A Highly Step-Economical Synthesis of Dictyostatin

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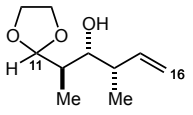
Supporting Information

General Information. All reactions were carried out under an atmosphere of nitrogen in flame-dried glassware with magnetic stirring unless otherwise indicated. Degassed solvents were purified by passage through an activated alumina column. Thin-layer chromatography (TLC) was carried out on glass backed silica gel TLC plates (250 mm) from Silicycle; visualization by UV light and/or phosphomolybdic acid (PMA). HPLC analysis was carried out on an Agilent 1200 Series using either a Chiralpak AD-H (250 x 4.5 mm ID) column or Chiralcel OD-H (250x4.5 mm ID) column. ^{1}H NMR spectra were recorded on a Bruker AVIII 300 (300 MHz), AVIII 400 (400 MHz), AVIII 500 (500 MHz) or AVIII 500 Ascend (500 MHz) spectrometer and are reported in ppm, relative to residual protonated solvent peak ($CDCl_3$, 7.26 ppm; C_6D_6, 7.16 ppm). Data are reported as follows: (bs= broad singlet, s = singlet, d = doublet, t = triplet, m = multiplet, dd = doublet of doublets, ddd = doublet of doublet of doublets, ddt = doublet of doublet of triplets, td = triplet of doublets; coupling constant(s) in Hz; integration). Proton decoupled ^{13}C NMR spectra were recorded on a Bruker AVIII 400 (100 MHz), AVIII 500 (126 MHz) or AVIII 500 Ascend (126 MHz) spectrometer and are reported in ppm from $CDCl_3$ internal standard (77.23 ppm). Infrared spectra were recorded on a Nicolet Avatar 370DTGS FT-IR. Optical rotations were recorded on a Jasco DIP-1000 digital polarimeter. (APCI)-MS was conducted on a JMS-LCmate LCMS (JEOL). Melting points were determined using a Stanford Research Systems DigiMelt apparatus.



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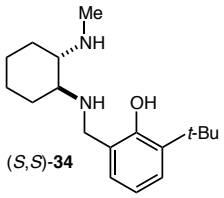


(*S*,*S*)-**34**

Hydroformylation procedure adapted from: 1) Wong, G. W.; Adint, T. T.; Landis, C. R. Landis. *Org. Synth.* **2012**, *89*, 243-254; 2) McDonald, R. I.; Wong, G. W.; Neupane, R. P.; Stahl, S. S.; Landis, C. R. *J. Am. Chem. Soc.* **2010**, *132*, 14027-14029. Crotylation procedure adapted from: Suen, L. M.; Steigerwald, M. L.; Leighton, J. L. *Submitted.*

To the metal cylinder of a Parr bomb (without a glass liner) was added 2-vinyl-1,3-dioxolane (1g, 10 mmol, 1 equiv), $Rh(acac)(CO)_2$ (0.4 mg, 0.015 mol%, dissolved in 50 μL Tol), and Bis[(*R*,*R*,*S*)-Diazaphos-SPE] (2 mg, 0.015 mol%, dissolved in 8 μL THF). The Parr bomb was charged to 200 psi with 1/1 H_2/CO and vented (repeated 5X). The bomb was then pressurized to 200 psi and heated to 70°C. The pressure was maintained between 150-200 psi during the reaction. After 10h, the bomb was allowed to cool to RT and de-pressurized. Aliquot ^{1}H-NMR indicated full conversion of dioxolane. The enantiomeric excess of **5** was determined to be 86% ee by chiral GC (see trace below).

In the interim, (*S*,*S*)-**6** was prepared: To a cooled (0°C) solution of (*S*,*S*)-**34** (3.2 g, 11 mmol, 1.1 equiv) in CH_2Cl_2 (50 mL, 0.2 M) was added DBU (4.9 mL, 33 mmol, 3.3 equiv) and *cis*-crotyltrichlorosilane (1.8 mL, 12 mmol, 1.2 equiv). After 90 min, the reaction mixture was cooled to -78°C, and a solution of crude aldehyde **5** (1 equiv) in CH_2Cl_2 (5 mL) was added. The reaction mixture was allowed to warm to 0°C as the dry ice bath expired. After 2h, the reaction mixture was quenched at 0°C with TBAF-$3H_2O$ (3.8 g, 12 mmol, 1.2 equiv). After 1h, the reaction mixture was concentrated and re-suspended in Et_2O (50 mL) in order to precipitate the DBU-HCl salts. After stirring overnight, the mixture was filtered, concentrated, and purified by silica gel flash column chromatography (5-25% EtOAc/Hex) affording alcohol **7** (1.15g, 62% yield) as a colorless oil.

TLC R_f = 0.28 (20% EtOAc/Hex)

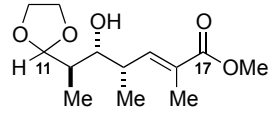
$[\alpha]^{21}_D$ -3.1 (*c* = 1.0, CH_2Cl_2)

IR (thin film) 3523, 2974, 2886, 1636, 1458, 1401, 1113, 1044, 999, 965, 924 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.91 (ddd, *J* = 17.4, 10.4, 7.0 Hz, 1H, $C_{15}H$), 5.11 – 5.04 (m, 2H, $C_{16}H_2$), 4.96 (d, *J* = 4.0 Hz, 1H, $C_{11}H$), 4.03 – 3.95 (m, 2H), 3.92 – 3.83 (m, 2H), 3.57 (app. dt, *J* = 7.8, 3.8 Hz, 1H, $C_{13}H$), 3.01 (d, *J* = 3.5 Hz, 1H, OH), 2.41 – 2.34 (m, 1H, $C_{14}H$), 1.99 (app. pd, *J* = 7.1, 4.0 Hz, 1H, $C_{12}H$), 1.03 (d, *J* = 6.8 Hz, 3H), 0.95 (d, *J* = 6.9 Hz, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 142.4, 114.4, 106.6, 75.8, 65.2, 65.0, 40.3, 39.2, 12.6, 11.3

LRMS calcd for $C_{10}H_{19}O_3$ $[M+H]^+$: 187.13; found 186.91 (APCI+)



9

To a cooled (-78 °C) solution of **7** (1.1 g, 5.9 mmol, 1 equiv) in CH_2Cl_2 (59 mL, 0.1 M) was bubbled in ozone. Immediately after the solution began turning blue (15 min), the reaction mixture was purged with oxygen until colorless. Further reaction oxidizes the acetal. PPh_3 (1.7g, 6.5 mmol, 1.1 equiv) was added, and the reaction mixture was allowed to warm to RT. After 11h, the reaction mixture was diluted with toluene (59 mL). Phosphonium **8** (2.5 g, 7.1 mmol, 1.2 equiv) was added, and the reaction mixture was heated to 45°C. After 5h, the reaction mixture was cooled to RT and concentrated to approx. 15 mL. Purification was accomplished by silica gel flash column chromatography (5% EtOAc/Hex; then 20% EtOAc/Hex) affording methyl ester **9** (1.3 g, 82% yield).

TLC R_f = 0.19 (25% EtOAc/Hex)

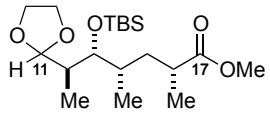
$[\alpha]^{20}_D$ 7.1 (*c* = 1.0, CH_2Cl_2)

IR (thin film) 3519, 2970, 2884, 1713, 1437, 1243, 1109 cm^{-1}

^1H NMR (500 MHz, $CDCl_3$) δ 6.78 (dd, *J* = 9.9, 1.5 Hz, 1H, $C_{15}H$), 4.84 (d, *J* = 4.2 Hz, 1H, $C_{11}H$), 4.03 – 3.94 (m, 2H), 3.90 – 3.82 (m, 2H), 3.72 (s, 3H), 3.56 – 3.51 (m, 1H, $C_{13}H$), 3.25 (d, *J* = 4.2 Hz, 1H, OH), 2.73 – 2.64 (m, 1H, $C_{14}H$), 1.95 (app. pd, *J* = 7.0, 4.1 Hz, 1H, $C_{12}H$), 1.85 (d, *J* = 1.5 Hz, 3H, $C_{16}CH_3$), 1.05 (d, *J* = 6.7 Hz, 3H, $C_{14}CH_3$), 0.99 (d, *J* = 7.1 Hz, 3H, $C_{12}CH_3$)

^{13}C NMR (125 MHz, $CDCl_3$) δ 168.9, 145.2, 126.7, 106.7, 75.8, 65.1, 65.0, 51.9, 39.4, 36.4, 13.7, 12.7, 11.9

LRMS calcd for $C_{13}H_{23}O_5$ $[M+H]^+$: 259.15; found 258.73 (APCI+)



10

To the glass liner of a Parr bomb was added **9** (2.4 g, 9.3 mmol, 1 equiv) and CH_2Cl_2 (23 mL, 0.4M). The Parr bomb was charged to 300 psi with H_2 and stirred overnight in order to saturate the solution with H_2. Then, Crabtree's catalyst (150 mg, 0.19 mmol, 0.02 equiv) was added, and the bomb was charged to 300 psi with H_2. After 21h, aliquot ^{1}H-NMR indicated complete conversion of starting material. The glass liner was removed from the bomb and cooled to -78°C. 2,6-lutidine (4.3 mL, 37.2 mmol, 4 equiv) and TBS-OTf (4.3 mL, 18.6 mmol, 2 equiv) were added. After 6h, the reaction mixture was quenched with saturated aqueous NH_4Cl (20 mL). The aqueous layer was separated and extracted with CH_2Cl_2 (3x100 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. Purification was accomplished by silica gel flash column chromatography (5-10% EtOAc/Hex) affording **10** (2.94 g, 84% yield) as a colorless oil.

TLC R_f = 0.69 (25% EtOAc/Hex)

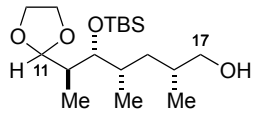
$[\alpha]^{20}_D$ -21.0 (*c* = 0.6, CH_2Cl_2)

IR (thin film) 2955, 2932, 2883, 2857, 1738, 1464, 1253, 1194, 1088, 836, 776 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.91 (d, *J* = 3.2 Hz, 1H, $C_{11}H$), 3.98 – 3.88 (m, 2H), 3.86 – 3.77 (m, 2H), 3.65 (s, 3H), 3.61 (dd, *J* = 7.9, 1.8 Hz, 1H, $C_{13}H$), 2.58 – 2.50 (m, 1H, $C_{16}H$), 1.95 (app. pd, *J* = 7.2, 3.3 Hz, 1H, $C_{12}H$), 1.74 – 1.60 (m, 2H, $C_{15}H_a$, $C_{14}H$), 1.29 (ddd, *J* = 12.9, 8.7, 5.8 Hz, 1H, $C_{15}H_b$), 1.15 (d, *J* = 7.0 Hz, 3H, $C_{16}CH_3$), 0.89 (s, 9H, TBS), 0.86 (d, *J* = 6.7 Hz, 3H, $C_{12}CH_3$), 0.83 (d, *J* = 7.0 Hz, 3H, $C_{14}CH_3$), 0.06 (s, 3H, TBS), 0.05 (s, 3H, TBS)

^{13}C NMR (125 MHz, $CDCl_3$) δ 177.4, 104.7, 76.5, 65.2, 65.0, 51.6, 41.4, 39.9, 37.5, 33.5, 26.3, 18.7, 18.0, 13.3, 9.2, -3.7, -4.2

Exact mass calcd for $C_{19}H_{37}O_5Si$ $[M–H]^-$: 373.2411; found 373.2413 (FAB+)



11

To a cooled (-78°C) solution of methyl ester **10** (1.9g, 5.1 mmol, 1 equiv) in toluene (51 mL, 0.1M) was added DIBAL (1M Hex, 13.7 mL, 13.7 mmol, 2.7 equiv) dropwise. After 6h, the reaction mixture was quenched with methanol (4 mL) and then a saturated aqueous solution of Rochelle's salt (100 mL). After vigorously stirring for 10h, the aqueous layer was separated and extracted with 50% EtOAc/Hex (4x50 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. Purification was accomplished by silica gel flash column chromatography (20% EtOAc/Hex) affording alcohol **11** (1.5g, 86% yield) as a colorless oil.

TLC R_f = 0.23 (25% EtOAc/Hex)

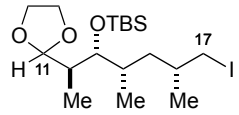
$[\alpha]^{20}_D$ -13.7 (*c* = 1.0, CH_2Cl_2)

IR (thin film) 3390, 2958, 2930, 2885, 2858, 1463, 1386, 1252, 1048, 836, 774 cm^{-1}

^1H NMR (500 MHz, $CDCl_3$) δ 4.89 (d, *J* = 3.6 Hz, 1H, $C_{11}H$), 3.94 – 3.88 (m, 2H), 3.85 – 3.76 (m, 2H), 3.58 (dd, *J* = 7.3, 2.3 Hz, 1H, $C_{13}H$), 3.50 (dd, *J* = 10.7, 4.5 Hz, 1H, $C_{17}H_a$), 3.37 (dd, *J* = 10.7, 6.6 Hz, 1H, $C_{17}H_b$), 1.97 (app. pd, *J* = 7.0, 3.4 Hz, 1H, $C_{12}H$), 1.80 – 1.73 (m, 2H, $C_{14}H$, OH), 1.72 – 1.64 (m, 1H, $C_{16}H$), 1.38 (dt, *J* = 13.5, 6.8 Hz, 1H, $C_{15}H_a$), 0.97 (dt, *J* = 13.5, 7.4 Hz, 1H, $C_{15}H_b$), 0.92 (d, *J* = 6.7 Hz, 3H, $C_{16}CH_3$), 0.88 (s, 9H, TBS), 0.86 (d, *J* = 6.9 Hz, 3H, $C_{12}CH_3$), 0.85 (d, *J* = 6.8 Hz, 3H, $C_{14}CH_3$), 0.04 (s, 3H, TBS), 0.03 (s, 3H, TBS)

^{13}C NMR (125 MHz, $CDCl_3$) δ 104.9, 76.4, 67.9, 65.1, 64.9, 41.5, 38.7, 33.2, 33.0, 26.3, 18.7, 17.8, 14.7, 9.8, -3.6, -4.1

Exact mass calcd for $C_{18}H_{39}O_4Si$ $[M+H]^+$: 347.2618; found 347.2605 (FAB+)



1

To a cooled (0°C) solution of PPh_3 (71 mg, 0.27 mmol, 1.17 equiv) and imidazole (20 mg, 0.29 mmol, 1.25 equiv) in CH_2Cl_2 (2.3 mL, 0.1 M) was added iodine (70 mg, 0.28 mmol, 1.2 equiv). After 10 min, alcohol **11** (80 mg, 0.23 mmol, 1 equiv) was added, and the reaction mixture was allowed to warm to RT. After 12h, the reaction mixture was diluted with hexanes (5 mL) and filtered over a plug of silica gel, eluting with hexanes (30 mL). The filtrate was concentrated and purified by pH 7.0 buffered silica gel flash column chromatography (5-10% EtOAc/Hex) affording iodide **1** (100 mg, 95% yield).

TLC R_f = 0.50 (10% EtOAc/Hex)

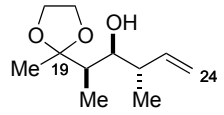
$[\alpha]^{20}_D$ -18.6 (*c* = 1.0, CH_2Cl_2)

IR (thin film) 2956, 2929, 2883, 2857, 1462, 1382, 1252, 1070, 836, 774 cm^{-1}

^1H NMR (400 MHz, $CDCl_3$) δ 4.92 (d, *J* = 3.4 Hz, 1H, $C_{11}H$), 3.96 – 3.91 (m, 1H), 3.86 – 3.79 (m, 1H), 3.61 (dd, *J* = 7.7, 1.8 Hz, 1H, $C_{13}H$), 3.27 (dd, *J* = 9.6, 3.5 Hz, 1H, $C_{17}H_a$), 3.11 (dd, *J* = 9.6, 6.3 Hz, 1H, $C_{17}H_b$), 1.97 (m, 1H, $C_{12}H$), 1.77 – 1.67 (m, 1H, $C_{14}H$), 1.51 – 1.42 (m, 1H, $C_{16}H$), 1.32 (ddd, *J* = 13.6, 7.5, 5.8 Hz, 1H, $C_{15}H_a$), 1.16 (ddd, *J* = 13.6, 8.5, 6.5 Hz, 1H, $C_{15}H_b$), 0.97 (d, *J* = 6.4 Hz, 3H, $C_{16}CH_3$), 0.90 (s, 9H, TBS), 0.87 (d, *J* = 7.1 Hz, 3H, $C_{12}CH_3$), 0.85 (d, *J* = 6.9 Hz, 3H, $C_{14}CH_3$), 0.07 (s, 3H, TBS), 0.06 (s, 3H, TBS)

^{13}C NMR (100 MHz, $CDCl_3$) δ 104.8, 76.4, 65.2, 65.0, 42.3, 41.6, 32.9, 32.0, 26.4, 21.6, 18.7, 18.0, 13.7, 9.5, -3.6, -4.1

Exact mass calcd for $C_{18}H_{36}O_3SiI$ $[M–H]^-$: 455.1479; found 455.1480 (FAB+)



14

Procedure adapted from: 1) Wong, G. W.; Adint, T. T.; Landis, C. R. Landis. *Org. Synth.* **2012**, *89*, 243-254; 2) McDonald, R. I.; Wong, G. W.; Neupane, R. P.; Stahl, S. S.; Landis, C. R. *J. Am. Chem. Soc.* **2010**, *132*, 14027-14029.

To the metal cylinder of a Parr bomb (without a glass liner) was added 2-methyl-2-vinyl-1,3-dioxolane (1 mL, 8.36 mmol, 1 equiv), $Rh(acac)(CO)_2$ (0.66 mg, 0.03 mol%, dissolved in 150 μL Tol), and Bis[(*R*,*R*,*S*)-Diazaphos-SPE] (3.3 mg, 0.03 mol%, dissolved in 13.5 μL THF). The Parr bomb was charged to 200 psi with 1/1 H_2/CO and vented (repeated 5X). The bomb was then pressurized to 200 psi and heated to 70°C. The pressure was maintained between 150-200 psi during the reaction. After 16h, the bomb was allowed to cool to RT and de-pressurized. Aliquot ^{1}H-NMR indicated full conversion of dioxolane. The enantiomeric excess was determined to be 91% ee by chiral GC (see trace below).

Crude aldehyde **12** (1 equiv) was dissolved in Toluene (15 mL, 0.56 M), and *trans*-crotylborane **13** (1.89 mL, 9.2 mmol, 1.1 equiv) was added. After 24h, the reaction mixture was quenched at 0°C with MeOH (5 mL). After 30 min, the reaction mixture was concentrated and azeotroped with pentane (3x50 mL) in order to remove residual MeOH. Purification was accomplished by silica gel flash column chromatography (1% EtOAc/Hex; then 5-10 % EtOAc/Hex) affording **14** (850 mg, 51% yield) as a colorless oil.

TLC R_f = 0.39 (30% EtOAc/Hex)

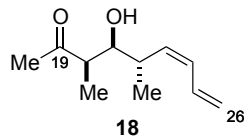
$[\alpha]^{21}_D$ -17.6 (*c* = 1.0, CH_2Cl_2)

IR (thin film) 3526, 2977, 2886, 1457, 1375, 1169, 1079, 1040, 974 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.84 (ddd, *J* = 17.7, 10.2, 7.9 Hz, 1H, $C_{23}H$), 5.08 (d, *J* = 17.7 Hz, 1H, $C_{24}H_a$), 5.04 (d, *J* = 10.2 Hz, 1H, $C_{24}H_b$), 4.01 – 3.93 (m, 4H), 3.69 (d, *J* = 9.2 Hz, 1H, $C_{21}H$), 2.84 (s, 1H, OH), 2.24 (app. h, *J* = 7.0 Hz, 1H, $C_{22}H$), 1.92 (q, *J* = 6.9 Hz, 1H, $C_{20}H$), 1.32 (s, 3H, $C_{18}H_3$), 0.96 (d, *J* = 7.2 Hz, 3H, $C_{22}CH_3$), 0.91 (d, *J* = 6.9 Hz, 3H, $C_{20}CH_3$)

^{13}C NMR (125 MHz, $CDCl_3$) δ 142.4, 114.7, 112.7, 73.7, 65.0, 64.4, 42.0, 41.8, 22.3, 16.6, 7.2

Exact mass calcd for $C_{11}H_{21}O_3$ $[M+H]^+$: 201.1491; found 201.1483 (FAB+)



18

To a cooled (-78°C) solution of **14** (77 mg, 0.38 mmol, 1 equiv) in CH_2Cl_2 (3.8 mL, 0.1 M) was bubbled in ozone. After the solution turned blue, the reaction mixture was purged with oxygen until colorless. PPh_3 (111 mg, 0.42 mmol, 1.1 equiv) was added, and the reaction mixture was allowed to warm to RT. After 16h, the reaction mixture was concentrated and azeotroped with benzene (3x10 mL). The crude aldehyde was used immediately without further purification.

To a cooled (0°C) solution of aldehyde (1 equiv) in Et_2O (1 mL) was added powdered 4Å mol sieves (100 mg) and Matteson's reagent **19** (231 mg, 0.96 mmol, 2.5 equiv). After 72h, aliquot ^{1}H-NMR indicated complete conversion of aldehyde. The reaction mixture was cooled to 0°C. EtOH (1.6 mL) was added, followed by 6M KOH (1.6 mL, 9.6 mmol, 25 equiv). The reaction mixture was allowed to warm to RT. After 36h, the reaction mixture was slowly acidified at 0°C to ~pH 2 with 6M HCl (~2 mL). Excess acid can result in enolization and elimination of water. The reaction mixture was allowed to warm to RT. After 24h, the reaction mixture was quenched at 0°C with saturated aqueous $NaHCO_3$ (20 mL). The aqueous layer was separated and extracted with 50% EtOAc/Hex (3x100mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. Purification was accomplished by silica gel flash column chromatography (10-25% EtOAc/Hex) affording keto-alcohol **18** (50 mg, 71% yield).

TLC R_f = 0.47 (30% EtOAc/Hex)

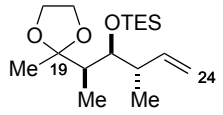
$[\alpha]^{21}_D$ 97.3 (*c* = 1.0, CH_2Cl_2)

IR (thin film) 3457, 2967, 2932, 1708, 1456, 1359, 985, 905, 736, 663 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.57 (m, 1H, $C_{25}H$), 6.13 (t, *J* = 11.0 Hz, 1H, $C_{24}H$), 5.37 (t, *J* = 10.5 Hz, 1H, $C_{23}H$), 5.24 (m, 1H, $C_{26}H_a$), 5.14 (d, *J* = 10.2 Hz, 1H, $C_{26}H_b$), 3.78 – 3.72 (m, 1H, $C_{21}H$), 2.77 (m, 1H, $C_{22}H$), 2.67 (qd, *J* = 7.1, 4.2 Hz, 1H, $C_{20}H$), 2.19 (s, 3H, $C_{18}H_3$), 1.18 (d, *J* = 7.1 Hz, 3H, $C_{20}CH_3$), 0.99 (d, *J* = 6.8 Hz, 3H, $C_{22}CH_3$)

^{13}C NMR (125 MHz, $CDCl_3$) δ 212.8, 134.1, 132.1, 131.0, 118.7, 75.1, 49.1, 35.8, 29.1, 17.5, 10.2

Exact mass calcd for $C_{11}H_{19}O_2$ $[M+H]^+$: 183.1385; found 183.1389 (FAB+)



15

To a cooled (-78°C) solution of alcohol **14** (1.32 g, 6.6 mmol, 1 equiv) in CH_2Cl_2 (66 mL, 0.1 M) was added 2,6-lutidine (1.14 mL, 7.9 mmol, 1.2 equiv) and TES-OTf (1.64 mL, 7.3 mmol, 1.1 equiv). After 3h, the reaction mixture was quenched with saturated aqueous NH_4Cl (10 mL). The aqueous layer was separated and extracted with CH_2Cl_2 (3x25mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. Purification was accomplished by silica gel flash column chromatography (1% EtOAc/Hex) affording TES ether **15** (2.01g, 97% yield) as a colorless oil.

TLC R_f = 0.67 (30% EtOAc/Hex)

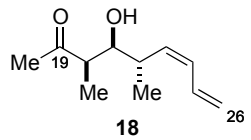
$[\alpha]^{21}_D$ 2.9 (*c* = 1.0, CH_2Cl_2)

IR (thin film) 2979, 2959, 2929, 1355, 1324, 1144, 966, 847, 738 cm^{-1}

^1H NMR (500 MHz, $CDCl_3$) δ 5.83 (ddd, *J* = 16.3, 11.3, 6.5 Hz, 1H, $C_{23}H$), 5.04 – 4.99 (m, 2H, $C_{24}H_2$), 3.97 (dd, *J* = 3.7, 2.3 Hz, 1H, $C_{21}H$), 3.93 – 3.89 (m, 2H), 3.87 – 3.83 (m, 2H), 2.44 – 2.36 (m, 1H, $C_{22}H$), 1.78 (qd, *J* = 7.2, 2.3 Hz, 1H, $C_{20}H$), 1.26 (s, 3H, $C_{18}H_3$), 1.02 (d, *J* = 6.9 Hz, 3H, $C_{22}CH_3$), 0.98 (t, *J* = 8.0 Hz, 9H, TES), 0.93 (d, *J* = 7.2 Hz, 3H, $C_{20}CH_3$), 0.63 (q, *J* = 8.0 Hz, 6H, TES)

^{13}C NMR (125 MHz, $CDCl_3$) δ 141.3, 114.3, 112.6, 73.7, 64.4, 64.3, 45.4, 42.2, 20.8, 14.6, 11.3, 7.3, 5.7

LRMS calcd for $C_{17}H_{35}O_3Si$ $[M+H]^+$: 315.24; found 315.40 (FAB+)

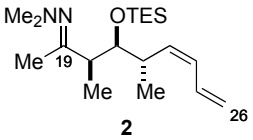


18

To a cooled (-78°C) solution of TES ether **15** (12.6 g, 39.8 mmol, 1 equiv) in CH_2Cl_2 (398 mL, 0.1 M) was bubbled in ozone. After the solution turned blue, the reaction mixture was purged with oxygen until colorless. PPh_3 (11.6 g, 43.8 mmol, 1.1 equiv) was added, and the reaction mixture was allowed to warm to RT. After 16h, the reaction mixture was concentrated, triturated with hexanes (2x100 mL), and azeotroped with benzene (2x100 mL). Aldehyde **16** was used immediately without further purification.

To a cooled (0°C) solution of aldehyde **16** (1 equiv) in THF (796 mL, 0.05 M) was added anhydrous $CrCl_2$ (21 g, 171 mmol, 4.3 equiv) and 1-bromoallyltrimethylsilane **17** (42.3 g, 219 mmol, 5.5 equiv). The reaction mixture was stirred for 15 min at 0°C, 2h at RT, and re-cooled to 0°C. EtOH (150 mL) was added, followed by 6M KOH (166 mL, 995 mmol, 25 equiv). The reaction mixture was allowed to warm to RT. After 27h, the reaction mixture was slowly acidified at 0°C to ~pH 1 with 6M HCl (100 mL). The reaction mixture was again allowed to warm to RT. After 24h, the reaction mixture was quenched at 0°C with saturated aqueous $NaHCO_3$ (100 mL) and then diluted with brine (500 mL). The aqueous layer was separated and extracted with EtOAc (2x1L). The combined organic layers were dried over $MgSO_4$, filtered over celite, and concentrated. Purification was accomplished by silica gel flash column chromatography (2-20% EtOAc/Hex) affording keto-alcohol **18** (4.7 g, 65% yield).

See above for data for **18**.



2

To a cooled (-78°C) solution of keto-alcohol **18** (10.4 g, 57.1 mmol, 1 equiv) in CH_2Cl_2 (285 mL, 0.2 M) was added 2,6-lutidine (13.2 mL, 114 mmol, 2 equiv) and TES-OTf (13.5 mL, 59.9 mmol, 1.05 equiv). After 2.5h, 1,1-dimethyl hydrazine (285 mL, 0.2 M) was added over 15 min, followed by TMS-Cl (8.0 mL, 62.8 mmol, 1.1 equiv). The reaction mixture was allowed to warm to RT. After 12h, the reaction mixture was quenched at 0°C with saturated aqueous $NaHCO_3$ (100 mL) and then diluted with brine (200 mL). The aqueous layer was separated and extracted with EtOAc (3x500 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. Purification was accomplished by silica gel flash column chromatography (2-10% EtOAc/Hex) affording hydrazone **2** (17.4 g, 90% yield).

TLC R_f = 0.21 (10% EtOAc/Hex)

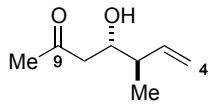
$[\alpha]^{21}_D$ 12.4 (*c* = 1.0, CH_2Cl_2)

IR (thin film) 2957, 2877, 1810, 1721, 1635, 1460, 1239, 1076, 1020, 738 cm^{-1}

^1H NMR (500 MHz, $CDCl_3$) δ 6.55 – 6.44 (m, 1H, $C_{25}H$), 5.98 (t, *J* = 11.1 Hz, 1H, $C_{24}H$), 5.51 (t, *J* = 10.4 Hz, 1H, $C_{23}H$), 5.19 – 5.13 (m, 1H, $C_{26}H_a$), 5.05 (d, *J* = 10.1 Hz, 1H, $C_{26}H_b$), 3.80 (dd, *J* = 9.2, 2.3 Hz, 1H, $C_{21}H$), 2.80 – 2.73 (m, 1H, $C_{22}H$), 2.40 (s, 6H), 2.43 – 2.37 (m, 1H, $C_{20}H$), 1.82 (s, 3H, $C_{18}H_3$), 1.05 (d, *J* = 7.0 Hz, 3H, $C_{20}CH_3$), 1.02 (d, *J* = 7.0 Hz, 3H, $C_{22}CH_3$), 0.99 (t, *J* = 8.0 Hz, 9H, TES), 0.65 (q, *J* = 8.0 Hz, 6H, TES)

^{13}C NMR (125 MHz, $CDCl_3$) δ 169.4, 134.2, 132.9, 129.4, 117.1, 78.3, 47.0, 47.0, 36.8, 18.6, 16.6, 15.5, 7.3, 5.8

Exact mass calcd for $C_{19}H_{39}ON_2Si$ $[M+H]^+$: 339.2832; found 339.2835 (FAB+)



22

To a cooled (0 °C) solution of aldehyde **20** (830 mg, 6.4 mmol, 1 equiv) in CH_2Cl_2 (32 mL, 0.2 M) was added (*S*,*S*)-**21** (3.8g, 6.7 mmol, 1.05 equiv) and then scandium triflate (78 mg, 0.16 mmol, 0.025 equiv). After vigorously stirring for 2h, the reaction mixture was concentrated, re-suspended in Et_2O (32 mL), and quenched at 0°C with 1N HCl (20 mL). After 3h, the reaction mixture was filtered to recover the (*S*,*S*)-diamine (3.3 g, 94% yield). The aqueous layer was separated and extracted with 50% EtOAc/Hex (3x100 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (50 mL), dried over $MgSO_4$, filtered, and concentrated. Purification was accomplished by silica gel flash column chromatography (25% EtOAc/Hex) affording methyl ketone **22** (780 mg, 86% yield).

TLC R_f = 0.26 (40% EtOAc/Hex)

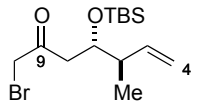
$[\alpha]^{20}_D$ -0.7 (*c* = 0.7, CH_2Cl_2)

IR (thin film) 3416, 2925, 2858, 1723, 1462, 1378, 1253, 1030, 836, 774 cm^{-1}

^1H NMR (400 MHz, $CDCl_3$) δ 5.79 (ddd, *J* = 16.9, 10.6, 7.9 Hz, 1H, C_5H), 5.13 – 5.05 (m, 2H, C_4H_2), 3.97 (dtd, *J* = 8.0, 4.9, 3.3 Hz, 1H, C_7H), 2.78 (d, *J* = 3.3 Hz, 1H, OH), 2.58 – 2.54 (m, 2H, $C_{10}H_2$, 2.30 – 2.21 (m, 1H, C_6H), 2.19 (s, 3H, C_8H_3), 1.06 (d, *J* = 6.9 Hz, 3H, C_6CH_3)

^{13}C NMR (125 MHz, $CDCl_3$) δ 209.9, 139.9, 116.1, 70.8, 47.4, 43.4, 31.0, 15.9

LRMS calcd for $C_8H_{15}O_2$ $[M+H]^+$: 143.11; found 142.91 (APCI+)



23

To a cooled (-78°C) solution of methyl ketone **22** (5.8 g, 41 mmol, 1 equiv) in CH_2Cl_2 (204 mL, 0.2 M) was added 2,6-lutidine (19.8 mL, 171 mmol, 4.2 equiv) and TBS-OTf (19.7 mL, 86 mmol, 2.1 equiv). The reaction mixture was allowed to warm to -20°C as the dry ice bath expired. After 6h, the reaction mixture was re-cooled to -78 °C, and a solution of *N*-bromosuccinimide (8.7 g, 49 mmol, 1.2 equiv) in THF (102 mL) was added over 30 min. After 2h, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ (50 mL). The aqueous layer was separated and extracted with CH_2Cl_2 (3x100 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. Purification was accomplished by pH 7.0 buffered silica gel flash column chromatography (1% EtOAc/Hex) affording bromoketone **23** (11 g, 80% yield, >90% purity as judged by ^{1}H NMR). Further chromatography did not result in cleaner product and may be detrimental, so the material was used without further purification.

TLC R_f = 0.68 (10% EtOAc/Hex)

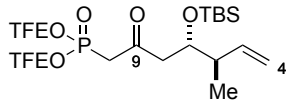
$[\alpha]^{20}_D$ -37.5 (*c* = 0.7, CH_2Cl_2)

IR (thin film) 2956, 2930, 2857, 1708, 1459, 1369, 1322, 1253, 1048, 834, 776 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.74 (ddd, *J* = 17.4, 10.4, 7.2 Hz, 1H, C_5H), 5.07 – 5.00 (m, 2H, C_4H_2), 4.19 (app. dt, *J* = 7.8, 3.9 Hz, 1H, C_7H), 3.91 (d, *J* = 1.4 Hz, 2H, $C_{10}H_2$), 2.75 (dd, *J* = 15.8, 7.8 Hz, 1H, C_8H_a), 2.56 (dd, *J* = 15.8, 4.5 Hz, 1H, C_8H_b), 2.37 – 2.30 (m, 1H, C_6H), 1.03 (d, *J* = 6.9 Hz, 3H, C_6CH_3), 0.87 (s, 9H, TBS), 0.08 (s, 3H, TBS), 0.01 (s, 3H, TBS)

^{13}C NMR (125 MHz, $CDCl_3$) δ 200.9, 140.0, 115.7, 72.2, 43.7, 43.6, 36.1, 26.0, 18.2, 14.3, -4.5, -4.6

LRMS calcd for $C_{14}H_{28}BrO_2Si$ $[M+H]^+$: 335.10; found 335.58 (APCI+)



24

Bromoketone **23** (2.4 g, 7.2 mmol, 1 equiv) and methyldiphenylphosphite (3.1 mL, 14.3 mmol, 2 equiv) were heated together neat at 140°C. After 10h, aliquot ^{1}H-NMR indicated full conversion to the bis-phenyl phosphonate (this reaction time may vary depending on the scale of the reaction). The reaction mixture was cooled to 0°C. Trifluoroethanol (31 mL, 60 equiv), THF (15 mL), and DBU (2.1 mL, 14.3 mmol, 2 equiv) were added. The reaction mixture was heated to 45°C. After 1h, the reaction mixture was cooled to RT and filtered over a silica gel plug, eluting with 50% EtOAc/Hex (600 mL). The filtrate was concentrated and purified by silica gel flash column chromatography (2-20% EtOAc/Hex) affording bis-trifluoroethyl phosphonate **24** (2.6 g, 72% yield). Residual THF may cause streaking of the phenol byproduct during chromatography; in this case, a second column may be required to completely remove phenol.

NMR Data for Bis-Phenyl Phosphonate

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 – 7.30 (m, 4H), 7.22 – 7.17 (m, 6H), 5.74 (ddd, J = 17.5, 10.5, 7.3 Hz, 1H, C_5H), 5.05 – 4.98 (m, 2H, C_4H_2), 4.22 (ddd, J = 7.2, 4.8, 3.4 Hz, 1H, C_7H), 3.44 – 3.31 (m, 2H, $C_{10}H_2$), 2.85 (dd, J = 16.7, 7.2 Hz, 1H, C_8H_a), 2.72 (dd, J = 16.7, 4.8 Hz, 1H), 2.35 (app. pd, J = 6.9, 3.4 Hz, 1H, C_6H), 1.03 (d, J = 6.9 Hz, 3H, C_6CH_3), 0.86 (s, 9H, TBS), 0.09 (s, 3H, TBS), 0.02 (s, 3H, TBS)

^{13}C NMR (125 MHz, $CDCl_3$) δ 199.9 (d, $^2J_{C,P}$ = 6.7 Hz), 150.1 (d, $^2J_{C,P}$ = 9.0 Hz), 150.1 (d, $^2J_{C,P}$ = 8.7 Hz), 139.8, 130.0, 125.7, 120.8 (d, $^3J_{C,P}$ = 4.4 Hz), 115.7, 71.7, 48.3, 43.5, 43.3 (d, $^1J_{C,P}$ = 129.7 Hz), 26.0, 18.2, 14.6, -4.5, -4.6

Data for 24

TLC R_f = 0.48 (25% EtOAc/Hex)

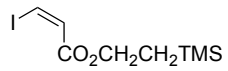
$[\alpha]^{19}_D$ -15.2 (c = 1.0, CH_2Cl_2)

IR (thin film) 2946, 1719, 1295, 1259, 1171, 1066, 962, 834, 776, 655 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.72 (ddd, J = 17.5, 10.4, 7.2 Hz, 1H, C_5H), 5.10 – 4.97 (m, 2H, C_4H_2), 4.49 – 4.37 (m, 4H, TFE), 4.16 (app. dt, J = 7.7, 4.2 Hz, 1H, C_7H), 3.35 – 3.21 (m, 2H, $C_{10}H_2$), 2.67 (dd, J = 16.3, 7.2 Hz, 1H, C_8H_a), 2.56 (dd, J = 16.3, 4.6 Hz, 1H, C_8H_b), 2.33 (app. pd, J = 6.8, 3.5 Hz, 1H, C_6H), 1.01 (d, J = 6.8 Hz, 3H, C_6CH_3), 0.87 (s, 9H, TBS), 0.08 (s, 3H, TBS), 0.02 (s, 3H, TBS)

^{13}C NMR (125 MHz, $CDCl_3$) δ 200.4 (d, $^2J_{C,P}$ = 7.0 Hz), 139.7, 122.6 (qd, J = 277.3, 8.1 Hz), 122.6 (qd, J = 277.3, 8.1 Hz), 115.8, 71.6, 62.6 (qd, J = 38.1, 5.5 Hz), 62.4 (qd, J = 38.3, 5.9 Hz), 48.2 (d, $^3J_{C,P}$ = 5.0 Hz), 43.5, 42.9 (d, $^1J_{C,P}$ = 139.0 Hz), 25.9, 18.2, 14.3, -4.6, -4.6

Exact mass calcd for $C_{18}H_{32}F_6O_5PSi$ $[M+H]^+$: 501.1661; found 501.1672 (FAB+)



25

(2*Z*)-3-Iodo-2-propenoic acid is commercially available. It may be prepared by the procedure described in: Ma, S.; Lu, X.; Li, Z. *J. Org. Chem.* **1992**, *57*, 709-713.

To a cooled (0°C) solution of (2*Z*)-3-iodo-2-propenoic acid (28 g, 141 mmol, 1.5 equiv) and 2-(trimethylsilyl)ethanol (21 mL, 146 mmol, 1.55 equiv) in CH_2Cl_2 (705 mL, 0.2 M) was added DMAP (288 mg, 2.4 mmol, 0.025 equiv) and DCC (19.5 g, 94 mmol, 1 equiv). The reaction mixture was allowed to warm to RT. After 12h, the reaction mixture was filtered over celite, eluting with hexanes. The filtrate was concentrated and purified by pH 7.0 buffered silica gel flash column chromatography (1% EtOAc/Hex) affording vinyl iodide **25** (20.5 g, 73% yield) as a colorless oil.

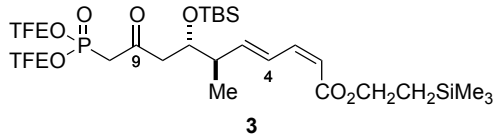
TLC R_f = 0.38 (5% EtOAc/Hex)

IR (thin film) 2954, 2898, 1723, 1598, 1322, 1250, 1190, 1159, 836 cm^{-1}

^1H NMR (500 MHz, $CDCl_3$) δ 7.40 (d, *J* = 8.8 Hz, 1H), 6.85 (d, *J* = 8.8 Hz, 1H), 4.30 – 4.23 (m, 2H), 1.07 – 1.00 (m, 2H), 0.03 (s, 9H)

^{13}C NMR (125 MHz, $CDCl_3$) δ 164.8, 130.1, 94.6, 63.1, 17.5, -1.4

LRMS calcd for $C_8H_{16}IO_2Si$ $[M+H]^+$: 299.00; found 298.20 (FAB+)



3

To a solution of phosphonate **24** (4 g, 8 mmol, 1 equiv) and vinyl iodide **25** (4.8 g, 16 mmol, 2 equiv) in MeCN (53 mL, 0.15 M) was added AgOAc (2.7 g, 16 mmol, 2 equiv) and $Pd(OAc)_2$ (54 mg, 0.24 mmol, 0.03 equiv). The reaction mixture was heated to 45ºC. After 12h, additional $Pd(OAc)_2$ (54 mg) was added. After a total reaction time of 36h, the reaction mixture was cooled to RT and filtered over celite, eluting with 50% EtOAc/Hex (500 mL) The filtrate was washed with pH 7.0 buffer solution (200 mL). The aqueous layer was separated and extracted with 50% EtOAc/Hex (2x200 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. Purification was accomplished by pH 7.0 buffered silica gel flash column chromatography (5-10% EtOAc/Hex) affording dienoate **3** (3.99 g, 74% yield).

TLC R_f = 0.50 (20% EtOAc/Hex)

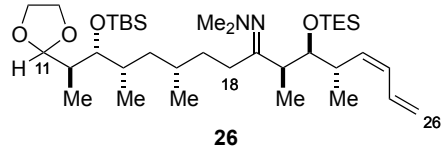
$[\alpha]^{20}_D$ -5.8 (*c* = 1.0, CH_2Cl_2)

IR (thin film) 2956, 1711, 1639, 1601, 1419, 1256, 1170, 1070, 963, 836 cm^{-1}

^1H NMR (500 MHz, $CDCl_3$) δ 7.37 (dd, *J* = 15.5, 11.3 Hz, 1H, C_4H), 6.52 (t, *J* = 11.3 Hz, 1H, C_3H), 5.93 (dd, *J* = 15.5, 7.8 Hz, 1H, C_5H), 5.61 (d, *J* = 11.3 Hz, 1H, C_2H), 4.49 – 4.39 (m, 4H, TFE), 4.24 – 4.18 (m, 3H, TMSE, C_7H), 3.34 – 3.21 (m, 2H, $C_{10}H_2$), 2.68 (dd, *J* = 16.7, 7.0 Hz, 1H, C_8H_a), 2.57 (dd, *J* = 16.7, 4.9 Hz, 1H, C_8H_b), 2.52 – 2.44 (m, 1H, C_6H), 1.08 (d, *J* = 6.8 Hz, 3H, C_6CH_3), 1.04 – 1.00 (m, 2H, TMSE), 0.87 (s, 9H, TBS), 0.09 (s, 3H, TBS), 0.05 (s, 9H, TMSE), 0.02 (s, 3H, TBS)

^{13}C NMR (125 MHz, $CDCl_3$) δ 200.1 (d, $^2J_{C,P}$ = 6.9 Hz), 166.7, 145.1, 144.6, 127.8, 122.60 (qd, *J* = 277.5, 7.8 Hz, 2C), 117.2, 71.4, 62.5 (qd, *J* = 38.2, 5.6 Hz), 62.5 (qd, *J* = 38.1, 5.7 Hz), 62.3, 48.7 (d, $^3J_{C,P}$ = 5.1 Hz), 43.0, 42.8 (d, $^1J_{C,P}$ = 138.6 Hz), 25.9, 18.2, 17.5, 14.9, -1.4, -4.6

LRMS calcd for $C_{26}H_{45}F_6NaO_7PSi_2$ $[M+Na]^+$: 693.22; found 693.29 (FAB+)



26

To a cooled (-10°C) solution of diisopropylamine (176 μL, 1.25 mmol, 1.25 equiv) in THF (2.5 mL, 0.4 M) was added MeLi (1.55 M Et_2O, 774 μL, 1.2 mmol, 1.2 equiv) under Argon. After 10 min, hydrazone **2** (372 mg, 1.1 mmol, 1.1 equiv) was added. After an additional 30 min, the reaction mixture was cooled to -78°C and DMPU (0.5 mL) was added, followed by iodide **1** (456 mg, 1 mmol, 1 equiv). The resulting solution was allowed to warm to -20°C. After 24h at -20°C, the reaction mixture was quenched with pH 7.0 buffer solution (10 mL). The aqueous layer was separated and extracted with EtOAc (5x50 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. Purification was accomplished by silica gel flash column chromatography (2-5% EtOAc/Hex) affording **26** (480 mg, 72% yield).

TLC R_f = 0.43 (10% EtOAc/Hex)

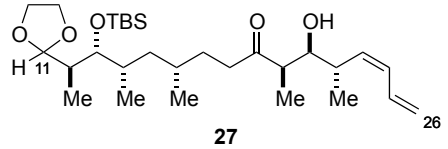
$[\alpha]^{20}_D$ -30.2 (*c* = 1.0, CH_2Cl_2)

IR (thin film) 2957, 1632, 1463, 1379, 1251, 1076, 774, 676 cm^{-1}

^1H NMR (500 MHz, $CDCl_3$) δ 6.46 (dt, *J* = 16.9, 10.8 Hz, 1H, $C_{25}H$), 5.99 (t, *J* = 11.0 Hz, 1H, $C_{24}H$), 5.63 (t, *J* = 10.5 Hz, 1H, $C_{23}H$), 5.14 (dd, *J* = 16.9, 2.0 Hz, 1H, $C_{26}H_a$), 5.04 (d, *J* = 10.2 Hz, 1H, $C_{26}H_b$), 4.93 (d, *J* = 3.1 Hz, 1H, $C_{11}H$), 3.96 – 3.87 (m, 3H, $C_{21}H$), 3.86 – 3.77 (m, 2H), 3.60 (dd, *J* = 8.2, 1.7 Hz, 1H, $C_{13}H$), 2.84 – 2.76 (m, 1H, $C_{22}H$), 2.42 – 2.36 (m, 1H, $C_{18}H_a$), 2.35 (s, 6H), 2.33 – 2.27 (m, 1H, $C_{20}H$), 2.14 (td, *J* = 12.4, 4.0 Hz, 1H, $C_{18}H_b$), 2.00 – 1.92 (m, 1H, $C_{12}H$), 1.76 – 1.68 (m, 1H, $C_{14}H$), 1.52 – 1.39 (m, 2H, $C_{16}H$, $C_{17}H_a$), 1.30 – 1.22 (m, 1H, $C_{15}H_a$), 1.19 – 1.11 (m, 1H, $C_{17}H_b$), 1.06 (d, *J* = 6.9 Hz, 3H, $C_{20}CH_3$), 1.08 – 1.02 (m, 1H, $C_{15}H_b$), 1.01 (d, *J* = 6.9 Hz, 3H, $C_{22}CH_3$), 0.99 (t, *J* = 8.0 Hz, 9H, TES), 0.89 (s, 9H, TBS), 0.85 (dd, *J* = 6.7, 1.6 Hz, 6H, $C_{16}CH_3$, $C_{12}CH_3$), 0.82 (d, *J* = 6.8 Hz, 3H, $C_{14}CH_3$), 0.66 (d, *J* = 8.0 Hz, 6H, TES), 0.05 (s, 3H, TBS), 0.04 (s, 3H, TBS)

^{13}C NMR (125 MHz, $CDCl_3$) δ 174.9, 134.1, 132.9, 129.3, 117.1, 104.7, 79.2, 76.2, 65.2, 64.9, 47.6, 44.9, 42.4, 41.4, 35.9, 33.1, 32.7, 30.9, 28.5, 26.4, 19.8, 19.6, 18.7, 17.7, 13.7, 9.3, 7.3, 5.8, -3.6, -4.1

Exact mass calcd for $C_{37}H_{75}N_2O_4Si_2$ $[M+H]^+$: 667.5265; found 667.5243 (FAB+)



27

To a cooled (0°C) solution of **26** (560 mg, 0.84 mmol, 1 equiv) in 9:1 THF/H_2O (5 mL) in a Nalgene tube was added 2 mL of a freshly prepared pyridinium hydrofluoride solution buffered with excess pyridine (stock solution prepared from 500 μL HF-pyridine, 1 mL pyridine, and 4 mL THF). The reaction mixture was allowed to warm to RT. After 12h, additional HF-pyridine (100 μL) was added. After a total reaction time of 20h, the reaction mixture was quenched at 0°C with pH 7.0 buffer solution (10 mL). The aqueous layer was separated and extracted with EtOAc (5x50 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. Purification was accomplished by silica gel flash column chromatography (4-10% EtOAc/Hex) affording keto-alcohol **27** (390 mg, 91% yield).

TLC R_f = 0.33 (20% EtOAc/Hex)

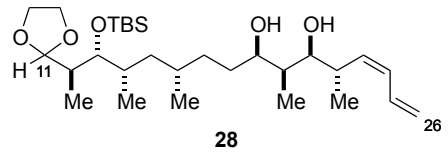
$[\alpha]^{20}_D$ 0.5 (*c* = 1.0, CH_2Cl_2)

IR (thin film) 3399, 2958, 2926, 2855, 1726, 1711, 1625, 1461, 1259, 1073 836 cm^{-1}

^1H NMR (500 MHz, $CDCl_3$) δ 6.60 – 6.51 (m, 1H, $C_{25}H$), 6.11 (t, *J* = 11.0 Hz, 1H, $C_{24}H$), 5.42 – 5.36 (m, 1H, $C_{23}H$), 5.25 – 5.20 (m, 1H, $C_{26}H_a$), 5.12 (d, *J* = 10.2 Hz, 1H, $C_{26}H_b$), 4.91 (d, *J* = 3.3 Hz, 1H, $C_{11}H$), 3.96 – 3.88 (m, 2H), 3.86 – 3.77 (m, 2H), 3.75 – 3.70 (m, 1H, $C_{21}H$), 3.59 (dd, *J* = 8.0, 1.7 Hz, 1H, $C_{13}H$), 2.79 – 2.71 (m, 1H, $C_{22}H$), 2.67 (qd, *J* = 7.1, 4.4 Hz, 1H, $C_{20}H$), 2.46 (t, *J* = 7.8 Hz, 2H, $C_{18}H_2$), 2.35 (d, *J* = 3.2 Hz, 1H, OH), 2.00 – 1.92 (m, 1H, $C_{12}H$), 1.80 – 1.71 (m, 1H, $C_{14}H$), 1.68 – 1.60 (m, 1H, $C_{17}H$), 1.51 – 1.40 (m, 1H, $C_{16}H$), 1.30 – 1.21 (m, 2H, $C_{15}H_a$, $C_{17}H_b$), 1.16 (d, *J* = 7.1 Hz, 3H, $C_{20}CH_3$), 1.10 – 1.03 (m, 1H, $C_{15}H_b$), 0.99 (d, *J* = 6.8 Hz, 3H, $C_{22}CH_3$), 0.89 (s, 9H, TBS), 0.87 – 0.81 (m, 9H, $C_{12}CH_3$, $C_{16}CH_3$, $C_{14}CH_3$), 0.05 (s, 3H, TBS), 0.04 (s, 3H, TBS)

^{13}C NMR (125 MHz, $CDCl_3$) δ 215.2, 134.2, 132.1, 130.7, 118.5, 104.8, 76.3, 75.2, 65.1, 64.9, 48.4, 42.8, 41.4, 39.4, 35.6, 32.8, 30.0, 29.7, 26.3, 20.0, 18.7, 17.7, 13.9, 10.6, 9.4, -3.6, -4.2

Exact mass calcd for $C_{29}H_{53}O_5Si$ $[M–H]^-$: 509.3663; found 509.3663 (FAB+)



28

To a cooled (-78°C) solution of keto-alcohol **27** (110 mg, 0.22 mmol, 1 equiv) in 1:1 THF/MeOH (4.3 mL, 0.05M) was added Et_2B-OMe (1M THF, 650 µL, 0.65 mmol, 3 equiv) dropwise. After 1h, $NaBH_4$ (16 mg, 0.43 mmol, 2 equiv) was added. After an additional 6h, the reaction mixture was quenched with AcOH (100 µL) and then saturated aqueous $NaHCO_3$ (20 mL). The aqueous layer was separated and extracted with EtOAc (5x50 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The crude mixture was azeotroped with methanol (3x20 mL) in order to hydrolyze the boronate. Purification was accomplished by silica gel flash column chromatography (5-20% EtOAc/Hex) affording diol **28** (100 mg, 91% yield) as a colorless oil.

TLC R_f = 0.17 (20% EtOAc/Hex)

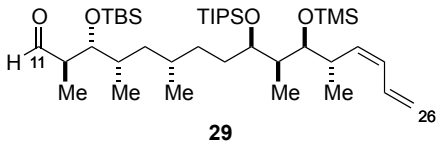
$[\alpha]^{20}_D$ -18.8 (*c* = 0.8, CH_2Cl_2)

IR (thin film) 3424, 2958, 2929, 2857, 1462, 1380, 1252, 1057, 836, 774 cm^{-1}

^1H NMR (500 MHz, $CDCl_3$) δ 6.63 (dt, *J* = 16.5, 10.3 Hz, 1H, $_{25}H$), 6.18 (t, *J* = 11.0 Hz, 1H, $C_{24}H$), 5.28 – 5.23 (m, 2H, $C_{23}H$, $C_{26}H_a$), 5.17 (d, *J* = 10.1 Hz, 1H, $C_{26}H_b$), 4.92 (d, *J* = 3.0 Hz, 1H, $C_{11}H$), 3.96 – 3.89 (m, 2H), 3.85 – 3.78 (m, 2H), 3.76 (app. t, *J* = 6.0 Hz, 1H, $C_{19}H$), 3.60 (dd, *J* = 8.0, 1.8 Hz, 1H, $C_{13}H$), 3.46 (d, *J* = 9.0 Hz, 1H, $C_{21}H$), 3.27 (bs, 1H, OH), 2.81 (app. tq, *J* = 9.6, 6.7 Hz, 1H, $C_{22}H$), 2.29 (bs, 1H, OH), 2.00 – 1.91 (m, 1H, $C_{12}H$), 1.78 – 1.72 (m, 1H, $C_{14}H$), 1.73 – 1.66 (m, 1H, $C_{20}H$), 1.57 – 1.39 (m, 4H, $C_{16}H$, $C_{17}H_a$, $C_{18}H_2$), 1.32 – 1.24 (m, 1H, $C_{15}H_a$), 1.11 – 1.03 (m, 1H, $C_{15}H_b$), 1.01 – 0.95 (m, 1H, $C_{17}H_b$), 0.94 (d, *J* = 7.3 Hz, 3H, $C_{20}CH_3$), 0.93 (d, *J* = 6.7 Hz, 3H, $C_{22}CH_3$), 0.90 – 0.86 (12H, TBS, $C_{16}CH_3$), 0.85 (d, *J* = 7.0 Hz, 3H, $C_{12}CH_3$), 0.83 (d, *J* = 6.8 Hz, 3H, $C_{14}CH_3$), 0.05 (s, 3H, TBS), 0.04 (s, 3H, TBS)

^{13}C NMR (125 MHz, $CDCl_3$) δ 134.6, 132.1, 132.0, 119.1, 104.8, 80.8, 77.4, 76.4, 65.1, 64.9, 43.0, 41.4, 37.1, 36.5, 32.9, 32.9, 32.3, 30.2, 26.4, 20.3, 18.7, 16.8, 14.0, 9.4, 4.4, -3.6, -4.2

Exact mass calcd for $C_{29}H_{55}O_5Si$ $[M–H]^-$: 511.3819; found 511.3814 (FAB+)



29

To a cooled (-78°C) solution of diol **28** (170 mg, 0.33 mmol, 1 equiv) in CH_2Cl_2 (6.6 mL, 0.05M) was added 2,6-lutidine (382 μL, 3.3 mmol, 10 equiv) and TIPS-OTf (94 μL, 0.35 mmol, 1.05 equiv). After 4h, TMS-OTf (299 μL, 1.66 mmol, 5 equiv) was added, and the reaction mixture was warmed to 0°C. After 3h at 0°C, the reaction mixture was quenched with water (5 mL). After vigorously stirring for 2h, the aqueous layer was separated and extracted with CH_2Cl_2 (5x10 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. Purification was accomplished by pH 7.0 buffered silica gel flash column chromatography (1-5% EtOAc/Hex) affording aldehyde **30** (190 mg, 82% yield) as a colorless oil.

TLC R_f = 0.30 (5% EtOAc/Hex)

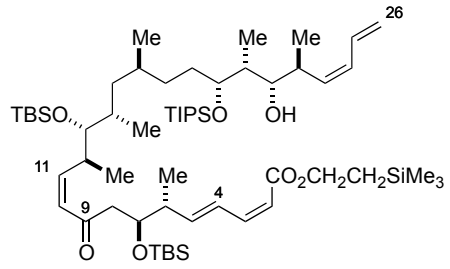
$[\alpha]^{20}_D$ -23.0 (*c* = 1.8, CH_2Cl_2)

IR (thin film) 2948, 2867, 1728, 1463, 1380, 1251, 1029, 883, 835, 774, 676 cm^{-1}

^1H NMR (500 MHz, $CDCl_3$) δ 9.75 (d, *J* = 2.6 Hz, 1H, $C_{11}H$), 6.54 (dt, *J* = 16.8, 10.6 Hz, 1H, $C_{25}H$), 5.99 (t, *J* = 11.0 Hz, 1H, $C_{24}H$), 5.55 (t, *J* = 10.6 Hz, 1H, $C_{23}H$), 5.15 (dd, *J* = 16.8, 2.0 Hz, 1H, $C_{26}H_a$), 5.06 (d, *J* = 10.1 Hz, 1H, $C_{26}H_b$), 3.84 (ddd, *J* = 9.7, 4.2, 2.1 Hz, 1H, $C_{19}H$), 3.73 – 3.69 (m, 2H, $C_{13}H$, $C_{21}H$), 3.00 – 2.92 (m, 1H, $C_{22}H$), 2.57 – 2.50 (m, 1H, $C_{12}H$), 1.72 – 1.60 (m, 2H, $C_{14}H$, $C_{18}H_a$), 1.51 – 1.46 (m, 1H, $C_{20}H$), 1.44 – 1.33 (m, 2H, $C_{16}H$, $C_{18}H_b$), 1.20 (ddd, *J* = 13.4, 8.3, 5.2 Hz, 1H, $C_{15}H_a$), 1.09 – 1.04 (25H, TIPS, $C_{12}CH_3$, $C_{17}H_a$), 1.01 (d, *J* = 6.9 Hz, $C_{22}CH_3$), 0.99 – 0.94 (m, 1H, $C_{15}H_b$), 0.87 (12H, TBS, $C_{20}CH_3$), 0.84 (d, *J* = 6.9 Hz, $C_{14}CH_3$), 0.83 (d, *J* = 6.6 Hz, $C_{16}CH_3$), 0.81 – 0.75 (m, 1H, $C_{17}H_b$), 0.14 (s, 9H, TMS), 0.05 (s, 3H, TBS), 0.03 (s, 3H, TBS)

^{13}C NMR (125 MHz, $CDCl_3$) δ 205.1, 134.3, 132.7, 128.9, 117.1, 78.7, 78.0, 73.0, 50.7, 41.5, 40.7, 34.8, 34.8, 33.1, 31.3, 30.8, 26.2, 20.4, 19.5, 18.5, 18.5, 18.4, 14.9, 13.4, 12.2, 9.6, 1.2, -3.7, -4.0

LRMS calcd for $C_{39}H_{80}NaO_4Si_3$ $[M+Na]^+$: 719.5; found 719.8 (FAB+)



30

To a cooled (-78°C) solution of phosphonate **3** (201 mg, 0.30 mmol, 1.3 equiv) in THF (4.6 mL, 0.05 M) was added NaHMDS (1M THF, 277 μL, 0.28 mmol, 1.2 equiv). After 20 min, aldehyde **29** (161 mg, 0.23 mmol, 1 equiv) was added, and the reaction mixture was allowed to warm to RT. After 48h, the reaction mixture was quenched at 0°C with a solution of PPTS (5 mg) in MeOH (2 mL) in order to deprotect the TMS ether. After 4h, the reaction mixture was diluted with pH 7.0 buffer solution (10 mL). The aqueous layer was separated and extracted with EtOAc (5x50 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. Purification was accomplished by silica gel flash column chromatography (4% EtOAc/Hex) affording enone **30** (174 mg, 73% yield) as a colorless oil.

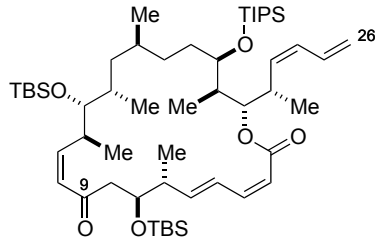
TLC R_f = 0.57 (10% EtOAc/Hex)

$[\alpha]^{20}_D$ 3.3 (*c* = 0.5, CH_2Cl_2)

IR (thin film) 2955, 2928, 2862, 1696, 1716, 1700, 1462, 1251, 1172, 835 cm^{-1}

^1H NMR (500 MHz, $CDCl_3$) δ 7.36 (dd, *J* = 15.4, 11.4 Hz, 1H, C_4H), 6.64 (dt, *J* = 16.8, 10.6 Hz, 1H, $C_{25}H$), 6.53 (t, *J* = 11.4 Hz, 1H, C_3H), 6.29 (dd, *J* = 11.6, 9.7 Hz, 1H, $C_{11}H$), 6.07 (t, *J* = 11.0 Hz, 1H, $C_{24}H$), 6.04 – 5.98 (m, 2H, $C_{10}H$, C_5H), 5.57 (d, *J* = 11.4 Hz, 1H, C_2H), 5.46 (t, *J* = 10.2 Hz, 1H, $C_{23}H$), 5.19 (dd, *J* = 16.8, 2.2 Hz, 1H, $C_{26}H_a$), 5.09 (d, *J* = 10.3 Hz, 1H, $C_{26}H_b$), 4.27 – 4.19 (m, 3H, C_7H, TMSE), 3.97 – 3.93 (m, 1H, $C_{19}H$), 3.73 – 3.67 (m, 1H, $C_{12}H$), 3.55 (dd, *J* = 8.1, 2.4 Hz, 1H, $C_{21}H$), 3.48 (t, *J* = 3.5 Hz, 1H, $C_{13}H$), 2.85 – 2.78 (m, 1H, $C_{22}H$), 2.76 (bs, 1H, OH), 2.54 (dd, *J* = 16.4, 6.6 Hz, 1H, C_8H_a), 2.47 (dd, *J* = 16.4, 5.5 Hz, 1H, C_8H_b), 2.50 – 2.44 (m, 1H, C_6H), 1.75 – 1.66 (m, 2H, $C_{18}H_a$, $C_{20}H$), 1.66 – 1.58 (m, 1H, $C_{14}H$), 1.46 – 1.33 (m, 2H, $C_{18}H_b$, $C_{16}H$), 1.33 – 1.26 (m, 1H, $C_{15}H_a$), 1.24 – 1.16 (m, 1H, $C_{17}H_a$), 1.11 – 1.06 (24H, TIPS, C_6CH_3), 1.06 – 1.01 (m, 2H, TMSE), 1.00 (d, *J* = 6.8 Hz, 3H, $C_{12}CH_3$), 0.95 (d, *J* = 6.8 Hz, 3H, $C_{22}CH_3$), 0.93 – 0.89 (13H, TBS, $C_{20}CH_3$, $C_{15}H_b$), 0.87 (s, 9H, TBS), 0.83 (d, *J* = 6.5 Hz, 3H, $C_{16}CH_3$), 0.82 (d, *J* = 6.8 Hz, 3H, $C_{14}CH_3$), 0.80 – 0.75 (m, 1H, $C_{17}H_b$), 0.09 (s, 3H, TBS), 0.07 (s, 3H, TBS), 0.05 (12H, TMSE, TBS), 0.00 (s, 3H, TBS)

^{13}C NMR (125 MHz, $CDCl_3$) δ 199.5, 166.8, 152.2, 146.2, 145.1, 135.9, 132.6, 129.6, 127.5, 125.5, 117.5, 116.6, 79.9, 79.3, 78.5, 71.7, 62.2, 49.4, 43.4, 41.2, 37.4, 36.5, 36.2, 36.1, 32.7, 31.9, 30.9, 26.3, 26.1, 20.7, 19.3, 18.6, 18.5, 18.4, 18.2, 18.1, 17.6, 15.9, 15.8, 13.6, 5.9, -1.3, -3.5, -3.8, -4.2, -4.6



32

To a cooled (0°C) solution of TMSE ester **30** (75 mg, 0.073 mmol, 1 equiv) in DMF (7.3 mL, 0.01M) was added a solution of TAS-F (21 mg, 0.076, 1.05 equiv) in DMF (0.5 mL). The reaction mixture was allowed to warm to RT. After 20h, the reaction mixture was diluted with Et_2O (10 mL) and quenched at 0°C with 1M $NaHSO_4$ (5 mL). The reaction mixture was further diluted with brine (5 mL) and extracted with Et_2O (5x10 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. Acid **31** was used immediately without purification.

To a solution of acid **31** in Toluene (73 mL, 0.001M) was added 2-methyl-6-nitrobenzoic anhydride (75 mg, 0.22 mmol, 3 equiv), DMAP (8 mg, 0.073 mmol, 1 equiv), and NEt_3 (101 μL, 0.73 mmol, 10 equiv). After 24h, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ (20 mL) The aqueous layer was separated and extracted with EtOAc (3x50 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. Purification was accomplished by silica gel flash column chromatography (1-5% EtOAc/Hex) affording macrocycle **32** (40 mg, 61% yield over 2 steps) as a colorless oil.

TLC R_f = 0.46 (5% EtOAc/Hex)

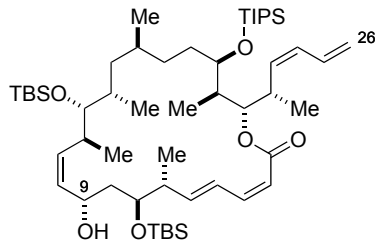
$[\alpha]^{20}_D$ -13.0 (*c* = 0.5, CH_2Cl_2)

IR (thin film) 2929, 2859, 1708, 1463, 1254, 1025, 835, 774, 676 cm^{-1}

^1H NMR (500 MHz, $CDCl_3$) δ 7.13 (dd, *J* = 15.5, 11.2 Hz, 1H, C_4H), 6.57 (dt, *J* = 16.8, 10.3 Hz, 1H, $C_{25}H$), 6.55 (t, *J* = 11.4 Hz, 1H, C_3H), 6.38 (dd, *J* = 11.7, 10.1 Hz, 1H, $C_{11}H$), 6.12 (d, *J* = 11.7 Hz, 1H, $C_{10}H$), 6.06 (t, *J* = 11.3 Hz, 1H, $C_{24}H$), 6.00 (dd, *J* = 15.7, 8.2 Hz, 1H, C_5H), 5.59 (d, *J* = 11.6 Hz, 1H, C_2H), 5.48 (t, *J* = 10.7 Hz, 1H, $C_{23}H$), 5.33 (dd, *J* = 8.8, 3.1 Hz, 1H, $C_{21}H$), 5.21 (dd, *J* = 16.8, 1.9 Hz, 1H, $C_{26}H_a$), 5.12 (d, *J* = 10.2 Hz, 1H, $C_{26}H_b$), 4.12 – 4.05 (m, 1H, C_7H), 3.82 (bs, 1H, $C_{19}H$), 3.73 (bs, 1H, $C_{12}H$), 3.30 (dd, *J* = 6.1, 1.7 Hz, 1H, $C_{13}H$), 3.18 – 3.10 (m, 1H, $C_{22}H$), 2.59 (dd, *J* = 14.1, 6.3 Hz, 1H, C_8H_a), 2.51 (dd, *J* = 14.1, 5.3 Hz, 1H, C_8H_b), 2.44 – 2.36 (m, 1H, C_6H), 1.77 – 1.68 (m, 1H, $C_{20}H$), 1.66 – 1.55 (m, 1H, $C_{18}H_a$), 1.48 – 1.39 (m, 2H, $C_{14}H$, $C_{16}H$), 1.34 – 1.25 (m, 2H, $C_{17}H_a$, $C_{18}H_b$), 1.13 – 1.07 (m, 25H, TIPS, C_6CH_3, $C_{15}H_a$), 1.03 (d, *J* = 7.0 Hz, 3H, $C_{12}CH_3$), 1.01 (d, *J* = 6.8 Hz, 3H, $C_{22}CH_3$), 0.94 (s, 9H, TBS), 0.93 – 0.90 (m, 1H, $C_{15}H_b$), 0.89 (s, 9H, TBS), 0.83 (d, *J* = 6.7 Hz, 3H, $C_{20}CH_3$), 0.78 (d, *J* = 6.9 Hz, 3H, $C_{16}CH_3$), 0.77 (d, *J* = 7.2 Hz, 3H, $C_{14}CH_3$), 0.67 – 0.55 (m, 1H, $C_{17}H_b$), 0.08 (s, 3H, TBS), 0.07 (s, 3H, TBS), 0.07 (s, 3H, TBS), 0.04 (s, 3H, TBS)

^{13}C NMR (125 MHz, $CDCl_3$) δ 199.2, 166.7, 151.1, 144.6, 142.9, 133.2, 132.0, 130.0, 128.5, 125.5, 118.4, 118.2, 81.0, 78.7, 73.1, 52.3, 44.5, 42.5, 39.5, 37.4, 36.0, 34.0, 32.1, 30.2, 29.9, 26.4, 26.0, 20.7, 19.0, 18.7, 18.5, 18.5, 18.4, 18.2, 15.9, 13.6, 13.4, 9.1, -3.2, -3.4, -4.0, -4.5

LRMS calcd for $C_{53}H_{97}O_6Si_3$ $[M–H]^-$: 913.66; found 913.62 (FAB+)



33

To a cooled (-78°C) solution of enone **32** (25 mg, 27 μmol, 1 equiv) in Toluene (546 μL, 0.05M) was added (*R*)-2-Methyl-CBS oxazaborolidine (1M Tol, 109 μL, 109 μmol, 4 equiv) and catecholborane (50% w/w Toluene, 60 μL, 218 μmol, 8 equiv). After 24h, the reaction mixture was quenched with MeOH (2 mL) and then saturated aqueous $NaHCO_3$ (2 mL). The aqueous layer was separated and extracted with Et_2O (5x10 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. Purification was accomplished by silica gel flash column chromatography (5-10% EtOAc/Hex) affording **33** (20 mg, 80% yield) as a colorless oil.

TLC R_f = 0.30 (10% EtOAc/Hex)

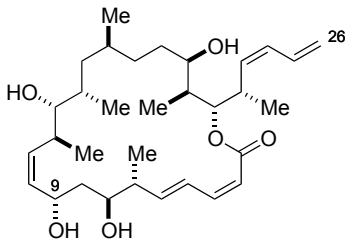
$[\alpha]^{20}_D$ -19.2 (*c* = 1.2, CH_2Cl_2)

IR (thin film) 3462, 2956, 2865, 1716, 1640, 1463, 1379, 962, 775, 677 cm^{-1}

^1H NMR (500 MHz, $CDCl_3$, 315 K) δ 7.05 (dd, *J* = 15.5, 11.3 Hz, 1H, C_4H), 6.59 (dt, *J* = 16.7, 10.6 Hz, 1H, $C_{25}H$), 6.53 (t, *J* = 11.3 Hz, 1H, C_3H), 6.10 – 6.03 (m, 2H, C_5H, $C_{24}H$), 5.69 (t, *J* = 10.2 Hz, 1H, $C_{11}H$), 5.61 (d, *J* = 11.3 Hz, 1H, C_2H), 5.45 – 5.35 (m, 2H, $C_{10}H$, $C_{23}H$), 5.24 – 5.16 (m, 2H, $C_{26}H_a$, $C_{21}H$), 5.10 (d, *J* = 10.1 Hz, 1H, $C_{26}H_b$), 4.58 (td, *J* = 8.8, 3.9 Hz, 1H, C_9H), 4.10 (dt, *J* = 8.5, 3.8 Hz, 1H, C_7H), 3.78 (bs, 1H, $C_{19}H$), 3.22 (dd, *J* = 6.9, 2.4 Hz, 1H, $C_{13}H$), 3.13 – 3.04 (m, 1H, $C_{22}H$), 2.75 – 2.66 (m, 1H, $C_{12}H$), 2.64 – 2.56 (m, 1H, C_6H), 1.89 – 1.81 (m, 1H, $C_{20}H$), 1.75 – 1.66 (m, 1H, $C_{18}H_a$), 1.58 – 1.49 (m, 1H, $C_{14}H$), 1.48 – 1.38 (m, 3H, $C_{16}H$, C_8H_2), 1.35 – 1.26 (m, 1H, $C_{17}H_a$), 1.23 – 1.14 (m, 1H, $C_{18}H_b$), 1.11 – 1.06 (25H, TIPS, C_6CH_3, $C_{15}H_a$), 1.03 (d, *J* = 6.9 Hz, 3H, $C_{12}CH_3$), 1.00 (d, *J* = 6.9 Hz, 3H, $C_{20}CH_3$), 0.98 (d, *J* = 6.9 Hz, 3H, $C_{22}CH_3$), 0.94 (s, 9H, TBS), 0.93 (s, 9H, TBS), 0.91 – 0.86 (m, 1H, $C_{15}H_b$), 0.81 (d, *J* = 6.4 Hz, 3H, $C_{16}CH_3$), 0.77 (d, *J* = 6.6 Hz, 3H, $C_{14}CH_3$), 0.65 – 0.54 (m, 1H, $C_{17}H_b$), 0.15 (s, 3H, TBS), 0.12 (s, 3H, TBS), 0.07 (s, 3H, TBS), 0.06 (s, 3H, TBS)

^{13}C NMR (125 MHz, Toluene-d_8, 333 K) δ 165.9, 143.2, 142.3, 134.2, 133.6, 132.6, 131.8, 130.5, 128.4, 118.9, 118.1, 81.2, 77.9, 74.6, 70.6, 64.8, 43.4, 42.8, 40.8, 40.1, 36.1, 35.6, 35.3, 33.4, 32.9, 31.2, 30.3, 26.6, 26.3, 18.9, 18.7, 18.6, 18.4, 16.3, 13.8, 12.4, 10.5, -3.1, -3.2, -4.3, -4.4

LRMS calcd for $C_{53}H_{99}O_6Si_3$ $[M–H]^-$: 915.68; found 915.77 (FAB+)



Dictyostatin

To a cooled (0°C) solution of **33** (13 mg, 0.014 mmol, 1 equiv) in THF (3.5 mL) in a Nalgene tube was added pyridinium hydrofluoride (173 μL). The reaction mixture was allowed to warm to RT. Over four days, four aliquots of pyridinium hydrofluoride (173 μL) were added, one per day. After complete conversion to product, as monitored by TLC, the reaction mixture was slowly quenched at 0°C with saturated aqueous $NaHCO_3$ (30 mL) and then diluted with EtOAc (30 mL). The aqueous layer was separated and extracted with EtOAc (3x30 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. Purification was accomplished by silica gel flash column chromatography (50-70% EtOAc/Hex) affording dictyostatin (5.5 mg, 73% yield) as a white solid.

TLC R_f = 0.52 (100% EtOAc)

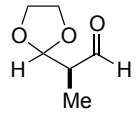
$[\alpha]^{21}_D$ -37.9 (*c* = 0.2, MeOH)

IR (thin film) 3404, 2924, 1694, 1636, 1598, 1378, 1264, 1180, 965 cm^{-1}

^1H NMR (500 MHz, CD_3OD) δ 7.18 (dd, *J* = 15.5, 11.1 Hz, 1H, C_4H), 6.68 (dt, *J* = 16.9, 10.6 Hz, 1H, $C_{25}H$), 6.62 (t, *J* = 11.3 Hz, 1H, C_3H), 6.14 (dd, *J* = 15.5, 6.8 Hz, 1H, C_5H), 6.03 (t, *J* = 11.0 Hz, 1H, $C_{24}H$), 5.53 (d, *J* = 11.4 Hz, 1H, C_2H), 5.55 – 5.50 (m, 1H, $C_{11}H$), 5.38 (dd, *J* = 11.2, 8.6 Hz, 1H, $C_{10}H$), 5.31 (t, *J* = 10.6 Hz, 1H, $C_{23}H$), 5.22 (dd, *J* = 16.9, 1.9 Hz, 1H, $C_{26}H_a$), 5.14 – 5.09 (m, 2H, $C_{26}H_b$, $C_{21}H$), 4.62 (td, *J* = 9.6, 3.5 Hz, 1H, C_9H), 4.02 (dt, *J* = 10.7, 2.9 Hz, 1H, C_7H), 3.36 – 3.31 (m, 1H, $C_{19}H$), 3.17 – 3.10 (m, 1H, $C_{22}H$), 3.07 (dd, *J* = 8.1, 3.0 Hz, 1H, $C_{13}H$), 2.77 – 2.69 (m, 1H, $C_{12}H$), 2.61 – 2.53 (m, 1H, C_6H), 1.90 – 1.76 (m, 2H, $C_{20}H$, $C_{18}H_a$), 1.62 – 1.49 (m, 3H, $C_{14}H$, $C_{17}H_a$, $C_{16}H$), 1.47 (ddd, *J* = 14.1, 10.7, 3.5 Hz, 1H, C_8H_a), 1.38 (ddd, *J* = 14.1, 10.0, 2.9 Hz, 1H, C_8H_b), 1.26 – 1.18 (m, 1H, $C_{15}H_a$), 1.12 (d, *J* = 6.9 Hz, 3H, C_6CH_3), 1.09 (d, *J* = 6.9 Hz, 3H, $C_{12}CH_3$), 1.09 – 1.06 (m, 1H, $C_{18}H_b$), 1.04 (d, *J* = 6.7 Hz, 3H, $C_{20}CH_3$), 0.98 (d, *J* = 6.7 Hz, 3H, $C_{22}CH_3$), 0.92 (d, *J* = 6.5 Hz, 3H, $C_{14}CH_3$), 0.89 (d, *J* = 6.5 Hz, 3H, $C_{16}CH_3$), 0.89 – 0.85 (m, 1H, $C_{15}H_b$), 0.73 – 0.63 (m, 1H, $C_{17}H_b$)

^{13}C NMR (125 MHz, CD_3OD) δ 168.0, 146.3, 144.8, 134.9, 134.5, 133.4, 131.3, 131.1, 128.5, 118.5, 118.0, 80.3, 78.6, 73.7, 70.2, 65.4, 44.0, 42.2, 40.8, 40.4, 35.8, 35.7, 35.3, 32.7, 32.5, 31.2, 21.8, 19.3, 18.0, 16.0, 13.6, 10.3

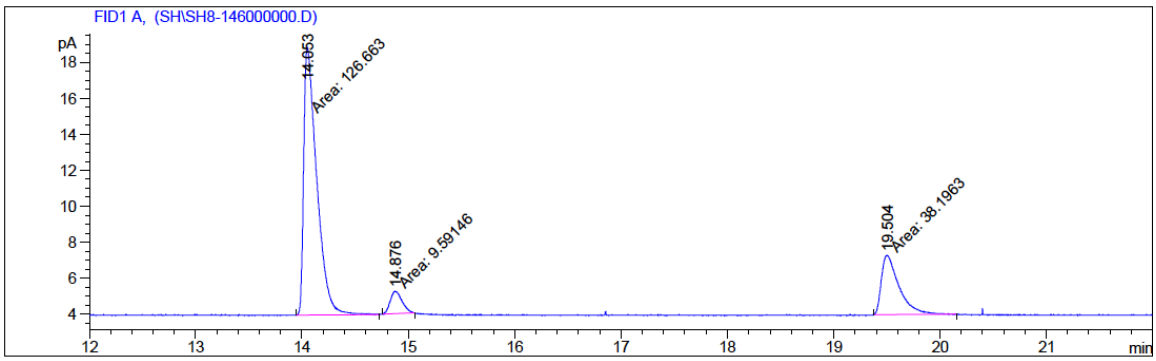
LRMS calcd for $C_{32}H_{51}O_6$ $[M–H]^-$: 531.37; found 531.32 (FAB+)



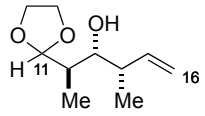
5

^{1}H NMR (500 MHz, $CDCl_3$)
of crude aldehyde mixture

GC Chromatogram (Supelco β-DEX 325, Isothermal 90°C, 1 mL/min)
Enantiomeric excess determined to be 86% ee
Major(R) = 14.1 min, Minor(S) = 14.9 min, Linear = 19.5 min

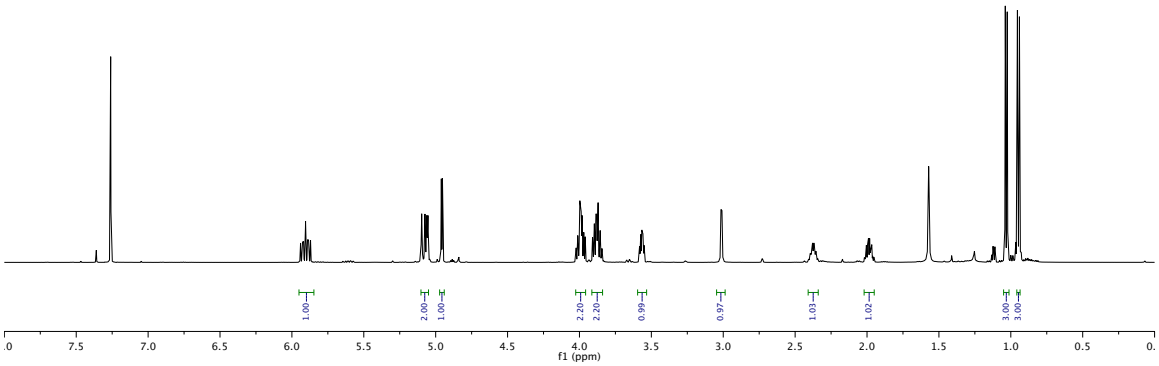


Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	14.053	MM	0.1417	126.66331	14.90113	72.60680
2	14.876	MM	0.1282	9.59146	1.24649	5.49808
3	19.504	MM	0.1934	38.19626	3.29131	21.89512

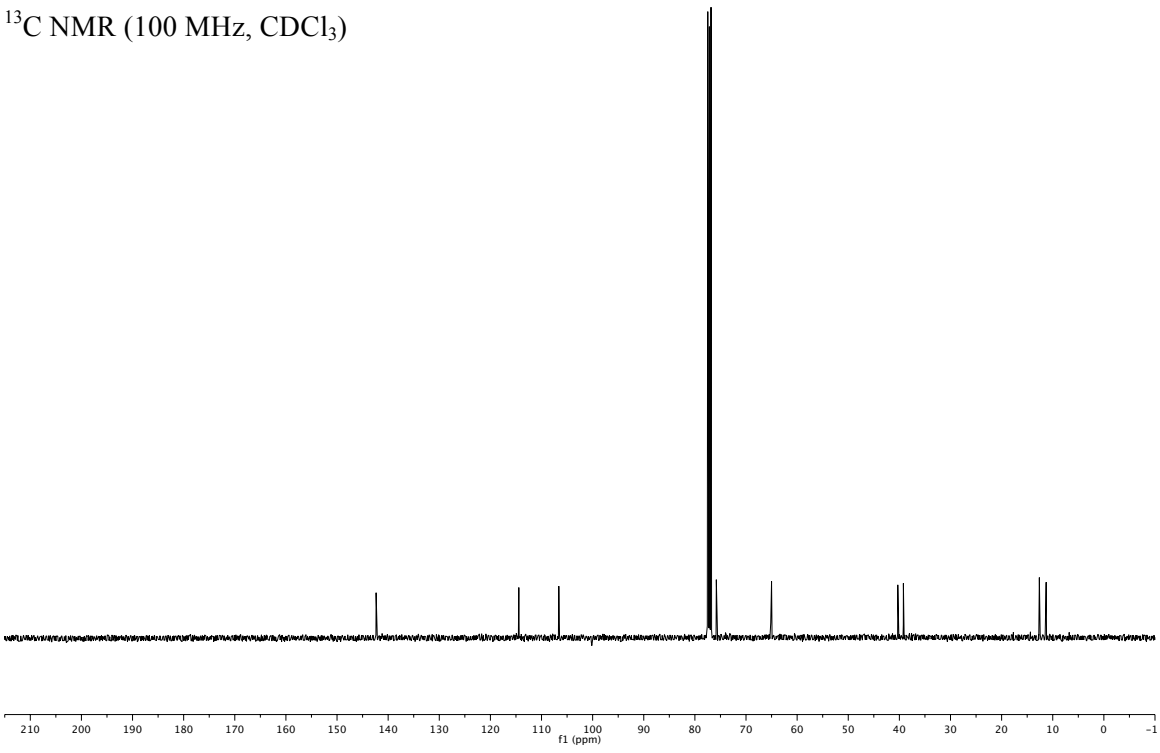


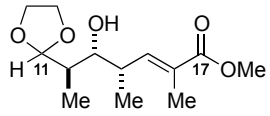
7

^{1}H NMR (500 MHz, $CDCl_3$)



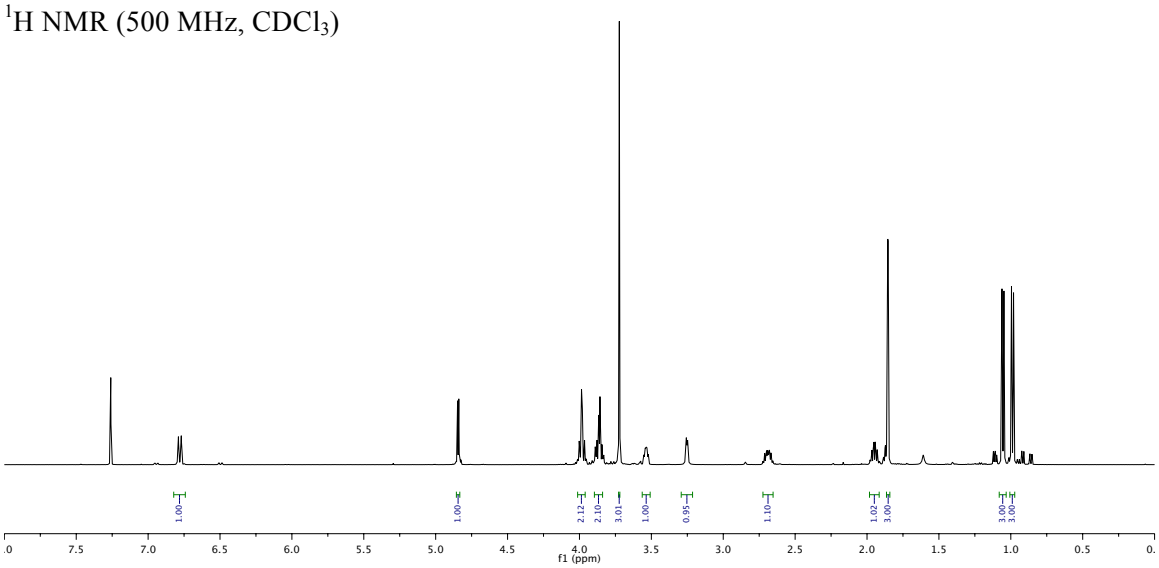
^{13}C NMR (100 MHz, $CDCl_3$)



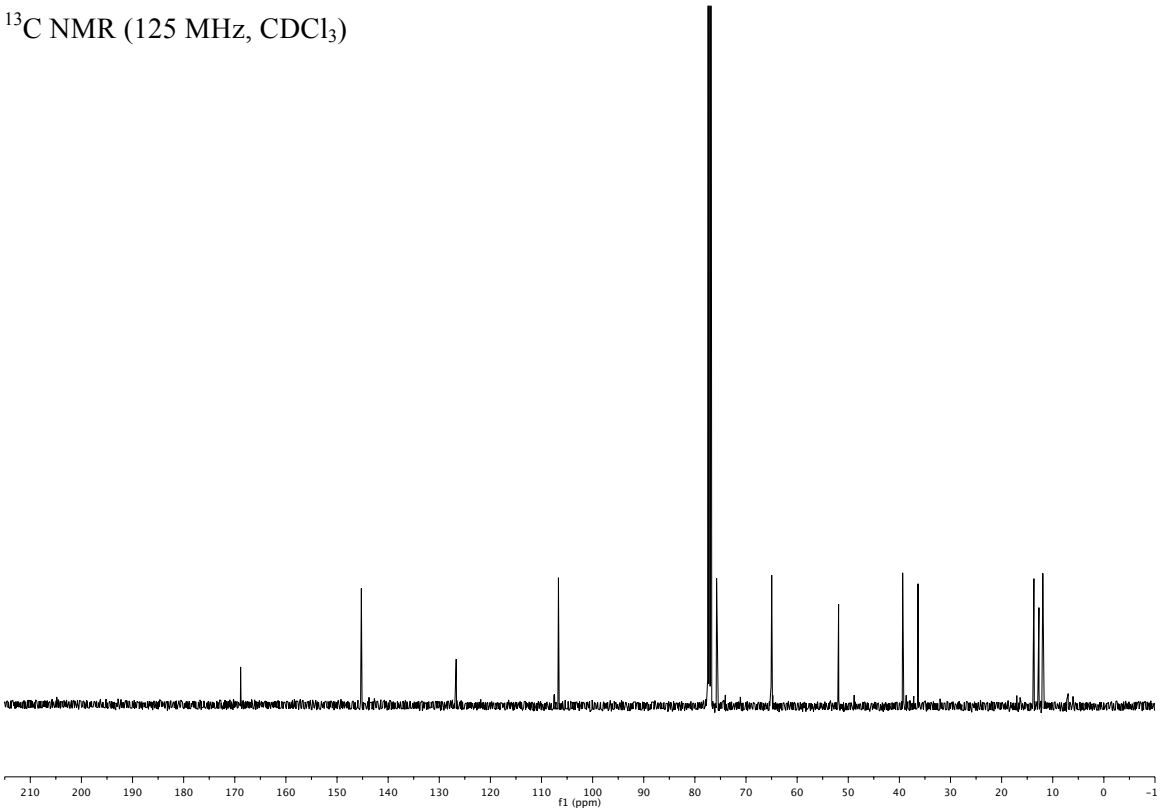


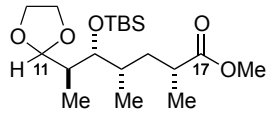
9

^{1}H NMR (500 MHz, $CDCl_3$)



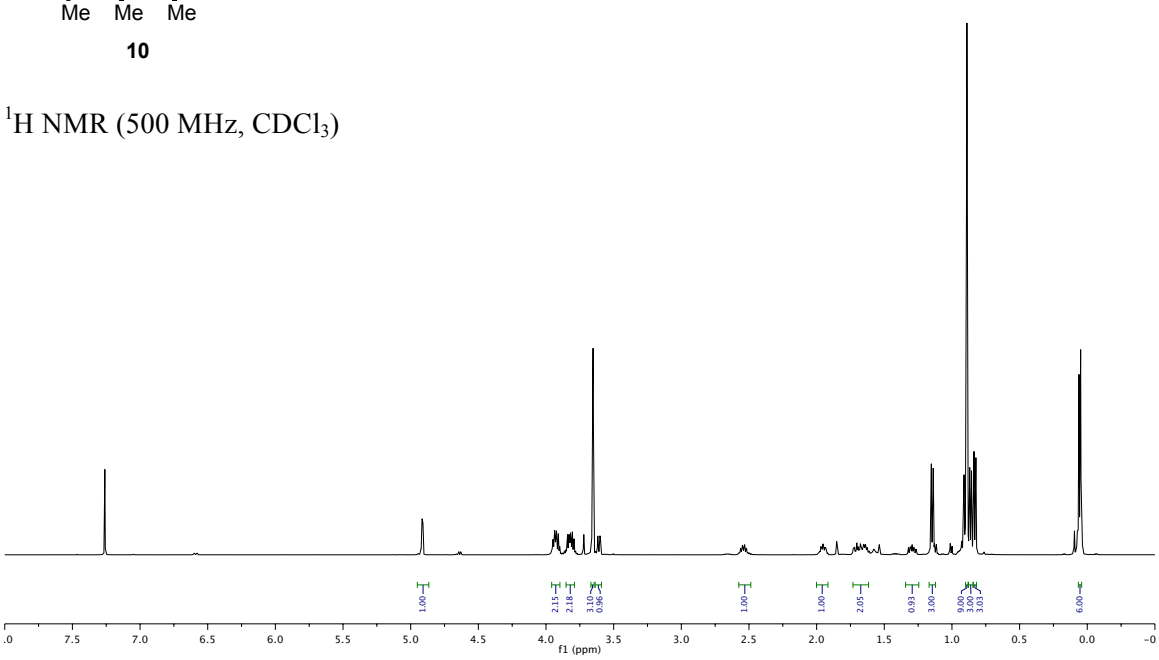
^{13}C NMR (125 MHz, $CDCl_3$)



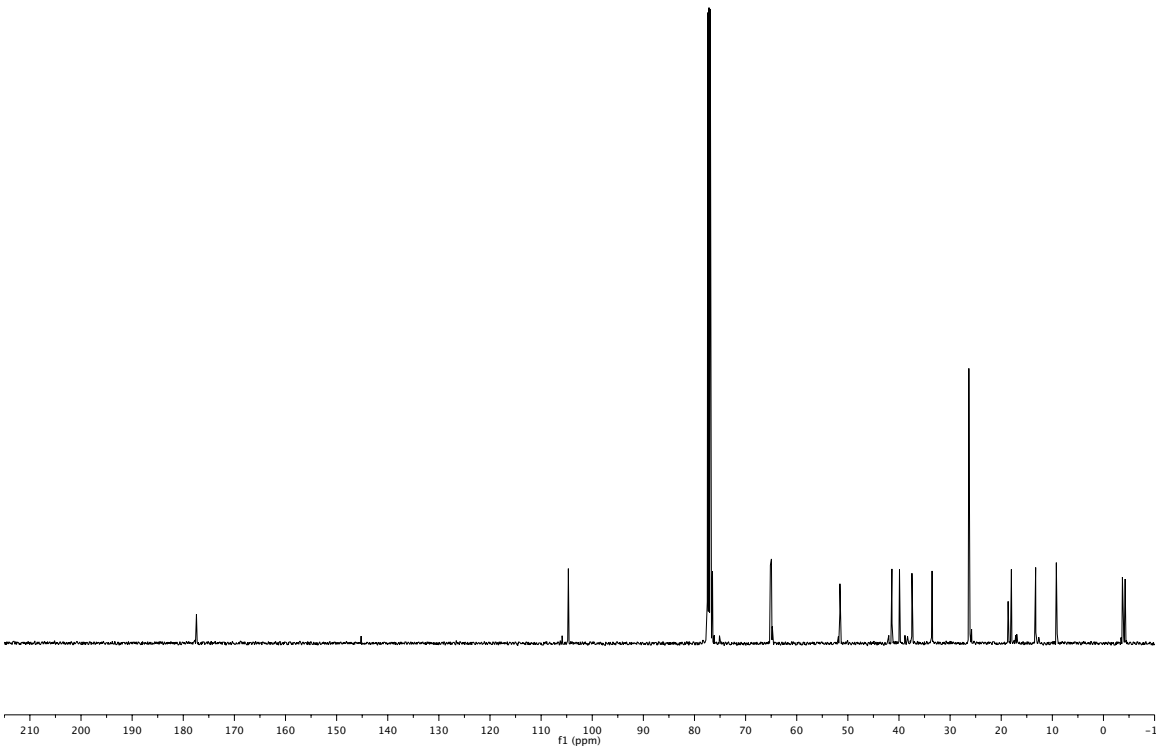


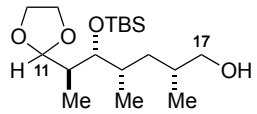
10

^{1}H NMR (500 MHz, $CDCl_3$)



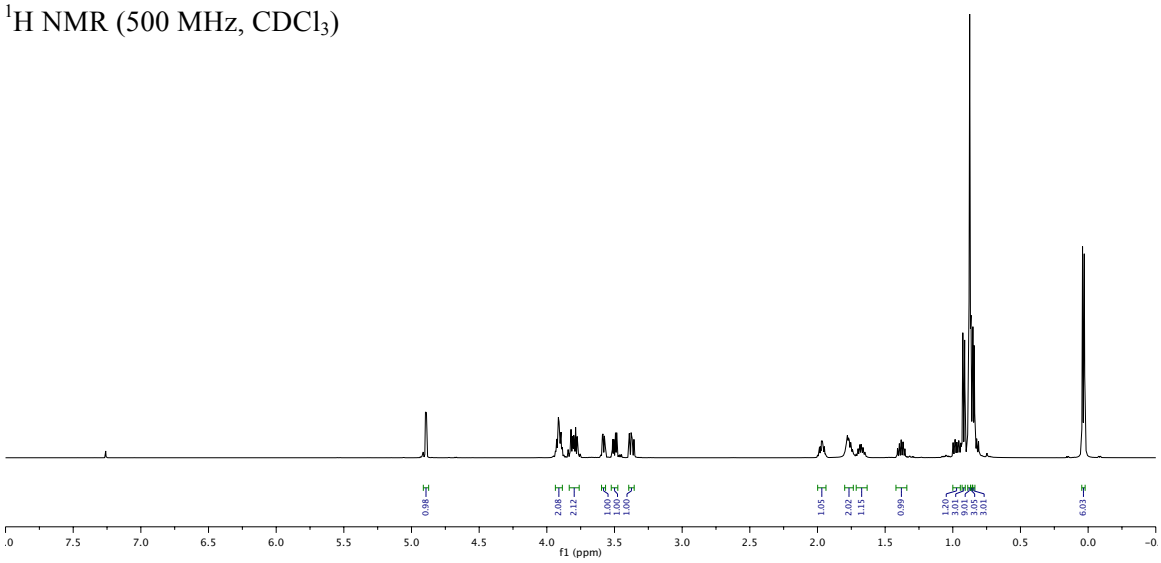
^{13}C NMR (125 MHz, $CDCl_3$)



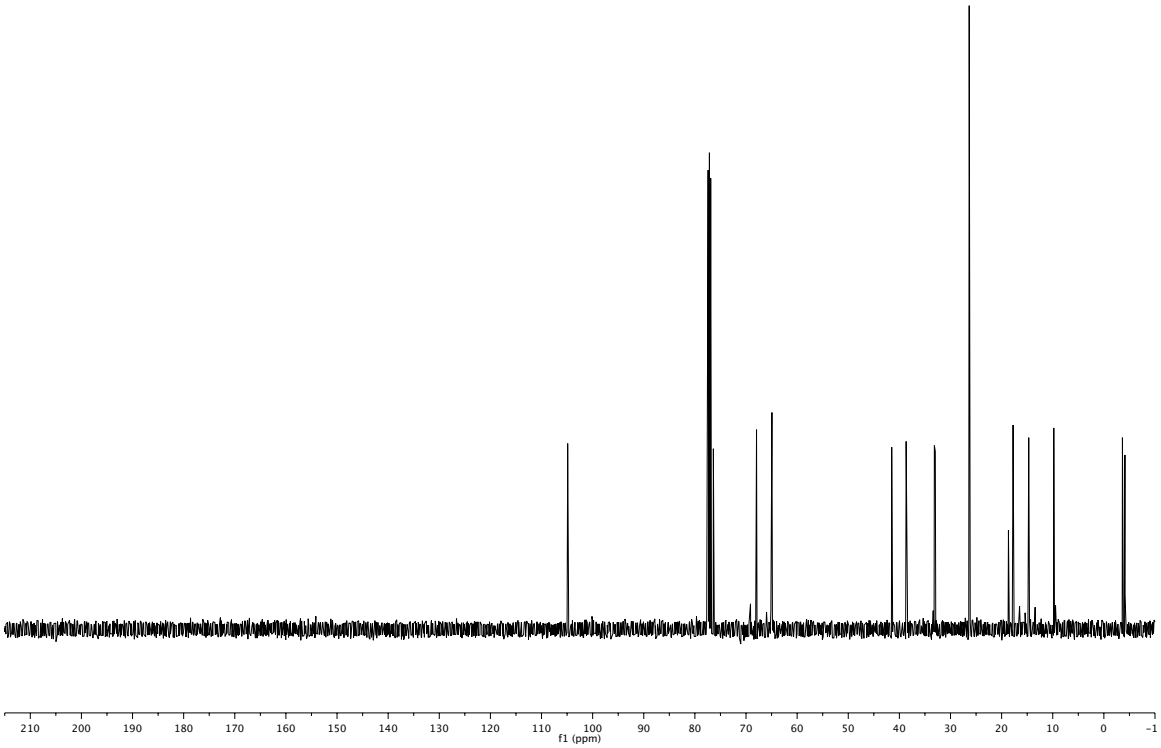


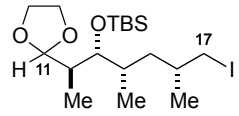
11

^{1}H NMR (500 MHz, $CDCl_3$)



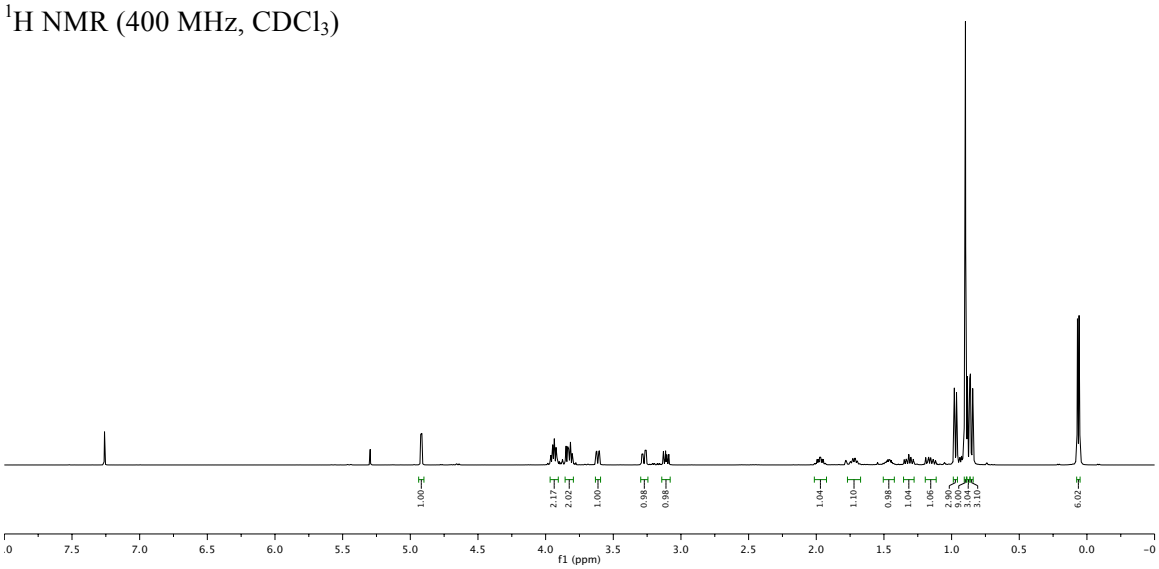
^{13}C NMR (125 MHz, $CDCl_3$)



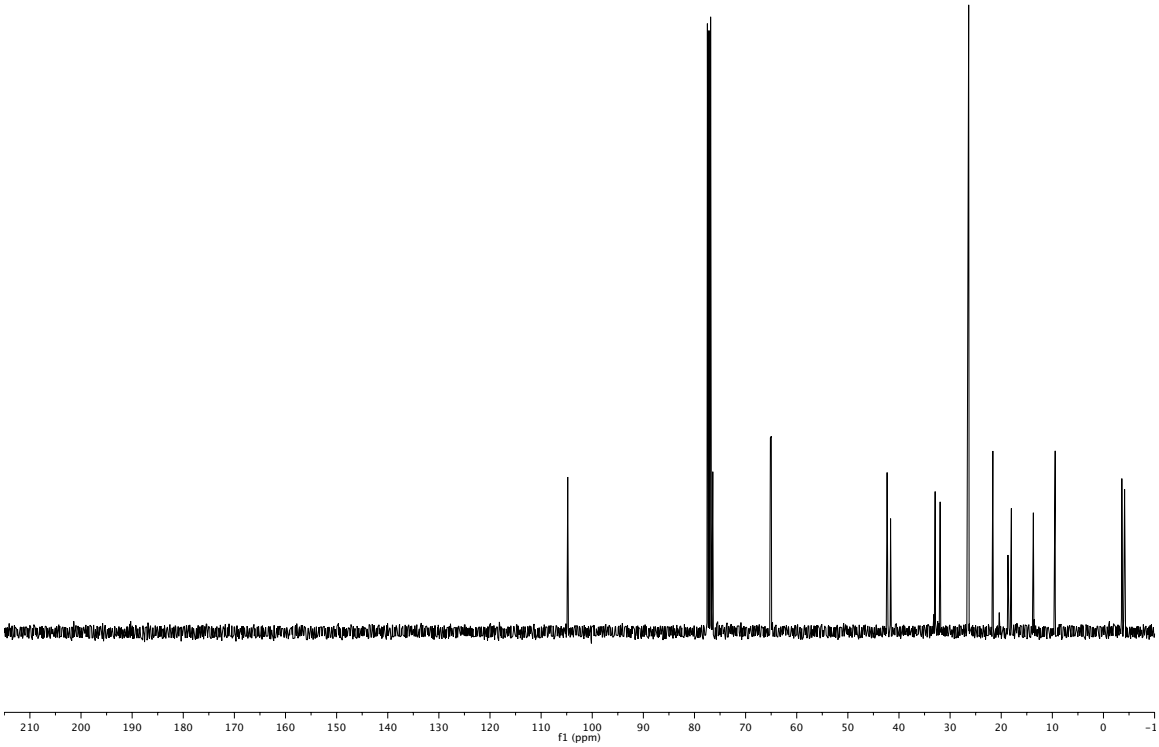


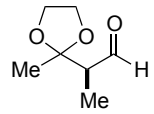
1

^{1}H NMR (400 MHz, $CDCl_3$)



^{13}C NMR (100 MHz, $CDCl_3$)

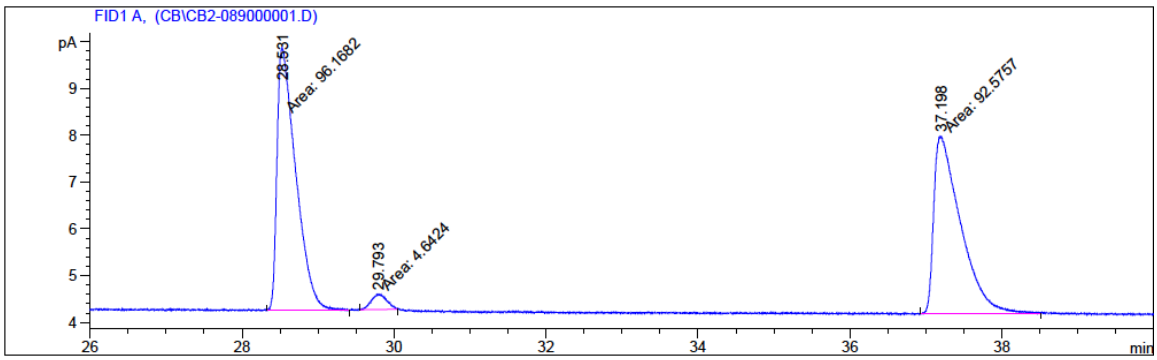




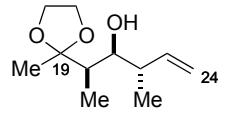
12

^{1}H NMR (300 MHz, $CDCl_3$)
of crude aldehyde mixture

GC Chromatogram (Supelco β-DEX 325, Isothermal 80°C, 1 mL/min)
Enantiomeric excess determined to be 91% ee
Major(R) = 28.5 min, Minor(S) = 29.8 min, Linear = 37.2 min

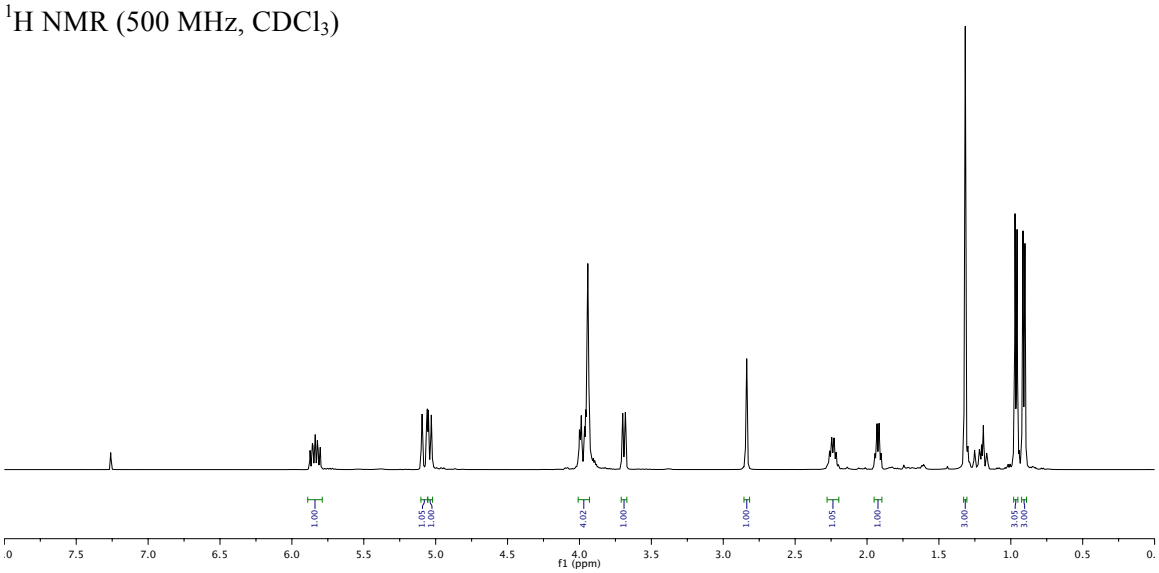


Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	28.531	MM	0.2845	96.16822	5.63448	49.72856
2	29.793	MM	0.2329	4.64240	3.32249e-1	2.40059
3	37.198	MM	0.4070	92.57568	3.79063	47.87086

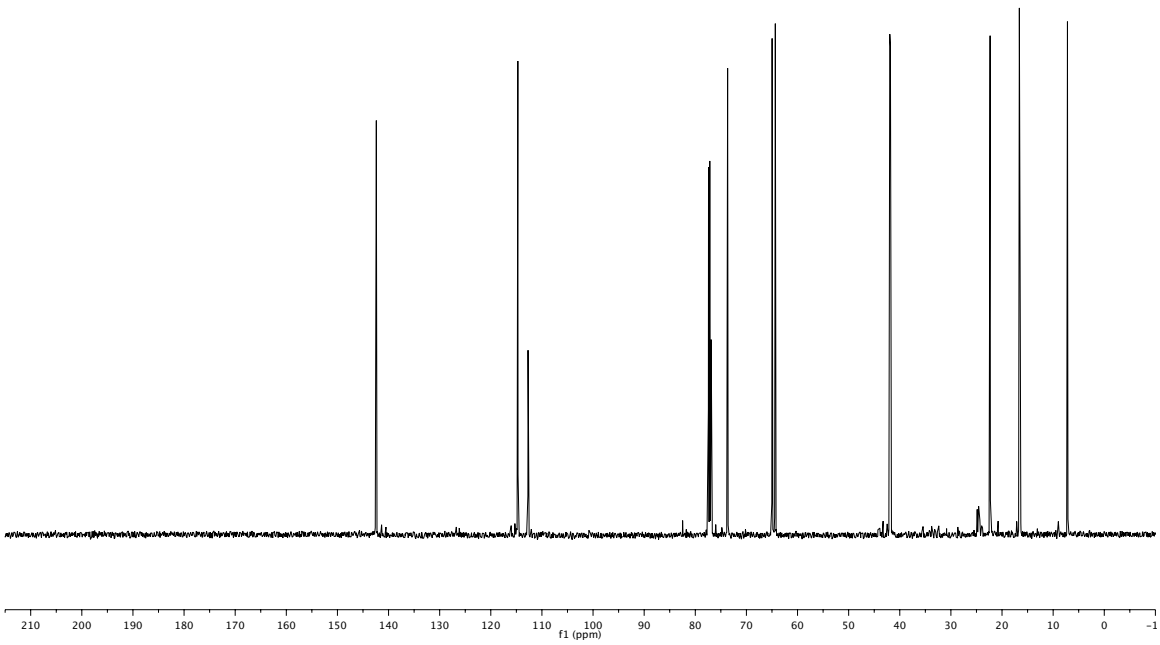


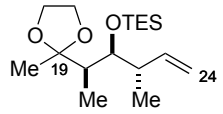
14

^{1}H NMR (500 MHz, $CDCl_3$)



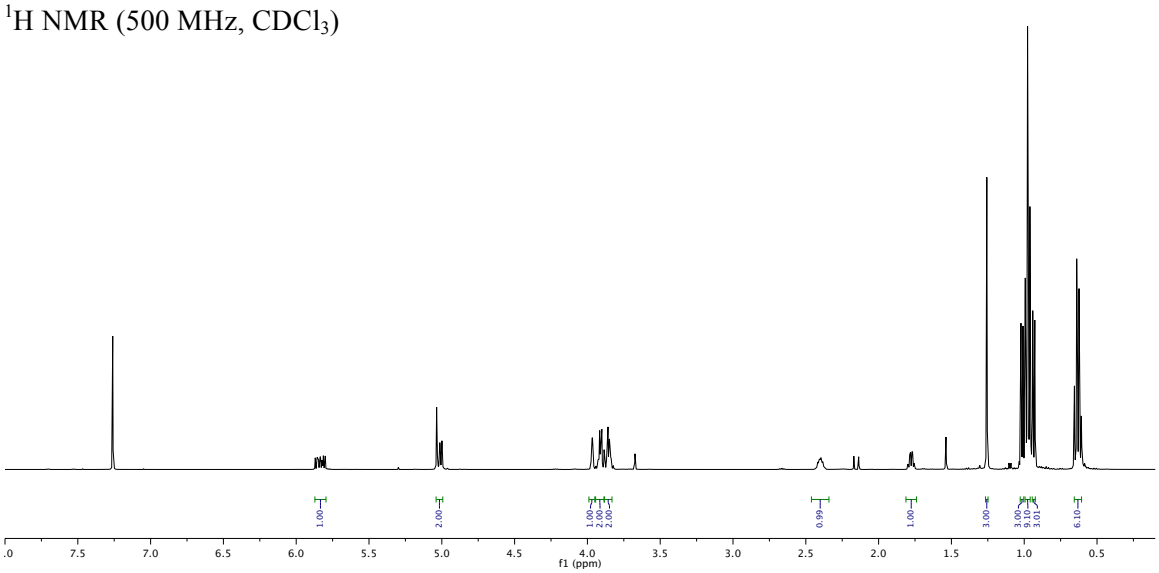
^{13}C NMR (125 MHz, $CDCl_3$)



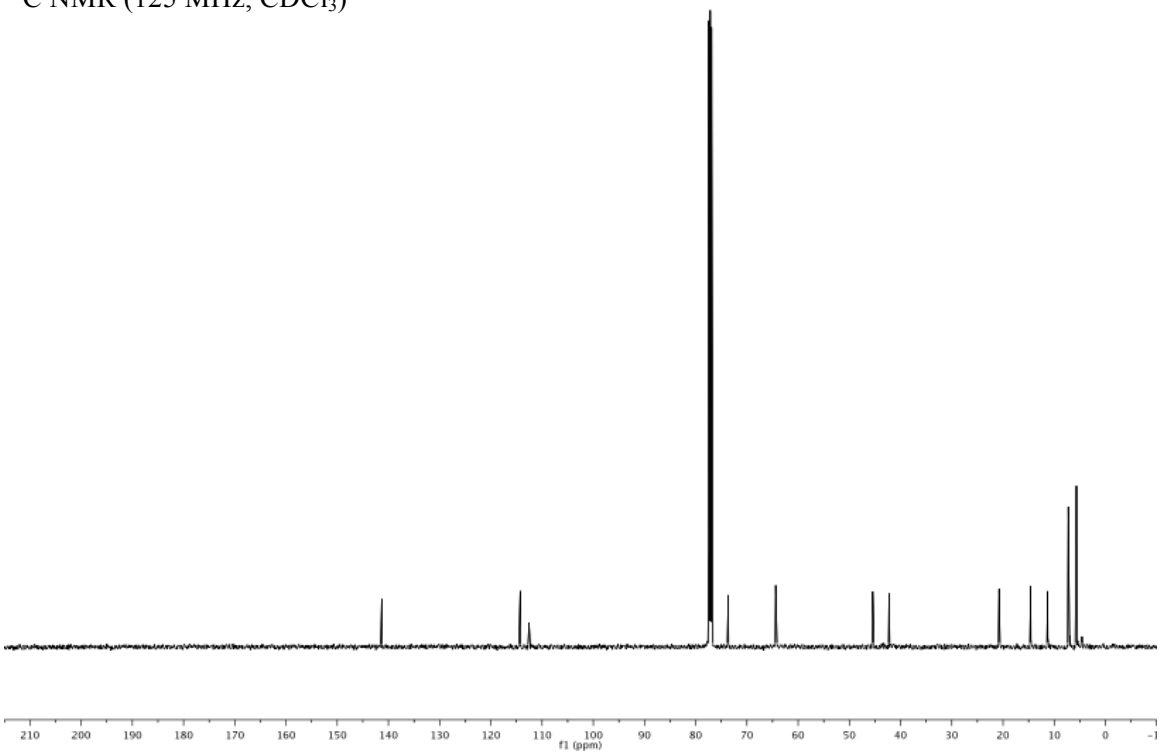


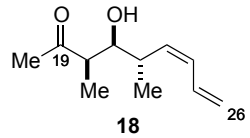
15

^{1}H NMR (500 MHz, $CDCl_3$)



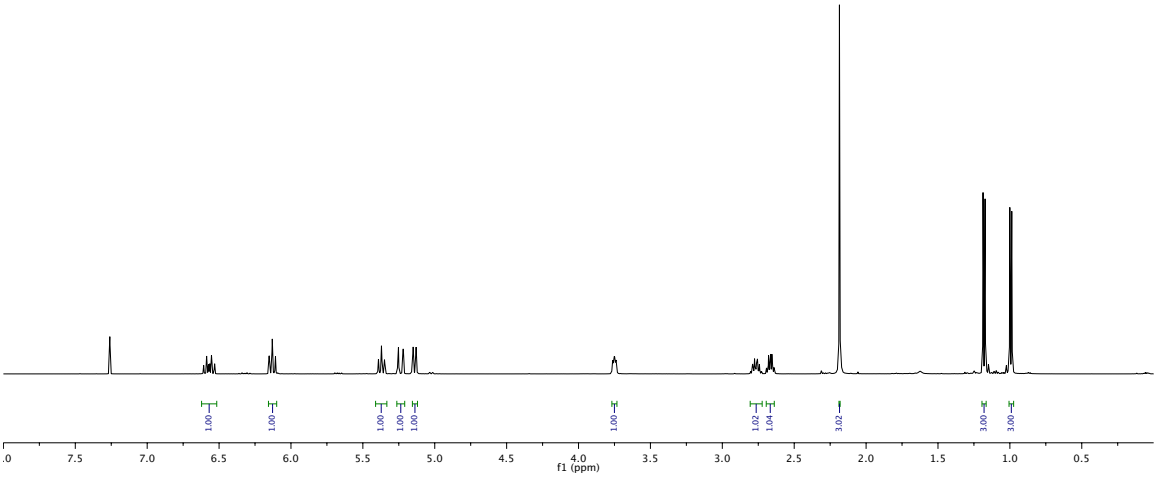
^{13}C NMR (125 MHz, $CDCl_3$)



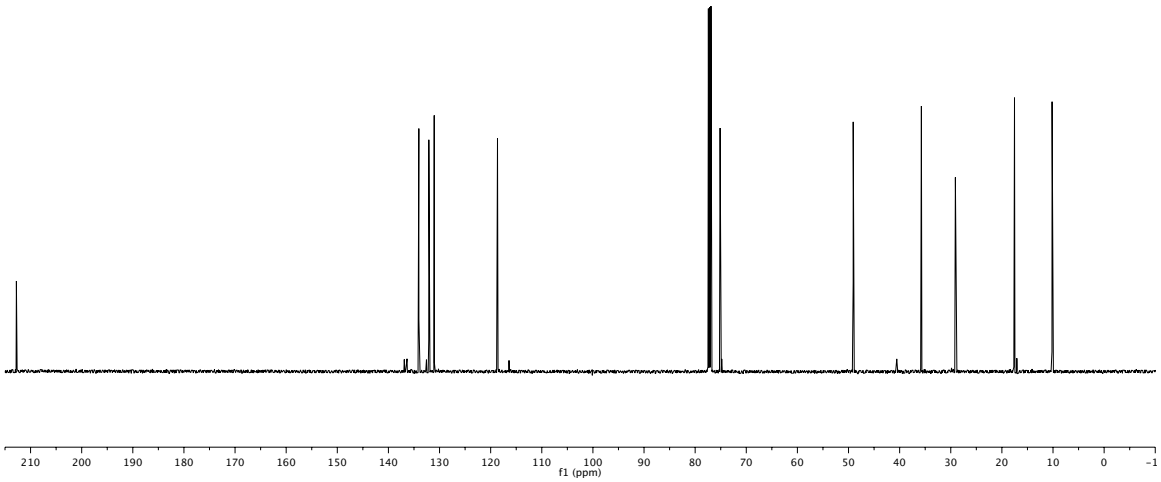


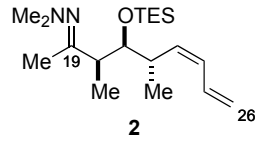
18

^{1}H NMR (500 MHz, $CDCl_3$)



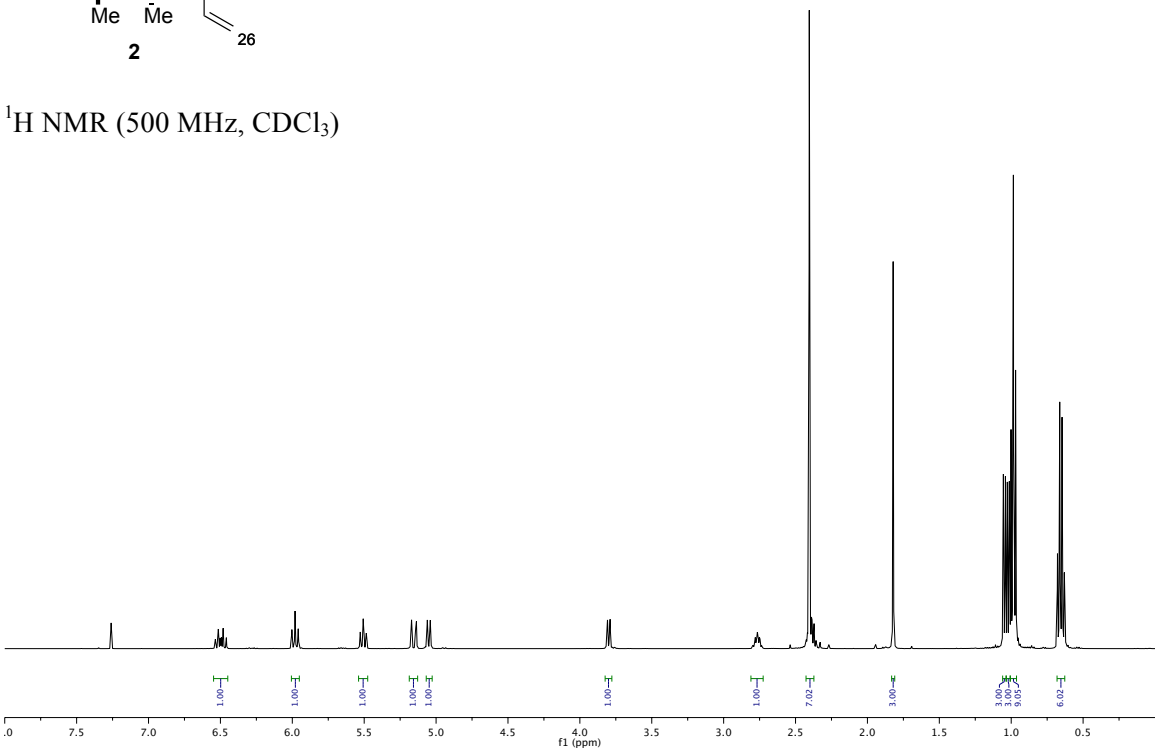
^{13}C NMR (125 MHz, $CDCl_3$)



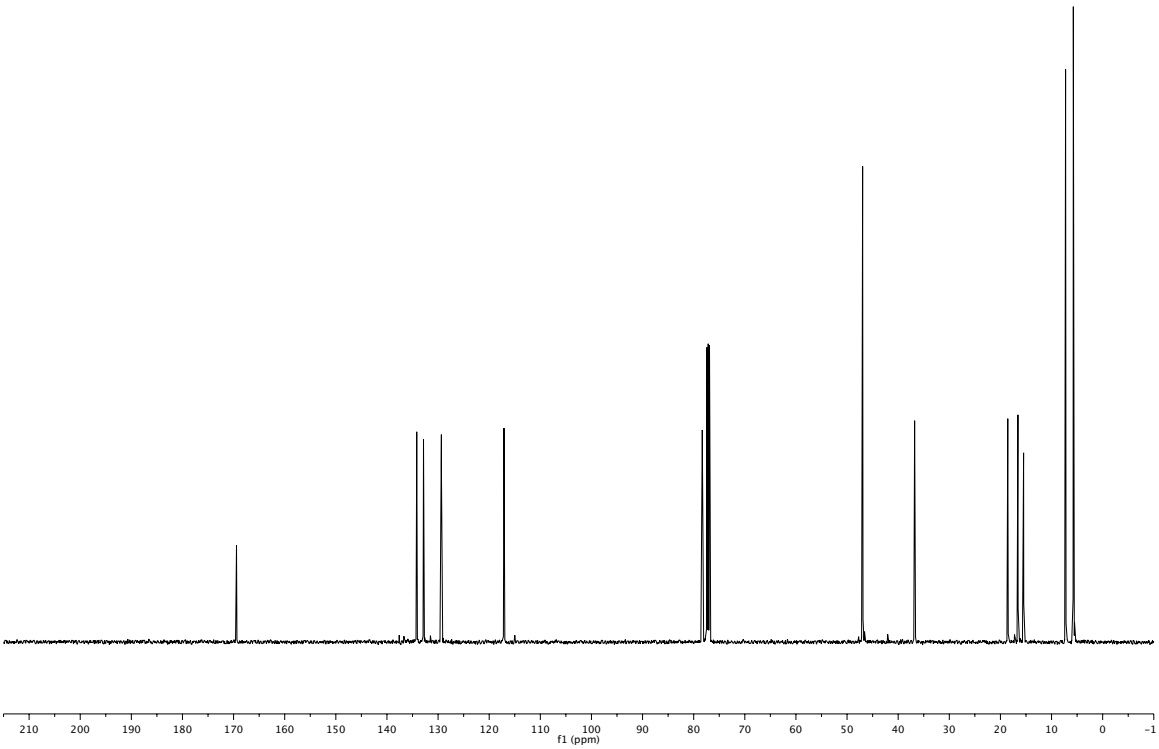


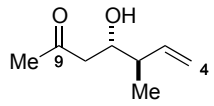
2

^{1}H NMR (500 MHz, $CDCl_3$)



^{13}C NMR (125 MHz, $CDCl_3$)

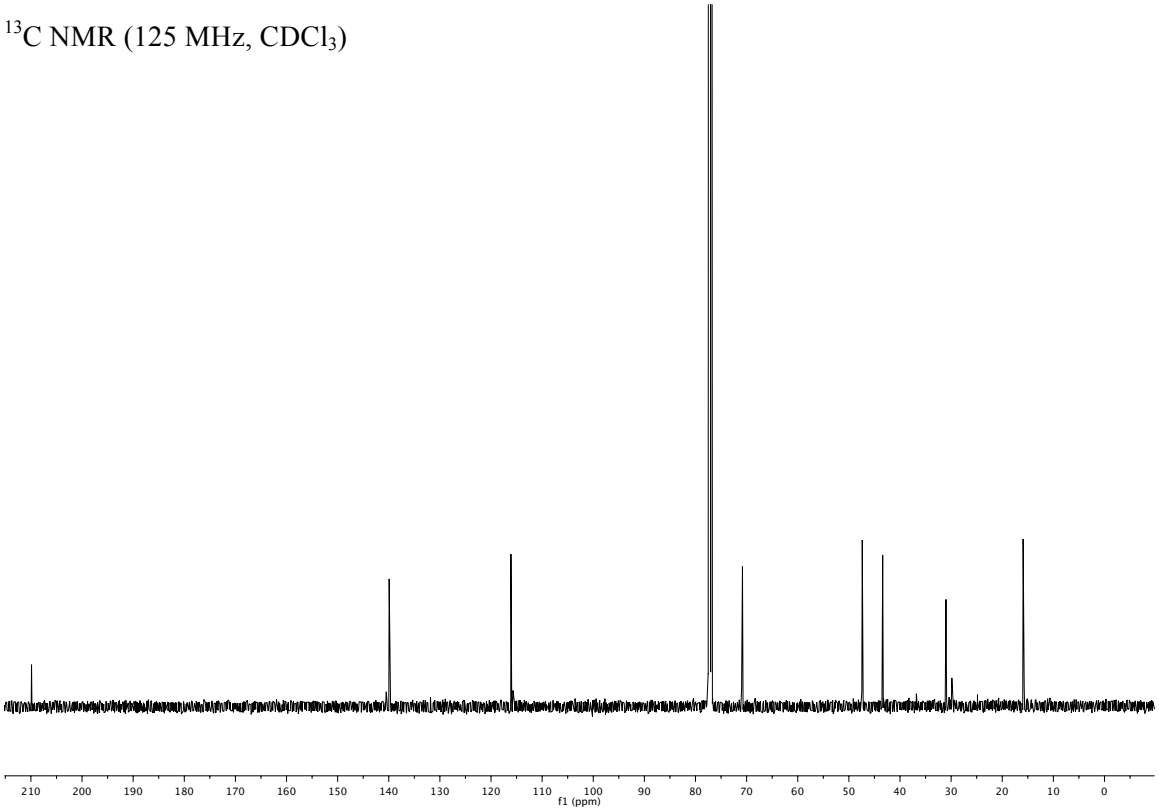


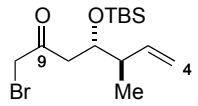


22

^{1}H NMR (400 MHz, $CDCl_3$)

^{13}C NMR (125 MHz, $CDCl_3$)

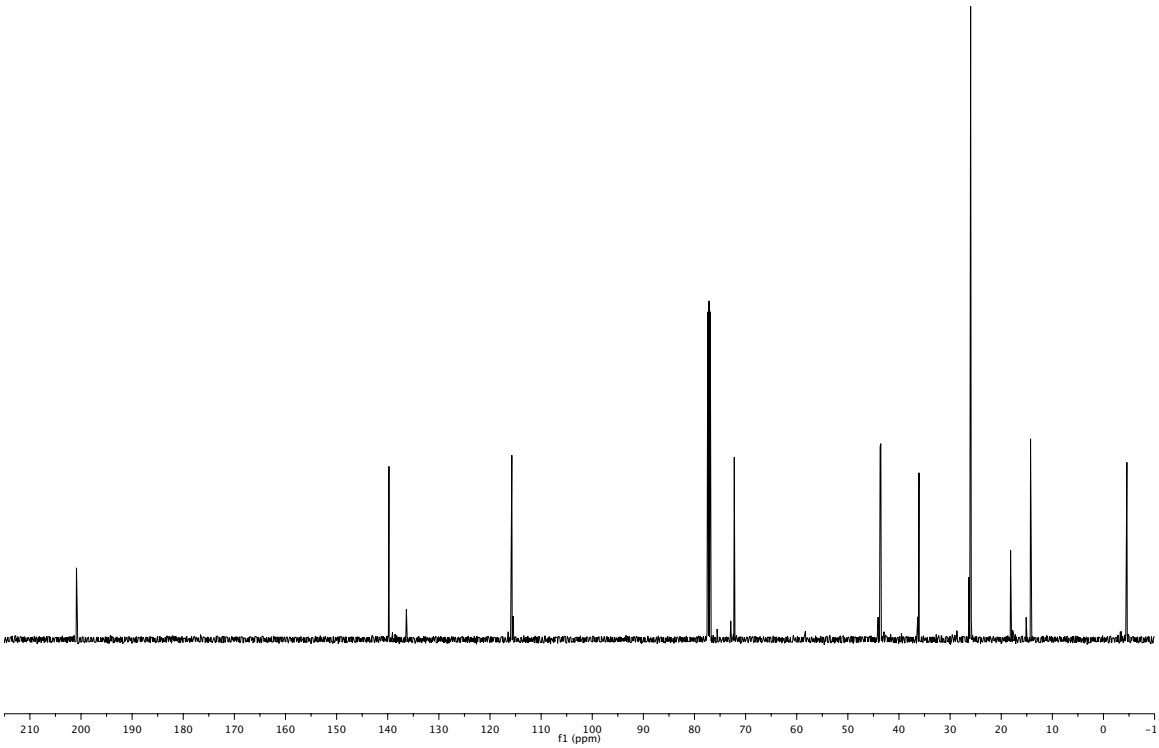


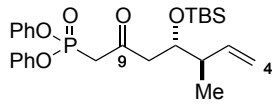


23

^{1}H NMR (500 MHz, $CDCl_3$)

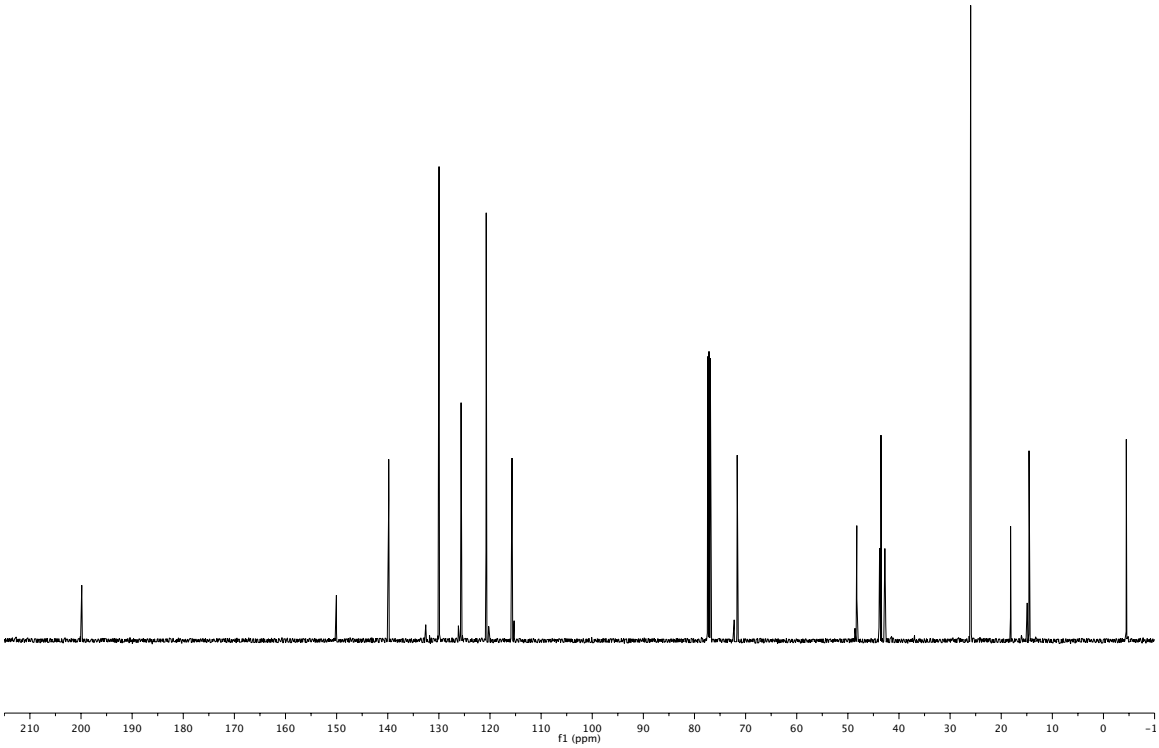
^{13}C NMR (125 MHz, $CDCl_3$)

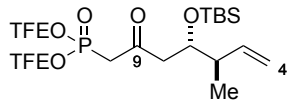




^{1}H NMR (500 MHz, $CDCl_3$)

^{13}C NMR (125 MHz, $CDCl_3$)

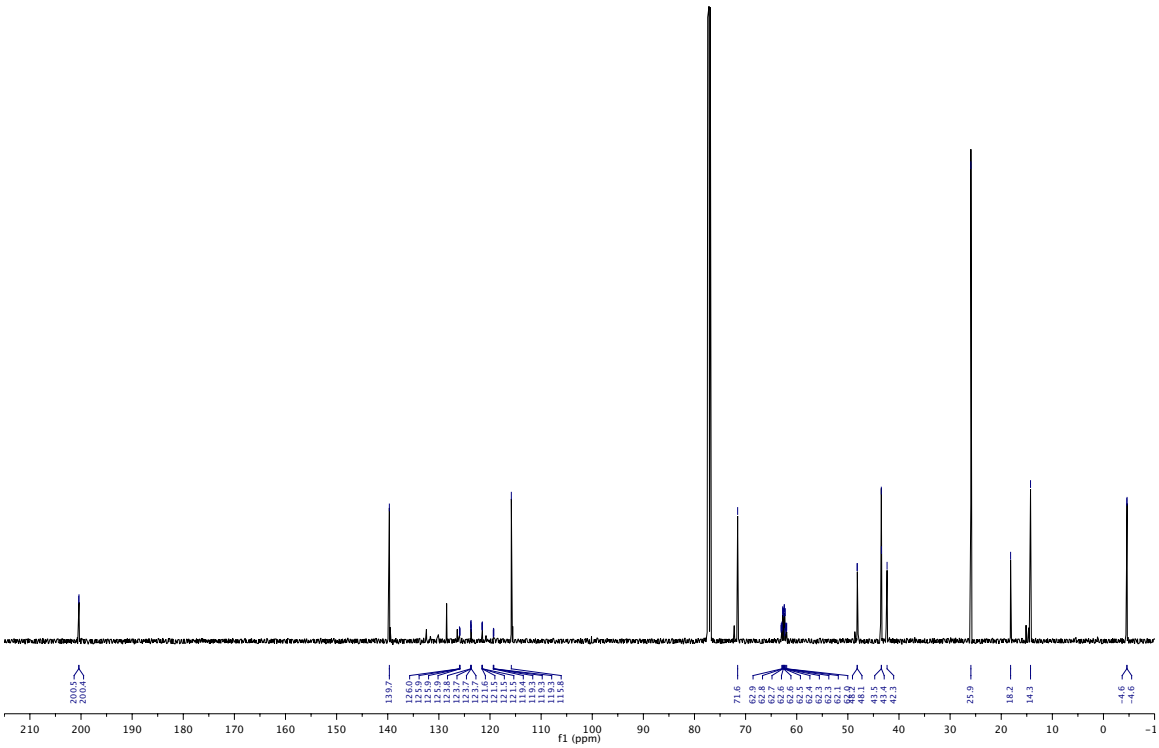


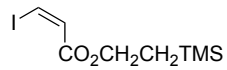


24

^{1}H NMR (500 MHz, $CDCl_3$)

^{13}C NMR (125 MHz, $CDCl_3$)

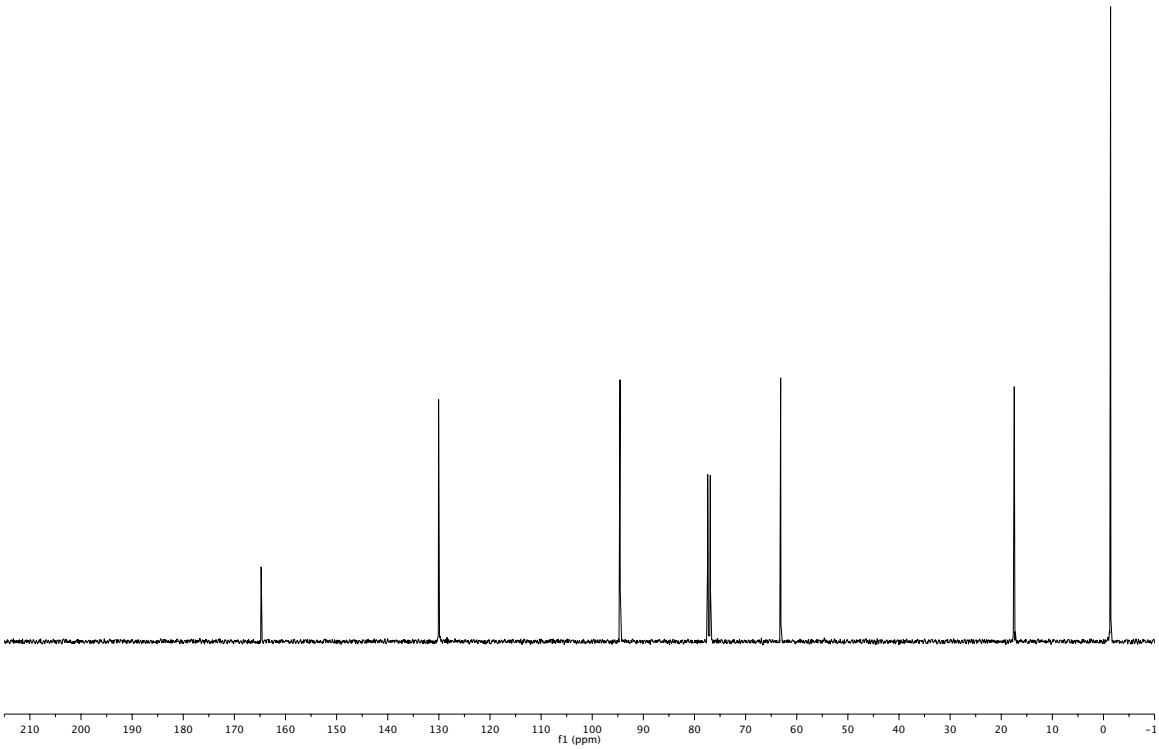


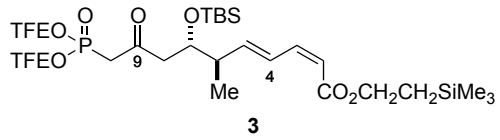


25

^{1}H NMR (500 MHz, $CDCl_3$)

^{13}C NMR (125 MHz, $CDCl_3$)

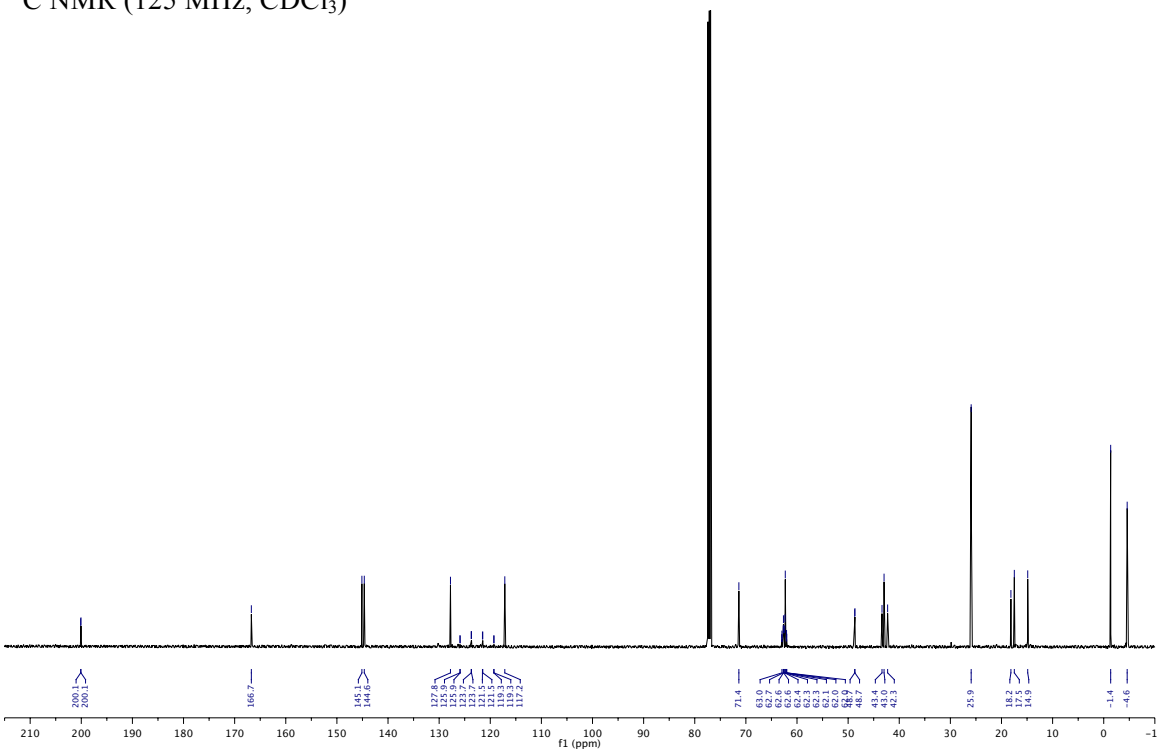


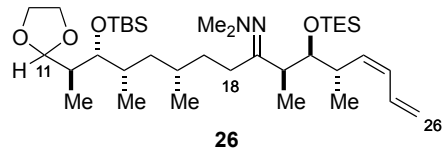


3

^{1}H NMR (500 MHz, $CDCl_3$)

^{13}C NMR (125 MHz, $CDCl_3$)

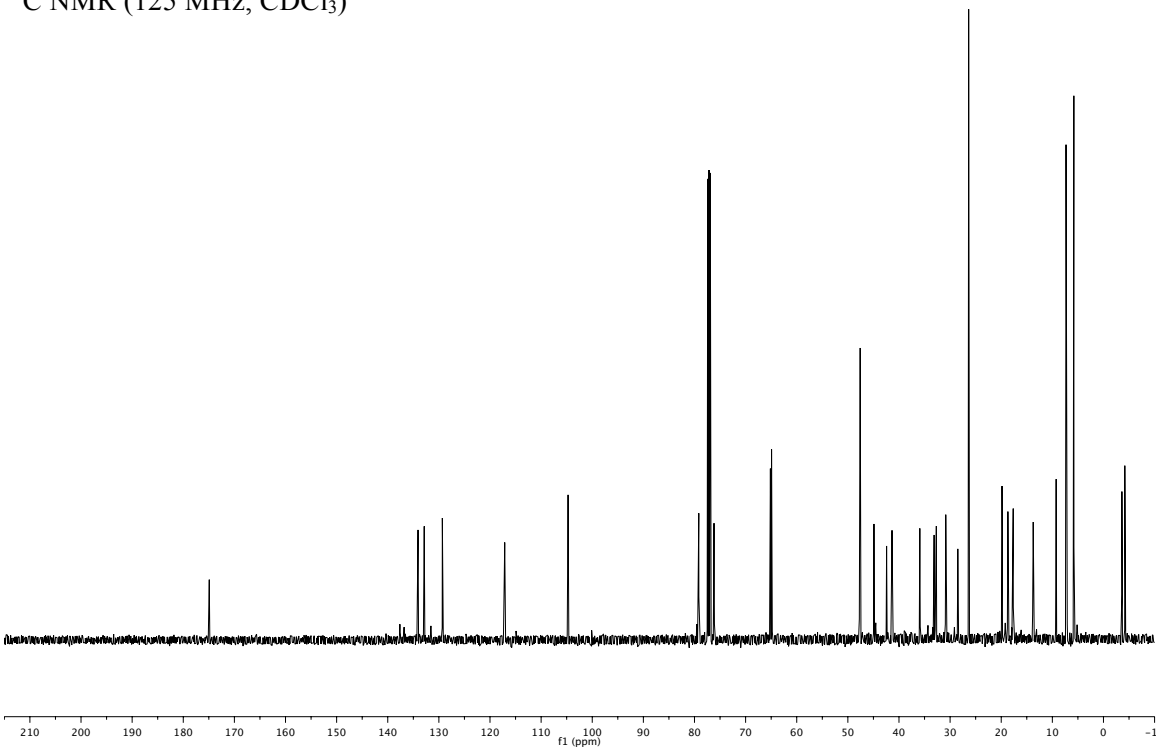


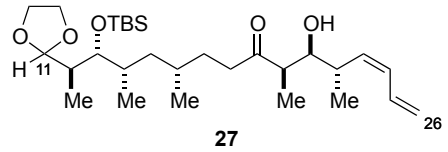


26

^{1}H NMR (500 MHz, $CDCl_3$)

^{13}C NMR (125 MHz, $CDCl_3$)

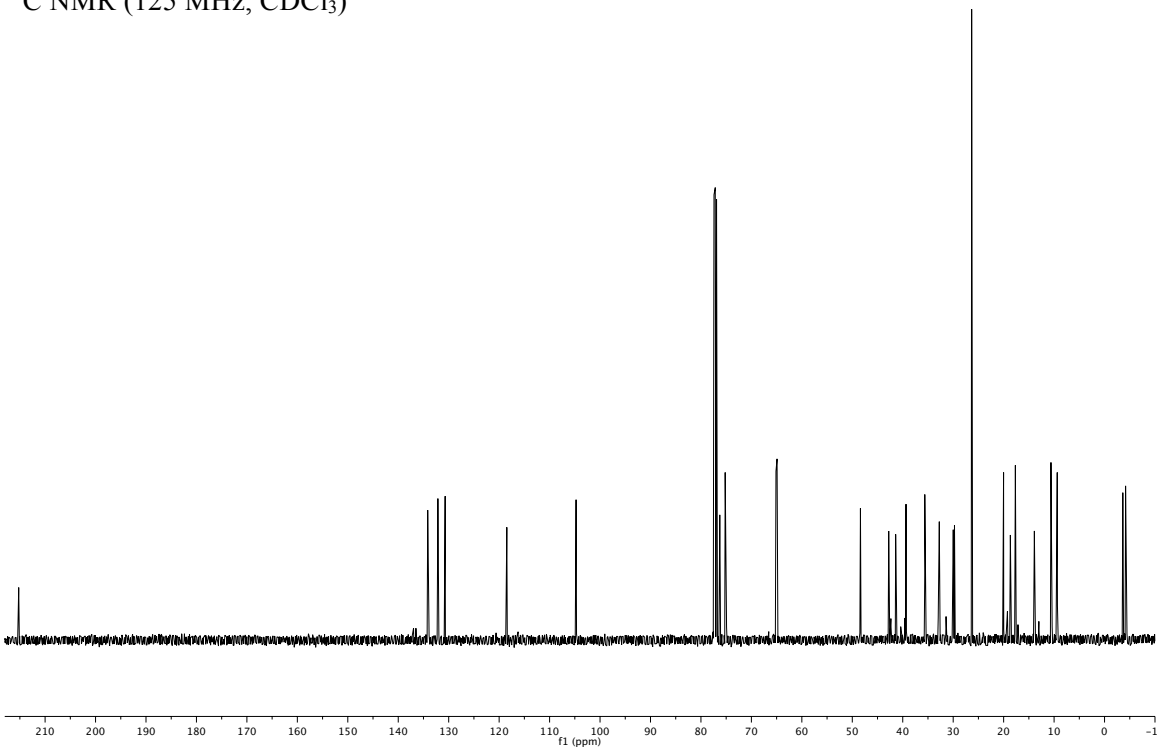


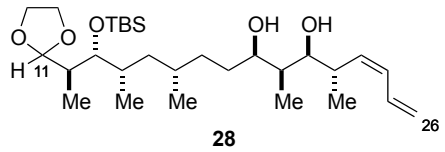


27

^{1}H NMR (500 MHz, $CDCl_3$)

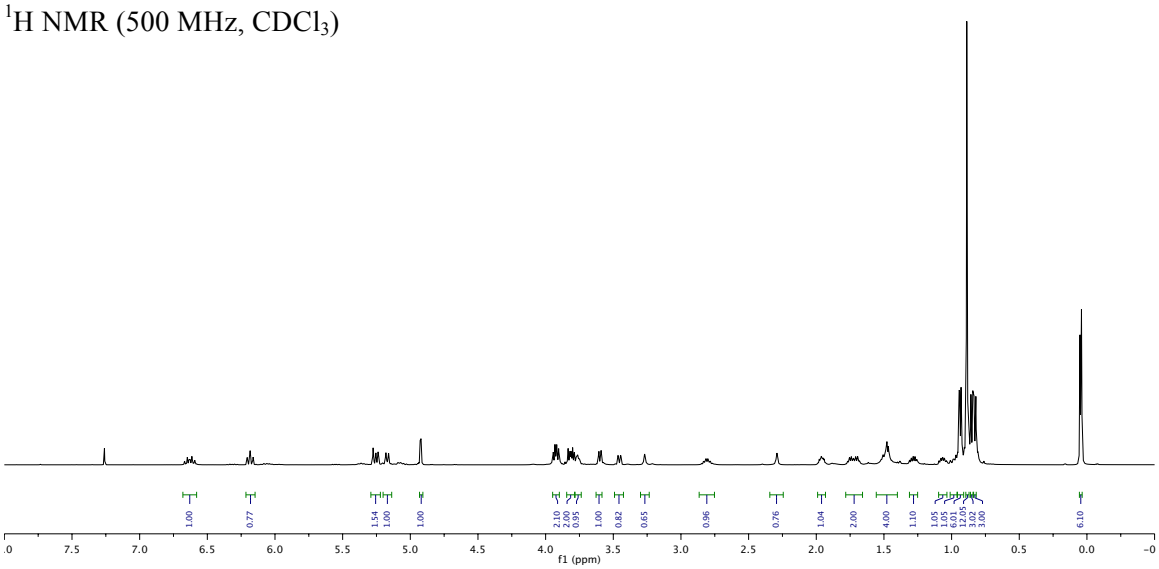
^{13}C NMR (125 MHz, $CDCl_3$)



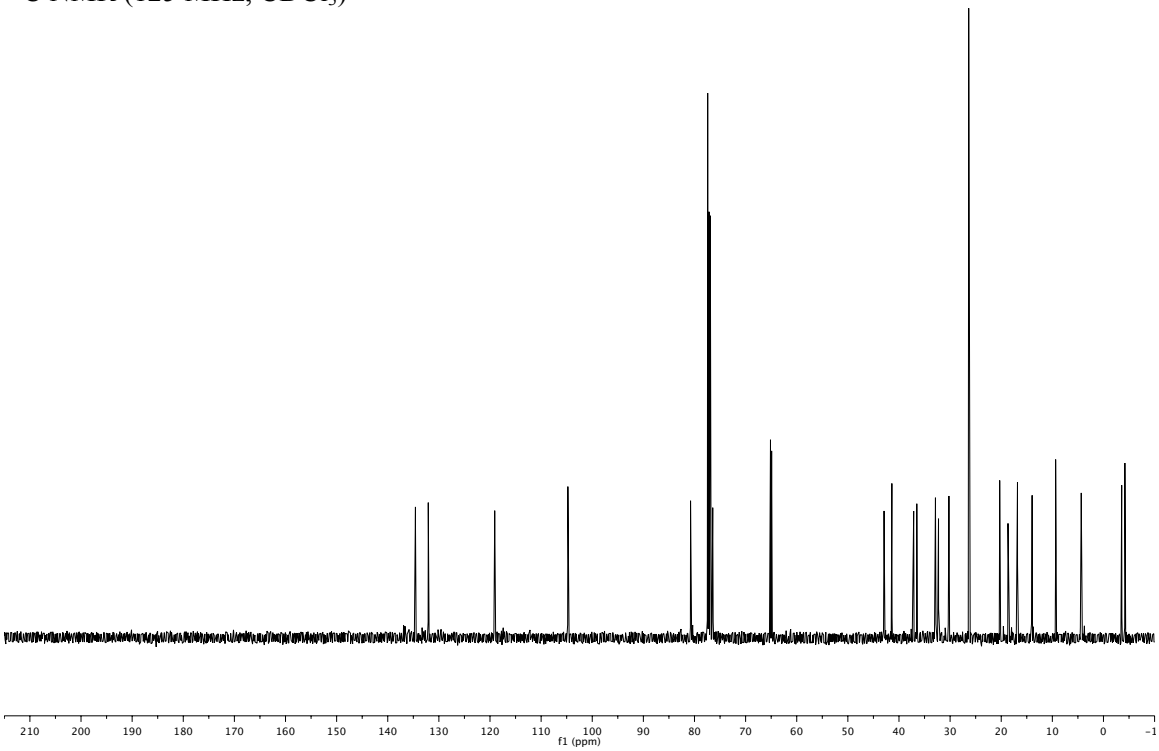


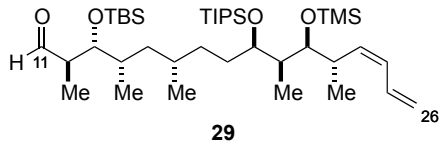
28

^{1}H NMR (500 MHz, $CDCl_3$)



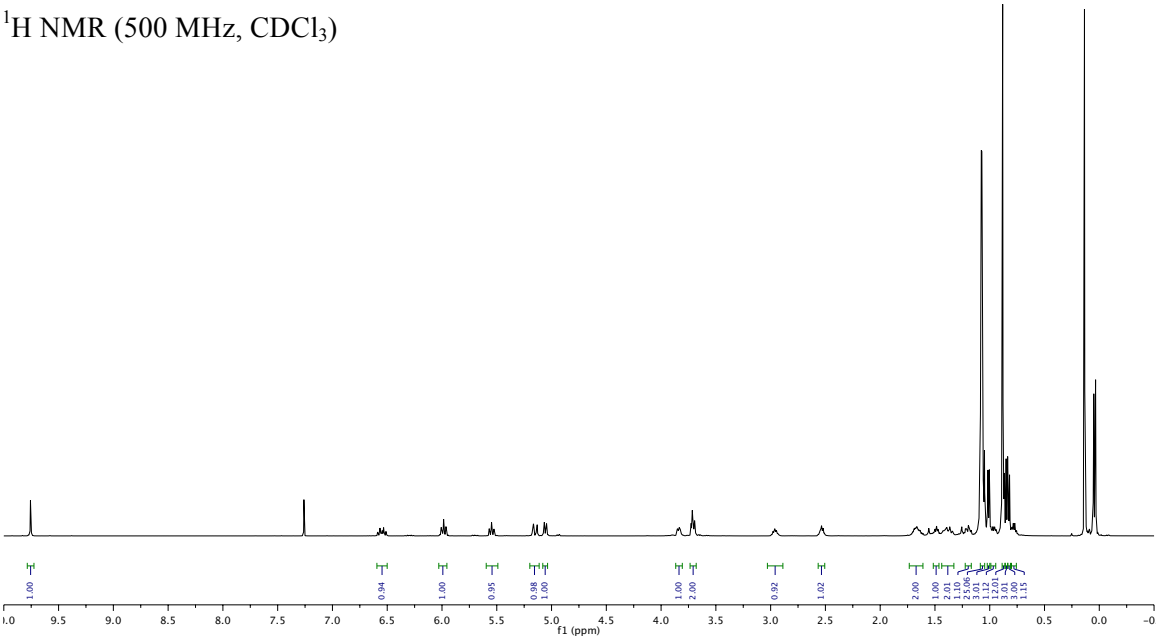
^{13}C NMR (125 MHz, $CDCl_3$)



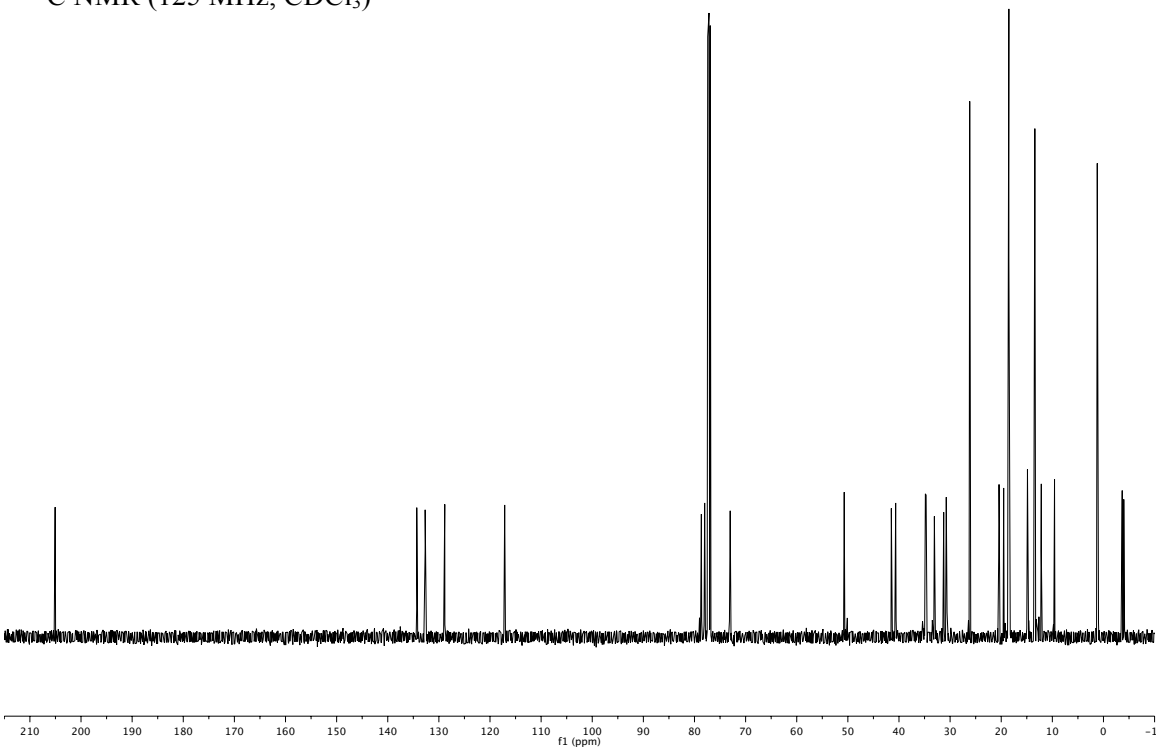


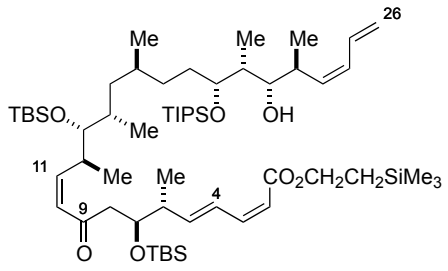
29

^{1}H NMR (500 MHz, $CDCl_3$)



^{13}C NMR (125 MHz, $CDCl_3$)

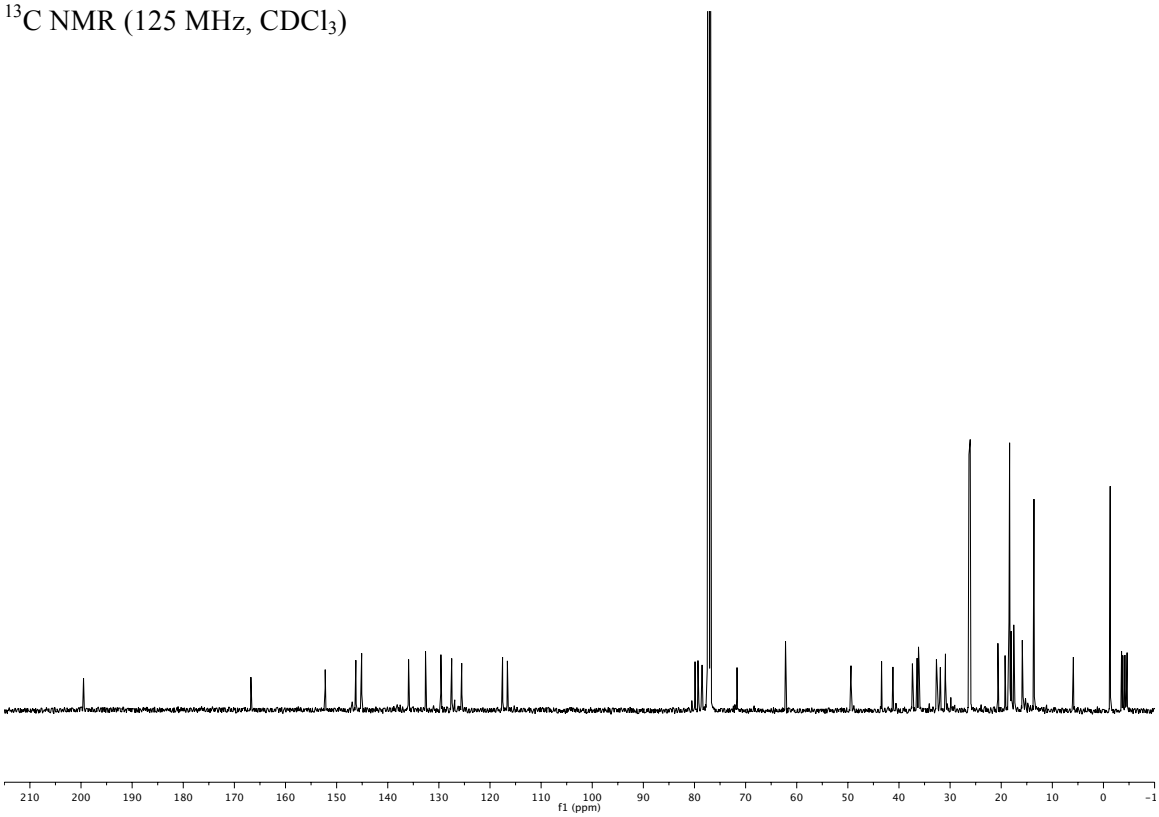


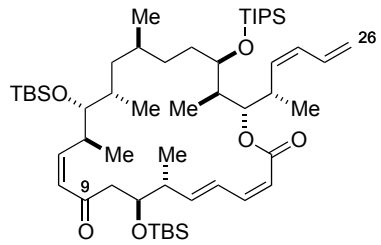


30

^{1}H NMR (500 MHz, $CDCl_3$)

^{13}C NMR (125 MHz, $CDCl_3$)

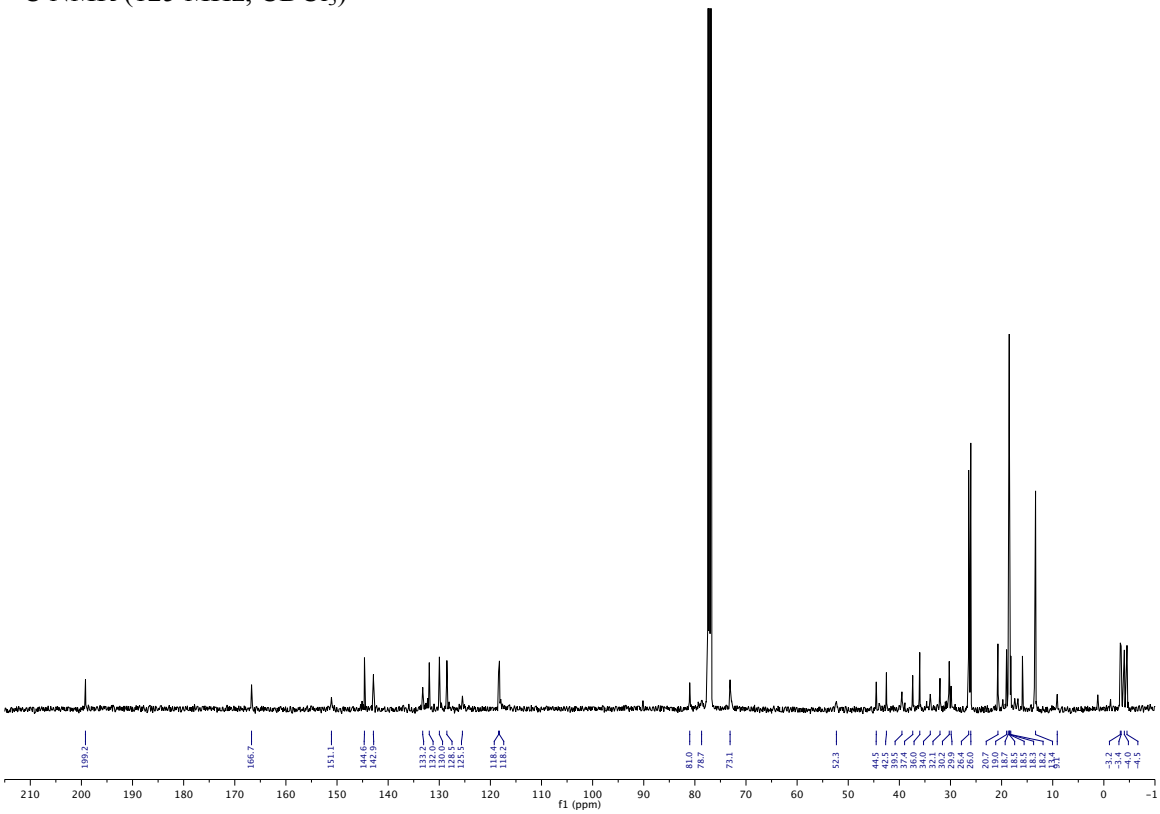


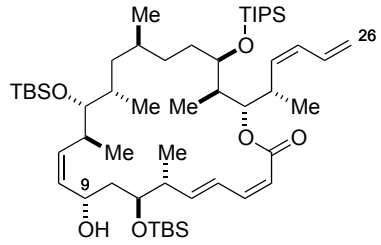


32

^{1}H NMR (500 MHz, $CDCl_3$)

^{13}C NMR (125 MHz, $CDCl_3$)

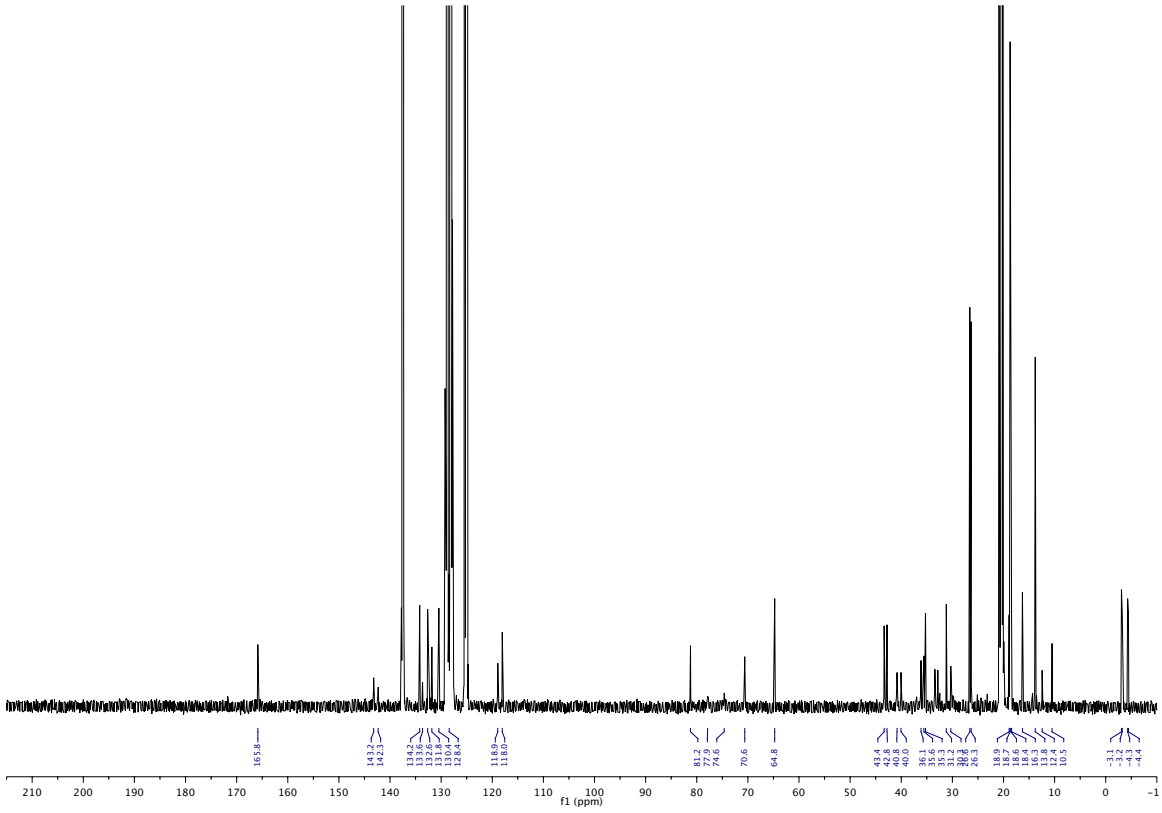


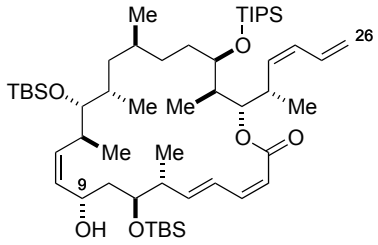


33

^{1}H NMR (500 MHz, $CDCl_3$, 315 K)

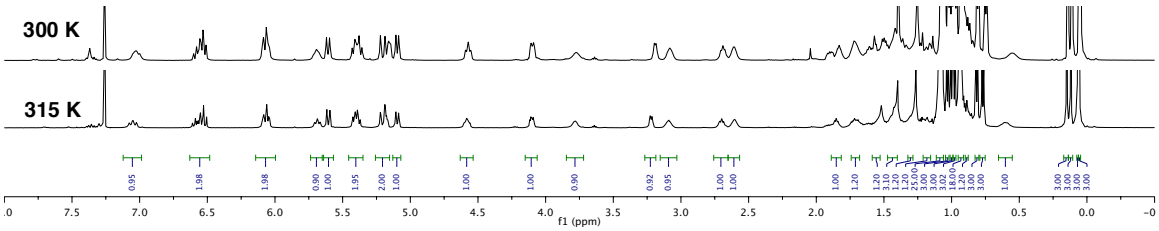
^{13}C NMR (125 MHz, Toluene-d_6, 333 K)



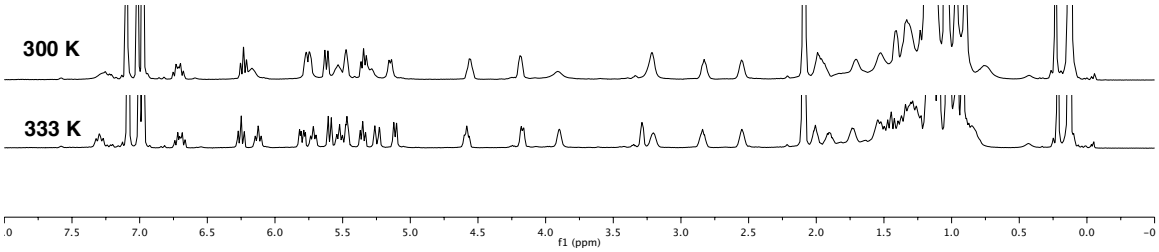


33

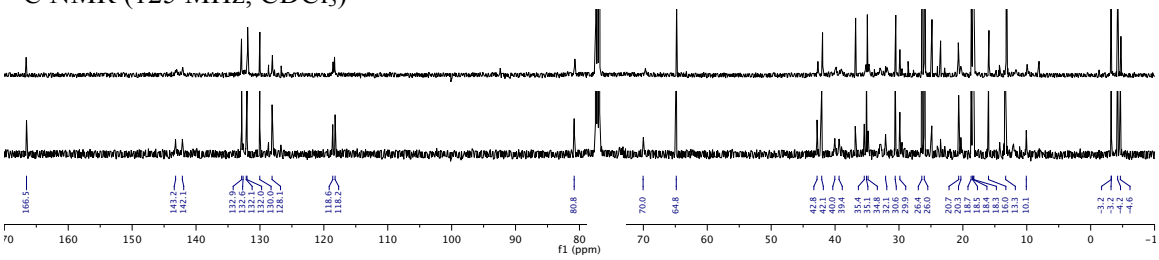
^{1}H NMR (500 MHz, $CDCl_3$)



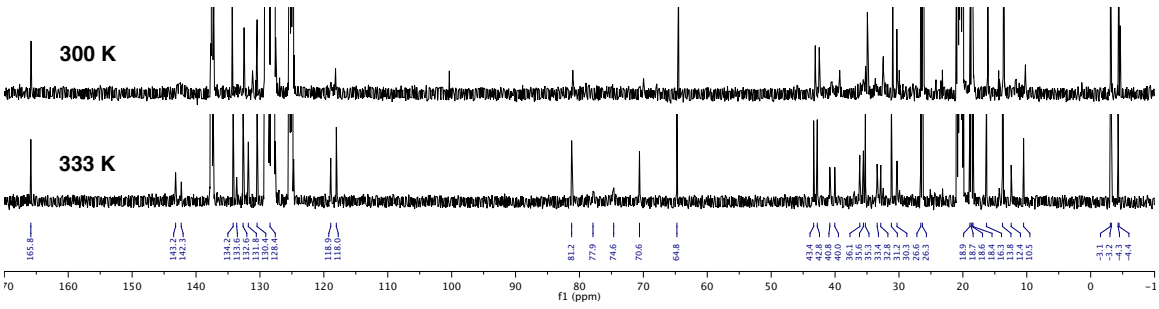
^{1}H NMR (500 MHz, Toluene-d_6)

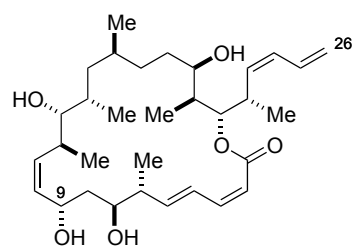


^{13}C NMR (125 MHz, $CDCl_3$)



^{13}C NMR (125 MHz, Toluene-d_6)

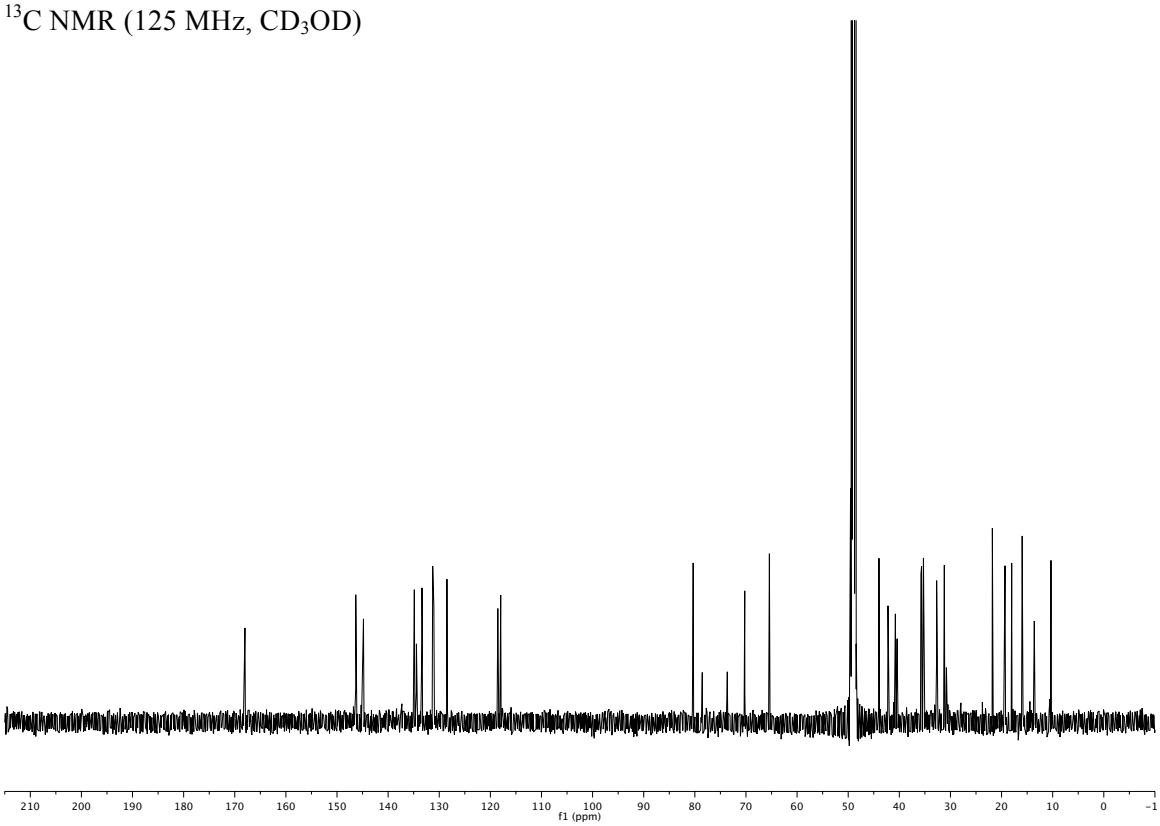




Dictyostatin

^{1}H NMR (500 MHz, CD_3OD)

^{13}C NMR (125 MHz, CD_3OD)



^{1}H and ^{13}C NMR spectra of Curran's synthetic Dictyostatin (see: *JACS* **2010**, *132*, 9175-9187)