

Supporting Information for

Synthesis (and Alternative Proof of Configuration) of the Scyphostatin C(1')-C(20') Trienoyl Fragment

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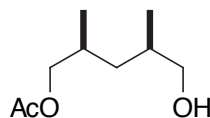
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General Information.

All reactions requiring anhydrous conditions were carried out in oven dried glassware under an argon atmosphere using freshly distilled solvents. ^1H and ^{13}C NMR spectra were recorded on a Varian VI-500 spectrometer. Proton chemical shifts are referenced to TMS (0.00ppm) for spectra collected in CDCl_3 and to residual CHCD_2OD (3.31 ppm) for spectra taken in CD_3OD . Carbon chemical shifts are referenced to CDCl_3 (77.00 ppm) and CD_3OD (49.49 ppm). Infrared (IR) spectra were obtained in a Prospect MIDAC FT-IR spectrometer. High resolution mass spectra were recorded either on a VG 7070E-HF, or a Finnegan MAT 95 instrument. Optical rotations were measured on a JASCO-DIP-370 polarimeter using a 3.5 i.d. x 50 mm cell.

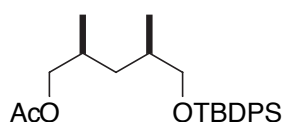
Note that roman numerals (*i - iii*) have been assigned to intermediates not shown in the paper.



(+)-3

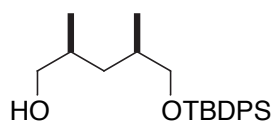
To the *meso*-2,4-dimethyl-1,5-pentanediol (8.50 g, 0.064 mol) in THF (285 mL) was added water (360 μL), Porcine Pancreatic Lipase (24.8 g, purchased from Sigma), and vinyl acetate (57.2 mL, 0.615 mol). This mixture was stirred at room temperature and monitored by ^1H NMR spectroscopy until the ratio of mono acetate to bis acetate was ~38:62 (7

hours). The reaction mixture was filtered, concentrated, and purified on silica gel [2:1 to 1:1 (hexanes: ethyl acetate) gradient elution] to give 4.15g (37%) of the mono acetate **(+)-3** as a colorless oil. $[\alpha]_D^{25} = +9.31$ (c 1.31, CHCl_3), 92% *ee* by Mosher Analysis; ^1H NMR (500 MHz, CDCl_3): δ 3.97 (dd, $J = 11.0, 5.0$ Hz, 1H), 3.86 (dd, $J = 11.0, 7.0$ Hz, 1H), 3.51 (dd, $J = 10.5, 5.5$ Hz, 1H), 3.42 (dd, $J = 10.5, 6.5$ Hz, 1H), 2.06 (s, 3H), 1.90 (m, 1H), 1.74 (m, 1H), 1.44 (m, 1H), 1.00 (m, 1H), 0.96 (d, $J = 6.5$ Hz, 3H), and 0.95 (d, $J = 6.5$ Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3): δ 171.1, 68.9, 67.1, 36.9, 32.5, 29.5, 20.4, 17.4, and 16.9; IR (thin film): 3431, 2957, 2924, 1738, 1462, 1391, 1371, 1243, and 1030 cm^{-1} .



i

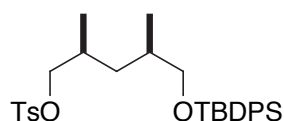
To a solution of *tert*-butyldiphenylsilyl chloride (5.95 mL, 22.9 mmol), triethylamine (3.80 mL, 27.3 mmol), and DMAP (244 mg, 2.00 mmol) in CH_2Cl_2 (25 mL) at 0°C was added alcohol **(+)-3** dropwise in CH_2Cl_2 (5 mL). The reaction mixture was allowed to warm to room temperature and stirred for 6 h. This mixture was diluted with CH_2Cl_2 , washed with 1N HCl and saturated NaHCO_3 , and dried with Na_2SO_4 . The organic extract was concentrated to give 8.90 g (99%) of the TBDPS protected mono acetate **i** as a colorless oil. ^1H NMR (500 MHz, CDCl_3): δ 7.66 (m, 4H), 7.44-7.36 (m, 6H), 3.93 (dd, $J = 10.5, 5.5$ Hz, 1H), 3.80 (dd, $J = 10.5, 6.5$ Hz, 1H), 3.49 (dd, $J = 10.0, 5.5$ Hz, 1H), 3.43 (dd, $J = 10.0, 6.0$ Hz, 1H), 2.03 (s, 3H), 1.83 (m, 1H), 1.74 (m, 1H), 1.52 (m, 1H), 1.05 (s, 9H), 0.94 (d, $J = 6.5$ Hz, 3H), 0.94 (m, 1H), and 0.89 (d, $J = 6.5$ Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3): δ 171.2, 135.6, 133.8, 130.0, 127.7, 69.3, 68.5, 37.3, 32.3, 30.0, 26.8, 20.9, 19.2, 17.6, and 17.5; IR (thin film): 3070, 3049, 2958, 2857, 1739, 1471, 1427, 1389, 1364, 1238, 1189, and 1112 cm^{-1} ; $[\alpha]_D^{23} = +7.23$ (c 2.24, CHCl_3); HR-FABMS: m/z calcd for MH^+ ($\text{C}_{25}\text{H}_{37}\text{O}_3\text{Si}$) 413.2496, found 413.2512



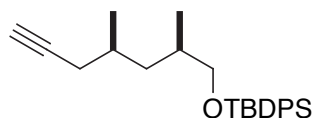
ii

The TBDPS protected mono acetate **i** (8.90 g, 21.6 mmol) was refluxed overnight with K_2CO_3 (9.02 g, 65.0 mmol) in a 1:1 (v/v) mixture of methanol and water (200

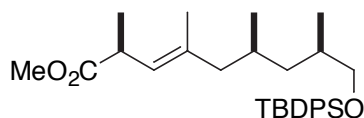
mL). The mixture was neutralized with concentrated HCl, extracted with CH₂Cl₂, dried with Na₂SO₄, and concentrated. Purification on silica gel (6:1, hexanes: ethyl acetate) gave 7.00 g (88%) of **ii** as a colorless oil. ¹H NMR (500 MHz, CDCl₃): δ 7.66 (m, 4H), 7.44-7.36 (m, 6H), 3.51 (dd, J = 10.0, 5.5 Hz, 1H), 3.47 (dd, J = 10.5, 5.5 Hz, 1H), 3.42 (dd, J = 10.0, 6.5 Hz, 1H), 3.50 (dd, J = 10.5, 6.5 Hz, 1H), 1.74 (m, 1H), 1.63 (m, 1H), 1.46 (m, 1H), 1.05 (s, 9H), 0.95 (d, J = 6.5 Hz, 3H), 0.92 (m, 1H), and 0.88 (d, 6.5 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃): δ 135.6, 133.9, 129.5, 127.6, 68.7, 68.2, 37.1, 33.1, 26.9, 26.5, 19.3, 17.9, and 17.4; IR (thin film): 3353, 3073, 3053, 2954, 2849, 1461, 1421, 1077, and 813 cm⁻¹; [α]²³_D = +0.14 (c 2.7, CHCl₃); HR-FABMS: *m/z* calcd for MH⁺ (C₂₃H₃₅O₂Si) 371.2406, found 371.2401.

**iii**

To a solution of alcohol **ii** (7.00 g, 18.9 mmol) in CH₂Cl₂ (20.0 mL), was added *p*-toluenesulfonyl chloride (3.78 g, 19.8 mmol), triethylamine (8.36 ml, 60.0 mmol), and DMAP (24.0 mg, 0.20 mmol). After stirring for 4 h at room temperature, the reaction mixture was diluted with CH₂Cl₂, poured into saturated aqueous NH₄Cl, extracted with CH₂Cl₂, dried with Na₂SO₄, and concentrated. Purification on silica gel (7:1, hexanes: ethyl acetate) gave 9.80 g (99%) of tosylate **iii** as a pale yellow oil. ¹H NMR (500 MHz, CDCl₃): δ 7.76 (m, 2H), 7.63 (m, 4H), 7.44-7.35 (m, 6H), 7.30 (m, 2H), 3.87 (dd, J = 9.4, 5.2 Hz, 1H), 3.72 (dd, J = 9.4, 7.0 Hz, 1H), 3.43 (dd, J = 9.9, 5.4 Hz, 1H), 3.36 (dd, J = 9.9, 6.0 Hz, 1H), 2.43 (s, 3H), 1.82 (m, 1H), 1.63 (m, 1H), 1.38 (m, 1H), 1.05 (s, 9H), 0.91 (m, 1H), 0.88 (d, J = 6.7 Hz, 3H), and 0.85 (d, J = 6.7 Hz, 1H); ¹³C NMR (125 MHz, CDCl₃): δ 144.5, 135.5, 134.7, 133.7, 129.7, 129.5, 127.8, 127.5, 75.0, 68.3, 36.6, 32.7, 30.2, 26.8, 21.5, 19.1, 17.5, and 17.1; IR (thin film): 3067, 2959, 2933, 2860, 2360, 1465, 1362, 1179, 1107, 964, and 703 cm⁻¹; [α]²³_D = +4.44 (c 2.70, CHCl₃); HR-FABMS: *m/z* calcd for MH⁺ (C₃₀H₄₁O₄SSi) 525.2495, found 525.2534.

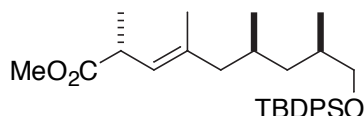
**4**

To a stirred solution of trimethylsilylacetylene (7.95 mL, 56.0 mmol) in THF (12 mL) at -78°C was added *n*-BuLi (2.47 M in hexanes, 22.6 mL, 56.0 mmol). After one hour, tosylate **iii** dissolved in THF (8 mL) was added dropwise. The reaction was warmed to 0°C , DMSO (20 mL) was added, and the mixture was allowed to warm to room temperature. After 3 h the reaction mixture was quenched by the careful addition of water, and the product was extracted with hexanes, dried with Na_2SO_4 , and concentrated. The residue was re-dissolved in methanol (20 mL) and stirred with K_2CO_3 (8.29 g, 0.060 mol) for another 2 h. Methanol was removed *in vacuo*, the residue was partitioned between diethyl ether and water, and the organic layer was dried with Na_2SO_4 and concentrated. Purification on silica gel (19:1, hexanes: ethyl acetate) gave 7.10 g (67%, for 2 steps) of alkyne **4** as a yellow oil. ^1H NMR (500 MHz, CDCl_3): δ 7.66 (m, 4H), 7.44–7.36 (m, 6H), 3.50 (dd, $J = 10.0, 5.0$ Hz, 1H), 3.42 (dd, $J = 10.0, 6.0$ Hz, 1H), 2.17 (ddd, $J = 7.5, 5.0, 3.0$ Hz, 1H), 2.13 (ddd, $J = 7.5, 5.0, 3.0$ Hz, 1H), 2.02 (ddd, $J = 10.0, 7.5, 3.0$ Hz, 1H), 1.98 (ddd, $J = 10.0, 7.5, 3.0$ Hz, 1H), 1.93 (t, $J = 3.0$ Hz, 1H), 1.72 (m, 2H), 1.51 (m, 1H), 1.05 (s, 9H), 1.00 (m, 1H), 0.96 (d, $J = 6.5$ Hz, 3H), and 0.93 (d, $J = 7.0$ Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3): δ 135.6, 133.9, 129.5, 127.6, 83.1, 69.2, 68.8, 39.8, 33.1, 29.6, 26.9, 25.5, 20.0, 19.3, and 17.5; IR (thin film): 3307, 3070, 2957, 2929, 2859, 1467, 1428, 1109, 882, 703, and 617 cm^{-1} ; $[\alpha]_D^{23} = +9.68$ (c 2.50, CHCl_3); HR-FABMS: m/z calcd for MH^+ ($\text{C}_{25}\text{H}_{35}\text{OSi}$) 379.2457, found 379.2449.

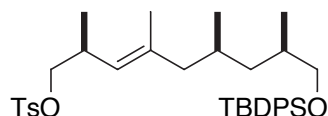
**7ss**

To zirconocene dichloride (1.24 g, 4.23 mmol) dissolved in CH_2Cl_2 (10 mL) in a Schlenk flask was added trimethylaluminum (2.0 M in toluene, 5.00 mL, 10.0 mmol). The mixture was stirred for 15 min at room temperature and alkyne **4** (1.60 g, 4.23 mmol) was added in CH_2Cl_2 (1.50 mL). The reaction mixture was allowed to stir overnight, the flask was cooled in an ice bath, and all solvents were carefully removed while the mixture was stirred *in vacuo* (0.8 mm Hg). The solid residue was washed twice with hexanes while maintaining the argon atmosphere, and the hexane soluble alkenylalane was cannulated into a

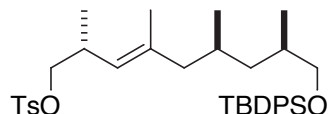
fresh pear shaped flask under argon. This solution was cooled to $-40\text{ }^{\circ}\text{C}$ and methyllithium (1.51 M in Et_2O , 2.80 mL, 4.23 mmol) was added. The reaction mixture was stirred for 5 min, and triflate (**S**)-**6** (2.18 g, 10.6 mmol) was added. The mixture was allowed to warm to room temperature and stirred for 48 h. The reaction was quenched with saturated aqueous NaHCO_3 , the aluminum salts filtered, and the residue partitioned between diethyl ether and water. The combined organic layers were washed with brine, dried with Na_2SO_4 , and concentrated. Purification on silica gel (19:1, hexanes: ethyl acetate) gave 0.49 g (51%) of ester **7ss** as a colorless oil. ^1H NMR (500 MHz, CDCl_3): δ 7.66 (m, 4H), 7.44-7.36 (m, 6H), 5.12 (d, $J = 9.6$ Hz, 1H), 3.64 (s, 3H), 3.50 (dd, $J = 9.8, 5.2$ Hz, 1H), 3.39 (dd, $J = 9.8, 6.5$ Hz, 1H), 3.33 (dq, $J = 9.6, 6.9$ Hz, 1H), 2.02 (m, 1H), 1.75 (m, 1H), 1.62 (m, 2H), 1.58 (d, $J = 1.5$ Hz, 3H), 1.30 (m, 1H), 1.19 (d, $J = 7.0$ Hz, 3H), 1.05 (s, 9H), 0.93 (d, $J = 6.5$ Hz, 3H), 0.90 (m, 1H), and 0.73 (d, $J = 6.0$ Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3): δ 175.9, 136.4, 135.6, 133.9, 129.5, 127.5, 125.1, 68.8, 51.1, 47.4, 41.2, 38.7, 33.1, 28.0, 26.0, 19.2, 18.0, 17.8, and 16.0; IR (thin film); 3071, 2962, 2931, 2859, 1739, 1461, 1424, 1161, 1115, 1079, 815, and 700 cm^{-1} ; $[\alpha]^{23}_{\text{D}} = +44.8$ (c 1.03, CHCl_3); HR-FABMS: m/z calcd for MH^+ ($\text{C}_{30}\text{H}_{45}\text{O}_3\text{Si}$) 481.3138, found 481.3123.

**7as**

Alkyne **4** was coupled with the triflate of methyl-(*R*)-(+)-lactate [(*R*)-**6**] using the preceding protocol to furnish **7as** (47%). ^1H NMR (500 MHz, CDCl_3): δ 7.66 (m, 4H), 7.44-7.35 (m, 6H), 5.10 (d, $J = 9.6$ Hz, 1H), 3.65 (s, 3H), 3.49 (dd, $J = 9.8, 5.1$ Hz, 1H), 3.40 (dd, $J = 9.8, 6.5$ Hz, 1H), 3.33 (dq, $J = 9.6, 6.9$ Hz, 1H), 2.00 (m, 1H), 1.74 (m, 1H), 1.66-1.61 (m, 2H), 1.58 (d, $J = 1.3$ Hz, 3H), 1.31 (m, 1H), 1.19 (d, $J = 6.7$ Hz, 3H), 1.05 (s, 9H), 0.93 (d, $J = 6.5$ Hz, 3H), 0.90 (m, 1H), and 0.74 (d, $J = 6.1$ Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3): δ 175.9, 136.6, 134.1, 134.0, 129.5, 127.6, 125.1, 68.8, 51.6, 47.5, 41.2, 38.8, 33.1, 28.2, 26.9, 19.9, 19.3, 17.9, 17.8 and 16.2; IR (thin film); 3066, 2963, 2929, 2866, 1739, 1459, 1429, 1172, 1109, and 700 cm^{-1} ; $[\alpha]^{29}_{\text{D}} = -44.5$ (c 1.05, CHCl_3); HR-FABMS: m/z calcd for MH^+ ($\text{C}_{30}\text{H}_{45}\text{O}_3\text{Si}$) 481.3138, found 481.3139

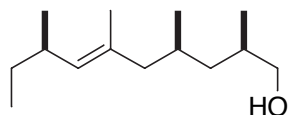
**8ss**

To a stirred solution of ester **7ss** (1.11 g, 2.31 mmol) in CH₂Cl₂ (15 mL) at -78°C was slowly added DIBAL (1.0 M in hexanes, 11.6 mL, 11.6 mmol). The reaction mixture was stirred at -78°C for 10 min, and then at 0°C for 2 h. This mixture was re-cooled to -78°C and quenched by the dropwise addition of MeOH (5 mL). The solution was poured into saturated aqueous NH₄Cl, diluted with CH₂Cl₂, and stirred until layers separated. The aqueous layer was extracted with CH₂Cl₂, washed with brine, dried with Na₂SO₄, and concentrated. The product was passed through a short plug of silica gel to give 810 mg (77%) of the corresponding alcohol. To a stirred solution of this alcohol (686 mg, 1.51 mmol) in CH₂Cl₂ (5 mL) was added triethylamine (0.67 mL, 4.80 mmol), *p*-toluenesulfonyl chloride (303 mg, 1.60 mmol), and DMAP (24 mg, 0.20 mmol). The mixture was stirred at room temperature for 3 h, diluted with CH₂Cl₂, washed with saturated aqueous NH₄Cl, dried with Na₂SO₄, and concentrated. Purification on silica gel (8:1, hexanes: ethyl acetate) gave 887 mg (97%) of tosylate **8ss** as a colorless oil. ¹H NMR (500 MHz, CDCl₃): 7.77 (d, *J* = 8.0 Hz, 2H), 7.66 (m, 4H), 7.44-7.35 (m, 6H), 7.32 (d, *J* = 8.0 Hz, 2H), 4.72 (d, *J* = 9.0 Hz, 1H), 3.83 (dd, *J* = 9.5, 6.2 Hz, 1H), 3.74 (dd, *J* = 9.5, 7.8 Hz, 1H), 3.50 (dd, *J* = 9.8, 5.3 Hz, 1H), 3.40 (dd, *J* = 9.8, 6.6 Hz, 1H), 2.71 (m, 1H), 2.43 (s, 3H), 1.96 (dd, *J* = 12.8, 4.0 Hz, 1H), 1.73 (m, 1H), 1.57 (m, 1H), 1.50 (dd, *J* = 12.8, 9.5 Hz, 1H), 1.48 (d, *J* = 1.2 Hz, 3H), 1.27 (m, 1H), 1.05 (s, 9H), 0.92 (d, *J* = 7.0 Hz, 6H), 0.89 (m, 1H), and 0.70 (d, *J* = 6.5 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃): δ 144.5, 136.7, 135.6, 134.0, 133.2, 129.7, 129.5, 127.9, 127.5, 125.9, 74.4, 68.9, 47.4, 41.3, 33.1, 32.2, 27.9, 26.8, 21.6, 19.6, 19.3, 17.7, 17.3, and 16.2; IR (thin film): 3066, 3048, 2964, 2929, 2859, 1434, 1355, 1178, 1115, 966, and 828 cm⁻¹; [α]_D²⁹ = +13.8 (*c* 1.10, CHCl₃); HR-FABMS: *m/z* caclcd for MH⁺ (C₃₆H₅₁O₄SSi) 607.3277, found 607.3267.

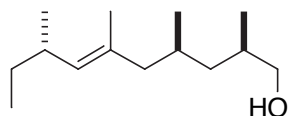
**8as**

The preceding protocol was used to derive **8as** from **7as**. ¹H NMR (500 MHz, CDCl₃): δ 7.78 (d, *J* = 8.5 Hz, 2H), 7.66 (m, 4H), 7.44-7.35 (m, 6H), 7.32 (d, *J* = 8.5 Hz, 2H), 4.73 (d, *J* = 9.1 Hz, 1H), 3.82 (dd, *J* = 9.4, 6.3 Hz, 1H), 3.74 (dd, *J* = 9.4, 7.7 Hz,

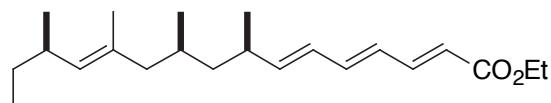
¹H), 3.48 (dd, *J* = 9.8, 5.3 Hz, 1H), 3.39 (dd, *J* = 9.8, 6.6 Hz, 1H), 2.71 (m, 1H), 2.44 (s, 3H), 1.95 (m, 1H), 1.72 (m, 1H), 1.58-1.51 (m, 2H), 1.48 (d, *J* = 1.4 Hz, 3H), 1.29 (m, 1H), 1.04 (s, 9H), 0.92 (d, *J* = 6.9 Hz, 6H), 0.87 (m, 1H), and 0.70 (d, *J* = 6.6 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃): δ 144.5, 136.8, 135.6, 134.0, 133.3, 129.7, 129.5, 127.9, 127.5, 126.0, 74.3, 68.8, 47.7, 41.1, 33.1, 32.3, 27.9, 26.8, 21.7, 19.9, 19.3, 17.8, 17.2, and 16.1; IR (thin film): 3066, 3049, 2963, 2934, 2860, 1457, 1429, 1367, 1189, 1114, 954, and 823 cm⁻¹; HR-FABMS: *m/z* calcd for MH⁺ (C₃₆H₅₁O₄SSi) 607.3277, found 607.3285.

**9ss**

To a solution of CuI (1.37 g, 7.20 mmol) in Et₂O (5 mL) at -10 °C was added methyllithium (1.55 M in Et₂O, 9.30 mL, 14.4 mmol). This mixture was stirred at -10 °C for 10 min, cooled to -40 °C, and tosylate **8ss** (870 mg, 1.43 mmol) was added dropwise in Et₂O (3 mL). The reaction mixture was allowed to warm to room temperature and stirred overnight, diluted with NH₄OH (conc., 30 mL) and NH₄Cl (satd, 30 mL), and stirred open to air until bright blue. This mixture was extracted with Et₂O, dried with Na₂SO₄, and concentrated. To a stirred solution of this crude product in THF (8 mL) was added TBAF (418 mg, 1.60 mmol). The mixture was stirred for 4 h and then quenched with saturated aqueous NaHCO₃, extracted with Et₂O, dried with Na₂SO₄, and concentrated. Purification on MPLC using silica gel (6:1, hexanes: ethyl acetate) furnished 220 mg (72%, 2 steps) of alcohol **9ss** as a colorless oil. ¹H NMR (500 MHz, CDCl₃): δ 4.86 (d, *J* = 9.8 Hz, 1H), 3.54 (dd, *J* = 10.5, 5.0 Hz, 1H), 3.37 (dd, *J* = 10.5, 7.2 Hz, 1H), 2.24 (m, 1H), 2.0 (m, 1H), 1.74 (m, 1H), 1.70-1.65 (m, 2H), 1.56 (d, *J* = 1.4 Hz, 3H), 1.36-1.26 (m, 2H), 1.25-1.15 (m, 2H), 0.94 (d, *J* = 6.7 Hz, 3H), 0.91 (d, *J* = 6.7 Hz, 3H), 0.83 (d, *J* = 6.4 Hz, 3H), and 0.83 (t, *J* = 7.5 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃): δ 133.0, 132.1, 68.2, 47.6, 40.8, 34.0, 33.1, 30.5, 28.1, 21.0, 20.1, 17.5, 16.2, and 12.0; IR (thin film): 3330, 2962, 2917, 2868, 1455, 1376 and 1036 cm⁻¹; [α]_D²⁵ = -14.4 (*c* 1.10, CHCl₃); HR-FABMS: *m/z* calcd for MH⁺ (C₁₄H₂₉O) 213.2218, found 213.2218.

**9as**

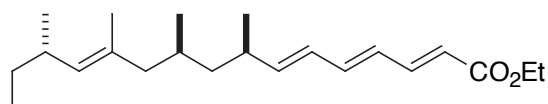
The preceding protocol was used to generate **9as** from **8as**. ^1H NMR (500 MHz, CDCl_3): δ 4.86 (d, J = 9.3 Hz, 1H), 3.53 (dd, J = 10.4, 5.0 Hz, 1H), 3.37 (dd, J = 10.4, 6.7 Hz, 1H), 2.24 (m, 1H), 2.03 (m, 1H), 1.74 (m, 1H), 1.70-1.62 (m, 2H), 1.56 (d, J = 1.1 Hz, 3H), 1.37-1.27 (m, 2H), 1.25-1.15 (m, 2H), 0.94 (d, J = 6.7 Hz, 3H), 0.91 (d, J = 6.7 Hz, 3H), 0.84 (t, J = 7.5 Hz, 3H), and 0.83 (d, J = 6.1 Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3): δ 133.0, 132.2, 68.3, 47.7, 41.0, 34.1, 33.1, 30.6, 28.2, 21.0, 20.1, 17.3, 16.1, and 12.0; IR (thin film): 3330, 2960, 2917, 2875, 1457, 1378 and 1031 cm^{-1} ; $[\alpha]_D^{25}$ = +37.4 (*c* 1.27, CH_3OH); HR-FABMS: m/z calcd for MH^+ ($\text{C}_{14}\text{H}_{29}\text{O}$) 213.2218, found 213.2236.

**12ss**

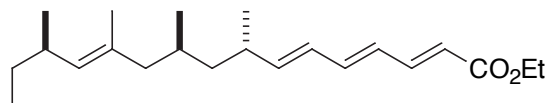
To a stirred solution of alcohol **9ss** (13 mg, 0.06 mmol) in CH_2Cl_2 was added powdered 4Å molecular sieves (~10 mg), TPAP (2 mg, 0.01 mmol), and NMO (25 mg, 0.21 mmol). After 1 h the reaction mixture was filtered with CH_2Cl_2 through a short plug of silica gel. The volatile aldehyde **10ss** was concentrated *in vacuo* (waterbath $<25^\circ\text{C}$) and used immediately in the next step.

To a stirred solution of diisopropylamine (25 μL , 0.18 mmol) in THF (300 μL) at -78°C was added *n*-BuLi (2.30 M in hexanes, 78 μL , 0.18 mmol). This mixture was warmed to 0°C for 15 min, and re-cooled to -78°C . Phosphonate **11** in THF (200 μL) was then added dropwise. After 30 min **10ss** was added dropwise in THF (200 μL). The reaction mixture was stirred at -78°C for 30 min and at 0°C for 30 min before it was quenched with saturated aqueous NH_4Cl , extracted with Et_2O , dried with Na_2SO_4 , and concentrated. Purification by MPLC on silica gel (1% ethyl acetate in hexanes) gave 17 mg (81%, 2 steps) of triene **12ss** as a colorless oil. ^1H NMR (500 MHz, CD_3OD): δ 7.307 (dd, J = 15.1, 11.2 Hz, 1H), 6.605 (dd, J = 15.1, 10.9 Hz, 1H), 6.312 (dd, J = 15.1, 11.2 Hz, 1H), 6.179 (dd, J = 15.1, 10.9 Hz, 1H), 5.869 (d, J = 15.1 Hz, 1H), 5.777 (dd, J = 15.1, 8.7 Hz, 1H), 4.850 (d, J = 9.7 Hz, 1H), 4.178 (q, J = 7.3 Hz, 2H), 2.370 (m, 1H), 2.263 (m, 1H), 1.905 (dd, J = 13.1, 7.1 Hz, 1H), 1.802 (dd, J = 13.1, 7.1 Hz, 1H), 1.592 (m, 1H), 1.550 (d, J = 1.2 Hz, 3H), 1.367 (ddd, J = 14.0, 10.0, 5.0 Hz, 1H), 1.351 (ddq, J = 13.5,

7.5, 5.0 Hz, 1H), 1.280 (t, $J = 7.4$ Hz, 3H), 1.192 (ddq, $J = 13.5, 8.5, 7.5$ Hz, 1H), 1.031 (ddd, $J = 14.0, 9.6, 4.5$ Hz, 1H), 1.010 (d, $J = 6.9$ Hz, 3H), 0.912 (d, $J = 6.7$ Hz, 3H), 0.858 (t, $J = 7.4$ Hz, 3H), and 0.835 (d, $J = 6.7$ Hz, 3H); ^{13}C NMR (125 MHz, CD_3OD): δ 169.44, 147.75, 147.00, 143.36, 134.74, 134.01, 130.37, 129.65, 121.26, 61.87, 50.09, 45.70, 36.80, 35.89, 32.17, 31.26, 22.36, 22.02, 20.40, 16.88, 15.08, and 13.03; $[\alpha]_{\text{D}}^{25} = -2.35$ (c 0.34, CHCl_3); HR-FABMS: m/z calcd for MH^+ ($\text{C}_{22}\text{H}_{37}\text{O}_2$) 333.2794, found 333.2809.

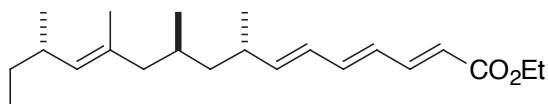
**12as**

Compound **12as** was prepared from **9as** following the preceding protocol. ^1H NMR (500 MHz, CD_3OD): δ 7.307 (dd, $J = 15.2, 11.3$ Hz, 1H), 6.612 (dd, $J = 15.0, 10.7$ Hz, 1H), 6.314 (dd, $J = 15.0, 11.3$ Hz, 1H), 6.179 (dd, $J = 15.1, 10.7$ Hz, 1H), 5.868 (d, $J = 15.2$ Hz, 1H), 5.781 (dd, $J = 15.1, 8.3$ Hz, 1H), 4.848 (d, $J = 9.4$ Hz, 1H), 4.178 (q, $J = 7.3$ Hz, 2 H), 2.372 (m, 1H), 2.266 (m, 1H), 1.934 (dd, $J = 13.2, 6.5$ Hz, 1H), 1.770 (dd, $J = 13.2, 8.1$ Hz, 1H), 1.601 (m, 1H), 1.544 (d, $J = 1.1$ Hz, 3H), 1.345 (ddq, $J = 13.5, 7.5, 5.5$ Hz, 1H), 1.341 (ddd, $J = 13.9, 9.4, 5.0$ Hz, 1H), 1.280 (t, $J = 7.3$ Hz, 3H), 1.187 (ddq, $J = 13.5, 8.0, 7.5$ Hz, 1H), 1.057 (ddd, $J = 13.5, 9.4, 5.0$ Hz, 1H), 1.014 (d, $J = 6.7$ Hz, 3H), 0.915 (d, $J = 6.8$ Hz, 3H), 0.847 (t, $J = 7.4$ Hz, 3H), and 0.829 (d, $J = 6.5$ Hz, 3H); ^{13}C NMR (125 MHz, CD_3OD): δ 169.46, 148.29, 147.04, 143.50, 134.67, 134.16, 129.94, 129.59, 121.18, 61.87, 49.28, 46.00, 36.60, 35.89, 32.19, 29.99, 21.98, 21.18, 20.79, 16.86, 15.08, and 12.98; $[\alpha]_{\text{D}}^{25} = +4.0$ (c 0.55, CH_3OH); HR-FABMS: m/z calcd for MH^+ ($\text{C}_{22}\text{H}_{37}\text{O}_2$) 333.2794, found 333.2791.

**12sa**

To the crude aldehyde **10ss** (13 mg, 0.06 mmol) in MeOH (2 mL) was added florisil[®] (0.100g) and potassium fluoride (0.100g). The reaction mixture was stirred for 6 h, filtered through a plug of silica gel, and concentrated *in vacuo* (waterbath <25 °C) to give a mixture of **10ss** and **10sa** (1:1.5). This mixture of aldehydes was coupled with phosphonate **11** (as described in the synthesis of **12ss**) to give 31 mg (76%, 3 steps) of a 1:1.5 mixture of **12ss** : **12sa**. Careful separation by MPLC on silica gel (0.5% ethyl

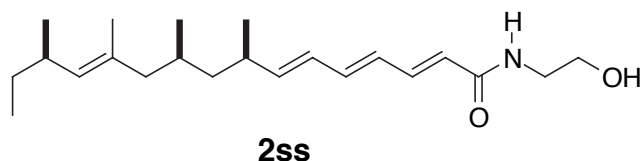
acetate in hexanes) furnished a pure sample of **12sa**. ^1H NMR (500 MHz, CD_3OD): δ 7.309 (dd, $J = 15.2, 11.1$ Hz, 1H), 6.621 (dd, $J = 14.9, 10.8$ Hz, 1H), 6.308 (dd, $J = 14.9, 11.1$ Hz, 1H), 6.184 (dd, $J = 15.1, 10.8$ Hz, 1H), 5.865 (d, $J = 15.2$ Hz, 1H), 5.855 (dd, $J = 15.1, 8.1$ Hz, 1H), 4.856 (d, $J = 10.0$ Hz, 1H), 4.178 (q, $J = 7.0$ Hz, 2 H), 2.377 (m, 1H), 2.266 (m, 1H), 2.037 (dd, $J = 13.0, 5.2$ Hz, 1H), 1.715 (dd, $J = 13.0, 8.2$ Hz, 1H), 1.656 (m, 1H), 1.560 (d, $J = 1.4$ Hz, 3H), 1.347 (ddq, $J = 13.0, 7.5, 7.5$ Hz, 1H), 1.295 (ddd, $J = 14.0, 7.0, 7.0$ Hz, 3H), 1.280 (t, $J = 7.0$ Hz, 3H), 1.188 (ddq, $J = 13.0, 9.0, 7.0$ Hz, 1H), 1.148 (ddd, $J = 14.0, 7.0, 7.0$ Hz, 1H), 0.993 (d, $J = 6.7$ Hz, 3H), 0.910 (d, $J = 6.7$ Hz, 3H), 0.848 (t, $J = 7.4$ Hz, 3H), and 0.823 (d, $J = 6.4$ Hz, 3H); ^{13}C NMR (125 MHz, CD_3OD): δ 169.46, 147.81, 147.02, 143.39, 134.71, 134.03, 130.32, 129.64, 121.24, 61.87, 50.02, 45.89, 36.80, 35.88, 32.17, 30.05, 22.24, 22.01, 20.33, 16.86, 15.08, and 12.98; $[\alpha]_D^{25} = +8.12$ (c 0.27, CH_3OH); HR-FABMS: m/z calcd for MH^+ ($\text{C}_{22}\text{H}_{37}\text{O}_2$) 333.2794, found 333.2808.

**12aa**

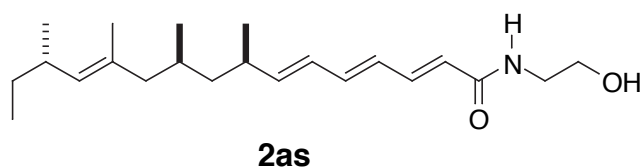
Compound **12aa** was prepared from **9as** following the preceding protocol. ^1H NMR (500 MHz, CD_3OD): δ 7.310 (dd, $J = 15.2, 11.2$ Hz, 1H), 6.311 (dd, $J = 14.9, 11.2$ Hz, 1H), 6.187 (dd, $J = 15.3, 10.7$ Hz, 1H), 5.866 (d, $J = 15.2$ Hz, 1H), 5.851 (dd, $J = 15.3, 8.3$ Hz, 1H), 5.624 (dd, $J = 14.9, 10.7$ Hz, 1H), 4.856 (d, $J = 9.5$ Hz, 1H), 4.178 (q, $J = 7.2$ Hz, 2 H), 2.381 (m, 1H), 2.266 (m, 1H), 2.066 (dd, $J = 11.5, 4.0$ Hz, 1H), 1.685 (dd, $J = 11.5, 8.5$ Hz, 1H), 1.661 (m, 1H), 1.554 (d, $J = 1.4$ Hz, 3H), 1.349 (ddq, $J = 13.9, 7.5, 7.5$ Hz, 1H), 1.280 (t, $J = 7.0$ Hz, 3H), 1.258 (ddd, $J = 14.0, 7.0, 7.0$ Hz, 3H), 1.197 (ddd, $J = 14.0, 7.0, 7.0$ Hz, 1H), 1.187 (m, 1H), 0.998 (d, $J = 6.6$ Hz, 3H), 0.910 (d, $J = 6.5$ Hz, 3H), 0.847 (t, $J = 7.4$ Hz, 3H), and 0.821 (d, $J = 6.3$ Hz, 3H); ^{13}C NMR (125 MHz, CD_3OD): δ 169.46, 148.35, 147.04, 143.50, 134.73, 134.12, 129.85, 129.59, 121.18, 61.87, 49.32, 45.79, 36.55, 35.08, 32.14, 30.04, 22.01, 21.07, 20.76, 16.90, 15.09, and 12.99; $[\alpha]_D^{25} = +57.0$ (c 0.20, CH_3OH); HR-FABMS: m/z calcd for MH^+ ($\text{C}_{22}\text{H}_{37}\text{O}_2$) 333.2794, found 333.2820.

General procedure for conversion of esters 12ss-12aa to amides 2ss-2aa: To *O*-TBS protected amino ethanol (4 equiv)ⁱ in CH_2Cl_2 was added dropwise trimethylaluminum (4 equiv, 2.0M in toluene) and the mixture was allowed to stir at room temperature for 30 min. The ester

(1 equiv) in CH_2Cl_2 was added and this mixture was allowed to stir at 45 °C. After 4 h the reaction was carefully quenched with saturated aqueous NH_4Cl , extracted with CH_2Cl_2 , dried with Na_2SO_4 and concentrated. This crude mixture was re-dissolved in THF, and TBAF (2 equiv) was added. The reaction was allowed to stir overnight, quenched with NaHCO_3 , extracted with CH_2Cl_2 , dried with Na_2SO_4 , and concentrated. Purification on column chromatography with 100% ethyl acetate furnished the amides **2ss-2aa**.

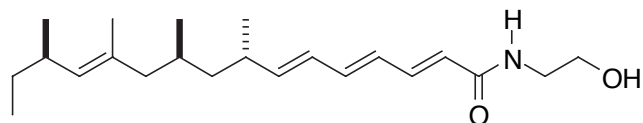


^1H NMR (500 MHz, CD_3OD): δ 7.170 (dd, $J = 15.1, 11.2$ Hz, 1H), 6.535 (dd, $J = 14.9, 10.9$ Hz, 1H), 6.271 (dd, $J = 14.9, 11.2$ Hz, 1H), 6.156 (dd, $J = 15.1, 10.9$ Hz, 1H), 5.993 (d, $J = 15.1$ Hz, 1H), 5.701 (dd, $J = 15.1, 8.7$ Hz, 1H), 4.846 (d, $J = 10.0$ Hz, 1H), 3.620 (t, $J = 5.5$ Hz, 2 H), 3.369 (t, $J = 5.5$ Hz, 2 H), 2.353 (m, 1H), 2.268 (m, 1H), 1.899 (dd, $J = 13.1, 7.1$ Hz, 1H), 1.803 (dd, $J = 13.1, 7.1$ Hz, 1H), 1.592 (m, 1H), 1.543 (d, $J = 1.2$ Hz, 3H), 1.363 (ddd, $J = 14.0, 10.0, 5.0$ Hz, 1H), 1.356 (ddq, $J = 13.5, 7.5, 5.0$ Hz, 1H), 1.191 (ddq, $J = 13.5, 8.5, 7.5$ Hz, 1H), 1.022 (ddd, $J = 14.0, 9.6, 4.5$ Hz, 1H), 1.005 (d, $J = 6.9$ Hz, 3H), 0.912 (d, $J = 6.7$ Hz, 3H), 0.859 (t, $J = 7.4$ Hz, 3H), and 0.834 (d, $J = 6.7$ Hz, 3H); ^{13}C NMR (125 MHz, CD_3OD): δ 169.82, 146.57, 142.65, 141.78, 134.71, 134.04, 130.45, 129.91, 124.31, 62.17, 50.10, 45.73, 43.58, 36.77, 35.88, 32.18, 30.02, 22.43, 22.01, 20.41, 16.86, and 13.01; HR-FABMS: m/z calcd for MH^+ ($\text{C}_{22}\text{H}_{38}\text{N}_1\text{O}_2$) 348.2903, found 348.2910.



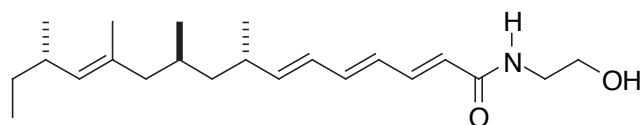
^1H NMR (500 MHz, CD_3OD): δ 7.170 (dd, $J = 15.2, 11.3$ Hz, 1H), 6.541 (dd, $J = 15.0, 10.7$ Hz, 1H), 6.272 (dd, $J = 15.0, 11.3$ Hz, 1H), 6.158 (dd, $J = 15.1, 10.7$ Hz, 1H), 5.994 (d, $J = 15.2$ Hz, 1H), 5.721 (dd, $J = 15.1, 8.3$ Hz, 1H), 4.845 (d, $J = 9.4$ Hz, 1H), 3.620 (t, $J = 5.5$ Hz, 2 H), 3.369 (t, $J = 5.5$ Hz, 2 H), 2.357 (m, 1H), 2.267 (m, 1H), 1.930 (dd, $J = 13.2, 6.5$ Hz, 1H), 1.771 (dd, $J = 13.2, 8.1$ Hz, 1H), 1.596 (m, 1H), 1.555 (d, $J = 1.1$ Hz, 3H), 1.338 (ddd, $J = 13.9, 10.0, 5.5$ Hz, 1H), 1.344 (ddd, $J = 15.5, 13.5, 7.5$ Hz, 1H), 1.186 (ddq, $J = 13.5, 8.0, 7.5$ Hz, 1H), 1.049 (ddd, $J = 13.9, 9.4, 5.0$ Hz, 1H), 1.009 (d, $J = 6.7$

Hz, 3H), 0.915 (d, J = 6.8 Hz, 3H), 0.847 (t, J = 7.4 Hz, 3H), and 0.830 (d, J = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, CD_3OD): δ 169.81, 146.62, 142.65, 141.80, 134.67, 134.04, 130.39, 129.91, 124.30, 62.16, 50.00, 45.91, 43.58, 36.75, 35.88, 32.17, 30.03, 22.32, 22.02, 20.36, 16.87, and 12.99; HR-FABMS: m/z calcd for MH^+ ($\text{C}_{22}\text{H}_{38}\text{N}_1\text{O}_2$) 348.2903, found 348.2895.

**2sa**

^1H NMR (500 MHz, CD_3OD): δ 7.172 (dd, J

= 15.2, 11.1 Hz, 1H), 6.547 (dd, J = 15.0, 10.5 Hz, 1H), 6.268 (dd, J = 15.0, 11.1 Hz, 1H), 6.162 (dd, J = 15.2, 10.5 Hz, 1H), 5.991 (d, J = 15.2 Hz, 1H), 5.793 (dd, J = 15.2, 8.1 Hz, 1H), 4.855 (d, J = 10.0 Hz, 1H), 3.620 (t, J = 5.5 Hz, 2 H), 3.369 (t, J = 5.5 Hz, 2 H), 2.363 (m, 1H), 2.265 (m, 1H), 2.039 (dd, J = 12.6, 5.5 Hz, 1H), 1.710 (dd, J = 12.6, 8.4 Hz, 1H), 1.656 (m, 1H), 1.559 (d, J = 1.0 Hz, 3H), 1.334 (ddq, J = 13.0, 7.5, 7.5 Hz, 1H), 1.290 (ddd, J = 14.0, 7.0, 7.0 Hz, 1H), 1.188 (ddq, J = 13.0, 9.0, 7.0, Hz, 1H), 1.144 (ddd, J = 14.0, 7.0, 7.0 Hz, 1H), 0.988 (d, J = 6.5 Hz, 3H), 0.910 (d, J = 6.8 Hz, 3H), 0.849 (t, J = 7.5 Hz, 3H), and 0.822 (d, J = 6.3 Hz, 3H); ^{13}C NMR (125 MHz, CD_3OD): δ 169.82, 147.17, 142.67, 141.91, 134.71, 134.15, 129.87, 129.95, 124.25, 62.16, 49.32, 45.84, 43.58, 36.50, 35.89, 32.14, 30.04, 22.00, 21.14, 20.75, 16.89, and 12.98.; HR-FABMS: m/z calcd for MH^+ ($\text{C}_{22}\text{H}_{38}\text{N}_1\text{O}_2$) 348.2903, found 348.2915.

**2aa**

^1H NMR (500 MHz, CD_3OD): δ 7.172 (dd, J

= 15.2, 11.2 Hz, 1H), 6.268 (dd, J = 14.9, 11.2 Hz, 1H), 6.164 (dd, J = 15.3, 10.7 Hz, 1H), 5.991 (d, J = 15.2 Hz, 1H), 5.790 (dd, J = 15.0, 8.3 Hz, 1H), 5.549 (dd, J = 15.0, 10.7 Hz, 1H), 4.853 (d, J = 9.5 Hz, 1H), 3.621 (t, J = 5.5 Hz, 2 H), 3.369 (t, J = 5.5 Hz, 2 H), 2.367 (m, 1H), 2.264 (m, 1H), 2.067 (dd, J = 11.5, 4.0 Hz, 1H), 1.682 (dd, J = 11.5, 8.5 Hz, 1H), 1.661 (m, 1H), 1.553 (d, J = 1.0 Hz, 3H), 1.349 (ddq, J = 14.0, 6.0, 7.5 Hz, 1H), 1.240 (ddd, J = 14.0, 7.0, 7.0 Hz, 1H), 1.183 (m, 2H), 0.994 (d, J = 6.6 Hz, 3H), 0.911 (d, J = 6.5 Hz, 3H), 0.847 and 0.820 (d, J = 6.3 Hz, 3H); ^{13}C NMR (125 MHz, CD_3OD): δ 169.81, 147.10, 142.67, 141.89, 134.66, 134.19, 130.03, 129.87, 124.27, 62.16, 49.27, 46.06, 43.58, 36.56, 35.89, 32.19, 29.10, 21.98, 21.26,

20.80, 16.87, and 12.98; HR-FABMS: m/z calcd for MH^+ ($C_{22}H_{38}N_1O_2$) 348.2903, found 348.2932.

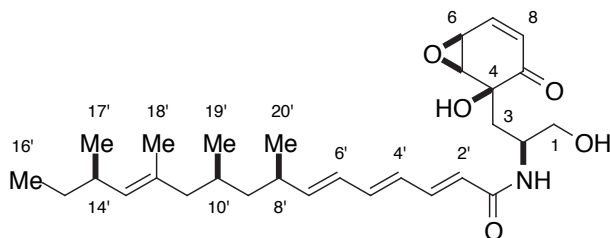
Table A. Proton Chemical Shifts (ppm, referenced to $\delta_{\text{CHD}_2\text{OD}} = 3.310$) for the Trienoyl Side Chain Protons [H(2')-H(20')] in Compounds **1**, **2ss**, **2as**, **2sa**, and **2aa** in CD₃OD.

Proton Number	Proton Chemical Shifts (ppm)				
	1	2ss	2as	2sa	2aa
2'	5.903	5.993	5.994	5.991	5.991
3'	7.154	7.170	7.170	7.172	7.172
4'	6.255	6.271	6.272	6.268	6.268
5'	6.538	6.535	6.541	6.547	5.549
6'	6.150	6.156	6.158	6.162	6.164
7'	5.706	5.701	5.721	5.793	5.790
8'	2.352	2.353	2.357	2.363	2.367
9a'	1.022	1.022	1.049	1.144	1.183
9b'	1.363	1.363	1.338	1.290	1.240
10'	1.590	1.592	1.596	1.656	1.661
11a'	1.801	1.803	1.771	1.710	1.682
11b'	1.899	1.899	1.930	2.039	2.067
13'	4.850	4.846	4.845	4.855	4.853
14'	2.268	2.268	2.267	2.265	2.264
15a'	1.355	1.356	1.344	1.334	1.349
15b'	1.190	1.191	1.186	1.188	1.183
16'	0.859	0.859	0.847	0.849	0.847
17'	0.911	0.912	0.915	0.910	0.911
18'	1.542	1.543	1.555	1.559	1.553
19'	0.834	0.834	0.830	0.822	0.820
20'	1.004	1.005	1.009	0.988	0.994

Table B. Carbon Chemical Shifts (ppm, referenced to $\delta_{\text{CD}_3\text{OD}} = 49.49$) for the Trienoyl Side Chain Carbons [C(1')-C(20')] in Compounds **1**, **2ss**, **2as**, **2sa**, and **2aa** in CD₃OD.

Carbon Number	Carbon Chemical Shifts (ppm)				
	1	2ss	2as	2sa	2aa
1'	169.00	169.82	169.81	169.82	169.81
2'	124.21	124.31	124.30	124.25	124.27
3'	142.89	142.65	142.65	142.67	142.67
4'	129.90	129.91	129.91	129.87	129.87
5'	141.87	141.78	141.80	141.91	141.89
6'	130.40	130.45	130.39	129.95	130.03
7'	146.34	146.57	146.62	147.17	147.10
8'	36.69	36.77	36.75	36.50	36.56
9'	45.70	45.73	45.91	45.84	46.06
10'	30.00	30.02	30.03	30.04	29.10
11'	50.07	50.10	50.00	49.32	49.27
12'	134.00	134.04	134.04	134.15	134.19
13'	134.68	134.71	134.67	134.71	134.66
14'	35.85	35.88	35.88	35.89	35.89
15'	32.16	32.18	32.17	32.14	32.19
16'	13.00	13.01	12.99	12.98	12.98
17'	22.00	22.01	22.02	21.14	21.26
18'	16.87	16.86	16.87	16.89	16.87
19'	20.41	20.41	20.36	20.75	20.80
20'	22.39	22.43	22.32	22.00	21.98

Table C. Proton and Carbon Chemical Shifts (ppm, referenced to $\delta = 3.310$ for ^1H and $\delta = 49.49$ for ^{13}C) in CD_3OD of all Resonances in Scyphostatin (**1**) as Recorded from the Spectra Provided to us by Dr. M. Tanaka.



Position Number	Chemical Shift (ppm)		Position Number	Chemical Shift (ppm)	
	^1H	^{13}C		^1H	^{13}C
1	3.461	65.60	7'	5.706	146.34
	3.524		8'	2.352	36.69
2	4.055	48.47	9'	1.022	45.70
3	1.887	40.27		1.363	
	2.084		10'	1.590	30.00
4		78.00	11'	1.801	50.07
5	3.673	58.68		1.899	
6	3.594	49.79	12'		134.00
7	7.145	146.63	13'	4.850	134.68
8	6.080	132.50	14'	2.268	35.85
9		200.00	15'	1.355	32.16
1'		169.00		1.190	
2'	5.903	124.21	16'	0.859	13.00
3'	7.154	142.89	17'	0.911	22.00
4'	6.255	129.90	18'	1.542	16.87
5'	6.538	141.87	19'	0.834	20.41
6'	6.150	130.40	20'	1.004	22.39