Supporting Information

Total Syntheses of Amphidinolides T1 and T4 via Catalytic, Stereoselective Reductive Macrocyclizations

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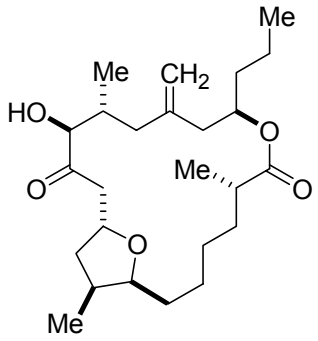
General Information. Unless otherwise noted, all reactions performed in organic solvents were conducted under an atmosphere of argon with rigorous exclusion of moisture from reagents and glassware. THF and Et_2O were distilled from a blue solution of sodium benzophenone ketyl. CH_2Cl_2 was distilled from calcium hydride. Toluene was distilled from sodium metal. Anhydrous DMF and CH_3CN were purchased from Aldrich and used without purification. Analytical thin layer chromatography (TLC) was performed using EM Science silica gel 60 F_{254} plates and UV light, 12-molybdophosphoric acid (PMA stain), or potassium permanganate ($KMnO_4$ stain) for analysis of the developed plates. Flash chromatography was performed using silica gel 60 (40-63 μm) from Silicycle. NMR spectra were recorded on a Varian 500 MHz spectrometer in $CDCl_3$ or C_6D_6. IR spectra were recorded on a Perkin-Elmer 2000 FT-IR. High resolution mass spectra (HRMS) were obtained on a Bruker Daltonics APEXII 3 Tesla Fourier Transform Mass Spectrometer by Dr. Li Li of the Massachusetts Institute of Technology Department of Chemistry Instrumentation Facility. GC analysis was performed on a Varian CP-3800 gas chromatograph fitted with Chiraldex B-PH, B-DA, and G-TA capillary columns. HPLC was performed on a Hewlett-Packard 1100 chromatograph equipped with a variable wavelength detector and Chiralcel OD, AD, or OJ column. Specific rotations ($[\alpha]_D$) values for chiral compounds were measured on a Perkin-Elmer 241 polarimeter at 589 nm.



(+)-Amphidinolide T1 (1). A 2 mL plastic Eppendorf tube was charged with a solution of **50** (2.2 mg, 0.004 mmol) in CH_3CN (0.70 ml) and a Teflon-coated stirbar. Anhydrous HF-pyridine was added via syringe (0.10 ml), and the reaction was stirred 72 h at ambient temperature. After this time, the mixture was partitioned between H_2O and EtOAc (1 mL each), and the layers were separated. The aqueous phase was extracted with EtOAc (5 x 1 mL) and the combined organic layers were washed with brine (1 x 2 mL), dried over Na_2SO_4, filtered and concentrated. The crude residue was purified via Pasteur pipet column chromatography (9:1 hexane-EtOAc) to give the title compound as a clear, colorless oil (1.6 mg, 94% yield). R_f (80:20, hexane-EtOAc) = 0.32.

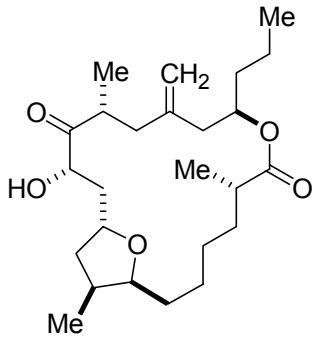
IR (thin film/NaCl): 3485, 2925, 2854, 1727 cm^{-1}.

^1H NMR (C_6D_6, 500 MHz): δ 5.37-5.32 (m, 1H), 5.13 (s, 1H), 4.92 (s, 1H), 4.51-4.46 (m, 1H), 4.30 (dd, *J* = 1.5, 5.8 Hz, 1H), 3.64 (ddd, *J* = 2.5, 4.4, 10.8 Hz, 1H), 3.60 (d, *J* = 5.8 Hz, 1H), 2.53 (dd, *J* = 10.4, 13.4 Hz, 1H), 2.47-2.41 (m, 3H), 2.33-2.23 (m, 3H), 1.88 (dd, *J* = 2.7, 14.3 Hz, 1H), 1.70-1.65 (m, 1H), 1.62-1.48 (m, 5H), 1.46-1.20 (m, 7H), 1.19-1.11 (m 1H), 1.07 (d, *J* = 7.0 Hz, 3H), 1.05-1.02 (m, 1H), 0.93 (d, *J* = 6.4 Hz, 3H), 0.86 (t, *J* = 7.3 Hz, 3H), 0.62 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (C_6D_6, 125 MHz): δ 212.5, 175.4, 144.0, 116.7, 78.9, 78.6, 74.1, 72.2, 45.5, 42.3, 41.7, 40.5, 40.2, 37.0, 36.1, 35.6, 32.4, 30.2, 27.3, 26.7, 19.6, 18.6, 14.6, 14.5, 14.3.

HRMS (ESI) $[M+Na]^+$: *m/z* calcd for $C_{25}H_{42}NaO_5$ 445.2924, obsd 445.2938.

$[\alpha]_D$ = +6.7 (23 °C, *c* = 0.3, $CHCl_3$)



(−)-Amphidinolide T4 (4). A 2 mL plastic Eppendorf tube was charged with a solution of **61** (3.0 mg, 0.0055 mmol) in CH_3CN (0.70 ml) and a Teflon-coated stirbar. Anhydrous HF-pyridine was added via syringe (0.10 ml), and the reaction was stirred 17 h at ambient temperature. After this time, the mixture was partitioned between H_2O and EtOAc (5 mL each), and the layers were separated. The aqueous phase was extracted with EtOAc (5 x 3 mL). The combined organic phase was dried over Na_2SO_4, filtered and concentrated. The crude residue was purified via Pasteur pipet column chromatography (9:1 hexane-EtOAc) to give the title compound as a clear, colorless oil (2.0 mg, 87% yield). R_f (80:20 hexane-EtOAc) = 0.17.

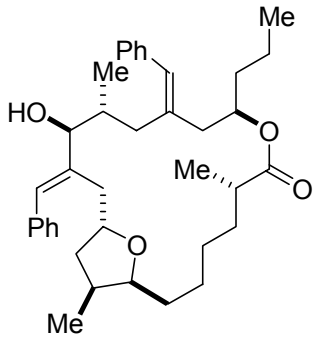
IR (thin film/NaCl): 3465, 2960, 2873, 1725, 1071 cm^{-1}.

^1H NMR (C_6D_6, 500 MHz): δ 5.23-5.18 (m, 1H), 4.83 (s, 2H), 4.56-4.53 (m, 1H), 4.33-4.29 (m, 1H), 4.03 (d, *J* = 6.7 Hz, 1H), 3.79-3.75 (m, 1H), 3.36-3.32 (m, 1H), 2.73 (dd, *J* = 4.0, 14.0 Hz, 1H), 2.54 (dd, *J* = 4.9, 13.4 Hz, 1H), 2.42-2.40 (m, 1H), 2.10 (dd, *J* = 8.7, 13.6 Hz, 1H), 2.02 (dd, *J* = 10.1, 14.0 Hz, 1H), 1.99-1.94 (m, 1H), 1.88-1.86 (m, 1H), 1.71-1.66 (m, 1H), 1.63-1.26 (br m, 13H), 1.19-1.13 (m, 1H), 1.10 (d, *J* = 7.0 Hz, 3H), 0.97 (d, *J* = 6.7 Hz, 3H), 0.85 (t, *J* = 7.3 Hz, 3H), 0.70 (d, *J* = 7.3 Hz, 3H).

^{13}C NMR (C_6D_6, 125 MHz): δ 216.2, 176.0, 143.5, 116.0, 79.7, 75.4, 75.0, 72.3, 41.5, 41.2, 40.64, 40.57, 39.9, 38.8, 36.5, 35.9, 34.3, 29.1, 27.1, 26.4, 19.2, 18.5, 16.4, 14.6, 14.4.

HRMS (ESI)$[M+Na]^+$: *m/z* calcd for $C_{25}H_{42}NaO_5$ 445.2924, obsd 445.2929.

$[\alpha]_D$ = − 7.5 (23 °C, *c* = 0.8, $CHCl_3$)



(−)-11,15-Dibenzylidene-(14*S*)-hydroxy-(6*S*,13*R*,19*R*)-trimethyl-(9*R*)-propyl-8,20-dioxa-bicyclo[15.2.1]icosan-7-one (6). A stock solution of catalyst was prepared in the following manner: in a glovebox, $Ni(cod)_2$ (26 mg, 0.095 mmol) was placed in a flask containing a stirbar. The flask was sealed with a rubber septum, removed from the glovebox, and immediately placed under argon. Tributylphosphine (26 μL, 0.188 mmol), toluene (4.74 ml, previously degassed by bubbling argon through for 10 minutes), and triethylborane (0.26 ml, 1.80 mmol) were added sequentially, producing a clear yellow catalyst solution. A 2 ml Woodward reaction tube equipped with a stirbar, rubber septum, and septum screw cap on the side-arm was purged with argon. Stock catalyst solution was added to the tube (500 μL), and the tube was immediately placed in an oil bath at 60 °C for 3 min. A solution of **8** in degassed toluene (27 mg, 0.047 mmol in 500 μL) was added to the tube dropwise, causing the solution to turn red-brown. The reaction was allowed to stir at 60 °C for 14 h. After this time, the solution was cooled to ambient temperature, diluted with 1.5 ml EtOAc, and stirred open to the air 1 h; then concentrated. The crude residue was purified via Pasteur pipet column chromatography (90:10 hexane-EtOAc) to give the title compound as a clear, yellow oil (12 mg, 44% yield). R_f (90:10, hexane-EtOAc) = 0.20.

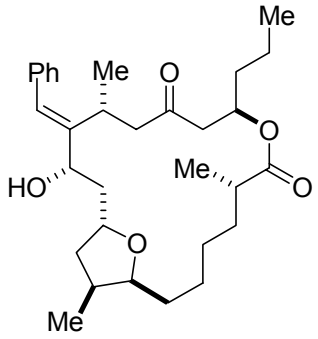
IR (thin film/NaCl): 3377, 2959, 2932, 2872, 1726, 1599, 1462, 1453 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ 7.32-7.13 (m, 10H), 6.49 (s, 1H), 6.45 (s, 1H), 5.29-5.27 (m, 1H), 4.15-4.08 (m, 2H), 3.98 (d, *J* = 4.6 Hz, 1H), 3.90-3.87 (m, 1H), 2.73 (dd, *J* = 5.8, 13.7 Hz, 1H), 2.53-2.42 (m, 3H), 2.37 (dd, *J* = 7.5, 13.9 Hz, 1H), 2.21 (dd, *J* = 7.3, 13.4 Hz, 1H), 2.14-2.10 (m, 2H), 2.06-1.98 (m, 1H), 1.75-1.69 (m, 1H), 1.68-1.28 (br m, 13H), 1.20 (d, *J* = 7.0 Hz, 3H), 0.93 (t, *J* = 7.3 Hz, 3H), 0.91 (d, *J* = 6.1 Hz, 3H), 0.83 (d, *J* = 7.3 Hz, 3H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 176.2, 142.7, 139.1, 138.5, 138.1, 129.01, 128.98 (2C), 128.96 (2C), 128.5 (2C), 128.4 (2C), 128.0, 126.5 (2C), 79.3, 77.3, 72.7, 42.9, 41.7, 40.4, 38.5, 36.5, 36.3, 35.0, 34.8, 34.1, 30.2, 27.5, 25.9, 18.64, 18.62, 14.9, 14.5, 14.3 (missing one C under $CDCl_3$ signal; when spectrum taken in C_6D_6 there are four signals in the 70-80 ppm region: δ 79.7, 77.6, 76.8, 72.5).

HRMS (ESI) $[M+Na]^+$: *m/z* calcd for $C_{38}H_{52}NaO_4$ 595.3758, obsd 595.3746.

$[\alpha]_D$ = −67.8 (23 °C, *c* = 1.8, C_6D_6)



(−)-14-Benzylidene-(15*S*)-hydroxy-(6*S*,13*R*,19*S*)-trimethyl-(9*R*)-propyl-8,20-dioxa-bicyclo[15.2.1]icosane-7,11-dione (7b). A stock solution of catalyst was prepared in the following manner: in a glovebox, $Ni(cod)_2$ (26 mg, 0.095 mmol) was placed in a flask containing a stirbar. The flask was sealed with a rubber septum, removed from the glovebox, and immediately placed under argon. Tributylphosphine (26 μL, 0.188 mmol), toluene (4.74 ml, previously degassed by bubbling argon through for 10 minutes), and triethylborane (0.26 ml, 1.80 mmol) were added sequentially, producing a clear yellow catalyst solution. A 2 ml Woodward reaction tube equipped with a stirbar, rubber septum, and septum screw cap on the side-arm was purged with argon. Stock catalyst solution was added to the tube (240 μL), and the tube was immediately placed in an oil bath at 60 °C for 3 min. A solution of **9b** in degassed toluene (12 mg, 0.024 mmol in 760 μL) was added to the tube dropwise, causing the solution to turn red-brown. The reaction was allowed to stir at 60 °C for 14 h. After this time, the solution was cooled to ambient temperature, diluted with 1.5 ml EtOAc, and stirred open to the air 1 h; then concentrated. The crude residue was purified via gradient Pasteur pipet column chromatography (85:15 hexane-EtOAc polarity increased to 73:30 hexane-EtOAc) to give the title compound as a clear, yellow oil (7.0 mg, 58% yield). R_f (50:50 hexane-EtOAc) = 0.41.

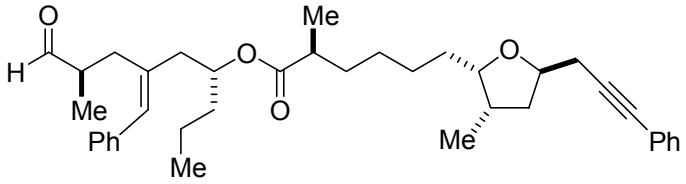
IR (thin film/NaCl): 3432 (br), 2960, 2935, 2873, 1780, 1732, 1458 cm^{-1}.

^1H NMR (C_6D_6, 500 MHz): δ 7.33-7.31 (m, 2H), 7.18 (app t, J = 7.6 Hz, 2H), 7.03 (app t, J = 7.3 Hz, 1H), 6.86 (s, 1H), 5.36-5.31 (m, 1H), 4.58 (d, J = 8.9 Hz, 1H), 4.44-4.39 (m, 1H), 3.71-3.63 (m, 2H), 2.52-2.46 (m, 2H), 2.41 (dd, J = 7.9, 17.1 Hz, 1H), 2.37-2.33 (m, 1H), 2.11 (dd, J = 5.0, 14.5 Hz, 1H), 2.05 (br s, 1H), 1.83-1.79 (m, 1H), 1.74-1.60 (m, 3H), 1.57-1.37 (m, 7H), 1.33-1.24 (m, 2H), 1.23-1.09 (m, 4H), 1.08-1.05 (m, 6H), 0.78-0.74 (m, 6H).

^{13}C NMR (C_6D_6, 125 MHz): δ 206.9, 175.1, 150.4, 138.9, 130.4, 127.2 (2C), 125.2 (2C), 122.0, 79.2, 74.4, 71.9, 69.0, 50.0, 47.8, 46.0, 40.72, 40.70, 37.3, 37.0, 35.3, 30.7, 30.6, 27.6, 27.3, 21.1, 18.9, 17.1, 14.9, 14.4.

HRMS (ESI)$[M+Na]^+$: *m/z* calcd for $C_{31}H_{46}O_5Na$ 519.3081, obsd 519.3077.

$[\alpha]_D$ = −2.5 (23 °C, c = 2.4, C_6H_6)



(+)-(2*S*)-Methyl-6-[(3*S*)-methyl-(5*R*)-(3-phenyl-prop-2-ynyl)-tetrahydro-furan-(2*S*)-yl]-hexanoic acid 3-benzylidene-(5*R*)-methyl-6-oxo-(1*R*)-propyl-hexyl ester (8). Dess-Martin periodinane was dissolved in CH_2Cl_2 (124 mg, 0.30 mmol, 2.4 mL) and a solution of **47** in CH_2Cl_2 was added dropwise via syringe (80 mg, 0.14 mmol, 1.2 mL). The resulting solution was stirred at ambient temperature for 75 min, diluted with Et_2O (15 ml), and poured into 10 ml saturated $NaHCO_3$ containing 2.5 g $Na_2S_2O_3$. When the organic layer cleared, the layers were separated. The organic phase was washed with saturated $NaHCO_3$ (1 x 15 ml), H_2O (1 x 15 ml), and brine (1 x 15 ml), then dried over Na_2SO_4, filtered, and concentrated. The crude residue was purified via column chromatography (90:10 hexane-EtOAc) to give the title compound as a clear, colorless oil (67 mg, 84% yield). R_f (70:30, hexane-EtOAc) = 0.55.

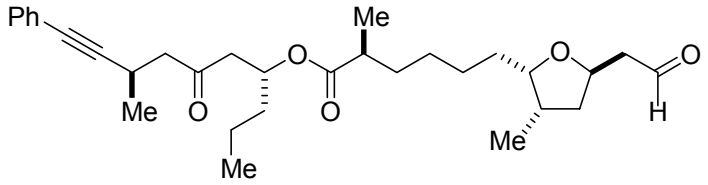
IR (thin film/NaCl): 2961, 2934, 2873, 1726, 1599, 1491, 1460 cm^{-1}.

^1H NMR (C_6D_6, 500 MHz): δ 9.21 (d, *J* = 1.8 Hz, 1H), 7.50-7.48 (m, 2H), 7.16-7.13 (m, 5H), 7.05-6.97 (m, 3H), 6.40 (s, 1H), 5.28-5.23 (m, 1H), 4.24-4.19 (m, 1H), 3.88-3.85 (m, 1H), 2.79-2.73 (m, 1H), 2.60 (dd, *J* = 4.9, 16.5 Hz, 1H), 2.51 (dd, *J* = 7.0, 16.5 Hz, 1H), 2.43-2.30 (m, 4H), 2.22 (dd, *J* = 4.9, 14.0 Hz, 1H), 2.03-1.98 (m, 1H), 1.88 (ddd, *J* = 7.0, 9.0, 10.8 Hz, 1H), 1.79-1.74 (m, 1H), 1.63-1.58 (m, 1H), 1.55-1.42 (m, 4H), 1.40-1.21 (m, 7H), 1.11 (d, *J* = 7.0 Hz, 3H), 0.88 (d, *J* = 7.3 Hz, 3H), 0.75 (d, *J* = 7.0 Hz, 3H), 0.71 (d, *J* = 6.7 Hz, 3H).

^{13}C NMR (C_6D_6, 125 MHz): δ 203.4, 176.5, 138.3, 136.7, 132.3 (2C), 131.0, 129.5 (2C), 128.95 (2C), 128.92 (2C), 128.7, 127.2, 125.0, 88.2, 82.7, 82.2, 75.6, 71.5, 45.1, 43.3, 40.4, 39.9, 37.2, 36.7, 34.6, 31.7, 31.2, 28.2, 27.8, 27.4, 19.5, 17.9, 14.49, 14.47, 13.8.

HRMS (ESI) $[M+Na]^+$: *m/z* calcd for $C_{38}H_{50}NaO_4$ 593.3601, obsd 593.3601.

$[\alpha]_D$ = +0.60 (23 °C, *c* = 3.4, CH_2Cl_2)



(−)-(2*S*)-Methyl-6-[(3*S*)-methyl-(5*R*)-(2-oxo-ethyl)-tetrahydro-furan-(2*S*)-yl]-hexanoic acid (5*R*)-methyl-3-oxo-7-phenyl-(1*R*)-propyl-hept-6-ynyl ester (9b). A solution of **58** in CH_2Cl_2 (91 mg, 0.16 mmol in 50 mL) was cooled to −78 °C. Ozone was bubbled through the solution until a blue color persisted. Argon was immediately bubbled through until the solution was colorless. Dimethylsulfide was added (0.8 ml) and the solution was allowed to slowly warm to ambient temperature over 3 h. The solution was concentrated and immediately purified by gradient column chromatography (85:15 hexane-EtOAc, polarity increased to 70:30 hexane-EtOAc). Two products were isolated: a diastereomeric ketoalkynyl-ozonide (less polar) and the desired ketoalkynal **9b** (more polar). The ozonide was dissolved in 10 ml CH_2Cl_2 and stirred with triphenylphosphine (256 mg) for 40 min. Concentration and purification on a silica gel column (elution with 80:20 hexane-EtOAc) afforded pure ketoynal which was combined with the original portion (combined: 63 mg, 80% overall yield). R_f (50:50 hexane-EtOAc) = 0.46.

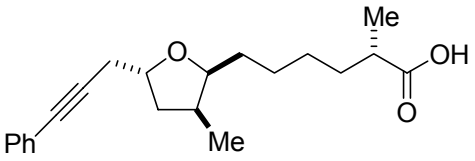
IR (thin film/NaCl): 2962, 2935, 2874, 1727 (br) cm^{-1}.

^1H NMR (C_6D_6, 500 MHz): δ 9.51 (dd, *J* = 1.8, 2.8 Hz, 1H), 7.48-7.46 (m, 2H), 7.16-6.97 (m, 3H), 5.50-5.45 (m, 1H), 4.23-4.18 (m, 1H), 3.66-3.63 (m, 1H), 3.25-3.21 (m, 1H), 2.52-2.46 (m, 2H), 2.41-2.37 (m, 1H), 2.27-2.21 (m, 2H), 2.16 (dd, *J* = 7.0, 16.5 Hz, 1H), 1.96 (ddd, *J* = 1.7, 5.3, 15.9 Hz, 1H), 1.85-1.81 (m, 1H), 1.77-1.72 (m, 1H), 1.58-1.38 (m, 5H), 1.36-1.19 (m, 8H), 1.16 (d, *J* = 6.7 Hz, 3H), 1.13 (d, *J* = 7.0 Hz, 3H), 0.82 (t, *J* = 7.3 Hz, 3H), 0.69 (d, *J* = 7.3 Hz, 3H).

^{13}C NMR (C_6D_6, 125 MHz): δ 205.8, 201.9, 176.4, 131. 8 (2C), 128.4 (2C), 128.0, 123.7, 93.2, 81.7, 81.2, 71.7, 69.9, 50.7, 50.1, 47.9, 40.2, 39.8, 36.5, 36.0, 33.8, 30.4, 27.6, 26.7, 22.4, 21.0, 18.7, 17.2, 14.06, 14.04.

HRMS (ESI)$[M+Na]^+$: *m/z* calcd for $C_{31}H_{44}O_5Na$ 519.3081, obsd 519.3077.

$[\alpha]_D$ = −2.5 (23 °C, *c* = 2.4, C_6H_6)



(+)-(2*S*)-Methyl-6-[(3*S*)-methyl-(5*R*)-(3-phenyl-prop-2-ynyl)-tetrahydro-furan-(2*S*)-yl]-hexanoic acid (10).[1] A flask containing lithium chloride (549 mg, 12.95 mmol) was flame-dried under a stream of Ar for five minutes, cooled to ambient temperature, and charged with THF (2.5 mL) and diisopropylamine (0.62 mL, 4.40 mmol). The heterogenous mixture was cooled to −78 °C and n-butyllithium was added (1.63 mL, 2.5M in hexane). The mixture was stirred 5 min at −78 °C, warmed to 0 °C for 30 min, then re-cooled to −78 °C. An ice-cooled solution of *N*-(2-Hydroxy-1-methyl-2-phenyl-ethyl)-*N*-methyl-propionamide in THF (474 mg, 2.14 mmol in 4.6 mL) was added slowly via cannula, followed by a 1.0 mL wash portion of THF. The mixture was allowed to stir 60 min at −78 °C, 15 min at 0 °C, and 5 min at ambient temperature before re-cooling to 0 °C. An ice-cooled solution of **26** in THF (391 mg, 1.02 mmol, in 1.8 mL) was added, followed by a 1.0 ml wash portion of THF. The mixture was stirred at 0 °C for 5h, at which point the reaction was quenched with saturated NH_4Cl (5 ml). H_2O and EtOAc were added (5 ml each), the layers were separated, and the aqueous phase extracted with EtOAc (3 x 10ml). The combined organic phases were dried over Na_2SO_4, filtered and concentrated to give a crude orange oil. The crude oil was purified by gradient column chromatography (90:10 CH_2Cl_2-EtOAc, polarity increased to 50:50) to afford the alkylated amide (R_f 50:50 CH_2Cl_2-EtOAc = 0.47). The amide was taken up in a 1:1 mixture of *t*-BuOH and CH_3OH (3.4 mL) and transferred to a sealable reaction tube equipped with a magnetic stirbar. NaOH was added (3.3 mL, 3.22N aqueous solution), the tube was sealed, and the mixture was heated to refluxed 48h. After cooling to ambient temperature, the volatile organic components were removed in vacuo. The remaining residue was stirred in CH_2Cl_2 and H_2O (20 ml each), forming an emulsion which was carefully acidified to pH < 2 by the addition of 6 N H_2SO_4. The resulting layers (now clearly distinct) were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 20 ml). The combined organic phases were dried over Na_2SO_4, filtered and concentrated to give a clear, pale yellow oil which was diastereomerically pure by ^{1}H NMR (298 mg, 89% yield over two steps). R_f (EtOAc) = 0.30.

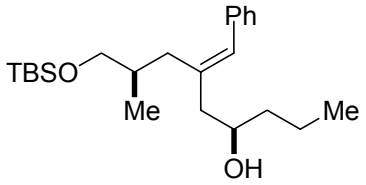
IR (thin film/NaCl): 3055 (br), 2936, 2860, 2241, 1950, 1705 cm^{-1}.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.41-7.39 (m, 2H), 7.29-7.27 (m, 3H), 4.33-4.28 (m, 1H), 4.00-3.97 (m, 1H), 2.68 (dd, *J* = 4.6, 16.6 Hz, 1H), 2.60 (dd, *J* = 7.0, 16.6 Hz, 1H), 2.50-2.43 (m, 1H), 2.35-2.28 (m, 1H), 2.09-2.03 (m, 1H), 1.87 (ddd, *J* = 3.7, 7.0, 12.5, 1H), 1.75-1.68 (m, 1H), 1.52-1.25 (m, 7H), 1.18 (d, *J* = 6.7 Hz, 3H), 0.94 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 182.7, 131.8 (2C), 128.4 (2C), 127.9, 124.0, 87.1, 82.3, 82.0, 75.2, 39.44, 39.37, 36.1, 33.7, 30.4, 27.6, 27.2, 26.7, 17.0, 14.2.

HRMS (ESI)[M-H]$^-$: *m/z* calcd for $C_{21}H_{27}O_3$ 327.1966, obsd 327.1963.

$[\alpha]_D$ = +2.9 (23 °C, *c* = 4.1, $CDCl_3$)



(+)-2-[3-(tert-Butyldimethylsilanyloxy)-(2*R*)-methylpropyl]-1-phenyl-hept-1-en-(4*R*)-ol (11). In a glovebox, $Ni(cod)_2$ (28 mg, 0.10 mmol) was placed in a 10 ml flask which was then sealed with a rubber septum. The flask was removed from the glovebox and placed under Ar. To this flask was added tributylphosphine (28 μL, 0.20 mmol), (*R*)-*n*-propyloxirane (**16**)[2] (degassed by bubbling Ar through for 10 min, 0.70 ml, 6.75 mmol), triethylborane (0.30 mL, 2.0 mmol), and **14** (290 mg, 1.0 mmol). The resulting dark brown solution was stirred at ambient temperature 14 h, then opened to the air for 1 h. Volatile organics were evaporated, and the crude residue was purified via gradient column chromatography (50:1 hexane-EtOAc, polarity gradually increased to 9:1) to afford the title compound as a clear, colorless oil (304 mg, 81% yield, 1 diastereomer by ^{1}H NMR). R_f (90:10, hexane-EtOAc) = 0.22.

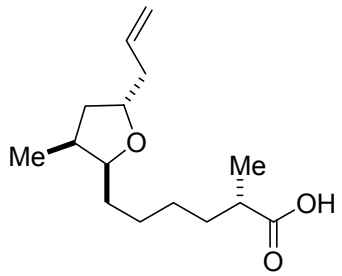
IR (thin film/NaCl): 3376, 2956, 2930, 2857, 1463 cm $^{-1}$.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.33-7.30 (m, 2H), 7.27-7.26 (m, 2H), 7.22-7.19 (m, 1H), 6.44 (s, 1H), 3.85-3.82 (m, 1H), 3.40 (dd, *J* = 6.0, 9.7 Hz, 1H), 3.32 (dd, *J* = 6.2, 9.9 Hz, 1H), 2.50 (dd, *J* = 6.4, 13.7 Hz, 1H), 2.42 (dd, *J* = 4.3, 13.7 Hz, 1H), 2.28-2.23 (m, 1H), 2.09-1.90 (m, 1H), 1.85 (s, 1H), 1.58-1.50 (m, 3H), 1.46-1.40 (m, 1H), 0.98 (t, *J* = 7.0 Hz, 3H), 0.88 (s, 9H), 0.85 (d, *J* = 6.7 Hz, 3H), 0.02 (s, 3H), 0.01 (s, 3H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 139.1, 138.0, 129.5, 129.1 (2C), 128.3 (2C), 126.4, 69.4, 68.2, 46.5, 39.5, 34.5, 34.3, 26.1 (3C), 19.2, 18.5, 17.1, 14.4, -5.21, -5.23.

HRMS (ESI) $[M+Na]^+$: *m/z* calcd for $C_{23}H_{40}NaO_2Si$ 399.2690, obsd 399.2675.

$[\alpha]_D$ = +10.5 (23 °C, *c* = 15.2, CH_2Cl_2).



(+)-6-[(5*R*)-Allyl-(3*S*)-methyl-tetrahydro-furan-(2*S*)-yl]-(2*S*)-methyl-hexanoic acid (12). A flask containing lithium chloride (490 mg, 11.56 mmol) was flame-dried under a

stream of Ar for five minutes, cooled to ambient temperature, and charged with THF (2.0 mL) and diisopropylamine (0.48 mL, 3.40 mmol). The heterogenous mixture was cooled to −78 °C and n-butyllithium was added (1.26 mL, 2.5M in hexane). The mixture was stirred 5 min at −78 °C, warmed to 0 °C for 30 min, then re-cooled to −78 °C. An ice-cooled solution of *N*-(2-hydroxy-1-methyl-2-phenyl-ethyl)-*N*-methyl-propionamide in THF (350 mg, 1.58 mmol in 3.3 mL) was added slowly via cannula, followed by a 1.0 mL wash portion of THF. The mixture was allowed to stir 60 min at −78 °C, 15 min at 0 °C, and 5 min at ambient temperature before re-cooling to 0 °C. An ice-cooled solution of iodide **35** in THF (262 mg, 0.85 mmol, in 1.2 mL) was added, followed by a 1.0 ml wash portion of THF. The mixture was stirred at 0 °C for 3h, at which point the reaction was quenched with saturated NH_4Cl (5 ml). H_2O and EtOAc were added (5 ml each), the layers were separated, and the aqueous phase extracted with EtOAc (3 x 10ml). The combined organic phases were dried over Na_2SO_4, filtered and concentrated to give a crude yellow oil. The crude oil was purified by gradient column chromatography (90:10 CH_2Cl_2-EtOAc, polarity increased to 50:50) to afford the alkylated amide (R_f 50:50 CH_2Cl_2-EtOAc = 0.35). The amide was taken up in a 1:1 mixture of *t*-BuOH and CH_3OH (2.64 mL) and transferred to a 25 mL flask equipped with a magnetic stirbar. NaOH was added (2.64 mL, 3.22N aqueous solution), the flask was equipped with a reflux condensor, and the mixture was heated to reflux 48h. After cooling to ambient temperature, CH_2Cl_2 and H_2O were added (20 ml each). Acidification to pH < 2 was effected by the addition of 6 N H_2SO_4. The resulting layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 20 ml). The combined organic phases were dried over Na_2SO_4, filtered and concentrated to give a clear, pale yellow oil which was diastereomerically pure by ^{1}H NMR (191 mg, 88% yield over two steps). R_f (EtOAc) = 0.85.

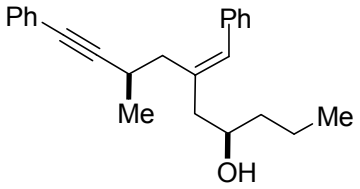
IR (thin film/NaCl): 3077 (br), 2965, 2937, 2862, 1706, 1642 cm^{-1}.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 10.8 (br s, 1H), 5.83-5.75 (m, 1H), 5.09-5.02 (m, 2H), 4.15-4.09 (m, 1H), 3.87-3.83 (m, 1H), 2.48-2.41 (m, 1H), 2.36-2.30 (m, 1H), 2.25-2.16 (m, 2H), 1.79-1.65 (m, 3H), 1.52-1.33 (m, 6H), 1.32-1.25 (m, 1H), 1.16 (d, *J* = 7.0 Hz, 3H), 0.89 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 183.0, 135.2, 117.0, 81.5, 76.2, 41.2, 39.5, 39.4, 36.0, 33.7, 30.4, 27.6, 26.7, 17.0, 14.2.

HRMS (ESI)$[M-H]^-$: *m/z* calcd for $C_{15}H_{25}O_3$ 253.1798, obsd 253.1801.

$[\alpha]_D$ = +8.4 (23 °C, *c* = 4.5, CH_2Cl_2)



(+)-6-Benzylidene-(8*R*)-methyl-10-phenyl-dec-9-yn-(4*R*)-ol (13). Copper (I) iodide (100 mg, 0.54 mmol) and palladium tetrakis(triphenylphosphine) (39 mg, 0.033 mmol) were combined in a round bottom flask. The flask was evacuated and back-filled with Ar three times. Pyrrolidine (3.0 mL), alkyne **54** (132 mg, 0.51 mmol in 0.5 ml pyrrolidine), and iodobenzene (200 μL, 1.79 mmol) were added sequentially and the mixture was stirred at ambient temperature 16 h. Et_2O was added (20 mL) and the mixture was filtered through a plug of silica gel. Solvent was evaporated, and the crude residue was purified via column chromatography (9:1 hexane-EtOAc) to afford the title compound as a clear, yellow oil (147 mg, 86% yield). R_f (90:10, hexane-EtOAc) = 0.15.

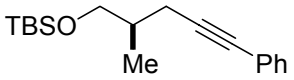
IR (thin film/NaCl): 3417, 2958, 2930, 2871, 1598, 1491, 1442 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ 7.40-7.32 (m, 6H), 7.28-7.22 (m, 4H), 6.56 (s, 1H), 3.90-3.86 (m, 1H), 2.99-2.93 (m, 1H), 2.74 (dd, *J* = 9.8, 13.7 Hz, 1H), 2.68-2.56 (m, 1H), 2.35 (dd, *J* = 5.8, 13.7 Hz, 1H), 2.26 (dd, *J* = 9.8, 13.8 Hz, 1H), 1.87 (br s, 1H), 1.57-1.39 (m, 4H), 1.27 (d, *J* = 6.7 Hz, 3H), 0.96 (t, *J* = 7.0 Hz, 3H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 137.9, 137.7, 131.7 (2C), 130.7, 129.1, 128.39 (2C), 128.36 (2C), 127.8 (2C), 126.7, 123.8, 93.8, 81.9, 69.3, 45.6, 39.5, 37.4, 25.3, 21.5, 19.2, 14.4.

HRMS (ESI) $[M+Na]^+$: *m/z* calcd for $C_{24}H_{28}ONa$ 355.2032, obsd 355.2021.

$[\alpha]_D$ = +12.2 (23 °C, *c* = 3.2, $CDCl_3$)



(+)-1-(*t*-butyldimethylsiloxy)-(2*R*)-methyl-5-phenyl-4-pentyne (14). A 50 mL round bottom flask was charged with **33** (1.1 g, 6.3 mmol), imidazole (0.79 g, 11.6 mmol), *t*-butyldimethylsilylchloride (1.6 g, 10.6 mmol) and DMF (6.3 ml). The solution was stirred 20 h at ambient temperature, then partitioned between H_2O and Et_2O (80 mL each). The ethereal layer was washed with H_2O (3 x 100 mL), brine (3 x 100 mL), dried over $MgSO_4$, filtered and concentrated in vacuo. The crude residue was purified via gradient column chromatography (50:1 hexane-EtOAc, polarity gradually increased to 19:1) to afford the title compound as a clear, colorless oil (1.74 g, 96% yield). R_f (hexane) = 0.21.

IR (thin film/NaCl): 2956, 2929, 2857, 1490, 1471 cm^{-1}.

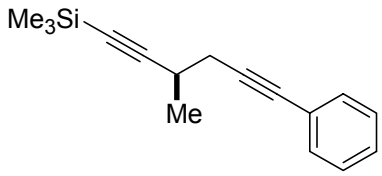
^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.42-7.40 (m, 2H), 7.32-7.27 (m, 3H), 3.60-3.54 (m, 2H), 2.52 (dd, *J* = 5.8, 16.5 Hz, 1H), 2.37 (dd, *J* = 7.0, 16.7 Hz, 1H), 1.97-1.93 (m, 1H), 1.05 (d, *J* = 6.7 Hz, 3H), 0.93 (s, 9H), 0.09 (s, 6H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 131.7 (2C), 128.4 (2C), 127.7, 124.3, 89.1, 81.7, 67.1, 35.7, 26.2, 26.1, 23.2, 18.6, 16.4, -5.13, -5.15, -5.18.

HRMS (ESI) $[M+Na]^+$: *m/z* calcd for $C_{18}H_{28}NaOSi$ 311.1802, obsd 311.1806.

$[\alpha]_D$ = +1.2 (23 °C, *c* = 10.7, CH_2Cl_2).

ent-**14**: $[\alpha]_D$ = −15.1 (23 °C, *c* = 4.1, CH_2Cl_2).



(−)-Trimethyl-[(3*R*)-methyl-6-phenyl-hexa-1,5-diynyl]-silane (15). A solution of dibromide **52** in THF (421 mg, 1.29 mmol in 3.5 mL) was cooled to −78 °C. A 1.6 M solution of methyllithium in Et_2O was added dropwise (2.0 mL, 3.23 mmol) and the solution was stirred 1.5 h at −78 °C. Chlorotrimethylsilane was filtered through basic alumina and immediately added dropwise (0.49 ml, 3.87 mmol) to the reaction. The solution was stirred 14 h, warming to ambient temperature slowly. Saturated NH_4Cl was added (1 mL), and the mixture was diluted with Et_2O and H_2O (2 ml each). The aqueous phase was extracted with Et_2O (3 x 5 mL), and the combined organic layers were washed with brine (3 x 15 ml), dried over $MgSO_4$, filtered and concentrated. The crude residue was purified via gradient column chromatography (50:1 hexanes:EtOAc, polarity gradually increased to 19:1) to afford the product as a clear, colorless oil (284 mg, 92% yield). R_f (90:10, hexane:EtOAc) =0.62.

IR (thin film/NaCl): 2962, 2932, 2907, 2170, 1491, 1280 cm^{-1}.

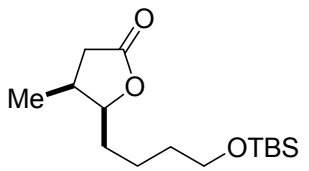
^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.43-7.41 (m, 2H), 7.30-7.29 (m, 3H), 2.80-2.73 (m, 1H), 2.67 (dd, *J* = 5.5, 16.8 Hz, 1H), 2.52 (dd, *J* = 7.9, 16.8 Hz, 1H), 1.34 (d, *J* = 7.0 Hz, 3H), 0.17 (s, 9H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 131.8 (2C), 128.4 (2C), 127.9, 123.9, 110.3, 87.7, 85.2, 82.4, 27.5, 27.0, 20.4, 0.4 (3C).

HRMS (ESI) $[M+Na]^+$: *m/z* calcd for $C_{16}H_{20}NaSi$ 263.1226, obsd 263.1227.

$[\alpha]_D = -3.0$ (23 °C, $c = 5.4$, CH_2Cl_2).

ent-**15**: $[\alpha]_D = +27.6$ (23 °C, $c = 5.4$, CH_2Cl_2).



(−)-(5*S*)-[4-(tert-Butyldimethylsilanyloxy)-butyl]-(4*S*)-methyl-dihydro-furan-2-one (20).[3] A 100 mL flask was charged with 3Ä powdered molecular sieves (8.1 g) and 4-*N*-methylmorpholine-*N*-oxide (5.70 g, 49.1 mmol). A solution of **45** in dry CH_3CN (4.75 g, 16.4 mmol in 160 mL) was added via cannula and the mixture was stirred 5 min. Tetrapropylammonium perruthenate was added slowly (0.86 g, 2.5 mmol), and the mixture was stirred 14h. Silica gel was added, and the solvent was evaporated. The dry silica gel was loaded onto a slurry-packed column (70:30 hexanes-EtOAc), eluted and concentrated to give the title compound as a clear, colorless oil (3.35 g, 71% yield, 93% ee). R_f (70:30, hexane-EtOAc) = 0.34.

IR (thin film/NaCl): 2930, 2858, 1780 cm $^{-1}$.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 4.45-4.41 (m, 1H), 3.64-3.59 (m, 2H), 2.69 (dd, J = 7.9, 17.0 Hz, 1H), 2.60-2.55 (m, 1H), 2.19 (dd, J = 3.8, 17.0 Hz, 1H), 1.70-1.59 (m, 1H), 1.58-1.47 (m, 4H), 1.45-1.40 (m, 1H), 1.00 (d, J = 7.0 Hz, 3H), 0.88 (s, 9H), 0.04 (s, 6H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 177.1, 83.8, 63.0, 37.7, 33.1, 32.7, 29.9, 26.1 (3C), 22.5, 18.5, 14.0, -5.1 (2C).

HRMS (ESI) $[M+Na]^+$: *m/z* calcd for $C_{15}H_{30}NaO_3Si$ 309.1856, obsd 309.1840.

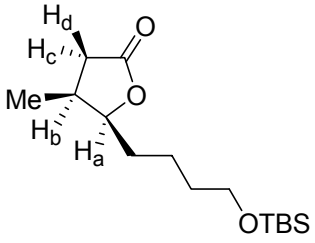
$[\alpha]_D = -37.0$ (23 °C, $c = 10.6$, CH_2Cl_2).

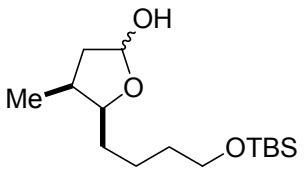
Chiral GC analysis was performed on the acetate derivative (OAc instead of OTBS): (G-TA, isothermal, column = 150 °C, injector = 200 °C, flow (H_2) = 1.5 ml/min): $t_R[(S,S)]$ = 21.32 min; $t_R[(R,R)]$ = 21.86 min).

Relative configuration confirmed by nOe studies:

Summary of nOe data:

H_a-H_b: 5.7%
H_a-H_c: 1.8%
H_{Me}-H_b: 2.0%
H_{Me}-H_d: 2.3%





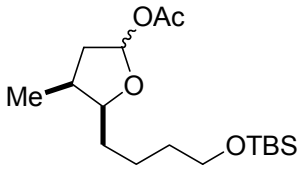
(5*S*)-[4-(tert-Butyldimethylsilanyloxy)-butyl]-(4*S*)-methyl-tetrahydro-furan-2-ol (21a).[3] Diisobutylaluminum hydride (4.3 ml, 1.0 M in hexane, 4.3 mmol) was added to a cooled solution (−78 °C) of **20** in CH_2Cl_2 (1.02 g, 3.6 mmol, in 70 ml CH_2Cl_2). The solution was stirred 1 h, then quenched with saturated NH_4Cl (5 ml) and allowed to warm to ambient temperature. The aqueous phase was extracted with CH_2Cl_2 (3 x 10 ml), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated to give the title compound as a clear, colorless oil that was used without purification (1.00 g, 97% yield, 2.4:1 d.r.). R_f (70:30, hexane-EtOAc) = 0.29.

IR (thin film/NaCl): 3411, 2935, 2858 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ major 5.52-5.51(m, 1H), minor 5.43 (m, 1H), major 4.13-4.10 (m, 1H), 3.92 (s, 1H, OH) minor 3.88-3.86 (m, 1H), 3.61-3.58 (m, 2H), major 2.40-2.33 (m, 1H), minor 2.23-2.21 (m, 1H), 2.00-1.96 (m, 1H), 1.79-1.75 (m, 1H), 1.61-1.52 (m, 2H), 1.50-1.30 (m, 4H), minor 1.03 (d, J = 6.9 Hz, 3H), 0.87-0.83 (m, 9H + 3H from major diastereomer), 0.03 (s, 6H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 98.4 (minor 97.4), 82.9 (minor 80.7), 63.3 (minor 63.2), 42.1 (minor 41.3), 34.5 (minor 35.0), 33.1 (minor 33.0), 30.3 (minor 31.0), 26.1, 22.89 (minor 22.93), 18.5, 14.6 (minor 14.8), -5.1.

HRMS (ESI) $[M+Na]^+$: *m/z* calcd for $C_{15}H_{32}NaO_3Si$ 311.2013, obsd 311.2004.



Acetic acid (5*S*)-[4-(tert-butyldimethylsilanyloxy)-butyl]-(4*S*)-methyl-tetrahydro-furan-2-yl ester (21b). A solution of **20** in CH_2Cl_2 was cooled to -78 °C (0.86 g, 3.0 mmol, in 60 mL). DIBAL-H was added via syringe (3.6 mL, 1.0 M in CH_2Cl_2, 3.6 mmol) and the solution was stirred at -78 °C for 2h. 4-Dimethylaminopyridine (0.44 g, 3.6 mmol), acetic anhydride (2.83 mL, 30 mmol), and pyridine (1.94 mL, 24 mmol) were added sequentially. The mixture was stirred at -78 °C for 15 min, then allowed to warm to ambient temperature and stir 18h. The reaction was quenched by addition of saturated NH_4Cl (30 mL), and the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (5 x 30 mL) and concentrated. The crude residue was partitioned between Et_2O and H_2O (50 mL each). The ethereal layer was washed with saturated NH_4Cl (2 x 25

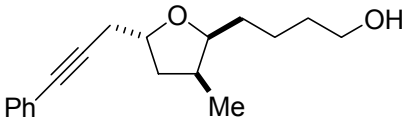
mL) and brine (2 x 50 mL), dried over $MgSO_4$, filtered and concentrated. The crude oil was purified via column chromatography (90:10 hexanes:EtOAc) to afford the title compound as a clear, slightly yellow oil (0.79 g, 80% yield, 1.3:1 d.r.). R_f (95:5, EtOAc:hexane) = 0.14.

IR (NaCl): 2931, 2858, 1749, 1250 cm $^{-1}$.

^{1}H NMR ($CDCl_3$, 500 MHz): δ major 6.24 (dd, *J* = 2.3, 5.6 Hz, 1H), minor 6.16 (dd, *J* = 1.8, 6.1 Hz, 1H), major 4.12-4.08 (m, 1H), minor 3.98-3.96 (m, 1H), 3.61-3.57 (m, 2H), 2.43-2.36 (m, 1H), major 2.10 (ddd, *J* = 2.4, 7.3, 13.7 Hz, 1H), 2.02 (s, 3H), major 1.88 (dt, *J* = 5.8, 13.7 Hz, 1H), minor 1.75 (ddd, *J* = 2.0, 4.3, 13.6 Hz, 1H), 1.57-1.32 (m, 6H), minor 1.02 (d, *J* = 7.0 Hz, 3H), major 0.91 (d, *J* = 7.0 Hz, 3H), 0.87 (s, 9H), 0.03 (s, 6H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 170.8 (minor 170.7), 98.3 (minor 98.8), 82.6 (minor 84.4), 63.2, 40.6 (minor 40.1), 33.9 (minor 34.3), 33.0, 30.2 (minor 30.7), 26.1, 22.7 (minor 22.8), 21.60 (minor 21.64), 18.5, 14.4 (minor 14.3), -5.1.

HRMS (ESI) $[M+Na]^+$: *m/z* calcd for $C_{17}H_{34}NaO_4Si$ 353.2119, obsd 353.2108.



(+)-4-[(3*S*)-Methyl-(5*R*)-(3-phenyl-prop-2-ynyl)-tetrahydro-furan-(2*S*)-yl]-butan-1-ol (23). A solution of **21a** (480 mg, 1.65 mmol) and trimethyl-(1-phenyl-propa-1,2-dienyl)-silane (**22**)[4] (1.39mL, 0.89 g/mL, 6.60 mmol) in 3.3 mL CH_2Cl_2 was cooled to −78 °C. $BF_3{\cdot}OEt_2$ (0.63 mL, 4.95 mmol) was added dropwise via syringe, and the mixture was stirred for 2 h, then allowed to warm to ambient temperature slowly over 14 h. The reaction was quenched by dropwise addition of saturated $NaHCO_3$ (2 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 4 mL), dried over Na_2SO_4, filtered and concentrated. The crude residue was purified by gradient column chromatography (90:10 CH_2Cl_2-EtOAc, polarity increased to 50:50) to afford the title compound as a clear, yellow oil (180 mg, 41% yield). R_f (50:50, EtOAc-CH_2Cl_2) = 0.47.

IR (thin film/NaCl): 3395, 2936, 2870, 2361 cm $^{-1}$.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.41-7.39 (m, 2H), 7.29-7.28 (m, 3H), 4.33-4.28 (m, 1H), 4.02-3.98 (m, 1H), 3.67 (t, *J* = 6.6 Hz, 2H), 2.67 (dd, *J* = 4.8, 16.6 Hz, 1H), 2.60 (dd, *J* = 7.0, 16.6 Hz, 1H), 2.34-2.32 (m, 1H), 2.07 (ddd, *J* = 7.0, 9.0, 10.8 Hz, 1H), 1.89 (ddd, *J* = 3.7, 7.0, 12.5 Hz, 1H), 1.65-1.61 (m, 2H), 1.54-1.50 (m, 2H), 1.46-1.41 (m, 2H), 0.94 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 131.8 (2C), 128.4 (2C), 127.9, 124.0, 87.1, 82.3, 82.0, 75.3, 63.1, 39.4, 36.2, 33.0, 30.3, 27.2, 23.0, 14.2.

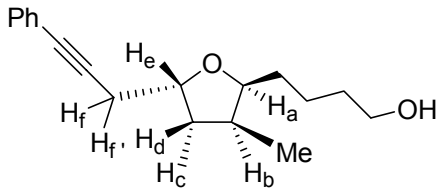
HRMS (ESI) $[M+H]^+$: *m/z* calcd for $C_{18}H_{24}O_2$ 273.1849, obsd 273.1856.

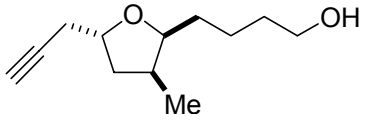
$[\alpha]_D$ = +1.0 (23 °C, *c* = 7.8, CH_2Cl_2).

Relative configuration confirmed by nOe studies:

Summary of nOe data:

H_a-H_b: 3.4%
H_a-H_c: 0.3%
H_e-H_d: 2.9%
H_e-H_f/$H_{f'}$: 2.9%





(−)-4-[(3*S*)-Methyl-(5*R*)-(prop-2-ynyl)-tetrahydro-furan-(2*S*)-yl]-butan-1-ol (25). A solution of **21a** (340 mg, 1.20 mmol) and triphenyl-propa-1,2-dienyl-stannane (**24**)[5] (930 mg, 2.39 mmol) in 3.6 mL CH_2Cl_2 was cooled to −78 °C. $BF_3{\cdot}OEt_2$ (0.46 mL, 3.60 mmol) was added dropwise via syringe, and the mixture was stirred for 2 h, then allowed to warm to ambient temperature slowly over 14 h. The reaction was quenched by dropwise addition of saturated $NaHCO_3$ (2 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 5 mL), dried over Na_2SO_4, filtered and concentrated. The crude residue was purified by gradient column chromatography (90:10 hexane-EtOAc, polarity increased to 50:50) to afford the title compound as a clear, colorless oil (207 mg, 88% yield). R_f (50:50, EtOAc-hexane) = 0.26.

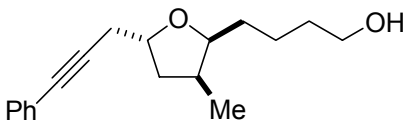
IR (thin film/NaCl): 3384, 3294, 2934, 2870, 2119 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ 4.25-4.19 (m, 1H), 3.97-3.93 (m, 1H), 3.65 (t, *J* = 6.7 Hz, 2H), 2.44 (ddd, *J* = 2.6, 5.2, 16.6 Hz, 1H), 2.37 (ddd, *J* = 2.7, 6.8, 16.6 Hz, 1H), 2.32-2.27 (m, 1H), 1.99-1.93 (m, 2H), 1.82 (ddd, *J* = 3.7, 7.0, 12.5 Hz, 1H), 1.64-1.58 (m, 2H), 1.55-1.46 (m, 2H), 1.43-1.35 (m, 2H), 0.92 (d, *J* = 7.3 Hz, 3H).

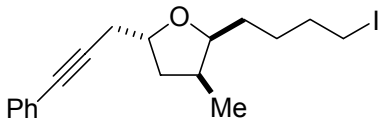
^{13}C NMR ($CDCl_3$, 125 MHz): δ 82.2, 81.5, 75.0, 69.8, 63.0, 39.3, 36.1, 33.0, 30.2, 26.2, 22.9, 14.1.

HRMS (ESI) $[M+Na]^+$: *m/z* calcd for $C_{12}H_{20}NaO_2$ 219.1356, obsd 219.1351.

$[\alpha]_D$ = −1.0 (23 °C, *c* = 3.0, CH_2Cl_2)



23. Prepared from terminal alkyne **25**: Copper (I) iodide (83 mg, 0.44 mmol) and palladium tetrakis(triphenylphosphine) (170 mg, 0.15 mmol) were combined in a round bottom flask with alkyne **25** (296 mg, 1.48 mmol). The flask was evacuated and back-filled with Ar three times. Pyrrolidine (5.0 mL) and iodobenzene (0.50 mL, 4.46 mmol) were added sequentially and the mixture was stirred at ambient temperature 3.5 h. Et_2O was added (10 mL) and the mixture was filtered through a plug of silica gel. Solvent was evaporated, and the crude residue was purified via column chromatography (70:30 hexane-EtOAc, polarity gradually increased to 50:50 hexane-EtOAc) to afford the title compound as a clear, yellow oil (395 mg, 98% yield).



(+)-(2*S*)-(4-Iodo-butyl)-(3*S*)-methyl-(5*R*)-(3-phenyl-prop-2-ynyl)-tetrahydro-furan (26). A solution of **23** in a 2:3 mixture of CH_3CN-Et_2O (383 mg, 1.40 mmol, in 4.2 mL) was cooled to 0 °C. Imidazole (124 mg, 1.82 mmol), triphenylphosphine (440 mg, 1.68 mmol), and iodine (497 mg, 1.96 mmol) were added sequentially, and the brown heterogeneous mixture was stirred at 0 °C for 3.5 h. Silica gel was added, and the solvents were removed in vacuo. The dry silica gel was loaded onto a slurry-packed column (95:5 hexane-EtOAc), the title compound was eluted and concentrated to give a clear, pale yellow oil (391 mg, 73% yield). R_f (90:10 hexane-EtOAc) = 0.30.

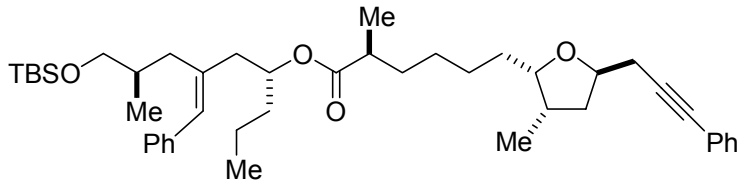
IR (thin film/NaCl): 3055, 2960, 2934, 2872, 1598 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ 7.43-7.38 (m, 2H), 7.33-7.26 (m, 3H), 4.31 (ddd, *J* = 5.0, 6.8, 14.0 Hz, 1H), 4.03-3.97 (m, 1H), 3.22 (t, *J* = 6.9 Hz, 2H), 2.70 (dd, *J* = 5.0, 16.5 Hz, 1H), 2.62 (dd, *J* = 6.9, 16.5 Hz, 1H), 2.39-2.31 (m, 1H), 2.13-2.04 (m, 1H), 1.95-1.85 (m, 3H), 1.61-1.39 (m, 4H), 0.97 (d, *J* = 6.9 Hz, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 131.6 (2C), 128.2 (2C), 127.7, 123.8, 87.0, 81.92, 81.89, 75.2, 39.4, 36.2, 33.9, 29.6, 27.8, 27.3, 14.3, 7.3.

HRMS (ESI) $[M+Na]^+$: *m/z* calcd for $C_{18}H_{23}INaO$ 405.0763, obsd 405.0679.

$[\alpha]_D$ = +16.0 (23 °C, *c* = 7.5, $CHCl_3$)



(+)-(2*S*)-Methyl-6-[(3*S*)-methyl-(5*R*)-(3-phenyl-prop-2-ynyl)-tetrahydro-furan-(2*S*)-yl]-hexanoic acid 3-benzylidene-6-(tert-butyl-dimethyl-silanyloxy)-(5*R*)-methyl-(1*R*)-propyl-hexyl ester (27). A flask containing **10** (21 mg, 0.064 mmol) was charged with **11** (31 mg, 0.083 mmol), dicyclohexylcarbodiimide (21 mg, 0.102 mmol), 4-pyrrolidinopyridine (15 mg, 0.101 mmol), and CH_2Cl_2 (0.42 ml). The mixture was stirred 24 h at ambient temperature. Silica gel was added, and the solvents were removed in vacuo. The dry silica gel was loaded onto a slurry-packed column (90:10 hexane-EtOAc) and the title compound was eluted to give a clear, colorless oil (28 mg, 72% yield) upon concentration. R_f (90:10, hexane-EtOAc) = 0.39.

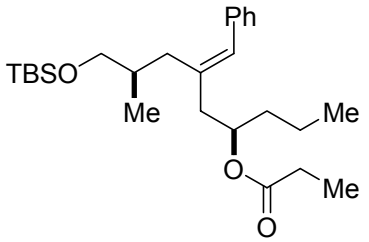
IR (thin film/NaCl): 2933, 2857, 1730, 1463 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ 7.41-7.39 (m, 2H), 7.31-7.28 (m, 5H), 7.19-7.16 (m, 3H), 6.36 (s, 1H), 5.14-5.11 (m, 1H), 4.31-4.26 (m, 1H), 3.96-3.92 (m, 1H), 3.40 (dd, *J* = 5.5, 9.8 Hz, 1H), 3.23 (dd, *J* = 6.6, 9.8 Hz, 1H), 2.68 (dd, *J* = 4.9, 16.5 Hz, 1H), 2.59 (dd, *J* = 7.0, 16.5 Hz, 1H), 2.44-2.34 (m, 3H), 2.32-2.27 (m, 1H), 2.14 (dd, *J* = 8.2, 14.0 Hz, 1H), 2.05 (ddd, *J* = 7.0, 9.0, 10.8 Hz, 1H), 1.92-1.84 (m, 2H), 1.69-1.63 (m, 1H), 1.60-1.56 (m, 2H), 1.51-1.22 (m, 10H), 1.09 (d, *J* = 6.7 Hz, 3H), 0.93 (t, *J* = 7.3 Hz, 3H), 0.92 (d, *J* = 7.0 Hz, 3H), 0.86 (s, 9H), 0.82 (d, *J* = 6.7 Hz, 3H), -0.01 (s, 3H), -0.02 (s, 3H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 176.7, 138.3, 138.0, 131.8 (2C), 129.3, 129.1 (2C), 128.4 (2C), 128.2 (2C), 127.9, 126.3, 124.0, 87.1, 82.3, 81.9, 75.2, 71.9, 68.2, 42.8, 40.0, 39.4, 36.6, 36.1, 34.3, 34.01, 33.95, 30.5, 27.7, 27.2, 26.7, 26.1 (3C), 18.9, 18.5, 17.4, 17.1, 14.23, 14.19, -5.20, -5.22.

HRMS (ESI) $[M+Na]^+$: *m/z* calcd for $C_{44}H_{66}NaO_4Si$ 709.4623, obsd 709.4611.

$[\alpha]_D$ = +1.0 (23 °C, *c* = 4.9, $CDCl_3$)



(+)-Propionic acid 3-benzylidene-6-(tert-butyl-dimethyl-silanyloxy)-(5*R*)-methyl-(1*R*)-propyl-hexyl ester (28). To a solution of alcohol **11** in CH_2Cl_2 (96 mg, 0.25 mmol, in 1.5 mL) was added propionic anhydride (50 μL, 0.38 mmol), pyridine (31 μL, 0.38 mmol), and 4-dimethylaminopyridine (3 mg, 0.025 mmol). The solution was allowed to

stir at ambient temperature 16h. After concentration, the crude residue was taken up in 30 mL Et_2O, washed with saturated NH_4Cl (3 x 15ml) and brine (3 x 15 mL), dried over $MgSO_4$, filtered and concentrated. Purification via column chromatography (50:1 hexanes-EtOAc) afforded the title compound as a colorless oil (110 mg, >99% yield). R_f (95:5, hexane-EtOAc) = 0.28.

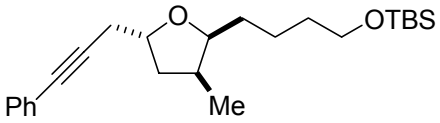
IR (thin film/NaCl): 2958, 2930, 2857, 1735, 1463 cm $^{-1}$.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.30-7.28 (m, 2H), 7.20-7.16 (m, 2H), 7.06-7.03 (m, 1H), 6.46 (s, 1H), 5.40-5.35 (m, 1H), 3.40 (dd, *J* = 5.5, 9.8 Hz, 1H), 3.27 (dd, *J* = 6.1, 9.8 Hz, 1H), 2.61 (dd, *J* = 6.4, 14.0 Hz, 1H), 2.47 (dd, *J* = 7.9, 13.5 Hz, 1H), 2.38-2.31 (m, 2H), 2.15-2.12 (m, 2H), 2.09-2.04 (m, 1H), 1.65-1.46 (m, 2H), 1.43-1.32 (m, 2H), 1.00 (t, *J* = 7.6 Hz, 3H), 0.96 (s, 9H), 0.91-0.87 (m, 6H), 0.034 (s, 3H), 0.028 (s, 3H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 173.8, 139.0, 138.7, 130.0, 129.6 (2C), 128.8 (2C), 126.9, 72.1, 68.6, 43.7, 37.1, 35.0, 34.6, 28.3, 26.5 (3C), 19.5, 18.9, 17.4, 14.5, 9.8, -4.9 (2C).

HRMS (ESI) $[M+Na]^+$: *m/z* calcd for $C_{26}H_{44}NaO_3Si$ 433.3132, obsd 433.3123.

$[\alpha]_D$ = +0.77 (23 °C, *c* = 2.6, CH_2Cl_2).



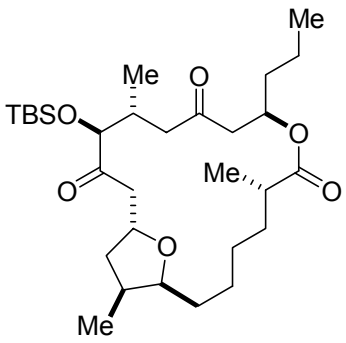
tert-Butyldimethyl-{4-[(3*S*)-methyl-(5*R*)-(3-phenyl-prop-2-ynyl)-tetrahydro-furan-2-yl]-butoxy}-silane (30). Obtained in some reactions. R_f (90:10, hexane-EtOAc) = 0.34.

IR (thin film/NaCl): 2956, 2930, 2857, 1254 cm $^{-1}$.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.41-7.39 (m, 2H), 7.29-7.28 (m, 3H), 4.30 (d^4, *J* = 4.9, 7.0, 7.0, 7.0 Hz, 1H), 3.99 (m, 1H), 3.65-3.60 (m, 2H), 2.68 (dd, *J* = 4.7, 16.6 Hz, 1H), 2.60 (dd, *J* = 7.2, 16.6 Hz, 1H), 2.34-2.28 (m, 1H), 2.06 (ddd, *J* = 7.3, 9.0, 10.8 Hz, 1H), 1.87 (ddd, *J* = 3.4, 7.0, 12.5 Hz, 1H), 1.60-1.32 (m, 6H), 0.94 (d, *J* = 7.0 Hz, 3H), 0.90 (s, 9H), 0.05 (s, 6H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 131.8 (2C), 128.4 (2C), 127.9, 124.0, 87.1, 82.3, 81.9, 75.2, 63.3, 39.4, 36.1, 33.2, 30.4, 27.2, 26.20, 26.19 (3C), 22.9, 14.2, -5.0 (2C).

HRMS (ESI) $[M+Na]^+$: *m/z* calcd for $C_{24}H_{38}NaO_2Si$ 409.2535, obsd 409.2529.



(−)-(14*S*)-(tert-Butyl-dimethyl-silanyloxy)-(6*S*,13*R*,19*R*)-trimethyl-(9*R*)-propyl-8,20-dioxa-bicyclo[15.2.1]icosane-7,11,15-trione (32). A solution of **49** in CH_2Cl_2 was prepared (9.1 mg, 0.013 mmol in 2.0 ml) and cooled to −78 °C. Ozone was bubbled through the solution until a persistent blue color was observed. The ozone source was removed, and the saturated solution was stirred 15 min. After this time, Ar was bubbled through the solution until it was colorless. Methyl sulfide (0.10 ml) was added via syringe. The solution was allowed to warm to ambient temperature over 6 h; then concentrated. The crude residue was purified via Pasteur pipet gradient column chromatography (50:1 hexane-EtOAc, polarity gradually increased to 9:1 hexane-EtOAc) to give the title compound as a clear, yellow oil (3.0 mg, 43% yield). R_f (90:10, hexane-EtOAc) = 0.21.

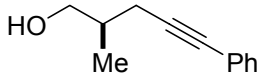
IR (thin film/NaCl): 2960, 2932, 2857, 1730, 1728, 1713, 1259 cm^{-1}.

^{1}H NMR (C_6D_6, 500 MHz): δ 5.64-5.59 (m, 1H), 4.71-4.66 (m, 1H), 4.47 (d, *J* = 1.5 Hz, 1H), 3.82-3.80 (m, 1H), 3.08-3.03 (m, 1H), 3.05 (dd, *J* = 10.7, 14.0 Hz, 1H), 2.67 (dd, *J* = 10.1, 19.2 Hz, 1H), 2.43-2.37 (m, 2H), 2.17 (dd, *J* = 2.4, 19.2 Hz, 1H), 1.97 (dd, *J* = 2.4, 14.8 Hz, 1H), 1.83 (dd, *J* = 1.7 Hz, 14.2 Hz, 1H), 1.67-1.62 (m, 1H), 1.61-1.53 (m, 2H), 1.50-1.43 (m, 2H), 1.41-1.35 (m, 3H), 1.31-1.20 (m, 3H), 1.18-1.09 (m, 4H), 1.08-1.07 (m, 12H), 1.01 (d, *J* = 7.0 Hz, 3H), 0.80 (t, *J* = 7.0 Hz, 3H), 0.65 (d, *J* = 7.0 Hz, 3H), 0.25 (s, 3H), 0.03 (s, 3H).

^{13}C NMR (C_6D_6, 125 MHz): δ 208.7, 208.2, 174.3, 81.1, 77.7, 74.6, 71.2, 50.1, 46.5, 46.3, 43.2, 40.8, 37.3, 37.1, 37.0, 31.4, 28.2, 27.6, 27.3, 26.5 (3C), 26.3, 18.9, 18.8, 14.6, 14.5, 14.2, -3.8, -4.9.

HRMS (ESI) $[M+Na]^+$: *m/z* calcd for $C_{30}H_{54}NaO_6Si$ 561.3582, obsd 561.3587.

$[\alpha]_D$ = −5.0 (23 °C, *c* = 0.8, $CDCl_3$)



(+)-(2*R*)-methyl-5-phenyl-pent-4-yn-1-ol (33). A solution of **43** (0.69 g, 2.3 mmol in 8 mL THF) was cooled to 0 °C. $LiAlH_4$ was added slowly in one portion (0.26 g, 6.9

mmol). The slurry was stirred 1 h at 0 °C, then quenched with 0.75 mL H_2O. Saturated Rochelle's salt solution (10 mL) and Et_2O (15 mL) were added, and the mixture was stirred 30 min to aid in disrupting the emulsion. After this time, the opaque aqueous phase was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (3 x 40 mL), dried over $MgSO_4$, filtered and concentrated in vacuo. The crude residue was purified via column chromatography (95:5 CH_2Cl_2-EtOAc) to afford the title compound as a pale yellow oil (315 mg, 79% yield, 98% ee). R_f (95:5, CH_2Cl_2-EtOAc) = 0.35.

IR (thin film/NaCl): 3330, 2958, 2924, 2873, 1490 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ 7.42-7.39 (m, 2H), 7.32-7.28 (m, 3H), 3.68-3.64 (m, 2H), 2.51 (dd, *J* = 6.1, 16.8 Hz, 1H), 2.45 (dd, *J* = 6.4, 16.8 Hz, 1H), 2.02-1.96 (m, 1H), 1.65 (br s, 1H), 1.08 (d, *J* = 6.7 Hz, 3H).

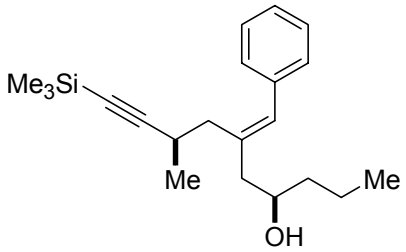
^{13}C NMR ($CDCl_3$, 125 MHz): δ 131.7 (2C), 128.4 (2C), 127.9, 123.9, 88.3, 82.2, 67.3, 35.5, 23.4, 16.5.

HRMS (EI) $[M^+]^{\cdot}$: *m/z* calcd for $C_{12}H_{14}O$ 174.1039, obsd 174.1035.

$[\alpha]_D$ = +2.0 (23 °C, *c* = 3.0, CH_2Cl_2).

ent-**33**: $[\alpha]_D$ = −12.5 (23 °C, *c* = 7.2, CH_2Cl_2).

Chiral HPLC analysis was performed on the Mosher ester derivative[6] (alcohol was coupled with *R*-MTPA using DCC/DMAP conditions): (OD, isocratic, 98:2 hexane:*i*-propanol, 1 ml/min): t_R[(*R*,*R*)] = 9.23 min; t_R[(*R*,*S*)] = 11.86 min).



(+)-6-Benzylidene-(8*R*)-methyl-10-trimethylsilanyl-dec-9-yn-(4*R*)-ol (34). In a glovebox, $Ni(cod)_2$ (36 mg, 0.13 mmol) was placed in a 10 ml flask which was then sealed with a rubber septum. The flask was removed from the glovebox and placed under Ar. To this flask was added tributylphosphine (36 μL, 0.26 mmol), **16** (degassed by bubbling Ar through for 10 min, 0.70 ml, 6.7 mmol), triethylborane (0.36 mL, 2.3 mmol), and diyne **15** (267 mg, 1.11 mmol). The resulting dark brown solution was stirred at ambient temperature 14 h, then opened to the air for 1 h. Volatile organics were evaporated, and the crude residue was purified via gradient column chromatography

(50:1 hexane-EtOAc, polarity gradually increased to 9:1) to afford the title compound as a clear, yellow oil (158 mg, 45% yield). R_f (90:10, hexane-EtOAc) = 0.23.

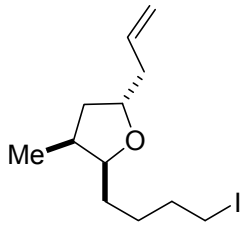
IR (thin film/NaCl): 3416 (br), 2959, 2931, 2873, 2162, 1599 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ 7.36-7.30 (m, 3H), 7.25-7.21 (m, 2H), 6.53 (s, 1H), 3.85-3.83 (m, 1H), 2.79-2.74 (m, 1H), 2.61 (dd, *J* = 9.8, 13.7 Hz, 1H), 2.53-2.50 (m, 1H), 2.27-2.19 (m, 2H), 1.95 (d, *J* = 2.4 Hz, 1H), 1.58-1.42 (m, 4H), 1.17 (d, *J* = 7.0 Hz, 3H), 0.98 (t, *J* = 7.0 Hz, 3H), 0.12 (s, 9H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 137.9, 137.6, 130.5, 129.1 (2C), 128.3 (2C), 126.6, 111.2, 85.7, 69.3, 45.5, 39.5, 37.4, 25.5, 21.4, 19.2, 14.4, 0.3 (3C).

HRMS (ESI) $[M+Na]^+$: *m/z* calcd for $C_{21}H_{32}ONa$ 351.2115, obsd 351.2128.

$[\alpha]_D$ = + 116.6 (23 °C, *c* = 4.1, CH_2Cl_2)



(−)-(5*R*)-Allyl-(2*S*)-(4-iodo-butyl)-(3*S*)-methyl-tetrahydro-furan (35). A solution of **57** in a 2:3 mixture of CH_3CN-Et_2O (220 mg, 1.11 mmol, in 3.2 mL) was cooled to 0 °C. Imidazole (98 mg, 1.44 mmol), triphenylphosphine (350 mg, 1.33 mmol), and iodine (398 mg, 1.57 mmol) were added sequentially, and the brown heterogeneous mixture was stirred at 0 °C for 4 h. Silica gel was added, and the solvents were removed in vacuo. The dry silica gel was loaded onto a slurry-packed column (95:5 hexane-EtOAc), the title compound was eluted and concentrated to give a clear, pale yellow oil (295 mg, 86% yield). R_f (90:10 hexane-EtOAc) = 0.31.

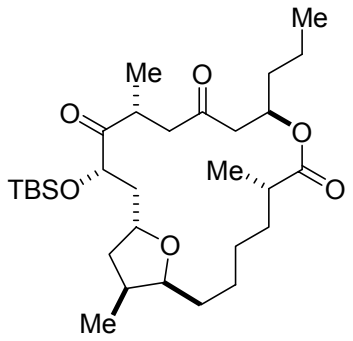
IR (thin film/NaCl): 3074, 2960, 2935, 2873, 1641 cm^{-1}.

^1H NMR (C_6D_6, 500 MHz): δ 5.91-5.83 (m, 1H), 5.10-5.04 (m, 2H), 4.04-3.98 (m, 1H), 3.65-3.62 (m, 1H), 2.72 (t, *J* = 7.0 Hz, 2H), 2.34-2.28 (m, 1H), 2.15-2.10 (m, 1H), 1.91-1.86 (m, 1H), 1.54-1.48 (m, 3H), 1.42-1.36 (m, 2H), 1.35-1.28 (m, 1H), 1.27-1.15 (m, 1H), 1.10-1.03 (m, 1H), 0.70 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (C_6D_6, 125 MHz): δ 136.1, 117.0, 81.2, 76.5, 41.9, 39.9, 36.6, 34.2, 30.0, 28.2, 14.5, 7.2.

HRMS (ESI) $[M+Na]^+$: *m/z* calcd for $C_{12}H_{21}IONa$ 331.0529, obsd 331.0521.

$[\alpha]_D = -1.1$ (23 °C, $c = 4.5$, C_6H_6)



(+)-(15*S*)-(tert-Butyl-dimethyl-silanyloxy)-(6*S*,13*R*,19*S*)-trimethyl-(9*R*)-propyl-8,20-dioxa-bicyclo[15.2.1]icosane-7,11,14-trione (36). A solution of **60** in CH_2Cl_2 (6.7 mg, 0.011 mmol in 35 mL) was cooled to −78 °C. Ozone was bubbled through the solution until a blue color persisted. Argon was immediately bubbled through until the solution was colorless. Dimethylsulfide was added (0.8 ml) and the solution was allowed to slowly warm to ambient temperature over 3 h. The solution was concentrated and purified by gradient column chromatography (50:1 hexane-EtOAc, polarity increased to 93:7 hexane-EtOAc) to give the title compound as a clear oil (4.5 mg, 78% yield). R_f (80:20 hexane-EtOAc) = 0.45.

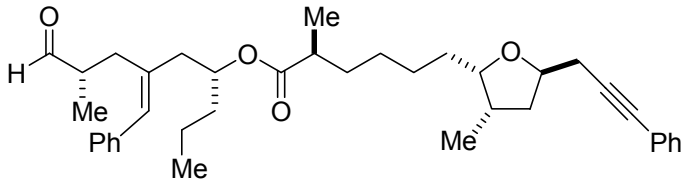
IR (thin film/NaCl): 2932, 2858, 1732, 1717 (br) cm^{-1}.

^{1}H NMR (C_6D_6, 500 MHz): δ 5.40-5.34 (m, 1H), 4.92 (t, J = 4.3 Hz, 1H), 4.43-4.38 (m, 1H), 4.02-4.00 (m, 1H), 3.60-3.56 (m, 1H), 3.09 (dd, J = 9.6, 18.8 Hz, 1H), 2.83-2.78 (m, 1H), 2.42-2.38 (m, 1H), 2.27 (dd, J = 11.1, 14.8 Hz, 1H), 2.09 (dd, J = 3.0, 18.8 Hz, 1H), 1.82 (dd, J = 2.6, 14.8 Hz, 1H), 1.77-1.66 (m, 3H), 1.59-1.43 (m, 6H), 1.36-1.28 (m, 3H), 1.26-1.15 (m, 4H), 1.07-1.04 (m, 15H), 0.77-0.74 (m, 6H), 0.26 (s, 3H), 0.14 (s, 3H).

^{13}C NMR (C_6D_6, 125 MHz): δ 211.8, 207.0, 174.3, 77.1, 76.5, 76.1, 71.4, 48.0, 45.9, 42.71, 42.67, 40.8, 37.5, 36.9, 36.7, 36.2, 30.5, 27.8, 27.2, 26.5 (3C), 19.0, 18.7, 18.6, 18.1, 14.8, 14.4, -3.6, -4.2.

HRMS (ESI)$[M+Na]^+$: *m/z* calcd for $C_{30}H_{54}O_6NaSi$ 561.3582, obsd 561.3576.

$[\alpha]_D = +3.3$ (23 °C, $c = 0.9$, C_6D_6)



(−)-(2*S*)-Methyl-6-[(3*S*)-methyl-(5*R*)-(3-phenyl-prop-2-ynyl)-tetrahydro-furan-(2*S*)-yl]-hexanoic acid 3-benzylidene-(5*S*)-methyl-6-oxo-(1*R*)-propyl-hexyl ester (40). Dess-Martin periodinane (56 mg, 0.132 mmol) was added to a solution of **48** in CH_2Cl_2 (21 mg, 0.037 mmol, 1.2 mL). The resulting solution was stirred at ambient temperature for 90 min, then partially concentrated and purified via column chromatography (90:10 hexane-EtOAc) to give the title compound as a clear, colorless oil (17 mg, 81% yield). R_f (90:10, hexane-EtOAc) = 0.11.

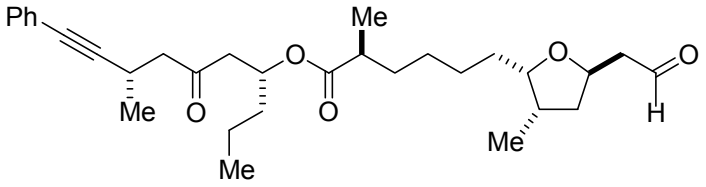
IR (thin film/NaCl): 2960, 2932, 2871, 1724, 1597, 1490 cm^{-1}.

^1H NMR (C_6D_6, 500 MHz): δ 9.22 (d, *J* = 1.8 Hz, 1H), 7.51-7.48 (m, 2H), 7.18-7.13 (m, 5H), 7.04-6.95 (m, 3H), 6.41 (s, 1H), 5.32-5.27 (m, 1H), 4.25-4.19 (m, 1H), 3.89-3.85 (m, 1H), 2.66 (dd, *J* = 6.4, 14.3 Hz, 1H), 2.60 (dd, *J* = 4.6, 16.5 Hz, 1H), 2.52 (dd, *J* = 7.3, 16.5 Hz, 1H), 2.46 (dd, *J* = 8.5, 14.3 Hz, 1H), 2.43-2.40 (m, 1H), 2.28-2.20 (m, 3H), 2.03-1.98 (m, 1H), 1.89 (ddd, *J* = 7.0, 8.8, 10.7 Hz, 1H), 1.80-1.75 (m, 1H), 1.63-1.58 (m, 1H), 1.57-1.50 (m, 1H), 1.49-1.45 (m, 2H), 1.43-1.38 (m, 2H), 1.37-1.30 (m, 4H), 1.29-1.20 (m, 2H), 1.11 (d, *J* = 7.0 Hz, 3H), 0.89 (t, *J* = 7.0 Hz, 3H), 0.75 (d, *J* = 7.0 Hz, 3H), 0.68 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (C_6D_6, 125 MHz): δ 203.1, 176.3, 138.4, 136.8, 132.3 (2C), 131.0, 129.9, 129.5 (2C), 128.92 (2C), 128.89 (2C), 128.7, 127.2, 125.0, 88.2, 82.7, 82.2, 75.6, 71.4, 45.3, 43.3, 40.4, 39.9, 37.4, 36.7, 34.6, 31.4, 31.2, 28.2, 27.8, 27.4, 19.5, 17.9, 14.5, 13.6.

HRMS (ESI) $[M+Na]^+$: *m/z* calcd for $C_{38}H_{50}NaO_4$ 593.3601, obsd 593.3602.

$[\alpha]_D$ = −7.8 (23 °C, *c* = 6.8, CH_2Cl_2)



(+)-(2*S*)-Methyl-6-[(3*S*)-methyl-(5*R*)-(2-oxo-ethyl)-tetrahydro-furan-(2*S*)-yl]-hexanoic acid (5*S*)-methyl-3-oxo-7-phenyl-(1*R*)-propyl-hept-6-ynyl ester (41). A solution of **59** in CH_2Cl_2 (35 mg, 0.062 mmol in 20 mL) was cooled to −78 °C. Ozone was bubbled through the solution until a blue color persisted. Argon was immediately bubbled through until the solution was colorless. Dimethylsulfide was added (0.4 ml) and the solution was allowed to slowly warm to ambient temperature over 3 h. The

solution was concentrated and immediately purified by gradient column chromatography (85:15 hexane-EtOAc, polarity increased to 70:30 hexane-EtOAc). Two products were isolated: a diastereomeric ketoalkynyl-ozonide (less polar) and the desired ketoalkynal **39** (more polar). The ozonide was dissolved in 5 ml CH_2Cl_2 and stirred with triphenylphosphine (90 mg) for 40 min. Concentration and purification on a silica gel column (elution with 80:20 hexane-EtOAc) afforded pure ketoynal which was combined with the original portion (combined: 19 mg, 63% overall yield). R_f (80:20 hexane-EtOAc) = 0.26.

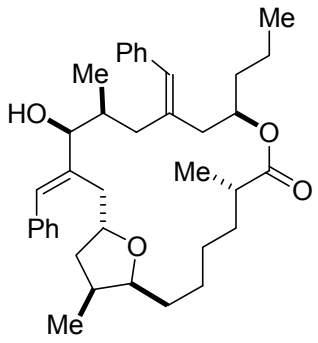
IR (thin film/NaCl): 2963, 2935, 2874, 2729, 2234, 1728 (br) cm^{-1}.

^1H NMR (C_6D_6, 500 MHz): δ 9.51 (dd, *J* = 1.7, 2.6 Hz, 1H), 7.48-7.46 (m, 2H), 7.02-6.95 (m, 3H), 5.48-5.43 (m, 1H), 4.23-4.18 (m, 1H), 3.66-3.63 (m, 1H), 3.23-3.19 (m, 1H), 2.53-2.44 (m, 2H), 2.40-2.36 (m, 1H), 2.27-2.18 (m, 3H), 1.96 (ddd, *J* = 1.8, 5.2, 15.9 Hz, 1H), 1.86-1.82 (m, 1H), 1.76-1.69 (m, 2H), 1.52-1.35 (m, 5H), 1.34-1.19 (m, 7H), 1.17 (d, *J* = 6.7 Hz, 3H), 1.12 (d, *J* = 7.0 Hz, 3H), 0.81 (t, *J* = 7.3 Hz, 3H), 0.69 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (C_6D_6, 125 MHz): δ 204.6, 200.4, 176.0, 132.3 (2C), 128.9 (2C), 128.6, 124.7, 94.1, 81.9, 81.7, 72.0, 70.0, 50.9, 50.0, 48.1, 40.42, 40.39, 37.1, 36.4, 34.5, 31.0, 28.2, 27.3, 22.8, 21.3, 19.2, 17.8, 14.4, 14.3.

HRMS (ESI)$[M+Na]^+$: *m/z* calcd for $C_{31}H_{44}O_5Na$ 519.3081, obsd 519.3086.

$[\alpha]_D$ = +4.8 (23 °C, *c* = 4.8, C_6D_6)



11,15-Dibenzylidene-(14*S*)-hydroxy-(6*S*,13*S*,19*R*)-trimethyl-(9*R*)-propyl-8,20-dioxa-bicyclo[15.2.1]icosan-7-one (42). A stock solution of catalyst was prepared in the following manner: in a glovebox, $Ni(cod)_2$ (26 mg, 0.095 mmol) was placed in a flask containing a stirbar. The flask was sealed with a rubber septum, removed from the glovebox, and immediately placed under argon. Tributylphosphine (26 μL, 0.188 mmol), toluene (4.74 ml, previously degassed by bubbling argon through for 10 minutes), and triethylborane (0.26 ml, 1.80 mmol) were added sequentially, producing a clear yellow catalyst solution. A 2 ml Woodward reaction tube equipped with a stirbar, rubber

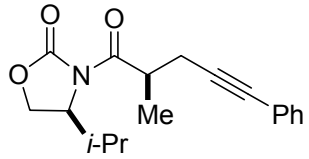
septum, and septum screw cap on the side-arm was purged with argon. Stock catalyst solution was added to the tube (500 μL), and the tube was immediately placed in an oil bath at 60 °C for 3 min. A solution of **40** in degassed toluene (15 mg, 0.026 mmol in 500 μL) was added to the tube dropwise, causing the solution to turn red-brown. The reaction was allowed to stir at 60 °C for 14 h. After this time, the solution was cooled to ambient temperature, diluted with 1.0 ml EtOAc, and stirred open to the air 1 h; then concentrated. The crude residue was purified via Pasteur pipet column chromatography (93:7 hexane-EtOAc) to give the title compound as a clear, colorless oil (6 mg, 35% yield, 8:1 dr 14*S*:14*R*). R_f (90:10, hexane-EtOAc) = 0.21.

IR (thin film/NaCl): 3377, 2959, 2932, 2872, 1726, 1599, 1462, 1453 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz, major diastereomer): δ 7.37-7.33 (m, 2H), 7.30-7.20 (3H), 7.14-7.11 (m, 2H), 7.08-7.06 (m, 2H), 7.03-7.00 (m, 1H), 6.56 (s, 1H), 6.33 (s, 1H), 5.51-5.47 (m, 1H), 5.08 (d, *J* = 7.5 Hz, 1H), 4.18-4.14 (m, 1H), 3.75-3.71 (m, 1H), 3.65 (dd, *J* = 7.9, 9.5 Hz, 1H), 3.14 (dd, *J* = 2.4, 15.3 Hz, 1H), 2.81 (dd, *J* = 9.5, 13.1 Hz, 1H), 2.73-2.64 (m, 2H), 2.55-2.52 (m, 3H), 1.97-1.88 (3H), 1.86-1.80 (m, 2H), 1.75-1.67 (m, 2H), 1.64-1.58 (m, 2H), 1.54-1.25 (m, 6H), 1.23 (d, *J* = 6.8 Hz, 3H), 0.90 (t, *J* = 7.3 Hz, 3H), 0.67 (d, *J* = 6.7 Hz, 3H), 0.56 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (C_6D_6, 125 MHz, major diastereomer): δ 175.5, 142.3, 139.6, 139.5, 138.4, 131.6, 130.4, 129.9 (2C), 129.5 (2C), 128.9 (2C), 127.5 (2C), 127.2, 126.8, 84.3, 79.3, 78.0, 74.0, 42.8, 41.0, 40.6, 38.8, 36.9, 36.6, 35.6, 35.2, 34.7, 30.4, 30.3, 27.8, 26.2, 19.8, 18.8, 16.8, 14.5.

HRMS (ESI) $[M+Na]^+$: *m/z* calcd for $C_{38}H_{52}NaO_4$ 595.3758, obsd 595.3762.



(+)-(4*S*)-Isopropyl-3-[(2*R*)-methyl-5-phenyl-pent-4-ynoyl]-oxazolidin-2-one (43).[7] A solution of diisopropylamine in THF (0.51g, 5.0 mmol amine in 7.0 mL THF) was cooled to 0 °C. A solution of *n*-butyllithium in hexane was added (2.1 mL, 2.5 M, 5.2 mmol), and the resulting solution was stirred 30 min at 0 °C. After this time, the solution was cooled to −78 °C and stirred 10 min. A separate solution of (*S*)-4-isopropyl-3-propionyl-oxazolidin-2-one[7a] in THF (0.87 g, 4.7 mmol, in 1.5 mL THF) was slowly added via syringe down the side of the reaction flask. The mixture was stirred 30 min at −78 °C. A solution of 3-bromo-1-propynylbenzene[8] in THF (2.5 g, 12.8 mmol, in 1.3 mL) was added via syringe down the side of the reaction flask. The mixture was stirred 15 min at −78 °C, then 2 h at 0 °C. The reaction was quenched at 0 °C with saturated NH_4Cl (5 mL), diluted with H_2O (5 mL) and Et_2O (10ml). The aqueous phase was extracted with Et_2O (3 x 25 mL), washed with brine (3 x 25 mL), dried over $MgSO_4$, filtered and

concentrated in vacuo. The crude residue was purified via column chromatography (70:30 CH_2Cl_2-hexane, a second column was necessary to separate diastereomers) to afford the title compound as a yellow oil (1.30 g, 92% yield, >95:5 dr). R_f (80:20, hexane-EtOAc) = 0.19.

IR (thin film/NaCl): 2966, 2877, 1779, 1703, 1387 cm $^{-1}$.

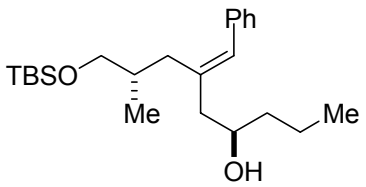
^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.38-7.34 (m, 2H), 7.28-7.25 (m, 3H), 4.51-4.47 (m, 1H), 4.29 (app t, J = 8.9 Hz, 1H), 4.20 (dd, J = 3.2, 9.2 Hz, 1H), 4.10-4.03 (m, 1H), 2.80 (dd, J = 6.9, 16.8 Hz, 1H), 2.70 (dd, J = 6.4, 16.8 Hz, 1H), 2.40-2.34 (m, 1H), 1.31 (d, J = 6.9 Hz, 3H), 0.89 (d, J = 7.2 Hz, 3H), 0.84 (d, J = 6.9 Hz, 3H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 175.4, 153.9, 131.8 (2C), 128.3 (2C), 127.9, 123.7, 87.0, 82.4, 63.5, 58.7, 37.9, 28.6, 24.1, 18.1, 16.8, 14.8.

HRMS (ESI) $[M+Na]^+$: *m/z* calcd for $C_{18}H_{21}NaNO_3$ 322.1414, obsd 322.1415.

$[\alpha]_D$ = +37.1 (23 °C, c = 4.8, CH_2Cl_2).

ent-**43**: $[\alpha]_D$ = −43.0 (23 °C, c = 6.3, CH_2Cl_2).



(−)-2-[3-(tert-Butyldimethylsilanyloxy)-(2*S*)-methylpropyl]-1-phenyl-hept-1-en-(4*R*)-ol (44). Prepared as described for **11** (same scale) except *ent*-**14** was used: (264 mg, 70% yield, >95:5 dr by ^{1}H NMR). R_f (90:10, hexane-EtOAc) = 0.22.

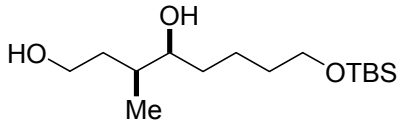
IR (thin film/NaCl): 3403, 2956, 2930, 2857, 1600, 1463 cm $^{-1}$.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.34-7.31 (m, 2H), 7.27-7.20 (m, 3H), 6.49 (s, 1H), 3.82-3.80 (m, 1H), 3.41 (dd, J = 5.8, 9.8 Hz, 1H), 3.37 (dd, J = 6.2, 9.9 Hz, 1H), 2.51-2.48 (m, 1H), 2.34-2.27 (m, 2H), 2.12 (dd, J = 9.8, 13.6 Hz, 1H), 1.88-1.85 (m, 2H), 1.58-1.41 (m, 4H), 0.98 (t, J = 7.0 Hz, 3H), 0.90 (s, 9H), 0.77 (d, J = 6.7 Hz, 3H), 0.03 (s, 6H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 139.0, 138.0, 130.1, 129.1 (2C), 128.3 (2C), 126.5, 68.8, 68.4, 45.8, 39.6, 34.7, 33.3, 26.1 (3C), 19.2, 18.5, 16.3, 14.4, -5.19, -5.21.

HRMS (ESI) $[M+Na]^+$: *m/z* calcd for $C_{23}H_{40}NaO_2Si$ 399.2690, obsd 399.2693.

$[\alpha]_D$ = −55.9 (23 °C, c = 2.2, CH_2Cl_2).



(−)-8-(tert-Butyl-dimethyl-silanyloxy)-(3*S*)-methyl-octane-(1,4*S*)-diol (45).[9] Gaseous *cis*-2-butene was condensed (15 ml, 150 mmol) and transferred via cannula to a cooled suspension (−78 °C) of potassium *t*-butoxide in THF (4.21 g, 37.6 mmol in 15 ml THF). A solution of *n*-butyllithium was added via syringe (15 mL, 2.5 M in hexane, 37.6 mmol), causing the mixture to turn bright yellow. The mixture was stirred 5 min at −78 °C, warmed to −45 °C for 20 min, then re-cooled to −78 °C. A solution of (+)-Ipc_2BOMe in Et_2O was prepared (14.2 g, 45.0 mmol in 45 ml) and transferred to the reaction via cannula. After stirring 30 min at −78 °C, $BF_3{\cdot}OEt_2$ (8.51 g, 7.6 ml, 60.3 mmol) was added via syringe and the mixture was stirred 5 min. Aldehyde **19**[10] was added (9.75 g, 45.0 mmol), and the viscous mixture was allowed to stir 3 h at −78 °C. A mixture of 3N NaOH and 30% H_2O_2 (27.0 mL NaOH, 11.0 mL H_2O_2) was added, and the reaction was allowed to warm to ambient temperature with stirring for 3 h. H_2O and Et_2O were added (50 mL each) and the phases were separated. The organic phase was washed with H_2O (2 x 50 mL) and brine (3 x 50 mL), dried over $MgSO_4$, filtered and concentrated. The crude oil was then taken up in 300 ml THF and cooled to 0 °C. $BH_3{\cdot}THF$ was added via syringe (150 mL, 1 M in THF, 150 mmol) and the solution was stirred 14 h, warming to ambient temperature. The solution was re-cooled to 0 °C and methanol was added slowly (50 mL). After bubbling ceased, a mixture of 1.8 N NaOH and 30% H_2O_2 was added (30.0 mL NaOH, 12.0 mL H_2O_2) and the mixture was stirred at ambient temperature 3 h. Brine and Et_2O were added (150 mL each), the layers were separated, and the aqueous phase was extracted with 80:20 EtOAc:Et_2O (3 x 150 mL). The combined organic phases were washed with brine (3 x 150 mL), dried over Na_2SO_4, filtered and concentrated. The crude residue was purified via gradient column chromatography (70:30 hexane-EtOAc, polarity increased to 50:50) to afford the title compound as a viscous, clear oil (4.75 g, 43% yield over two steps). R_f (80:20, EtOAc-hexane) = 0.25.

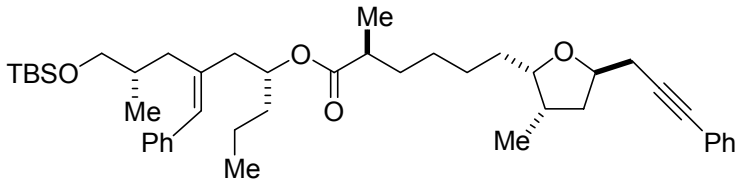
IR (thin film/NaCl): 3321, 2928, 2855 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ 7.9 (br s, 1H, OH), 3.81-3.76 (m, 1H), 3.70-3.60 (m, 4H), 2.3 (br s, 1H, OH), 1.80-1.70 (m, 2H), 1.60-1.37 (m, 7H), 0.91 (d, J = 7.0 Hz, 3H), 0.90 (s, 9H), 0.06 (s, 6H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 74.9, 63.4, 60.6, 36.28, 36.26, 33.4, 32.9, 26.1 (3C), 22.9, 18.5, 14.1, -5.1 (2C).

HRMS (ESI) $[M+Na]^+$: *m/z* calcd for $C_{15}H_{34}NaO_3Si$ 313.2169, obsd 313.2169.

$[\alpha]_D$ = −8.9 (23 °C, *c* = 10.0, CH_2Cl_2).



(−)-(2*S*)-Methyl-6-[(3*S*)-methyl-(5*R*)-(3-phenyl-prop-2-ynyl)-tetrahydro-furan-(2*S*)-yl]-hexanoic acid 3-benzylidene-6-(tert-butyl-dimethyl-silanyloxy)-(5*S*)-methyl-(1*R*)-propyl-hexyl ester (46). A flask containing acid **10** (110 mg, 0.33 mmol) was charged with alcohol **44** (200 mg, 0.53 mmol), dicyclohexylcarbodiimide (120 mg, 0.58 mmol), 4-pyrrolidinopyridine (90 mg, 0.61 mmol), and CH_2Cl_2 (5.5 ml). The mixture was stirred 24 h at ambient temperature. Silica gel was added, and the solvents were removed in vacuo. The dry silica gel was loaded onto a slurry-packed column (90:10 hexane-EtOAc) and the title compound was eluted to give a clear, colorless oil (120 mg, 53% yield) upon concentration. R_f (90:10, hexane-EtOAc) = 0.32.

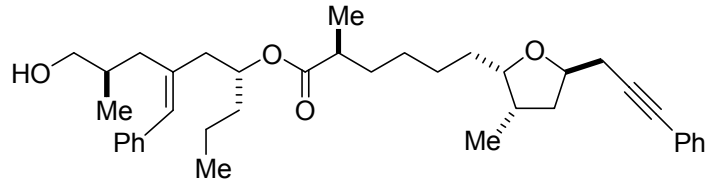
IR (thin film/NaCl): 2957, 2933, 2857, 1729, 1599, 1462 cm^{-1}.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.41-7.39 (m, 2H), 7.30-7.24 (m, 5H), 7.19-7.16 (m, 3H), 6.36 (s, 1H), 5.16-5.12 (m, 1H), 4.31-4.26 (m, 1H), 3.96-3.92 (m, 1H), 3.41 (dd, *J* = 5.5, 9.8 Hz, 1H), 3.32 (dd, *J* = 6.4, 9.8 Hz, 1H), 2.68 (dd, *J* = 4.6, 16.5 Hz, 1H), 2.59 (dd, *J* = 7.3, 16.5 Hz, 1H), 2.41-2.28 (m, 4H), 2.23-2.19 (m, 1H), 2.08-2.02 (m, 1H), 1.88-1.81 (m, 2H), 1.69-1.62 (m, 1H), 1.60-1.55 (m, 2H), 1.48-1.25 (m, 10H), 1.08 (d, *J* = 7.0 Hz, 3H), 0.95-0.91 (m, 6H), 0.88 (s, 9H), 0.74 (d, *J* = 6.7 Hz, 3H), 0.02 (s, 3H), 0.01 (s, 3H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 176.7, 138.4, 137.9, 131.8 (2C), 129.4, 129.1 (2C), 128.4 (2C), 128.2 (2C), 127.9, 126.2, 124.0, 87.1, 82.3, 81.9, 75.2, 71.6, 68.4, 42.8, 40.0, 39.4, 37.0, 36.0, 34.5, 33.9, 33.4, 30.5, 27.7, 27.2, 26.7, 26.1 (3C), 19.0, 18.5, 17.4, 16.5, 14.20, 14. 18, -5.2 (2C).

HRMS (ESI) $[M+Na]^+$: *m/z* calcd for $C_{44}H_{66}NaO_4Si$ 709.4623, obsd 709.4643.

$[\alpha]_D$ = −23.0 (23 °C, *c* = 1.0, CH_2Cl_2)



(+)-(2*S*)-Methyl-6-[(3*S*)-methyl-(5*R*)-(3-phenyl-prop-2-ynyl)-tetrahydro-furan-(2*S*)-yl]-hexanoic acid 3-benzylidene-6-hydroxy-(5*R*)-methyl-(1*R*)-propyl-hexyl ester (47). A solution of tetrabutylammonium fluoride (0.33 mL, 1.0 M in THF, 0.33 mmol) was added to a stirred solution of **27** in THF (150 mg, 0.22 mmol in 1.8 mL). The mixture was allowed to stir 2 h, then EtOAc and saturated NaCl (aqueous) were added (5 ml each). The layers were separated, the aqueous phase was extracted with EtOAc (3 x 5

ml), and the combined organic phases were concentrated. The crude residue was purified via column chromatography (70:30 hexane-EtOAc) to give the title compound as a clear, colorless oil (122 mg, 97% yield). R_f (70:30, hexane-EtOAc) = 0.31.

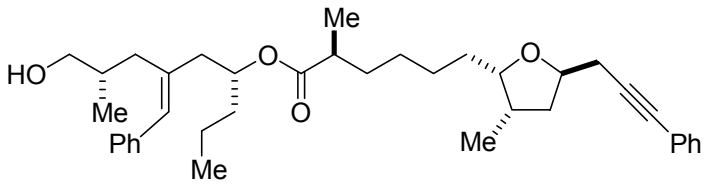
IR (thin film/NaCl): 3447, 2959, 2934, 2872, 2360, 1727, 1458 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ 7.41-7.39 (m, 2H), 7.32-7.28 (m, 5H), 7.22-7.17 (m, 3H), 6.40 (s, 1H), 5.14-5.09 (m, 1H), 4.32-4.26 (m, 1H), 3.97-3.93 (m, 1H), 3.36 (t, *J* = 5.8 Hz, 2H), 2.68 (dd, *J* = 4.6, 16.5 Hz, 1H), 2.59 (dd, *J* = 7.0, 16.5 Hz, 1H), 2.49-2.40 (m, 3H), 2.39-2.34 (m, 1H), 2.32-2.28 (m, 1H), 2.15 (dd, *J* = 7.3, 14.0 Hz, 1H), 2.05 (ddd, *J* = 7.0, 9.0, 10.8 Hz, 1H), 1.91-1.84 (m, 2H), 1.70-1.64 (m, 1H), 1.61-1.57 (m, 2H), 1.49-1.26 (m, 10H), 1.10 (d, *J* = 6.7 Hz, 3H), 0.94 (t, *J* = 7.3 Hz, 3H), 0.92 (d, *J* = 7.0 Hz, 3H), 0.85 (d, *J* = 6.7 Hz, 3H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 176.9, 138.0, 137.9, 131.8 (2C), 129.6, 129.0 (2C), 128.37 (2C), 128.35 (2C), 127.9, 126.5, 123.9, 87.0, 82.2, 81.9, 75.2, 71.8, 67.8, 42.7, 39.9, 39.3, 36.5, 36.1, 34.3, 33.9, 33.6, 30.4, 27.6, 27.2, 26.6, 18.9, 17.4, 17.1, 14.2 (2C).

HRMS (ESI) $[M+Na]^+$: *m/z* calcd for $C_{38}H_{52}NaO_4$ 595.3758, obsd 595.3748.

$[\alpha]_D$ = +0.16 (23 °C, *c* = 12.6, CH_2Cl_2)



(−)-(2*S*)-Methyl-6-[(3*S*)-methyl-(5*R*)-(3-phenyl-prop-2-ynyl)-tetrahydro-furan-(2*S*)-yl]-hexanoic acid 3-benzylidene-6-hydroxy-(5*S*)-methyl-(1*R*)-propyl-hexyl ester (48). A solution of tetrabutylammonium fluoride (0.050 mL, 1.0 M in THF, 0.050 mmol) was added to a stirred solution of **46** in THF (27 mg, 0.039 mmol in 0.6 mL). The mixture was allowed to stir 1 h, then EtOAc and saturated NaCl (aqueous) were added (1 ml each). The layers were separated, the aqueous phase was extracted with EtOAc (3 x 1 ml), and the combined organic phases were concentrated. The crude residue was purified via column chromatography (70:30 hexane-EtOAc) to give the title compound as a clear, colorless oil (23 mg, 95% yield). R_f (70:30, hexane-EtOAc) = 0.29.

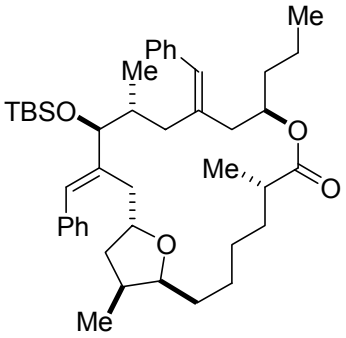
IR (thin film/NaCl): 3439, 2932, 2869, 1725, 1490 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ 7.41-7.39 (m, 2H), 7.31-7.27 (m, 5H), 7.21-7.16 (m, 3H), 6.40 (s, 1H), 5.15-5.13 (m, 1H), 4.30-4.27 (m, 1H), 3.96-3.93 (m, 1H), 3.44-3.41 (m, 1H), 3.37-3.34 (m, 1H), 2.67 (dd, *J* = 4.8, 16.6 Hz, 1H), 2.59 (dd, *J* = 7.2, 16.6 Hz, 1H), 2.43-2.35 (m, 4H), 2.30-2.27 (m, 1H), 2.22-2.18 (m, 1H), 2.08-2.02 (m, 1H), 1.90-1.83 (m, 2H), 1.69-1.65 (m, 1H), 1.62-1.56 (m 2H), 1.48-1.25 (m, 10H), 1.10 (d, *J* = 7.0 Hz, 3H), 0.95-0.91 (m, 6H), 0.79 (d, *J* = 6.7 Hz, 3H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 176.8, 138.1, 137.6, 131.8 (2C), 129.8, 129.0 (2C), 128.4 (2C), 128.3 (2C), 127.9, 126.4, 123.9, 87.1, 82.2, 81.9, 75.2, 71.7, 68.2, 42.6, 39.9, 39.4, 36.8, 36.1, 34.3, 33.9, 33.5, 30.4, 27.7, 27.2, 26.6, 18.9, 17.4, 16.6, 14.19, 14.17.

HRMS (ESI) $[M+Na]^+$: *m/z* calcd for $C_{38}H_{52}NaO_4$ 595.3758, obsd 595.3749.

$[\alpha]_D = -0.16$ (23 °C, *c* = 3.0, $CDCl_3$)



(+)-11,15-Dibenzylidene-(14*S*)-(tert-butyl-dimethyl-silanyloxy)-(6*S*,13*R*,19*R*)-trimethyl-(9*R*)-propyl-8,20-dioxa-bicyclo[15.2.1]icosan-7-one (49). A solution of **6** in CH_2Cl_2 was prepared (9.0 mg, 0.016 mmol in 2.0 ml) and cooled to −78 °C. 2,6-Lutidine (30 μL, 0.24 mmol) and *t*-butyldimethylsilyl trifluoromethanesulfonate (30 μL, 0.13 mmol) were added via microliter syringe, and the resulting solution was stirred 2 h at −78 °C. A minimal amount of MeOH was added to quench the reaction (5 drops); then the solution was warmed to ambient temperature and concentrated. The crude residue was purified via Pasteur pipet column chromatography (50:1 hexane-EtOAc) to give the title compound as a clear, yellow oil (9.1 mg, 84% yield). R_f (90:10, hexane-EtOAc) = 0.44.

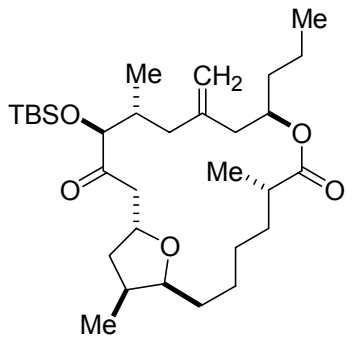
IR (thin film/NaCl): 2958, 2931, 2856, 1728, 1599, 1461 cm^{-1}.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.39-7.35 (m, 3H), 7.24-7.19 (m, 5H), 7.09-7.06 (m, 2H), 6.81 (br s, 1H), 6.57 (s, 1H), 5.38-5.36 (m, 1H), 4.37-4.31 (m, 2H), 3.87-3.70 (m, 1H), 2.93 (app t, *J* = 12.4 Hz, 1H), 2.71 (dd, *J* = 8.0, 14.6 Hz, 1H), 2.64-2.59 (m, 2H), 2.53 (dd, *J* = 4.1, 14.6 Hz, 1H), 2.46-2.44 (m, 2H), 2.27 (dd, *J* = 5.8, 13.6 Hz, 1H), 1.96-1.91 (m, 1H), 1.83-1.72 (m, 2H), 1.71-1.62 (m, 2H), 1.60-1.29 (br m, 10H), 1.17 (d, *J* = 6.7 Hz, 3H), 1.03 (d, *J* = 6.4 Hz, 3H), 1.01 (s, 9H), 0.91 (t, *J* = 7.3 Hz, 3H), 0.70 (d, *J* = 7.0 Hz, 3H), 0.15 (s, 3H), 0.13 (s, 3H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 176.7, 140.6, 139.0, 138.7, 138.4, 129.4, 129.2 (2C), 129.0 (2C), 128.4, 128.3 (2C), 128.2 (2C), 126.3, 126.2, 80.0, 74.8, 74.5, 40.2, 39.7, 39.0, 36.8, 36.5, 36.2, 36.0, 34.8, 33.2, 29.9, 28.6, 26.4, 26.2 (3C), 24.7, 18.7, 18.4, 17.5, 14.6, 14.3, -3.9, -4.7 (missing one C under $CDCl_3$ signal; when spectrum taken in C_6D_6 there are three signals in the 70-80 ppm region: δ 80.8, 75.0 (2C), 74.8).

HRMS (ESI) $[M+Na]^+$: *m/z* calcd for $C_{44}H_{66}NaO_4Si$ 709.4623, obsd 709.4615.

$[\alpha]_D = +2.1$ (23 °C, *c* = 3.8, C_6D_6)



(+)-(14*S*)-(tert-Butyl-dimethyl-silanyloxy)-(6*S*,13*R*,19*R*)-trimethyl-11-methylene-(9*R*)-propyl-8,20-dioxa-bicyclo[15.2.1]icosane-7,15-dione (50). A stock solution of methylenating reagent was prepared in the following manner: a 50 ml flask was charged with activated zinc[11] (0.51 g, 7.80 mmol), lead (II) chloride (0.093 g, 0.33 mmol), and THF (4.0 ml); then cooled to 0 °C. Diiodomethane (0.21 mL, 2.60 mmol) was added via syringe, and the mixture was stirred 30 min at 0 °C. During this time, a suspension of zirconium (IV) chloride in THF (0.25 g, 1.07 mmol in 3.0 mL) was prepared by stirring together 20 min at ambient temperature. The suspension of zirconium (IV) chloride transferred to the $Zn/PbCl_2/CH_2I_2$ mixture via cannula. The resulting heterogeneous mixture was stirred 30 minutes at 0 °C. (During this time, the mixture assumed a green color, which indicated the generation of the active methylenation reagent.) A solution of diketone **32** in THF (3.0 mg in 0.5 mL) was cooled to 0 °C. Methylenating reagent was transferred to the diketone solution via syringe (0.4 mL), and the reaction was stirred for 3.5 h at 0 °C. Water (0.5 mL) and Et_2O (5 mL) were added; then the cold bath was removed. The layers were separated, and the aqueous phase was extracted with Et_2O (5 x 5 mL). The combined organic phase was dried over Na_2SO_4, filtered and concentrated. The crude residue was purified via Pasteur pipet gradient column chromatography (50:1 hexane-EtOAc, polarity gradually increased to 13:1 hexane-EtOAc) to give the title compound as a clear, yellow oil (2.2 mg, 75% yield). R_f (90:10, hexane-EtOAc) = 0.37.

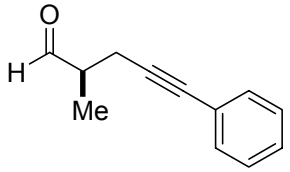
IR (thin film/NaCl): 2928, 2856, 1728, 1458 cm^{-1}.

^1H NMR (C_6D_6, 500 MHz): δ 5.37-5.33 (m, 1H), 5.04 (s, 1H), 4.90 (s, 1H), 4.61-4.55 (m, 1H), 4.25 (d, *J* = 2.1 Hz, 1H), 3.77 (ddd, *J* = 3.5, 6.0, 8.2 Hz, 1H), 2.49-2.40 (m, 3H), 2.30 (app d, *J* = 5.5 Hz, 2H), 2.12 (dd, *J* = 3.4, 15.3 Hz, 1H), 1.86-1.80 (m, 1H), 1.61-1.43 (m, 7H), 1.39-1.29 (m, 6H), 1.26-1.16 (m 2H), 1.15-1.07 (m, 13H), 1.05 (d, *J* = 6.1 Hz, 3H), 0.89 (t, *J* = 7.3 Hz, 3H), 0.69 (d, *J* = 7.0 Hz, 3H), 0.30 (s, 3H), 0.11 (s, 3H).

^{13}C NMR (C_6D_6, 125 MHz): δ 208.9, 175.5, 144.4, 116.2, 81.5, 78.8, 73.6, 72.3, 45.8, 42.1, 42.0, 40.5, 40.0, 36.9, 36.1, 35.3, 32.6, 30.6, 29.8, 27.1, 26.6 (3C), 26.2, 19.6, 18.5, 14.7, 14.6, 14.5, -3.3, -4.3.

HRMS (ESI) $[M+Na]^+$: *m/z* calcd for $C_{31}H_{56}NaO_5Si$ 559.3789, obsd 559.3781.

$[\alpha]_D$ = +5.7 (23 °C, *c* = 0.7, $CHCl_3$)



(+)-(2*R*)-Methyl-5-phenyl-pent-4-ynal (51). Dess-Martin periodinane (0.85g, 2.0 mmol) was added carefully to a solution of **33** in CH_2Cl_2 (174 mg, 1.0 mmol in 25 mL) and the mixture was stirred at ambient temperature 2.5 h. The volume of the solution was reduced to approximately 2 ml by concentration in vacuo and loaded onto a slurry-packed column (90:10 hexane-EtOAc) and the title compound was eluted to give a clear, colorless oil (160 mg, 92% yield) upon concentration. R_f (90:10, hexane-EtOAc) =0.22.

IR (thin film/NaCl): 2972, 1728, 1490 cm^{-1}.

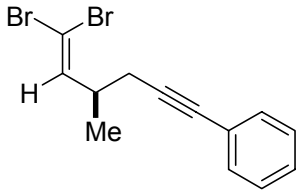
^1H NMR ($CDCl_3$, 500 MHz): δ 9.78 (d, J = 0.9 Hz, 1H), 7.41-7.39 (m, 2H), 7.31-7.29 (m, 3H), 2.77 (dd, J = 5.1, 15.9 Hz, 1H), 2.69-2.60 (m, 2H), 1.30 (d, J = 7.0 Hz, 3H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 203.6, 131.82, 131.78 (2C), 128.4 (2C), 123.5, 86.6, 82.8, 45.6, 21.0, 13.4.

HRMS (ESI) $[M+Na]^+$: *m/z* calcd for $C_{12}H_{12}NaO$ 195.0780, obsd 195. 0785.

$[\alpha]_D$ = +7.1 (23 °C, c = 3.1, CH_2Cl_2)

ent-**51**: $[\alpha]_D$ = −6.9 (23 °C, c = 1.6, CH_2Cl_2)



(+)-[6,6-Dibromo-(4*R*)-methyl-hex-5-en-1-ynyl]-benzene (52). A solution of carbon tetrabromide in CH_2Cl_2 (1.26 g, 3.8 mmol in 5.0 ml) was cooled to 0 °C. Triphenylphosphine was added (1.99 g, 7.6 mmol) and the bright orange solution was stirred 40 min. Aldehyde **51** was added as a solution in CH_2Cl_2 (0.32 g, 1.9 mmol in 2.0 ml) and the mixture was stirred 16 h, warming slowing to ambient temperature. The heterogeneous mixture was diluted with hexane, filtered through Celite and concentrated. The residue was taken up in hexane, filtered to remove solid triphenylphosphine oxide, and re-concentrated. The crude residue was purified via column chromatography (19:1 hexane-EtOAc) to give the title compound as a clear, light yellow oil (0.42 g, 69% yield). R_f (90:10, hexane-EtOAc) =0.47.

IR (thin film/NaCl): 2966, 2927, 1598 cm^{-1}.

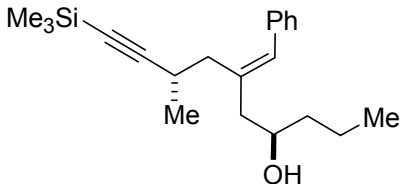
^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.46-7.43 (m, 2H), 7.35-7.30 (m, 3H), 6.42 (d, J = 9.2 Hz, 1H), 2.85-2.79 (m, 1H), 2.50 (dd, J = 1.2, 6.1 Hz, 2H), 1.21 (d, J = 6.7 Hz, 3H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 142.3, 131.8 (2C), 128.4 (2C), 128.0, 123.7, 88.9, 87.1, 82.7, 37.8, 25.8, 18.6.

HRMS (EI) M^+: *m/z* calcd for $C_{13}H_{12}Br_2$ 325.9300, obsd 325.9303.

$[\alpha]_D$ = +5.1 (23 °C, c = 6.3, CH_2Cl_2).

ent-**52**: $[\alpha]_D$ = −37.5 (23 °C, c = 6.3, CH_2Cl_2).



(−)-6-Benzylidene-(8*S*)-methyl-10-trimethylsilanyl-dec-9-yn-(4*R*)-ol (53). Procedure and scale exactly as described above except the opposite enantiomer of the diyne was used (*ent*-**15**). The title compound was isolated as a colorless oil (120 mg, 33% yield). R_f (90:10, hexane-EtOAc) = 0.16.

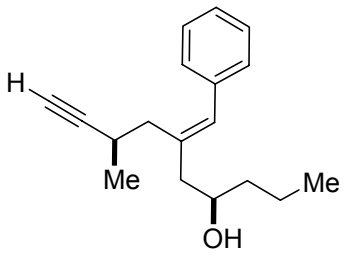
IR (thin film/NaCl): 3419 (br), 2959, 2932, 2873, 2163, 1599 cm^{-1}.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.35-7.29 (m, 4H), 7.25-7.22 (m, 1H), 6.51 (s, 1H), 3.88-3.84 (m, 1H), 2.76-2.71 (m, 1H), 2.56 (dd, J = 3.0, 13.7 Hz, 1H), 2.48 (dd, J = 9.2, 13.4 Hz, 1H), 2.39 (dd, J = 6.4, 13.4 Hz, 1H), 2.22 (dd, J = 9.5, 13.7 Hz, 1H), 1.90 (d, J = 2.7 Hz, 1H), 1.58-1.49 (m, 3H), 1.48-1.42 (m, 1H), 1.15 (d, J = 7.0 Hz, 3H), 0.98 (t, J = 7.3 Hz, 3H), 0.14 (s, 9H).

^{13}C NMR (C_6D_6, 125 MHz): δ 138.6, 138.4, 131.2, 129.7 (2C), 128.8 (2C), 127.1, 112.2, 86.0, 69.8, 46.6, 40.5, 38.4, 26.5, 21.6, 19.8, 14.8, 0.6 (3C).

HRMS (ESI) $[M+Na]^+$: *m/z* calcd for $C_{21}H_{32}ONa$ 351.2115, obsd 351.2122.

$[\alpha]_D$ = − 105.8 (23 °C, c = 2.4, CH_2Cl_2)



(+)-6-Benzylidene-(8*R*)-methyl-dec-9-yn-(4*R*)-ol (54). A solution of alkyne **34** in THF (200 mg, 0.61 mmol in 6.0 mL) was cooled to 0 °C. A solution of tetrabutylammonium fluoride in THF was added dropwise (0.75 ml, 1.0 M). The solution was stirred 1 h at 0 °C, then partitioned between EtOAc and brine (6 mL each). The aqueous phase was extracted with EtOAc (3 x 6 mL), dried over $MgSO_4$, filtered and concentrated. The crude residue was purified by column chromatography (85:15 hexane-EtOAc) to afford the title compound as a clear, light yellow oil (132 mg, 80% yield). R_f (80:20, hexane-EtOAc) = 0.25.

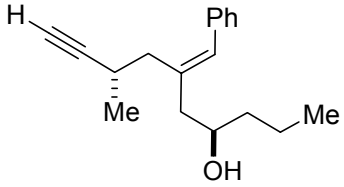
IR (thin film/NaCl): 3420, 3307, 2960, 2931, 2872, 2170, 1599 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ 7.35-7.26 (m, 3H), 7.25-7.22 (m, 2H), 6.54 (s, 1H), 3.85-3.83 (br m, 1H), 2.75-2.71 (m, 1H), 2.63 (dd, *J* = 9.5, 13.7 Hz, 1H), 2.53-2.47 (m, 1H), 2.30 (dd, *J* = 6.1, 13.7 Hz, 1H), 2.26-2.21 (m, 1H), 2.08 (d, *J* = 2.4 Hz, 1H), 1.85 (br s, 1H), 1.56-1.42 (m, 4H), 1.18 (d, *J* = 6.7 Hz, 3H), 0.97 (t, *J* = 6.7 Hz, 3H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 137.8, 137.4, 130.7, 129.0 (2C), 128.4 (2C), 126.7, 88.4, 69.4, 69.2, 45.6, 39.5, 37.2, 24.3, 21.2, 19.2, 14.4.

HRMS (ESI) $[M+Na]^+$: *m/z* calcd for $C_{18}H_{24}ONa$ 279.1719, obsd 279.1710.

$[\alpha]_D$ = +7.8 (23 °C, *c* = 3.6, $CDCl_3$)



(−)-6-Benzylidene-(8*S*)-methyl-dec-9-yn-(4*R*)-ol (55). A solution of alkyne **53** in THF (120 mg, 0.37 mmol in 3.7 mL) was cooled to 0 °C. A solution of tetrabutylammonium fluoride in THF was added dropwise (0.46 ml, 1.0 M). The solution was stirred 1 h at 0 °C, then partitioned between EtOAc and brine (4 mL each). The aqueous phase was extracted with EtOAc (3 x 4 mL), dried over $MgSO_4$, filtered and concentrated. The crude residue was purified by column chromatography (85:15 hexane-EtOAc) to afford the title compound as a clear, light yellow oil (53 mg, 52% yield). R_f (80:20, hexane-EtOAc) = 0.28.

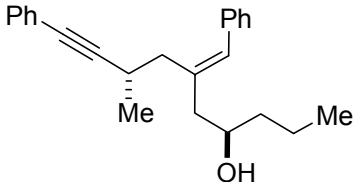
IR (thin film/NaCl): 3411, 3306, 2959, 2932, 2872, 2111, 1598 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ 7.35-7.32 (m, 2H), 7.29-7.25 (m, 2H), 7.24-7.22 (m, 1H), 6.52 (s, 1H), 3.88-3.84 (m, 1H), 2.72-2.67 (m, 1H), 2.55 (dd, *J* = 3.5, 13.8 Hz, 1H), 2.48 (d, *J* = 7.9 Hz, 2H), 2.22 (dd, *J* = 9.5, 14.6 Hz, 1H), 2.09 (d, *J* = 2.4 Hz, 1H), 1.88 (br s, 1H), 1.58-1.50 (m, 3H), 1.48-1.41 (m, 1H), 1.15 (d, *J* = 7.0 Hz, 3H), 0.98 (t, *J* = 6.7 Hz, 3H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 137.7, 137.6, 130.8, 129.0 (2C), 128.4 (2C), 125.7, 88.7, 69.4, 69.3, 45.8, 39.6, 37.4, 24.7, 21.0, 19.2, 14.4.

HRMS (ESI) $[M+Na]^+$: *m/z* calcd for $C_{18}H_{24}ONa$ 279.1719, obsd 279.1718.

$[\alpha]_D = -7.8$ (23 °C, *c* = 1.8, CH_2Cl_2)



(−)-6-Benzylidene-(8*S*)-methyl-10-phenyl-dec-9-yn-(4*R*)-ol (56). Copper (I) iodide (4 mg, 0.02 mmol) and palladium tetrakis(triphenylphosphine) (12 mg, 0.01 mmol) were combined in a round bottom flask. The flask was evacuated and back-filled with Ar three times. Pyrrolidine (1.2 mL), alkyne **55** (52 mg, 0.20 mmol in 0.3 ml pyrrolidine), and iodobenzene (85 μL, 0.76 mmol) were added sequentially and the mixture was stirred at ambient temperature 16 h. Et_2O was added (10 mL) and the mixture was filtered through a plug of silica gel. Solvent was evaporated, and the crude residue was purified via column chromatography (9:1 hexane-EtOAc) to afford the title compound as a clear, yellow oil (51 mg, 77% yield). R_f (90:10, hexane-EtOAc) = 0.14.

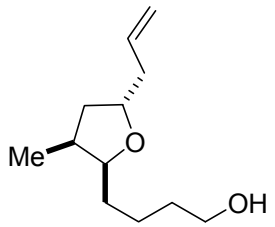
IR (thin film/NaCl): 3408, 2957, 2929, 2870, 1598, 1490 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ 7.38-7.25 (m, 6H), 7.24-7.20 (m, 4H), 6.54 (s, 1H), 3.93-3.89 (m, 1H), 2.95-2.90 (m, 1H), 2.63-2.51 (m, 3H), 2.28 (dd, *J* = 9.5, 13.9 Hz, 1H), 1.88 (s, 1H), 1.59-1.52 (m, 3H), 1.50-1.39 (m, 1H), 1.25 (d, *J* = 6.9 Hz, 3H), 0.96 (t, *J* = 7.0 Hz, 3H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 137.9, 137.8, 131.7 (2C), 130.7, 129.0 (2C), 128.4 (2C), 128.4 (2C), 127.8, 126.7, 123.8, 94.2, 81.8, 69.4, 45.9, 39.6, 37.7, 25.7, 21.3, 19.2, 14.4.

HRMS (ESI) $[M+Na]^+$: *m/z* calcd for $C_{24}H_{28}ONa$ 355.2032, obsd 355.2035.

$[\alpha]_D = -14.1$ (23 °C, *c* = 7.3, $CDCl_3$)



(−)-4-[(5*R*)-Allyl-(3*S*)-methyl-tetrahydro-furan-(2*S*)-yl]-butan-1-ol (57). A solution of lactol **21a** (0.29 g, 1.0 mmol) and allyltrimethylsilane (0.64 mL, 4.0 mmol) in 20 mL CH_2Cl_2 was cooled to −78 °C. Distilled boron trifluoride diethyl etherate was added dropwise (0.38 mL, 3.0 mmol), and the solution was allowed to stir, coming to ambient temperature, for 16 h. Saturated $NaHCO_3$ and H_2O were added (5 mL each), the layers were separated, and the organic phase was extracted with CH_2Cl_2 (3 x 15 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The crude residue was purified via gradient column chromatography (70:30 hex-EtOAc, polarity gradually increased to 50:50) to afford the title compound as a clear, colorless oil (0.18 g, 88% yield). R_f (50:50, hexane-EtOAc) = 0.25.

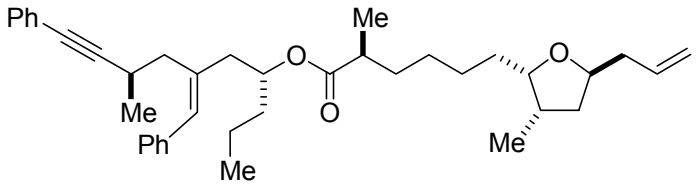
IR (thin film/NaCl): 3379, 3076, 2936, 2868, 1641 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ 5.85-5.76 (m, 1H), 5.10-5.04 (m, 2H), 4.15-4.09 (m, 1H), 3.89-3.85 (m, 1H), 3.66 (t, *J* = 6.4 Hz, 2H), 2.36-2.31 (m, 1H), 2.26-2.17 (m, 2H), 1.80-1.65 (m, 2H), 1.64-1.46 (m, 4H), 1.43-1.37 (m, 2H), 0.89 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 135.2, 117.0, 81.5, 76.3, 63.0, 41.2, 39.5, 36.1, 33.0, 30.3, 23.0, 14.2.

HRMS (ESI) $[M+Na]^+$: *m/z* calcd for $C_{12}H_{22}O_2Na$ 221.1521, obsd 221.1515.

$[\alpha]_D$ = −1.25 (23 °C, *c* = 4.8, CH_2Cl_2)



(+)-6-[(5*R*)-Allyl-(3*S*)-methyl-tetrahydro-furan-(2*S*)-yl]-(2*S*)-methyl-hexanoic acid 3-benzylidene-(5*R*)-methyl-7-phenyl-(1*R*)-propyl-hept-6-ynyl ester (58). Acid **12** (48 mg, 0.188 mmol) and alcohol **13** (31 mg, 0.093 mmol) were dissolved in 0.95 mL CH_2Cl_2. Dicyclohexylcarbodiimide (40 mg, 0.193 mmol) and 4-pyrrolidinopyridine (30 mg, 0.202 mmol) were added and the heterogeneous mixture was stirred at ambient temperature 14h. Silica gel was added, and the solvent was removed in vacuo. The dry silica gel was loaded onto a slurry-packed column (93:7 hexane-EtOAc) and the title

compound was eluted and concentrated to give a clear, pale yellow oil (38 mg, 72% yield). R_f (90:10 hexane-EtOAc) = 0.23.

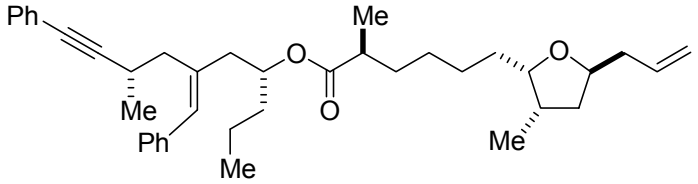
IR (thin film/NaCl): 2961, 2933, 2872, 2229, 1727, 1641, 1598 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ 7.36-7.29 (m, 10H), 6.45 (s, 1H), 5.85-5.77 (m, 1H), 5.20-5.15 (m, 1H), 5.10-5.04 (m, 2H), 4.13-4.08 (m, 1H), 3.84-3.80 (m, 1H), 2.99-2.94 (m, 1H), 2.70 (dd, *J* = 9.5, 13.7 Hz, 1H), 2.59-2.52 (m, 1H), 2.48-2.39 (m, 2H), 2.37-2.32 (m, 1H), 2.23-2.17 (m, 2H), 1.79-1.72 (m, 1H), 1.71-1.66 (m, 2H), 1.63-1.58 (m, 2H), 1.47-1.26 (m, 10H), 1.24 (d, *J* = 6.7 Hz, 3H), 1.10 (d, *J* = 7.0 Hz, 3H), 0.92 (t, *J* = 7.3 Hz, 3H), 0.89 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 176.8, 138.1, 136.8, 135.3, 131.7 (2C), 130.4, 129.1 (2C), 128.32, 128.28 (3C), 127.7, 126.4, 124.0, 117.0, 94.1, 81.4, 76.1, 71.7, 42.6, 41.2, 39.9, 39.4, 37.1, 36.8, 36.0, 33.9, 30.5, 27.7, 26.7, 25.2, 21.3, 19.0, 17.4, 14.2 (2C).

HRMS (ESI)$[M+Na]^+$: *m/z* calcd for $C_{39}H_{52}O_3Na$ 591.3809, obsd 591.3814.

$[\alpha]_D$ = +11.1 (23 °C, *c* = 6.3, $CDCl_3$)



(−)-6-[(5*R*)-Allyl-(3*S*)-methyl-tetrahydro-furan-(2*S*)-yl]-(2*S*)-methyl-hexanoic acid 3-be26nzylidene-(5*S*)-methyl-7-phenyl-(1*R*)-propyl-hept-6-ynyl ester (59). Acid **12** (83 mg, 0.3 mmol) and alcohol **56** (50 mg, 0.150 mmol) were dissolved in 2.0 mL CH_2Cl_2. Dicyclohexylcarbodiimide (61 mg, 0.295 mmol) and 4-pyrrolidinopyridine (44 mg, 0.296 mmol) were added and the heterogeneous mixture was stirred at ambient temperature 14h. Silica gel was added, and the solvent was removed in vacuo. The dry silica gel was loaded onto a slurry-packed column (93:7 hexane-EtOAc) and the title compound was eluted and concentrated to give a clear, pale yellow oil (71 mg, 84% yield). R_f (90:10 hexane-EtOAc) = 0.32.

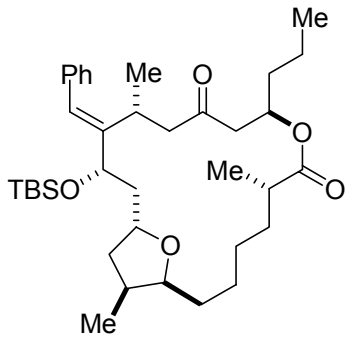
IR (thin film/NaCl): 2962, 2934, 2873, 2231, 1728, 1598, 1491 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ 7.38-7.35 (m, 2H), 7.34-7.29 (m, 2H), 7.28-7.26 (m, 4H), 7.25-7.21 (m, 2H), 6.45 (s, 1H), 5.87-5.78 (m, 1H), 5.22-5.17 (m, 1H), 5.12-5.05 (m, 2H), 4.14-4.09 (m, 1H), 3.85-3.81 (m, 1H), 2.93-2.89 (m, 1H), 2.64-2.58 (m, 2H), 2.54-2.42 (m, 3H), 2.40-2.33 (m, 1H), 2.24-2.18 (m, 2H), 1.80-1.67 (m, 3H), 1.64-1.58 (m, 2H), 1.48-1.41 (m, 4H), 1.40-1.24 (m, 5H), 1.22 (d, *J* = 6.7 Hz, 3H), 1.12 (d, *J* = 7.0 Hz, 3H), 0.94-0.89 (m, 6H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 176.8, 138.0, 137.2, 135.3, 131.7 (2C), 130.0, 129.0 (2C), 128.3 (4C), 127.7, 126.5, 124.0, 116.9, 94.4, 81.6, 81.4, 76.1, 71.7, 42.7, 41.2, 40.0, 39.4, 37.1, 36.7, 36.0, 33.9, 30.5, 27.7, 26.7, 25.5, 21.3, 19.0, 17.4, 14.2 (2C).

HRMS (ESI)[M+Na]$^+$: *m/z* calcd for $C_{39}H_{52}O_3Na$ 591.3809, obsd 591.3800.

$[\alpha]_D = -7.8$ (23 °C, *c* = 6.8, CH_2Cl_2)



(−)-14-Benzylidene-(15*S*)-(tert-butyl-dimethyl-silanyloxy)-(6*S*,13*R*,19*S*)-trimethyl-(9*R*)-propyl-8,20-dioxa-bicyclo[15.2.1]icosane-7,11-dione (60). Macrocyclic alcohol **7b** was dissolved in anhydrous DMF (21 mg, 0.042 mmol in 1.0 mL) and *t*-butyldimethylchlorosilane (46 mg, 0.31 mmol), imidazole (36 mg, 0.53 mmol), and *N,N*-dimethylaminopyridine (1 mg, 0.008 mmol) were added sequentially. The mixture was stirred at ambient temperature 20 h, then partitioned between 15 mL Et_2O and 10 ml H_2O. The organic phase was washed with H_2O (3 x 5 mL) and brine (3 x 10 mL), dried over Na_2SO_4, filtered and concentrated. The crude residue was purified via column chromatography (96:4 hexane-EtOAc) to afford the title compound as a clear, colorless oil (17 mg, 68% yield). R_f (90:10 hexane-EtOAc) = 0.29.

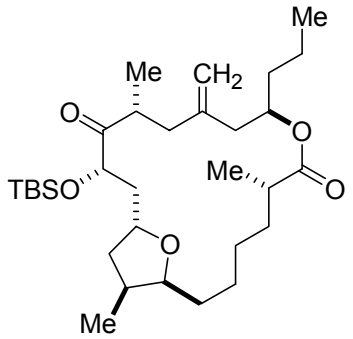
IR (thin film/NaCl): 2959, 2932, 2857, 1733 (br), 1463 cm^{-1}.

^{1}H NMR (C_6D_6, 500 MHz): δ 7.35 (app d, *J* = 7.6 Hz, 2H), 7.19-7.16 (m, 2H), 7.07 (s, 1H), 7.05-7.02 (m, 1H), 5.35-5.32 (m, 1H), 4.64 (d, *J* = 8.8 Hz, 1H), 4.46-4.41 (m, 1H), 3.78-3.75 (m, 1H), 3.67-3.62 (m, 1H), 2.58 (dd, *J* = 5.8, 17.4 Hz, 1H), 2.48-2.41 (m, 2H), 2.37-2.30 (m, 1H), 2.03-1.96 (m, 2H), 1.86-1.79 (m, 1H), 1.67-1.53 (m, 5H), 1.52-1.44 (m, 3H), 1.42-1.31 (m, 3H), 1.30-1.24 (m, 2H), 1.17 (d, *J* = 7.0 Hz, 3H), 1.14-1.08 (m, 2H), 1.07-1.04 (m, 12H), 0.78 (d, *J* = 7.0 Hz, 3H), 0.75 (t, *J* = 7.3 Hz, 3H), 0.29 (s, 3H), 0.24 (s, 3H).

^{13}C NMR (C_6D_6, 125 MHz): δ 206.3, 175.0, 149.8, 139.5, 129.4 (2C), 129.0 (2C), 127.0, 124.9, 78.3, 73.9, 71.6, 71.4, 50.0, 48.2, 47.9, 41.3, 41.0, 37.4, 37.0, 35.4, 30.7, 30.5, 27.7, 27.5, 26.6 (3C), 21.6, 18.90, 18.87, 17.5, 15.1, 14.4, -3.5, -4.1.

HRMS (ESI)[M+Na]$^+$: *m/z* calcd for $C_{37}H_{60}O_5Na$ 635.4102, obsd 635.4094.

$[\alpha]_D = -2.6$ (23 °C, *c* = 2.3, CH_2Cl_2)



(+)-(15*S*)-(tert-Butyl-dimethyl-silanyloxy)-(6*S*,13*R*,19*S*)-trimethyl-11-methylene-(9*R*)-propyl-8,20-dioxa-bicyclo[15.2.1]icosane-7,14-dione (61). A stock solution of methylenating reagent was prepared in the following manner: a 50 ml flask was charged with activated zinc[11] (0.51 g, 7.80 mmol), lead (II) chloride (0.093 g, 0.33 mmol), and THF (4.0 ml); then cooled to 0 °C. Diiodomethane (0.21 mL, 2.60 mmol) was added via syringe, and the mixture was stirred 30 min at 0 °C. During this time, a suspension of zirconium (IV) chloride in THF (0.25 g, 1.07 mmol in 3.0 mL) was prepared by stirring together 20 min at ambient temperature. The suspension of zirconium (IV) chloride transferred to the $Zn/PbCl_2/CH_2I_2$ mixture via cannula. The resulting heterogeneous mixture was stirred 30 minutes at 0 °C. (During this time, the mixture assumed a green color, which indicated the generation of the active methylenation reagent.) A solution of diketone **36** in THF (4.2 mg in 1.0 mL) was cooled to 0 °C. Methylenating reagent was transferred to the diketone solution via syringe (0.8 mL), and the reaction was stirred for 1 h at 0 °C. Water (0.5 mL) and Et_2O (5 mL) were added; then the cold bath was removed. The layers were separated, and the aqueous phase was extracted with Et_2O (5 x 5 mL). The combined organic phase was washed with saturated NaS_2O_3 (1 x 10 ml), dried over Na_2SO_4, filtered and concentrated. The crude residue was purified via Pasteur pipet gradient column chromatography (50:1 hexane-EtOAc, polarity gradually increased to 13:1 hexane-EtOAc) to give the title compound as a clear, colorless oil (3.6 mg, 85% yield). R_f (90:10 hexane-EtOAc) = 0.47.

IR (thin film/NaCl): 2933, 2857, 1725, 1461 cm^{-1}.

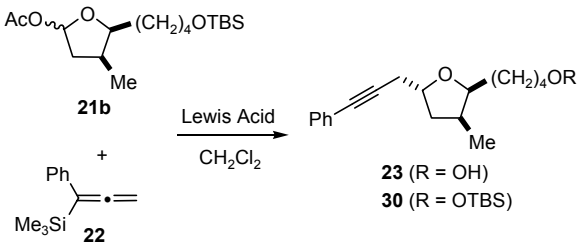
^1H NMR (C_6D_6, 500 MHz): δ 5.09-5.04 (m, 1H), 4.88 (s, 1H), 4.83 (s, 1H), 4.80 (dd, *J* = 2.1, 9.0 Hz, 1H), 4.46 (ddd, *J* = 2.4, 7.2, 15.8 Hz, 1H), 3.87 (ddd, *J* = 4.8, 4.8, 7.9 Hz, 1H), 3.27-3.23 (m, 1H), 2.57-2.50 (m, 2H), 2.41-2.36 (m, 1H), 2.21 (dd, *J* = 9.6, 14.3 Hz, 1H), 2.08 (app dd, *J* = 8.2, 13.4 Hz, 2H), 1.97-1.93 (m, 1H), 1.77-1.68 (m, 2H), 1.66-1.57 (m, 3H), 1.49-1.18 (br m, 10H), 1.10-1.05 (m, 15H), 0.83 (t, *J* = 7.3 Hz, 3H), 0.80 (d, *J* = 7.0 Hz, 3H), 0.27 (s, 3H), 0.14 (s, 3H).

^{13}C NMR (C_6D_6, 125 MHz): δ 212.8, 176.2, 143.4, 116.3, 78.4, 76.4, 73.7, 72.4, 41.4, 41.3, 41.2, 41.0, 40.4, 38.9, 36.3, 35.8, 33.8, 28.3, 26.54 (3C), 26.53, 26.0, 19.3, 19.1, 18.5, 17.5, 14.9, 14.3, −3.8, −4.5.

HRMS (ESI)$[M+Na]^+$: *m/z* calcd for $C_{31}H_{56}O_5NaSi$ 559.3789, obsd 559.3780.

$[\alpha]_D$ = + 0.7 (23 °C, *c* = 1.44, $CHCl_3$)

Table 1. Nucleophilic Addition of Allenylsilane **22** to Acetal **21b**.[a]



entry	Lewis acid	[**29b**] M	temperature	product(s)[b]
1	$TiCl_4$	0.05	−78 to 23 °C	**30** not observed
2	$SnBr_4$	0.05	−78 to 23 °C	**30** < 5%[c]
3	TBS-OTf	0.05	−78 to 23 °C	**23** 11%[d] + **30** 17%[d]
4	$BF_3 \cdot OEt_2$	0.05	−78 to 23 °C	**23** 13%[d]
5	$BF_3 \cdot OEt_2$	0.50	−78 to 23 °C	**23** 14%[d]
6	$BF_3 \cdot OEt_2$	0.05	−78 to 0 °C	**30** 13%[d]
7	$BF_3 \cdot OEt_2$	0.25	−78 °C	**30** not observed

a) 400 mol% **22** and 100 mol% **21b** were combined in CH_2Cl_2 and cooled to -78 °C before addition of 120 mol% Lewis acid. b) Characterized by ^1H NMR, ^{13}C NMR, and nOe experiments. c) Observed by ^1H NMR.
d) Isolated yield.

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[4] Prepared as reported in: Westmijze, H.; Vermeer, P. *Synthesis* **1979**, 390-392.

[5] Haruta, J.; Nishi, K.; Matsuda, S.; Akai, S.; Tamura, Y.; Kita, Y. *J. Org. Chem.* **1990**, *55*, 4853-4859.

[6] Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543-2549.

[7] For the general asymmetric alkylation procedure, see (a) Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 1737-1739. For asymmetric alkylation with a propargylic bromide, see (b) Savignac, M.; Durand, J.-O.; Genêt, J.-P. *Tetrahedron: Asymmetry* **1994**, *5*, 717-722.

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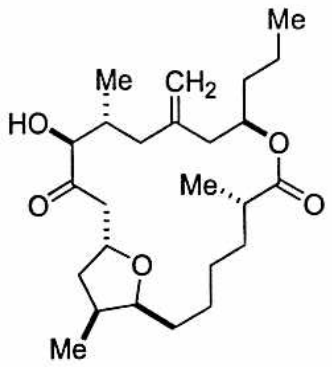
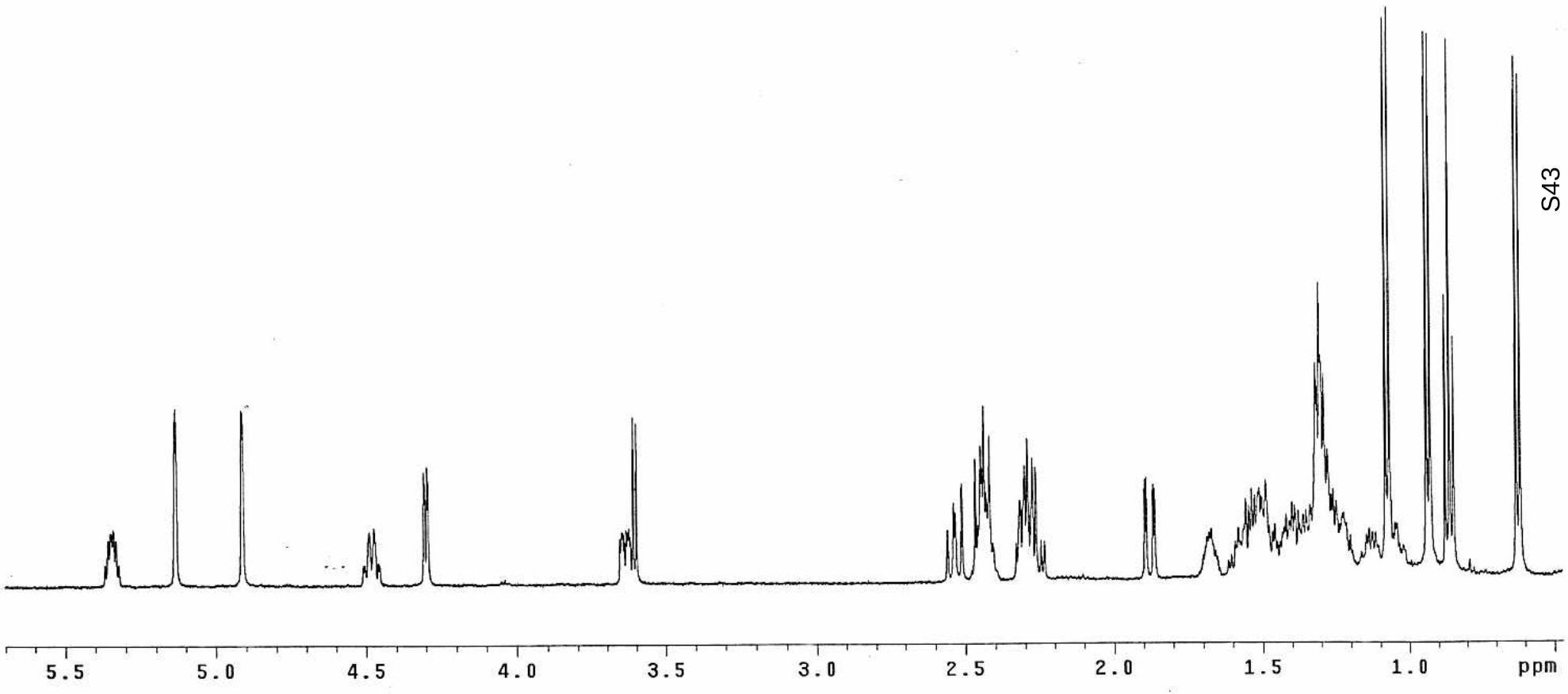
[9] Prepared according to the general procedure reported in: Brown, H. C.; Bhat, K. S. *J. Am. Chem. Soc.* **1986**, *108*, 5919-5923.

[10] Prepared as reported in: Marshall, J. A.; Shearer, B. G.; Crooks, S. L. *J. Org. Chem.* **1987**, *52*, 1236-1245.

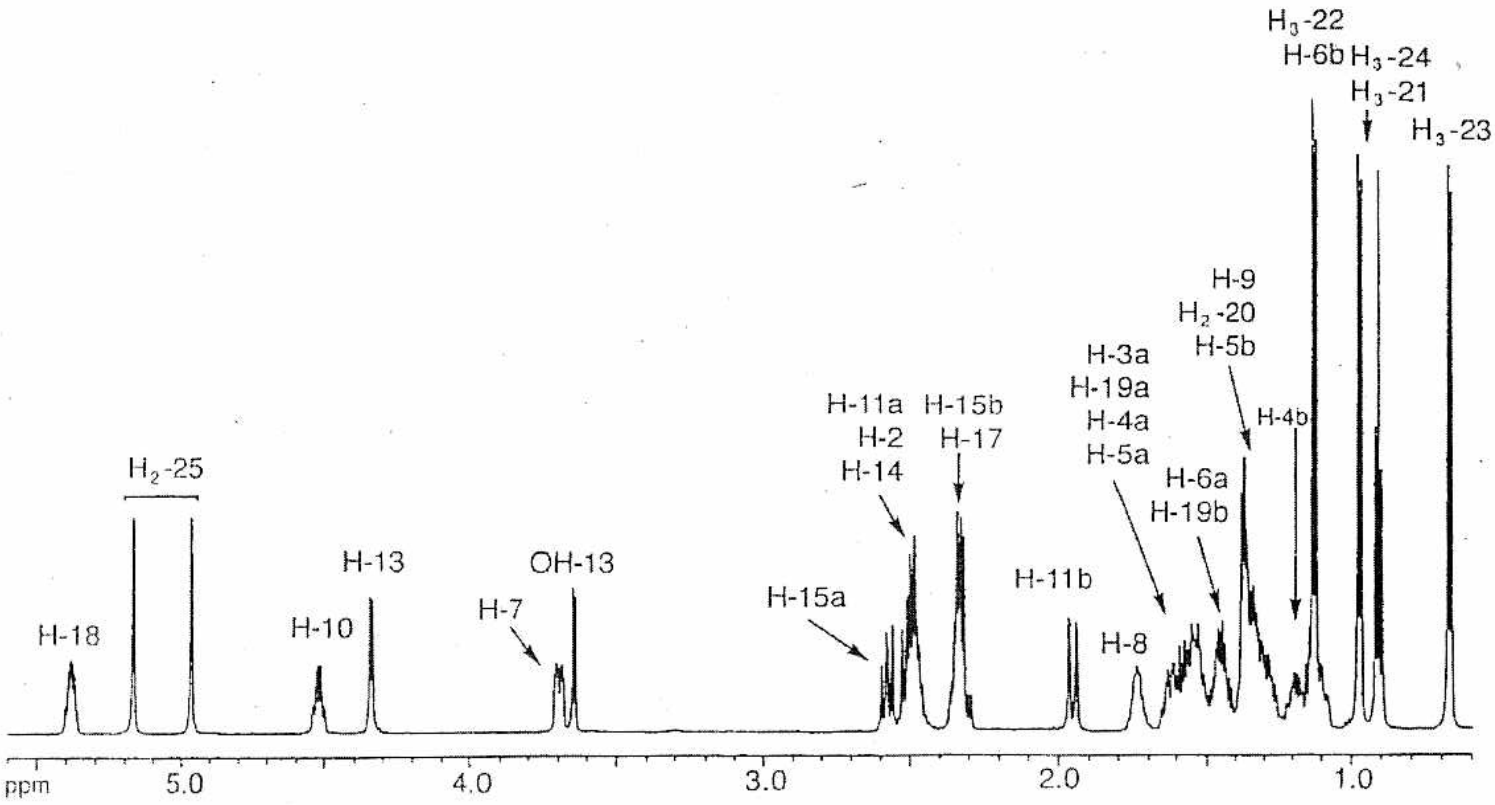
[11] Zinc was activated according to the procedure reported by Fieser and Fieser: Fieser, L. F.; Fieser, M. "Reagents for Organic Synthesis"; Wiley: New York, 1967, Vol. 1, p. 1276.

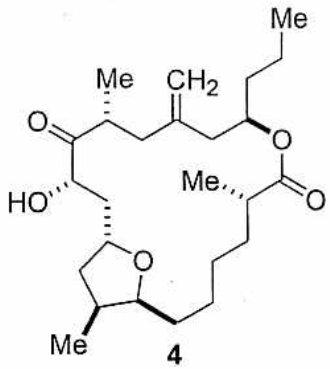


(+)-amphidinolide T1 (**1**)
synthetic

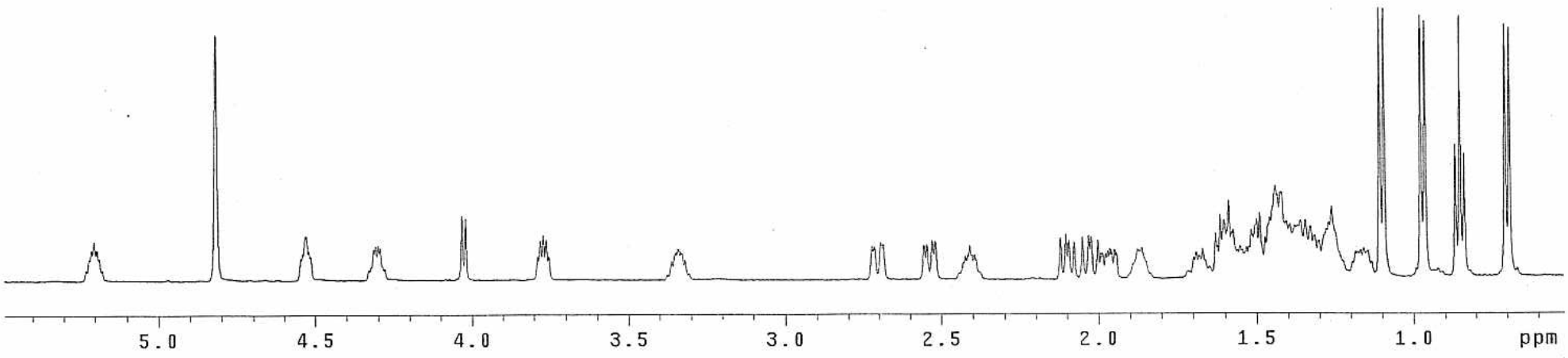


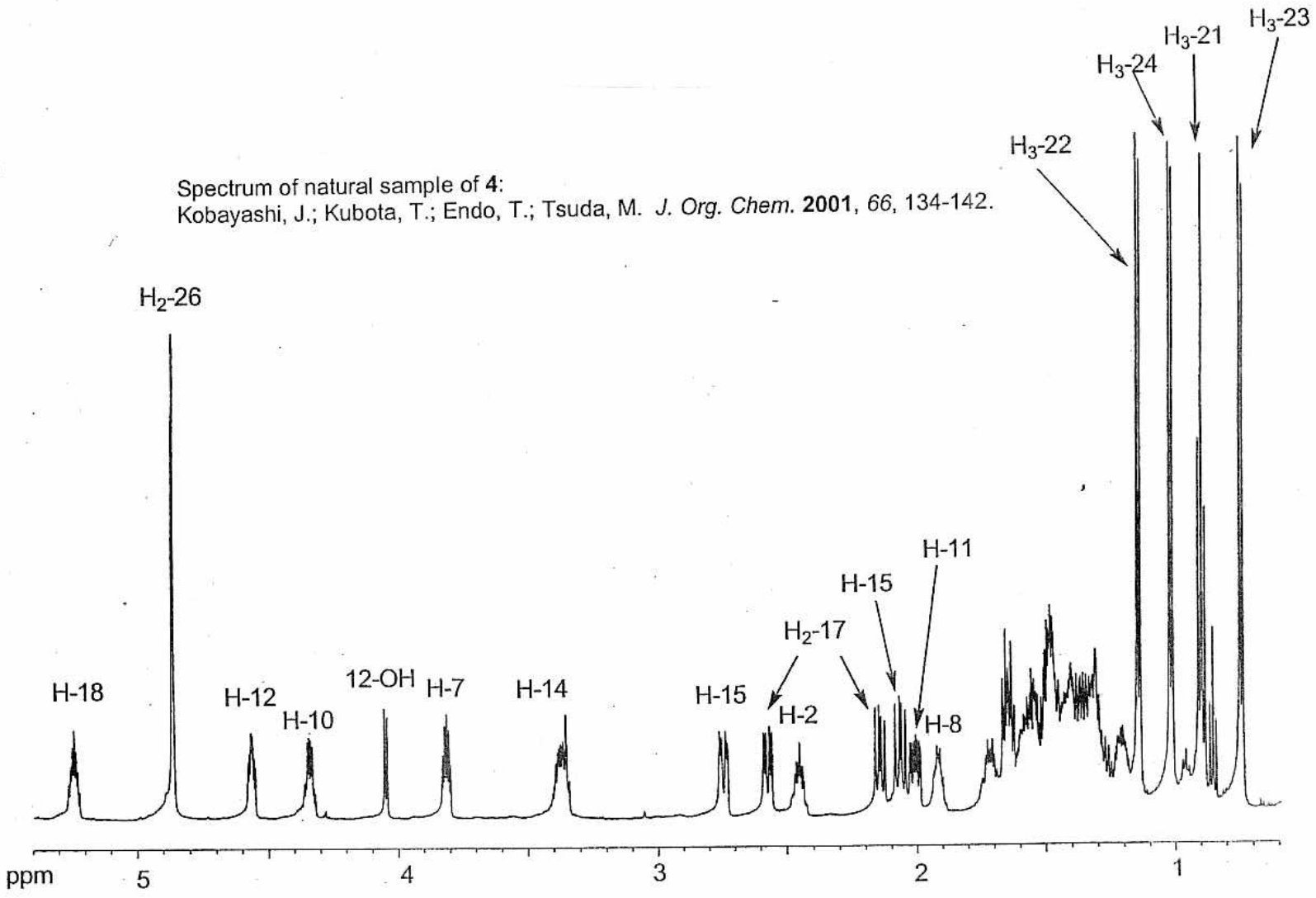
Spectrum of natural sample of **1**:
Tsuda, M.; Endo, T.; Kobayashi, J. *J. Org. Chem.* **2000**, *65*, 1349-1352.

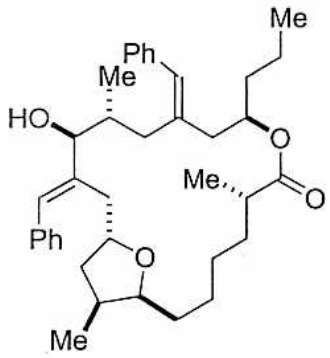




(–)-amphidinolide T4 (**4**)
synthetic




Spectrum of natural sample of 4:
Kobayashi, J.; Kubota, T.; Endo, T.; Tsuda, M. J. Org. Chem. 2001, 66, 134-142.
H3-23
H3-21
H3-24
H3-22
H2-26
H-18
H-12
H-10
12-OH
H-7
H-14
H-15
H2-17
H-2
H-15
H-11
H-8
ppm
5
4
3
2
1



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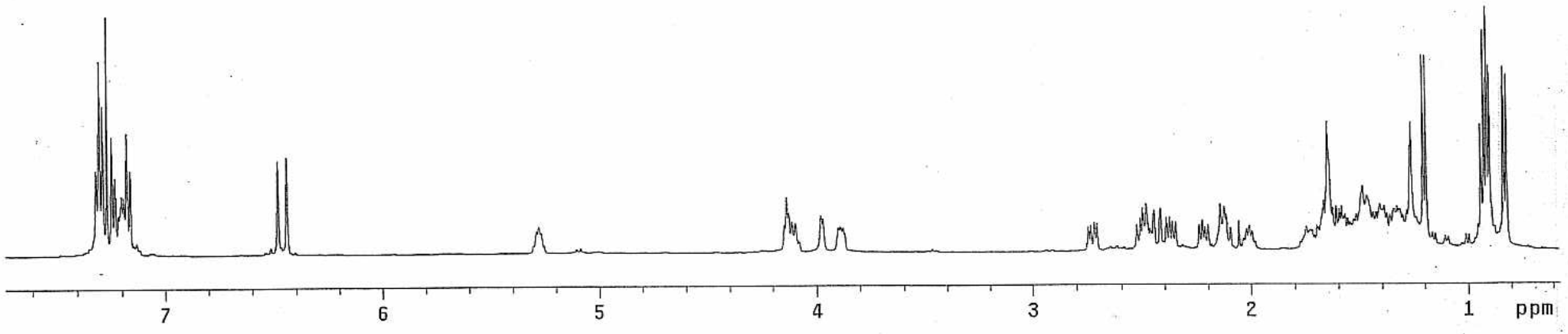

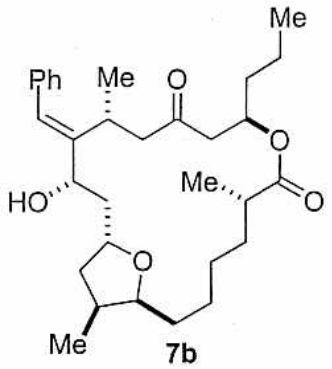

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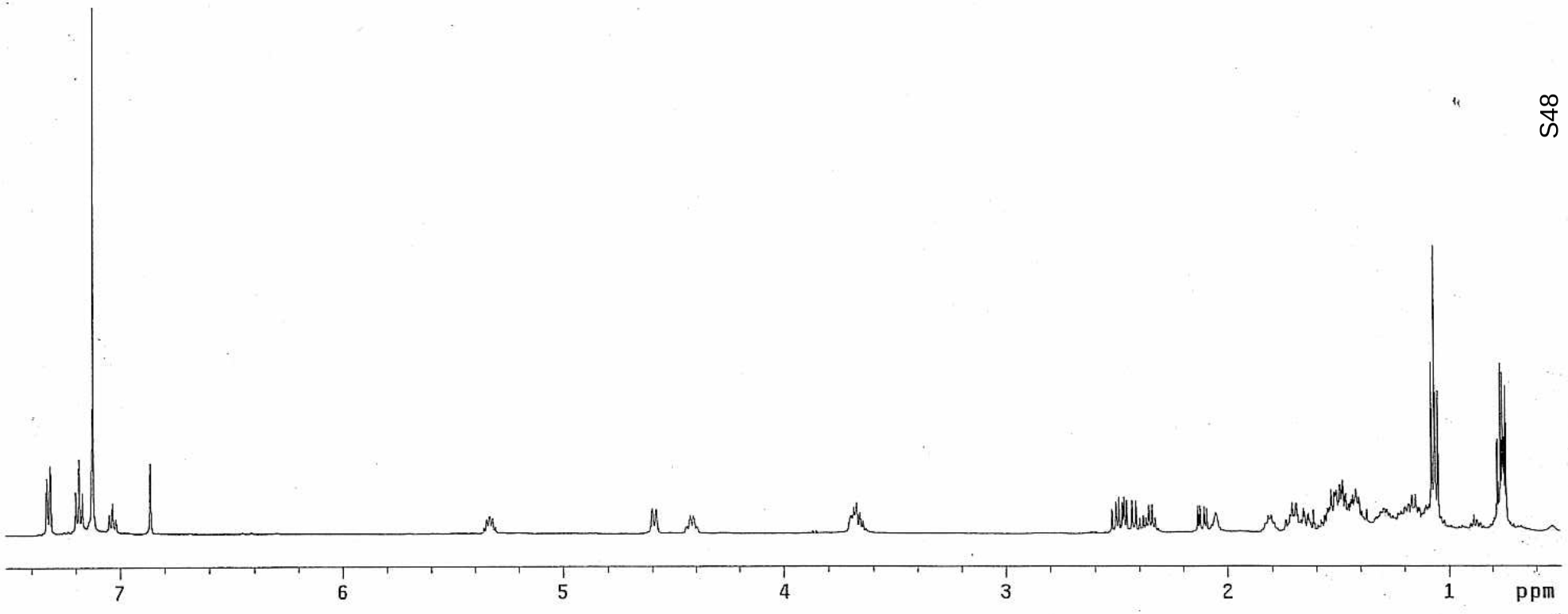

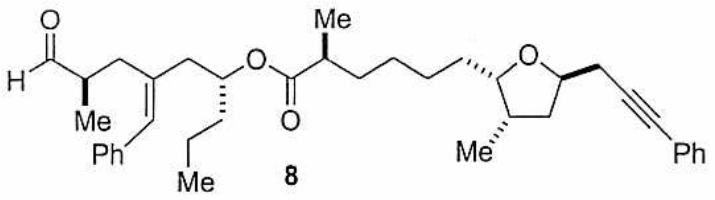

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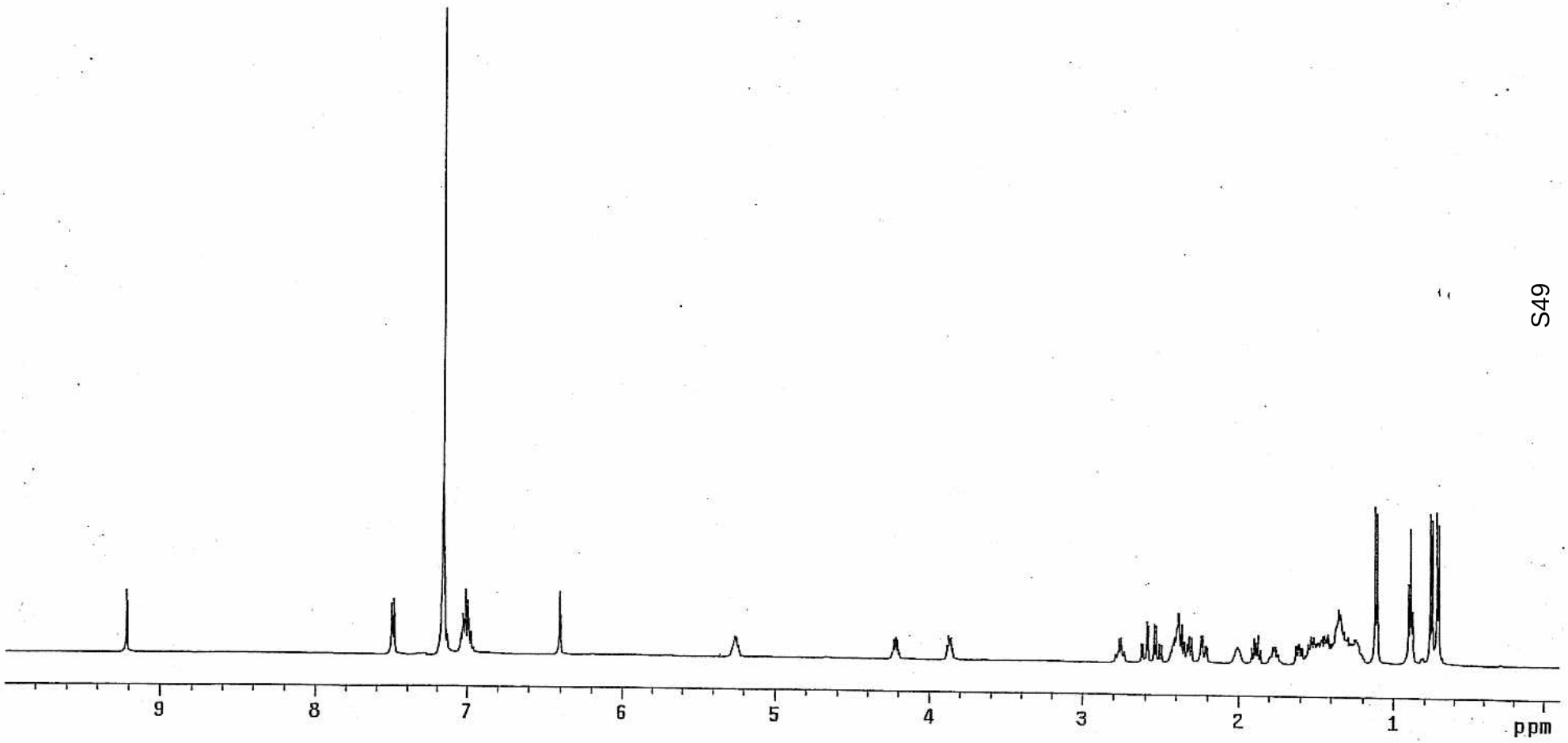

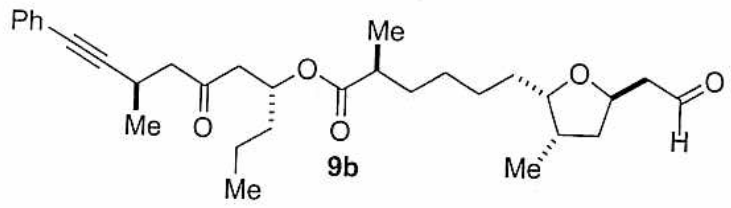

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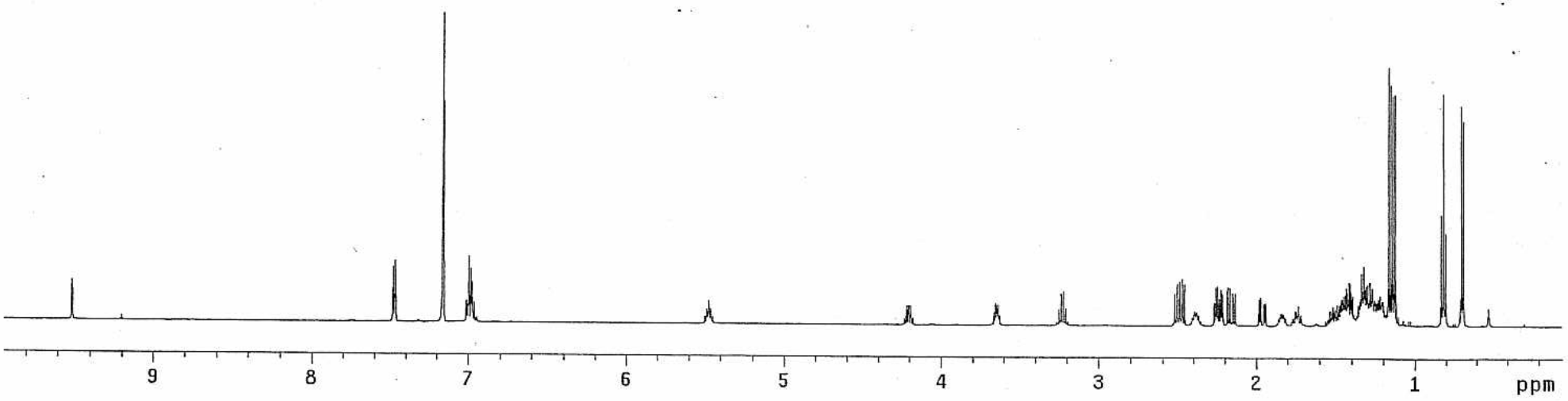

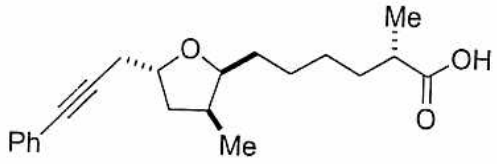

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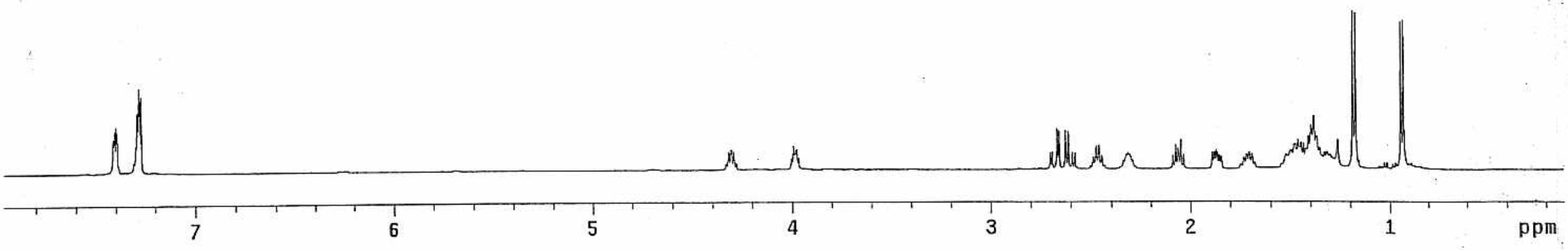

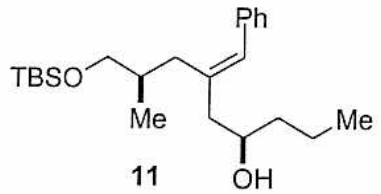
Ph
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OH

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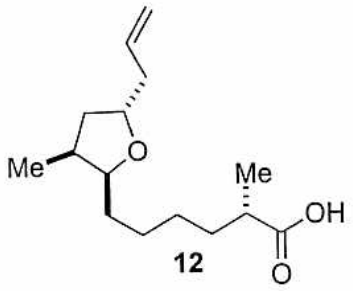
4
3
2
1
ppm



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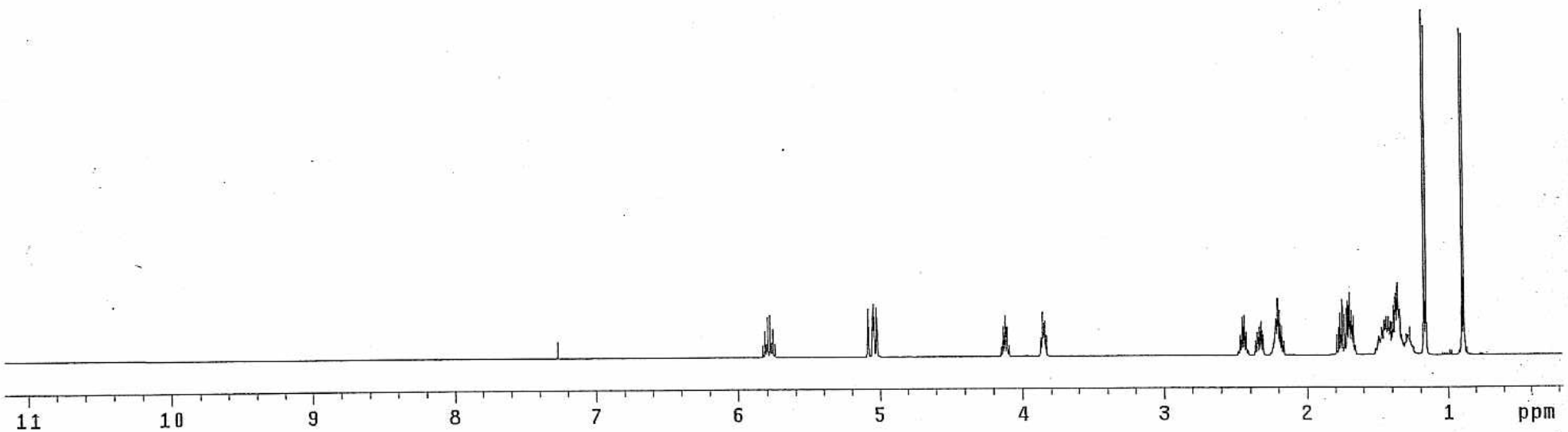

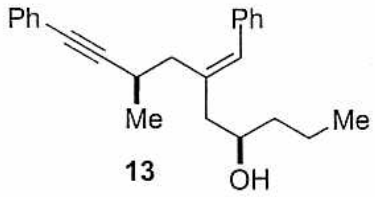

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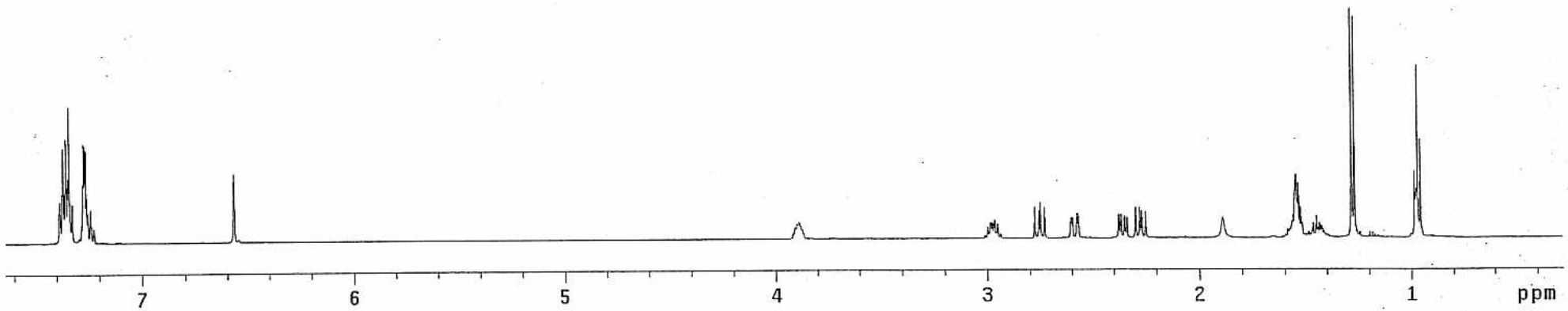

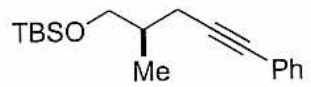

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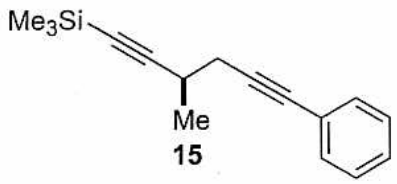

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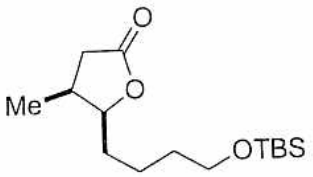

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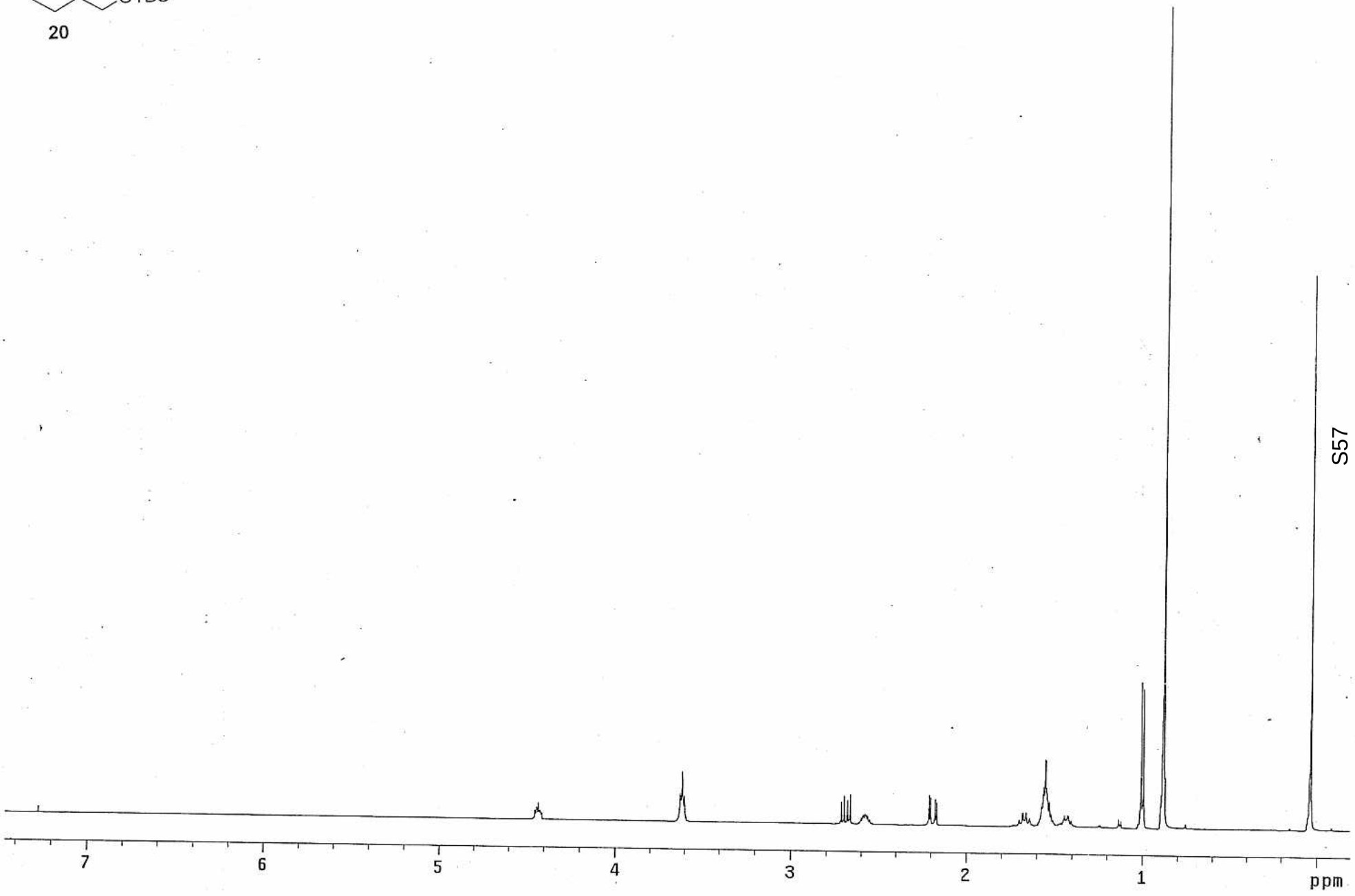

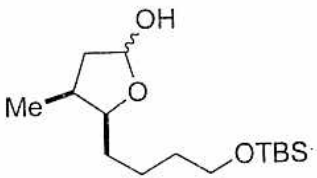

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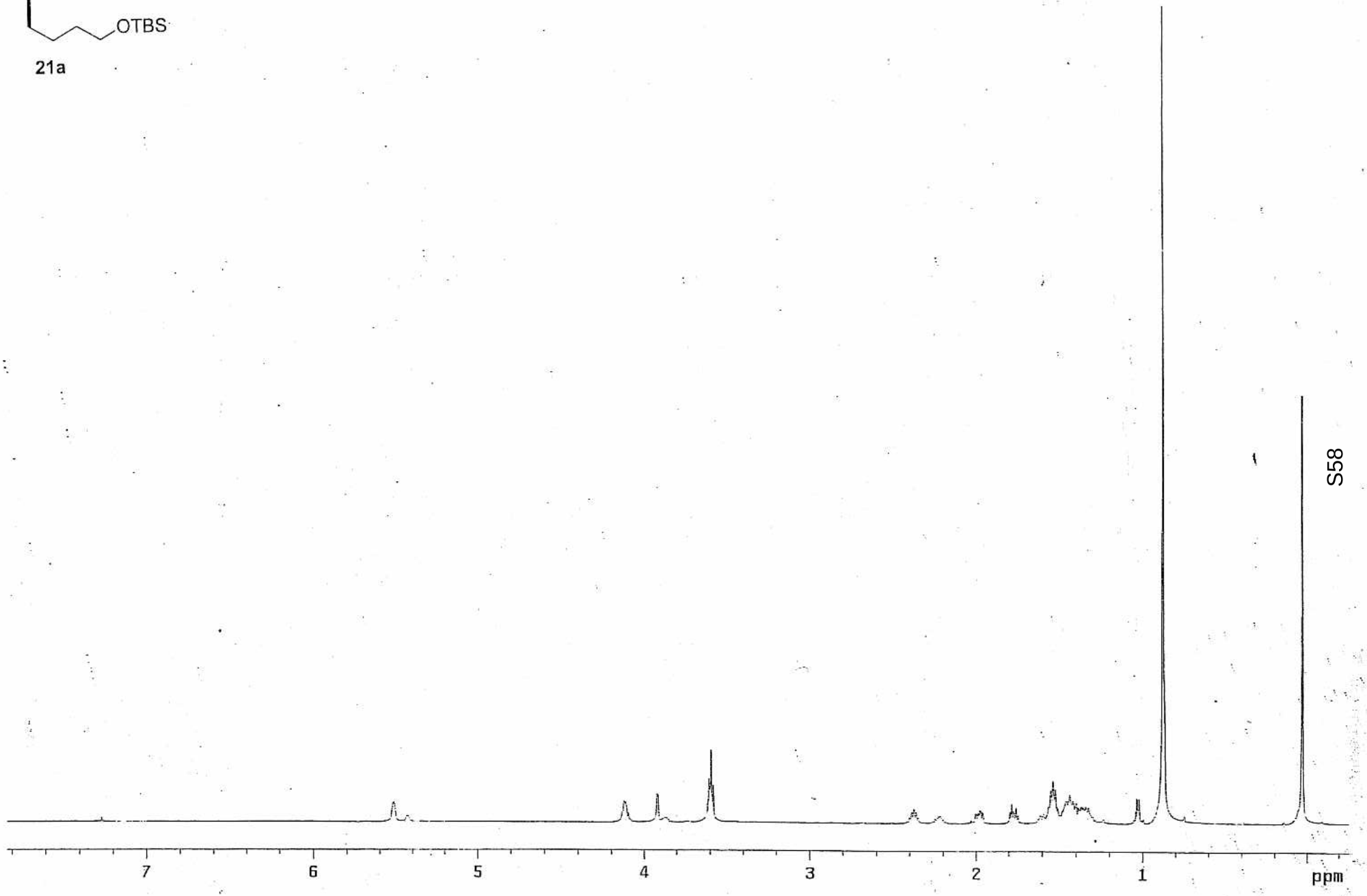

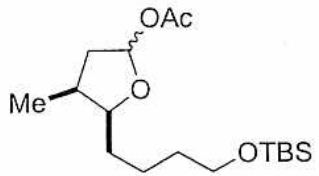

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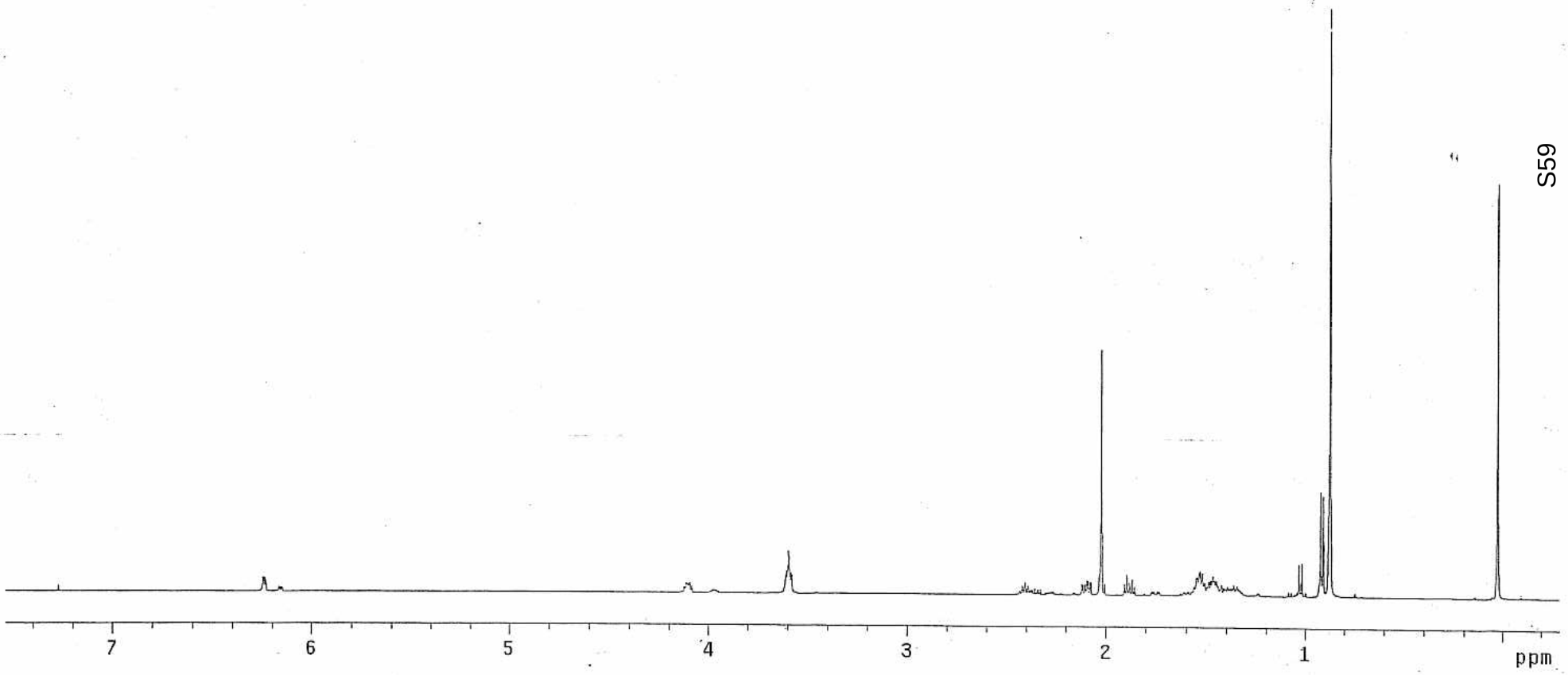

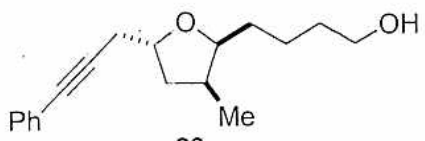

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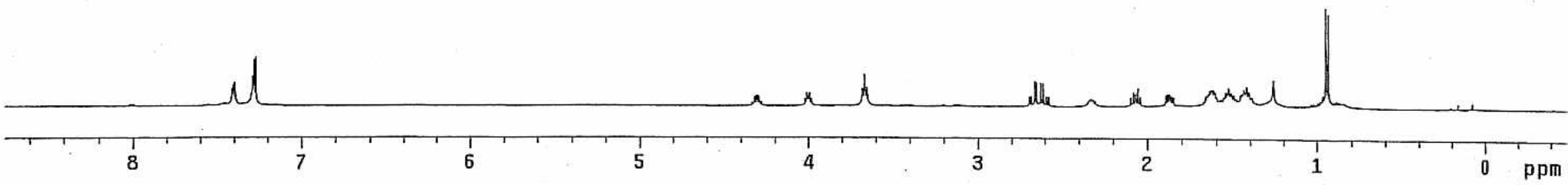

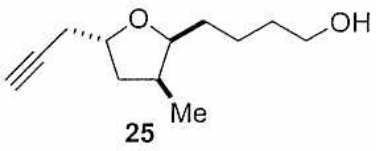

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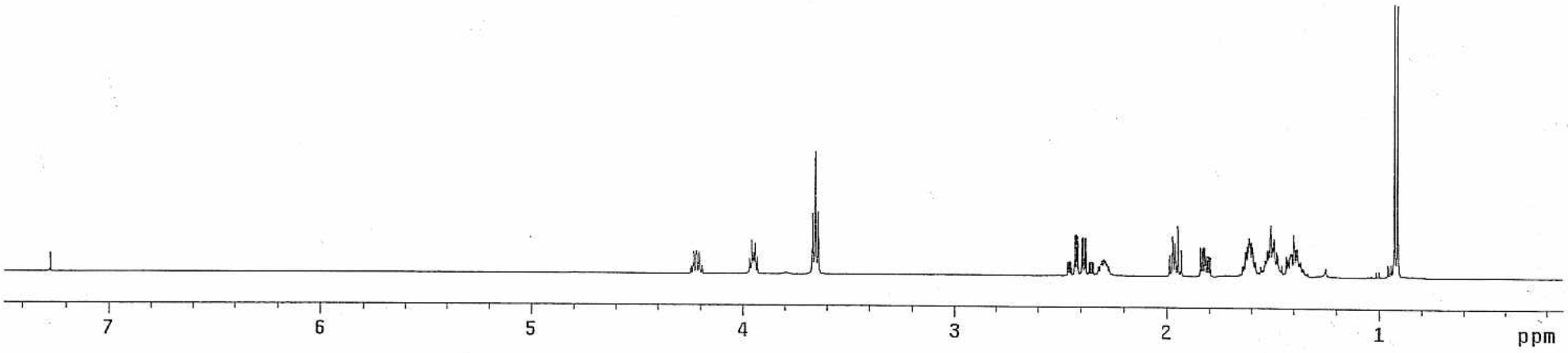

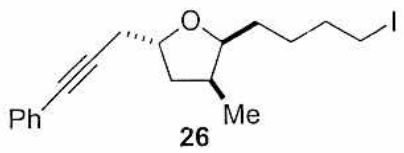

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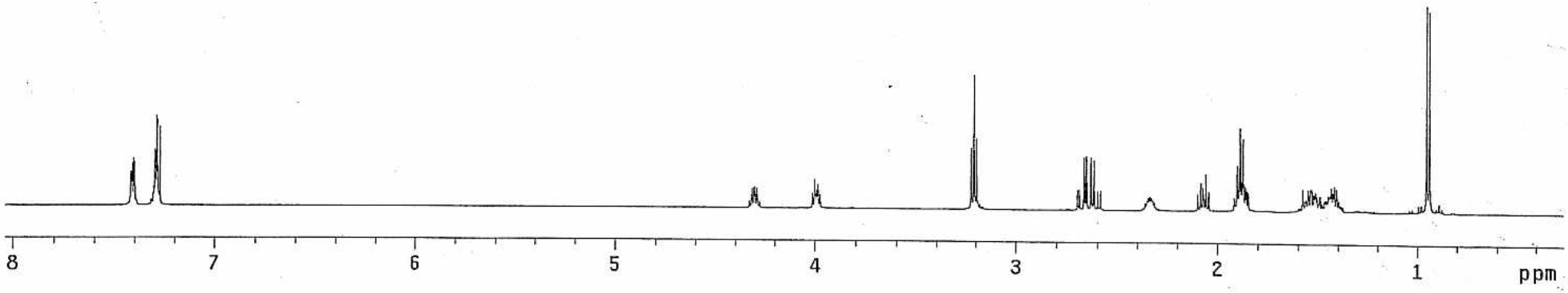

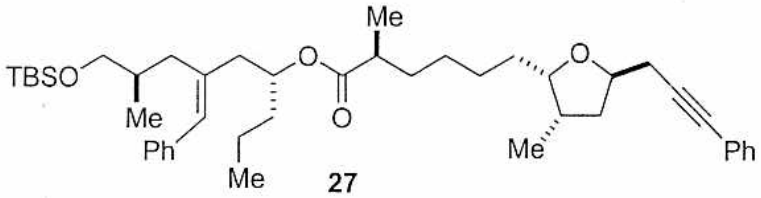

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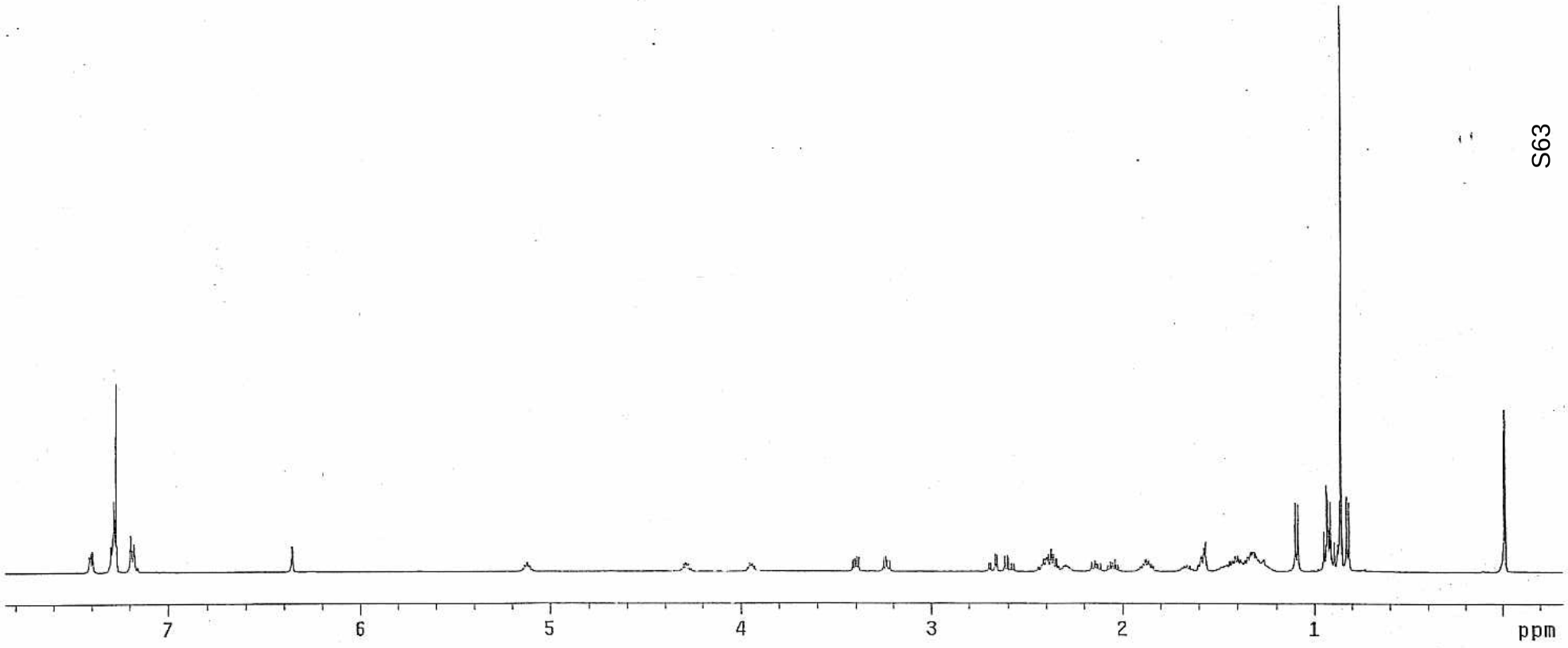

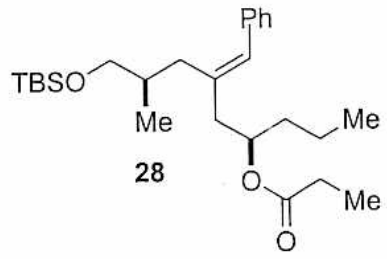
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Me
Me
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Me
O

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5
4
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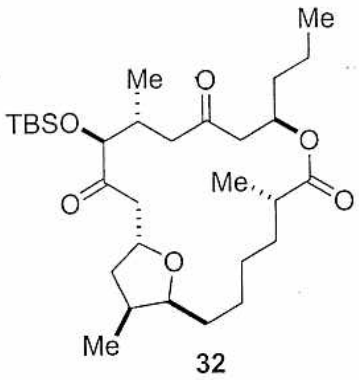

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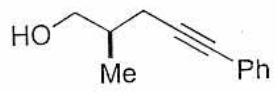

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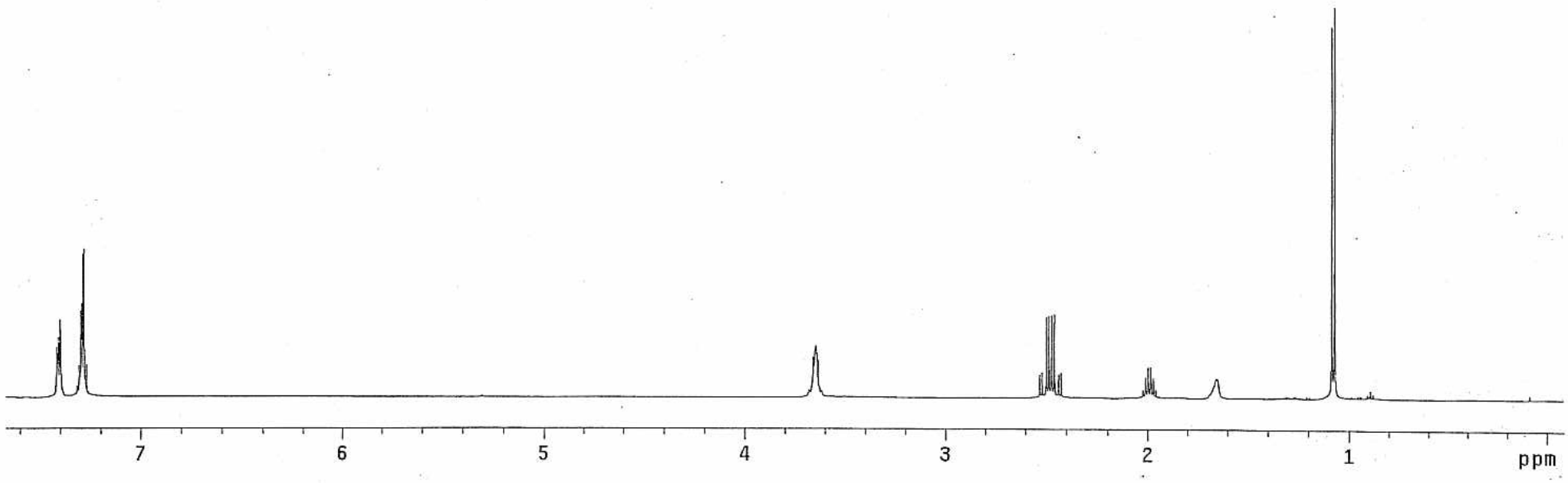

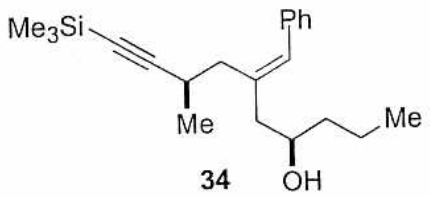

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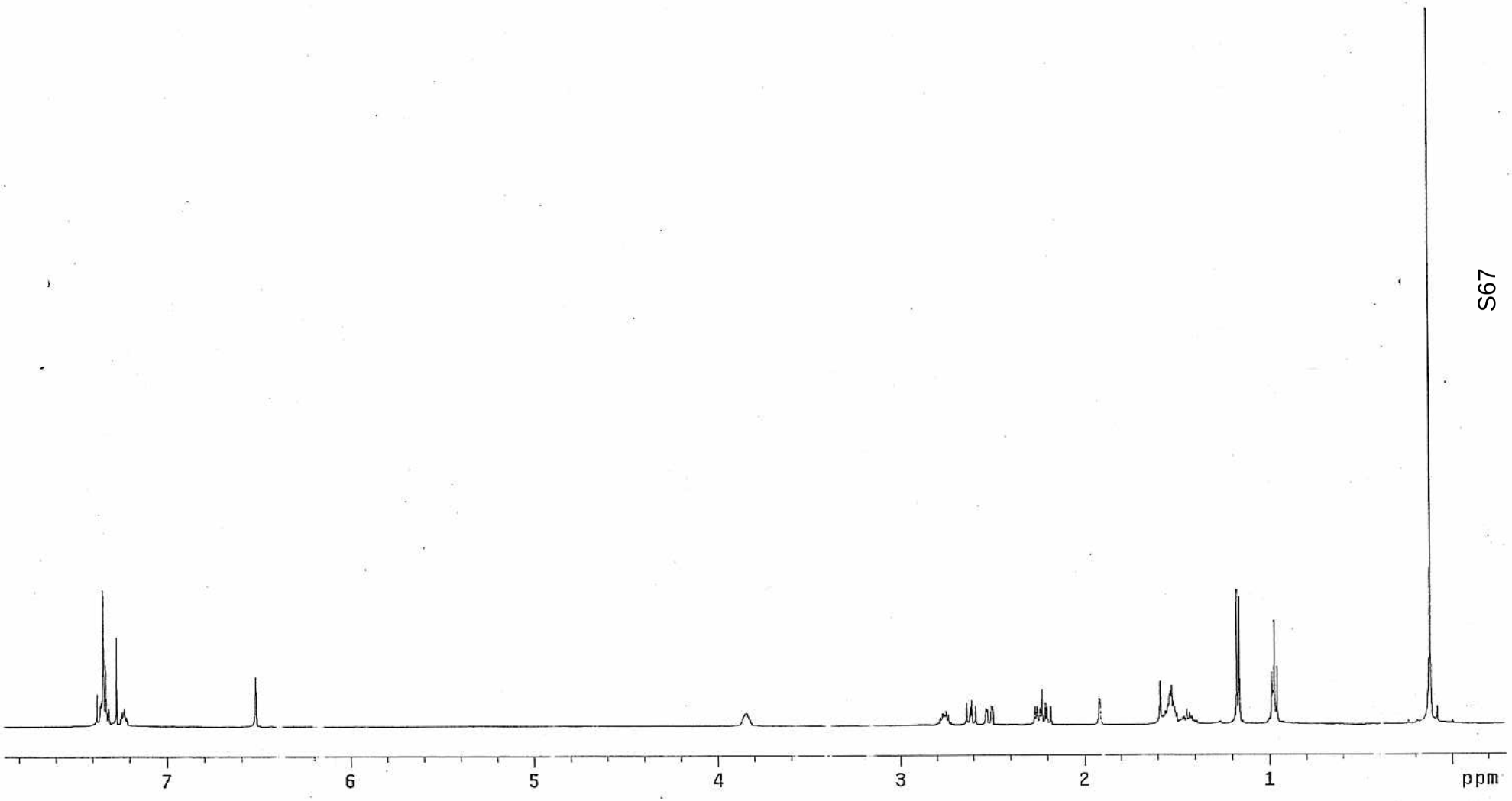

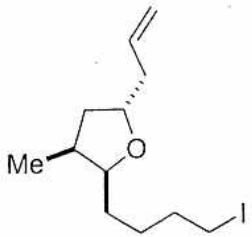

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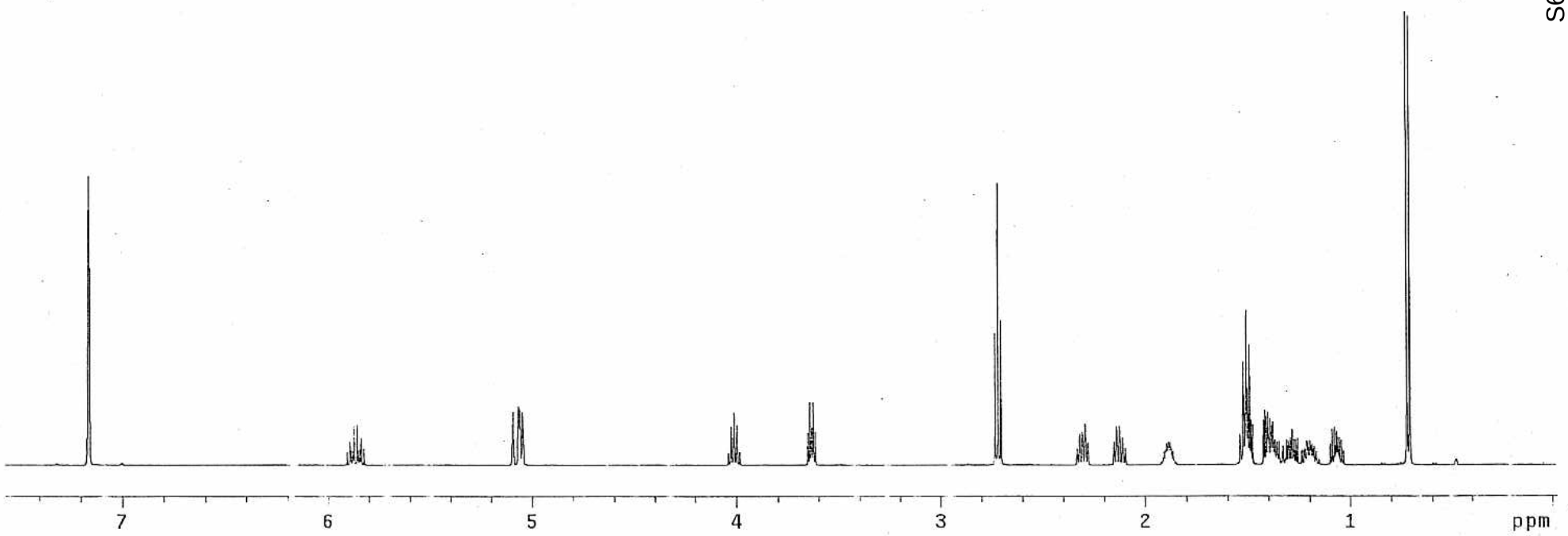

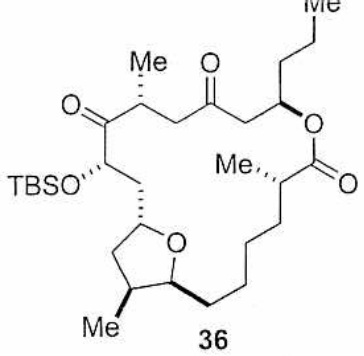

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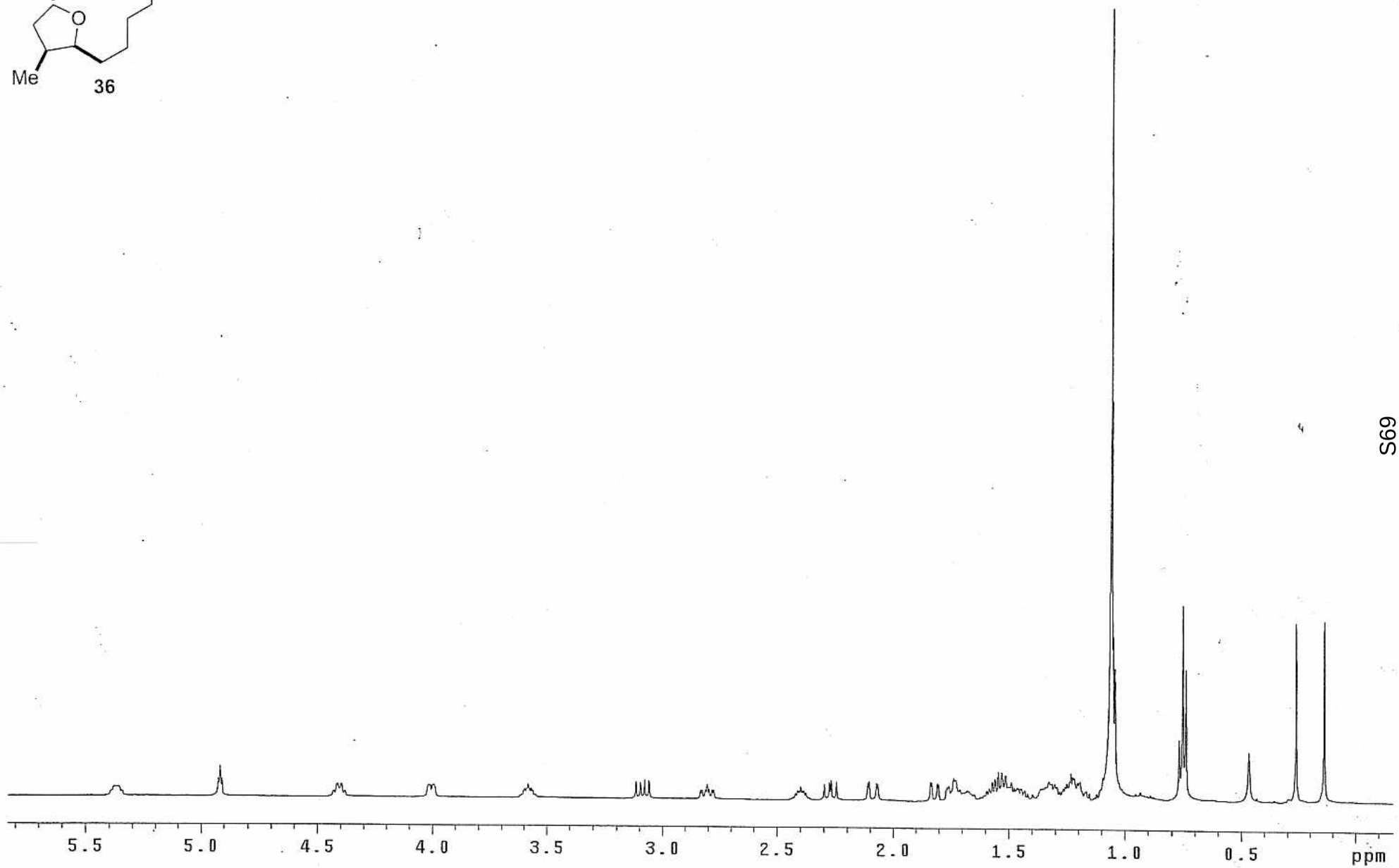

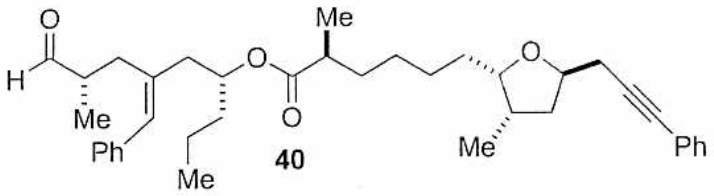

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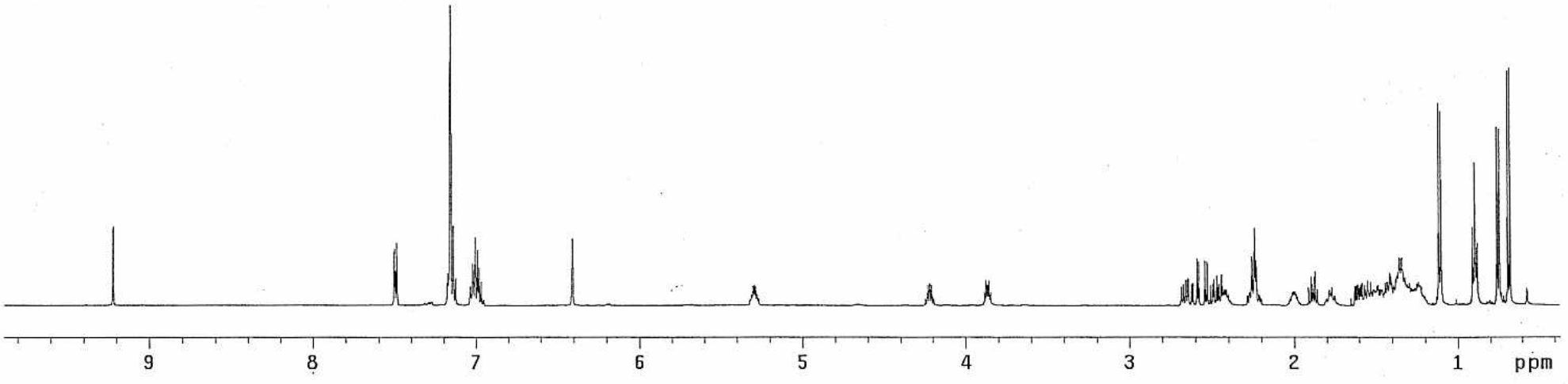

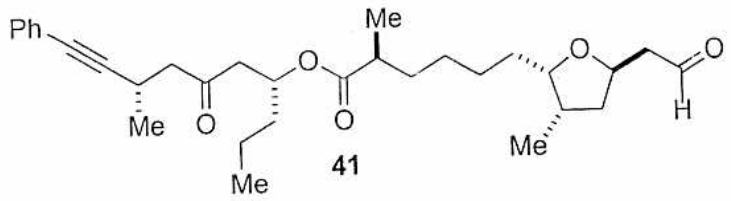

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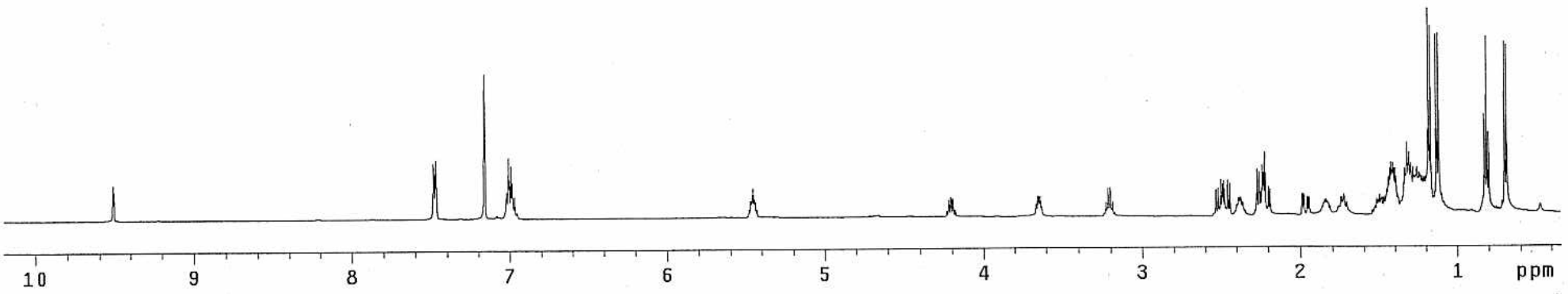

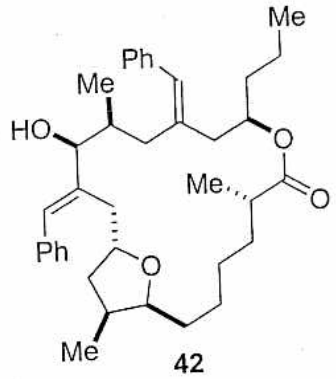

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