A Highly Convergent Total Synthesis of Leustroducsin B

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Supporting information

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1. Experimental part

1.1. General methods

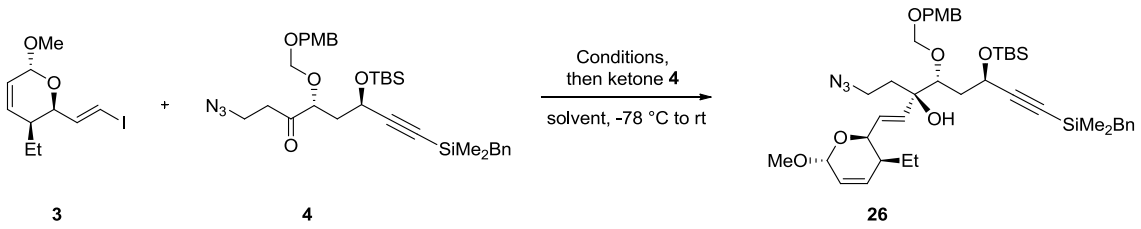
Air and/or moisture sensitive reactions were carried out under an argon atmosphere in oven-dried glassware and with anhydrous solvents. All compounds were purchased from commercial sources unless otherwise noted and used without further purification. Solvents were freshly distilled or dried by passing through an alumina column.

Thin layer chromatography was carried out on glass plates coated with silica gel SiO_2 60 F254 from Merck; visualization with a UV lamp (254 nm) or by staining with a *p*-anisaldehyde or potassium permanganate solution. Flash chromatography was performed with silica gel SiO_2 60 (0.040–0.063 μm, 230–400 mesh), technical solvents, and a head pressure of 0.2–0.4 bar. Melting points (m.p.) were measured on a Thomas Hoover capillary melting point apparatus in open capillaries and are uncorrected. Proton (^1H) and carbon (^{13}C) nuclear magnetic resonance (NMR) spectroscopy was performed on a Mercury NMR instrument at 400 MHz (1H) or 125 MHz (13C) and on a Unity NMR spectrometer at 500 MHz (^1H) or 150 MHz (^{13}C). Chemical shifts are reported in ppm relative to the residual protiated solvent ($CDCl_3$: δH = 7.26 ppm, δC = 77.16 ppm). All ^{13}C NMR spectra are proton decoupled. The resonance multiplicity is described as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), and br (broad). Infrared spectroscopic (IR) data were recorded on sodium chloride plates neat or as thin films on a Perkin-Elmer Paragon 500 FT-IR spectrometer. Absorption bands are reported in wavenumbers (cm^{-1}) in the range of 4000–600 cm^{-1}.

High-resolution mass spectrometry (HRMS) was measured on a Bruker micrOTOF-Q II electronspray ionization (ESI) mass spectrometer by the Vincent Coates Foundation Mass Spectrometry Laboratory at Stanford University. Mass peaks are reported in m/z units.

1.2. Optimization of the synthesis of 26

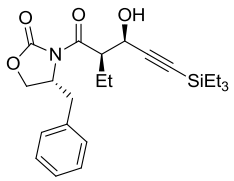
Table S1. Optimization table for the synthesis of **26**



3 **4** **26**

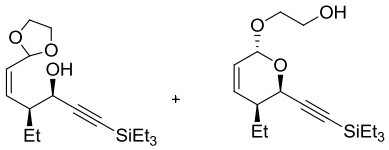
Entry	Conditions	Solvent	Results
1	*i*-PrMgCl, LiCl, THF, -30 °C	Ketone not added	No Mg-iodide exchange
2	*i*-PrMgCl, LiCl, THF, rt	Ketone not added	No Mg-iodide exchange
3	*n*-BuLi, $ZnMe_2$, THF, 1.1 eq. **4**	CH_2Cl_2	57%, > 20:1 dr
4	*n*-BuLi, $ZnMe_2$, THF, 2.0 eq. **4**	CH_2Cl_2	75%, > 20:1 dr
5	*n*-BuLi, THF, 1.1 eq. **4**	CH_2Cl_2	1:1.5 dr
6	*s*-BuLi, THF, 1.1 eq. **4**	CH_2Cl_2	Decomposition of **4**
7	$CrCl_2$, $NiCl_2$, DMSO, rt	NA	Decomposition of **4**
8	Mg, $BrCH_2CH_2Br$, THF	DCE	Mg-oxidative addition - Decomposition of **4**

1.3. Synthesis of Western Fragment 2



(*R*)-4-benzyl-3-((2R,3R)-2-ethyl-3-hydroxy-5-(triethylsilyl)pent-4-ynoyl)oxazolidin-2-one (7).

Et_3N (44.6 mmol, 6.00 mL) and Bu_2BOTf (1M in CH_2Cl_2, 44.6 mmol, 44.6 mL) were successively added dropwise to **5** in CH_2Cl_2 (190 mL) at 0°C. The reaction was stirred at the same temperature for 30 minutes, cooled to -78°C, aldehyde **6** in CH_2Cl_2 (20 mL) was added dropwise over 1 hour (syringe pump) and stirred for an extra hour to afford a clear orange solution. At -78°C, 20 mL of buffer (pH = 7 solution, 20 mL), MeOH (20 mL), H_2O_2 (30% aqueous solution, 20 mL) were added successively and the crude mixture stirred at room temperature for 2 hours. The organic fraction was recovered, dried over $MgSO_4$, concentrated under vacuum and the crude material purified by flash chromatography (gradient 5-10-15 mol% EtOAc/petroleum ether) to afford **7** as a thick colorless oil (87 %, 13.391g); R_f = 0.20 (10% EtOAc/ hexanes); $[\alpha]_D$ = + 20.2 (c 1.00, CH_2Cl_2); IR (neat) 3430, 2916, 2835, 1759, 1674, 1367, 1331, 1192, 1092, 1004, 724, 693 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.35-7.21 (5H), 4.73-4.64 (m, 2H), 4.19-4.11 (m, 3H), 3.33 (dd, J = 16.5, 4.0 Hz, 1H), 2.72 (dd, J = 16.5, 12.5 Hz, 1H), 2.61 (d, J = 7.5 Hz, 1H), 1.98-1.92 (m, 2H), 1.03 (t, J = 7.6 Hz, 3H), 0.96 (t, J = 8.0 Hz, 9H), 0.58 (q, J = 8.0 Hz, 6H); ^{13}C NMR (90 MHz, $CDCl_3$): 174.0, 153. 5, 135.4, 129.6, 129.2, 127.6, 105.4, 88.4, 66.3, 63.7, 55.7, 50.5, 38.2, 22.1, 11.7, 7.6, 4.5, 4.4; HRMS (ESI) Calcd for $C_{23}H_{33}NNaO_4Si$ $(M+Na)^+$: 438.2071; found 438.2066.



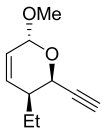
Alcohols 10 and 11.

DiBAL-H (1.2 M in toluene, 67.5 mmol, 81 mL) was added dropwise at -78°C to a solution of alcohol **7** (29.1 mmol, 12.1 g) in dry THF (500 mL). The reaction mixture was stirred at the same temperature for 2 hours, diluted with dry diethylether (300 mL) and Rochelle salt (saturated aqueous solution, 150 mL) was added. The crude mixture was stirred at room temperature for 2 hours, the organic fraction collected, dried over $MgSO_4$ and concentrated under vacuum at 0°C to recover a solution of aldehyde **8** in toluene (about 80 mL).

To the solution obtained above was added successively CH_2Cl_2 (300 mL), **9** (43.7 mmol, 18.73 g), tris[2-(2-methoxyethoxy)ethyl]amine TDA (58.3 mmol, 18.84 mL) and K_2CO_3 (aqueous saturated solution, 400 mL). The dark red reaction mixture was vigorously stirred at room temperature for 16 hours (pale red emulsion), diluted with diethyl ether (300 mL), the organic fraction recovered, rinsed with H_2O (2 x 100 mL), dried over $MgSO_4$, concentrated under vacuum and the crude material was purified by flash chromatography (gradient 10-20 mol% EtOAc/petroleum ether) to afford **10** and **11** as thick colorless oils (56 % combined yield, 5.11 g). For **10**, about 10% of *E*-isomer was observed by ^{1}H NMR.

10: R_f = 0.30 (20% EtOAc/ hexanes); $[\alpha]_D$ = + 11.9 (c 1.00, CH_2Cl_2); IR (neat) 3481, 2915, 2835, 1438, 1128, 1101, 1030, 993, 716 cm-^{1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.88 (d, J = 10.5 Hz, 1H), 5.74 (d, J = 10.5 Hz, 1H), 5.06 (s, 1H), 4.66 (d, J = 5.5 Hz, 1H), 3.91-3.73 (m, 4H), 2.95 (t, J = 6.3 Hz, 1H), 2.30-2.25 (m, 1H), 1.71-1.50 (m, 2H), 1.01-0.96 (m, 12H), 0.60 (q, J = 7.5 Hz, 6H); ^{13}C NMR (90 MHz, $CDCl_3$): 132.1, 125.5, 104.5, 96.0, 88.8, 70.9, 64.2, 62.4, 39.1, 24.3, 11.5, 7.60, 4.5; HRMS (ESI) Calcd for $C_{17}H_{30}NaO_3Si$ $(M+Na)^+$: 333.1856; found 333.1865.

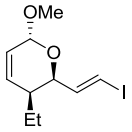
11: R_f = 0.15 (20% EtOAc/ hexanes); $[\alpha]_D^{22}$ = + 5.31 (c 1.00, CH_2Cl_2); IR (neat) 33.85, 2915, 2871, 2835, 1439, 1096, 1064, 1029, 991, 717 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.08 (dd, J = 10.5, 1.0 Hz, 1H), 5.75 (d, J = 10.5 Hz, 1H), 5.04 (s, 1H), 4.83 (d, J = 4.0 Hz, 1H), 3.90-3.71 (m, 4H), 2.56 (bs, 1H), 2.07-1.53 (m, 3H), 1.02-0.97 (m, 12H), 0.62 (q, J = 7.5 Hz, 6H); ^{13}C NMR (90 MHz, $CDCl_3$): 133.0, 124.8, 103.7, 95.6, 89.3, 70.9, 63.1, 62.6, 39.0, 22.8, 11.6, 7.6, 4.5; HRMS (ESI) Calcd for $C_{17}H_{30}NaO_3Si$ $(M+Na)^+$: 333.1856; found 333.1859.



(2*R*,3*S*,6*R*)-3-ethyl-2-ethynyl-6-methoxy-3,6-dihydro-2H-pyran (11a).[1]

To a solution of **10** and **11** combined (11.4 mmol, 3.54 g) in dry methanol (50 mL) was added $TsOH\cdot H_2O$ (3 mol%, 0.34 mmol, 65.0 mg) in one portion. The reaction mixture was stirred for one hour at room temperature to form a light pink solution. K_2CO_3 (22.8 mol, 3.15 g) was added in one portion at room temperature and the reaction was stirred at the same temperature for 16 hours, diluted with dry diethyl ether (100 mL) and rinsed with H_2O (2 x 100 mL). The organic fraction was recovered, dried over $MgSO_4$, concentrated under vacuum (no heating) and the crude material purified by flash chromatography (gradient 0-5 mol% EtOAc/petroleum ether) to afford **11a** as a colorless oil (88 %, 1.665 g); R_f = 0.57 (10% ethyl acetate/petroleum ether); $[\alpha]_D^{22}$ = 148.7 ± 0.1 (CH_2Cl_2, c = 2.23); IR (neat) 3295, 3045, 2963, 2935, 2879, 2828, 1657, 1464, 1402, 1382, 1336, 1187, 1110, 1071, 1046, 1023, 965, 906, 850, 792, 740 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.07 (dd, *J* = 5.5, 10.3 Hz, 1H), 5.71 (ddd, *J* = 1.1, 2.6, 10.1 Hz, 1H),

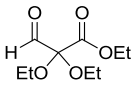
4.86 (d, *J* = 2.3 Hz, 1H), 4.78 (t, *J* = 2.9 Hz, 1H), 3.44 (s, 3H), 2.48 (d, *J* = 2.3 Hz, 1H), 1.98 (sextet, *J* = 4.3 Hz, 1H), 1.88 (ddq, *J* = 4.4, 13.4, 7.6 Hz, 1H), 1.54 (ddq, *J* = 9.3, 13.3, 7.4 Hz, 1H), 0.96 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$); δ 132.4, 124.7, 95.8, 81.2, 74.4, 61.8, 55.6, 38.6, 22.4, 11.3. HRMS Calcd for $C_9H_{11}O$ $(M\text{-}OCH_3)^+$ = 135.0810, found 135.0819.



(2*R*,3*S*,6*R*,*E*)-3-ethyl-2-(2-iodovinyl)-6-methoxy-3,6-dihydro-2*H*-pyran (2).

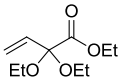
Schwartz reagent (Cp_2ZrHCl) (816.3 mg, 3.16 mmol) was suspended in dry CH_2Cl_2 (10 mL). Terminal alkyne **S1** (350.9 mg, 2.11 mmol) in dry CH_2Cl_2 (5 mL) was then added slowly at ambient temperature. The reaction was stirred for 15 min and iodine (885.5 mg, 3.5 mmol) in dry CH_2Cl_2 (5 mL) was added dropwise until the solution turn light brown. $Na_2S_2O_3$ (saturated aqueous solution, 30 mL) was immediately added followed by H_2O (10 mL) under vigorous stirring. The organic fraction was recovered, rinsed with H_2O (10 mL), dried over $MgSO_4$, concentrated under vacuum (no heating) and the crude material purified by flash chromatography (gradient 0-5 mol% EtOAc/petroleum ether) to afford **2** as a pale yellow oil (78 %, 485.6 mg); $[\alpha]_D^{25}$ = 134.5 ± 0.4 (CH_2Cl_2, c = 1.23). R_f (5% ethyl acetate/petroleum ether) = 0.39. IR (thin film) = 3043, 2962, 2932, 2876, 2825, 1652, 1614, 1464, 1398, 1337, 1278, 1188, 1111, 1051 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.57 (dd, *J* = 4.9, 14.5 Hz, 1H), 6.38 (dd, *J* = 1.5, 14.3 Hz, 1H), 6.09 (dd, *J* = 5.8, 10.2 Hz, 1H), 5.72 (ddd, *J* = 1.1, 2.7, 10.2 Hz, 1H), 4.84 (d, *J* = 2.3 Hz, 1H), 4.46 (m, 1H), 3.38 (s, 3H), 1.90 (sextet, *J* = 4.4 Hz, 1H), 1.50 (dq, *J* = 4.7, 7.6 Hz, 1H), 1.34 (dq, *J* = 9.3, 7.3 Hz, 1H), 0.89 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.3, 133.1, 124.9, 95.8, 76.8, 72.0, 55.3, 38.8, 21.7, 11.5; HRMS (EI) Calcd for $C_9H_{12}IO$ $(M\text{-}OCH_3)$ = 262.9933, found 262.9938.

1.4. Synthesis of Central Fragment 3



Ethyl 2,2-diethoxy-3-oxopropanoate (13).

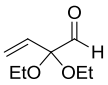
Diisopropylamine (25.8 mL, 183.3 mmol) was dissolved in THF (200 mL) and cooled to 0 °C. *n*-BuLi (2.4 M hexanes, 70.9 mL, 170 mmol) was added slowly and the reaction mixture was stirred for 15 min before it was cooled to -78 °C. Ethyldiethoxyacetate (**12**) (25 g, 141 mmol) was added dropwise over 5 min and the reaction was stirred for 15 min at the same temperature. Methyl formate (26 mL, 423 mmol) was added dropwise and the reaction warmed up to room temperature over 1 h. Hydrochloric acid (1N aqueous) was added dropwise to the solution under vigorous stirring until pH = 4 was reached. Et_2O (300 mL) and H_2O (100 mL) were added, the layers were separated and the aqueous layer was extracted twice with diethyl ether (2 x 100 mL). The combined organic layers were dried ($MgSO_4$), concentrated *in vacuo* and chromatographed gradiently with 10-30% EtOAc/petroleum ether to give aldehyde **13** (12.98 g, 45% yield) as a colorless oil. The spectral data were in accord with literature precedent.[2] R_f (20% ethyl acetate/petroleum ether) = 0.22. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.52 (s, 1H), 4.27 (q, *J* = 7.2 Hz, 2H), 3.63 (m, 4H), 1.30 (t, *J* = 7.2 Hz, 3H), 1.29 (t, *J* = 6.9 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 195.2, 165.3, 130.3, 99.5, 62.4, 59.8, 15.1, 14.1.



Ethyl 2,2-diethoxybut-3-enoate (13a).

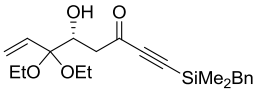
To a suspension of Ph_3PCH_3Br (24.5 g, 68.51 mmol) in THF (300 mL) was added *t*-BuONa (5.80 g, 60.4 mmol). The yellow mixture was stirred for 1 h at room temperature, and then aldehyde **13** (8.21 g, 40.3 mmol) was added. The reaction was stirred for 10 min and petroleum ether (300 mL) was added. The reaction mixture was then filtered, concentrated under vacuum, and triturated with petroleum ether (300 mL). The filtrate was recovered, concentrated under vacuum and the crude material purified by column chromatography gradiently with 10-20% ethyl acetate/petroleum ether to give the title compound **13a** (5.92 g, 73% yield). R_f (10% ethyl acetate/petroleum ether) = 0.30. IR (thin film) 2980, 2934, 2897, 1750, 1447, 1394, 1260, 1186, 1120, 1056 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$); δ 5.81 (dd, *J* = 10.5, 17.4 Hz, 1H), 5.66 (dd, *J* = 1.8, 17.4 Hz, 1H), 5.42 (dd, *J* = 1.8, 10.2 Hz, 1H), 4.24 (q, *J* = 6.9 Hz, 2H), 3.58 (m, 2H), 3.46 (m, 2H), 1.29 (t, *J* = 7.5 Hz, 3H), 1.25 (t, *J* = 7.2 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$); δ 168.9,

134.8, 120.0, 99.8, 61.7, 58.4, 15.1, 14.1. HRMS (EI) Calcd for $C_8H_{18}O_3$ (M-OEt) = 157.0865, found: 157.0860.



2,2-diethoxybut-3-enal (14).

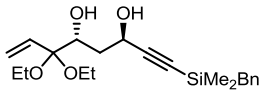
To a solution of ester **13a** (5.92 g, 29.3mmol) in DCM (120 mL) at -78 ºC was added DIBAL-H (1.2M in toluene, 61.0 mL, 73.3 mmol). The reaction was allowed to stir for 1.5 h when acetone (3 mL) was added to quench the reaction. The solution was allowed to warm to ambient temperature, diluted with diethyl ether (200 mL) and then sodium potassium tartrate (aqueous saturated solution, 200 mL) was added. The mixture was stirred vigorously until the layers quickly separated upon cessation of stirring. The layers were separated and the aqueous layer was extracted with diethyl ether (2 x 100 mL). The combined organic layers were washed with brine, and dried ($MgSO_4$). The crude mixture was concentrated under vacuum to give the title aldehyde **14** in solution in toluene (approximatively 50 mL) and was used directly in the next step. ^{1}H NMR analysis showed a conversion higher than 95%. IR (neat) 2980, 1749, 1407, 1179, 1056, 997 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$); δ 9.28 (s, 1H), 5.67 (m, 2H), 5.55 (m, 1H), 3.60 (m, 2H), 3.51 (m, 2H), 1.26 (t, *J* = 6.8 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$); δ 196.5, 132.7, 123.0, 102.1, 58.5, 15.5. HRMS (EI) Calcd for $C_6H_9O_2$ (M-OEt) = 113.0603, found 113.0603.



(R)-1-(benzyldimethylsilyl)-6,6-diethoxy-5-hydroxyoct-7-en-1-yn-3-one (16)

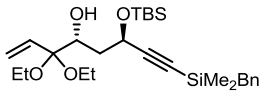
To a solution of (*S*,*S*)-Prophenol ligand (119 mg, 0.19 mmol) in THF (5 mL) at 0 °C was added diethylzinc (0.97 M toluene, 0.39 mL, 0.38 mmol) and the reaction was stirred for 30 min before addition to the substrates. To 4 Å molecular sieves (746 mg) was added a mixture of 2,2-diethoxybut-3-enal **14** (1.18 g, 7.46 mmol) and 4-(benzyldimethylsilyl)but-3-yn-2-one **15**[3] (1.94 g, 8.95 mmol) in THF (25 mL). The catalyst solution prepared above was then added. After 20 h at ambient temperature, pH 7 buffer and diethyl ether were added. The layers were separated, and the aqueous layer was extracted twice with ether. The combined organic layers were combined, washed with brine, dried ($MgSO_4$), concentrated *in vacuo*, and chromatographed gradiently with 10-20% diethyl ether/petroleum ether to give the title compound **16** (2.12 g, 76% yield). Chiral HPLC: OD column, 254 nm, 1.0 mL/min, 98:2 heptane: isopropanol, t_r (minor) = 8.8 min, t_r (major) = 9.7 min. 99% ee. $[\alpha]_D^{25} = -7.5 \pm 0.1$ (CH_2Cl_2, c = 1.8). R_f (10% ethyl acetate/petroleum ether) = 0.24. IR (thin film) 3567, 2976, 2897, 2151, 1996, 1684, 1601,

1559, 1494, 1456, 1410, 1253, 1208, 1074, 1055 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.25 (m, 2H), 7.12 (m, 1H), 7.07 (m, 2H), 5.75 (dd, *J* = 11.0, 17.5 Hz, 1H), 5.56 (dd, *J* = 2.0, 17.5 Hz, 1H), 5.43 (dd, *J* = 2.0, 10.5 Hz, 1H), 4.41 (dt, *J* = 9.5, 2.5 Hz, 1H), 3.49-3.58 (m, 3H), 3.41 (m, 1H), 2.74 (ddd, *J* = 1.0, 2.5, 16.5 Hz, 1H), 2.61 (dd, *J* = 9.5, 17.0 Hz, 1H), 2.38 (dd, *J* = 1.5, 3.0 Hz, 1H), 2.26 (s, 2H), 1.20 (t, *J* = 7.0 Hz, 3H), 1.17 (t, *J* = 7.0 Hz, 3H), 0.2 (s, 3H), 0.2 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 185.6, 137.9, 134.0, 128.4, 128.4, 124.8, 124.8, 120.2, 103.1, 100.8, 96.7, 69.1, 57.2, 56.9, 47.3, 25.4, 15.4, 15.4, -2.7, -2.7. Anal. Calcd for $C_{21}H_{30}O_4Si$: C, 67.34; H, 8.07. Found: C, 67.49; H, 7.87.



(3R,5R)-1-(benzyldimethylsilyl)-6,6-diethoxyoct-7-en-1-yne-3,5-diol (16a).

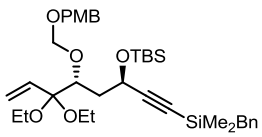
To a solution of ynone **16** (1.20 g, 3.2 mmol) in isopropanol (degassed for 15 min with Argon, 35 mL) at ambient temperature was added (*R,R*)-Noyori's catalyst (38 mg, 0.064 mmol). The reaction was stirred for 12 h and then the solvent was removed under vacuum. The residue was chromatographed gradiently with 10-15% ethyl acetate/petroleum ether to give the title compound **16a** (1.1 g, 91% yield) in greater than 20:1 dr. $[\alpha]_D^{25}$ = -3.9 ± 01 (CH_2Cl_2, c = 1.0). R_f (20% ethyl acetate/petroleum ether) = 0.31. IR (thin film) 3446, 3026, 2975, 2932, 2897, 2172, 1601, 1494, 1453, 1411, 1251, 1208, 1158, 1056, 986 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$); δ 7.23 (t, J = 7.7 Hz, 2H), 7.10 (t, *J* = 7.4 Hz, 1H), 7.07 (d, *J* = 7.2 Hz, 2H), 5.75 (dd, *J* = 10.9, 17.5 H, 1H), 5.53 (dd, *J* = 2.1, 17.6 Hz, 1H), 5.40 (dd, *J* = 2.0, 10.9 Hz, 1H), 4.61 (dt, *J* = 7.9, 4.8 Hz, 1H), 4.31 (ddd, *J* = 1.5, 5.4, 8.7 Hz, 1H), 3.50 (m, 3H), 3.43 (m, 1H), 3.37 (d, *J* = 7.9 Hz, 1H), 2.56 (s, 1H), 2.20(m, 2H), 1.79 (m, 2H), 1.20 (t, *J* = 7.1 Hz, 3H), 1.16 (t, *J* = 7.0 Hz, 3H), 0.13 (s, 3H), 0.12 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$); δ 138.7, 132.9, 128.3, 128.2, 124.4, 121.6, 110.4, 105.9, 89.5, 77.1, 66.6, 49.5, 40.7, 26.0, -2.3, -2.3; Anal. Calcd for $C_{21}H_{32}O_4Si$: C, 66.98; H, 8.57. Found: C, 66.79; H, 8.38.



(4R,6R)-8-(benzyldimethylsilyl)-6-((tert-butyldimethylsilyl)oxy)-3,3-diethoxyoct-1-en-7-yn-4-ol (17).

To diol **16a** (1.07 g, 2.84 mmol) in dimethylformamide (DMF) (15 mL) at ambient temperature was added imidazole (251 mg, 3.69 mmol) and TBSCl (449 mg, 2.98 mmol). The reaction was allowed to stir for 12 h. The mixture was then diluted with diethyl ether and washed with water. The aqueous layer was extracted twice with diethyl ether. The combined organic layers were washed with brine, dried ($MgSO_4$), concentrated *in vacuo* and chromatographed gradiently with 5-15% ethyl acetate/petroleum ether to give

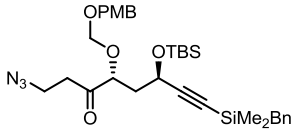
the TBS ether **17** (1.20 g, 88% yield). $[\alpha]_D^{25}$ = 51.6 ± 0.2 (CH_2Cl_2, c = 1.0). R_f (10% ethyl acetate/petroleum ether) = 0.63. IR (thin film) 3586, 3504, 3027, 2931, 2894, 2858, 2174, 1938, 1879, 1602, 1495, 1472, 1454, 1411, 1362, 1346, 1290, 1251, 1207, 1157 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$); δ 7.21 (t, *J* = 7.4 Hz, 2H), 7.08 (t, *J* = 7.2 Hz, 1H), 7.06 (d, *J* = 8.1 Hz, 2H), 5.78 (dd, *J* = 10.9, 17.5 Hz, 1H), 5.53 (dd, *J* = 2.2, 17.6 Hz, 1H), 5.39 (dd, *J* = 2.2, 11.0 Hz, 1H), 4.61 (dd, *J* = 2.9, 9.0 Hz, 1H), 4.09 (d, *J* = 10.5 Hz, 1H), 3.43-3.58 (m, 4H), 2.52 (s, 1H), 2.18 (s, 2H), 1.88 (dd, *J* = 9.0, 14.4 Hz, 1H), 1.60 (ddd, *J* = 2.9, 10.6, 14.3 Hz, 1H), 1.19 (t, *J* = 7.1 Hz, 3H), 1.17 (t, *J* = 7.1 Hz, 3H), 0.90 (s, 9H), 0.13 (s, 3H), 0.12 (s, 3H), 0.10 (s, 3H), 0.09 (s, 3H). ^1H NMR (400 MHz, d_6-benzene); δ 7.16 (m, 3H), 7.04 (m, 2H), 5.78 (dd, *J* = 10.8, 17.6 Hz, 1H), 5.62 (dd, *J* = 2.4, 17.6 Hz, 1H), 5.21 (dd, *J* = 2.4, 10.8 Hz, 1H), 4.97 (dd, *J* = 2.0, 10.4 Hz, 1H), 4.29 (dt, *J* = 10.8, 2.0 Hz, 1H), 3.36-3.56 (m, 4H), 2.30 (ddt, *J* = 10.8, 14.4, 2.0 Hz, 1H), 2.21 (t, *J* = 2.2 Hz, 1H), 2.12 (s, 2H), 1.98 (ddd, *J* = 2.4, 10.8, 13.2 Hz, 1H), 1.05 (t, *J* = 7.2 Hz, 3H), 1.04 (s, 9H), 1.01 (t, *J* = 6.8 Hz, 3H), 0.29 (s, 3H), 0.22 (s, 3H), 0.09 (s, 6H). ^{13}C NMR (100 MHz, d_6-benzene); δ 139.1, 134.9, 128.7, 128.5, 124.7, 119.4, 110.1, 101.6, 87.1, 69.5, 60.4, 57.2, 56.5, 40.6, 26.3, 26.0, 18.4, 15.5, 15.4, -2.2, -2.2, -4.3, -4.9. Anal. Calcd for $C_{27}H_{46}O_4Si_2$: C, 66.07; H, 9.45. Found: C, 66.21; H, 9.42.



(5R,7R)-7-((benzyldimethylsilyl)ethynyl)-5-(1,1-diethoxyallyl)-1-(4-methoxyphenyl)-9,9,10,10-tetramethyl-2,4,8-trioxa-9-silaundecane (19).

To 1-((chloromethoxy)methyl)-4-methoxybenzene ($PMBOCH_2Cl$) **18**[4] (2.16 g, 11.6 mmol) was added diisopropylethylamine (3 mL, 17.3 mmol), followed by alcohol **17** (1.42 g, 2.9 mmol) in DMF (8 mL). TBAI (107 mg, 0.29 mmol) was then added and the reaction was heated at 40 ºC for 20 h. Diethyl ether (20 mL) and water (20 mL) were added and the layers were separated. The aqueous layer was extracted 3 times with diethyl ether. The combined organic layers were washed with brine, dried ($MgSO_4$), concentrated *in vacuo*, and chromatographed isocratically with 5% ethyl acetate/petroleum ether to give the title compound **19** (1.77 g, 97% yield). $[\alpha]_D^{25}$ = 48.8 ± 0.1 (CH_2Cl_2, c = 1.3). R_f (10% ethyl acetate/petroleum ether) = 0.64. IR (thin film) 2931, 2895, 2858, 2172, 2067, 1996, 1940, 1879, 1662, 1614, 1587, 1514, 1494, 1464, 1411, 1389, 1361, 1303, 1250, 1208, 1160 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$); δ 7.28 (d, *J* = 8.5 Hz, 2H), 7.21 (t, *J* = 7.6 Hz, 2H), 7.08 (t, *J* = 7.3 Hz, 1H), 7.06 (d, *J* = 7.0 Hz, 2H), 6.87 (d, *J* = 8.5 Hz, 2H), 5.81 (dd, *J* = 10.9, 17.5 Hz, 1H), 5.53 (dd, *J* = 2.3, 17.6 Hz, 1H), 5.38 (dd, *J* = 2.2, 10.9 Hz, 1H), 4.91 (d, *J* = 6.3 Hz, 1H), 4.84 (d, *J* = 6.3 Hz, 1H), 4.63 (d, *J* = 11.6 Hz, 1H), 4.55 (d, *J* = 11.6 Hz, 1H), 4.55 (m, 1H), 3.93 (dd, *J* = 1.5, 9.9 Hz, 1H), 3.80 (s, 3H), 3.38-3.56 (m, 4H), 2.19 (s,

2H), 1.95 (ddd, *J* = 1.5, 10.5, 14.6 Hz, 1H), 1.62 (ddd, *J* = 2.4, 10.0, 14.6 Hz, 1H), 1.17 (t, *J* = 7.1 Hz, 3H), 1.13 (t, *J* = 7.1 Hz, 3H), 0.87 (s, 9H), 0.11 (s, 3H), 0.10 (s, 3H), 0.10 (s, 3H), 0.07 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$); δ 159.7, 139.0, 135.4, 130.6, 129.7, 128.5, 124.8, 119.0, 114.0, 110.1, 102.2, 96.1, 87.5, 77.6, 69.8, 60.6, 57.3, 55.9, 54.7, 41.6, 26.2, 26.1, 18.4, 15.5, 15.4, -2.2, -2.2, -4.0, -4.7. HRMS (EI) Calcd for $C_{36}H_{56}O_6NaSi_2$ = 663.3513, found 663.3518.

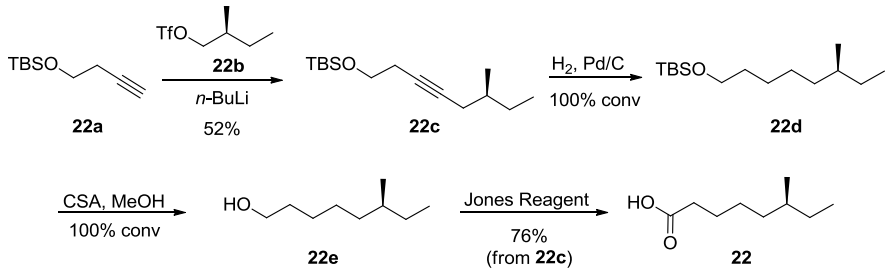


(4R,6R)-1-azido-8-(benzyldimethylsilyl)-6-((tert-butyldimethylsilyl)oxy)-4-(((4-methoxybenzyl)oxy)methoxy)oct-7-yn-3-one (3).

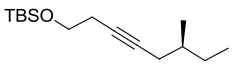
Ketal **19** (5.38 g, 8.39 mmol) was dissolved in acetone (42 mL) and aqueous acetic acid (80% AcOH/water, 42 mL). The mixture was stirred for 6 h at ambient temperature and then NaN_3 (1.64 g, 25.2 mmol) was added. The mixture was stirred for 2 h. The reaction was then diluted with diethyl ether and washed with water. Solid $NaHCO_3$ was added to neutralize the acetic acid. The layers were separated and the aqueous layer was extracted twice with diethyl ether. The combined organic layers were washed with brine, dried ($MgSO_4$), concentrated *in vacuo* and chromatographed gradiently with 6-7% ethyl acetate/petroleum ether to give the title compound **3** (4.6735 g, 91% yield). $[\alpha]_D^{25}$ = 12.2 ± 0.1 (CH_2Cl_2, c = 1.1). R_f (10% ethyl acetate/petroleum ether) = 0.40. IR (thin film) 2957, 2895, 2858, 2101, 1723, 1614, 1515, 1494, 1464, 1408, 1362, 1302, 1250, 1166, 1092, 1036 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 (m, 4H), 7.07 (m, 3H), 6.89 (m, 2H), 4.77 (d, *J* = 6.8 Hz, 1H), 4.68 (d, *J* = 6.8 Hz, 1H), 4.57 (d, *J* = 11.6 Hz, 1H), 4.54 (dd, *J* = 3.6, 9.2 Hz, 1H), 4.46 (dd, *J* = 3.6, 8.8 Hz, 1H), 3.80 (s, 3H), 3.49 (m, 2H), 2.78 (m, 2H), 2.18 (s, 2H), 1.96 (m, 2H), 0.90 (s, 9H), 0.14 (s, 3H), 0.11 (s, 3H), 0.11 (s, 3H), 0.09 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.1, 159.4, 138.8, 129.6, 129.3, 128.4, 128.3, 124.5, 113.9, 107.8, 95.2, 88.4, 79.9, 70.1, 59.3, 55.3, 45.6, 40.8, 37.9, 26.0, 25.9, 18.2, -2.2, -2.3, -4.1, -4.8. HRMS (EI) Calcd for $C_{32}H_{47}N_3O_5Si_2$ = 609.3054, found 609.3040.

1.5. Synthesis of Eastern 4.

1.5.1. Synthesis of (S)-6-methyloctanoic acid (22).



Scheme S1. Synthesis of **22**.

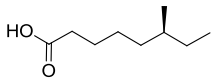


(*S*)-tert-butyldimethyl(6-methyloct-3-ynyloxy)silane (22c)

Triflate **22b** was synthesized according to literature precedent.[5] (*S*)-(-)-2-Methyl-1-butanol (3 mL, 28 mmol) was dissolved in DCM (100 mL) and cooled to -78 ºC. Pyridine (2.7 mL, 33 mmol) was then added followed by syringe pump addition of triflic anhydride (4.8 mL, 28.5 mmol) over 30 min. The reaction was stirred for 2 h and then quenched with brine, diluted with diethyl ether, washed with water, twice with aqueous $CuSO_4$, and brine. The organic layer was then dried ($MgSO_4$), filtered, and concentrated *in vacuo* to give the desired triflate **22b** (3.85 g, 62% mass balance), which was stored at -15 ºC and then used in the following reaction without further purification. The spectral data were in accord with literature values.[24] ^{1}H NMR (200 MHz, $CDCl_3$); δ 4.37 (m, 2H), 1.87 (m, 1H), 1.50 (m, 1H), 1.30 (m, 1H), 1.02 (d, J = 6.8 Hz, 3H), 0.95 (t, J = 7.4 Hz, 3H).

Alkyne **22a** (3.66 mL, 17.7 mmol) was dissolved in THF (100 mL) and cooled to -78 ºC. *n*-BuLi (1.6 M hexanes, 11 mL, 17.6 mmol) was added, followed by 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU) (4.3 mL, 35.7 mmol). The reaction was stirred for 2 h while slowly warming to -30 ºC. Triflate **22b** (3.72 g, 16.9 mmol) was then added as a solution in THF (40 mL) via cannula. The reaction was stirred for 4 h while slowly warming to ambient temperature. The reaction was then diluted with diethyl ether, washed with saturated aqueous $NaHCO_3$ and brine, dried ($MgSO_4$), concentrated *in vacuo*, and triturated with 10% ethyl acetate/petroleum ether to remove polymerized THF. The solution was then concentrated *in vacuo* and chromatographed isocratically with 1% ethyl acetate/petroleum ether to give the title compound **22c** (2.69 g, 52% yield). $[\alpha]_D^{24}$ = 4.2 ± 0.1 (CH_2Cl_2, c = 2.3). R_f (2% ethyl acetate/ petroleum ether) = 0.30. IR (thin film) 2960, 2930, 2738, 1472, 1463, 1380, 1362, 1256, 1220,

1106, 1058, 1006 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$); δ 3.67 (t, *J* = 7.2 Hz, 2H), 2.35 (tt, *J* = 2.7, 7.5 Hz, 2H), 2.10 (ddt, *J* = 5.4, 16.2, 2.4 Hz, 1H), 1.99 (ddt, *J* = 6.6, 16.2, 2.1 Hz, 1H), 1.45 (m, 2H), 1.18 (m, 1H), 0.92 (d, *J* = 6.6 Hz, 3H), 0.88 (s, 9H), 0.85 (t, *J* = 7.2 Hz, 3H), 0.05 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$); δ 79.9, 77.4, 62.2, 34.2, 28.4, 25.7, 25.6, 23.0, 18.8, 18.1, 11.3, -5.5. HRMS (ESI) Calcd for $C_{11}H_{21}OSi$ (M-*t*-Bu) = 197.1362, found 197.1369.



(*S*)-6-methyloctanoic acid (22).

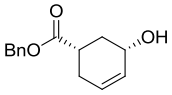
Alkyne **22c** (2.69 g, 8.71 mmol) was dissolved in ethyl acetate (80 mL) and added to 10% Pd/C (514 mg, 0.48 mmol) via cannula. The reaction vessel was evacuated and then filled with hydrogen from a balloon. The reaction was stirred for 14 h and then the hydrogen was bubbled through the reaction mixture for 30 min. The reaction mixture was then filtered through a pad of celite, rinsed with diethyl ether and concentrated *in vacuo* to give the desired alkane **22d**, which was used without further purification in the next step. $[\alpha]_D^{24}$ = 2.5 ± 0.2 ($CHCl_3$, c = 1.5). R_f (2% ethyl acetate/petroleum ether) = 0.18. IR (thin film) 2931, 2858, 1464, 1388, 1362, 1256, 1220, 1103, 1006 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$); δ 3.60 (t, *J* = 6.5 Hz, 2H), 1.51 (m, 2H), 1.30 (m, 7H), 1.10 (m, 2H), 0.89 (s, 9H), 0.85 (t, *J* = 7.2 Hz, 3H), 0.84 (d, *J* = 6.5 Hz, 3H), 0.05 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$); δ 63.6, 36.9, 34.6, 33.2, 29.7, 27.2, 26.4, 26.2, 19.5, 18.6, 11.7, -5.0. HRMS (ESI) Calcd for $C_{11}H_{25}OSi$ (M-*t*-Bu) = 201.1675, found 201.1690.

Silyl ether **22d** (8.71 mmol) was dissolved in DCM (40 mL) and methanol (40 mL). CSA (214 mg, 0.92 mmol) was then added and the reaction was stirred at ambient temperature for 2 h and then quenched with aqueous $NaHCO_3$. The reaction was diluted with diethyl ether and the layers separated. The aqueous layer was extracted with diethyl ether and DCM. The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo* to give the known[55] desired free alcohol **22e** (1.32 g), which was used without further purification in the next reaction. ^1H NMR (300 MHz, $CDCl_3$); δ 3.64 (t, *J* = 6.6 Hz, 2H), 1.56 (m, 2H), 1.08-1.42 (m, 9H), 0.85 (m, 6H).

Primary alcohol **22e** (1.32 g) was dissolved in acetone (50 mL). Jones' reagent was added dropwise at ambient temperature until the color remained orange. Isopropanol was then added to quench the excess Jones' reagent. The reaction was diluted with diethyl ether, filtered to remove the blue solids, washed with aqueous $NaHSO_4$ and brine. The aqueous layers were extracted twice with ether. The combined organic layers were dried ($MgSO_4$), concentrated *in vacuo* and chromatographed with 10-15% ethyl

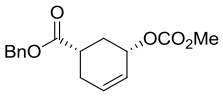
acetate/petroleum ether to give the title compound **22** (1.044g, 76% yield over 3 steps). The spectral data were in accord with literature values.[6] $[\alpha]_D^{24}$ = 4.6 ± 0.2 ($CHCl_3$, c = 1.41). IR (thin film) 2927, 1713, 1463, 1413, 1379, 1287, 1113, 938, 836, 773, 733 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$); δ 2.36 (t, *J* = 7.2 Hz, 2H), 1.63 (m, 2H), 1.33 (m, 5H), 1.13 (m, 2H), 0.86 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$); δ 179.2, 35.8, 33.9, 33.7, 29.1, 26.2, 24.7, 18.8, 11.0.

*1.5.2. Completion of the synthesis of **4**.*



(±)-benzyl 5-hydroxycyclohex-3-enecarboxylate (20a).

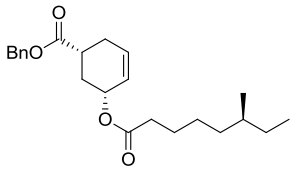
Benzyl alcohol (784 mg, 7.25 mmol) was dissolved in THF (10 mL) then *t*-BuOK (7 mg, 0.061 mmol) was added. The solution was cooled to 0 ºC and lactone **20**[7] (300 mg, 2.42 mmol) was added as a solution in THF (5 mL). The reaction was stirred for 30 min and then aqueous NH_4Cl was added. The layers were separated and the aqueous layer was extracted 3 times with diethyl ether. The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, concentrated *in vacuo*, and chromatographed gradiently with 15-25% ethyl acetate/petroleum ether to give the title alcohol **20a** (403 mg, 72% yield). The spectral data were in accord with literature values.[8] R_f (20% ethyl acetate/petroleum ether) = 0.23. IR (thin film) 3406, 3032, 2929, 1728, 1499, 1454, 1390, 1243, 1169, 1116, 1046, 1000 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$); δ 7.37 (m, 5H), 5.75 (m, 2H), 5.14 (s, 2H), 4.28 (m, 1H), 2.76 (m, 1H), 2.32 (m, 3H), 1.77 (ddd, *J* = 8.1, 10.8, 12.9 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$); δ 175.0, 135.9, 130.9, 128.6, 128.3, 128.1, 126.9, 66.5, 66.1, 38.0, 34.2, 27.4.



(±)-benzyl 5-(methoxycarbonyloxy)cyclohex-3-enecarboxylate (21).

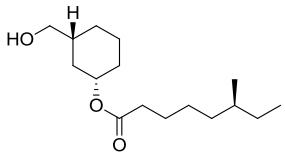
Alcohol **20a** (321 mg, 1.38 mmol) and pyridine (0.56 mL, 6.92 mmol) were dissolved in DCM (8 mL). Methyl chloroformate (391 mg, 4.14 mmol) was then added at ambient temperature. The solution was stirred for 2 h and then aqueous NH_4Cl was added. The layers were separated and the aqueous layer was extracted 3 times with DCM. The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, concentrated *in vacuo* and chromatographed gradiently with 8-10% ethyl acetate/petroleum ether to give the title compound **21** (668 mg, 97% yield). R_f (8% ethyl acetate/petroleum ether) = 0.25. IR (thin film) 3037, 2926, 2852, 1744, 1678, 1665, 1587, 1499, 1443, 1392, 1333, 1264, 1122 cm^{-1}. ^1H NMR (500

MHz, $CDCl_3$); δ 7.47 (m, 5H), 5.89 (ddt, *J* = 1.5, 3.5, 10.0 Hz, 1H), 5.71 (dddd, *J* = 1.0, 2.5, 4.5, 10.0 Hz, 1H), 5.26 (m, 1H), 5.15 (d, *J* = 12.0 Hz, 1H), 5.12 (d, *J* = 12.5 Hz, 1H), 3.76 (s, 3H), 2.78 (dddd, *J* = 3.0, 7.0, 10.5, 12.0 Hz, 1H), 2.45 (dddd, *J* = 1.0, 2.5, 6.0, 11.5 Hz, 1H), 2.34 (m, 2H), 1.86 (dt, *J* = 9.5, 12.5 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$); δ 173.8, 155.4, 135.9, 129.7, 128.6, 128.3, 128.2, 126.2, 73.0, 66.6, 54.8, 37.8, 30.4, 27.2. HRMS (ESI) Calcd for $C_{16}H_{18}O_5$ (M^+) = 290.1154, found 290.1157.



(1*R*,5*R*)-benzyl 5-((*S*)-6-methyloctanoyloxy)cyclohex-3-enecarboxylate (23).

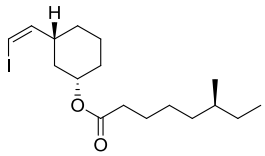
(*S*)-6-Methyloctanoic acid **22** from above (445 mg, 2.8 mmol) was added to a mixture of NaH (60% in mineral oil, 96 mg) and THAB (1.043 g, 2.4 mmol) in DCM (10 mL). A solution obtained by mixing allylpalladium dimer (11 mg, 0.03 mmol) and (*S*,*S*)-standard Trost ligand (62 mg, 0.09 mmol) in CH_2Cl_2 (2 mL) was added to the above mixture. After 15 min methyl carbonate **21** (348 mg, 1.2 mmol) was added and the reaction was stirred for 1.5 h. Silica gel was added to the reaction and the volatile organics were removed *in vacuo*. The silica gel was loaded for isocratic chromatography with 10% ethyl acetate/petroleum ether to give the title compound **23** (416 mg, 93% yield). HPLC: 99:1 heptane:isopropanol, 1.0 mL/min, 254 nm, OD column, t_R (minor) = 12.6 min, t_R (major) = 14.3 min. $[\alpha]_D^{24}$ = 28.0 ± 0.2 (CH_2Cl_2, c = 1.05). R_f (5% ethyl acetate/petroleum ether) = 0.25. IR (thin film) 3036, 2859, 2873, 1792, 1656, 1610, 1588, 1498, 1456, 1379, 1269, 1160, 1119, 1070 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$); δ 7.35 (m, 5H), 5.86 (ddd, *J* = 1.8, 3.8, 7.3, 9.6 Hz, 1H), 5.63 (m, 1H), 5.41 (m, 1H), 5.15 (d, *J* = 12.5 Hz, 1H), 5.11 (d, *J* = 12.3 Hz, 1H), 2.78 (dddd, *J* = 2.8, 7.9, 8.3, 15.4 Hz, 1H), 2.39 (ddd, *J* = 2.4, 5.2, 12.2 Hz, 1H), 2.33 (m, 2H), 2.28 (t, *J* = 7.6 Hz, 2H), 1.76 (dt, *J* = 9.4, 12.3 Hz, 1H), 1.58 (m, 2H), 1.30 (m, 4H), 1.10 (m, 2H), 0.85 (t, *J* = 7.2 Hz, 3H), 0.83 (d, *J* = 6.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$); δ 174.1, 173.5, 135.9, 129.1, 128.7, 128.3, 128.1, 127.0, 69.0, 66.5, 38.1, 36.2, 34.6, 34.2, 30.5, 29.5, 27.3, 26.3, 25.4, 19.2, 11.4. HRMS (ESI) Calcd for $C_{23}H_{32}O_4Na$ (M+Na) = 395.2198, found 395.2203.



(*S*)-((1*S*,3*R*)-3-(hydroxymethyl)cyclohexyl) 6-methyloctanoate (24)

Benzyl ester **23** (975.7 mg, 2.62 mmol) in ethyl acetate (26 mL) was added to 10% Pd/C (282.5 mg, 0.028 mmol). Hydrogen gas was bubbled through this suspension for 50 min, then continued stirring under an atmosphere of hydrogen without bubbling for 14 h. The reaction was filtered through Celite, rinsed with ethyl acetate and concentrated *in vacuo* to give the desired saturated compound (735.7 mg, 99% mass balance), which was used without further purification. $[\alpha]_D^{23}$ = -19.0 ± 0.2 (CH_2Cl_2, c = 1.1). IR (thin film) 2933, 2864, 1732, 1709, 1454, 1417, 1172, 1029 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$); δ 4.74 (tt, *J* = 4, 10.5 Hz, 1H), 2.46 (tt, *J* = 3.5, 11.5 Hz, 1H), 2.27 (t, *J* = 7.5 Hz, 2H), 2.24 (m, 1H), 1.96 (m, 2H), 1.90 (m, 1H), 1.58 (m, 2H), 1.52 (q, *J* = 12 Hz, 1H), 1.23-1.42 (m, 8H), 1.11 (m, 2H), 0.85 (t, *J* = 7.5 Hz, 3H), 0.84 (d, *J* = 6 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$); δ 180.4, 173.3, 71.5, 41.3, 36.2, 34.7, 34.3, 31.1, 29.5, 27.8, 26.6, 25.4, 23.1, 19.2, 11.5. HRMS (EI) Calcd for $C_{16}H_{28}O_4$ = 284.1988, found 284.1994. Anal. Calcd for $C_{16}H_{28}O_4$: C, 67.57; H, 9.92. Found: C, 67.70; H, 9.77.

The above carboxylic acid (735.7 mg, 2.59 mmol) was dissolved in THF (21 mL) and cooled to 0 °C. Borane dimethyl sulfide complex (0.3 mL, 3.16 mmol) was added and the reaction was stirred for 2 h while slowly warming to ambient temperature. Methanol (2 mL) and aqueous $NaHCO_3$ (12 mL) were then added to quench the reaction. The layers were separated and the aqueous layer was extracted 5 times with DCM. The combined organic layers were dried ($MgSO_4$), filtered, concentrated *in vacuo* and chromatographed gradiently with 15-25% ethyl acetate/petroleum ether to give the title compound **24** (671.6 mg, 95% yield over two steps). $[\alpha]_D^{23}$ = -5.0 ± 0.2 (CH_2Cl_2, c = 1.5). IR (thin film) 3446, 2933, 2861, 1733, 1456, 1379, 1173, 1101, 1030 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$); δ 4.74 (tt, *J* = 4.5, 11 Hz, 1H), 3.50 (d, *J* = 6 Hz, 2H), 2.27 (t, *J* = 7.5 Hz, 2H), 2.03 (m, 1H), 1.98 (m, 1H), 1.84 (ddt, *J* = 7, 13.5, 3.5 Hz, 1H), 1.74 (m, 1H), 1.21-1.45 (m, 12H), 1.01-1.16 (m, 3H), 0.91 (m, 1H), 0.85 (t, *J* = 7.5 Hz, 3H), 0.83 (d, *J* = 6 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$); δ 173.5, 72.7, 67.9, 39.2, 36.2, 34.9, 34.8, 34.2, 31.9, 29.5, 28.3, 26.6, 25.4, 23.5, 19.2, 11.4. LRMS (ESI) Calcd for $C_{16}H_{30}NaO_3$ (M+Na) = 293.2, found 293.2. HRMS (EI) Calc'd for $C_9H_{19}O_2$ ((*S*)-methyloctanoic acid+H) = 159.1385, found 159.1378; Calc'd for $C_7H_{13}O_2$ (M-(*S*)-methyloctanoic acid) = 129.0916, found 129.0911.



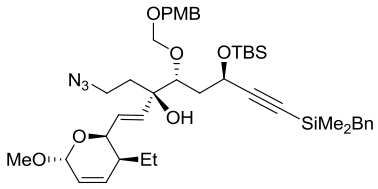
(*S*)-((1*S*,3*R*)-3-((*Z*)-2-iodovinyl)cyclohexyl) 6-methyloctanoate (4)

To a solution of the alcohol **24** (446.3 mg, 2 mmol) in DCM (20 mL) was added Dess-Martin periodinane (861 mg, 2 mmol) and $NaHCO_3$ (170.8 mg, 2 mmol). The reaction was stirred for 25 min and then diluted with diethyl ether and washed with aqueous $NaHCO_3$ and brine. The aqueous layer was extracted with ether and the combined organic layers were dried ($MgSO_4$), filtered, concentrated *in vacuo* and chromatographed gradiently with 5-10% ethyl acetate/petroleum ether to give the desired aldehyde **24a** (374.9 mg, 85% yield) along with starting material (26.1 mg, 90% yield BRSM). $[\alpha]_D^{23}$ = -19.3 ± 0.3 (CH_2Cl_2, c = 1.05). R_f (10% ethyl acetate/petroleum ether) = 0.44. IR (thin film) 2927, 2856, 1732, 1463, 1379, 1171, 1108 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$); δ 9.64 (s, 1H), 4.80 (tt, *J* = 4, 10 Hz, 1H), 2.38 (dtt, *J* = 0.5, 3.5, 11 Hz, 1H), 2.28 (t, *J* = 7.5 Hz, 2H), 2.22 (m, 1H), 1.93 (m, 3H), 1.58 (m, 3H), 1.20-1.45 (m, 7H), 1.10 (m, 3H), 0.85 (t, *J* = 7 Hz, 3H), 0.83 (d, *J* = 6 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$); δ 202.7, 173.3, 71.5, 48.5, 36.2, 34.7, 34.3, 31.2, 29.8, 29.5, 26.7, 25.4, 24.9, 22.5, 19.2, 11.5. LRMS (ESI) Calc'd for $C_{32}H_{57}O_6$ (2M+H) =537.4, found 537.5. HRMS (EI) Calc'd for $C_9H_{19}O_2$ ((*S*)-methyloctanoic acid+H) = 159.1385, found 159.1385; Calc'd for $C_7H_{11}O_2$ (M-(*S*)-methyloctanoic acid) = 127.0759, found 127.0748.

Iodomethyltriphenylphosphonium iodide ($[Ph_3PCH_2I]I$) (89 mg, 0.168 mmol) was suspended in THF (0.5 mL). NaHMDS (2 M THF, 0.8 mL, 0.168 mmol) was then added and the reaction stirred for 5 min to give a bright yellow color. The solution was then cooled to -78 °C and the above aldehyde (15.0 mg, 0.056 mmol) was added slowly down the side of the flask as a solution in THF (0.5 mL) and DMPU (0.1 mL). The reaction was stirred for 10 min and then quenched with aqueous NH_4Cl and warmed to ambient temperature. The layers were separated and the aqueous was extracted 3 times with diethyl ether. The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, concentrated *in vacuo* and chromatographed gradiently with 2-4% diethyl ether/petroleum ether to give the title compound **6.4** (14 mg, 64% yield) in >20:1 dr [as judged by comparison of the integration of the alkene protons at 6.46 ppm (minor diastereomer) and 5.98 ppm (major diastereomer) or the other alkene protons at 6.14 ppm (major diastereomer) and 6.03 ppm (minor diastereomer)]. $[\alpha]_D^{26}$ = 63.1 ± 0.2 (CH_2Cl_2, c = 1.1). IR (thin film) 2929, 2857, 1734, 1457, 1283, 1169 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$); δ 6.14 (dd, *J* = 0.8, 7.3 Hz, 1H), 5.98 (dd, *J* = 7.5, 8.5 Hz, 1H), 4.78 (tt, *J* = 4.3, 11.1 Hz, 1H), 2.46 (m, 1H), 2.27 (t, *J* = 7.5 Hz, 2H), 1.99 (m, 2H), 1.83 (d pentet, *J* = 13.7, 3.4 Hz, 1H), 1.70 (m, 1H), 1.58 (m, 3H), 1.44 (m, 1H), 1.18-1.36 (m,

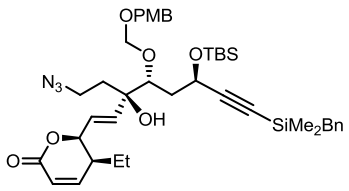
5H), 1.00-1.16 (m, 4H), 0.85 (t, *J* = 7 Hz, 3H), 0.83 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$); δ 173.3, 144.5, 80.8, 71.8, 42.3, 36.4, 36.3, 34.8, 34.3, 32.0, 31.4, 30.2, 29.5, 26.7, 25.5, 23.5, 22.8, 19.2, 11.5. HRMS (EI) Calc'd for $C_{17}H_{29}IO_2$ = 392.1212, found 392.1203.

1.6. Completion of the synthesis of Leustroducsin B (1)



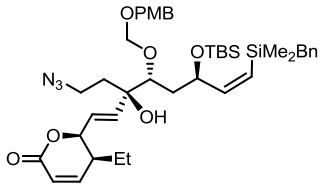
(3*R*,4*R*,6*R*,*E*)-4-((4-methoxybenzyloxy)methoxy)-3-(2-azidoethyl)-8-(benzyldimethylsilyl)-6-(*tert*-butyldimethylsilyloxy))-1-((2*S*,3*S*,6*R*)-3-ethyl-6-methoxy-3,6-dihydro-2*H*-pyran-2-yl)oct-1-en-7-yn-3-ol (26).

Freshly prepared vinyl iodide **2** (308.3 mg, 1.05 mmol) was dissolved in THF (1.5 mL) and cooled to -78 °C. *n*-BuLi (2.2 M hexanes, 430 μL, 0.94 mmol) and dimethylzinc (Acros new bottle of 1.2 M toluene, 780 μL, 0.94 mmol) were then added and the reaction was stirred for 30 min. Ketone **3** (319.1 mg, 0.52 mmol) was then added as a solution in dry CH_2Cl_2 (3.0 mL). The reaction was stirred for 9 h at -78 °C. The reaction was then poured over aqueous NaH_2PO_4 and extracted with ethyl acetate. The organic layer was then washed with brine, dried ($MgSO_4$), filtered, concentrated *in vacuo* and chromatographed isocratically with 10% ethyl acetate/petroleum ether to give the title compound **26** (306.4 mg, 75% yield) in >20:1 dr (as judged by ^{1}H NMR of the alkene proton at 6.12 ppm vs. 6.02 ppm for the diastereomer, or by comparison of the OH peak at 4.02 ppm vs. 3.99 ppm for the diastereomer, or by comparison of one of the protons adjacent to an OH group at 3.69 ppm vs. 3.77 ppm for the diastereomer). $[\alpha]_D^{24}$ = 41.0 ± 0.3 (CH_2Cl_2, c = 1.11). R_f (10% ethyl acetate/petroleum ether) = 0.25. IR (thin film) 3425, 2957, 2929, 2857, 2172, 2096, 1728, 1613, 1587, 1515, 1494, 1464, 1401, 1380, 1362, 1338, 1303, 1250, 1209, 1186, 1166, 1092, 1046, 965, 905, 838, 779, 764, 699 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$); δ 7.25 (d, *J* = 8.7 Hz, 2H), 7.20 (t, *J* = 7.6 Hz, 2H), 7.08 (t, *J* = 7.3 Hz, 1H), 7.03 (d, *J* = 7.4 Hz, 2H), 6.87 (d, *J* = 8.7 Hz, 2H), 6.13 (dd, *J* = 5.6, 10.1 Hz, 1H), 5.92 (dd, *J* = 4.6, 15.5 Hz, 1H), 5.74 (dd, *J* = 2.3, 9.9 Hz, 1H), 5.68 (d, *J* = 15.5 Hz, 1H), 4.87 (s, 1H), 4.86 (d, *J* = 7.0 Hz, 1H), 4.69 (d, *J* = 7.0 Hz, 1H), 4.66 (d, *J* = 11.4 Hz, 1H), 4.53 (d, *J* = 11.1 Hz, 1H), 4.44 (m, 1H), 4.04 (s, 1H), 3.79 (s, 3H), 3.49 (m, 1H), 3.37 (s, 3H), 3.28 (m, 1H), 2.16 (s, 2H), 1.96 (m, 2H), 1.89 (m, 2H), 1.78 (m, 1H), 1.72 (m, 1H), 1.48 (m, 1H), 1.32 (m, 2H), 0.88 (t, *J* = 7.4 Hz, 3H), 0.83 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H), 0.08 (s, 3H), 0.04 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$); δ 159.5, 138.7, 133.7, 130.6, 130.3, 129.7, 128.7, 128.3, 128.1, 125.0, 124.4, 113.9, 108.5, 96.8, 95.8, 87.8, 86.6, 74.9, 70.4, 69.5, 59.8, 55.2, 55.0, 47.2, 40.8, 39.0, 33.9, 25.9, 25.7, 21.6, 18.0, 11.4, -2.3, -2.4, -4.0, -4.8. LRMS (ESI) Calcd for $C_{42}H_{63}N_3NaO_7Si_2$ $(M+Na)^+$ = 800.41, found 800.41. HRMS (ESI) Calcd for $C_{42}H_{63}N_3NaO_7Si_2$ $(M+Na)^+$ = 800.4102, found 800.4124.



(5S,6S)-6-((3R,4R,6R,E)-3-(2-azidoethyl)-8-(benzyldimethylsilyl)-6-((tert-butyldimethylsilyl)oxy)-3-hydroxy-4-(((4-methoxybenzyl)oxy)methoxy)oct-1-en-7-yn-1-yl)-5-ethyl-5,6-dihydro-2H-pyran-2-one (30).

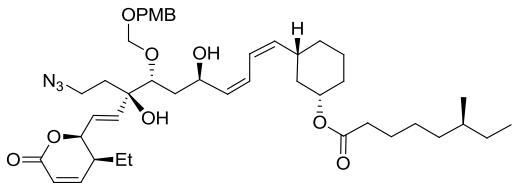
Acetal **26** (168.4 mg, 0.22 mmol) was dissolved in CH_2Cl_2 (2.0 mL) and PCC (186.2 mg, 0.86 mmol) was added. MS 4Å (100 mg) was also added, the reaction stirred for 3 h and then directly applied to column chromatography, gradient 0-5% EtOAc/CH_2Cl_2 to give the title compound **27** (104.3mg, 62%). $[\alpha]_D^{25}$ = 55.2 ± 0.1 (CH_2Cl_2, c = 1.0). R_f (20% ethyl acetate/petroleum ether = 0.18. IR (thin film) 3422, 2958, 2858, 2361, 2096, 1727, 1612, 1515, 1459, 1381, 1303, 1250, 1166, 1089, 1032 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$); δ 7.27 (d, *J* = 8.7 Hz, 2H), 7.22 (t, *J* = 7.6 Hz, 2H), 7.10 (t, *J* = 7.4 Hz, 1H), 7.06 (d, *J* = 6.8 Hz, 2H), 6.96 (dd, *J* = 5.4, 9.6 Hz, 1H), 6.90 (d, *J* = 8.7 Hz, 2H), 6.06 (d, *J* = 9.9 Hz, 1H), 5.97 (dd, *J* = 4.9, 15.4 Hz, 1H), 5.85 (d, *J* = 15.0 Hz, 1H), 5.02 (m, 1H), 4.88 (d, *J* = 6.8 Hz, 1H), 4.71 (d, *J* = 7.1 Hz, 1H), 4.68 (d, *J* = 11.1 Hz, 1H), 4.55 (d, *J* = 11.6 Hz, 1H), 4.46 (dd, *J* = 2.4, 10.3 Hz, 1H), 4.15 (br s, 1H), 3.81 (s, 3H), 3.49 (d, *J* = 7.2 Hz, 1H), 3.36 (ddd, *J* = 6.2, 9.8, 12.0 Hz, 1H), 3.27 (ddd, *J* = 5.6, 9.6, 12.6 Hz, 1H), 2.41 (m, 1H), 2.20 (s, 2H), 1.89-2.00 (m, 2H), 1.70-1.82 (m, 2H), 1.44 (m, 1H), 1.26 (m, 1H), 0.95 (t, *J* = 7.3 Hz, 1H), 0.85 (s, 9H), 0.12 (s, 3H), 0.11 (s, 6H), 0.07 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$); δ 164.1, 159.6, 150., 138.9, 134.2, 129.8, 128.8, 128.4, 128.3, 126.4, 124.5, 121.0, 114.1, 108.2, 96.8, 88.2, 86.2, 79.9, 75.1, 70.6, 60.0, 55.4, 47.2, 40.8, 39.3, 34.2, 26.1, 25.9, 21.7, 18.2, 11.1, -2.2, -2.3, -3.9, -4.7. LRMS (ESI) Calc'd for $C_{41}H_{59}N_3NaO_7Si_2$ (M+Na) = 784.4, found 784.4. HRMS (ESI) Calc'd for $C_{41}H_{59}N_3NaO_7Si_2$ = 784.3789, found 784.3785.



(5S,6S)-6-((1E,3R,4R,6R,7Z)-3-(2-azidoethyl)-8-(benzyldimethylsilyl)-6-((tert-butyldimethylsilyl)oxy)-3-hydroxy-4-(((4-methoxybenzyl)oxy)methoxy)octa-1,7-dien-1-yl)-5-ethyl-5,6-dihydro-2H-pyran-2-one (32).

Alkyne **30** (101.3 mg, 0.13 mmol) was dissolved in THF/*i*-PrOH (2.8 mL, 1:1), Et_3N (23 μL, 0.17 mmol) and *o*-nitrobenzenesulfonylhydrazide **31**[9] (31.5 mg, 1.15 mmol) were added. The reaction was stirred at ambient temperature for 24 h **<u>in the dark</u>**, diluted with diethyl ether (5 mL) and washed with water (2 x 5

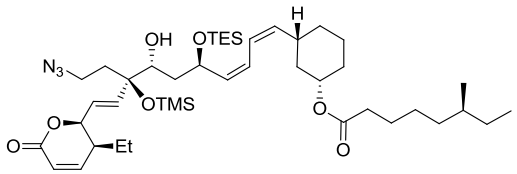
mL). The organic layer was washed with brine, dried ($MgSO_4$), filtered, concentrated *in vacuo*, and chromatographed gradiently with 5-10-15% ethyl acetate/petroleum ether to give the title compound **32** (42.3 mg, 45% yield) and recovered starting material **30** (31.0 mg, 73% brsm). $[\alpha]_D^{35}$ = 25.4 ± 0.1 (CH_2Cl_2, c = 1.3). R_f (20% ethyl acetate/petroleum ether) = 0.25. IR (thin film) 3418, 2957, 2991, 2857, 2096, 1729, 1613, 1515, 1494, 1463, 1381, 1303, 1250, 1162, 1083, 1031 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$); δ 7.26 (d, *J* = 8.5 Hz, 2H), 7.22 (t, *J* = 7.6 Hz, 2H), 7.09 (t, *J* = 7.3 Hz, 1H), 7.01 (d, *J* = 7.6 Hz, 2H), 6.94 (dd, *J* = 5.4, 9.9 Hz, 1H), 6.89 (d, *J* = 8.7 Hz, 2H), 6.25 (dd, *J* = 8.7, 14.6 Hz, 1H), 6.05 (dd, *J* = 1.0, 9.9 Hz, 1H), 5.95 (dd, *J* = 4.9, 15.3 Hz, 1H), 5.77 (d, *J* = 15.4 Hz, 1H), 5.49 (d, *J* = 14.5 Hz, 1H), 4.99 (dt, *J* = 1.5, 4.0 Hz, 1H), 4.93 (d, *J* = 7.0 Hz, 1H), 4.72 (d, *J* = 11.7 Hz, 1H), 4.70 (d, *J* = 7.2 Hz, 1H), 4.53 (d, *J* = 11.4 Hz, 1H), 4.45 (d, *J* = 1.0 Hz, 1H), 4.37 (t, *J* = 9.2 Hz, 1H), 3.81 (s, 3H), 3.50 (d, J = 8.5 Hz, 1H), 3.34 (ddd, *J* = 5.7, 9.8, 12.5 Hz, 1H), 3.23 (ddd, *J* = 5.5, 9.9, 12.2 Hz, 1H), 2.40 (sextet, *J* = 4.8 Hz, 1H), 2.17 (s, 2H), 1.92 (ddd, *J* = 5.7, 9.6, 13.6 Hz, 1H), 1.67 (ddd, *J* = 5.6, 9.9, 13.8 Hz, 1H), 1.55-1.66 (m, 2H), 1.45 (ddd, *J* = 7.6, 9.3, 13.5 Hz, 1H), 1.31 (ddd, *J* = 1.7, 10.1, 13.7 Hz, 1H), 0.94 (t, *J* = 7.4 Hz, 3H), 0.82 (s, 9H), 0.13 (s, 6H), 0.00 (s, 3H), -0.03 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$); δ 164.1, 159.1, 152.5, 150.5, 139.7, 134.4, 129.9, 128.6, 128.3, 128.3, 126.6, 126.2, 124.3, 121.0, 114.1, 97.1, 87.8, 79.9, 74.9, 70.7, 70.1, 55.4, 47.2, 40.7, 39.3, 33.8, 26.6, 25.9, 21.7, 18.1, 11.1, -1.5, -1.7, -3.1, -4.4. LRMS (ESI) Calc'd for $C_{41}H_{61}N_3NaO_7Si_2$ (M+Na) = 786.4, found 786.4. HRMS (ESI) Calc'd for $C_{41}H_{61}N_3NaO_7Si_2$ (M+Na) = 786.3946, found 786.3940.



(*S*)-((1*S*,3*R*)-3-((1*Z*,3*Z*,5*R*,7*R*,8*R*,9*E*)-7-((4-methoxybenzyloxy)methoxy)-8-(2-azidoethyl)-10-((2*S*,3*S*,6*R*)-3-ethyl-6-methoxy-3,6-dihydro-2*H*-pyran-2-yl)-5,8-dihydroxydeca-1,3,9-trienyl)cyclohexyl) 6-methyloctanoate (33).

Vinyl silane **32** (3 mg, 0.004 mmol) and vinyl iodide **4** (4 mg, 0.010 mmol) in degassed THF (0.1 mL) were added to $Pd_2dba_3{\cdot}CHCl_3$ (dba = dibenzylideneacetone) (0.9 mg, 0.0009 mmol) under argon. Acetic acid (1 μL, 0.017 mmol) was then added, followed by slow addition of TBAF (1M THF, 0.02 mL, 0.02 mmol) over 2 h at ambient temperature. The reaction was stirred for 14 h and then chromatographed gradiently from 0-50% ethyl acetate/petroleum ether to give the title compound **33** (2.1 mg, 70% yield). $[\alpha]_D^{24}$ = 3.9 ± 0.8 (CH_2Cl_2, c = 0.42). ^1H NMR (500 MHz, $CDCl_3$); δ 7.27 (d, *J* = 8.7 Hz, 2H), 6.89 (d, *J* = 8.7 Hz, 2H), 6.26 (t, *J* = 11.2 Hz, 1H), 6.15 (dd, *J* = 5.5, 9.9 Hz, 1H), 6.14 (t, *J* = 11.0 Hz, 1H), 5.90 (dd, *J*

= 4.3, 15.9 Hz, 1H), 5.76 (dd, *J* = 1.8, 10.5 Hz, 1H), 5.72 (dd, *J* = 1.7, 15.4 Hz, 1H), 5.44 (t, *J* = 10.1 Hz, 1H), 5.31 (t, *J* = 10.0 Hz, 1H), 4.88 (d, *J* = 1.8 Hz, 1H), 4.87 (d, *J* = 6.6 Hz, 1H), 4.80 (d, *J* = 6.8 Hz, 1H), 4.70-4.80 (m, 2H), 4.63 (s, 2H), 4.56 (m, 1H), 3.81 (s, 3H), 3.67 (dd, *J* = 3.7, 9.6 Hz, 1H), 3.43 (m, 1H), 3.38 (s, 3H), 3.33 (m, 1H), 2.57 (m, 1H), 2.46 (m, 1H), 2.34 (m, 1H), 2.27 (t, *J* = 7.3 Hz, 2H), 1.88-2.00 (m, 4H), 1.80-1.85 (m, 2H), 1.75-1.80 (m, 1H), 1.70-1.75 (m, 1H), 1.66-1.69 (m, 1H), 1.00-1.66 (m, 13H), 0.91 (t, *J* = 7.6 Hz, 3H), 0.85 (t, *J* = 7.1 Hz, 3H), 0.83 (d, *J* = 6.3 Hz, 3H). ^{13}C NMR (126 MHz, d_6-benzene); δ 172.4, 160.3, 143.6, 136.3, 132.8, 129.8, 129.6, 127.3, 126.0, 124.2, 123.4, 115.8, 114.1, 96.8, 96.3, 88.9, 85.2, 71.7, 70.3, 69.6, 64.8, 54.7, 54.5, 48.1, 47.1, 38.7, 37.0, 34.6, 34.5, 34.4, 33.1, 31.5, 30.2, 30.0, 29.8, 26.3, 23.6, 22.8, 22.2, 19.1, 11.6, 11.0. HRMS (ESI) Calc'd for $C_{44}H_{67}N_3NaO_9$ (M+Na) = 804.4775, found 804.4752.

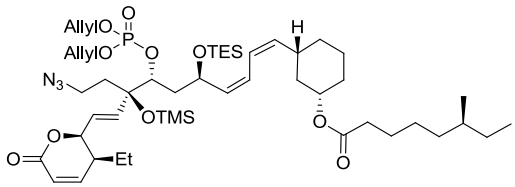


(*S*)-((1*S*,3*R*)-3-((1*Z*,3*Z*,5*R*,7*R*,8*R*,9*E*)-8-(2-azidoethyl)-10-((2*S*,3*S*)-3-ethyl-6-oxo-3,6-dihydro-2*H*-pyran-2-yl)-7-hydroxy-5-(triethylsilyloxy)-8-(trimethylsilyloxy)deca-1,3,9-trienyl)cyclohexyl) 6-methyloctanoate (35).

Diol **33** (41.2 mg, 0.053 mmol) was dissolved in DCM (1.0 mL) and cooled to -78 ºC. 2,6-Lutidine (92 μL, 0.80 mmol) and TESOTf (18 μL, 0.080 mmol) and the reaction was stirred for 1 h and then TMSOTf (96 μL, 0.53 mmol) was added. The reaction was stirred for 1 h and then quenched with pH 7 phosphate buffer. The reaction was warmed to ambient temperature and extracted 5 times with diethyl ether, concentrated *in vacuo* to afford **34** as a light yellow gum which was used in the next step without further purification. $[\alpha]_D^{25}$ = 38.2 ± 0.9 (CH_2Cl_2, c = 0.41). R_f (10% ethyl acetate/petroleum ether) = 0.15. IR (thin film) 2931, 2095, 1730, 1514, 1462, 1379, 1250, 1034, 841, 738 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$); δ 7.31 (d, *J* = 8.8 Hz, 2H), 6.97 (dd, *J* = 5.4, 9.8 Hz, 1H), 6.91 (d, *J* = 8.8 Hz, 2H), 6.15 (t, *J* = 11.7 Hz, 1H), 6.10 (m, 1H), 6.07 (dd, *J* = 1.1, 9.9 Hz, 1H), 5.88 (dd, *J* = 1.1, 15.5 Hz, 1H), 5.77 (dd, *J* = 6.0, 15.5 Hz, 1H), 5.38 (t, *J* = 9.6 Hz, 1H), 5.27 (t, *J* = 9.5 Hz, 1H), 5.04 (t, *J* = 4.4 Hz, 1H), 4.89 (d, *J* = 6.6 Hz, 1H), 4.83 (d, *J* = 6.5 Hz, 1H), 4.80 (m, 1H), 4.76 (m, 1H), 4.63 (s, 2H), 3.84 (s, 3H), 3.76 (d, *J* = 8.9 Hz), 3.32 (m, 2H), 2.57 (m, 1H), 2.40 (m, 1H), 2.28 (t, *J* = 7.2 Hz, 2H), 2.20 (ddd, *J* = 5.9, 11.4, 13.9 Hz, 1H), 1.95-2.01 (m, 2H), 1.89-1.95 (m, 1H), 1.84 (dt, *J* = 13.3, 3.4 Hz, 1H), 1.75 (dd, *J* = 10.6, 13.2 Hz, 1H), 1.40-1.52 (m, 2H), 1.08-1.40 (m, 14H), 1.04 (m, 1H), 0.96 (t, *J* = 7.4 Hz, 3H), 0.93 (t, *J* = 7.9 Hz, 9H), 0.87 (t, *J* = 7.2 Hz, 3H), 0.86 (d, *J* = 6.3 Hz, 3H), 0.56 (q, *J* = 8.1 Hz, 6H), 0.21 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$); δ 173.4, 164.0, 159.2, 149.9, 137.4, 135.5, 135.2, 129.8, 129.2, 125.3, 122.4, 122.0, 120.8,

113.8, 96.7, 82.3, 80.2, 79.2, 72.2, 70.0, 65.2, 55.3, 47.2, 39.8, 39.6, 38.1, 36.2, 36.1, 34.9, 34.7, 34.2, 31.9, 31.3, 29.7, 29.4, 26.6, 25.4, 23.7, 21.6, 19.1, 11.4, 11.1, 6.9, 5.2, 2.5. HRMS (ESI) Calc'd for $C_{52}H_{85}N_3NaO_9Si_2$ (M+Na) = 974.5722, found 974.5726.

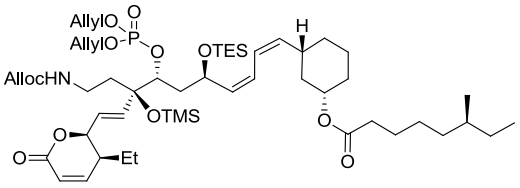
PMBM ether **34** obtained above was dissolved in CH_2Cl_2 (2.5 mL) and water (200 μL). DDQ (120.3 mg, 0.53 mmol) was then added and the reaction **vigorously** stirred for 1 h. **An emulsion must form in order for the reaction to proceed.** The reaction mixture was then quenched by addition of $Na_2S_2O_3$ (saturated aqueous solution, 2 mL) and $NaHCO_3$ (saturated aqueous solution, 2 mL) and the organic fraction rinsed multiple times with water. The crude material was chromatographed gradiently with 5-20% ethyl acetate/hexanes to give the title compound **35** (28.0 mg, 66% from **33**). $[\alpha]_D^{23}$ = 42.9 ± 0.1 (CH_2Cl_2, c = 0.19). R_f (10% ethyl acetate/petroleum ether) = 0.06. IR (thin film) 2955, 2919, 2875, 2851, 2095, 1767, 1728, 1462, 1380, 1253, 1081, 1017, 841, 738 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$); δ 6.98 (dd, *J* = 5.4, 9.9 Hz, 1H), 6.24 (t, *J* = 11.4 Hz, 1H), 6.09 (t, *J* = 10.3 Hz, 1H), 6.08 (dd, *J* = 1.2, 9.8 Hz, 1H), 5.94 (dd, *J* = 1.3, 15.7 Hz, 1H), 5.77 (dd, *J* = 5.9, 15.7 Hz, 1H), 5.57 (t, *J* = 9.8 Hz, 1H), 5.36 (t, *J* = 9.9 Hz, 1H), 5.05 (m, 1H), 4.96 (m, 1H), 4.77 (m, 1H), 3.86 (d, *J* = 10.0 Hz), 3.35 (m, 2H), 2.60 (m, 1H), 2.43 (m, 1H), 2.28 (t, *J* = 7.6 Hz, 2H), 2.10 (ddd, *J* = 6.5, 10.1, 14.0 Hz, 1H), 1.95-2.06 (m, 2H), 1.88-1.95 (m, 1H), 1.85 (m, 1H), 1.00-1.74 (m, 18H), 0.99 (t, *J* = 7.4 Hz, 3H), 0.96 (t, *J* = 8.1 Hz, 9H), 0.87 (t, *J* = 7.2 Hz, 3H), 0.86 (d, *J* = 6.3 Hz, 3H), 0.60 (q, *J* = 7.8 Hz, 6H), 0.15 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$); δ 173.3, 164.0, 150.0, 138.0, 135.3, 133.9, 125.5, 122.9, 121.6, 120.8, 80.2, 79.2, 73.6, 72.1, 67.5, 47.0, 39.5, 38.2, 38.1, 36.1, 35.3, 34.9, 34.7, 34.2, 31.9, 31.3, 29.7, 29.4, 26.6, 25.4, 23.7, 21.6, 19.1, 11.4, 11.1, 6.7, 4.7, 2.5. HRMS (ESI) Calc'd for $C_{43}H_{75}N_3NaO_7Si_2$ (M+Na) = 824.5041, found 824.5037.



(*S*)-((1*S*,3*R*)-3-((1*Z*,3*Z*,5*R*,7*R*,8*R*,9*E*)-8-(2-azidoethyl)-7-(bis(allyloxy)phosphoryloxy)-10-((2*S*,3*S*)-3-ethyl-6-oxo-3,6-dihydro-2*H*-pyran-2-yl)-5-(triethylsilyloxy)-8-(trimethylsilyloxy)deca-1,3,9-trienyl)cyclohexyl) 6-methyloctanoate (37).

Secondary alcohol **35** (9.2 mg, 0.0115 mmol) and 1*H*-tetrazole (8.0 mg, 0.115 mmol) were dissolved in CH_2Cl_2 (150 μL) and MeCN (150 μL). Diallyl diisopropylphosphoramidite (15.2 μL, 0.0575 mmol) was then added and the reaction was stirred for 1 h. The reaction was cooled to 0 ºC and MeOH (20 μL) and *tert*-butylhydroperoxide (5.5 M decane, 20 μL) were then added. The reaction was stirred for 1 h and then quenched with $NaSO_3$. The aqueous layer was extracted six times with diethyl ether and then

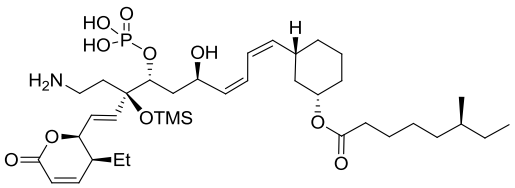
concentrated *in vacuo* and chromatographed gradiently with 10-40% ethyl acetate/hexanes to give the title phosphate **37** (5.5 mg, 50%). $[\alpha]_D^{23}$ = 21.2 ± 1.9 (CH_2Cl_2, c = 0.08). R_f (20% ethyl acetate/petroleum ether) = 0.31. IR (thin film) 3383, 2958, 2919, 2850, 2096, 1728, 1612, 1514, 1463, 1379, 1260, 1098, 1024, 801 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$); δ 6.98 (dd, *J* = 5.5, 9.8 Hz, 1H), 6.17 (m, 2H), 6.07 (dd, *J* = 1.1, 9.8 Hz, 1H), 5.98 (m, 2H), 5.88 (dd, *J* = 1.3, 15.6 Hz, 1H), 5.79 (dd, *J* = 5.6, 15.6 Hz, 1H), 5.43 (m, 1H), 5.39 (m, 1H), 5.37 (t, *J* = 9.3 Hz, 1H), 5.27-5.32 (m, 3H), 5.05 (brt, *J* = 4.3 Hz, 1H), 4.96 (t *J* = 10.0 Hz, 1H), 4.76 (m, 1H), 4.40-4.50 (m, 5H), 3.40 (ddd, *J* = 5.4, 10.1, 17.3 Hz, 1H), 3.30 (ddd, *J* = 6.2, 10.3, 16.7 Hz, 1H), 2.58 (m, 1H), 2.42 (m, 1H), 2.28 (t, *J* = 6.8 Hz, 2H), 2.11 (m, 2H), 1.98 (m, 1H), 1.93 (m, 1H), 1.86 (m, 1H), 1.00-1.84 (m, 16H), 0.97 (t, *J* = 7.4 Hz, 3H), 0.96 (t, *J* = 8.1 Hz, 9H), 0.87 (t, *J* = 7.2 Hz, 3H), 0.86 (d, *J* = 6.5 Hz, 3H), 0.62 (q, *J* = 7.8 Hz, 6H), 0.23 (s, 9H). ^{31}P NMR (162 MHz, $CDCl_3$); δ -0.6.^{13}C NMR (150 MHz, $CDCl_3$); δ 173.6, 159.7, 148.9, 139.3, 136.3, 135.6, 133.3, 132.7, 130.2, 127.4, 125.7, 79.7, 79.3, 71.6, 67.7, 67.5, 64.8, 46.1, 39.7, 39.6, 39.3, 39.0, 37.4, 37.4, 37.1, 34.5, 34.0, 31.1, 30.9, 26.6, 25.7, 24.3, 24.0, 22.8, 19.9, 10.8, 10.5, 6.2, 4.5, 1.7. HRMS (ESI) Calc'd for $C_{49}H_{84}N_3NaO_{10}PSi_2$ (M+Na) = 984.5331, found 984.5333.



(S)-(1S,3R)-3-((1Z,3Z,5R,7R,8R,9E)-8-(2-(((allyloxy)carbonyl)amino)ethyl)-7-((bis(allyloxy)phosphoryl)oxy)-10-((2S,3S)-3-ethyl-6-oxo-3,6-dihydro-2H-pyran-2-yl)-5-((triethylsilyl)oxy)-8-((trimethylsilyl)oxy)deca-1,3,9-trien-1-yl)cyclohexyl 6-methyloctanoate (38).

To a solution of phosphonate **37** (4.2 mg, 0.0044 mmol) in THF/H_2O (220 μL, 10:1) was added PPh_3 (3.4 mg, 0.013 mmol). The reaction mixture was stirred for 24 h at room temperature. Pyridine was added (3 μL, 0.022 mmol) and allyl chloroformate (2 μL, 0.013 mmol) was added in one portion under vigorous stirring. After 10 min, $NaHCO_3$ (saturated aqueous solution, 1mL) and EtOAC (2 mL) were added. The aqueous layer was extracted twice with ethyl acetate, concentrated *in vacuo* and purified by preparative silica gel chromatography 30% ethyl acetate/hexanes to give the title carbamate **38** (3.2 mg, 72%). $[\alpha]_D^{23}$ = 74.5 ± 0.4 (CH_2Cl_2, c = 0.61). R_f (20% ethyl acetate/petroleum ether) = 0.31. IR (thin film) 3322, 2886, 2835, 2812, 1704, 2201, 1441, 1360, 1235, 1150, 1069, 1006, 913, 831, 723 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$); δ 6.96 (dd, *J* = 5.5, 9.8 Hz, 1H), 6.14 (m, 2H), 6.04 (d, *J* = 9.8 Hz, 1H), 5.98-5.87 (m, 3H), 5.78 (dd, *J* = 5.5, 15.5 Hz, 1H), 5.39-5.17 (m, 6H), 5.06 (t, J = 4.0 Hz, 1H), 5.02 (t, J = 4.5 Hz, 1H), 4.90 (t, J = 9.5 Hz, 1H), 4.75-4.71 (m, 1H), 4.62 (t, J = 9.0 Hz, 1H), 4.56-4.53 (m, 6H), 3.28-3.21 (m, 2H), 2.58-2.52

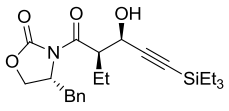
(m, 2H), 2.41-2.36 (m, 2H), 2.25 (t, J = 7.5 Hz, 2H), 2.04-1.80 (m, 3H), 1.84-1.00 (m, 16H), 0.97 (t, *J* = 7.4 Hz, 3H), 0.96 (t, *J* = 8.1 Hz, 9H), 0.87 (t, *J* = 7.2 Hz, 3H), 0.86 (d, *J* = 6.5 Hz, 3H), 0.62 (q, *J* = 7.8 Hz, 6H), 0.23 (s, 9H). ^{31}P NMR (162 MHz, $CDCl_3$); δ -0.6.^{13}C NMR (150 MHz, $CDCl_3$); δ 173.6, 173.5, 164.0, 156.4, 150.1, 137.7, 135.3, 134.7, 133.3, 132.8, 132.7, 132.7, 126.7, 123.0, 122.4, 121.2, 118.7, 118.6, 117.6, 80.6, 80.5, 80.3, 78.8, 78.7, 72.4, 68.5, 65.5, 65.2, 46.1, 39.7, 39.6, 39.3, 39.0, 37.4, 37.4, 37.1, 34.5, 34.0, 31.1, 30.9, 26.6, 25.7, 24.3, 24.0, 22.8, 19.9, 10.8, 10.5, 6.2, 4.5, 1.7. HRMS (ESI) Calcd for $C_{53}H_{90}NNaO_{12}PSi_2$ $(M+Na)^+$ = 1042.5631, found 1042.5648.



(S)-(1S,3R)-3-((1Z,3Z,5R,7R,8R,9E)-8-(2-aminoethyl)-10-((2S,3S)-3-ethyl-6-oxo-3,6-dihydro-2H-pyran-2-yl)-5-hydroxy-7-(phosphonooxy)-8-((trimethylsilyl)oxy)deca-1,3,9-trien-1-yl)cyclohexyl 6-methyloctanoate – Leustroducsin B (1).

Carbamate **36** (2.3 mg, 0.002 mmol), PPh_3 (0.5 mg, 0.002 mmol) and Et_3N (3 μL, 0.02 mmol) were combined in dry THF (200 μL). Formic acid (3.8 μL, 0.1 mmol) was added rapidly followed by $Pd(PPh_3)_4$ (0.5 mg, 0.0004 mmol, 20 mol%). The reaction flask was flushed with argon and heated at 50°C for 2 hours. The flask was cooled to room temperature and the pale yellow/light green solution was directly applied to preparative reverse phase TLC plate (Merck RP–18 F_{254}) (eluant: water/acetonitrile 35/65) to give Leustroduscin B **1** (0. 7 mg, 55%) as a white waxy solid. $[\alpha]_D^{23}$ = 91.2 ± 1.1 (MeOH, c = 0.05). R_f (30% H_2O/MeCN) = 0.10 on C18 reverse phase TLC plate. ^{1}H NMR (400 MHz, CD_3OD): δ 7.07 (dd, J = 9.9, 5.5 Hz, 1H), 6.32-6.23 (m, 2H), 6.10-5.84 (m, 3H), 5.45 (brt, J = 9.0 Hz, 1H), 5.30 (brt, J = 9.4 Hz, 1H), 5.09 (brt, J = 5.0 Hz, 1H), 4.93 (brt, J = 9.0 Hz, 1H), 4.34-4.25 (m, 1H), 3.11-2.97 (m, 2H), 2.67-2.52 (m, 2H), 2.27 (t, J = 7.3 Hz, 2H), 2.24-2.14 (m, 1H), 1.98-1.78 (m, 4H), 1.75-1.22 (m, 15H), 1.20-1.01 (m, 3H), 0.95 (t, J = 7.5 Hz, 3H), 0.89-0.84 (m, 6H). ^{13}C NMR (150 MHz, CD_3OD): δ 175.1, 166.3, 152.7, 138.1, 137.4, 153.2, 133.8, 133.1, 130.0, 127.6, 124.2, 123.7, 121.0, 82.3, 73.8, 64.6, 40.5, 39.4, 37.3, 37.1, 36.1, 35.5, 35.4, 33.1, 32.4, 30.8, 30.5, 27.6, 26.5, 24.6, 23.7, 22.7, 19.6, 14.4, 11.7, 11.4. HRMS (ESI) Calcd for $C_{34}H_{56}NNaO_{10}P$ (M+Na) = 692.3534, found 692.3541.

2. ^{1}H and ^{13}C NMR spectra of new compounds



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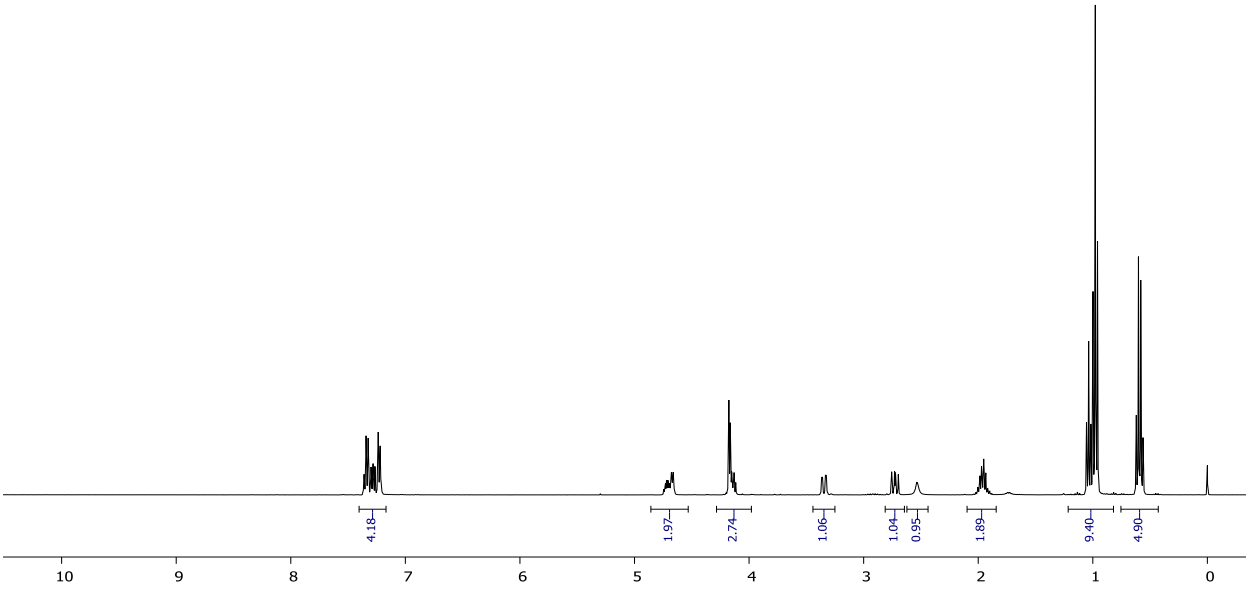

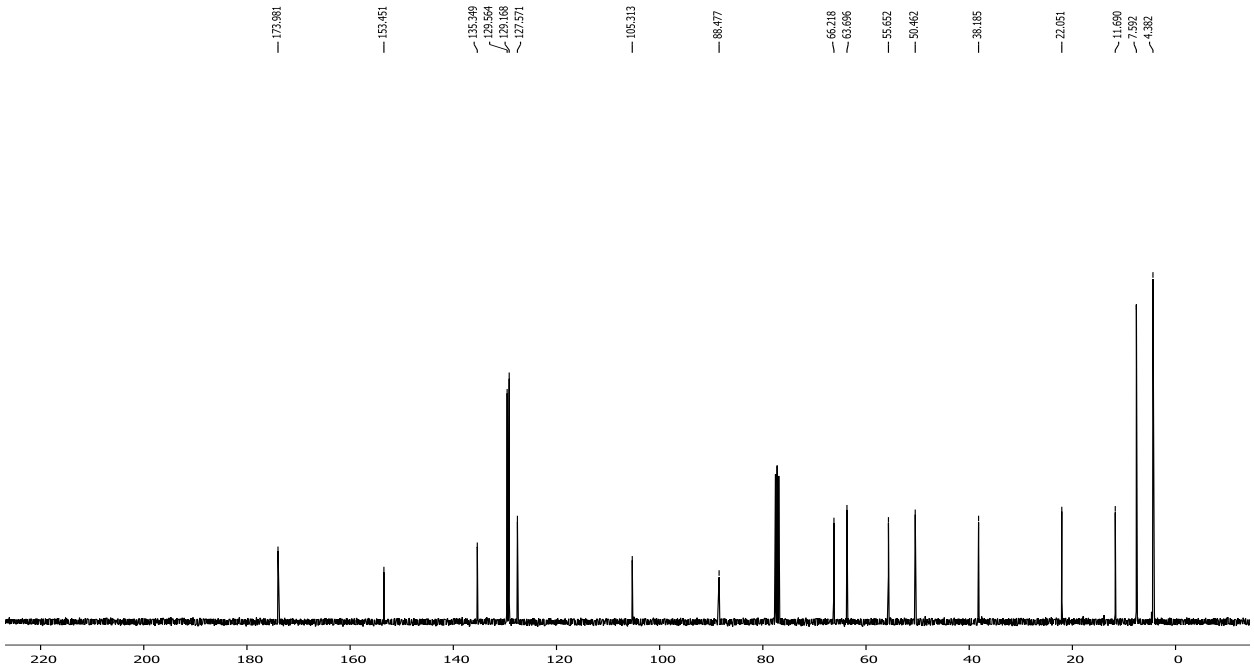
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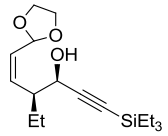
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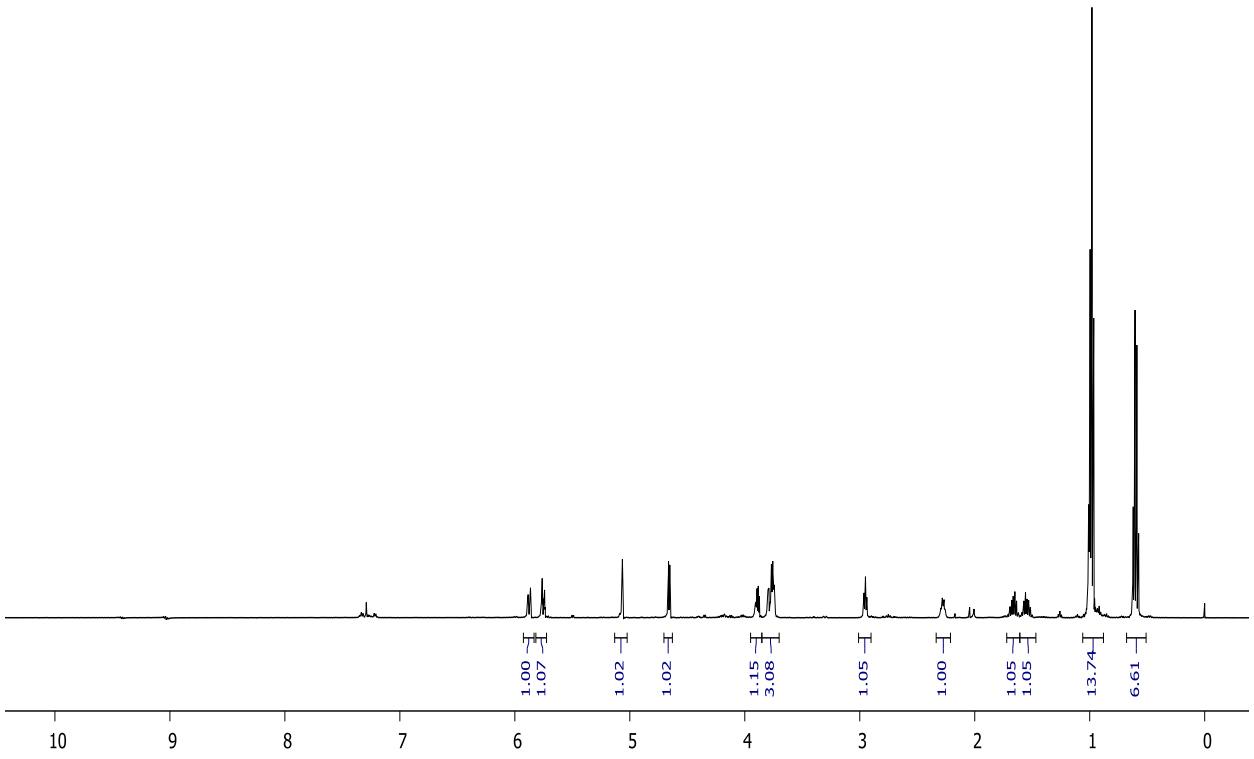
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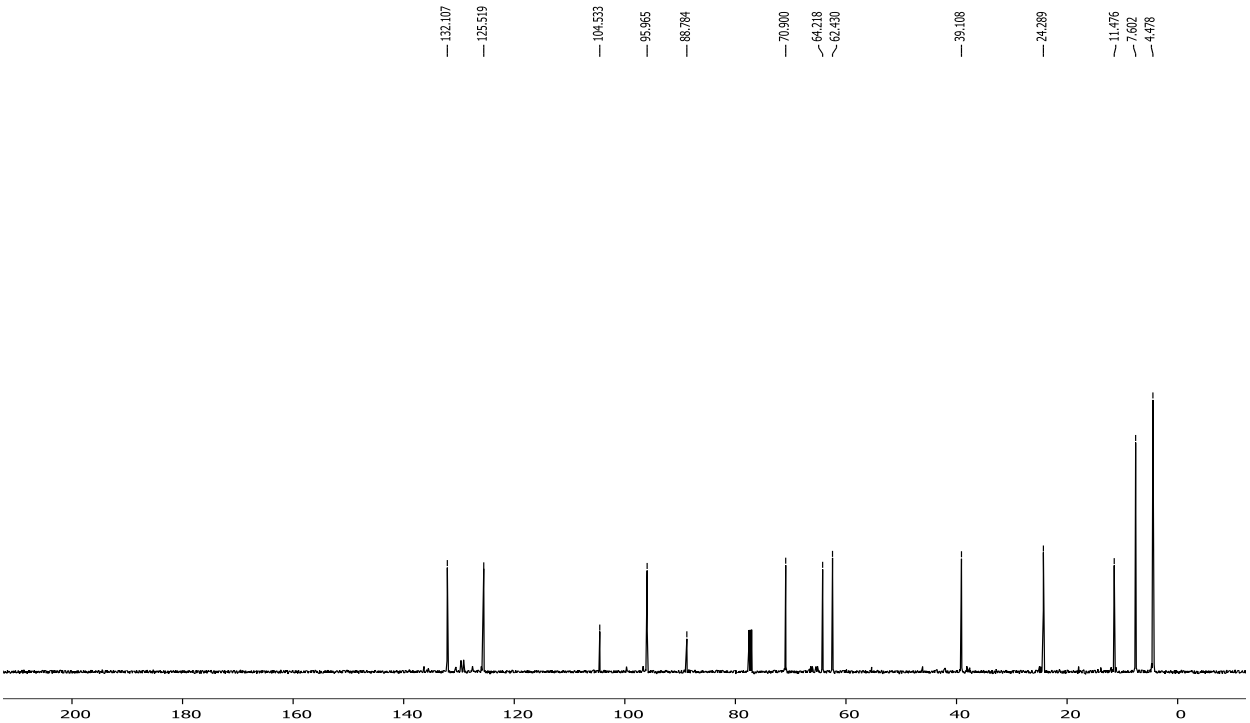
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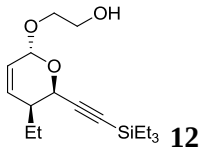
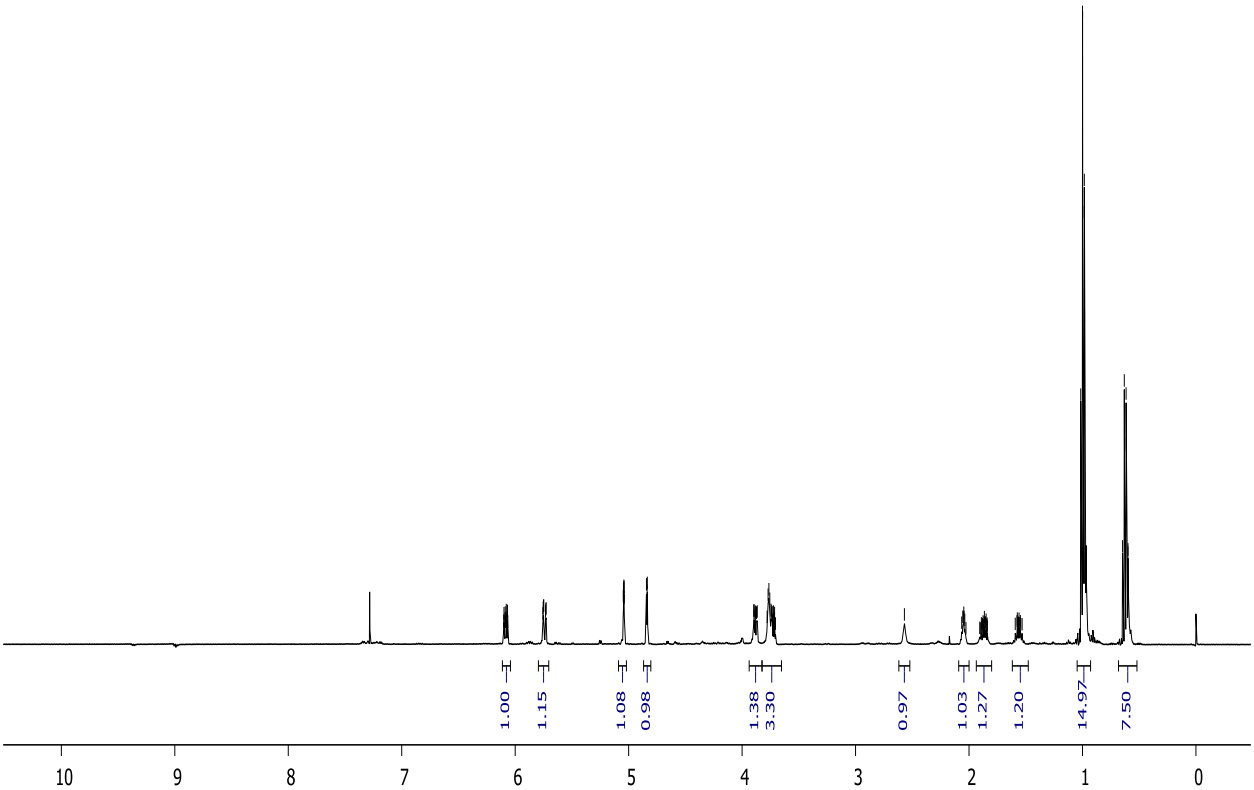
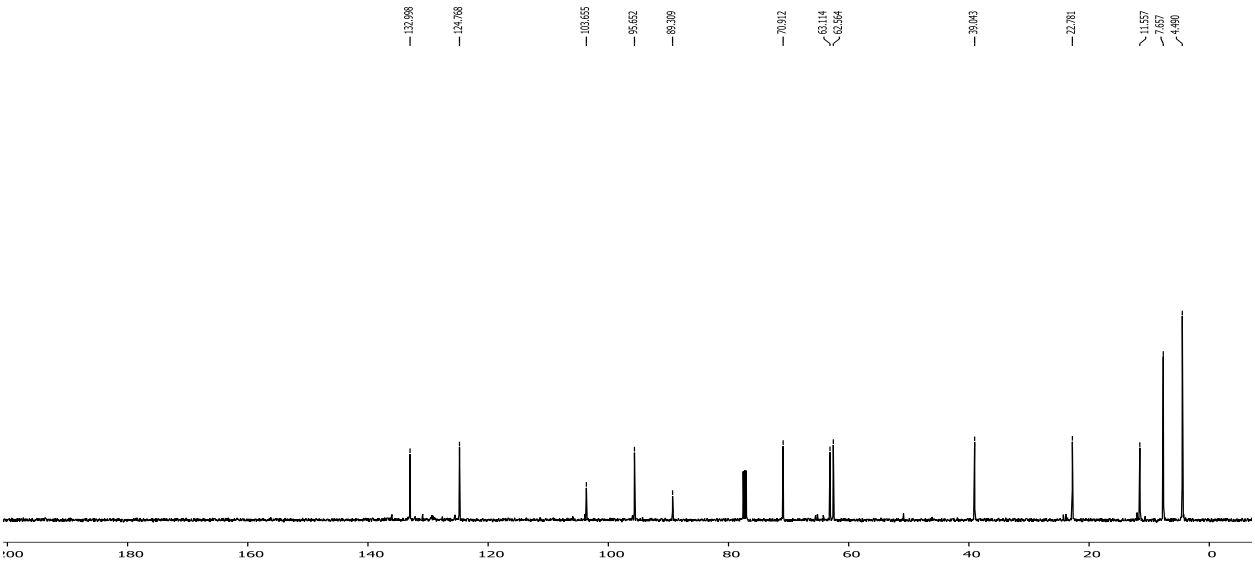
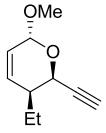
20
0


OH
O
O
Et
SiEt3

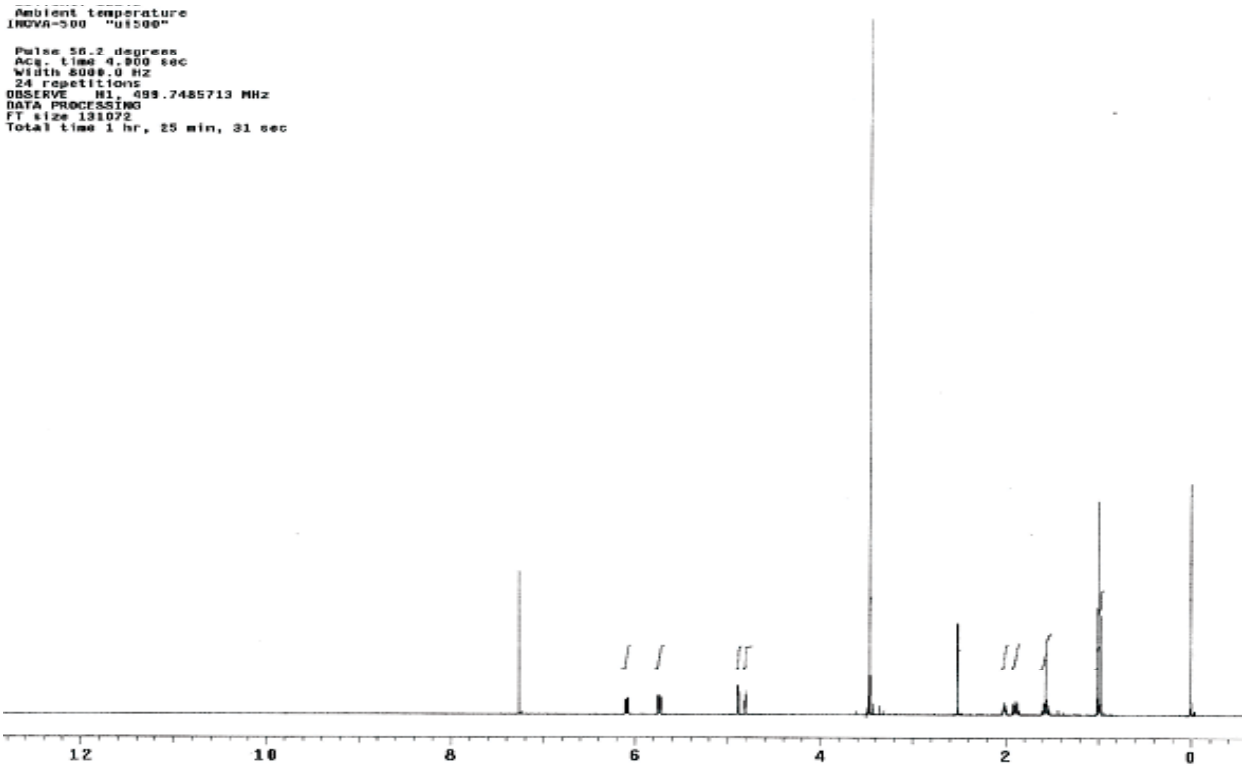
12

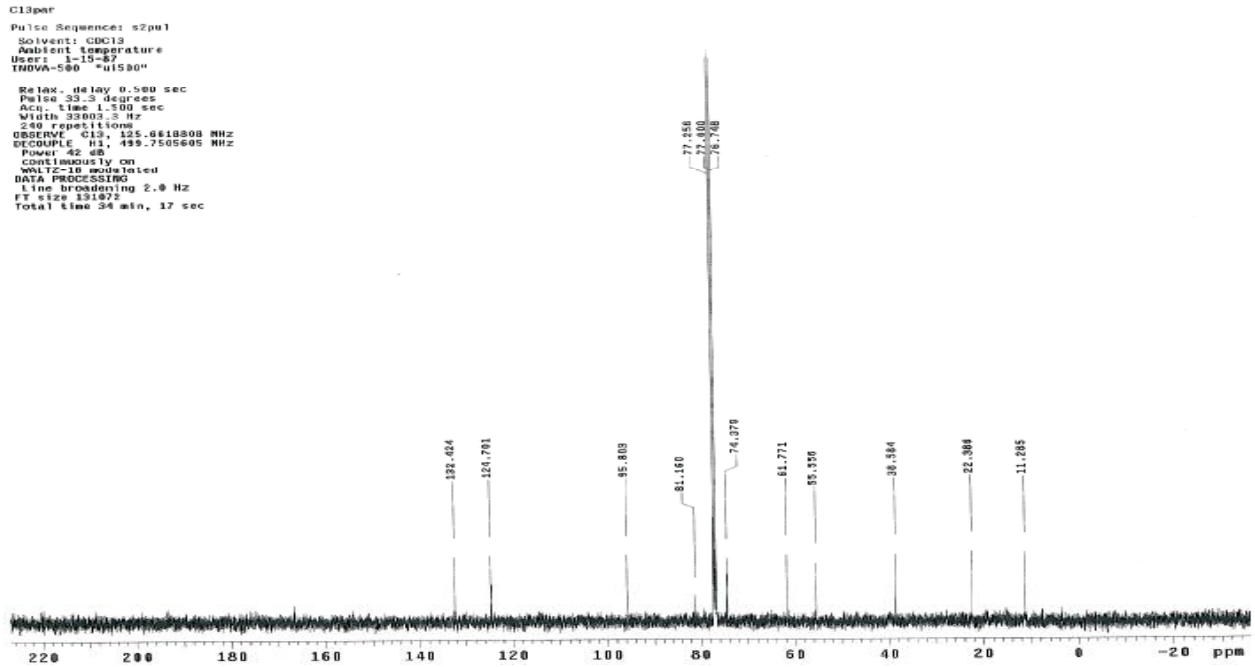

1.00
1.15
1.08
0.98
1.38
3.30
0.97
1.03
1.27
1.20
14.97
7.50
10
9
8
7
6
5
4
3
2
1
0

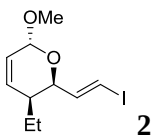

132.998
124.768
103.655
95.652
89.309
70.912
63.114
62.564
39.043
22.781
11.557
7.657
4.490
180
160
140
120
100
80
60
40
20
0


OMe
O
Et

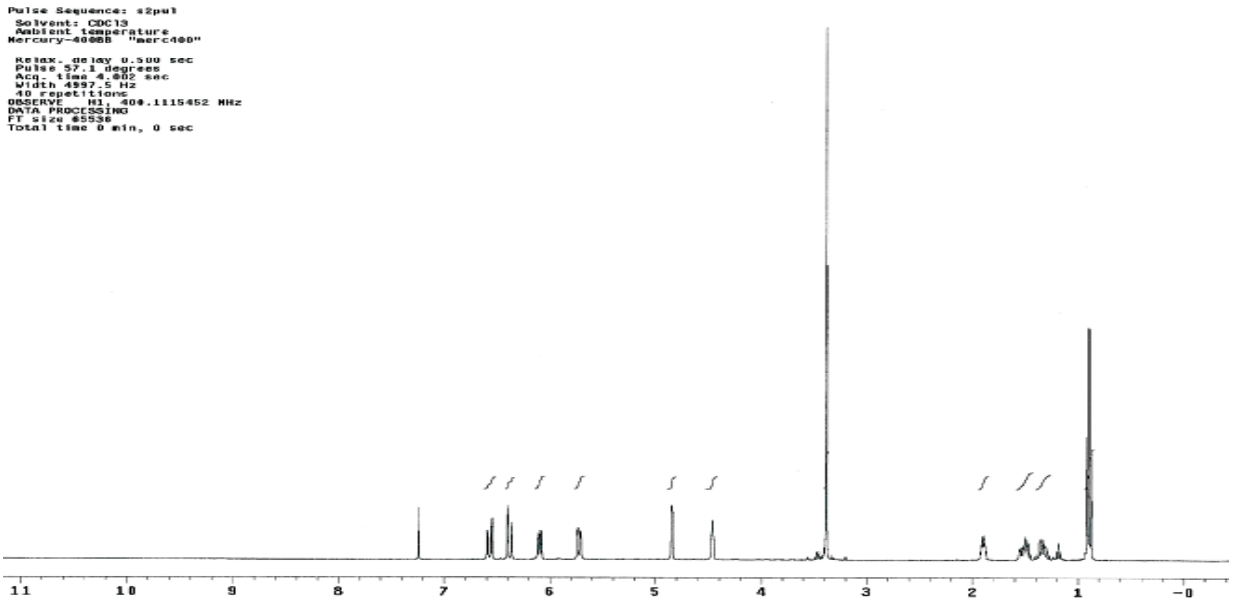
11a

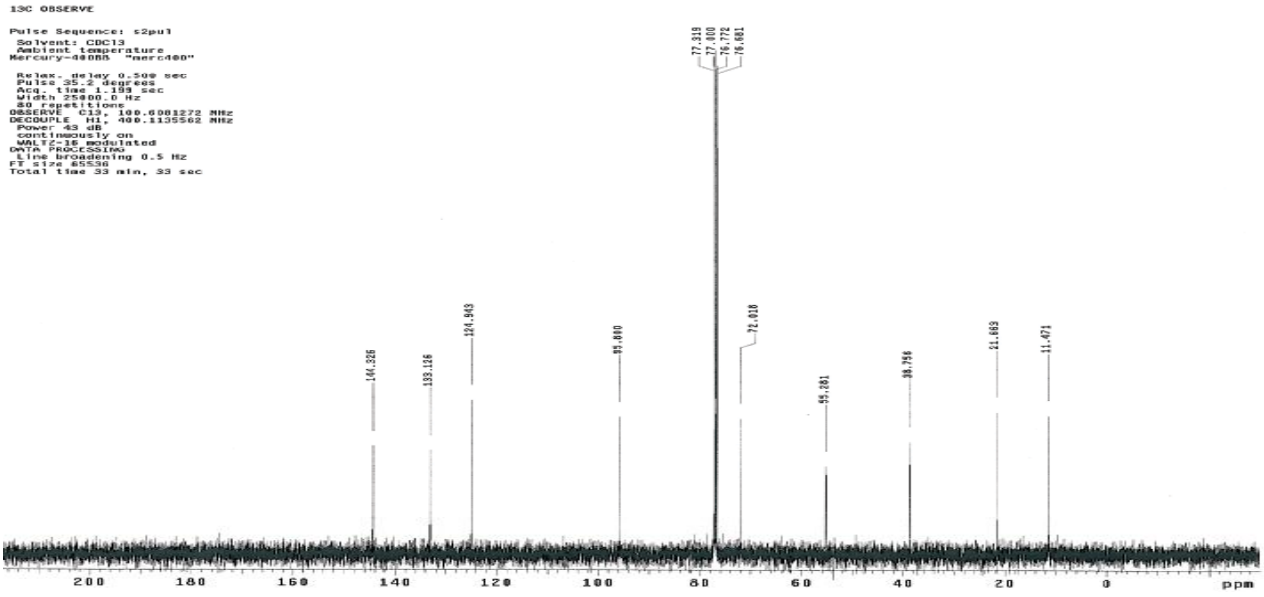

Ambient temperature
INOVA-500 "ui500"
Pulse 56.2 degrees
Acq. time 4.000 sec
Width 8000.0 Hz
24 repetitions
OBSERVE H1, 499.7485713 MHz
DATA PROCESSING
FT size 131072
Total time 1 hr, 25 min, 31 sec
12
10
8
6
4
2
0

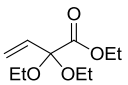

C13par
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
User: 1-15-07
INOVA-500 "ui500"
Relax. delay 0.500 sec
Pulse 33.3 degrees
Acq. time 1.500 sec
Width 33003.3 Hz
240 repetitions
OBSERVE C13, 125.6618808 MHz
DECOUPLE H1, 499.7505605 MHz
Power 42 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 2.0 Hz
FT size 131072
Total time 34 min, 17 sec
77.456
77.800
78.748
132.624
124.701
95.803
81.160
74.079
61.771
55.556
30.584
22.384
11.285
220
200
180
160
140
120
100
80
60
40
20
0
-20
ppm


OMe
O
I
Et

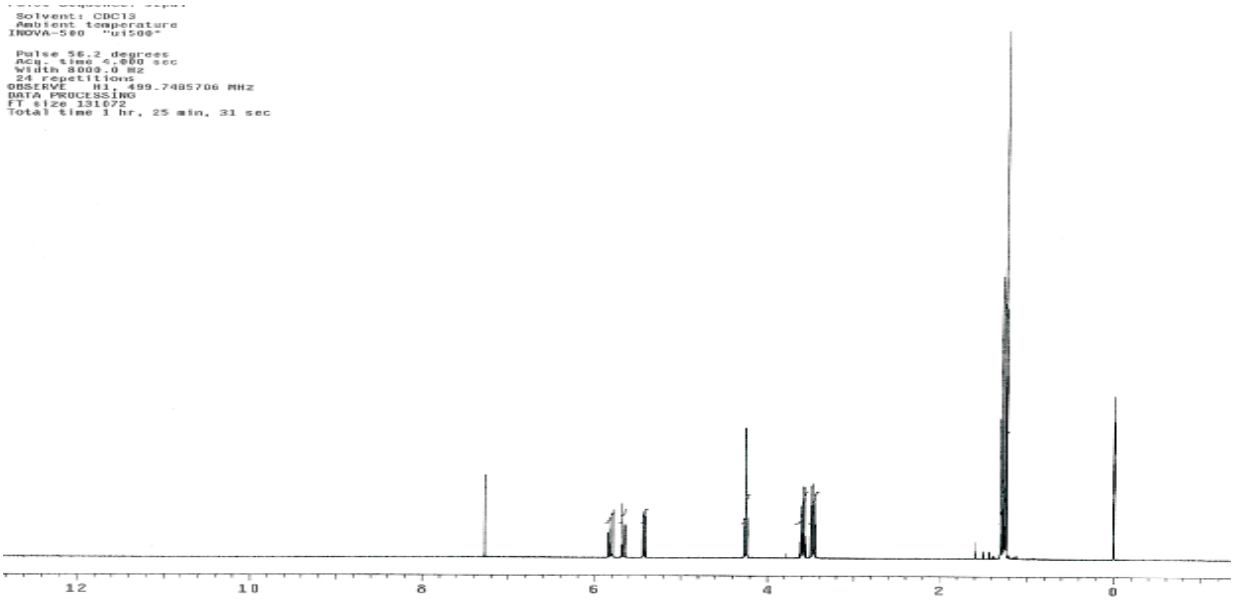
2

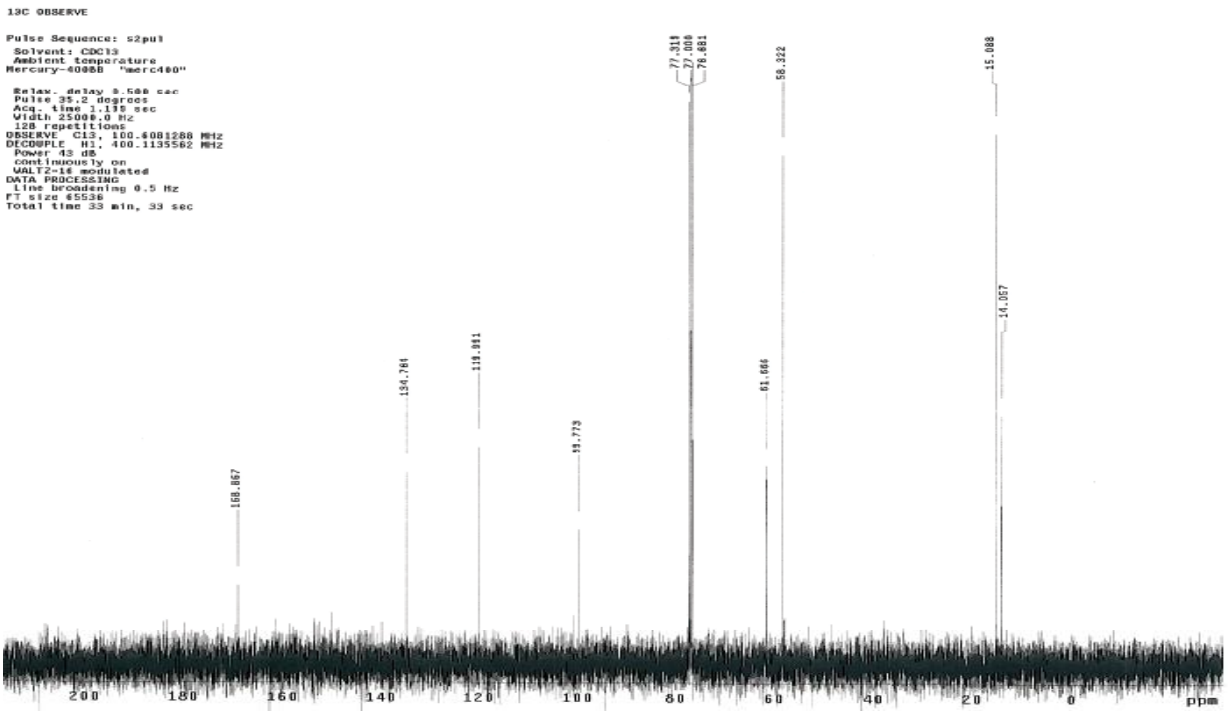

Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
Mercury-400BB "merc400"
Relax. delay 0.500 sec
Pulse 57.1 degrees
Acq. time 4.002 sec
Width 4997.5 Hz
40 repetitions
OBSERVE H1, 400.1115452 MHz
DATA PROCESSING
FT size 65536
Total time 0 min, 0 sec

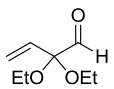

13C OBSERVE
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
Mercury-400BB "merc400"
Relax. delay 0.500 sec
Pulse 35.2 degrees
Acq. time 1.189 sec
Width 25400.0 Hz
80 repetitions
OBSERVE C13, 100.6081272 MHz
DECOUPLE H1, 400.1135562 MHz
Power 43 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 33 min, 33 sec
77.319
77.000
76.772
76.681
144.356
133.126
124.843
95.880
72.010
55.281
38.756
11.469
11.471
ppm


O
OEt
EtO
OEt

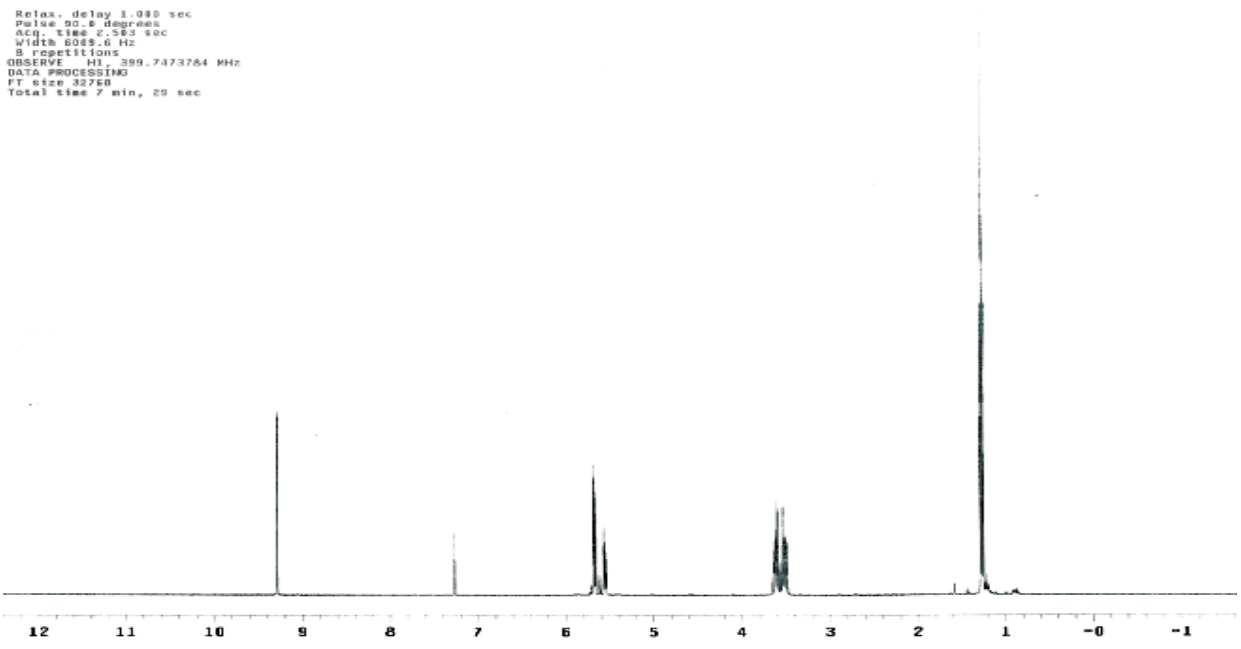
13a

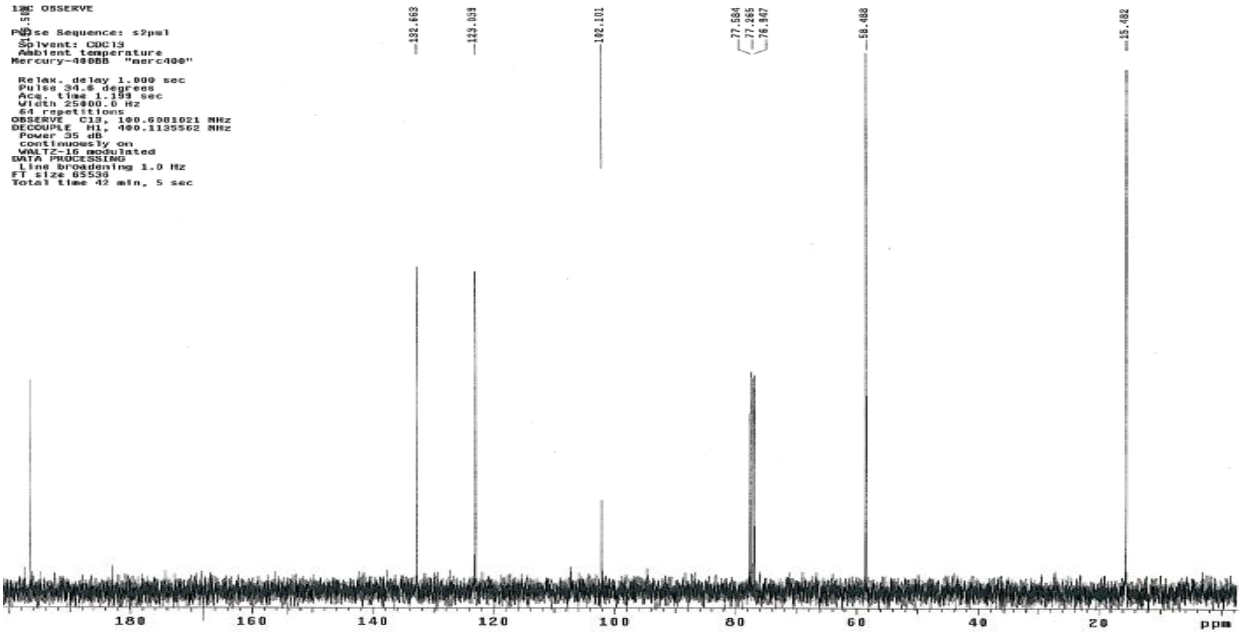

Solvent: CDCl3
Ambient temperature
INOVA-500 "u1500"
Pulse 56.2 degrees
Acq. time 4.000 sec
Width 8000.0 Hz
24 repetitions
OBSERVE H1, 499.7485706 MHz
DATA PROCESSING
FT size 131072
Total time 1 hr, 25 min, 31 sec
12
10
8
6
4
2
0

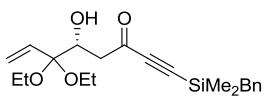

13C OBSERVE
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
Mercury-400BB "merc400"
Relax. delay 3.500 sec
Pulse 35.2 degrees
Acq. time 1.135 sec
Width 25000.0 Hz
128 repetitions
OBSERVE C13, 100.6081288 MHz
DECOUPLE H1, 400.1135562 MHz
Power 43 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 33 min, 33 sec
77.311
77.008
76.681
58.322
15.088
14.057
134.761
119.991
99.773
61.666
168.867
200
180
160
140
120
100
80
60
40
20
0
ppm


O
H
EtO
OEt

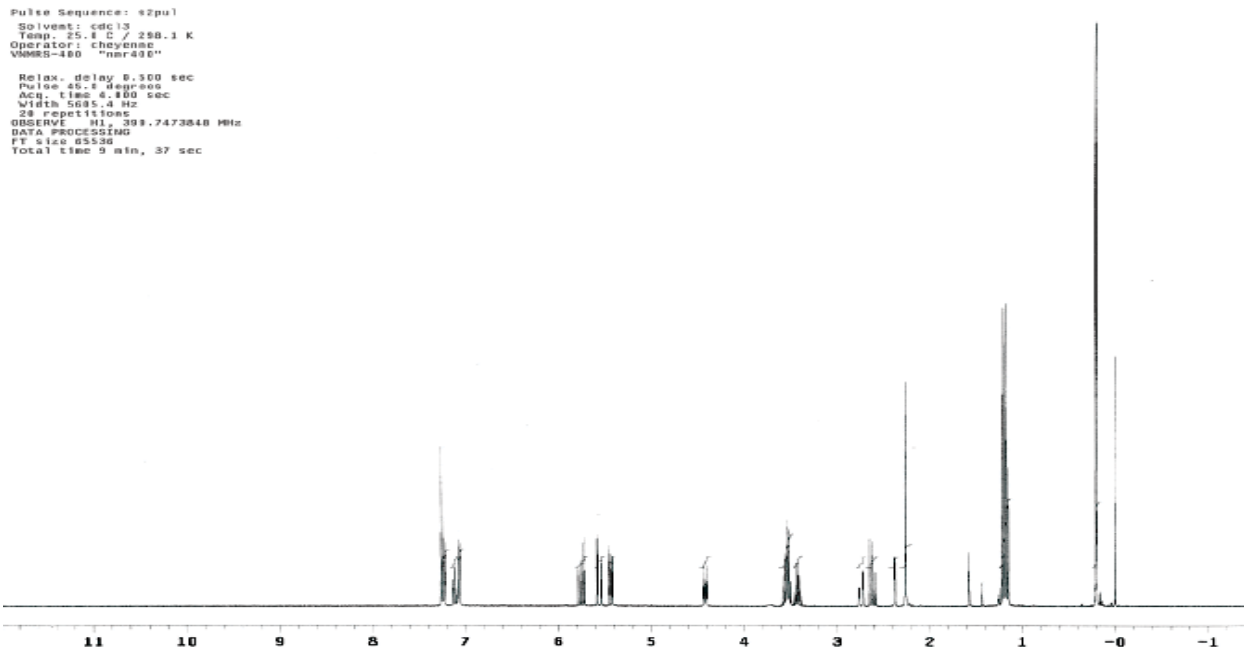
14

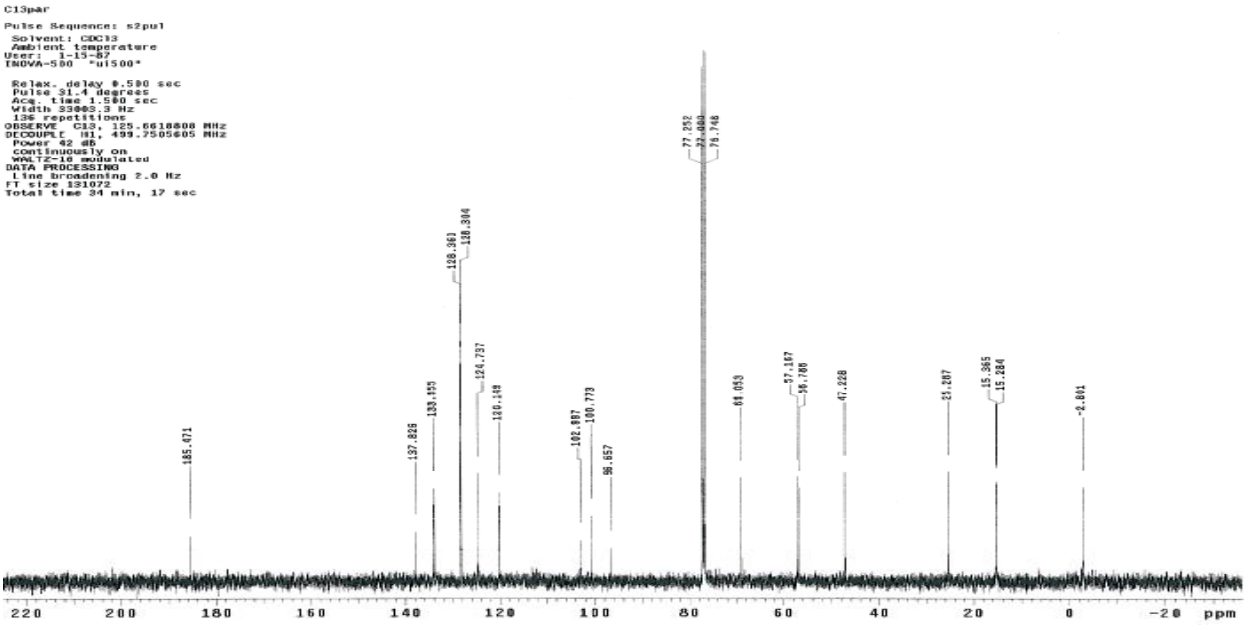

Relax. delay 1.000 sec
Pulse 90.0 degrees
Acq. time 2.583 sec
Width 6069.6 Hz
8 repetitions
OBSERVE H1, 399.7473784 MHz
DATA PROCESSING
FT size 32768
Total time 7 min, 29 sec
12
11
10
9
8
7
6
5
4
3
2
1
-0
-1

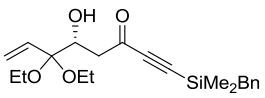

Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
Mercury-400BB "merc400"
Relax. delay 1.000 sec
Pulse 30.6 degrees
Acq. time 1.199 sec
Width 25000.0 Hz
64 repetitions
OBSERVE C13, 100.6081021 MHz
DECOUPLE H1, 400.1135562 MHz
Power 35 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 65536
Total time 42 min, 5 sec
182.693
169.809
102.101
77.584
77.365
76.947
58.488
15.482
180
160
140
120
100
80
60
40
20
ppm


OH
O
EtO
OEt
SiMe2Bn

16


Pulse Sequence: s2pul
Solvent: cdcl3
Temp. 25.8 C / 298.1 K
Operator: cheyenne
VNMRS-400 "nmr400"
Relax. delay 8.500 sec
Pulse 45.8 degrees
Acq. time 4.000 sec
Width 5605.4 Hz
28 repetitions
OBSERVE H1, 399.7473848 MHz
DATA PROCESSING
FT size 65536
Total time 9 min, 37 sec
11
10
9
8
7
6
5
4
3
2
1
-0
-1

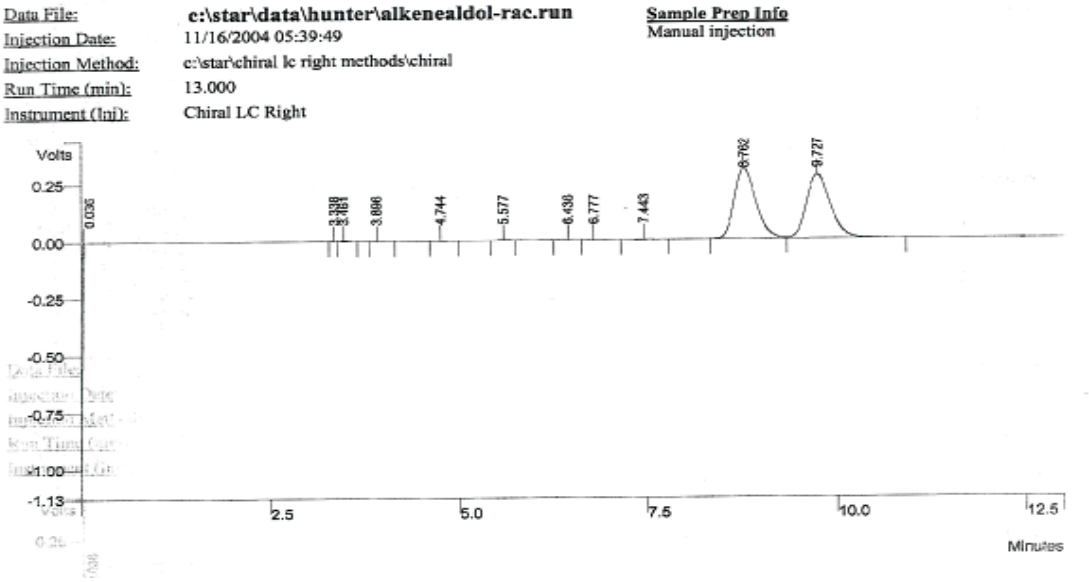

C13par
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
User: 1-15-87
INOVA-500 "ui500"
Relax. delay 8.590 sec
Pulse 31.4 degrees
Acq. time 1.580 sec
Width 33003.3 Hz
136 repetitions
OBSERVE C13, 125.6618808 MHz
DECOUPLE H1, 499.7505605 MHz
Power 42 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
line broadening 2.0 Hz
FT size 131072
Total time 34 min, 17 sec
185.471
137.828
133.155
128.361
128.304
124.737
120.148
102.897
100.773
86.657
77.252
77.000
76.748
64.053
57.187
56.780
47.228
21.287
15.365
15.284
-2.891
220
200
180
160
140
120
100
80
60
40
20
0
-20
ppm



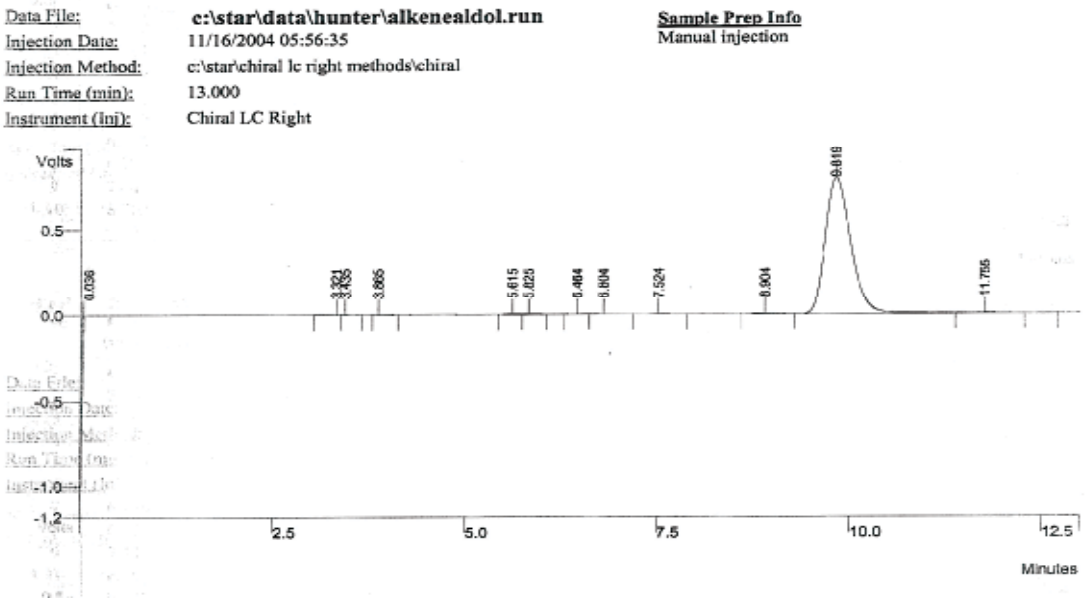
16

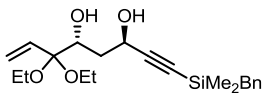
HPLC Conditions: OD column, 98:2 heptane:isopropanol, 1.0 mL/min, 254 nm

racemic:

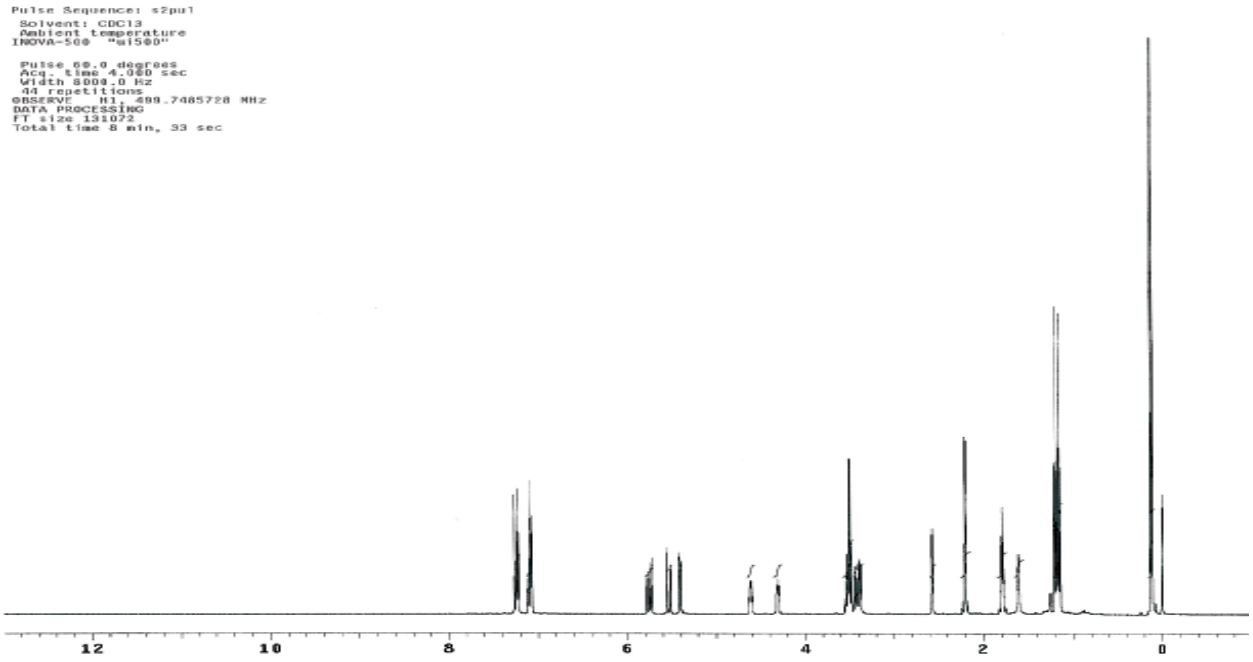


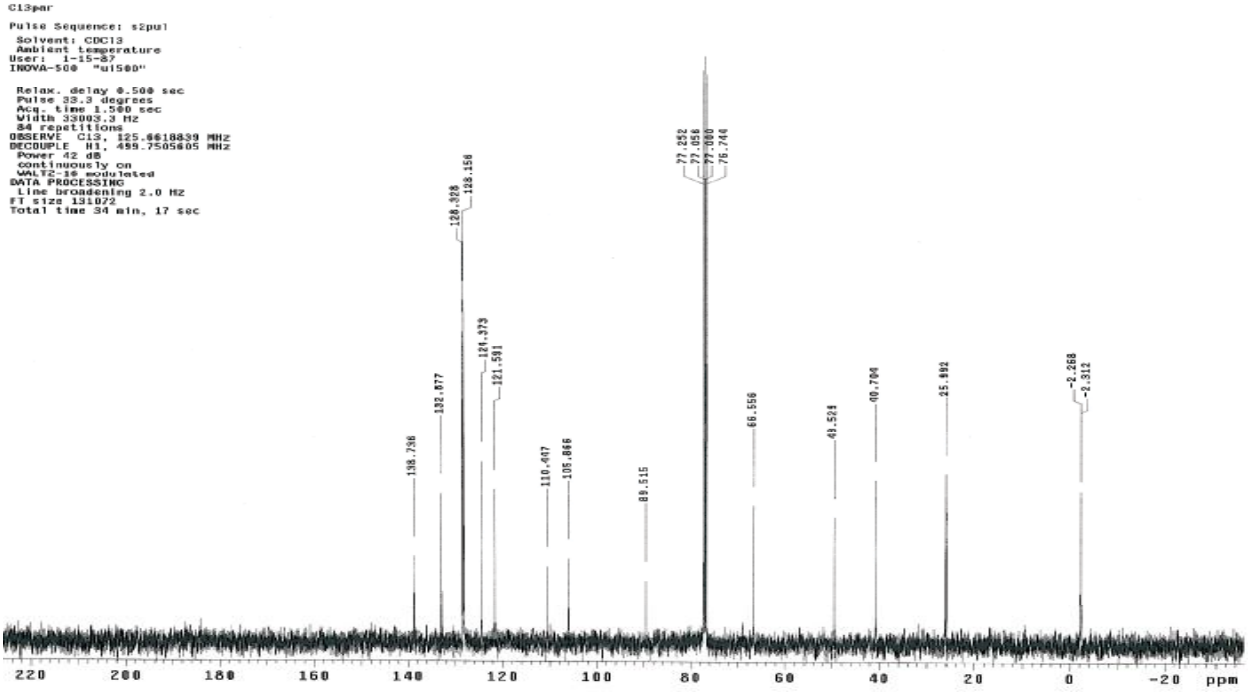
99% ee:

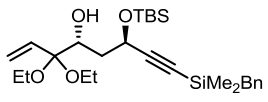



OH
OH
EtO
OEt
SiMe2Bn

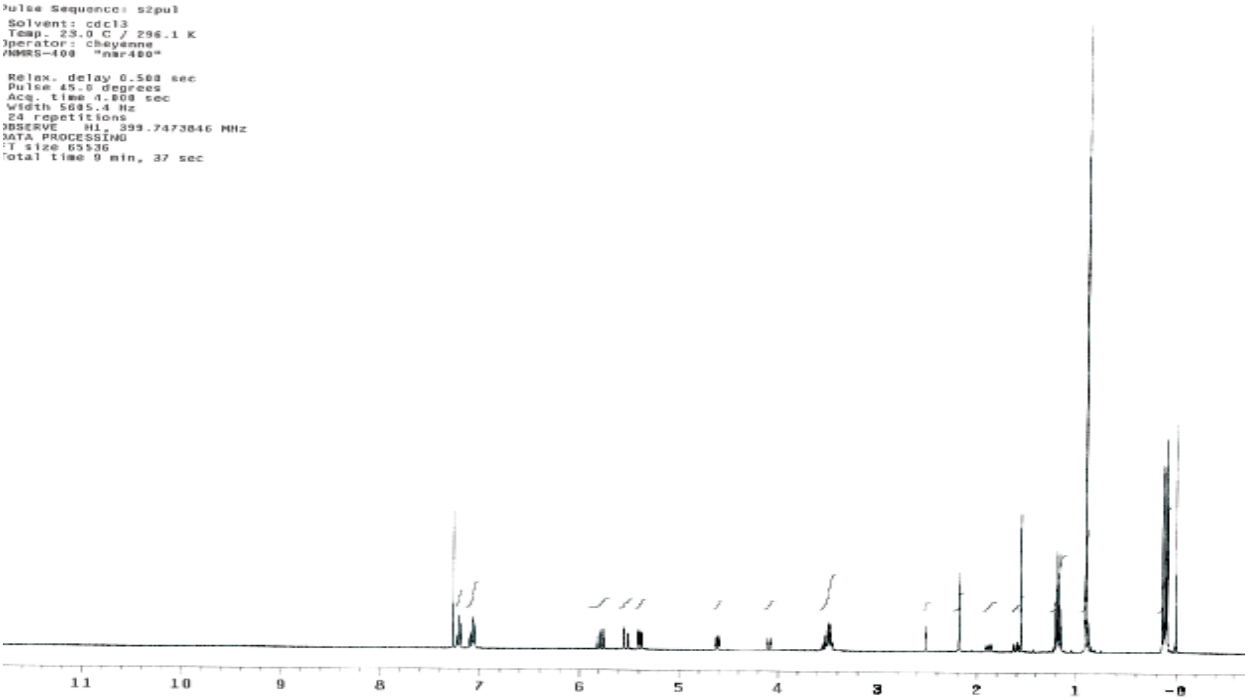
16a

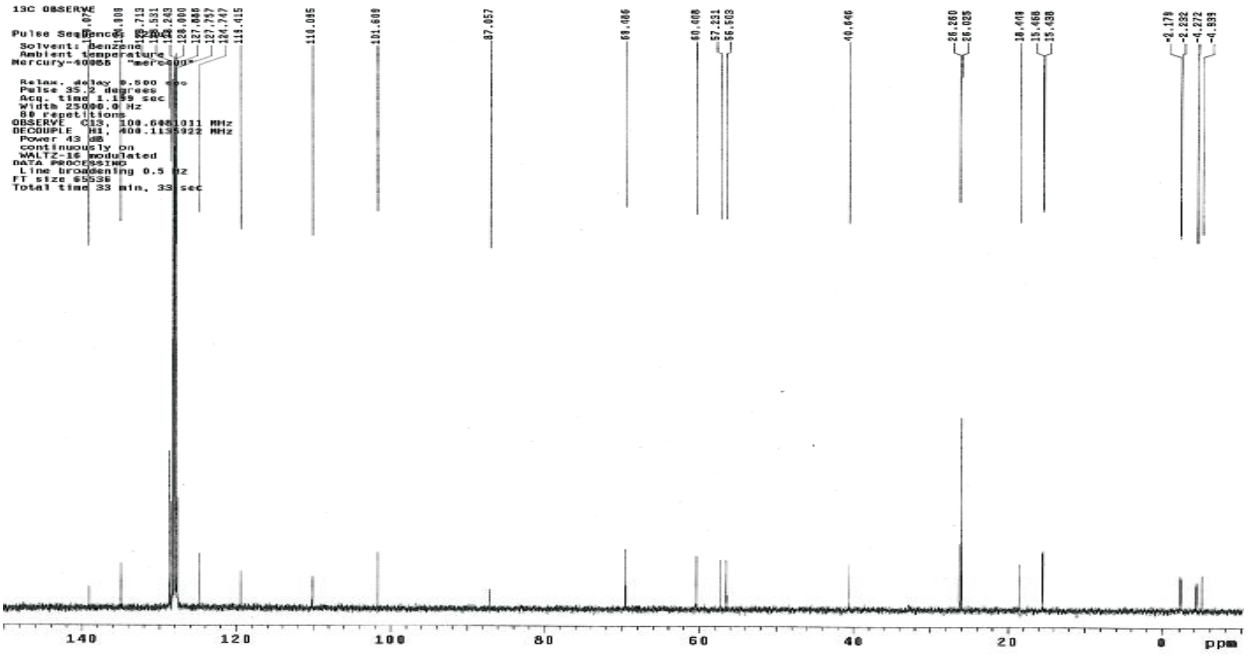

Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
INOVA-500 "ul500"
Pulse 60.0 degrees
Acq. time 4.980 sec
Width 8000.0 Hz
44 repetitions
OBSERVE H1, 499.7485728 MHz
DATA PROCESSING
FT size 131072
Total time 8 min, 33 sec
12
10
8
6
4
2
0

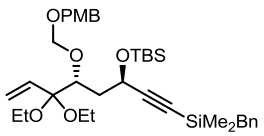

C13par
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
User: 1-15-87
INOVA-500 "ul500"
Relax. delay 0.500 sec
Pulse 33.3 degrees
Acq. time 1.500 sec
Width 33003.3 Hz
84 repetitions
OBSERVE C13, 125.6618839 MHz
DECOUPLE H1, 499.7505605 MHz
Power 42 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 2.0 Hz
FT size 131072
Total time 34 min, 17 sec
138.736
132.877
128.308
128.156
124.373
121.591
110.647
105.866
89.515
77.252
77.056
77.000
76.744
68.556
49.529
40.704
25.892
-2.268
-2.312
220
200
180
160
140
120
100
80
60
40
20
0
-20
ppm


OH
OTBS
EtO
OEt
SiMe2Bn

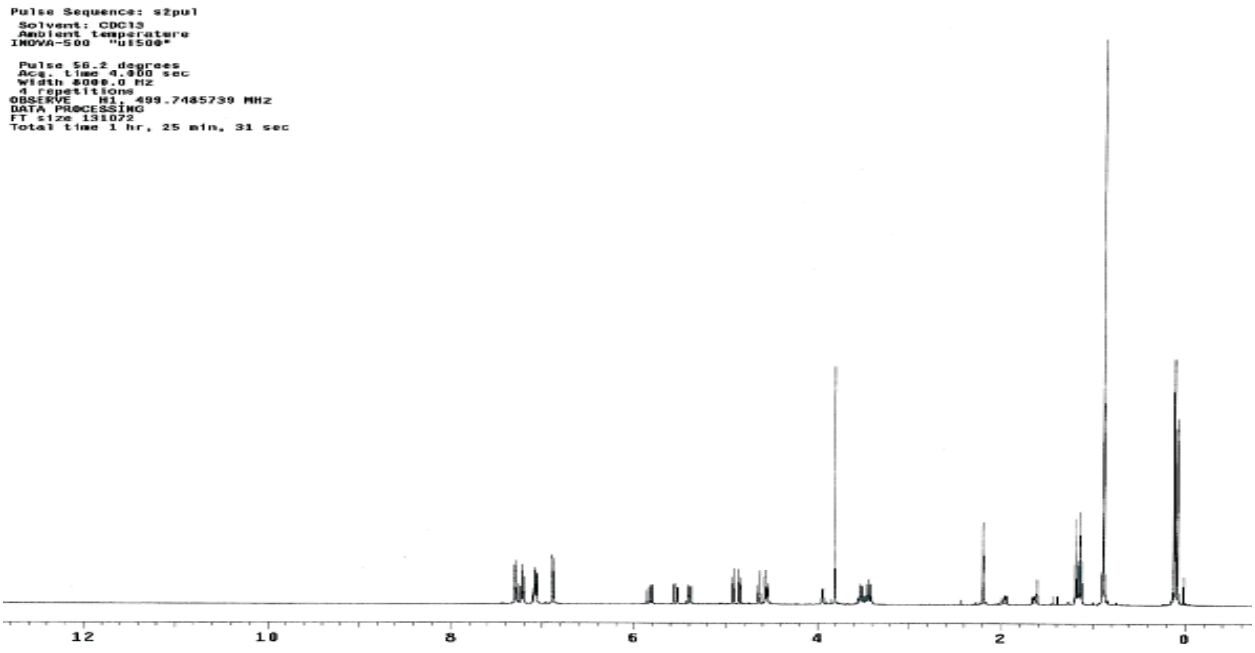
17

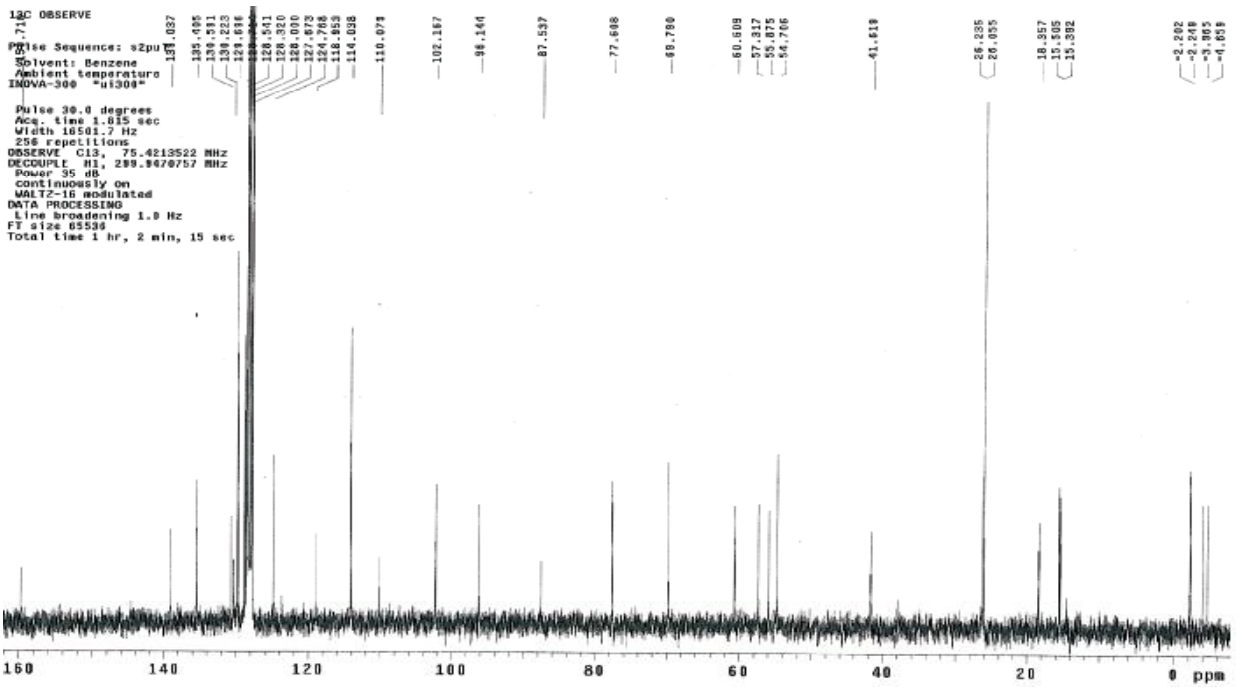

Pulse Sequence: s2pul
Solvent: cdcl3
Temp. 23.0 C / 296.1 K
Operator: cheyenne
VNMRS-400 "nmr400"
Relax. delay 0.500 sec
Pulse 45.0 degrees
Acq. time 4.808 sec
Width 5005.4 Hz
24 repetitions
OBSERVE H1, 399.7473846 MHz
DATA PROCESSING
FT size 65536
Total time 0 min, 37 sec
11
10
9
8
7
6
5
4
3
2
1
0

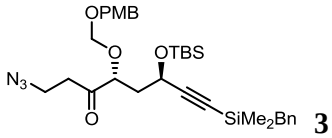

13C OBSERVE
Pulse Sequence: s2pul
Solvent: Benzene
Ambient temperature
Mercury-400BB "merc400"
Relax. delay 5.000 sec
Pulse 35.2 degrees
Acq. time 1.159 sec
Width 25000.0 Hz
80 repetitions
OBSERVE C13, 100.6481031 MHz
DECOUPLE H1, 400.1135922 MHz
Power 43 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 33 min, 33 sec
140
120
100
80
60
40
20
0
ppm


OPMB
O
OTBS
EtO
OEt
SiMe2Bn

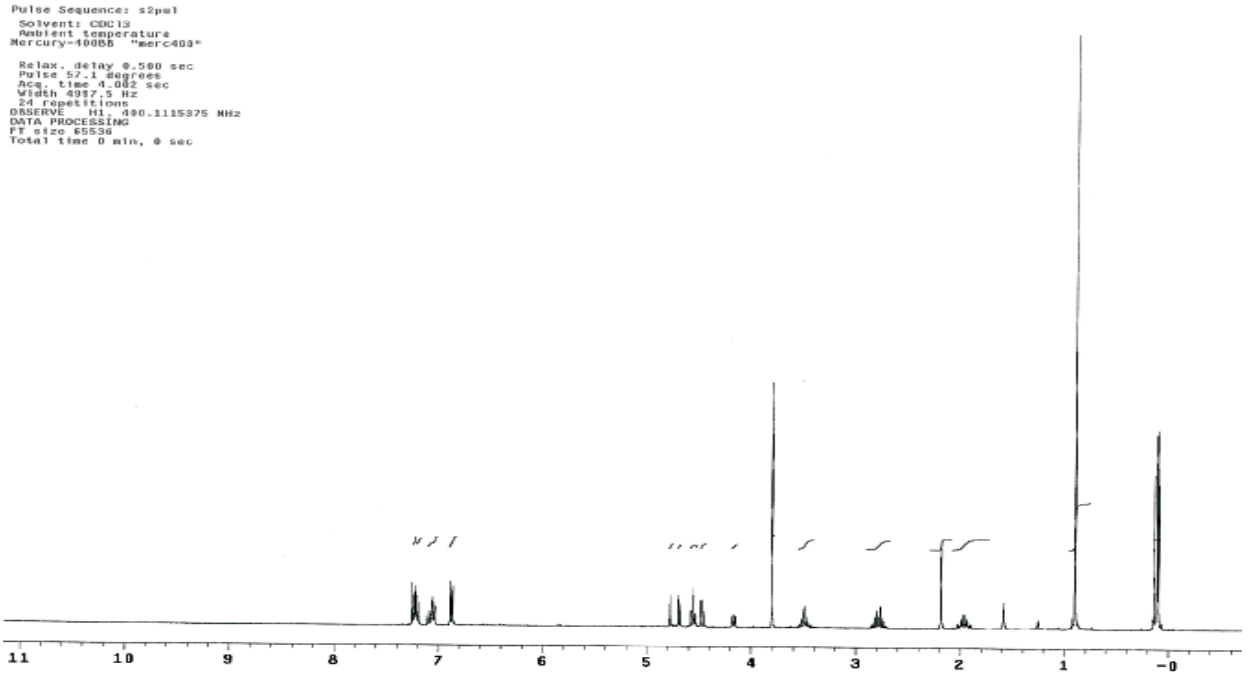
19

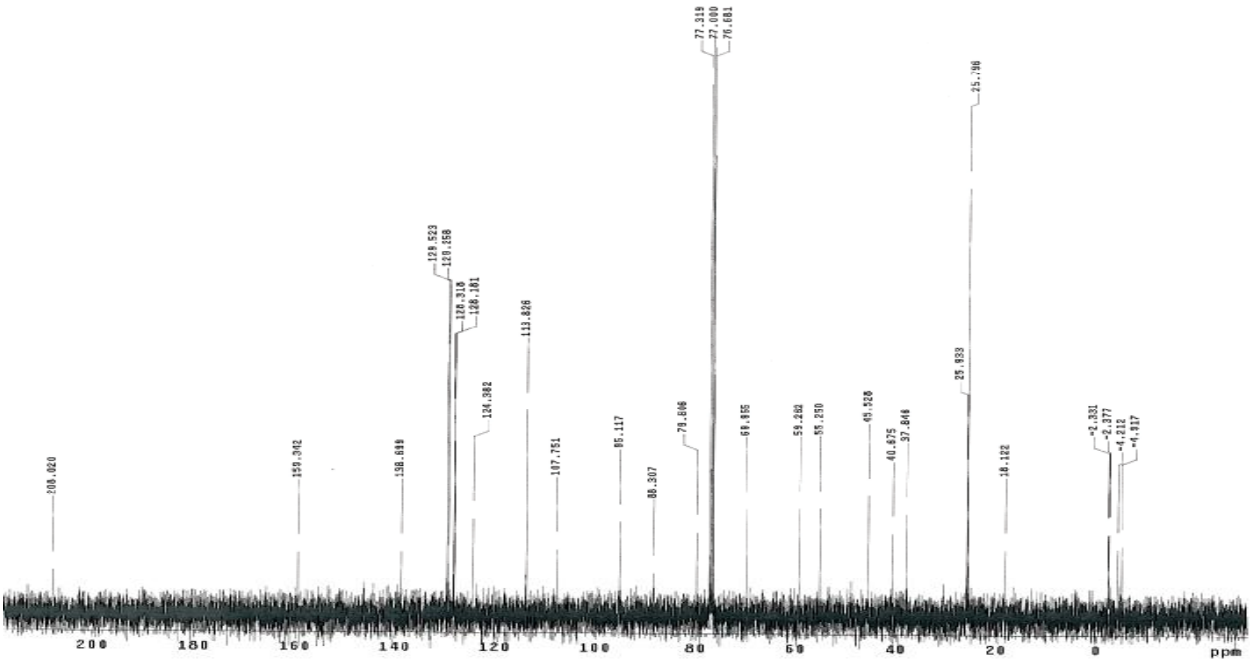

Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
INOVA-500 "ui500"
Pulse 56.2 degrees
Acq. time 4.000 sec
Width 4000.0 Hz
8 repetitions
OBSERVE H1, 499.7485739 MHz
DATA PROCESSING
FT size 131072
Total time 1 hr, 25 min, 31 sec
12
10
8
6
4
2
0

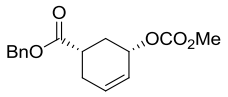

13C OBSERVE
Pulse Sequence: s2pu
Solvent: Benzene
Ambient temperature
INOVA-300 "ui300"
Pulse 30.0 degrees
Acq. time 1.815 sec
Width 18501.7 Hz
256 repetitions
OBSERVE C13, 75.4213522 MHz
DECOUPLE H1, 299.9470757 MHz
Power 35 dB
continuously On
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 65536
Total time 1 hr, 2 min, 15 sec
160
140
120
100
80
60
40
20
0 ppm


OPMB
O
OTBS
N3
O
SiMe2Bn

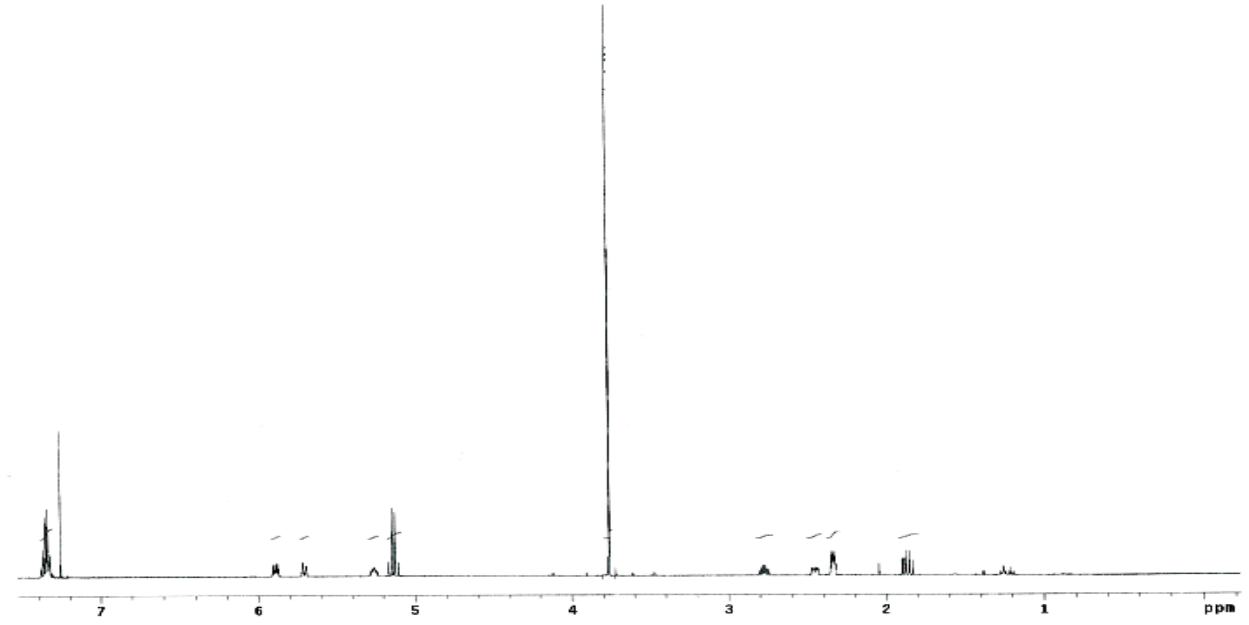
3

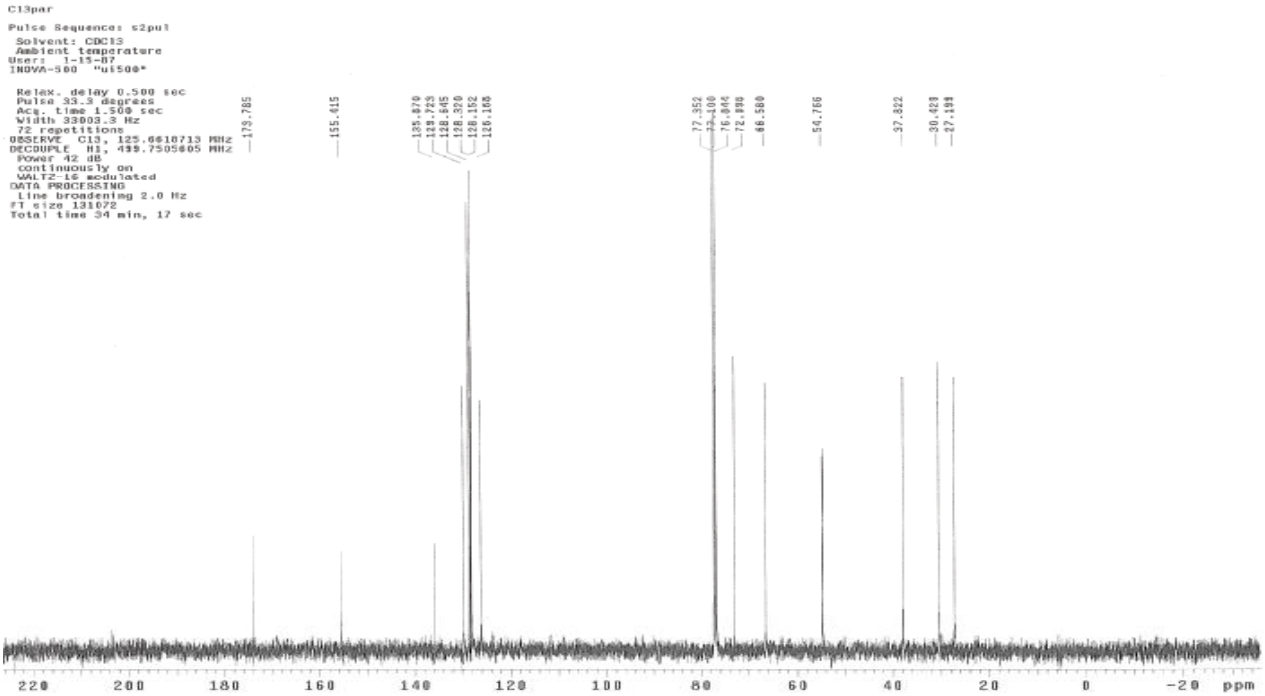

Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
Mercury-400BB "merc400"
Relax. delay 0.500 sec
Pulse 57.1 degrees
Acq. time 4.002 sec
Width 4937.5 Hz
24 repetitions
OBSERVE H1, 400.1115375 MHz
DATA PROCESSING
FT size 65536
Total time 0 min, 0 sec
11
10
9
8
7
6
5
4
3
2
1
-0

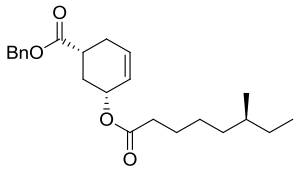

77.319
77.000
76.681
129.523
128.858
128.316
128.161
133.826
124.382
107.751
85.117
80.307
79.696
69.855
59.269
55.250
43.526
40.675
37.844
25.798
25.033
18.182
-2.331
-2.377
-4.212
-4.817
198.020
159.342
138.688
200
180
160
140
120
100
80
60
40
20
0
ppm


O
BnO
OCO2Me

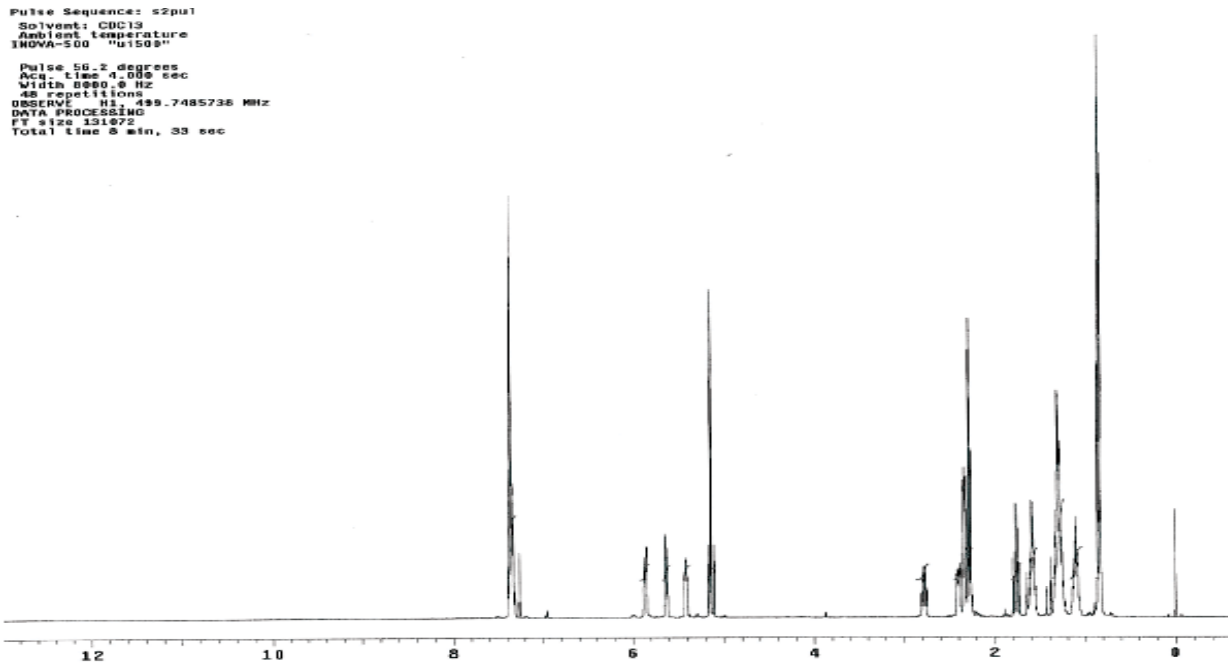
21

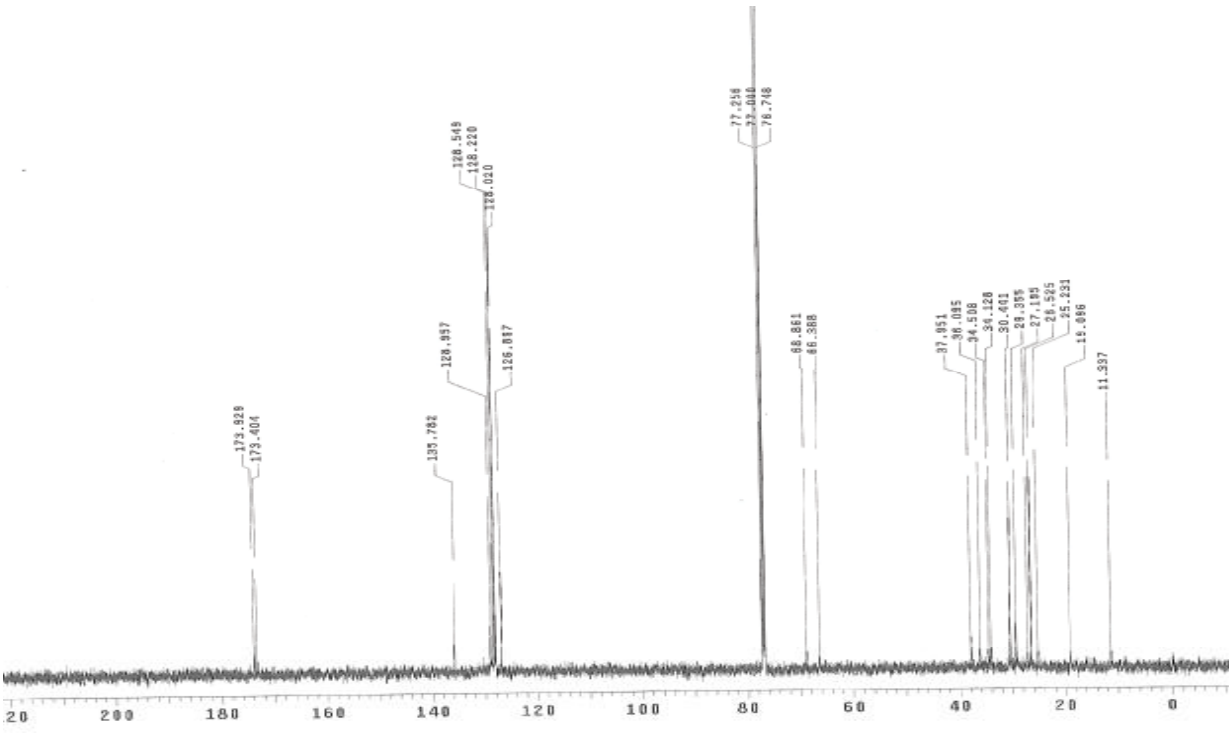

7
6
5
4
3
2
1
ppm

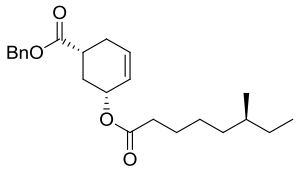

C13par
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
User: 1-15-07
INOVA-500 "ui500"
Relax. delay 0.500 sec
Pulse 33.3 degrees
Acq. time 1.500 sec
Width 33003.3 Hz
72 repetitions
OBSERVE C13, 125.6610713 MHz
DECOUPLE H1, 499.7505605 MHz
Power 42 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
line broadening 2.0 Hz
FT size 131072
Total time 34 min, 17 sec
170.785
155.415
135.870
129.725
128.545
128.320
128.152
126.168
77.352
77.100
76.844
72.898
66.580
54.766
37.822
30.428
27.194
220
200
180
160
140
120
100
80
60
40
20
0
-20
ppm



23


Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
INOVA-500 "u1509"
Pulse 56.2 degrees
Acq. time 4.000 sec
Width 8000.0 Hz
48 repetitions
OBSERVE H1, 499.7485738 MHz
DATA PROCESSING
FT size 131072
Total time 8 min, 33 sec
12
10
8
6
4
2
0

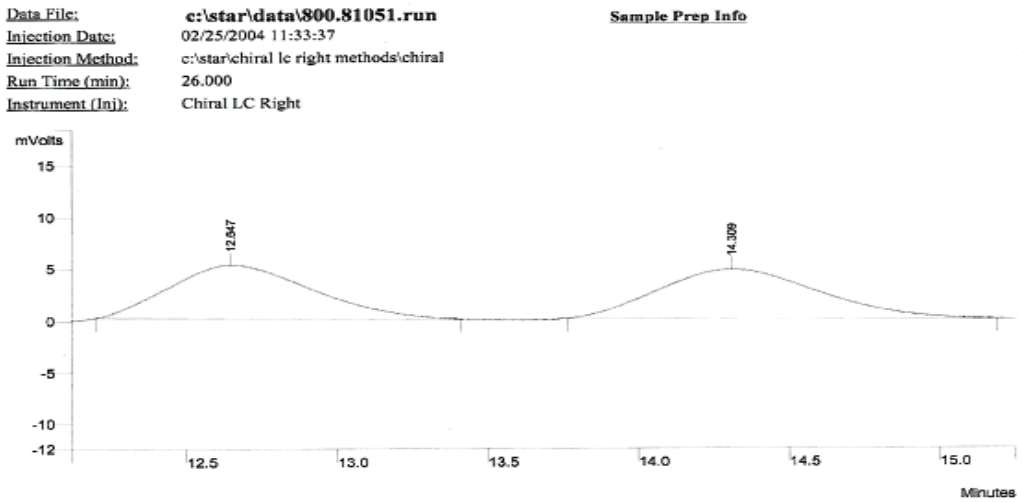

173.928
173.404
135.782
129.937
128.549
128.220
128.020
126.817
77.256
77.000
76.748
68.861
66.388
37.951
36.095
34.508
34.128
30.461
29.955
27.185
26.525
25.231
19.086
11.597
200
180
160
140
120
100
80
60
40
20
0



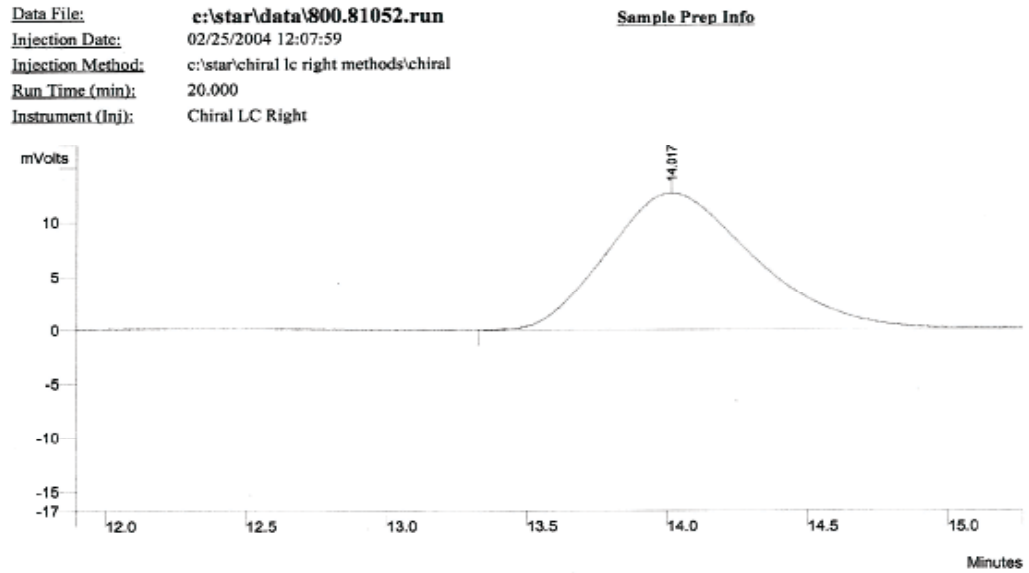
23

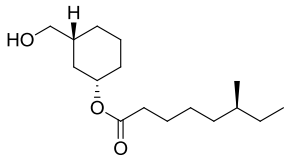
HPLC Conditions: OD column, 99:1 heptane:isopropanol, 1.0 mL/min, 254 nm

racemic:

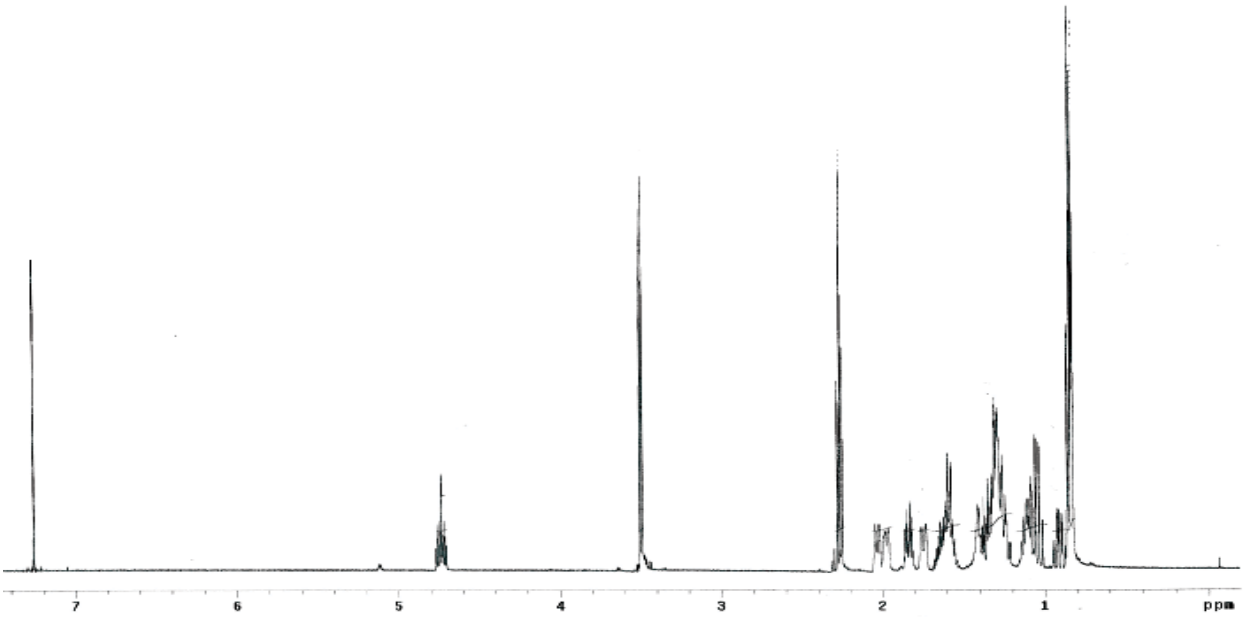


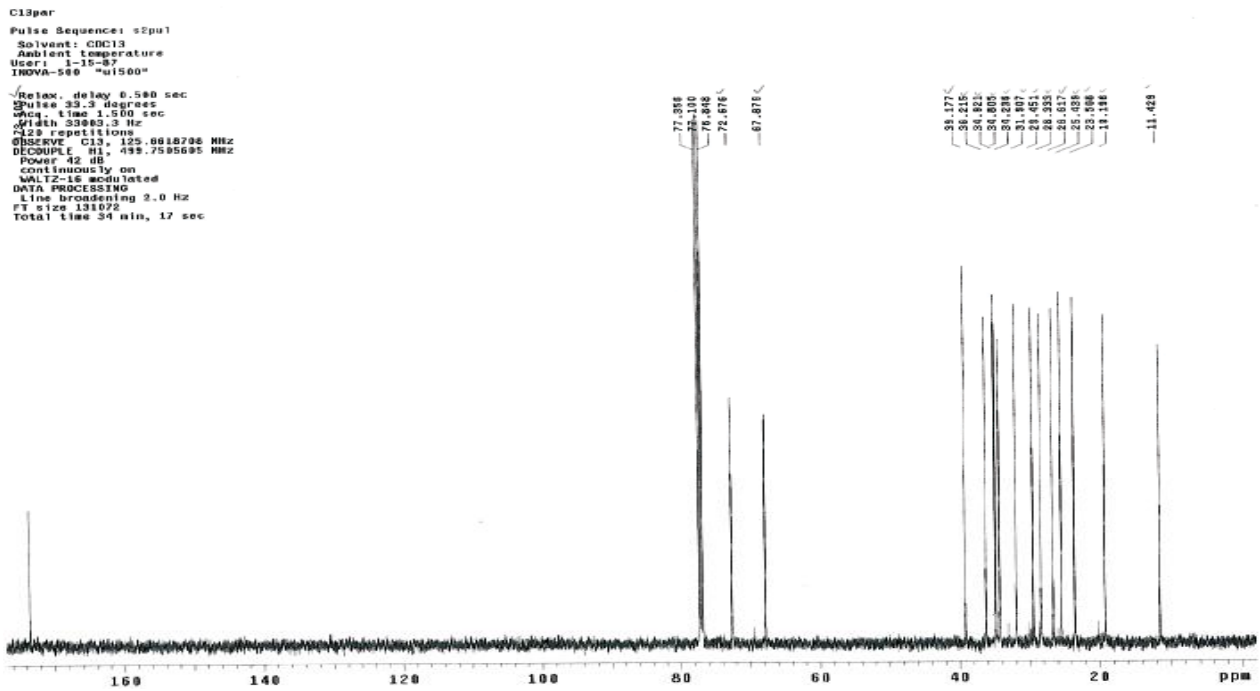
99% ee:

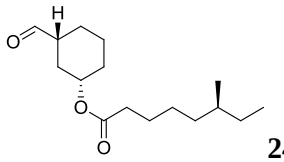



H
HO
O
O

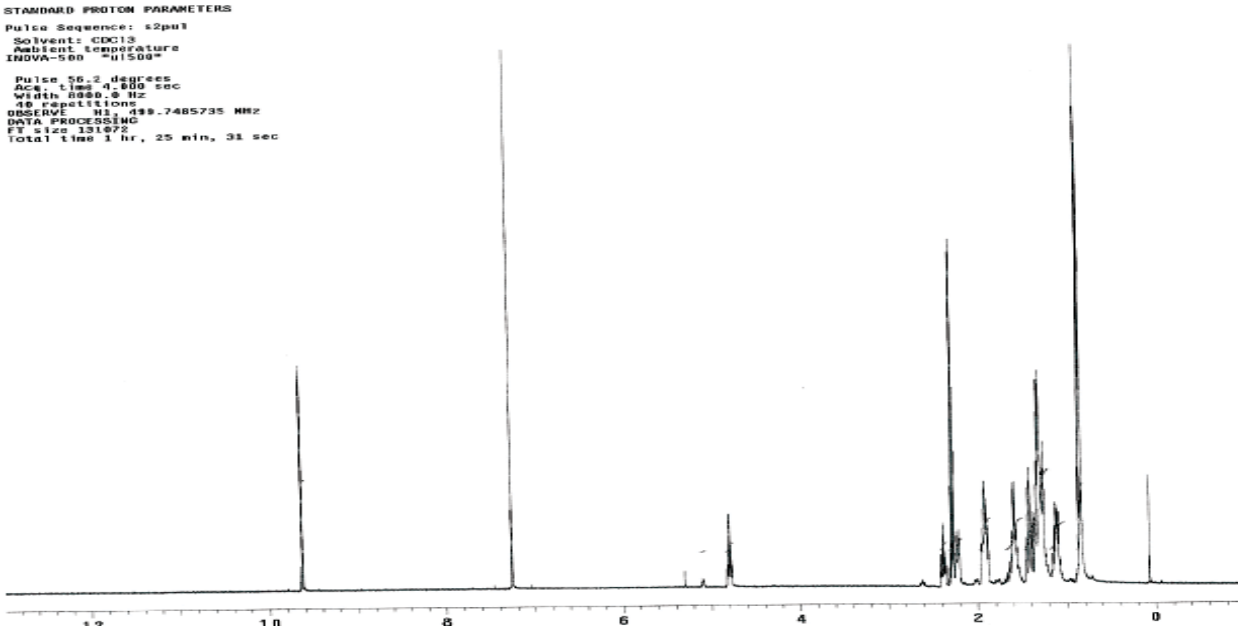
24

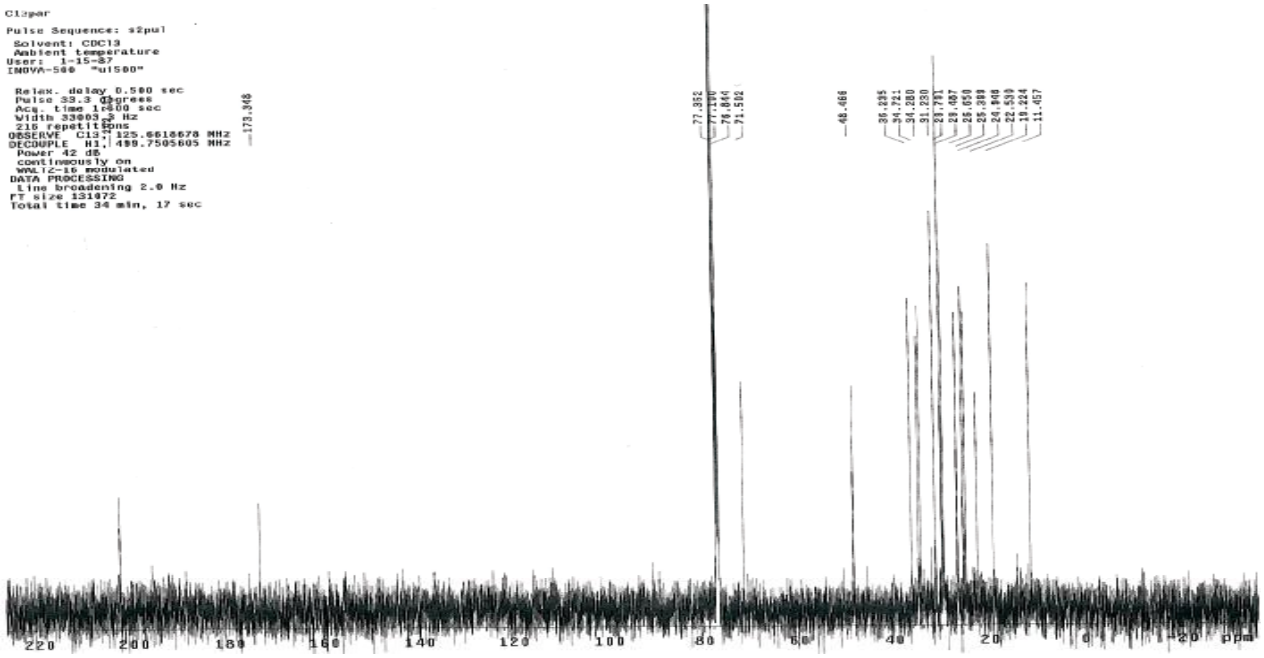

7
6
5
4
3
2
1
ppm

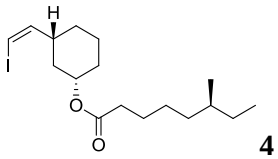

C13par
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
User: 1-15-07
INOVA-500 "wl500"
Relax. delay 0.500 sec
Pulse 33.3 degrees
Acq. time 1.500 sec
Width 33003.3 Hz
128 repetitions
OBSERVE C13, 125.8818706 MHz
DECOUPLE H1, 499.7595695 MHz
Power 42 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 2.0 Hz
FT size 131072
Total time 34 min, 17 sec
77.358
77.100
76.842
72.676
67.878
59.177
56.215
54.821
54.805
50.298
31.807
29.451
28.935
26.617
25.438
23.508
19.148
11.428
160
140
120
100
80
60
40
20
ppm



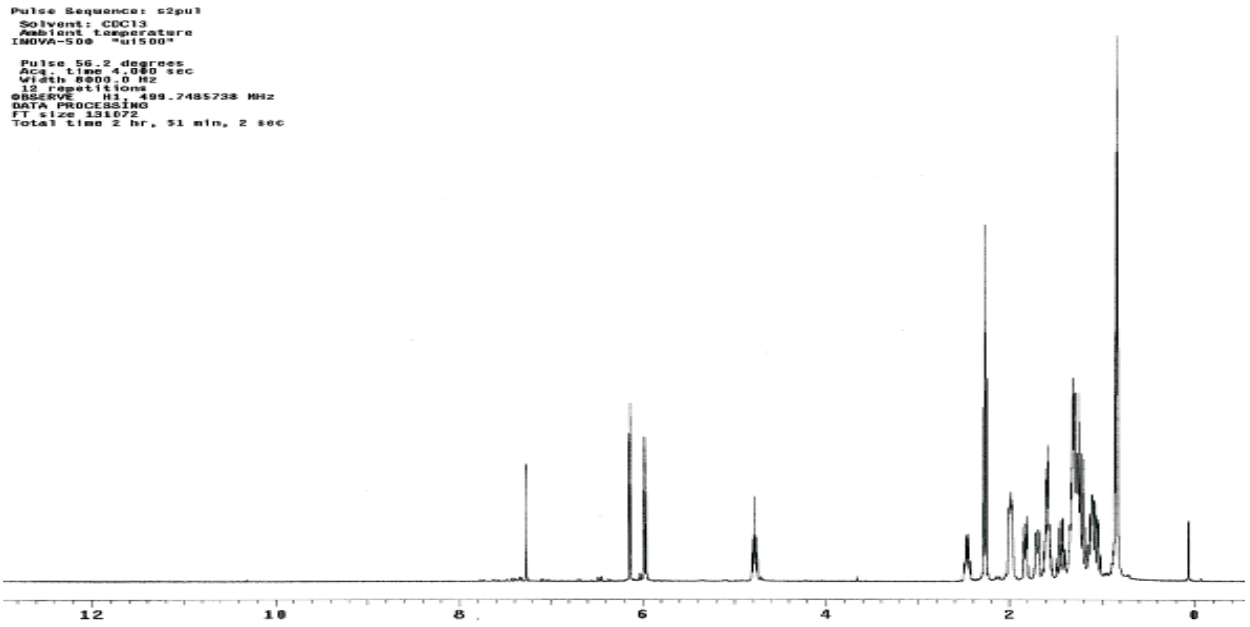
24a

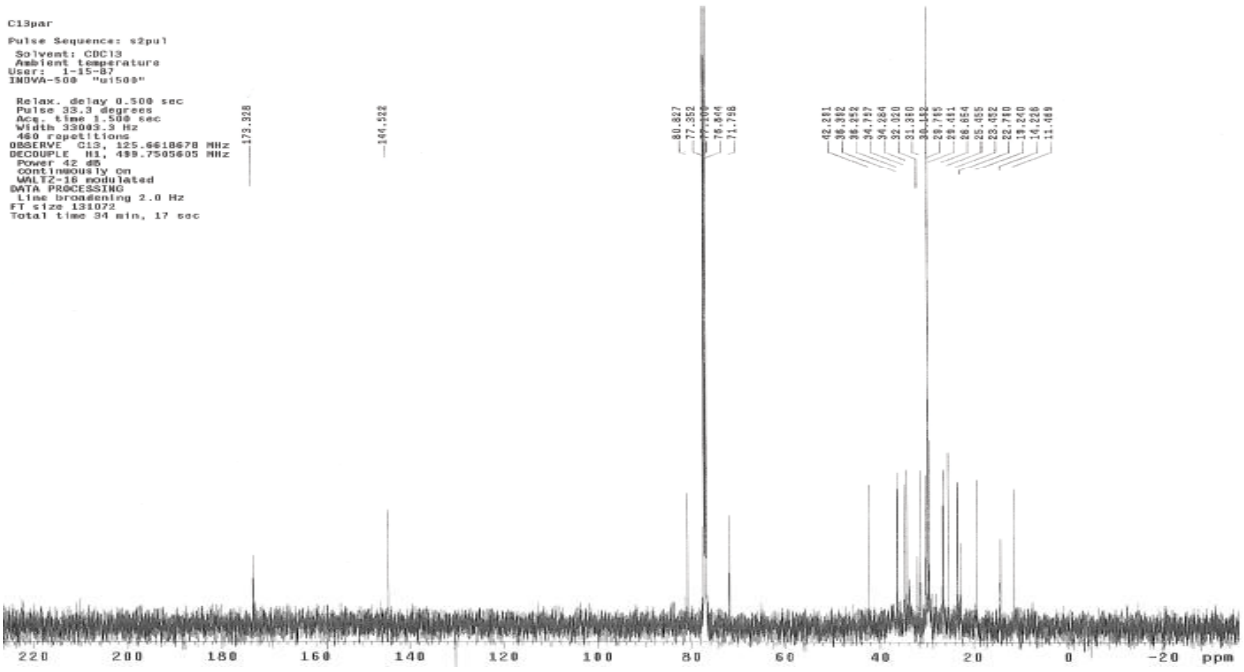

STANDARD PROTON PARAMETERS
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
INOVA-500 "ul500"
Pulse 56.2 degrees
Acq. time 4.000 sec
Width 8000.0 Hz
40 repetitions
OBSERVE H1, 499.7485735 MHz
DATA PROCESSING
FT size 131072
Total time 1 hr, 25 min, 31 sec

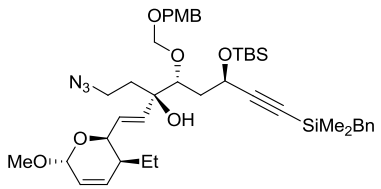

Clapar
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
User: 1-15-87
INOVA-500 "ul500"
Relax. delay 0.500 sec
Pulse 33.3 degrees
Acq. time 1.600 sec
Width 33003.3 Hz
216 repetitions
OBSERVE C13, 125.6618678 MHz
DECOUPLE H1, 499.7505605 MHz
Power 42 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 2.0 Hz
FT size 131072
Total time 34 min, 17 sec
173.348
77.352
77.100
76.844
71.582
48.466
36.235
34.721
34.280
31.230
28.791
28.487
25.650
25.389
24.848
22.539
19.224
11.457



4

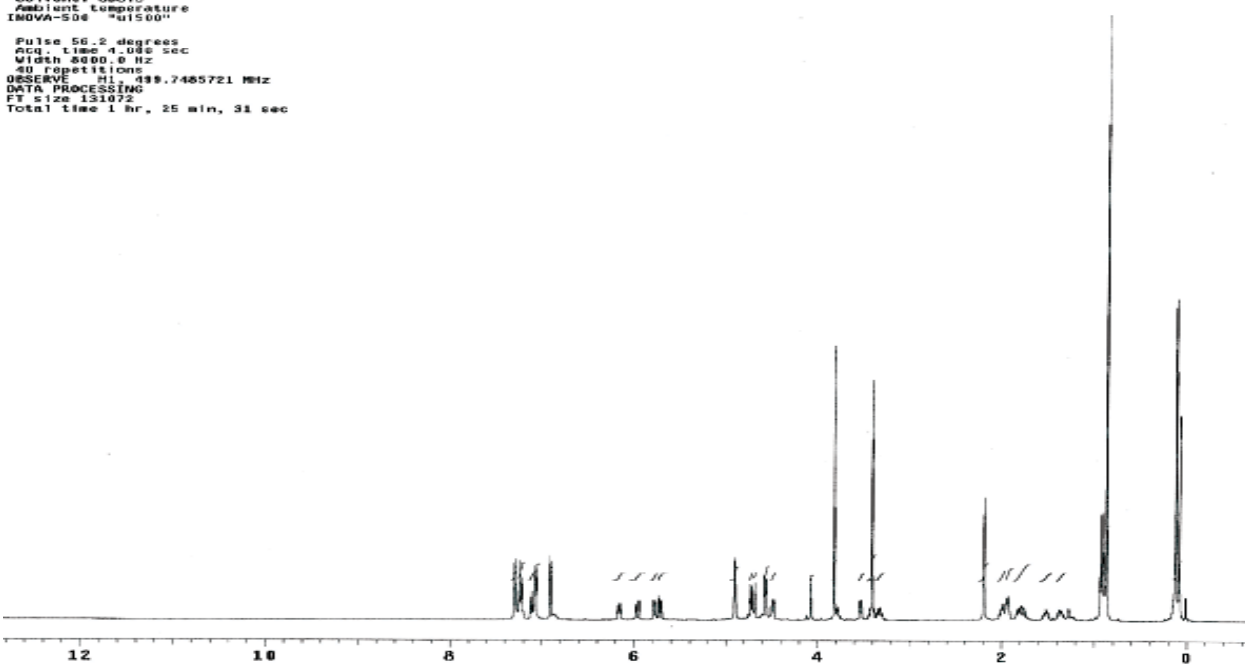

Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
INOVA-500 "u1500"
Pulse 56.2 degrees
Acq. time 4.000 sec
Width 6000.0 Hz
12 repetitions
OBSERVE H1, 499.7485738 MHz
DATA PROCESSING
FT size 131072
Total time 2 hr, 51 min, 2 sec
12
10
8
6
4
2
0


C13par
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
User: 1-15-87
INOVA-500 "u1500"
Relax. delay 0.500 sec
Pulse 33.3 degrees
Acq. time 1.500 sec
Width 33003.3 Hz
460 repetitions
OBSERVE C13, 125.6618678 MHz
DECOUPLE H1, 499.7505605 MHz
Power 42 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 2.0 Hz
FT size 131072
Total time 34 min, 17 sec
173.328
144.328
80.827
77.352
77.100
76.844
71.798
42.281
38.382
36.852
34.797
34.284
32.920
31.380
29.795
29.411
28.854
25.955
23.482
22.710
19.240
14.226
11.489
220
200
180
160
140
120
100
80
60
40
20
0
-20
ppm

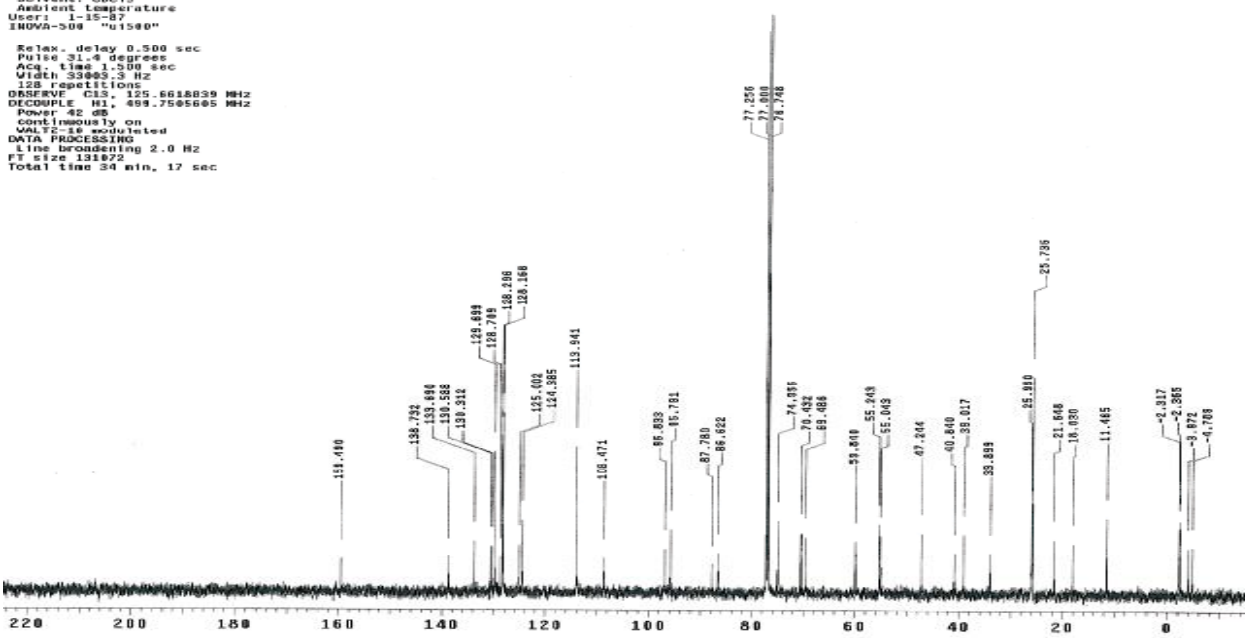


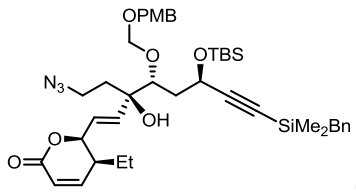
26

```
Pulse Sequence: s2pul
 Solvent: CDCl3
 Ambient temperature
INOVA-500  "u1500"

 Pulse 56.2 degrees
 Acq. time 4.000 sec
 Width 8000.0 Hz
  40 repetitions
OBSERVE   H1, 499.7485721 MHz
DATA PROCESSING
FT size 131072
Total time 1 hr, 25 min, 31 sec
```



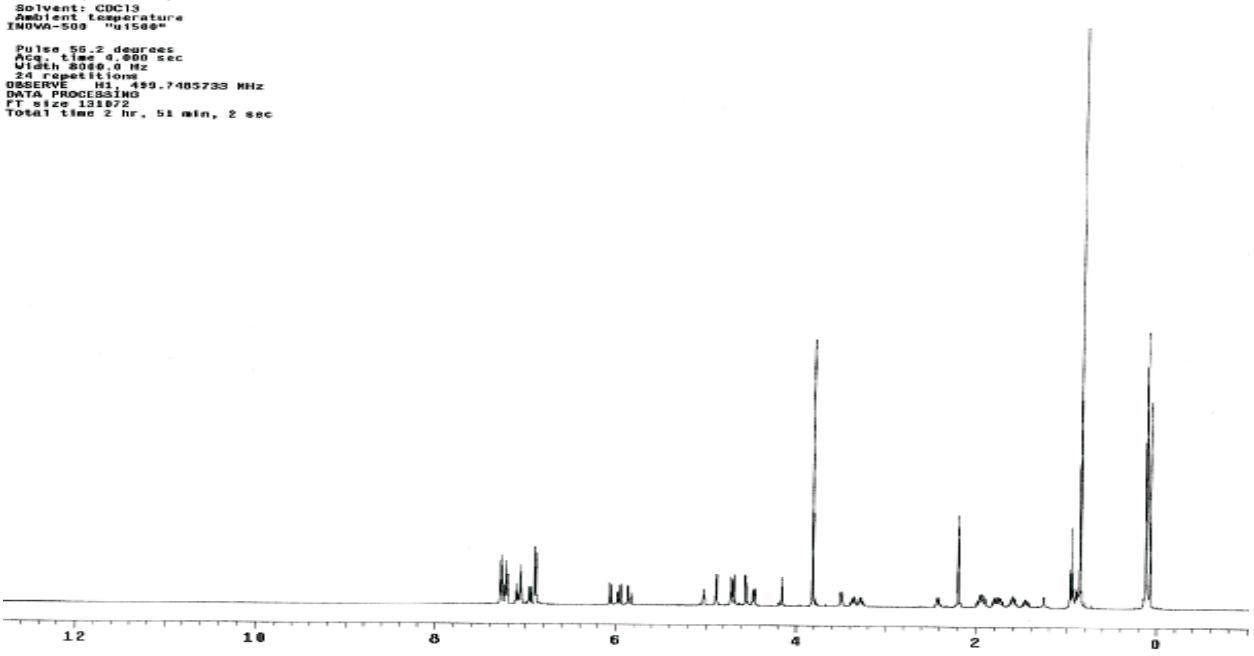

```
Pulse Sequence: s2pul
 Solvent: CDCl3
 Ambient temperature
User:  1-15-87
INOVA-500  "u1500"

 Relax. delay 0.500 sec
 Pulse 31.4 degrees
 Acq. time 1.500 sec
 Width 33003.3 Hz
  128 repetitions
OBSERVE   C13, 125.6618839 MHz
DECOUPLE   H1, 499.7505605 MHz
 Power 42 dB
 continuously on
 WALTZ-16 modulated
DATA PROCESSING
 Line broadening 2.0 Hz
FT size 131072
Total time 34 min, 17 sec
```



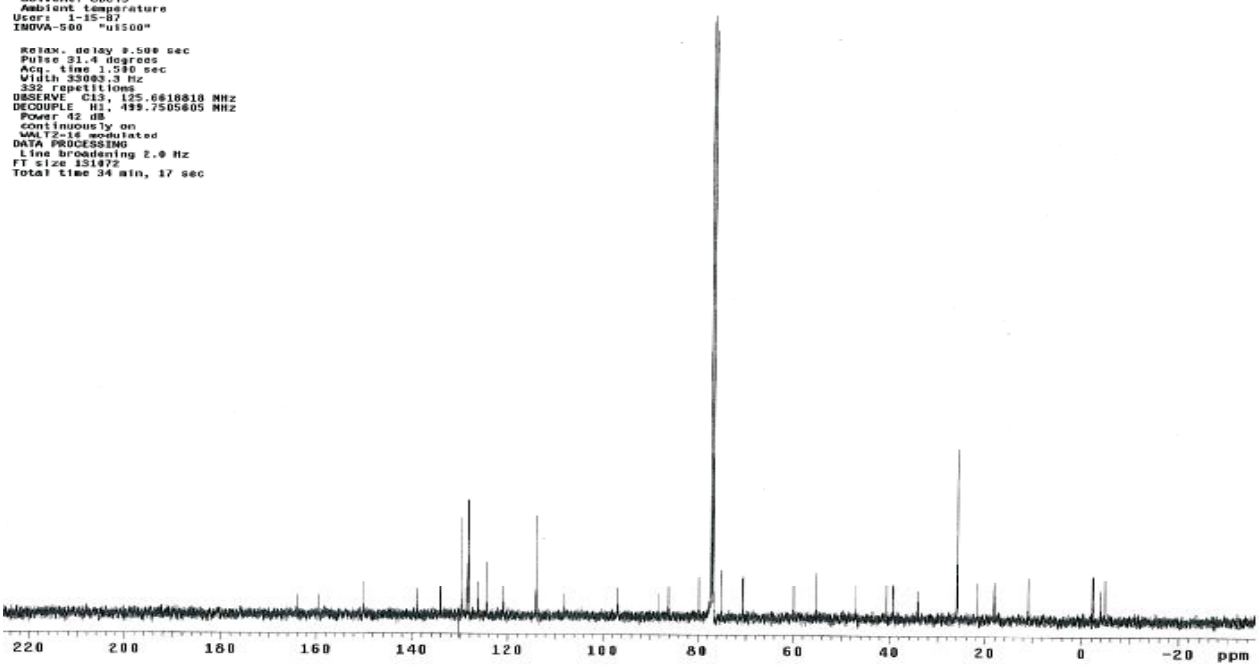


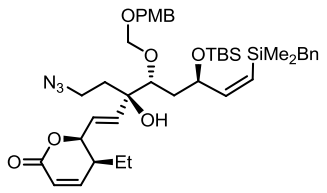
30

```
Pulse Sequence: s2pul
 Solvent: CDCl3
 Ambient temperature
INOVA-500  "u1500"

 Pulse 56.2 degrees
 Acq. time 4.000 sec
 Width 8060.0 Hz
 24 repetitions
OBSERVE    H1, 499.7485733 MHz
DATA PROCESSING
FT size 131072
Total time 2 hr, 51 min, 2 sec
```

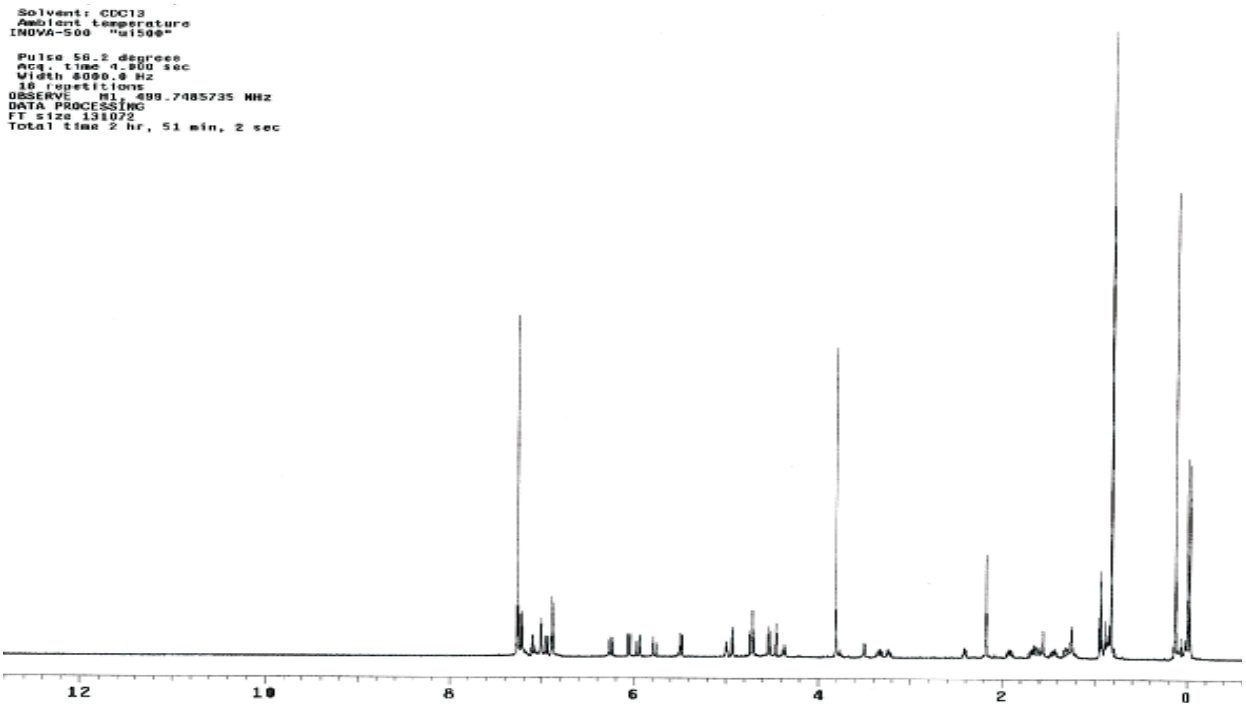


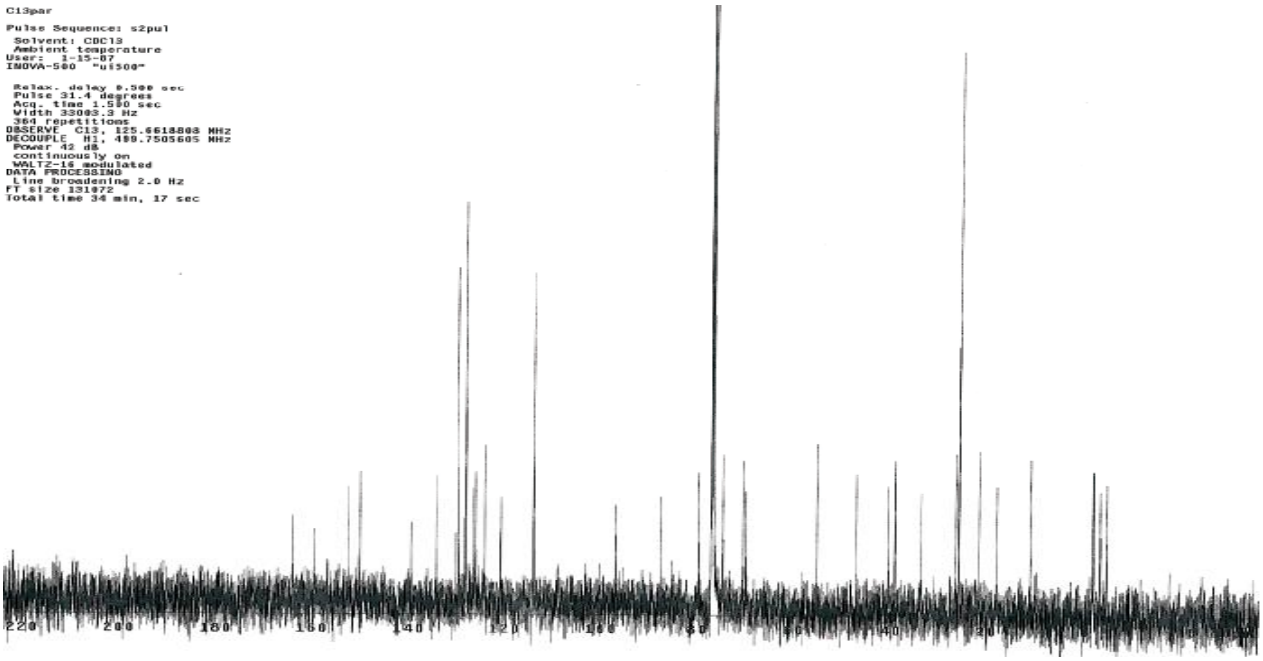

```
C13par

Pulse Sequence: s2pul
 Solvent: CDCl3
 Ambient temperature
User:  1-15-87
INOVA-500  "u1500"

 Relax. delay 0.500 sec
 Pulse 31.4 degrees
 Acq. time 1.500 sec
 Width 33003.3 Hz
 332 repetitions
OBSERVE  C13, 125.6618810 MHz
DECOUPLE  H1, 499.7505605 MHz
 Power 42 dB
 continuously on
 WALTZ-16 modulated
DATA PROCESSING
 Line broadening 2.0 Hz
FT size 131072
Total time 34 min, 17 sec
```

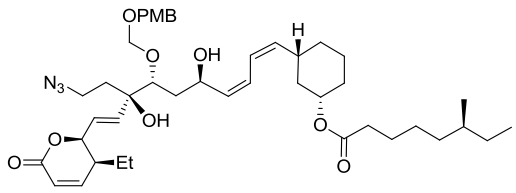



OPMB
O
OTBS SiMe2Bn
N3
OH
O
O
Et

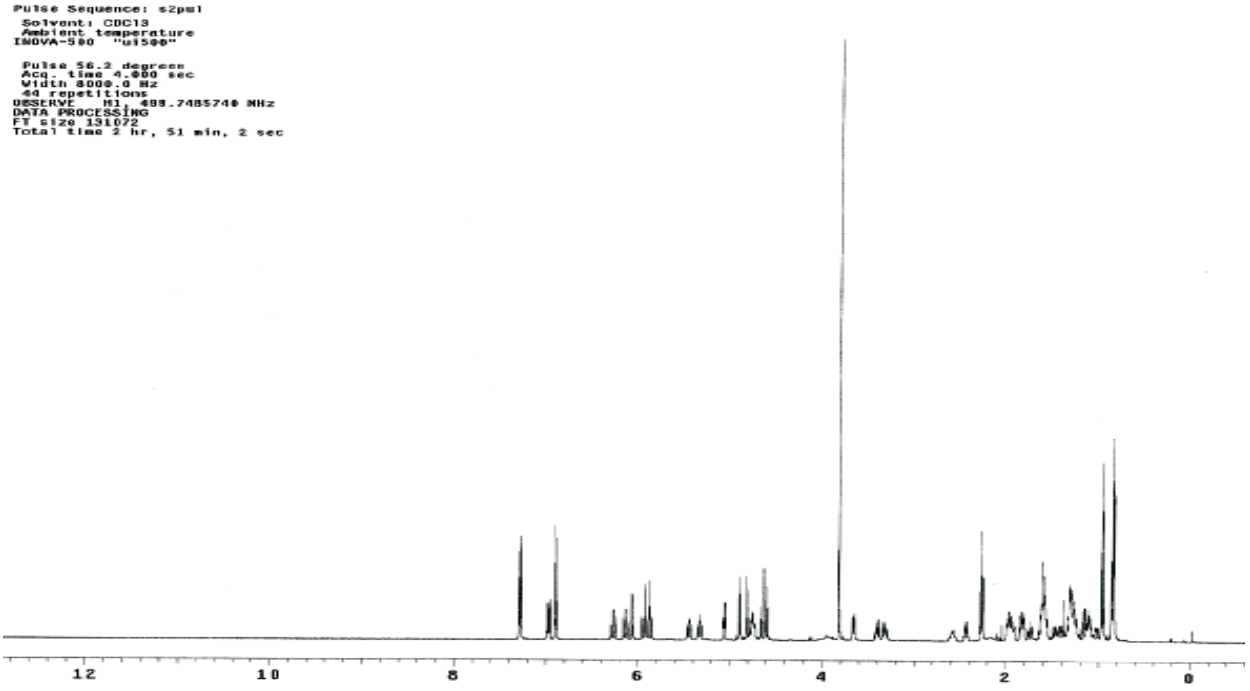
32

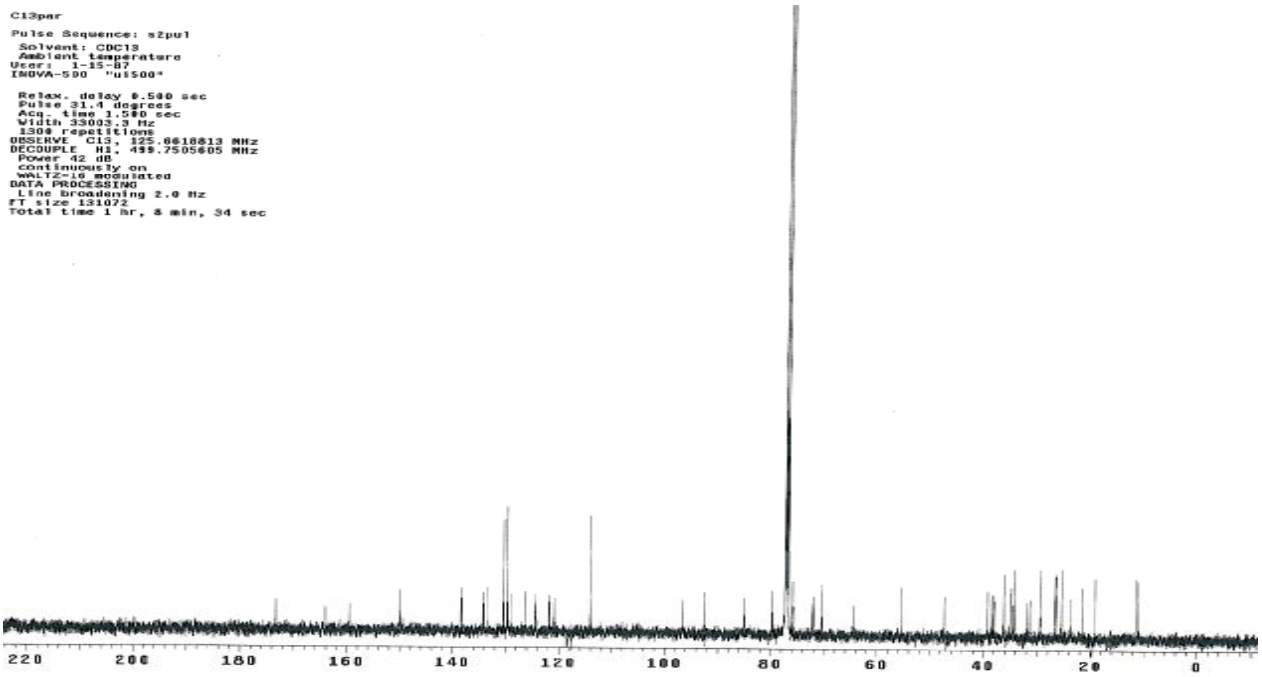

Solvent: CDCl3
Ambient temperature
INOVA-500 "u1500"
Pulse 58.2 degrees
Acq. time 4.000 sec
Width 8000.0 Hz
16 repetitions
OBSERVE H1, 499.7485735 MHz
DATA PROCESSING
FT size 131072
Total time 2 hr, 51 min, 2 sec
12
10
8
6
4
2
0

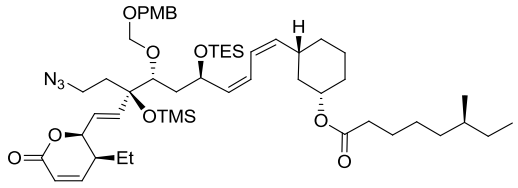

C13par
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
User: 1-15-07
INOVA-500 "u1500"
Relax. delay 0.500 sec
Pulse 31.4 degrees
Acq. time 1.590 sec
Width 33093.3 Hz
364 repetitions
OBSERVE C13, 125.6618803 MHz
DECOUPLE H1, 499.7505605 MHz
Power 42 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 2.0 Hz
FT size 131072
Total time 34 min, 17 sec
220
200
180
160
140
120
100
80
60
40
20
0


OPMB
O
OH
H
N3
OH
O
O
O
Et
O

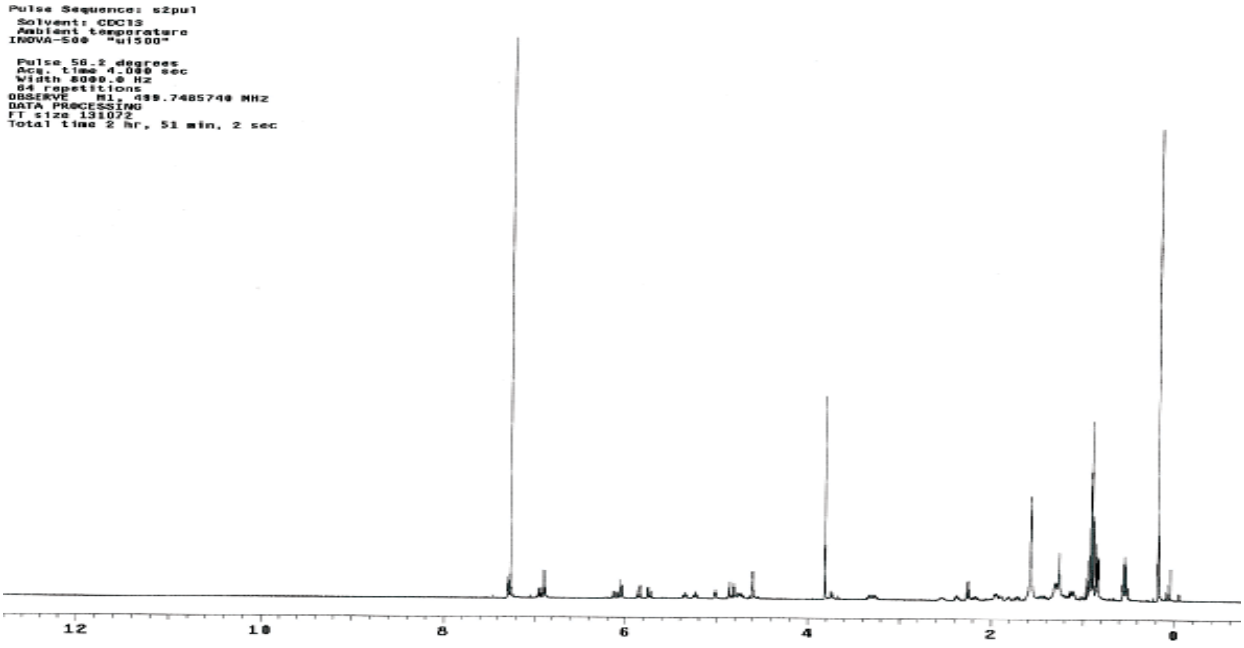
33

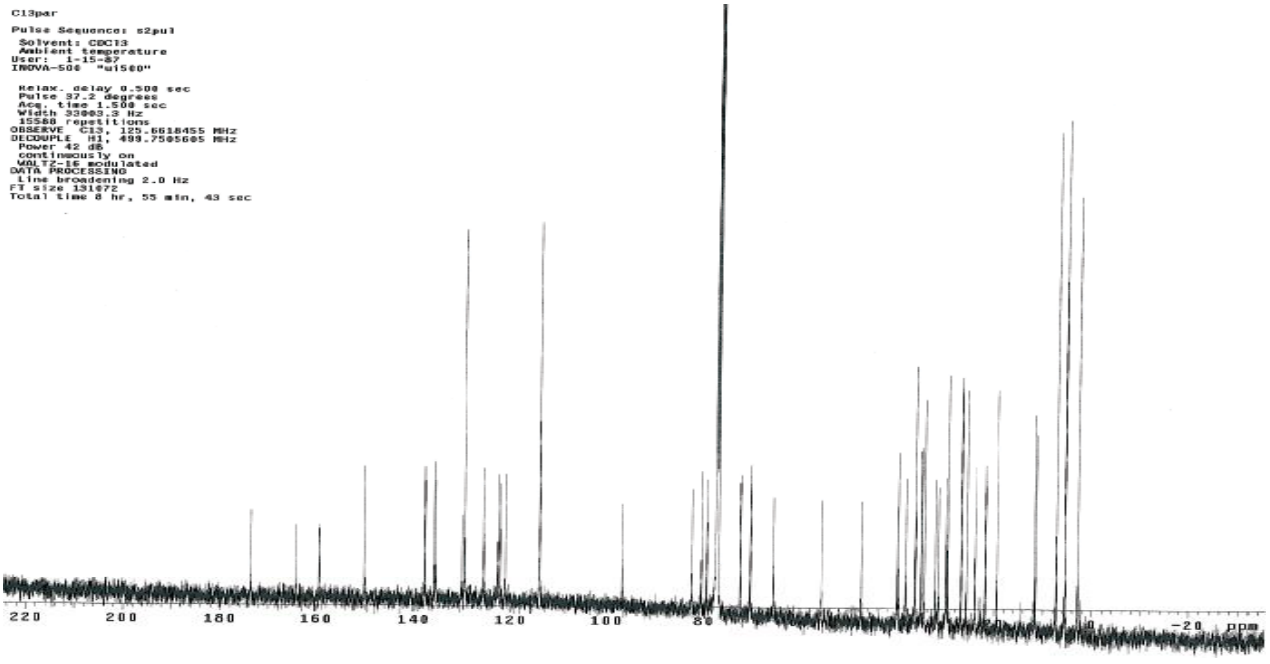

Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
INOVA-500 "ui500"
Pulse 56.2 degrees
Acq. time 4.000 sec
Width 8000.0 Hz
40 repetitions
OBSERVE H1, 499.7485740 MHz
DATA PROCESSING
FT size 131072
Total time 2 hr, 51 min, 2 sec
12
10
8
6
4
2
0

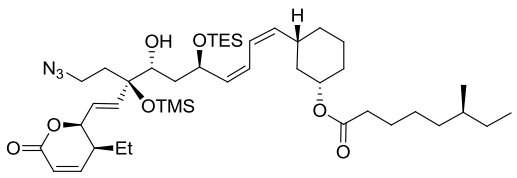

C13par
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
User: 1-15-87
INOVA-500 "ui500"
Relax. delay 0.500 sec
Pulse 31.4 degrees
Acq. time 1.580 sec
Width 33003.3 Hz
1308 repetitions
OBSERVE C13, 125.6618813 MHz
DECOUPLE H1, 499.7505605 MHz
Power 42 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 2.0 Hz
FT size 131072
Total time 1 hr, 8 min, 34 sec
220
200
180
160
140
120
100
80
60
40
20
0


OPMB
O
OTES
H
N3
OTMS
O
O
O
O
Et

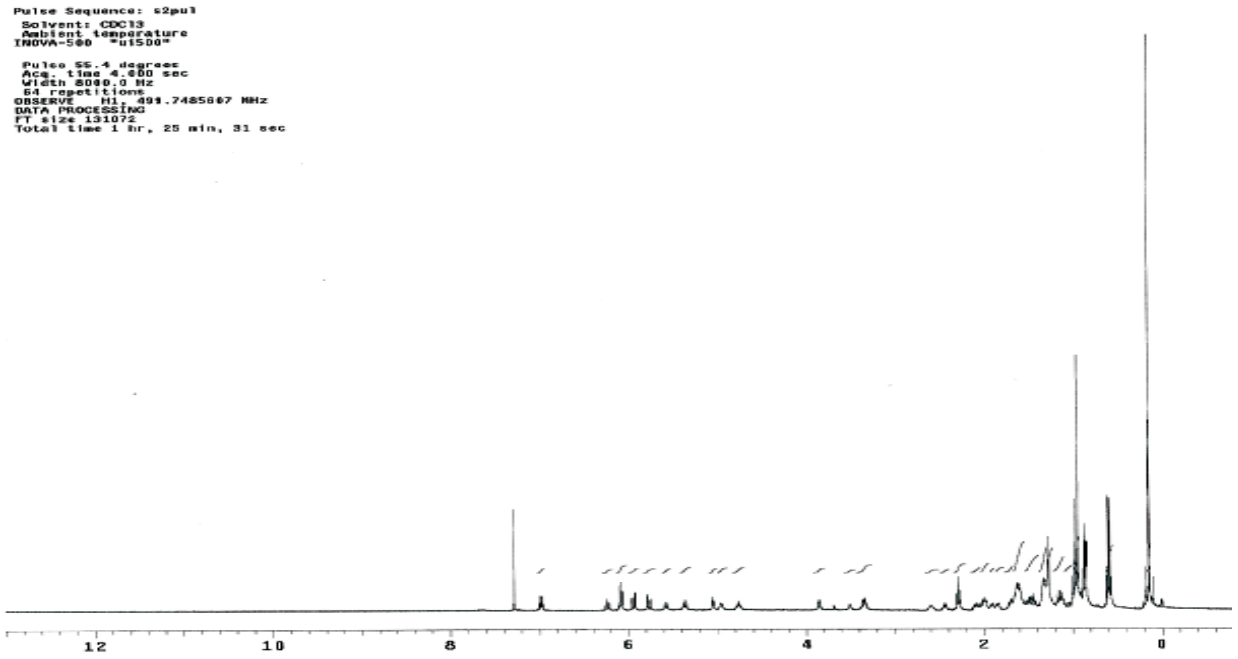
34

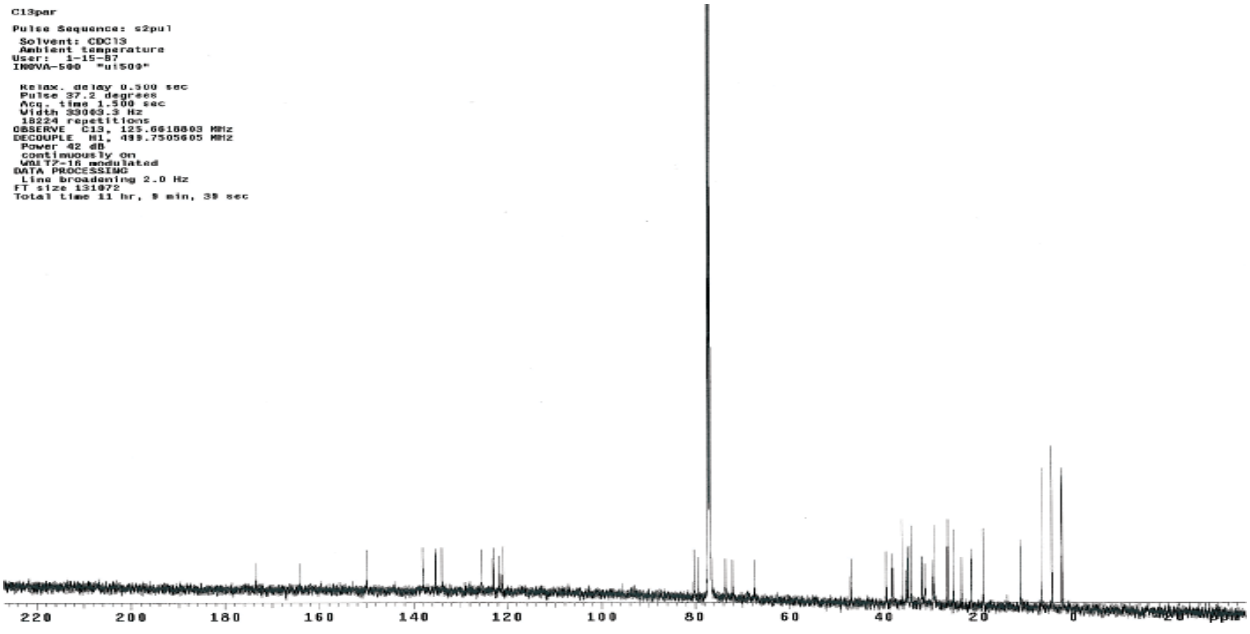

Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
INOVA-500 "ui500"
Pulse 56.2 degrees
Acq. time 4.000 sec
Width 8000.0 Hz
64 repetitions
OBSERVE H1, 499.7485740 MHz
DATA PROCESSING
FT size 131072
Total time 2 hr, 51 min, 2 sec
12
10
8
6
4
2
0

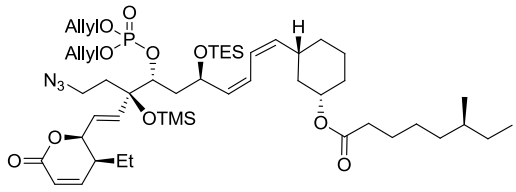

C13par
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
User: 1-15-07
INOVA-500 "ui500"
Relax. delay 0.500 sec
Pulse 37.2 degrees
Acq. time 1.508 sec
Width 33003.3 Hz
15580 repetitions
OBSERVE C13, 125.6618455 MHz
DECOUPLE H1, 499.7505605 MHz
Power 42 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 2.0 Hz
FT size 131072
Total time 8 hr, 55 min, 43 sec
220
200
180
160
140
120
100
80
-20
ppm


H
OH
OTES
N3
OTMS
O
O
Et
O
O

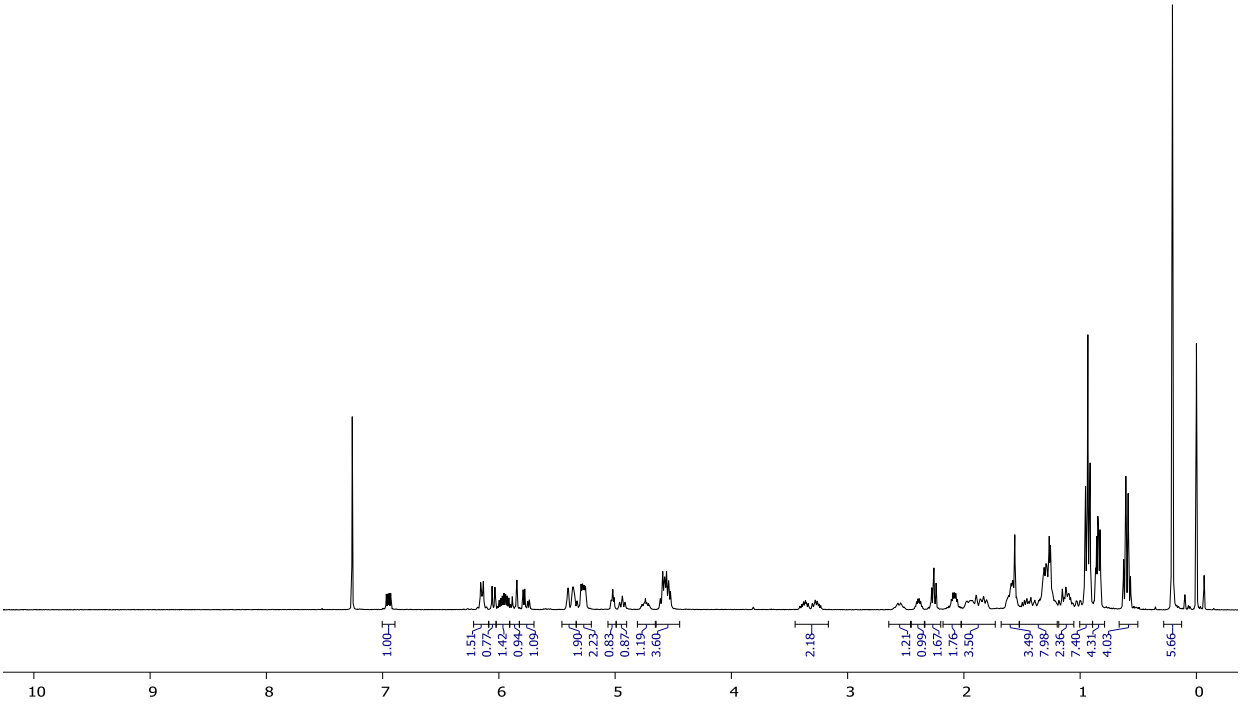
35

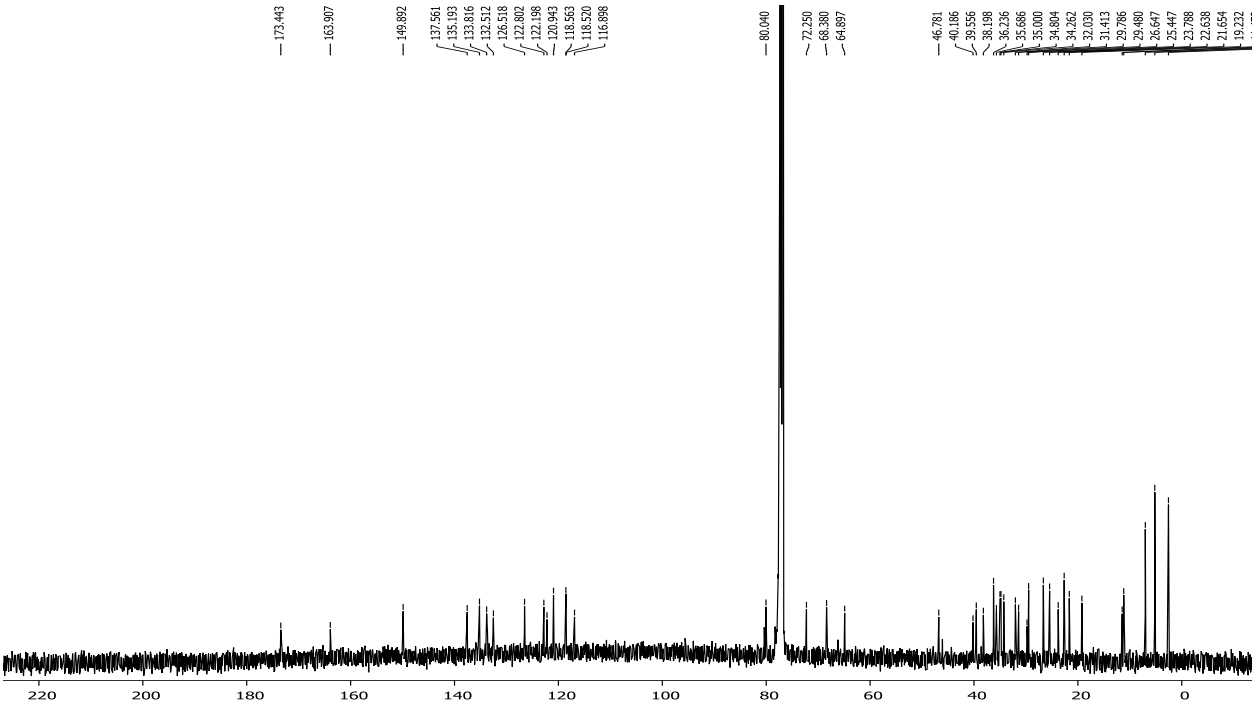

Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
INOVA-500 "ui500"
Pulse 55.4 degrees
Acq. time 4.000 sec
Width 8000.0 Hz
64 repetitions
OBSERVE H1, 499.7485807 MHz
DATA PROCESSING
FT size 131072
Total time 1 hr, 25 min, 31 sec
12
10
8
6
4
2
0

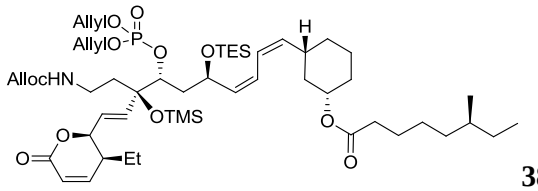

C13par
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
User: 1-15-87
INOVA-500 "ui500"
Relax. delay 0.500 sec
Pulse 37.2 degrees
Acq. time 1.500 sec
Width 33083.3 Hz
18224 repetitions
OBSERVE C13, 125.6618803 MHz
DECOUPLE H1, 499.7505605 MHz
Power 42 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 2.0 Hz
FT size 131072
Total time 11 hr, 9 min, 38 sec
220
200
180
160
140
120
100
80
60
40
20
0
ppm


AllylO
AllylO
P
O
O
OTES
H
N3
OTMS
O
O
Et
O
O

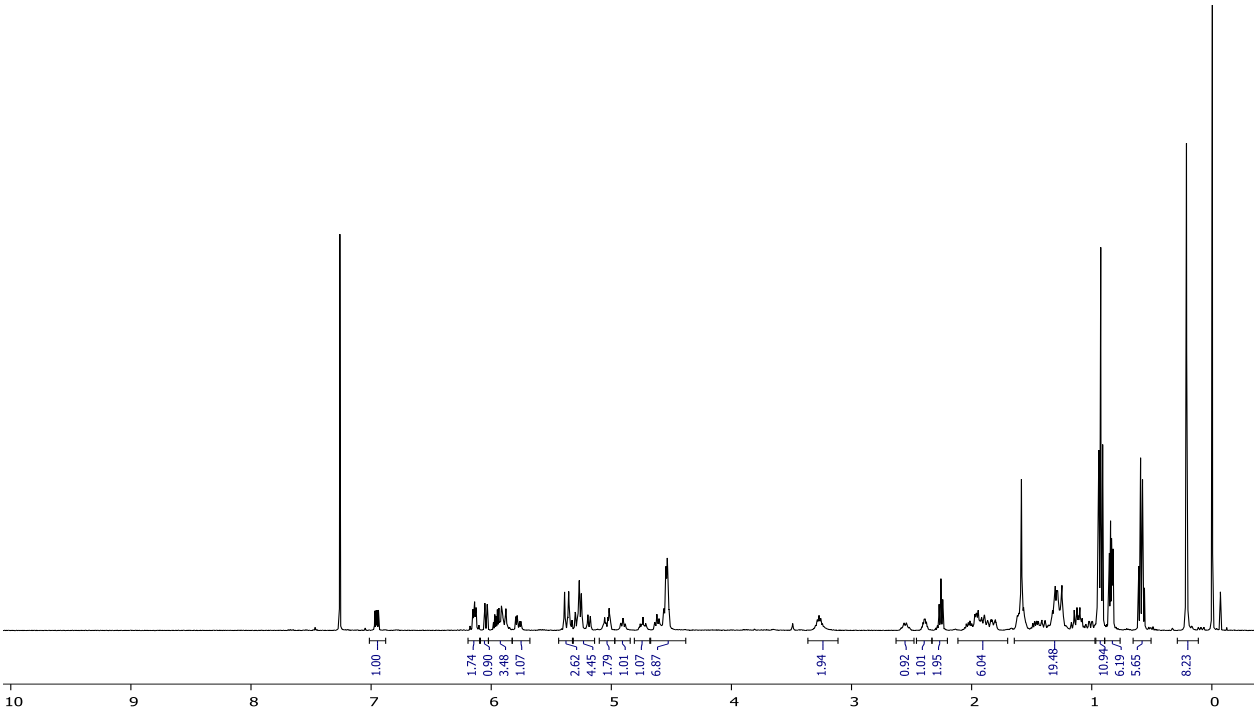
37

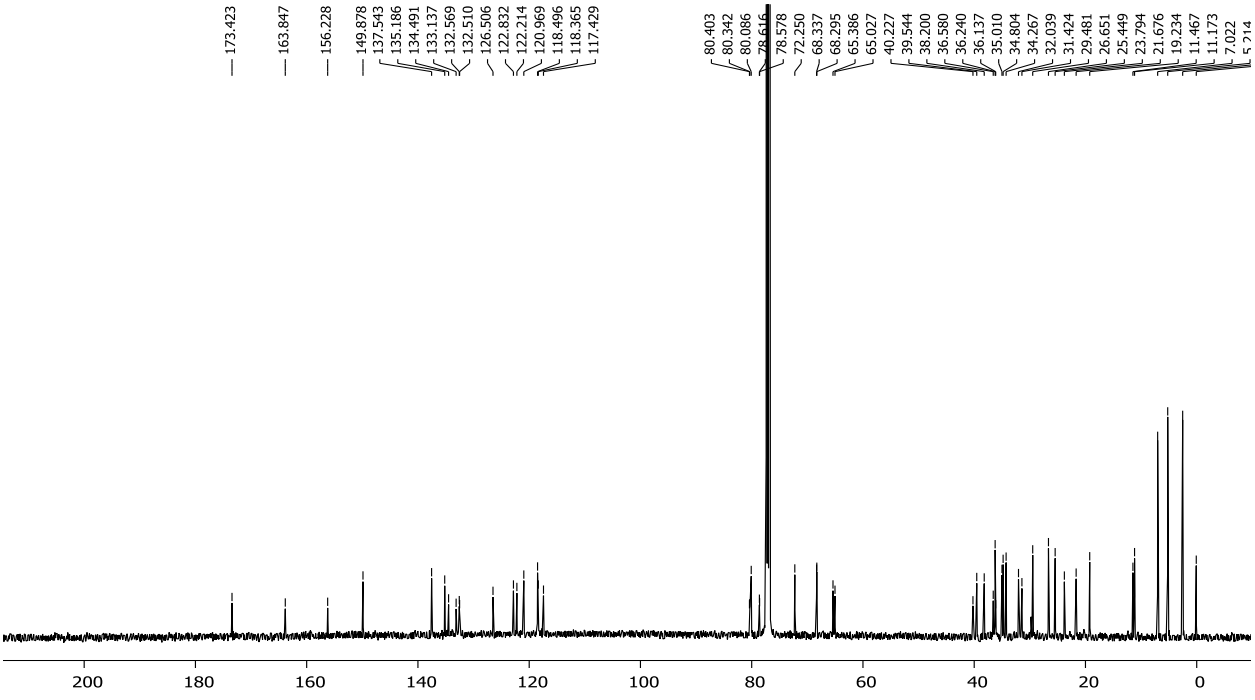

1.00
1.51
0.77
1.42
0.94
1.09
1.90
2.23
0.83
0.87
1.19
3.60
2.18
1.21
0.99
1.67
1.76
3.50
3.49
7.99
2.36
7.40
4.31
4.03
5.66
10
9
8
7
6
5
4
3
2
1
0

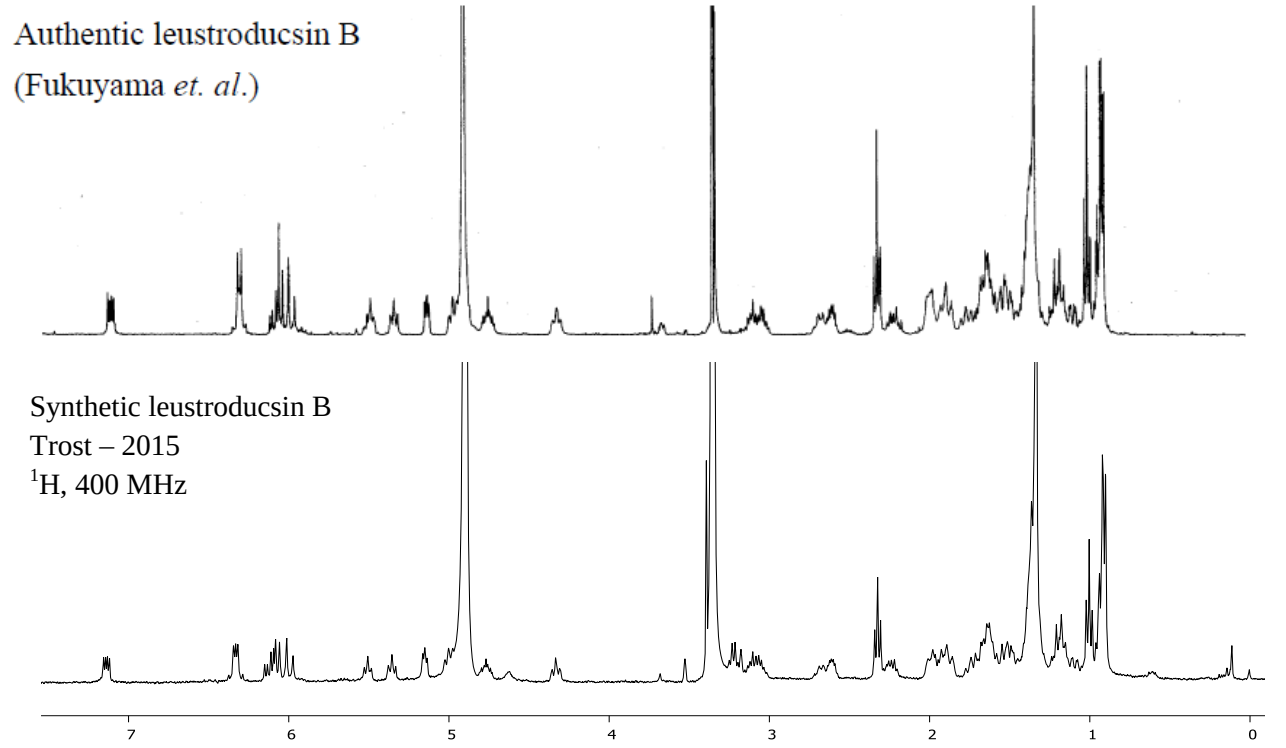

173.443
163.907
149.892
137.561
135.193
133.816
132.512
126.518
122.802
122.198
120.943
118.563
118.520
116.898
80.040
72.250
68.380
64.897
46.781
40.186
39.556
38.198
36.236
35.686
35.000
34.804
34.262
32.030
31.413
29.786
29.480
26.647
25.447
23.788
22.638
21.654
19.232
220
200
180
160
140
120
100
80
60
40
20
0

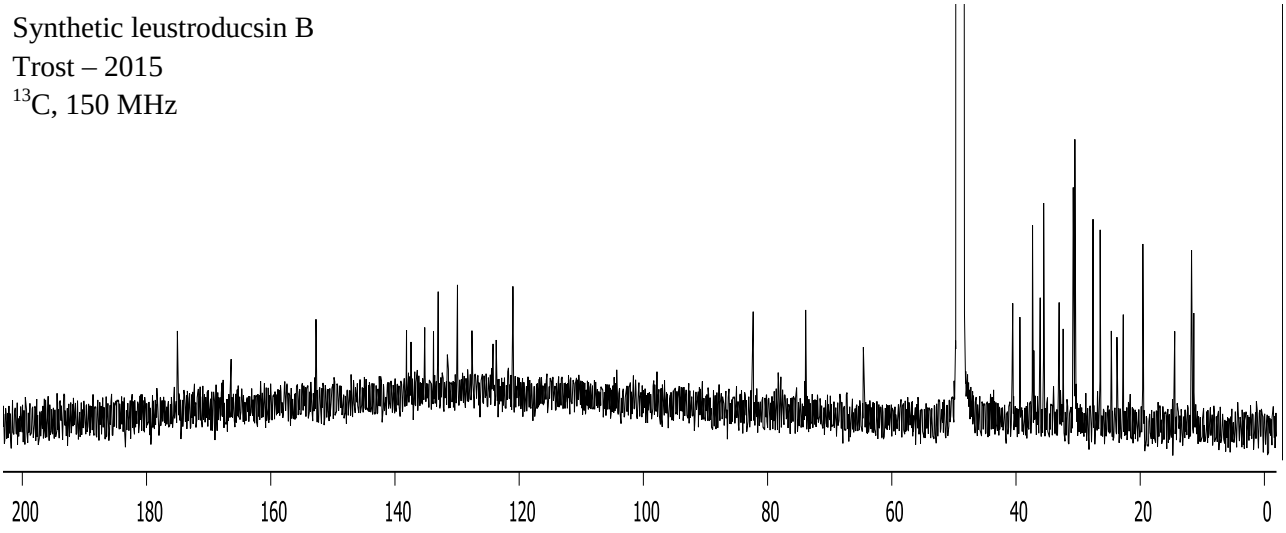

AllylO
AllylO
P
O
O
OTES
H
AllocHN
OTMS
O
O
Et
O
O

38


1.00
1.74
0.90
3.48
1.07
2.62
4.45
1.79
1.01
1.07
6.87
1.94
0.92
1.01
1.95
6.04
19.48
10.94
6.19
5.65
8.23
10
9
8
7
6
5
4
3
2
1
0


173.423
163.847
156.228
149.878
137.543
135.186
134.491
133.137
132.569
132.510
126.506
122.832
122.214
120.969
118.496
118.365
117.429
80.403
80.342
80.086
78.616
78.578
72.250
68.337
68.295
65.386
65.027
40.227
39.544
38.200
36.580
36.240
36.137
35.010
34.804
34.267
32.039
31.424
29.481
26.651
25.449
23.794
21.676
19.234
11.467
11.173
7.022
200
180
160
140
120
100
80
60
40
20
0





The picture of the ^{1}H spectrum of natural leustroducsin B was taken from : Miyashita, K.; Tsunemi, T.; Hosokawa, T.; Ikejiri, M.; Imanishi, T. *J. Org. Chem.* **2008**, *73*, 5360-5370.

(1) Structure **11a** does not appear in the manuscript.

(2) Trost, B. M.; Fettes, A.; Shireman, B. T. *J. Am. Chem. Soc.* **2004**, *126*, 2660-2661.

(3) Ynone **15** was prepared following the procedure described in : Trost, B. M.; Frederiksen, M. U.; Papillon, J. P. N.; Harrington, P. E.; Shin, S.; Shireman, B. T. *J. Am. Chem. Soc.* **2005**, *127*, 3666-3667.

(4) $PMBOCH_2Cl$ (**18)** was prepared following the procedure described in: Benneche, T.; Strande, P.; Undheim, K. *Synthesis* **1983**, 762-763.

(5) Organ, M. G.; Bilokin, Y. V.; Bratovanov, S. *J. Org. Chem.* **2002**, *67*, 5176-5183.

(6) Matsuhashi, H.; Shimada, K. *Tetrahedron* **2002**, *58*, 5619-5626.

(7) Lactone **20** was synthesized following a procedure described in: Trost, B. M.; Richardson, J.; Yong, K. *J. Am. Chem. Soc.* **2006**, *128*, 2540-2541.

(8) Shimada, K.; Kaburagi, Y.; Fukuyama, T. *J. Am. Chem. Soc.* **2003**, *125*, 4048-4049.

(9) **31** was prepared following the procedure described in: Myers, A. G.; Zheng, B.; Movassaghi, M. *J. Org. Chem.* **1997**, *62*, 7507-7507.