Supporting Information

For

De novo total synthesis of mycolactone A/B and its [^{2}H]-isotopologue

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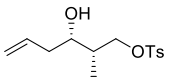
1. Material and methods

NMR spectra were recorded on Brucker AV 300 or AV 400 spectrometer at 300 MHz or 400 MHz for ^{1}H NMR, at 75 or 100 MHz for ^{13}C NMR and at 376 MHz MHz for ^{19}F NMR. The spectra were calibrated using undeuterated solvent as internal reference, unless otherwise indicated. The following abbreviations were used to explain multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, and b = broad. Coupling constant (*J*) were reported in Hertz. High resolution mass spectra (HRMS) in positive mode were recorded using a 6520 series quadrupole time-of-flight (Q-TOF) mass spectrometer (Agilent) fitted with a multimode ion source (in mixed mode that enables both electrospray ionization, ESI, and atmospheric pressure chemical ionization, APCI). Samples were directly infused into the source using 50/50-methanol/formic acid 0.2 % in water. Specific optical rotations are expressed in (deg·mL)/(g·dm) and were recorded on a Perkin-Elmer polarimeter at a light wavelength of sodium D line (λ = 589 nm) and at 20 °C. Tetrahydrofuran (THF) was distilled under nitrogen from sodium-benzophenone. Reagents were purchased from Aldrich, Apollo Scientific or Alfa Aesar and used without further purification, unless otherwise noted. Yields refer to chromatographically and spectroscopically (^{1}H, ^{13}C and ^{19}F NMR) homogeneous materials, unless otherwise noted. Reactions were monitored by thin-layer chromatography (TLC) carried out on Merck TLC silica gel 60 F254 aluminum plates, using UV light or potassium permanganate as visualizing agents. All separations were performed by chromatography on Merck silica gel 60 (40-63 µm), on a Combiflash Companion from Teledyne Isco or by preparative TLC chromatography (layer thickness of 500 µm). Preparative HPLC was carried out on an Interchim puriFlash®4250 instrument and using Interchim columns (Si, 5 µm, 250 × 10.0 mm; Si, 5 µm, 250 × 21.2 mm). Sonication was performed on the Transsonic 275/H Prolabo instrument.

2. Experimental details and analytical data

(2*S*,3*S*)-3-Hydroxy-2-methylhex-5-enyl 4-methylbenzenesulfonate (**10**)



The alcohol **9** (6 g, 24.56 mmol) was dissolved in CH_2Cl_2 (25 mL) and the solution was cooled to 10 °C before addition of iodobenzene diacetate (8.70 g, 27.02 mmol) and TEMPO (0.383 g, 2.46 mmol). The orange solution was stirred and allowed to warm up to room temperature. After 2 hours, water was added to the reaction mixture and the aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were dried over anhydrous sodium sulfate and concentrated to yield the corresponding aldehyde **143** that was used without further purification. Next, to a cooled (-78 °C) commercial solution of (–)-*B*allyldiisopinocampheylborane (25.00 mmol in 25 mL of pentane) in diethyl ether (50 mL) was slowly added the aldehyde dissolved in diethyl ether (70 mL). The temperature of the reaction mixture was maintained below -70 °C during the whole addition. The solution was then stirred for another 3 hours at -78 °C before addition of methanol (7 mL), water (25 mL) and $NaBO_3$•$4H_2O$ (11.50 g, 74.74 mmol) 10 minutes later. The reaction mixture was allowed to warm up to room temperature overnight. The following morning more water was added and the aqueous layer was extracted with diethyl ether. The organic phase was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated. The crude alcohol obtained was purified by flash chromatography on silica gel (elution with petroleum ether/ethyl acetate 10:0 to 7:3) to yield alcohol **10** (3.61 g, 51%) as a colorless oil.

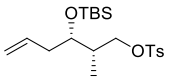
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80 (d, *J* = 8.1 Hz, 2H), 7.36 (d, *J* = 8.1 Hz, 2H), 5.76 (m, 1H), 5.14-5.09 (2H), 4.09 (m, 1H), 3.91 (m, 1H), 3.75 (m, 1H), 2.46 (s, 3H), 2.21-2.16 (2H), 1.94 (m, 1H), 1.59 (br s, 1H), 0.89 (d, *J* = 6.9 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 144.8, 134.6, 132.9, 129.8, 127.9, 118.3, 72.5, 69.3, 39.1, 37.3, 21.6, 9.7.

The spectral data are in agreement with those reported in the literature.[1]

[1] Aïssa, C.; Riveiros, R.; Ragot, J.; Fürstner, A. *J. Am. Chem. Soc.,* **2003**, *125*, 15512.

(2*S*,3*S*)-3-(*tert*-Butyldimethylsilyloxy)-2-methylhex-5-enyl 4-methylbenzenesulfonate (**SI-1**)



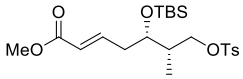
To a solution of alcohol **10** (1.00 g, 3.51 mmol) in CH_2Cl_2 (15 mL) were added imidazole (0.96 g, 14.1 mmol) and *tert*-butyldimethylsilyl chloride (1.27 g, 8.4 mmol). The solution was stirred at room temperature for 3 days. Then, water was added and the aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were dried over anhydrous sodium sulfate, filtered and concentrated. The resulting oil was purified by flash chromatography on silica gel (elution with petroleum ether/ethyl acetate 10:0 to 8:2) to afford compound **SI-1** (0.97 g, 69%) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.4 Hz, 2H), 7.35 (d, *J* = 8.1 Hz, 2H), 5.66 (m, 1H), 5.04-4.99 (2H), 3.98 (m, 1H); 3.85 (m, 1H), 3.75 (m, 1H), 2.46 (s, 3H), 2.20-2.12 (2H), 1.93 (m, 1H), 0.84 (d, *J* = 7.2 Hz, 3H), 0.82 (s, 9H), 0.02 (s, 3H), -0.03 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 144.6, 134.5, 133.0, 129.8, 127.9, 117.2, 72.8, 71.0, 39.0, 37.0, 25.7, 25.7, 25.5, 21.6, 18.0, 10.1, -4.1, -5.0.

The spectral data are in agreement with those reported in the literature.[2]

Methyl (2*E*,5*S*,6*S*)-5-[(*tert*-butyldimethylsilyl)oxy]-6-methyl-7-{[(4-methylphenyl) sulfonyl]oxy}hept-2-enoate (**11**)



A solution of **SI-1** (2 g, 5.02 mmol) and methyl acrylate (1.81 mL, 20.1 mmol) in dichloroethane (20.3 mL) was heated to 60 °C. Then Grubbs 2nd generation precatalyst (0.213 g, 0.251 mmol) diluted in dichloroethane (7.71 mL) was added dropwise to the solution over 15 minutes. After stirring for 3 hours at 60 °C, 20 mg of Grubbs 2nd generation precatalyst diluted in 1 ml of dichloroethane was added to the mixture, and then the resultant solution was stirred for further 30 minutes at 60 °C. The mixture was cooled to room temperature and filtrated through a pad of silica gel (elution with cyclohexane/EtOAc 6:4). The filtrate was evaporated and the crude residue was purified by flash chromatography on silica gel (elution with petroleum ether/ethyl acetate 10:0 to 8:2) to afford **11** (2.15 g, 94%) as a yellowish oil.

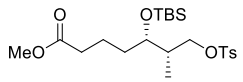
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.3 Hz, 2H), 7.35 (d, *J* = 7.9 Hz, 2H), 6.82 (dt, *J* = 15.4, 7.3 Hz, 1H), 5.81 (d, *J* = 15.6 Hz, 1H), 3.98 (dd, *J* = 9.3, 6.7 Hz, 1H), 3.89-3.81 (m, 2H), 3.74 (s, 3H), 2.46 (s, 3H), 2.37-2.25 (m, 2H), 1.90 (m, 1H), 0.85 (d, *J* = 7.2 Hz, 3H), 0.82 (s, 9H), 0.02 (s, 3H), -0.02 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3, 144.9, 144.7, 132.8, 129.7, 127.7, 123.1, 77.2, 71.9, 70.4, 51.3, 37.6, 37.1, 25.6, 21.4, 17.8, 10.5, 10.3, -4.5, -5.1.

$[\alpha]_D^{20}$ -3.2 (*c* 0.5, $CHCl_3$).

HRMS calculated for $C_{22}H_{36}O_6SSi + H^+$ 457.2075; found 457.2065 $[M + H]^+$.

Methyl (5*S*,6*S*)-5-[(*tert*-butyldimethylsilyl)oxy]-6-methyl-7-{[(4-methylphenyl) sulfonyl]oxy}heptanoate (**SI-2**)



To a solution of **11** (1.97 g, 4.31 mmol) in ethyl acetate (119 mL) was added PtO_2 (0.12 g, 0.526 mmol). Then the resultant solution was stirred for 1.5 hours at room temperature under an atmosphere of hydrogen. The mixture was filtered over Celite® and concentrated. The product **SI-2** (1.96 g, quantitative yield) was obtained as a light yellowish oil.

[2] Sasmal, P. K.; Abbineni, C.; Iqbal, J.; Mukkanti, K. *Tetrahedron*, **2010**, *66*, 5000.

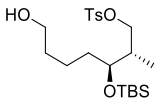
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.3 Hz, 2H), 7.35 (d, *J* = 7.9 Hz, 2H), 4.01 (dd, *J* = 9.2, 6.4 Hz, 1H), 3.85 (dd, *J* = 9.3, 7.3 Hz, 1H), 3.67 (s, 3H), 3.64 (m, 1H), 2.46 (s, 3H), 2.28 (t, *J* = 7.2 Hz, 2H), 1.93 (m, 1H), 1.55-1.45 (m, 2H), 1.44-1.33 (m, 2H), 0.84 (d, *J* = 6.8 Hz, 3H), 0.81 (s, 9H), 0.01 (s, 3H), -0.04 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 173.5, 144.6, 132.9, 129.7, 127.8, 72.5, 71.4, 51.3, 37.2, 33.7, 33.0, 25.6, 21.4, 21.0, 17.8, 10.5, -4.4, -4.9.

$[\alpha]_D^{20}$ +1.2 (*c* 0.6, $CHCl_3$).

HRMS calculated for $C_{22}H_{38}O_6SSi_2 + H^+$ 459.2231; found 459.2231 $[M + H]^+$.

(5*S*,6*S*)-5-[(*tert*-Butyldimethylsilyl)oxy]-6-methyl-7-{[(4-methylphenyl)sulfonyl]oxy}heptan-1-ol 1(**12**)



To a solution of **SI-2** (1.96 g, 4.27 mmol) dissolved in toluene (8 mL) and cooled at -78 °C, a solution of DIBAL-H (1.5 M in toluene, 7.52 mL, 9.4 mmol) was added dropwise. The mixture was allowed to warm up to room temperature and stirred for 2.5 hours. The solution was then quenched with a cooled saturated solution of Rochelle salt, and then the resultant solution was stirred at room temperature for 1 hour. The aqueous layer was extracted with Et_2O, washed with a 0.5 M aqueous HCl solution, a saturated aqueous $NaHCO_3$ solution and brine. The combined organic extracts were dried over anhydrous sodium sulfate, filtered and concentrated, affording **12** (1.82 g, quantitative yield) as a yellowish oil.

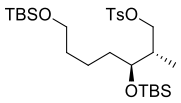
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.3 Hz, 2H), 7.35 (d, *J* = 7.9 Hz, 2H), 4.01 (dd, *J* = 9.3, 6.5 Hz, 1H), 3.85 (dd, *J* = 9.2, 7.2 Hz, 1H), 3.69-3.61 (m, 3H), 2.46 (s, 3H), 1.93 (m, 1H), 1.55-1.45 (m, 2H), 1.44-1.33 (m, 2H), 1.30-1.25 (m, 2H), 0.84 (d, *J* = 6.8 Hz, 3H), 0.81 (s, 9H), 0.01 (s, 3H), -0.04 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 144.6, 133.0, 129.8, 129.0, 128.2, 127.9, 125.2, 72.8, 71.7, 62.6, 37.3, 33.5, 32.7, 25.7, 21.8, 21.5, 17.9, 10.5, -4.2, -4.8.

$[\alpha]_D^{20}$ +1.1 (*c* 1.0, $CHCl_3$).

HRMS calculated for $C_{21}H_{38}O_5SSi_2 + H^+$ 431.2282; found 431.2283 $[M + H]^+$.

(2*S*,3*S*)-3,7-bis[(*tert*-Butyldimethylsilyl)oxy]-2-methylheptyl-4 methylbenzene-1-sulfonate (**SI-3**)



To a solution of **12** (1.79 g, 4.16 mmol) in dry DMF (41 mL) was added *tert*-butyldimethylsilyl chloride (0.689 g, 4.57 mmol) and imidazole (0.622 g, 9.14 mmol). The resulting mixture was stirred for 15 hours at room temperature. The reaction was then quenched with water and extracted with Et_2O. The combined organic extracts were washed with brine, then dried over anhydrous sodium sulfate, filtered and concentrated to give **SI-3** (2.40 g, quantitative yield) as a yellowish oil.

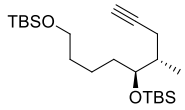
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.3 Hz, 2H), 7.35 (d, *J* = 7.9 Hz, 2H), 4.01 (dd, *J* = 9.2, 6.2 Hz, 1H), 3.85 (dd, *J* = 9.2, 6.5 Hz, 1H), 3.65 (m, 1H), 3.58 (t, *J* = 6.4 Hz, 2H), 2.46 (s, 3H), 1.93 (m, 1H), 1.55-1.45 (m, 2H), 1.44-1.33 (m, 2H), 1.30-1.25 (m, 2H), 0.90 (s, 9H), 0.84 (d, *J* = 6.7 Hz, 3H), 0.80 (s, 9H), 0.05 (s, 6H), 0.01 (s, 3H), -0.04 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 144.6, 133.1, 129.7, 127.9, 72.9, 71.9, 62.9, 37.4, 33.5, 32.8, 25.9, 25.7, 22.0, 21.6, 18.3, 17.9, 10.6, -4.3, -4.9, -5.4.

$[\alpha]_D^{20}$ +0.8 (*c* 1.0, $CHCl_3$).

HRMS calculated for $C_{27}H_{52}O_5SSi_2 + H^+$ 545.3147; found 545.3138 $[M + H]^+$.

(5*S*)-2,2,3,3,11,11,12,12-Octamethyl-5-[(2*S*)-pent-4-yn-2-yl]-4,10-dioxa-3,11-disilatridecane (**13**)



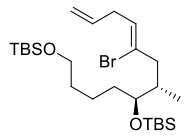
To a solution of **SI-3** (1.05 g, 1.93 mmol) in a 1:1 mixture of dry THF/DMSO (11.5 mL) was added at 0 °C the commercial lithium acetylide ethylenediamine complex (1.58 g, 15.4 mmol). The mixture was stirred at 0 °C for 8.5 hours. The reaction was then carefully quenched with addition of a 1 M aqueous solution of HCl and extracted with EtOAc. The organic layer was washed with water then brine. The combined organic extracts were dried over anhydrous sodium sulfate, filtered and concentrated. The crude residue was purified by flash chromatography on silica gel (elution with petroleum ether/ethyl acetate 10:0 to 9:1) to give **13** (0.70 g, 72%) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.70 (td, *J* = 6.1, 3.3 Hz, 1H), 3.61 (t, *J* = 6.5 Hz, 2H), 2.28 (ddd, *J* = 16.6, 6.4, 2.6 Hz, 1H), 2.04 (ddd, *J* = 16.8, 7.9, 2.6 Hz, 1H), 1.95 (t, *J* = 2.6 Hz, 1H), 1.80 (m, 1H), 1.55-1.47 (m, 2H), 1.45-1.36 (m, 2H), 1.22-1.10 (m, 2H), 0.92 (s, 9H), 0.87 (s, 9H), 0.84 (d, *J* = 6.7 Hz, 3H), 0.06 (s, 12H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 84.2, 74.0, 68.8, 63.1, 37.4, 33.6, 33.0, 26.0, 25.9, 22.3, 22.0, 18.3, 18.1, 13.6, -4.2, -4.6, -5.3.

The spectral data are in agreement with those reported in the literature.[3]

(5*S*)-5-[(2*S*,4*Z*)-4-Bromoocta-4,7-dien-2-yl]-2,2,3,3,11,11,12,12-octamethyl-4,10-dioxa-3,11-disilatridecane (**14**)



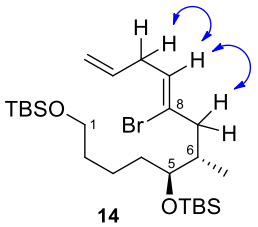
A round bottom flask was charged with $PdBr_2(PhCN)_2$ (61 mg, 0.129 mmol), $NaHCO_3$ (1.08 g, 12.9 mmol) and allyl bromide (11.2 mL, 128 mmol). The resulting solution was stirred for 20 minutes at room temperature. Then, a solution of **13** (1.03 g, 2.58 mmol) in THF (2.45 mL) was then added dropwise at room temperature over a period of 7 hours. After addition, the reaction was stirred for further 30 minutes before being filtered through a pad of silica gel and evaporated. The crude residue was then purified by flash chromatography on silica gel (elution with petroleum ether/dichloromethane 10:0 to 9:1) to afford **14** (1.30 g, 97%) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.81 (ddt, *J* = 16.9, 10.3, 6.3, 1H), 5.66 (t, *J* = 6.9 Hz, 1H), 5.13-5.09 (m, 2H), 3.61 (t, *J* = 6.3 Hz, 2H), 3.56 (m, 1H), 2.94 (t, *J* = 6.1 Hz, 2H), 2.60 (dd, *J* = 13.4, 4.1 Hz, 1H), 2.21 (m, 1H), 2.03 (m, 1H), 1.55-1.48 (m, 2H), 1.46-1.37 (m, 2H), 1.35-1.22 (m, 2H), 0.92 (s, 18H), 0.78 (d, *J* = 6.7 Hz, 3H), 0.06 (s, 12H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 135.0, 129.1, 126.9, 115.4, 74.9, 63.1, 44.7, 35.8, 35.7, 33.5, 33.0, 26.0, 22.4, 18.4, 18.2, 13.0, -4.1, -4.4, -5.3.

$[\alpha]_D^{20}$ -14.5 (*c* 0.6, $CHCl_3$).

HRMS calculated for $C_{25}H_{51}BrO_2Si_2 + Na^+$ 541.2503; found 541.2505 $[M + Na]^+$.



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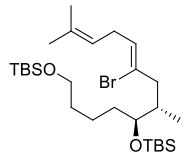
[3] Wang, G.; Yin, N.; Negishi, E.-i. *Chem. Eur. J.*, **2011**, *17*, 4118.

(*S*)-5-((*S*,*Z*)-4-Bromo-7-methylocta-4,6-dien-2-yl)-2,2,3,3,11,11,12,12-octamethyl-4,10-dioxa-3,11-disilatridecane (**15**)



To a solution of **14** (0.50 g, 0.962 mmol) dissolved in CH_2Cl_2 (0.4 mL) was added 2-methyl-2-butene (3.7 mL, 34.8 mmol). Then Grubbs 2nd generation precatalyst (16.3 mg, 0.0192 mmol) was added and the reaction mixture was stirred at room temperature overnight. The reaction mixture was filtered through a pad of silica and concentrated. The crude residue was purified by flash chromatography (elution with petroleum ether/dichloromethane 10:0 to 9:1) to give after evaporation **15** (521 mg, 99%) as a colorless oil.

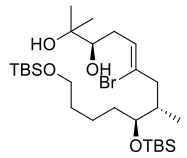
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.59 (t, *J* = 6.9, 1H), 5.14 (tsept, *J* = 7.5, 1.5 Hz, 1H), 3.61 (t, *J* = 6.4 Hz, 2H), 3.57 (m, 1H), 2.86 (t, *J* = 7 Hz, 2H), 2.56 (dd, *J* = 13.8, 3.5 Hz, 1H), 2.18 (dd, *J* = 13.8, 9.6 Hz, 1H), 2.01 (m, 1H), 1.71 (s, 3H), 1.66 (s, 3H), 1.53-1.47 (m, 2H), 1.46-1.37 (m, 2H), 1.36-1.25 (m, 2H), 0.91 (s, 18H), 0.78 (d, *J* = 6.8 Hz, 3H), 0.06 (s, 12H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 133.0, 128.5, 127.6, 120.9, 74.8, 63.1, 44.7, 35.7, 33.6, 33.1, 30.7, 26.0, 25.6, 22.3, 18.4, 18.2, 17.9, 12.9, -4.1, -4.4, -5.3.

$[\alpha]_D^{20}$ -10.0 (*c* 0.7, $CHCl_3$).

HRMS calculated for $C_{27}H_{55}BrO_2Si_2 + Na^+$ 569.2816; found 569.2822 $[M + Na]^+$.

(3*R*,8*S*,9*S*,*Z*)-6-Bromo-9,13-bis((*tert*-butyldimethylsilyl)oxy)-2,8-dimethyltridec-5-ene-2,3-diol (**16**)



A solution of AD-mix beta (2.42 g, 3.100 mmol) in H_2O (8.63 mL) and *tert*-butanol (8.63 mL) was stirred at room temperature until both phases were clear. Then, methanesulfonamide (164 mg, 1.730 mmol) was added before cooling the mixture to 0 °C. To this solution, **15** (945 mg, 1.730 mmol) was added at once. The heterogeneous slurry was vigorously stirred at 4 °C overnight. The reaction mixture was quenched by addition of solid Na_2SO_3 (300 mg) at 0 °C and then allowed to warm at room temperature and stirred for further 45 minutes. The mixture was partitioned between water and EtOAc. The organic layer was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated. The crude residue was purified by flash chromatography (elution with petroleum ether/EtOAc 10:0 to 7:3) to give after evaporation **16** (895 mg, 89%) as a light yellowish oil.

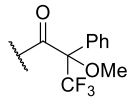
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.82 (t, *J* = 6.8 Hz, 1H), 3.61 (t, *J* = 6.4 Hz, 2H), 3.59 (m, 1H), 3.51 (dd, *J* = 10.4, 2.4 Hz, 1H), 2.61 (dd, *J* = 13.8, 3.6 Hz, 1H), 2.45 (m, 1H), 2.31-2.21 (m, 2H), 2.13 (m, 1H), 2.02 (m, 1H), 1,90 (m, 1H), 1,59 (m, 1H), 1.57-1.48 (m, 2H), 1.45-1.35 (m, 3H), 1.28 (s, 3H), 1.21 (s, 3H), 0.90 (s, 18H), 0.79 (d, *J* = 6.8 Hz, 3H), 0.06 (s, 12H).

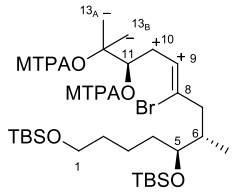
^{13}C NMR (100 MHz, $CDCl_3$) δ 130.3, 126.5, 77.6, 75.0, 72.9, 63.1, 44.7, 35.9, 34.1, 33.4, 33.0, 26.5, 26.0, 25.9, 23.5, 22.3, 18.4, 18.1, 13.0, -4.1, -4.4, -5.3.

$[\alpha]_D^{20}$ +6.4 (*c* 0.5, $CHCl_3$)

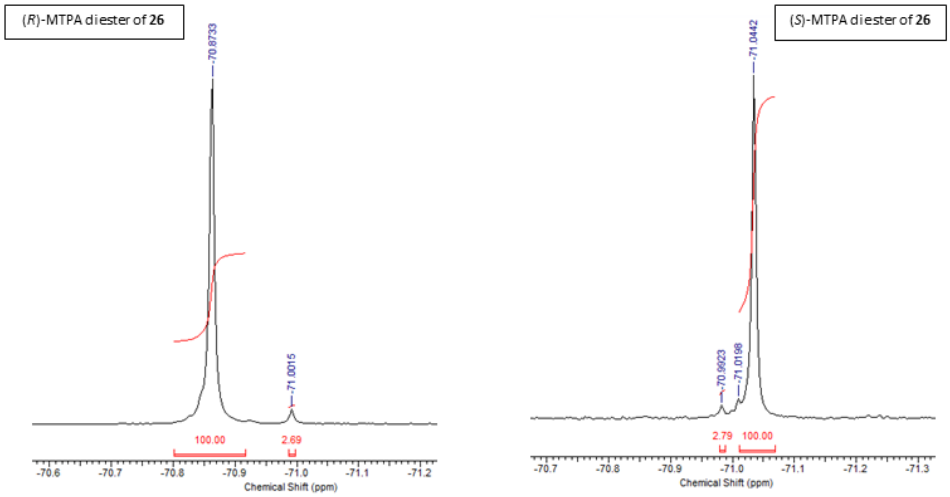
HRMS calculated for $C_{27}H_{57}BrO_4Si_2 + H^+$ 581.3052; found 581.3032 $[M + H]^+$.

(*R*)-(−)-MTPA (18 µL, 0.10 mmol), DMAP (12.6 mg, 0.103 mmol) and DCC (21 mg, 0.103 mmol) were added to a solution of **26** (10 mg, 17.2 µmol) in CH_2Cl_2 (130 µL) and stirred at 25 °C for 24 hours at which time the reaction was concentrated to dryness under reduced pressure. The crude residue was purified on preparative TLC (elution with petroleum ether/EtOAc 8:2) yielded the (*S*)-MTPA diester of **26** (9 mg) as a yellowish oil. The (*R*)-MTPA diester of **26** (9.5 mg) was obtained from **26** (10 mg, 17.2 µmol) by using (*S*)-(+)-MTPA through the same procedure as described previously.

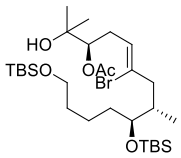
MTPA = 



	S **(ppm)**	***R*** **(ppm)**	**Δδ = Δ*S* – Δ*R* (ppm)**
H9	5,6739	5,5621	+0,1118
H10	2,6328	2,5977	+0,0351
H10'	2,5312	2,5054	+0,0258
H11	5,1416	5,0989	+0,0427
H13$_A$	1,2018	1,2689	-0,0671
H13$_B$	1,1823	1,2212	-0,0389



(3*R*,8*S*,9*S*,*Z*)-6-Bromo-9,13-bis((*tert*-butyldimethylsilyl)oxy)-2-hydroxy-2,8-dimethyltridec-5-en-3-yl acetate (**SI-4**)



To a solution of **16** (335 mg, 0.576 mmol) in pyridine (595 µL, 7.360 mmol) was added acetic anhydride (595 µL, 6.340 mmol). The reaction mixture was stirred at room temperature for 3 hours. The reaction mixture was diluted with EtOAc and water. The organic layer was washed with a saturated aqueous solution of $NaHCO_3$, brine, dried over anhydrous sodium sulfate, filtered and concentrated to give **SI-4** (359 mg, quantitative yield) as a yellowish oil. Due to instability issue on silica gel after a purification test, the crude residue was used directly and without further purification for the next step.

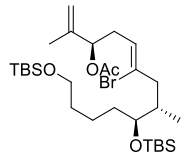
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.64 (t, *J* = 6.5 Hz, 1H), 4.90 (dd, *J* = 9.2, 3.7 Hz, 1H), 3.61 (t, *J* = 6.4 Hz, 2H), 3.55 (m, 1H), 2.62-2.48 (m, 3H), 2.15 (m, 1H), 2.10 (s, 3H), 2.00 (ddd, *J* = 10.2, 6.8, 3.3 Hz, 1H), 1.70-1.59 (m, 2H), 1.54-1.48 (m, 2H), 1.44-1.36 (m, 2H), 1.31 (m, 1H), 1.25 (s, 6H), 0.90 (s, 18H), 0.76 (d, *J* = 6.8 Hz, 3H), 0.06 (s, 12H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8, 130.5, 125.3, 78.6, 75.2, 72.3, 63.2, 44.4, 39.2, 33.1, 32.0, 26.7, 26.0, 26.0, 25.1, 22.4, 21.0, 18.1, 13.2, -4.2, -4.3, -5.3.

[α]$_D^{20}$ -8.6 (*c* 0.5, $CHCl_3$)

HRMS calculated for $C_{29}H_{59}BrO_5Si_2 + H^+$ 623.3157; found 623.3147 $[M + H]^+$.

(3*R*,8*S*,9*S*,*Z*)-6-Bromo-9,13-bis((*tert*-butyldimethylsilyl)oxy)-2,8-dimethyltrideca-1,5-dien-3-yl acetate (**SI-5**)



A solution of **SI-4** (359 mg, 0.575 mmol) in dry CH_2Cl_2 (2.67 mL) and pyridine (0.86 mL, 10.60 mmol) was stirred at 0 °C for 10 minutes Then, $SOCl_2$ (104 µL, 1.44 mmol) was added and the mixture was stirred at 0 °C for 5 minutes. Then, the reaction mixture was poured into a suspension of ice, water and Et_2O. The organic layer was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated to give **SI-5** (349 mg, quantitative yield) as a yellowish oil. Due to instability issue on silica gel after a purification test, the crude residue was used directly and without further purification for the next step.

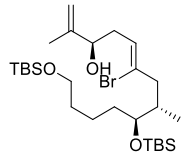
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.57 (t, *J* = 6.3 Hz, 1H), 5.26 (t, *J* = 6.5 Hz, 1H), 4.97 (s, 1H), 4.92 (s, 1H), 3.61 (t, *J* = 6.4 Hz, 2H), 3.55 (m, 1H), 2.65-2.48 (m, 3H), 2.18 (m, 1H), 2.08 (s, 3H), 2.00 (ddd, *J* = 10.0, 6.5, 3.4 Hz, 1H), 1.76 (s, 3H), 1.60-1.48 (m, 2H), 1.45-1.36 (m, 2H), 1.35-1.28 (m, 2H), 0.90 (s, 18H), 0.76 (d, *J* = 6.8 Hz, 3H), 0.06 (s, 12H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 170.1, 142.5, 130.5, 124.4, 112.9, 75.7, 75.0, 63.1, 44.5, 36.0, 34.8, 33.2, 33.1, 30.3, 29.7, 26.0, 26.0, 22.4, 21.2, 18.1, 13.1, -4.2, -4.3, -5.3.

[α]$_D^{20}$ -5.3 (*c* 0.6, $CHCl_3$)

HRMS calculated for $C_{29}H_{57}BrO_4Si_2 + H^+$ 605.3052; found 605.3055 $[M + H]^+$.

(3*R*,8*S*,9*S*,*Z*)-6-Bromo-9,13-bis((*tert*-butyldimethylsilyl)oxy)-2,8-dimethyltrideca-1,5-dien-3-ol (**SI-6**)



To a solution of **SI-5** (349 mg, 0.574 mmol) in CH_2Cl_2 (5.50 mL) cooled at -78 °C was added a solution of DIBAL-H (1.5 M in toluene, 0.957 mL, 1.44 mmol). The reaction mixture was then allowed to reach room temperature and stirred for 1.5 hours. The solution was then quenched with a cooled saturated solution of Rochelle salt, and then the resultant solution was stirred at room temperature for 1 hour. The aqueous layer was extracted with Et_2O, washed with a 0.5 M aqueous HCl solution, a saturated aqueous $NaHCO_3$ solution and brine. The combined organic extracts were dried over anhydrous sodium sulfate, filtered and concentrated to give **SI-6** (324 mg, quantitative yield) as a yellowish oil. Due to instability issue on silica gel after a purification test, the crude residue was used directly and without further purification for the next step.

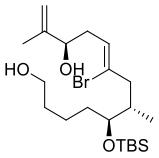
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.68 (t, *J* = 6.7 Hz, 1H), 4.99 (s, 1H), 4.88 (s, 1H), 4.19 (m, 1H), 3.61 (t, *J* = 6.4 Hz, 2H), 3.48 (m, 1H), 2.61 (m, 1H), 2.55-2.42 (m, 2H), 2.20 (m, 1H), 2.00 (m, 1H), 1.77 (s, 3H), 1.62-1.48 (m, 3H), 1.43-1.31 (m, 2H), 1.29-1.22 (m, 2H), 0.90 (s, 18H), 0.78 (d, *J* = 6.8 Hz, 3H), 0.06 (s, 12H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 146.8, 130.2, 125.4, 111.3, 75.7, 75.0, 63.1, 44.7, 32.2, 35.9, 34.4, 33.0, 26.0, 25.9, 22.3, 18.1, 17.9, 13.1, -4.1, -4.4, -5.3.

[α]$_D^{20}$ +1.2 (*c* 0.7, $CHCl_3$)

HRMS calculated for $C_{27}H_{55}BrO_3Si_2 + H^+$ 563.2946; found 563.2927 $[M + H]^+$.

(5*S*,6*S*,11*R*,*Z*)-8-Bromo-5-((*tert*-butyldimethylsilyl)oxy)-6,12-dimethyltrideca-8,12-diene-1,11-diol (**17**)



To a solution of **SI-6** (324 mg, 0.573 mmol) in THF (31.0 mL) was slowly added a solution of TBAF (1 M in THF, 1.15 mL, 1.15 mmol) at 0 °C. The reaction was stirred at 0 °C overnight. Then, the reaction was quenched with water and extracted with EtOAc. The combined organic phases were washed with a saturated aqueous $NaHCO_3$ solution, brine, dried over anhydrous sodium sulfate, filtered and concentrated. The crude residue was purified by flash chromatography (elution with petroleum ether/EtOAc 10:0 to 7:3) to give **17** (138 mg, 54% over 4 steps) as a light yellowish oil.

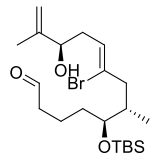
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.68 (t, *J* = 6.7 Hz, 1H), 4.99 (s, 1H), 4.88 (s, 1H), 4.18 (t, *J* = 6.3 Hz, 1H), 3.66 (t, *J* = 6.7 Hz, 2H), 3.58 (td, *J* = 5.9, 3.3 Hz, 1H), 2.58 (dd, *J* = 14.0, 3.4 Hz, 1H), 2.56-2.41 (m, 2H), 2.21 (dd, *J* = 14.0, 9.7 Hz, 1H), 2.01 (m, 1H), 1.77 (s, 3H), 1.61-1.51 (m, 4H), 1.49-1.36 (m, 2H), 1.33-1.25 (m, 2H), 0.90 (s, 9H), 0.79 (d, J = 6.8 Hz, 3H), 0.06 (d, *J* = 5.0 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 146.8, 130.1, 125.5, 111.3, 74.8, 74.7, 62.9, 44.8, 37.2, 35.8, 33.4, 32.9, 25.9, 25.9, 22.1, 18.1, 17.9, 13.1, -4.1, -4.4.

$[\alpha]_D^{20}$ +2.3 (*c* 0.6, $CHCl_3$)

HRMS calculated for $C_{21}H_{41}BrO_3Si + Na^+$ 471.1901; found 471.1903 $[M + Na]^+$.

(5*S*,6*S*,11*R*,*Z*)-8-Bromo-5-((*tert*-butyldimethylsilyl)oxy)-11-hydroxy-6,12-dimethyltrideca-8,12-dienal (**SI-7**)



To a solution of **17** (300 mg, 0.667 mmol) in CH_2Cl_2 (7.7 mL) were added TEMPO (10.4 mg, 0.067 mmol) and iodobenzene diacetate (322 mg, 1.00 mmol). The reaction was vigorously stirred at room temperature for 25 hours. Then, the reaction was quenched with a saturated aqueous $NaHCO_3$ solution and extracted with CH_2Cl_2. The organic phase was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated to give **SI-7** (298 mg, quantitative yield) as a yellowish oil. The crude residue was used directly and without further purification for the next step.

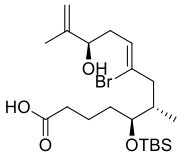
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.77 (t, *J* = 1.6 Hz, 1H), 5.68 (t, *J* = 6.7 Hz, 1H), 4.99 (s, 1H), 4.88 (s, 1H), 4.18 (t, *J* = 6.3 Hz, 1H), 3.58 (m, 1H), 2.62 (dd, *J* = 14.1, 3.8 Hz, 1H), 2.52-2.40 (m, 3H), 2.18 (m, 1H), 2.02 (ddd, *J* = 10.1, 6.7, 3.5 Hz, 1H), 1.77 (s, 3H), 1.74-1.57 (m, 2H), 1.55-1.41 (m, 2H), 1.40-1.28 (m, 2H), 0.90 (s, 9H), 0.79 (d, *J* = 6.8 Hz, 3H), 0.06 (d, *J* = 8.1 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 202.4, 146.8, 132.0, 125.7, 111.3, 75.8, 74.7, 62.9, 44.4, 43.9, 37.2, 36.0, 33.8, 32.9, 29.7, 25.9, 18.7, 18.1, 17.9, 13.2, -4.2, -4.3.

$[\alpha]_D^{20}$ -1.5 (*c* 0.2, $CHCl_3$)

HRMS calculated for $C_{21}H_{39}BrO_3Si + Na^+$469.1744; found 469.1749 $[M + Na]^+$.

(5*S*,6*S*,11*R*,*Z*)-8-Bromo-5-((*tert*-butyldimethylsilyl)oxy)-11-hydroxy-6,12-dimethyltrideca-8,12-dienoic acid (**18**)



To a solution of **SI-7** (298 mg, 0.666 mmol) in *tert*-BuOH (17.7 mL), H_2O (8.85 mL) and 2-methyl-2-butene (8.85 mL) were added NaH_2PO_4 (479 mg, 4.00 mmol) and $NaClO_2$ (246 mg, 2.73 mmol). The reaction was vigorously stirred at room temperature for 4 hours. Then, the reaction was quenched with a saturated aqueous NH_4Cl solution and extracted with EtOAc. The combined organic phases were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated to give **18** (309 mg, quantitative yield) as a yellowish oil. Due to instability issue on silica gel after a purification test, the crude residue was used directly and without further purification for the next step.

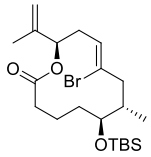
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.68 (t, *J* = 6.7 Hz, 1H), 4.99 (s, 1H), 4.88 (s, 1H), 4.18 (t, *J* = 6.3 Hz, 1H), 3.60 (m, 1H), 2.62 (dd, *J* = 14.0, 3.9 Hz, 1H), 2.55-2.43 (m, 2H), 2.37 (t, *J* = 7.3 Hz, 1H), 2.20 (m, 1H), 2.04 (m, 1H), 1.77 (s, 3H), 1.72-1.55 (m, 2H), 1.51-1.38 (m, 2H), 1.34-1.21 (m, 2H), 0.90 (s, 9H), 0.80 (d, *J* = 6.8 Hz, 3H), 0.08-0.06 (m, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 169.2, 146.8, 132.2, 128.4, 111.3, 74.7, 74.5, 44.5, 37.2, 35.9, 32.8, 29.7, 25.9, 22.7, 21.2, 18.1, 17.9, 13.3, -4.2, -4.3.

$[\alpha]_D^{20}$ -3.5 (*c* 0.4, $CHCl_3$)

HRMS calculated for $C_{21}H_{39}O_4Si + Na^+$ 485.1693; found 485.1699 $[M + Na]^+$.

(6*S*,7*S*,12*R*,*Z*)-9-Bromo-6-((*tert*-butyldimethylsilyl)oxy)-7-methyl-12-(prop-1-en-2-yl)oxacyclododec-9-en-2-one (**19**)



To a solution of **18** (309 mg, 0.700 mmol) in benzene (13.1 mL) were added *i*-Pr_2NEt (0.859 mL, 5.20 mmol) and 2,4,6-trichlorobenzoyl chloride (0.412 mL, 2.63 mmol). The mixture was stirred at room temperature for 1 hour. In a separate flask, DMAP (305 mg, 2.50 mmol) was dissolved in benzene (283 mL). To this solution was added dropwise the anhydride solution via a syringe pump over 12 hours. The mixture was then stirred for 6 more hours. The reaction mixture was quenched with a saturated aqueous $NaHCO_3$ solution and extracted with EtOAC. The organic layer was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated. The crude residue was purified by column chromatographic (elution with petroleum ether/EtOAc 10:0 to 9:1) to give after evaporation **19** (141 mg, 48% over 3 steps) as a yellowish oil.

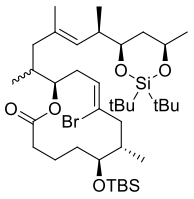
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.55 (dd, *J* = 10.6, 3.8 Hz, 1H), 5.40 (dd, *J* = 12.0, 2.6 Hz, 1H), 5.02 (s, 1H), 4.92 (s, 1H), 3.45 (ddd, *J* = 9.0, 4.7, 2.1 Hz, 1H), 2.94 (m, 1H), 2.59 (dt, *J* = 12.4, 4.1 Hz, 1H), 2.35-2.24 (m, 3H), 2.09 (ddd, *J* = 9.3, 6.1, 3.8 Hz, 1H), 2.01 (td, *J* = 12.6, 4.0 Hz, 1H), 1.79 (s, 3H), 1.76-1.64 (m, 2H), 1.62-1.51 (m, 2H), 1.00 (d, *J* = 6.8 Hz, 3H), 0.90 (s, 9H), 0.05 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 173.0, 143.0, 132.9, 124.7, 112.3, 76.6, 73.6, 46.5, 36.5, 35.9, 34.5, 33.6, 25.9, 20.8, 18.6, 18.5, 18.1, 14.1, -4.2, -4.8.

$[\alpha]_D^{20}$ -35.5 (*c* 0.5, $CHCl_3$)

HRMS calculated for $C_{21}H_{37}BrO_3Si + H^+$ 445.1768; found 445.1762 $[M + H]^+$.

(6*S*,7*S*,12*R*,*Z*)-9-Bromo-6-((*tert*-butyldimethylsilyl)oxy)-12-((2*S*,6*R*,*E*)-6-((4*R*,6*R*)-2,2-di-*tert*-butyl-6-methyl-1,3,2-dioxasilinan-4-yl)-4-methylhept-4-en-2-yl)-7-methyloxacyclododec-9-en-2-one (**20**)



To a solution of **19** (100 mg, 0.225 mmol) dissolved in THF (0.854 mL) and cooled at 0 °C was added 9-BBN dimer (109 mg, 0.450 mmol). The mixture was then allowed to warm up to room temperature and stirred for 2 hours under ultrasounds

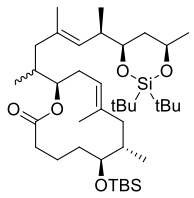
radiation (sonication). In the meantime, a mixture of **4** (114 mg, 0.269 mmol), Cs_2CO_3 (248 mg, 0.761 mmol) and $AsPh_3$ (20.6 mg, 0.0671 mmol) in a mix of DMF (1.38 mL) and H_2O (0.256 mL) was prepared in a separate flask. The borane solution was cooled down to room temperature before being cannulated into the previously prepared compound **4** solution. The mixture was degassed by freeze-pump-thaw cycles and then $Pd(dppf)Cl_2$ (24.6 mg, 0.0336 mmol) was added. The reaction was protected from light and stirred at room temperature overnight. Then, the reaction mixture was quenched by addition of water and Et_2O. The layers were separated and the aqueous layer was extracted twice with Et_2O. The combined organic extracts were washed with brine, dried over anhydrous sodium sulfate and evaporated. The crude residue was purified by column chromatography (elution with petroleum ether/EtOAc 10:0 to 95:5) to give **20** (100 mg, 60% over 2 steps) as a yellowish oil and as a mixture of isomers that was not separated (C12-(*R*)/C12-(*S*) 2:8).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.45 (dd, *J* = 10.7, 3.7 Hz, 1H), 4.97 (d, *J* = 9.8 Hz, 1H), 4.91 (ddd, *J* = 11.8, 5.9, 3.0 Hz, 1H), 4.14 (m, 1H), 3.70 (m, 1H), 3.44 (m, 1H), 2.80 (m, 1H), 2.56 (dt, *J* = 12.2, 4.0 Hz, 1H), 2.35 (m, 1H), 2.28-2.22 (m, 2H), 2.20-2.14 (m, 2H), 2.08-1.87 (m, 3H), 1.80-1.70 (m, 4H), 1.61 (s, 3H), 1.58-1.48 (m, 2H), 1.44-1.23 (m, 2H), 1.19 (d, *J* = 6.0 Hz, 3H), 1.17-1.10 (m, 2H), 1.01 (s, 9H), 1.00-0.99 (m, 3H), 0.98 (s, 9H), 0.89 (s, 9H), 0.85 (d, *J* = 6.5 Hz, 3H), 0.05 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 173.5, 132.6, 132.5, 129.9, 125.1, 77.8, 76.3, 74.5, 70.5, 46.4, 43.2, 41.7, 40.4, 35.9, 34.8, 34.5, 33.8, 33.6, 29.7, 27.6, 27.2, 25.9, 24.9, 22.7, 20.8, 19.6, 18.5, 18.1, 16.7, 16.1, 14.5, -4.2, -4.8.

HRMS calculated for $C_{38}H_{71}BrO_5Si_2 + H^+$ 743.4096; found 743.4095 $[M + H]^+$.

(6*S*,7*S*,12*R*,*E*)-6-((*tert*-Butyldimethylsilyl)oxy)-12-((2*S*,6*R*,*E*)-6-((4*R*,6*R*)-2,2-di-*tert*-butyl-6-methyl-1,3,2-dioxasilinan-4-yl)-4-methylhept-4-en-2-yl)-7,9-dimethyloxacyclododec-9-en-2-one (**21a**)



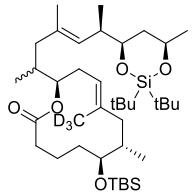
To a dried sealable vial was added $Pd(PPh_3)_4$ (1.74 mg, 1.51 µmol). The vial was pumped out under high vacuum and backfilled with nitrogen (three times). Then, a solution of dimethylzinc (1.2 M in toluene, 108 µL, 0.129 mmol) was added and the yellow resulting mixture was cooled to 0 °C before the slow addition of **20** (16 mg, 21.5 µmol) dissolved in THF (240 µL). The reaction mixture was then stirred at 90 °C for 15 hours. The mixture was carefully quenched with water and extracted with Et_2O. The organic layer was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated. The crude residue was purified by flash chromatography (elution with petroleum ether/dichloromethane 10:0 to 9:1) to give **21a** (11 mg, 75%) as a colorless oil and as a mixture of isomers that was not separated (C12-(*R*)/C12-(*S*) 2:8).

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.96 (d, *J* = 9.8 Hz, 2H), 4.83 (ddd, *J* = 11.7, 5.7, 3.0 Hz, 1H), 4.14 (m, 1H), 3.69 (ddd, *J* = 11.2, 7.7, 1.5 Hz, 1H), 3.37 (dd, *J* = 9.1, 2.3 Hz, 1H), 2.54-2.30 (m, 3H), 2.10 (dd, *J* = 13.1, 5.0 Hz, 1H), 2.04-1.90 (m, 2H), 1.88-1.76 (m, 3H), 1.74-1.69 (m, 2H), 1.67 (s, 3H), 1.62 (d, *J* = 1.0 Hz, 3H), 1.58 (m, 1H), 1.44-1.32 (m, 2H), 1.19 (d, *J* = 6.0 Hz, 3H), 1.01 (s, 9H), 0.98 (s, 9H), 0.97 (m, 9H), 0.90 (s, 9H), 0.85 (d, *J* = 6.5 Hz, 3H), 0.04 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 173.5, 137.3, 132.8, 129.8, 121.4, 77.9, 77.5, 75.5, 70.5, 45.4, 43.4, 41.7, 40.5, 36.0, 35.3, 34.7, 33.4, 30.9, 29.6, 27.6, 27.2, 25.9, 24.9, 22.7, 21.7, 19.6, 18.6, 18.1, 16.7, 16.1, 15.7, 14.8, 14.5, -4.2, -4.7.

HRMS calculated for $C_{39}H_{74}O_5Si_2 + Na^+$ 701.4967; found 701.4974 $[M + Na]^+$.

(6*S*,7*S*,12*R*,*E*)-6-((*tert*-Butyldimethylsilyl)oxy)-12-((2*S*,6*R*,*E*)-6-((4*R*,6*R*)-2,2-di-*tert*-butyl-6-methyl(d3)-1,3,2-dioxasilinan-4-yl)-4-methylhept-4-en-2-yl)-9-methyl(d3)-7methyloxacyclododec-9-en-2-one (**21b**)



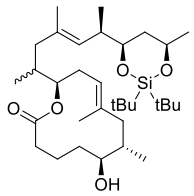
To a dried sealable vial was added $Pd(PPh_3)_4$ (2.1 mg, 1.79 µmol). The vial was pumped out under high vacuum and backfilled with nitrogen (three times). Then, a solution of d_6-dimethylzinc (306 µL, 0.153 mmol, prepared from commercially available CD_3Li and a 0.5 M stock solution of flame-dried $ZnCl_2$ in Et_2O) was added and the yellow resulting mixture was cooled to 0 °C before the slow addition of **20** (19 mg, 0.026 mmol) dissolved in THF (570 µL). The reaction mixture was then stirred at 90 °C for 20 hours. The mixture was carefully quenched with water and extracted with Et_2O. The organic layer was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated. The crude residue was purified by flash chromatography (elution with petroleum ether/EtOAc 10:0 to 95:5) to give **21b** (13 mg, 75%) as a colorless oil and as a mixture of isomers that was not separated (C12-(*R*)/C12-(*S*) 2:8).

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.96 (d, *J* = 10.3 Hz, 2H), 4.83 (ddd, *J* = 11.8, 5.5, 3.0 Hz, 1H), 4.14 (m, 1H), 3.69 (dd, *J* = 10.3, 8.6 Hz, 1H), 3.36 (ddd, *J* = 11.2, 7.7, 1.5 Hz, 1H), 2.52-2.28 (m, 3H), 2.10 (dd, *J* = 13.1, 5.0 Hz, 1H), 2.04-1.90 (m, 2H), 1.88-1.76 (m, 3H), 1.74-1.66 (m, 2H), 1.62 (d, *J* = 0.5 Hz, 3H), 1.60 (m, 1H), 1.44-1.32 (m, 2H), 1.19 (d, *J* = 6.0 Hz, 3H), 1.01 (s, 9H), 0.98-096 (m, 18H), 0.90 (s, 9H), 0.85 (d, *J* = 6.5 Hz, 3H), 0.04 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 173.5, 137.3, 132.8, 129.8, 121.5, 77.8, 77.5, 75.5, 70.5, 45.3, 43.4, 41.7, 40.5, 36.0, 35.3, 34.8, 33.4, 29.7 29.5, 27.6, 27.2, 25.9, 24.9, 22.7, 21.7, 19.6, 18.6, 18.1, 16.7, 16.1, 14.8, 14.5, -4.2, -4.8.

HRMS calculated for $C_{39}H_{71}D_3O_5Si_2 + Na^+$ 704.5155; found 704.5143 $[M + Na]^+$.

(6*S*,7*S*,12*R*,*E*)-12-((2S,6*R*,*E*)-6-((4*R*,6*R*)-2,2-di-*tert*-Butyl-6-methyl-1,3,2-dioxasilinan-4-yl)-4-methylhept-4-en-2-yl)-6-hydroxy-7,9-dimethyloxacyclododec-9-en-2-one (**22a**)



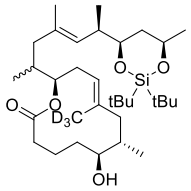
To a solution of **21a** (33 mg, 0.049 mmol) in THF (1.41 mL) were added AcOH (1.57 mL, 27.5 mmol) and the commercial Dowex® 50WX8-400 hydrogen form resin pre-washed with MeOH (50 mg). The reaction mixture was stirred at 65 °C overnight. Then, the reaction mixture was cooled down to room temperature, filtered and partitioned between water and EtOAc. The organic layer was then washed with a saturated aqueous $NaHCO_3$ solution, brine, dried over anhydrous sodium sulfate, filtered and concentrated. The crude residue was purified by preparative TLC (elution with CH_2Cl_2/MeOH 98:2) to give **22a** (17.2 mg, 63%) as a light yellowish oil and as a mixture of isomers (C12-(*R*)/C12-(*S*) 2:8).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.04-4.95 (m, 3H), 4.14 (m, 1H), 3.70 (ddd, *J* = 11.5. 7.4, 1.8 Hz, 1H), 3.50 (m, 1H), 2.45 (td, *J* = 14.3, 11.2 Hz, 1H), 2.33-2.22 (m, 3H), 2.15-2.04 (m, 2H), 2.00-1.79 (m, 4H), 1.80-1.55 (m, 5H), 1.62 (s, 3H), 1.60 (d, *J* = 1.3 Hz, 3H), 1.40-1.25 (m, 3H), 1.18 (d, *J* = 6.3 Hz, 3H), 1.02-0.91 (m, 6H), 1.01 (s, 9H), 0.98 (s, 9H), 0.86 (d, *J* = 6.4 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 175.2, 137.0, 132.6, 129.9, 123.1, 77.8, 77.2, 71.0, 70.5, 45.4, 43.3, 41.7, 40.4, 35.0, 34.9, 34.8, 34.0, 30.0, 27.6, 27.2, 24.9, 22.7, 20.3, 19.6, 16.7, 16.5, 16.1, 14.7.

The spectral data are in agreement with those reported in the literature.[4]

(6*S*,7*S*,12*R*,*E*)-12-((2S,6*R*,*E*)-6-((4*R*,6*R*)-2,2-di-*tert*-Butyl-6-methyl-1,3,2-dioxasilinan-4-yl)-4-methylhept-4-en-2-yl)-6-hydroxy-9-methyl(d3)-7-methyloxacyclododec-9-en-2-one (**22b**)



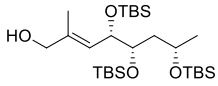
To **21a** (13 mg, 0.019 mmol) were added AcOH (1.21 mL, 21.17 mmol) and the commercial Dowex® 50WX8-400 hydrogen form resin pre-washed with MeOH (40 mg). The reaction mixture was stirred at 50 °C overnight. Then, the reaction mixture was cooled down to room temperature, filtered and partitioned between water and EtOAc. The organic layer was then washed with a saturated aqueous $NaHCO_3$ solution, brine, dried over anhydrous sodium sulfate, filtered and concentrated. The crude residue was purified by preparative TLC (elution with CH_2Cl_2/MeOH 98:2) to give **22b** (6 mg, 55%) as a light yellowish oil and as a mixture of isomers (C12-(*R*)/C12-(*S*) 2:8).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.08-4.95 (m, 3H), 4.14 (m, 1H), 3.70 (m, 1H), 3.52 (m, 1H), 2.46 (td, *J* = 14.2, 11.4 Hz, 1H), 2.36-2.22 (m, 3H), 2.15-2.04 (m, 2H), 2.00-1.79 (m, 4H), 1.80-1.55 (m, 5H), 1.61 (d, *J* = 1.0 Hz, 3H), 1.40-1.25 (m, 3H), 1.19 (d, *J* = 6.0 Hz, 3H), 1.02-0.91 (m, 6H), 1.01 (s, 9H), 0.98 (s, 9H), 0.86 (d, *J* = 6.5 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 175.2, 137.0, 132.6, 129.9, 123.1, 77.8, 77.2, 71.0, 70.5, 45.3, 43.3, 41.7, 40.4, 35.0, 34.9, 34.8, 34.0, 30.0, 29.7, 27.6, 27.2, 24.9, 22.7, 20.3, 19.6, 16.7, 16.1, 14.7.

HRMS calculated for $C_{33}H_{57}D_3O_5Si + Na^+$ 590.4291; found 590.4286 $[M + Na]^+$.

(4*S*,5*S*,7*S*,*E*)-4,5,7-tris((*tert*-Butyldimethylsilyl)oxy)-2-methyloct-2-en-1-ol (**SI-8**)



To a stirred solution of **23** (300 mg, 0.52 mmol) in dry CH_2Cl_2 (5.5 mL) was added a solution of DIBAL-H (1.5 M in toluene 1.46 mL, 2.20 mmol) at -78 °C. The reaction mixture was allowed to reach 0 °C and was stirred this temperature for 1 hour. The solution was then quenched with a cooled saturated aqueous solution of Rochelle salt, and then the resultant solution was stirred at room temperature for 3 hours. The aqueous layer was extracted with Et_2O and the combined organic extracts were washed with water, brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give **SI-8** (271 mg, 97%) as a colorless oil.

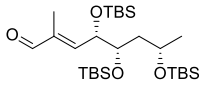
^{1}H NMR (300 MHz, $CDCl_3$) δ 5.46 (dd, *J* = 9.1, 1.1 Hz, 1H), 4.33 (dd, *J* = 9.1, 3.8 Hz, 1H), 4.01 (s,2H), 3.91 (m, 1H), 3.60 (dt, *J* = 7.9, 3.8 Hz, 1H), 1.83 (ddd, *J* = 13.3, 8.4, 3.9, 8.4 Hz, 1H), 1.71 (q, *J* = 1.1 Hz, 3H), 1.59 (ddd, *J* = 13.3, 8.3, 5.0 Hz, 1H), 1.29 (m, 1H), 1.13 (d, *J* = 6.0 Hz, 3H), 0.88 (s, 9H), 0.87 (s, 9H), 0.86 (s, 9H), 0.05 (s, 6H), 0.04 (s, 3H), 0.03 (s, 3H), 0.02 (s, 3H), -0.02 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 136.4, 125.8, 73.4, 70.9, 68.9, 66.1, 42.5, 25.9, 25.8, 23.4, 18.2, 18.1, 18.0, 14.6, -4.1, -4.2, -4.3, -4.5, -4.6, -4.7.

The spectral data are in agreement with those reported in the literature.[5]

[4] Gersbach, P.; Jantsch, A.; Feyen, F.; Scherr, N.; Dangy, J.-P.; Pluschke, G.; Altmann, K.-H. *Chem. Eur. J.*, **2011**, *17*, 13017.
[5] Song, F.; Fidanze, S.; Benowitz, A. B.; Kishi, Y. *Org. Lett.*, **2002**, *4*, 647.

(4*S*,5*S*,7*S*,*E*)-4,5,7-tris((*tert*-Butyldimethylsilyl)oxy)-2-methyloct-2-enal (**SI-9**)



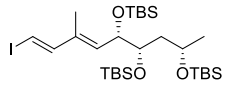
To a stirred solution of **SI-8** (250 mg, 0.469 mmol) in CH_2Cl_2 (2.71 mL) was added MnO_2 (611 mg, 7.04 mmol). The resulting mixture was warmed up to 40 °C and stirred for 24 hours. The reaction mixture was then cooled to room temperature, filtered through a pad of Celite® with CH_2Cl_2, and concentrated under reduced pressure to afford **SI-9** (250 mg, quantitative yield) as a yellowish oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.45 (s, 1H), 6.44 (dd, *J* = 8.4, 1.3 Hz, 1H), 4.56 (dd, *J* = 8.4, 3.7 Hz, 1H), 3.91 (m, 1H) , 3.72 (dt, *J* = 8.1, 3.9 Hz, 1H) , 1.90 (ddd, *J* = 13.2, 8.2, 4.0 Hz, 1H), 1.80 (q, *J* = 1.3 Hz, 3H), 1.61 (m, 1H), 1.15 (d, *J* = 6.0 Hz, 3H), 0.88 (s, 9H), 0.87 (s, 9H), 0.86 (s, 9H), -0.02 (18H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 195.6, 152.8, 138.9, 73.3, 71.2, 65.7, 42.4, 25.9, 25.8, 25.7, 23.3, 18.1, 18.0, 17.9, 10.2, -4.1, -4.3, -4.4, -4.5, -4.6.

The spectral data are in agreement with those reported in the literature.[5]

(1*E*,3*E*)-(*5S,6S,8S*)-tris-(*tert*-Butyldimethylsilyloxy)-1-iodo-3-methyl-nona-1,3-diene (**SI-10**)



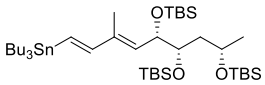
To a stirred solution of $CrCl_2$ (347 mg, 2.82 mmol) in THF (3.02 mL) under nitrogen atmosphere was added dropwise a solution of **SI-9** (250 mg, 0.471 mmol) and CHI_3 (200 mg, 1.41 mmol) dissolved in THF (2.07 mL). The reaction mixture was stirred at room temperature for 12 hours. Then, the mixture was quenched with water and diluted with Et_2O. The aqueous layer was extracted three times with Et_2O and the combined organic extracts were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude residue was purified by column chromatography (elution with petroleum ether/ CH_2Cl_2 10:0 to 9:1) to give after evaporation **SI-10** (262 mg, 85%) as a red oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.00 (d, *J* = 14.9 Hz, 1H), 5.99 (d, *J* = 14.9 Hz, 1H), 5.52 (d, *J* = 9.2 Hz, 1H), 4.48 (dd, *J* = 9.2, 3.8 Hz, 1H), 4.08 (dt, *J* = 7.5, 5.9 Hz, 1H), 3.81 (dt, *J* = 7.8, 3.8 Hz, 1H), 2.09 (ddd, *J* = 13.4, 7.8, 4.4 Hz, 1H), 1.86 (ddd, *J* = 13.4, 7.5, 5.6 Hz, 1H), 1.55 (q, *J* = 1.1 Hz, 3H), 1.26 (d, *J* = 5.9 Hz, 3H), 1.00 (s, 9H), 0.96 (s, 9H), 0.92 (s, 9H), 0.13 (s, 6H), 0.09 (s, 3H), 0.08 (s, 3H), 0.05 (s, 3H), 0.01 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 149.2, 135.2, 133.8, 76.5, 71.4, 73.9, 66.3, 43.4, 26.1, 26.0, 25.9, 23.9, 18.3, 12.9, -4.0, -4.1, -4.3, -4.5.

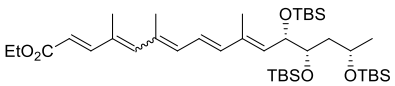
The spectral data are in agreement with those reported in the literature.[3]

(1*E*,3*E*)-(*5S,6S,8S*)-tris-(*tert*-Butyldimethylsilyloxy)-1-tributylstannyl-3-methyl-nona-1,3-diene (**24**)



To a solution of **SI-10** (205 mg, 0.313 mmol) in Et_2O (1.64 mL) at -78 °C was added a solution of *n*-BuLi (2.3 M in hexane, 0.204 mL, 0.47 mmol) and the reaction was stirred for 20 minutes before the addition of tributyltin chloride (0.127 mL, 0.47 mmol). The reaction mixture was then allowed to warm to room temperature and was stirred for 1 hour. The reaction mixture was quenched with a saturated aqueous $NaHCO_3$ solution and diluted with Et_2O. The organic layer was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated to give **24** (256 mg) as a yellowish oil. The crude product was used without further purification for the next step.

(*2E,4E,6E,8E,10E*)-(*12S,13S,15S*)-Ethyl-12,13,15-tris(*tert*-butyldimethylsilyloxy)-4,6,10- trimethylhexadeca-2,4,6,8,10-pentaenoate (**SI-11**)



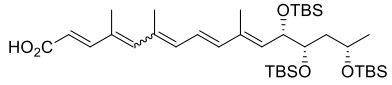
A degassed solution of **24** (256 mg, 0.314 mmol) and **25** (100 mg, 0.327 mmol) in DMF (1.98 mL) was added at room temperature to a flask containing a flamme-dried tetrabutylammonium diphenyl phosphinate (185 mg, 0.377 mmol). After 5 minutes of stirring, CuTc (89.8 mg, 0.471 mmol) followed by $Pd(PPh_3)_4$ (29 mg, 0.0251 mmol) were added. The resulting black-brown mixture was stirred at room temperature for 1 hour. Then, the reaction mixture was quenched with water and diluted with Et_2O. The organic layer was washed with brine, dried over anhydrous sodium sulfate, filtered throught a short pad of silica and evaporated. The crude residue was purified by flash chromatography (elution with petroleum ether/EtOAC 10:0 to 9:1) to give **SI-11** (197 mg, 89%) as a yellowish oil as a mixture of isomers that was not separated (*E*-$\Delta^{4'\text{-}5'}$/*Z*-$\Delta^{4'\text{-}5'}$ 75:25).

^{1}H NMR *E*-$\Delta^{4'\text{-}5'}$ (400 MHz, $CDCl_3$) δ 7.37 (d, *J* = 15.5 Hz, 1H), 6.50 (dd, *J* = 15.5, 11.1, 1H), 6.37 (d, *J* = 15.5 Hz, 1H), 6.35 (s, 1H), 6.27 (d, *J* = 11.2 Hz, 1H), 5.86 (d, *J* = 15.5 Hz, 1H), 5.58 (d, *J* = 8.9 Hz, 1H), 4.43 (dd, *J* = 8.9, 3.6 Hz, 1H), 4.22 (q, *J* = 7.1 Hz, 2H), 3.91 (dt, *J* = 7.6, 5.8 Hz, 1H), 3.64 (dt, *J* = 7.6, 3.6 Hz, 1H), 2.05 (s, 3H), 2.02 (s, 3 H), 1.85 (s, 3H), 1.80 (m, 1H), 1.62 (m, 1H), 1.31 (t, *J* = 7.1 Hz, 3H), 1.14 (d, *J* = 5.8 Hz, 3H), 0.88 (s, 9H), 0.87 (s, 9H), 0.86 (s, 9H), 0.05 (s, 9H), 0.04 (s, 3H), 0.02 (s, 3H), -0.02 (s, 3H).

^{13}C NMR *E*-$\Delta^{4'\text{-}5'}$ (100 MHz, $CDCl_3$) δ 167.5, 150.7, 143.7, 139.8, 135.1, 134.6, 134.3, 134.0, 132.2, 123.7, 116.2, 73.7, 71.4, 66.1, 60.2, 42.7, 25.9, 25.8, 23.5, 18.1, 18.0, 17.9, 17.1, 14.4, 14.2, 13.5, -4.1, -4.3, -4.5, -4.6, -4.7.

The spectral data are in agreement with those reported in the literature.[6]

(2*E*,4*E*,6*E*,8*E*,10*E*,12*S*,13*S*,15*S*)-12,13,15-tris(*tert*-Butyldimethylsilyloxy)-4,6,10-trimethylhexadeca- 2,4,6,8,10-pentaenoic acid (**26**)



To a stirred solution of **SI-11** (197 mg, 0.279 mmol) in a 4:1:1 mixture of THF (7 mL)/H_2O (1.75 mL)/EtOH (1.75 mL) was added LiOH•H_2O (116 mg, 2.79 mmol). The resulting mixture was stirred at room temperature for 38 hours. Then, the reaction mixture was quenched by addition of a saturated aqueous NH_4Cl solution and was diluted with EtOAc. The organic layer was washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude residue was purified by flash chromatography (elution with CH_2Cl_2/MeOH 10:0 to 9:1) to afford **26** (153 mg, 81%) as a yellowish oil and as a mixture of isomers that was not separated (*E*-$\Delta^{4'\text{-}5'}$/*Z*-$\Delta^{4'\text{-}5'}$ 75:25).

^{1}H NMR *E*-$\Delta^{4'\text{-}5'}$ (400 MHz, Acetone-d6) δ 7.36 (d, *J* = 15.5 Hz, 1H), 6.67 (dd, *J* = 15.0, 11.2 Hz, 1H), 6.48 (d, *J* = 15.0 Hz, 1 H), 6.46 (s, 1H), 6.39 (d, *J* = 11.2 Hz, 1H), 5.87 (d, *J* = 15.5 Hz, 1H), 5.67 (d, *J* = 9.1 Hz, 1H), 4.58 (dd, *J* = 9.1, 3.4 Hz, 1H), 4.01 (m, 1H), 3.78 (m, 1H), 2.09 (s, 3H), 2.06 (s, 3H), 1.94 (s, 3H), 1.87 (m, 1H), 1.66 (m, 1H), 1.17 (d, *J* = 6.0 Hz, 3H), 0.91 (27H), 0.09 (18H).

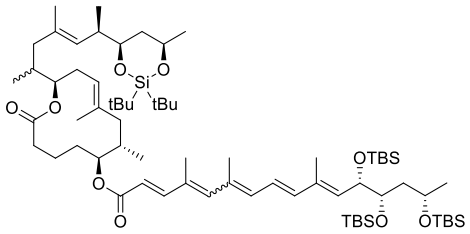
^{13}C NMR *E*-$\Delta^{4'\text{-}5'}$ (100 MHz, Acetone-d6) δ 169.2, 152.6, 145.3, 141.2, 137.1, 136.4, 136.0, 135.7, 134.2, 126.3, 118.1, 76.3, 73.0, 67.7, 44.9, 27.4, 27.3, 25.2, 22.2, 18.2, 15.3, 14.8, -2.7, -2.9,-3.0, -3.1, -3.3, -3.4.

The carboxylic acid **26** was then photoisomerized in acetone for 1 hour, using a green fluorescent bulb, in order to obtain **26** with a *E*-$\Delta^{4'\text{-}5'}$/*Z*-$\Delta^{4'\text{-}5'}$ = 1:1 ratio, as detected by ^{1}H NMR. The spectrum emission of the fluorescent bulb at 5 cm is the following: 365, 405, 435, 486, 541, 545, 576, 578 and 610 nm; the intensity integrated on 300-800 nm is 12 mW/cm^2.

The spectral data are in agreement with those reported in the literature.[5]

[6] Chany, A.-C.; Casarotto, V.; Schmitt, M.; Tarnus, C.; Guenin-Macé, L.; Demangel, C.; Mirguet, O.; Eustache, J.; Blanchard, N. *Chem. Eur. J.*, **2011**, *17*, 14413.

(2*E*,8*E*,10*E*,12*S*,13*S*,15*S*)-(6*S*,7*S*,12*R*,*E*)-12-((2*S*,6*R*,*E*)-6-((4*R*,6*R*)-2,2-di-*tert*-Butyl-6-methyl-1,3,2-dioxasilinan-4-yl)-4-methylhept-4-en-2-yl)-7,9-dimethyl-2-oxooxacyclododec-9-en-6-yl 12,13,15-tris((*tert*-butyldimethylsilyl)oxy)-4,6,10-trimethylhexadeca-2,4,6,8,10-pentaenoate (**SI-12a**)



To a solution of **26** (28.9 mg, 0.0425 mmol) in THF (2.48 mL) were added *i*-Pr_2NEt (28.4 µL, 0.172 mmol), 2,4,6-trichlorobenzoyl chloride (14 µL, 0.0871 mmol) followed by DMAP (26 mg, 0.212 mmol). Then, **22a** (12 mg, 0.0212 mmol) dissolved in THF (0.920 mL) was added and the reaction was stirred at room temperature protected from light for 2 hours. The reaction mixture was quenched with a saturated aqueous $NaHCO_3$ solution and extracted with EtOAC. The organic layer was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated. The crude residue was purified by preparative TLC (elution with petroleum ether/EtOAc 9:1) to give after evaporation **SI-12a** (24 mg, 92%) as a yellowish oil and as a mixture of isomers that was not separated (*E*-$\Delta^{4'\text{-}5'}$/*Z*-$\Delta^{4'\text{-}5'}$ 1:1; C12-(*R*)/C12-(*S*) 2:8).

^{1}H NMR *Z*-$\Delta^{4'\text{-}5'}$ (400 MHz, Acetone-d6) δ 7.93 (d, *J* = 15.6 Hz, 1H), 6.66 (dd, *J* = 15.1, 11.1 Hz, 1H), 6.41 (d, *J* = 15.5 Hz, 1H), 6.34 (s 1H), 6.19 (d, *J* = 10.6 Hz, 1H), 5.93 (d, *J* = 15.4 Hz, 1H), 5.67 (m, 1H), 5.12-5.05 (m, 2H), 4.88 (m, 1H), 4.71 (m, 1H), 4.58 (dd, *J* = 9.2, 3.1 Hz, 1H), 4.21 (m, 1H), 4.00 (m, 1H), 3.82-3.76 (m, 2H), 2.54-2.37 (m, 3H), 2.12-1.88 (m, 10H), 1.98 (s, 3H), 1.95 (s, 3H), 1.82-1.57 (m, 6H), 1.71 (br. s, 3H), 1.66 (s, 3H), 1.43-1.30 (m, 3H), 1.20 (d, *J* = 5.8 Hz, 3H), 1.17 (d, *J* = 6.0 Hz, 3H), 1.05 (br. s, 3H), 1.03 (s, 9H), 1.00 (s, 9H), 0.96-0.85 (m, 33H), 0.11-0.06 (m, 12H), 0.04 (s, 3H), 0.03 (s, 3H).

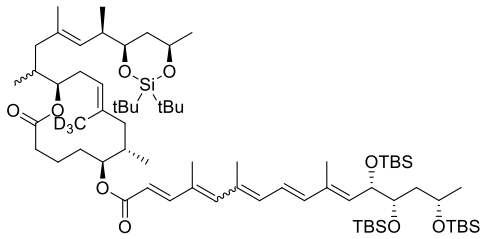
^{13}C NMR *Z*-$\Delta^{4'\text{-}5'}$ (100 MHz, Acetone-d6) δ 173.3, 167.0, 143.1, 141.9, 140.1, 137.4, 135.8, 135.1, 134.8, 134.0, 132.1, 130.5, 125.3, 123.9, 119.8, 79.3, 79.0, 76.3, 74.4, 72.2, 71.5, 66.8, 46.5, 44.5, 44.1, 42.7, 41.4, 36.1, 35.5, 32.9, 31.7, 29.7 (obscured by acetone-d6), 28.1, 27.7, 26.4-26.3 (m, 9C), 25.4, 24.3, 23.4, 21.2, 20.8, 20.6, 20.2, 18.8, 18.7, 17.7, 17.2, 16.3, 16.0, 15.1, 13.9, -3.8, -3.9, -4.1, -4.2, -4.3.

^{1}H NMR *E*-$\Delta^{4'\text{-}5'}$ (400 MHz, Acetone-d6) δ 7.37 (d, *J* = 15.6 Hz, 1H), 6.69 (dd, *J* = 15.1, 11.0 Hz, 1H), 6.48 (d, *J* = 15.4 Hz, 1H), 6.47 (s, 1H), 6.37 (d, *J* = 10.8 Hz, 1H), 5.89 (d, *J* = 15.2 Hz, 1H), 5.67 (m, 1H), 5.12-5.05 (m, 2H), 4.88 (m, 1H), 4.71 (m, 1H), 4.58 (dd, *J* = 9.2, 3.1 Hz, 1H), 4.21 (m, 1H), 4.00 (m, 1H), 3.82-3.76 (m, 2H), 2.54-2.37 (m, 3H), 2.12-1.88 (m, 10H), 2.09 (s, 3H), 2.03 (s, 3H), 1.82-1.57 (m, 6H), 1.71 (br. s, 3H), 1.66 (s, 3H), 1.43-1.30 (m, 3H), 1.20 (d, *J* = 5.8 Hz, 3H), 1.17 (d, *J* = 6.0 Hz, 3H), 1.05 (br. s, 3H), 1.03 (s, 9H), 1.00 (s, 9H), 0.96-0.85 (m, 33H), 0.11-0.06 (m, 12H), 0.04 (s, 3H), 0.03 (s, 3H).

^{13}C NMR *E*-$\Delta^{4'\text{-}5'}$ (100 MHz, Acetone-d6) δ 173.3, 167.0, 151.3, 144.4, 140.4, 137.4, 136.0, 135.8, 135.5, 135.0, 134.0, 133.3, 130.5, 125.3, 123.9, 117.5, 79.3, 79.0, 76.3, 74.4, 72.2, 71.5, 66.8, 46.5, 44.5, 44.1, 42.7, 41.4, 36.1, 35.5, 32.9, 31.7, 29.7 (obscured by acetone-d6), 28.1, 27.7, 26.4-26.3 (m, 9C), 25.4, 24.3, 23.4, 20.9, 20.8, 20.6, 20.2, 18.8, 18.7, 17.7, 17.2, 16.3, 16.0, 15.1, 13.9, -3.8, -3.9, -4.1, -4.2, -4.3.

The spectral data are in agreement with those reported in the literature.[4]

(2*E*,8*E*,10*E*,12*S*,13*S*,15*S*)-(6*S*,7*S*,12*R*,*E*)-12-((2*S*,6*R*,*E*)-6-((4*R*,6*R*)-2,2-di-*tert*-Butyl-6-methyl-1,3,2-dioxasilinan-4-yl)-4-methylhept-4-en-2-yl)-9-methyl(d3)-7-methyl-2-oxooxacyclododec-9-en-6-yl 12,13,15-tris((*tert*-butyldimethylsilyl)oxy)-4,6,10-trimethylhexadeca-2,4,6,8,10-pentaenoate (**SI-12b**)



To a solution of **26** (13.2 mg, 0.019 mmol) in THF (1.13 mL) were added *i*-Pr_2NEt (13.0 µL, 0.078 mmol), 2,4,6-trichlorobenzoyl chloride (6 µL, 0.040 mmol) followed by DMAP (11.8 mg, 0.097 mmol). Then, **22b** (5.5 mg, 9.68 µmol) dissolved in THF (0.420 mL) was added and the reaction was stirred at room temperature protected from light for 2 hours. The reaction mixture was quenched with a saturated aqueous $NaHCO_3$ solution and extracted with EtOAC. The organic layer was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated. The crude residue was purified by preparative TLC (elution with petroleum ether/EtOAc 9:1) to give after evaporation **SI-12b** (6 mg, 50%) as a yellowish oil and as a mixture of isomers that was not separated (*E*-$\Delta^{4'\text{-}5'}$/*Z*-$\Delta^{4'\text{-}5'}$ 1:1; C12-(*R*)/C12-(*S*) 2:8).

^{1}H NMR *Z*-$\Delta^{4'\text{-}5'}$ (400 MHz, Acetone-d6) δ 7.92 (d, *J* = 15.9 Hz, 1H), 6.65 (m, 1H), 6.53 (d, *J* = 15.4 Hz, 1H), 6.41 (s 1H), 6.19 (d, *J* = 10.8 Hz, 1H), 5.95 (m, 1H), 5.68 (m, 1H), 5.10-5.05 (m, 2H), 4.88 (m, 1H), 4.71 (m, 1H), 4.58 (dd, *J* = 9.1, 3.5 Hz, 1H), 4.22 (m, 1H), 4.00 (m, 1H), 3.82-3.76 (m, 2H), 2.53-2.37 (m, 3H), 2.12-1.83 (m, 10H), 1.98 (s, 3H), 1.95 (s, 3H), 1.80-1.57 (m, 6H), 1.66 (s, 3H), 1.43-1.30 (m, 3H), 1.20 (d, *J* = 6.0 Hz, 3H), 1.17 (d, *J* = 5.8 Hz, 3H), 1.05 (br. s, 3H), 1.03 (s, 9H), 1.00 (s, 9H), 0.96-0.85 (m, 33H), 0.11-0.06 (m, 12H), 0.04 (s, 3H), 0.03 (s, 3H).

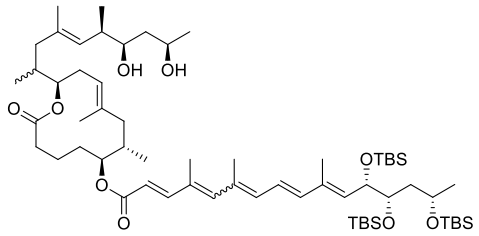
^{13}C NMR *Z*-$\Delta^{4'\text{-}5'}$ (100 MHz, Acetone-d6) δ 173.3, 167.0, 143.2, 141.9, 140.1, 137.8, 135.8, 135.1, 134.8, 134.0, 132.1, 130.5, 125.3, 123.9, 119.8, 79.3, 79.0, 76.2, 74.4, 72.2, 71.5, 66.8, 46.5, 44.5, 44.1, 42.7, 41.4, 36.1, 35.4, 32.9, 31.7, 29.7 (obscured by acetone-d6), 28.1, 27.7, 26.4-26.3 (m, 9C), 25.4, 24.3, 23.4, 21.2, 20.8, 20.6, 20.2, 18.8, 18.7, 17.7, 17.2, 16.3, 15.1, 13.9, -3.8, -3.9, -4.1, -4.2, -4.3.

^{1}H NMR *E*-$\Delta^{4'\text{-}5'}$ (400 MHz, Acetone-d6) δ 7.52 (d, *J* = 15.4 Hz, 1H), 6.68 (m, 1H), 6.47 (d, *J* = 14.4 Hz, 1H), 6.45 (s, 1H), 6.35 (d, *J* = 8.3 Hz, 1H), 5.92 (m, 1H), 5.67 (m, 1H), 5.10-5.05 (m, 2H), 4.88 (m, 1H), 4.71 (m, 1H), 4.58 (dd, *J* = 9.1, 3.5 Hz, 1H), 4.22 (m, 1H), 4.00 (m, 1H), 3.82-3.76 (m, 2H), 2.53-2.37 (m, 3H), 2.12-1.83 (m, 10H), 2.10 (s, 3H), 2.03 (s, 3H), 1.80-1.57 (m, 6H), 1.66 (s, 3H), 1.43-1.30 (m, 3H), 1.20 (d, *J* = 5.8 Hz, 3H), 1.17 (d, *J* = 6.0 Hz, 3H), 1.05 (br. s, 3H), 1.03 (s, 9H), 1.00 (s, 9H), 0.96-0.85 (m, 33H), 0.11-0.06 (m, 12H), 0.04 (s, 3H), 0.03 (s, 3H).

^{13}C NMR *E*-$\Delta^{4'\text{-}5'}$ (100 MHz, Acetone-d6) δ 173.3, 167.0, 155.2, 144.4, 140.1, 137.8, 136.4, 135.8, 135.6, 135.1, 134.0, 133.2, 130.5, 125.3, 123.9, 115.7, 79.3, 79.0, 76.2, 74.4, 72.2, 71.5, 66.8, 46.5, 44.5, 44.1, 42.7, 41.4, 36.1, 35.4, 32.9, 31.7, 29.7 (obscured by acetone-d6), 28.1, 27.7, 26.4-26.3 (m, 9C), 25.4, 24.3, 23.4, 21.1, 20.8, 20.6, 20.2, 18.8, 18.7, 17.7, 17.2, 16.3, 15.1, 13.9, -3.8, -3.9, -4.1, -4.2, -4.3.

HRMS calculated for $C_{70}H_{125}D_3O_9Si_4 + Na^+$ 1250.8716; found 1250.8698 $[M + Na]^+$.

(2*E*,4*E*,6*E*,8*E*,10*E*,12*S*,13*S*,15*S*)-(6*S*,7*S*,12*R*,*E*)-12-((2*S*,6*R*,7*R*,9*R*,*E*)-7,9-Dihydroxy-4,6-dimethyldec-4-en-2-yl)-7,9-dimethyl-2-oxooxacyclododec-9-en-6-yl 12,13,15-tris((*tert*-butyldimethylsilyl)oxy)-4,6,10-trimethylhexadeca-2,4,6,8,10-pentaenoate (**SI-13a**)



To a polypropylene vial containing **SI-12a** (27 mg, 22.0 µmol) in THF (2.21 mL) and pyridine (466 µL) was added HF•pyridine 70% (57.2 µL, 2.202 mmol). The reaction mixture was stirred at room temperature for 1 hour. The solution was then cooled in an ice bath and a saturated aqueous $NaHCO_3$ solution was added until gas evolution stopped. The reaction mixture was diluted with EtOAc and the layers were separated. The organic layer was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated. The crude residue was purified by preparative TLC (eluent petroleum ether/EtOAc 6:4) to give **SI-13a** (23 mg, quantitative yield) as a yellowish oil and as a mixture of isomers that was not separated (*E*-$\Delta^{4'\text{-}5'}$/*Z*-$\Delta^{4'\text{-}5'}$ 1:1; C12-(*R*)/C12-(*S*) 2:8).

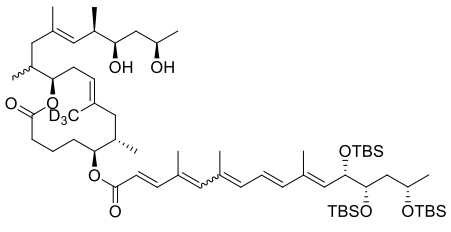
^{1}H NMR *Z*-$\Delta^{4'\text{-}5'}$ (400 MHz, Acetone-d6) δ 7.93 (d, *J* = 15.6 Hz, 1H), 6.70 (m, 1H), 6.47 (m, 1H), 6.34 (s 1H), 6.19 (d, *J* = 10.7 Hz, 1H), 5.92 (d, *J* = 15.6 Hz, 1H), 5.68 (m, 1H), 5.14 (m, 1H), 5.04 (d, *J* = 9.8 Hz, 1H), 4.90 (m, 1H), 4.71 (m, 1H), 4.58 (dd, *J* = 9.0, 3.4 Hz, 1H), 4.24-4.15 (m, 2H), 4.06-3.92 (m, 2H), 3.78 (m, 1H), 3.52 (m, 1H), 2.55 (m, 1H), 2.44-2.35 (m, 2H), 2.28-1.83 (m, 8H), 2.03 (s, 3H), 1.98 (br. s, 3H), 1.95 (s, 3H), 1.89-1.56 (m, 7H), 1.71 (br. s, 3H), 1.65 (s, 3H), 1.39 (m, 1H), 1.17 (d, *J* = 5.8 Hz, 3H), 1.14 (d, *J* = 6.0 Hz, 3H), 0.98 (d, *J* = 6.8 Hz, 3H), 0.96-0.85 (m, 33H), 0.13-0.07 (m, 15H), 0.05-0.02 (m, 3H).

^{1}H NMR *E*-$\Delta^{4'\text{-}5'}$ (400 MHz, Acetone-d6) δ 7.37 (d, *J* = 15.5 Hz, 1H), 6.70 (m, 1H), 6.47 (m, 1H), 6.46 (s 1H), 6.35 (m, 1H), 5.89 (d, *J* = 15.5 Hz, 1H), 5.68 (m, 1H), 5.14 (m, 1H), 5.04 (d, *J* = 9.8 Hz, 1H), 4.90 (m, 1H), 4.71 (m, 1H), 4.58 (dd, *J* = 9.0, 3.4 Hz, 1H), 4.24-4.15 (m, 2H), 4.06-3.92 (m, 2H), 3.78 (m, 1H), 3.52 (m, 1H), 2.55 (m, 1H), 2.44-2.35 (m, 2H), 2.28-1.83 (m, 8H), 2.09 (s, 3H), 2.06 (br. s, 3H), 1.95 (s, 3H), 1.89-1.56 (m, 7H), 1.71 (br. s, 3H), 1.65 (s, 3H), 1.39 (m, 1H), 1.17 (d, *J* = 5.8 Hz, 3H), 1.14 (d, *J* = 6.0 Hz, 3H), 0.98 (d, *J* = 6.8 Hz, 3H), 0.96-0.85 (m, 33H), 0.13-0.07 (m, 15H), 0.05-0.02 (m, 3H).

HRMS calculated for $C_{62}H_{112}O_9Si_3 + Na^+$ 1107.7506; found 1107.7513 $[M + Na]^+$.

The spectral data are in agreement with those reported in the literature.[4]

(2*E*,4*E*,6*E*,8*E*,10*E*,12*S*,13*S*,15*S*)-(6*S*,7*S*,12*R*,*E*)-12-((2*S*,6*R*,7*R*,9*R*,*E*)-7,9-Dihydroxy-4,6-dimethyldec-4-en-2-yl)-9-methyl(d3)-7-methyl-2-oxooxacyclododec-9-en-6-yl 12,13,15-tris((*tert*-butyldimethylsilyl)oxy)-4,6,10-trimethylhexadeca-2,4,6,8,10-pentaenoate (**SI-13b**)



To a polypropylene vial containing **SI-12b** (6 mg, 4.88 µmol) in THF (490 µL) and pyridine (103 µL) was added HF•pyridine 70% (9 µL, 0.488 mmol). The reaction mixture was stirred at room temperature for 1 hour. The solution was then cooled in an ice bath and a saturated aqueous $NaHCO_3$ solution was added until gas evolution stopped. The reaction mixture was diluted with EtOAc and the layers were separated. The organic layer was washed with brine, dried over

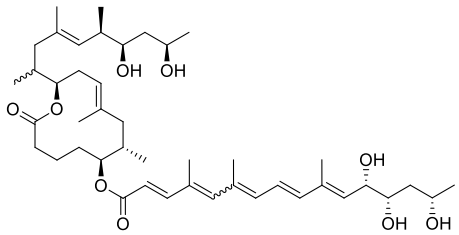
anhydrous sodium sulfate, filtered and concentrated to give **SI-13b** (5.3 mg, quantitative yield) as a yellowish oil and as a mixture of isomers that was not separated (*E*-$\Delta^{4'\text{-}5'}$/*Z*-$\Delta^{4'\text{-}5'}$ 1:1; C12-(*R*)/C12-(*S*) 2:8). The product was used without further purification for the next step.

^{1}H NMR *Z*-$\Delta^{4'\text{-}5'}$ (400 MHz, Acetone-d6) δ 7.93 (d, *J* = 15.4 Hz, 1H), 6.67 (m, 1H), 6.49 (m, 1H), 6.34 (s 1H), 6.19 (d, *J* = 11.3 Hz, 1H), 5.93 (m, 1H), 5.67 (m, 1H), 5.13 (m, 1H), 5.03 (d, *J* = 9.3 Hz, 1H), 4.88 (m, 1H), 4.70 (m, 1H), 4.58 (dd, *J* = 9.1, 3.0 Hz, 1H), 4.25-4.20 (m, 2H), 4.03-3.89 (m, 2H), 3.78 (m, 1H), 3.51 (m, 1H), 2.49 (m, 1H), 2.44-2.35 (m, 2H), 2.28-1.83 (m, 8H), 2.01 (s, 3H), 1.97 (br. s, 3H), 1.96 (s, 3H), 1.89-1.80 (m, 3H), 1.69-1.54 (m, 4H), 1.64 (s, 3H), 1.40 (m, 1H), 1.17 (d, *J* = 6.3 Hz, 3H), 1.13 (d, *J* = 5.8 Hz, 3H), 0.98 (d, *J* = 6.5 Hz, 3H), 0.96-0.85 (m, 33H), 0.13-0.07 (m, 15H), 0.05-0.02 (m, 3H).

^{1}H NMR *E*-$\Delta^{4'\text{-}5'}$ (400 MHz, Acetone-d6) δ 7.56 (d, *J* = 15.3 Hz, 1H), 6.70 (m, 1H), 6.48 (m, 1H), 6.41 (s 1H), 6.36 (m, 1H), 5.89 (m, 1H), 5.67 (m, 1H), 5.13 (m, 1H), 5.03 (d, *J* = 9.3 Hz, 1H), 4.88 (m, 1H), 4.70 (m, 1H), 4.58 (dd, *J* = 9.1, 3.0 Hz, 1H), 4.25-4.20 (m, 2H), 4.03-3.89 (m, 2H), 3.78 (m, 1H), 3.51 (m, 1H), 2.49 (m, 1H), 2.44-2.35 (m, 2H), 2.28-1.83 (m, 8H), 2.09 (s, 3H), 2.07 (br. s, 3H), 1.95 (s, 3H), 1.89-1.80 (m, 3H), 1.69-1.54 (m, 4H), 1.64 (s, 3H), 1.39 (m, 1H), 1.17 (d, *J* = 6.3 Hz, 3H), 1.13 (d, *J* = 5.8 Hz, 3H), 0.98 (d, *J* = 6.5 Hz, 3H), 0.96-0.85 (m, 33H), 0.13-0.07 (m, 15H), 0.05-0.02 (m, 3H).

HRMS calculated for $C_{62}H_{109}D_3O_9Si_3 + Na^+$ 1110.7695; found 1110.7660 $[M + Na]^+$.

(2*E*,4*E*,6*E*,8*E*,10*E*,12*S*,13*S*,15*S*)-(6*S*,7*S*,12*R*,*E*)-12-((2*S*,6*R*,7*R*,9*R*,*E*)-7,9-Dihydroxy-4,6-dimethyldec-4-en-2-yl)-7,9-dimethyl-2-oxooxacyclododec-9-en-6-yl 12,13,15-trihydroxy-4,6,10-trimethylhexadeca-2,4,6,8,10-pentaenoate (**Mycolactone A/B**)



To a stirred solution of **SI-13a** (24 mg, 22.1 µmol) in THF (3.127 mL) was added a 1M solution of TBAF in THF (313 µL, 0.313 mmol). The resulting mixture was stirred at room temperature for 75 minutes. Then, $CaCO_3$ (10 mg), the commercial Dowex® 50WX8-400 hydrogen form resin (15 mg) and MeOH (0.1 mL) were added and the reaction mixture was stirred for 20 more minutes. The crude product was then filtered, concentrated under reduced pressure and purified on preparative TLC (elution with CH_2Cl_2/MeOH 9:1) to give **mycolactone A/B** (16 mg, 97%) as a yellowish oil and as a mixture of isomers that was not separated (*E*-$\Delta^{4'\text{-}5'}$/*Z*-$\Delta^{4'\text{-}5'}$ 1:1; C12-(*R*)/C12-(*S*) 2:8).

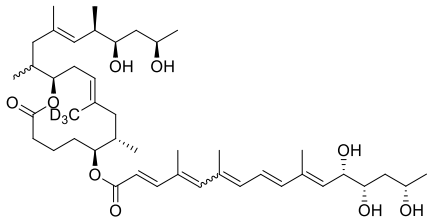
^{1}H NMR *Z*-$\Delta^{4'\text{-}5'}$ (400 MHz, Acetone-d6) δ 7.92 (d, *J* = 15.6 Hz, 1H), 6.64 (dd, *J* = 15.5, 11.3 Hz, 1H), 6.40 (d, *J* = 15.9 Hz, 1H), 6.34 (s, 1H), 6.16 (d, *J* = 10.6 Hz, 1H), 5.94 (d, *J* = 15.6 Hz, 1H), 5.60 (m, 1H), 5.14 (m, 1H), 5.04 (d, *J* = 9.3 Hz, 1H), 4.89 (m, 1H), 4.71 (m, 1H), 4.28 (m, 1H), 4.22-4.16 (m, 2H), 4.03-3.92 (m, 4H), 3.66 (m, 1H), 3.50 (m, 1H), 2.54 (m, 1H), 2.44-2.34 (m, 2H), 2.22-1.94 (m, 7H), 2.02 (s, 3H), 1.98 (br. s, 3H), 1.91 (br. s, 3H), 1.83 (m, 1H), 1.72-1.63 (m, 4H), 1.70 (br. s, 3H), 1.64 (br. s, 3H), 1.62-1.45 (m, 4H), 1.39 (m, 1H), 1.14 (d, *J* = 6.5 Hz, 3H), 1.11 (d, *J* = 6.3 Hz, 3H), 0.98 (d, *J* = 6.5 Hz, 3H), 0.90 (d, *J* = 6.5 Hz, 3H), 0.89 (d, *J* = 6.5 Hz, 3H).

^{1}H NMR *E*-$\Delta^{4'\text{-}5'}$ (400 MHz, Acetone-d6) δ 7.37 (d, *J* = 15.5 Hz, 1H), 6.67 (dd, *J* = 15.4, 11.3 Hz, 1H), 6.47 (s, 1H), 6.40 (d, *J* = 15.9 Hz, 1H), 6.36 (m, 1H), 5.89 (d, *J* = 15.6 Hz, 1H), 5.60 (m, 1H), 5.14 (m, 1H), 5.04 (d, *J* = 9.3 Hz, 1H), 4.89 (m, 1H), 4.71 (m, 1H), 4.28 (m, 1H), 4.22-4.16 (m, 2H), 4.03-3.92 (m, 4H), 3.66 (m, 1H), 3.50 (m, 1H), 2.54 (m, 1H), 2.44-2.34 (m, 2H), 2.22-1.94 (m, 7H), 2.09 (s, 3H), 2.07 (br. s, 3H), 1.91 (br. s, 3H), 1.83 (m, 1H), 1.72-1.63 (m, 4H), 1.70 (br. s, 3H), 1.64 (br. s, 3H), 1.62-1.45 (m, 4H), 1.39 (m, 1H), 1.14 (d, *J* = 6.5 Hz, 3H), 1.11 (d, *J* = 6.3 Hz, 3H), 0.98 (d, *J* = 6.5 Hz, 3H), 0.90 (d, *J* = 6.5 Hz, 3H), 0.89 (d, *J* = 6.5 Hz, 3H).

HRMS calculated for $C_{44}H_{70}O_9 + Na^+$ 765.4912; found 765.4908 $[M + Na]^+$.

The spectral data are in agreement with those reported in the literature.[4]

(2*E*,4*E*,6*E*,8*E*,10*E*,12*S*,13*S*,15*S*)-(6*S*,7*S*,12*R*,*E*)-12-((2*S*,6*R*,7*R*,9*R*,*E*)-7,9-Dihydroxy-4,6-dimethyldec-4-en-2-yl)-9-methyl(d3)-7-methyl-2-oxooxacyclododec-9-en-6-yl 12,13,15-trihydroxy-4,6,10-trimethylhexadeca-2,4,6,8,10-pentaenoate (**[22,22,22-^{2}H$_3$]-Mycolactone A/B**)



To a stirred solution of **SI-13b** (5 mg, 4.59 µmol) in THF (650 µL) was added a 1M solution of TBAF in THF (65 µL, 0.065 mmol). The resulting mixture was stirred at room temperature for 75 minutes. Then, $CaCO_3$ (10 mg), the commercial Dowex® 50WX8-400 hydrogen form resin (15 mg) and MeOH (0.1 mL) were added and the reaction mixture was stirred for 20 more minutes. The crude product was then filtered, concentrated under reduced pressure and purified on preparative TLC (elution with CH_2Cl_2/MeOH 9:1) to give **[22,22,22-^{2}H$_3$]-Mycolactone A/B** (2.1 mg, 61%) as a yellowish oil and as a mixture of isomers that was not separated (*E*-$\Delta^{4'\text{-}5'}$/*Z*-$\Delta^{4'\text{-}5'}$ 1:1; C12-(*R*)/C12-(*S*) 2:8).

^{1}H NMR *Z*-$\Delta^{4'\text{-}5'}$ (400 MHz, Acetone-d6) δ 7.92 (d, *J* = 15.9 Hz, 1H), 6.63 (m, 1H), 6.41 (d, *J* = 15.9 Hz, 1H), 6.33 (s, 1H), 6.16 (d, *J* = 11.1 Hz, 1H), 5.95 (m, 1H), 5.59 (m, 1H), 5.12 (m, 1H), 5.04 (d, *J* = 9.8 Hz, 1H), 4.89 (m, 1H), 4.71 (m, 1H), 4.28 (m, 1H), 4.22-4.18 (m, 2H), 4.02-3.89 (m, 4H), 3.65 (m, 1H), 3.51 (m, 1H), 2.51 (m, 1H), 2.45-2.33 (m, 2H), 2.15-1.89 (m, 7H), 2.02 (s, 3H), 1.98 (br. s, 3H), 1.91 (br. s, 3H), 1.83 (m, 1H), 1.72-1.63 (m, 4H), 1.64 (br. s, 3H), 1.61-1.45 (m, 4H), 1.41 (m, 1H), 1.14 (d, *J* = 6.0 Hz, 3H), 1.11 (d, *J* = 6.3 Hz, 3H), 0.98 (d, *J* = 5.8 Hz, 3H), 0.90 (d, *J* = 6.5 Hz, 3H), 0.89 (d, *J* = 6.9 Hz, 3H).

^{13}C NMR *Z*-$\Delta^{4'\text{-}5'}$ (100 MHz, Acetone-d6) δ 173.4, 167.0, 143.2, 141.9, 140.0, 137.3, 137.3, 135.0, 135.0, 134.8, 133.5, 132.2, 131.3, 125.2, 124.0, 119.7, 79.4, 77.1, 76.4, 75.9, 72.5, 69.1, 67.8, 46.4, 44.5, 43.9, 42.0, 40.6, 36.1, 35.5, 32.9, 31.4, 29.7 (obscured by acetone-d6), 24.7, 24.3, 21.1, 20.9, 20.6, 17.7, 17.2, 16.3, 15.1, 13.5.

^{1}H NMR *E*-$\Delta^{4'\text{-}5'}$ (400 MHz, Acetone-d6) δ 7.37 (d, *J* = 15.6 Hz, 1H), 6.67 (m, 1H), 6.47 (s, 1H), 6.43 (d, *J* = 16.1 Hz, 1H), 6.36 (m, 1H), 5.89 (m, 1H), 5.59 (m, 1H), 5.12 (m, 1H), 5.04 (d, *J* = 9.8 Hz, 1H), 4.89 (m, 1H), 4.71 (m, 1H), 4.28 (m, 1H), 4.22-4.18 (m, 2H), 4.02-3.89 (m, 4H), 3.65 (m, 1H), 3.51 (m, 1H), 2.51 (m, 1H), 2.45-2.33 (m, 2H), 2.15-1.89 (m, 7H), 2.09 (s, 3H), 2.06 (br. s, 3H), 1.91 (br. s, 3H), 1.83 (m, 1H), 1.72-1.63 (m, 4H), 1.64 (br. s, 3H), 1.61-1.45 (m, 4H), 1.41 (m, 1H), 1.14 (d, *J* = 6.0 Hz, 3H), 1.11 (d, *J* = 6.3 Hz, 3H), 0.98 (d, *J* = 5.8 Hz, 3H), 0.91 (d, *J* = 6.5 Hz, 3H), 0.89 (d, *J* = 6.9 Hz, 3H).

^{13}C NMR *E*-$\Delta^{4'\text{-}5'}$ (100 MHz, Acetone-d6) δ 173.4, 167.0, 151.3, 144.4, 140.4, 137.4, 137.4, 136.2, 135.0, 135.0, 134.7, 133.5, 132.2, 131.3, 125.2, 124.0, 117.5, 79.4, 77.1, 76.4, 75.9, 72.5, 69.1, 67.8, 46.4, 44.5, 43.9, 42.0, 40.6, 36.1, 35.5, 32.9, 31.4, 29.7 (obscured by acetone-d6), 24.7, 24.3, 20.9, 20.6, 17.2, 16.3, 15.1, 14.4, 13.5.

HRMS calculated for $C_{44}H_{67}D_3O_9 + Na^+$ 768.5100; found 768.5096 $[M + Na]^+$.

3. Assay of immunosuppressive activity

Immunosuppressive activity of synthetic and natural mycolactones was evaluated on Jurkat T cells by measuring the suppression of IL-2 production. Jurkat cells were seeded in a 96-well plate at a density of 1 x 105 cells per well in the presence of increasing doses of synthetic or natural mycolactone or with vehicle as control, 30 minutes before 16 hours of activation with PMA/ calcimycin at 100ng/ml and 250 ng/ml respectively. The production of IL-2 was measured in the culture supernatants by ELISA assay (human IL-2 ELISA set CDK079C), according to the manufacturer's protocol.

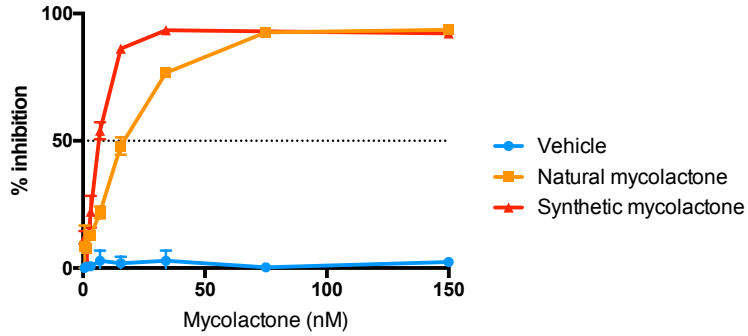
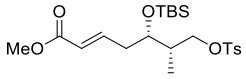


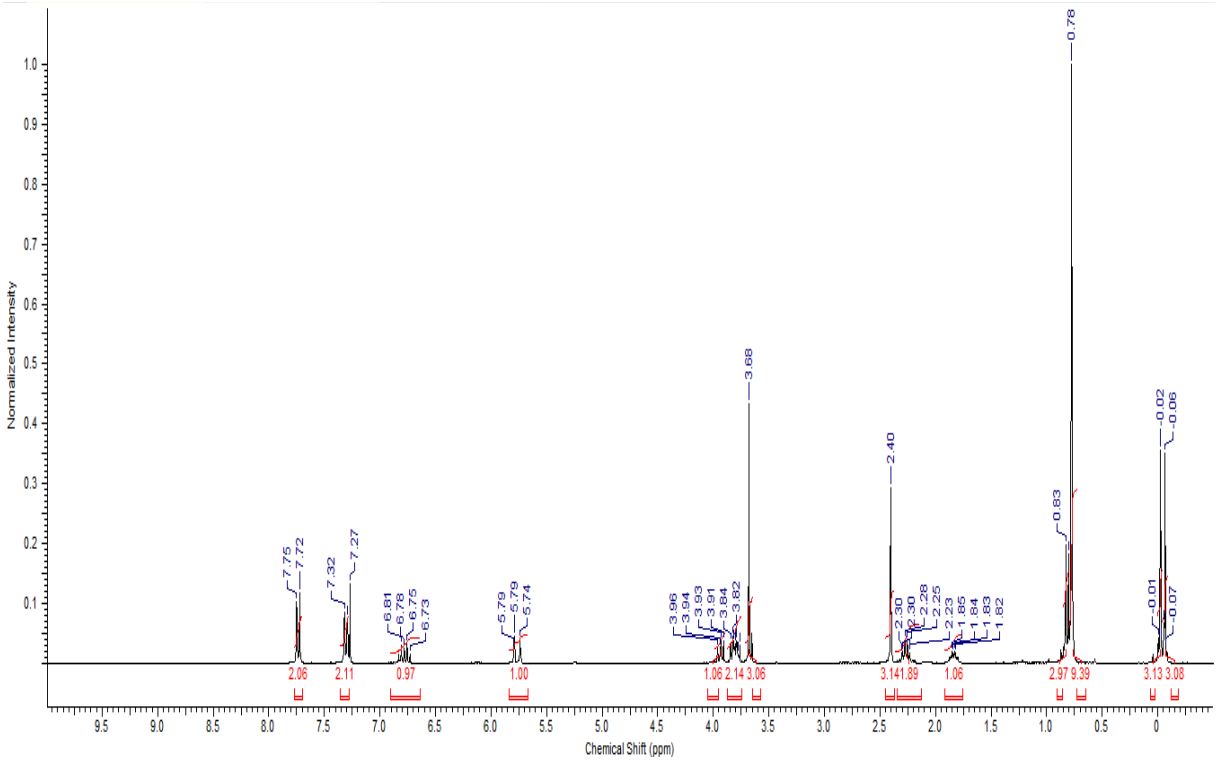
Figure: Comparative immuno-suppressive activities of synthetic and natural mycolactones as evaluated by inhibition of IL-2 production by activated human T cells. Jurkat cells were exposed to increasing doses of synthetic or natural mycolactones 30 minutes prior to 16 hours stimulation with PMA/ Calcimycin. The calculated IC_{50} were of 17 nM and 6 nM for respectively synthetic and natural mycolactone.

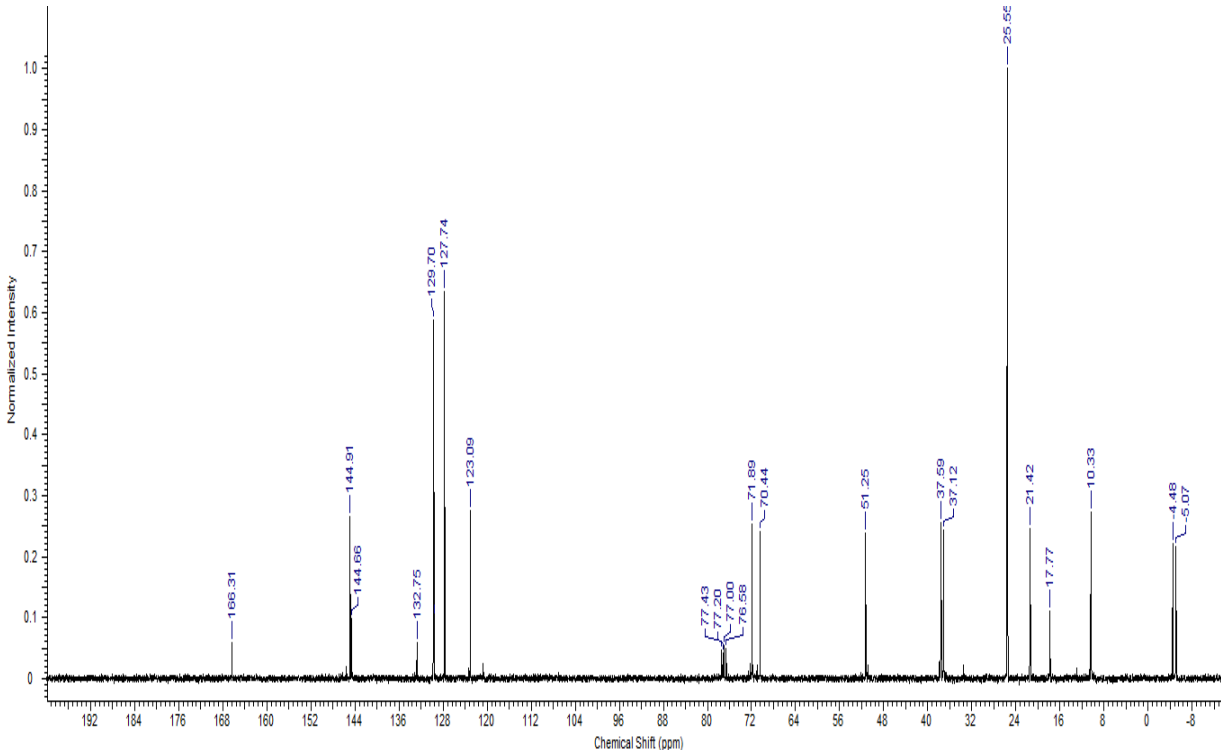
4. NMR Spectra

Methyl (2*E*,5*S*,6*S*)-5-[(*tert*-butyldimethylsilyl)oxy]-6-methyl-7-{[(4-methylphenyl) sulfonyl]oxy}hept-2-enoate (**11**)

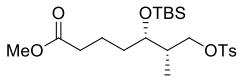


Chemical Formula: $C_{22}H_{36}O_6SSi$
Molecular Weight: 456,67

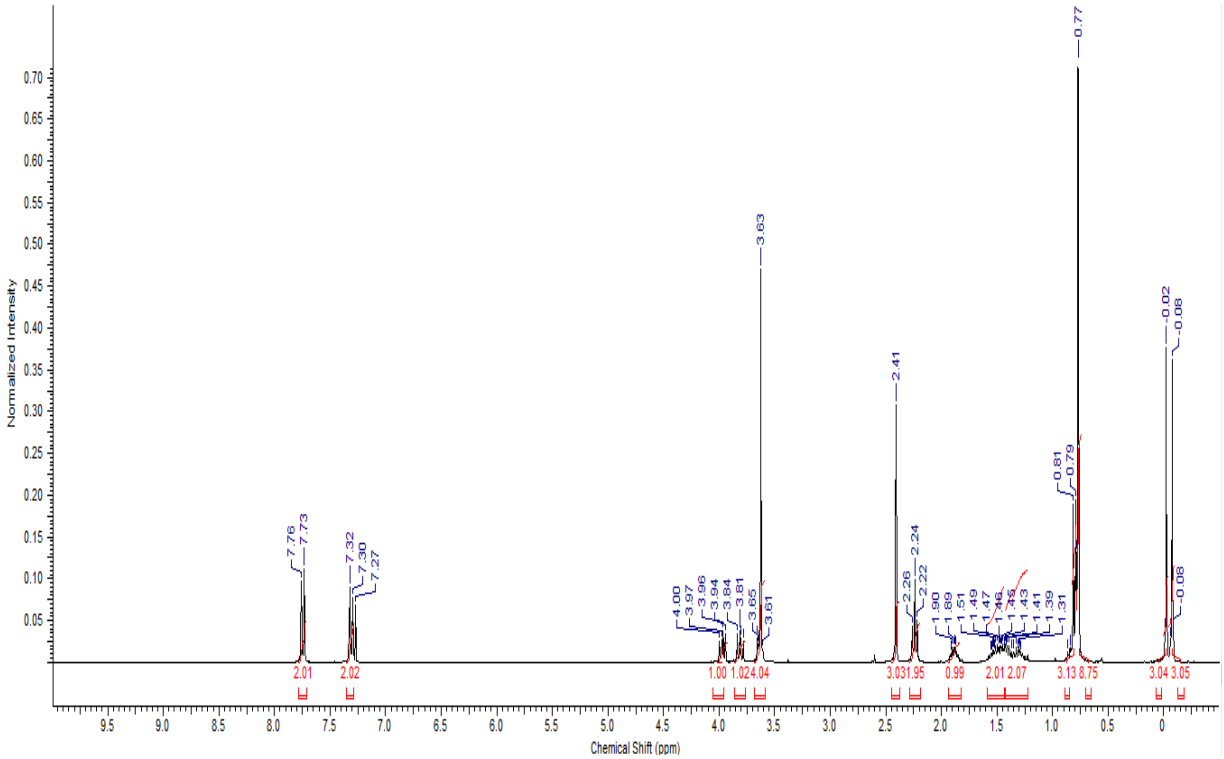


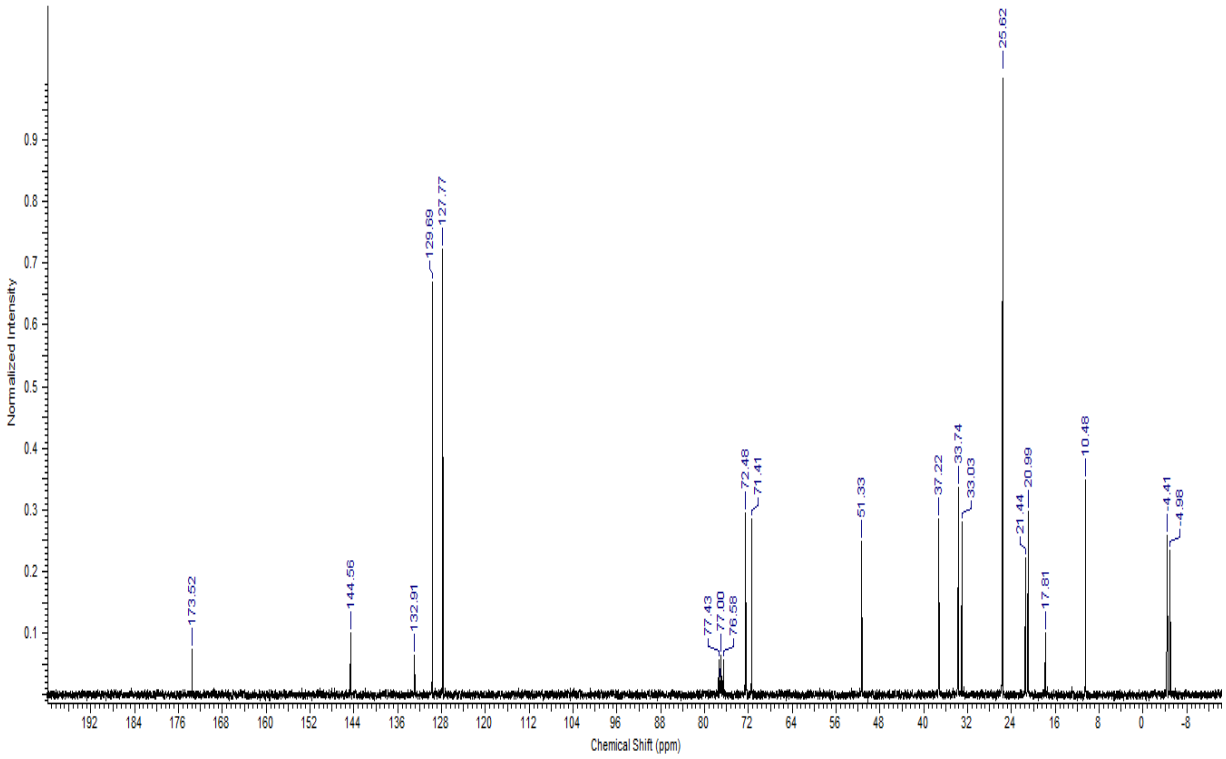


Methyl (5*S*,6*S*)-5-[(*tert*-butyldimethylsilyl)oxy]-6-methyl-7-{[(4-methylphenyl) sulfonyl]oxy}heptanoate (**SI-2**)

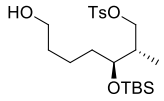


Chemical Formula: $C_{22}H_{38}O_6SSi$
Molecular Weight: 458,68

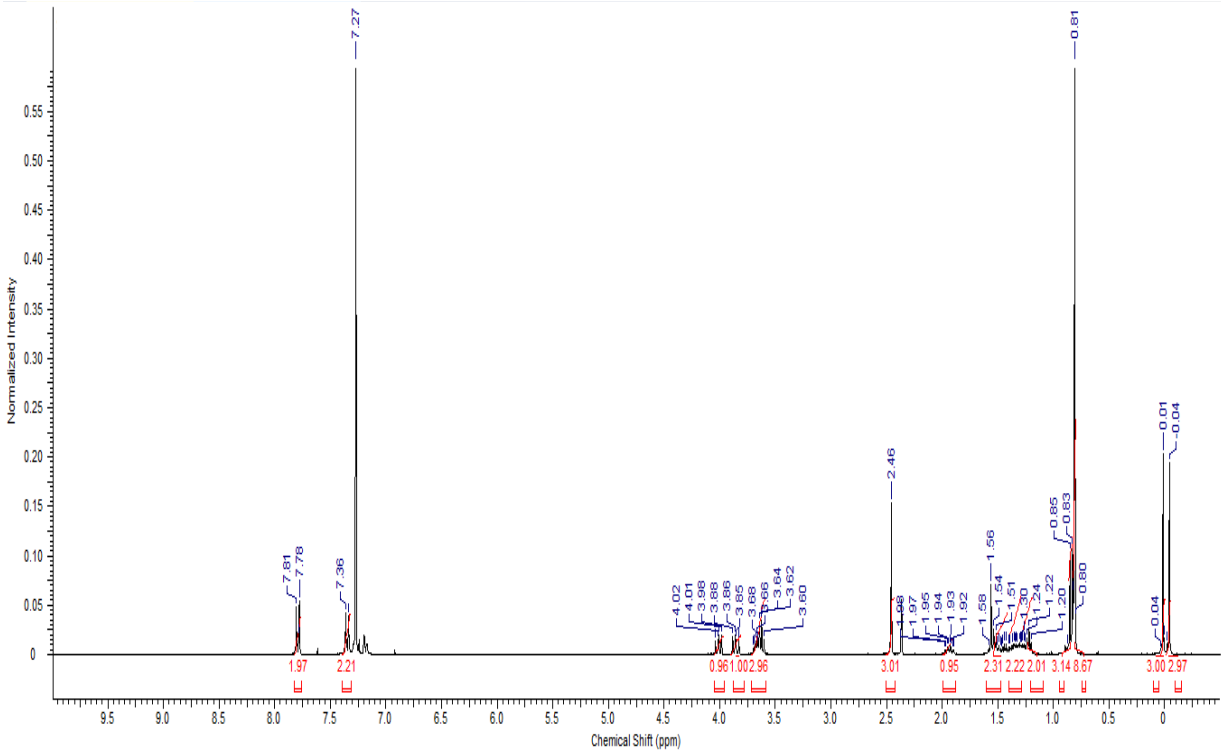


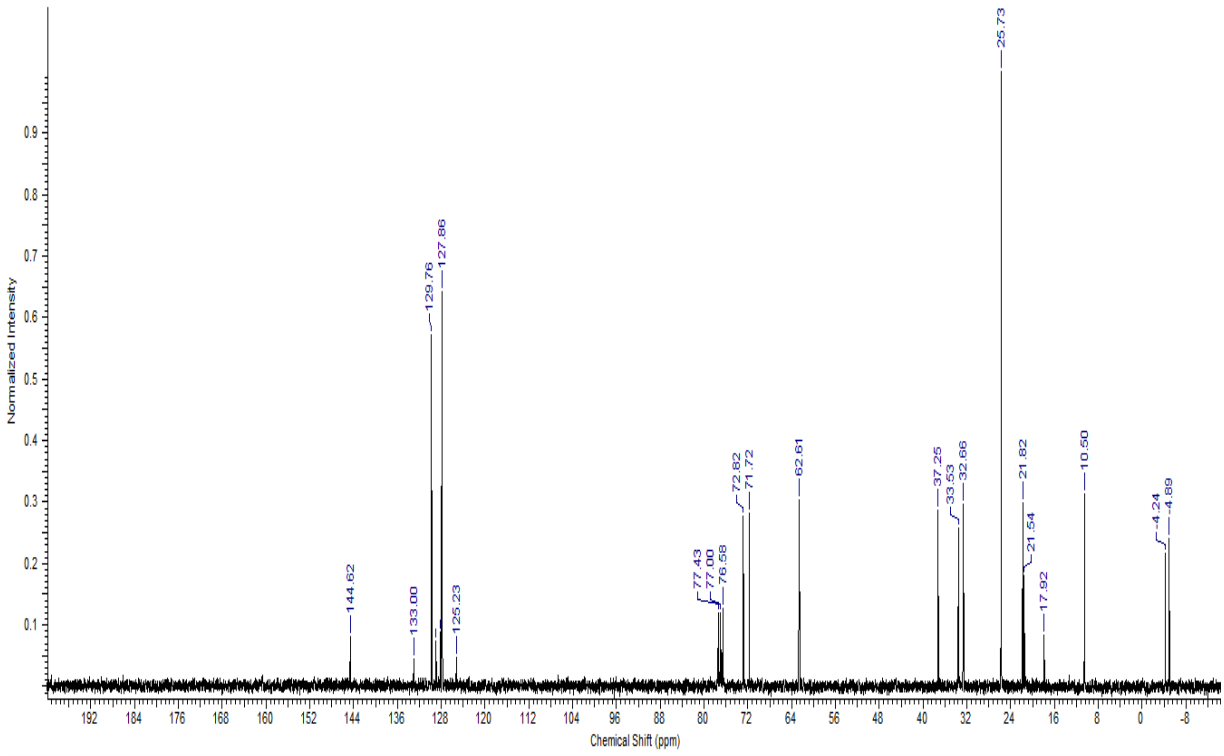


(5*S*,6*S*)-5-[(*tert*-Butyldimethylsilyl)oxy]-6-methyl-7-{[(4-methylphenyl)sulfonyl]oxy}heptan-1-ol (**12**)

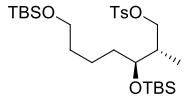


Chemical Formula: $C_{21}H_{38}O_5SSi$
Molecular Weight: 430,67

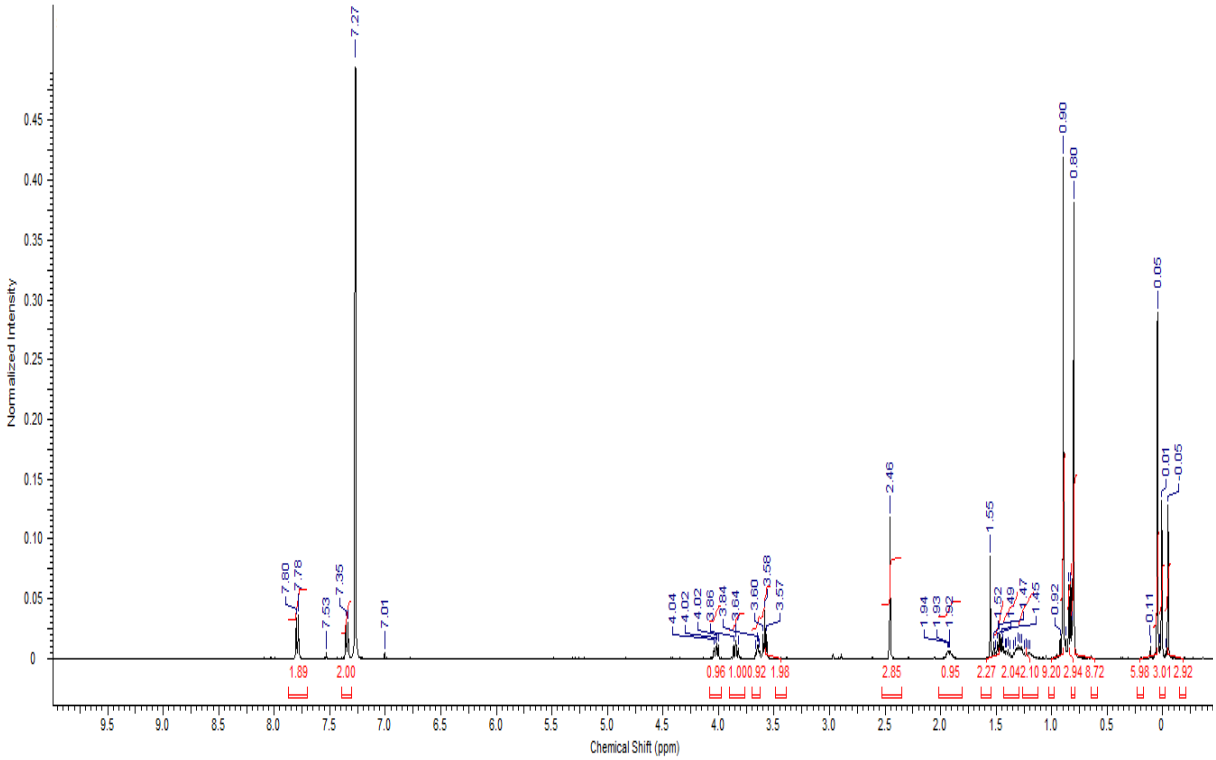


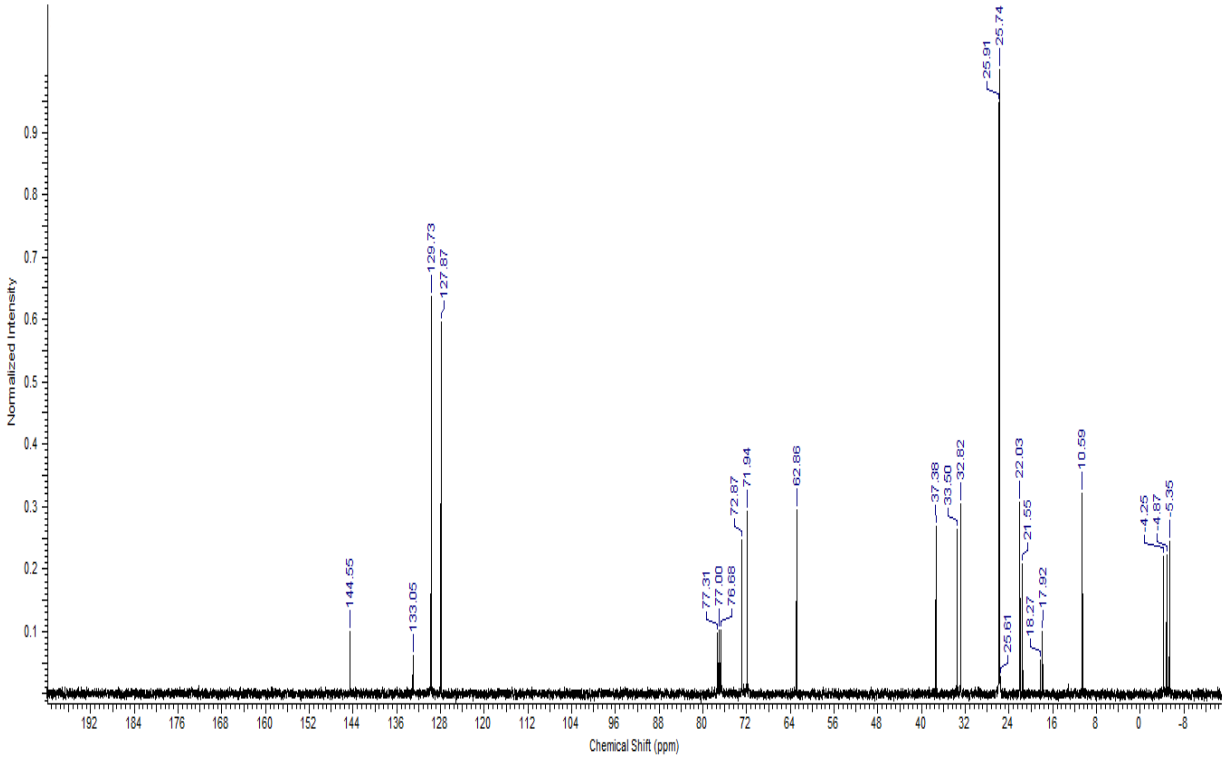


(2*S*,3*S*)-3,7-bis[(*tert*-Butyldimethylsilyl)oxy]-2-methylheptyl-4 methylbenzene-1-sulfonate (**SI-3**)

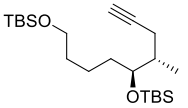


Chemical Formula: $C_{27}H_{52}O_5SSi_2$
Molecular Weight: 544,93

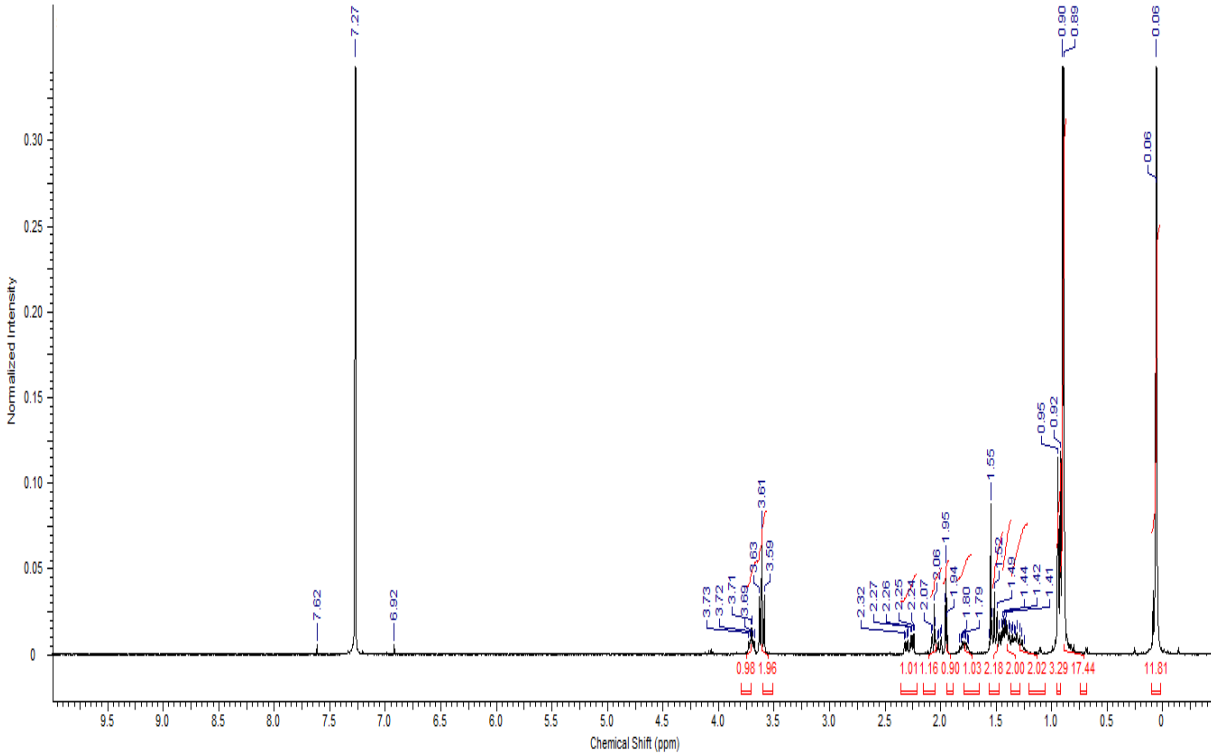


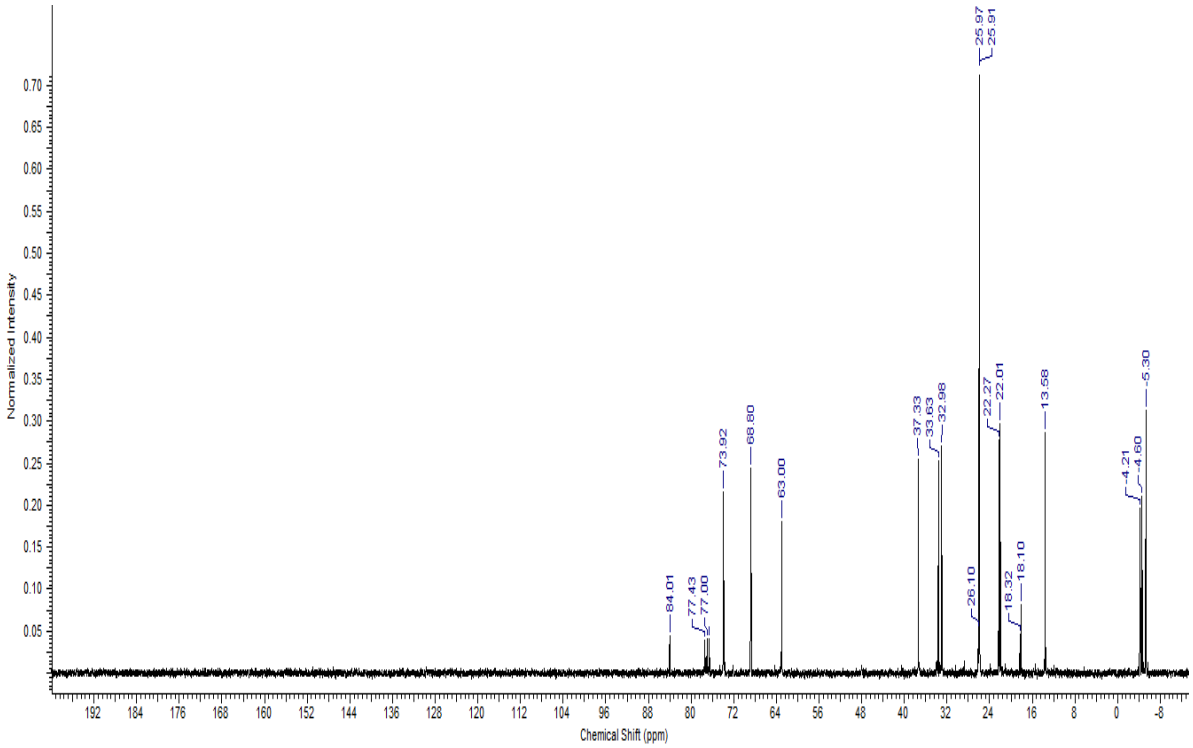


(5*S*)-2,2,3,3,11,11,12,12-Octamethyl-5-[(2*S*)-pent-4-yn-2-yl]-4,10-dioxa-3,11-disilatridecane (**13**)

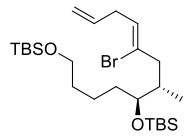


Chemical Formula: $C_{22}H_{46}O_2Si_2$
Molecular Weight: 398,77

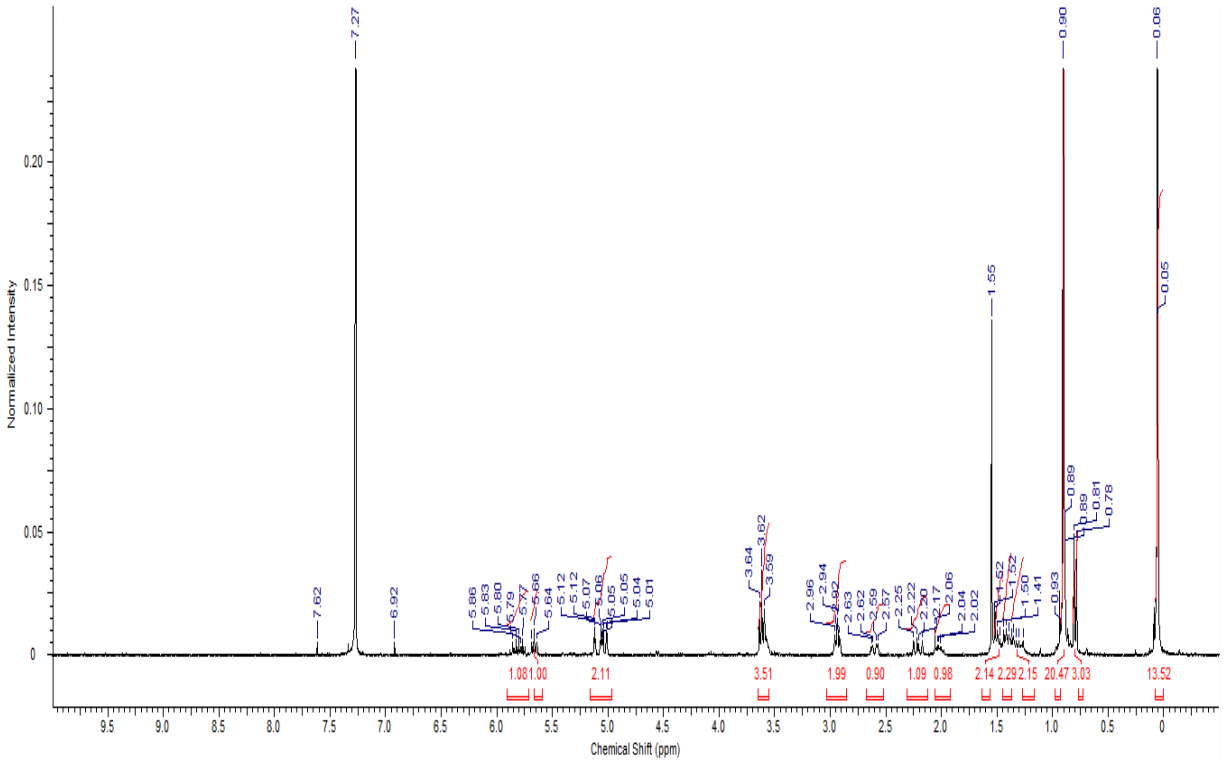


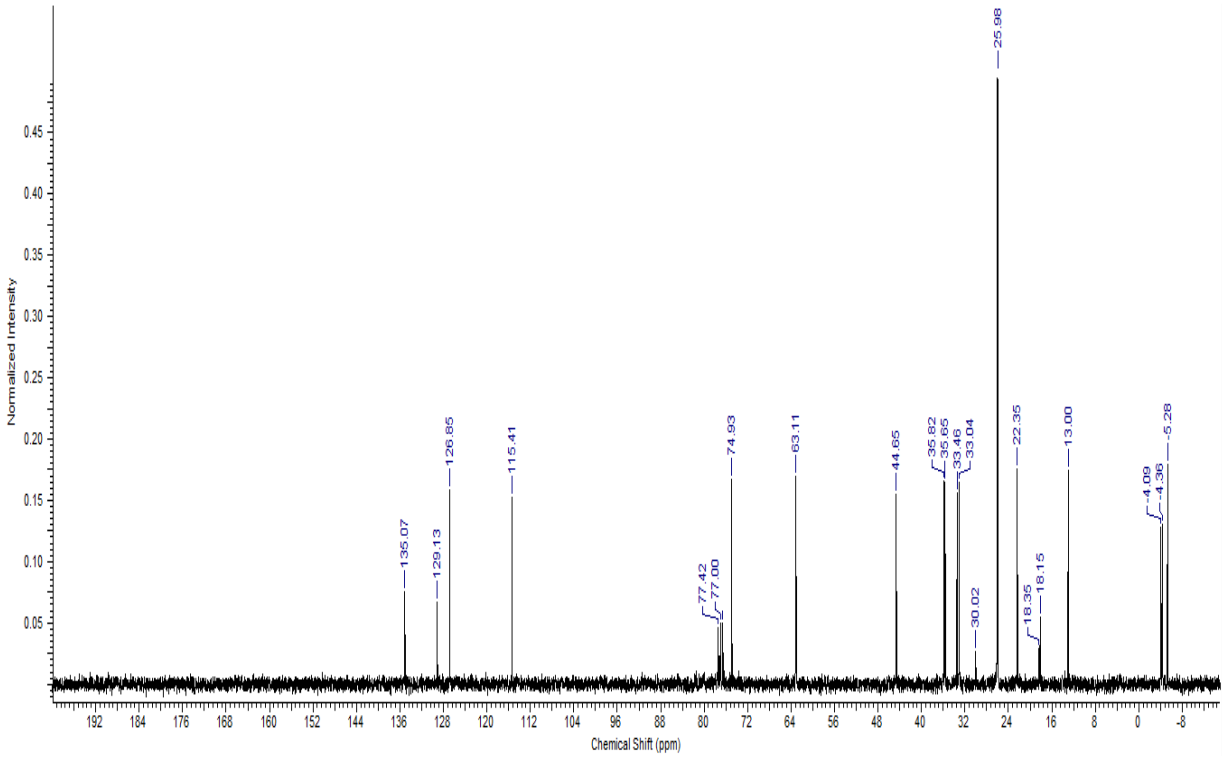


(5*S*)-5-[(2*S*,4*Z*)-4-Bromoocta-4,7-dien-2-yl]-2,2,3,3,11,11,12,12-octamethyl-4,10-dioxa-3,11-disilatridecane (**14**)

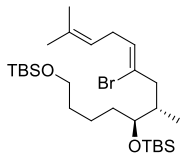


Chemical Formula: $C_{25}H_{51}BrO_2Si_2$
Molecular Weight: 519,75

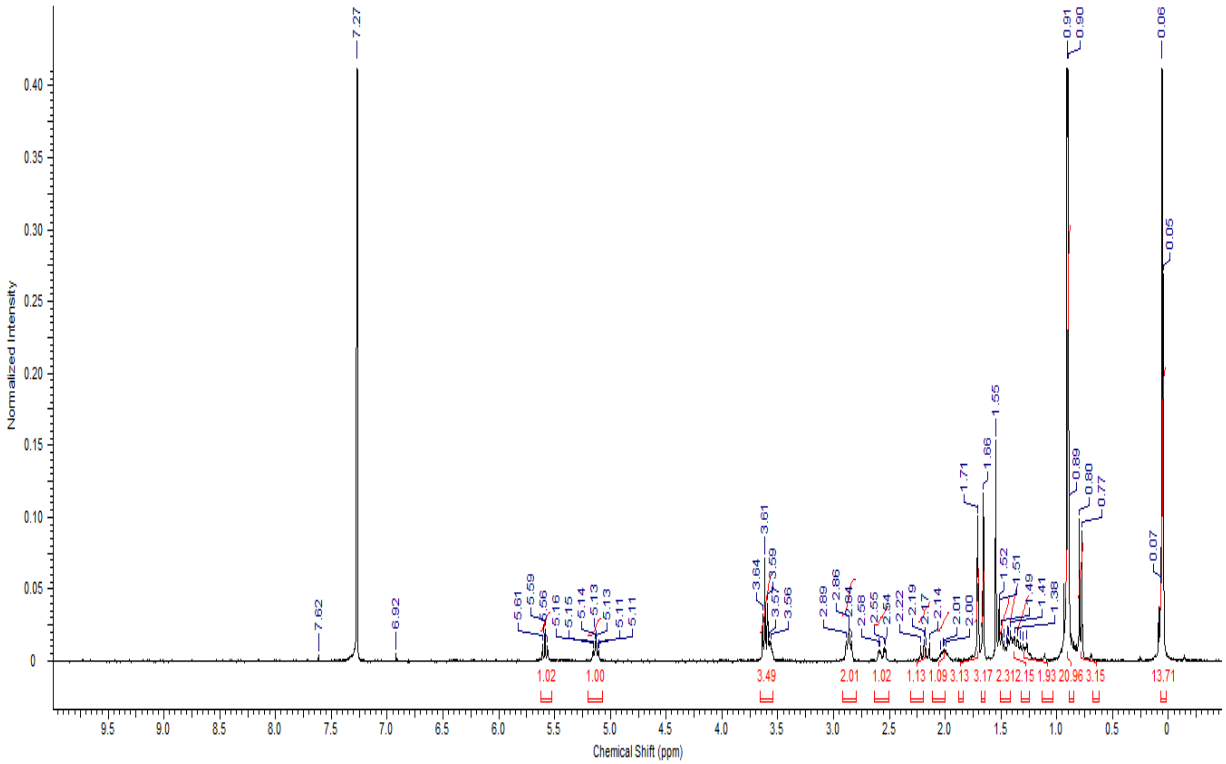


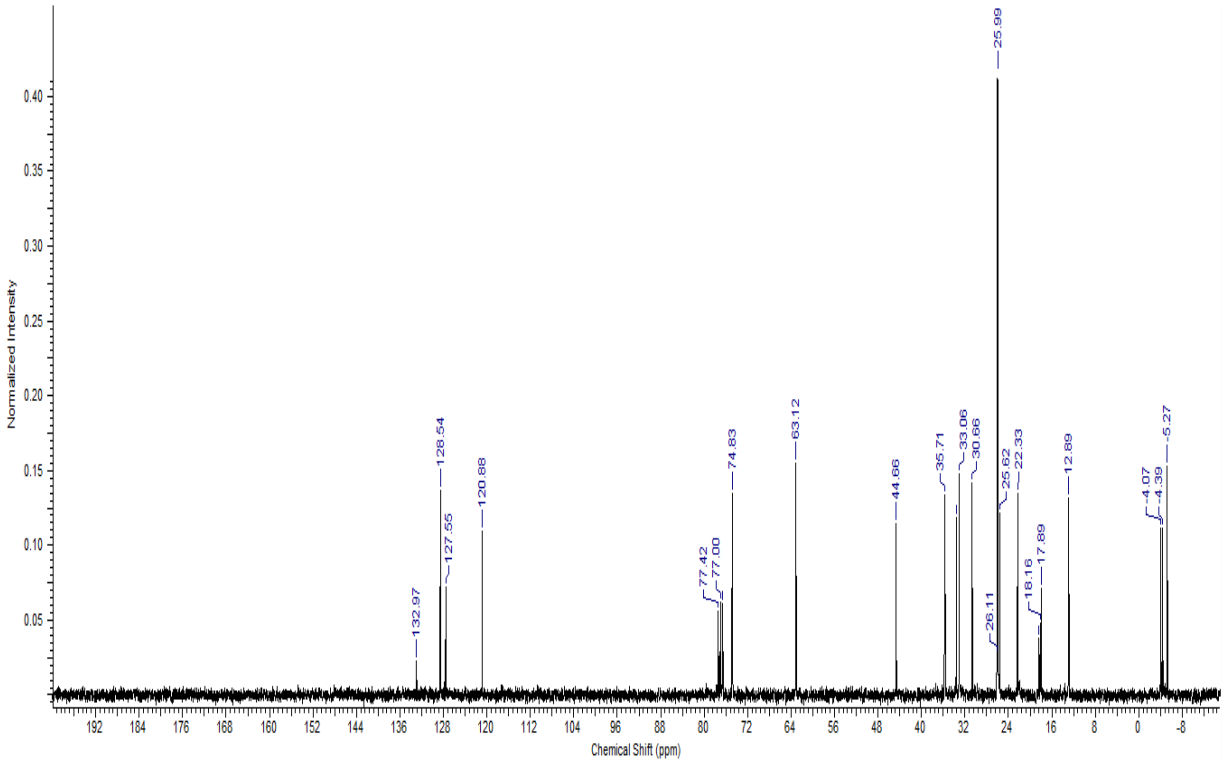


(*S*)-5-((*S*,*Z*)-4-Bromo-7-methylocta-4,6-dien-2-yl)-2,2,3,3,11,11,12,12-octamethyl-4,10-dioxa-3,11-disilatridecane (**15**)

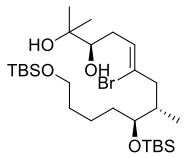


Chemical Formula: $C_{27}H_{55}BrO_2Si_2$
Molecular Weight: 547,80

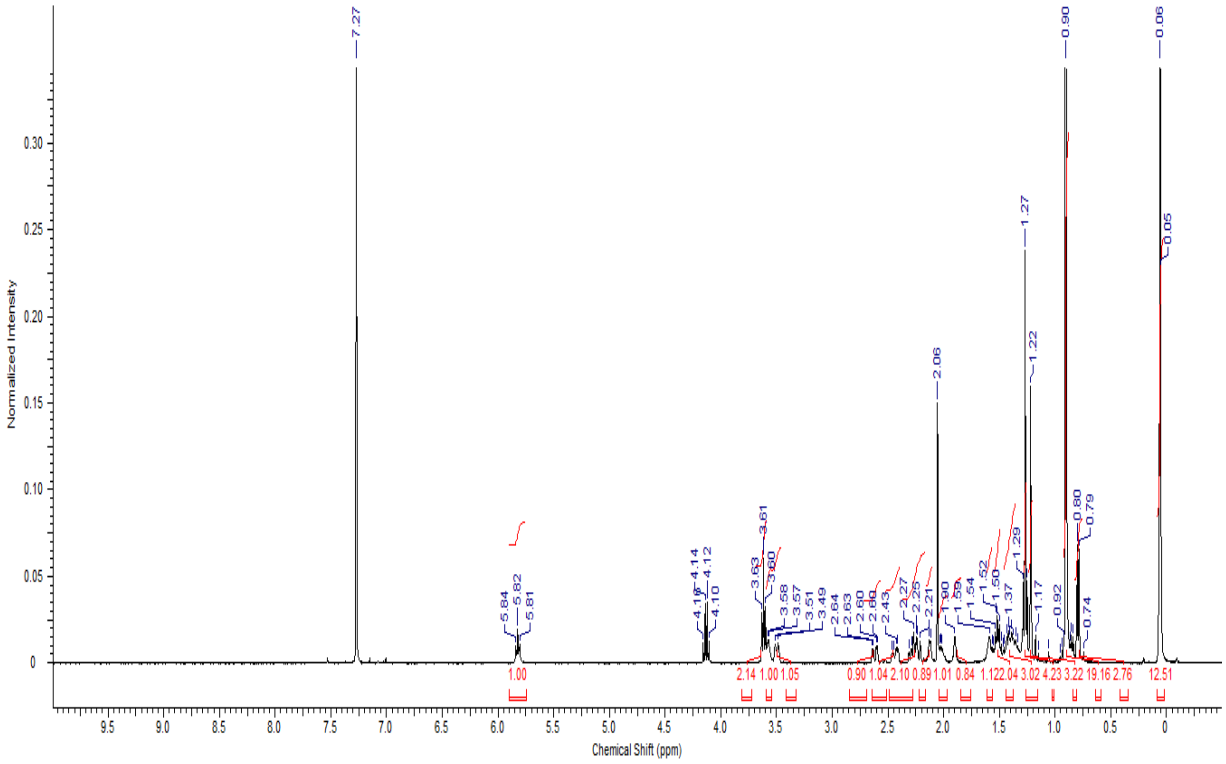


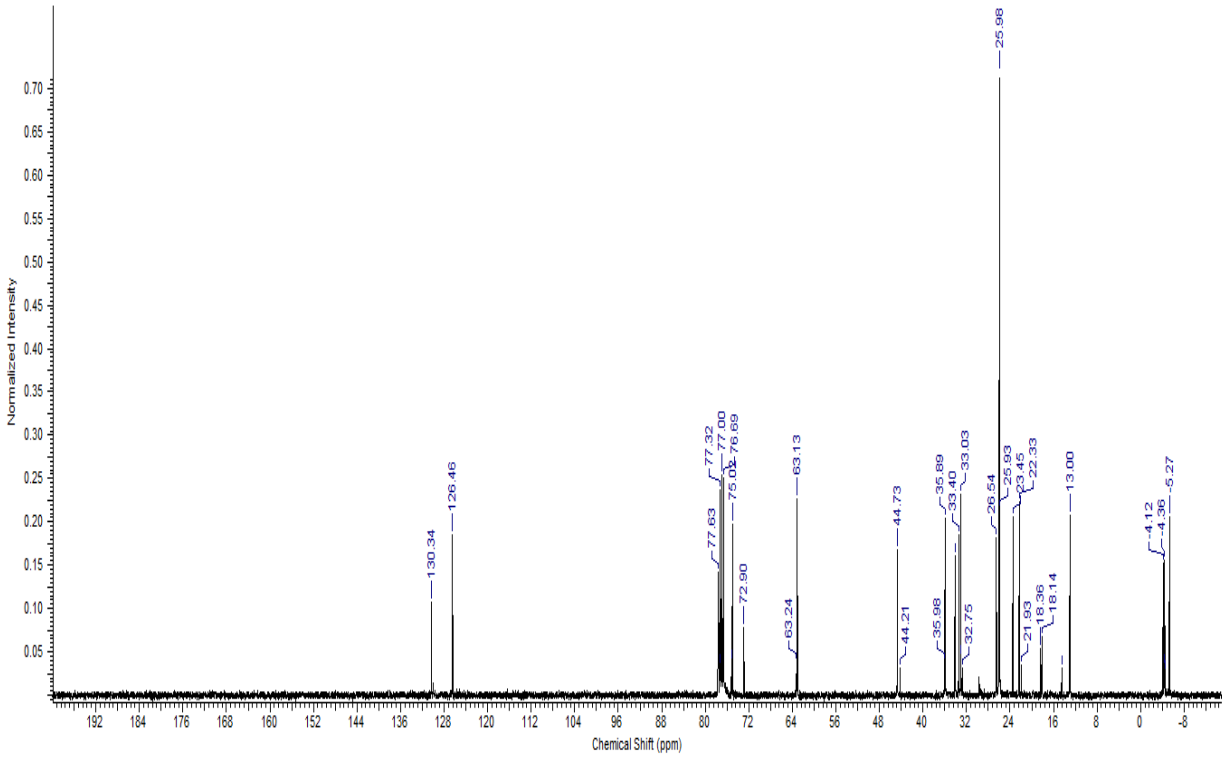


(3*R*,8*S*,9*S*,*Z*)-6-Bromo-9,13-bis((*tert*-butyldimethylsilyl)oxy)-2,8-dimethyltridec-5-ene-2,3-diol (**16**)

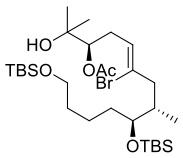


Chemical Formula: $C_{27}H_{57}BrO_4Si_2$
Molecular Weight: 581,81

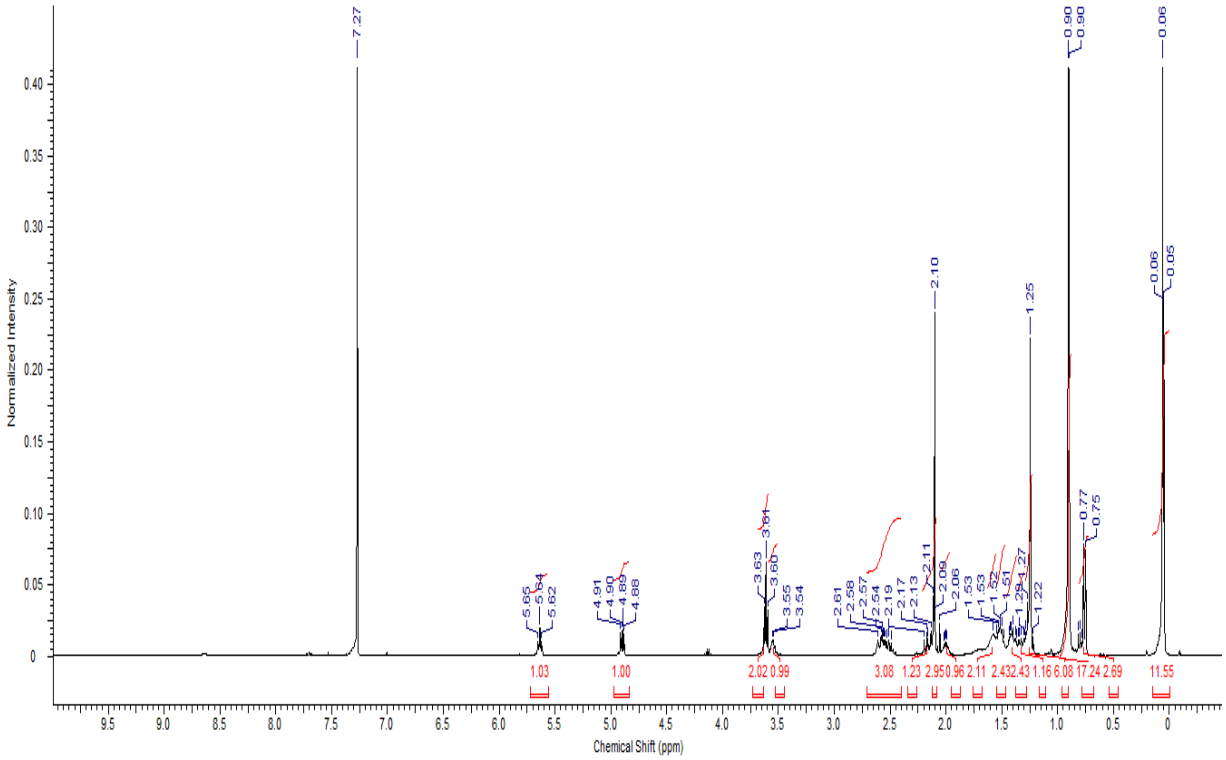


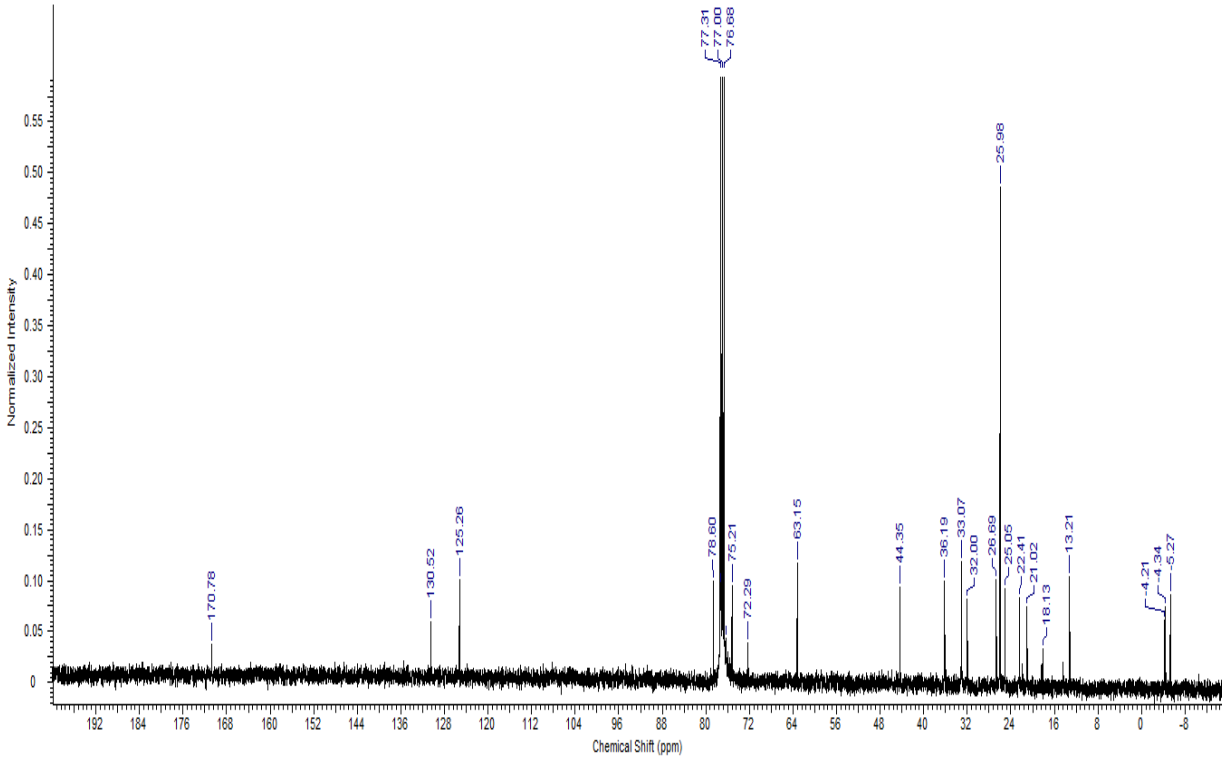


(3*R*,8*S*,9*S*,*Z*)-6-Bromo-9,13-bis((*tert*-butyldimethylsilyl)oxy)-2-hydroxy-2,8-dimethyltridec-5-en-3-yl acetate (**SI-4**)

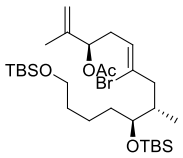


Chemical Formula: $C_{29}H_{59}BrO_5Si_2$
Molecular Weight: 623,85

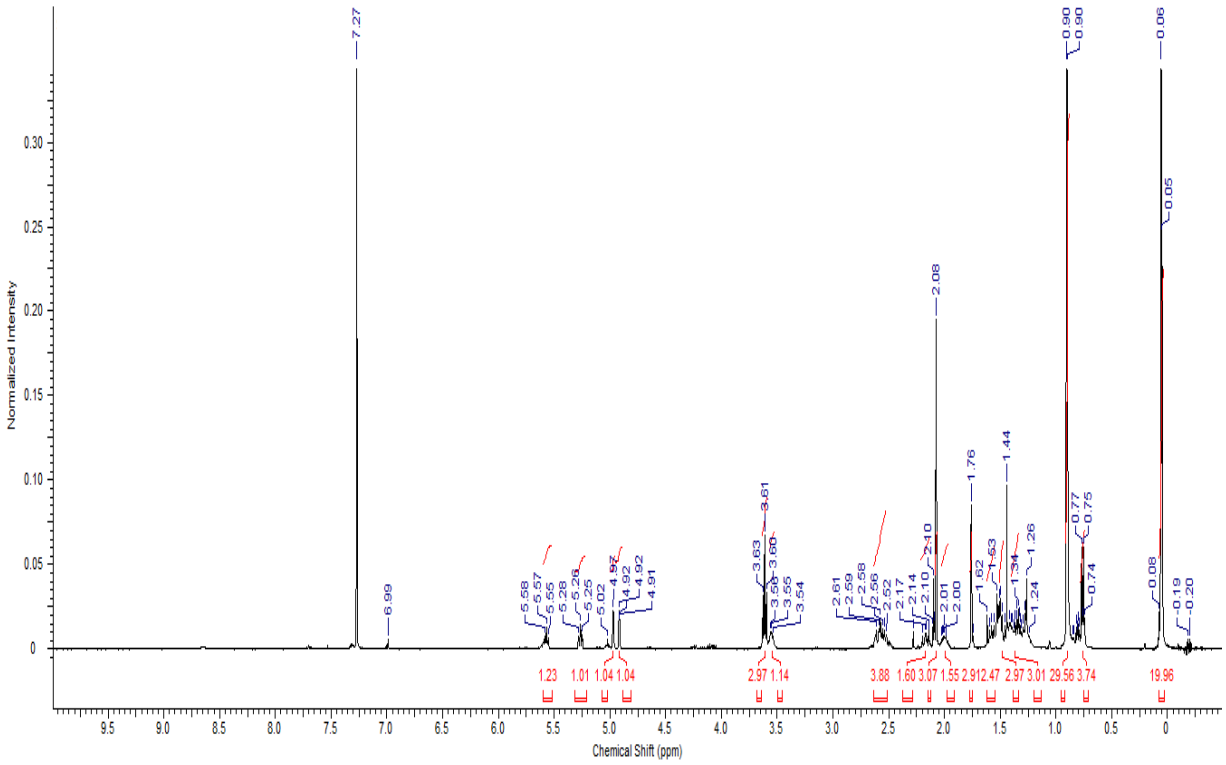


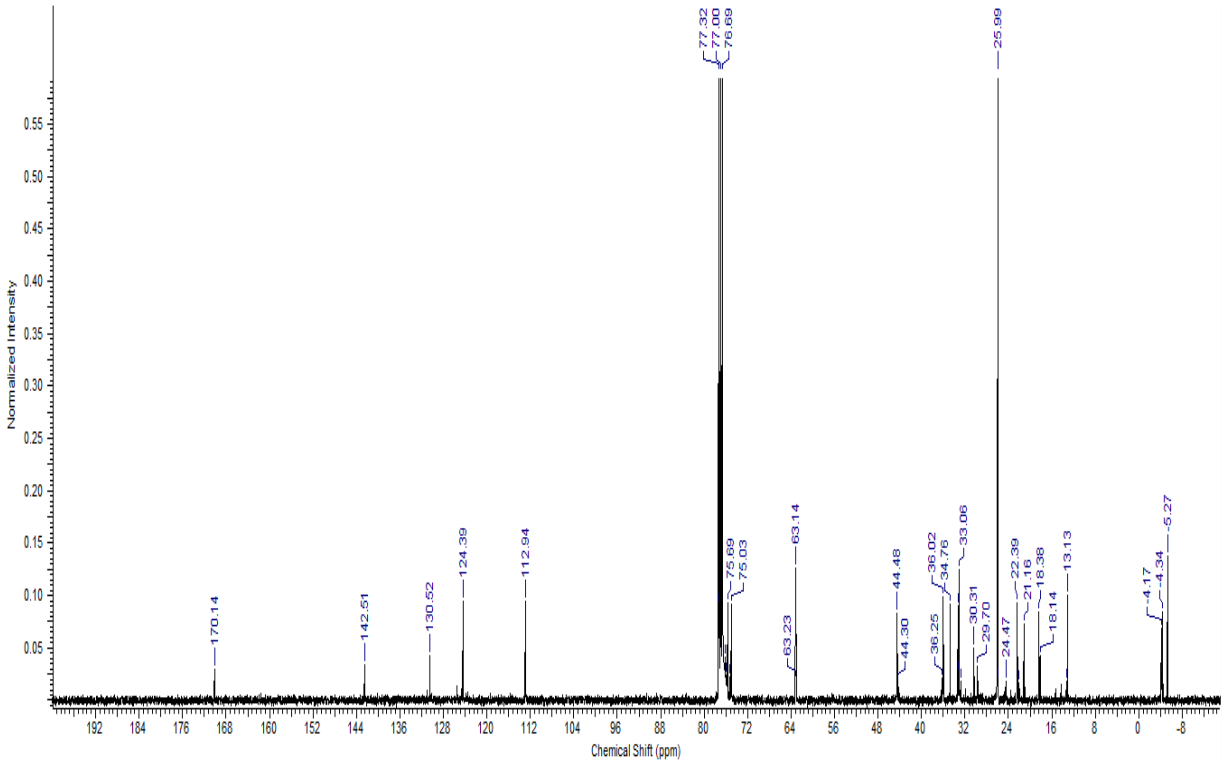


(3*R*,8*S*,9*S*,*Z*)-6-Bromo-9,13-bis((*tert*-butyldimethylsilyl)oxy)-2,8-dimethyltrideca-1,5-dien-3-yl acetate (**SI-5**)

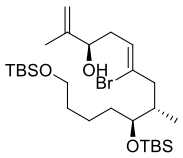


Chemical Formula: $C_{29}H_{57}BrO_4Si_2$
Molecular Weight: 605,84

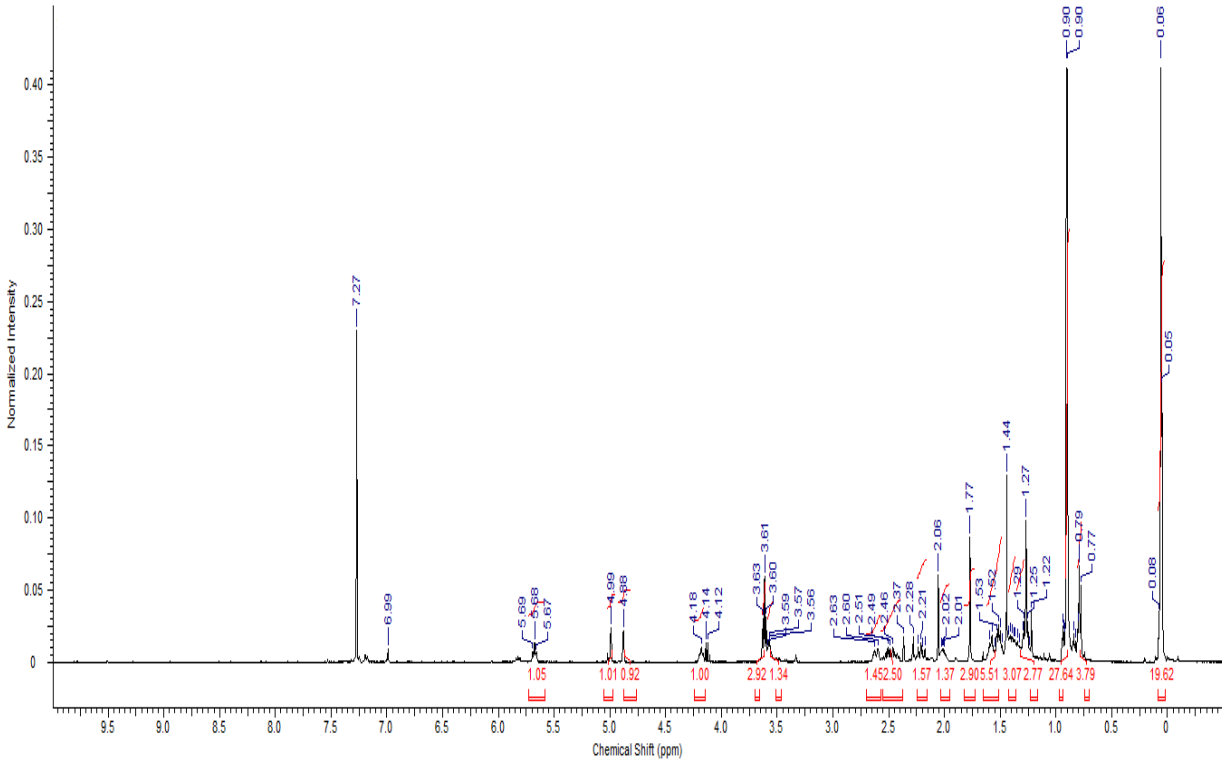


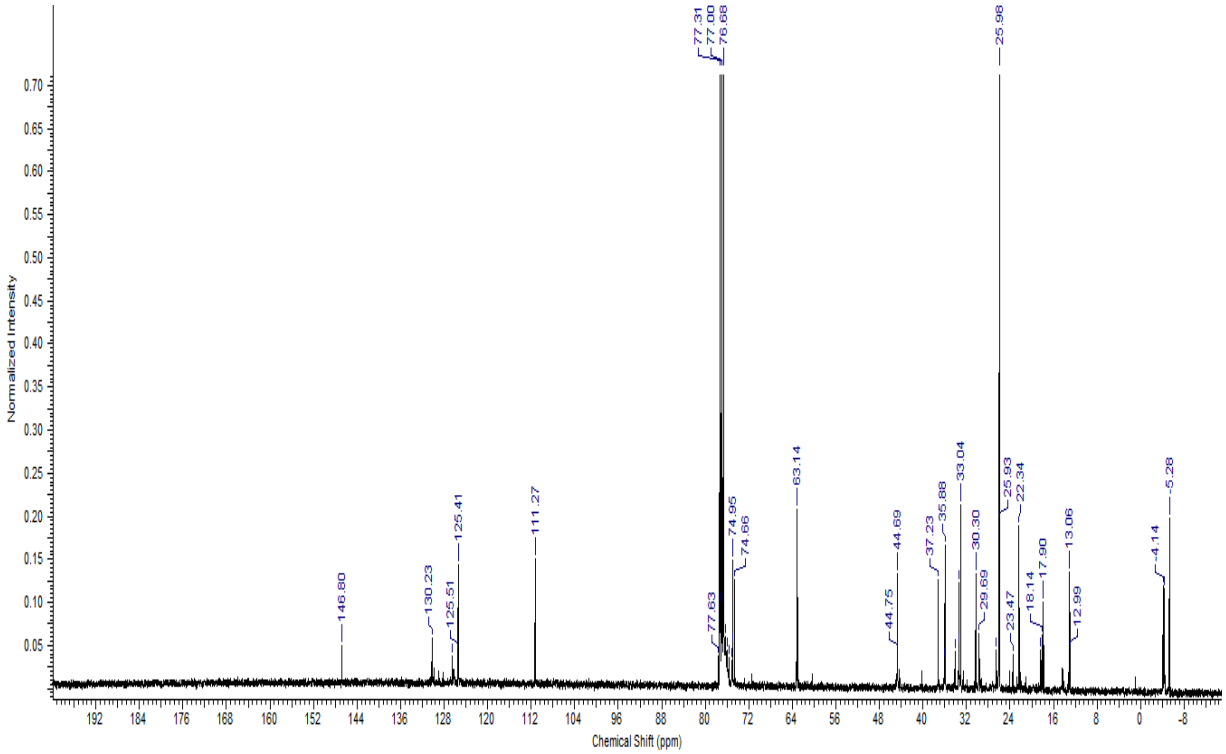


(3*R*,8*S*,9*S*,*Z*)-6-Bromo-9,13-bis((*tert*-butyldimethylsilyl)oxy)-2,8-dimethyltrideca-1,5-dien-3-ol (**SI-6**)

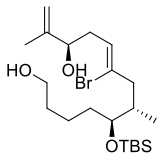


Chemical Formula: $C_{27}H_{55}BrO_3Si_2$
Molecular Weight: 563,80

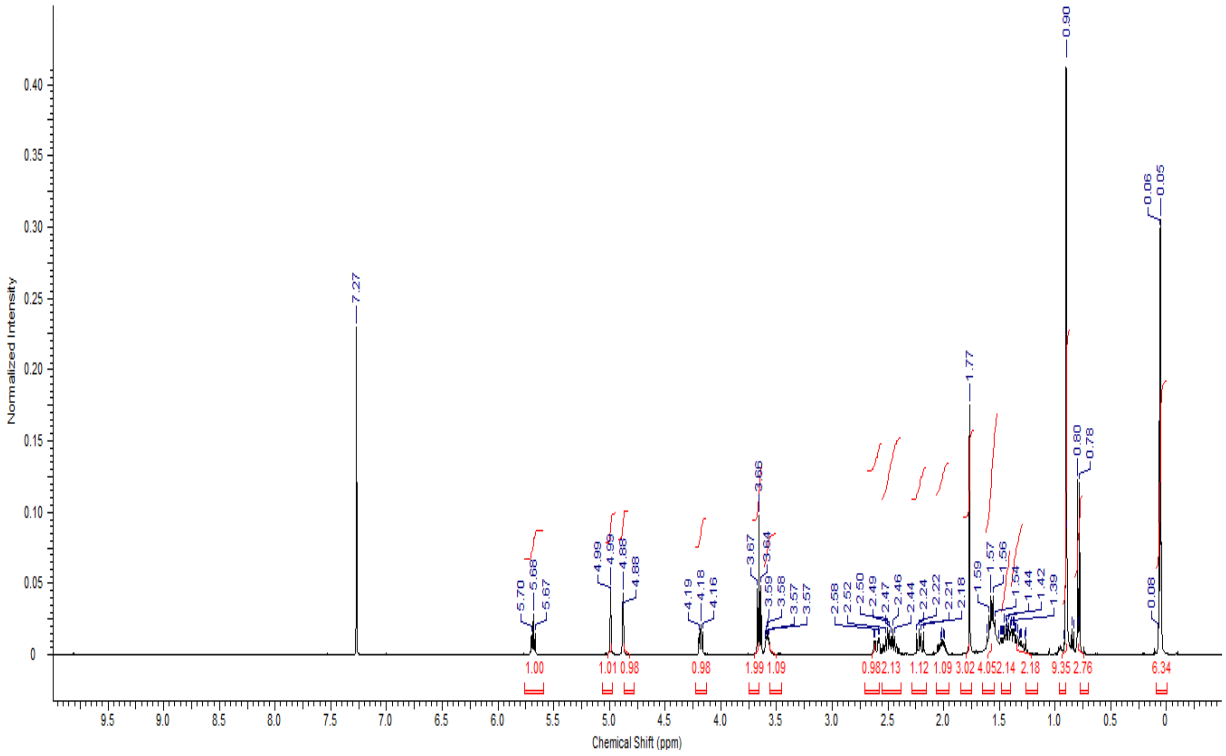


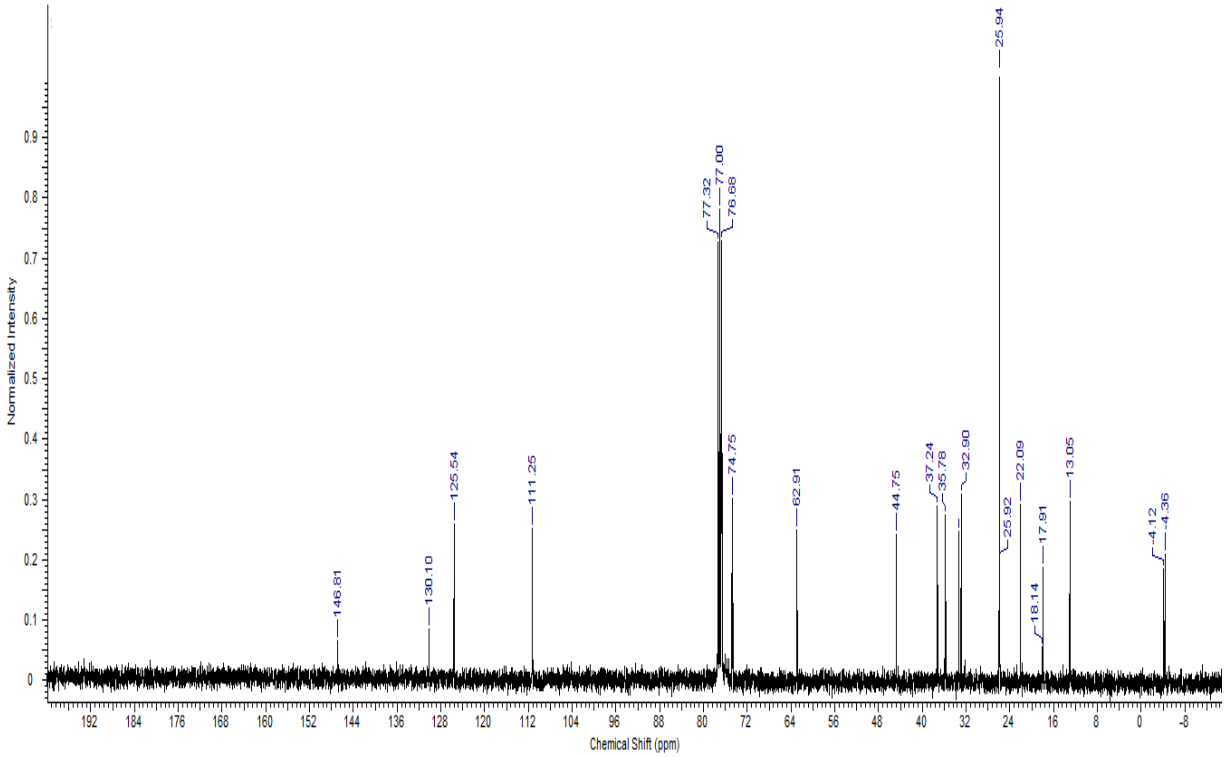


(5*S*,6*S*,11*R*,*Z*)-8-Bromo-5-((*tert*-butyldimethylsilyl)oxy)-6,12-dimethyltrideca-8,12-diene-1,11-diol (**17**)

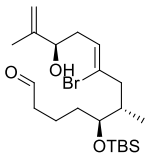


Chemical Formula: $C_{21}H_{41}BrO_3Si$
Molecular Weight: 449,54

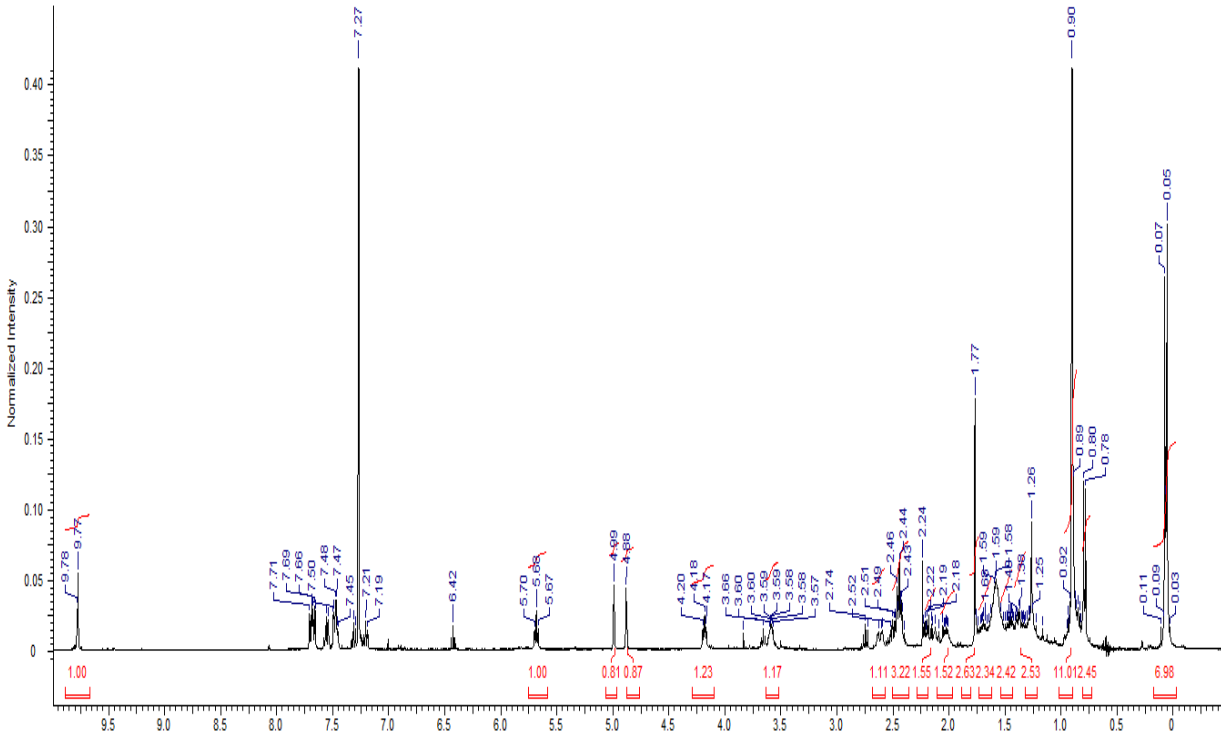


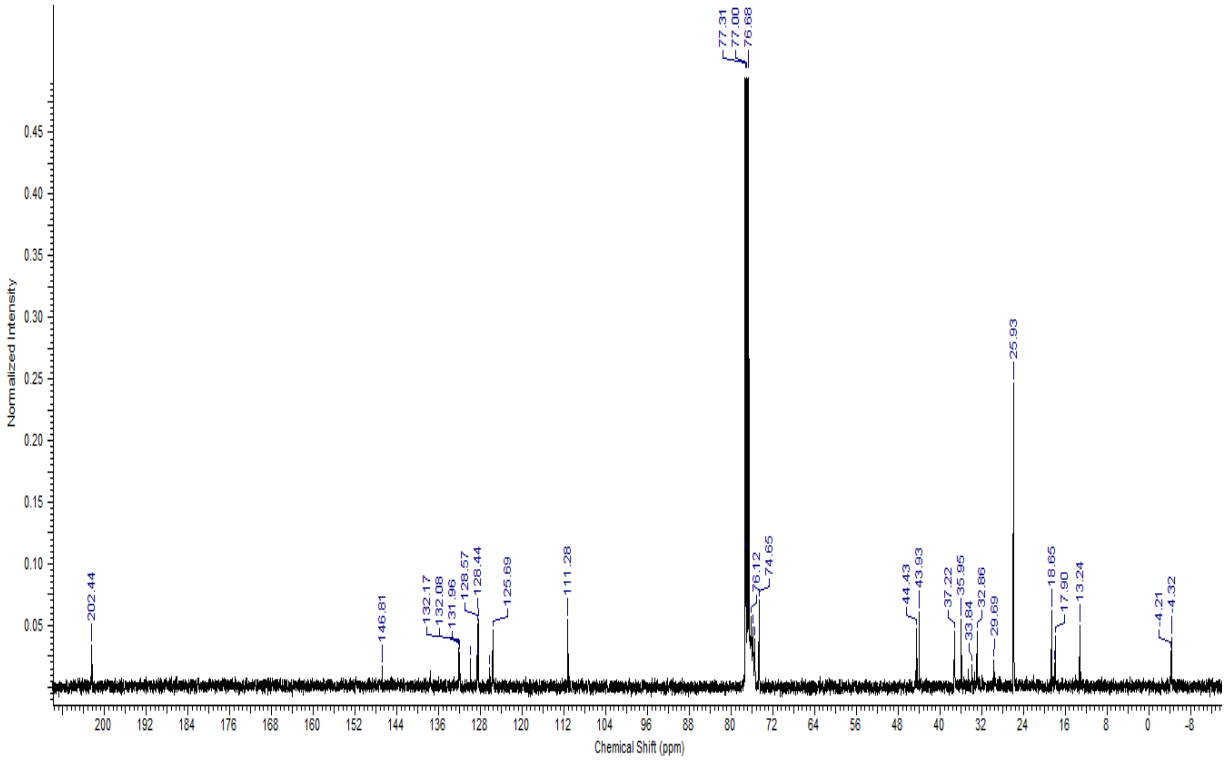


(5*S*,6*S*,11*R*,*Z*)-8-Bromo-5-((*tert*-butyldimethylsilyl)oxy)-11-hydroxy-6,12-dimethyltrideca-8,12-dienal (**SI-7**)

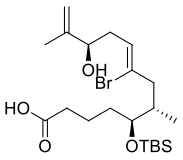


Chemical Formula: $C_{21}H_{39}BrO_3Si$
Molecular Weight: 447,52

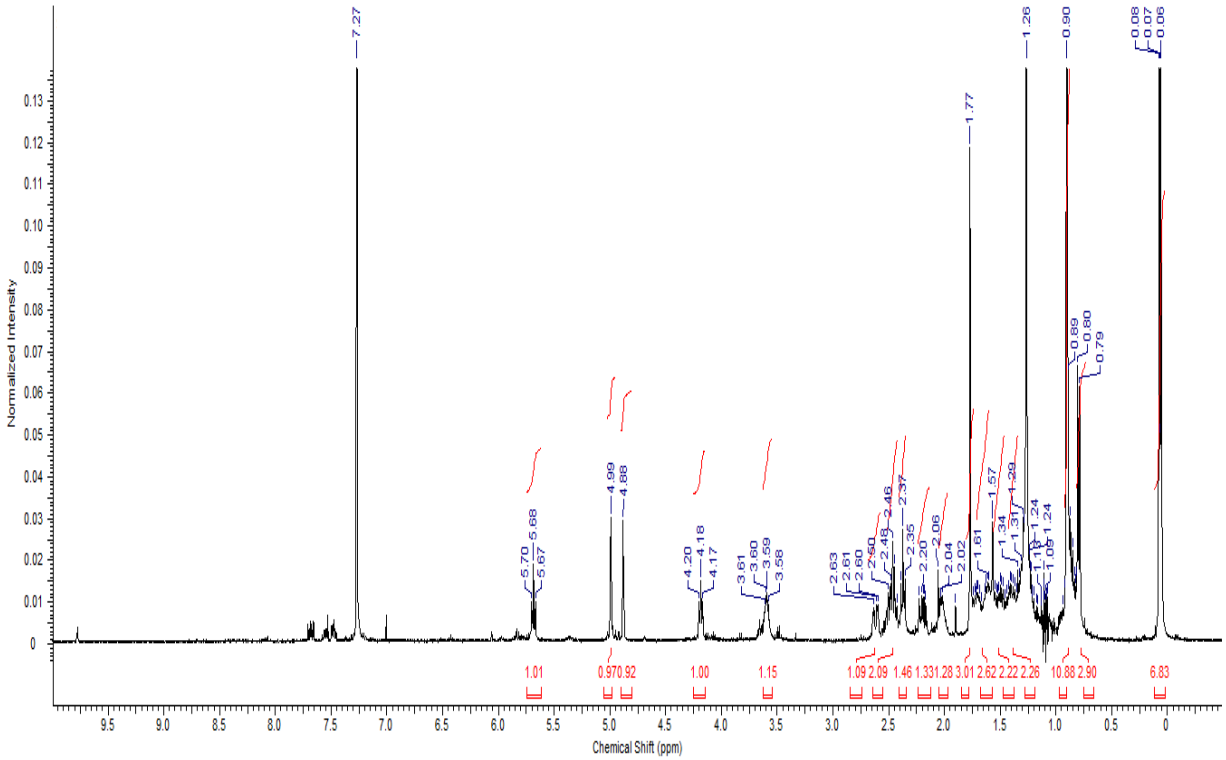


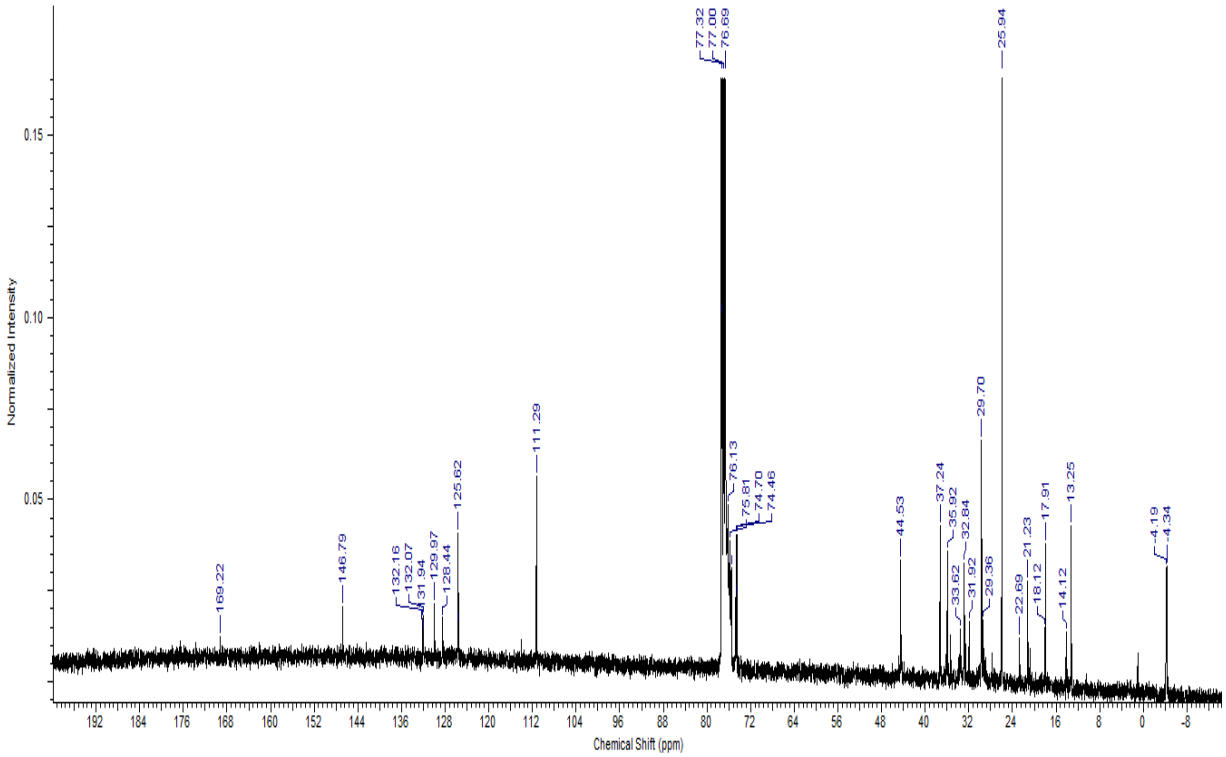


(5*S*,6*S*,11*R*,*Z*)-8-Bromo-5-((*tert*-butyldimethylsilyl)oxy)-11-hydroxy-6,12-dimethyltrideca-8,12-dienoic acid (**18**)

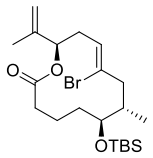


Chemical Formula: $C_{21}H_{39}BrO_4Si$
Molecular Weight: 463,52

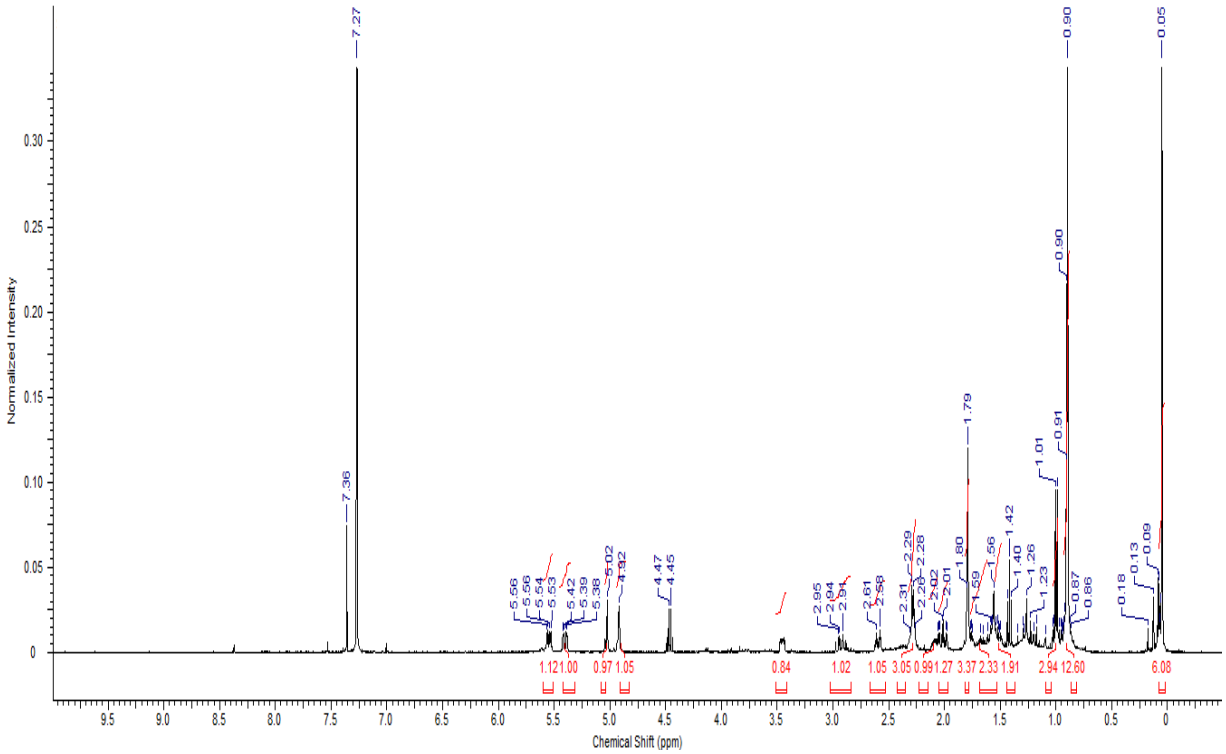


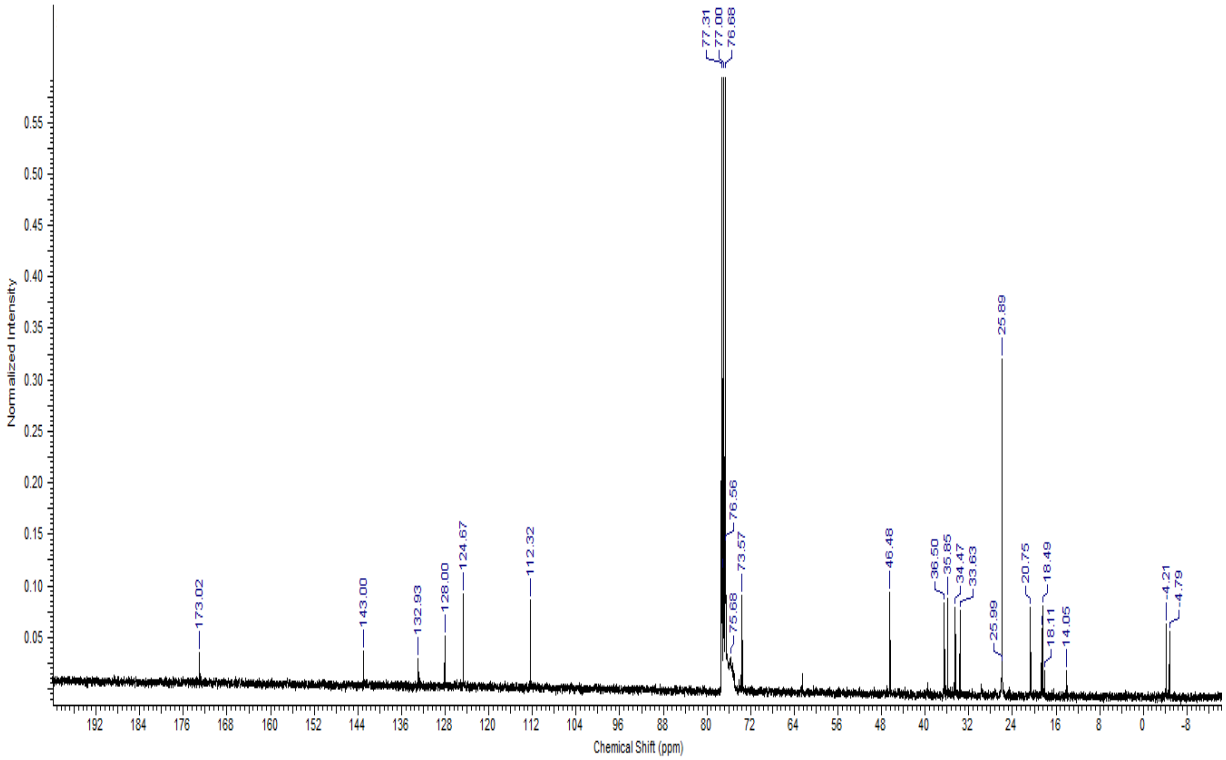


(6*S*,7*S*,12*R*,*Z*)-9-Bromo-6-((*tert*-butyldimethylsilyl)oxy)-7-methyl-12-(prop-1-en-2-yl)oxacyclododec-9-en-2-one (**19**)

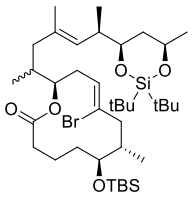


Chemical Formula: $C_{21}H_{37}BrO_3Si$
Molecular Weight: 445,51

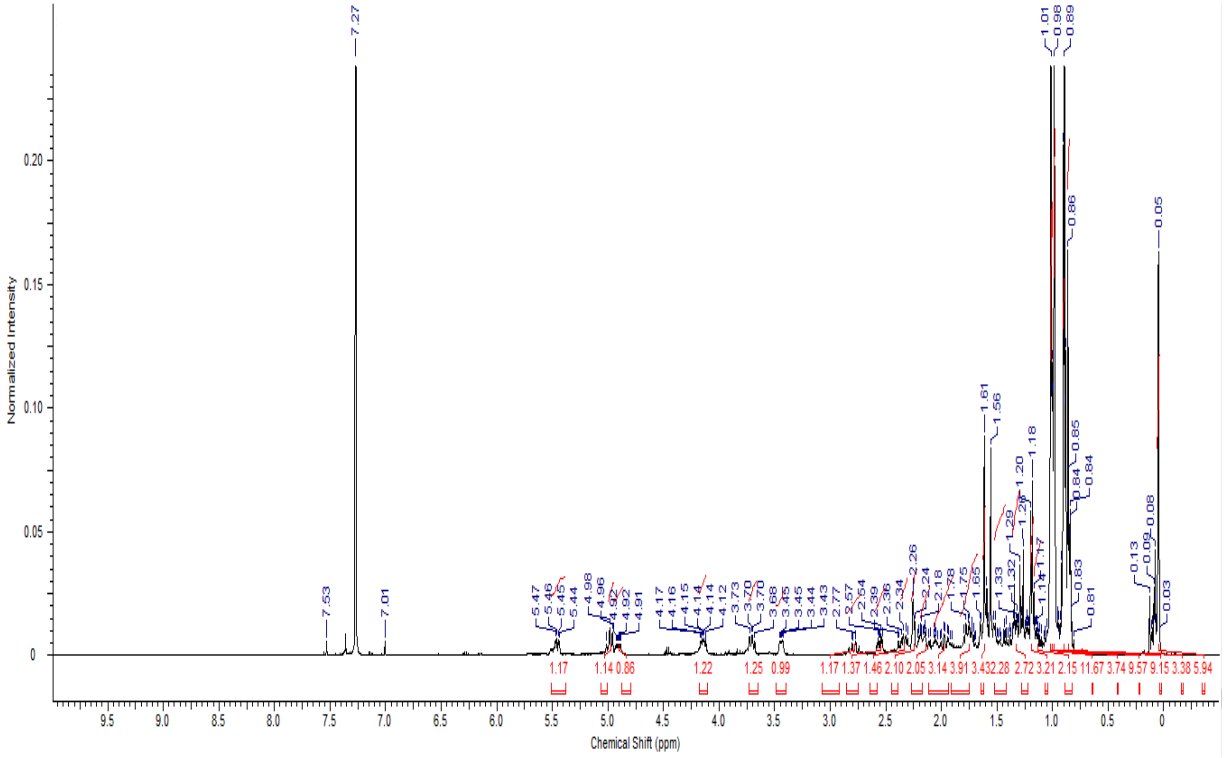


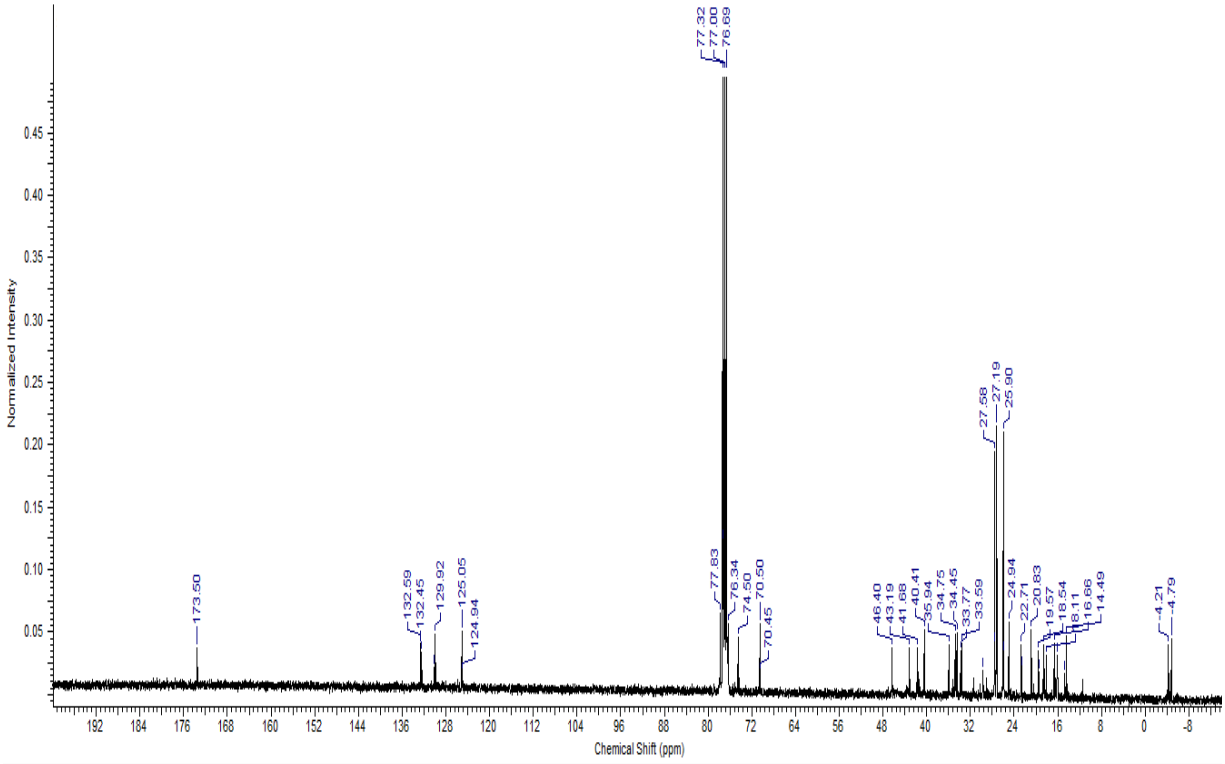


(6*S*,7*S*,12*R*,*Z*)-9-Bromo-6-((*tert*-butyldimethylsilyl)oxy)-12-((2*S*,6*R*,*E*)-6-((4*R*,6*R*)-2,2-di-*tert*-butyl-6-methyl-1,3,2-dioxasilinan-4-yl)-4-methylhept-4-en-2-yl)-7-methyloxacyclododec-9-en-2-one (**20**)

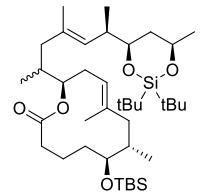


Chemical Formula: $C_{38}H_{71}BrO_5Si_2$
Molecular Weight: 744,04

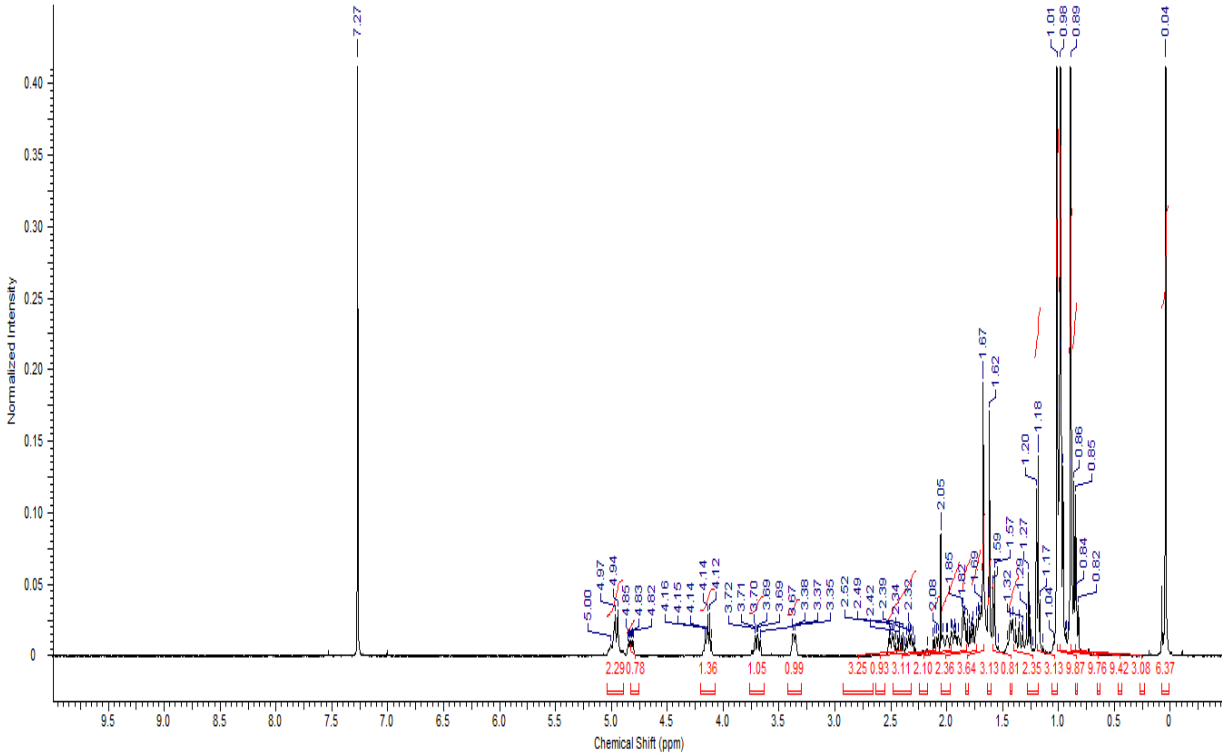


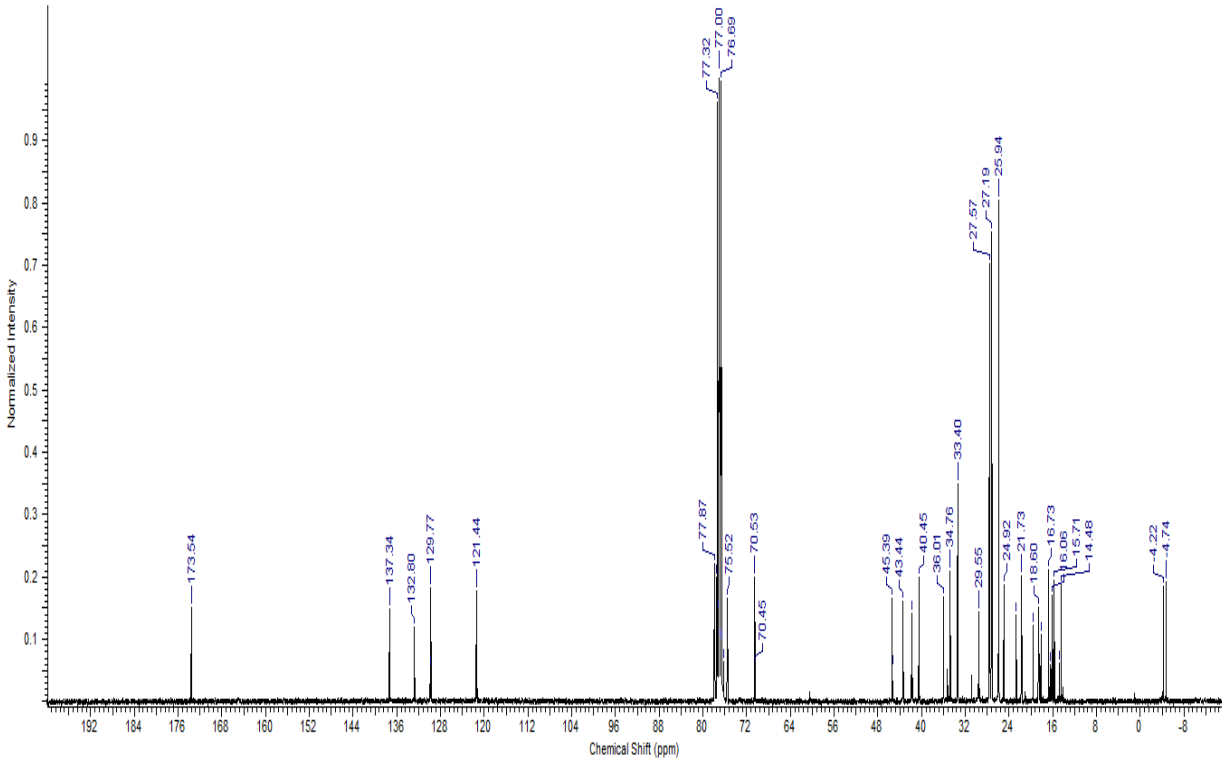


(6*S*,7*S*,12*R*,*E*)-6-((*tert*-Butyldimethylsilyl)oxy)-12-((2*S*,6*R*,*E*)-6-((4*R*,6*R*)-2,2-di-*tert*-butyl-6-methyl-1,3,2-dioxasilinan-4-yl)-4-methylhept-4-en-2-yl)-7,9-dimethyloxacyclododec-9-en-2-one (**21a**)

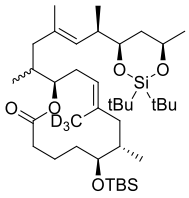


Chemical Formula: $C_{39}H_{74}O_5Si_2$
Molecular Weight: 679,17

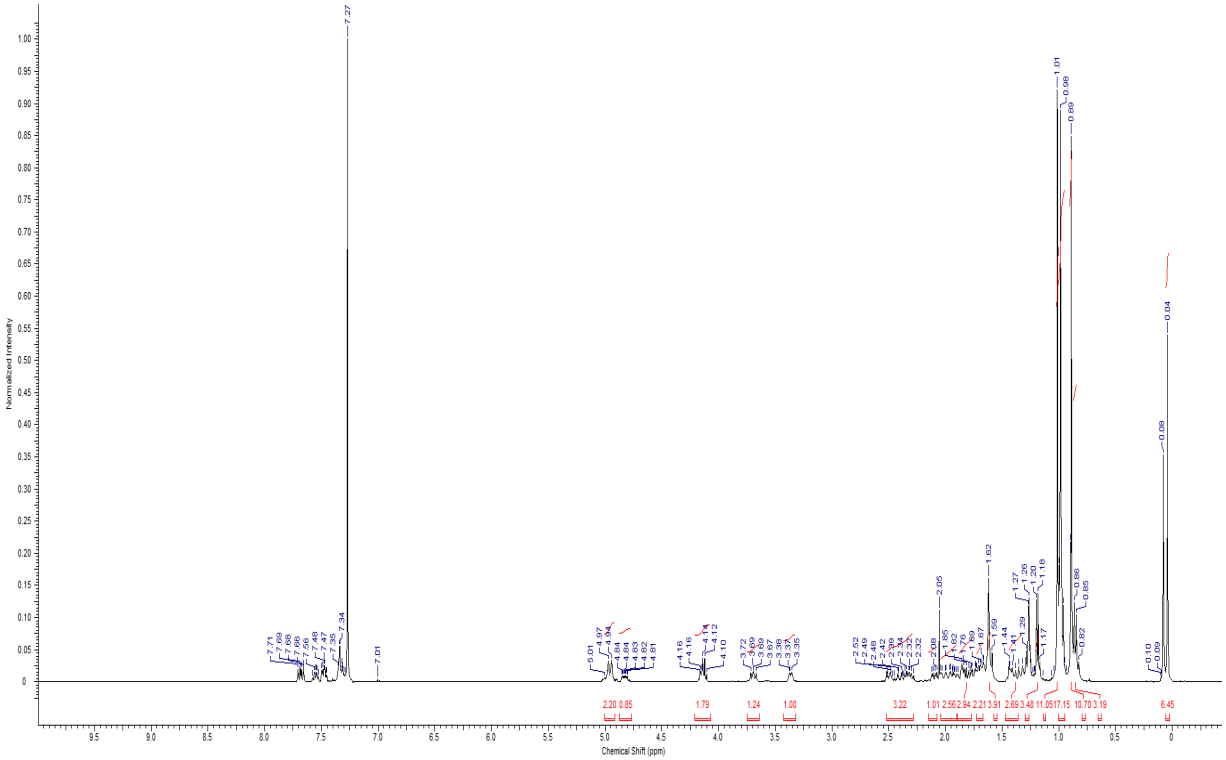


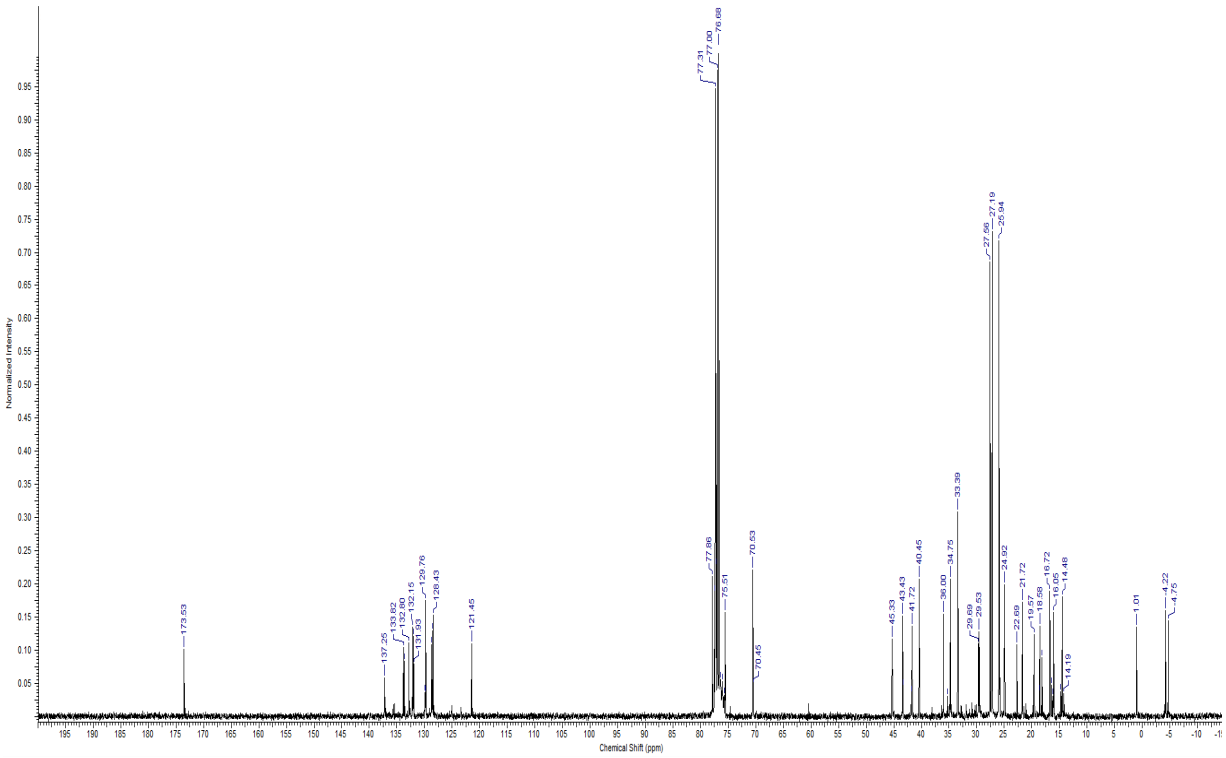


(6*S*,7*S*,12*R*,*E*)-6-((*tert*-Butyldimethylsilyl)oxy)-12-((2*S*,6*R*,*E*)-6-((4*R*,6*R*)-2,2-di-*tert*-butyl-6-methyl(d3)-1,3,2-dioxasilinan-4-yl)-4-methylhept-4-en-2-yl)-9-methyl(d3)-7methyloxacyclododec-9-en-2-one (**21b**)

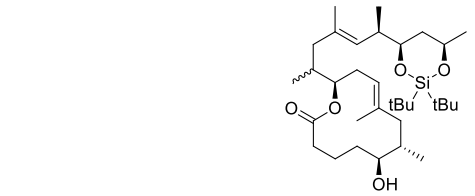


Chemical Formula: $C_{39}H_{71}D_3O_5Si_2$
Molecular Weight: 682,19

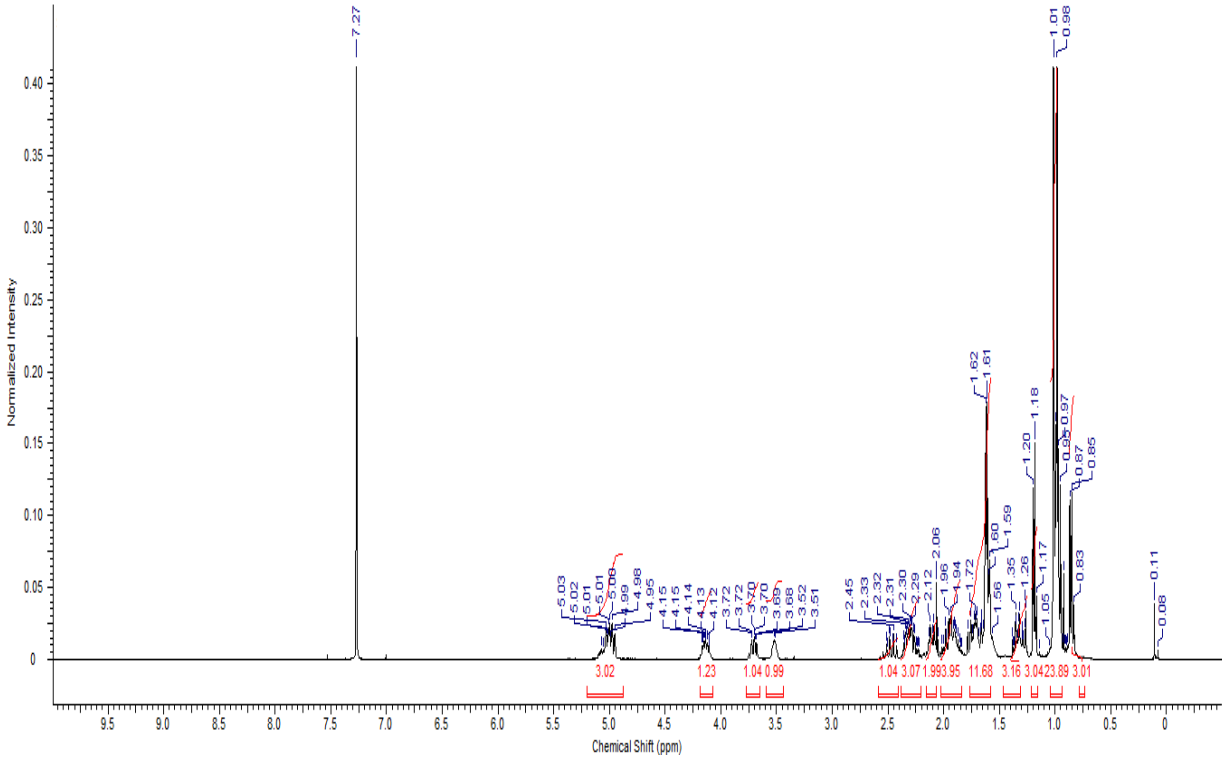


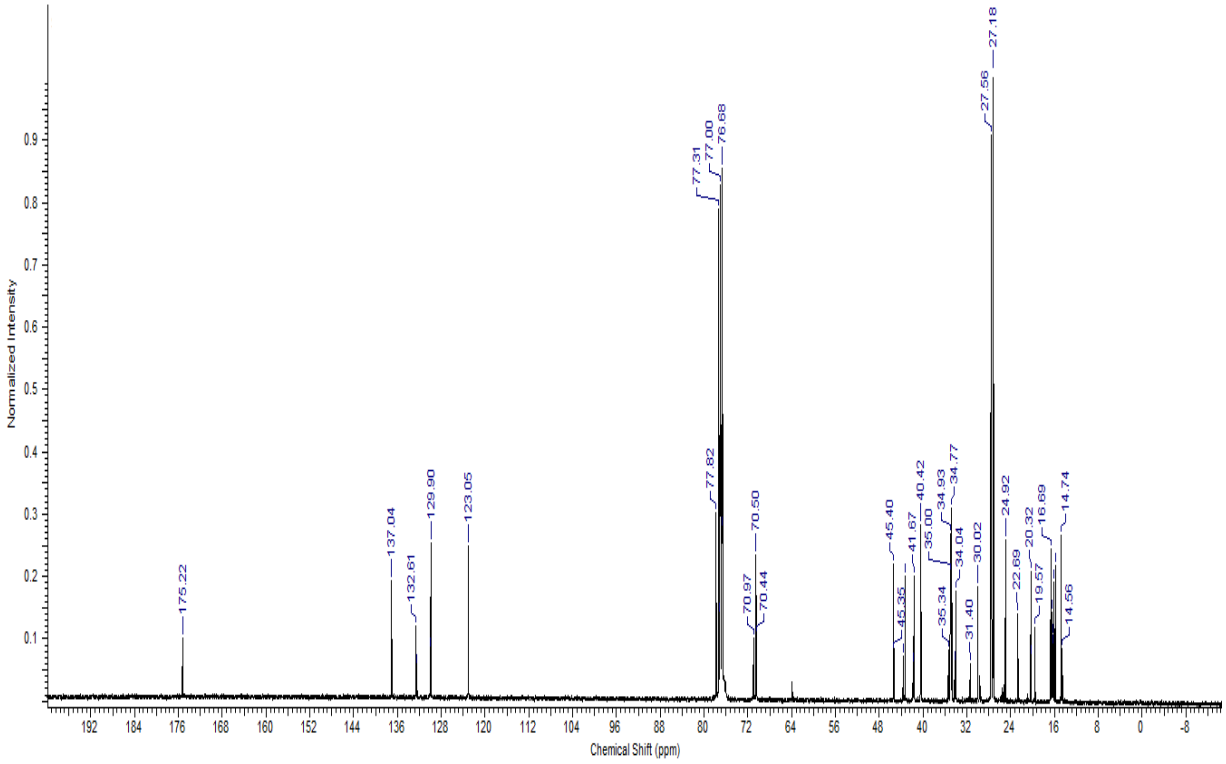


(6*S*,7*S*,12*R*,*E*)-12-((2S,6*R*,*E*)-6-((4*R*,6*R*)-2,2-di-*tert*-Butyl-6-methyl-1,3,2-dioxasilinan-4-yl)-4-methylhept-4-en-2-yl)-6-hydroxy-7,9-dimethyloxacyclododec-9-en-2-one (**22a**)

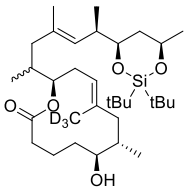


Chemical Formula: $C_{33}H_{60}O_5Si$
Molecular Weight: 564,91

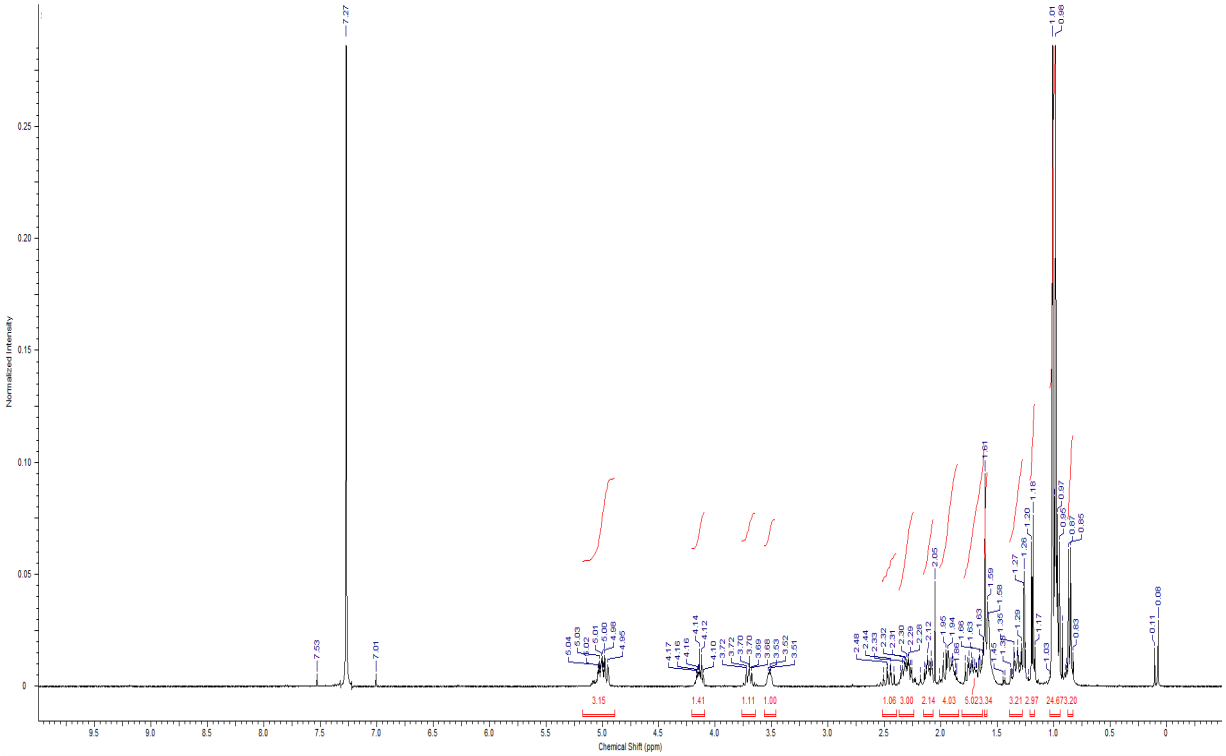


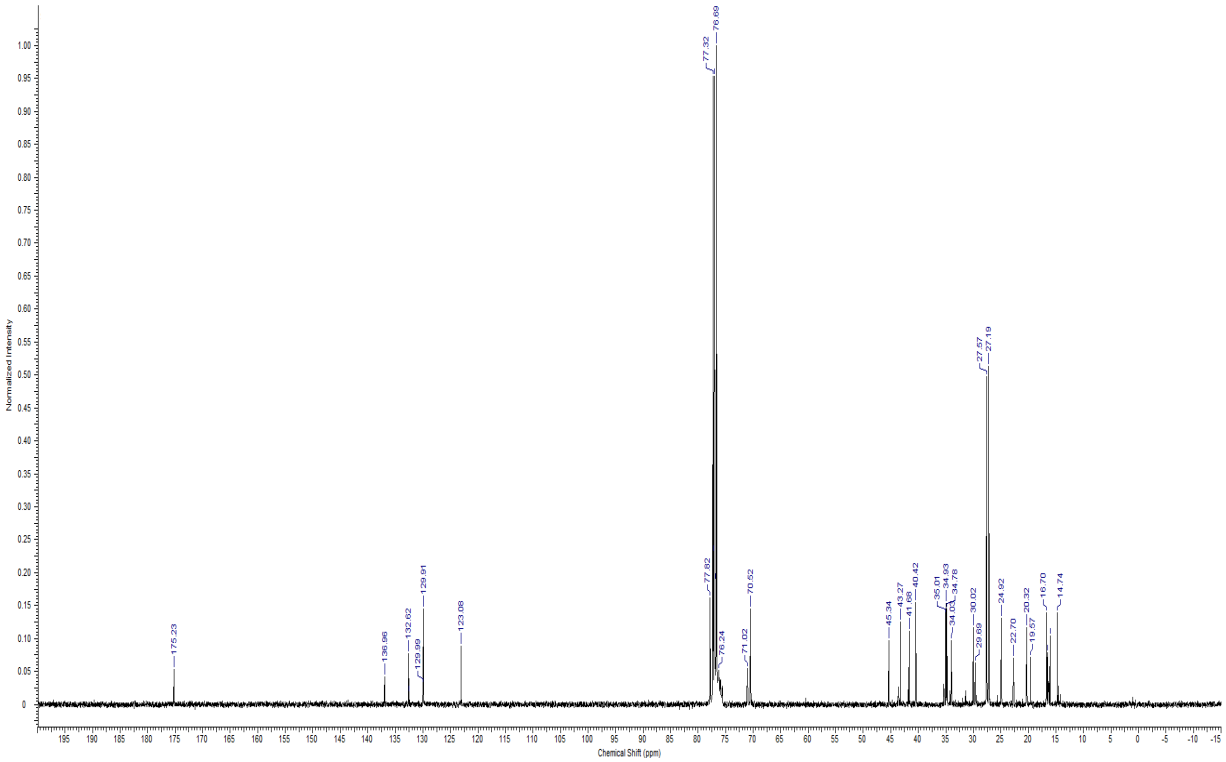


(6*S*,7*S*,12*R*,*E*)-12-((2S,6*R*,*E*)-6-((4*R*,6*R*)-2,2-di-*tert*-Butyl-6-methyl-1,3,2-dioxasilinan-4-yl)-4-methylhept-4-en-2-yl)-6-hydroxy-9-methyl(d3)-7-methyloxacyclododec-9-en-2-one (**22b**)

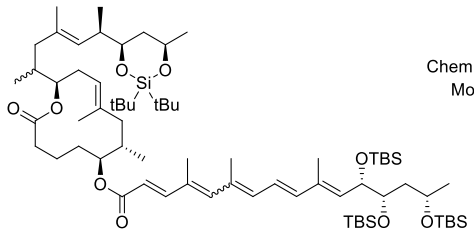


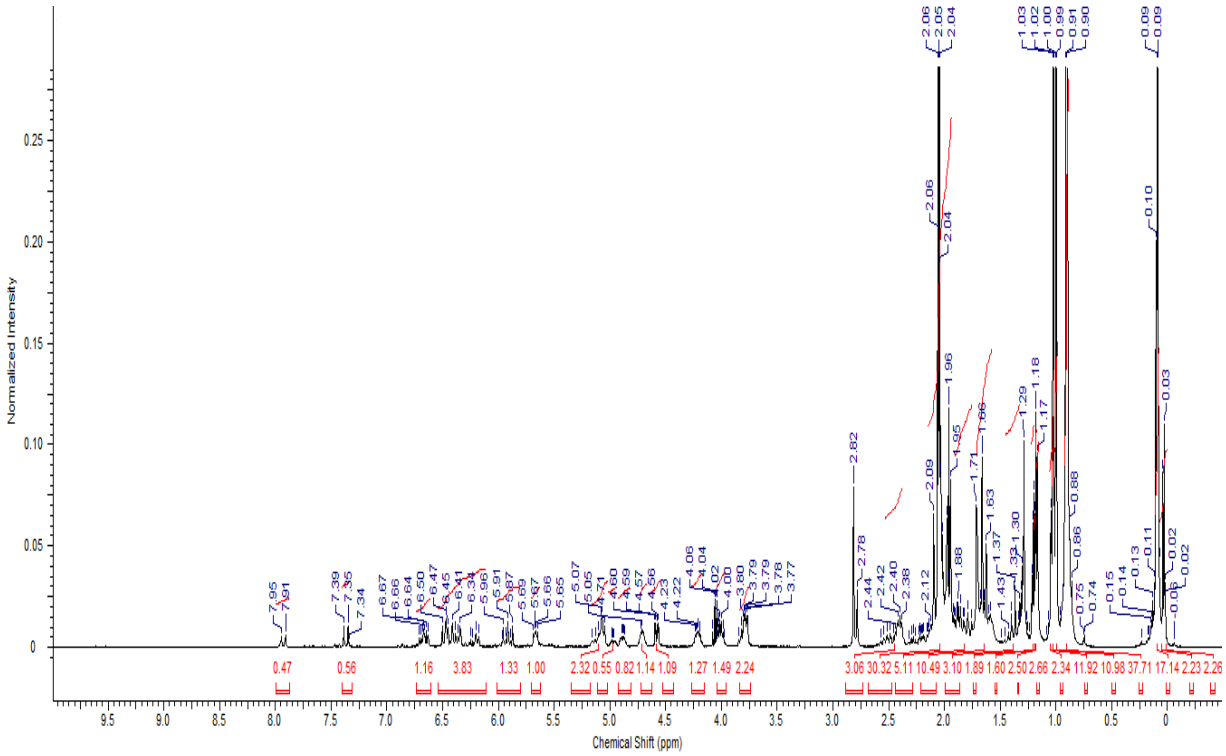
Chemical Formula: $C_{33}H_{57}D_3O_5Si$
Molecular Weight: 567,93

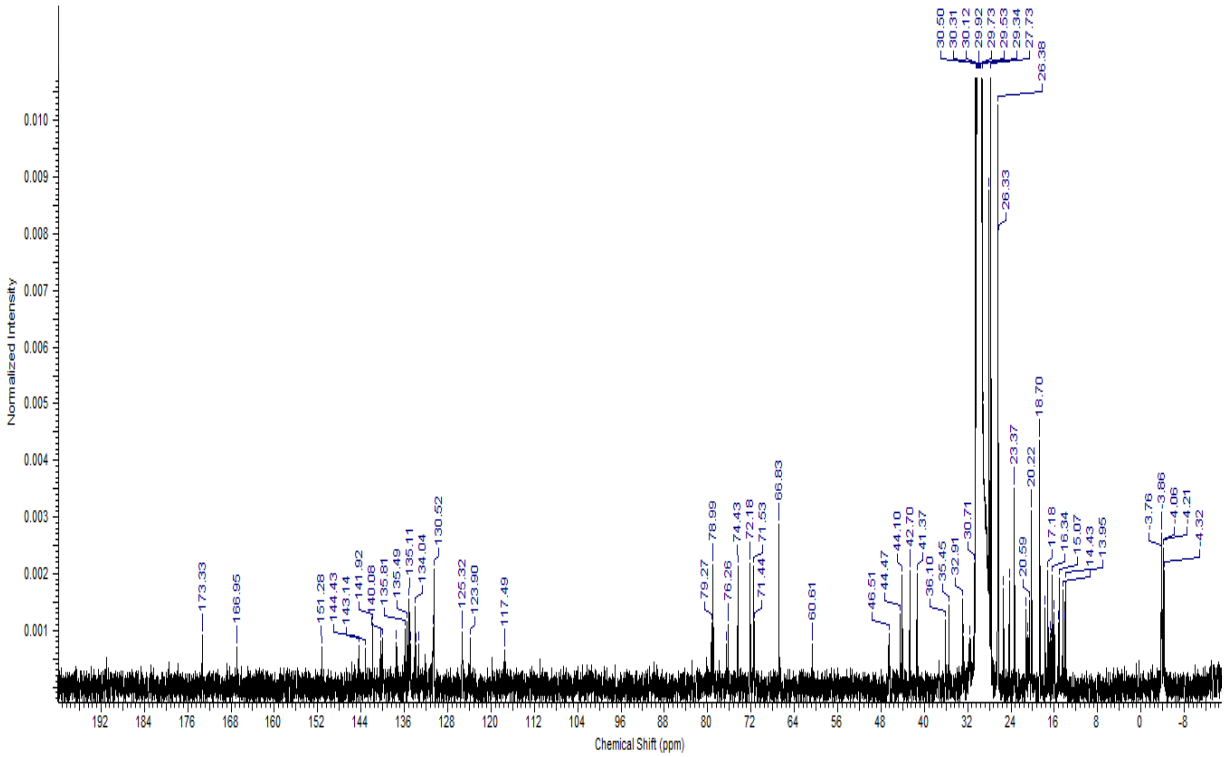




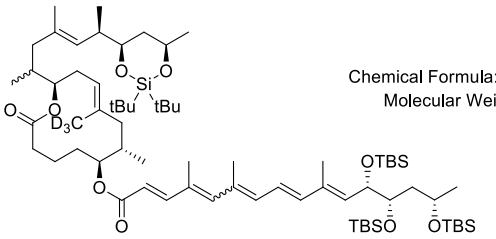
(2*E*,8*E*,10*E*,12*S*,13*S*,15*S*)-(6*S*,7*S*,12*R*,*E*)-12-((2*S*,6*R*,*E*)-6-((4*R*,6*R*)-2,2-di-*tert*-Butyl-6-methyl-1,3,2-dioxasilinan-4-yl)-4-methylhept-4-en-2-yl)-7,9-dimethyl-2-oxooxacyclododec-9-en-6-yl 12,13,15-tris((*tert*-butyldimethylsilyl)oxy)-4,6,10-trimethylhexadeca-2,4,6,8,10-pentaenoate (**SI-12a**)

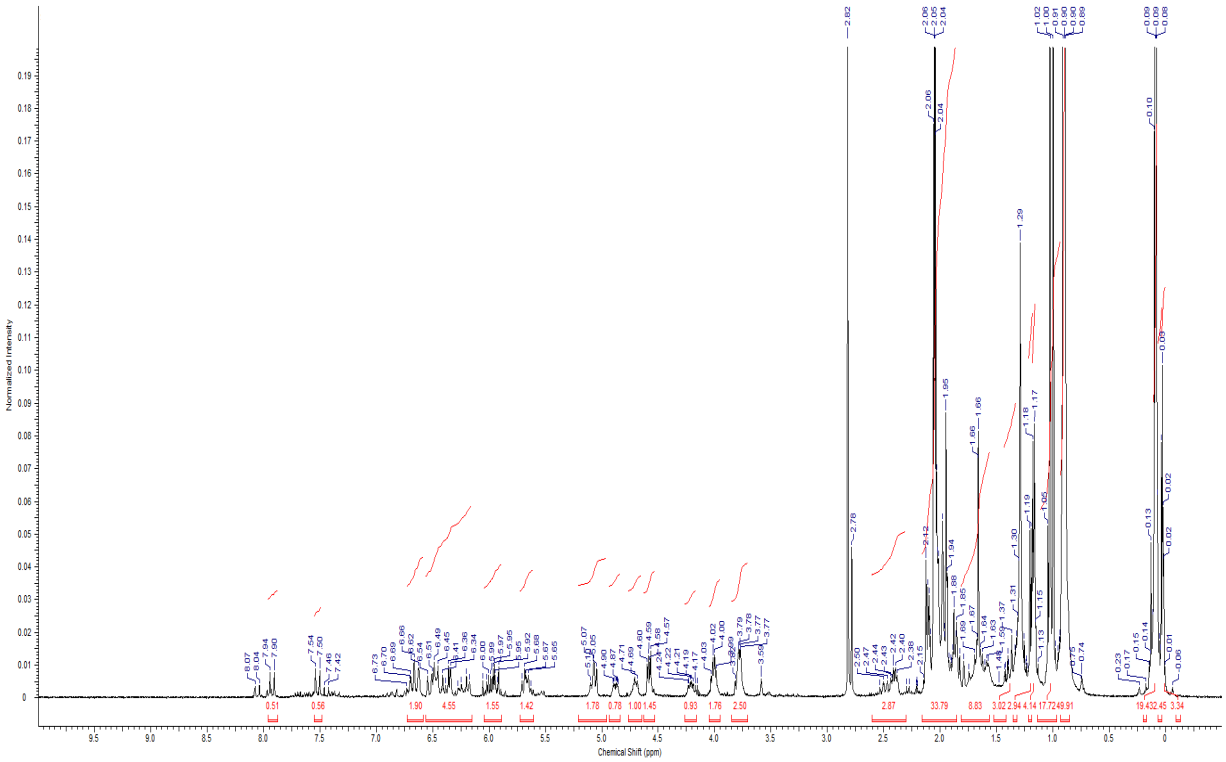


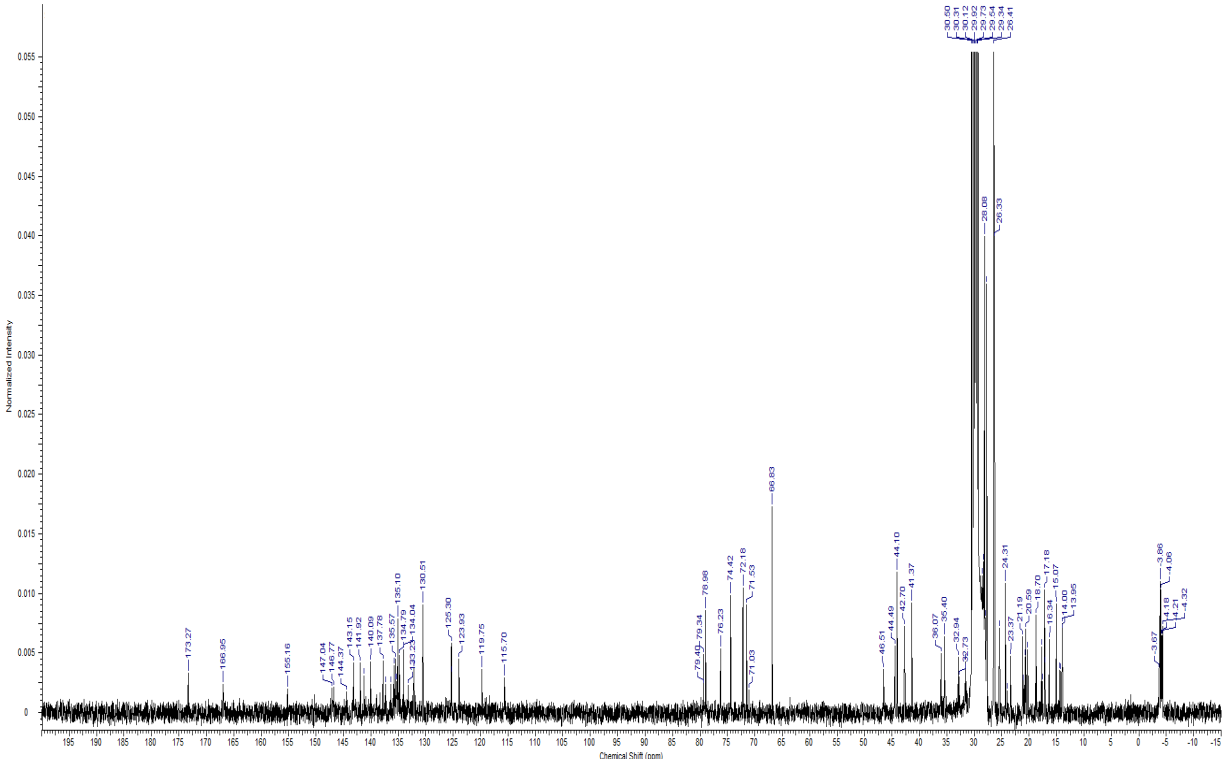



Normalized Intensity
Chemical Shift (ppm)
173.33
166.95
151.28
144.43
143.14
141.92
140.08
135.81
135.49
135.11
134.04
130.52
125.32
123.90
117.49
79.27
78.99
76.26
74.43
72.18
71.44
71.53
66.83
60.61
48.51
44.47
44.10
42.70
41.37
36.10
35.45
32.91
30.71
30.50
30.31
30.12
29.92
29.73
29.53
29.34
27.73
26.38
26.33
23.37
20.59
20.22
18.70
17.18
16.34
15.07
14.43
13.95
-3.76
-3.86
-4.06
-4.21
-4.32

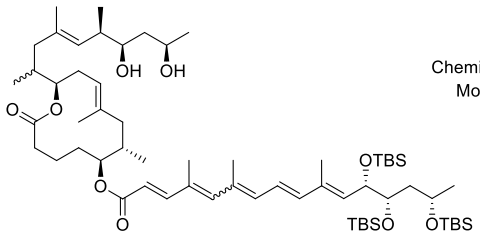
(2*E*,8*E*,10*E*,12*S*,13*S*,15*S*)-(6*S*,7*S*,12*R*,*E*)-12-((2*S*,6*R*,*E*)-6-((4*R*,6*R*)-2,2-di-*tert*-Butyl-6-methyl-1,3,2-dioxasilinan-4-yl)-4-methylhept-4-en-2-yl)-9-methyl(d3)-7-methyl-2-oxooxacyclododec-9-en-6-yl 12,13,15-tris((*tert*-butyldimethylsilyl)oxy)-4,6,10-trimethylhexadeca-2,4,6,8,10-pentaenoate (**SI-12b**)



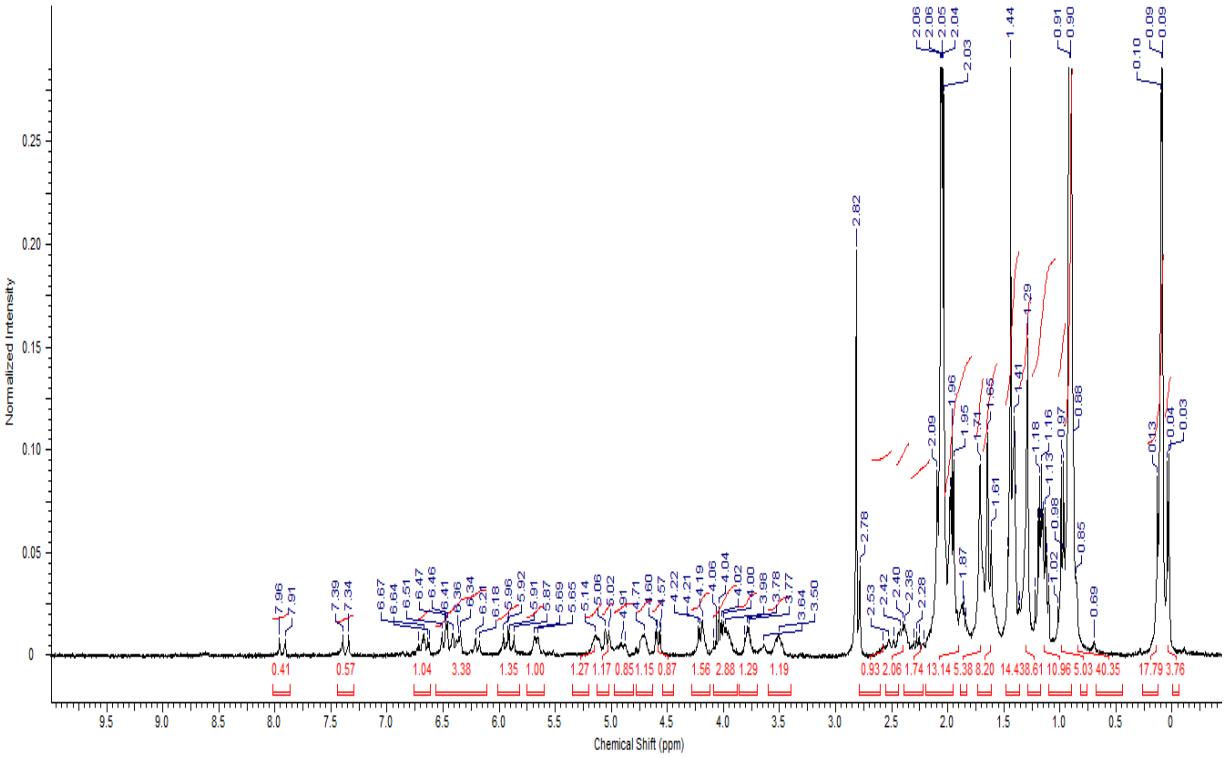



Normalized Intensity
Chemical Shift (ppm)
30.60
30.31
30.12
29.92
29.73
29.54
29.34
29.41
28.08
26.33
24.31
23.37
21.19
20.59
18.70
17.18
16.34
15.07
14.00
13.95
3.98
4.06
4.21
4.32
3.67
14.18
69.83
74.42
72.18
71.53
71.03
79.98
79.34
79.45
76.23
44.10
44.49
46.51
42.70
41.37
36.07
35.40
32.94
32.73
173.27
166.95
155.16
147.04
146.77
144.37
143.15
141.92
140.09
137.78
135.57
135.10
134.04
133.21
130.51
125.30
123.93
119.75
115.70

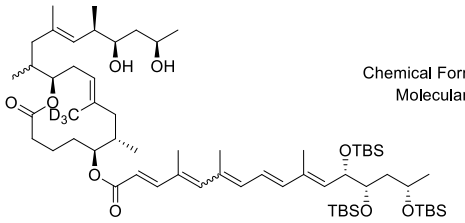
(2*E*,4*E*,6*E*,8*E*,10*E*,12*S*,13*S*,15*S*)-(6*S*,7*S*,12*R*,*E*)-12-((2*S*,6*R*,7*R*,9*R*,*E*)-7,9-Dihydroxy-4,6-dimethyldec-4-en-2-yl)-7,9-dimethyl-2-oxooxacyclododec-9-en-6-yl 12,13,15-tris((*tert*-butyldimethylsilyl)oxy)-4,6,10-trimethylhexadeca-2,4,6,8,10-pentaenoate (**SI-13a**)



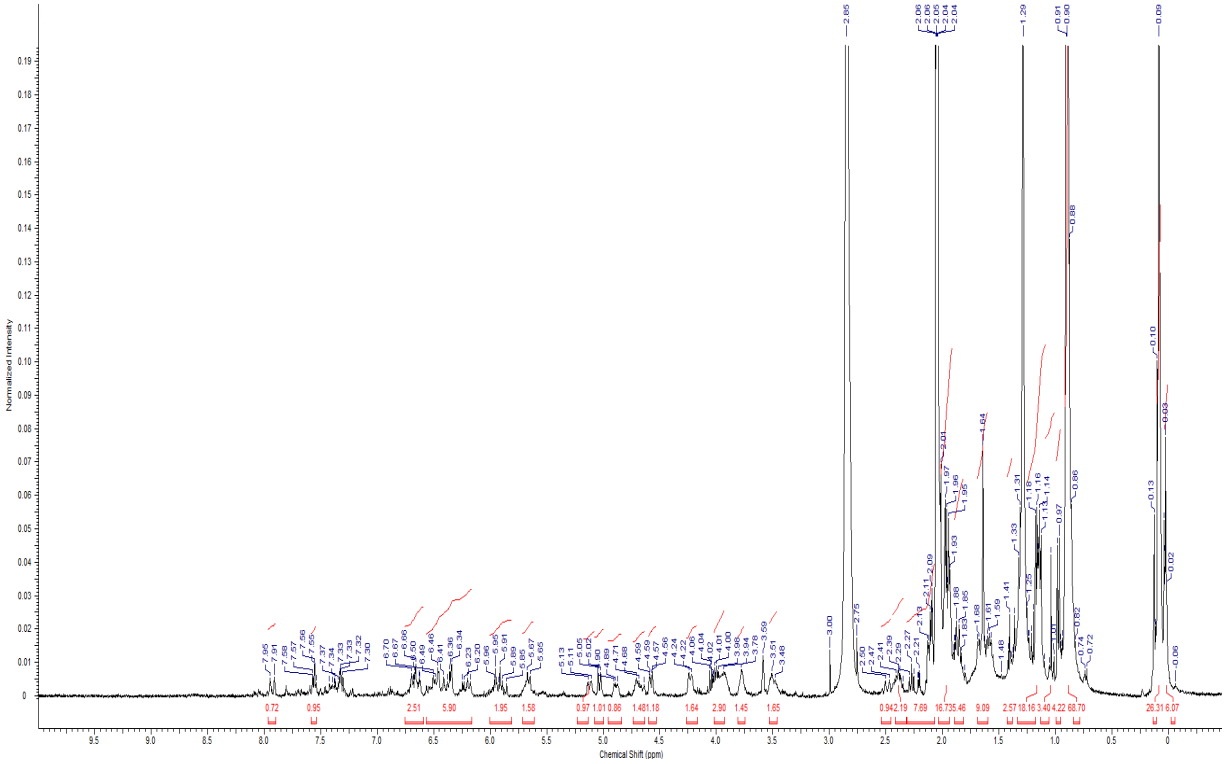
Chemical Formula: $C_{62}H_{112}O_9Si_3$
Molecular Weight: 1085,80



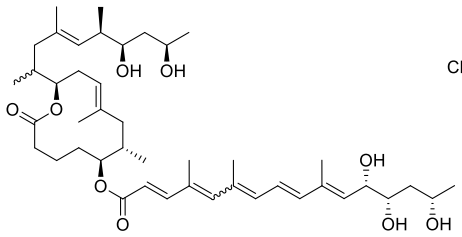
(2*E*,4*E*,6*E*,8*E*,10*E*,12*S*,13*S*,15*S*)-(6*S*,7*S*,12*R*,*E*)-12-((2*S*,6*R*,7*R*,9*R*,*E*)-7,9-Dihydroxy-4,6-dimethyldec-4-en-2-yl)-9-methyl(d3)-7-methyl-2-oxooxacyclododec-9-en-6-yl 12,13,15-tris((*tert*-butyldimethylsilyl)oxy)-4,6,10-trimethylhexadeca-2,4,6,8,10-pentaenoate (**SI-13b**)



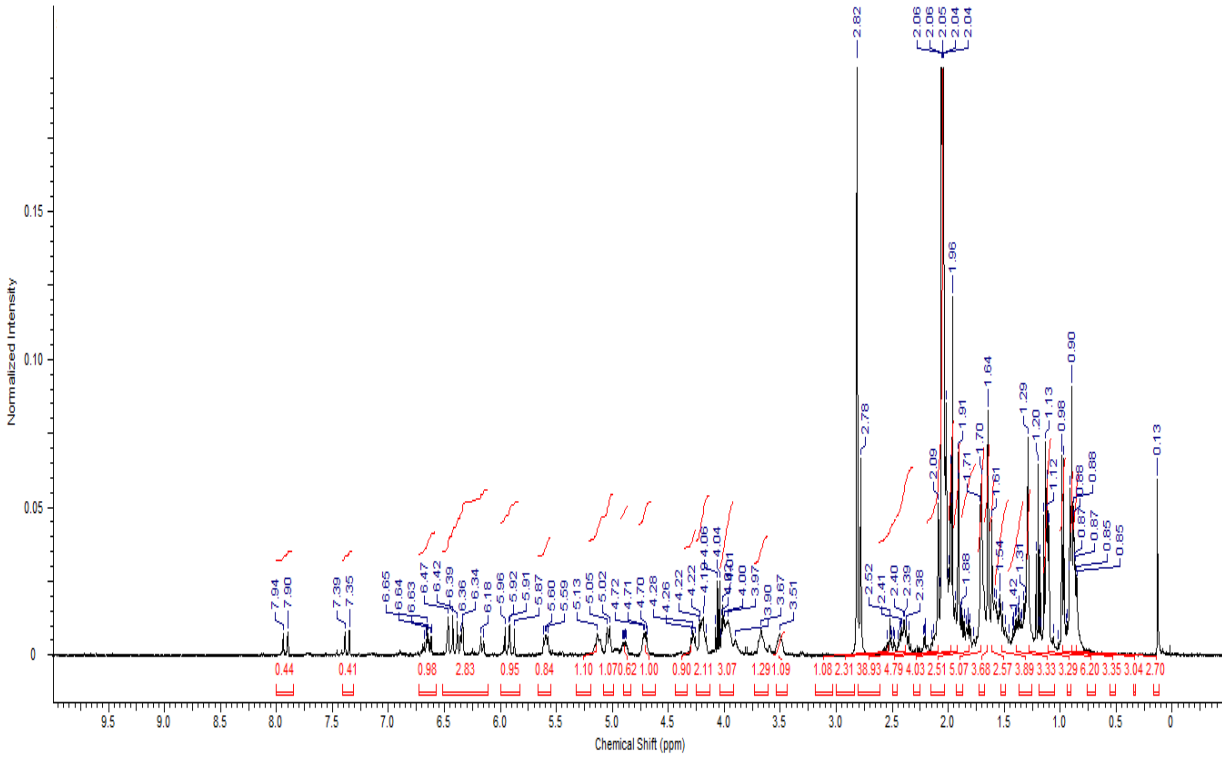
Chemical Formula: $C_{62}H_{109}D_3O_9Si_3$
Molecular Weight: 1088,82



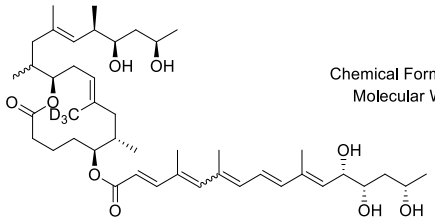
(2*E*,4*E*,6*E*,8*E*,10*E*,12*S*,13*S*,15*S*)-(6*S*,7*S*,12*R*,*E*)-12-((2*S*,6*R*,7*R*,9*R*,*E*)-7,9-Dihydroxy-4,6-dimethyldec-4-en-2-yl)-7,9-dimethyl-2-oxooxacyclododec-9-en-6-yl 12,13,15-trihydroxy-4,6,10-trimethylhexadeca-2,4,6,8,10-pentaenoate **(Mycolactone A/B)**



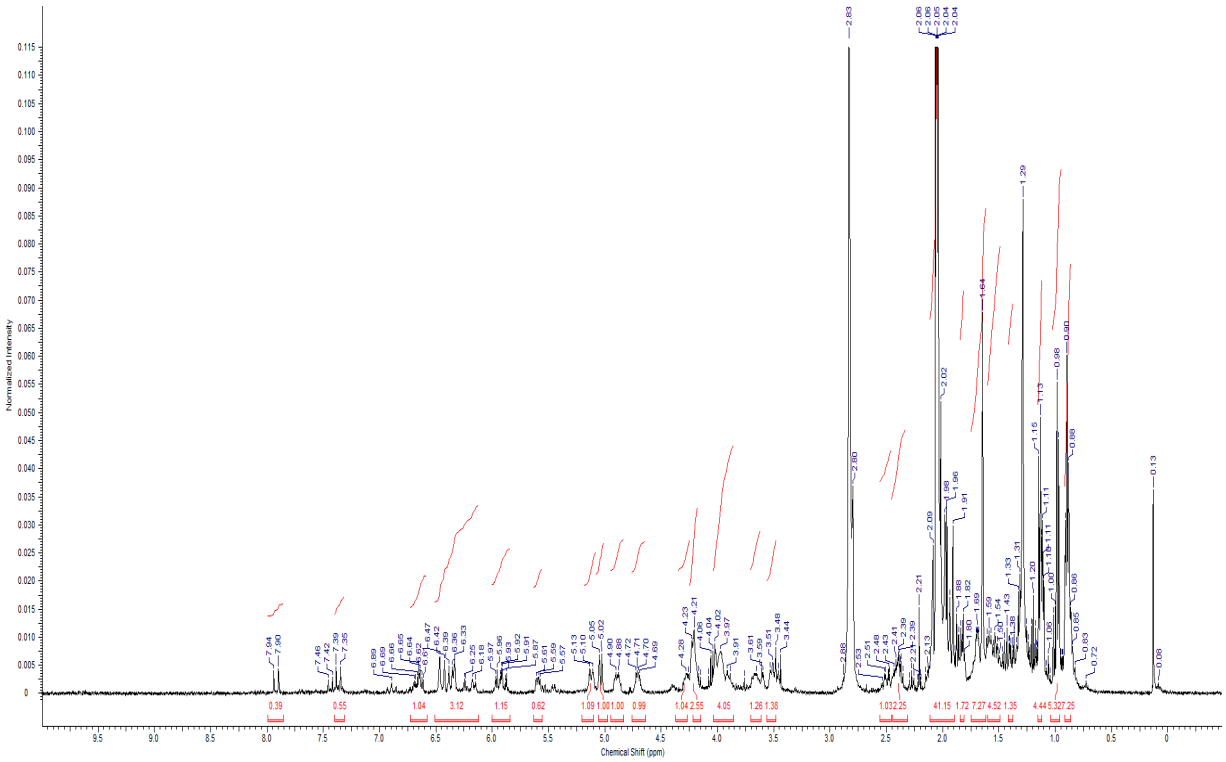
Chemical Formula: $C_{44}H_{70}O_9$
Molecular Weight: 743,02

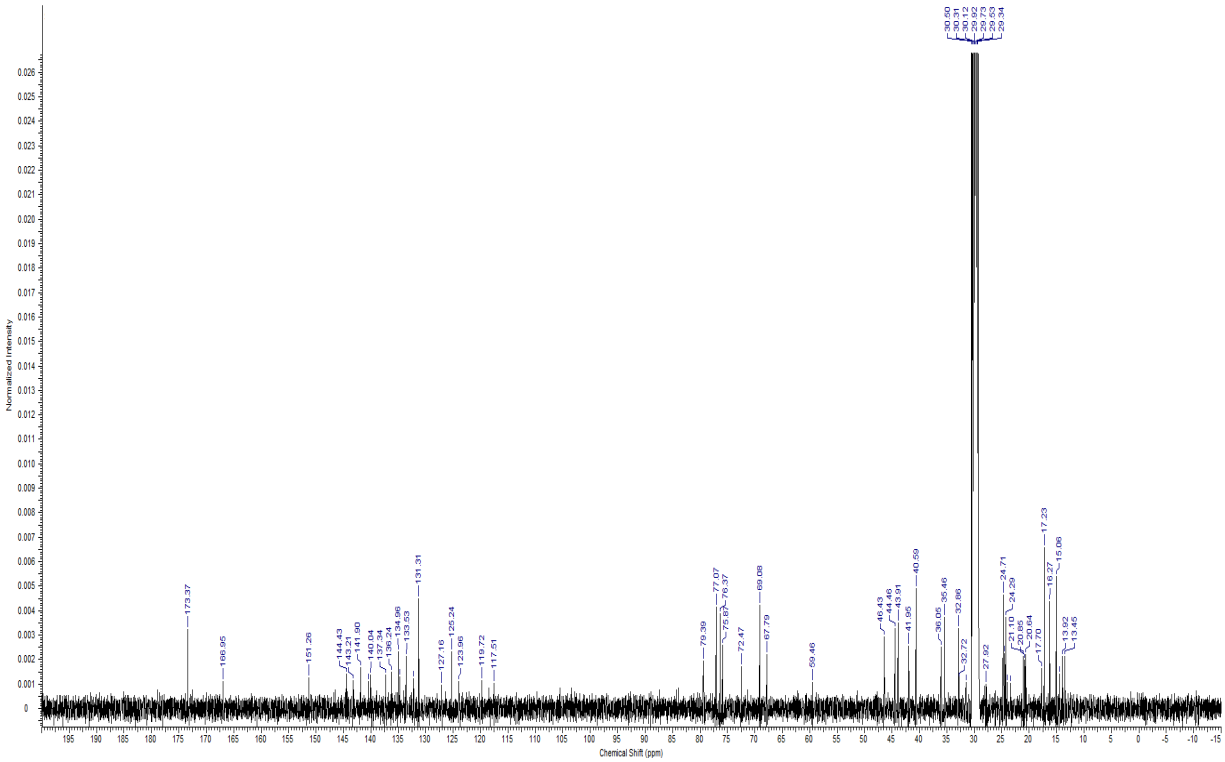


(2*E*,4*E*,6*E*,8*E*,10*E*,12*S*,13*S*,15*S*)-(6*S*,7*S*,12*R*,*E*)-12-((2*S*,6*R*,7*R*,9*R*,*E*)-7,9-Dihydroxy-4,6-dimethyldec-4-en-2-yl)-9-methyl(d3)-7-methyl-2-oxooxacyclododec-9-en-6-yl 12,13,15-trihydroxy-4,6,10-trimethylhexadeca-2,4,6,8,10-pentaenoate (**[22,22,22-$^2H_3$]-Mycolactone A/B**)



Chemical Formula: $C_{44}H_{67}D_3O_9$
Molecular Weight: 746,04




Normalized Intensity
Chemical Shift (ppm)
30.60
30.31
30.12
29.92
29.73
29.63
29.34
173.37
166.95
151.26
144.43
144.21
141.90
140.04
137.34
136.74
134.86
133.53
131.31
127.16
125.24
123.96
119.72
117.51
79.39
77.07
75.69
76.37
72.47
69.08
67.79
59.46
46.45
44.46
43.91
41.85
40.59
36.05
35.46
32.86
32.72
27.92
24.71
24.29
21.10
20.91
20.64
17.70
17.23
16.27
15.06
13.92
13.45