Supporting Information for:

Synthesis and Supramolecular Properties of Conformationally Restricted and Flexible Phospholipids

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1. Physicochemical Methods

Materials All polar lipids were obtained from Avanti Polar Lipids Inc. The fluorescent markers 1-hydroxypyrene-3,6,8-trisulfonic acid (HPTS) and N,N'-*p*-xylenebis(pyridinium bromide) (DPX) were obtained from Molecular Probes, Inc. and carboxyfluorescein from Eastman Kodak Co.

Preparation of Unilamellar Vesicles Measured aliquots of the appropriate phospholipids in chloroform were placed in a 10 mL round-bottomed flask. The chloroform was evaporated under reduced pressure on a rotary evaporator and dried under vacuum for at least one hour. The dried lipids were hydrated with aqueous solutions of 5mM HPTS/7.14 mM DPX/100 mM NaCl/5 mM TES buffer (pH 7.4) or 50 mM carboxyfluorescein/100 mM NaCl, while vortexing using a glass bead to promote removal of the lipids from the flask walls. The vesicle solution then underwent a rapid freeze/thaw procedure ten times unless they were to be used for membrane ^{31}P NMR, DLS or DCS measurements, where this procedure was omitted. The vesicle solution was then extruded, at room temperature, twenty nine times through a polycarbonate filter with 100 nm diameter pores using a hand-held Basic LiposoFast extruder from Avestin, Inc. With the HPTS/DPX leakage assay, the unencapsulated marker compounds were removed by overnight dialysis against isotonic NaCl solution, while gel filtration through a Sephadex G-50 column was employed in the carboxyfluorescein assay.

Leakage of the Aqueous Contents Vesicles were prepared as above, encapsulating 5 mM HPTS/7.14 mM DPX/100 mM NaCl/5mM TES buffer(pH 7.4) or 50mM carboxyfluorescein/100 mM NaCl/5 mM TES buffer (pH 7.4). For the HPTS/DPX release experiments the excitation wavelength was set at 413 nm (pH insensitive region for HPTS)[1,2] with emission measured at 510 nm. For the carboxyfluorescein leakage experiments these values were 495 nm and 520 nm, respectively. The vesicles were added to 3 mL of 100 mM NaCl/5 mM TES buffer (pH 7.4). Fluorescence intensity was monitored over time. Zero% and 100% leakage were determined from the initial fluorescence of the sample, and after addition of 0.2% octaethylene glycol monododecyl ether, respectively.

Dynamic Light Scattering Dynamic Light Scattering measurements were performed on a Beckman Coulter N4 Plus instrument. Vesicles were prepared as described above, but instead of fluorescent probes, only buffer was used. Software provided by the manufacturer was used to determine the distribution of particle hydrodynamic radius in the solution. Extreme care was taken to reduce the contamination by dust. Measurements were made at temperature 25°C and a scattering angle of 90°.

^{31}P NMR Vesicles were prepared as described above in the presence of 10% D_2O. The proton-decoupled ^{31}P NMR spectra (121 MHz) were acquired at 25 °C using a phase-cycled Hahn spin-echo sequence.[3] In each case, about 1000 scans were collected with a recycling delay of 3 sec and line broadening of 100 Hz. The chemical shifts are relative to phosphoric acid at 0 ppm.

Differential Scanning Calorimetry Vesicles were prepared as above, using pure dipalmitoleoylphosphatidylethanolamine (DiPoPE), or mixtures of 99 mol% DiPoPE and 1 mol% of the compounds **1b** or **2b**, with a final phospholipid concentration of 14.5 mM in 100 mM NaCl/5 mM TES buffer (pH 7.4). All the samples and the buffers were degassed prior to use. A VP-DSC (Microcal, Amherst, USA) high-sensitivity scanning microcalorimeter was used with a cell volume of 0.5 ml. Continuous scans were recorded at a rate of 60° C/h from 10 to 90° C.

Langmuir-Blodgett Films The π-A isotherms were recorded at 25.0° C with a computer-controlled Kibron MicroTrough S Langmiur-Blodgett trough (Kibron, Helsinki, Finland). Pure water was used as a subphase (18 MΩ cm) and a compression rate of 10 mm/min. Samples of **1b**, **2b**, or DiPOPE were dissolved in chloroform at a concentration 1 mg/mL and spread over the subphase using a microsyringe. The π-A isotherms for each compound were measured at least three times to confirm reproducibility.

2. Syntheses

General methods: THF was distilled from sodium/benzophenone. All reactions were carried out in oven dried glassware unless water was used as a reaction medium. Commercial reagents were generally used as received, unless otherwise indicated. Butyl lithium was purchased as a stock solution (2.5 M in hexanes). TLC analyses were performed on Merck aluminum-backed F254 silica gel plates, using UV light, potassium permanganate and phosphomolybdic acid for visualization. Drying of organic phases obtained from extractive workup was generally done with $MgSO_4$. Flash chromatography was performed as described by Still and coworkers[4] using either Merck silica gel 60 (230-400 mesh), or Baker silica gel (60-200 mesh). NMR spectra were recorded in $CDCl_3$ unless otherwise indicated, using $CHCl_3$ (δ 7.26 ppm) and $CDCl_3$ (δ 77.0 ppm) as internal references for ^1H and ^{13}C, respectively. IR spectra were recorded neat on thin films using KBr plates.

Diisopropyl (3-chloro-allyl)-phosphonate, 7. A mixture of triisopropylphosphite (15 mL, 57.7 mmol) and 1,3-dichloropropene (Aldrich, mixture of *cis* and *trans* isomers, 5.1 mL, 74.8 mmol) was heated under reflux for 20 h. The product was distilled under reduced pressure to give 12.2 g (88%) of **7** as a colorless oil and a 3:2 mixture of two geometric isomers. **Major isomer:** NMR (400 MHz, selected data) δ 6.19 (app ttt, *J* = 7, 4.2, 1.6 Hz, 1H), 5.92-5.80 (m, 1H), 4.74-4.64 (m, 2H), 2.79 (dd, *J* = 7.6, 1.6 Hz, 1H), 2.73 (dd, *J* = 7.6, 1.6 1H), 1.31 (br d, *J* = 6.2 Hz, 6H); ^{13}C NMR (75 MHz) δ 121.6 (d, *J* = 10.4 Hz), 121.2 (d, *J* = 16.4 Hz), 70.3 (d, *J* = 6.5 Hz), 26.6 (d, *J* = 142.1 Hz), 23.7 (d, *J* = 5.5 Hz). **Minor isomer:** NMR (400 MHz, selected data) δ 6.08 (app ttt, *J* = 13.3, 5.3, 1.3 Hz, 1H), 5.92-5.80 (m, 1H),), 5.92-5.80 (m, 1H), 4.74-4.64 (m, 2H), 2.55 (dd, *J* = 7.8, 1.3 Hz, 1H), 2.50 (dd, *J* = 7.8, 1.3 Hz, 1H), 1.30 (br d, *J* = 7.8 Hz, 6H); ^{13}C NMR (75 MHz) δ 123.2 (d, *J* = 10.9 Hz), 120.8 (d, *J* = 18 Hz), 70.4 (d, *J* = 6.5 Hz), 29.7 (d, *J* = 142.7 Hz), 23.7 (d, *J* = 5.5 Hz). FAB-HRMS (*m/z*) $[M+H]^+$ calcd for $C_9H_{18}ClO_3P$ 241.0760, found 241.0747.

Diisopropyl [2-(2-oxo-3-oxa-bicyclo[3.1.0]hex-6-yl)-vinyl]-phosphonate, 6. A typical procedure goes as follows: To a -78 °C solution of chloroallylphosphonate (1.085 g, 4.508 mmol) in dry THF (40 mL) was added *n*-BuLi (1.68 mL of 2.23 M solution in hexanes, 3.75

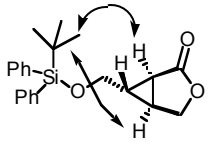
mmol). A precooled (-78 °C) solution of 2(*5H*)-furanone (293 μL, 4.13 mmol) in dry THF (10 mL) was added immediately via cannula. The reaction mixture was stirred at -78 °C for 2 h, quenched with a saturated solution of ammonium chloride (3 mL) and allowed to warm to room temperature. The mixture was diluted with brine and extracted twice with EtOAc. The combined organic layers were dried and concentrated to give a yellowish oil as the crude reaction product. Purification by flash chromatography (0.5…6% MeOH in CH_2Cl_2) afforded 630 mg (58%) of *ca* 85:15 mixture of stereoisomers of **6** as a colorless oil. *Rf* = 0.25 (MeOH/CH_2Cl_2 19:1). **Major isomer:** ^{1}H NMR (300 MHz, selected data) δ 4.54-4.39 (m, 2H), 4.25 (ddd, *J* = 9.9, 4.5, 1.8 Hz, 1H), 4.15 (br d, *J* = 9.9 Hz, 1H); ^{13}C NMR (75 MHz, selected data) δ 173.5, 146.8 (d, *J* = 6.3 Hz), 119.5 (d, *J* = 189.2 Hz), 70.1 (m), 68.7, 28.3 (d, *J* = 28.7 Hz). **Minor isomer:** ^{1}H NMR (300 MHz, selected data) δ 4.54-4.39 (m, 2H), 4.33 (ddd, *J* = 10.2, 5.1, 1.8 Hz, 1H), 4.10 (br d, *J* = 10.2 Hz, 1H); ^{13}C NMR (75 MHz, selected data) δ 172.9, 141.8 (d, *J* = 5.9 Hz), 124.5 (d, *J* = 188.7 Hz), 70.1 (m), 66.0. FAB-HRMS (*m/z*) $[M+1]^+$ calcd for $C_{13}H_{21}O_5P$ 289.1205, found 289.1201.

6-Formyl-3-oxa-bicyclo[3.1.0]hexane-2-one, 5. A -78 °C solution of alkene **6** (589 mg, 2.045 mmol) in dichloromethane (50 mL) was treated with a stream of O_3 in O_2 for 25 min. The reaction mixture was flushed with nitrogen for 10 min. to remove the excess O_3 and then Me_2S (5 mL) was added in one portion and the reaction mixture allowed to warm to room temperature. Solvent was removed under reduced pressure and the residual oil was purified by flash chromatography (20…60% EtOAc in hexanes) to afford 278 mg of *ca* 2:1 mixture of aldehyde **5** and phosphorus-positive by-product. The actual amount of **5** was calculated from ^{1}H NMR spectra to be 156.3 mg (61%). The aldehyde isolated was diastereomerically pure. **5:** R*f* = 0.3 (hexanes/EtOAc 1/1). ^{1}H NMR (300 MHz) δ 9.57 (br d, *J* = 2.4 Hz, 1H), 4.45 (dd, *J* = 9.9, 4.2 Hz, 1H), 4.33 (dd, *J* = 9.9, 0.6 Hz, 1H), 2.79-2.72 (m, 1H), 2.63 (br dd, *J* = 6.6, 2.4 Hz, 1H), 2.30 (br q, *J* = 2.7 Hz, 1H); ^{13}C NMR (75 MHz) δ 195.4, 173.0, 68.8, 32.4, 26.1, 25.6.

6-Hydroxymethyl-3-oxa-bicyclo[3.1.0]hexan-2-one, 15. To a solution of aldehyde **5** (27.2 mg, 0.21 mmol)[5] in MeOH :CH_2Cl_2 1:1 (4 mL) at 0 °C was added 10 mg (0.26 mmol) of $NaBH_4$. After stirring for 15 min at 0 °C, 0.2 mL of water was added and the slurry was filtered through a plug of $MgSO_4$ to afford 29 mg of crude alcohol **15** (^{13}C NMR (75 MHz) δ 176.2, 69.3, 61.1, 27.3, 21.6, 21.5) which was used in next step without purification. **15:** ^{1}H NMR (300 MHz) δ 4.33 (br dd, *J* = 9.3, 4.8 Hz, 1H), 4.26 (dt, *J* = 9.3, 0.9 Hz, 1H), 3.68-3.55 (m, 2H), 2.69 (br s, 1H), 2.27-2.21 (m, 1H), 2.07 (ddd, *J* = 6, 2.7, 0.9 Hz, 1H), 1.52-1.45 (m, 1H); ^{13}C NMR (75 MHz) δ 176.2, 69.4, 61.6, 27.3, 21.8, 21.7; IR 3401, 1770, 1373, 1185, 1044 cm^{-1}. FAB HRMS (*m/z*) $[M+H]^+$ calcd for $C_6H_8O_3$ 129.0552, found 129.0542.

6-(*tert*-Butyl-diphenyl-silyloxymethyl)-3-oxa-bicyclo[3.1.0]hexan-2-one, 16. To a solution of crude alcohol **15** in 1 mL of DMF, was added 38 mg (0.56 mmol) of imidazole and 93 μL (0.36 mmol) of TBDPSCl. After stirring the reaction mixture for 20 h at RT, EtOAc was added and the organic layer was washed with water, dried and concentrated. Purification by flash chromatography (2%…10% EtOAc in hexanes) afforded 52.1 mg of **16** as a white crystalline compound (40% from **6**). **16:** R*f* = 0.29 (EtOAc/hexanes 1/4); ^{1}H NMR (500 MHz) δ 7.66-7.62 (m, 8H), 7.47-7.38 (m, 12H), 4.31 (dd, *J* = 9, 4.5 Hz, 1H), 4.19 (d, *J* = 9 Hz, 1H), 3.81 (dd, *J* = 11, 4.5 Hz, 1H), 3.69 (dd, *J* = 11, 4.5 Hz, 1H), 2.20 (br q, *J* = 5 Hz, 1H), 2.09 (dd, *J* = 5 Hz, 1H),

1.44-1.39 (m, 1H), 1.05 (s, 9H); ^{13}C NMR (75 MHz) □ 175.9, 135.5, 133.0, 129.9, 127.8, 69.2, 61.8, 26.4, 26.8, 21.4, 21.3, 19.2; IR 2931, 2858, 1776, 1113, 703 cm^{-1}. mp. 107-110 °C.



Arows indicate the observed nOe effects

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6-(*tert*-Butyl-diphenyl-silyloxymethyl)-3-oxa-bicyclo[3.1.0]hexan-2-ol, 17. To a solution of lactone **16** (96 mg, 0.262 mmol) in 5 mL of CH_2Cl_2 at -78 °C was added dropwise DIBALH (786 □L, 1 M in CH_2Cl_2, 0.786 mmol). After 1.5 h at -78 °C, 1 mL of EtOH was added followed by 0.5 mL of water. The reaction mixture was allowed to warm up to –50 °C, then celite/Na_2SO_4 (1/1, total *c.a.* 3 g) was added. When the reaction mixture reached room temperature, the slurry was filtered and concentrated to give 94 mg (97%) of a colorless oil as a 95:5 mixture of bicyclic lactol **17** and the corresponding monocyclic hydroxy aldehyde based on ^{1}H NMR analysis. Lactol **17** was used in the next step without further purification. **17:** *Rf* = 0.33 (hexanes/EtOAc 2/1); ^{1}H NMR (300 MHz) □ 7.69-7.63 (m, 8H), 7.46-7.34 (m, 12H), 5.22 (s, 1H), 3.98 (br dd, *J* = 8.1, 2.7 Hz, 1H), 3.78 (br dd, *J* = 8.1, 1.5 Hz, 1H), 3.61 (dd, *J* = 6, 2.1 Hz, 2H), 1.59 (br t, 3.3 Hz, 1H), 1.05 (s, 9H), 0.94-0.88 (m, 2H); ^{13}C NMR (75 MHz) □ 135.5, 133.6, 129.6, 127.6, 98.3, 67.6, 63.8, 27.4, 26.8, 22.3, 20.1, 19.2. Hydroxy aldehyde: ^{1}H NMR (300 MHz, selected data) □ 9.64 (br d, 3.9 Hz, 1H).

3-(*tert*-Butyl-diphenyl-silyloxymethyl)-1,2-di(hydroxymethyl)-cyclopropane, 18. To a solution of lactol **17** (40 mg, 0.108 mmol) in 3 mL of EtOH was added $NaBH_4$ (35mg, 0.92 mmol) in one portion. After stirring the reaction mixture for 1.5 h at RT, 0.2 mL of water was added followed by filtration through a plug of $MgSO_4$ and concentration. Purification by flash chromatography (33…50% EtOAc in hexanes) afforded 35 mg (87%) of diol **18** as a white crystalline compound. **18:** R*f* = 0.36 (EtOAc/hexanes 1/1); ^{1}H NMR (300 MHz) □ 7.68-7.63 (m, 8H), 7.46-7.35 (m, 12H), 4.03 (dd, *J* = 11.7, 5.4 Hz, 2H), 3.61 (d, *J* = 6.3 Hz, 2H), 3.32 (br s, 2H), 3.258 (br t, *J* = 11 Hz, 2H), 1.29-1.18 (m, 2H), 1.05 (s, 9H), 0.92 (br t, 5Hz, 1H); ^{13}C NMR (75 MHz) □ 135.5, 133.6, 129.6, 127.6, 65.3, 62.0, 26.8, 25.0, 22.5, 19.1. IR 3339, 2931, 2958, 1428, 1112, 702 cm^{-1}. mp. 79-80 °C. FAB HRMS (*m/z*) [M-H]$^+$ calcd for $C_{38}H_{72}O_5$ 369.1886, found 369.1893.

Silyl ether 19a. To a solution of diol **18** (114 mg, 0.308 mmol) in CH_2Cl_2 (9 mL), was added palmitoyl chloride (233 □L, 0.77 mmol) and Et_3N (129 □L, 0.924 mmol). After stirring for 40 min at RT, 0.5 mL of water and 5 mL of *i*-PrOH were added. Concentration, followed by flash chromatography (3% EtOAc in hexanes) afforded 260 mg (99%) of diester **19a** as a colorless oil which slowly solidified. **19a:** R*f* = 0.34 (hexanes/EtOAc 9/1); ^{1}H NMR (300 MHz) □ 7.71-7.64 (m, 8H), 7.48-7.36 (m, 12H), 4.23 (ddd, *J* = 12, 4.5, 2.1 Hz, 2H), 3.99 (ddd, *J* = 12, 5.4, 2.4 Hz, 2H), 3.63 (dd, *J* = 5.4, 2.4 Hz, 2H), 2.30 (td, *J* = 8.1, 2.7 Hz, 4H), 1.63 (br pentet, *J* = 6 Hz, 4H), 1.36-1.22 (m, 51H), 1.06 (s, 9H), 0.90 (td, *J* = 7.2, 3 Hz, 6H); ^{13}C NMR (75 MHz, some signals in aliphatic region overlap) □ 173.6, 135.5, 133.6, 129.6, 127.6, 65.1, 63.4, 34.3, 31.9, 29.65, 29.61, 29.57, 29.4, 29.3, 29.2, 29.1, 26.8, 24.9, 24.8, 22.6, 19.5, 19.1, 14.0. IR 2925, 2854, 1738, 1466, 1113, 702 cm^{-1}.

Silyl ether 19b. To a solution of diol **18** (206 mg, 0.557 mmol) in CH_2Cl_2 (15 mL), was added palmitoleoyl chloride (382 mg, 1.4 mmol) and Et_3N (233 μL, 1.67 mmol). After stirring for 1 h at RT, the reaction mixture was concentrated. Purification by flash chromatography (4% EtOAc in hexanes) afforded 469 mg (99%) of diester **19b** as a colorless oil. **19b:** R*f* = 0.55 (hexanes/EtOAc 9/1); ^{1}H NMR (300 MHz) δ 7.68-7.63 (m, 4H), 7.44-7.35 (m, 6H), 5.41-5.29 (m, 4H), 4.21 (ddd, *J* = 12, 5.4, 2.1 Hz, 2H), 3.98 (ddd, *J* = 11.7, 5.7, 2.1 Hz, 2H), 3.61 (d, *J* = 5.7 Hz, 2H), 2.29 (t, *J* = 7.2 Hz, 4H), 2.02 (br q, *J* = 6 Hz, 8H), 1.61 (br pentet, *J* = 6.9 Hz, 4H), 1.38-1.22 (m, 31H), 1.05 (s, 9H), 0.89 (t, *J* = 6.9 Hz, 6H); ^{13}C NMR (75 MHz, two signals in aliphatic region overlap) δ 173.7, 135.5, 133.6, 129.9, 129.70, 129. 65, 127.6, 65.1, 63.4, 34.3, 31.7, 29.7, 29.13, 29.08, 28.9, 27.2, 27.1, 26.8, 24.91, 24.85, 22.6, 19.4, 19.1, 14.1. IR 2997, 2856, 1738, 1113, 702 cm^{-1}.

Alcohol 20a. To a solution of diester **19a** (260 mg, 0.306 mmol) in 10 mL of THF, was added TBAF (460 μL, 1 M in THF, 0.46 mmol). After stirring for 14 h at RT, the reaction mixture was concentrated and purified by flash chromatography (10…30% EtOAc in hexanes) to afford 173.5 mg (93%) of alcohol **20a** as a white solid. **20a:** ^{1}H NMR (500 MHz) δ 4.24 (ddd, *J* = 12, 5.5, 2 Hz, 2H), 4.00 (ddd, *J* = 12, 5.5, 2 Hz, 2H), 3.52 (d, *J* = 6 Hz, 2H), 2.29 (t, *J* = 8 Hz, 4H), 1.61 (pentet, *J* = 7.5 Hz, 4H), 1.32-1.23 (m, 50H), 1.15-1.08 (m, 1H), 0.872 (t, *J* = 7 Hz, 6H); ^{13}C NMR (125 MHz, some signals overlap in aliphatic region) δ 173.8, 65.0, 63.2, 34.3, 31.9, 29.7, 29.64, 29.60, 29.5, 29.34, 29.27, 29.2, 25.3, 25.0, 22.7, 20.1, 14.1. IR 3480, 2917, 2849, 1732, 1715, 1471, 1456 cm^{-1}. FAB HRMS (*m/z*) [M-H]$^+$ calcd for $C_{38}H_{72}O_5$ 607.5302, found 607.5333.

Alcohol 20b. To a solution of silyl ether **19b** (177 mg, 0.21 mmol) in 8 mL of THF, was added TBAF (315 μL, 1 M in THF, 0.315 mmol). After stirring for 14 h at RT, the reaction mixture was concentrated and purified by flash chromatography (10…30% EtOAc in hexanes) to afford 128 mg (>99%) of alcohol **20b** as a colorless oil. **20b:** R*f* = 0.42 (hexanes/EtOAc 2/1); ^{1}H NMR (300 MHz) δ 5.38-5.26 (m, 4H), 4.24 (ddd, *J* = 12, 5.1, 2.4 Hz, 2H), 3.98 (ddd, *J* = 11.7, 5.4, 2.1 Hz, 2H), 3.50 (d, *J* = 6.3 Hz, 2H), 2.28 (t, *J* = 7.2 Hz, 4H), 1.99 (br q, *J* = 6 Hz, 8H), 1.60 (br pentet, *J* = 7.2 Hz, 4H), 1.38-1.18 (m, 31H), 0.86 (t, *J* = 6.9 Hz, 6H);); ^{13}C NMR (75 MHz) δ 173.8, 129.9, 129.7, 64.8, 63.2, 34.3, 31.7, 29.6, 29.12, 29.08, 29.06, 28.9, 27.2, 27.1, 25.2, 24.9, 22.6, 20.0, 14.0. IR 3446, 2923, 2855, 1732, 1456, 1175 cm^{-1}. FAB-HRMS (*m/z*) [M-OH]$^+$ calcd for $C_{38}H_{68}O_5$ 587.5040, found 587.5063.

Phospholipid 1a. To a solution of alcohol **20a** in 1 mL of CH_2Cl_2, was added imidazole (7 mg, 0.1 mmol) and diphenylchlorophosphate (10 μL, 0.049 mmol). After stirring for 14 h at RT, the reaction was concentrated. Purification by flash chromatography (10% EtOAc in hexanes) afforded 23.2 mg (92%) of diphenyl-protected phospholipid as a colorless oil which slowly solidified. *Rf* = 0.63 (hexanes/EtOAc 2/1); ^{1}H NMR (500 MHz) δ 7.38-7.30 (m, 4H), 7.24-7.15 (m, 6H), 4.19 (ddd, *J* = 12, 7, 2 Hz, 2H), 4.1 (br dd, *J* = 9, 7.5 Hz, 2H), 3.95 (ddd, *J* = 12, 7.5, 2 Hz, 2H), 2.26 (t, 7.5 Hz, 4H), 1.59 (pentet, *J* = 7 Hz, 4H), 1.39-1.21 (m, 51H). 0.88 (t, *J* = 7 Hz, 6H); ^{13}C NMR (75 MHz, some signals overlap in aliphatic region) δ 173.5, 150.5 (d, *J* = 7 Hz), 129.8, 125.3, 120.0 (d, *J* = 4.8 Hz), 71.2 (d, *J* = 6 Hz), 62.5, 34.2, 31.9, 29.64, 29.60, 29.57, 29.4, 29.3, 29.2, 29.1, 24.9, 22.6, 22.5 (d, *J* = 7 Hz), 20.6, 14.1. IR 2926, 2854. 1735, 1495, 1189, 765. FAB HRMS (*m/z*) [M+H]$^+$ calcd for $C_{50}H_{81}O_8P$ 841.5747, found 841.5723. The

protecting phenyl groups were removed in a following way: a stream of H_2 was bubbled through the solution of PtO_2 (12 mg, 0.05 mmol) in AcOH (3 mL) for 2 min. followed by the addition of diphenyl-protected phospholipid in 2 mL of AcOH. After stirring for 8 h at RT under H_2 atmosphere, the reaction mixture was filtered and concentrated to afford 79 mg (99%) of phospholipid **1a** as an amorphous solid. **1a:** ^{1}H NMR (500 MHz) δ 4.32 (br s, 2H), 3.90 (br s, 4H), 2.28 (br q, J = 7Hz, 4H), 1.59 (br s, 4H), 1.38-2.20 (m, 57H), 0.87 (t, J = 7Hz, 6H); ^{13}C NMR (125 MHz, some signals overlap in aliphatic region) δ 173.9, 69.0 (br s), 63.0, 34.2, 31.9, 29.7, 29.6, 29.5, 29.32, 29.29, 29.2, 24.9, 22.6, 20.3, 14.1. IR 3352, 2926, 2855, 2071, 1728, 909, 735 cm^{-1}. FAB-HRMS (*m/z*) $[M+Na]^+$ calcd for $C_{38}H_{73}O_8P$ 711.4941, found 711.4965.

Phospholipid 1c. To a solution of alcohol **20a** (65.9 mg, 0.108 mmol) and triethylamine (17 μL, 0.119 mmol) in 2 mL of benzene, was added 2-chloro-1,3,2-dioxaphospholane-2-oxide (11 μL, 0.119 mmol). After stirring for 21 h at RT, the reaction mixture was filtered and concentrated. The residue was dissolved in the mixture of acetonitrile/benzene (4/4 mL) and a stream of ammonia was bubbled through the solution. After 5.5 h at RT no more intermediate oxalane was detected by TLC. The resulting slurry was purified by flash chromatography (first eluting with 5% MeOH in $CHCl_3$ followed by 20:4:1 $CHCl_3$:MeOH:NH_4OH, no attempt was made to separate any dissolved silica gel) to afford 4.6 mg (7%) of unreacted alcohol **20a** and 49.2 mg (62%) of phospholipid as a practically insoluble waxy solid. Due to the low solubility, NMR analysis was impossible. Rf = 0.57 ($CHCl_3$/MeOH/NH_4OH 10:4:1). FAB-HRMS (*m/z*) $[M+H]^+$ calcd for $C_{40}H_{78}NO_8P$ 732.5543, found 732.5557.

Phospholipid 1b. The two-step procedure to make **1c** was used to make **1b**. The crude product was purified by flash chromatography (5-30% MeOH in $CHCl_3$, final samples taken up in chloroform and filtered to separate silica) to afford 89 mg (26%) of unreacted alcohol **20b** and 254 mg (62%) of phospholipid. **1b:** Rf = 0.58 ($CHCl_3$/MeOH/H_2O 62/25/4); ^{1}H NMR (300 MHz) δ 7.44 (br s, 3H), 5.39-5.26 (m, 4H), 4.35 (br dd, J = 12.3, 5.1 Hz, 2H), 3.95-3.82 (m, 4H), 3.79-3.64 (m, 4H), 2.27 (t, J = 7.5 Hz, 4H), 2.00 (br d, J = 5.7 Hz, 8H), 1.65-1.54 (m, 4H), 1.29 (br s, 30H), 1.18-1.09 (m, 1H), 0.87 (t, J = 7.2 Hz, 6H); ^{13}C NMR (75 MHz, some signals in aliphatic region overlap) δ 173.8, 130.0, 129.7, 68.0 (br), 67.4 (br), 63.1, 61.6 (br), 34.3, 31.8, 29.7, 29.25, 29.20, 29.17, 29.0, 27.2, 24.9, 22.6, 20.2, 14.1. IR 3233, 2926, 2855, 1734, 1457, 1200, 1086, 1037 cm^{-1}. FAB-HRMS (*m/z*) $[M+H+Na]^+$ calcd for $C_{40}H_{74}NO_8P$ 751.5128, found 751.5153.

4-Ethoxycarbonyl-1,6-heptadiene, 13. A mixture of diethyl diallylmalonate (8 g, 33.28 mmol), lithium chloride (3.1 g, 73 mmol), water (0.67 mL) and dimethyl sulfoxide (60 mL) were heated at reflux for 6 h. After cooling, the mixture was diluted with brine (50 mL) and the product was extracted into diethyl ether. The organic phase was dried and concentrated to give 4.8 g (86%) of viscous oil. The product was used in next step without further purification. **13:** ^{1}H NMR (300 MHz) δ 5.76-5.62 (m, 2H), 5.08-4.94 (m, 4H), 4.07 (q, J = 7.5 Hz, 2H), 2.50-2.40 (m, 1H), 2.37-2.14 (m, 4H), 1.19 (t, J = 7 Hz, 6H); ^{13}C NMR (75 MHz) δ 174.7, 135.1, 116.7, 60.0, 44.7, 35.6, 14.2.

4-Hydroxymethyl-1,6-heptadiene, 12. To a solution of ester **13** (2.71 g, 16.1 mmol) in 20 mL of dry CH_2Cl_2, a solution of DIBAL (40 mL, 1 M in CH_2Cl_2, 40 mmol) was added over 10 min. at –78 °C. After sirring for 1 h at –78 °C, the reaction was worked up according to the procedure described by Baeckström.[6] The crude product 1.42 g (69%) was used in the next step

without further purification.[7] **12:** *Rf* = 0.23 (hexanes/ EtOAc 9/1); ^{1}H NMR (300 MHz) δ 5.86-5.70 (m, 2H), 5.08-4.97 (m, 4H), 3.53 (d, *J* = 5.7 Hz, 2H), 2.12-2.01 (m, 4H), 1.89 (br s, 1H), 1.68 (septet, *J* = 6 Hz, 1H); ^{13}C NMR (75 MHz) δ 136.7, 116.3, 65.1, 40.1, 35.3.

4-((*tert*-Butyl-diphenyl-silyloxy)methyl)-1,6-heptadiene, 21. To a solution of alcohol **12** (370 mg, 2.9 mmol) and imidazole (500 mg, 7.3 mmol) in 8 mL of DMF was added TBDPSCl (1.14 mL, 4.4 mmol). After stirring for 20 h at RT the reaction mixture was concentrated and the residue was purified by flash chromatography (1% EtOAc in hexanes) to give **21** (836 mg, 78%) as a colorless oil. **21:** *Rf* = 0.43 (hexanes/EtOAc 99/1); ^{1}H NMR (300 MHz) δ 7.73-7.66 (m, 8H), 7.48-7.36 (m, 12H), 5.85-5.68 (m, 2H), 5.08-4.96 (m, 4H), 3.61 (dd, *J* = 5.4, 1.5 Hz, 2H), 2.29-2.07 (m, 4H), 1.73 (septet, *J* = 5.4 Hz, 1H), 1.02 (s, 9H); ^{13}C NMR (75 MHz) δ 137.0, 135.6, 133.9, 129.5, 127.6, 116.1, 65.3, 40.5, 35.0, 26.9, 19.3.

3-((*tert*-Butyl-diphenyl-silyloxy)methyl)-1,5-pentanediol, 22. A -78 °C solution of **21** (432 mg, 1.18 mmol) in MeOH (15 mL) was treated with a stream of O_3 in O_2 for 35 min. The reaction mixtrure was then flushed with nitrogen for 20 min to remove the excess O_3 and then $NaBH_4$ (450 mg, 11.9 mmol) was added in one portion. The dry-ice bath was removed and the reaction mixture was allowed to warm up to room temperature. The reaction mixture was diluted with brine and extracted twice with EtOAc. The combined organic layers were dried, concentrated and filtered through the plug of celite to give 447 mg (>99%) of viscous colorless oil. The diol **22** was used in next step without further purification. **22:** ^{1}H NMR (500 MHz) δ 7.69-7.65 (m, 8H), 7.46-7.37 (m, 12H), 3.66-3.58 (m, 6H), 2.52 (br s, 2H), 1.84 (septet, *J* = 6 Hz, 1H), 1.65-1.53 (m, 4H), 1.07 (s, 9H); ^{13}C NMR (125 MHz) δ 135.6, 133.2, 129.8, 127.7, 67.3, 60.7, 34.8, 26.8, 19.2. IR 3350, 2931, 2858, 1428, 1113, 1050, 702 cm^{-1}.

Silyl ether 23a. To a solution of diol **22** (279 mg, 0.75 mmol) in 15 mL of dichloromethane, was added Et_3N (320 μL, 2.3 mmol) and palmitoyl chloride (570 μL, 1.87 mmol). After stirring the mixtrure for 1 h at RT, the solvent was removed at reduced pressure and the residue was purified by flash chromatography (1…3% EtOAc in hexanes) to give 444 mg (70%) of **23a** as an amorphous solid. **23a:** *Rf* = 0.56 (hexanes/EtOAc 9/1); ^{1}H NMR (500 MHz) δ 7.67-7.63 (m, 8H), 7.45-7.36 (m, 12H), 4.11-4.03 (m, 4H), 3.59 (d, *J*= 4.5 Hz, 2H), 2.25 (t, *J* = 8 Hz, 4H), 1.83-1.55 (m, 9H), 1.32-1.24 (m, 48H), 1.07 (s, 9H), 0.89 (t, *J* = 6.5 Hz, 6H); ^{13}C NMR (125 MHz, some signals in aliphatic region overlap) δ 173.8, 135.5, 133.5, 129.7, 127.7, 65.6, 62.4, 34.9, 34.3, 31.9, 30.1, 29.7 , 29.63 , 29.59, 29.5, 29.3, 29.3, 29.2, 26.8, 24.9, 22.7, 19.2, 14.1. IR 2923, 2854, 1738, 1465, 1172, 1113, 702 cm^{-1}.

Silyl ether 23b. To a solution of diol **22** (432 mg, 1.162 mmol) in 8 mL of dichloromethane, was added DMAP (378 mL, 3.1 mmol), DCC (913 mg, 4.4 mmol) and palmitoleic acid (591 mg, 2,32 mmol). After stirring the mixtrure for 20 h at RT, the precipitate was removed, and the filtrate concentrated. The residue was purified by flash chromatography (2% EtOAc in hexanes) to give 754 mg (77%) of **23b** as a colorless oil. R*f* = 0.27 (hexanes/EtOAc 9/1);); ^{1}H NMR (500 MHz) δ 7.68-7.63 (m, 8H), 7.45-7.36 (m, 12H), 5.39-5.31 (m, 4H), 4.11-4.02 (m, 4H), 3.59 (br d, *J* = 5 Hz, 2H), 2.25 (t, *J* = 7.5 Hz, 4H), 2.05-1.98 (m, 8H), 1.83-1.70 (m, 3H), 1.70-1.56 (m, 6H), 1.36-1.26 (m, 32H), 1.06 (s, 9H), 0.89 (t, *J* = 7H, 6H). IR 2927, 2856, 1738, 1464, 1428, 1173, 1113, 702 cm^{-1}. ^{13}C NMR (125 MHz) δ 173.7,

135.6, 133.5, 130.0, 129.7, 129.7, 127.7, 65.6, 34.9, 34.3, 31.8, 30.1, 29.71, 29.68, 29.2, 29.12, 29.09, 29.0, 27.2, 27.1, 26.9, 24.9, 22.6, 19.3, 14.1.

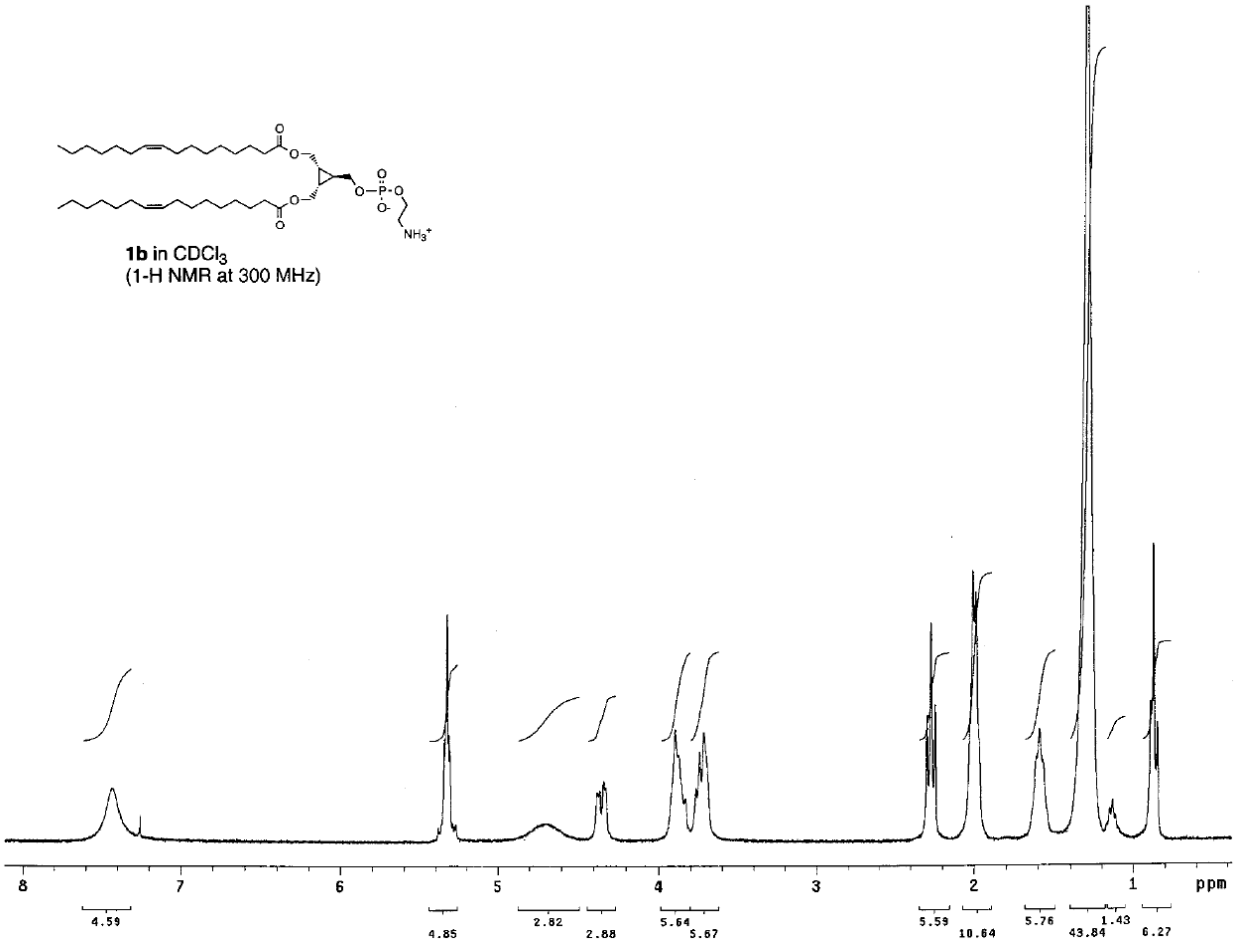
Alcohol 24a. A solution of TBAF (0.6 mL, 1 M in THF, 0.6 mmol) was added to a solution of silyl ether **23a** (275 mg, 0.32 mmol) in 10 mL of THF. After stirring for 16 h at RT, 0.5 mL of water was added and the reaction mixture was filtrated through the plug of $MgSO_4$, and concentrated. Purification by flash chromatography (5…20% EtOAc in hexanes) gave 156 mg (79%) of **24a** as a white solid. **24a:** *Rf* = 0.2 (hexanes/EtOAc 85/15); ^{1}H NMR (500 MHz) δ 4.18-4.10 (m, 4H), 3.61 (d, *J*= 3.5 Hz, 2H), 2.28 (t, *J* = 7 Hz, 4H), 1.78-1.55 (m, 9H), 1.32-1.22 (m, 48H), 0.87 (t, *J* = 7 Hz, 6H); ^{13}C NMR (125 MHz, some signals in aliphatic region overlap) δ 173.9, 64.6, 62.3, 34.8, 34.3, 31.9, 30.0, 29.7, 29.62, 29.58, 29.4, 29.3, 29.2, 29.1, 24.9, 22.6, 14.1. Mp. 50-52 °C. FAB-HRMS (*m/z*) $[M+H]^+$ calcd for $C_{38}H_{74}O_5$ 611.5618, found 611.5649.

Alcohol 24b. The same procedure to make **24a** was used to produce **24b** in 60% yield. **24b:** ^{1}H NMR (300 MHz) δ 5.40-5.27 (m, 4H), 4.14 (t, *J* = 6 Hz, 4H), 3.60 (br d, *J* = 3 Hz, 2H), 2.28 (t, *J* = 7.5 Hz, 4H), 2.00 (br q, *J* = 6 Hz, 8H), 1.82-1.55 (m, 9H), 1.36-1.23 (m, 32H), 0.87 (t, *J* = 7 Hz, 6H); ^{13}C NMR (75 MHz) δ 173.8, 130.0, 129.7, 64.8, 62.3, 35.0, 34.3, 31.7, 30.1, 29.69, 29.66, 29.14, 29.11, 29.08, 28.9, 27.2, 27.1, 24.9, 22.6, 14.1. IR 3468, 2924, 2854, 1736, 1464, 1175 cm^{-1}. FAB-HRMS (*m/z*) $[M+H]^+$ calcd for $C_{38}H_{70}O_5$ 607.5302, found 607.5319.

Phospholipid 2a. The two-step procedure to make **1a** was used to make **2a** in 94% yield. **2a:** ^{1}H NMR (500 MHz) δ 8.72 (br s, 2H), 4.18-4.09 (m, 4H), 3.94 (br s, 2H), 2.27 (t, *J* = 8 Hz, 4H), 1.90-1.83 (m, 1H), 1.80-1.71 (m, 2H), 1.71-1.62 (m, 2H), 1.62-1.54 (m, 4H), 1.32-1.22 (m, 48H), 0.87 (t, *J* = 7 Hz, 6H); ^{13}C NMR (125 MHz, some signals in aliphatic region overlap) δ 174.2, 68.3 (d, *J* = 4.4 Hz), 62.1, 34.3, 32.7 (d, *J* = 7.5 Hz), 31.9, 29.9, 29.73, 29.70, 29.67, 29.6, 29.37, 29.36, 29.2, 24.9, 22.7, 14.1. FAB-HRMS (*m/z*) $[M+H]^+$ calcd for $C_{58}H_{75}O_8P$ 691.5278, found 691.5250.

Phospholipid 2c. The two-step procedure to make **1c** was used to make **2c**. The crude product was purified by flash chromatography (first eluting with 15% MeOH in $CHCl_3$ followed by 20:4:1 $CHCl_3$:MeOH:NH_4OH) to afford 32 mg (43%) of **2c** as a waxy solid. Phospholipid **2c** is practically insoluble in common organic solvents and water. R*f* = 0.58 ($CHCl_3$/MeOH/NH_4OH 10:4:1). FAB-HRMS (*m/z*) $[M+H]^+$ calcd for $C_{40}H_{81}NO_8P$ 735.5778, found 735.5758.

Phospholipid 2b. The two-step procedure to make **1b** was used to make **2b**. The crude product was purified by flash chromatography (first eluting with 2-5% MeOH in $CHCl_3$ followed by 20:4:1 $CHCl_3$:MeOH:NH_4OH and 10:4:1 $CHCl_3$:MeOH:NH_4OH, final samples taken up in chloroform and filtered to separate silica) to afford 83.4 mg (81%) of **2b** as a semi-solid. **2b:** R*f* = 0.58 ($CHCl_3$/MeOH/H_2O 62/25/4). ^{1}H NMR (500 MHz) δ 5.37-5.29 (m, 4H), 4.17-4.06 (m, 4H), 3.90 (br s, 2H), 3.78 (br t, *J* = 4.5 Hz, 2H), 3.71 (br s, 2H), 2.26 (t, *J* = 7.5 Hz, 4H), 2.00 (q, *J* = 6.5 Hz, 8H), 1.84-1.78 (m, 1H), 1.78-1.70 (m, 2H), 1.70-1.63 (m, 2H), 1.62-1.54 (m, 4H), 1.36-1.23 (m, 32H), 0.87 (t, *J* = 7Hz, 6H); ^{13}C NMR (125 MHz) δ 174.1, 130.0, 129.7, 67.3 (d, *J* = 6 Hz), 66.3, 62.3, 61.6 (br d, *J* = 5.5 Hz), 34.3, 32.9 (d, *J* = 7.5 Hz), 31.8, 30.1, 29.72, 29.71, 29.24, 29.19, 29.17, 29.0, 27.20, 27.17, 24.9, 22.6, 14.1. FAB-HRMS (*m/z*) $[M+H]^+$ calcd for $C_{40}H_{77}NO_8P$ 731.5466, found 731.5437.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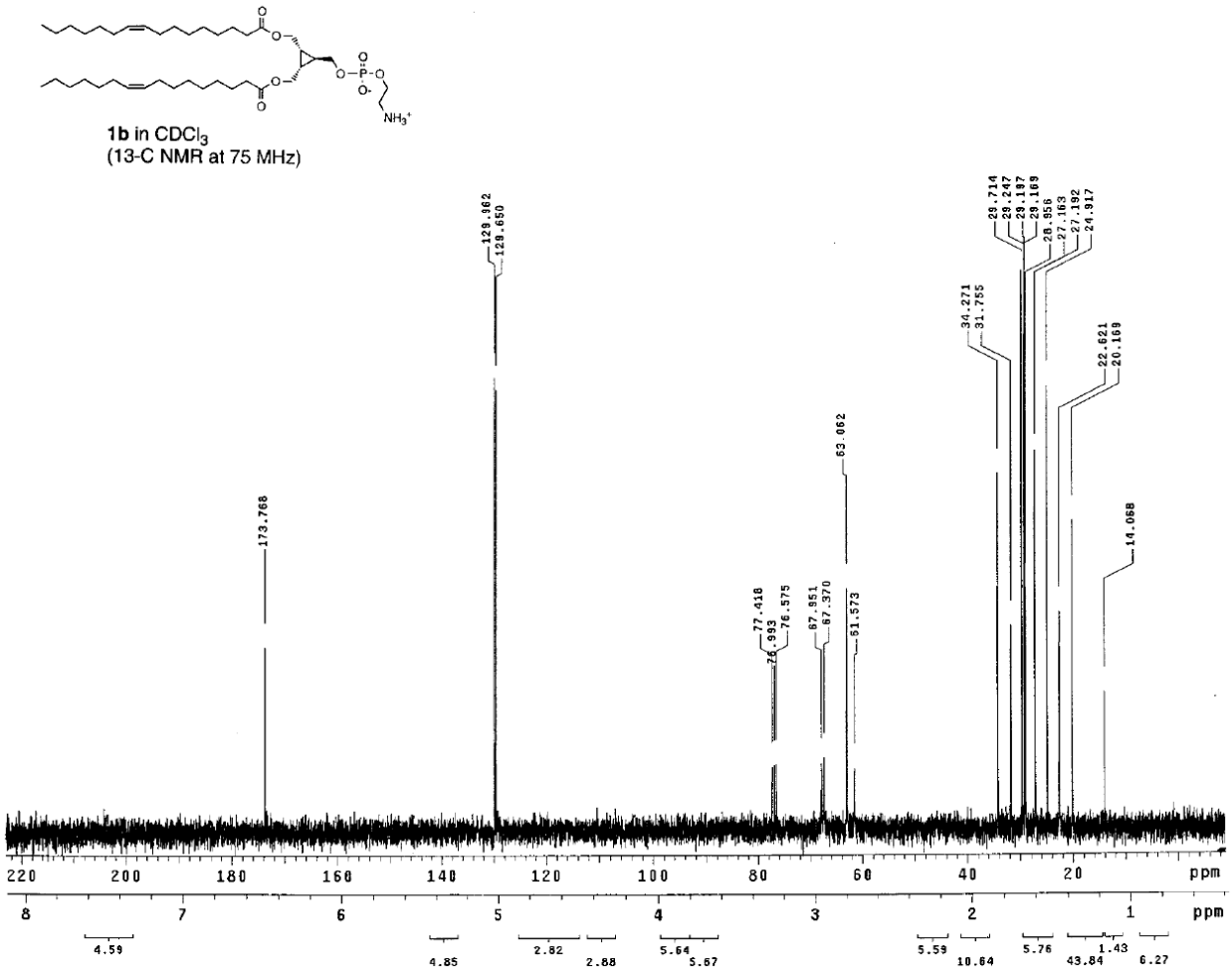
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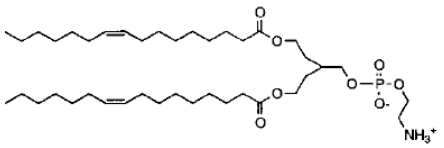

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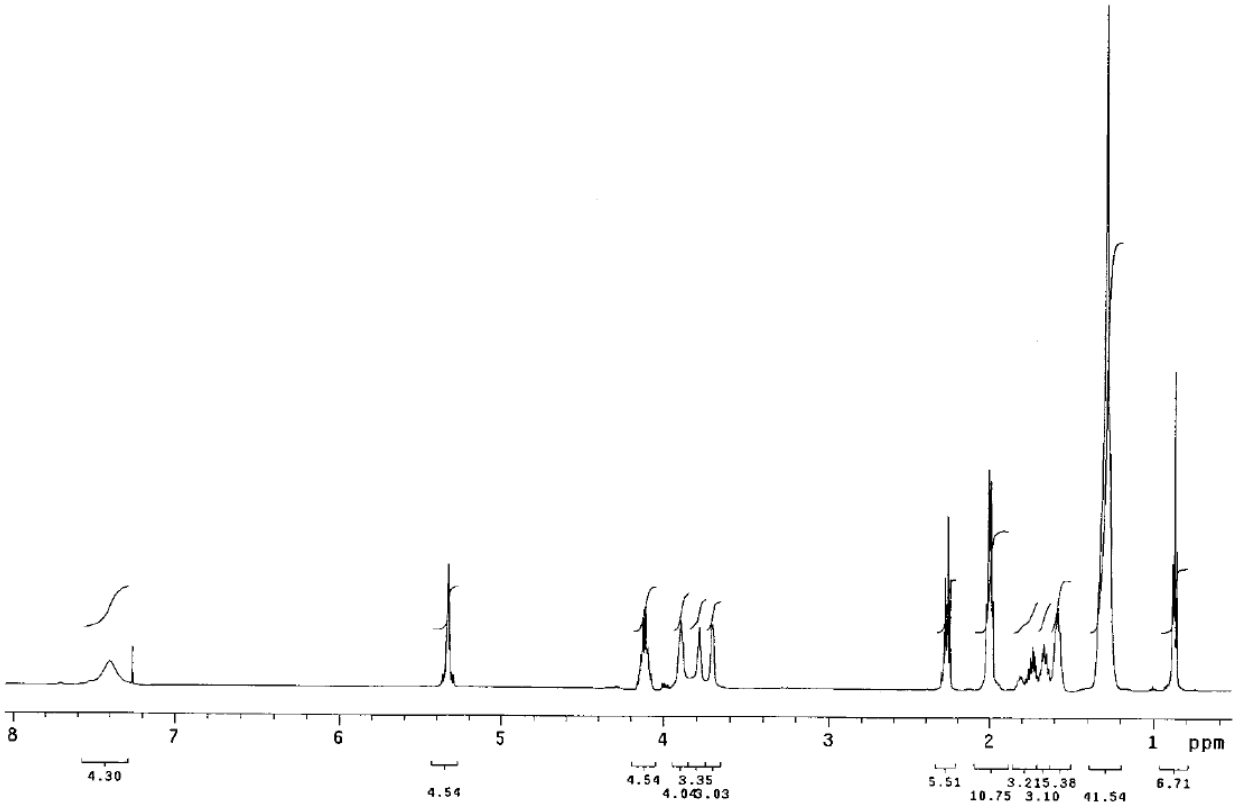

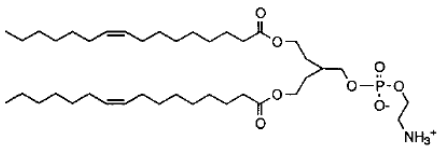

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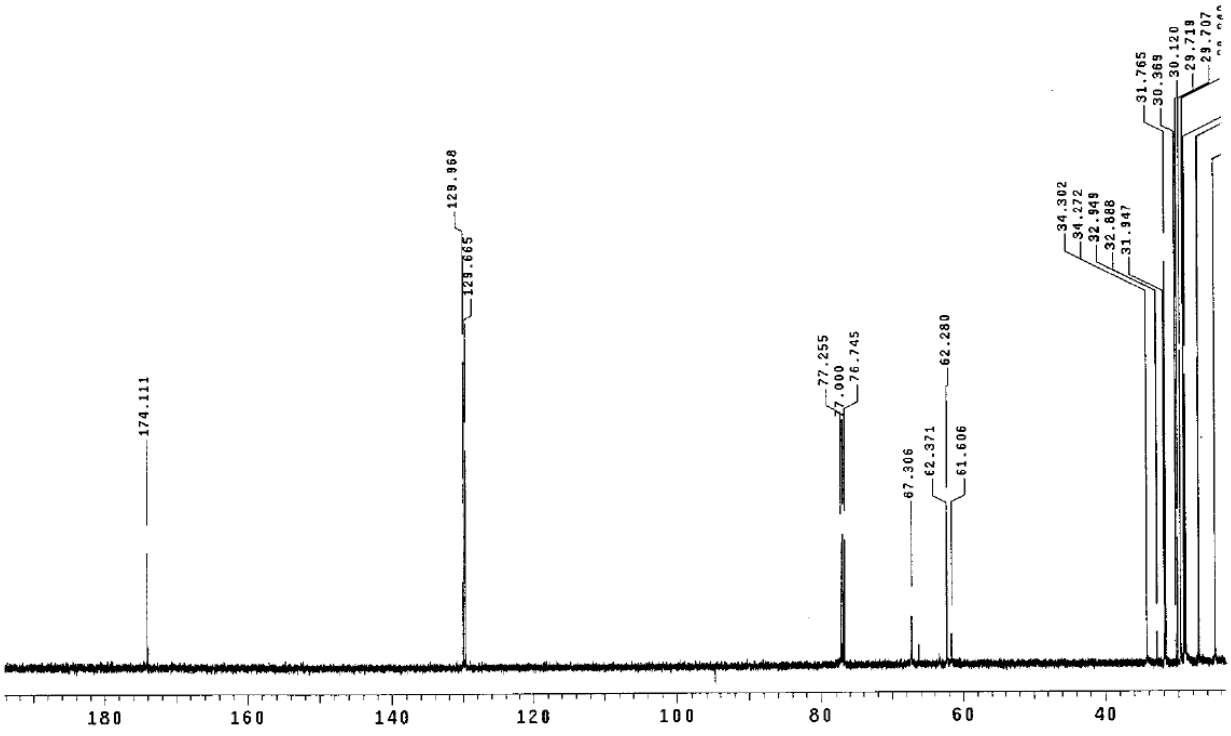

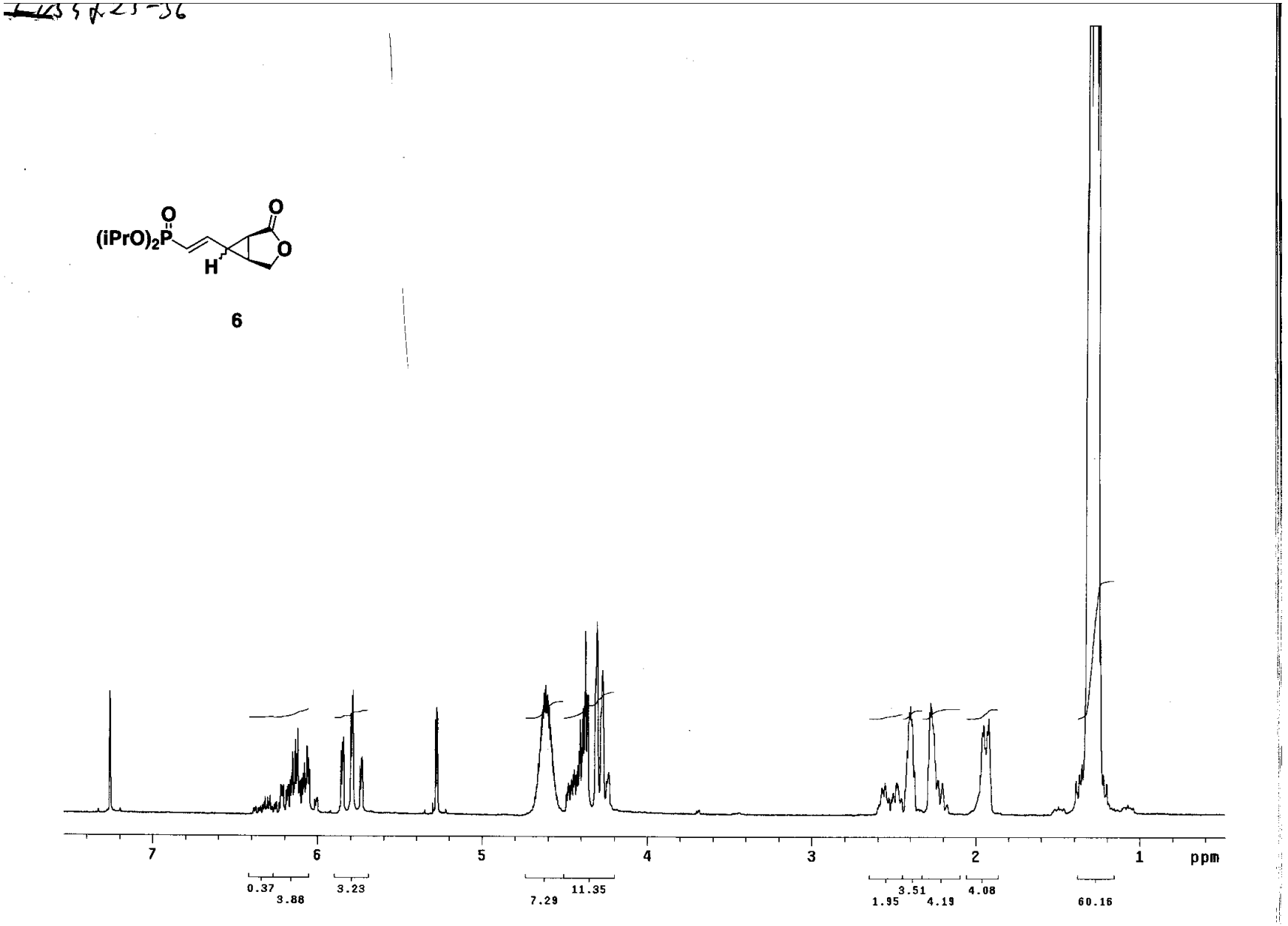
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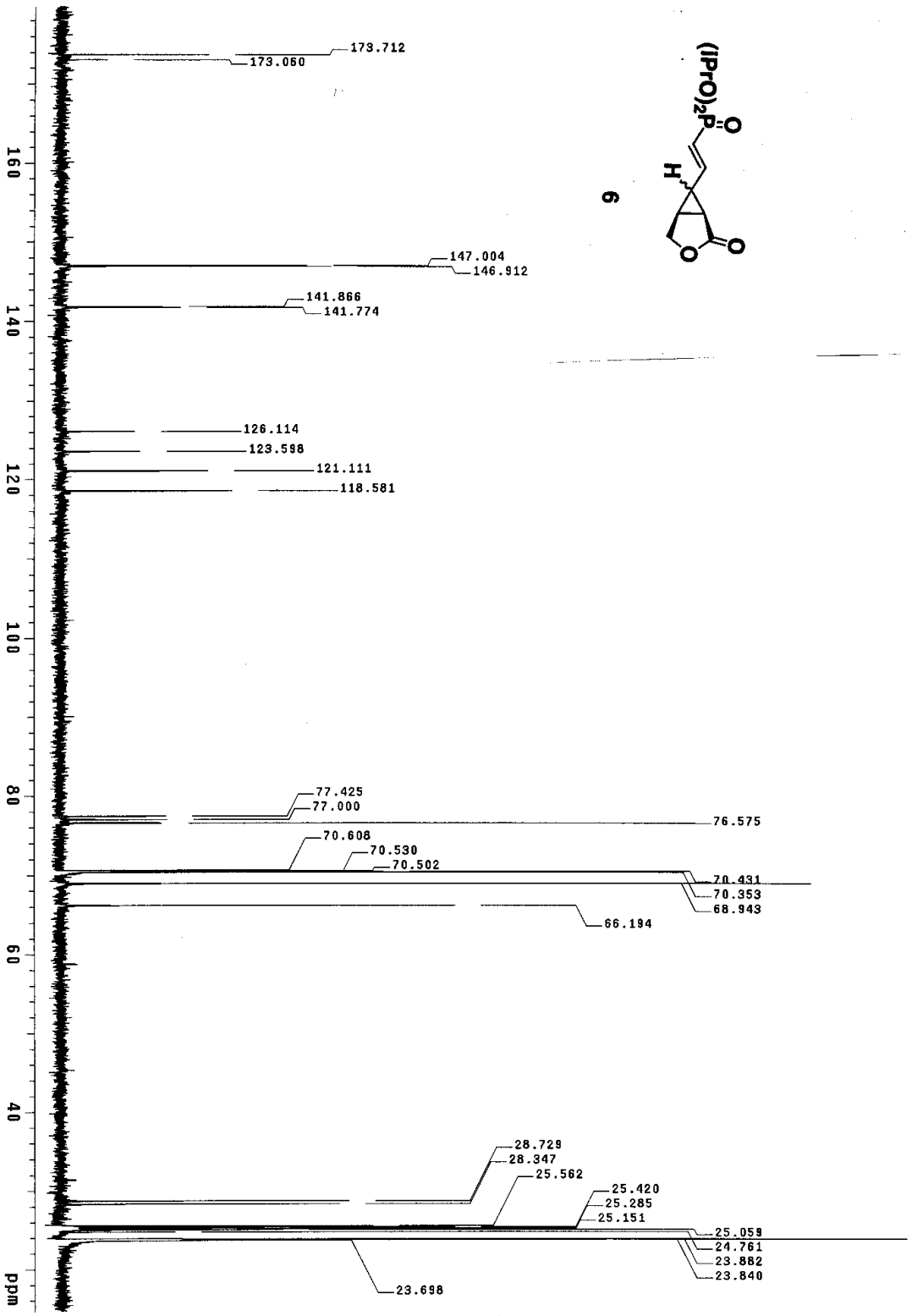
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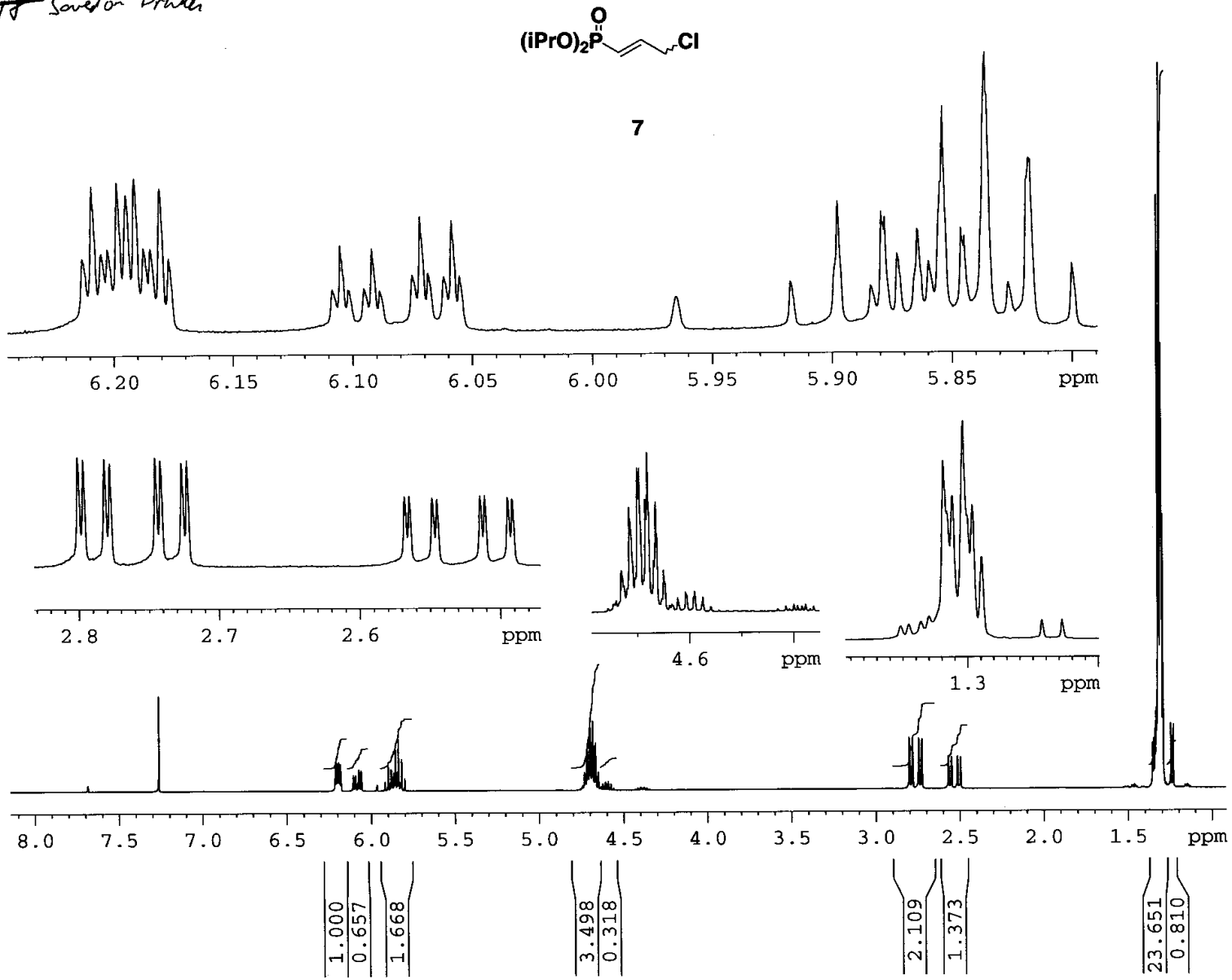

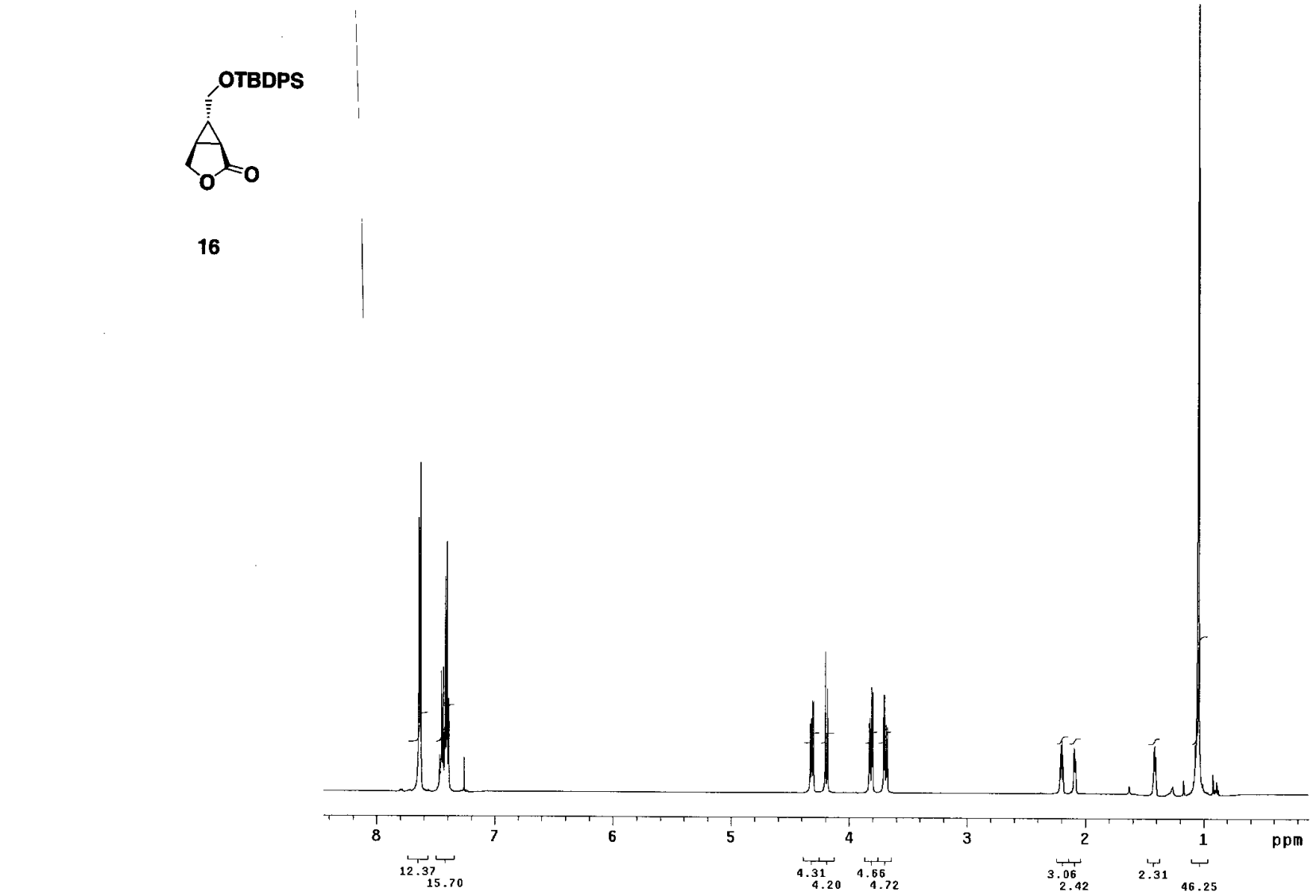
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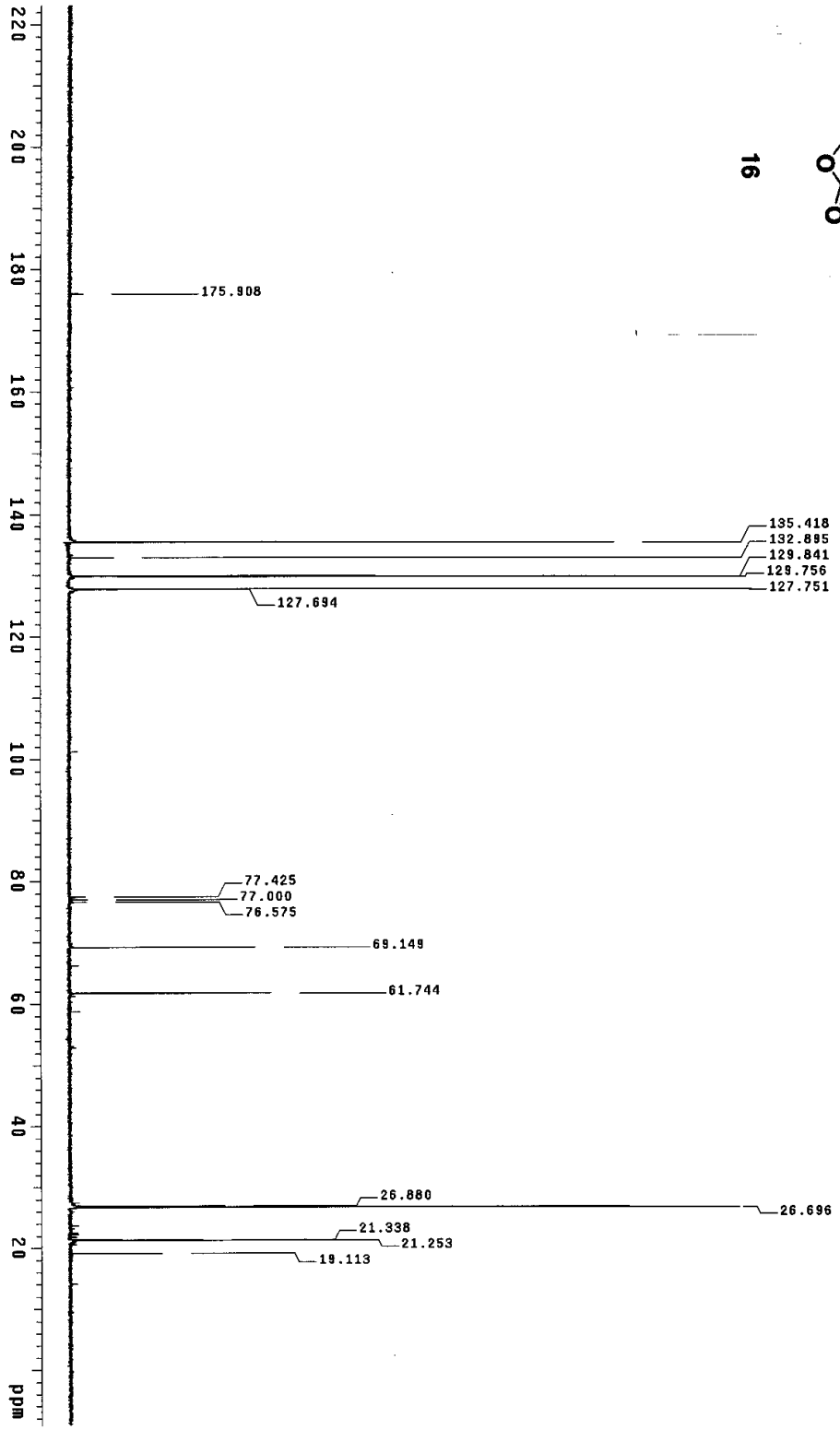
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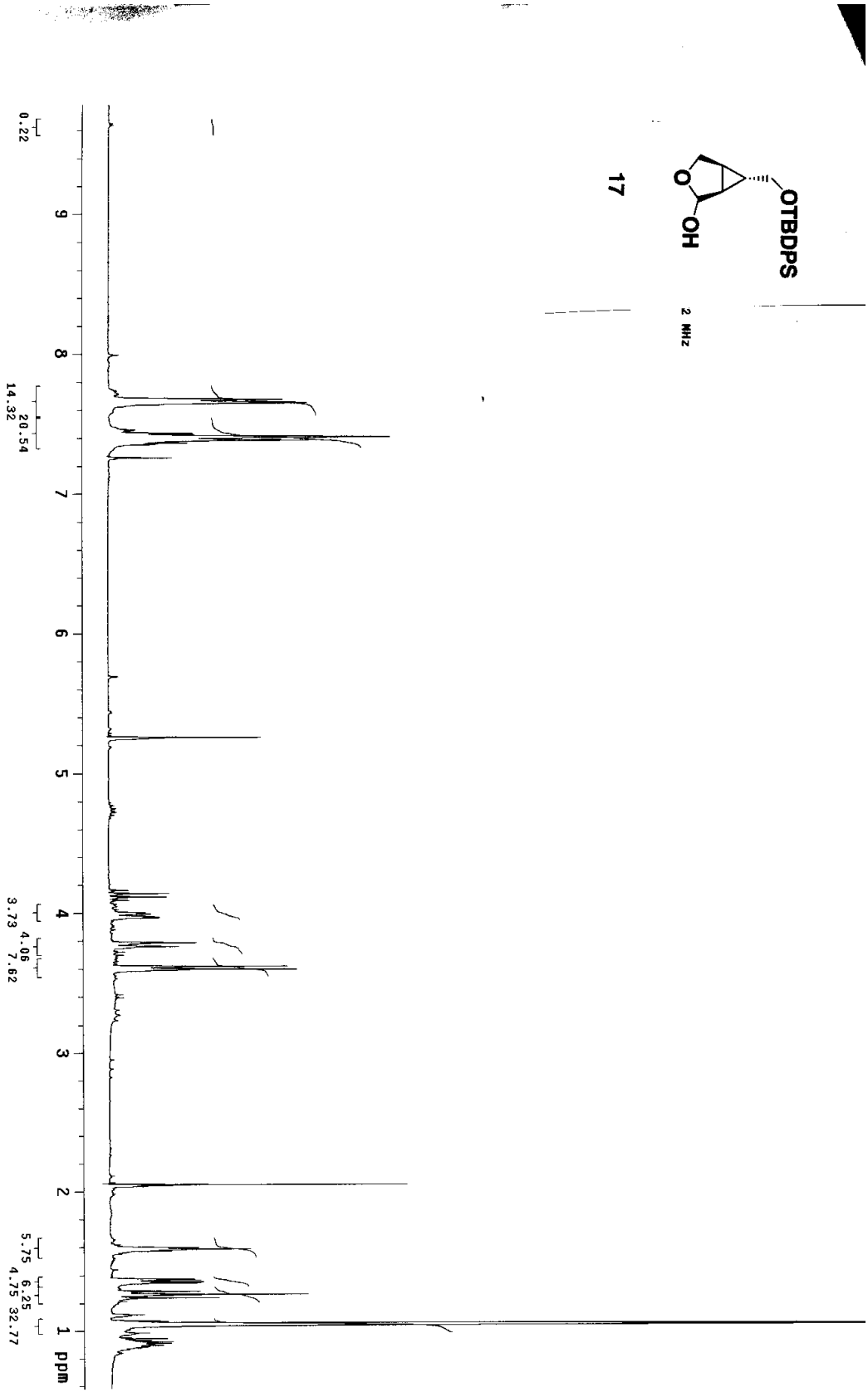
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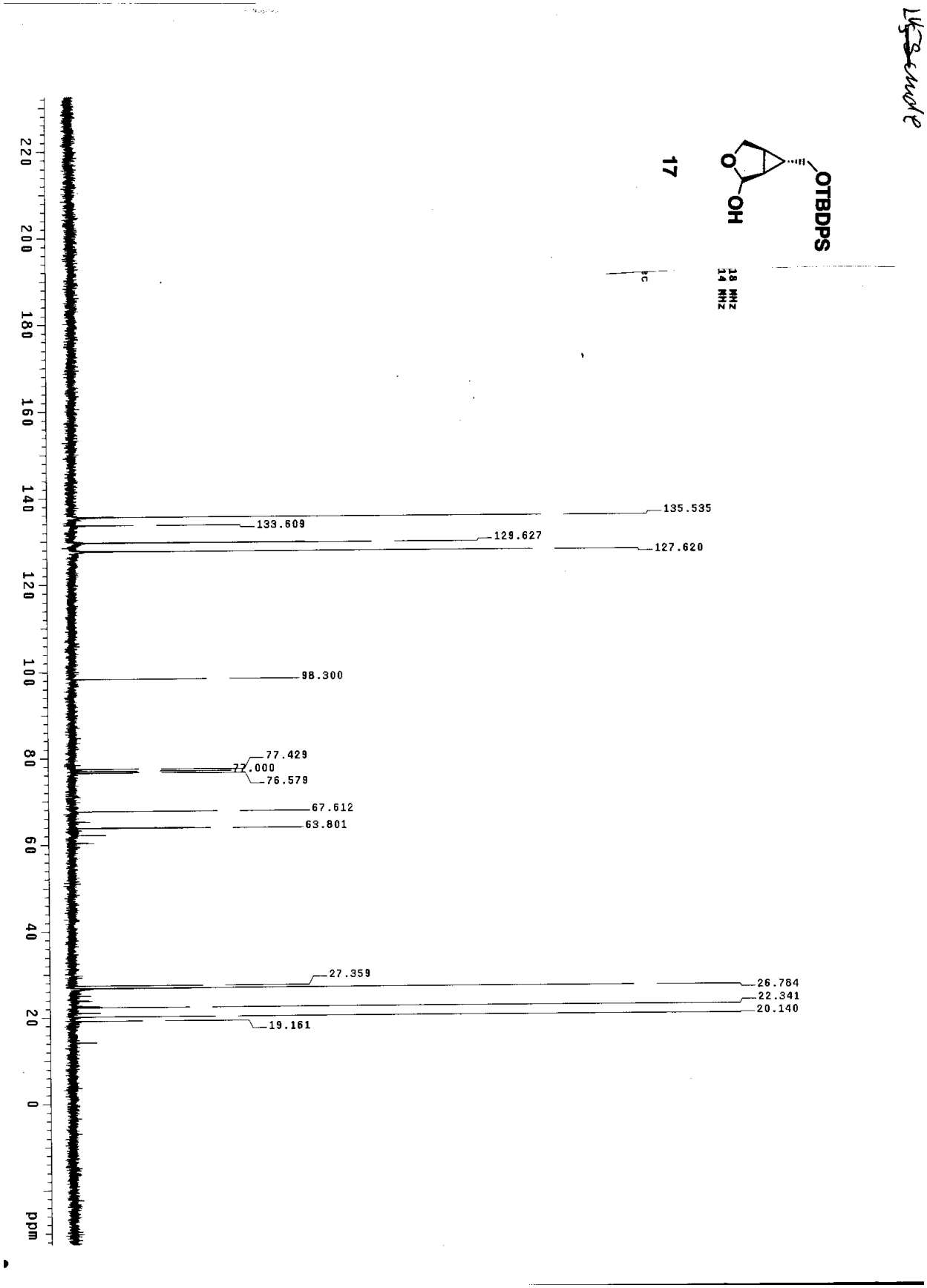
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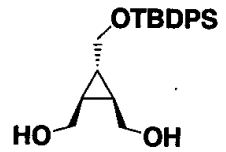
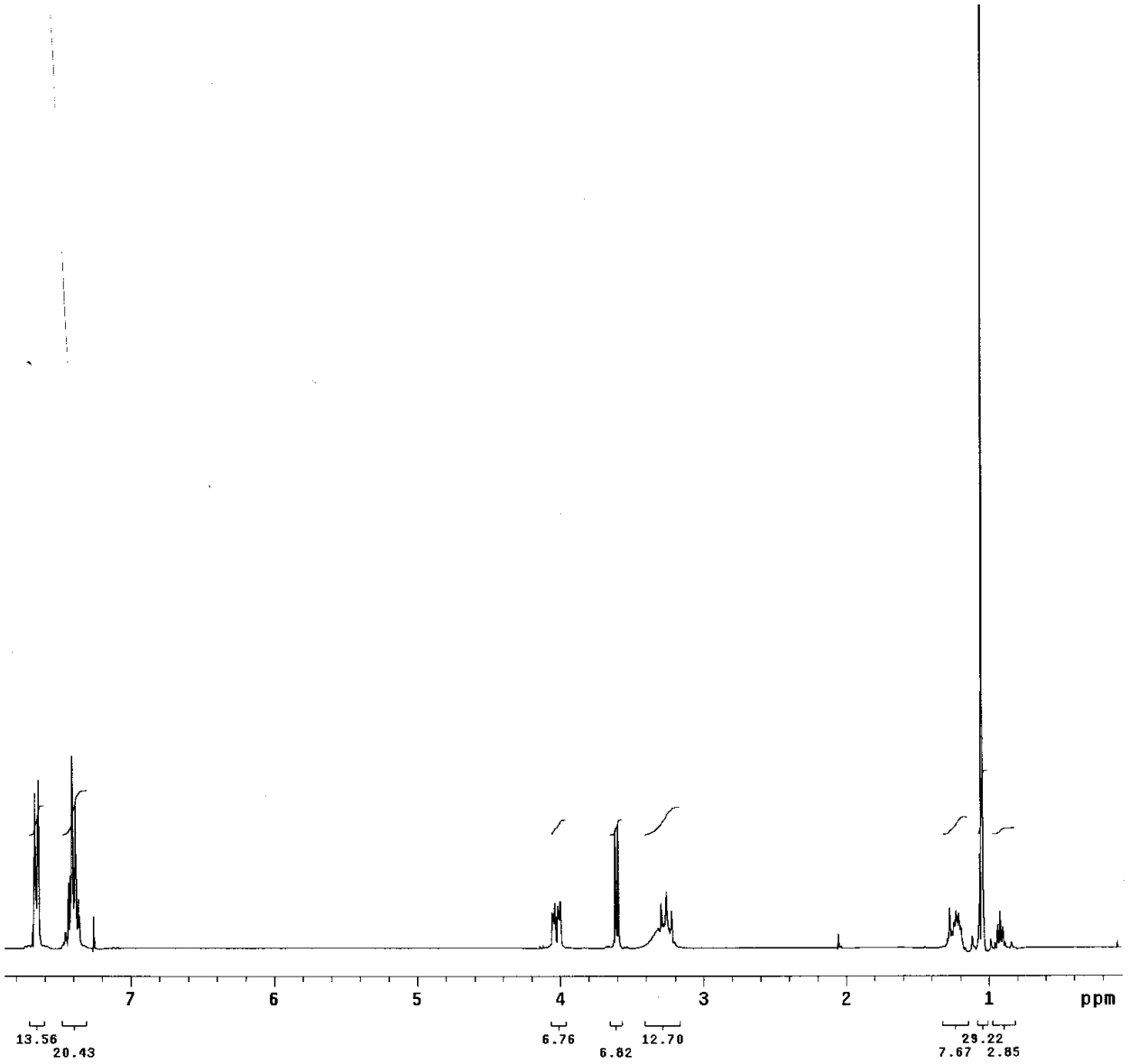
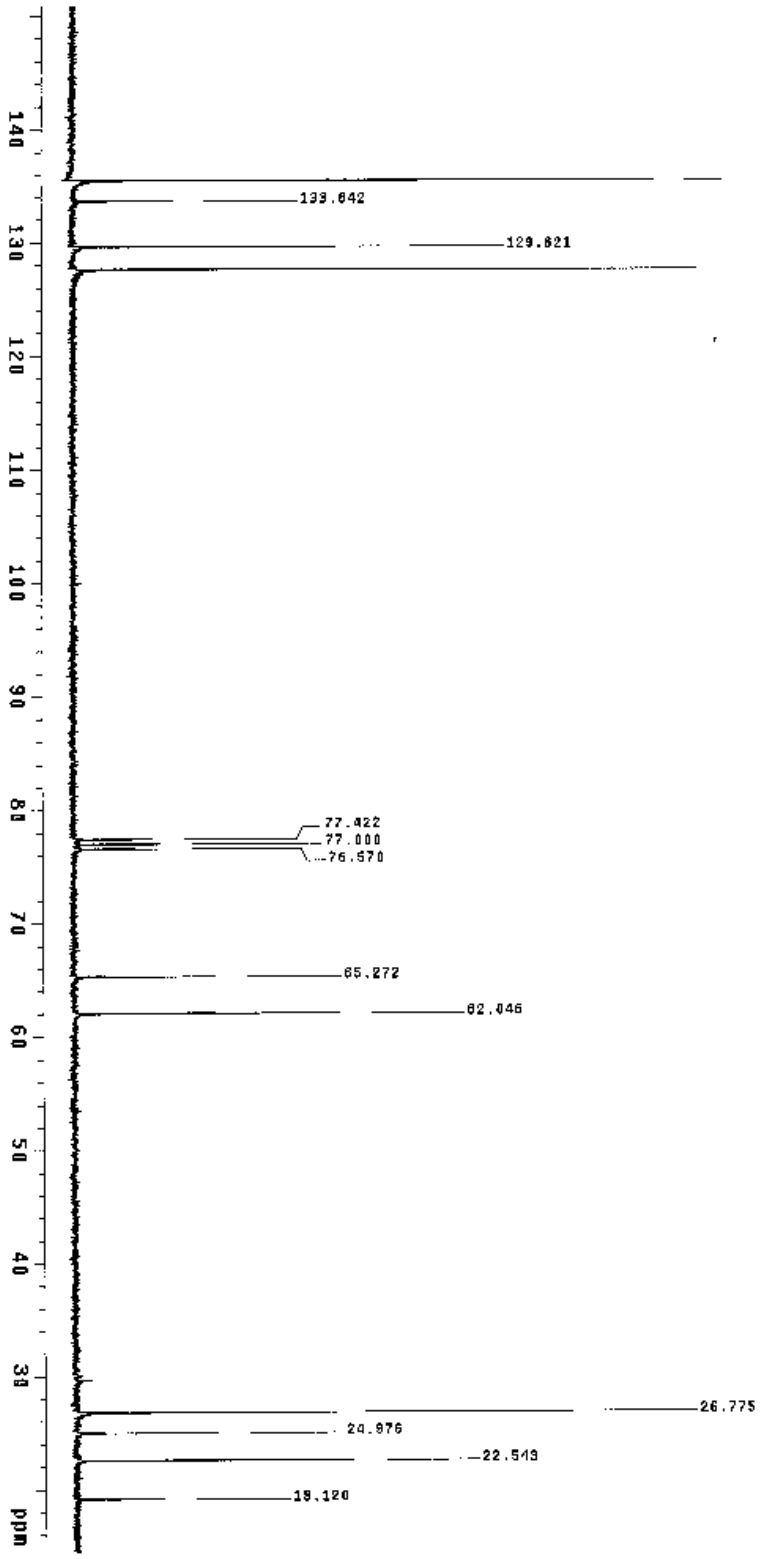
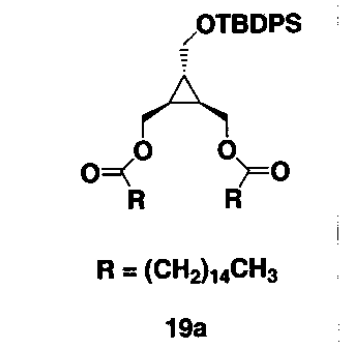


18

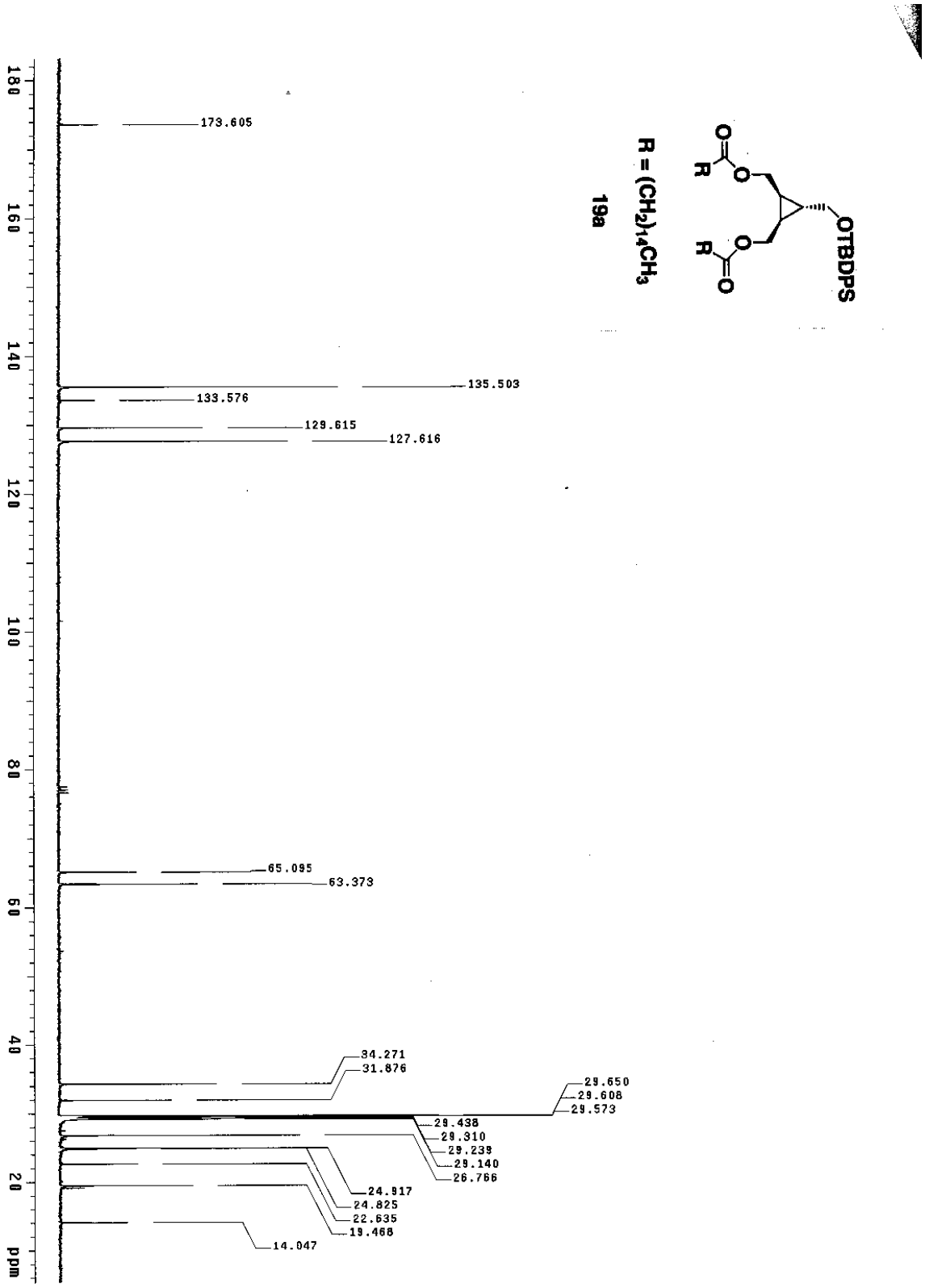



18
HO
OH
OTBDPS
133.642
129.821
77.422
77.000
76.570
65.272
62.046
26.775
24.976
22.543
18.120
ppm

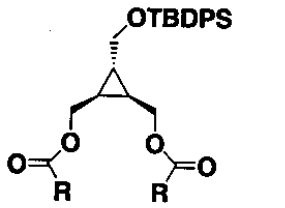


$R = (CH_2)_{14}CH_3$

19a

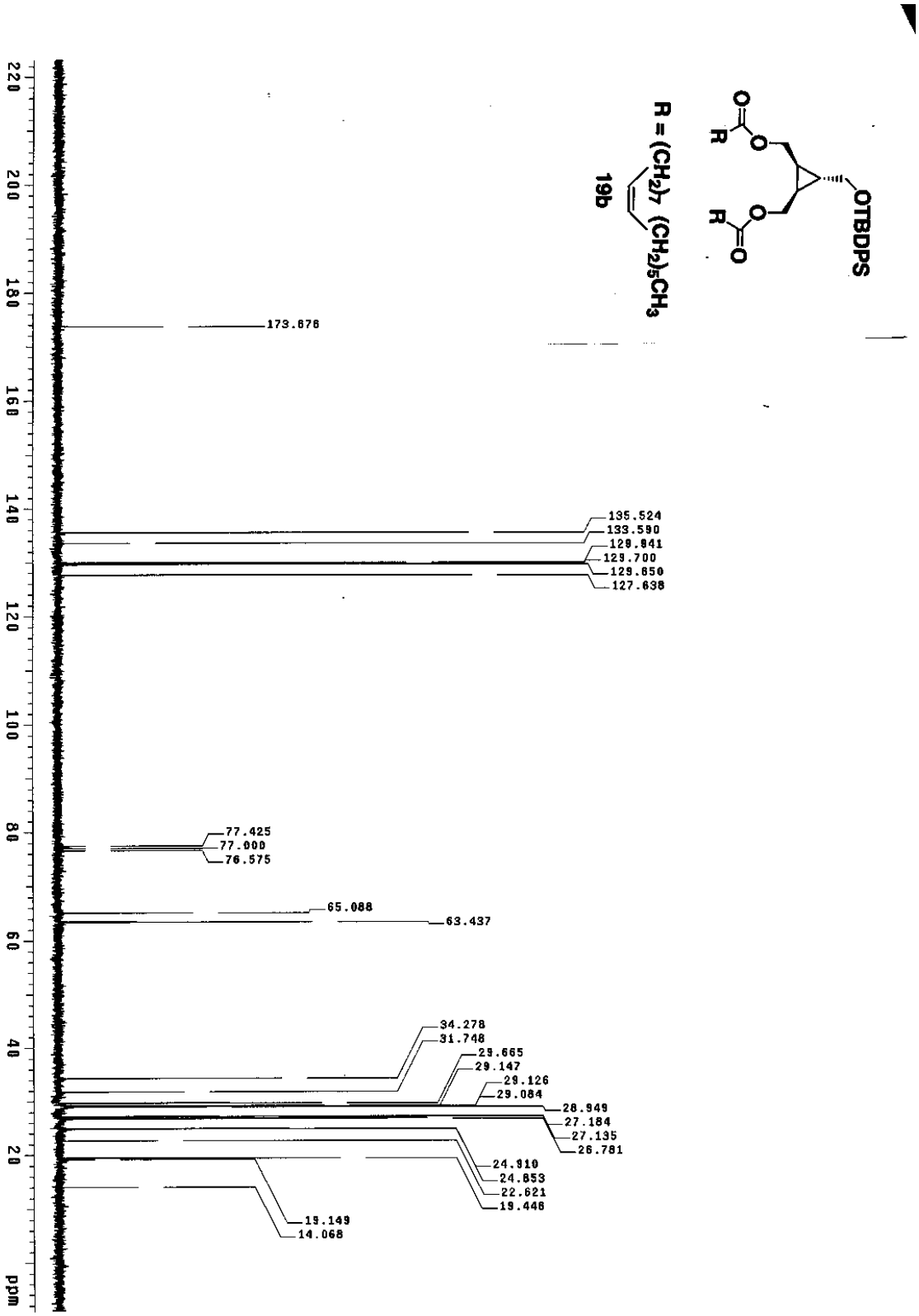

R = (CH2)14CH3
19a
OTBDPS
173.605
135.503
133.576
129.615
127.616
65.095
63.373
34.271
31.876
29.650
29.608
29.573
29.438
29.310
29.239
29.140
26.766
24.917
24.825
22.635
19.468
14.047
ppm

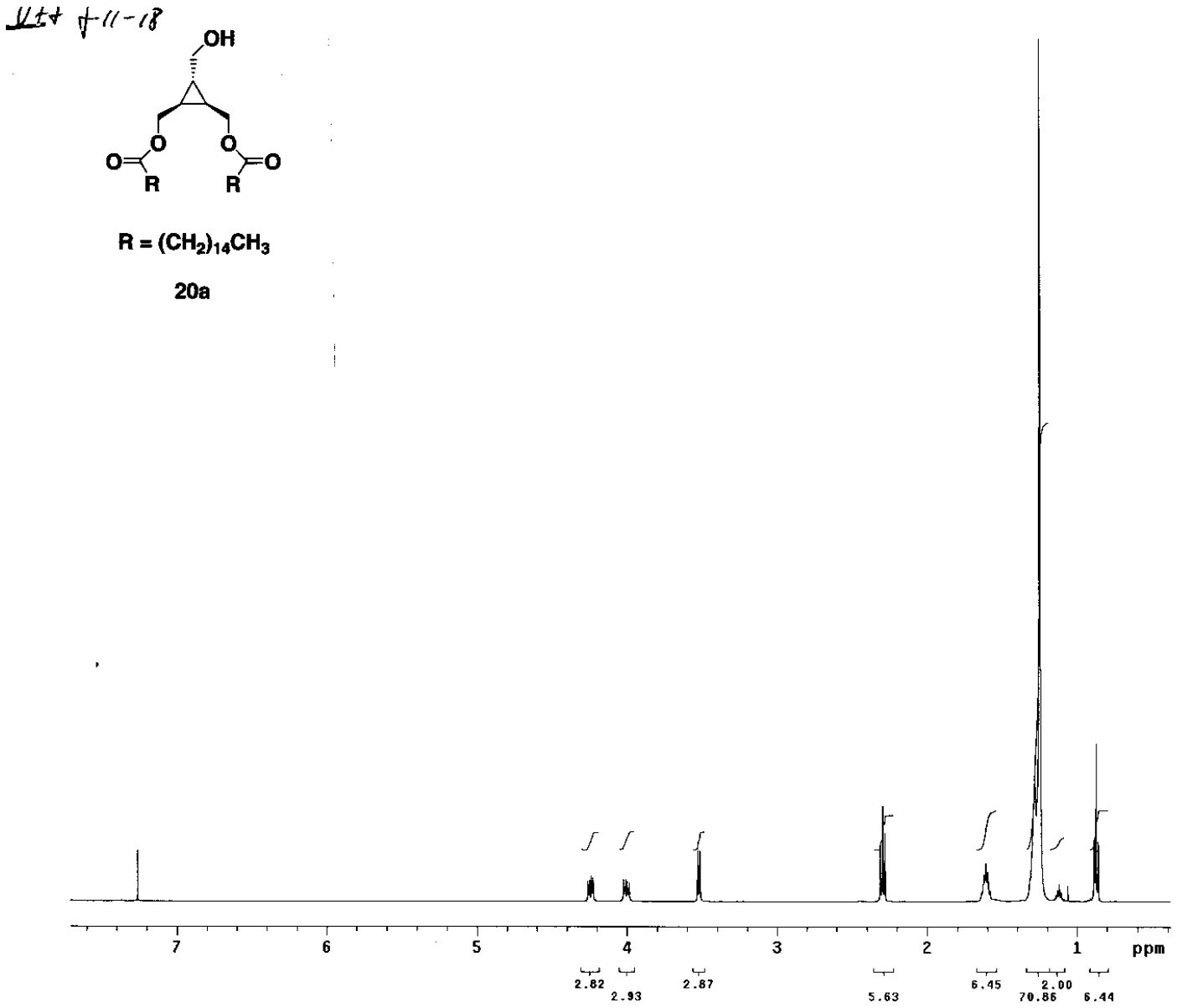
LV147 f.15-28

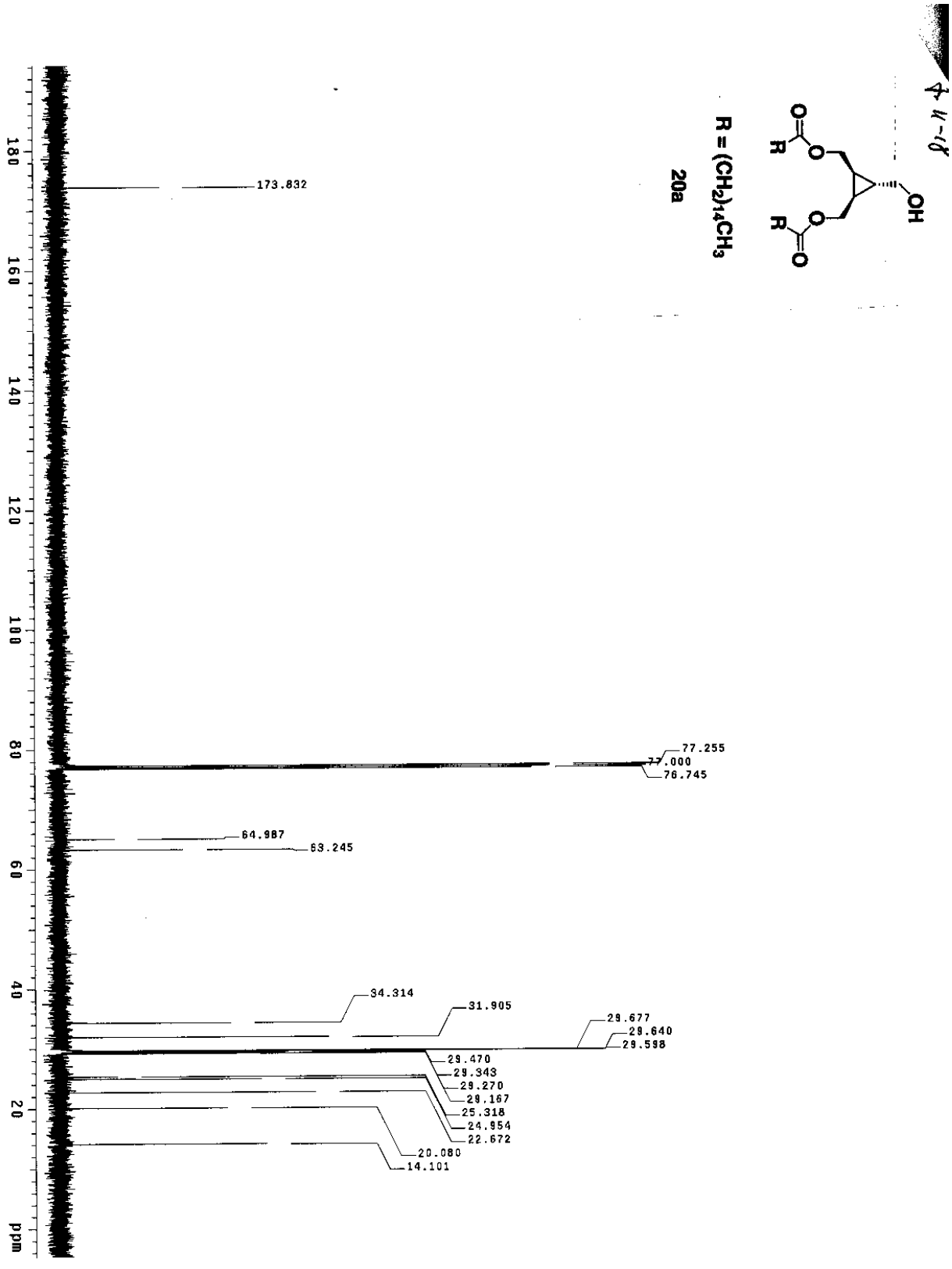


R = $(CH_2)_7$ $(CH_2)_5CH_3$

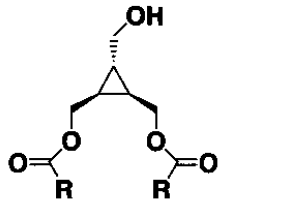
19b


R = (CH2)7 (CH2)5CH3
19b
OTBDPS
173.676
135.524
133.590
129.841
129.700
129.650
127.638
77.425
77.000
76.575
65.088
63.437
34.278
31.748
29.665
29.147
29.126
29.084
28.949
27.184
27.135
26.781
24.910
24.853
22.621
19.446
19.149
14.068
ppm


OH
O
O
O
O
R
R
R = (CH2)14CH3
20a
7
6
5
4
3
2
1
ppm
2.82
2.93
2.87
5.63
6.45
2.00
70.86
6.44

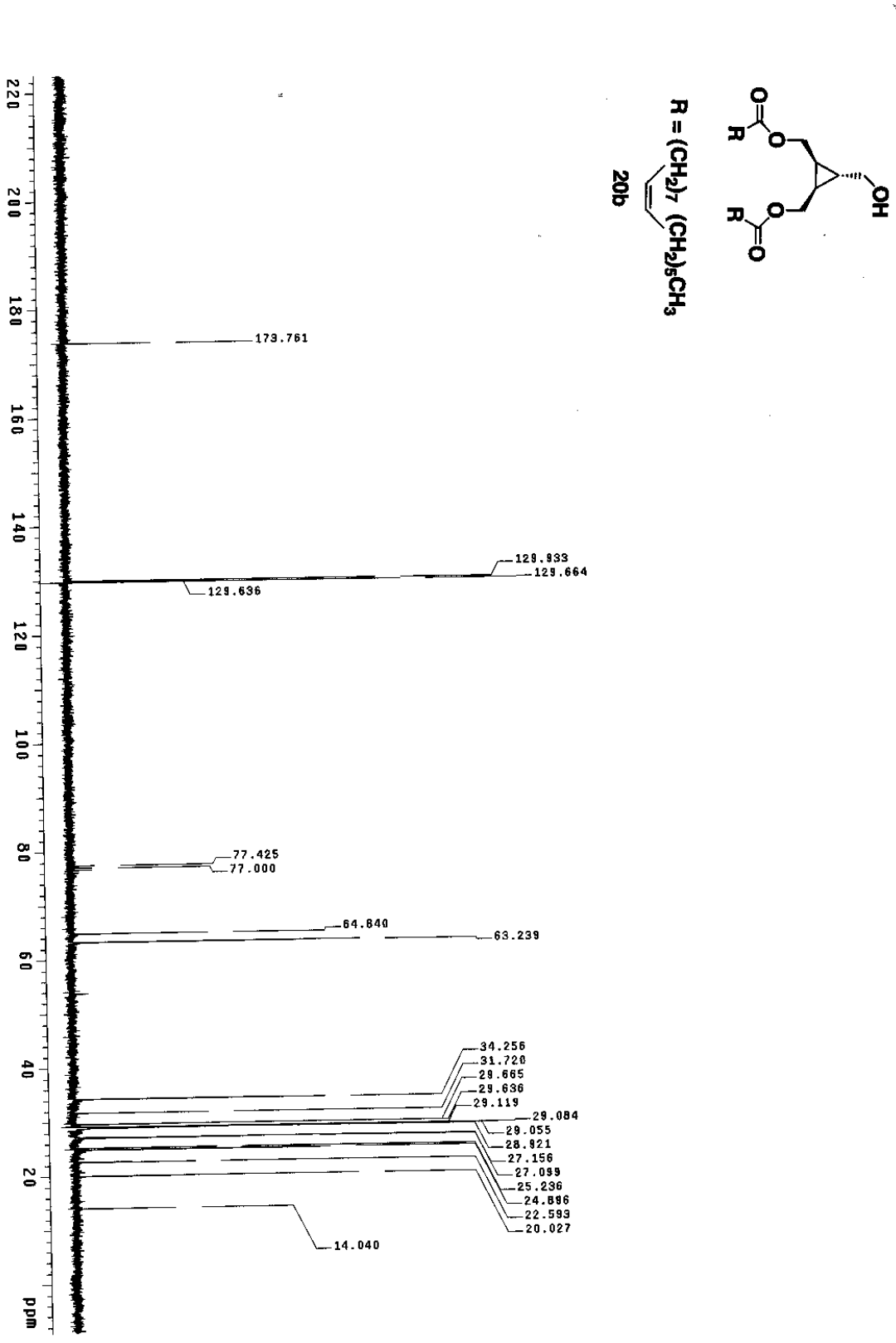

R = (CH2)14CH3
20a
173.832
77.255
77.000
76.745
64.987
63.245
34.314
31.905
29.677
29.640
29.598
29.470
29.343
29.270
29.167
25.318
24.954
22.672
20.080
14.101
ppm

~~148~~ f. 21-29

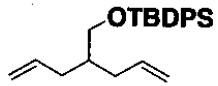


R = $(CH_2)_7$ $(CH_2)_5CH_3$

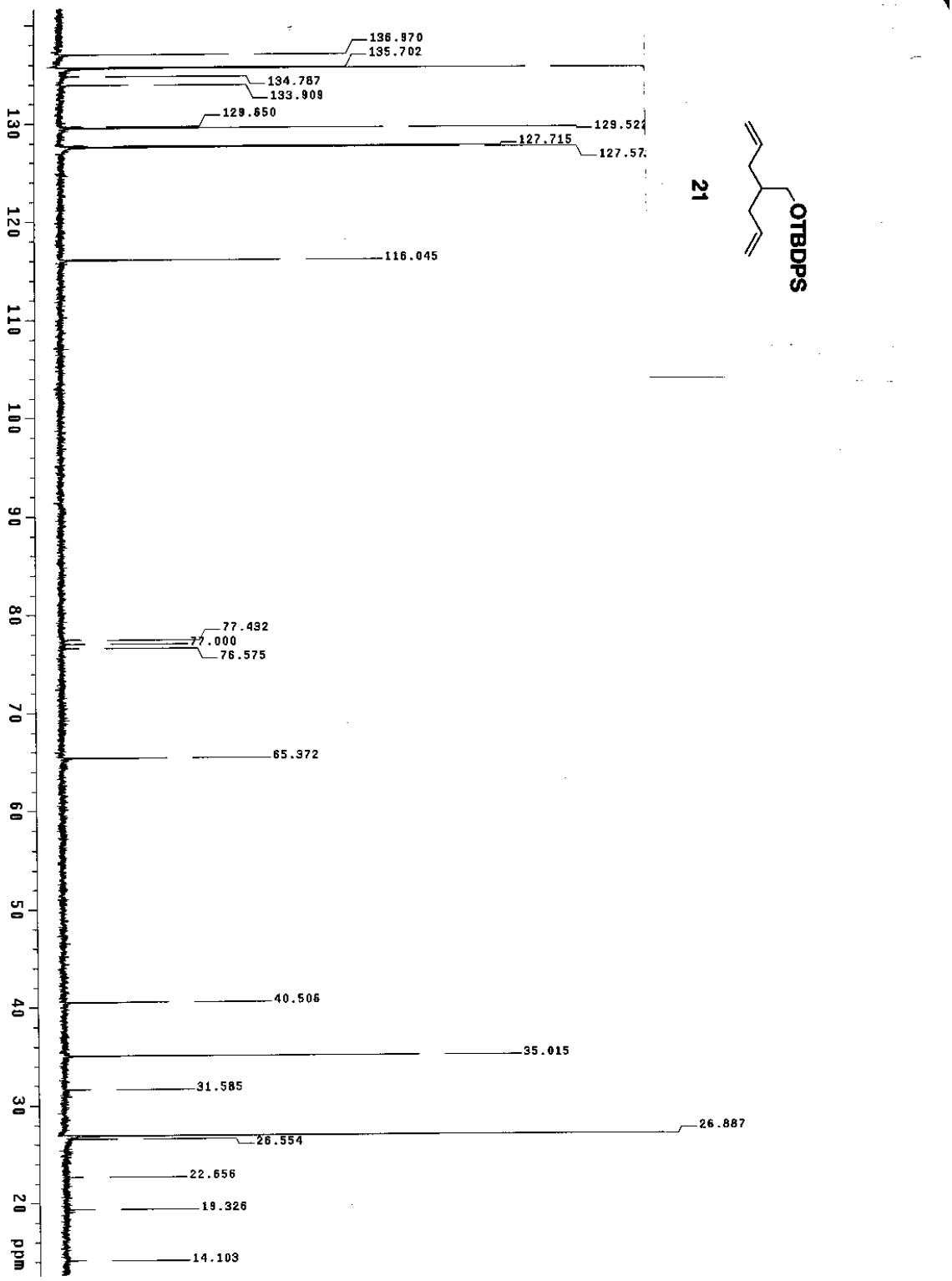
20b

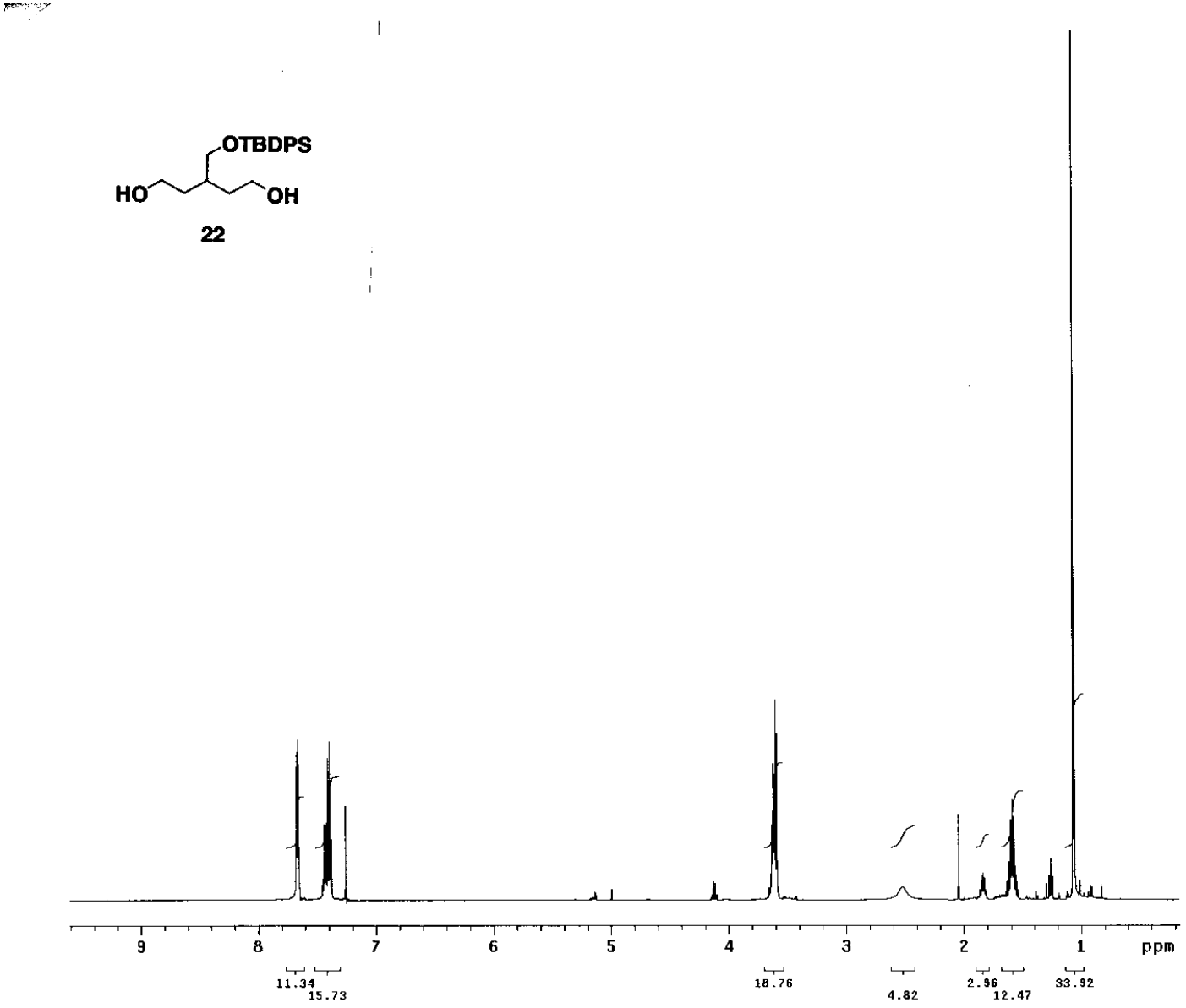

R = (CH2)7 (CH2)5CH3
20b
OH
O
R
220
200
180
160
140
120
100
80
60
40
20
ppm
173.761
129.933
129.664
129.636
77.425
77.000
64.840
63.239
34.256
31.720
29.665
29.636
29.119
29.084
29.055
28.921
27.156
27.099
25.236
24.886
22.593
20.027
14.040

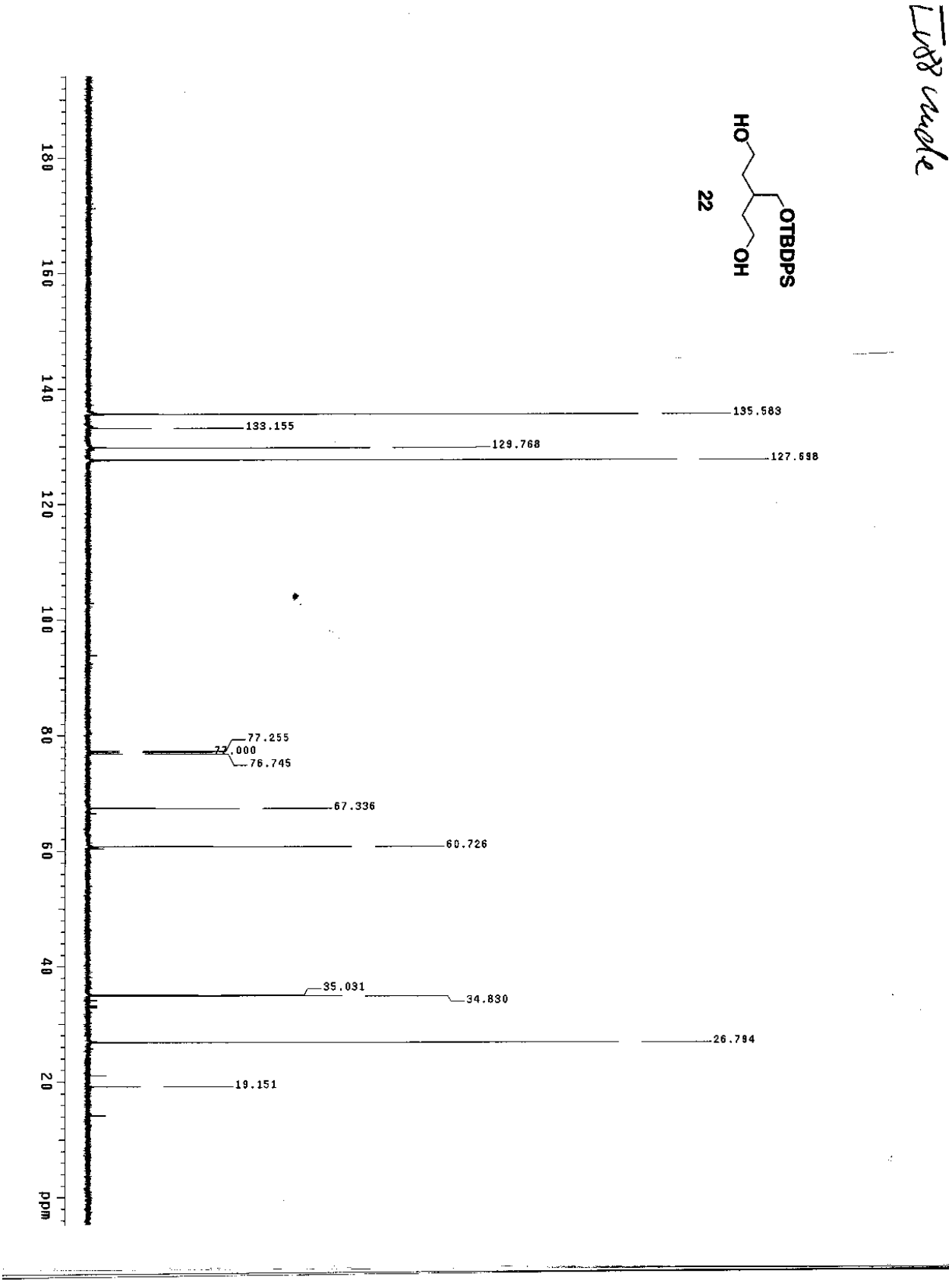
— LV102 1-3-7

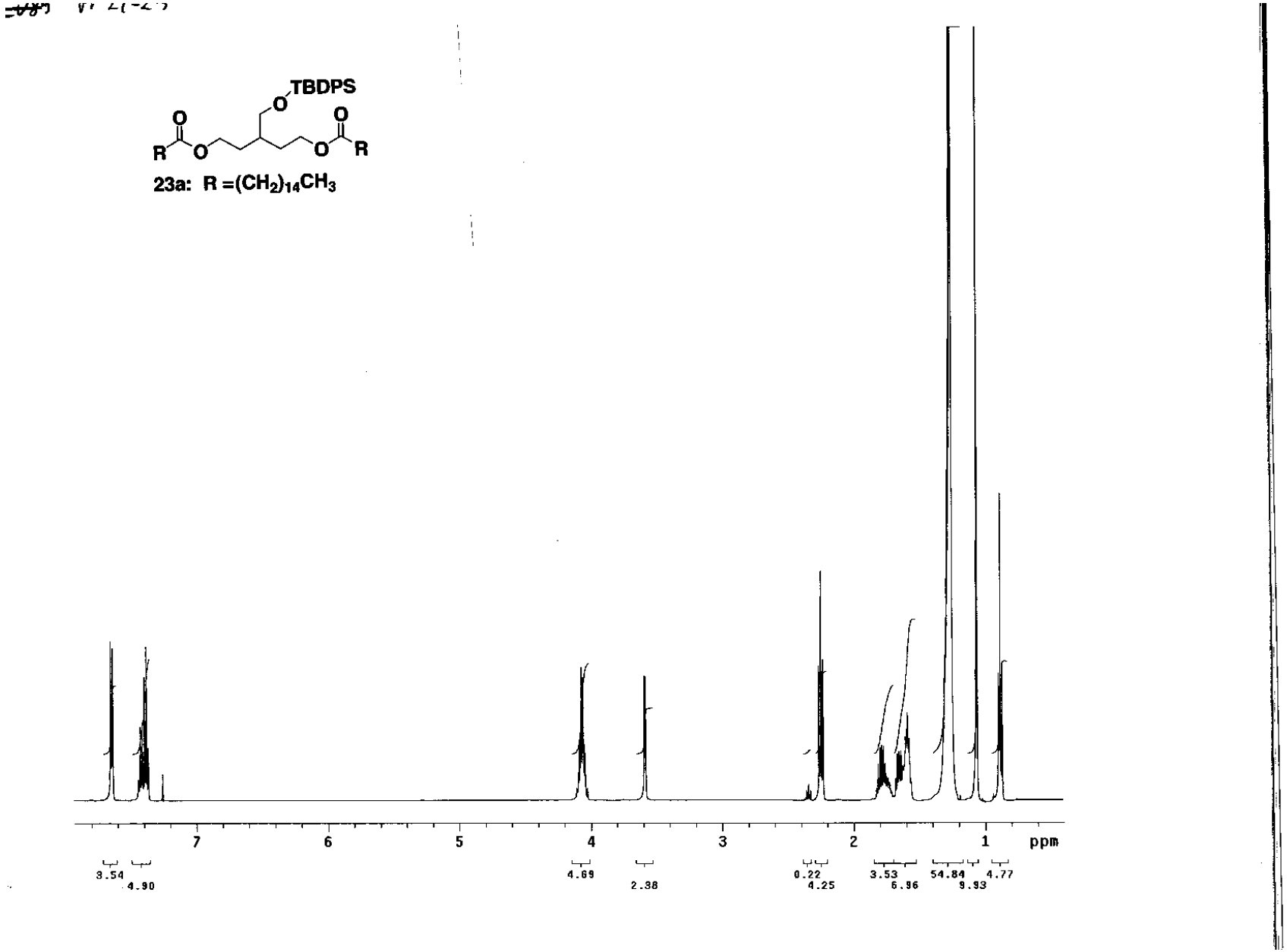


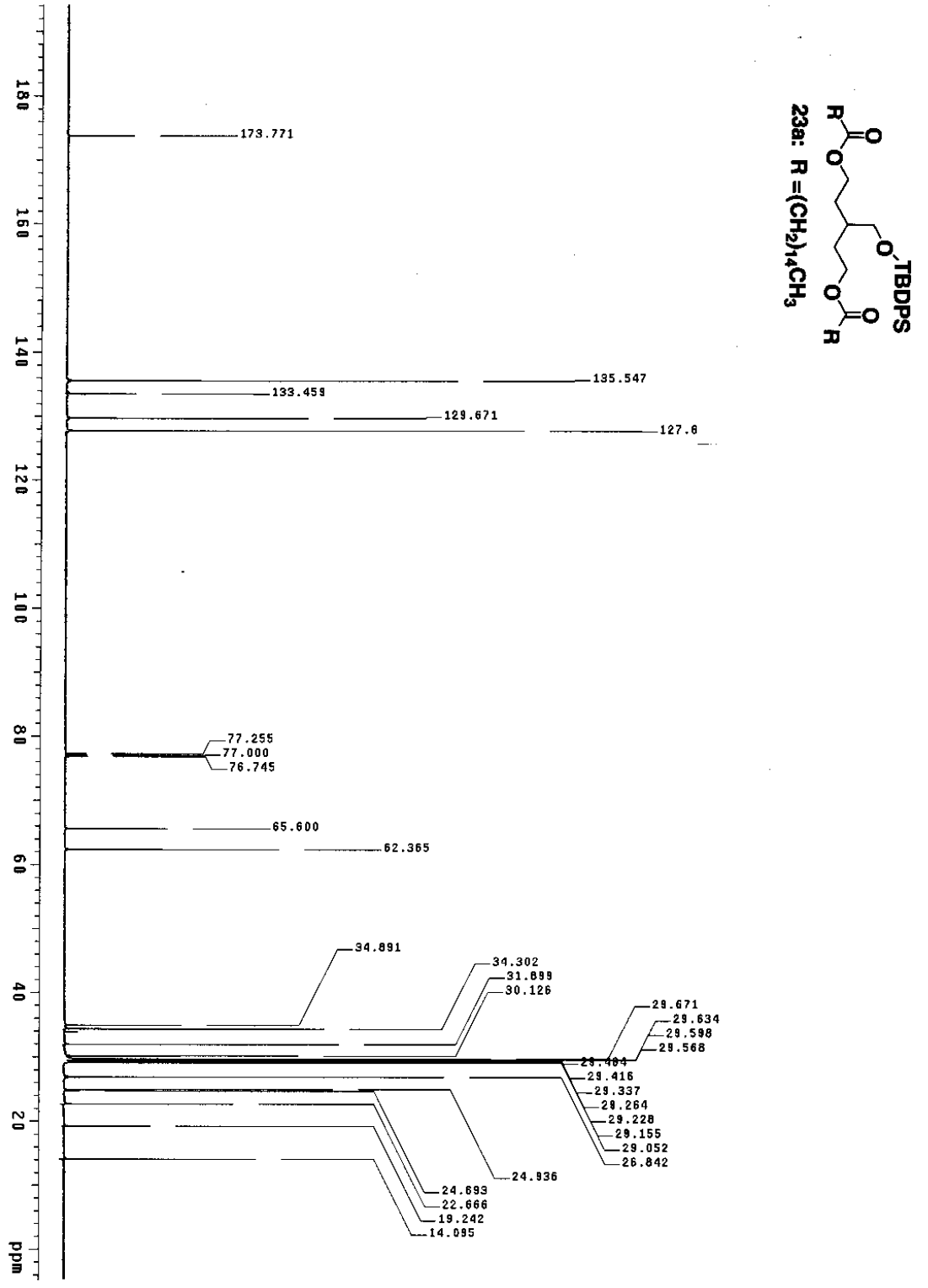
21


136.870
135.702
134.787
133.909
129.650
129.522
127.715
127.57
116.045
77.432
77.000
76.575
65.372
40.506
35.015
31.585
26.887
26.554
22.656
19.326
14.103
ppm
21
OTBDPS

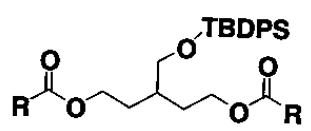

OTBDPS
HO
OH
22
9
8
7
6
5
4
3
2
1
ppm
11.34
15.73
18.76
4.82
2.96
12.47
33.92


Lu88 crude
HO
OTBDPS
OH
22
135.583
133.155
129.768
127.698
77.255
77.000
76.745
67.336
60.726
35.031
34.830
26.794
19.151
180
160
140
120
100
80
60
40
20
ppm

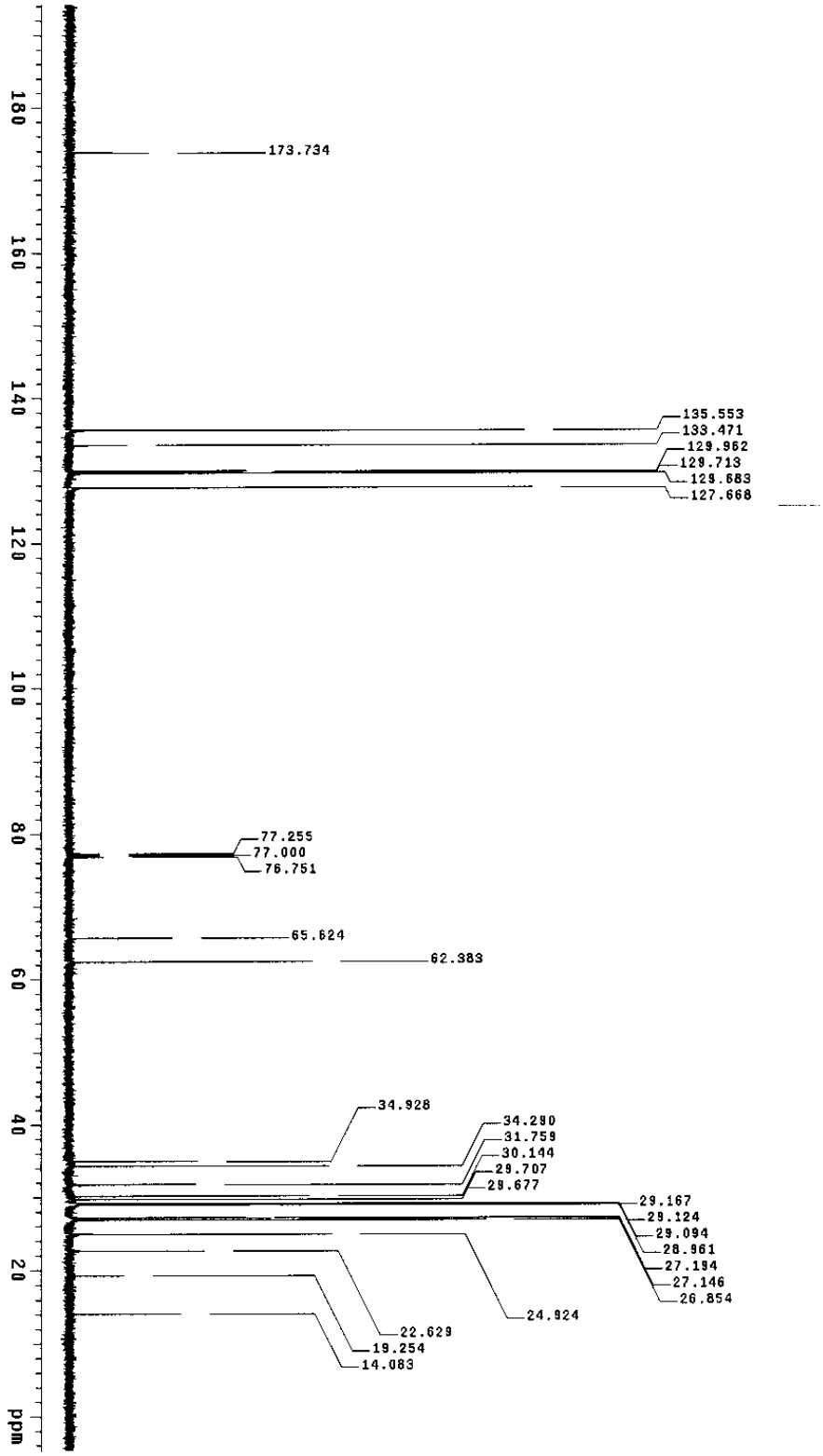

TBDPS
O
O
O
O
R
R
23a: R =(CH2)14CH3
7
6
5
4
3
2
1
ppm
3.54
4.90
4.69
2.38
0.22
4.25
3.53
6.96
54.84
9.93
4.77

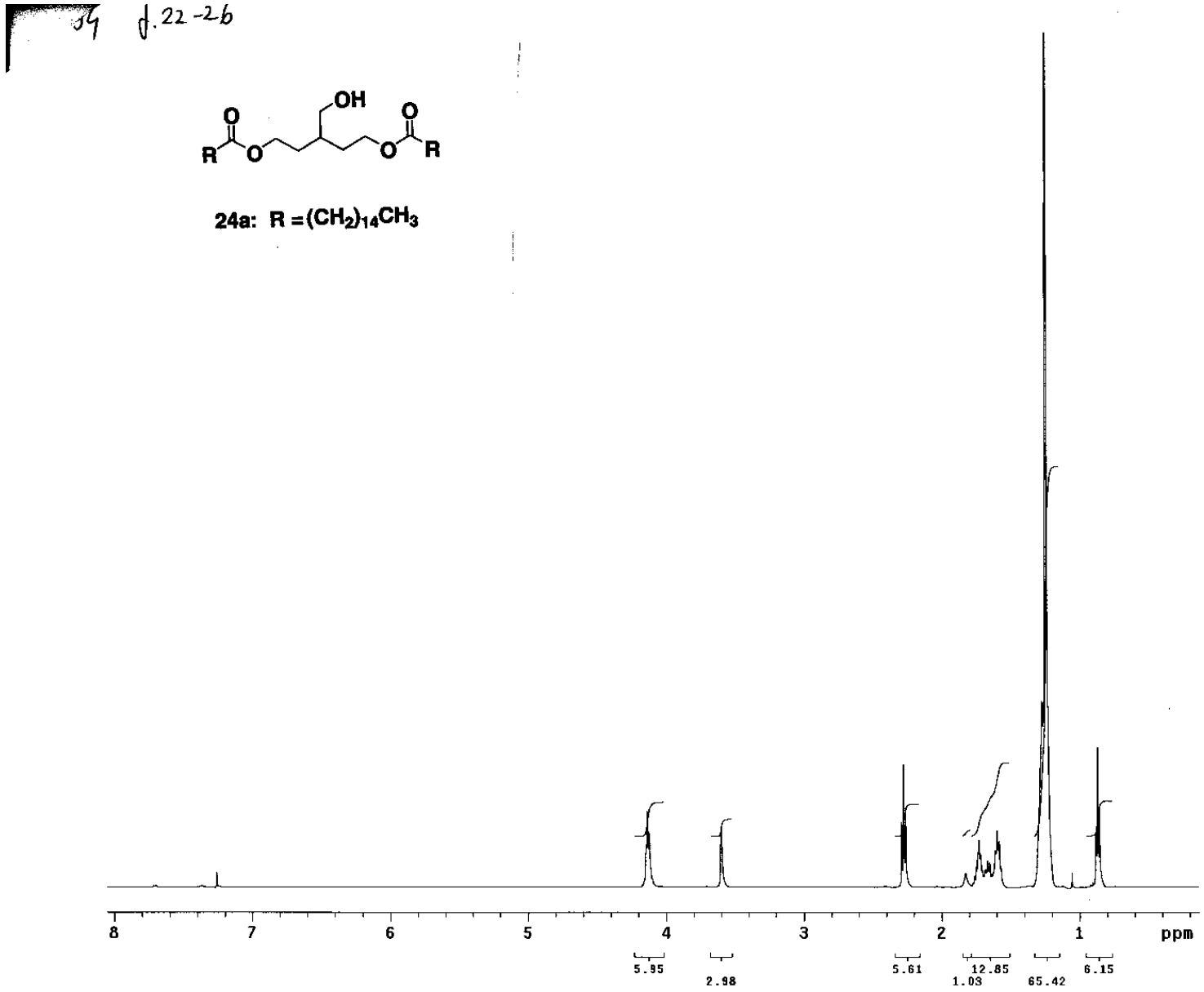

23a: R =(CH2)14CH3
TBDPS
173.771
135.547
133.459
129.671
127.6
77.255
77.000
76.745
65.600
62.365
34.891
34.302
31.899
30.126
29.671
29.634
29.598
29.568
29.484
29.416
29.337
29.264
29.228
29.155
29.052
26.842
24.936
24.693
22.666
19.242
14.095
ppm

LV 131 f. 13-17

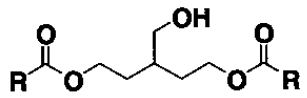


23b: R = $(CH_2)_7(CH_2)_5CH_3$

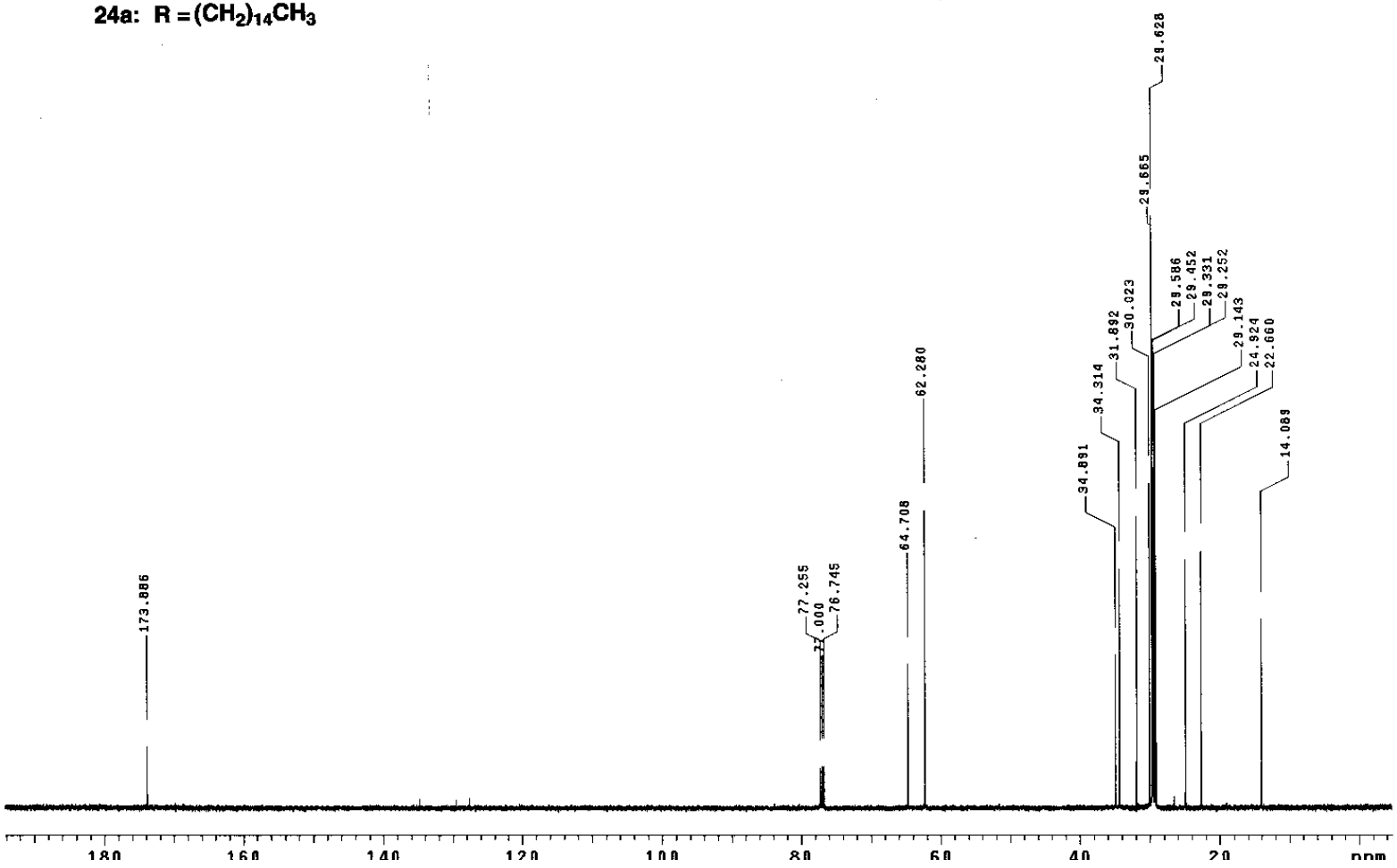

23b: R =(CH2)7CH=CH(CH2)5CH3
TBDPS
173.734
135.553
133.471
129.962
129.713
129.683
127.668
77.255
77.000
76.751
65.624
62.383
34.928
34.290
31.759
30.144
29.707
29.677
29.167
29.124
29.094
28.961
27.194
27.146
26.854
24.924
22.629
19.254
14.083
ppm


OH
O
O
R
O
O
R
24a: R =(CH2)14CH3
8
7
6
5
4
3
2
1
ppm
5.95
2.98
5.61
12.85
1.03
65.42
6.15

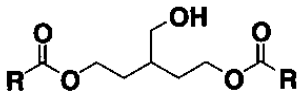
L054 #22-26



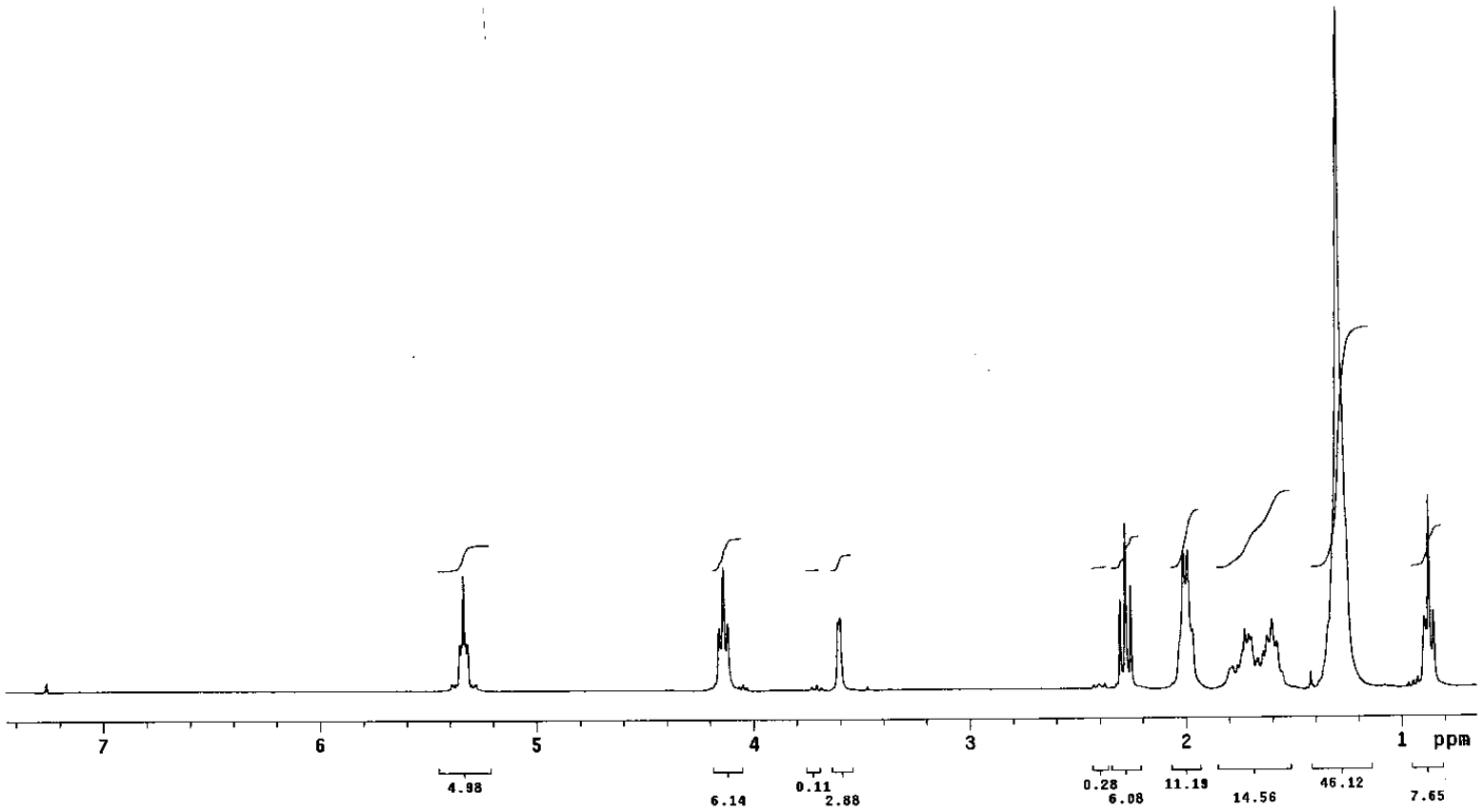
24a: R = $(CH_2)_{14}CH_3$

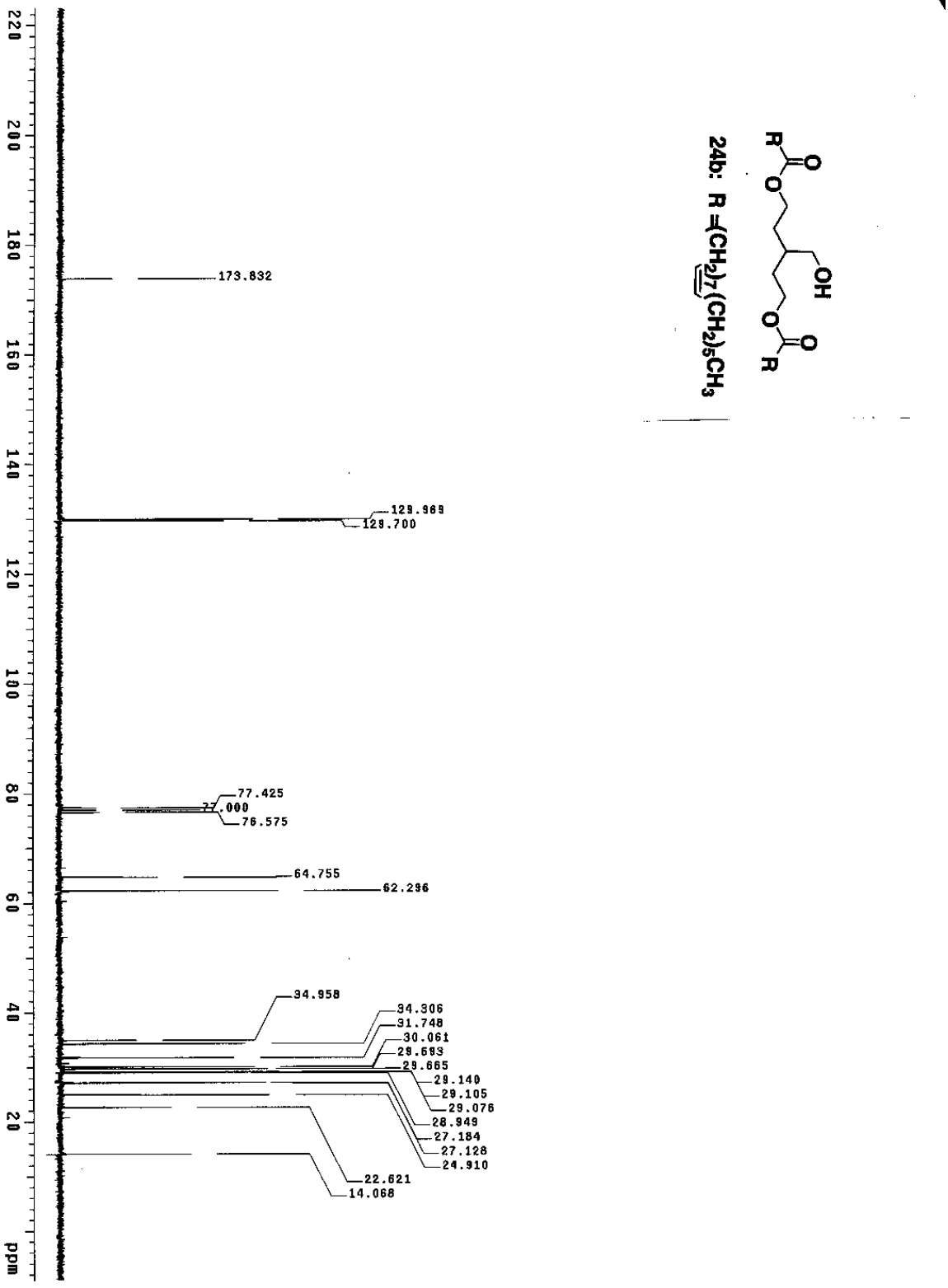


#4.28-31 LV132 in flask



24b: R = $(CH_2)_7(CH_2)_5CH_3$




24b: R =(CH2)7(CH2)5CH3
OH
220
200
180
160
140
120
100
80
60
40
20
ppm
173.832
129.969
129.700
77.425
77.000
76.575
64.755
62.296
34.958
34.306
31.748
30.061
29.693
29.665
29.140
29.105
29.076
28.949
27.184
27.128
24.910
22.621
14.068

4. References

1. Daleke, D. L.; Hong, K.; Papahadjopoulos, D. *Biochim. Biophys. Acta* **1990**, *1024*, 352-66.
2. Straubinger, R. M.; Papahadjopoulos, D.; Hong, K. L. *Biochemistry* **1990**, *29*, 4929-39.
3. Rance, M.; Byrd, A. *J. Magn. Reson.* **1983**, *52*, 221-240.
4. Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.
5. Contains *ca* 5 mg of unidentified phosphorus-positive byproduct.
6. Baeckström, P.; Li, L.; Wickramaratne, M.; Norin, T. *Synth. Comm.* **1990,** *20,* 423.
7. In some cases the reaction didn't go to completion and some intermediate aldehyde was detected by NMR. This problem was overcome by treating the crude product with $NaBH_4$ in MeOH for about 30 min.