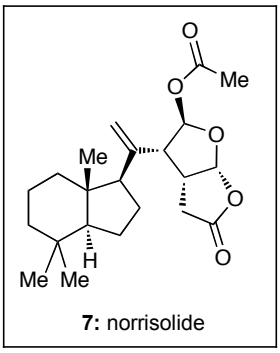
Chemical biology studies on norrisolide

Gianni Guizzunti,[b*] Thomas P. Brady,[a] Derek Fischer,[a] Vivek Malhotra,[c] and Emmanuel A. Theodorakis[a*]

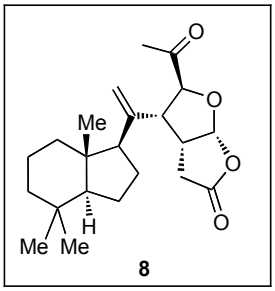
Supporting Information

General Chemical Techniques Compounds **1**, **3** and taxol were purchased from Sigma-Aldrich, **5** was purchased from Alexis Biochemicals and H-89 was purchased from BIOMOL Research Laboratories. Norrisolide was synthesized according to reference 23. All other chemical reagents were commercially obtained (Aldrich, Sigma Acros) at highest commercial quality and used without further purification except where noted. The synthesis of compounds **8-13** is described in references 16 and 23. The synthesis of compounds **14-18** is described in reference 25. The synthesis of compounds **19** and **21** is described in reference 26. Compounds **20** and **22** were synthesized by standard Pd(0)-catalyzed derivatization of iodinated compound **19**. Yields refer to chromatographically and spectroscopically (^{1}H NMR, ^{13}C NMR) homogeneous materials. Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60F-254) using UV light as the visualizing agent and 10% ethanolic phosphomolybdic acid (PMA) or *p*-anisaldehyde solution and heat as developing agents. E. Merck silica gel (60, particle size 0.040-0.063 mm) was used for flash chromatography. Preparative thin-layer chromatography separations were carried out on 0.25 or 0.50 mm E. Merck silica gel plates (60F-254). NMR spectra were recorded on Varian Mercury 400 and/or Unity 500 MHz instruments and calibrated using the residual undeuterated solvent as an internal reference. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad. High resolution mass spectra (HRMS) were recorded on a VG 7070 HS mass spectrometer under chemical ionization (CI) conditions or on a VG ZAB-ZSE mass spectrometer under fast atom bombardment (FAB) conditions.



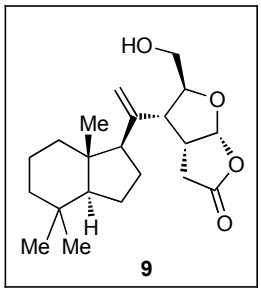
7: norrisolide

Norrisolide (**7**):[23] R_f= 0.6 (hex/ether: 3/7); $[\alpha]^{25}_D$: +3.5 (c= 0.13, CH_2Cl_2); ^{1}H NMR (400 MHz, C_6D_6) δ 6.63 (dd, *J*= 4.0, 1.6 Hz, 1H), 5.66 (dd, *J*= 6.4, 1.6 Hz, 1H), 4.90 (s, 1H), 4.77 (s, 1H), 2.70 (dd, *J*= 8.8, 3.6 Hz, 1H), 2.40-2.33 (m, 1H), 2.15 (dd, *J*= 18.0, 4.0 Hz, 1H), 1.76 (dd, *J*= 18.4, 10.8 Hz, 1H), 1.58 (s, 3H), 1.45-0.60 (m, 12H), 0.85 (s, 3H), 0.79 (s, 3H), 046 (s, 3H); ^{13}C NMR (100 MHz, C_6D_6) δ 173.5, 168.5, 143.4, 116.9, 107.1, 101.8, 58.7, 57.7, 50.0, 45.0, 41.7, 40.5, 38.6, 33.4, 33.3, 30.5, 24.2, 21.2, 20.7, 20.4, 19.9, 14.1; HRMS calcd for $C_{22}H_{32}O_5$ ($M-AcOH^+$) 316.2038, found 316.2051.



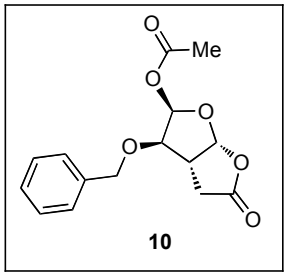
8

Compound **8**:[16] R_f= 0.3 (hex/ether: 1/1); $[\alpha]^{25}_D$: –4.51 (c= 0.52, CH_2Cl_2); IR (film) ν_{max} 2923, 1720, 1005 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.89 (d, *J*= 5.2 Hz, 1H), 5.14 (s, 1H), 5.12 (d, *J*= 4.8 Hz, 1H), 5.06 (s, 1H), 4.40 (d, *J*= 10.4 Hz, 1H), 3.37 (s, 3H), 3.22-3.14 (m, 1H), 2.84 (dd, *J*= 10.4, 8.0 Hz, 1H), 2.21 (s, 3H), 2.06-2.01 (m, 2H), 1.75-0.85 (m, 12H), 0.85 (s, 6H), 0.64 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.0, 142.7, 115.5, 108.4, 105.6, 84.0, 59.3, 58.1, 55.1, 50.4, 44.9, 44.4, 41.6, 38.9, 33.3 (2), 33.0, 26.5, 24.6, 20.7, 20.6, 19.8, 13.9; HRMS calcd for $C_{23}H_{36}O_4$ ($M+H^+$) 377.2691, found 377.2670.



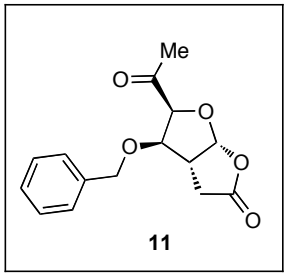
9

Compound **9**:[16] R_f= 0.2 (1/1: hex/ether); $[\alpha]^{25}_D$: +6.25 (c= 1.00, CH_2Cl_2); IR (film) ν_{max} 3462, 1025, 998 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.78 (d, *J*= 5.2 Hz, 1H), 5.11 (d, *J*= 4.8 Hz, 1H), 5.05 (s, 1H), 4.84 (s, 1H), 4.10-4.05 (m, 1H), 3.87 (dd, *J*= 12.0, 2.0 Hz, 1H), 3.55 (dd, *J*= 12.4, 4.0 Hz, 1H), 3.36 (s, 3H), 3.18-3.09 (m, 1H), 2.77 (dd, *J*= 10.8, 8.0 Hz, 1H), 2.08-0.81 (m, 14H), 0.85 (s, 6H), 0.69 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.2, 114.1, 107.8, 105.5, 80.2, 61.7, 59.3, 58.1, 55.0, 46.7, 44.7, 44.4, 41.7, 38.9, 33.3 (2), 32.9, 24.5, 20.7, 20.6, 19.8, 14.0; HRMS calcd for $C_{22}H_{36}O_4$ (M+Na^+) 387.3581, found 387.3599.



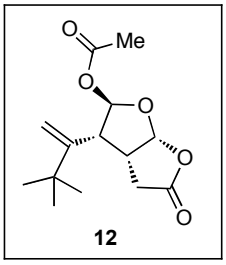
10

Compound **10**:[16] R_f= 0.30 (70% ether in hexanes); $[\alpha]^{25}_D$: +68.1 (c= 0.7, CH_2Cl_2); IR (film) ν_{max} 2919, 2854, 1788, 1745, 1374, 1235, 1138; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35 (3H, t, *J*= 7.2, 9.2 Hz), 7.30 (2H, d, *J*= 7.6 Hz), 6.45 (1H, d, *J*= 4.0 Hz), 6.04 (1H, d, *J*= 6.0 Hz), 4.63 (1H, d, *J*= 11.6 Hz), 4.487 (1H, d, *J*= 11.6 Hz), 3.88 (1H, qr, *J*= 4 Hz), 3.10 (1H, m), 2.79 (1H, dd, *J*= 9.2, 18.8 Hz), 2.48 (1H, dd, =2, *J*= 1.6, 18.8 Hz), 2.12 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.7, 169.2, 136.5, 128.6, 128.4, 127.8, 105.3, 95.1, 81.9, 73.5, 41.7, 33.2, 21.1; HRMS, calcd for $C_{15}H_{16}O_6$ (M+Na^+): 315.0845, found: 315.0859.



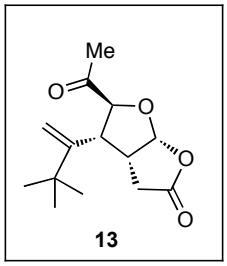
11

Compound **11**:[16] R_f= 0.40 (80% ether in hexanes); $[\alpha]^{25}_D$: –53.5 (c= 0.85, CH_2Cl_2); IR (film) ν_{max} 3634, 3528, 2918, 2861, 1780, 1731; ^1H NMR (400 MHz, $CDCl_3$) δ 7.34 (3H, t, *J*= 7.2, 10 Hz), 7.23 (2H, d, *J*= 6.4 Hz), 6.33 (1H, d, *J*= 5.6 Hz), 4.54 (2H, m), 4.46 (1H, d, *J*= 11.6 Hz), 4.15 (1H, d, *J*= 4 Hz), 3.23 (1H, q, *J*= 5.6, 6.0 Hz), 2.84 (1H, dd, *J*= 19.2, 11.6 Hz), 2.33 (1H, dd, *J*= 5.2, 18.8 Hz), 2.27 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.8, 173.5, 136.2, 128.5, 128.2, 127.6, 107.4, 85.4, 85.1, 72.2, 44.3, 31.1, 28.4; HRMS, calcd for $C_{15}H_{16}O_5$ (M+Cs^+): 409.0049, found: 409.0055.



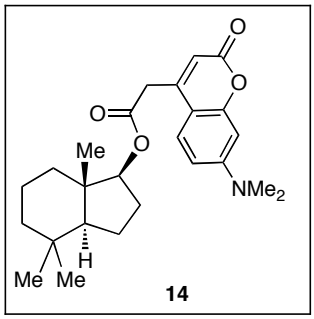
12

Compound **12**:[16] R_f= 0.5 (60% ether in hexanes). $[\alpha]^{25}_D$= +13.7, (c 0.3, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 6.24 (d, *J*= 5.6 Hz 1H), 5.42 (s, 1H), 4.87 (s, 1H), 4.48 (d, *J*= 10.8 Hz ,1H), 3.25 (m, 1H), 3.07 (t, *J*= 10.4 Hz, 1H), 2.68 (dd, *J*= 3.2, 18.8 Hz, 1H), 2.52 (dd, *J*= 10.8, 19.2 Hz, 1H), 2.23 (s, 3H), 1.03 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.2, 174.5, 151.2, 113.1, 107.7, 85.1, 45.6, 42.8, 36.6, 30.3, 28.8, 27.2, 19.9, 14.1; HRMS calcd for $C_{14}H_{20}O_4$ (M+Na^+) 275.1260, found 275.1281.



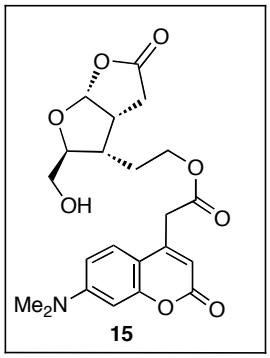
13

Compound **13**:[16] R_f= 0.4 (50% ether in hexanes); $[\alpha]^{25}_D$= +9.18, (c 0.43, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 6.44 (d, *J*= 5.2 Hz 1H), 5.65 (d, *J*= 6 Hz ,1H), 4.84 (s, 1H), 4.57 (s, 1H), 2.75 (m, 1H), 2.22 (m, 1H), 2.13 (dd, *J*= 5.2, 18 Hz, 1H), 1.65 (dd, *J*= 10.8, 18.8 Hz, 1H), 1.54 (s, 3H), 0.69 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.7, 168.6, 151.5, 136.1, 112.1, 106.8, 102.1, 47.3, 40.8, 36.3, 30.1, 28.4, 27.0, 20.3; HRMS calcd for $C_{14}H_{20}O_5$ (M+Na^+) 291.1209, found 291.1228.



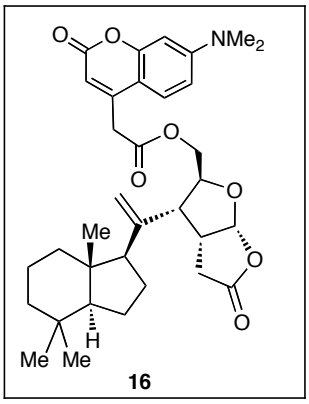
14

Compound **14**:[25] R_f= 0.4 (100% ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (d, J= 9.2 Hz, 1H), 6.60 (d, J= 8.8 Hz, 1H), 6.52 (s, 1H), 6.05 (s, 1H),4.54 (t, J= 8.4 Hz, 1 H), 3.67 (s, 2H), 3.05 (s, 6H), 2.09 (m, 1H) 1.60-1.09 (m, 6 H), 1.11-0.99 (m, 4H), 0.87 9s, 3H), 0.84 (s, 3H), 0.74 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.9, 161.7, 155.9, 152.9, 148.7, 125.4, 110.6, 108.9, 108.5, 98.4, 84.3, 52.6, 42.6, 41.3, 40.1, 38.6, 37.5, 33.0, 32.8, 26.2, 20.7, 20.2, 19.3, 12.6; HRMS FAB, calcd for $C_{25}H_{33}NO_4$ [M+]: 411.2410, found 411.2413.



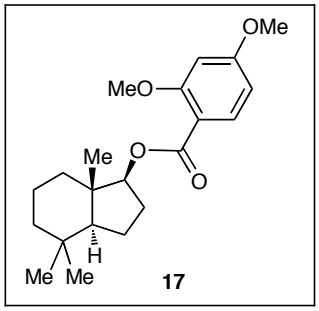
15

Compound **15**:[25] R_f= 0.3 (100% ether); $[\alpha]_{25}^{D}$= +9.2, c=0.21, CH_2Cl_2; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (d, J= 1.2 Hz, 1H), 6.63 (dd, J= 8.8, 2.4 Hz, 1H), 6.53 (d, J= 2.4 Hz, 1H), 6.05 (s, 1H), 5.99 (d, J= 5.6 Hz, 1H), 4.19-4.08 (m, 2H), 3.91-3.63 (m, 3H), 3.70 (s, 2H), 3.07 (s, 6H), 2.59-2.23 (m, 4H), 2.81-2.65 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.9, 166.8, 164.9, 125.5, 125.1, 110.7, 109.0, 106.7, 99.4, 82.4, 63.3, 61.0, 41.5, 40.1, 38.1, 37.5, 30.3, 29.7, 28.0, 25.7; HRMS, calcd for $C_{22}H_{25}NO_8$ [M+H$^+$] 432.1653, found: 432.1658.



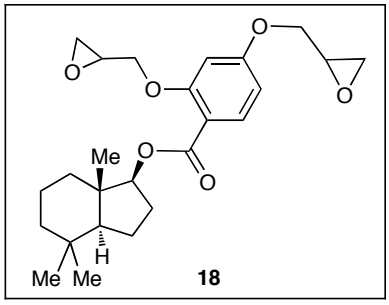
16

Compound **16**:[25] R_f= 0.3 (100% ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, J= 9.2 Hz, 1H), 6.63 (dd, J= 8.8, 2.8 Hz, 1H), 6.52 (d, J= 2.8 Hz, 1H), 6.05 (s, 1H), 6.00 (d, J= 5.6 Hz, 1H), 5.18 (s, 1H), 4.86 (s, 1H), 4.58 (dd, J= 12, 3 Hz, 1H), 4.18 (m, 1H), 4.05 (dd, J= 12.4, 5.2 Hz, 1H), 3.72 (s, 2H), 3.13 (m, 1H), 3.06 (s, 6H), 2.64-2.57 (m,2H), 2.49-2.42 (m, 1H), 1.92 (m, 1H), 1.71-0.99 (m, 11H), 0.83 (s, 3H), 0.83 (s, 3H), 0.52 (s, 3H); HRMS FAB, calcd for $C_{34}H_{43}NO_7$ [M+] 577.3040, found: 577.3041.

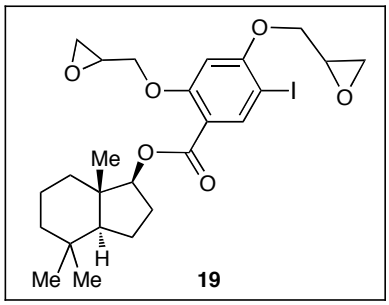


17

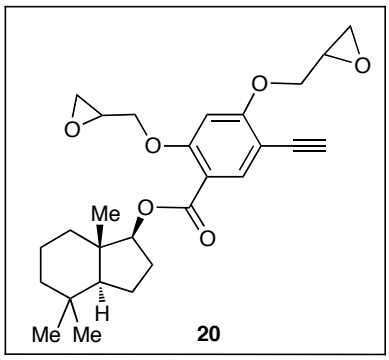
Compound **17**:[25] R_f= 0.7 (50% ether in hexanes); $[\alpha]_{25}^{D}$= +13.2 (c=0.4, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, J= 8.8 Hz, 1H), 6.49 (d, J= 2 Hz, 1H), 6.47 (s, 1H), 4.74 (t, J= 9.2 Hz, 1H), 3.87 (s, 3H), 3.84 (s, 3H), 2.23 (m, 1H), 1.69-1.03 (m, 10H), 0.99 (s, 3H), 0.90 (s, 3H), 0.87 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.5, 164.1, 161.4, 133.7, 112.9, 104.4, 98.9, 83.2, 55.8, 55.4, 52.7, 42.8, 41.5, 37.7, 33.1, 32.9, 26.7, 20.8, 20.4, 19.4, 13.0; HRMS, calcd for $C_{21}H_{30}O_4$ [M+Na$^+$]: 369.2042, found 369.2044.



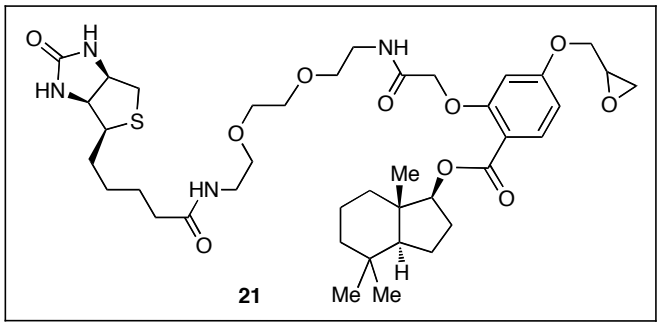
Compound **18**:[25] R_f= 0.3 (50% ether in hexanes); $[\alpha]_{25}^{D}$= +7.9 (c= 0.3, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, J= 8.4 Hz, 1H), 6.5 (m, 2H), 4.74 (m, 1H), 4.30-4.24 (m, 2H), 4.06-4.01 (m, 1H), 3.97-3.93 (m, 1H), 3.40-3.34 (m, 2H), 2.93- 2.90 (m, 2H), 2.86 (m, 1H), 2.76 (m, 1H), 2.24 (m, 1H), 1.75-1.34 (m, 6H), 1.26- 1.01 (m, 4H), 0.99 (s, 3H), 0.89 (s, 3H), 0.86 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.6, 160.0, 133.8, 113.9, 105.9, 105.8, 100.9, 83.4, 69.5, 68.9, 52.7, 50.1, 49.9, 44.9, 44.6, 42.8, 41.4, 37.7, 33.1, 32.8, 26.6, 20.8, 20.3, 19.4, 13.1; HRMS, calcd for $C_{25}H_{34}O_6$ [M+Na$^+$]: 453.2253, found 453. 2252.



Compound **19**:[26] R_f= 0.3 (70% ether in hexanes); $[\alpha]^{25}_{D}$= +22.2 (c= 0.1, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (s, 1H), 6.60 (d, J= 6.4 Hz, 1H), 4.73 (t, J= 7.6 Hz, 1H), 4.44-4.33 (m, 2H), 4.09-3.99 (m, 2H), 3.38 (m, 2H), 2.95- 2.87 (m, 4H), 2.83 (m, 1H), 2.22 (m, 1H), 1.75-1.01 (m, 11H), 0.99 (s, 3H), 0.90 (s, 3H), 0.86 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.2, 160.8, 160.5, 142.3, 115.7, 99.3, 83.7, 70.3, 69.8, 52.7, 50.1, 50.0, 49.9, 44.7, 44.5, 41.4, 37.7, 33.0, 32.8, 29.6, 26.5, 20.7, 20.3, 19.4, 13.1; HRMS, calcd for $C_{25}H_{33}IO_6$ [M+H$^+$]: 557.1400, found 557.1412.



Compound **20**: R_f = 0.3 (R_f = 0.4, 40% ether in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.86 (s, 3H), 0.90 (s, 3H), 0.99 (s, 3H), 1.01-1.63 (m, 8H), 1.69-1.77 (m, 1H), 2.18-2.26 (m, 1H), 2.82-2.26 (m, 1H), 2.82-2.88 (m, 2H), 2.92 (app. q, J = 4.4 Hz, 2H), 3.22 (s, 3H), 3.36-3.42 (m, 2H), 4.00-4.12 (m, 2H), 4.33-4.50 (m, 2H), 4.70-4.46 (m, 1H), 6.65 (app. d, J = 8.4 Hz, 1H), 7.99 (s, 1H); ^{13}C NMR (100 MHz, C_6D_6): δ 162.7, 159.7, 137.4, 137.3, (~ 127, signals obscured by C_6H_6), 113.8, 104.2, 98.4, 82.6, 80.2, 78.3, 69.2, 69.0, 68.8, 68.6, 51.6, 48.9, 48.8, 48.77, 48.71, 43.14, 43.07, 42.92, 42.86, 42.0, 40.6, 36.92, 36.87, 32.1, 31.8, 31.3, 30.9, 29.3, 29.2, 29.1, 28.8, 25.9, 25.86, 22.1, 22.0, 19.9, 19.4, 18.8, 13.4, 13.3, 12.2; HR-EI-MS: *m/z* calcd. for $C_{27}H_{34}O_6$: [M]$^+$ 454.2350, found: 454.2356.



Compound **21**: R_f= 0.3 (70% ether in hexanes); $[\alpha]^{25}_{D}$= +17.9 (c= 0.3, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 (bs, 1H), 7.88 (d, J= 8.8 Hz, 1H), 6.82 (m, 1H), 6.56 (dd, J= 8.8, 2.4 Hz, 1H), 6.48 (d, J= 2.4 Hz, 1H), 6.36 (s, 1H), 5.37 (s, 1H), 4.69 (t, J= 8 Hz, 1H), 4.57 (s, 2H), 4.48 (m, 1H), 4.32 (dd, J= 11.2, 2.8 Hz, 1H), 4.29 (m, 1H), 3.95 (dd, J= 10.8, 5.6 Hz, 1H), 3.67-3.53 (m, 12H), 3.43-3.34 (m, 2H), 3.11 (m, 1H), 2.95-2.86 (m, 3H), 2.78-2.68 (m, 2H) 2.21 (m, 2H), 2.01 (bs, 2H) 1.75-1.01(m, 13H), 0.99 (s, 3H), 0.90 (s, 3H), 0.87 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.3, 168.5, 164.6, 163.2, 159.6, 133.6, 112.5, 106.9, 100.8, 83.2, 70.2, 70.1, 69.9, 69.4, 69.1, 67.9, 61.7, 60.1, 55.2, 52.8, 49.9, 44.5, 43.8, 41.4, 40.5, 39.1, 38.9, 37.8, 35.9, 33.1, 32.9, 28.2, 28.0, 26.6, 25.6, 20.7, 20.3, 20.2, 19.4, 13.1; HRMS, calcd for $C_{40}H_{60}N_4O_{10}S$ [M+H$^+$]: 789.41084, found 789.4170.