A Concise, Phosphate-Mediated Approach to the Total Synthesis of (–)-Tetrahydrolipstatin

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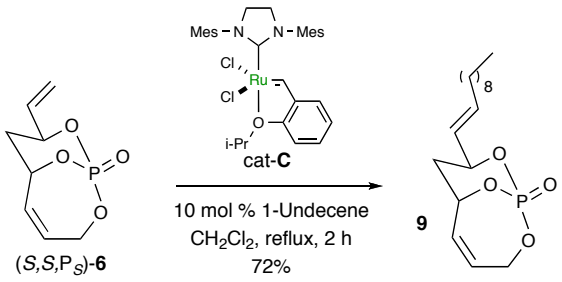
Experimental Section

General Methods. All reactions were carried out in oven- or flame-dried glassware under argon atmosphere using standard gas-tight syringes, cannulaes, and septa. Stirring was achieved with oven-dried magnetic stir bars. Et_2O, THF and CH_2Cl_2 were purified by passage through a purification system (Solv-Tek) employing activated Al_2O_3 (Grubbs, R. H.; Rosen. R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518-1520). Et_3N was purified by passage over basic alumina and stored over KOH. Butyl lithium was purchased from Aldrich and titrated prior to use. All olefin metathesis catalysts were acquired from Materia and used without further purification. Flash column chromatography was performed with Sorbent Technologies (30930M-25, Silica Gel 60A, 40-63 um) and thin layer chromatography was performed on silica gel $60F_{254}$ plates (EM-5717, Merck). Deuterated solvents were purchased from Cambridge Isotope laboratories. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ (unless otherwise mentioned) on a Bruker DRX-500 spectrometer operating at 500 MHz, and 125 MHz, respectively and calibrated to the solvent peak. ^{31}P NMR spectra was recorded on Bruker DRX-400 spectrometer operating at 162 MHz. High-resolution mass spectrometry (HRMS) was recorded on a LCT Premier Spectrometer (Micromass UK Limited) operating on ESI (MeOH). Observed rotations at 589 nm, were measured using AUTOPOL IV Model automatic polarimeter. IR was recorded on Shimadzu FTIR-8400S instrument.

(1*S*,6*S*,8*S*)-2,9,10-Trioxa-1-phosphabicyclo[4.3.1]dec-4-ene, 8-[(1*E*)- undecen-1-yl]-1-oxide (9).



To a stirring solution of Hoveyda-Grubbs 2nd G catalyst (cat-**C**) 0.4 g, 0.64 mmol) in degassed (15 min) CH_2Cl_2 (65 mL) was sequentially added bicyclic phosphate (*S*,*S*,P_S)-**6** (1.3 g, 6.43 mmol) and 1-undecene (1.5 mL, 7.1 mmol). The combined mixture was refluxed for 2 h with continuous argon flow. After reaction completion as monitored by TLC, the reaction mixture was concentrated under reduced pressure. Purification by flash column chromatography (1:1 Hexane/EtOAc) afforded 1.52 g of desired product **9** (72%) as a gray-colored solid.

R_f = 0.2 (1:3 Hexane/EtOAc);

M.P: 58-60 ºC;

FTIR (thin film): 3053, 2985, 2927, 1298, 1265 cm^{-1};

Optical Rotation: $[\alpha]_D$ = +81.84 (*c* = 1.25, CH_2Cl_2);

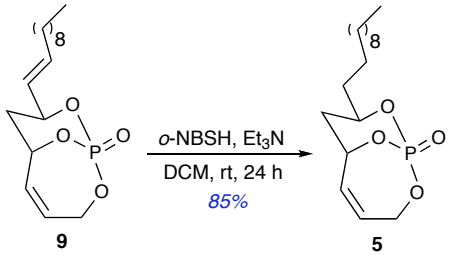
^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 6.04 (dddd, *J* = 11.8, 6.6, 3.0, 2.3 Hz, 1H), 5.83 (dt, *J* = 14.3, 6.9 Hz, 1H), 5.61 (ddd, *J* = 11.8, 3.8, 2.6 Hz, 1H), 5.49 (ddd, *J* = 15.4, 6.7, 1.1 Hz, 1H), 5.18 (br.d, J_{PH} = 24.5 Hz, 1H), 5.03-4.95 (m, 2H), 4.37 (ddd, *J* = 27.7, 14.7, 6.7, 1H), 2.24 (ddd, *J* = 14.7, 12.0, 6.2 Hz, 1H), 2.04 (q, *J* = 7.1 Hz, 2H), 1.75 (ddd, *J* = 14.7, 3.4, 2.3 Hz, 1H), 1.39-1.32 (m, 2H), 1.25 (br.s, 12H), 0.87 (t, *J* = 6.9 , 3H);

^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 135.5, 129.7, 127.9, 126.6 (d, J_{CP} = 10.1 Hz), 76.9 (d, J_{CP} = 6.4 Hz), 76.8 (d, J_{CP} = 6.4 Hz), 62.9 (d, J_{CP} = 6.4 Hz), 35.3 (d, J_{CP} = 5.7 Hz), 32.0, 31.8, 29.4, 29.5, 29.2, 29.0, 28.6, 22.6, 14.0;

^{31}P NMR (162 MHz, $CDCl_3$) δ (ppm) -3.55;

HRMS cald for $C_{17}H_{29}O_4PNa$ $(M+Na)^+$ 351.1701; found 351.1712 (TOF MS ES+).

(1*S*,6*S*,8*S*)-2,9,10-Trioxa-1-phosphabicyclo[4.3.1]dec-4-ene, 8-[undecan-1-yl]-1-oxide (5).



To a stirring solution of bicyclic phosphate **9** (700 mg, 2.13 mmol) in CH_2Cl_2 (27 mL) at room temperature was added *o*-nitro benzene sulfonyl hydrazine (*o*-NBSH) (5.30 g, 21.3 mmol) followed by Et_3N (10.6 mL, 2 mL/g of *o*-NBSH) producing an orange color reaction mixture. After stirring overnight, *o*-nitro benzene sulfonyl hydrazine (2.65 g, 10.65 mmol) and Et_3N (5.3 mL, 2 mL/g of *o*-NBSH) were added again and stirring was continued for an additional 12 h. The reaction was diluted with EtOAc (20 mL), extracted with sat. aq. $NaHCO_3$ (15 mL) followed by washing with EtOAc (2 x 25 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. Purification by flash column chromatography (1:1 hexane/EtOAc) afforded 597 mg of desired product **5** (85% yield) as a yellow colored solid. (**Note**: The reaction flask was wrapped with aluminum foil to avoid decomposition of *o*-NBSH due to light)

R_f = 0.2 (1:3 Hexane/EtOAc);

M.P: 85-86 ºC;

FTIR (thin film) 3053, 2985, 2927, 1298, 1265 cm^{-1};

Optical Rotation: $[\alpha]_D$ = +59.28 (*c* = 1.12, $CHCl_3$);

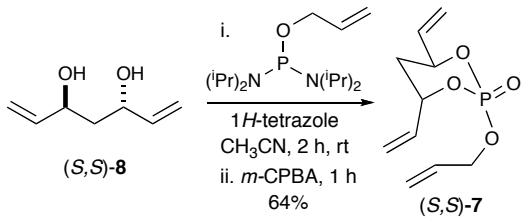
^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 6.02 (dddd, *J* = 11.9, 6.7, 3.1, 2.2 Hz, 1H), 5.58 (ddd, *J* = 11.9, 3.9, 2.5 Hz, 1H), 5.17 (br.d, J_{PH} = 24.5 Hz, 1H), 4.98 (dddd, *J* = 11.3, 8.3, 5.7, 2.7 Hz, 1H), 4.58-4.52 (m, 1H), 4.35 (ddd, *J* = 27.4, 14.8, 6.7 Hz, 1H), 2.16 (ddd, *J* = 14.6, 11.9, 6.3 Hz, 1H), 1.77-1.68 (m, 1H), 1.60-1.42 (m, 2H), 1.40-1.16 (br.s, 18H), 0.87 (t, *J* = 6.8 Hz, 3H);

^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 129.9, 127.8, 77.2 (d, J_{CP} = 6.9 Hz), 76.7 (d, J_{CP} = 6.9 Hz), 62.9 (d, J_{CP} = 6.3 Hz), 35.6 (d, J_{CP} = 9.2 Hz), 34.8 (d, J_{CP} = 5.9 Hz), 31.8, 29.6, 29.5, 29.4, 29.3, 29.2, 29.1, 24.5, 22.6, 14.0.;

^{31}P NMR (162 MHz, $CDCl_3$) δ (ppm) -2.97;

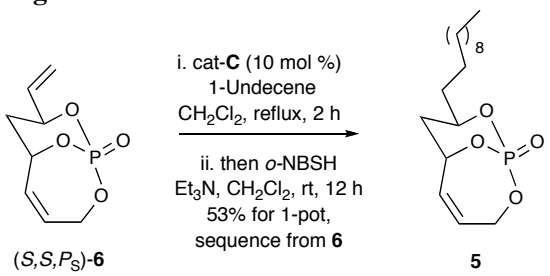
HRMS: cald for $C_{17}H_{31}O_4PNa$ $(M+Na)^+$ 353.1858; found 353.1854 (TOF MS ES+).

(4*S*,6*S*)-1,3,2-Dioxaphosphorinane, 4,6-diethenyl-2-(2-propen-1-yloxy)-2-oxide (7).



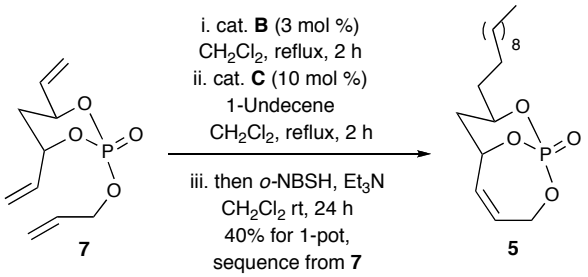
To a stirring solution of allyloxy tetraisopropylphosphorodiamidite (675 mg, 2.34 mmol) in CH_3CN (20 mL) under argon was added 1*H*-tetrazole (274 mg, 3.9 mmol) at RT producing a white cloudy reaction mixture. (*S,S)*-Diene-diol **8** (250 mg, 1.95 mmol) was added to above reaction mixture at RT and the white cloudy reaction mixture was stirred for 2 h. After consumption of starting material, oxidant *m*-CPBA (437 mg, 1.95 mmol) was added and stirring was continued for an additional 1 h. The reaction mixture was diluted with Et_2O (50 mL), quenched with 10% $NaHSO_3$ (20 mL) and the layers were separated. The organic layer was washed with 10% $NaHSO_3$ (2 x 15 mL), dried (Na_2SO_4) and concentrated under reduced pressure. Purification by flash column chromatography (2:1 hexane/EtOAc) afforded 260 mg of desired triene **7** (64%) as a colorless viscous oil.

One-pot sequential CM/Hydrogenation to 5:



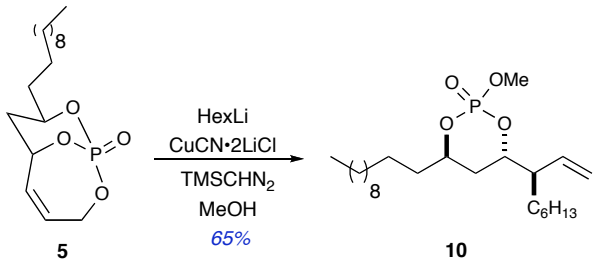
To a stirring solution of Hoveyda-Grubbs 2nd Gen. catalyst (cat. **C**) (15.5 mg, 0.0247mmol) in degassed CH_2Cl_2 (2.6 mL) was added phosphate **6** (50 mg, 0.247 mmol) followed by 1-undecene (56 μL, 0.272 mmol). The combined reaction mixture was refluxed for 2 h with continuous argon flow. After the completion of cross-metathesis, the reaction mixture was cooled to room temperature and diluted with CH_2Cl_2 (1 mL), followed by addition of *o*-NBSH (614mg, 2.46 mmol), and Et_3N (1.23 mL, 2 mL/g of *o*-NBSH) . The resulting yellow colored slurry was stirred for 12 h at room temperature. Additional *o*-NBSH (206 mg, 1.23 mmol) and Et_3N (0.6 mL, 2 mL/g of *o*-NBSH) were added and stirring was continued for another 12 h. The reaction mixture was diluted with EtOAc (10 mL), extracted with sat. $NaHCO_3$ (2 x 2 mL). The combined aqueous layers were washed with EtOAc (2 x 5 mL) and the combined organic layers were dried (Na_2SO_4) followed by concentration under reduced pressure. Further purification by flash column chromatography (1:1 Hexane/EtOAc) afforded 43 mg (53%) of desired phosphate **5** as a yellow-colored solid over two-steps.

One-pot sequential RCM/CM/Hydrogenation to 5:



To a stirring solution of triene **7** (68 mg, 0.296 mmol) in degassed CH_2Cl_2 (20 mL) was added Grubbs 2nd Gen. catalyst (cat-**B**) (8 mg, 0.0088 mmol). The reaction mixture was refluxed for 2.0 h with continuous argon flow. After the completion of RCM, excess CH_2Cl_2 was removed with continuous argon sparging to adjust the concentration. Hoveyda-Grubbs 2nd Gen catalyst (cat. **C**) (18 mg, 0.029 mmol) was added to the reaction mixture, followed by 1-undecene (50 mg, 0.32 mmol) and the mixture was refluxed for 2 h. TLC after 2 h showed product formation (phosphate **8**) with slight SM (phosphate **5**) still remaining. The reaction mixture was cooled to RT and *o*-NBSH (730 mg, 2.953 mmol), Et_3N (1.47 mL, 2 mL/g of *o*-NBSH) were added and stirring was continued for another 12 h. After overnight stirring, excess *o*-NBSH (365 mg, 1.47 mmol) and Et_3N (0.73 mL, 2 mL/g of *o*-NBSH) were added and stirring was continued for an additional 12 h. The reaction mixture was diluted with EtOAc (15 mL) and extracted with sat. $NaHCO_3$ (5 mL). The aqueous layer was washed with EtOAc (2 x 5 mL) and the combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. Purification by flash column chromatography (1:1 Hexane/EtOAc) afforded 38 mg of the desired phosphate **5** in 40% yield over 3 steps (Also 7 mg of hydrogenated product of the unreacted phosphate **6** during cross metathesis was obtained).

(4R,6S)-1,3,2-Dioxaphosphorinane, 2-methoxy-4-[1-undecan]-6-[(1R)-1-methyl-2-propen-1-yl]-2-oxide (10).



To a flask with CuCN (368 mg, 4.1 mmol) and LiCl (349 mg, 8.2 mmol), transferred in glove box, was added THF (7.8 mL) under argon and the reaction was stirred for 20 min at rt. The reaction mixture was then cooled to -78 ºC and *n*-hexyllithium (1.79 mL, 2.3 M soln in hexane, 4.1 mmol) was added dropwise producing a slightly yellow colored reaction mixture. To the combined mixture was added phosphate **5** (680 mg, 2.05 mmol, dissolved in 2 mL THF) *via* cannula at -78 ºC upon which time the reaction turned from yellow to a dark green color. The dry ice bath was removed and stirring was continued for additional 1 h at rt (consumption of starting material was monitored by TLC). The reaction mixture was then cooled to 0 ºC and quenched with 10% HCl (2 mL) followed by H_2O (4 mL) resulting in the formation of pepper-colored salts. The ice bath was removed and the reaction mixture was filtered thru Celite® with additional washing with EtOAc. The resulting crude was quenched again with addition 10% HCl (2 mL) and the layers were separated. The aqueous layer was washed with EtOAc (2 x 50 mL) and

the combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The resulting crude oil was then diluted with MeOH (10 mL), followed by slow addition of $TMSCHN_2$ (8 mL, added excess). During the addition, a black-colored precipitate was formed. After complete addition of $TMSCHN_2$, a few drops of glacial acetic acid were added to quench the excess $TMSCHN_2$. The resulting mixture was dried (Na_2SO_4), filtered with MeOH and concentrated under reduced pressure. Further purification by flash column chromatography (4:1 Hexane/EtOAc) produced 576 mg of the desired compound **10** as a viscous colorless oil in 65% yield.

R_f = 0.23 (4:1 Hexane/EtOAc);

FTIR (neat) 3018, 2927, 2956, 2854, 1274, 1215, 742 cm^{-1};

Optical Rotation: $[\alpha]_D$ = +14.9 (*c* = 2.04, $CHCl_3$);

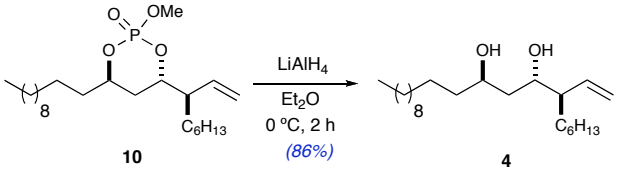
^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 5.73-5.60 (m, 1H), 5.17 (ddd, *J* = 10.2, 4.1, 1.8 Hz, 1H), 5.06 (dt, *J* = 17.2, 1.8 Hz, 1H), 4.55-4.35 (m, 2H), 3.78 (s, P-OMe), 3.76 (s, P-OMe), 2.21-2.08 (m, 2H), 1.94-1.72 (m, 2H), 1.62-1.37 (m, 5H), 1.25 (br.s, 24H), 0.87 (m, 6H);

^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 136.8, 136.5, 118.3, 118.1, 78.8 (d, J_{CP} = 7.6 Hz), 78.5(d, J_{CP} = 6.7 Hz), 77.8 (d, J_{CP} = 6.7 Hz), 77.4 (d, J_{CP} = 6.7 Hz), 54.3 (d, J_{CP} = 5.7 Hz), 53.8 (d, J_{CP} = 5.7 Hz), 49.1 (d, J_{CP} = 7.6 Hz), 48.9 (d, J_{CP} = 6.3 Hz), 35.4 (d, J_{CP} = 6.2 Hz), 34.1 (d, J_{CP} = 2.5 Hz), 32.8 (d, J_{CP} = 6.8 Hz), 32.7 (d, J_{CP} = 6.4 Hz), 31.8, 31.6 (d, J_{CP} = 2.4 Hz), 30.5, 30.3, 29.6, 29.5, 29.4, 29.3, 29.1, 26.9, 26.8, 25.5, 25.2, 22.6, 22.5, 14.1, 14.0;

^{31}P NMR (162 MHz, $CDCl_3$) δ (ppm) -3.40, -3.98;

HRMS cald. for $C_{24}H_{47}O_4PNa$ $(M+Na)^+$ 453.3110; found 453.3118 (TOF MS ES+)

(7*R*,8*S*,10*R*)-7-vinylhenicosane-8,10-diol (4):



To a stirring solution of phosphate **10** (560 mg, 1.3 mmol) in Et_2O (20 mL) was added $LiAlH_4$ (100 mg, 2.6 mmol) at 0 ºC under argon. The combined reaction mixture was stirred for 2 h at 0 ºC. After such time the reaction was quenched via slow addition of H_2O (100 mL), followed by 10% NaOH (100 mL) and H_2O (1 mL). The reaction was warmed to RT and stirred for another 30 min. The crude mixture was washed with 10% HCl (5 mL) and aqueous layer was extracted with Et_2O (3 x 50 mL). The combined organic layers were rinsed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. Purification by flash column chromatography (10% EtoAc/Hexane) afforded 396 mg (86%) of desired diol **4** as white colored solid.

R_f = 0.38 (4:1 Hexane/EtOAc); **MP:** 65-67 ºC;

Optical Rotation: $[\alpha]_D$ = -14.16 (*c* = 1.73, $CHCl_3$);

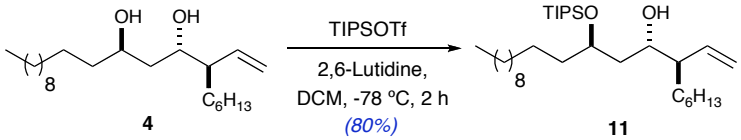
FTIR (thin film) 3517, 3076, 2918, 2848, 1463, 1265 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 5.62 (ddd, *J* = 17.2, 10.1, 9.5 Hz, 1H), 5.21 (dd, *J* = 10.3, 2.0 Hz, 1H), 5.12 (dd, *J* = 17.2, 1.6 Hz, 1H), 3.93-3.87 (m, 1H), 3.78-3.73 (m, 1H), 2.61 (s, 1H), 2.26 (s, 1H), 2.07-2.00 (m, 1H), 1.63 (dddd, *J* = 26.4, 11.6, 8.1, 3.2 Hz, 2H), 1.57-1.48 (m, 1H), 1.48-1.38 (m, 3H), 1.37-1.18 (m, 26H), 0.88 (t, *J* = 6.8 Hz, 3H), 0.87 (t, *J* = 6.8 Hz, 3H);

^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 139.1, 118.3, 70.8, 69.2, 50.8, 39.7, 37.4, 31.9, 31.7, 30.4, 29.7 (2C), 29.6 (3C), 29.3, 29.2, 27.2, 25.8, 22.7, 22.6, 14.1, 14.0;

HRMS: cald. for $C_{23}H_{46}O_2Na$ $(M+Na)^+$ 377.3396; found 377.3395 (TOF MS ES+).

(7*R*,8*S*,10*R*)-10-(triisopropylsilyloxy)-7-vinylhenicosan-8-ol (11):



To a stirring solution of diol **4** (190 mg, 0.54 mmol) in CH_2Cl_2 (8 ml) was added 2,6-lutidine (0.25 mL, 2.14 mmol) and the mixture was cooled to -78 °C. TIPSOTf (0.29 mL, 1.08 mmol) was added drop-wise and the colorless reaction mixture was stirred for 2 h and then allowed to slowly warm to 0 °C. After completion of the reaction as monitored by TLC, it was quenched with sat. NH_4Cl and extracted with EtOAc (2 x 10 mL), dried (Na_2SO_4) and concentrated under reduced pressure. Further purification by flash column chromatography (5% EtOAc/Hexane) afforded 220 mg (80%) of desired silyl ether **11** as viscous oil.

R_f = 0.6 (9:1 Hexane/EtOAc);

FTIR (neat) 3483, 3072, 2923, 2854, 1629, 1465 cm^{-1};

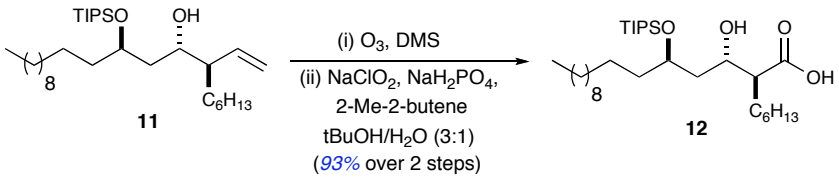
Optical Rotation: $[\alpha]_D$ = -21.85 (*c* = 2.32, $CHCl_3$);

^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 5.71 (ddd, *J* = 17.2, 10.2, 9.3 Hz, 1H), 5.11 (dd, *J* = 10.3, 2.2 Hz, 1H), 5.02 (dd, *J* = 17.7, 1.7 Hz, 1H), 4.13-4.08 (m, 1H), 3.97-3.93 (m, 1H), 3.58 (s, 1H), 1.92 (ddd, *J* = 13.5, 9.0, 4.0 Hz, 1H), 1.79-1.68 (m, 2H), 1.67-1.58 (m, 1H), 1.55-1.47 (m, 2H), 1.26 (br.s, 27H), 1.09-1.06 (m, 21H), 0.90-0.86 (m, 6H);

^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 139.4, 116.4, 72.3, 70.4, 50.7, 37.6, 35.7, 31.9, 31.8, 30.6, 29.7, 29.6 (2C), 29.5 (2C), 29.4, 29.3, 27.4, 25.7, 22.6 (2C), 18.1 (3C), 18.0 (3C), 14.1(2C), 12.3 (3C);

HRMS: cald. for $C_{32}H_{66}O_2SiNa$ $(M+Na)^+$ 533.4730; found 533.4731 (TOF MS ES+)

(2*S*,3*S*,5*R*)-2-hexyl-3-hydroxy-5-(triisopropylsilyloxy)hexadecanoic acid (12):



A flask with olefin **11** (230 mg, 0.45 mmol) dissolved in CH_2Cl_2 (9 mL) under argon was cooled to -78 ºC and Sudan III indicator was added producing an orange-colored reaction mixture. This reaction mixture was continuously sparged with ozone gas until the reaction mixture color changed from orange to colorless (approx. 30 min). The flow of ozone was stopped, DMS (7-8 drops) was added slowly at -78 ºC and stirring was continued for an additional 1 h at rt. The reaction was quenched with H_2O, extracted with EtOAc, washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure giving 230 mg of desired aldehyde as a viscous oil.

To the crude aldehyde (230 mg, 0.45 mmol), was added *t*BuOH/H_2O (3:1, 83 ml), 2-methyl-2-butene (2.0 M solution in THF, 0.92 mL, 1.84 mmol), NaH_2PO_4•$2H_2O$ (77 mg, 0.49 mmol), and $NaClO_2$ (138 mg, 1.53 mmol) and the reaction mixture was stirred overnight. After reaction completion as monitored by TLC, it was directly concentrated under reduced pressure to remove some excess *t*BuOH. The reaction was next quenched with sat. NH_4Cl, and extracted with EtOAc (50 mL), washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. Further purification by flash column chromatography (4:1 hexane/EtOAc) afforded 221 mg of desired carboxylic acid **12** as viscous oil in 93% yield over two steps.

R_f = 0.27 (4:1 Hexane/EtOAc);

FTIR (neat): 3500, 2925, 2856, 1706, 1643, 759 cm^{-1};

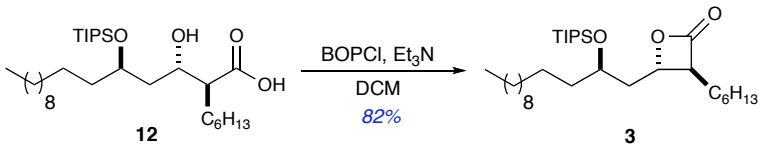
Optical Rotation: $[\alpha]_D$ = -22.52 (*c* = 1.03, $CHCl_3$);

^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 4.27-4.05 (m, 2H), 2.36 (s, 1H), 1.95-1.55 (m, 6H), 1.45-1.15 (m, 27H), 1.14-1.02 (m, 21H), 0.90-0.86 (m, 6H);

^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 177.2, 72.4, 68.9, 51.9, 37.4, 35.3, 31.9, 31.6, 29.6 (4C), 29.5 (2C), 29.3, 29.1, 27.2, 25.7, 22.6, 22.5, 18.1 (3C), 18.0 (3C), 14.1, 14.0, 12.3 (3C);

HRMS: cald. for $C_{31}H_{64}O_4SiNa$ $(M+Na)^+$ 551.4472; found 551.4475 (TOF MS ES+)

(3*S*,4*S*)-3-hexyl-4-((*R*)-2-(triisopropylsilyloxy)tridecyl)oxetan-2-one (3):



To a stirring solution of carboxylic acid **12** (50 mg, 0.095 mmol) at RT in CH_2Cl_2 (4 mL) was added Et_3N (40 µl, 0.28 mmol) followed by BOPCl (36 mg, 0.14 mmol). After one hour, the reaction was quenched with H_2O (2 mL), extracted with EtOAc (2 x 10 ml), dried (Na_2SO_4) and concentrated under reduced pressure. Purification by flash column chromatography (5% EtOAC/Hexane) afforded 40 mg (82%) of desired β-lactone as a viscous oil.

R_f = 0.50 (19:1 Hexane/EtOAc);

FTIR (neat): 2927, 1816, 1465, 1215, 760 cm^{-1};

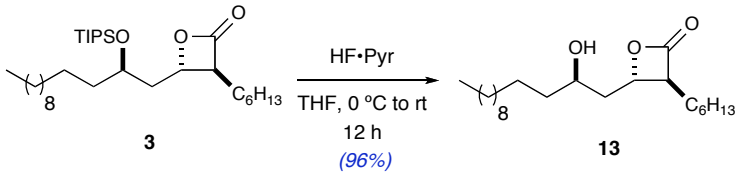
Optical Rotation: $[\alpha]_D$ = -31.96 (c = 0.66, $CHCl_3$);

^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 4.50 (dt, *J* = 9.3, 3.7 Hz, 1H), 3.99 (ddd, *J* = 11.6, 7.7, 3.7 Hz, 1H), 3.19 (ddd, *J* = 8.5, 6.6, 4.1 Hz, 1H), 1.94 (ddd, *J* = 14.3, 9.4, 3.5 Hz, 1H), 1.87-1.78 (m, 2H), 1.77-1.68 (m, 1H), 1.63-1.54 (m, 1H), 1.53-1.17 (m, 28H), 1.07 (br.s, 21H), 0.89 (t, *J* = 6.9, 3H), 0.88 (t, *J* = 6.9, 3H);

^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 171.7, 75.2, 69.2, 56.1, 41.8, 37.9, 31.7, 31.4, 29.8, 29.6 (3C), 29.5, 29.3, 28.9, 27.6, 26.7, 24.6, 22.6, 22.4, 18.2 (3C), 18.1 (3C), 14.1, 14.0, 12.7 (3C);

HRMS: Cald. for $C_{31}H_{62}O_3SiNa$ $(M+Na)^+$ 533.4366; found 533.4346 (TOF MS ES+)

(3*S*,4*S*)-3-hexyl-4-((*R*)-2-hydroxytridecyl)oxetan-2-one (13):



To a stirring solution of β-lactone (33 mg, 0.064 mmol) in a plastic vial under argon at 0 °C in THF (1.2 mL) was added HF•pyr (0.25 mL). After 2 h, the ice bath was removed and the reaction was stirred overnight. After reaction completion, it was diluted with Et_2O (1.5 mL), extracted with sat. $CuSO_4$ (aq.) (2 x 1 mL), washed with 10% HCl (0.5 mL), dried (Na_2SO_4) and concentrated under reduced pressure. Purification by flash column chromatography (20% EtOAc/Hexane) afforded 22 mg (96%) of desired compound **13** as a white solid.

R_f = 0.5 (4:1 Hexane/EtOAc);

MP: 59-60 °C;

FTIR (thin film): 3620, 2927, 1814, 1517, 1421, 1215 cm^{-1};

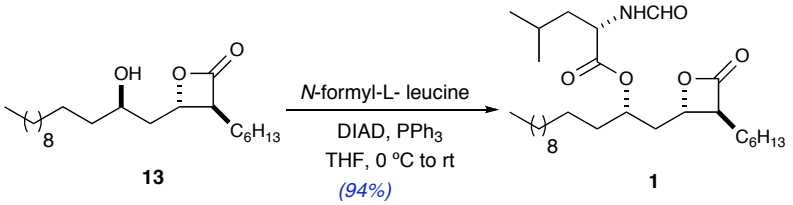
Optical Rotation: $[\alpha]_D$ = -40.7 (*c* = 0.95, $CHCl_3$);

^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 4.51(dt, *J* = 8.6, 4.3 Hz, 1H), 3.80 (br.d, *J* = 6.1 Hz, 1H), 3.26 (ddd, *J* = 8.3, 7.0, 4.0 Hz, 1H), 1.92 (ddd, *J* =14.7, 8.7, 2.8 Hz, 1H), 1.87-1.70 (m, 3H), 1.65 (br.s, 1H), 1.52-1.20 (m, 28H), 0.89 (t, *J* = 7.0 Hz, 3H), 0.88 (t, *J* = 7.0 Hz, 3H);

^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 171.6, 75.6, 68.4, 56.5, 41.8, 38.1, 31.9, 31.5, 29.6 (2C), 29.5 (2C), 29.4, 29.3, 28.9, 27.7, 26.7, 25.3, 22.6, 22.5, 14.1, 14.0;

HRMS: Cald. for $C_{22}H_{42}O_3Na$ $(M+Na)^+$ 377.3032; found 377.3049 (TOF MS ES+)

(*S*)-((*S*)-1-((2*S*,3*S*)-3-hexyl-4-oxooxetan-2-yl)tridecan-2-yl)-2-formamido-4-methylpentanoate (Tetrahydrolipstatin) (1):



To a flask with *β*-lactone **13** (16 mg, 0.045 mmol) was added THF (1.2 mL) under argon. PPh_3 (41 mg, 0.158 mmol), *N*-formyl-L-leucine (25 mg, 0.158 mmol) were next added at RT. The mixture was cooled to 0 ºC, followed by drop-wise addition of DIAD (25 μL, 0.126 mmol). The combined pale yellow colored reaction mixture was stirred at RT overnight and directly concentrated under reduced pressure. Further purification by flash column chromatography (10% EtOAc/toluene) gave 21 mg of desired (–)-Tetrahydrolipstatn (**1**) as a white solid in 94% yield.

R_f = 0.15 (4:1 Hexane/EtOAc);

MP: 38-39 ºC;

FTIR (thin film): 3423, 3055, 2958, 2927, 2856, 1820, 1735, 1691, 1265 cm^{-1};

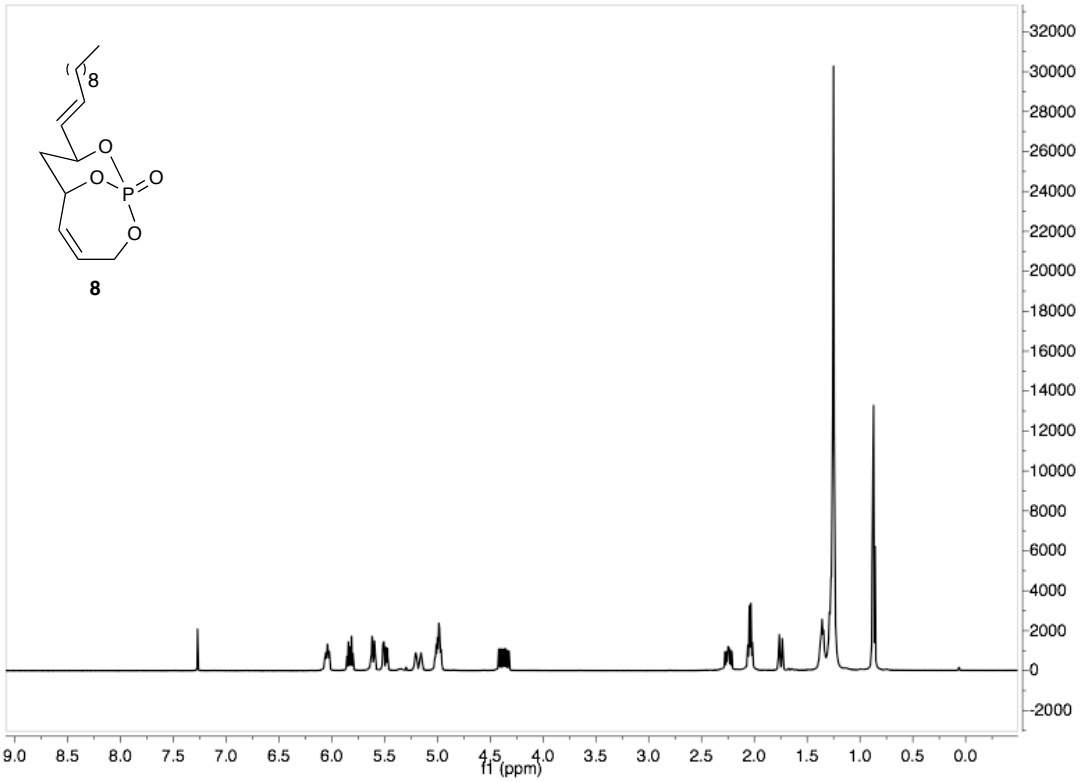
Optical Rotation: $[\alpha]_D$ = -32.0 (*c* = 0.77, $CHCl_3$);

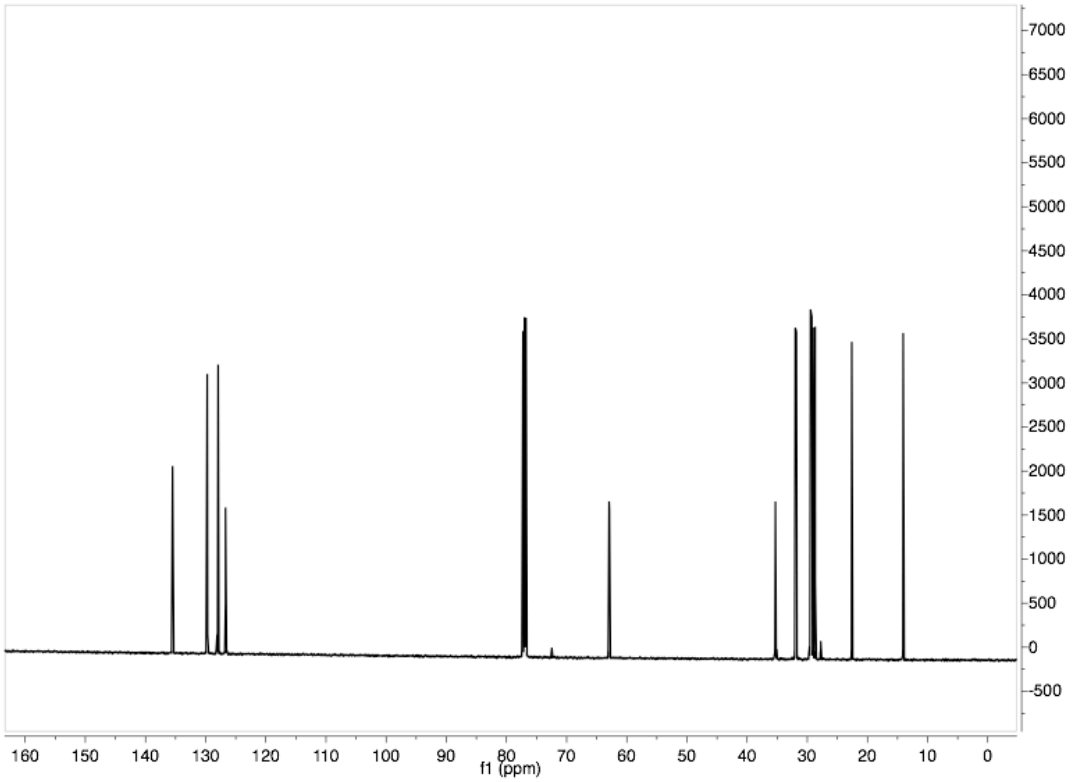
^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 8.22 (s, 1H), 5.96 (d, *J* = 8.4 Hz, 1H), 5.06-4.99 (m, 1H), 4.68 (td, *J* = 8.7, 4.1 Hz, 1H), 4.32-4.27 (m, 1H), 3.22 (ddd, *J* = 7.9, 7.2, 4.1 Hz, 1H), 2.21-2.12 (m, 1H), 1.99 (ddd, *J* = 14.9, 4.7, 4.1 Hz, 1H), 1.86-1.49 (m, 7H), 1.49-1.03 (m, 26H), 0.97 (dd, *J* = 6.1, 2.5 Hz, 6H), 0.89 (t, *J* = 6.9 Hz, 3H), 0.88 (t, *J* = 6.9 Hz, 3H);

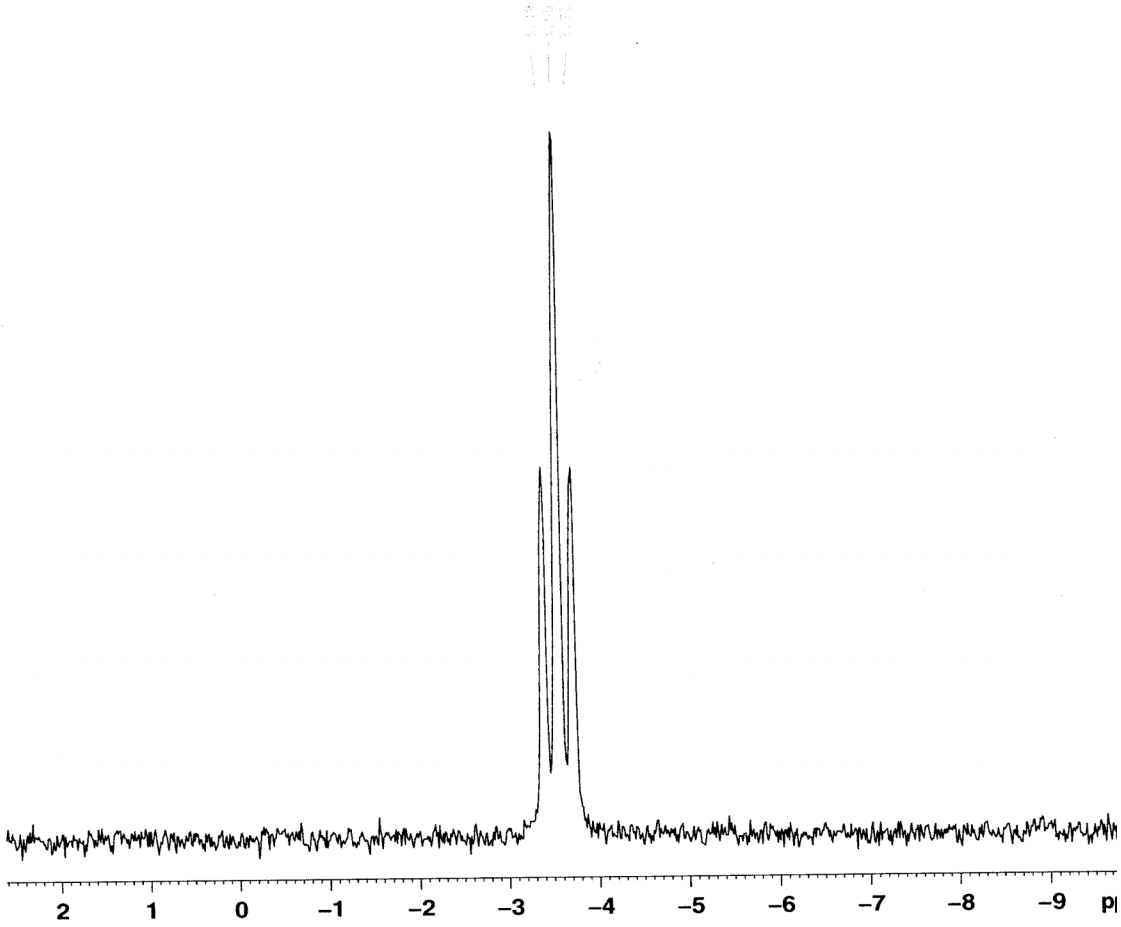
^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 171.9, 170.7, 160.6, 74.7, 72.7, 57.0, 49.6, 41.5, 38.7, 34.0, 31.9, 31.4, 29.6 (2C), 29.5, 29.4, 29.3, 29.2, 28.9, 27.6, 26.7, 25.0, 24.8, 22.8, 22.6, 22.5, 21.7, 14.1, 14.0;

HRMS: Cald. for $C_{29}H_{53}NO_5Na$ $(M+Na)^+$ 518.3821; found 518.3831 (TOF MS ES+)

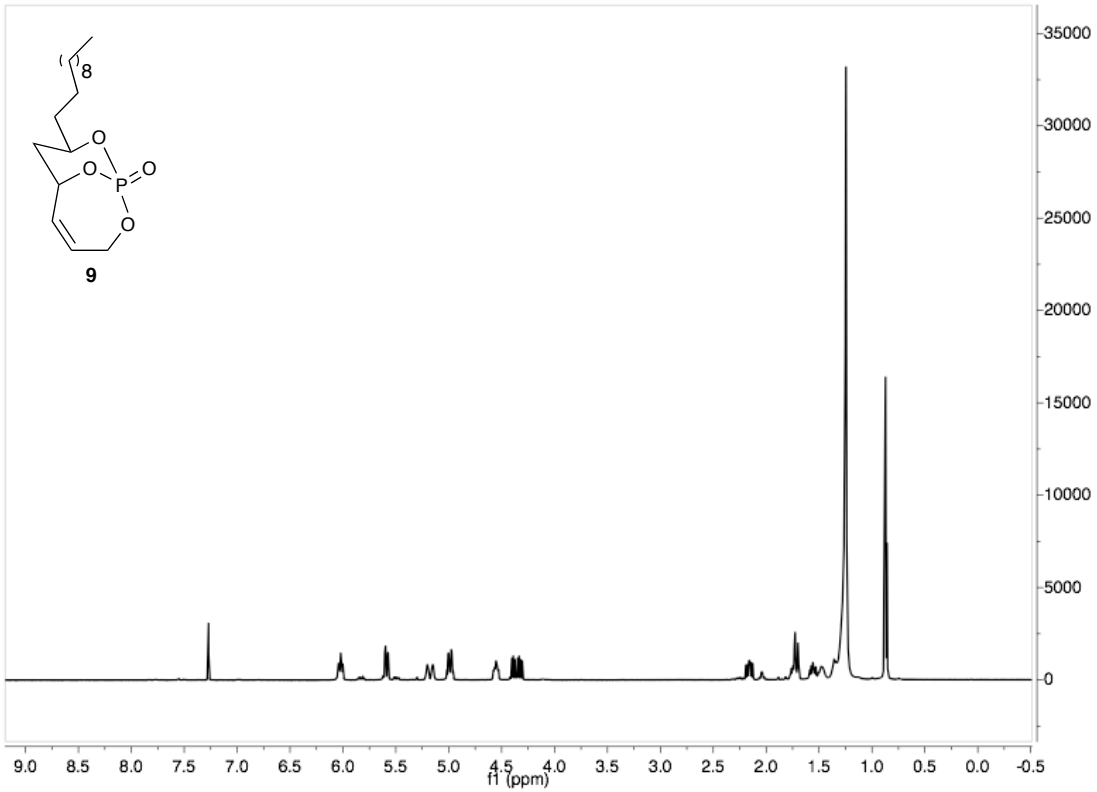
(1*S*,6*S*,8*S*)-2,9,10-Trioxa-1-phosphabicyclo[4.3.1]dec-4-ene, 8-[(1*E*)- undecen-1-yl]-1-oxide (9).

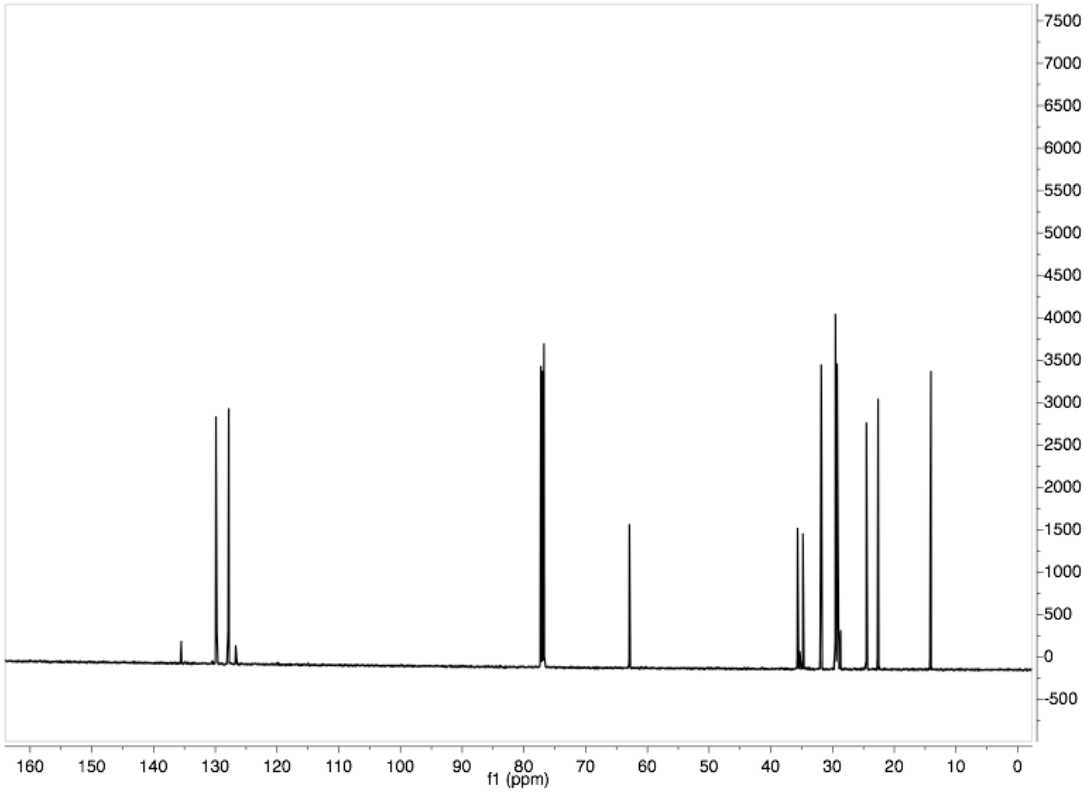


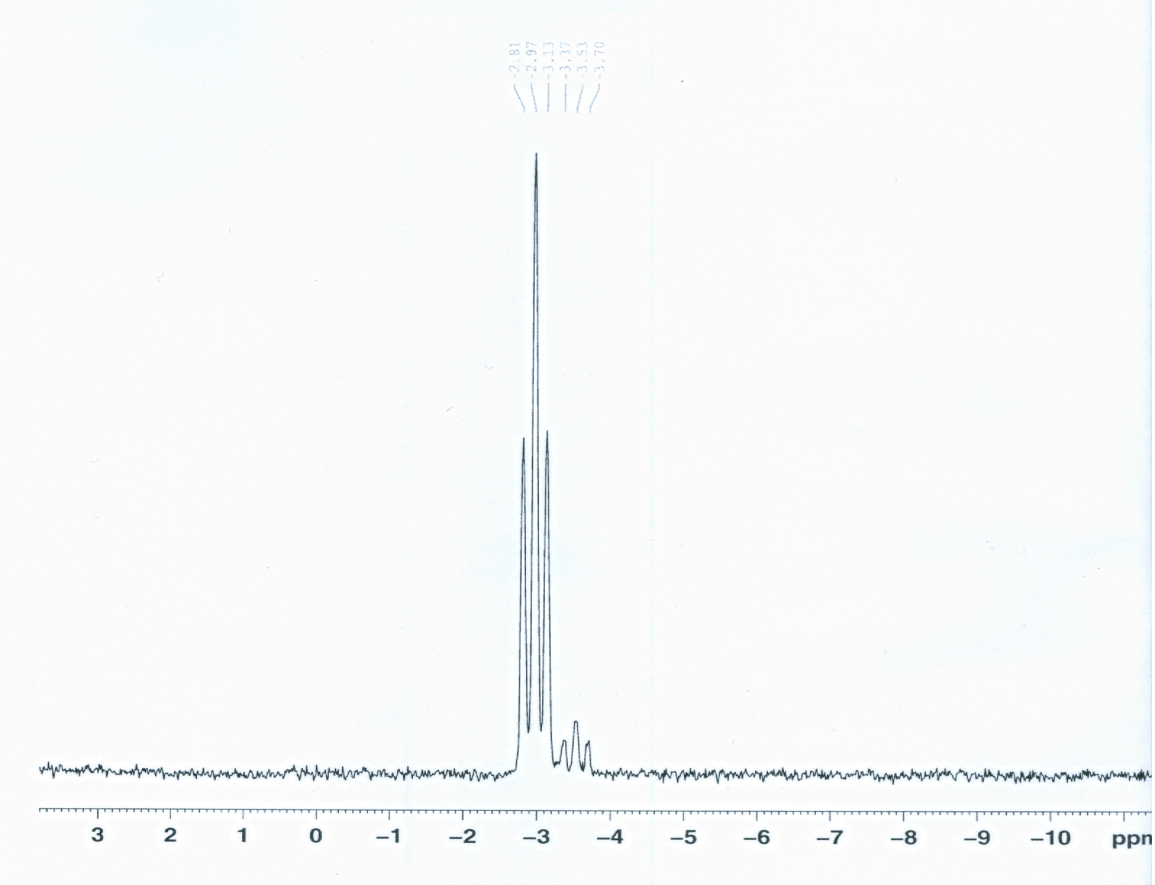



2
1
0
−1
−2
−3
−4
−5
−6
−7
−8
−9

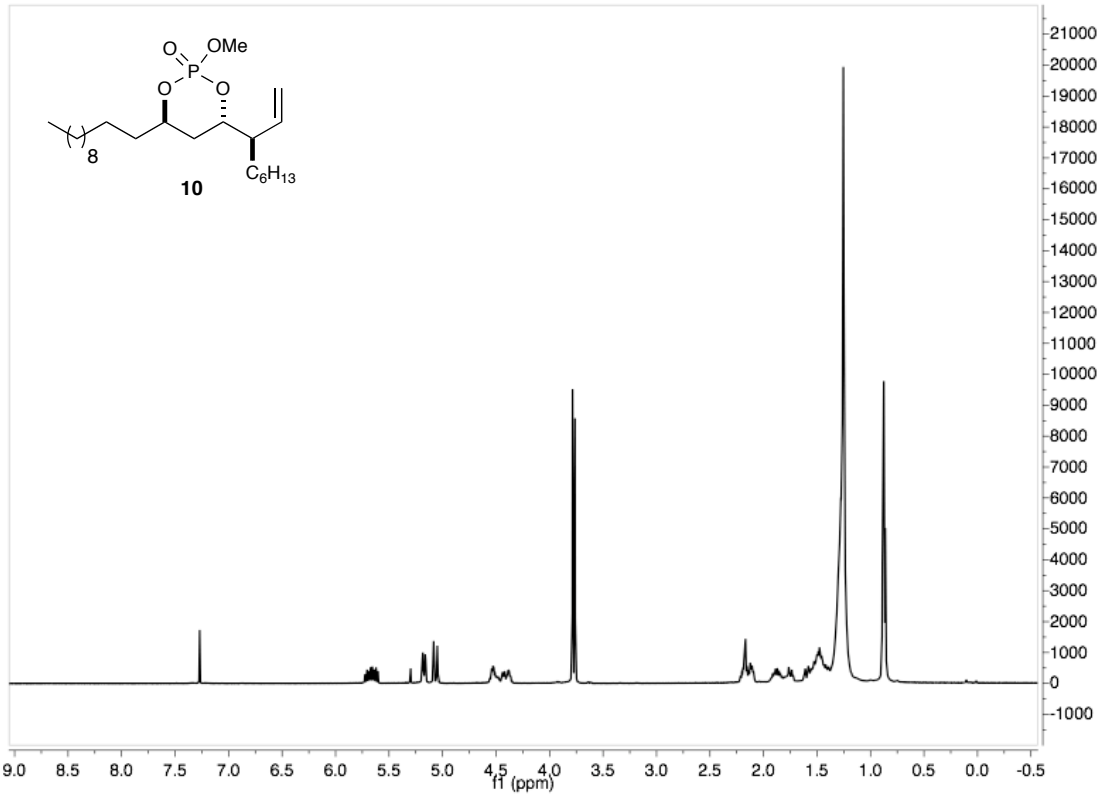
(1*S*,6*S*,8*S*)-2,9,10-Trioxa-1-phosphabicyclo[4.3.1]dec-4-ene, 8-[undecan-1-yl]-1-oxide (5).

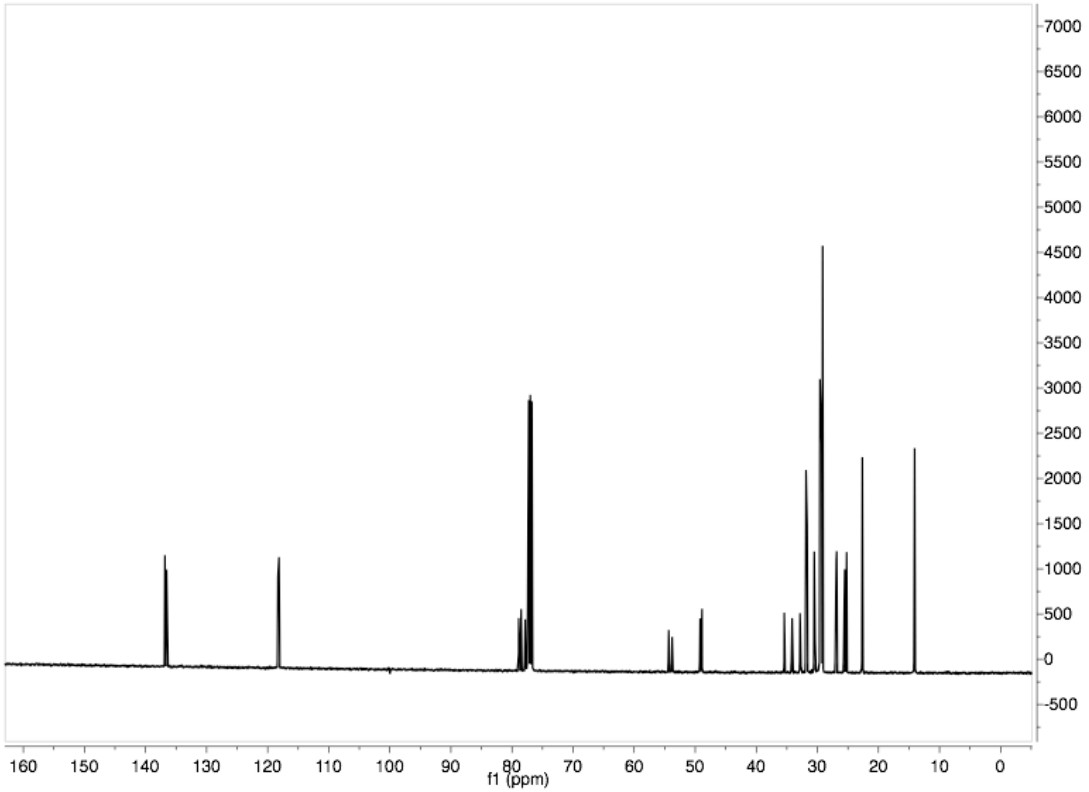


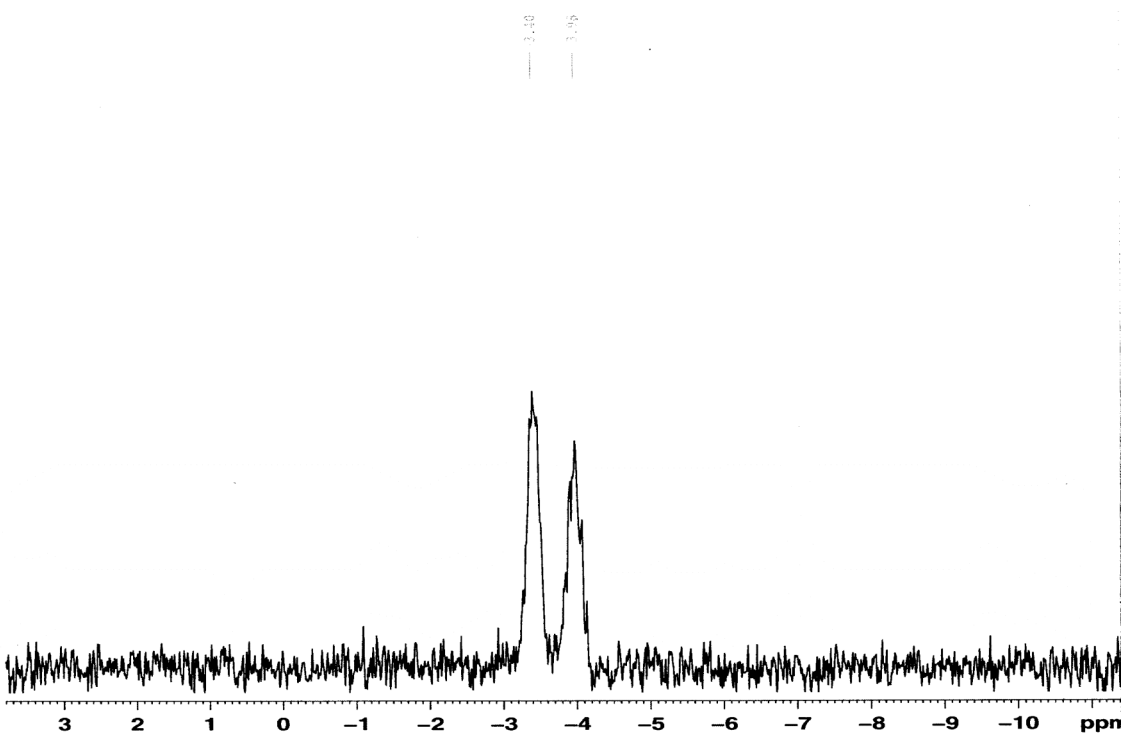



-2.81
-2.97
-3.13
-3.37
-3.53
-3.70
3
2
1
0
−1
−2
−3
−4
−5
−6
−7
−8
−9
−10
ppm

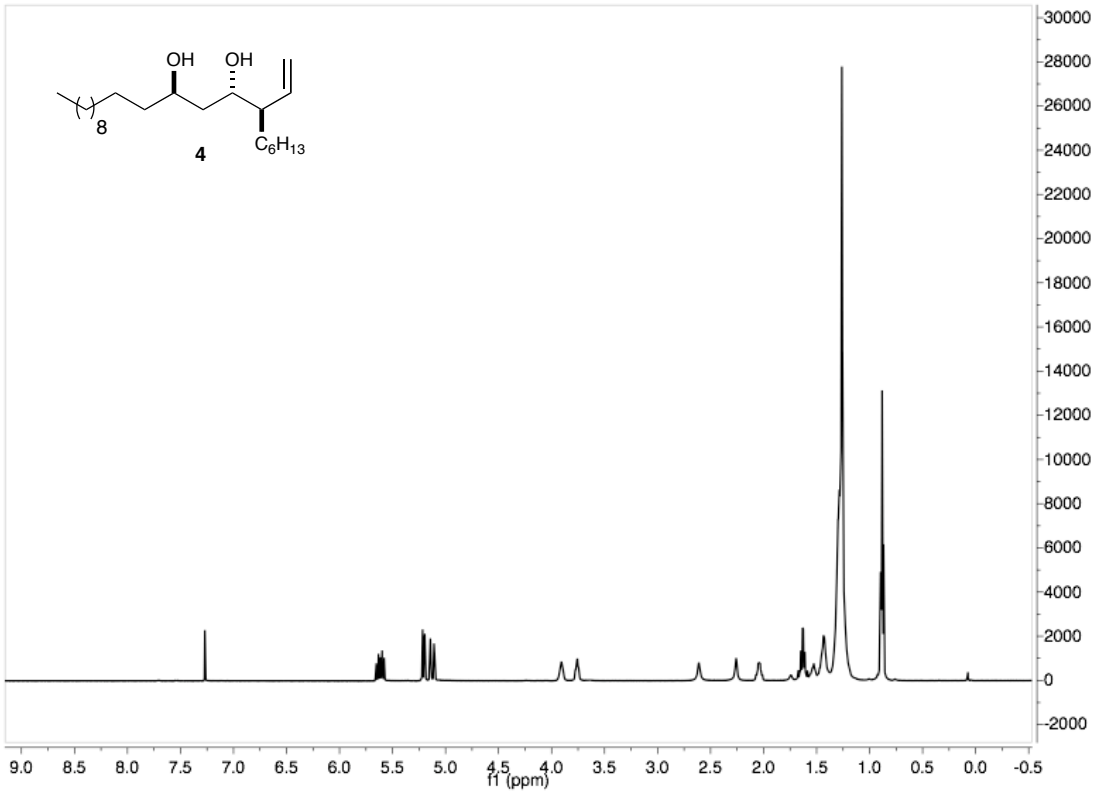
(4R,6S)-1,3,2-Dioxaphosphorinane, 2-methoxy-4-[1-undecan]-6-[(1R)-1-methyl-2-propen-1-yl]-2-oxide (10).

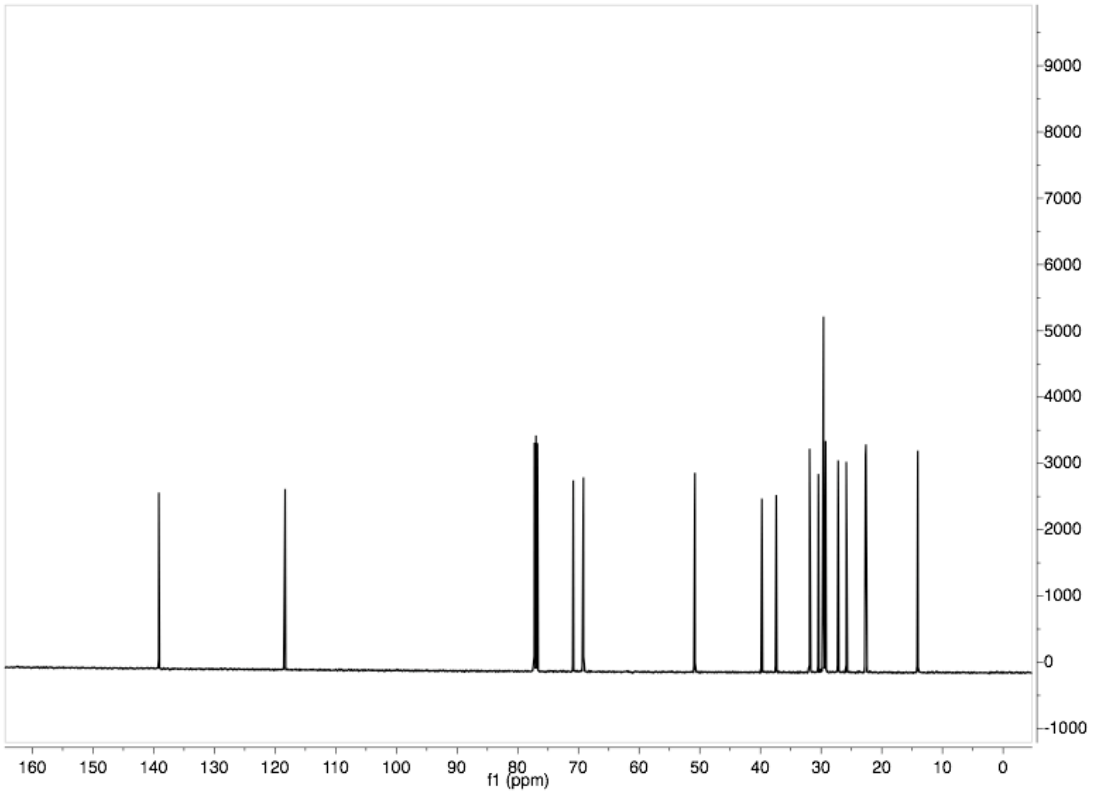




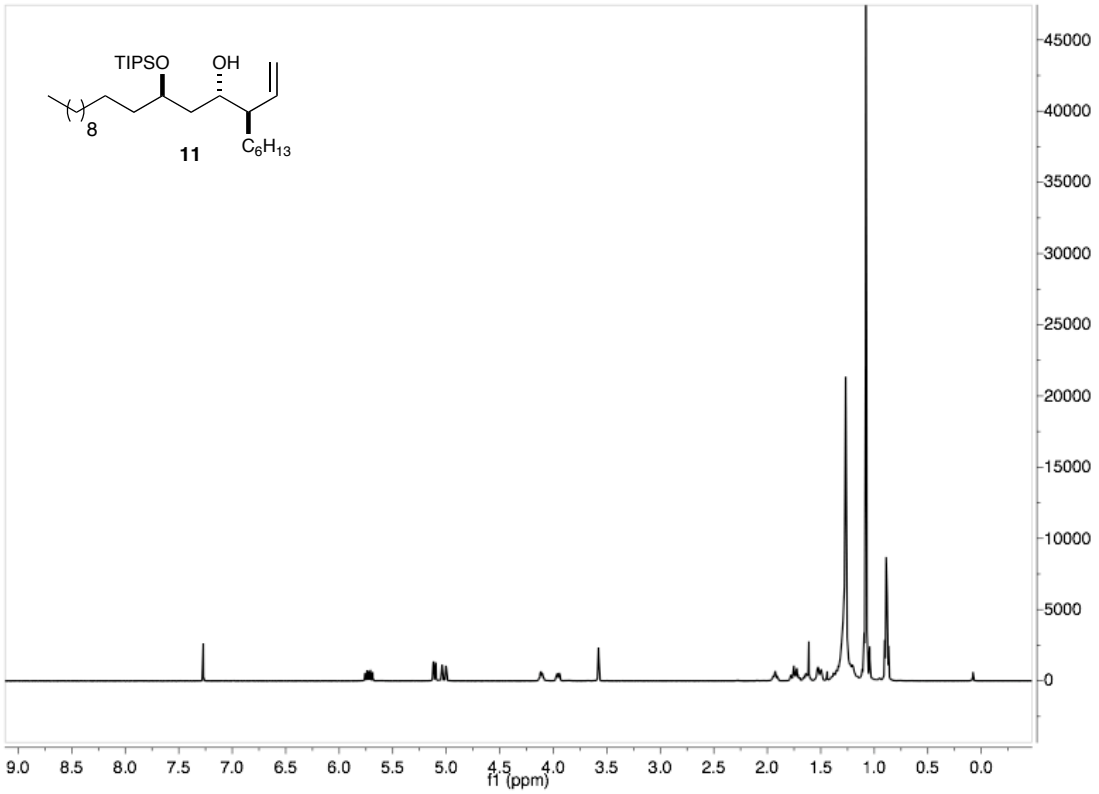

3
2
1
0
−1
−2
−3
−4
−5
−6
−7
−8
−9
−10
ppm

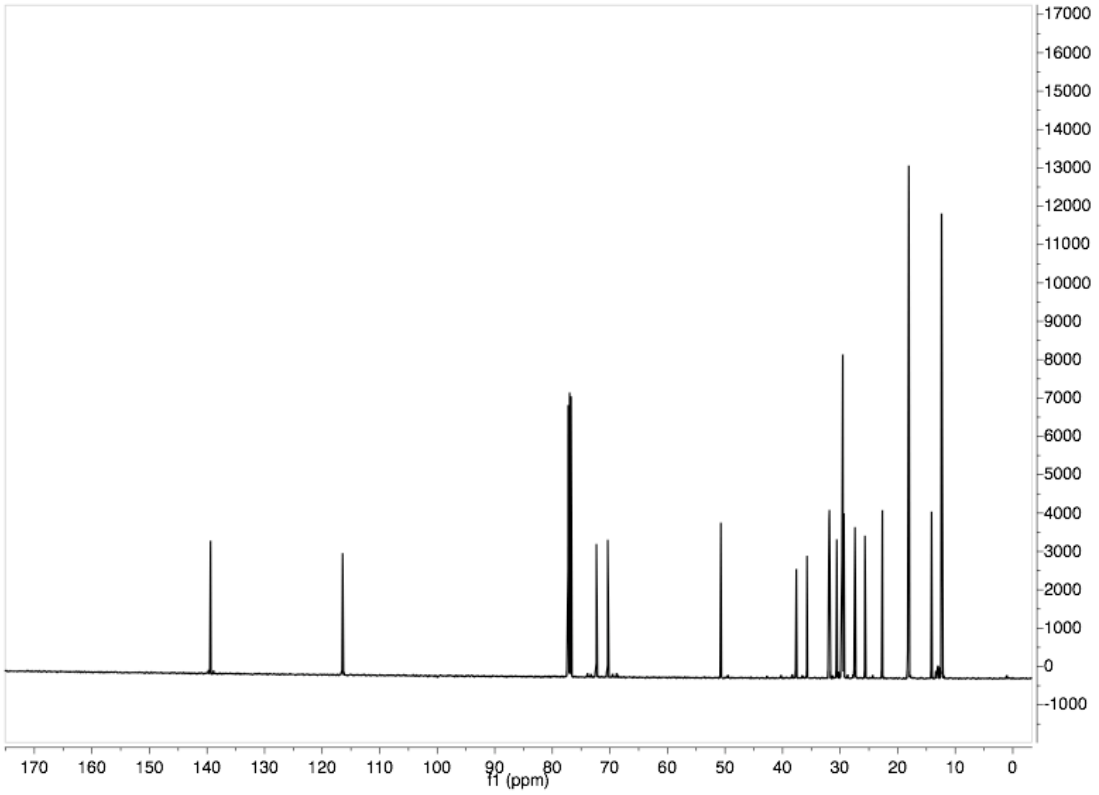
(7*R*,8*S*,10*R*)-7-vinylhenicosane-8,10-diol (4):



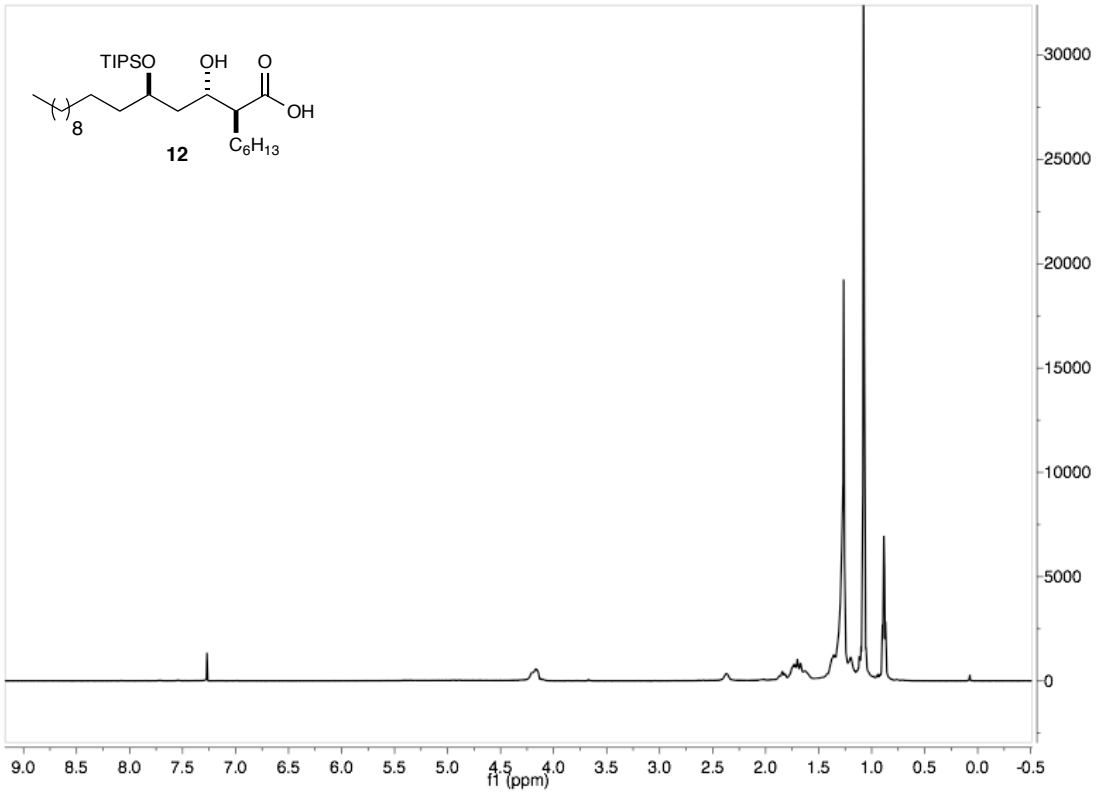


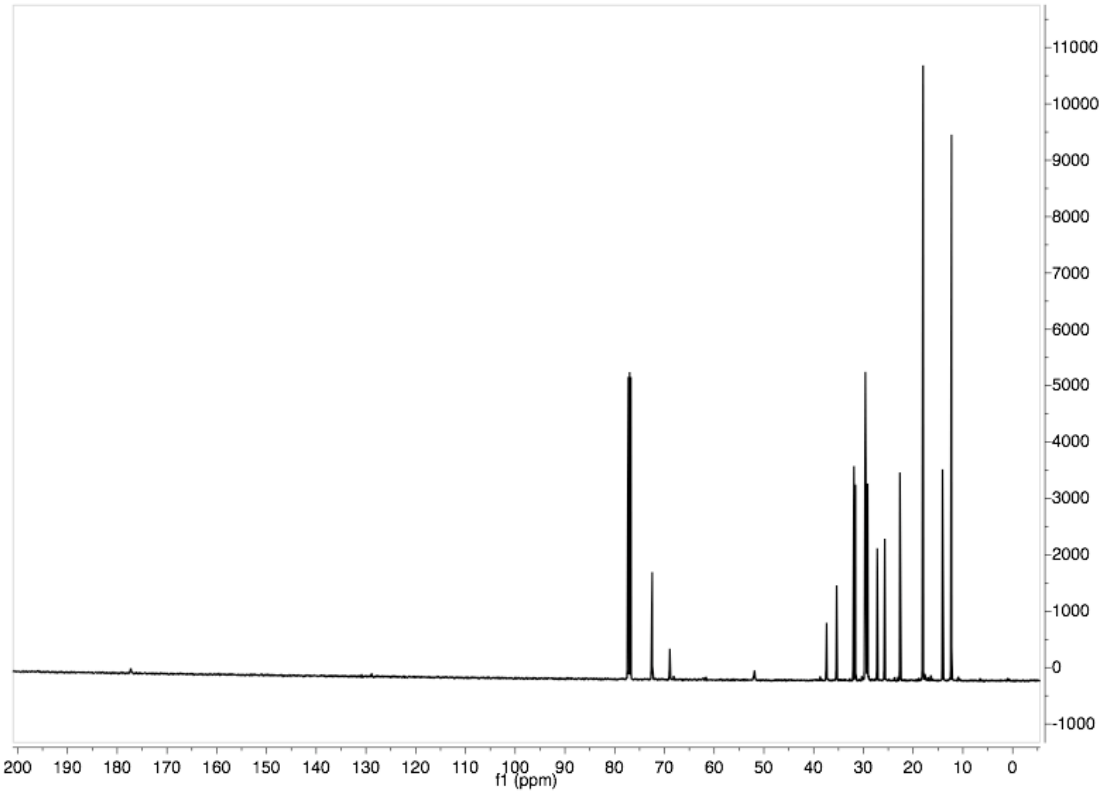
(7*R*,8*S*,10*R*)-10-(triisopropylsilyloxy)-7-vinylhenicosan-8-ol (11)



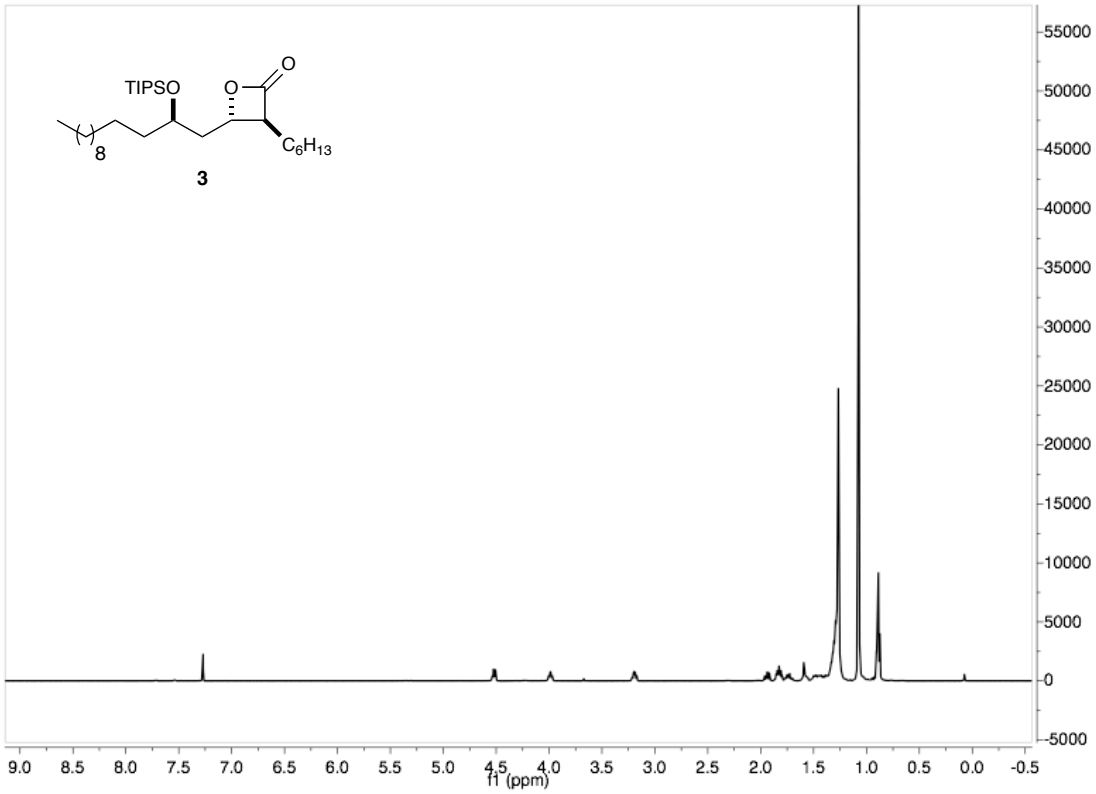


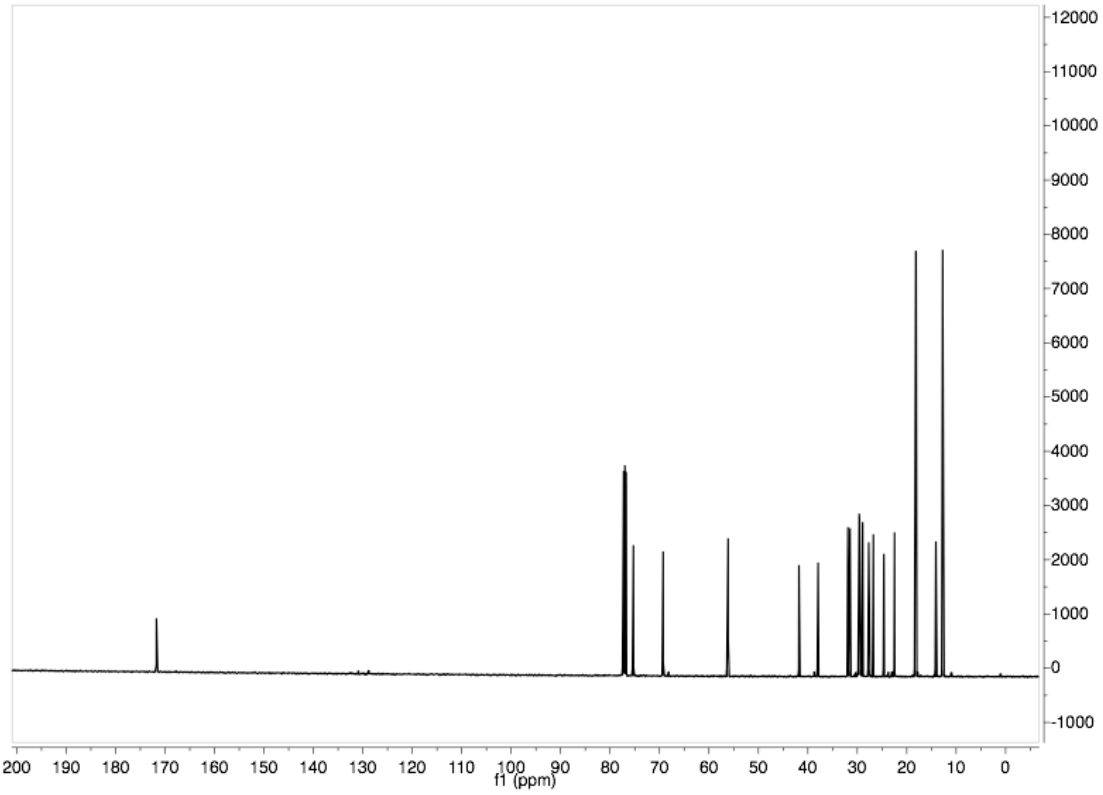
(2*S*,3*S*,5*R*)-2-hexyl-3-hydroxy-5-(triisopropylsilyloxy)hexadecanoic acid (12)



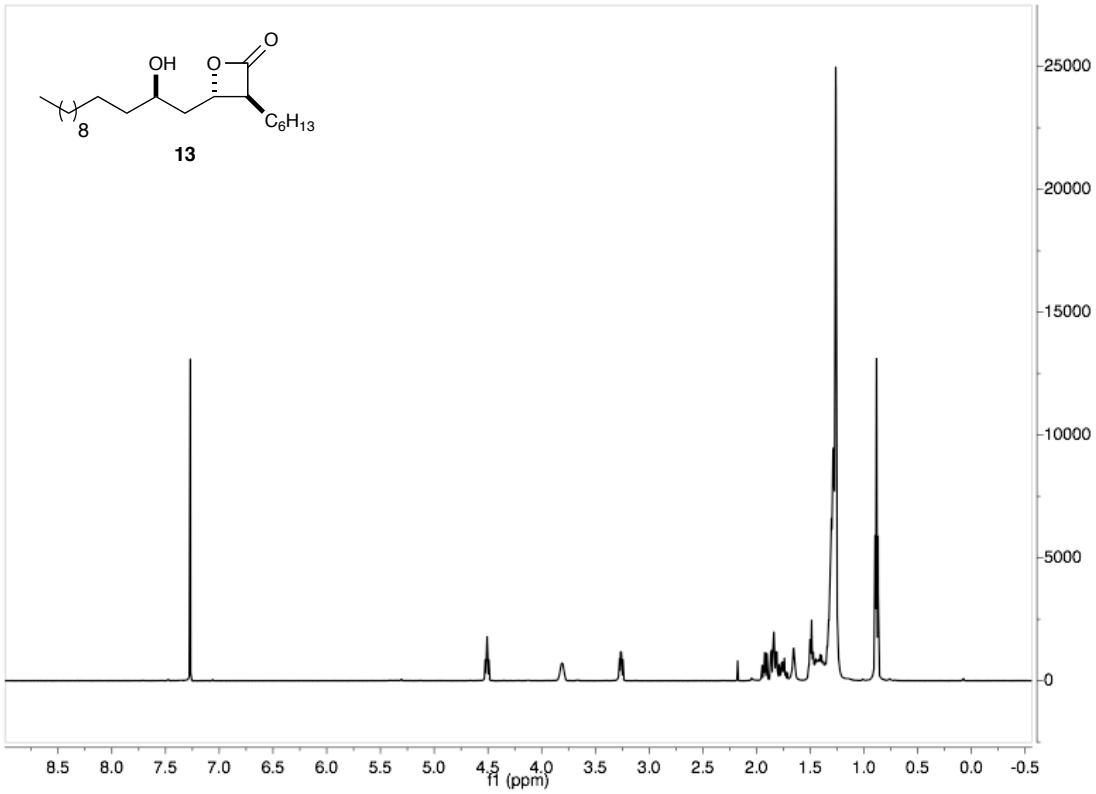


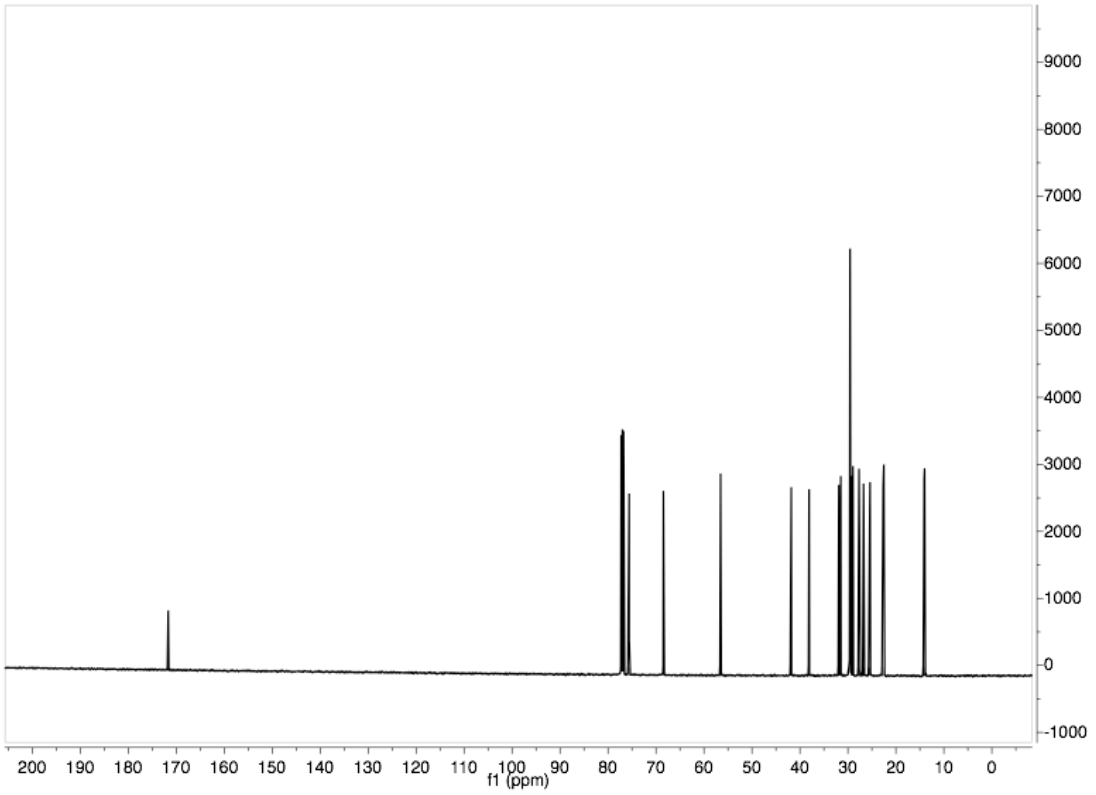
(3*S*,4*S*)-3-hexyl-4-((*R*)-2-(triisopropylsilyloxy)tridecyl)oxetan-2-one (3)





(3*S*,4*S*)-3-hexyl-4-((*R*)-2-hydroxytridecyl)oxetan-2-one (3)





(*S*)-((*S*)-1-((2*S*,3*S*)-3-hexyl-4-oxooxetan-2-yl)tridecan-2-yl)-2-formamido-4-methylpentanoate (Tetrahydrolipstatin 1):