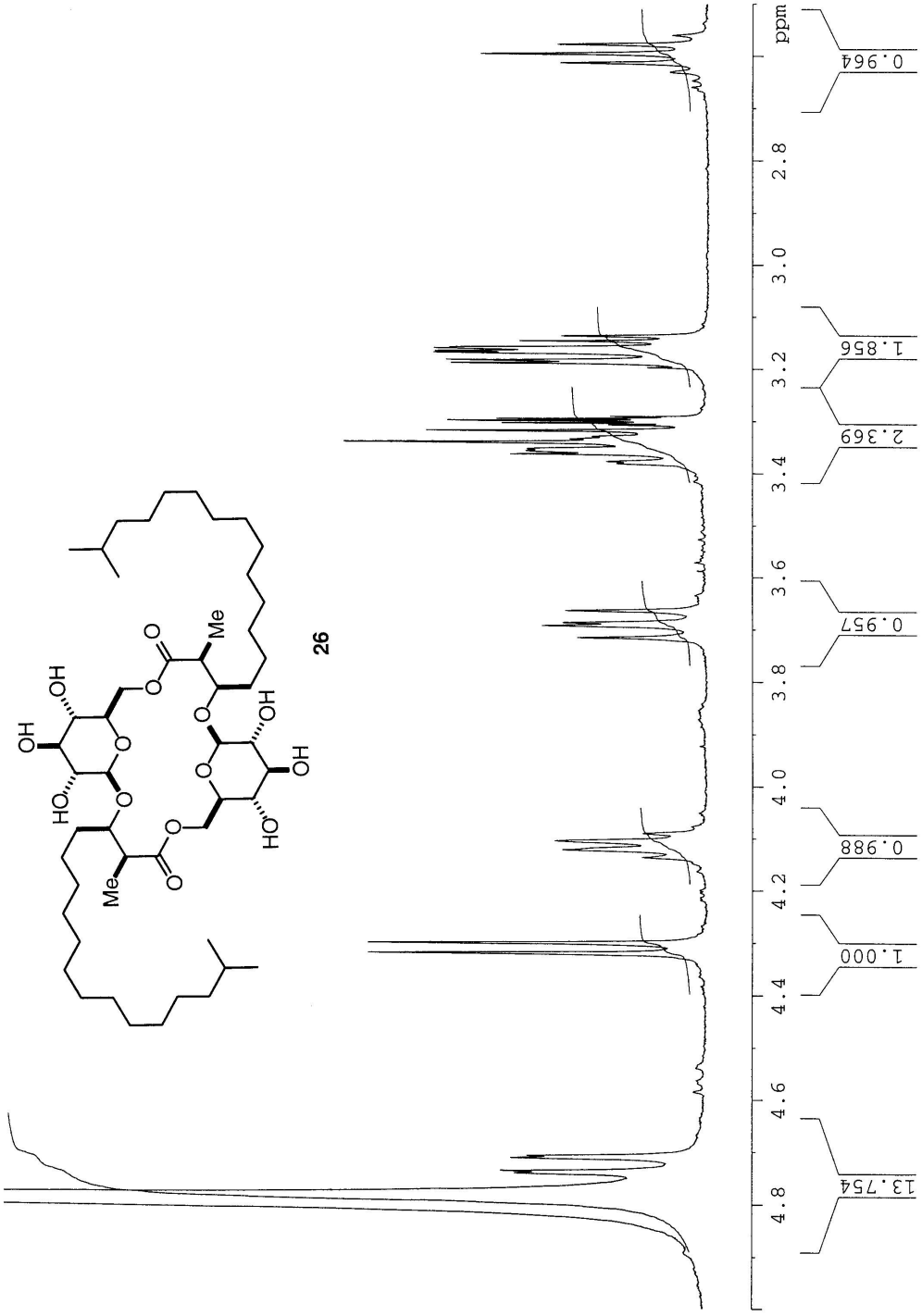
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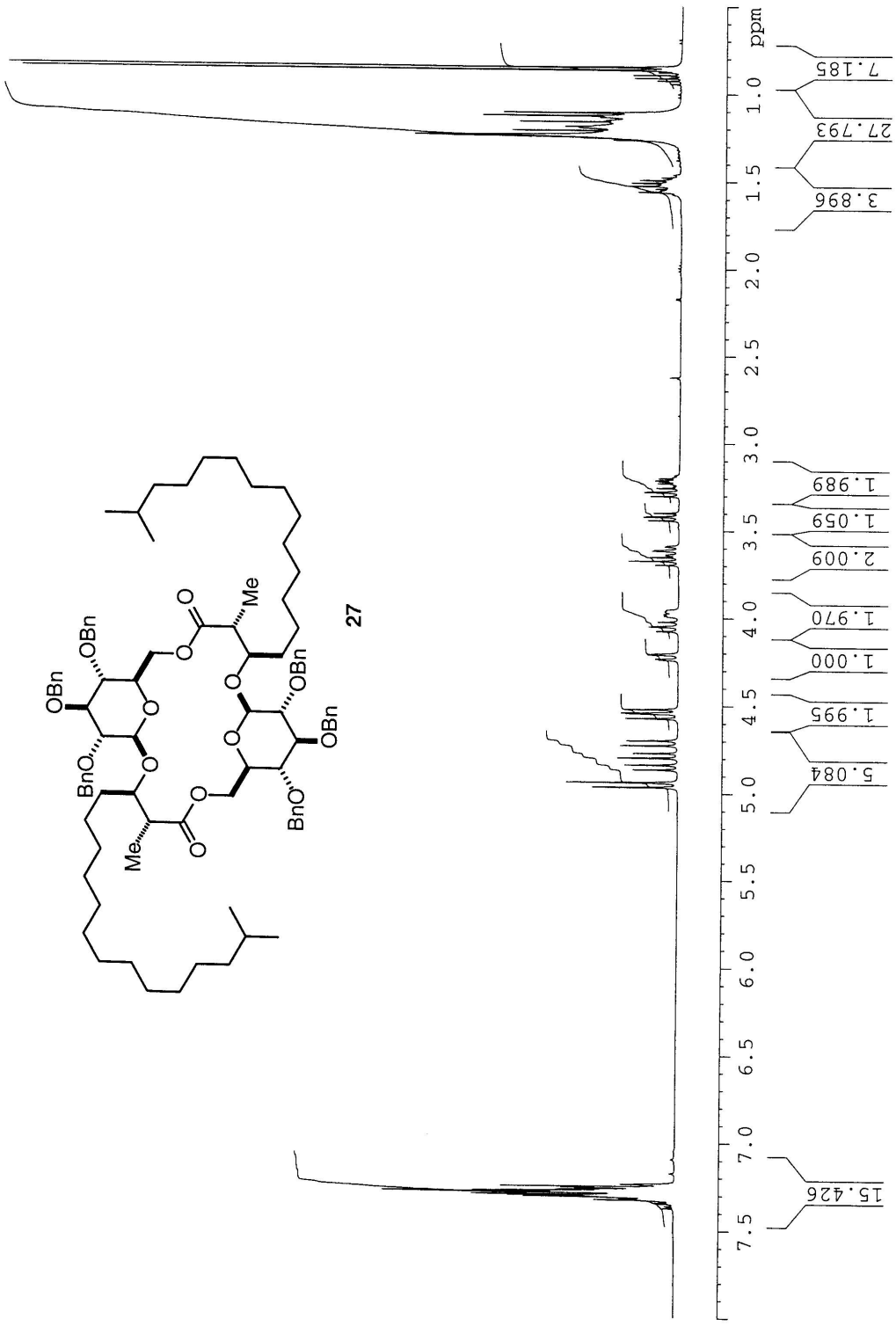
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6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
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1.000
1.970
2.009
1.059
1.989
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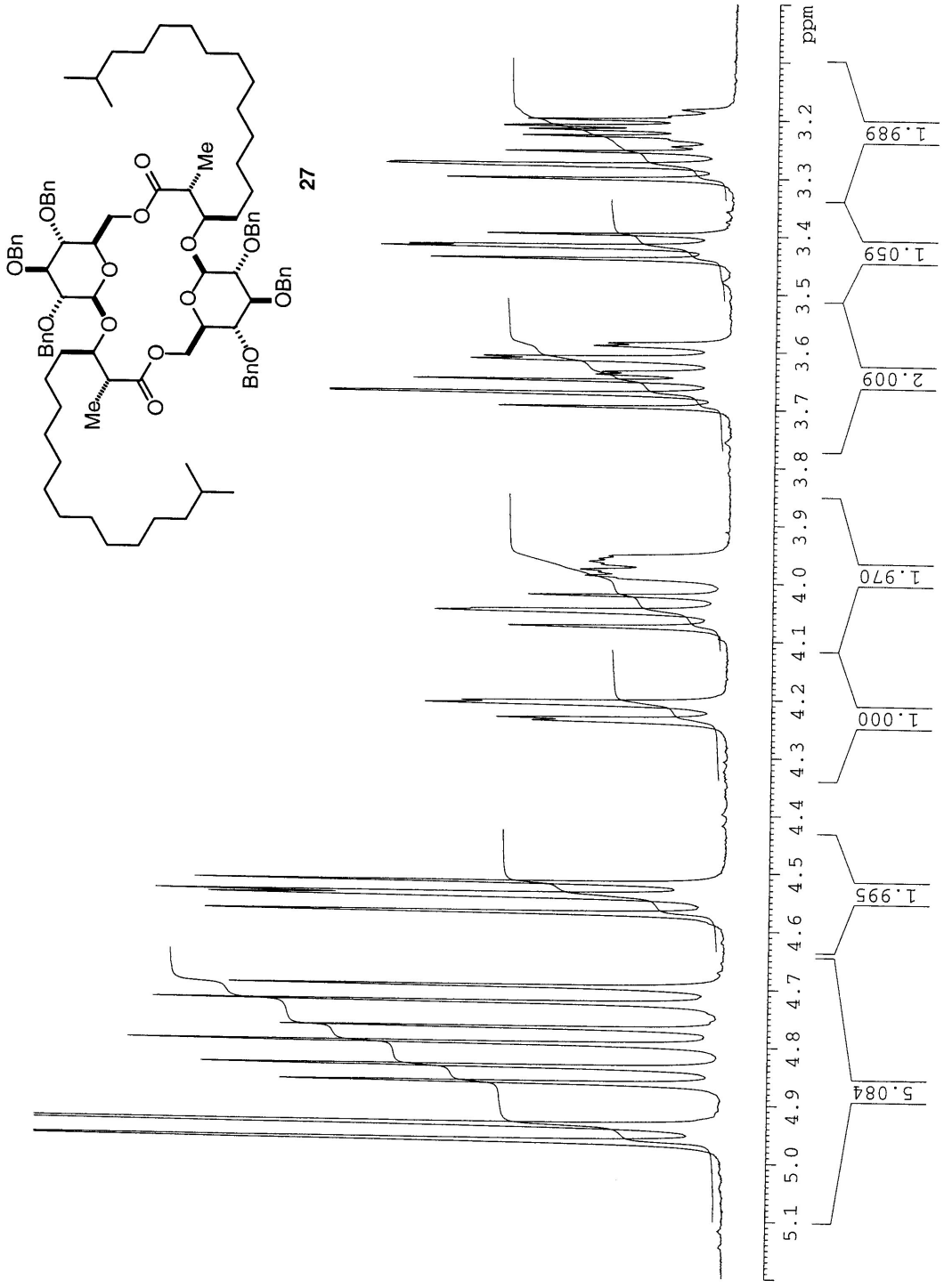
7.185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Me
Me
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OBn
BnO
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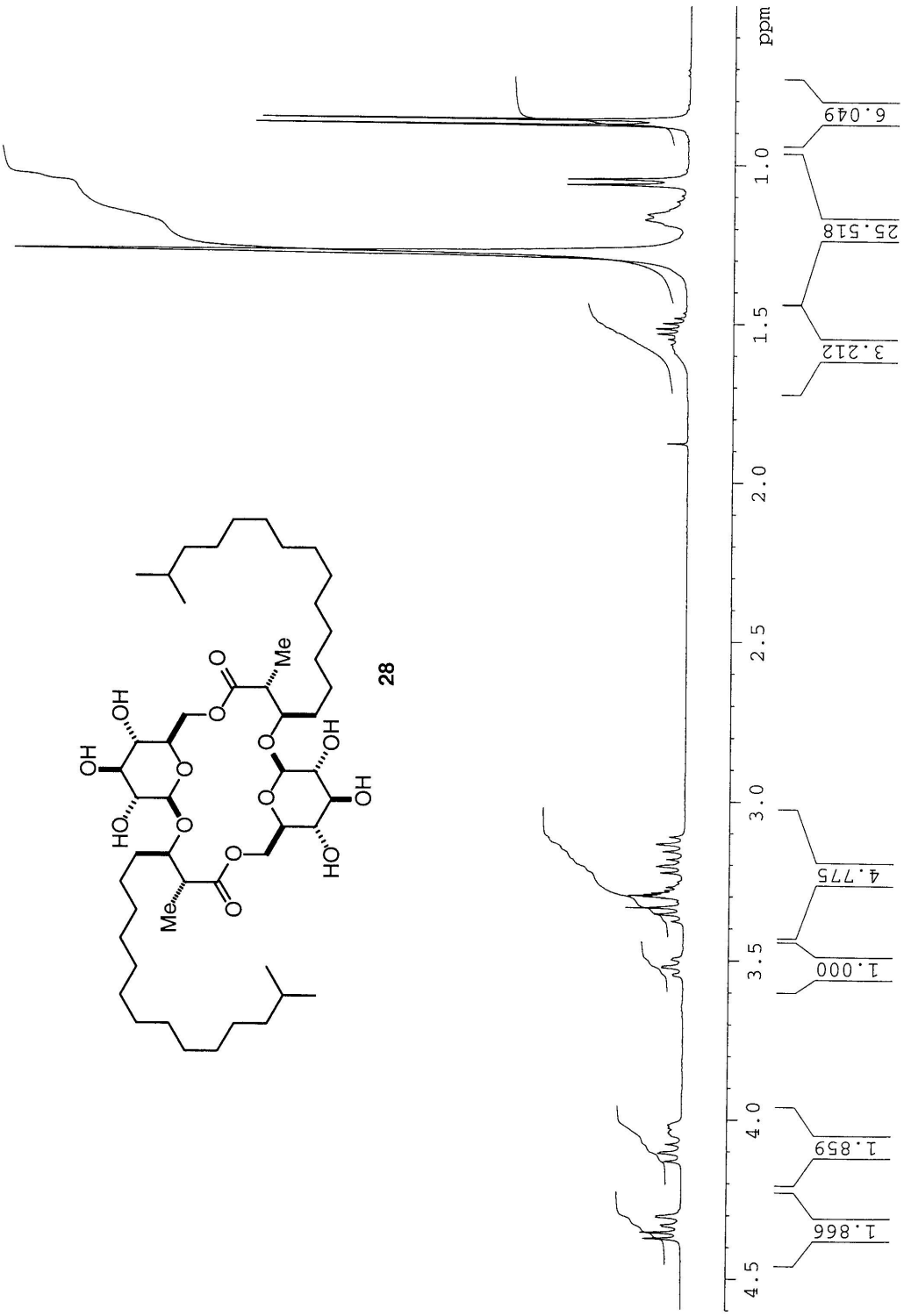
5.084
1.995
1.000
1.970
2.009
1.059
1.989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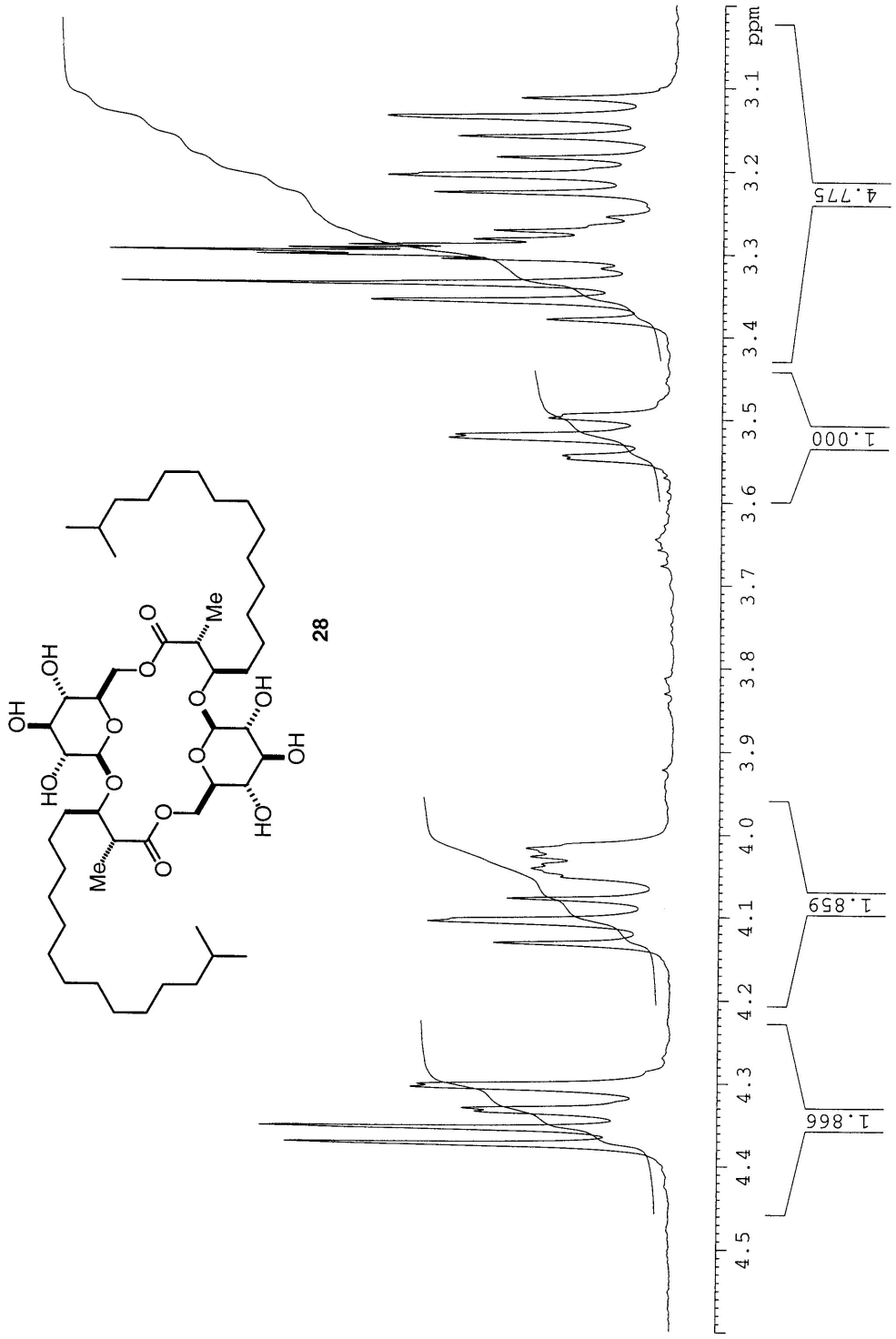
6.049


28
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HO
Me
Me
OH
OH
HO
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4.4
4.3
4.2
4.1
4.0
3.9
3.8
3.7
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3.5
3.4
3.3
3.2
3.1
ppm
1.866
1.859
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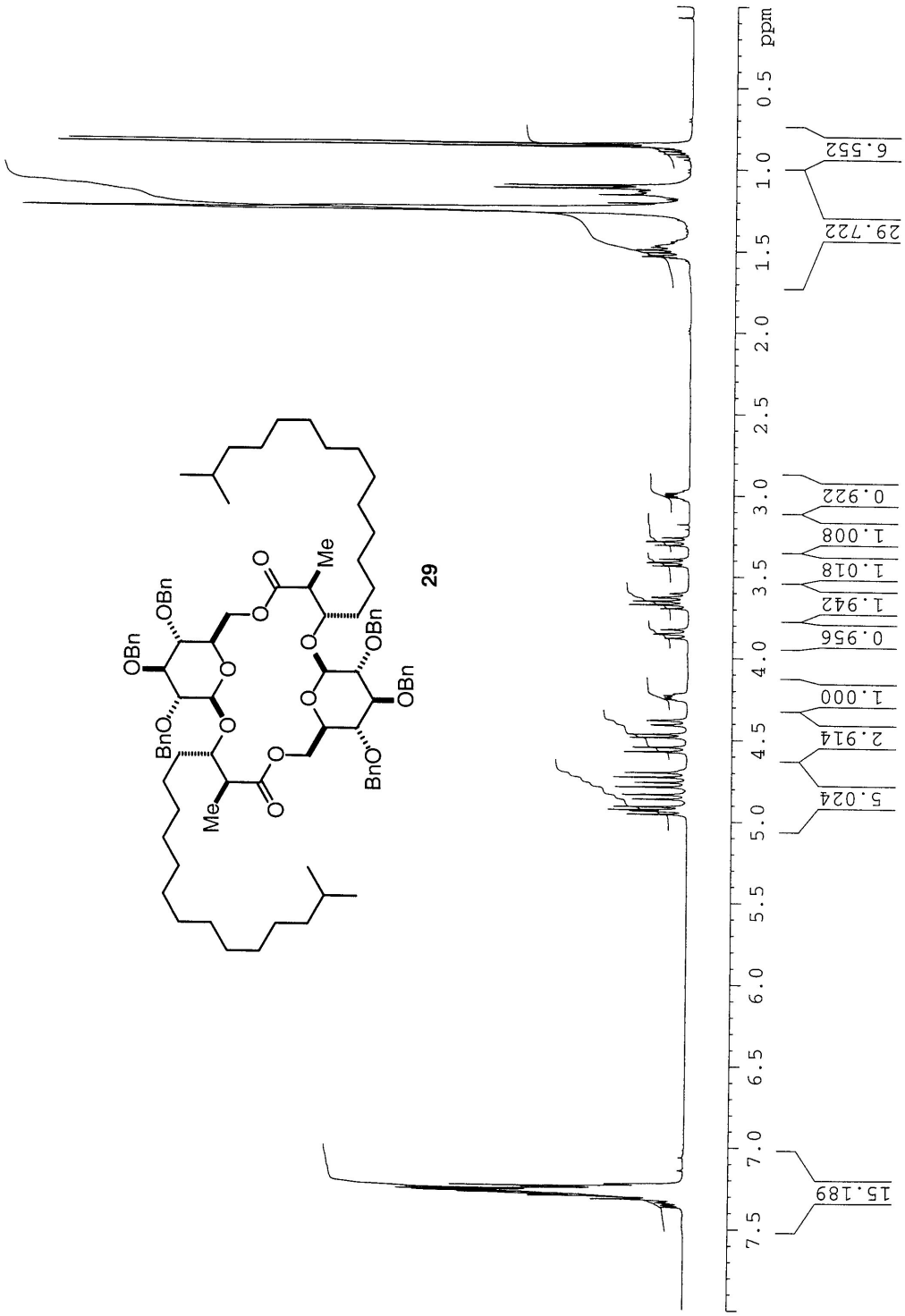
4.775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Me
Me
OBn
OBn
OBn
BnO
29
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1.942
1.018
1.008
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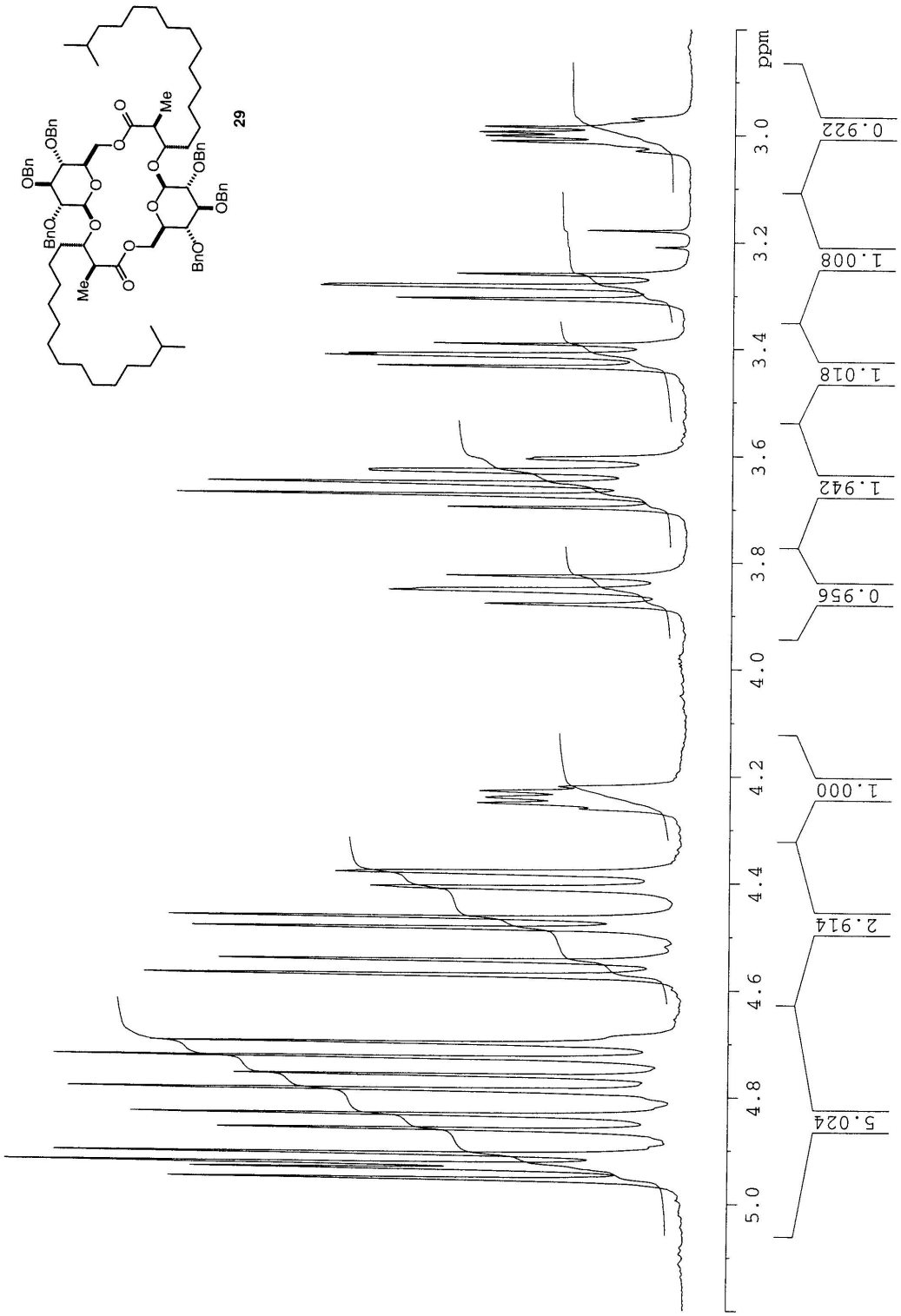
OBn
OBn
BnO
Me
O
O
Me
OBn
OBn
BnO
29
ppm
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4.8
4.6
4.4
4.2
4.0
3.8
3.6
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3.0
5.024
2.914
1.000
0.956
1.942
1.018
1.008
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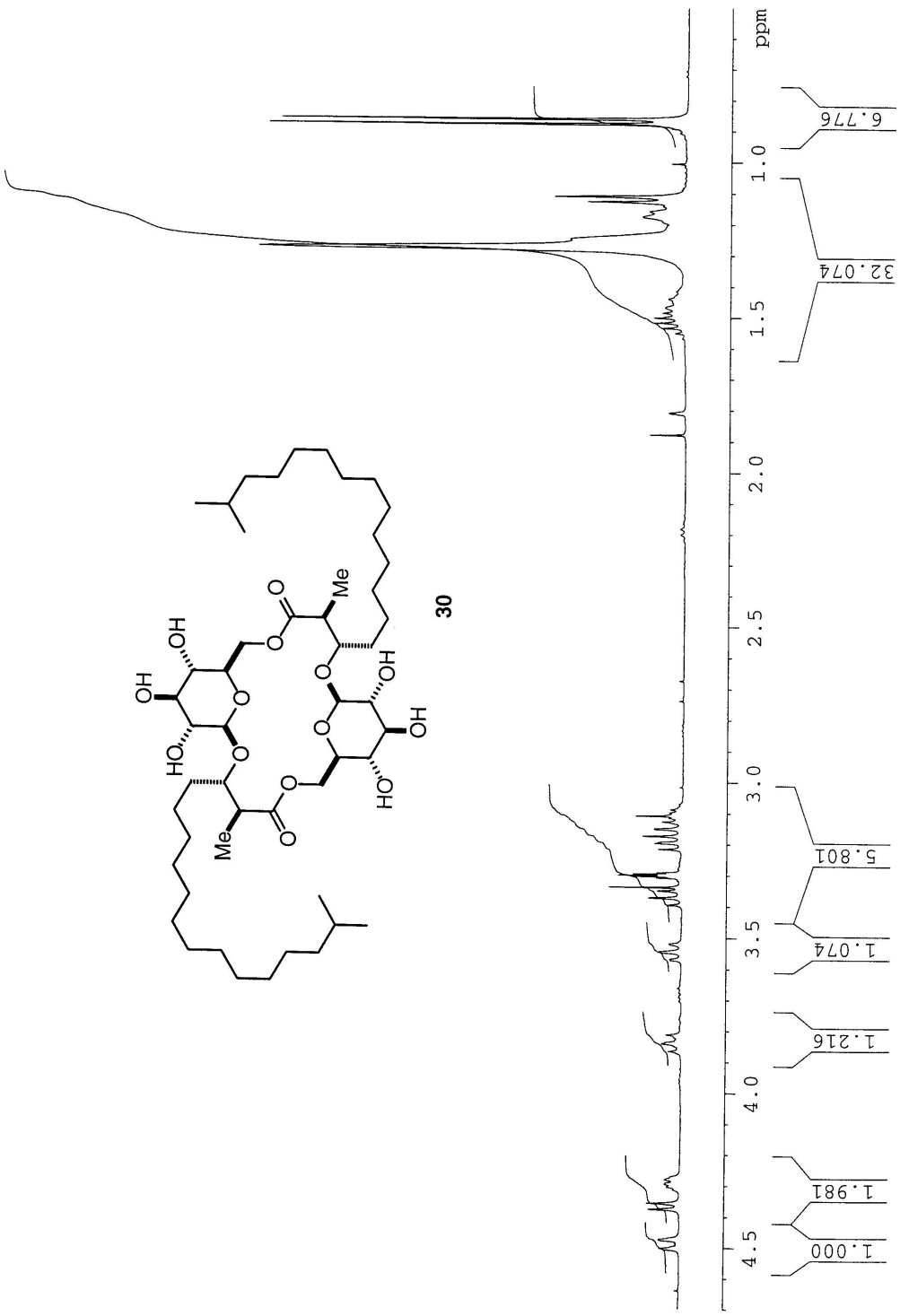
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3.0
2.5
2.0
1.5
1.0
1.000
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1.216
1.074
5.801
32.074
6.776
Me
Me
OH
OH
HO
HO
OH
HO
O
O
O
O
O
O
O
O
O
O

30