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Graphical Abstract

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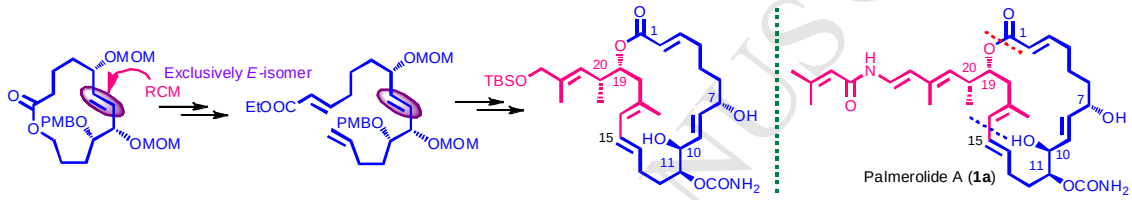

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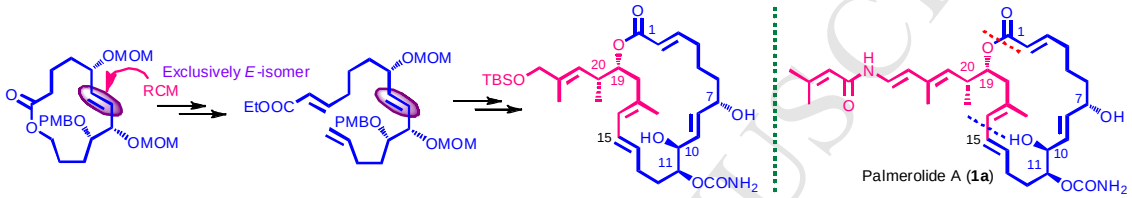

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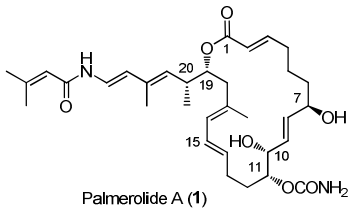
ABSTRACT

A stereoselective formal total synthesis of the 20-membered marine macrolide Palmerolide A, a highly potent antitumor agent, is described. The key steps involved in this synthesis are reductive elimination, Sharpless asymmetric dihydroxylation, protecting group dependent ring-closing metathesis reaction, Sharpless asymmetric epoxidation, Takai olefination and macrolactonization via Heck coupling reaction.

1. Introduction:

A significant number of macrocyclic natural products from marine flora and fauna have been extensively used in past and present for the treatment of many diseases and serve as compounds of interest both in their natural form and as templates for synthetic modification for the development of several novel therapeutic agents many of which are already been marketed as drugs.[1] A natural product enters into the drug discovery process through its potency, selectivity, and pharmacokinetic traits required for portraying it as a clinically useful drug agent. During the search for new potent drug molecules, Baker and co-workers[2] in 2006 reported the isolation and structural determination of Palmerolide A, the most prominent member of Palmerolide group, which is mainly due to its cytotoxicity, from the Antarctic marine tunicate *Synoicum adareanum*. Palmerolide A is a complex natural product comprising of a side chain containing an enamide, a 1,3-diene system, a carbamate moiety, five stereogenic centers, seven unsaturations with *E*-configuration and 20-membered macrolide ring. This natural product demonstrated extraordinary cytotoxic activity against the melanoma cell lines UACC-62 (LC_{50} =18 nM)[3] by inhibiting the proliferation of vacuolar ATPase with an IC_{50} of 2 nM. The remarkable 10^3 *in vitro* selectivity index for the melanoma cell lines prompted further biological evaluation of the compound. These findings coupled with the scarce natural abundance of Palmerolide A generated considerable interest in its chemical synthesis.[4] Several synthetic endeavours towards Palmerolide A led to the first total synthesis and revision of stereochemistry by De Brabander's group.[4a] Afterwards two more total syntheses by Nicolaou,[4b-d] and Hall,[4e] five formal syntheses[5] and several approaches,[6] including ours[6i] towards Palmerolide A have been reported in the literature.



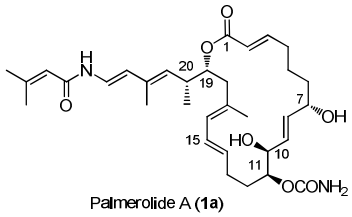


Figure 1. Structures of originally proposed (**1**) and revised Palmerolide A (**1a**).

Considering all these synthetic reports, a distinct retrosynthesis of macrolactone core **2** including intramolecular Heck coupling,[7] intermolecular Yamaguchi reaction,[8] protecting group dependent ring-closing metathesis reaction for the building of fragment **3**, regioselective reductive opening of epoxide by Me_3Al[9] and Takai olefination[10] of methyl ketone to form vinyl iodide for the construction of C16-C23 fragment was envisioned. Different established methodologies for the construction of intermediates were taken up to ensure an easy access to synthesize the required stereoisomers and other variants of Palmerolide A. As part of our ongoing research program on the synthesis of biologically active

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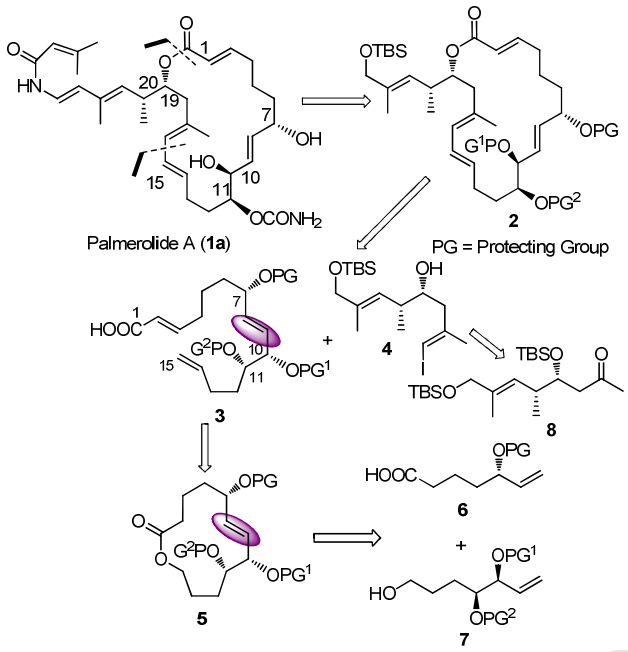
natural and unnatural products using protecting group dependent ring-closing metathesis approach,[11] the synthesis of macrolactone core **2** was targeted which is a late-stage intermediate of Palmerolide A leading to a formal total synthesis of the target molecule.

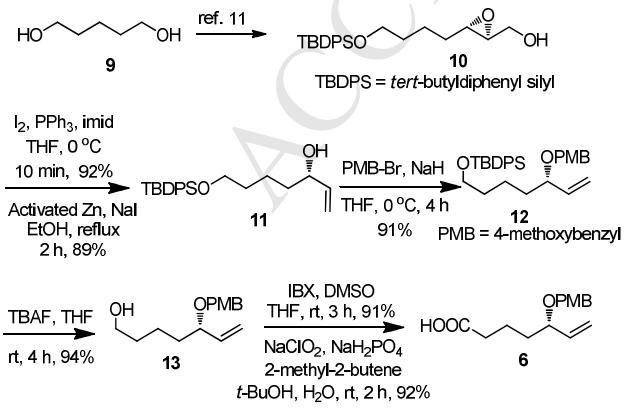
According to the retrosynthetic analysis of Palmerolide A (**1a**) as shown in Scheme 1, macrolactone core **2** could be constructed through esterification of **3** and **4**, followed by intramolecular Heck coupling.[7] Fragment **3** could be obtained from the 13-membered macrolactone **5**, which in turn could be prepared from **6** and **7** via coupling, followed by ring-closing metathesis reaction of the resulting diene compound.[12]



Scheme 1: Retrosynthetic analysis of Palmerolide A.

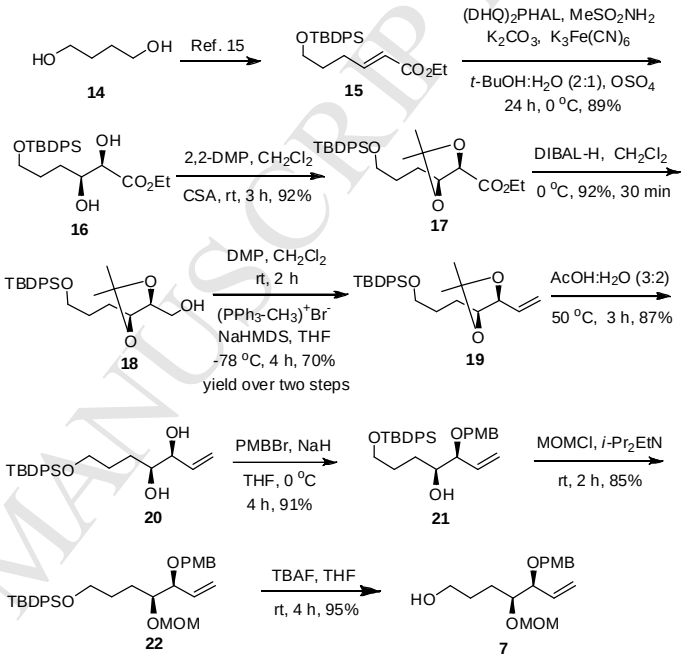
2. Result and discussion

The synthesis of acid fragment **6** commenced with 1,5-pentane diol **9**, which was converted to epoxy alcohol **10**[13] in 90% yield and with 97% ee through its corresponding allylic alcohol by treating with (+)-diethyl tartrate in presence of $Ti(O^iPr)_4$ and *t*-BuOOH under Katsuki-Sharpless[14] conditions. Conversion of alcohol **10** to the corresponding iodo derivative, subsequent reductive elimination using Zn/EtOH[15] afforded secondary allylic alcohol **11** in 82% yield over two steps (Scheme 2). The resulting alcohol was masked as its PMB-ether with PMB-Br in presence of NaH. Desilylation of **12** by treatment with TBAF generated primary alcohol **13** in 94% yield. The primary alcohol **13** was oxidized to corresponding aldehyde using IBX[16] followed by subsequent oxidation under Pinnick conditions using $NaClO_2$ furnishing acid fragment **6** in 84% yield over two steps.[17]



Scheme 2. Synthesis of the acid fragment **6**.

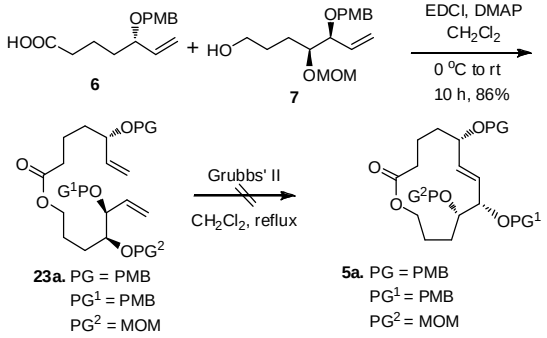
The synthesis of alcohol fragment **7** started with commercially available 1,4-butane diol following a literature protocol,[18] to obtain α,β-unsaturated ester **15**. The olefin was treated with osmium tetroxide and AD-mix-α under Sharpless asymmetric dihydroxylation conditions[19] to give diol **16** (89% yield with 98% ee). Protection of the diol moiety as its acetonide **17** was achieved by treating diol **16** with 2,2-dimethoxypropane in presence of catalytic amount of CSA in 92% yield. The ester group was then transformed to the corresponding terminal alkene by a three step sequence involving reduction of **17** using DIBAL-H in CH_2Cl_2 at −78 °C to afford primary alcohol **18**, which on oxidation with Dess-Martin periodinane in CH_2Cl_2 and subsequent one carbon homologation with $PPh_3{=}CH_2$ furnished alkene **19** in 70% yield over three steps (Scheme 3). Removal of isopropylidene group was effected with AcOH-H_2O leading to diol **20** in 87% yield.[20]



Scheme 3. Synthesis of the alcohol fragment **7**.

Selective PMB protection for the allylic hydroxyl group present in **20** with *p*-methoxybenzyl bromide (PMB-Br) in presence of NaH furnished **21** in 91% yield with 5-7% bis-PMB protected product.[21] The remaining free alcohol **21** was masked as its MOM-ether **22** with methoxymethyl chloride (MOMCl) and *N*,*N*-diisopropylethylamine (DIPEA) in CH_2Cl_2. Having synthesized **6** and **7**, the coupling of both the fragments was initially attempted under Yamaguchi conditions[8] which afforded the ester **23a** in low yield with the mixed anhydride as the byproduct. Similarly, coupling in the presence of dicyclohexyl carbodiimide (DCC)[22a-c] and 4-dimethylaminopyridine (DMAP) gave an inseparable mixture of insoluble dicyclohexyl urea along with the product. The best result was obtained when fragments **6** and **7** were treated with EDCI[22d-e] and DMAP in CH_2Cl_2 with

respect to purification and yield (86%) setting the stage for crucial ring-closing metathesis reaction (Scheme 4). Unfortunately, refluxing the diene ester with Grubbs' 2nd generation catalyst in CH_2Cl_2 under high dilution conditions failed to furnish the desired product leading to complete recovery of the starting material. We envisaged that steric congestion due to bulky PMB-protecting group around the reacting centers might act as a temporary constraint, preventing the ring-closing metathesis.



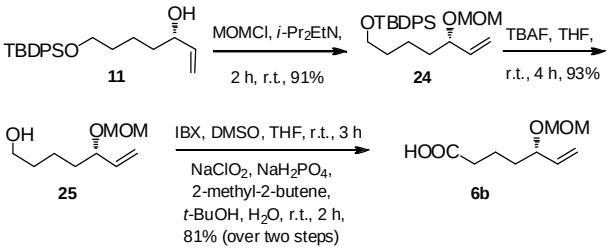
Scheme 4. RCM reaction on substrate **23a**.

After encountering failure in the endeavor to carry out RCM reaction, the above reaction was investigated with a set of ring-closing metathesis precursors by only changing the protecting group of allylic alcohol. During this process, precursors bearing dibenzyl (di-Bn) (**23b**), di-*tert*-butyldimethylsilyl (di-TBS) (**23c**) failed to produce the desired macrolactone with complete recovery of the starting material. Surprisingly, tri-MOM diene ester (**23d**) was transformed into the corresponding lactone in 70% yield with 20% starting material recovery in 12 h (entry **5d**, Table 1). When the above reaction was subjected to additional 24 h, complete conversion of starting material to lactone resulted in 78% yield (entry **5e**, Table 1). Taking this finding into account, when the RCM reaction was performed on diol-diene ester **23f** under high dilution conditions, required 13-membered macrolactone (entry **5f**, Table 1) was obtained in 82% yield with complete *E*-selectivity (J = 15.9 Hz) with no detectable amount of *Z*-isomer. This might be due to the tolerance of Grubbs' catalyst with activated nucleophile in the form of free allylic alcohol group.

Table 1 Protecting group dependent RCM for 13-membered lactone

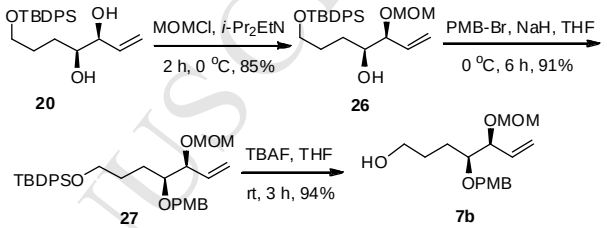
RCM Precursor	PG	PG^1	PG^2	Duration (in hour)	RCM Yield(%) (**5a-e**)	Starting Material Recovery (%)
23a	PMB	PMB	MOM	24	0	100
23b	Bn	Bn	MOM	24	0	100
23c	TBS	TBS	MOM	24	0	100
23d	MOM	MOM	MOM	12	70	20
23e	MOM	MOM	MOM	36	78	0
23f	H	H	MOM	12	82	0

Keeping in mind the formal total synthesis of Palmerolide A, protecting groups in the fragments **6** and **7** were manipulated few steps before esterification, which was achieved based on our previous approach. The subunit **6b** was synthesized in 3 steps, including MOM-protection of **11** with MOMCl, DIPEA in CH_2Cl_2 and subsequent (Scheme 5) desilylation. IBX oxidation of primary alcohol **25** and further oxidation under Pinnick conditions resulted carboxylic acid **6b** in 81% yield over two steps.



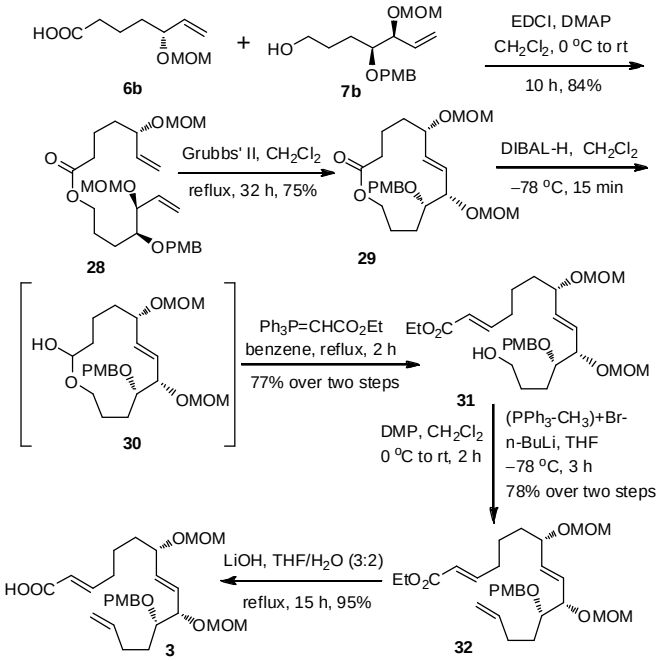
Scheme 5. Synthesis of the acid fragment **6b**.

The diol **20** was transformed to subunit **7b** via selective protection of allylic alcohol as a MOM ether **26** and subsequent formation of PMB ether **27** which on desilylation with TBAF in THF at room temperature afforded **7b** in 94% yield to complete the synthesis of alcohol fragment (Scheme 6).



Scheme 6. Synthesis of the alcohol fragment **7b.**

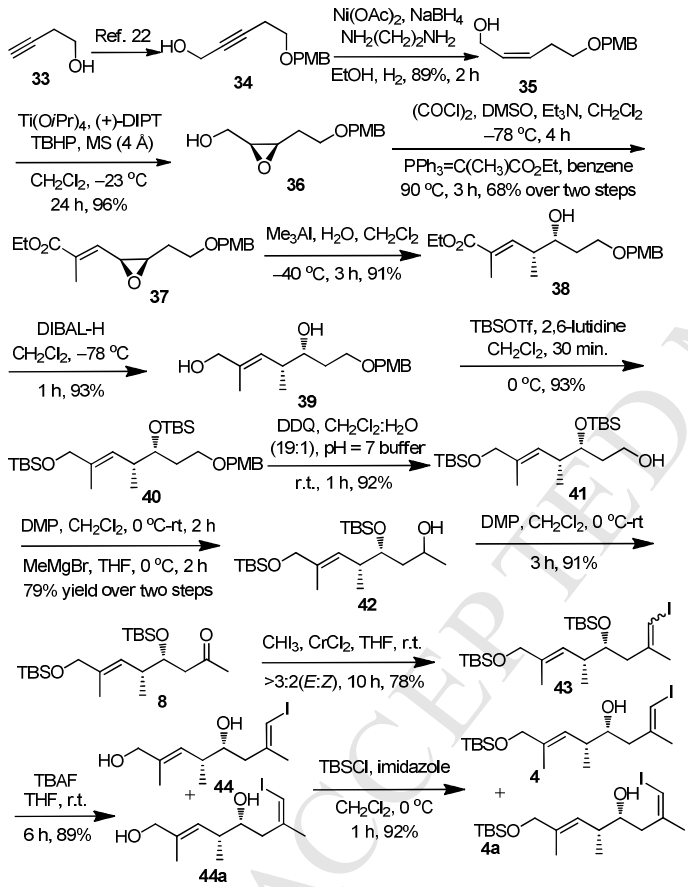
The required di-MOM protected diene ester **28** was synthesized following the earlier strategy as described in Scheme 4, which sets the stage for crucial RCM reaction. The 13-membered macrolactone formation proceeded smoothly with Grubbs 2nd generation catalyst under reflux conditions to afford **29** in 75% yield with exclusive formation of *E*-isomer. The controlled partial reduction of macrolactone **29** in CH_2Cl_2 was efficiently dealt with calculative amount of DIBAL-H at −78 °C into



Scheme 7. Synthesis of the acid fragment **3**.

the corresponding lactol **30** followed by two carbon homologation which afforded the α,β-unsaturated ester **31** in 77% yield over two steps (Scheme 7). The newly created primary alcohol was oxidized with Dess-Martin periodinane followed by one carbon Wittig olefination in THF to yield compound **32**. The ester functionality of **31** was saponified (Scheme 7) with LiOH in THF/H_2O (3:2) to furnish the required acid fragment **3** of Palmerolide A.

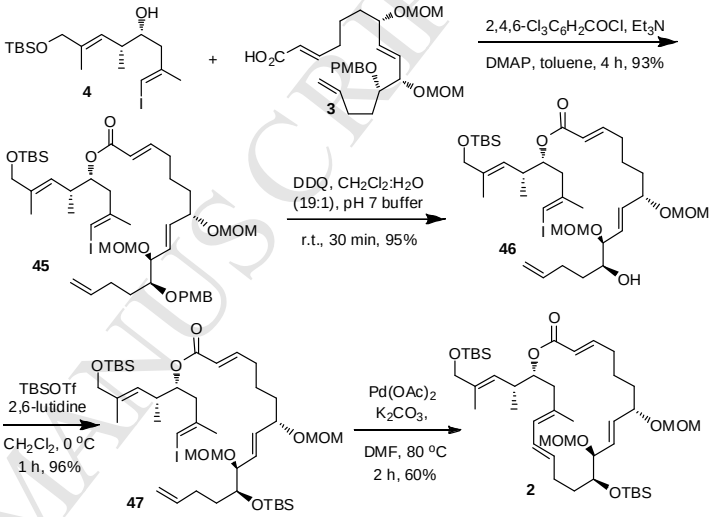
The preparation of fragment **4** was initiated from known alcohol **34** which was made available in two steps from homoproapargylic alcohol.[23] The acetylenic bond in compound **34** was selectively reduced to furnish *cis*-olefin **35** through nickel boride reduction[24] in 89% yield. The epoxide alcohol **36** was obtained through Sharpless asymmetric epoxidation with (+)-DIPT chiral ligand from *cis*-olefin **35** in 96% yield and 92% *ee*.[25] The epoxide unsaturated ester **37** was prepared from optically active epoxy alcohol in 68% yield through Swern oxidation followed by Horner-Wadsworth-Emmons reaction. Methylative opening of epoxide ring of **37** proceeded smoothly with Me_3Al in presence of small amount of water to afford a single diastereomer **38** (97% *de* as checked by HPLC) in 91%



Scheme 8. Synthesis of the alcohol fragment **4**.

yield.[9] Reduction of unsaturated ester **38** with DIBAL-*H* in CH_2Cl_2 followed by protection of the resulting diol **39** with TBSOTf and 2,6-lutidine afforded diTBS ether **40** in 93% yield. Oxidative removal of PMB ether compound **40** with DDQ[26] in CH_2Cl_2/H_2O at room temperature furnished **41** in 92% yield. The resulting primary alcohol **41** was transformed into methyl ketone **8** by a three step reaction sequence involving Dess-Martin periodinane oxidation[27] which furnished the corresponding aldehyde, followed by addition of MeMgBr in THF producing the secondary alcohol **42** in 79% yield. Subsequent oxidation with Dess-Martin periodinane provided methyl ketone **8** in 91% yield. The next task was the conversion of methyl ketone **8** to vinyl iodide **43** which involved Takai olefination reaction. Thus, Takai olefination of ketone with a mixture of $CrCl_2$ and CHI_3 in THF furnished vinyl iodide **43** with moderate *E*:*Z* (>3:2) ratio in 78% yield.[10] The di-TBS protected vinyl iodide **43** was subjected to TBAF in THF to obtain **44** in 89% yield. At this stage, both the isomers were separated by silica gel column chromatography. Finally, selective silylation (Scheme 8) of **44** with TBSCl and imidazole in CH_2Cl_2 formed vinyl iodide **4** in 92% yield.

After having achieved the synthesis of both the major fragments **3** and **4**, the next target was to couple these fragments with slight modification in protecting group to accomplish the formal synthesis of Palmerolide A. Following Yamaguchi's method the fragments **3** and **4** were coupled to obtain ester **45**, which on treatment with DDQ smoothly produced homoallylic alcohol **46** in 95% yield. The resulting homoallylic alcohol was masked



Scheme 9. Synthesis of macrocyclic core **2** of Palmerolide A.

using TBSOTf and 2,6-lutidine at 0 °C to furnish the requisite compound **47** in 96% yield. The final Heck coupling[7] following the procedure employed by Prasad et. al. furnished the macrocyclic core **2** of Palmerolide A (Scheme 9), whose spectral and analytical data were in good agreement with the reported one,[5a] which successfully completed the formal total synthesis of Palmerolide A.

3. Conclusion:

In conclusion, a stereocontrolled and convergent formal total synthesis of Palmerolide A having useful biological profile has been achieved. The key features of the synthesis were protecting group directed RCM reaction, regioselective epoxide opening by Me_3Al and macrolactonization via Heck coupling, novel Takai olefination which has not been applied for previous syntheses of Palmerolide A for the installation of *trans*-vinyl iodide (C16-C17).

4. Experimental section

4.1. General Remarks:

Air and/or moisture sensitive reactions were carried out in anhydrous solvents under an atmosphere of argon in an oven or flame-dried glassware. All anhydrous solvents were distilled prior to use: THF, benzene, toluene, diethyl ether from Na and benzophenone; CH_2Cl_2, DMSO, DMF, hexane from CaH_2; MeOH, EtOH from Mg cake. Commercial reagents were used

without purification. Column chromatography was carried out by using silica gel (60–120 mesh). Specific optical rotations $[\alpha]_D$ are given in 10^{-1} degcm^{2}g^{-1}. Infrared spectra were recorded in $CHCl_3$/neat (as mentioned) and reported in wave number (cm^{-1}). TOF analyzer type was used for the HRMS measurement. ^{1}H and ^{13}C NMR chemical shifts are reported in ppm downfield from tetramethylsilane and coupling constants (*J*) are reported in hertz (Hz). The following abbreviations are used to designate signal multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad.

4.2. (*S*)-7-(*tert*-Butyldiphenylsilyloxy)hept-1-en-3-ol (11)

To a stirred solution of epoxide **10** (5.2 g, 13.53 mmol) in THF (50 mL), was added triphenylphosphine (7.1 g, 27.07 mmol), Imidazole (1.84 g, 27.07 mmol) at 0 °C and stirred for 20 min under N_2 atmosphere. A solution of iodine (4.12 g, 16.24 mmol) in THF (20 mL) was added to the reaction mixture at 0 °C dropwise until decolourisation of reaction mixture ceases. After completion of the reaction (monitored by TLC), it was treated with saturated solution of sodium thiosulfate (30 mL). The organic layer was separated and the aqueous layer extracted with ethyl acetate (2 × 50 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and solvent removed under reduced pressure. The crude Iodo compound was taken to next reaction without purification (6.15 g).

Activated Zn (4.07 g, 62.23 mmol) and NaI (3.73 g, 24.9 mmol) were added to a stirred solution of crude iodo compound (6.15 g, 12.45 mmol) in MeOH (50 mL). The reaction mixture was stirred for 3 h at 70 °C. After completion of the reaction (monitored by TLC), the reaction mass was filtered through Celite pad. Methanol was removed under reduced pressure and the crude mass was washed with ethyl acetate. The organic layer was washed with saturated NH_4Cl solution (30 mL) and the aqueous layer was extracted with ethyl acetate (2 × 50 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and solvent removed under reduced pressure. The crude mass was purified by silica gel column chromatography (EtOAc/hexane = 1:4) to afford **11** (4.08 g, 81.8% over two steps) as a colorless liquid; R_f (EtOAc/hexane = 1:4) 0.45. $[\alpha]_D^{27}$ +4.7 (*c* 0.4, $CHCl_3$); IR (neat): 3362, 2932, 2859, 1716, 1428, 1390, 1260, 1111, 922,702 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.67-7.59 (m, 4H), 7.42-7.29 (m, 6H), 5.81 (m, 1H), 5.23-5.03 (m, 2H), 4.05 (m, 1H), 3.64 (t, *J* = 6.2 Hz, 2H), 1.64-1.36 (m, 6H), 1.04 (s, 9H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 141.1, 135.5, 134.0, 129.5, 127.6, 114.6, 73.1, 63.7, 36.6, 32.3, 26.8, 21.6, 19.2 ppm; ESI-HRMS Calcd for $C_{23}H_{32}O_2Na$ $[M + Na]^+$ 391.2069; found: 391.2077.

4.3. (*S*)-*tert*-Butyl(5-(4-methoxybenzyloxy)hept-6-enyloxy)-diphenylsilane (12)

To a solution of **11** (3.5 g, 9.50 mmol) in dry THF (45 mL), was added NaH (0.95 g, 23.75 mmol; 60% dispersion in mineral oil) at 0 °C, and the mixture was stirred for 30 min. Then, PMB-Br (1.64 g, 11.40 mmol), catalytic TBAI (0.1 g) was added and the solution was stirred for additional 3 h at 50 °C. After completion of the reaction (monitored by TLC), the reaction was warmed to 0 °C and quenched by H_2O drop-wise. The aqueous layer was extracted with ethyl acetate (2 × 35 mL), dried over anhydrous Na_2SO_4 and evaporation of the solvent was effected under reduced pressure. The crude mass was purified by silica gel column chromatography (EtOAc/hexane = 1:4) to afford **12** (4.22 g, 91%) as a yellow liquid; R_f (EtOAc/hexane = 1:4) 0.30. $[\alpha]_D^{27}$ −8.0 (*c* 0.90, $CHCl_3$); IR (neat): 3071, 2932, 2859, 1738, 1613, 1513, 1463, 1301, 1247, 1172, 1038, 926, 822 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.69-7.58 (m, 4H), 7.41-7.27 (m, 6H), 7.17 (d, *J* = 8.5 Hz, 2H), 6.78 (d, *J* = 8.5 Hz, 2H), 5.68 (m, 1H), 5.23-5.10 (m, 2H), 4.35 (AB_q, *J* = 11.5, 78.6 Hz, 2H), 3.74 (s, 3H), 3.69-3.57 (m, 3H), 1.68-1.31 (m, 6H), 1.04 (s, 9H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 159.0, 139.2, 135.5, 134.0, 129.4, 129.2, 127.5, 116.8, 113.7, 80.2, 69.6, 63.8, 55.1, 35.2, 32.4, 26.8, 21.7, 19.2 ppm; ESI-HRMS Calcd for $C_{31}H_{40}O_3Na$ $[M + Na]^+$ 511.2644; found: 511.2623.

4.4. (*S*)-5-(4-Methoxybenzyloxy)hept-6-en-1-ol (13)

TBAF (15.77 mL, 1 M in THF, 15.77 mmol) was added to a stirred solution of PMB ether compound (3.85 g, 7.88 mmol) in THF (30 mL) at 0 °C under N_2 atmosphere. The reaction mixture was stirred at room temperature for 4 h. After completion of the reaction (monitored by TLC), it was quenched with water (30 mL). The aqueous layer was extracted with ethyl acetate (3 × 30 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and solvent removed under reduced pressure. The crude mass was purified by silica gel chromatography (EtOAc/hexane = 1:4) to afford **13** (1.85 g, 94%) as a colorless liquid; R_f (EtOAc/hexane = 1:4) 0.25**.** $[\alpha]_D^{27}$ −12.6 (*c* 0.76, $CHCl_3$); IR (neat): 3481, 2934, 2884, 1736, 1613, 1514, 1465, 1248, 1036, 921, 822 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.19 (d, *J* = 8.7 Hz, 2H), 6.81 (d, *J* = 8.7 Hz, 2H), 5.70 (m, 1H), 5.23-5.12 (m, 2H), 4.49 (d, *J* = 11.5 Hz, 1H), 4.22 (d, *J* = 11.5 Hz, 1H), 3.78 (s, 3H), 3.67 (m, 1H), 3.56 (t, *J* = 6.2 Hz, 2H), 1.69-1.32 (m, 6H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 159.0, 139.0, 130.7, 129.3, 117.1, 113.7, 80.1, 69.7, 62.7, 55.2, 35.1, 32.5, 21.5 pm; ESI-HRMS Calcd for $C_{15}H_{22}O_3Na$ $[M + Na]^+$ 273.1466; found: 273.1476.

4.5. (*S*)-5-(4-Methoxybenzyl)oxy)hept-6-enoic acid (6)

To a stirred solution of 2-iodoxybenzoic acid (IBX) (1.82 g, 6.5 mmol) in DMSO (10 mL), was added a solution of alcohol **13** (1.42 g, 5.68 mmol) in anhydrous THF (20 mL) at room temperature. After stirring for 4 h, the reaction mixture was diluted with Et_2O (50 mL). The solid precipitated were filtered off and the residue was washed with Et_2O (60 mL). The combined filtrate and washings were successively washed with aqueous $NaHCO_3$ (50 mL), brine (2 × 50 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash column chromatography (EtOAc/hexane = 1:4) to afford aldehyde (1.24 g, 91%) as light yellow liquid which was used for the next step without further purification.

To a solution of resulting aldehyde (1.24 g, 5.0 mmol) in *t*-BuOH (15 mL), 2-methyl-2-butene (5 mL, 10 mmol, 2M solution in THF) was added at room temperature. Sodium dihydrogen phosphate (2.34 g, 15.0 mmol) and sodium chlorite (0.678 g, 7.5 mmol) were dissolved in water (15 mL) to make a clear solution and added to the above reaction mixture at 0 °C. The reaction mixture was stirred for another 3 h at room temperature. After completion of the reaction (monitored by TLC), the reaction mixture was extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (2 × 75 mL), dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The crude product was purified by silica gel chromatography (EtOAc/hexane = 3:2) to afford the desired acid **6** (1.21 g, 92%) as a colorless oil; R_f (EtOAc/hexane = 3:2) 0.45. $[\alpha]_D^{27}$ −6.2 (*c* 1.45, $CHCl_3$); IR (neat): 3075, 2928, 2856, 1708, 1612, 1514, 1422, 1248, 1172, 1035 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.18 (d, *J* = 8.3 Hz, 2H), 6.81 (d, *J* = 8.3 Hz, 2H), 5.70 (m, 1H)

5.24-5.14 (m, 2H), 4.36 (AB_q, J = 12.1, 80.1 Hz, 2H), 3.77 (s, 3H), 3.69 (m, 1H), 2.3 (t, J = 6.8 Hz, 2H), 1.79-1.45 (m, 4H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 179.5, 159.0, 138.5, 130.4, 129.3, 117.3, 113.7, 79.5, 69.6, 55.1, 34.6, 33.7, 20.5 ppm; ESI-HRMS Calcd for $C_{15}H_{20}O_4Na$ $[M + Na]^+$ 287.1259; found: 287.1256.

4.6. (*S*)-12,12-Dimethyl-11,11-diphenyl-5-vinyl-2,4,10-trioxa-11-silatridecane (24)

To a stirred solution of compound **11** (4.6 g, 12.49 mmol) in CH_2Cl_2 (45 mL), was added diisopropylethylamine (6.5 mL, 37.43 mmol) and stirred for 30 min at 0 °C under N_2 atmosphere. Methoxymethyl chloride (1.42 mL, 18.74 mmol) was added to the reaction mixture at same temperature and allowed to stir for 10 h at room temperature. After completion of the reaction (monitored by TLC), it was quenched with H_2O (30 mL). The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and solvent removed under reduced pressure. The crude mass was purified by silica gel column chromatography (EtOAc/hexane = 1:4) to afford MOM ether **24** (4.68 g, 91%) as a colorless liquid; R_f (EtOAc/hexane = 1:4) 0.40. $[\alpha]_D^{27}$ −15.0 (*c* 4.30, $CHCl_3$); IR (neat): 2935, 2861, 1468, 1428, 1104, 1037, 922, 822, 704, 613, 505 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.65-7.60 (m, 4H), 7.41-7.29 (m, 6H), 5.61 (m, 1H), 5.22-5.11 (m, 2H), 4.64 (d, J = 6.8 Hz, 1H), 4.45 (d, J = 6.8 Hz, 1H), 3.93 (m, 1H), 3.63 (t, J = 6.0 Hz, 2H), 3.32 (s, 3H), 1.65-1.40 (m, 6H), 1.03 (s, 9H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 138.4, 135.5, 134.0, 129.5, 127.6, 117.1, 93.6, 77.3, 63.8, 55.4, 35.1, 32.4, 26.8, 21.7, 19.2 ppm; ESI-HRMS Calcd for $C_{25}H_{36}O_3Na$ $[M + Na]^+$ 435.2330; found: 435.2325.

4.7. (*S*)-5-(Methoxymethoxy)hept-6-en-1-ol (25)

TBAF (21.58 mL, 1 M in THF, 21.58 mmol) was added to a stirred solution of MOM ether compound (4.45 g, 10.79 mmol) in THF (35 mL) at 0 °C under N_2 atmosphere. The reaction mixture was stirred at room temperature for 4 h. After completion of the reaction (monitored by TLC), it was quenched with water (30 mL). The aqueous layer extracted with ethyl acetate (2 × 35 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and solvent removed under reduced pressure. The crude mass was purified by silica gel chromatography (EtOAc/hexane = 1:4) to afford **25** (1.75 g, 93%) as a colorless liquid; R_f (EtOAc/hexane = 1:4) 0.35. $[\alpha]_D^{27}$ −35.9 (*c* 4.57, $CHCl_3$); IR (neat): 3412, 2936, 2879, 1726, 1443, 1248, 1149, 1036, 921, 772 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.60 (m, 1H), 5.20-5.11 (m, 2H), 4.62 (d, J = 6.7 Hz, 1H), 4.44 (d, J = 6.7 Hz, 1H), 3.93 (q, J = 6.7 Hz, 1H), 3.56 (t, J = 6.7 Hz, 2H), 3.31 (s, 3H), 2.25 (bs, 1H), 1.64-1.32 (m, 6H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 138.1, 117.2, 93.6, 77.2, 62.5, 55.3, 35.0, 32.4, 21.4 ppm; ESI-HRMS Calcd for $C_9H_{19}O_3$ $[M + H]^+$ 175.1328; found: 175.1321.

4.8. (*S*)-5-(Methoxymethoxy)hept-6-enoic acid (6b)

To a stirred solution of 2-iodoxybenzoic acid (IBX) (3.9 g, 14.0 mmol) in DMSO (20 mL), was added a solution of alcohol **24** (1.85 g, 10.75 mmol) in anhydrous THF (30 mL) at room temperature and stirring was continued for further 4 h. After completion of the reaction (monitored by TLC), Et_2O (60 mL) was added to the reaction mixture, precipitated solid was filtered off and the residue washed with Et_2O (50 mL). The combined filtrate and washings were successively washed with aqueous $NaHCO_3$ (75 mL), H_2O (2 × 75 mL), brine (75 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash column chromatography (EtOAc/hexane = 1:4) to afford (1.8 g, 89%) aldehyde as light yellow liquid which was used for the next step without further purification.

To a solution of resulting aldehyde (1.8 g, 10.47 mmol) in *t*-BuOH (20 mL), 2-methyl-2-butene (10.47 mL, 20.94 mmol, 2M solution in THF) was added at room temperature. Sodium dihydrogenphosphate (4.9 g, 31.41 mmol) and sodium chlorite (1.42 g, 15.70 mmol) were dissolved in water (15 mL) to make a clear solution and added to the above reaction mixture at 0 °C. The reaction mixture was stirred for another 3 h at room temperature. After completion of the reaction (monitored by TLC), the reaction mixture was extracted with EtOAc (3 × 60 mL). The combined organic layer were washed with brine (100 mL), dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The crude product was purified by silica gel chromatography (EtOAc/hexane = 3:2) to afford desired acid **6b** (1.79 g, 91%) as a colorless oil; R_f (EtOAc/hexane = 3:2) 0.40. $[\alpha]_D^{27}$ −34.4 (*c* 2.4, $CHCl_3$); IR (neat): 3082, 2935, 2890, 1712, 1419, 1150, 1097, 1033 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 5.66 (m, 1H), 5.25-5.16 (m, 2H), 4.70 (d, J = 6.8 Hz, 1H), 4.53 (d, J = 6.8 Hz, 1H), 4.00 (m, 1H), 3.37 (s, 3H), 2.41-2.35 (m, 2H), 1.82-1.50 (m, 4H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 179.3, 137.9, 117.5, 93.6, 76.9 , 55.4, 34.5, 33.8, 20.6 ppm; ESI-HRMS Calcd for $C_9H_{16}O_4Na$ $[M + Na]^+$ 211.0940; found: 211.0941.

4.9. (2*R*,3*S*)-Ethyl-6-(*tert*-butyldiphenylsilyloxy)-2,3-dihydroxyhexanoate (16)

To a stirred mixture of $K_3[Fe(CN)_6]$ (26.17 g, 79.50 mmol) and K_2CO_3 (10.97 g, 79.50 mmol) in H_2O (132.5 mL), $(DHQ)_2PHAL$ (0.21 g, 0.26 mmol) was added. After being stirred for 5 min, the α,β unsaturated ester **15** (10.5 g, 26.50 mmol) in *t*-BuOH (132.5 mL) was added to the reaction mixture at 0 °C. OsO_4 (0.04 mL, 10% solution in toluene) followed by methane sulfonamide (2.51 g, 26.5 mmol) was added at same temperature. The reaction mixture was then stirred at 0 °C for 24 h and then quenched with solid sodium metabisulfite (5 g). The stirring was continued for additional 1 h and then extracted with ethyl acetate (3 × 60 mL). The combined organic extracts were washed with saturated $NaHCO_3$ solution and then with brine, dried over Na_2SO_4 and solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/hexane = 1:4) to afford **16** (10.15 g, 89%) as a colorless viscous liquid; R_f (EtOAc/hexane = 1:4) 0.25. $[\alpha]_D^{27}$ −7.2 (*c* 6.80, $CHCl_3$); IR (neat): 3443, 2933, 2860, 1735, 1635, 1468, 1390, 1210, 1107, 821, 703 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.63 (d, J = 5.9, 4H), 7.41-7.32 (m, 6H), 4.27 (dd, J = 6.9, 14.8, 2H), 3.98 (m, 1H), 3.87 (m, 1H), 3.71-3.67 (m, 2H), 2.95 (d, J = 5.9, 1H), 2.24 (d, J = 7.9, 1H), 1.76-1.66 (m, 4H), 1.32 (t, J = 6.9 Hz, 3H), 1.04 (s, 9H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 173.5, 135.5, 133.6, 129.6, 127.6, 73.4, 72.3, 63.9, 62.0, 30.6, 28.7, 26.8, 19.2, 14.2 ppm; ESI-HRMS Calcd for $C_{24}H_{34}O_5SiNa$ $[M + Na]^+$ 453.2073; found: 453.2054.

4.10. (4*R*,5*S*)-Ethyl-5-(3-(*tert*-butyldiphenylsilyloxy)propyl)-2,2-di-methyl-1,3-dioxolane-4-carboxylate (17)

To a stirred solution of diol **16** (9.8 g, 22.78 mmol) in CH_2Cl_2

(40 mL), was added 2,2-dimethoxypropane (13.95 g, 113.89 mmol) and a catalytic amount of camphorsulfonic acid (264 mg) at 0 °C. The mixture was continued to stir at room temperature for 1 h under N_2 atmosphere. After completion of the reaction (monitored by TLC), the reaction mixture was quenched with saturated $NaHCO_3$ solution. The aqueous layer was extracted with CH_2Cl_2 and the combined organic solvent was dried with anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography (EtOAc/hexane = 1:4) to give **17** (9.85 g, 92%) as a yellow viscous oil; R_f (EtOAc/hexane = 1:4) 0.65. $[\alpha]_D^{27}$ −8.2 (*c* 9.39, $CHCl_3$); IR (neat): 3449, 2932, 2858, 1758, 1467, 1377, 1188, 1107, 704 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 7.65-7.60 (m, 4H), 7.40-7.30 (m, 6H), 4.27-4.14 (m, 2H), 4.12-4.00 (m, 2H), 3.73-3.65 (m, 2H), 1.96-1.60 (m, 4H), 1.41 (d, *J* = 7.9 Hz, 6H) 1.29 (t, *J* = 7.2 Hz, 3H), 1.04 (s, 9H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 170.9, 135.5, 133.9, 129.5, 127.6, 110.8, 79.1, 79.0, 63.4, 61.3, 29.9, 28.6, 27.2, 26.8, 25.7, 19.2, 14.1 ppm; ESI-HRMS Calcd for $C_{27}H_{38}O_5SiNa$ $[M + Na]^+$ 493.2386; found: 493.2373.

4.11. ((4*S*,5*S*)-5-(3-(*tert*-Butyldiphenylsilyloxy)propyl)-2,2-dimeth- yl-1,3-dioxolan-4-yl)methanol (18)

To a stirreded solution of the ester **17** (8.2 g, 17.43 mmol) in CH_2Cl_2 (85 mL), was added DIBAL-*H* in toluene (21.92 mL, 1.75 M, 38.36 mmol) dropwise at -78 °C. The solution was stirred at same temperature for 2 h under argon atmosphere. After completion of the reaction (monitored by TLC), the reaction was quenched by addition of saturated sodium potassium tartrate (70 mL) solution. The gelatinous mixture was stirred until two distinct layers formed. The layers were separated, and the aqueous layer extracted with CH_2Cl_2 (3 × 60 mL). The combined organic layers were dried over Na_2SO_4 and solvent was evaporated to dryness. The residue was purified by column chromatography (EtOAc/hexane = 1:4) to afford **18** (6.87 g, 92%) as colorless oil; R_f (EtOAc/hexane = 1:4) 0.25. $[\alpha]_D^{27}$ −8.9 (*c* 6.06, $CHCl_3$); IR (neat): 3461, 2933, 2860, 1467, 1376, 1247, 1108, 822, 707, 506 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 7.60-7.59 (m, 4H), 7.42-7.29 (m, 6H), 3.85 (m, 1H), 3.76-3.60 (m, 4H), 3.51 (m, 1H), 1.79-1.53 (m, 4H), 1.36 (d, *J* = 3.4 Hz, 6H), 1.04 (s, 9H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 135.5, 133.9, 129.5, 127.6, 108.6, 81.5, 76.7, 63.5, 62.1, 29.4, 28.9, 27.3, 27.0, 26.9, 19.2 ppm; ESI-HRMS Calcd for $C_{25}H_{36}O_4SiNa$ $[M + Na]^+$ 451.2280; found: 451.2273.

4.12. *tert*-Butyl(3-((4*S*,5*S*)-2,2-dimethyl-5-vinyl-1,3-dioxolan-4-yl)- propoxy) diphenylsilane (19)

To a stirred solution of primary alcohol **18** (7.0 g, 16.34 mmol) and solid anhydrous $NaHCO_3$ (1.65 g, 19.61) in CH_2Cl_2 (60 mL) at 0 °C, was added Dess-Martin periodinane (10.4 g, 24.51 mmol). The reaction mixture was stirred at 0 °C for 2 h under N_2 atmosphere. After completion of reaction (monitored by TLC), it was quenched with saturated aqueous $NaHCO_3$ solution (35 mL) and stirred for another 30 min. The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (2 × 60 mL). The combined organic layer was evaporated under reduced pressure to afford a crude residue which was immediately used for the next reaction.

Methyltriphenylphosphonium bromide (15.84 g, 44.34 mmol) was dissolved in THF (50 mL) and cooled to –78 ºC. *n*-Butyllithium (23.1 mL, 1.6 M in hexane, 36.95 mmol) was added drop wise to the above stirred solution which turned into light orange solution. It was then warmed to 0 ºC for 45 min and again cooled to –78 ºC. The crude aldehyde (6.3 g, 14.78 mmol) in THF (25 mL) was added to the reaction mixture drop wise. The reaction mixture was stirred at the same temperature for 4 h. After complete consumption of the starting material (monitored by TLC), the reaction was quenched with saturated NH_4Cl solution (40 mL) and warmed to room temperature. The organic phase was separated and the aqueous phase extracted with ethyl acetate (3 × 30 mL). The combined organic layers were washed with brine (2 × 25 mL), dried over Na_2SO_4 and concentrated. Purification by silica gel column chromatography (EtOAc/hexane = 1:4) afforded the desired compound **19** (4.76 g, 70% over two steps) as a colorless liquid; R_f (EtOAc/hexane = 1:4) 0.25. $[\alpha]_D^{27}$ +4.2 (*c* 5.28, $CHCl_3$); IR (neat): 2933, 2861, 1642, 1428, 1375, 1240, 1107, 1051, 929 ,702 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ = 7.62 (d, *J* = 7.0 Hz, 4H), 7.40-7.31 (m, 6H), 5.75 (m, 1H), 5.31 (d, *J* = 17.0 Hz, 1H), 5.19 (d, *J* = 10.0 Hz, 1H), 3.91 (m, 1H), 3.70-3.58 (m, 2H), 3.61 (dt, *J* = 3.0, 8.0, 16.0 Hz 1H), 1.76-1.53 (m, 4H), 1.36 (d, *J* = 8.0 Hz, 6H), 1.04 (s, 9H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 135.5, 134.0, 129.5, 127.6, 118.6, 108.5, 82.7, 80.4, 63.5, 28.9, 28.1, 27.3, 26.91, 26.85, 19.2 ppm; ESI-HRMS Calcd for $C_{26}H_{36}O_3SiNa$ $[M + Na]^+$ 447.2331; found: 447.2330.

4.13. (3*S*,4*S*)-7-(*tert*-Butyldiphenylsilyloxy)hept-1-ene-3,4-diol (20)

A stirred solution of **19** (4 g, 9.43 mmol) in a mixture of AcOH (42 mL) and H_2O (18 mL), was heated to 50 °C for 1.5 h. After completion of reaction (monitored by TLC), the solution was cooled to 0 °C and saturated $NaHCO_3$ solution was added slowly until pH is about 4. The mixture was diluted with EtOAc (50 mL). Then organic solvents were separated and the aqueous layer was extracted with EtOAc (3 × 30 mL). The combined organic solvents were washed with brine solution, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/hexane = 1:4) to provide diol **20** (3.15 g, 87%) as a viscous liquid; R_f (EtOAc/hexane = 1:4) 0.40. $[\alpha]_D^{27}$ −4.9 (*c* 1.26, $CHCl_3$); IR (neat): 3401, 2929, 2858, 1644, 1427, 1388, 1262, 1109, 929, 703 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ = 7.63 (d, *J* = 7.0 Hz, 4H), 7.42-7.33 (m, 6H), 5.83 (m, 1H), 5.33 (d, *J* = 17.9 Hz, 1H), 5.21 (d, *J* = 10.9 Hz, 1H), 3.88 (m, 1H), 3.68 (t, *J* = 5.0 Hz, 2H), 3.45 (m, 1H), 1.54-1.30 (m, 4H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 137.6, 135.5, 133.5, 129.6, 127.6, 117.3, 76.3, 74.1, 64.1, 29.9, 28.6, 26.8, 19.1 ppm; ESI-HRMS Calcd for $C_{23}H_{32}O_3SiNa$ $[M + Na]^+$ 407.2018; found: 407.2008.

4.14. (3*S*,4*S*)-7-(*tert*-Butyldiphenylsilyloxy)-3-(4-methoxyben-zyloxy)hept-1-en-4-ol (21)

To a solution of **20** (2.1 g, 5.46 mmol) in dry THF (30 ml), was added NaH (0.218 g, 5.46 mmol; 60% dispersion in mineral oil) at 0 °C and the reaction mixture was continued to stir for 30 min. Then, PMB-Br (0.70 g, 4.91 mmol) was added to the reaction mixture drop-wise and was allowed to stir for additional 3 h at same temperature. After completion of reaction, the reaction was quenched by cold H_2O and the aqueous layer was extracted with ethyl acetate (2 × 25 mL) and dried over anhydrous Na_2SO_4. Solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography (EtOAc/hexane = 1:4) to afford **21** (2.5 g, 91%) as a yellow oil; R_f (EtOAc/hexane = 1:4) 0.60. $[\alpha]_D^{27}$ +11.2 (*c* 0.43, $CHCl_3$); IR (neat): 3464, 2933, 2859, 1729, 1471,1428, 1279, 1108, 1036, 922, 704 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 7.65-7.59 (m, 4H), 7.42-7.30 (m, 6H), 7.19 (d, *J* = 9.1 Hz, 2H), 6.82 (d, *J* = 9.1 Hz, 2H), 5.71 (m, 1H), 5.37-5.24 (m, 2H), 4.55 (d, *J* = 11.3 Hz, 1H), 4.25 (d, *J* = 11.3 Hz, 1H), 3.79 (s, 3H),

3.68-3.61 (m, 2H), 3.56-3.42 (m, 2H), 1.76-1.57 (m, 2H), 1.42-1.32 (m, 2H), 1.03 (s, 9H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 159.2, 135.5, 135.4, 133.9, 130.1, 129.5, 127.6, 120.0, 113.8, 84.2, 73.1, 70.0, 63.8, 55.2, 29.7, 28.8, 28.5, 26.8 ppm; ESI-HRMS Calcd for $C_{31}H_{40}O_4SiNa$ $[M + Na]^+$ 527.2593; found: 527.2607.

4.15. (*S*)-5-((*S*)-1-(4-Methoxybenzyloxy)allyl)-11,11- dimethyl-10,10-diphen yl-2,4,9-trioxa-10-silado decane (22)

To a stirred solution of compound **21** (1.8 g, 3.57 mmol) in CH_2Cl_2 (30 mL), was added diisopropylethylamine (1.86 mL, 10.71 mmol) and stirred for 30 min at 0 ^oC under N_2 atmosphere. Methoxymethyl chloride (0.41 mL, 5.35 mmol) was added to the reaction mixture at same temperature. The reaction was continued to stir for 10 h at room temperature. After completion of the reaction (monitored by TLC), it was quenched with water (20 mL). The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (2 × 30 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and solvent removed under reduced pressure. The crude mass was purified by silica gel chromatography (EtOAc/hexane = 1:4) to afford **22** (1.66 g, 85%) as a colorless liquid; R_f (EtOAc/hexane = 1:4) 0.40. $[\alpha]_D^{27}$ −5.2 (*c* 0.67, $CHCl_3$); IR (neat): 2928, 2865, 1740, 1613, 1513, 1463, 1247, 1173, 1037, 822, 703 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.67-7.60 (m, 4H), 7.42-7.30 (m, 6H), 7.19 (d, *J* = 8.7 Hz, 2H), 6.80 (d, *J* = 8.7 Hz, 2H), 5.77 (m, 1H), 5.31-5.22 (m, 2H), 4.66 (AB_q, *J* = 6.8, 30.8 Hz, 2H), 4.53 (d, *J* = 11.7 Hz, 1H), 4.28 (d, *J* = 11.5 Hz, 1H), 3.79 (m, 1H), 3.77 (s, 3H), 3.62 (t, J = 6.0 Hz, 2H), 3.55 (m, 1H), 3.32 (s, 3H), 1.76-1.44 (m, 4H), 1.03 (s, 9H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 159.0, 135.5, 134.0, 130.6, 129.5, 129.3, 127.5, 118.6, 113.7, 97.0, 81.9, 79.7, 70.1, 63.9, 55.7, 55.2, 28.5, 27.3, 26.8, 19.2 ppm; ESI-HRMS Calcd for $C_{33}H_{44}O_5Na$ $[M + Na]^+$ 571.2855; found: 571.2836.

4.16. (4*S*,5*S*)-5-(4-Methoxybenzyl)oxy)-4-methoxymethoxy) hept-6-en-1-ol (7)

To a solution of **22** (3.81 g, 6.96 mmol) in anhydrous THF (45 mL), TBAF (10.44 mL, 1 M in THF, 10.44 mmol) was added drop wise at 0 ^oC under nitrogen atmosphere. After stirring for 4 h at room temperature, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ solution (40 mL) and the resulting mixture was extracted with EtOAc (3 × 60 mL). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography (EtOAc/hexane = 2:3) to afford the desired alcohol **7** (2.05 g, 95%) as a colorless liquid; R_f (EtOAc/hexane = 2:3) 0.25. $[\alpha]_D^{27}$ −5.5 (*c* 2.21, $CHCl_3$); IR (neat): 3398, 2936, 2863, 1735, 1612, 1513, 1459, 1301, 1248, 1173, 1035 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.20 (d, *J* = 9.1 Hz, 2H), 6.82 (d, *J* = 9.1 Hz, 2H), 5.78 (m, 1H), 5.35-5.25 (m, 2H), 4.69 (AB_q, *J* = 6.8, 35.5 Hz, 2H), 4.54 (AB_q, *J* = 11.3 Hz, 2H), 3.85-3.78 (m, 4H), 3.64-3.55 (m, 3H), 3.36 (s, 3H), 1.71-1.41 (m, 4H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 159.0, 135.2, 130.4, 129.2, 118.7, 113.6, 97.0, 81.8, 79.5, 70.1, 62.6, 55.7, 55.1, 28.6, 27.3 ppm; ESI-HRMS Calcd for $C_{17}H_{26}O_5SiNa$ $[M + Na]^+$ 333.1677; found: 333.1666.

4.17. (*S*)-((4*S*,5*S*)-5-(4-Methoxybenzyl)oxy)-4-(methoxyme-thoxy)-hept-6-enyl)-5-(4-methoxy benzyl)oxy) hept-6-enoate (23a)

To a stirred solution of acid **6** (1.72 g, 6.52 mmol) in CH_2Cl_2 (30 mL) at 0 ^oC, Et_3N (1.2 mL, 11.96 mmol) followed by EDCI (2.11 g, 13.6 mmol) and DMAP (0.732 g, 6.0 mmol) were added and stirred for 30 min. Alcohol **7** (1.68 g, 5.44 mmol) in CH_2Cl_2 (20 mL) was slowly added to the resulting reaction mixture at the same temperature and continued to stir for 12 h at room temperature. After completion of the reaction (monitored by TLC), it was quenched with water (30 mL). The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layer was washed with brine (100 mL), dried over Na_2SO_4 and the solvent was removed under reduced pressure to give crude residue which on purification by silica gel column chromatography (EtOAc/hexane = 1:4) afforded the desired coupled product **23a** (2.6 g, 86%) as a colorless liquid; R_f (EtOAc/hexane = 1:4) 0.45. $[\alpha]_D^{27}$ −11.4 (*c* 1.24, $CHCl_3$); IR (neat): 2952, 2935, 1738, 1613, 1514, 1465, 1365, 1301, 1247, 1037 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.17 (d, *J* = 8.2 Hz, 4H), 6.79 (d, *J* = 8.2 Hz, 4H), 5.79-5.64 (m, 2H), 5.30-5.14 (m, 4H), 4.70 (d, *J* = 6.4 Hz, 1H), 4.58 (d, *J* = 7.3 Hz, 1H), 4.53-4.45 (m,2H) 4.29-4.20 (m, 2H), 4.00 (t, *J* = 6.4 Hz, 2H), 3.76 (s, 6H), 3.73-3.64 (m, 2H), 3.53 (m, 1H), 3.32 (s, 3H), 2.25-2.17 (m, 2H), 1.73-1.65 (m, 3H), 1.64-1.54 (m, 5H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 173.5, 159.0, 138.8, 135.2, 130.4, 129.3, 118.8, 117.2, 113.7, 97.1, 81.6, 79.8, 79.3, 70.2, 69.7, 64.3, 55.8, 55.2, 34.9, 34.1, 27.3, 24.8, 20.9 ppm; ESI-HRMS Calcd for $C_{32}H_{44}O_8Na$ $[M + Na]^+$ 579.2933; found: 579.2912.

4.18. (*S*)-((4*S*,5*S*)-5-(*tert*-Butyldimethylsilyl)-4-(methoxyme-thyl)-hept-6-enyl)-5-(*tert*-butyldimethylsilyl)-hept-6-enoate (23c)

To a stirred solution of diol compound **23e** (0.16 g, 0.49 mmol) in CH_2Cl_2 (10 mL) was added 2,6-lutidine (0.2 mL, 1.47 mmol) followed by TBSOTf (0.31 mL, 1.47 mmol) at 0 ^oC under nitrogen atmosphere. The mixture was stirred for 4 h at room temperature and then quenched with saturated aq. $NaHCO_3$ solution (10 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 15 mL), and the combined organic layer was washed with brine (30 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography (EtOAc/hexane: 0.5:9.5) to afford di-TBS ether **23c** (0.235 g, 87%) as a colorless liquid; R_f (EtOAc/hexane: 0.5:9.5) 0.65. $[\alpha]_D^{27}$ −22.0 (*c* 1.24, $CHCl_3$); IR (neat): 2924, 2854, 1729, 1633, 1459, 1253, 1169, 1038 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 5.95-5.69 (m, 2H), 5.31-4.98 (m, 4H), 4.73 (d, *J* = 6.8 Hz, 1H), 4.61 (d, *J* = 6.8 Hz, 1H), 4.22 (m, 1H), 4.13-3.99 (m, 3H), 3.46-3.31 (m, 4H), 2.28 (t, *J* = 7.6 Hz, 2H), 1.81-1.45 (m, 8H), 0.9 (d, *J* = 2.3 Hz, 18H), 0.08-0.01 (m, 12H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 173.6, 141.4, 137.1, 115.9, 113.9, 97.3, 81.2, 74.8, 73.4, 64.3, 55.7, 37.4, 34.2, 26.3, 25.9, 25.8, 25.1, 20.7, 18.2, 18.1, −4.4, −4.7, −4.9, −5.0 ppm; ESI-HRMS Calcd for $C_{28}H_{56}O_6Si_2Na$ $[M + Na]^+$ 567.3513; found: 567.3492.

4.19. (*S*)-((4*S*,5*S*)-4,5-Bis(methoxymethyl)hept-6-enyl)-5-(methoxy- methyl) hept-6-enoate (23d)

To a stirred solution of the diol **23e** (0.104 g, 0.33 mmol) in anhydrous CH_2Cl_2 (10 mL), were added *N*,*N*-diisopropylethylamine (0.2 mL, 1.0 mmol), and DMAP (catalytic) at 0 ^oC. The reaction mixture was stirred for additional 30 min. Then MOMCl (0.15 mL, 1 mmol) was added dropwise to the reaction mixture and allowed to stir for another 12 h at room temperature. After completion of the reaction (monitored by TLC), it was quenched with saturated aqueous $NaHCO_3$ solution (10 mL). The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layer was washed with brine (30 mL) and dried over Na_2SO_4. The

residue obtained after evaporation of the solvent was purified by silica gel column chromatography (EtOAc/hexane: 1:4) to obtain the Tris-MOM ether **23d** (0.125 g, 94%) as a colorless liquid; R_f (EtOAc/hexane: 1:4) 0.45. $[\alpha]_D^{27}$ −5.8 (*c* 2.3, $CHCl_3$); IR (neat): 2924, 2853, 1735, 1462, 1371, 1102, 1034 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 5.81-5.57 (m, 2H), 5.34-5.15 (m, 4H), 4.86-4.44 (m, 6H), 4.12-4.02 (m, 3H), 3.97 (m, 1H), 3.57 (m, 1H), 3.39-3.33 (m, 9H), 2.34- 2.28 (m, 2H), 1.81-1.41 (m, 8H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 173.5, 138.0, 134.6, 119.0, 117.5, 97.0, 94.1, 93.7, 79.3 , 78.6, 76.8, 64.3, 55.9, 55.6, 55.5, 34.7, 34.0, 27.3, 24.7, 20.9 ppm; ESI-HRMS Calcd for $C_{20}H_{36}O_8Na$ $[M + Na]^+$ 427.2307; found: 427.2319.

4.20. (*S*)-((4*S*,5*S*)-5-Hydroxy-4-(methoxymethoxy)hept-6-enyl) 5-hydroxy hept-6-enoate (23e)

To a stirred solution of di-PMB ether **23a** (2.30 g, 4.14 mmol) in CH_2Cl_2 (40 mL), was added phosphate buffer (pH-7) solution (1 mL) at 0 °C followed by DDQ (2.82 g, 12.42 mmol). The reaction mixture was continued to stir for 2 h at room temperature. After completion of the reaction (monitored by TLC), it was quenched with saturated $NaHCO_3$ solution (20 mL). The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (3 × 40 mL). The combined organic layer was washed with brine (75 mL), dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to obtain the crude product which on purification by silica gel column chromatography (EtOAc/hexane = 3:7) furnished the corresponding diol **23e** (1.17 g, 90%) as a colorless oil; R_f (EtOAc/hexane = 3:7) 0.25. $[\alpha]_D^{27}$ +2.8 (*c* 1.4, $CHCl_3$); IR (neat): 3447, 2923, 2853, 1726, 1458, 1240, 1040, 924, 769, 607 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ = 5.89-5.78 (m, 2H), 5.35 (d, *J* = 17.1 Hz, 1H), 5.25-5.19 (m, 2H), 5.09 (d, *J* = 9.8 Hz, 1H), 4.74-4.64 (m, 2H), 4.12-4.05 (m, 3H), 4.01 (t, *J* = 6.1 Hz, 1H), 3.45-3.39 (m, 4H), 2.33 (t, *J* = 7.3 Hz, 2H), 1.79-1.61 (m, 5H), 1.57-1.50 (m, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 173.6, 140.8, 137.0, 117.1, 114.8, 97.3, 82.9, 74.6, 72.6, 64.2, 55.9, 36.2, 34.0, 27.6, 24.5, 20.7 ppm; ESI-HRMS Calcd for $C_{16}H_{28}O_6Na$ $[M + Na]^+$ 339.1783; found: 339.1777.

4.21. (6*S*,9*S*,10*S*,*E*)-6,9,10-*tris*(Methoxymethoxy)oxacyclotridec-7-en-2-one (5d)

A flame-dried round-bottomed flask was charged with a solution of ester **23d** (68 mg, 0.154 mmol) in CH_2Cl_2 (70 mL). The solution was degassed for 20 min under argon atmosphere. Grubbs' 2nd generation catalyst (15 mg, 0.015 mmol) in CH_2Cl_2 (10 mL) was subsequently added to the solution which was again degassed for 15 min. The reaction mixture was stirred for 48 h under refluxing conditions. After completion of the reaction (monitored by TLC), solvent was evaporated under reduced pressure. Purification of the crude residue by silica gel column chromatography (EtOAc/hexane = 3:7) afforded **5d** (46 mg, 78%) as a colorless oil; R_f (EtOAc/hexane = 3:7) 0.35. $[\alpha]_D^{27}$ −4.2 (*c* 1.1, $CHCl_3$); IR (neat): 2924, 2854, 1729, 1458, 1219, 1149, 1097, 1033 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 5.75 (dd, *J* = 4.7, 15.7 Hz, 1H), 5.56 (dd, *J* = 8.1, 16.4 Hz, 1H), 4.82 (m, 1H), 4.72-4.53 (m, 5H), 4.29-4.16 (m, 2H), 4.00 (m, 1H), 3.77 (m, 1H), 3.64 (m, 1H), 3.42-3.33 (m, 9H), 2.36- 2.24 (m, 2H), 1.79-1.55 (m, 8H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 172.9, 135.2, 127.0, 96.7, 94.2, 94.0, 78.9, 78.0, 73.7, 63.4, 55.5, 55.3, 34.6, 33.7, 28.0, 23.0, 19.4 ppm; ESI-HRMS Calcd for $C_{18}H_{32}O_8Na$ $[M + Na]^+$ 399.1992; found: 399.1989.

4.22. (6*S*,9*S*,10*S*,*E*)-6,9-Dihydroxy-10-(methoxymethoxy) oxacyclotridec-7-en-2-one (5e)

A flame-dried round-bottomed flask was charged with a solution of ester **23e** (0.158 g, 0.5 mmol) in CH_2Cl_2 (120 mL). The solution was degassed for 20 min under argon atmosphere. Grubbs' 2nd generation catalyst (0.45 mg, 0.05 mmol) in CH_2Cl_2 (30 mL) was subsequently added to the solution which was again degassed for 15 min. The reaction mixture was stirred for 12 h under refluxing conditions. After completion of the reaction (monitored by TLC), solvent was evaporated under reduced pressure. Purification of the crude residue by silica gel column chromatography (EtOAc/hexane = 1:1) afforded **5e** (0.119 g, 82%) as a colorless oil; R_f (EtOAc/hexane = 1:1) 0.55. $[\alpha]_D^{27}$ +16.0 (*c* 1.3, $CHCl_3$); IR (neat): 3445, 2924, 2856, 1724, 1453, 1250, 1157, 1032 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 5.79 (dddd, *J* = 3.8, 7.6, 15.1, 15.9 Hz, 1H), 5.52 (dddd, *J* = 8.3, 9.8, 15.1, 17.4 Hz, 1H), 4.76-4.64 (m, 2H), 4.35-4.20 (m, 2H), 4.13-3.85 (m, 3H), 3.46-3.32 (m, 5H), 2.35-2.22 (m, 2H), 1.80-1.49 (m, 8H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 172.9, 138.1, 129.6, 97.3, 83.3, 72.2, 69.5, 63.2, 55.8, 34.5, 23.4, 23.2, 19.7, 19.1 ppm; ESI-HRMS Calcd for $C_{14}H_{24}O_6Na$ $[M + Na]^+$ 311.1470; found: 311.1486.

4.23. (5*S*,6*S*)-12,12-Dimethyl-11,11-diphenyl-5-vinyl-2,4,10-trioxa-11-silatridecan-6-ol (26)

To a stirred solution of compound **20** (1.5 g, 3.9 mmol) in CH_2Cl_2 (30 mL), was added diisopropylethylamine (0.75 mL, 4.29 mmol) and stirred for 30 min at 0 °C under N_2 atmosphere. Methoxymethyl chloride (0.3 mL, 3.9 mmol) was added to the reaction mixture and the stirring was continued for 2 h at same temperature. After completion of the reaction (monitored by TLC), it was quenched with water (20 mL). The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (2 × 30 mL). The combined organic layer was washed with brine (20 mL) and dried over anhydrous Na_2SO_4 and solvent removed under reduced pressure. The crude mass was purified by silica gel chromatography (EtOAc/hexane = 1:4) to afford **26** (1.42 g, 85%) as a colorless liquid; R_f (EtOAc/hexane = 1:4) 0.50. $[\alpha]_D^{27}$ +20.4 (*c* 3.67, $CHCl_3$); IR (neat): 3464, 2933, 2859, 1729, 1471, 1428, 1279, 1108, 1036, 922, 704, 505 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 7.62 (d, *J* = 6.6 Hz, 4H), 7.42-7.29 (m, 6H), 5.73 (m, 1H), 5.38-5.13 (m, 2H), 4.73-4.50 (m, 2H), 3.95 (bs, 1H), 3.81 (m, 1H), 3.72-3.59 (m, 2H), 3.51 (m, 1H), 3.36 (s, 3H), 1.82-1.44 (m, 4H), 1.03 (s, 9H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 137.2, 135.5, 134.8, 129.5, 127.6, 119.8, 93.9, 83.4, 74.8, 63.8, 55.7, 29.1, 28.6, 26.8, 19.2 ppm; ESI-HRMS Calcd for $C_{25}H_{36}SiO_4Na$ $[M + Na]^+$ 451.2280; found: 451.2265.

4.24. (5*S*,6*S*)-6-(4-Methoxybenzyloxy)-12,12-dimethyl-11,11-diphe- nyl-5-vinyl-2,4,10-trioxa-11-silatri decane (27)

To a solution of **26** (1.2 g, 2.8 mmol) in dry THF (30 ml), was added NaH (0.167 g, 4.2 mmol; 60% dispersion in mineral oil) at 0 °C and the reaction mixture was continued to stir for 30 min. Then, PMB-Br (0.48 mL, 3.36 mmol) was added to the reaction mixture dropwise and was allowed to stir for additional 3 h at temperature. Then, the reaction was quenched by cold H_2O and the aqueous layer was extracted with ethyl acetate (2 × 25 mL) and dried over anhydrous Na_2SO_4. Solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography (EtOAc/hexane = 1:4) to afford **27** (1.39 g, 91%) as a yellow oil; R_f (EtOAc/hexane = 1:4) 0.60. $[\alpha]_D^{27}$ +8.0 (*c* 1.71, $CHCl_3$); IR (neat): 2933, 2860, 1612, 1513, 1467, 1248, 1105, 1037, 822, 704 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.64-7.59 (m, 4H), 7.40-7.30 (m, 6H), 7.18 (d, *J* = 8.6 Hz, 2H), 6.78 (d, *J* = 8.6 Hz, 2H), 5.73 (m, 1H), 5.29-5.21 (m, 2H), 4.72-4.40 (m, 4H), 4.09 (m, 1H), 3.76 (s, 3H), 3.64-3.56 (m, 2H),

3.40-3.30 (m, 4H), 1.71-1.37 (m, 4H), 1.03 (s, 9H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 159.1, 135.5, 135.1, 134.0, 130.8, 129.5, 127.6, 118.5, 113.6, 94.1, 80.6, 78.8, 72.6, 63.9, 55.5, 55.2, 28.6, 27.0, 26.8, 19.2 ppm; ESI-HRMS Calcd for $C_{33}H_{44}O_5SiNa$ $[M + Na]^+$ 571.2855; found: 571.2836.

4.25. (4*S*,5*S*)-4-(4-Methoxybenzyl)oxy)-5-(methoxymethoxy) hept-6-en-1-ol (7b)

To a solution of **27** (3.01 g, 5.5 mmol) in anhydrous THF (30 mL), TBAF (8.25 mL, 1 M in THF, 8.25 mmol) was added drop wise to the above stirred solution at 0 °C under nitrogen atmosphere. After stirring for 4 h at room temperature, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ solution (30 mL) and the resulting mixture was extracted with EtOAc (3 × 60 mL). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography (EtOAc/hexane = 2:3) to afford the desired alcohol **7b** (1.6 g, 94%) as a colorless liquid; R_f (EtOAc/hexane = 2:3) 0.30. $[\alpha]_D^{27}$ +6.64 (*c* 3.3, $CHCl_3$); IR (neat): 3427, 2946, 2879, 1613, 1514, 1247, 1149, 1058, 1017 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.22 (d, *J* = 8.6 Hz, 2H) , 6.82 (d, *J* = 8.6 Hz, 2H), 5.74 (m, 1H), 5.33-5.23 (m, 2H), 4.70-4.62 (m, 2H), 4.57-4.42 (m, 2H), 4.17 (t, *J* = 6.2 Hz, 1H), 3.78 (s, 3H), 3.58-3.51 (m, 2H), 3.45-3.32 (m, 4H), 1.75-1.38 (m, 4H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 159.1, 134.6, 130.4, 129.6, 118.7, 113.7, 94.1, 80.4, 78.3, 72.6, 62.7, 55.5, 55.2, 28.8, 26.9 ppm; ESI-HRMS Calcd for $C_{17}H_{26}O_5Na$ $[M + Na]^+$ 333.1677; found: 333.1666.

4.26. (*S*)-((4*S*,5*S*)-4-(4-Methoxybenzyl)oxy)-5-(methoxymeth-oxy)-hept-6-enyl)-5-(methoxy methoxy)-hept-6-enoate (28)

To a stirred solution of acid **6b** (0.670 g, 3.56 mmol) in CH_2Cl_2 (20 mL) at 0 °C, Et_3N (0.9 mL, 6.53 mmol) followed by EDCI (0.968 g, 6.23 mmol) and DMAP (0.264 g, 2.16 mmol) were added and stirred for 30 min. Alcohol **7b** (0.922 g, 2.97 mmol) in CH_2Cl_2 (15 mL) was slowly added to the resulting reaction mixture at the same temperature and continued to stir for 12 h at room temperature. After completion of the reaction (monitored by TLC), it was quenched with water (25 mL). The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (2 × 40 mL). The combined organic layer was washed with brine (75 mL), dried over Na_2SO_4 and the solvent was removed under reduced pressure to give crude residue which on purification by silica gel column chromatography afforded the desired coupled product **28** (1.2 g, 84 %) as a colorless liquid; R_f (EtOAc/hexane = 2.5:7.5) 0.40. $[\alpha]_D^{27}$ −5.3 (*c* 1.38, $CHCl_3$); IR (neat): 2927, 2857, 1734, 1514, 1460, 1248, 1151, 1097, 1035 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.21 (d, *J* = 9.0 Hz, 2H), 6.81 (d, *J* = 8.3 Hz, 2H), 5.80-5.56 (m, 2H), 5.31-5.13 (m, 4H), 4.67-4.61 (m, 3H), 4.56-4.43 (m, 3H), 4.12 (m, 1H), 4.03-3.92 (m, 3H), 3.78 (s, 3H), 3.40 (m, 1H), 3.32 (s, 6H), 2.28 (t, *J* = 7.5 Hz, 2H), 1.81-1.31 (m, 8H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 173.5, 159.2, 138.0, 134.6, 130.5, 129.6, 118.7, 117.4, 113.7,94.1, 93.7, 80.0, 78.4, 76.8, 72.6, 64.3, 55.5, 55.4, 55.2, 34.7, 34.0, 27.0, 24.9, 20.9 ppm; ESI-HRMS Calcd for $C_{26}H_{40}O_8Na$ $[M + Na]^+$ 503.26154; found: 503.26068.

4.27. (6*S*,9*S*,10*S*,*E*)-10-(4-Methoxybenzyl)oxy)-6,9-bis(metho-xymethoxy) oxacyclotridec-7-en-2-one (29)

A flame-dried round-bottomed flask was charged with a solution of ester **28** (0.681 g, 1.42 mmol) in CH_2Cl_2 (400 mL). The solution was degassed for 20 min under argon atmosphere. Grubbs' 2nd generation catalyst (95 mg, 0.11 mmol) in CH_2Cl_2 (60 mL) was subsequently added to the solution which was again degassed for 15 min. The reaction mixture was stirred for 36 h under refluxing conditions. After completion of the reaction (monitored by TLC), solvent was evaporated under reduced pressure. Purification of the crude residue by silica gel column chromatography (EtOAc/hexane = 3:7) afforded **29** (0.479 g, 75%) as a colorless liquid; R_f (EtOAc/hexane = 3:7) 0.25. $[\alpha]_D^{27}$ −7.2 (*c* 1.65, $CHCl_3$); IR (neat): 2930, 2884, 1731, 1513, 1458, 1247, 1036 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.27 (d, *J* = 12.8 Hz, 2H), 6.87 (d, *J* = 9.0 Hz, 2H), 5.74 (dd, *J* = 5.2, 15.9 Hz, 1H), 5.59 (dd, *J* = 7.5, 15.9 Hz, 1H), 4.71-4.52 (m, 6H), 4.23-4.07 (m, 3H), 3.96 (m, 1H), 3.81 (s, 3H), 3.48 (m, 1H), 3.35 (d, *J* = 2.2 Hz, 6H), 2.28 (d, *J* = 4.5 Hz, 2H), 1.77-1.52 (m, 8H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 172.8, 159.1, 134.5, 131.0, 129.2, 127.8, 113.7, 94.4, 94.2, 79.6, 79.0, 74.1, 72.4, 63.3, 55.3, 55.2, 34.6, 34.0, 27.5, 23.2, 19.6 ppm; ESI-HRMS Calcd for $C_{24}H_{36}O_8Na$ $[M + Na]^+$ 475.2302; found: 475.2293.

4.28. (2*E*,7*S*,8*E*,10*S*,11*S*)-Ethyl-14-hydroxy-11-(4-methoxy-benzyl)-oxy)-7,10-bis(methoxymethoxy)-tetra-deca-2,8-dienoate (31)

To a stirred solution of lactone **29** (0.231 g, 0.51 mmol) in CH_2Cl_2, DIBAL-H (0.5 mL, 1.4M solution in toluene, 0.70 mmol) was added slowly (Ca. 5 min) at −78 °C under nitrogen atmosphere. The solution was stirred for 30 min at same temperature and allowed to warm to 0 °C slowly. After completion of the reaction (monitored by TLC), MeOH (0.3 mL) was added slowly followed by the addition of cold aqueous saturated sodium potassium tartrate (8 mL). The biphasic mixture was stirred for further 2 h and then partitioned. Aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). Combined organic phase was dried over Na_2SO_4 and concentrated under reduced pressure. The crude residue (0.202 g, 87%) was used for the next step without further purification.

The lactol compound (0.202 g, 0.45 mmol) in benzene (12 mL), was added $Ph_3P{=}CHCO_2Et$ (0.233 g, 0.67 mmol) at room temperature. The reaction mixture was heated to 80 °C for 8 h. After completion of the reaction (monitored by TLC), the reaction mixture was concentrated under reduced pressure. Purification by silica gel column chromatography (EtOAc/hexane = 1:4) afforded α,β-unsaturated ester **31** (0.207 g, 89%) as a colorless oil; R_f (EtOAc/hexane = 1:4) 0.45. $[\alpha]_D^{27}$ −11.2 (*c* 2.2, $CHCl_3$); IR (neat): 3418, 2925, 2856, 1715, 1613, 1514, 1463, 1248, 1032 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.26 (d, *J* = 8.5 Hz, 2H), 6.95 (m, 1H), 6.87 (d, *J* = 8.5 Hz, 2H), 5.81 (d, *J* = 15.7 Hz, 1H) , 5.65-5.52 (m, 2H), 4.71-4.57 (m, 4H), 4.54-4.47 (m, 2H), 4.26-4.13 (m, 3H), 4.03 (m, 1H), 3.80 (s, 3H), 3.58 (t, *J* = 5.9 Hz, 2H), 3.46 (m, 1H), 3.35 (d, *J* = 3.4 Hz, 6H), 2.27-2.17 (m, 2H), 1.78-1.40 (m, 8H), 1.28 (t, *J* = 7.2 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 166.7, 159.2, 148.7, 134.0, 132.0, 129.5, 128.4, 121.5, 113.7, 94.3, 93.7, 80.5, 77.4, 76.1, 72.5, 62.6, 60.1, 55.5, 55.3, 55.2, 34.9, 31.9, 28.7, 27.1, 23.8, 14.2 ppm; ESI-HRMS Calcd for $C_{28}H_{44}O_9Na$ $[M + Na]^+$ 547.2877; found: 547.2871.

4.29. (2*E*,7*S*,8*E*,10*R*,11*R*)-Ethyl-11-(4-methoxybenzyl)oxy)-7,10-bis(methoxymethoxy)penta-deca-2,8,14-trienoate (32)

To a stirred solution of primary alcohol **31** (0.122 g, 0.23 mmol) and solid anhydrous $NaHCO_3$ (0.05 g) in CH_2Cl_2 (10 mL) at 0 °C, was added Dess-Martin periodinane (0.118 g, 0.28 mmol). The reaction mixture was stirred at 0 °C for 3 h. After completion of reaction (monitored by TLC), it was quenched with saturated aqueous $NaHCO_3$ solution (10 mL) and stirred for another 30

min. The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layer was evaporated under reduced pressure to afford a crude residue which was immediately used for the next reaction.

Methyltriphenylphosphonium bromide (0.225 g, 0.63 mmol) was dissolved in THF (10 mL) and cooled to –78 ºC. *n*-Butyllithium (0.3 mL, 1.6 M in hexane, 0.48 mmol) was added drop wise to the above stirred solution which turned into light orange solution. It was then warmed to 0 ºC for 45 min and again cooled to –78 ºC. The crude aldehyde (0.108 g, 0.21 mmol) in THF (5 mL) was added to the reaction mixture drop wise. The reaction mixture was stirred at the same temperature for 4 h. After complete consumption of the starting material (monitored by TLC), the reaction was quenched with saturated NH_4Cl solution (10 mL) and warmed to room temperature. The organic phase was separated and the aqueous phase extracted with ethyl acetate (2 × 15 mL). The combined organic layers were washed with brine (25 mL), dried over Na_2SO_4 and concentrated. Purification by silica gel column chromatography (EtOAc/hexane = 1:4) afforded the desired compound **31** (0.094 g, 78% over two steps) as a colorless liquid; R_f (EtOAc/hexane = 1:4) 0.20. $[\alpha]_D^{27}$ −10.3 (*c* 1.5, $CHCl_3$); IR (neat): 2925, 2851, 1723, 1511, 1457, 1248, 1097, 1035 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ = 7.23 (d, *J* = 9.0 Hz, 2H), 6.92 (m, 1H), 6.84 (d, *J* = 9.0 Hz, 2H), 5.82-5.70 (m, 2H), 5.63-5.50 (m, 2H), 4.99-4.90 (m, 2H), 4.67-4.54 (m, 4H), 4.50-4.44 (m, 2H), 4.20-4.13 (m, 2H), 4.01 (m, 1H), 3.79 (s, 3H), 3.41 (m, 1H), 3.34 (s, 7H), 2.24-2.14 (m, 2H), 2.09-2.00 (m, 2H), 1.68-1.45 (m, 6H), 1.29 (t, *J* = 7.0 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 166.6, 159.1, 148.6, 138.4, 133.8, 130.7, 130.0, 129.5, 121.6, 114.7, 113.7, 94.3, 93.6, 79.9, 77.3, 75.8, 72.6, 60.1, 55.5, 55.2, 35.0, 32.0, 29.9, 29.7, 23.9, 14.2 ppm; ESI-HRMS Calcd for $C_{29}H_{44}O_8Na$ $[M + Na]^+$ 543.2928; found: 543.2924.

4.30. (*Z*)-5-(4-Methoxybenzyloxy)pent-2-en-1-ol (35)

To a solution of nickel acetate tetrahydrate (3.76 g, 15.11 mmol) in ethanol (75 mL), sodium borohydride was added (0.57 g, 15.11 mmol) at room temperature under H_2 atmosphere. The mixture was stirred for 30 min and then ethylene diamine (2 mL, 30.2 mmol) followed by alkyne **34** (20 g, 60.4 mmol) in ethanol (50 mL) were added at same temperature and allowed to stir for additional 3 h under H_2 atmosphere. After completion of the reaction (monitored by TLC), the reaction mixture was filtered through a pad of Celite. Solvent (filtrate) was removed under reduced pressure and the residue was purified by flash column chromatography (EtOAc/hexane = 1:4) to provide allyl alcohol **35** (2.73 g, 89%) as a colorless oil; R_f (EtOAc/hexane = 1:4) 0.30. IR (neat): 3398, 2936, 2861, 1611, 1513, 1360, 1247, 1090, 1033, 820, 575 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ = 7.24 (d, *J* = 8.7 Hz, 2H), 6.87 (d, *J* = 8.7 Hz, 2H), 5.81 (qt, *J* = 1.4, 7.0, 9.5 Hz, 1H), 5.59 (qt, *J* = 1.1, 7.8, 9.8 Hz, 1H), 4.44 (s, 2H), 4.10 (d, *J* = 7.0 Hz, 2H), 3.79 (s, 3H), 3.46 (t, *J* = 6.1 Hz, 2H), 2.39 (qd, *J* = 1.2, 6.3 Hz, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 159.0, 130.7, 129.7, 129.2, 129.1, 113.6, 72.5, 68.5, 57.4, 55.0, 27.8 ppm; ESI-HRMS Calcd for $C_{13}H_{18}O_3Na$ $[M + Na]^+$ 245.1148; found: 245.1158.

4.31. ((2*S*,3*R*)-3-(2-(4-Methoxybenzyloxy)ethyl)oxiran-2-yl)methanol (36)

To a suspension of thoroughly dried molecular sieves 4 Å (7.2 g) in dry CH_2Cl_2 (60 mL), was added $Ti(OiPr)_4$ (2.87 mL, 9.7 mmol) followed by (+)-DET (2.42 mL, 11.52 mmol) at –20 °C under N_2 atmosphere. After stirring for 30 min, TBHP (6.5 M in toluene, 13.85 mL, 90.02 mmol) was slowly added and the resulting solution was stirred at –20 °C for a further 45 min. Allylic alcohol **35** (8 g, 36.01 mmol) in CH_2Cl_2 (320 mL) was then added and the reaction mixture was stirred at –20 °C for 24 h. After completion of the reaction (monitored by TLC), the reaction mixture was warmed to 0 °C and reaction mixture was filtered through sintered funnel. Then quenched by water (57.4 mL) and stirred vigorously for 30 min. The filtrate was again stirred along with 20% aqueous NaOH solution (14.4 mL) until both the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 40 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and solvent was evaporated under reduced pressure. The crude residue was purified by silica gel column chromatography (EtOAc/hexane = 1:3) to afford pure epoxide **36** (8.23 g, 96%) as a colorless oil; R_f (EtOAc/hexane = 1:4) 0.20. $[\alpha]_D^{27}$ +8.89 (*c* 1, $CHCl_3$); IR (neat): 3394, 2939, 1611, 1513, 1248, 1175, 1093, 1028, 819 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ = 7.25 (d, *J* = 8.7 Hz, 2H), 6.89 (d, *J* = 8.7 Hz, 2H), 4.46 (s, 2H), 3.84 (bs, 1H), 3.80 (s, 3H), 3.64 (m, 1H), 3.59 (m, 1H), 3.47 (dd, *J* = 8.1, 11.9 Hz, 1H), 3.21-3.14 (m, 2H), 3.03 (dt, *J* = 4.3, 8.9, 9.2 Hz, 1H), 2.06 (dq, *J* = 4.1, 14.7 Hz, 1H), 1.79-1.71 (m, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 159.3, 129.5, 129.0, 113.7, 73.0, 66.2, 59.8, 55.2, 55.0, 54.7, 27.9 ppm; ESI-HRMS Calcd for $C_{13}H_{18}O_4Na$ $[M + Na]^+$ 261.1097; found: 261.1107.

4.32. (*E*)-Ethyl-3-((2*S*,3*R*)-3-(2-(4-methoxybenzyloxy)ethyl) oxiran-2-yl)-2-methylacrylate (37)

To dimethyl sulfoxide (4.63 mL, 65.22 mmol) in CH_2Cl_2 (40 mL), was added oxalyl chloride (3.75 mL, 43.67 mmol) drop-wise at –78 °C under N_2 atmosphere. The reaction mixture was stirred for 30 min before alcohol **36** (5.2 g, 21.84 mmol) in CH_2Cl_2 (20 mL) was added slowly. The reaction mixture was stirred for 45 min at same temperature. Then triethylamine (15.23 mL, 109.2 mmol) was added drop-wise and allowed to stir for 1 h at –78 °C. The reaction was allowed to stir at room temperature for additional 1 h. After completion of the reaction (monitored by TLC), the reaction mixture was quenched with water. The aqueous phase was extracted with CH_2Cl_2 (3 × 40 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and evaporated to dryness under reduced pressure. The crude aldehyde was used immediately for the next reaction without further purification.

To a stirred solution of crude aldehyde (4.43 g, 18.76 mmol) in toluene (45 mL), was added (carbethoxyethylidene)triphenyl phosphorane (10.2 g, 28.14 mmol) at room temperature. The reaction mixture was heated to 90 °C for 3 h. After completion of the reaction (monitored by TLC), the reaction mixture was cooled to room temperature and solvent was evaporated under reduced pressure. The residue was purified by silica gel chromatography (EtOAc/hexane = 1:4) to afford **37** (4.74 g, 68% over two steps) as a colorless oil; R_f (EtOAc/hexane = 1:4) 0.65. $[\alpha]_D^{27}$ +18.3 (*c* 0.9, $CHCl_3$); IR (neat): 2959, 1711, 1513, 1461, 1245, 1097, 1033, 821, 566 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ = 7.25 (d, *J* = 8.6 Hz, 2H), 6.88 (d, *J* = 8.6 Hz, 2H), 6.49 (dd, *J* = 1.4, 7.9 Hz, 1H), 4.46 (ABq, *J* = 11.6, 13.7 Hz, 2H), 4.25-4.15 (m, 2H), 3.80 (s, 3H), 3.67-3.57 (m, 3H), 3.38-3.34 (m, 1H), 1.96 (d, *J* = 1.2 Hz, 3H), 1.95-1.79 (m, 2H), 1.29 (t, *J* = 7.2 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 166.9, 159.1, 135.0, 133.3, 130.1, 129.1, 113.7, 72.6, 66.9, 60.7, 56.7, 55.2, 53.0, 29.2, 14.1, 12.9 ppm; ESI-HRMS Calcd for $C_{18}H_{25}O_5$ $[M + H]^+$ 321.1696; found: 321.1714.

4.33. (4*R*,5*R*,*E*)-Ethyl-5-hydroxy-7-(4-methoxybenzyloxy)-2,4-dimethylhept-2-enoate (38)

To a stirred solution of epoxy unsaturated ester compound **37** (4.3 g, 13.43 mmol) in CH_2Cl_2 (70 mL), was added trimethylaluminium (67.2 mL, 134.3 mmol, 2 M in toluene) at –40 °C under N_2 atmosphere. The reaction mixture was allowed to stir for 30 min at the same temperature. Then, H_2O (1.45 mL, 80.58 mmol) was added very carefully (Caution: Me_3Al reacts violently and may ignite upon contact with water) and slowly so that the internal temperature did not change. After effervescence ceased, it was allowed to stir for further 3 h at –40 °C. After complete consumption of the starting material (shown by TLC), it was quenched very slowly with saturated NH_4Cl (50 mL) and diluted with CH_2Cl_2 (100 mL). HCl (1.0 N, 50 mL) was added and stirred vigorously until a clear separation of the two layers took place. The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (2 × 80 mL). The combined organic layer was washed with brine (2 × 50 mL), dried over anhydrous Na_2SO_4 and evaporated to dryness under reduced pressure. The crude mass was purified by silica gel column chromatography (EtOAc/ hexane = 1:5) to afford **38** (4.11 g, 91%) as a colorless oil; R_f (EtOAc/hexane = 1:5) 0.55. $[\alpha]_D^{27}$ +7.7 (*c* 1.1, $CHCl_3$); IR (neat): 3398, 2925, 2855, 1707, 1513, 1246, 1089, 1033, 821, 558 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 7.24 (d, *J* = 8.3 Hz, 2H), 6.88 (d, *J* = 8.3 Hz, 2H), 6.58 (dd, *J* = 1.5, 10.6 Hz, 1H), 4.44 (s, 2H), 4.18 (q, *J* = 6.8 Hz, 2H), 3.81 (s, 3H), 3.73-3.56 (m, 3H), 3.31 (bs, 1H), 2.62-2.48 (m, 1H), 1.84 (d, *J* = 1.5 Hz, 3H), 1.75-1.66 (m, 2H), 1.29 (t, *J* = 6.8 Hz, 3H), 1.07 (d, *J* = 6.8 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 168.1, 159.2, 143.7, 129.6, 129.3, 127.7, 113.8, 75.1, 73.0, 69.2, 60.5, 55.2, 39.7, 33.9, 15.6, 14.2, 12.6 ppm; ESI-HRMS Calcd for $C_{19}H_{28}O_5Na$ $[M + Na]^+$ 359.1829; found: 359.1845.

4.34. (4*R*,5*R*,*E*)-7-(4-Methoxybenzyloxy)-2,4-dimethylhept-2-ene-1,5-diol (39)

To a stirred solution of the ester **38** (3.2 g, 9.52 mmol) in CH_2Cl_2 (50 mL), was added DIBAL-H in toluene (11.42 mL, 1.75 M, 19.99 mmol) dropwise at −78 °C. The solution was stirred at same temperature for 2 h under N_2 atmosphere. After completion of the reaction (monitored by TLC), the reaction was quenched by addition of saturated aqueous sodium potassium tartrate (40 mL). The gelatinous mixture was stirred until two distinct layers formed. The layers were separated, and the aqueous layer extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers washed with brine (2 × 30 mL) and dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography (EtOAc/hexane = 1:4) to afford **39** (2.6 g, 93%) as colorless oil; R_f (EtOAc/hexane = 1:4) 0.20. $[\alpha]_D^{27}$ −10.2 (*c* 0.63, $CHCl_3$); IR (neat): 3384, 2950, 2865, 1612, 1513, 1457, 1248, 1084, 820 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 7.24 (d, *J* = 8.3 Hz, 2H), 6.87 (d, *J* = 9.0 Hz, 2H), 5.24 (d, *J* = 9.8 Hz, 1H), 4.44 (s, 2H), 3.96 (s, 2H), 3.80 (s, 3H), 3.71-3.54 (m, 3H), 2.46 (m, 1H), 1.82-1.68 (m, 2H), 1.65 (s, 3H), 1.00 (d, *J* = 6.8 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 159.1, 135.0, 129.8, 129.3, 128.2, 113.7, 75.3, 72.9, 69.1, 68.5, 55.2, 38.2, 33.6, 16.2, 14.0 ppm; ESI-HRMS Calcd for $C_{17}H_{27}O_4$ $[M + H]^+$ 295.1903; found: 295.1918.

4.35. (8*R*,9*R*,*E*)-9-(2-(4-Methoxybenzyloxy)ethyl)-2,2,3,3,6,8,11,11-12,12-decamethyl-4,10-dioxa-3,11-disilatridec-6-ene (40)

To a stirred solution of diol **39** (2.5 g, 8.50 mmol) in dry CH_2Cl_2 (40 mL), was added 2,6-lutidine (3.95 mL, 34.0 mmol) and TBSOTf (5.85 mL, 25.49 mmol) sequentially at 0 °C under N_2 atmosphere and allowed to stir for 30 min. After completion of the reaction (monitored by TLC), the reaction mixture was then quenched with H_2O (25 mL) and extracted with CH_2Cl_2 (2 × 50 mL). The organic extract was washed with brine (30 mL) and dried over Na_2SO_4 and solvent removed under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/hexane = 1:9) to afford **40** (4.12 g, 93%) as a clear liquid; R_f (EtOAc/hexane = 1:4) 0.75. $[\alpha]_D^{27}$ +7.1 (*c* 2.96, $CHCl_3$); IR (neat): 2955, 2931, 2857, 1613, 1513, 1465, 1251, 1090, 837, 775 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 7.24 (d, *J* = 8.6 Hz, 2H), 6.86 (d, *J* = 8.7 Hz, 2H), 5.26 (dd, *J* = 1.2, 9.8 Hz, 1H), 4.40 (dd, *J* = 11.4, 19.7 Hz, 2H), 3.98 (s, 2H), 3.79 (s, 3H), 3.63 (m, 1H), 3.53-3.44 (m, 2H), 2.46 (m, 1H), 1.84-1.68 (m, 2H), 1.57 (d, *J* = 1.1 Hz, 3H), 0.92-0.87 (m, 21H), 0.05 (s, 6H), 0.03 (d, *J* = 3.2 Hz, 6H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 159.0, 133.7, 130.6, 129.2, 127.7, 113.6, 73.5, 72.5, 68.7, 66.7, 55.2, 37.6, 34.6, 25.9, 18.4, 18.1, 16.4, 13.6, −4.4, −4.5, −5.2, −5.3 ppm; ESI-HRMS Calcd for $C_{29}H_{54}O_4Si_2Na$ $[M + Na]^+$ 545.3452; found: 545.3477.

4.36. (3*R*,4*R*,*E*)-3,7-Bis(*tert*-butyldimethylsilyloxy)-4,6-dimethylhe-pt-5-en-1-ol (41)

To a solution of PMB protected compound **40** (2.3 g, 4.40 mmol) in CH_2Cl_2:H_2O (19:1, 40 mL), phosphate buffer solution (pH = 7) (2 mL) followed by DDQ (1.5 g, 6.60 mmol) was added at 0 °C and allowed to stir for 2 h at room temperature. After completion of the reaction (monitored by TLC), it was quenched with saturated $NaHCO_3$ (30 mL) solution. The two layers were separated and the aqueous layer extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layer was washed with brine (2 × 30 mL), dried over anhydrous Na_2SO_4 and solvent was removed under reduced pressure to give red colored crude product which on purification by silica gel column chromatography (EtOAc/hexane = 1:4) to afford the desired primary alcohol **41** (1.63 g, 92%) as a colorless liquid; R_f (EtOAc/hexane = 1:4) 0.25. $[\alpha]_D^{27}$ +5.1 (*c* 0.93, $CHCl_3$); IR (neat): 3362, 2957, 2873, 1734, 1613, 1515, 1245, 1033, 821 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 5.20 (d, *J* = 9.8 Hz, 1H), 3.98 (s, 2H), 3.79 (m, 1H), 3.72-3.62 (m, 2H), 2.67-2.54 (m, 1H), 2.33 (bs, 1H), 1.87-1.75 (m, 1H), 1.72-1.63 (m, 1H), 1.61 (s, 3H), 0.95 (d, *J* = 6.8 Hz, 3H), 0.89 (m, 18H), 0.08 (d, *J* = 7.6 Hz, 6H), 0.04 (s, 6H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 134.2, 126.8, 75.6, 68.5, 60.0, 37.2, 36.0, 25.92(3C), 25.89(3C), 18.4, 18.0, 17.5, 13.7, −4.3, −4.5, −5.2, −5.3 ppm; ESI-HRMS Calcd for $C_{21}H_{47}O_3Si_2$ $[M + H]^+$ 403.3058; found: 403.3081.

4.37. (4*R*,5*R*,*E*)-4,8-Bis(*tert*-butyldimethylsilyloxy)-5,7-dimethyl-oct-6-en-2-ol (42)

To a stirred solution of **41** (1.2 g, 2.98 mmol) in dry CH_2Cl_2 (40 mL), was added $NaHCO_3$ (0.3 g, 3.57 mmol) and Dess-Martin periodinane (2.53 g, 5.96 mmol) at 0 °C under N_2 atmosphere and allowed to stir for 1 h at room temperature. After completion of the reaction (monitored by TLC), it was quenched with saturated aqueous $NaHCO_3$ (20 mL) and $Na_2S_2O_3$ (10 mL) and extracted with CH_2Cl_2 (2 × 35 mL). The combined organic extracts were washed with brine (20 mL), dried over Na_2SO_4 and solvent was removed under reduced pressure furnished crude aldehyde and used as such for the next reaction.

To a stirred solution of crude aldehyde (1.09 g, 2.72 mmol) in THF (30 mL) at 0 °C under N_2 atmosphere, was added MeMgBr (5.44 mL, 1 M solution in toluene, 5.44 mmol) dropwise. The solution was stirred for additional 2 h at room temperature. After completion of the reaction (monitored by TLC), the reaction was quenched by addition of saturated aqueous NH_4Cl (20 mL) and extracted with ethyl acetate (2 × 35 mL). The combined organic layers were dried over Na_2SO_4 and evaporated to dryness. The

residue was purified by silica gel column chromatography (EtOAc/hexane = 1:4) to afford **42** (0.973 g, 79% over two steps) as a mixture of diastereomers; R_f (EtOAc/hexane = 1:4) 0.35. IR (neat): 3450, 2957, 2858, 1719, 1460, 1379, 1254, 1077, 836, 773, 667 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 5.35 (dd, *J* = 1.5, 9.8 Hz, 1H), 5.13 (dd, *J* = 1.5, 9.8 Hz, 1H), 4.13-4.02 (m, 1H), 3.99 (s, 2H), 3.97 (s, 2H), 3.95-3.87 (m, 1H), 3.80-3.73 (m, 1H), 3.72-3.66 (m, 1H), 2.77-2.65 (m, 1H), 2.64-2.54 (m, 1H), 1.64-1.60 (m, 10H), 1.16 (d, *J* = 6.0 Hz, 3H), 1.09 (d, *J* = 6.8 Hz, 3H), 0.97 (d, *J* = 6.8 Hz, 3H), 0.93-0.87 (m, 39H), 0.09-0.03 (m, 24H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 134.5, 134.2, 126.7, 126.6, 76.4, 76.0, 68.6, 68.4, 66.5, 64.8, 42.1, 42.0, 37.8, 37.0, 25.93, 25.90, 24.0, 23.8, 18.4, 18.02, 17.99, 16.5, 13.74, 13.70, −4.1, −4.2, −4.5, −4.6, −5.2, −5.3 ppm; ESI-HRMS Calcd for $C_{22}H_{49}O_3Si_2$ $[M + H]^+$ 417.3214; found: 417.3236.

4.38. (4*R*,5*R*,*E*)-4,8-Bis(*tert*-butyldimethylsilyloxy)-5,7-dimethyloct-6-en-2-one (8)

To a stirred solution of secondary alcohol **42** (0.85 g, 2.04 mmol) in CH_2Cl_2, anhydrous $NaHCO_3$ (0.21 g, 2.45 mmol) and Dess-Martin periodinane (1.73 g, 4.08 mmol) were added at 0 °C under nitrogen atmosphere. Then the reaction mixture was stirred for 2 h at room temperature. After completion of reaction (monitored by TLC), the reaction mixture was quenched with saturated $NaHCO_3$ (30 mL) solution. The aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layer was washed with brine (2 × 20 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude mass was purified by silica gel chromatography (EtOAc/hexane = 1:4) to afford **8** (0.77 g, 91%) as a colorless liquid; R_f (EtOAc/hexane = 1:4) 0.65. $[\alpha]_D^{27}$ +6.3 (*c* 1.8, $CHCl_3$); IR (neat): 2956, 2858, 1720, 1465, 1361, 1254, 1072, 837, 775, 668 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 5.19 (d, *J* = 9.8 Hz, 1H), 4.02 (q, *J* = 6.0 Hz, 1H), 3.97 (s, 2H), 2.54 (d, *J* = 6.0 Hz, 2H), 2.51-2.42 (m, 1H), 2.11 (s, 3H), 1.61 (d, *J* = 1.5 Hz, 3H), 0.93 (d, *J* = 6.8 Hz, 3H), 0.87 (d, *J* = 10.6 Hz, 18H), 0.05 (d, *J* = 3.0 Hz, 9H), 0.01 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 207.5, 134.7, 127.1, 72.6, 68.5, 49.5, 38.6, 31.5, 25.9, 18.4, 18.1, 16.4, 13.7, −4.5, −4.6, −5.3 ppm; ESI-HRMS Calcd for $C_{22}H_{46}O_3Si_2Na$ $[M + Na]^+$ 437.2877; found: 437.2899.

4.39. (8*R*,9*R*,*E*)-9-((*E*)-3-Iodo-2-methylallyl)-2,2,3,3,6,8,11,11,12,12-decamethyl-4,10-dioxa-3,11-disilatridec-6-ene (43)

Anhydrous $CrCl_2$ (1.48 g, 12.06 mmol) was transferred to a round bottom flask under N_2 atmosphere and treated with THF (15 mL) at room temperature. To the resulting grey suspension was added a solution of ketone **8** (0.5 g, 1.2 mmol) and CHI_3 (1.32 mg, 3.36 mmol) in THF (5 mL) via cannula (2 × 2 mL THF). The resulting dark red-brown mixture was stirred at room temperature for 4 h. The reaction was quenched by addition of H_2O (15 mL) and the resulting mixture was stirred for 15 min. The aqueous layer was extracted with ethyl acetate (3 × 20 mL). The combined organic extracts were washed with brine (2 × 10 mL), dried over Na_2SO_4 and evaporated to dryness under reduced pressure. The crude mass was purified by silica gel chromatography (EtOAc/hexane = 1:9) to afford **43** (0.504 g, 78%) as a colorless liquid; R_f (EtOAc/hexane = 1:9) 0.60. $[\alpha]_D^{27}$ +15.6 (*c* 0.7, $CHCl_3$); IR (neat): 3398, 2936, 2863, 1735, 1612, 1513, 1459, 1301, 1248, 1173, 1035 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 5.90 (d, *J* = 8.3 Hz, 1H), 5.29 (dd, *J* = 9.8, 21.9 Hz, 1H), 3.98 (s, 2H), 3.73-3.56 (m, 1H), 2.50-2.11 (m, 3H), 1.86 (d, *J* = 24.9 Hz, 3H), 1.63 (d, *J* = 40.8 Hz, 3H), 0.99 (d, *J* = 6.8 Hz, 3H), 0.92-0.86 (m, 18H), 0.7-0.3 (m, 12H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ = 145.4, 145.0, 134.1, 133.7, 128.0, 127.4, 77.6, 75.9, 74.2, 74.1, 68.7, 68.5, 45.1, 43.6, 37.3, 37.2, 26.0, 25.9, 25.3, 24.5, 18.4, 18.1, 15.9, 15.4, 13.8, 13.7, −4.1, −4.0, −4.37, −4.44, −5.22, −5.23 ppm; ESI- HRMS Calcd for $C_{23}H_{51}IO_2Si_2N$ $[M + NH_4]^+$ found: 556.2497; found: 556.2483.

4.40. (2*E*,4*R*,5*R*,7*E*)-8-Iodo-2,4,7-trimethylocta-2,7-diene-1,5-diol (44)

TBAF (3.34 mL, 1 M in THF, 3.344 mmol) was added to a stirred solution of di-TBS ether compound (0.45 g, 0.836 mmol) in THF (12 mL) at 0 °C under N_2 atmosphere. The reaction mixture was stirred at room temperature for 6 h. After completion of the reaction (monitored by TLC), it was quenched with water (15 mL). The aqueous layer extracted with ethyl acetate (3 × 20 mL), the combined organic layer was dried over anhydrous Na_2SO_4 and solvent removed under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/hexane = 2:3) to afford **44** (0.23 g, 89%) as a colorless liquid; R_f (EtOAc/hexane = 2:3) 0.30. $[\alpha]_D^{27}$ +6.2 (*c* 1.1, $CHCl_3$); IR (neat): 3398, 2936, 2863, 1735, 1612, 1513, 1459, 1301, 1248, 1173, 1035 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ = 6.01 (s, 1H), 5.29 (d, *J* = 10.0 Hz, 1H), 4.02 (s,2H), 3.58-3.52 (m, 1H), 2.53-2.46 (m, 1H), 2.43 (d, *J* = 14.0 Hz, 1H), 2.24 (dd, *J* = 10.0, 14.0 Hz, 1H), 1.87 (s, 3H), 1.68 (s, 3H), 1.03 (d, *J* = 7.0 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 145.3, 135.7, 127.5, 77.0, 72.8, 68.5, 44.9, 38.0, 23.9, 16.3, 14.1 ppm; ESI-HRMS Calcd for $C_{11}H_{19}O_2INa$ $[M + Na]^+$ 333.0322; found: 333.0321.

4.41. (2*E*,4*R*,5*R*,7*Z*)-8-Iodo-2,4,7-trimethylocta-2,7-diene-1,5-diol (44a)

$[\alpha]_D^{27}$ +16.5 (*c* 0.85, $CHCl_3$); IR (neat): 3420, 2921, 1629, 1377, 1271, 1007, 763, 670 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ = 5.99 (s, 1H), 5.36 (d, *J* = 10.0 Hz, 1H), 4.03 (s, 2H), 3.70-3.64 (m, 1H), 2.60-2.53 (m, 1H), 2.42-2.35 (m, 2H), 1.96 (s, 3H), 1.72 (s, 3H), 1.07 (d, *J* = 7.0 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 145.6, 135.9, 127.7, 76.4, 74.3, 68.7, 43.5, 38.8, 24.4, 16.2, 14.2 ppm; ESI-HRMS Calcd for $C_{11}H_{19}O_2INa$ $[M + Na]^+$ 333.0322; found: 333.0334.

4.42. (1*E*,4*R*,5*R*,6*E*)-8-(*tert*-Butyldimethylsilyloxy)-1-iodo-2,5,7-trimethylocta-1,6-dien-4-ol (4)

To a stirred solution of **41** (0.12 g, 0.387 mmol) in dry CH_2Cl_2 (20 mL), was added imidazole (0.04 g, 0.581 mmol) followed by TBSCl (0.088 g, 0.0581 mmol) at 0 °C under N_2 atmosphere and allowed to stir for 1 h. After completion of the reaction (monitored by TLC), the reaction mixture was quenched with saturated aqueous NH_4Cl (10 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried over Na_2SO_4 and evaporated to dryness under reduced pressure. The crude mass was purified by silica gel column chromatography (EtOAc/hexane = 1:4) to afford **4** (0.151 g, 92%) as a colorless liquid; R_f (EtOAc/hexane = 1:4) 0.45. $[\alpha]_D^{27}$ +14.2 (*c* 1.40, $CHCl_3$); IR (neat): 3446, 2926, 2856, 1723, 1461, 1375, 1254, 1073, 839, 773, 674 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ = 5.99 (s, 1H), 5.25 (d, *J* = 9.1 Hz, 1H), 4.01 (s, 2H), 3.51 (t, *J* = 9.1 Hz, 1H), 2.51-2.42 (m, 2H), 2.42-2.17 (m, 1H), 1.86 (s, 3H), 1.61 (s, 3H), 1.56 (bs, 2H), 1.03 (d, *J* = 7.1 Hz, 3H), 0.91 (s, 9H), 0.06 (s, 6H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 145.5, 135.6, 125.8, 73.0, 68.2, 45.0, 38.1, 25.9, 24.0, 18.4, 16.6, 13.9, −5.2 ppm; ESI-HRMS Calcd for $C_{17}H_{33}O_2ISiNa$ $[M + Na]^+$ 447.1197; found: 447.1186.

4.43. (1*Z*,4*R*,5*R*,6*E*)-8-(*tert*-Butyldimethylsilyloxy)-1-iodo-2,5,7-trimethyl-octa-1,6-dien-4-ol (4a)

$[\alpha]_D^{27}$ +16.6 (*c* 0.3, $CHCl_3$); IR (neat): 3398, 2936, 2863, 1735, 1612, 1513, 1459, 1301, 1248, 1173, 1035 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ = 5.99 (s, 1H), 5.32 (d, *J* = 10.1 Hz, 1H), 4.03 (s,2H), 3.65 (m, 1H), 2.56 (m, 1H), 2.39-2.36 (m, 2H), 1.95 (s, 3H), 1.65 (s, 3H), 1.54 (bs, 2H), 1.07 (d, *J* = 7.1 Hz, 3H), 0.91 (s, 9H), 0.07 (s, 6H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 145.6, 135.8, 125.9, 74.4, 68.3, 43.5, 38.8, 25.9, 24.4, 18.4, 16.5, 13.9, −5.2 ppm; ESI-HRMS Calcd for $C_{17}H_{33}O_2ISiNa$ $[M + Na]^+$ 447.1197; found: 447.1192.

4.44. (2*E*,7*S*,8*E*,10*S*,11*S*)-11-(4-Methoxybenzyloxy)-7,10-bis(meth- oxymeth oxy) pentadeca-2,8,14-trienoic acid (3)

To a stirred solution of the ester **31** (0.05 g, 0.096 mmol) in THF (5 mL), was added aqueous solution of LiOH (0.021 g, 0.864 mmol) at room temperature. The reaction mixture was allowed to stir at 80 °C for 15 h. After completion of the reaction (monitored by TLC), it was cooled to 0 °C. The reaction mixture was acidified with 1 M HCl (until pH = 2.0) and the organic layer separated. The aqueous layer was extracted with ethyl acetate (3 × 15 mL). The combined organic layer were washed with brine (2 × 25 mL) and dried over anhydrous Na_2SO_4. The solvent was evaporated to dryness under reduced pressure and the crude mass purified by silica gel column chromatography (EtOAc/hexane = 1:1) to afford **3** (0.044 g, 95%) as a colorless liquid; R_f (EtOAc/hexane = 1:1) 0.25. $[\alpha]_D^{27}$ −15.8 (*c* 0.4, $CHCl_3$); IR (neat): 3430, 2925, 2854, 1723, 1649, 1513, 1467, 1250, 1035, 757 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 7.26 (d, *J* = 8.3 Hz, 2H), 7.11-6.99 (m, 1H), 6.87 (d, *J* = 8.5 Hz, 2H), 5.86-5.69 (m, 2H), 5.63-5.52 (m, 2H), 5.02-4.91 (m, 2H), 4.72-4.57 (m, 4H), 4.53-4.45 (m, 2H), 4.20 (t, *J* = 5.9 Hz, 1H), 4.08-4.00 (m, 1H), 3.80 (s, 3H), 3.50-3.41 (m, 1H), 3.36 (d, *J* = 1.3 Hz, 6H), 2.31-1.99 (m, 4H), 1.71-1.45 (m, 6H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 170.8, 151.5, 138.4, 133.7, 130.7, 130.0, 129.5, 129.4, 120.7, 114.7, 113.7, 94.2, 93.6, 79.9, 77.3, 75.8, 72.6, 55.53, 55.45, 55.2, 35.0, 32.1, 29.9, 29.7, 23.7 ppm; ESI-HRMS Calcd for $C_{27}H_{40}O_8Na$ $[M + Na]^+$ 515.2617; found: 515.2615.

4.45. (2*E*,7*S*,8*E*,10*S*,11*S*)-((1*E*,4*R*,5*R*,6*E*)-8-(*tert*-Butyldimethylsilyloxy)-1-iodo-2,5,7-trimethylocta-1,6-dien-4-yl)11-(4-methoxybenzyloxy)-7,10-bis(methoxymethoxy)pentadeca-2,8,14-trienoate (45)

To a stirred solution of the acid **3** (0.49 g, 2.01 mmol) in dry toluene (10 mL), Et_3N (0.31 mL, 4.02 mmol) followed by 2,4,6-trichlorobenzoyl chloride (0.63 mL, 4.02 mmol) was added at 0 °C under N_2 atmosphere and continued to stir for 45 min at room temperature. DMAP (1.22, 10.04 mmol) and alcohol **4** (0.45 g, 1.004 mmol) dissolved in dry toluene (10 mL) was added to reaction mixture dropwise at 0 °C and allowed to stir for 6 h at room temperature. After completion of the reaction (monitored by TLC), it was diluted with water (25 mL) and ethyl acetate (50 mL). The aqueous layer was extracted with ethyl acetate (2 × 40 mL). The combined organic layer was washed with brine (2 × 50 mL), dried over anhydrous Na_2SO_4 and solvent evaporated under reduced pressure. The crude mass was purified by silica gel column chromatography (EtOAc/hexane = 1:12) to furnish **45** (0.63 g, 93%, based on the starting alcohol) as a colorless liquid; R_f (EtOAc/hexane = 1:12) 0.30. $[\alpha]_D^{27}$ +3.8 (*c* 0.8, $CHCl_3$); IR (neat): 2924, 2854, 1728, 1460, 1266, 1076, 772 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 7.29-7.25 (m, 2H), 6.98-6.91 (m, 1H), 6.87 (d, *J* = 8.3 Hz, 2H), 5.88 (s, 1H), 5.84-5.71 (m, 2H), 5.64-5.55 (m, 2H), 5.23 (d, *J* = 9.8 Hz, 1H), 5.02-4.89 (m, 3H), 4.71-4.57 (m, 4H), 4.49 (d, *J* = 9.1 Hz, 2H), 4.19 (t, *J* = 6.0 Hz, 1H), 4.08-3.98 (m, 3H), 3.81 (s, 3H), 3.50-3.40 (m, 1H), 3.36 (s, 6H), 2.70-2.57 (m, 1H), 2.50-2.32 (m, 2H), 2.28-2.00 (m, 4H), 1.82 (s, 3H), 1.70-1.48 (m, 9H), 0.95 (d, *J* = 6.8 Hz, 3H), 0.91 (s, 9H), 0.06 (s, 6H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ = 166.1, 159.2, 149.0, 144.3, 138.4, 135.8, 133.9, 130.7, 129.9, 129.5, 128.1, 125.1, 121.3, 114.7, 113.7, 94.3, 93.7, 80.0, 77.4, 75.9, 74.8, 72.6, 68.1, 55.6, 55.5, 55.3, 42.2, 36.1, 35.1, 32.1, 31.9, 29.9, 25.9, 24.0, 23.9, 18.4, 16.8, 13.9, −5.2 ppm; ESI-HRMS Calcd for $C_{44}H_{71}O_9ISiNa$ $[M + Na]^+$ 921.3835; found: 921.3804.

4.46. (2*E*,7*S*,8*E*,10*S*,11*S*)-((1*E*,4*R*,5*R*,6*E*)-8-(*tert*-Butyldimethylsilyloxy)-1-iodo-2,5,7-trimethyl-octa-1,6-dien-4-yl)-11-hydroxy-7,10-bis(methoxy-methoxy)pentadeca-2,8,14-trienoate (46)

To a stirred solution of PMB protected compound **45** (16 mg, 0.018 mmol) in CH_2Cl_2:H_2O (19:1, 10 mL), 1 mL phosphate buffer solution (pH = 7) followed by DDQ (6.2 mg, 0.027 mmol) was added at 0 °C. The reaction mixture was allowed to stir for 2 h at room temperature. After completion of the reaction (monitored by TLC), it was quenched with saturated $NaHCO_3$ (5 mL) solution. The two layers were separated and the aqueous layer extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layer was washed with brine (10 mL), dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to give the residue which on purification by silica gel column chromatography (EtOAc/hexane = 1:7) afforded primary alcohol **46** (13.3 mg, 95%) as a colorless liquid; R_f (EtOAc/hexane = 1:4) 0.45. $[\alpha]_D^{27}$ +11.2 (*c* 0.4, $CHCl_3$); IR (neat): 3448, 2924, 2854, 1719, 1652, 1258, 1097, 1033, 770 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 6.91 (dt, *J* = 7.0, 15.7 Hz, 1H), 5.88 (s, 1H), 5.86-5.76 (m, 2H), 5.63 (m, 1H), 5.53 (m, 1H), 5.23 (d, *J* = 8.7 Hz, 1H), 5.03 (d, *J* = 15.7 Hz, 1H), 4.98-4.90 (m, 2H), 4.67 (AB_q, *J* = 7.0, 24.4 Hz, 2H), 4.56 (dd, *J* = 7.0, 15.7 Hz, 2H), 4.06-3.99 (m, 3H), 3.89 (t, *J* = 7.0 Hz, 1H), 3.57 (m, 1H), 3.37 (d, *J* = 12.2 Hz, 6H), 2.67-2.61 (m, 1H), 2.54 (bs, 1H), 2.48-2.34 (m, 2H), 2.30-2.14 (m, 4H), 1.83 (s, 3H), 1.57-1.46 (m, 9H), 0.95 (d, *J* = 6.1 Hz, 3H), 0.91 (s, 9H), 0.06 (s, 6H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 166.1, 148.9, 144.3, 138.3, 136.1, 135.8, 129.3, 128.1, 125.0, 121.4, 114.8, 94.0, 93.9, 80.2, 77.1, 76.2, 74.8, 72.9, 68.0, 55.7, 55.5, 42.2, 36.1, 35.0, 32.0, 30.9, 29.6, 25.9, 24.0, 23.9, 18.4, 16.9, 13.9, −5.3 ppm; ESI-HRMS Calcd for $C_{36}H_{63}O_8ISiNa$ $[M + Na]^+$ 801.3222; found: 801.3229.

4.47. (2*E*,7*S*,8*E*,10*S*,11*S*)-((1*E*,4*R*,5*R*,6*E*)-8-(*tert*-Butyldimethylsilyloxy)-1-iodo-2,5,7-trimethyl-octa-1,6-dien-4-yl)-11-(*tert*-butyldimethylsilyloxy)-7,10-bis(methoxymethoxy)pentadeca-2,8, 14-trienoate (47)

To a solution of homoallylic alcohol **46** (11 mg, 0.014 mmol) in CH_2Cl_2 (5 mL), was added 2,6-lutidine (3.3 µL, 0.028 mmol) and TBSOTf (3.85 µL, 0.017 mmol) at 0 °C under N_2 atmosphere. The reaction mixture was allowed to stir for 30 min at same temperature. After completion of the reaction (monitored by TLC), the reaction mixture was then quenched with H_2O (5 mL). The reaction mixture was diluted with CH_2Cl_2 and aqueous layer was extracted with CH_2Cl_2 (2 × 10 ml). The organic layer dried over Na_2SO_4 and solvent removed under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/hexane = 1:15) to afford **47** (12.1 mg, 96%) as a clear liquid; R_f (EtOAc/hexane = 1:15) 0.55. $[\alpha]_D^{27}$ −5.1 (*c* 0.7, $CHCl_3$); IR (neat): 2925, 2851, 1723, 1511, 1457, 1248, 1097, 1035 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ = 6.91 (dt, *J* = 7.0, 15.4 Hz, 1H), 5.87 (s, 1H), 5.84-5.75 (m, 2H), 5.60 (dd, *J* = 6.4, 15.7 Hz, 1H), 5.54 (dd, *J* = 7.2, 15.7 Hz, 1H), 5.22 (d, *J* = 9.8 Hz, 1H), 5.03-4.89 (m, 3H), 4.68 (d, *J* = 6.7 Hz, 1H), 4.64 (d, *J* = 6.6 Hz, 1H), 4.57 (d, *J* = 6.7 Hz, 1H), 4.49 (d, *J* = 6.7 Hz, 1H), 4.09-3.96 (m, 4H), 3.75-3.68 (m, 1H), 3.36 (s, 3H), 3.35 (s, 3H), 2.68-2.57 (m,

1H), 2.48-2.32 (m, 2H), 2.27-1.98 (m, 4H), 1.82 (s, 3H), 1.72-1.35 (m, 9H), 0.94 (d, *J* = 6.7 Hz, 3H), 0.90 (s, 9H), 0.89 (s, 9H), 0.07 (d, *J* = 6.3 Hz, 6H), 0.06 (s, 6H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ = 166.1, 149.1, 144.3, 138.7, 135.8, 133.8, 129.6, 125.0, 121.3, 114.4, 94.5, 93.6, 78.9, 77.2, 75.8, 74.8, 73.5, 68.0, 55.47, 55.44, 42.2, 36.1, 35.1, 32.1, 31.7, 29.6, 25.92(3C), 25.88(3C), 24.0, 23.9, 18.4, 18.1, 16.9, 13.9, −4.3, −4.7, −5.2 ppm; ESI-HRMS Calcd for $C_{42}H_{81}O_8NISi_2$ $[M + NH_4]^+$ 910.4539; found: 910.4600.

4.48. (3*E*,8*S*,9*E*,11*S*,12*S*,15*E*,17*E*,20*R*)-12-(*tert*-Butyldimethylsilyloxy)-20-((*R*,*E*)-5-(*tert*-butyldimethylsilyloxy)-4-methylpent-3-en-2-yl)-8,11-bis(methoxymethoxy)-18-methyloxacyclicosa-3,9,15,17-tetraen-2-one (2)

To a stirred solution of vinyl iodide **47** (9.7 mg, 0.011 mmol) in dry DMF (5 mL), was added K_2CO_3 (12.6 mg, 0.09 mmol) and $Pd(OAc)_2$ (3 mg, 0.014 mmol) at room temperature under Ar atmosphere. The reaction mixture was heated to 65 ^oC and continued to stir for 5 h at same temperature. After complete consumption of the starting material (monitored by TLC), the reaction mixture was cooled to room temperature and quenched with water (2 mL). The aqueous layer was extracted with ethyl acetate (3 × 5 mL), washed with brine (5 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The crude mass was purified by silica gel column chromatography (EtOAc/hexane = 1:4) to afford **2** (5 mg, 60%) as a viscous liquid; R_f (EtOAc/hexane = 1:4) 0.55. $[\alpha]_D^{27}$ −121.6 (*c* 0.4, $CHCl_3$); IR (neat): 2928, 2856, 2310, 1720, 1655, 1531, 1465, 1255, 1102, 1036, 836, 775 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 6.82 (ddd, *J* = 4.7, 10.4, 15.3 Hz, 1H), 6.10 (dd, *J* = 11.1, 14.7 Hz, 1H), 5.73 (dd, *J* = 1.2, 15.6 Hz, 1H), 5.68 (dd, *J* = 3.0, 15.7 Hz, 1H), 5.63 (d, *J* = 10.3 Hz, 1H), 5.51-5.46 (m, 1H), 5.45-5.38 (m, 1H), 5.23 (dd, *J* = 1.1, 9.9 Hz, 1H), 4.95-4.89 (m, 1H), 4.69 (d, *J* = 6.7 Hz, 1H), 4.63 (s, 2H), 4.50 (d, *J* = 6.7 Hz, 1H), 4.17-4.09 (m, 1H), 4.01 (s, 2H), 3.99-3.92 (m, 1H), 3.67 (dddd, *J* = 1.5, 4.4, 9.8, 14.0 Hz, 1H), 3.37 (s, 3H), 3.36 (s, 3H), 2.64-2.57 (m, 1H), 2.27-1.95 (m, 6H), 1.80-1.40 (m, 12H), 0.95 (d, *J* = 6.6 Hz, 3H), 0.92 (s, 9H), 0.91(s, 9H), 0.09 (s, 3H), 0.08 (s, 3H), 0.06 (s, 6H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ = 166.4, 148.8, 135.5, 132.5, 131.9, 130.4, 129.9, 128.1, 126.5, 125.5, 121.1, 95.6, 93.2, 78.1, 77.2, 74.6, 74.0, 68.2, 55.5, 55.3, 43.9, 36.8, 35.8, 33.2, 33.0, 30.5, 25.9, 25.0, 18.4, 18.1, 17.3, 16.4, 13.9, −4.5, −4.7, −5.2 ppm; ESI-HRMS Calcd for $C_{42}H_{80}O_8NSi_2$ $[M + NH_4]^+$ 782.5417; found: 782.5401.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at http://dx.doi.org.

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Supporting Information

Formal Total Synthesis of Palmerolide A

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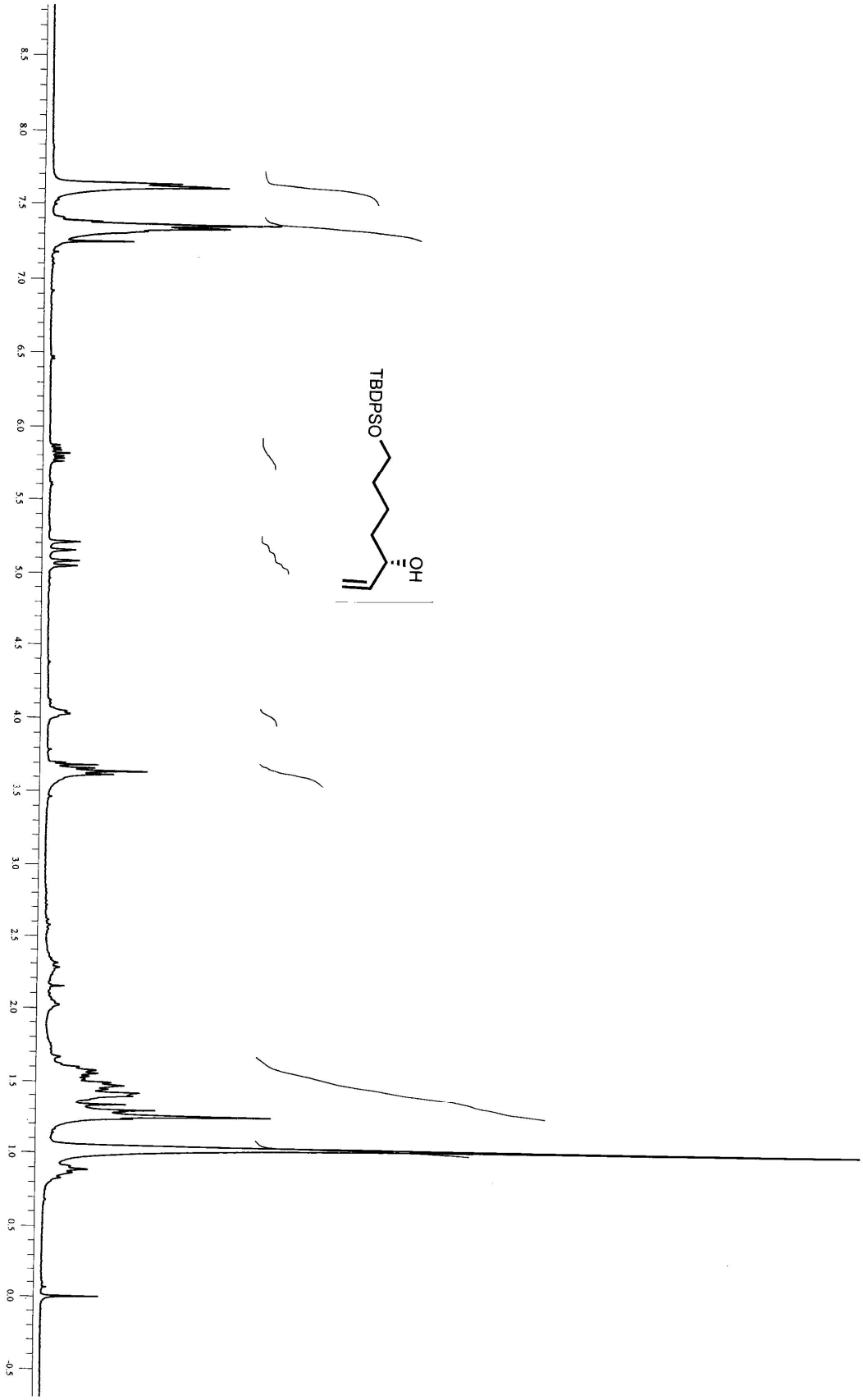

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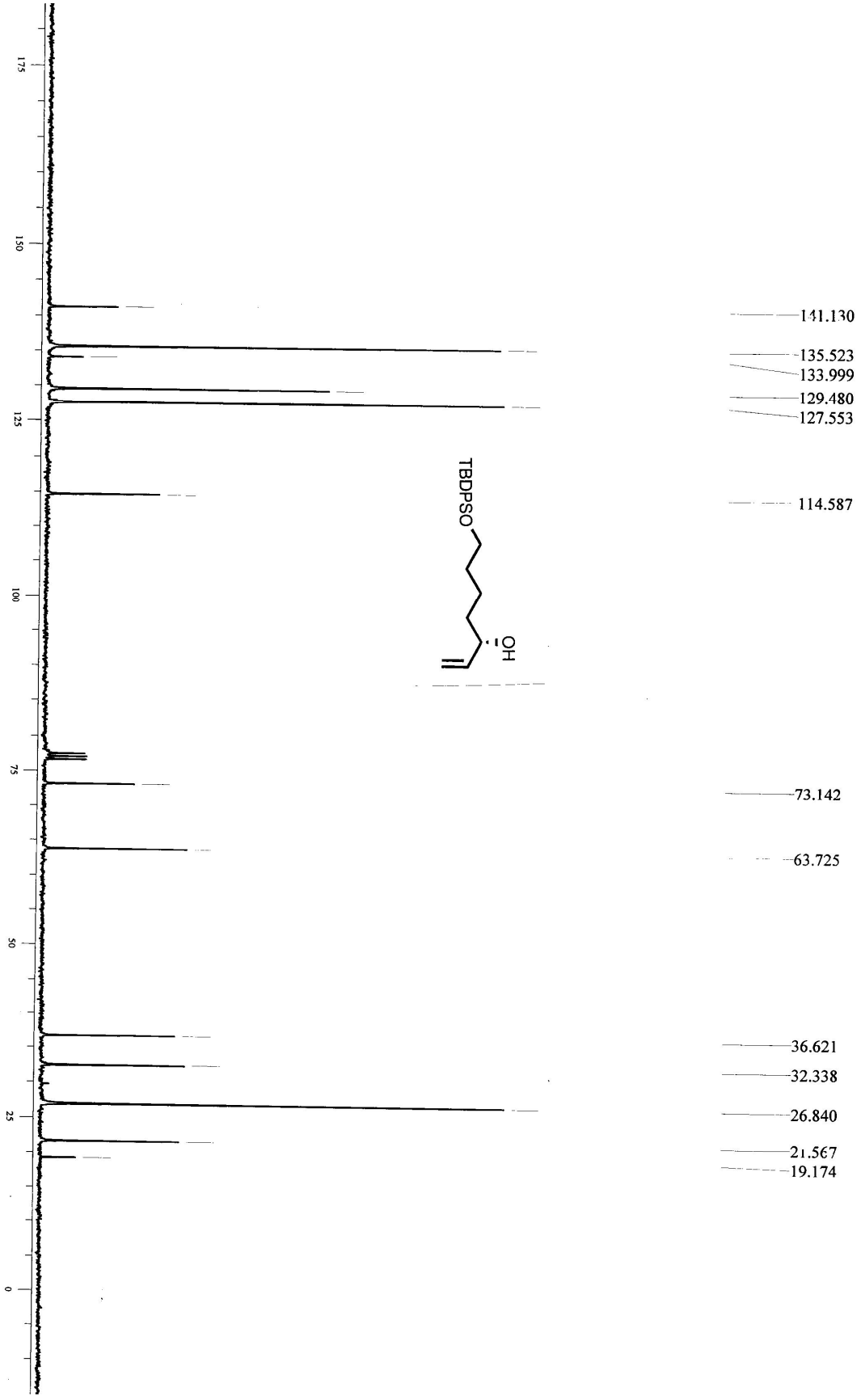

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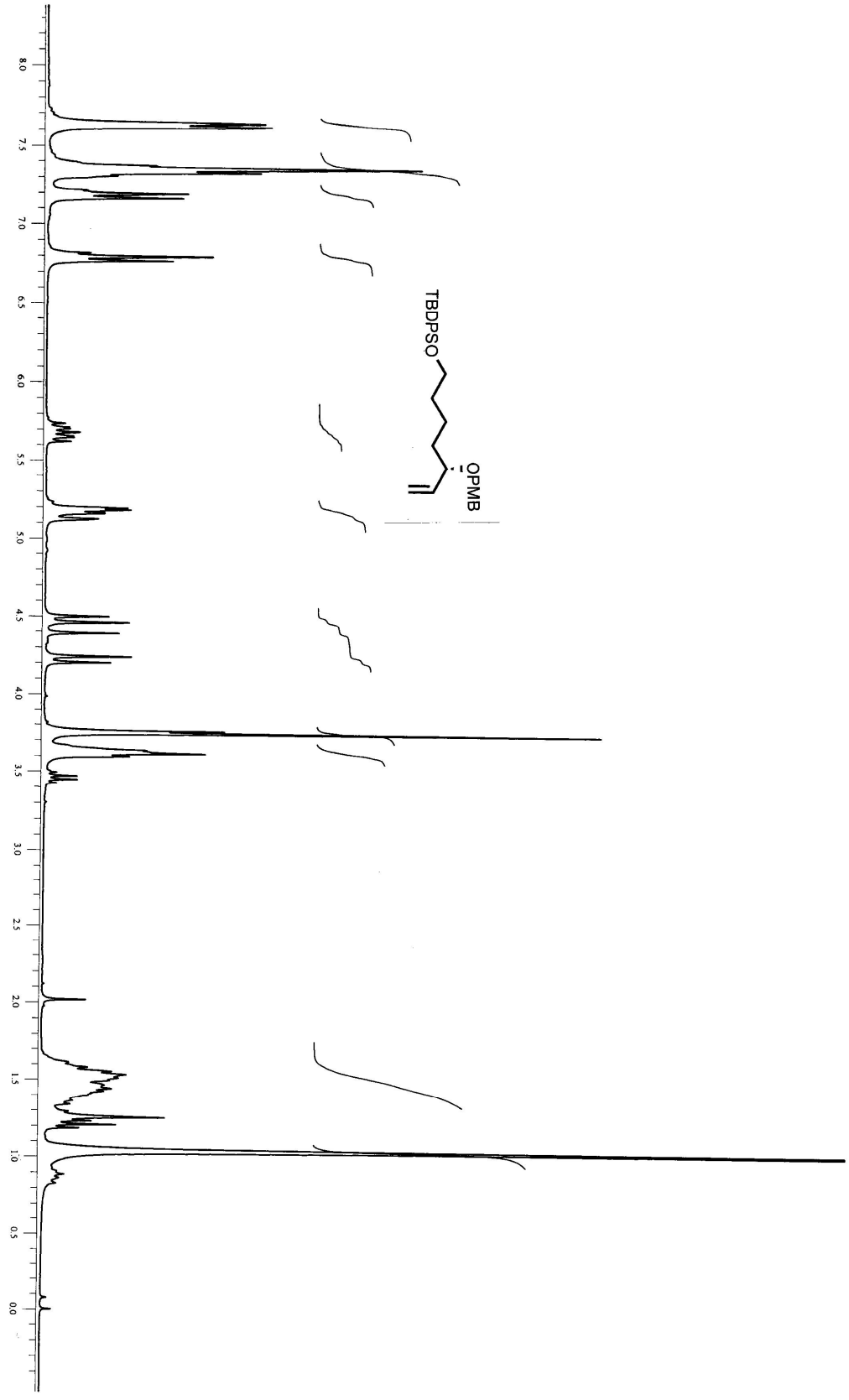

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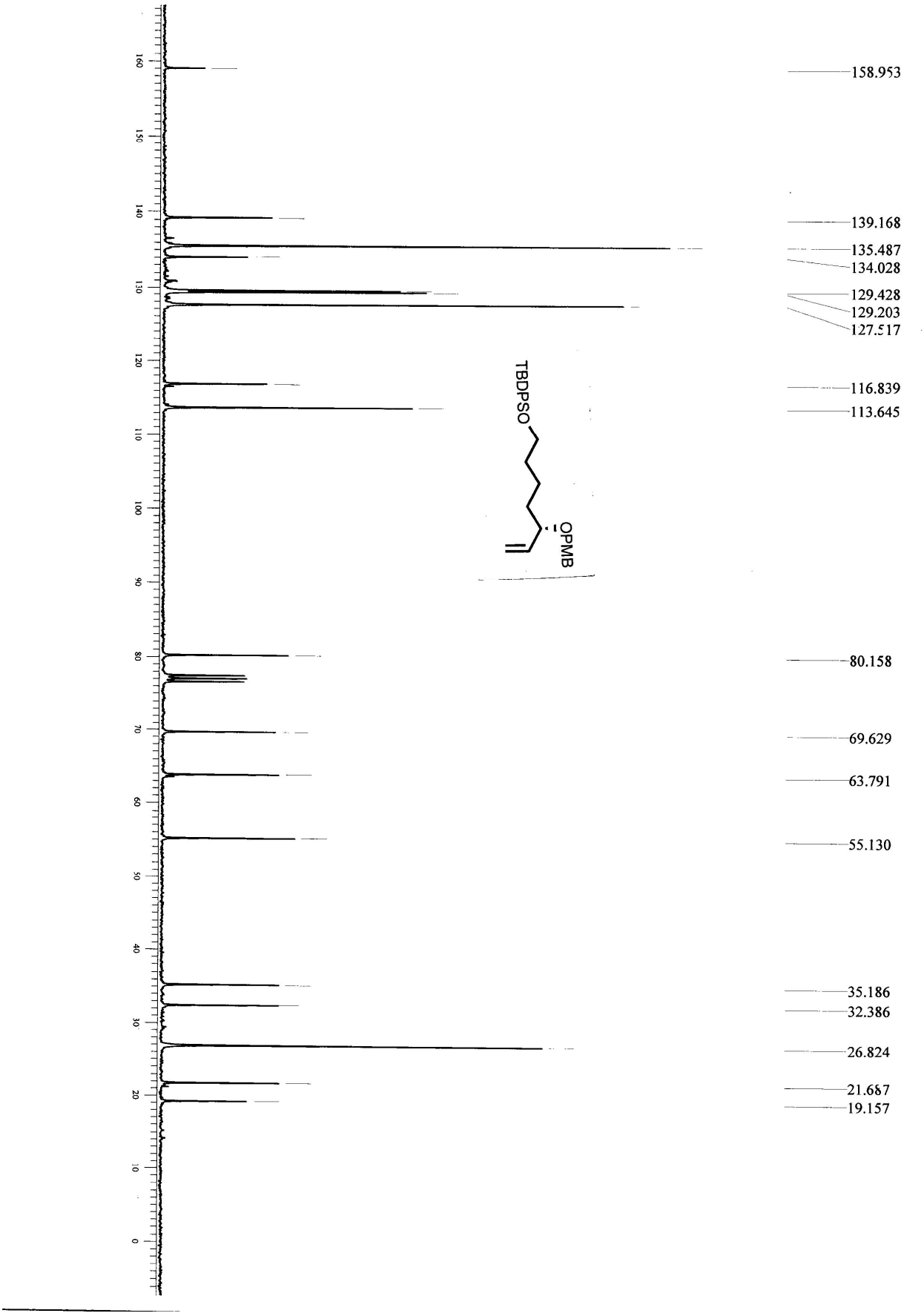

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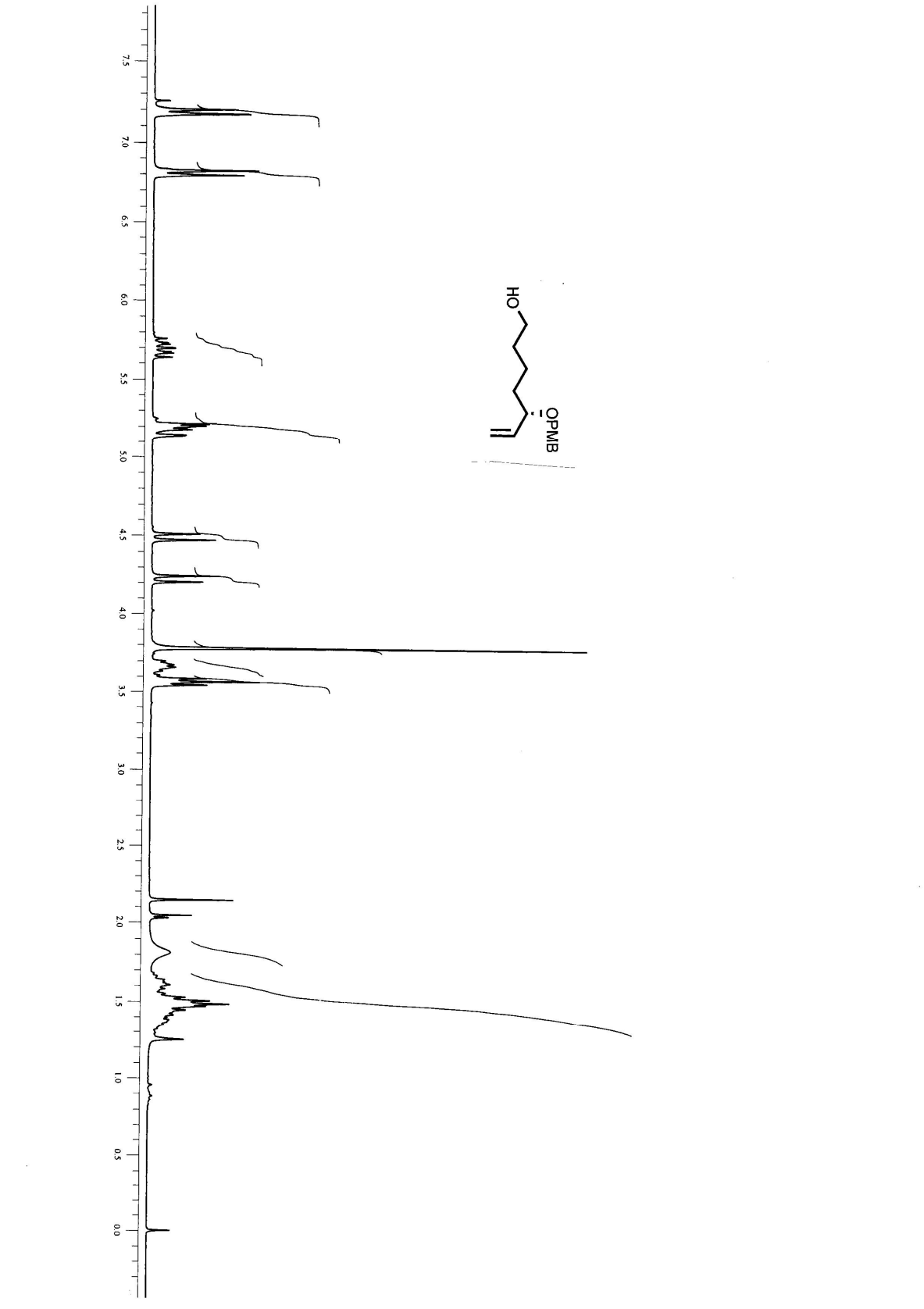

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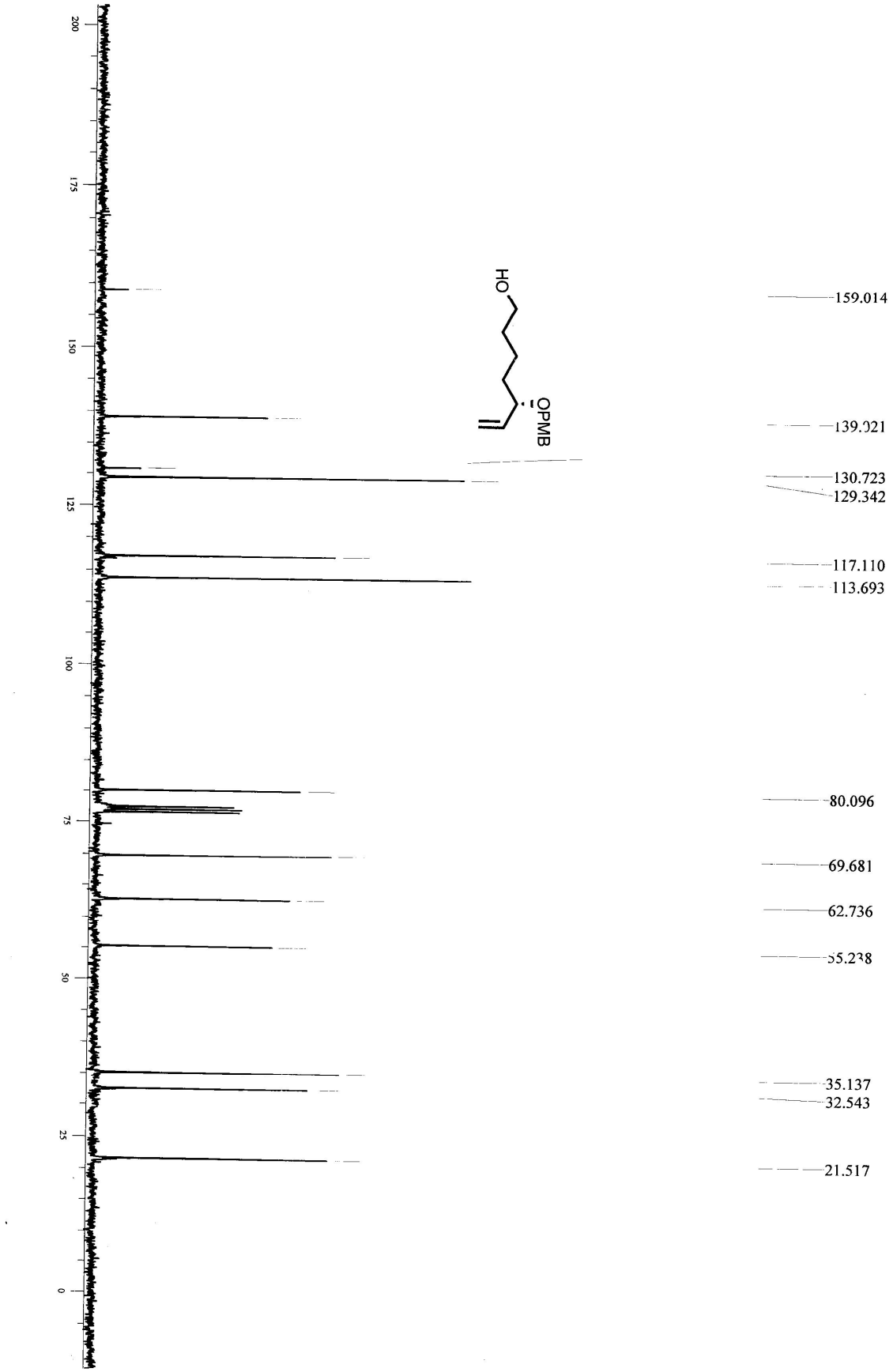

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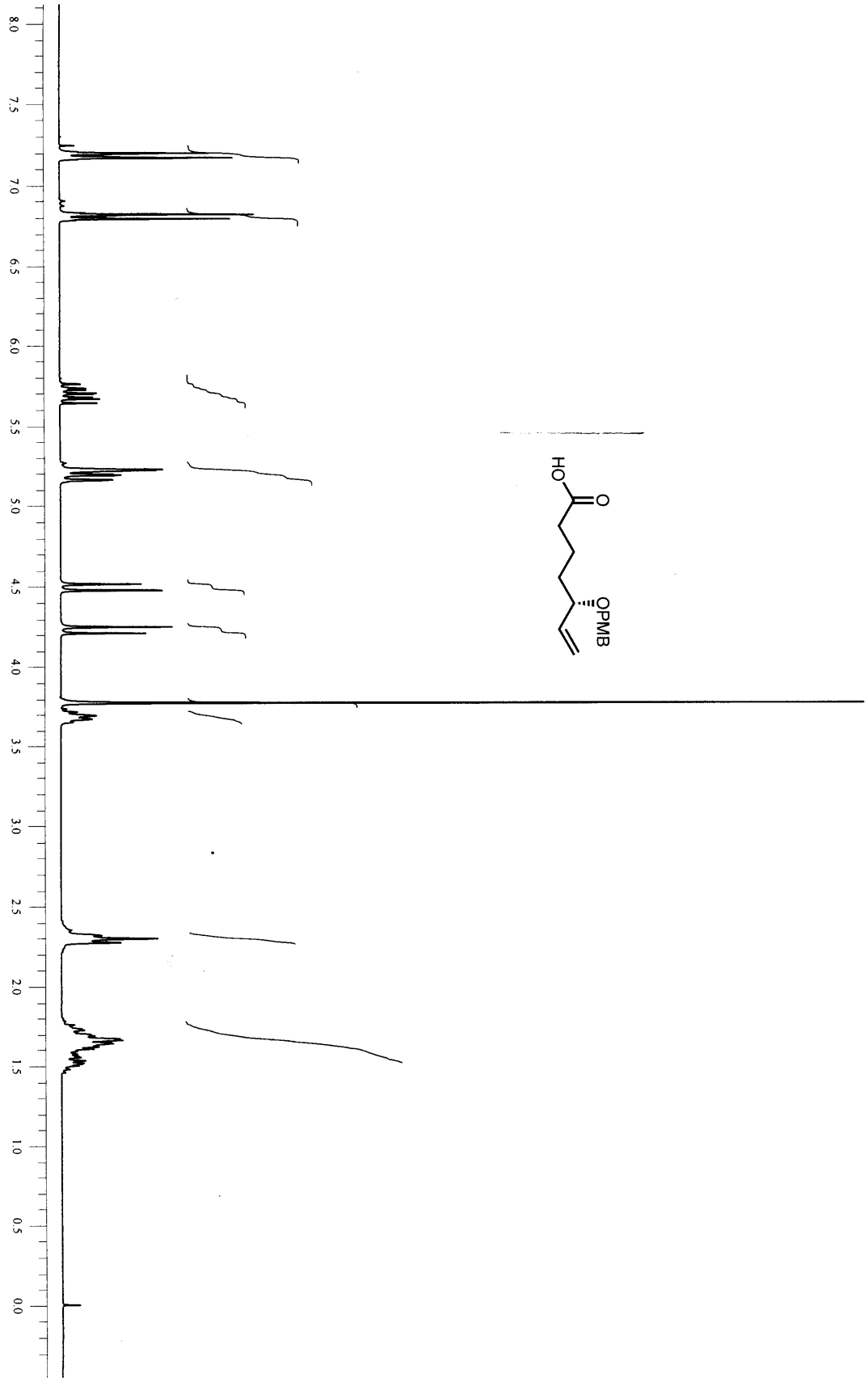

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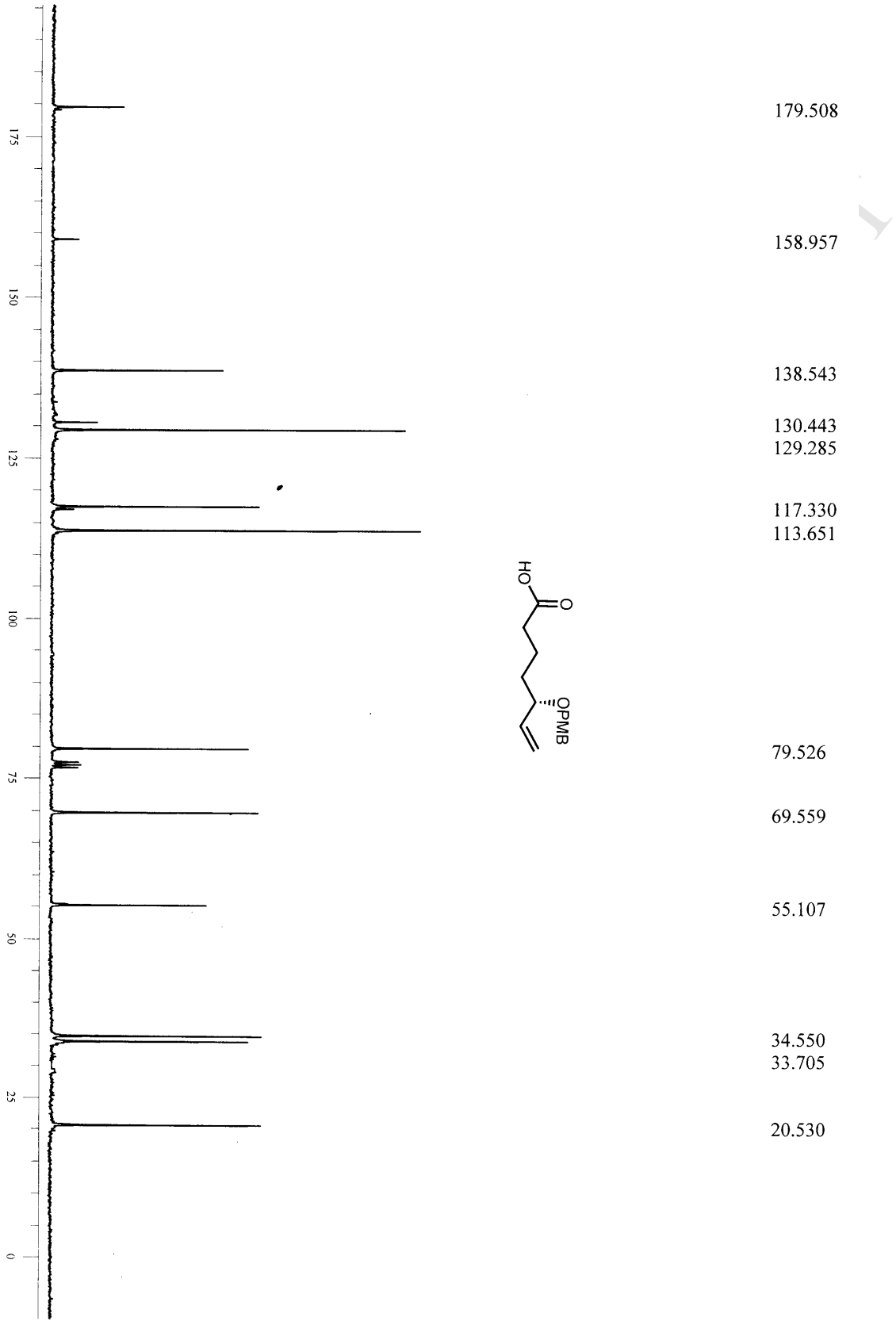

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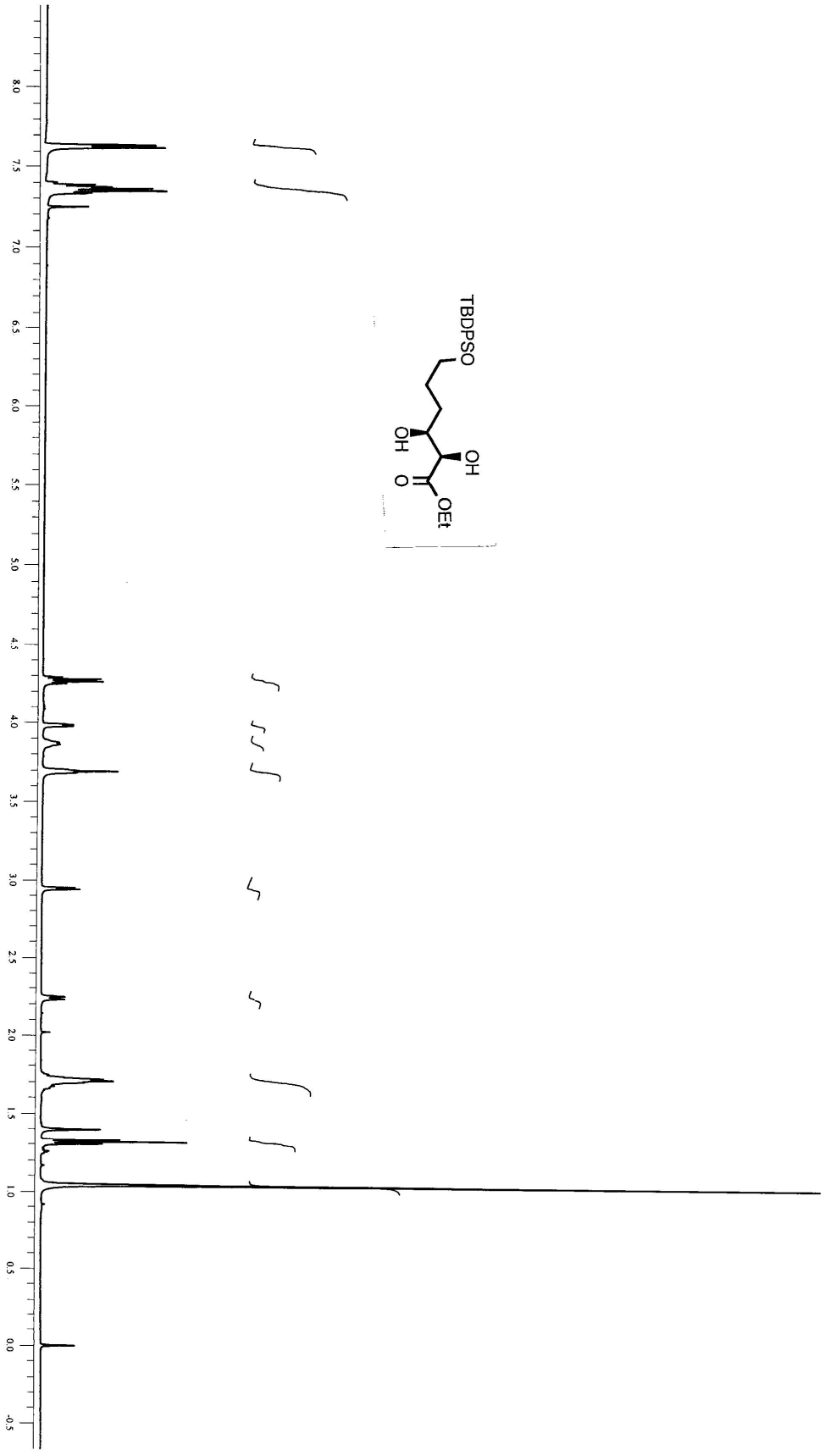

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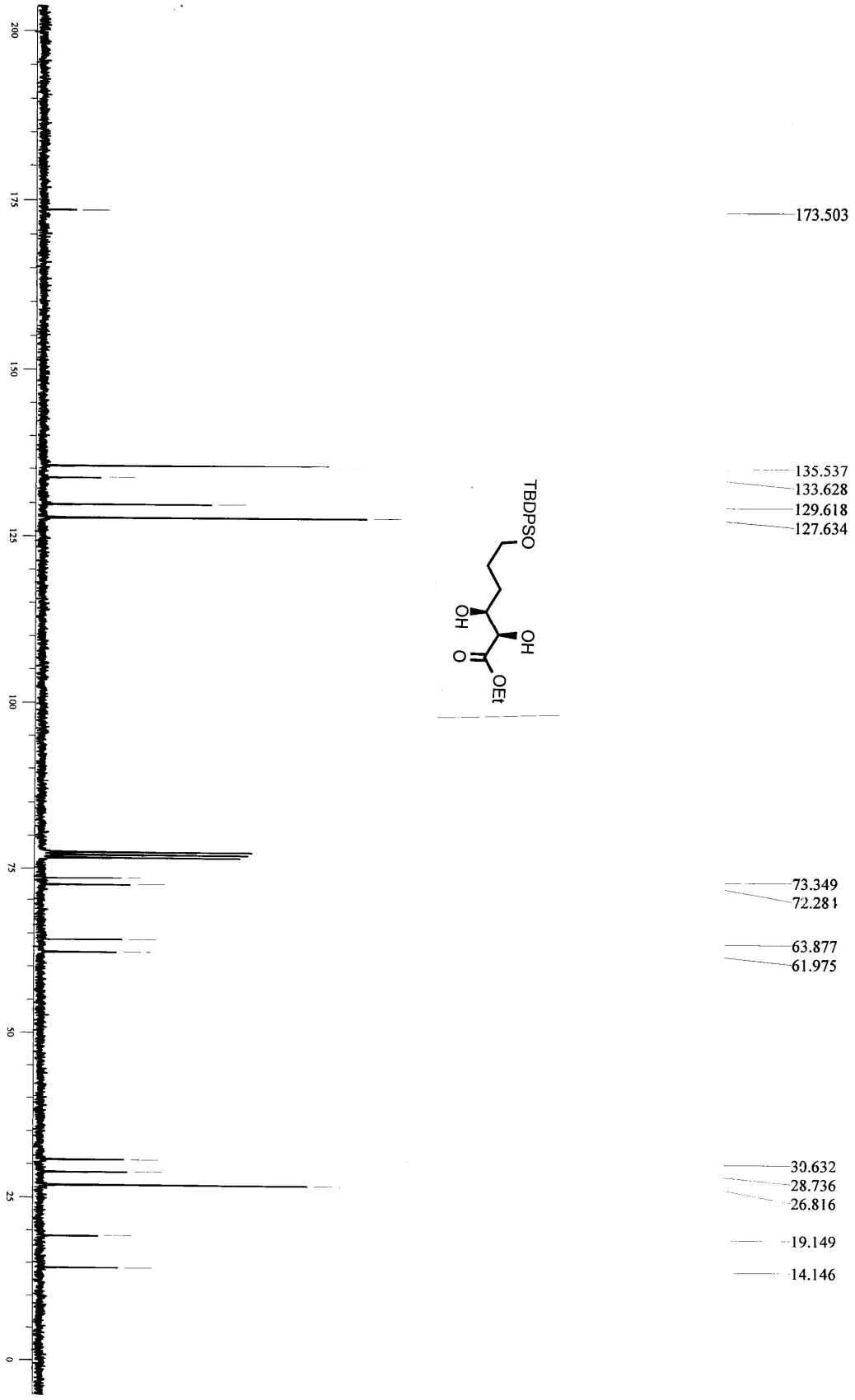

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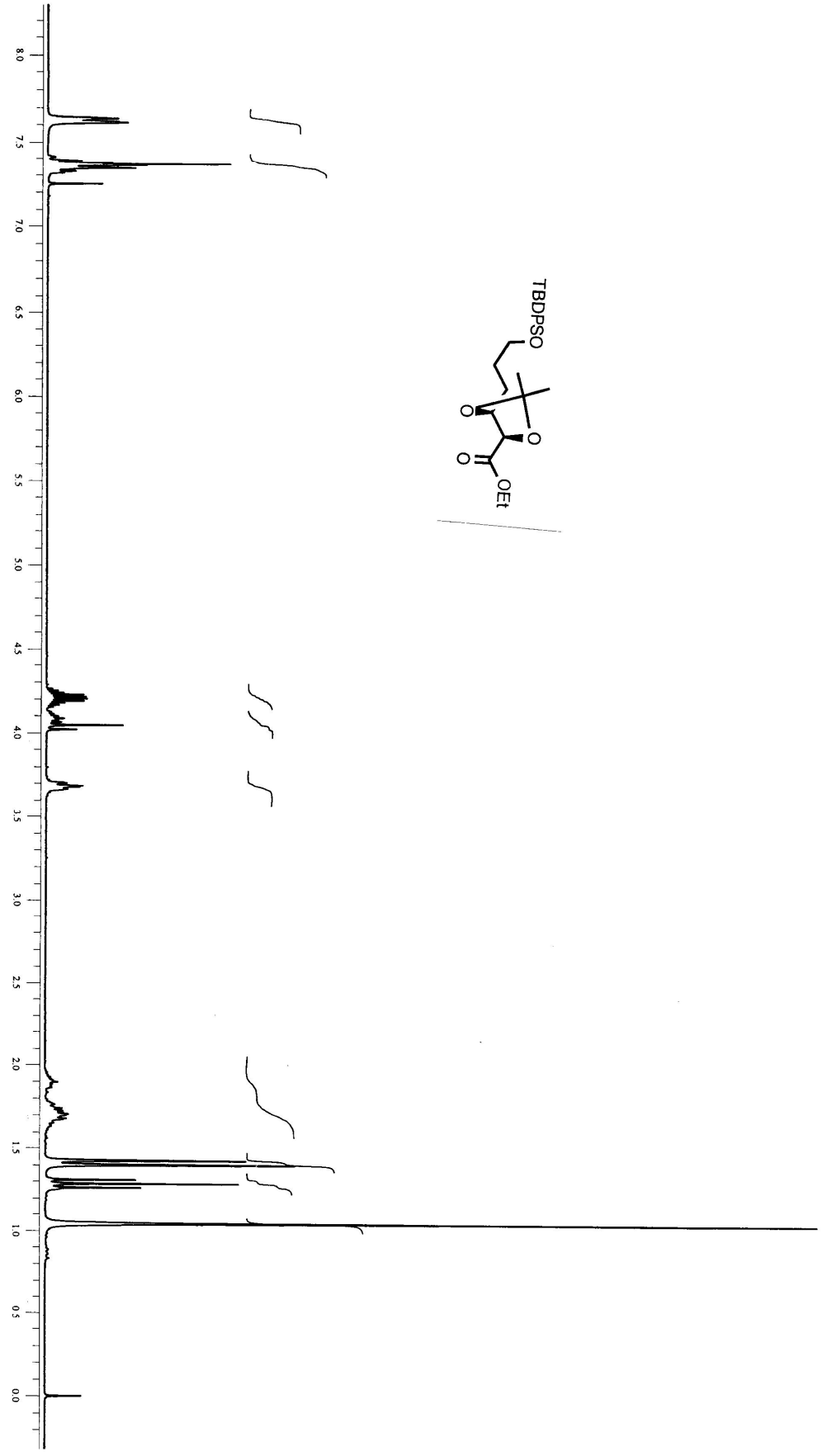

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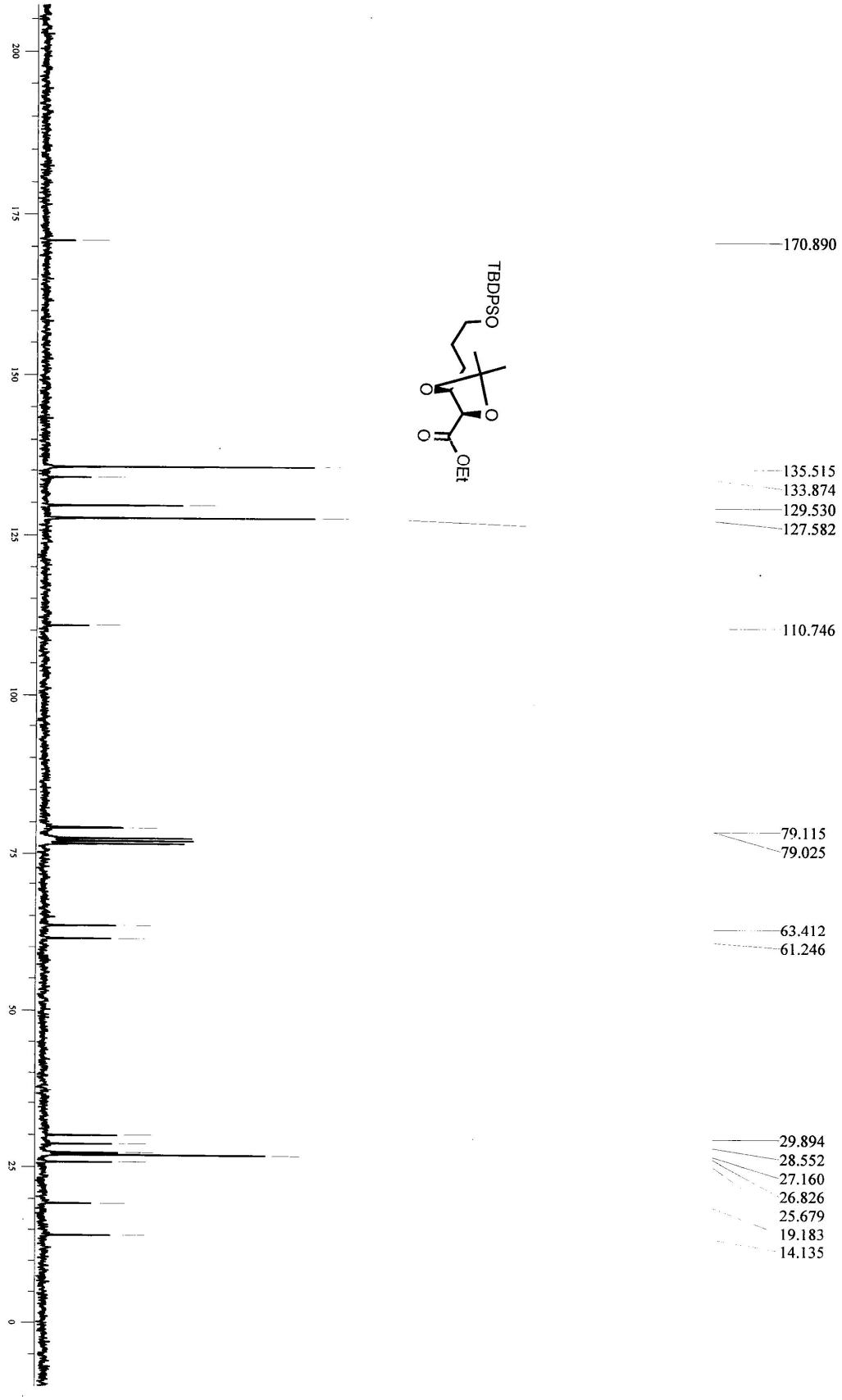
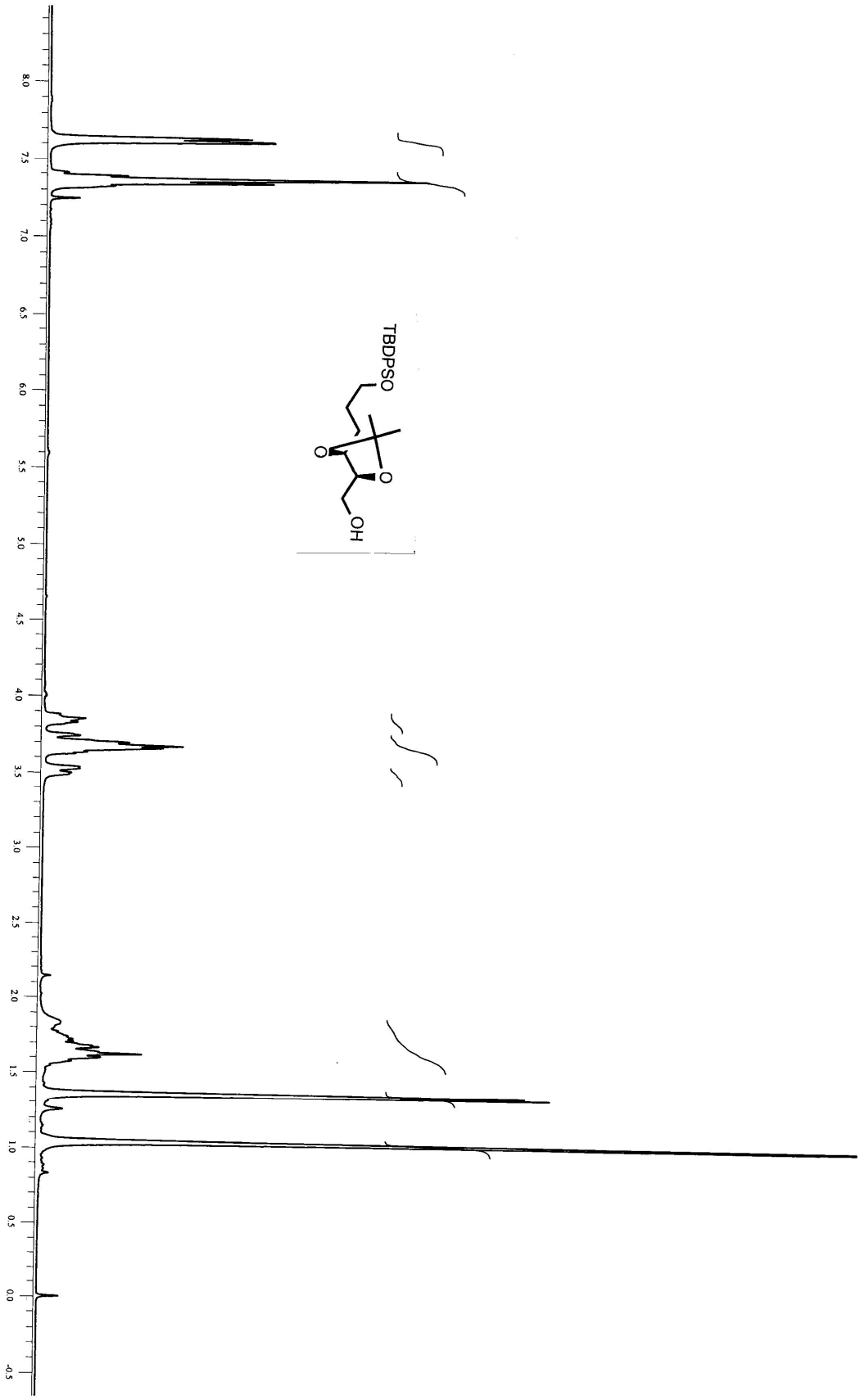
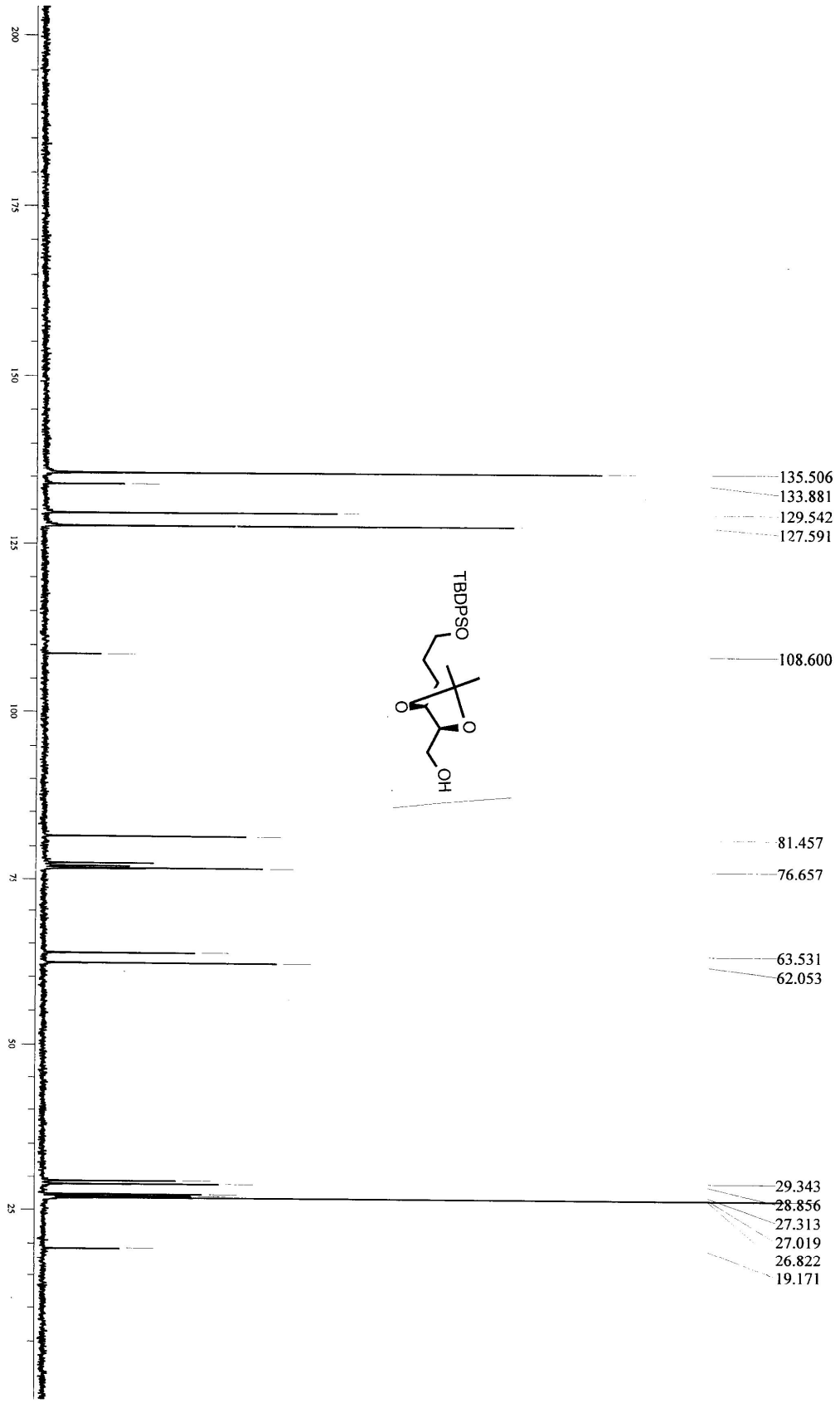


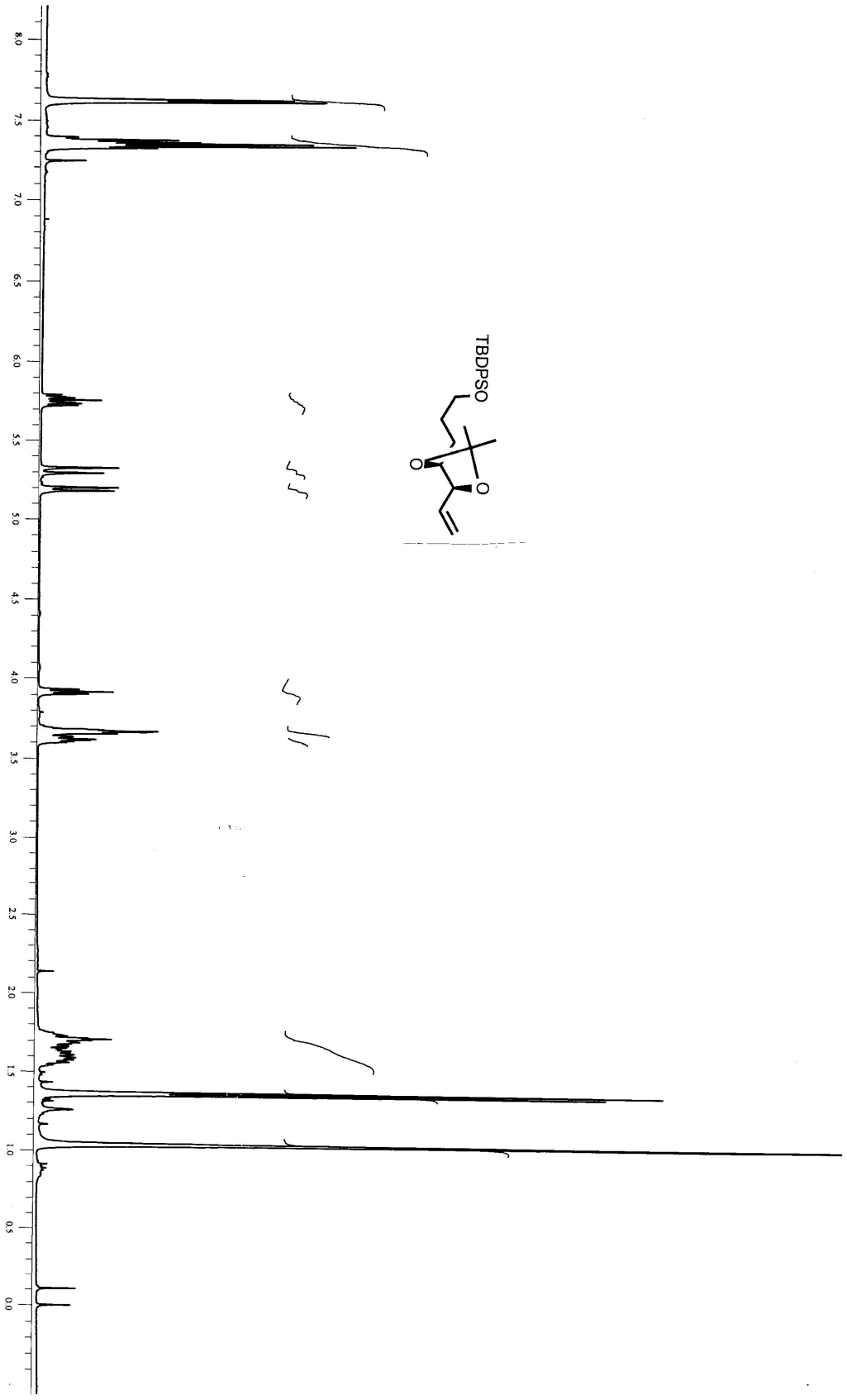
^{13}C NMR of Compound **16** ($CDCl_3$, 75 MHz)



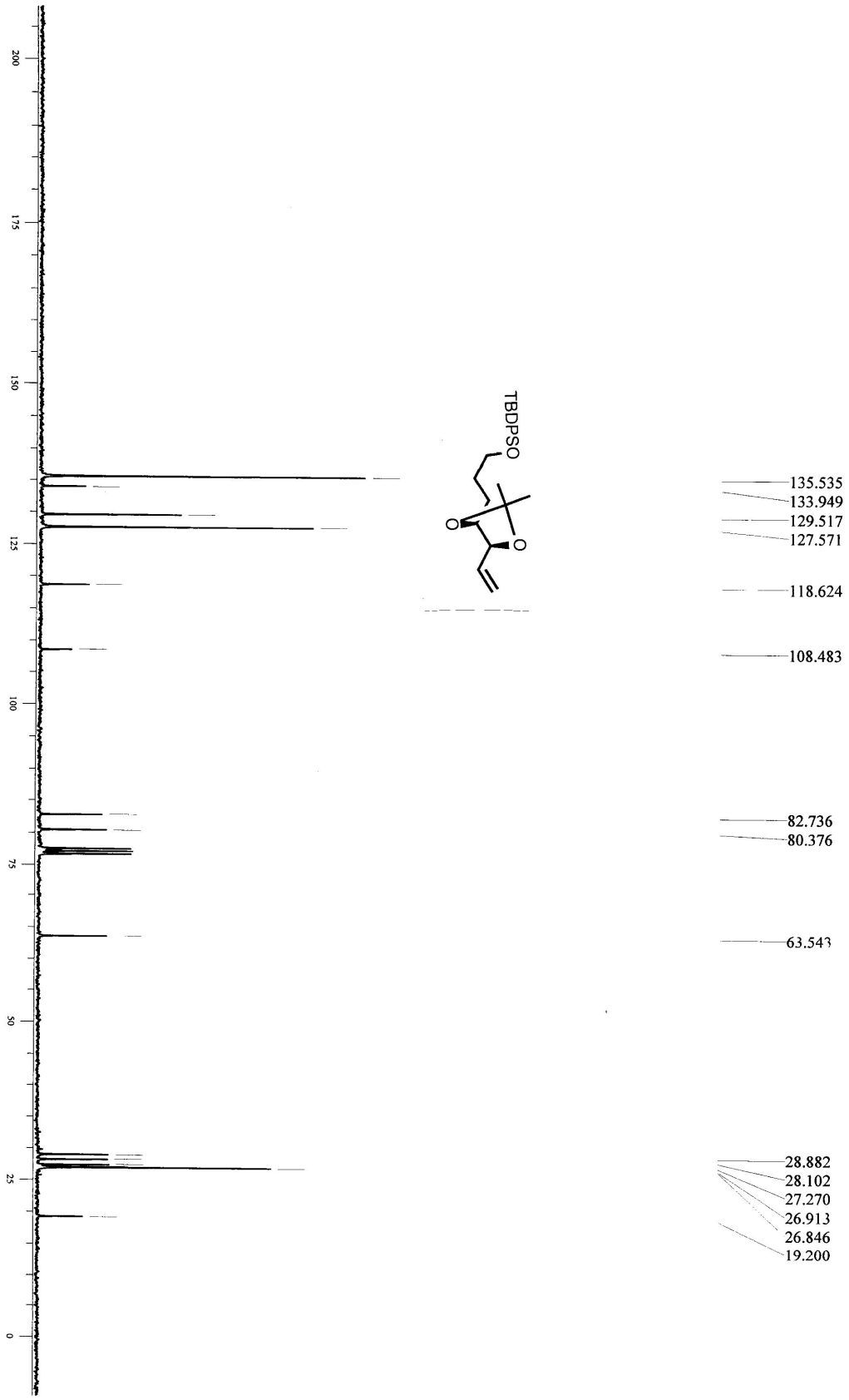
^{1}H NMR of Compound **17** ($CDCl_3$, 300 MHz)



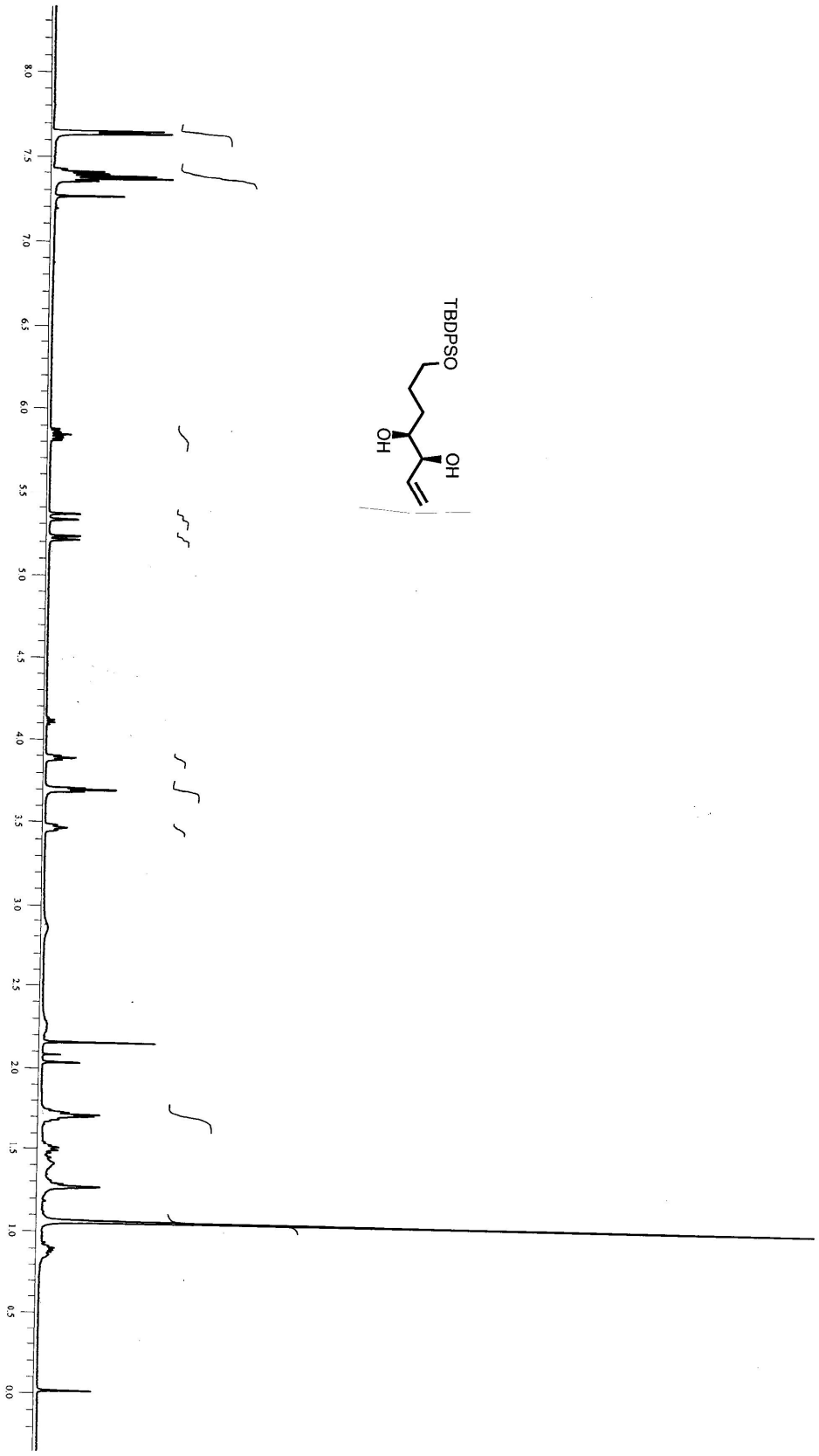
^{13}C NMR of Compound **17** ($CDCl_3$, 75 MHz)



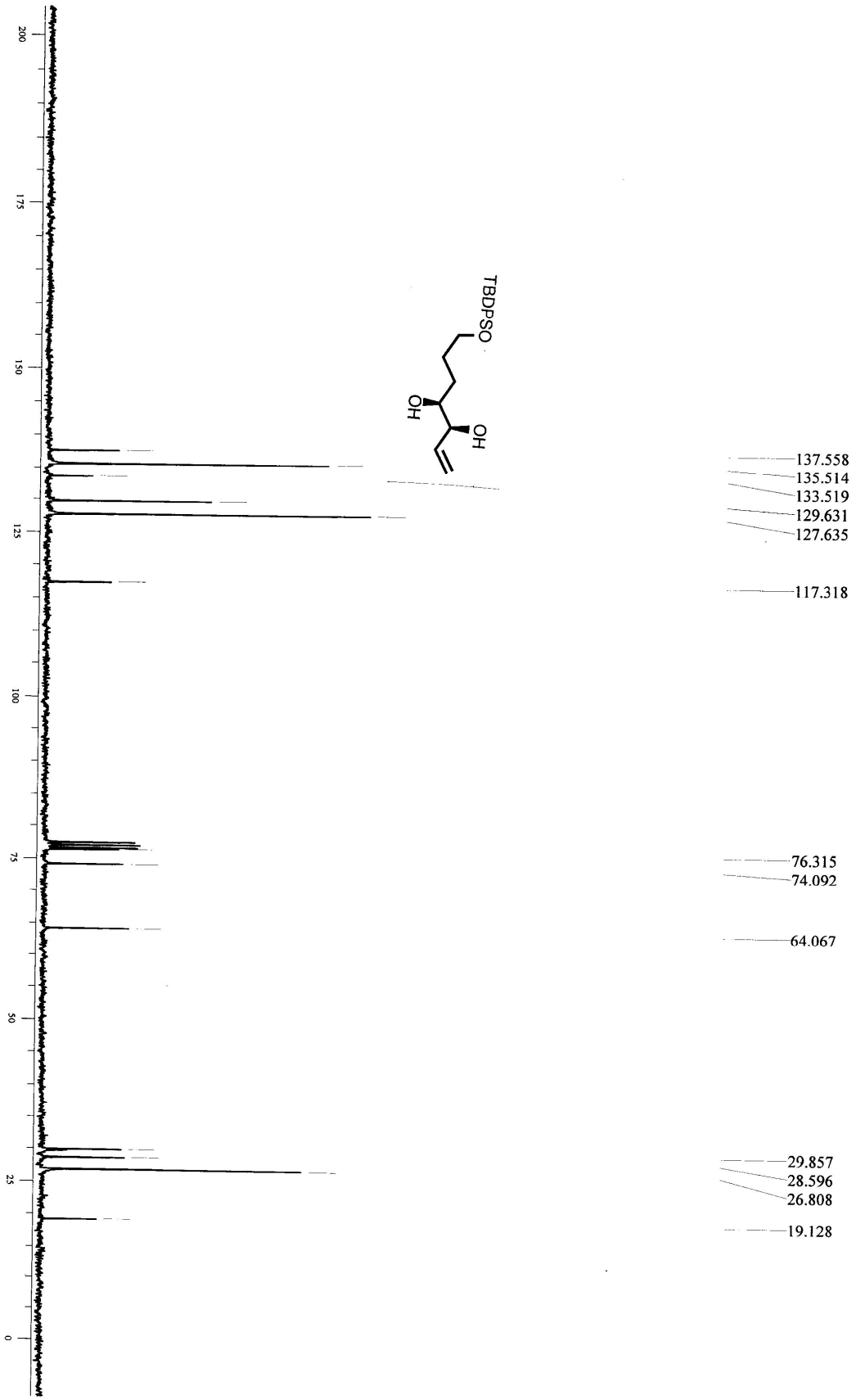
^{1}H NMR of Compound **18** ($CDCl_3$, 500 MHz)



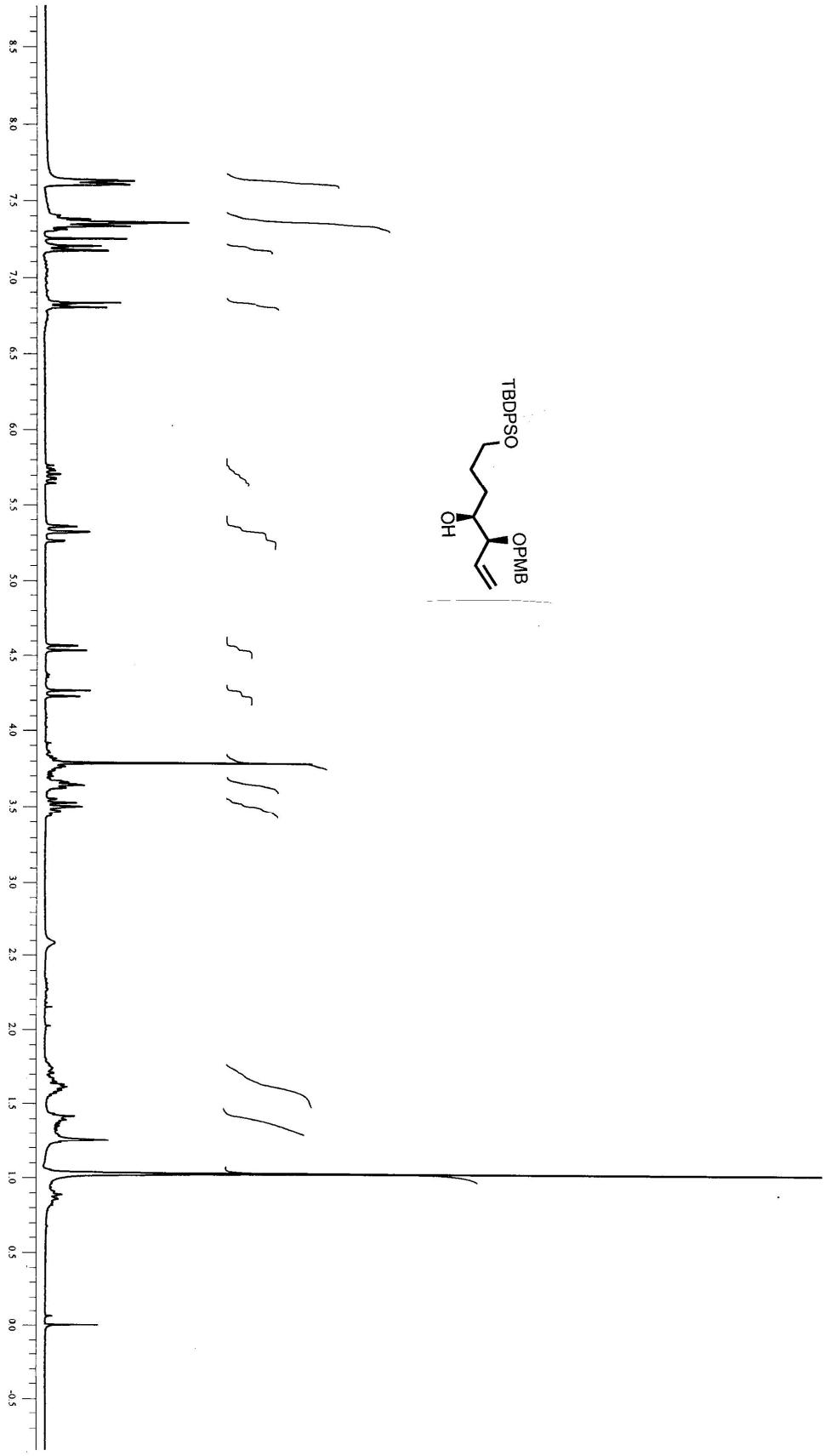
^{13}C NMR of Compound **18** ($CDCl_3$, 75 MHz)



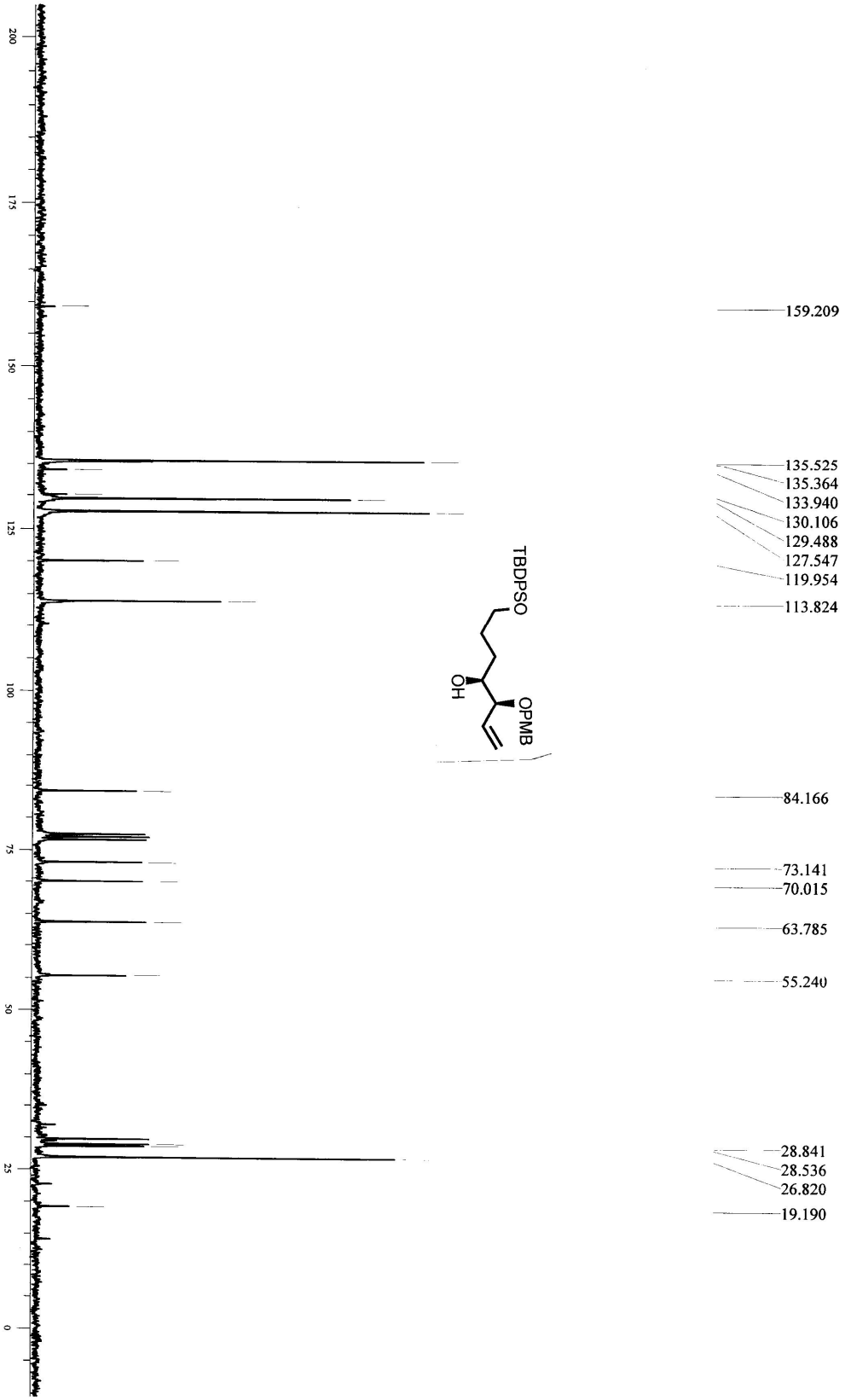
^{1}H NMR of Compound **19** ($CDCl_3$, 500 MHz)



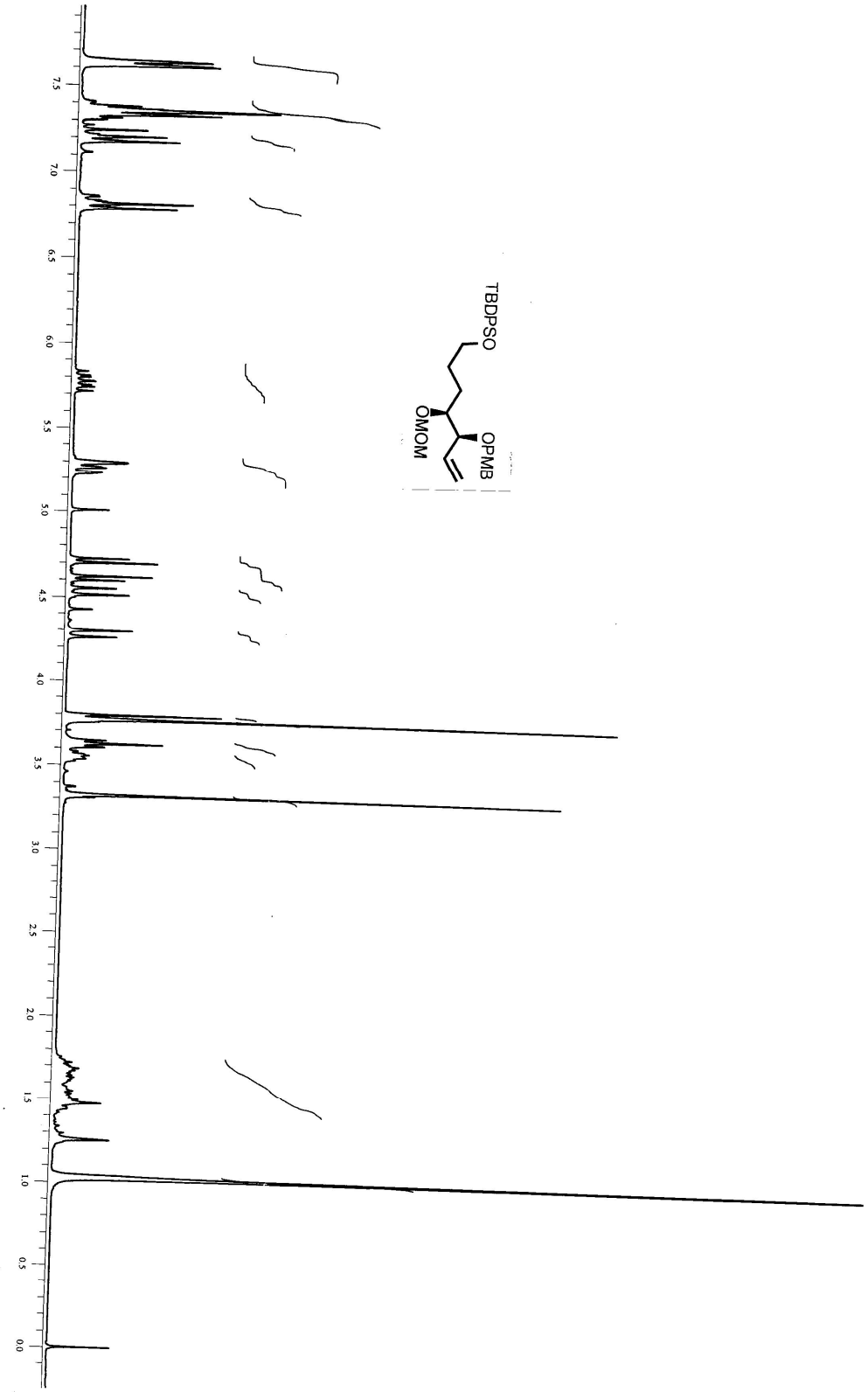
^{13}C NMR of Compound **19** ($CDCl_3$, 75 MHz)



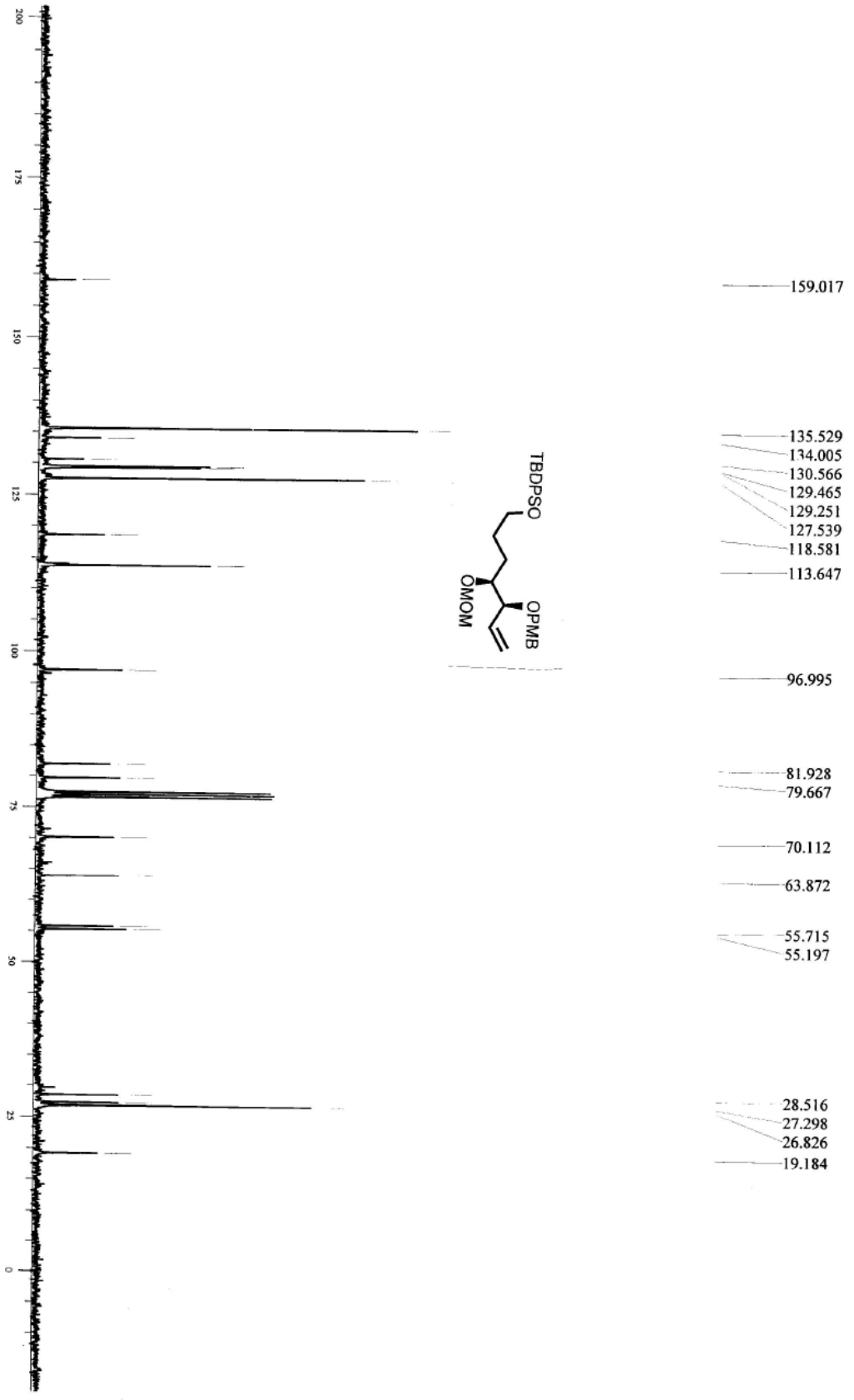
^{1}H NMR of Compound **20** ($CDCl_3$, 300 MHz)



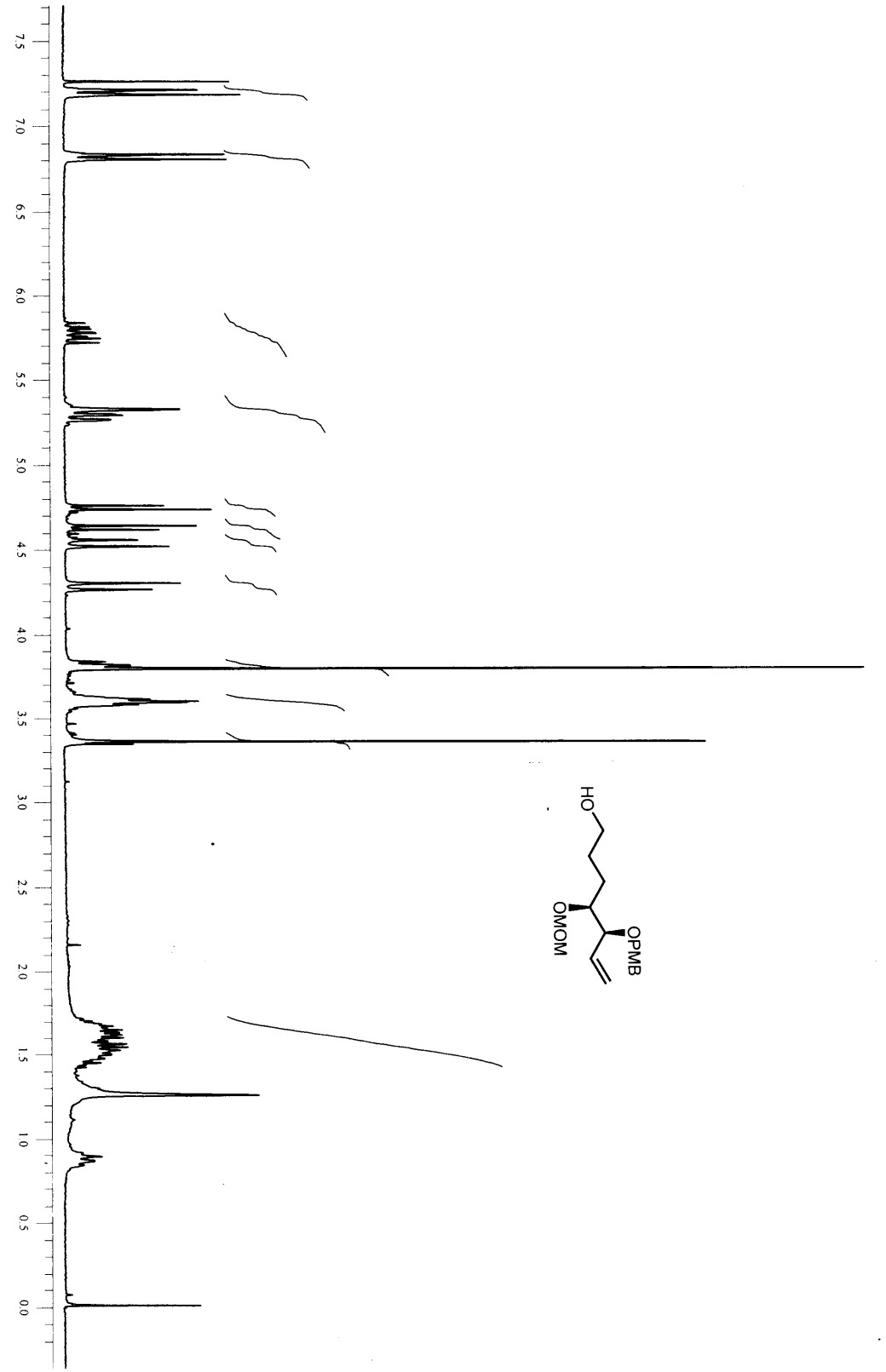
^{13}C NMR of Compound **20** ($CDCl_3$, 75 MHz)



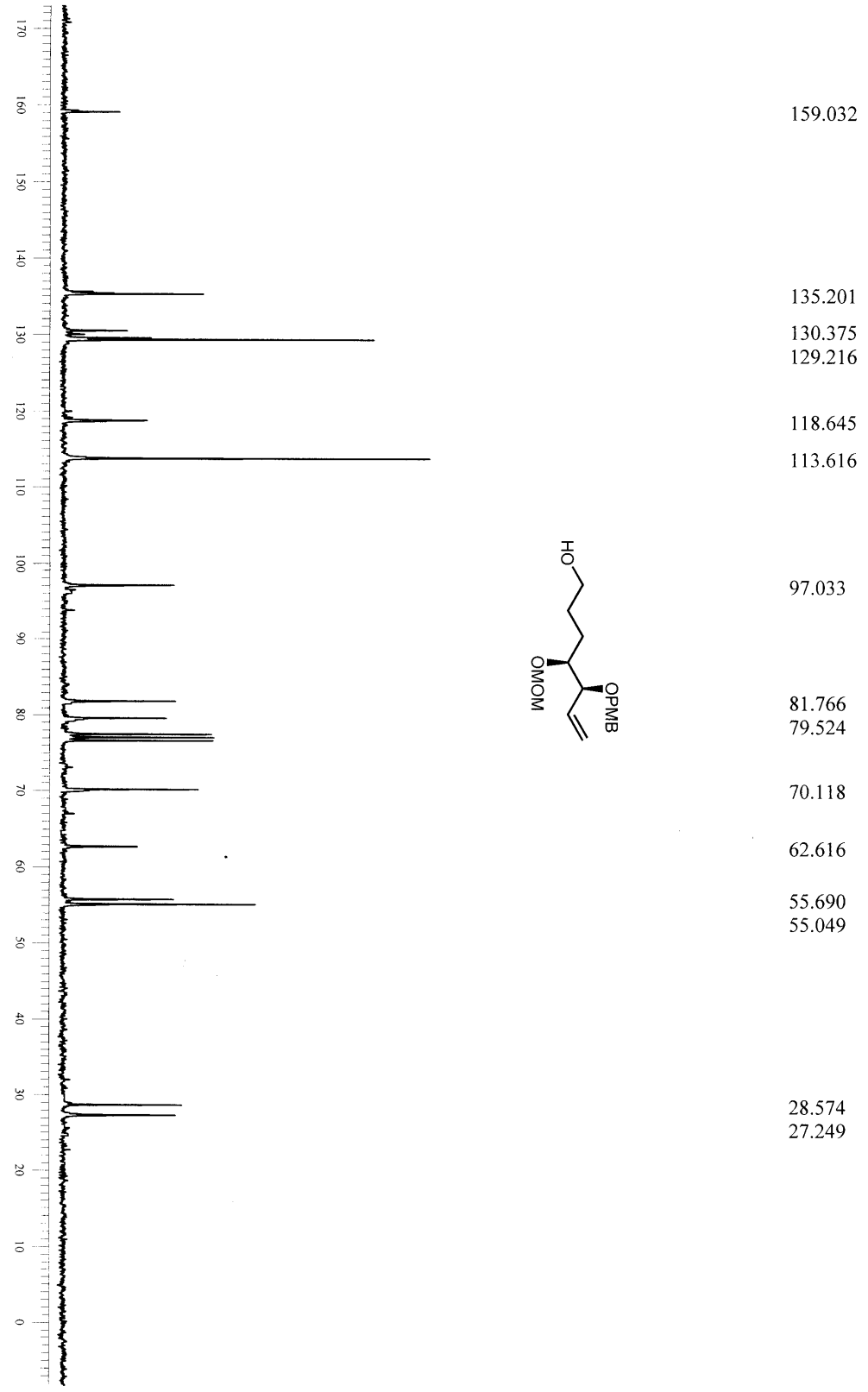
^{1}H NMR of Compound **21** ($CDCl_3$, 300 MHz)



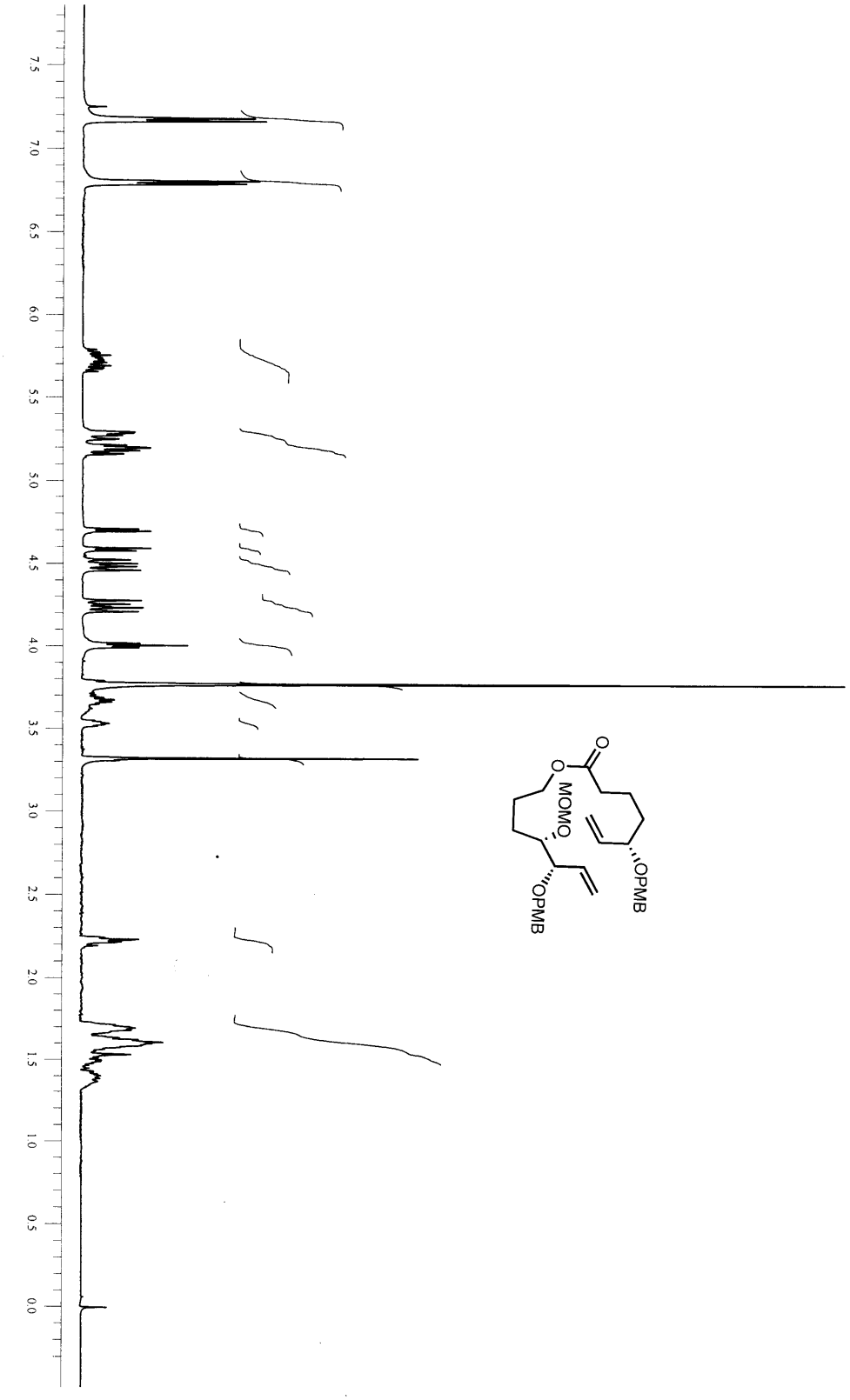
^{13}C NMR of Compound **21** ($CDCl_3$, 75 MHz)



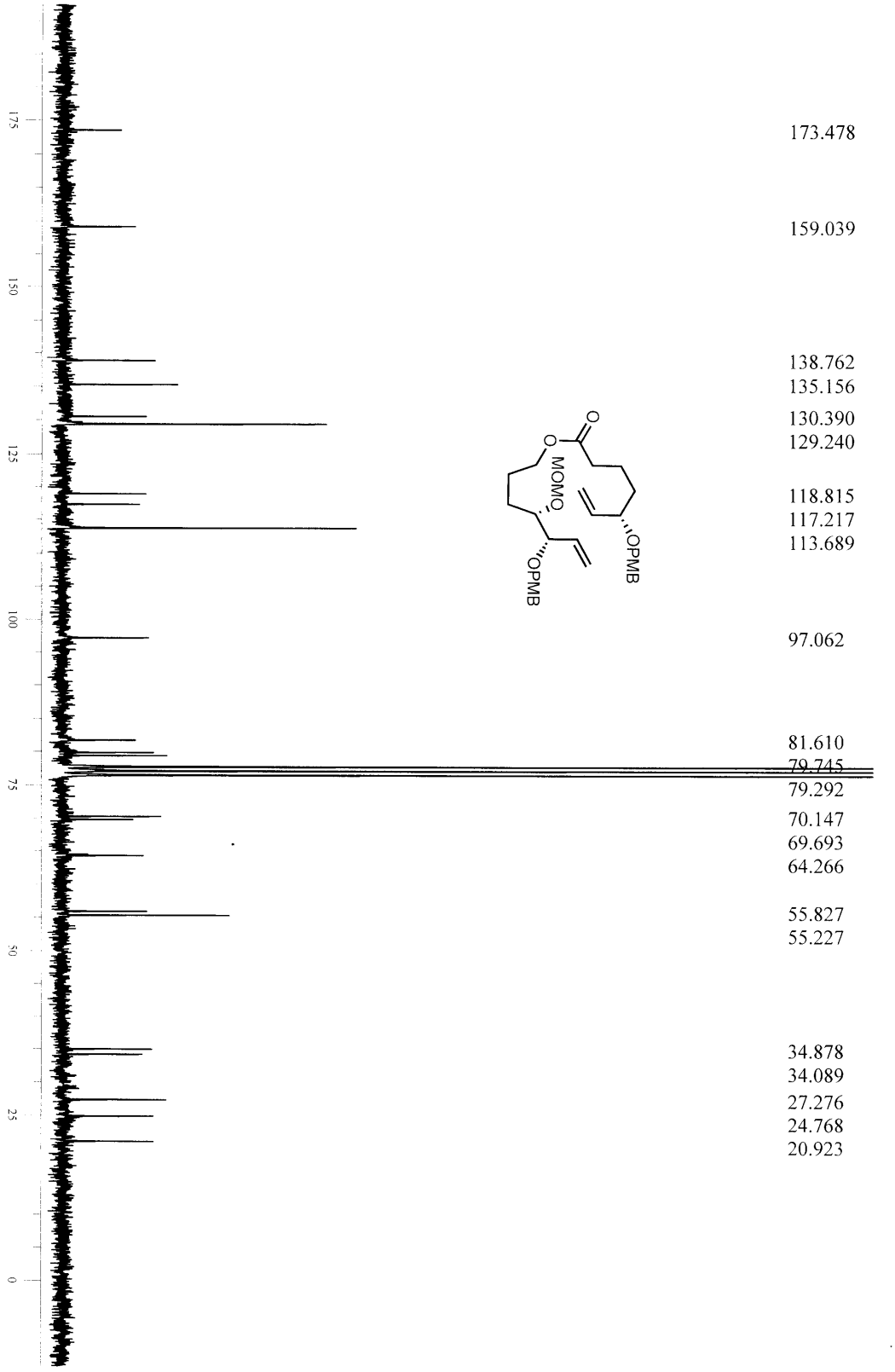
^{1}H NMR of Compound **7** ($CDCl_3$, 300 MHz)



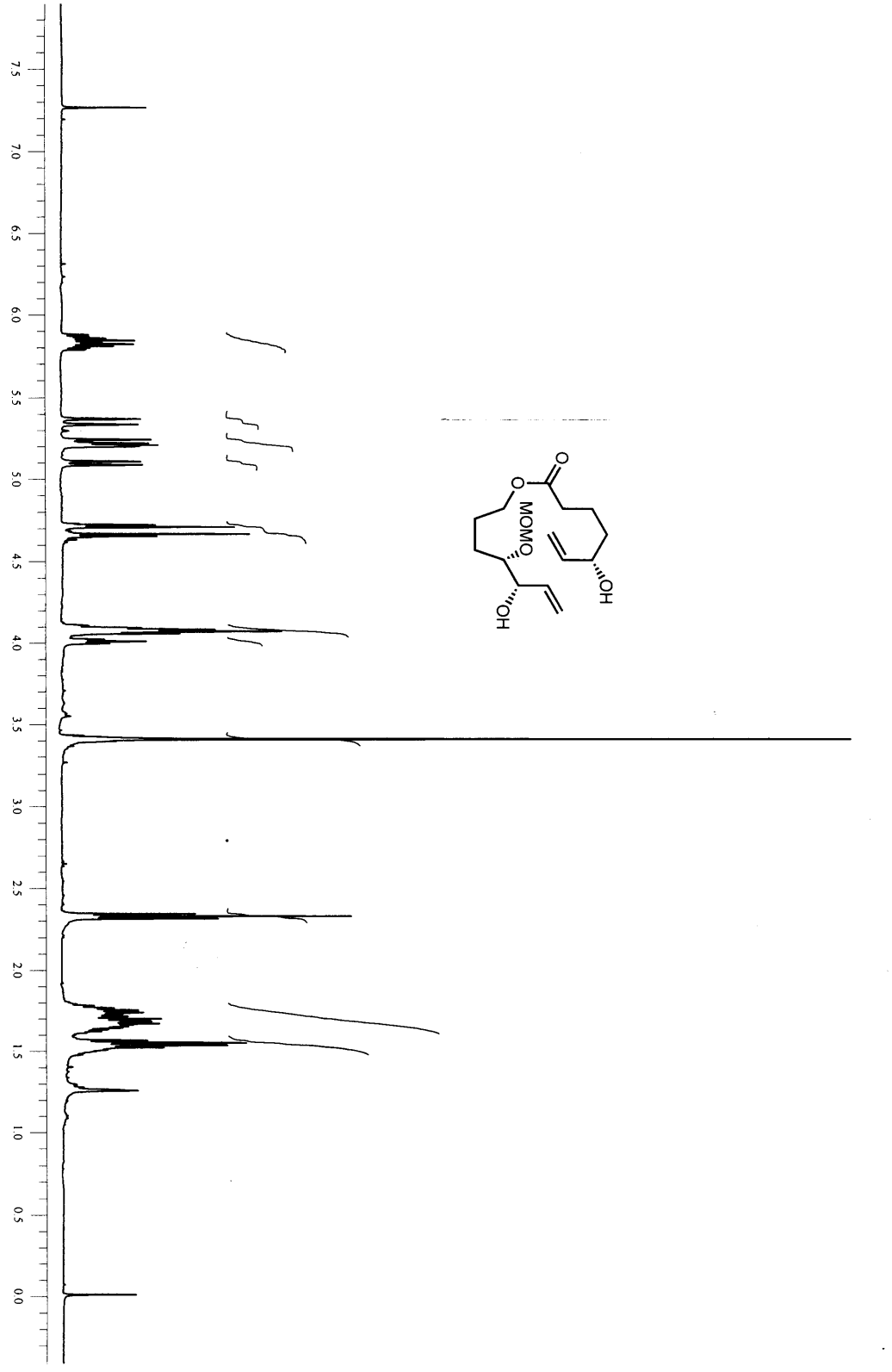
^{13}C NMR of Compound **7** ($CDCl_3$, 75 MHz)



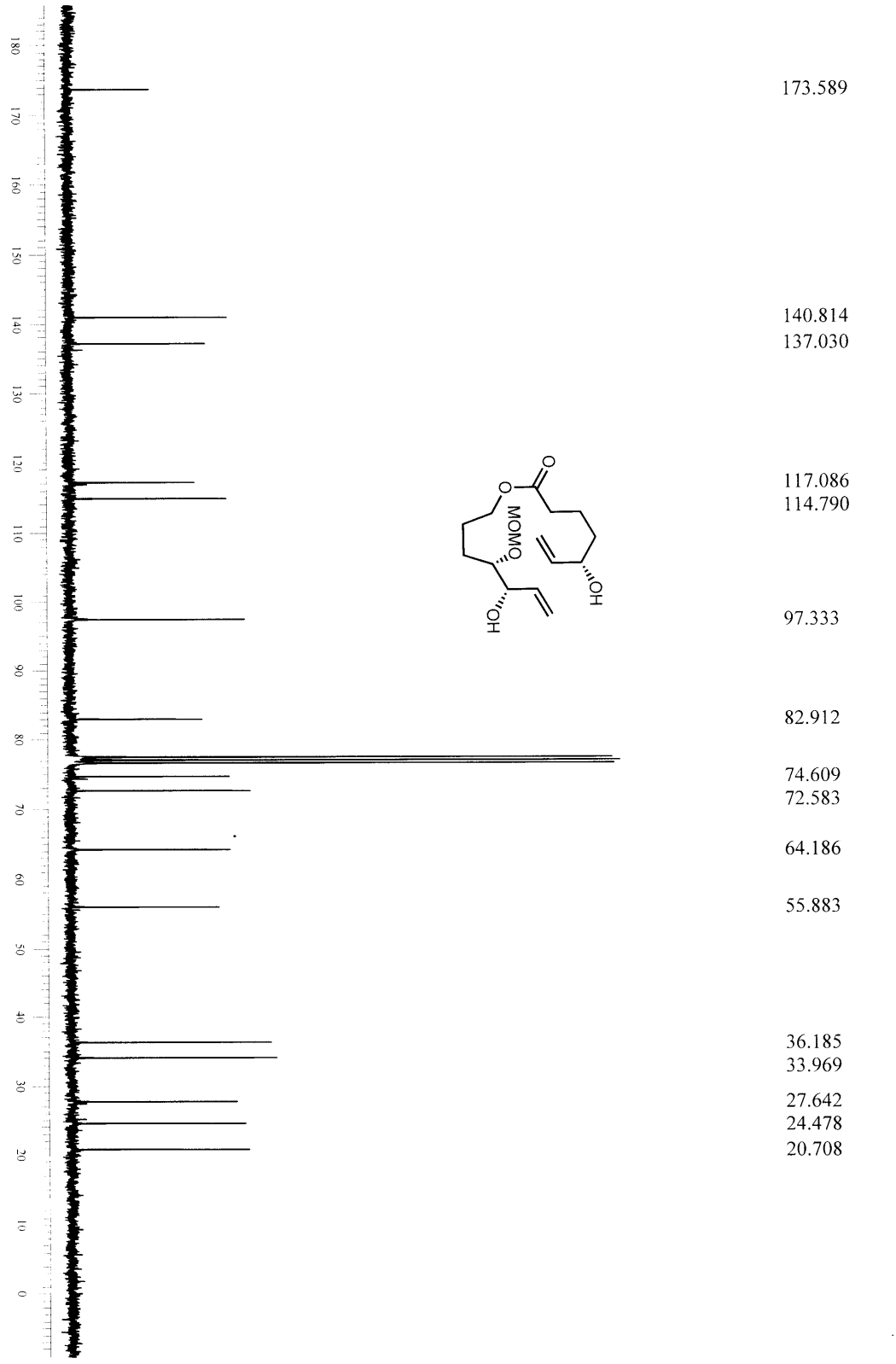
^{1}H NMR of Compound **21a** ($CDCl_3$, 500 MHz)



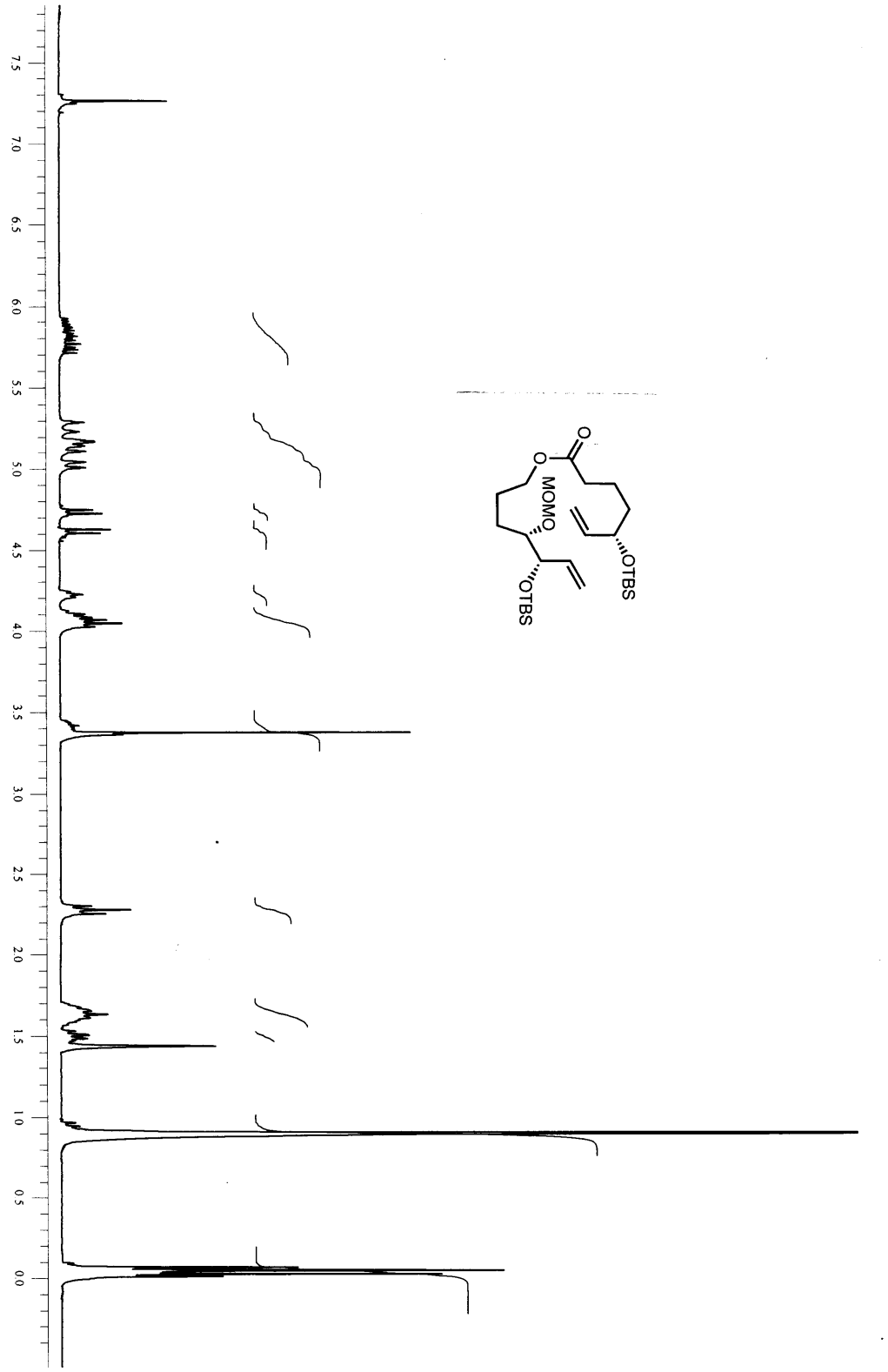
^{13}C NMR of Compound **21a** ($CDCl_3$, 75 MHz)



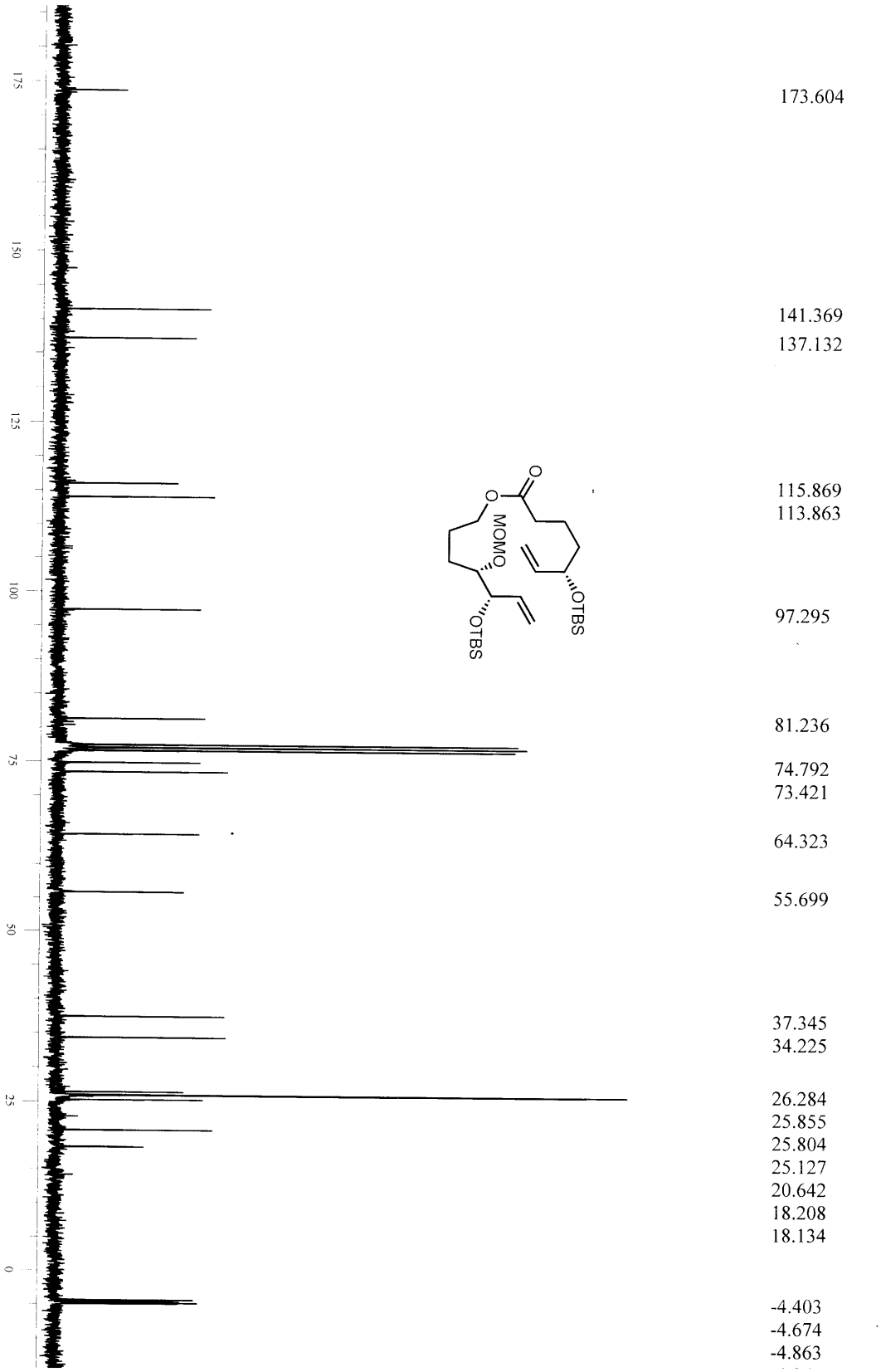
^{1}H NMR of Compound **21f** ($CDCl_3$, 500 MHz)



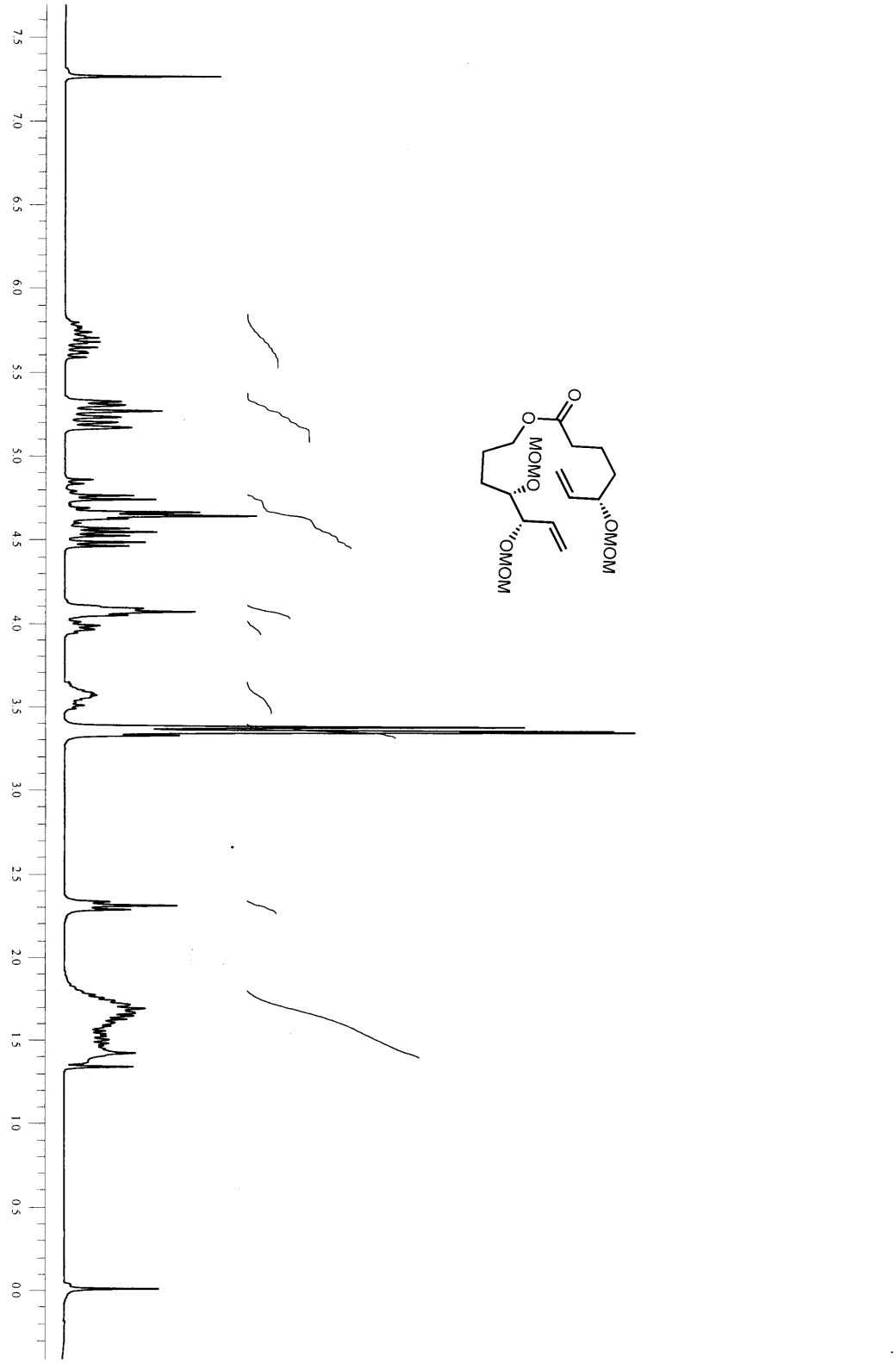
^{1}H NMR of Compound **21f** ($CDCl_3$, 75 MHz)



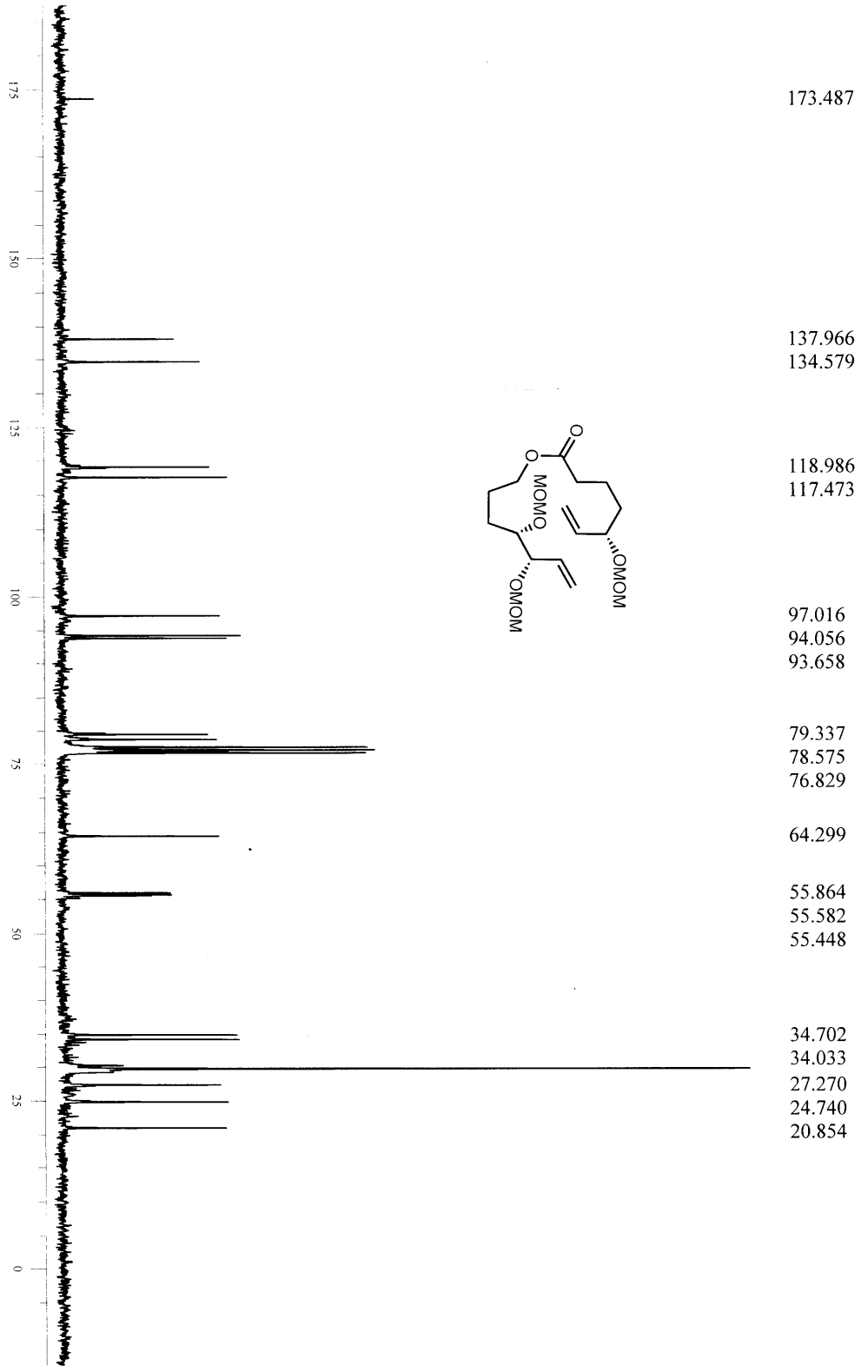
^{1}H NMR of Compound **21c** ($CDCl_3$, 300 MHz)



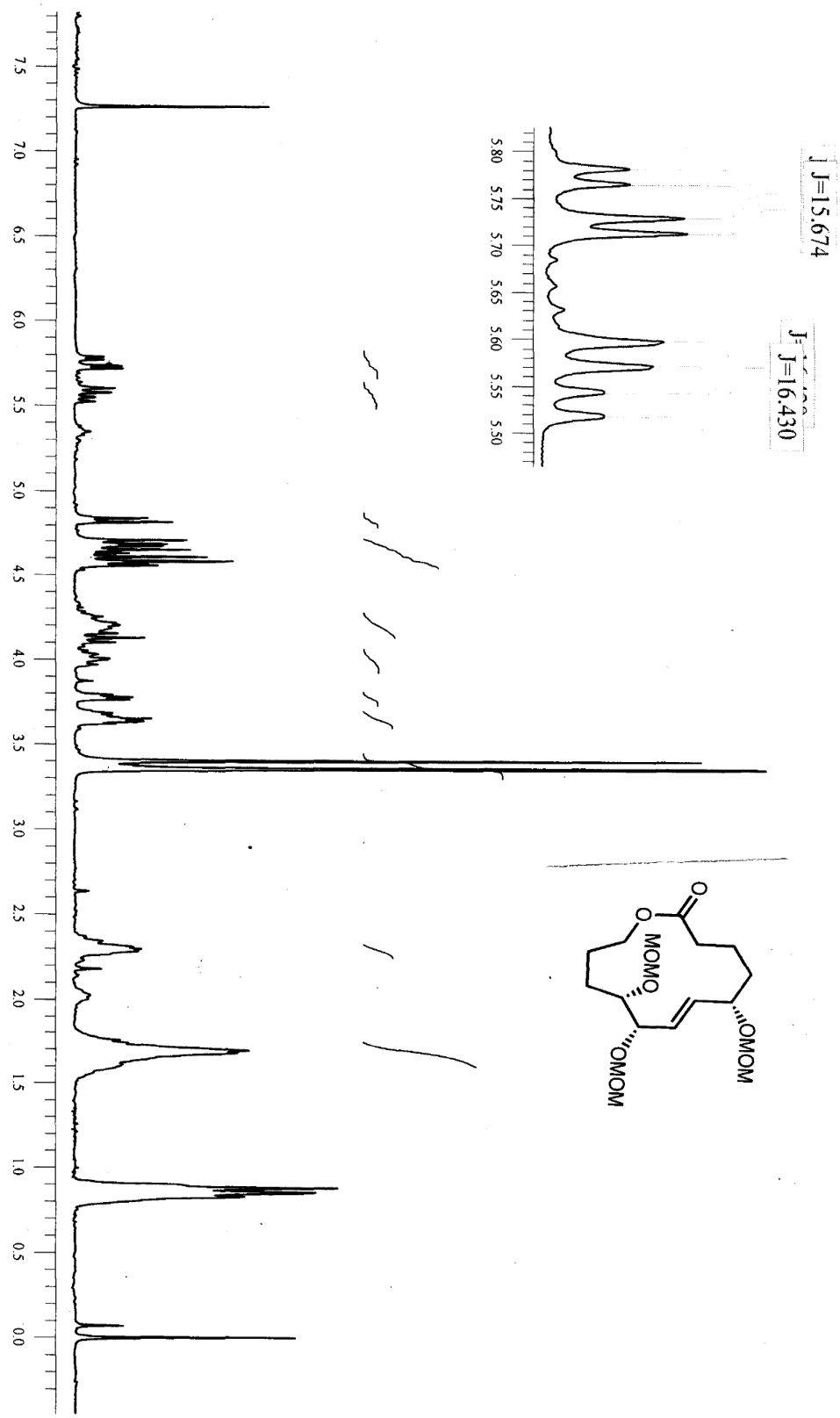
^{13}C NMR of Compound **21c** ($CDCl_3$, 75 MHz)



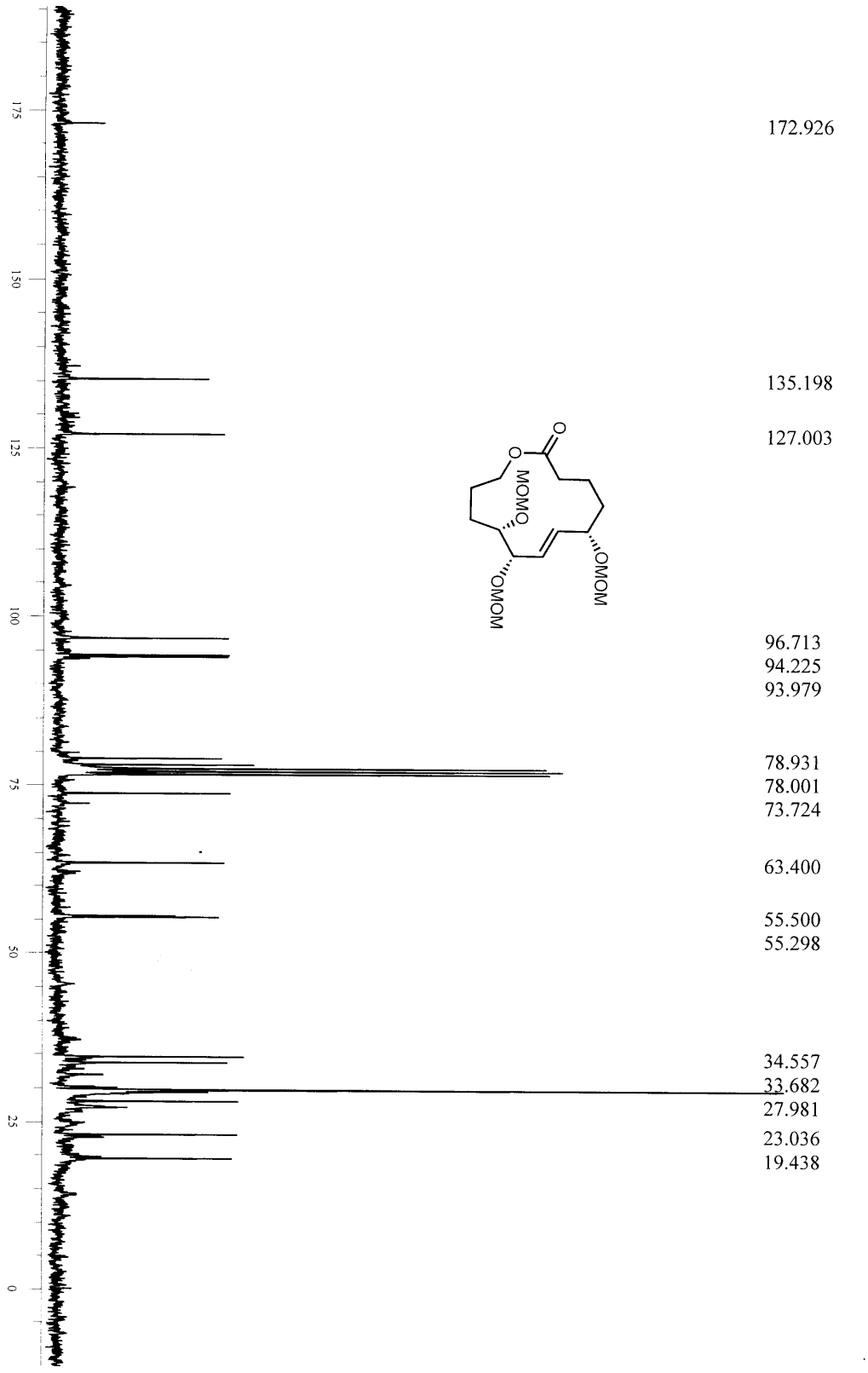
^{1}H NMR of Compound **21d** ($CDCl_3$, 300 MHz)



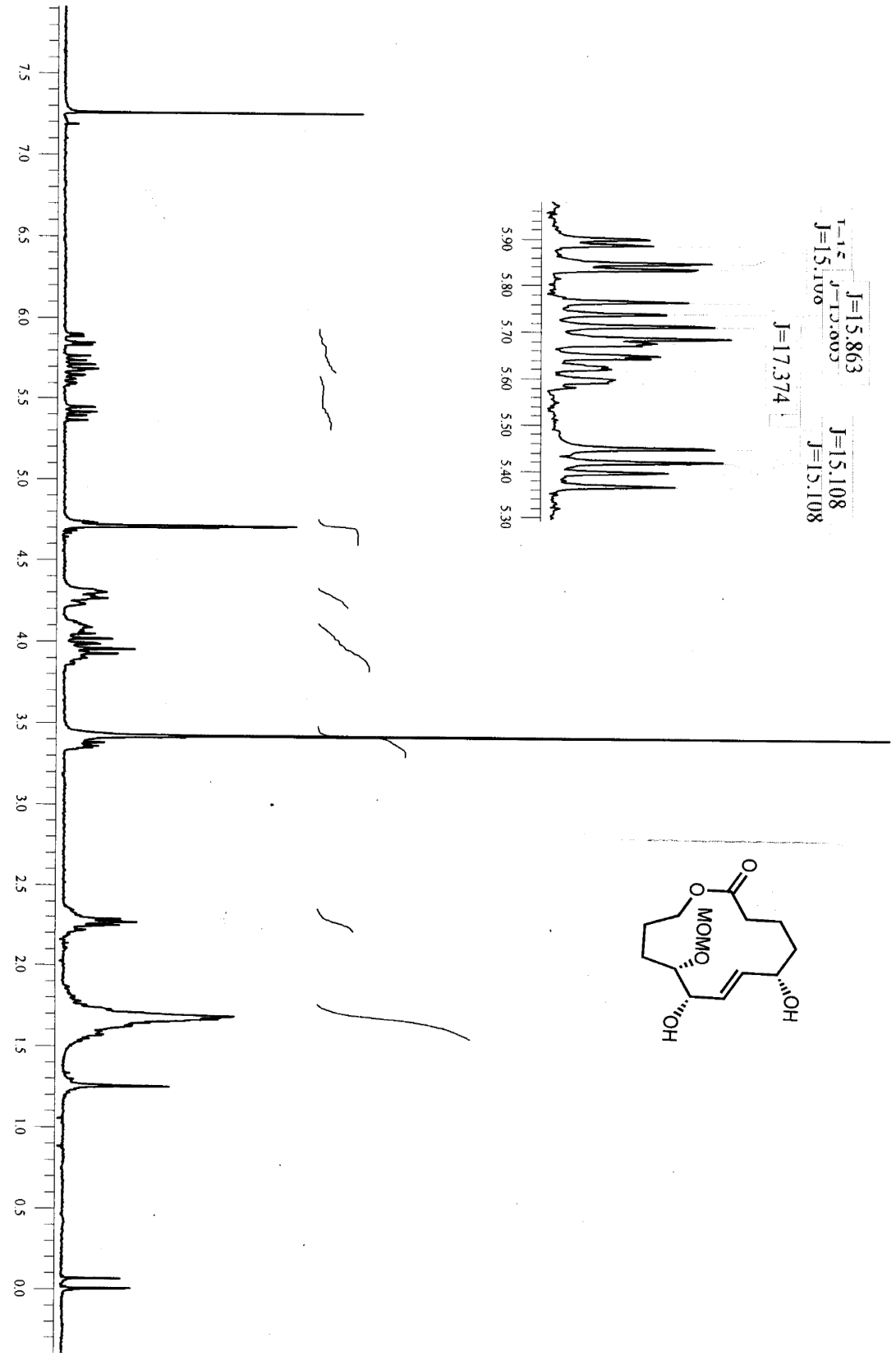
^{13}C NMR of Compound **21d** ($CDCl_3$, 75 MHz)



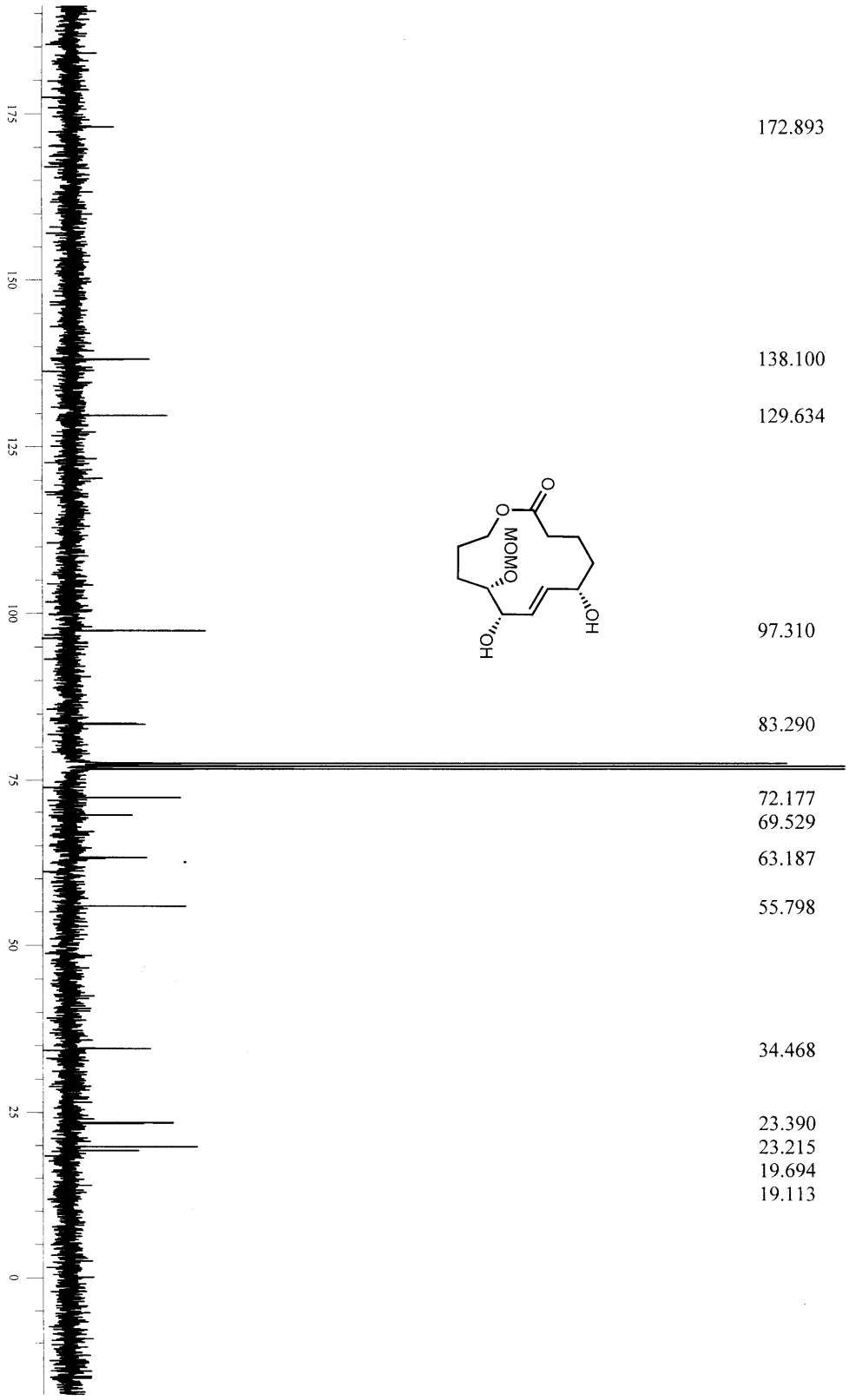
^{1}H NMR of Compound **5d** ($CDCl_3$, 300 MHz)



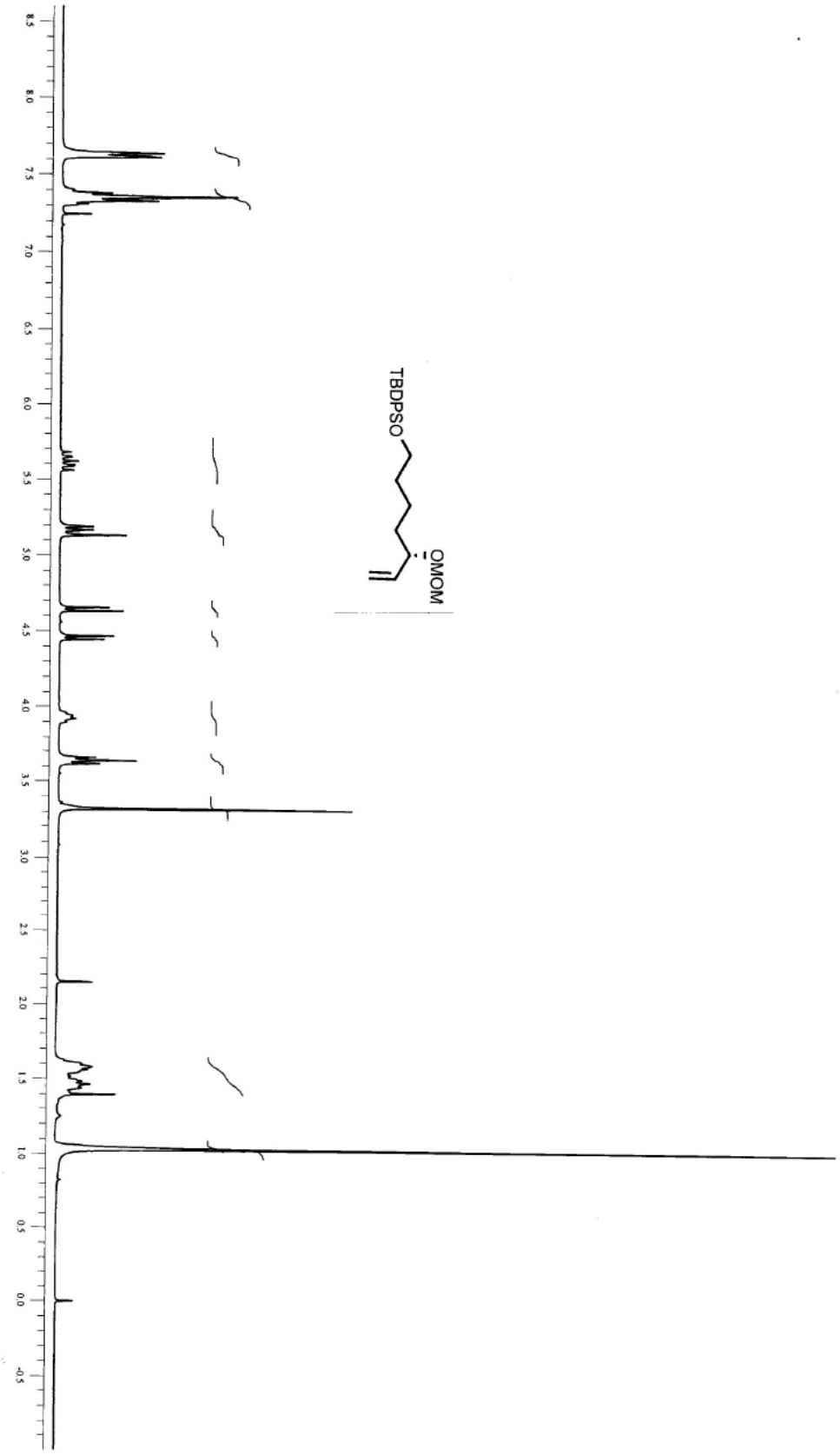
^{13}C NMR of Compound **5d** ($CDCl_3$, 75 MHz)



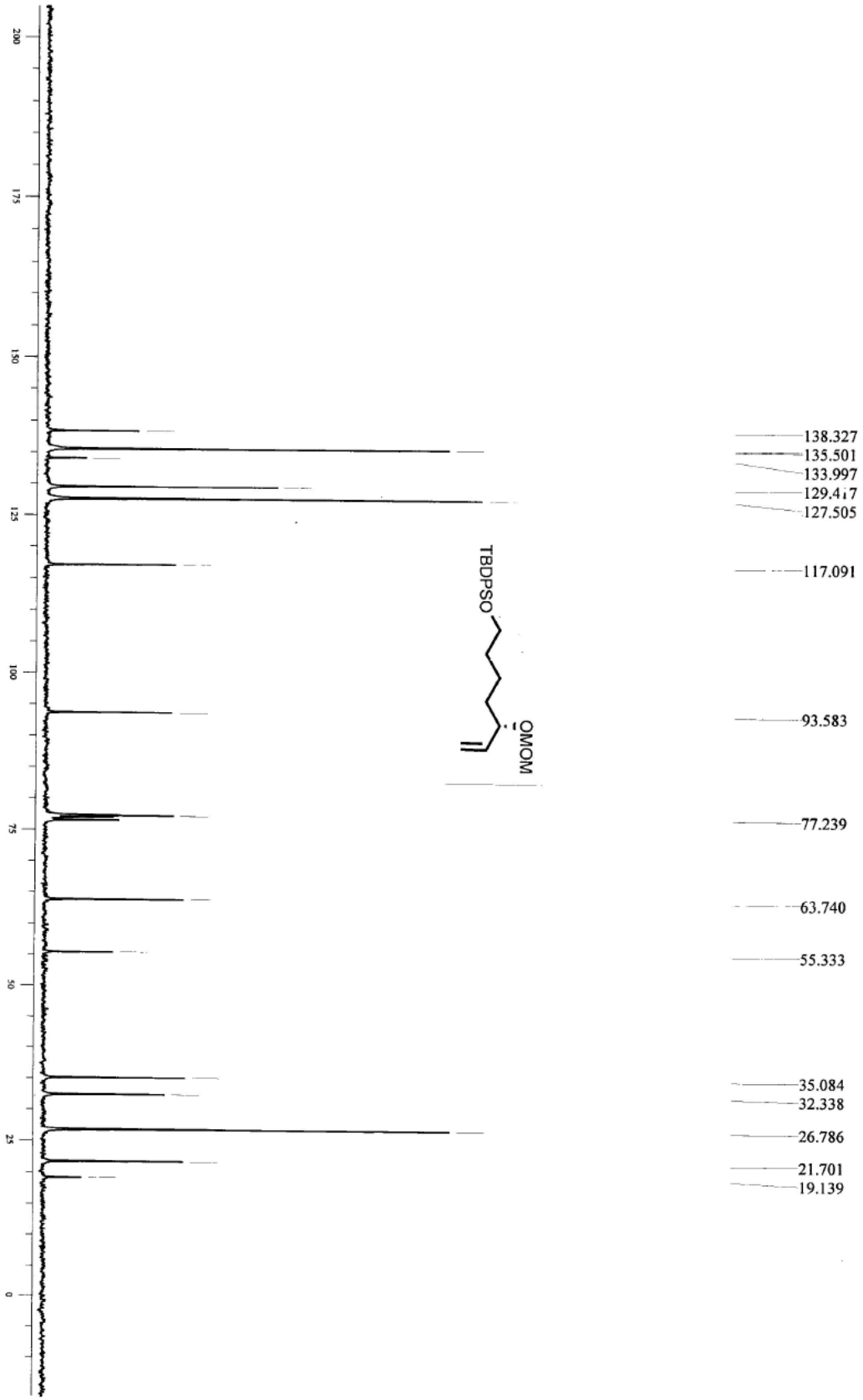
^{1}H NMR of Compound **5f** ($CDCl_3$, 300 MHz)



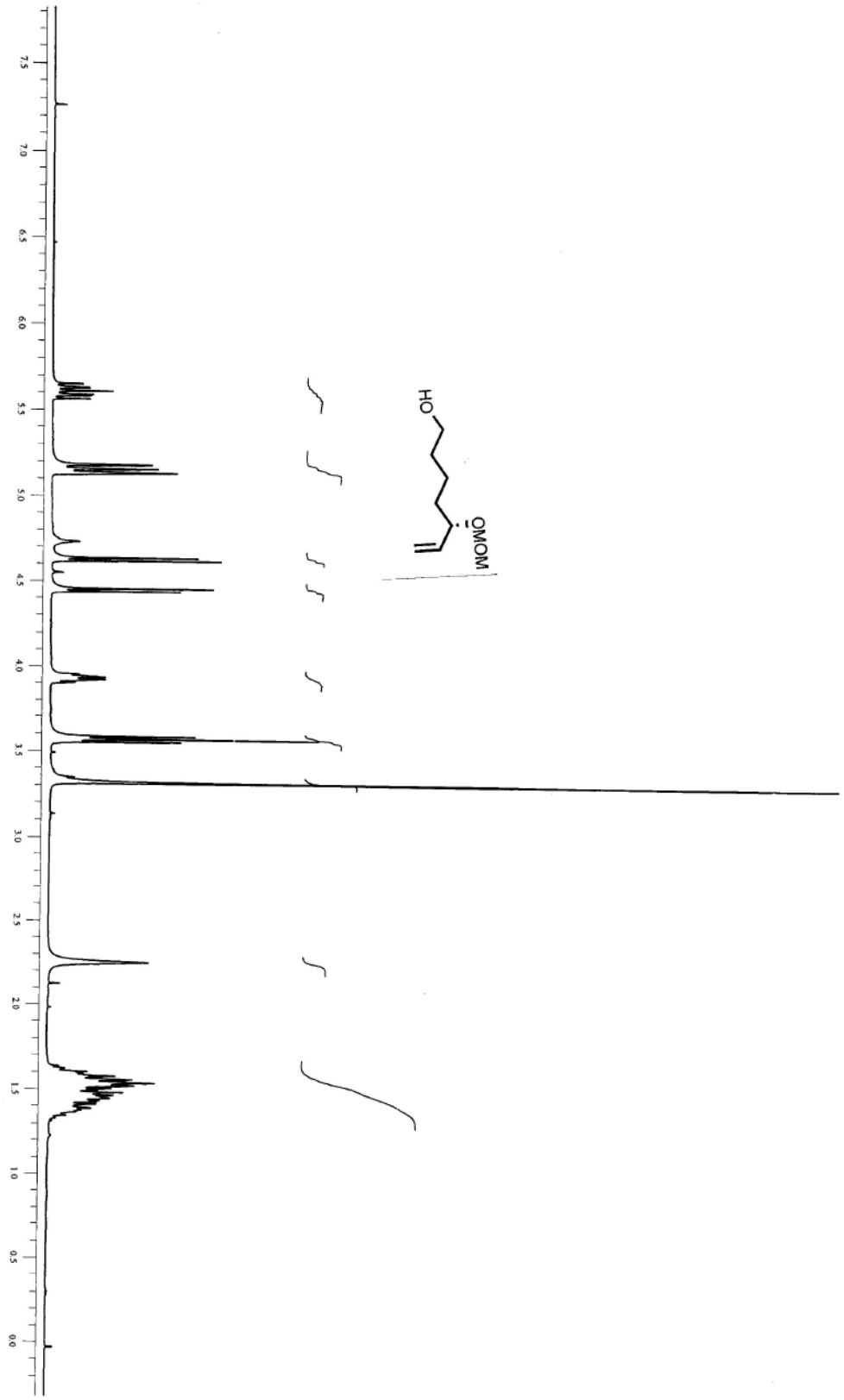
^{13}C NMR of Compound **5f** ($CDCl_3$, 75 MHz)



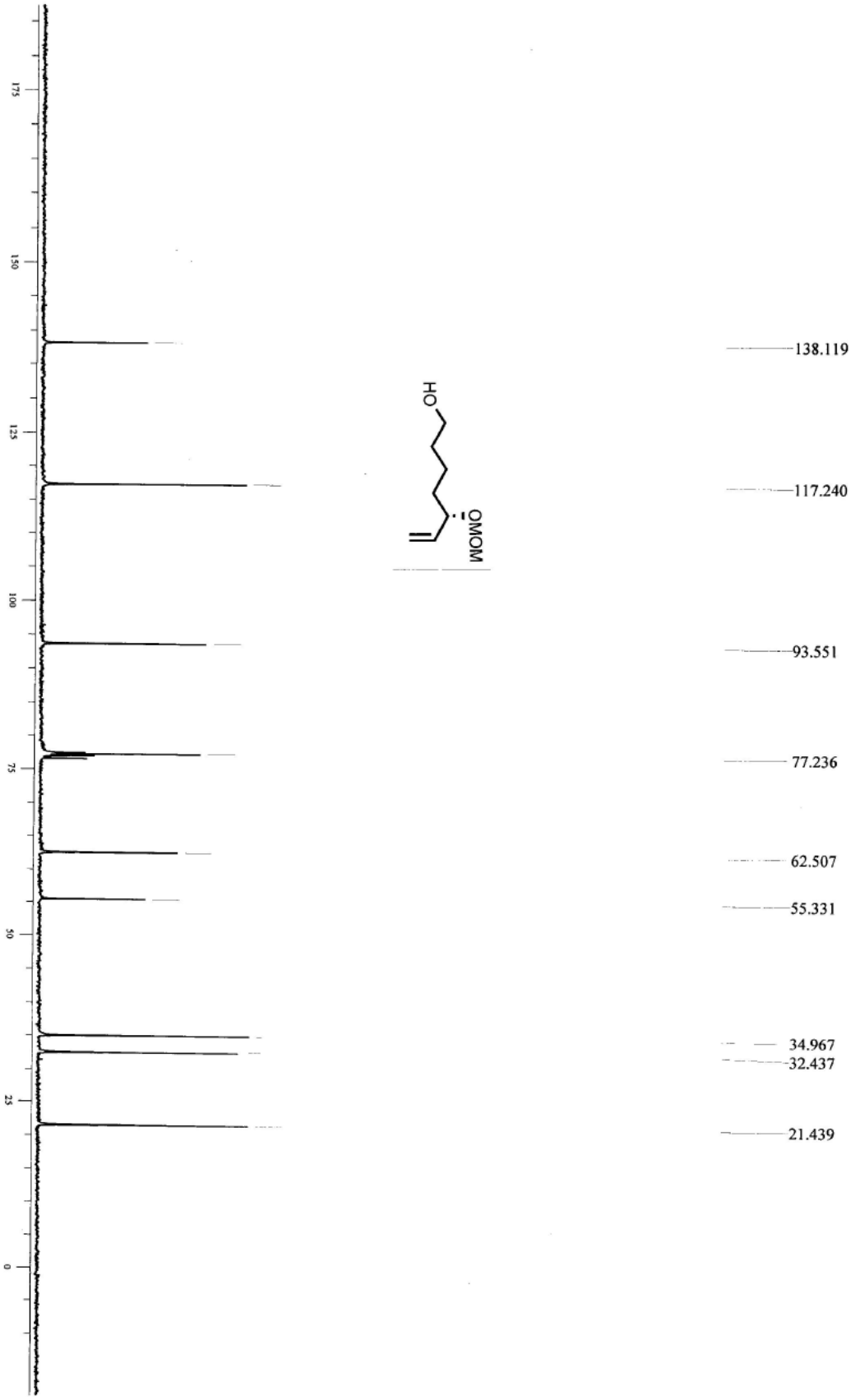
^{1}H NMR of Compound **23** ($CDCl_3$, 300 MHz)



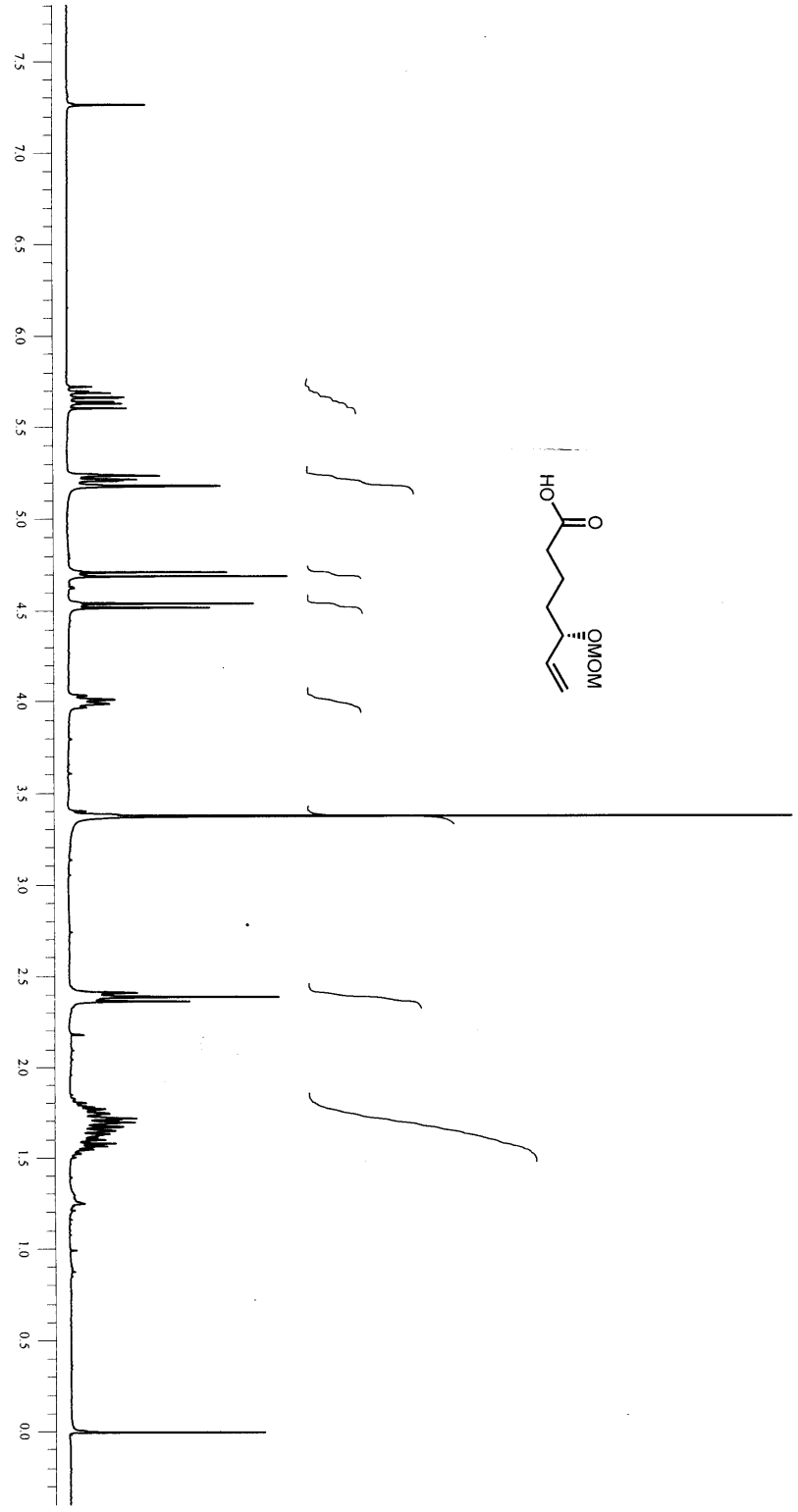
^{13}C NMR of Compound **23** ($CDCl_3$, 75 MHz)



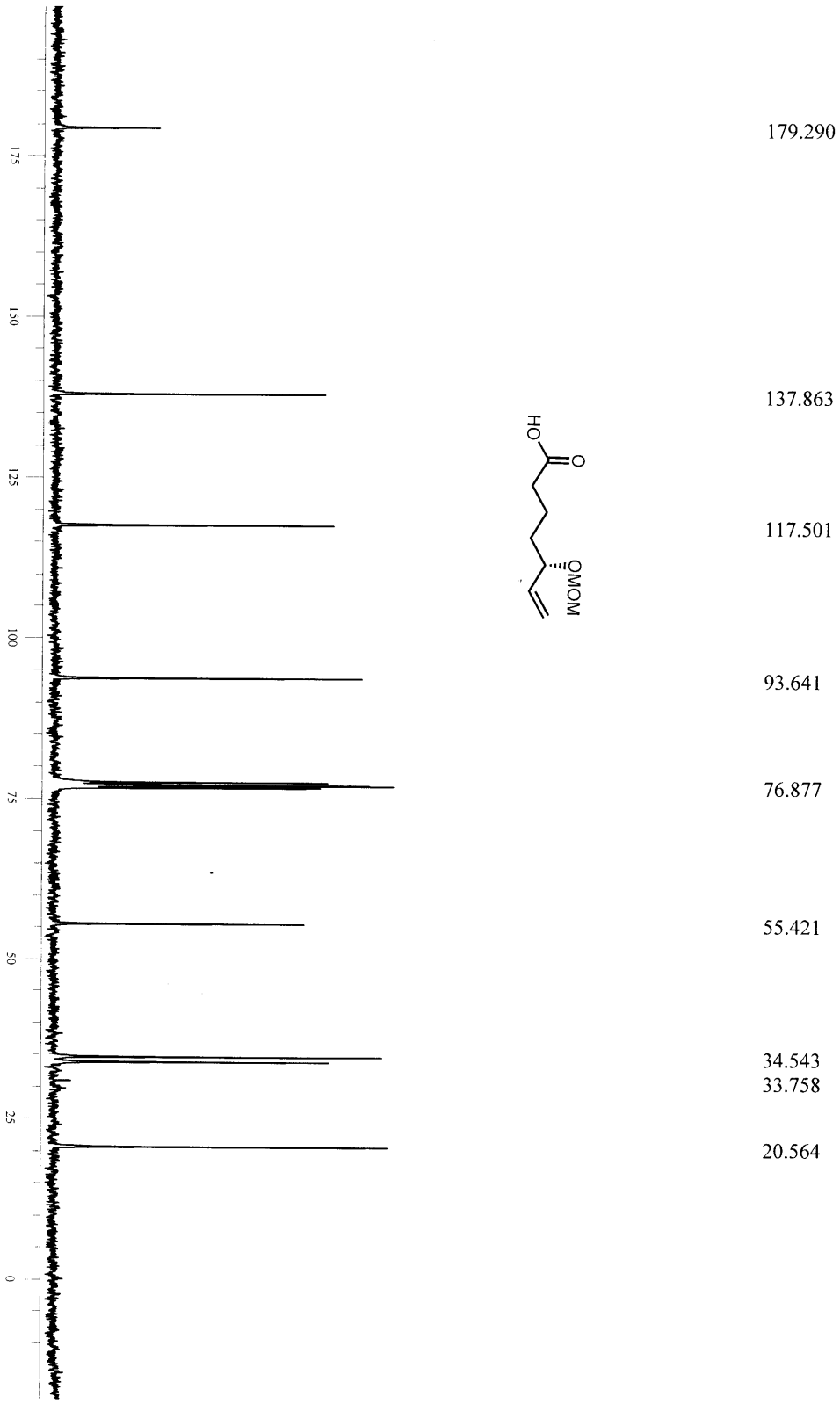
^{1}H NMR of Compound **24** ($CDCl_3$, 400 MHz)



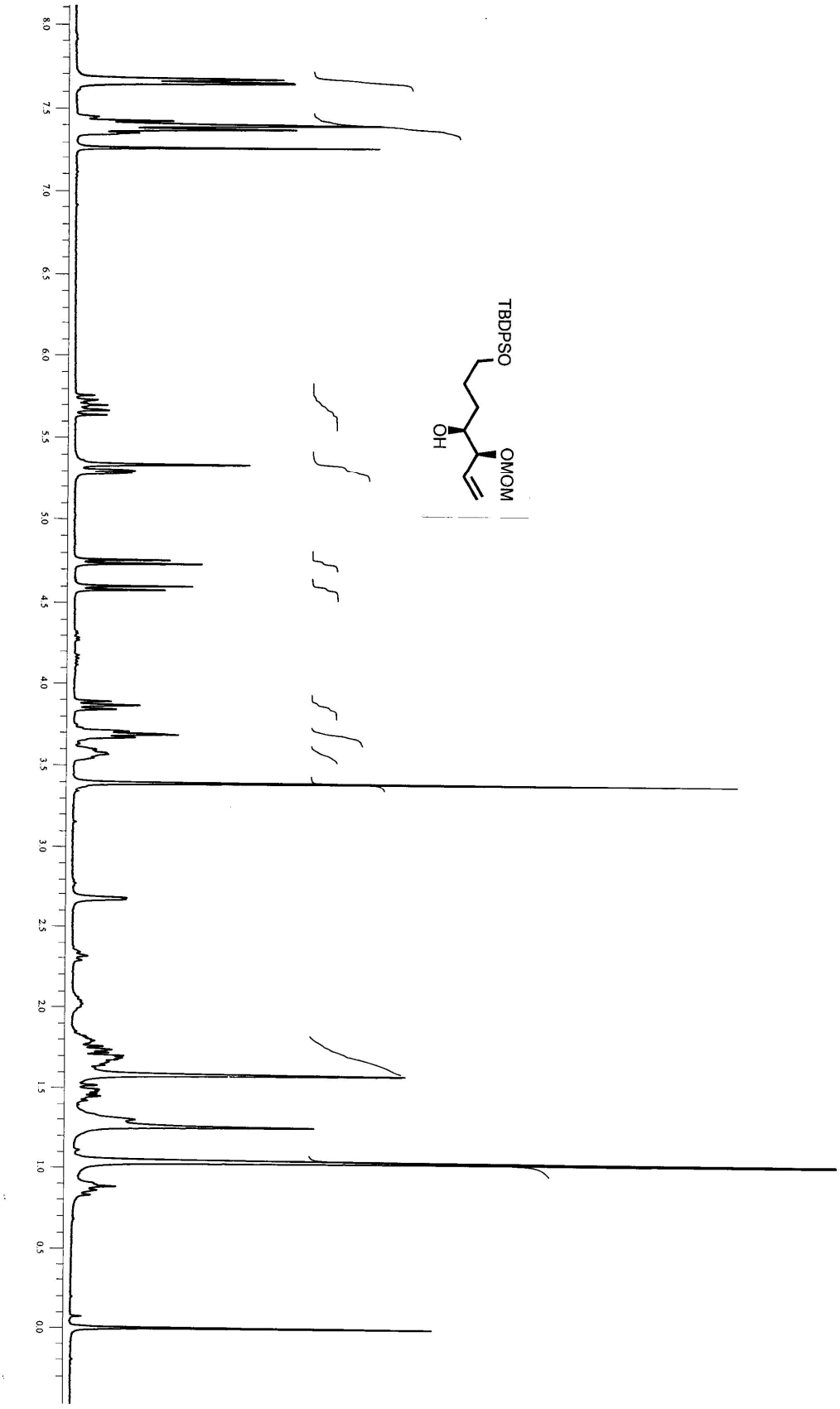
^{13}C NMR of Compound **24** ($CDCl_3$, 75 MHz)



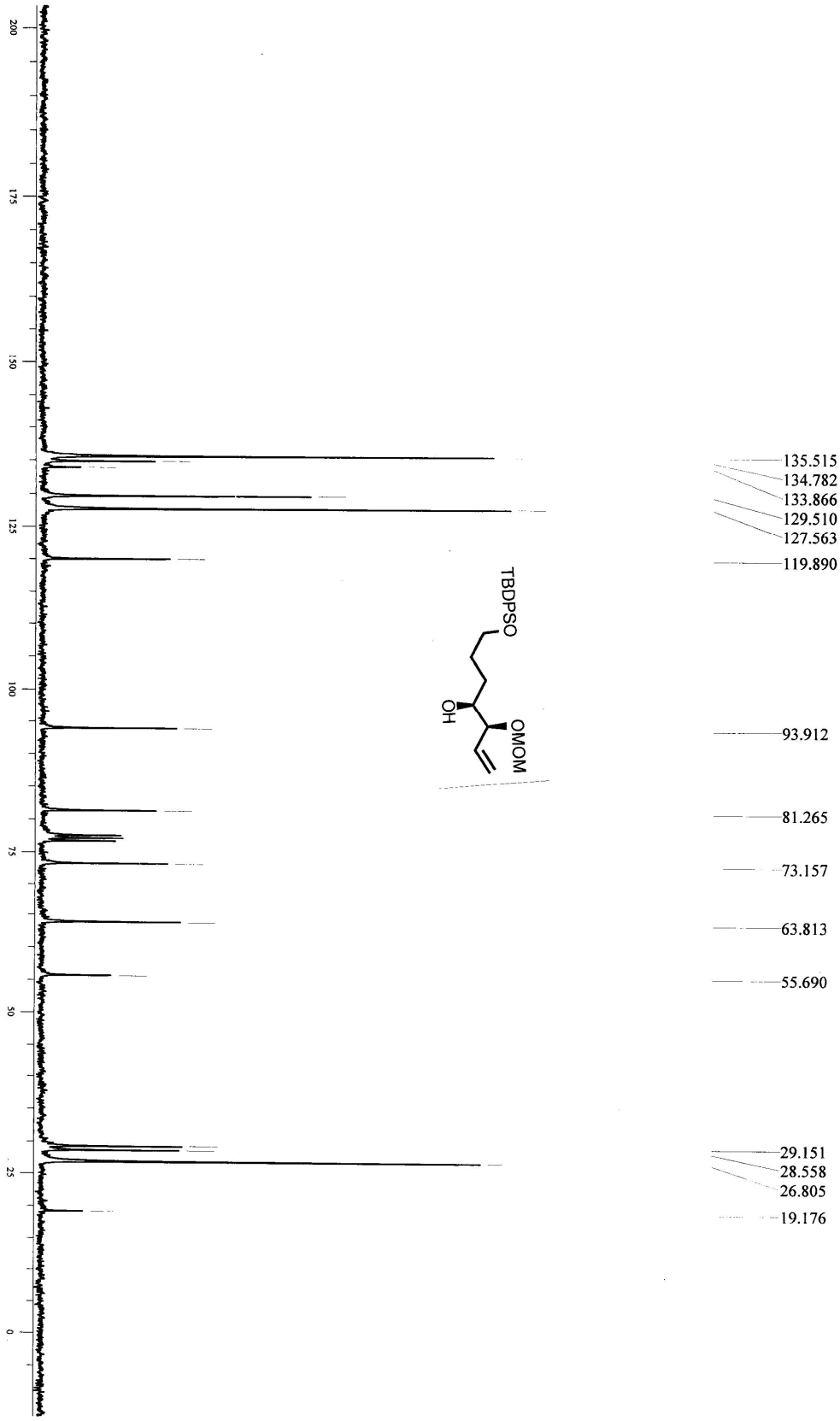
^{1}H NMR of Compound **6b** ($CDCl_3$, 300 MHz)



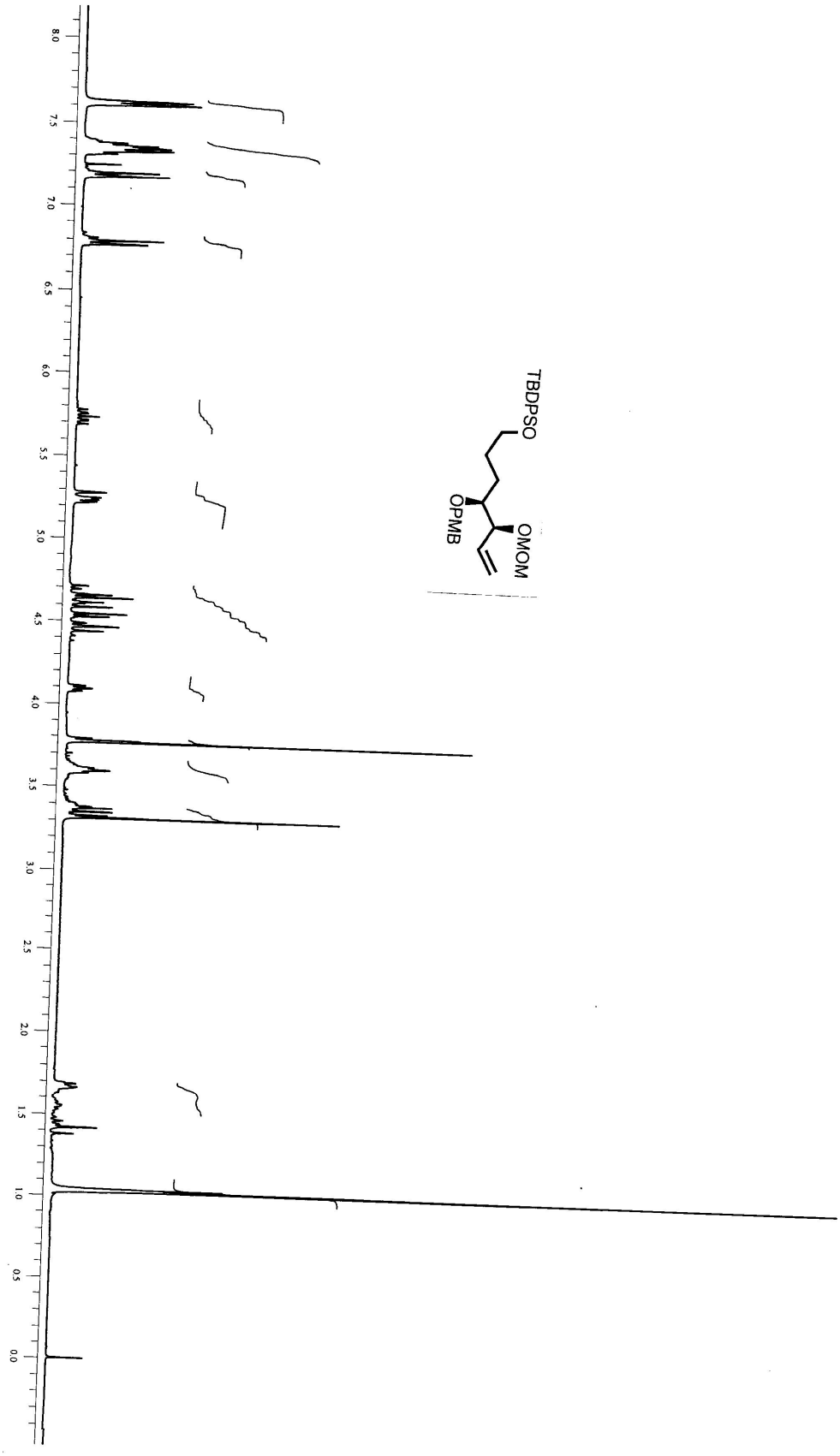
^{13}C NMR of Compound **6b** ($CDCl_3$, 75 MHz)



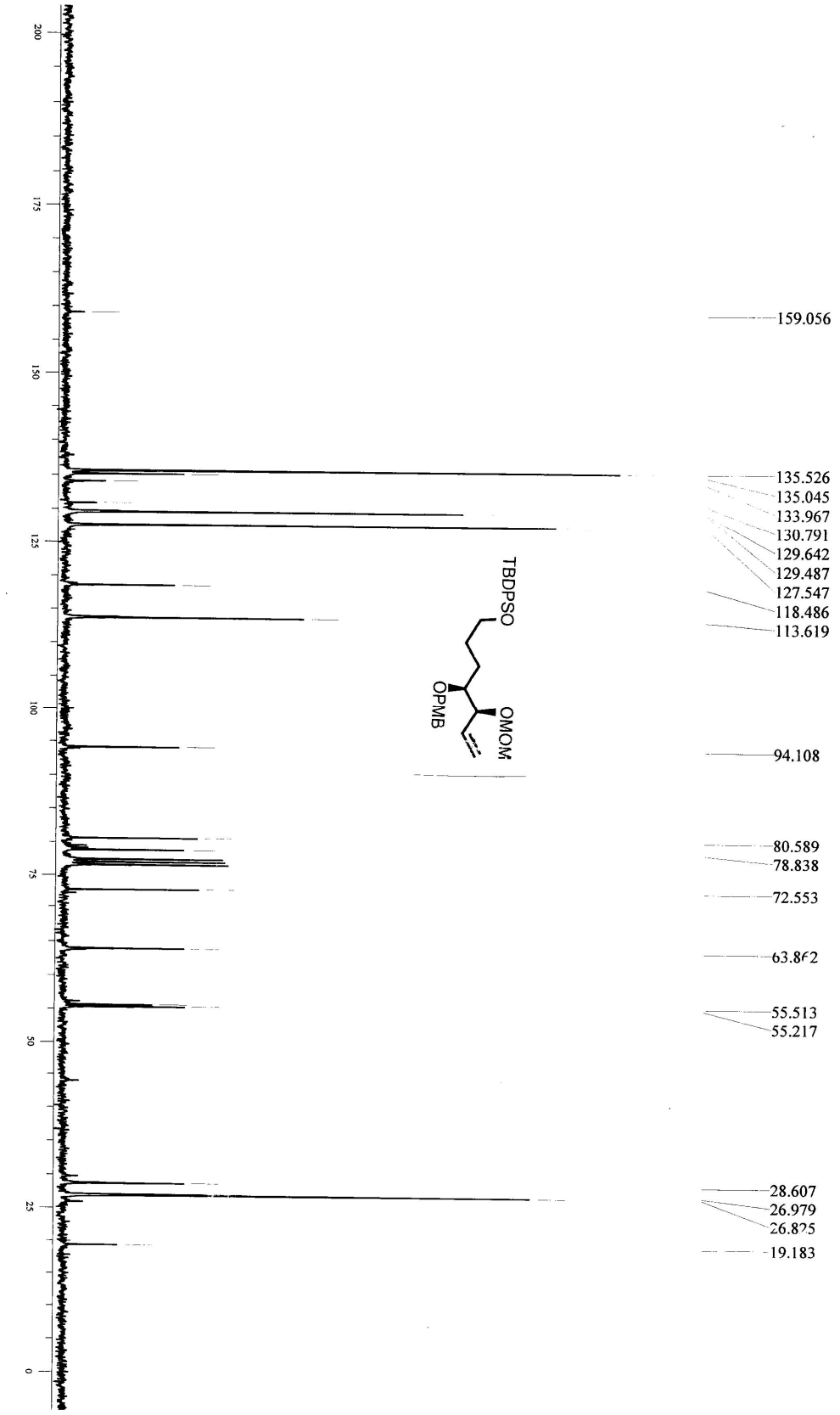
^{1}H NMR of Compound **25** ($CDCl_3$, 300 MHz)



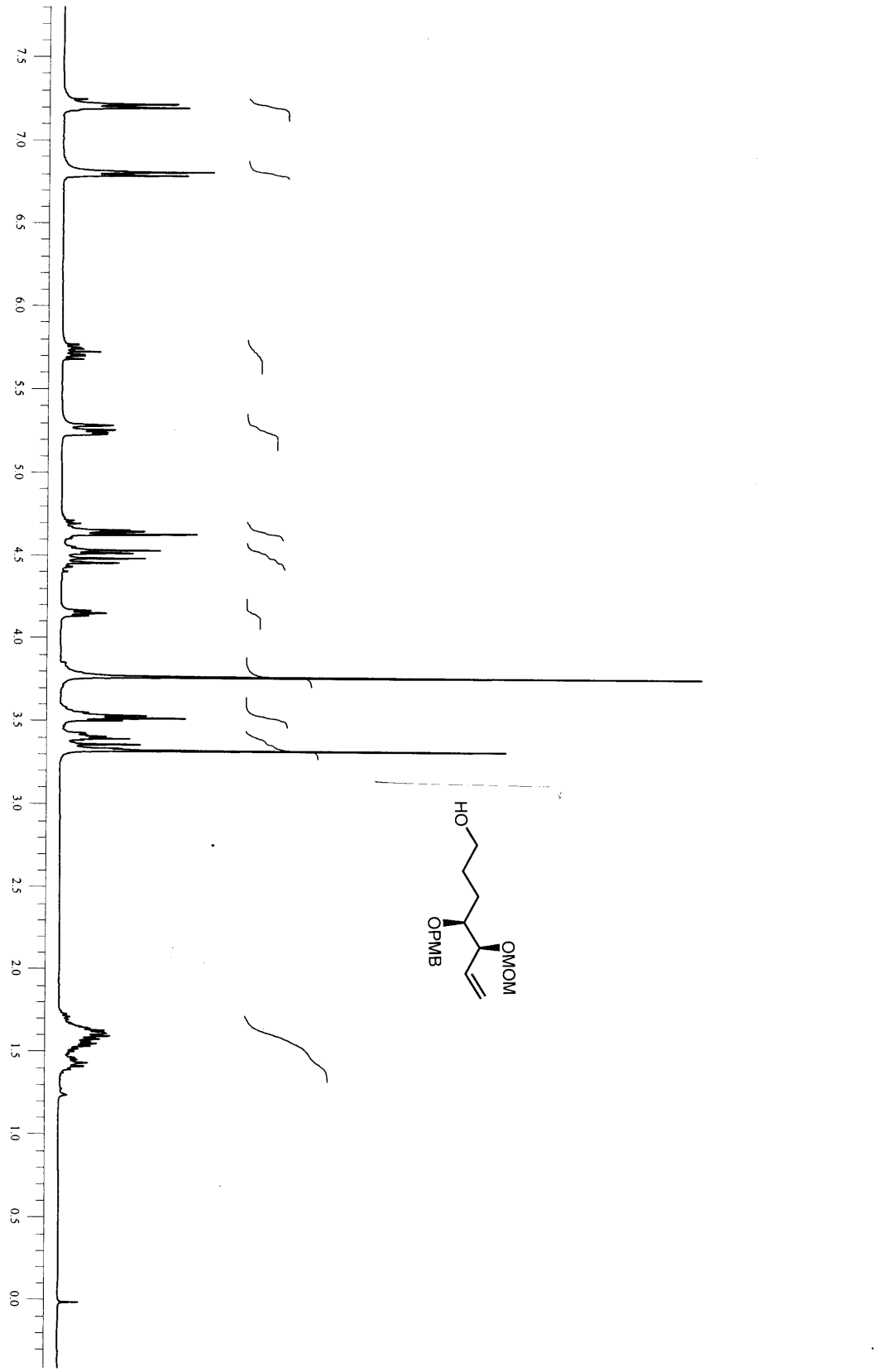
^{13}C NMR of Compound **25** ($CDCl_3$, 75 MHz)



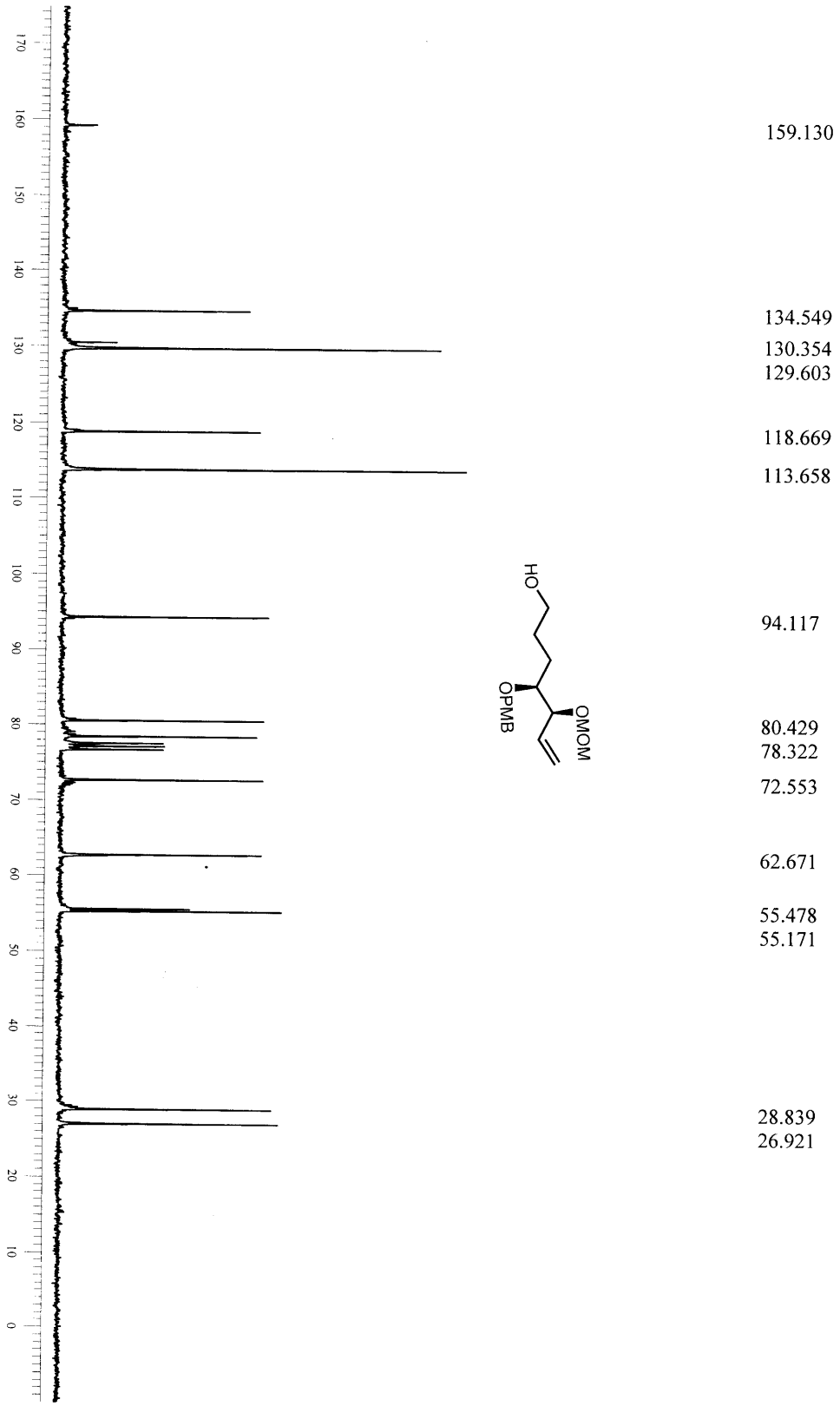
^{1}H NMR of Compound **26** ($CDCl_3$, 400 MHz)



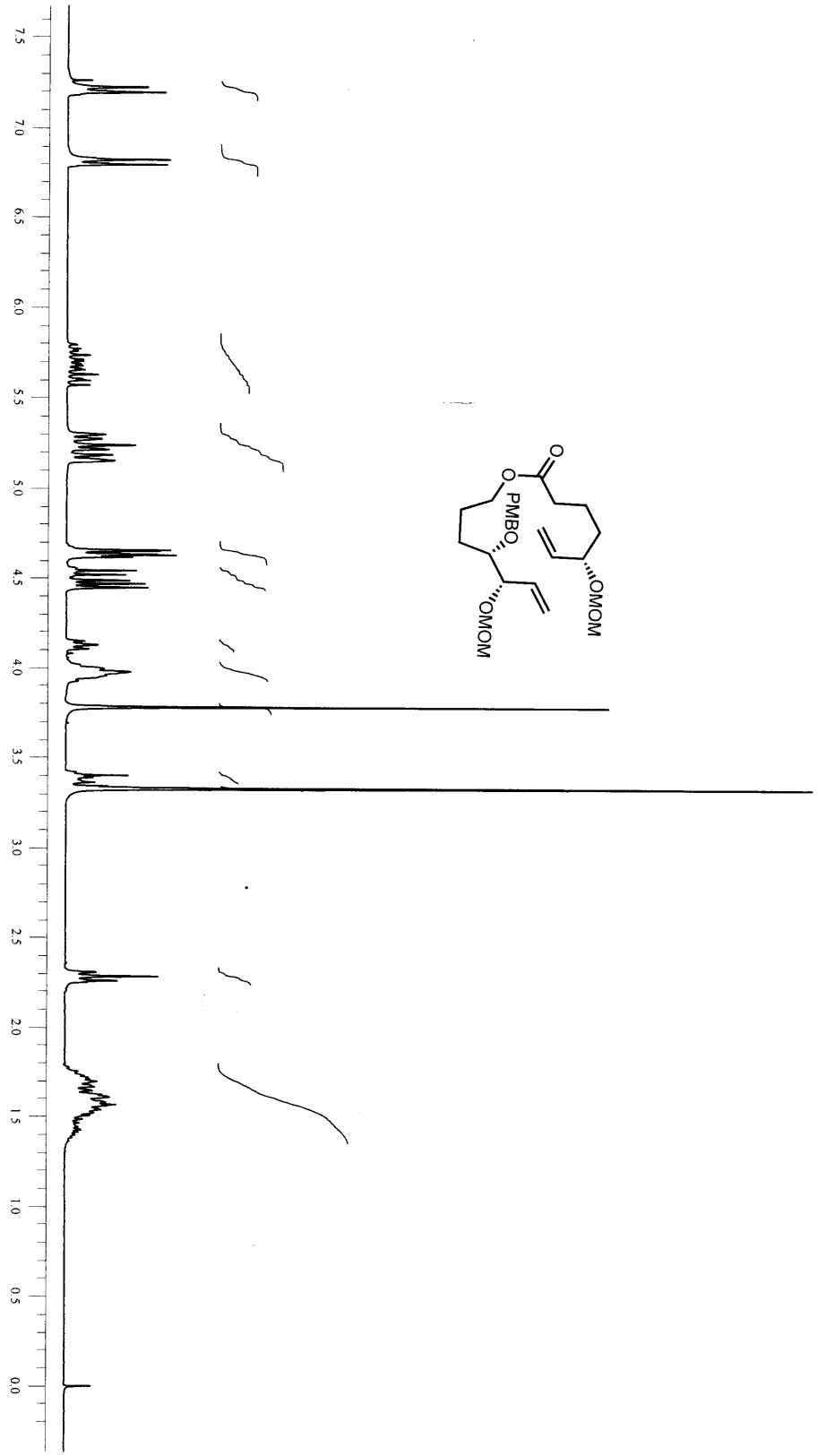
^{13}C NMR of Compound **26** ($CDCl_3$, 75 MHz)



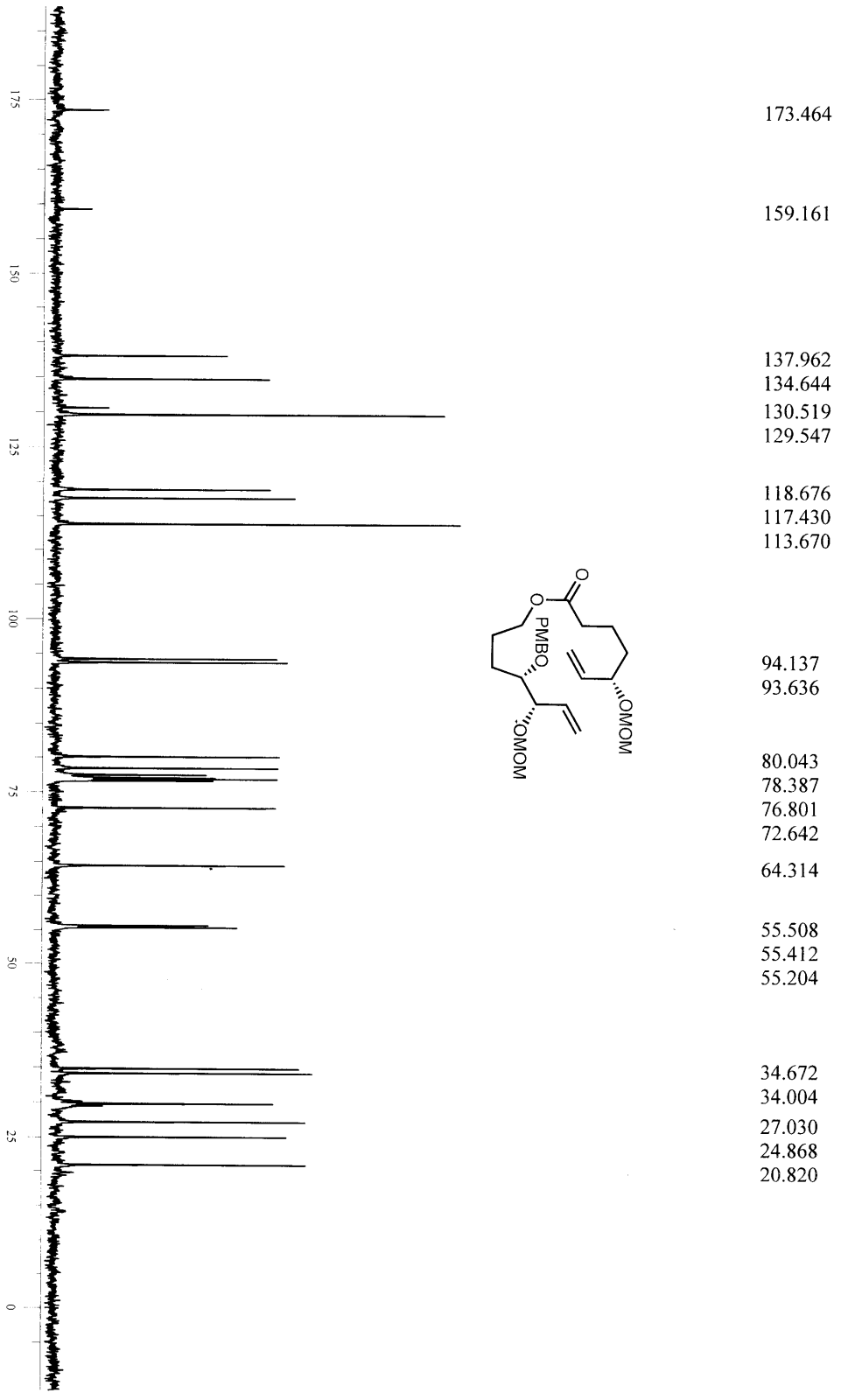
^{1}H NMR of Compound **7b** ($CDCl_3$, 400 MHz)



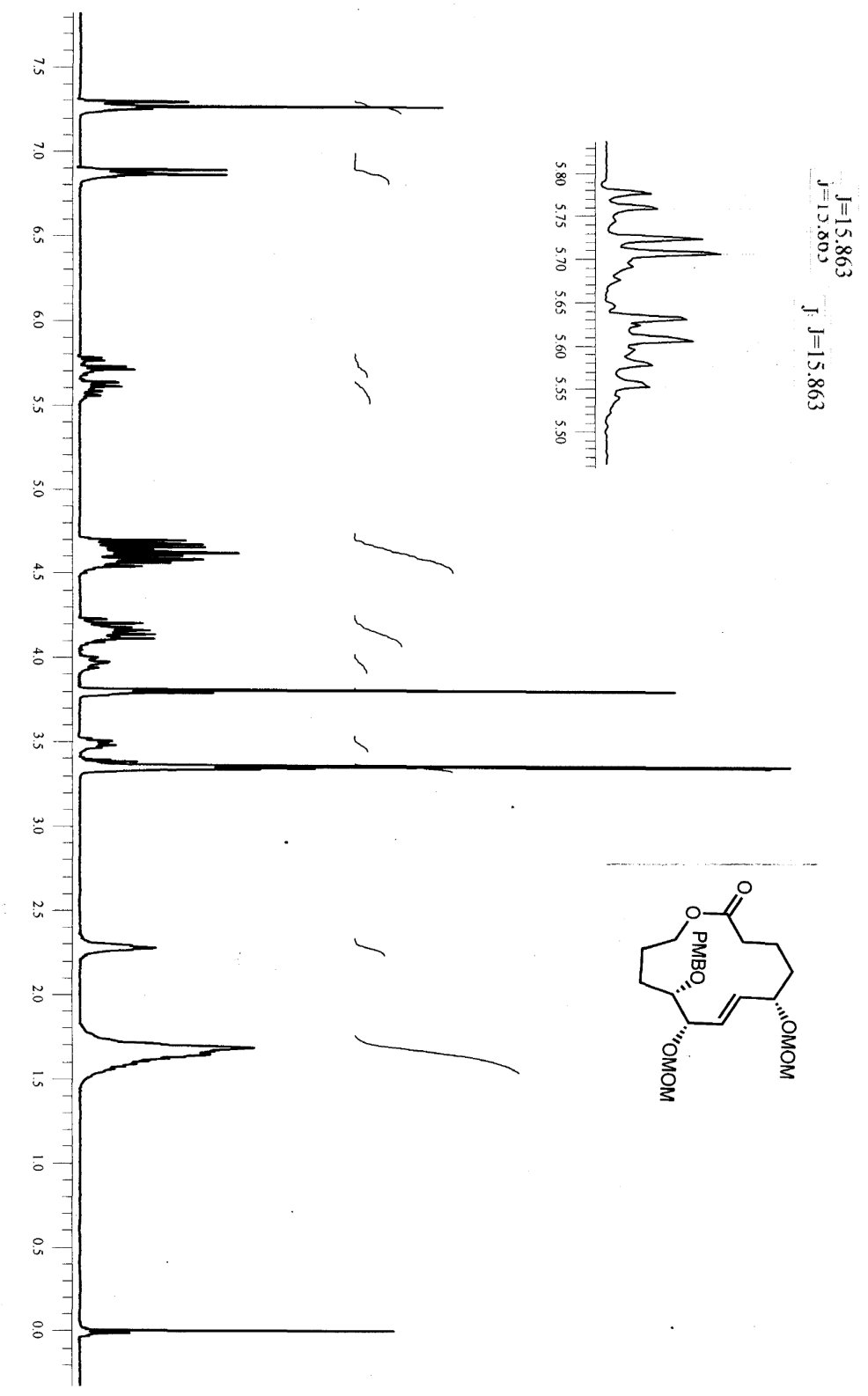
^{13}C NMR of Compound **7b** ($CDCl_3$, 75 MHz)



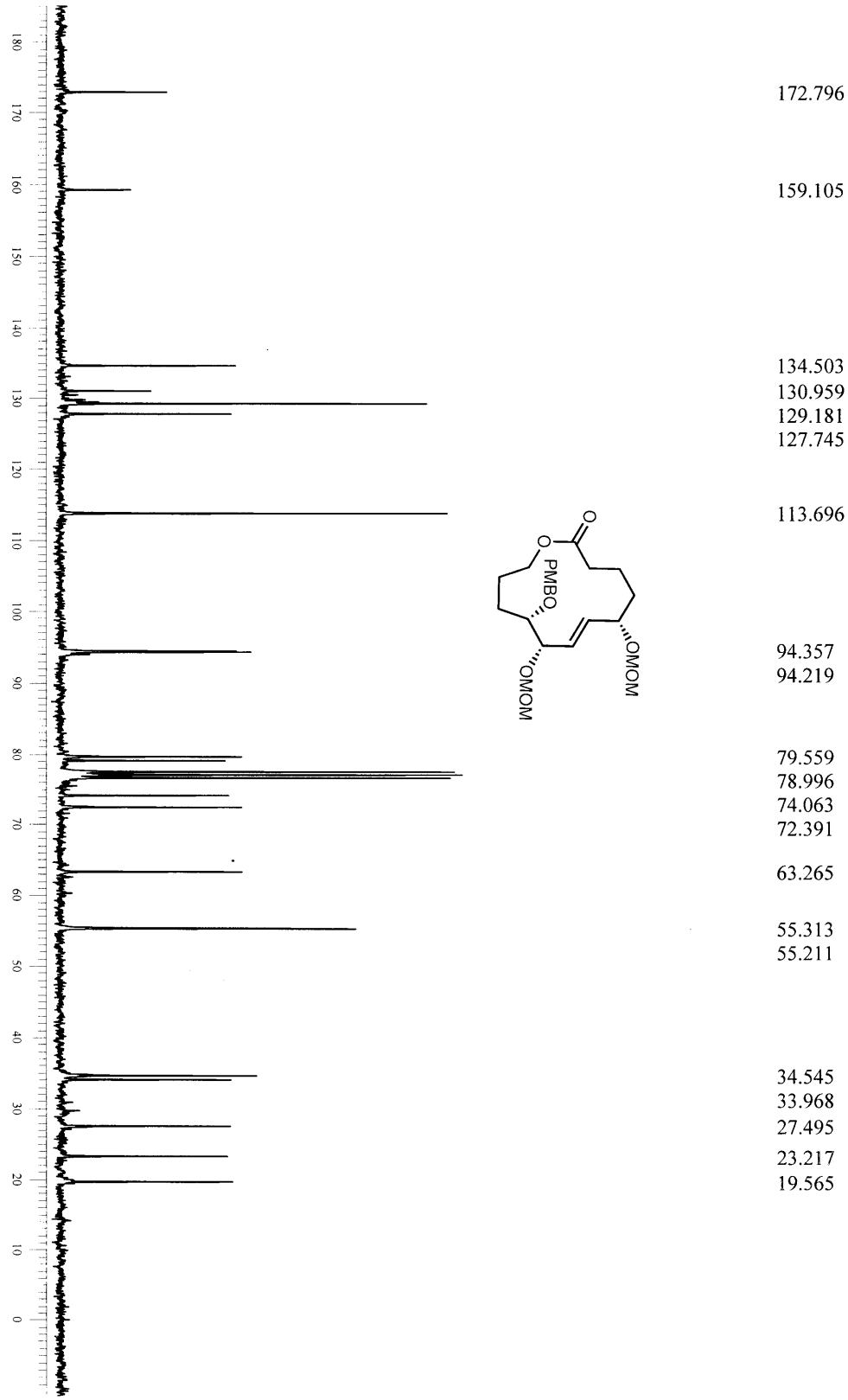
^{1}H NMR of Compound **27** ($CDCl_3$, 300 MHz)



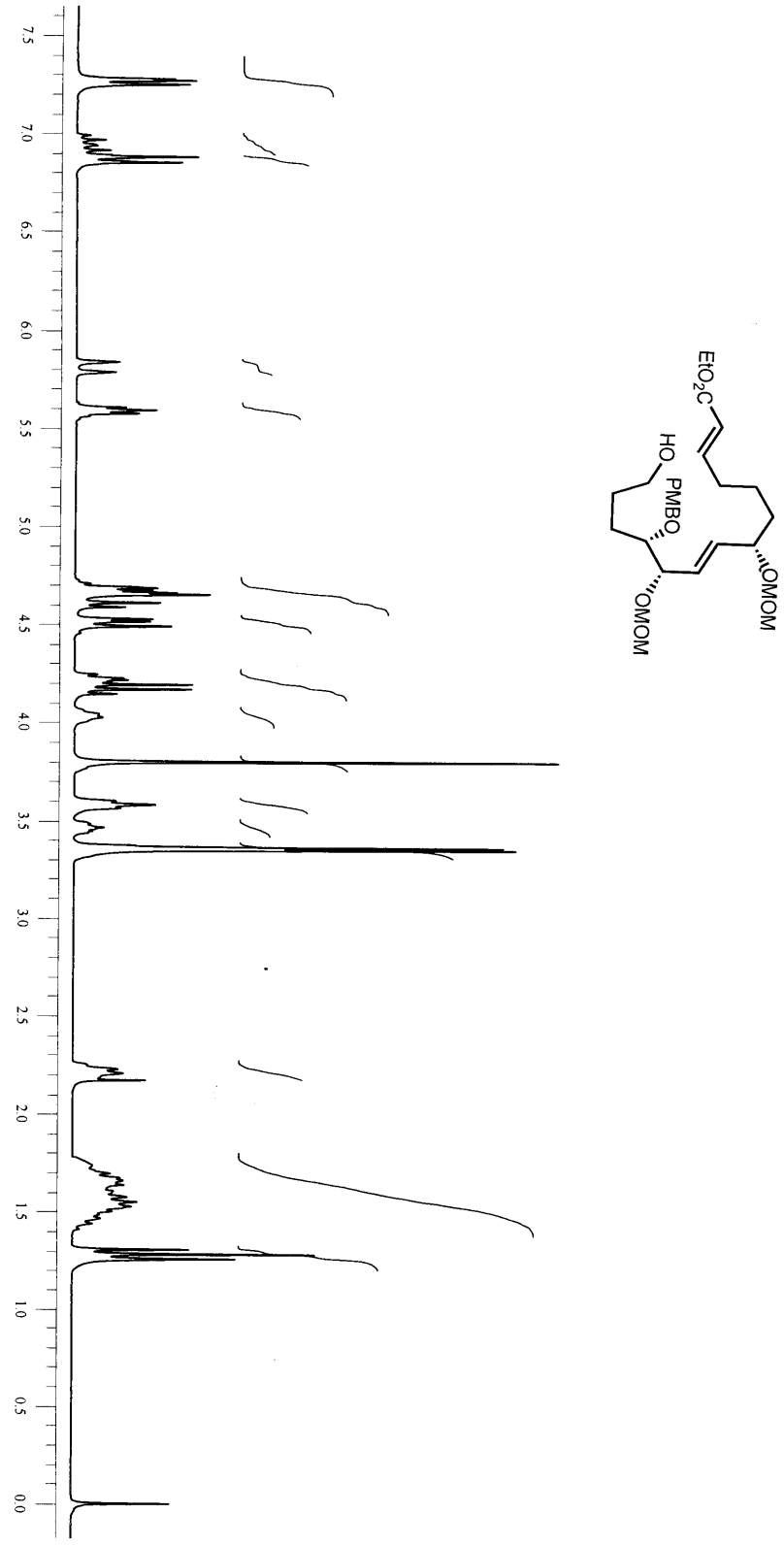
^{13}C NMR of Compound **27** ($CDCl_3$, 75 MHz)



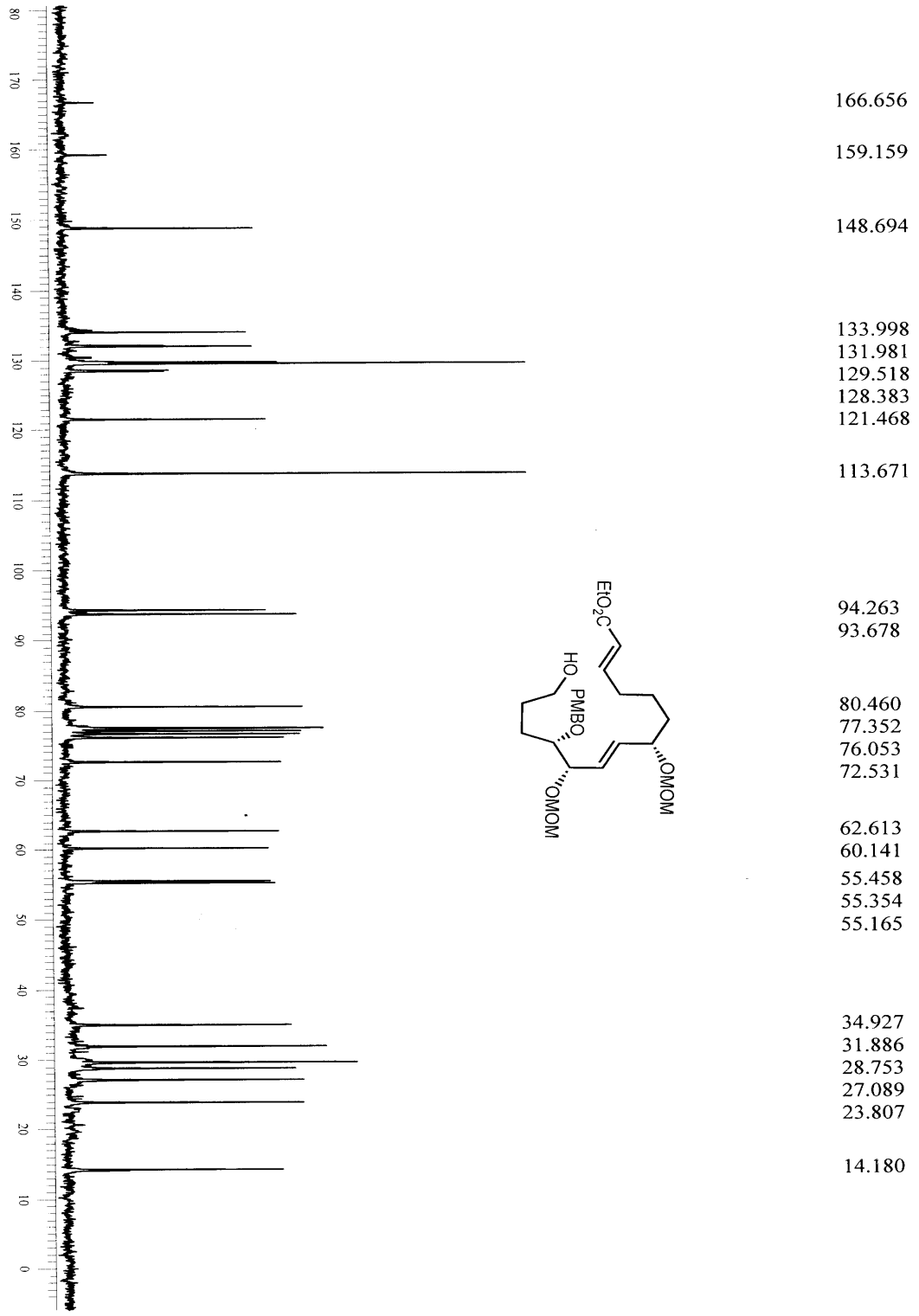
^{1}H NMR of Compound **28** ($CDCl_3$, 500 MHz)



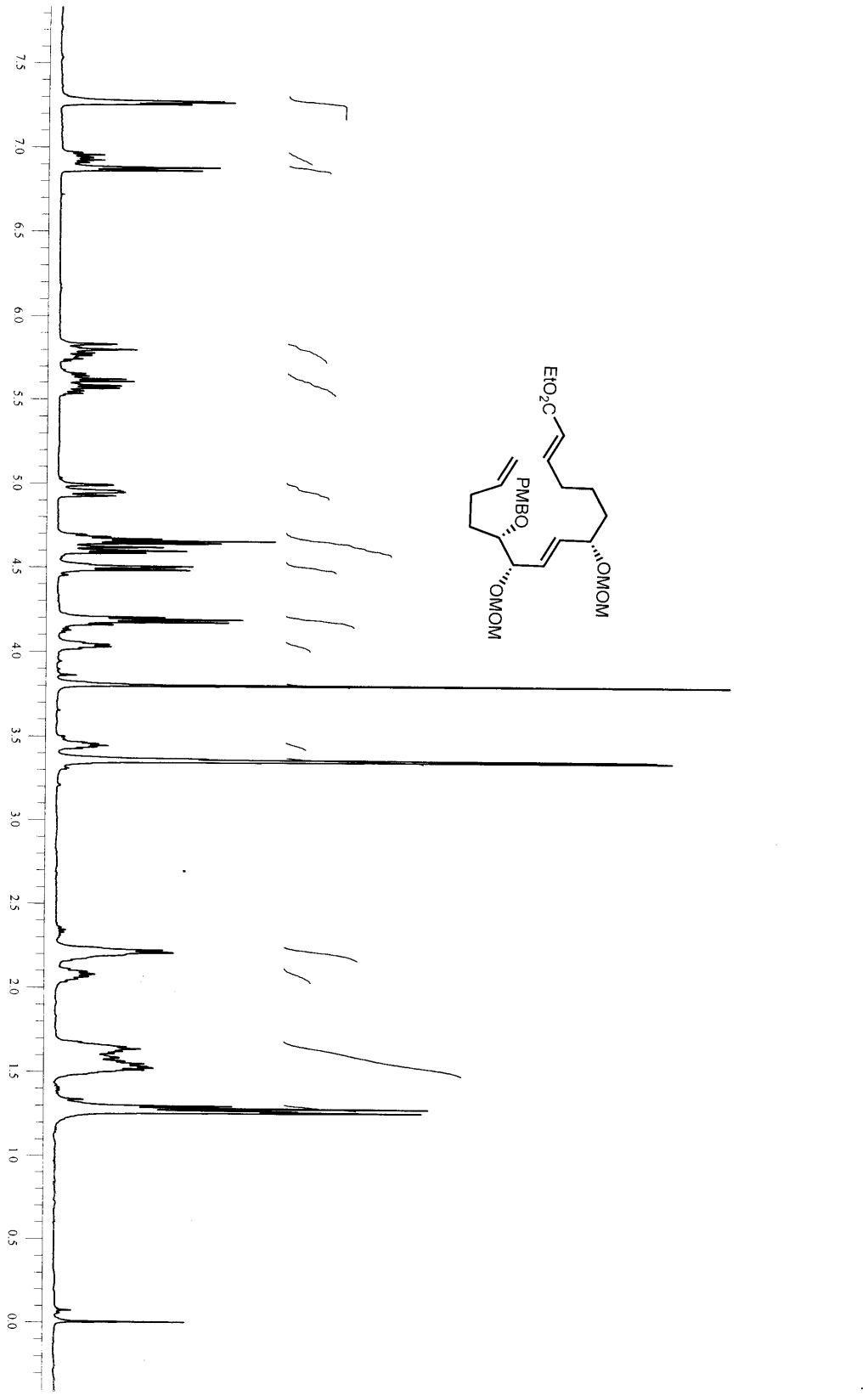
^{13}C NMR of Compound **28** ($CDCl_3$, 75 MHz)



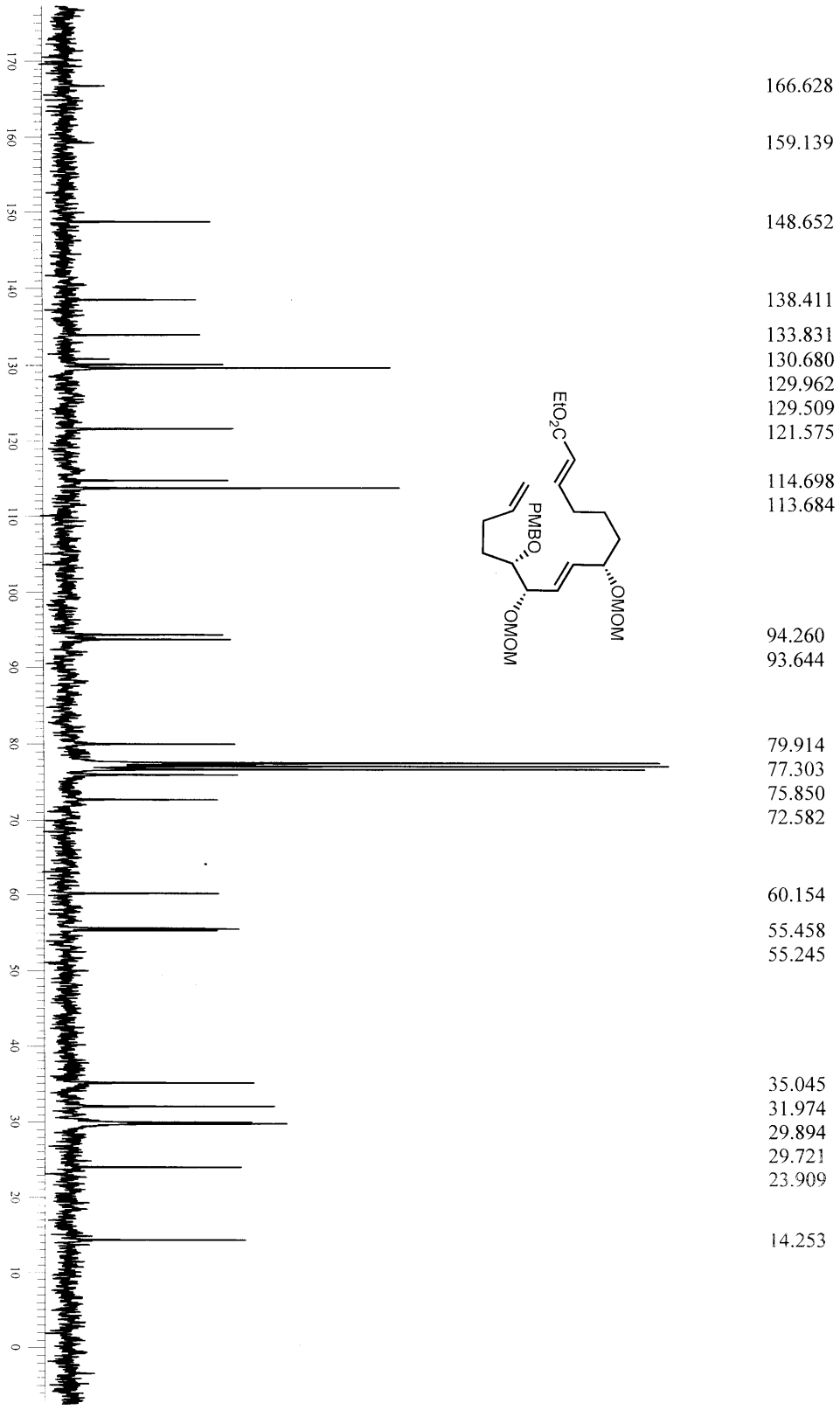
^{1}H NMR of Compound **30** ($CDCl_3$, 300 MHz)



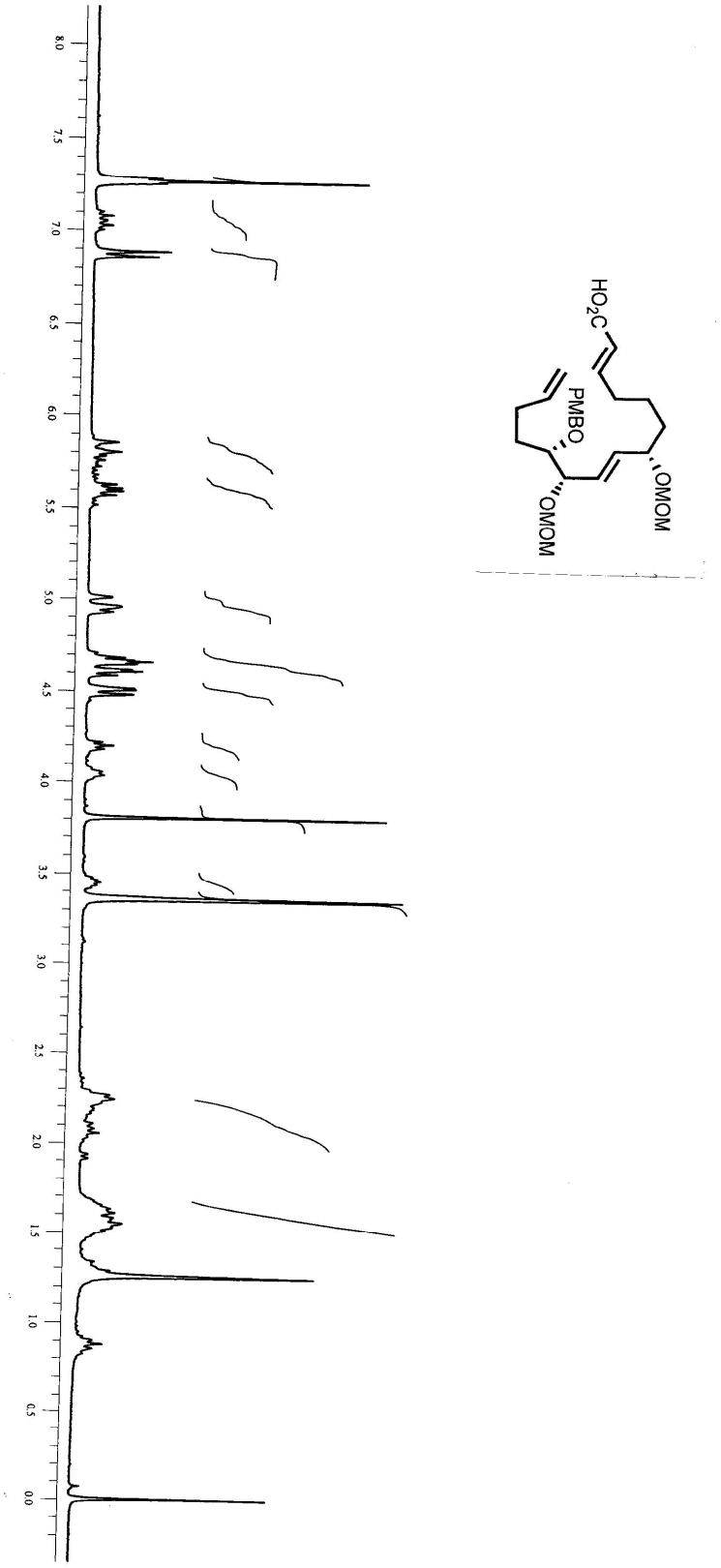
^{13}C NMR of Compound **30** ($CDCl_3$, 75 MHz)



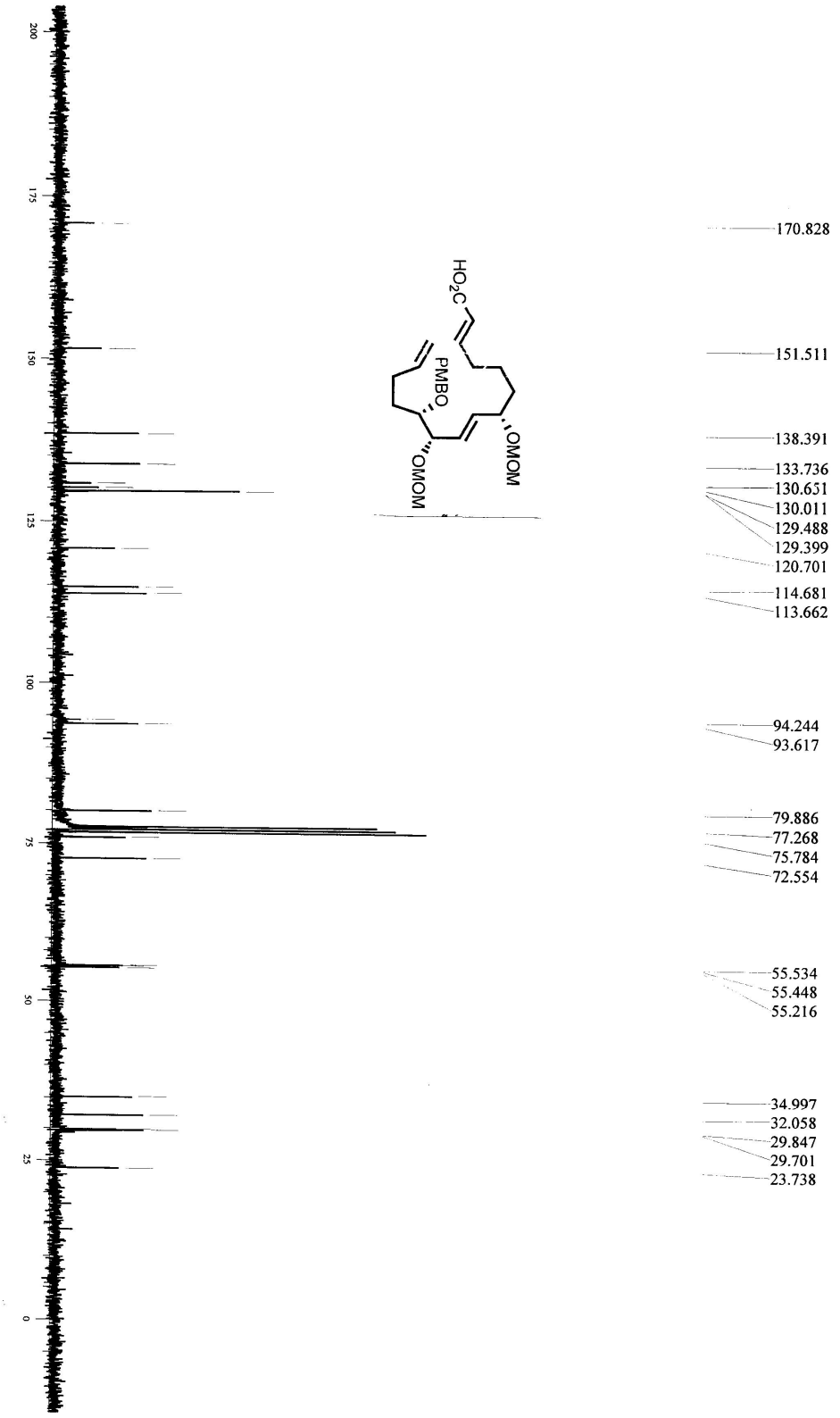
^{1}H NMR of Compound **31** ($CDCl_3$, 500 MHz)



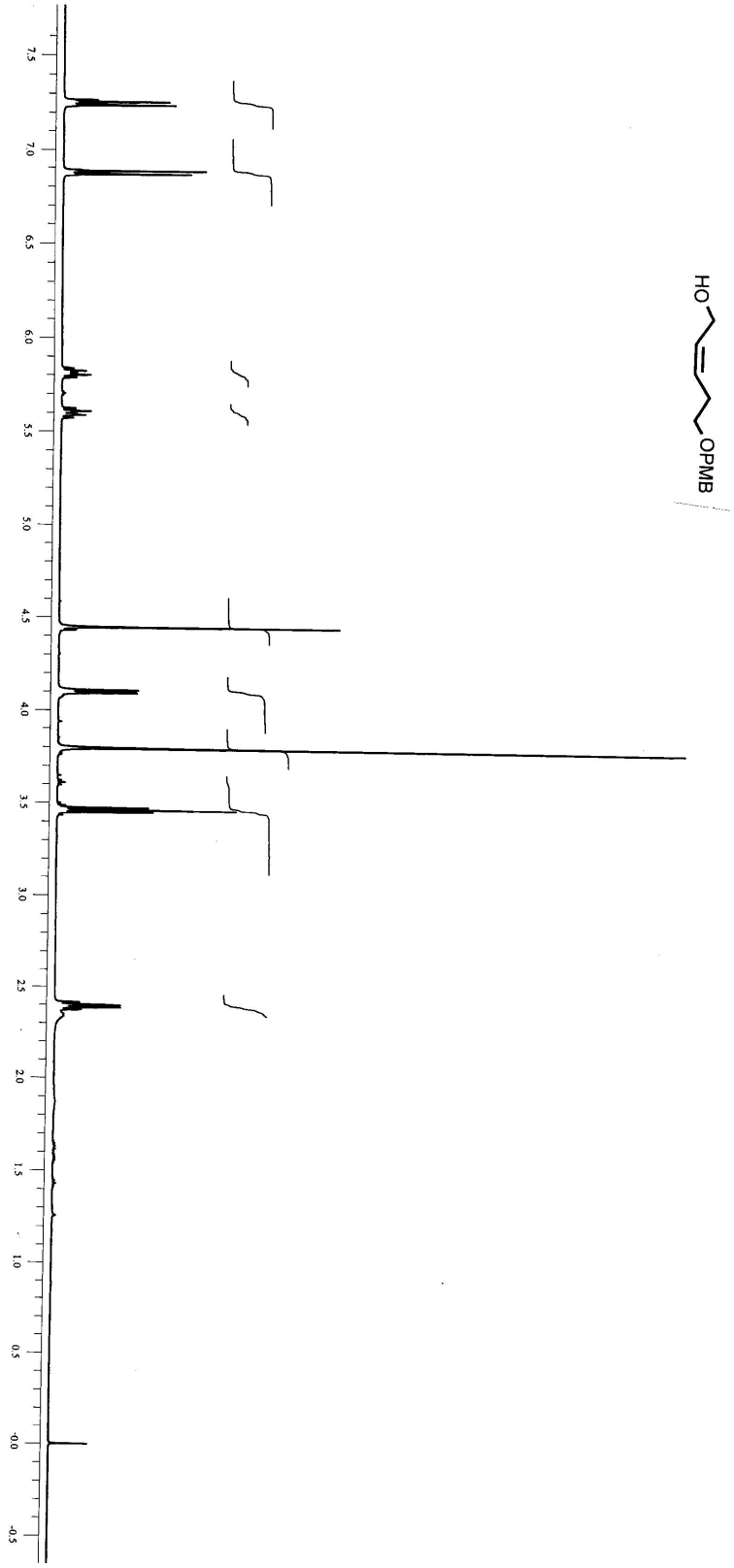
^{13}C NMR of Compound **31** ($CDCl_3$, 75 MHz)



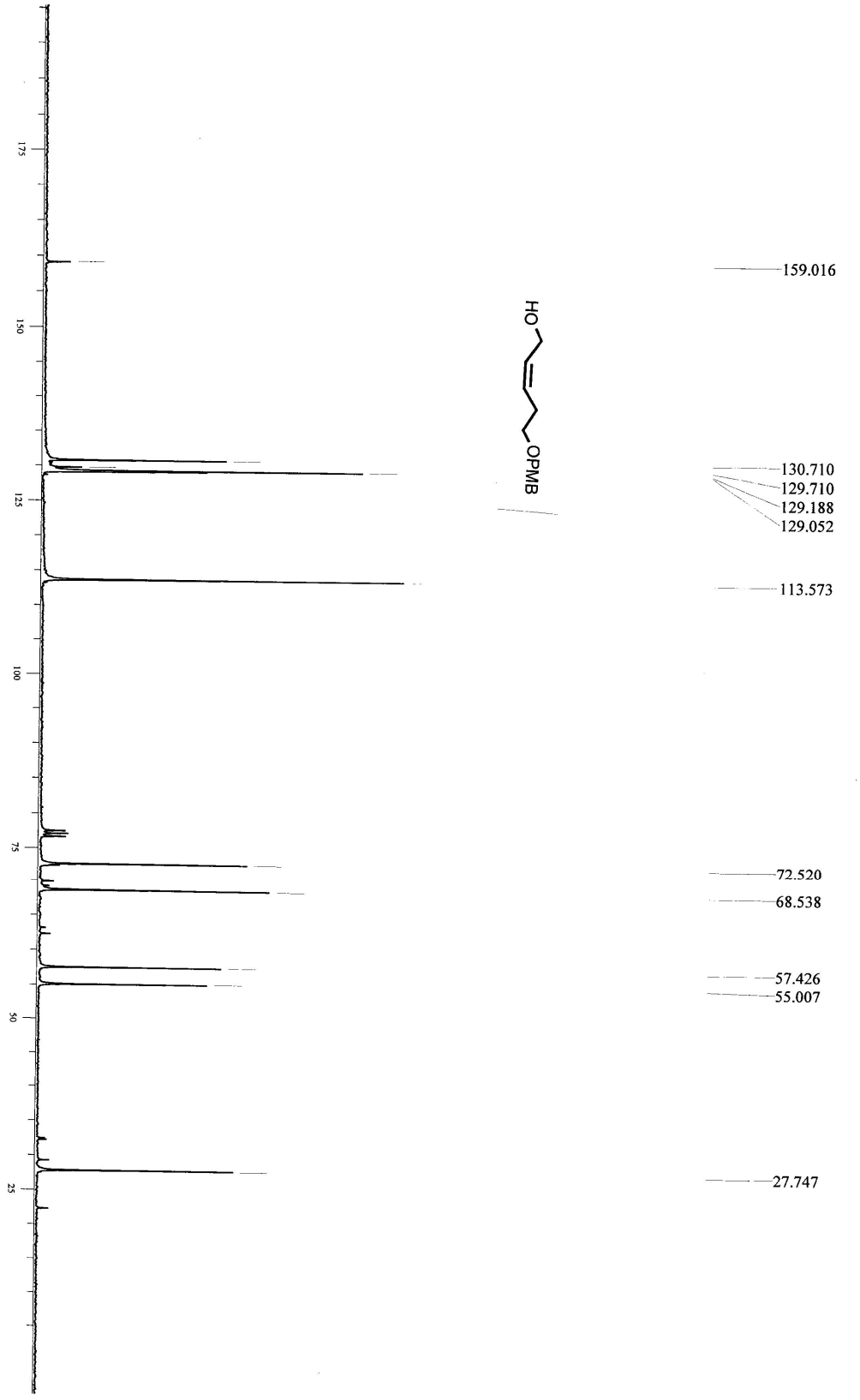
^{1}H NMR of Compound **3** ($CDCl_3$, 300 MHz)



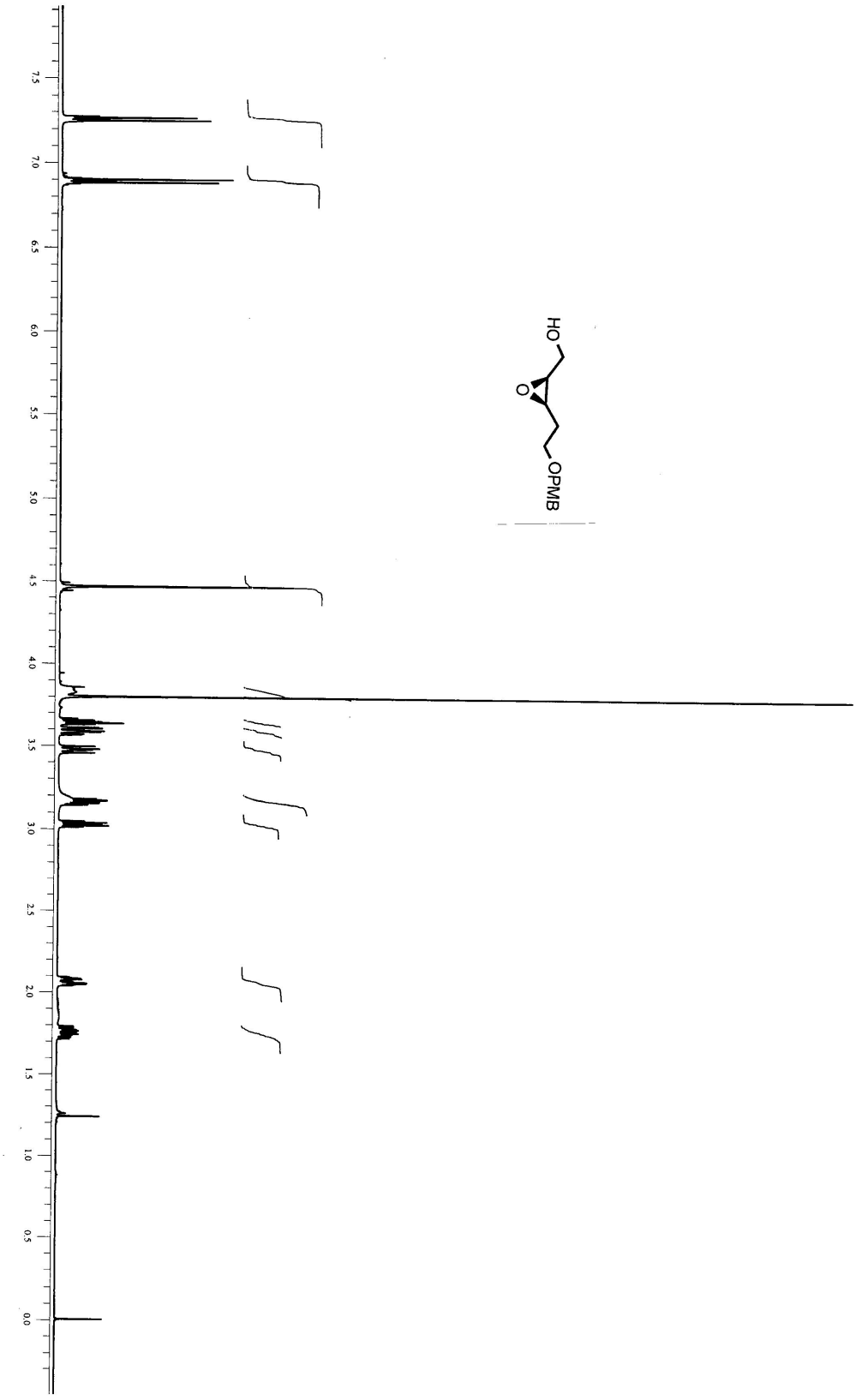
^{13}C NMR of Compound **3** ($CDCl_3$, 75 MHz)



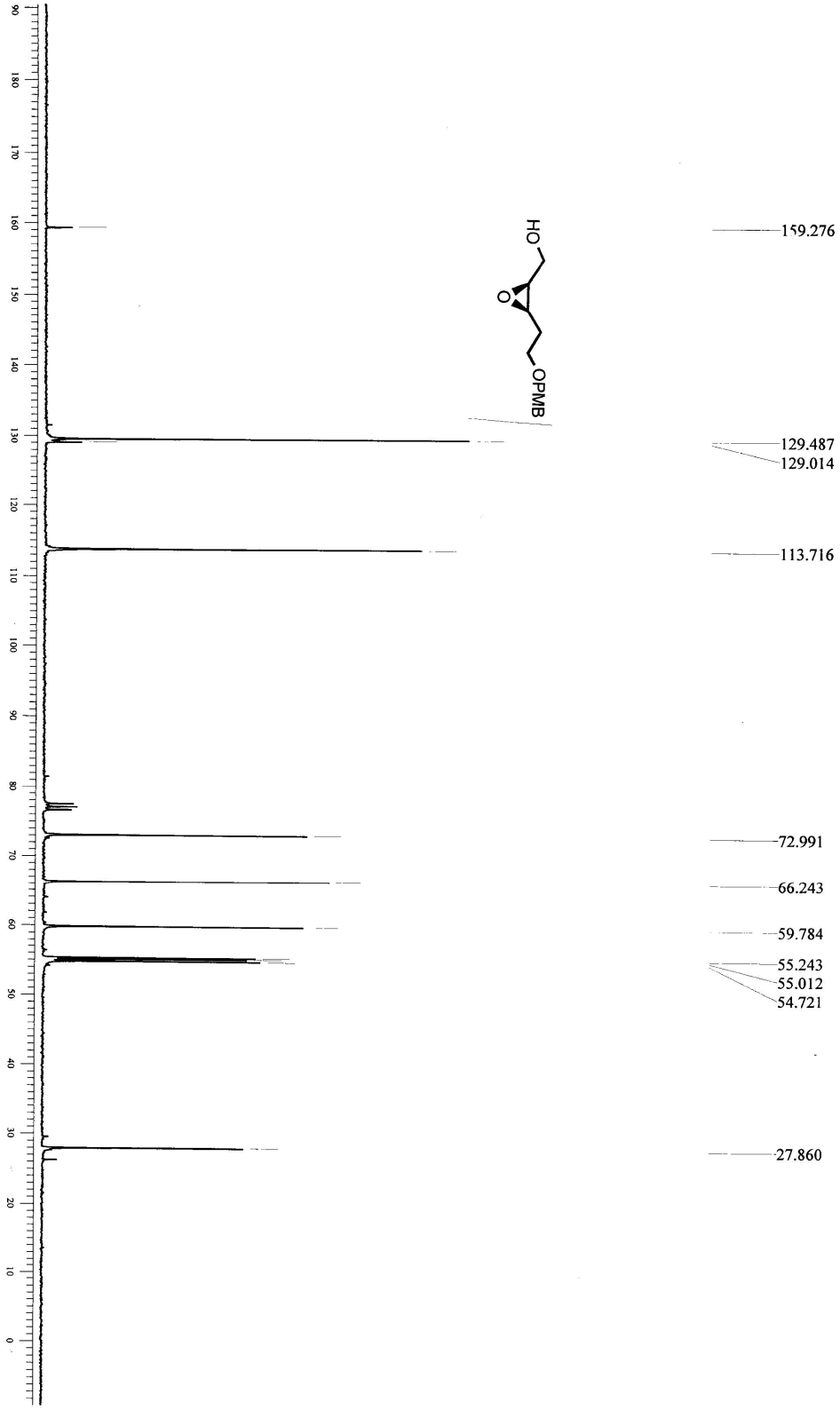
^{1}H NMR of Compound **34** ($CDCl_3$, 500 MHz)



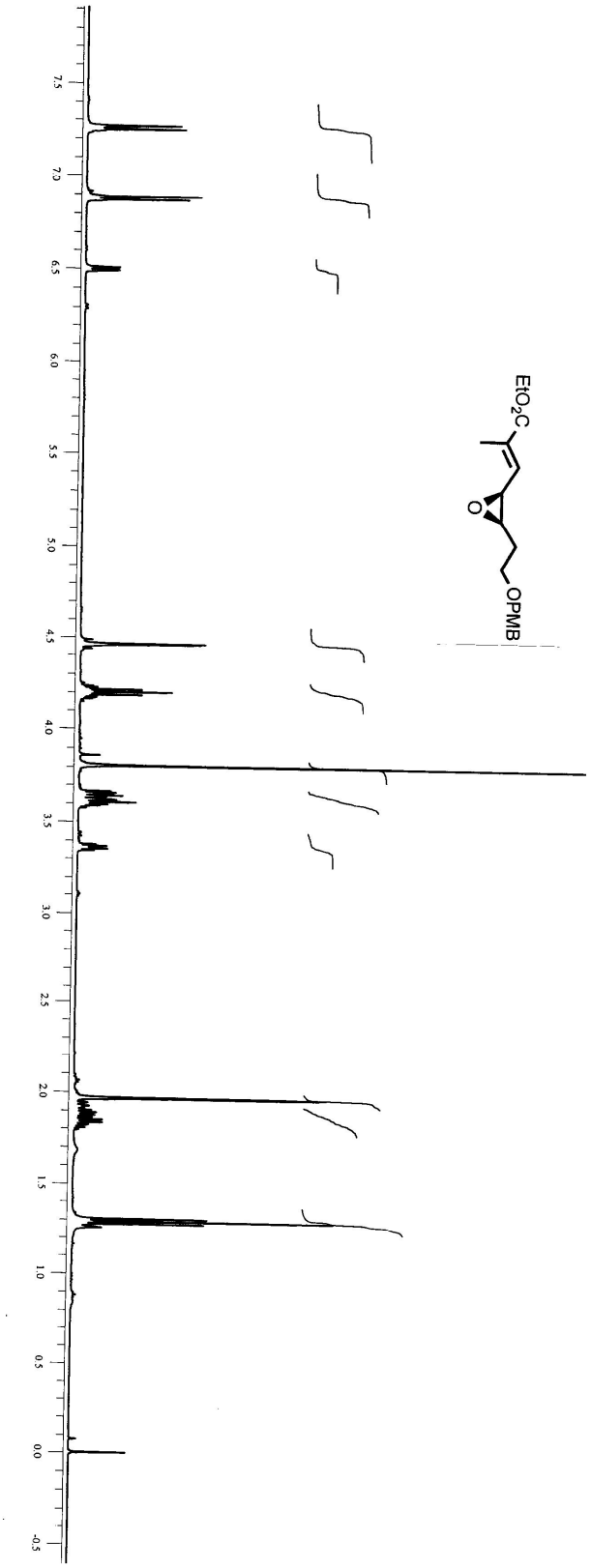
^{13}C NMR of Compound **34** ($CDCl_3$, 75 MHz)



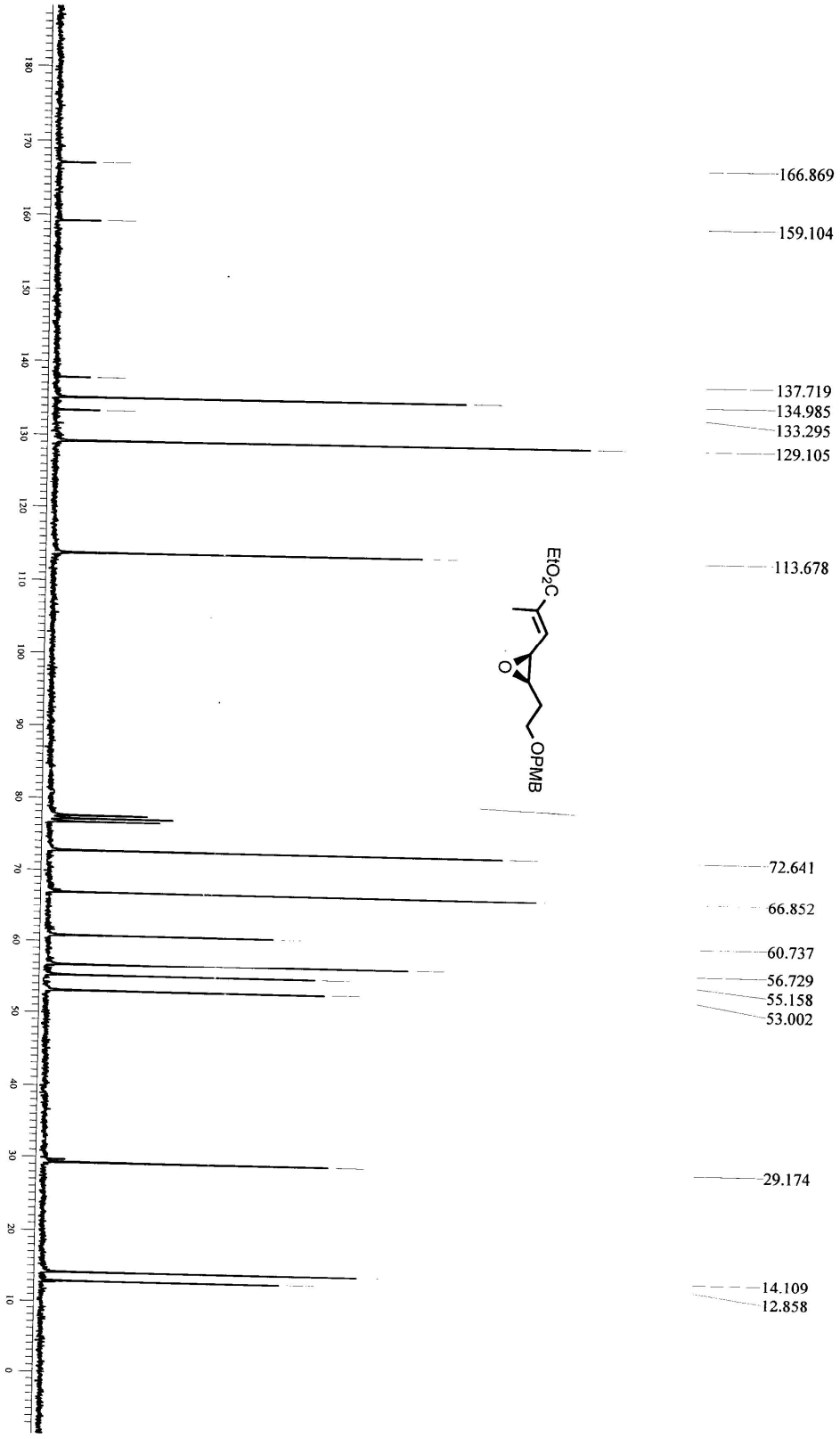
^{1}H NMR of Compound **35** ($CDCl_3$, 500 MHz)



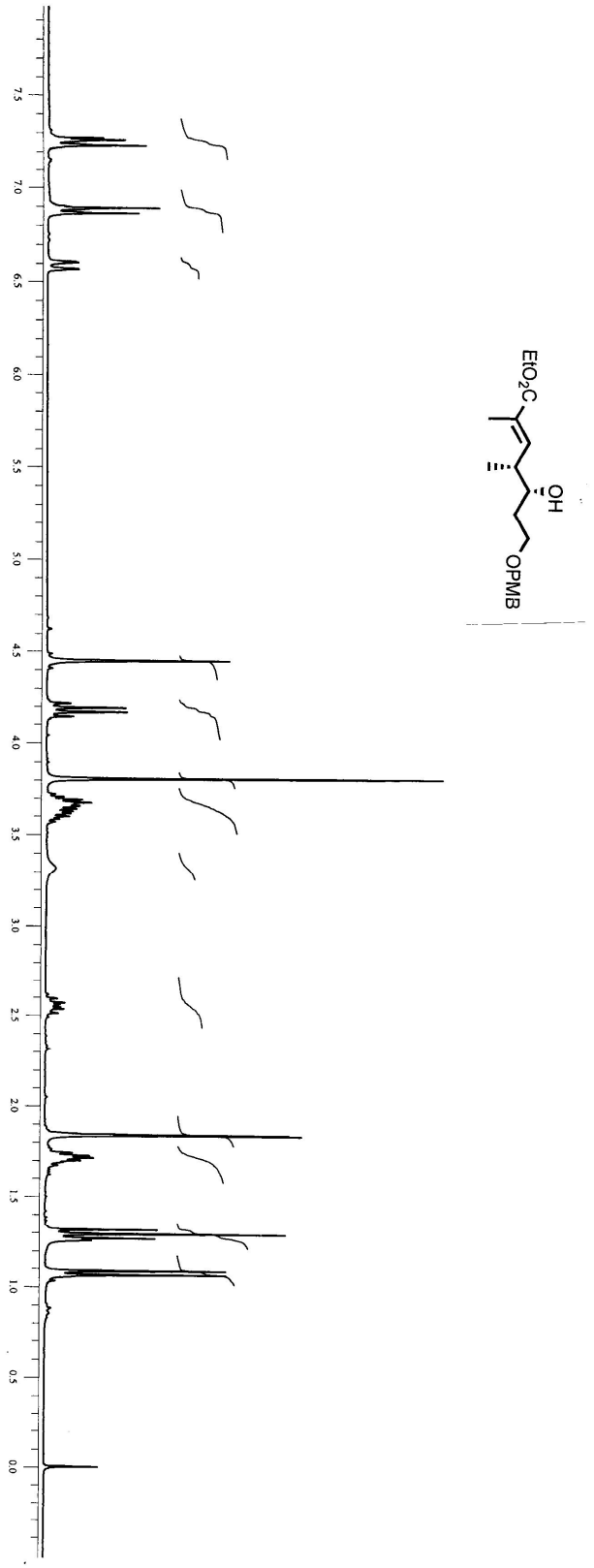
^{13}C NMR of Compound **35** ($CDCl_3$, 75 MHz)



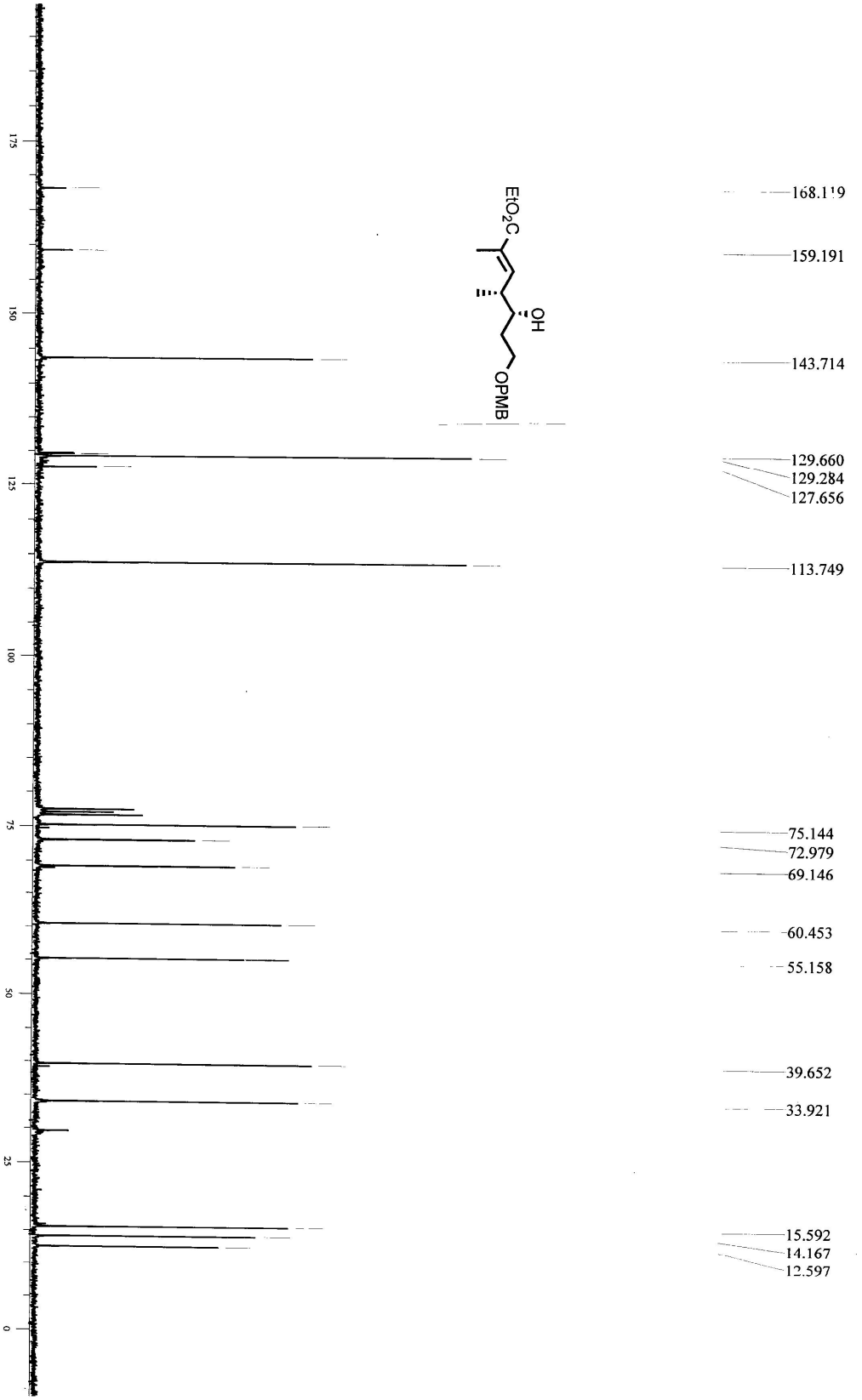
^{1}H NMR of Compound **36** ($CDCl_3$, 500 MHz)



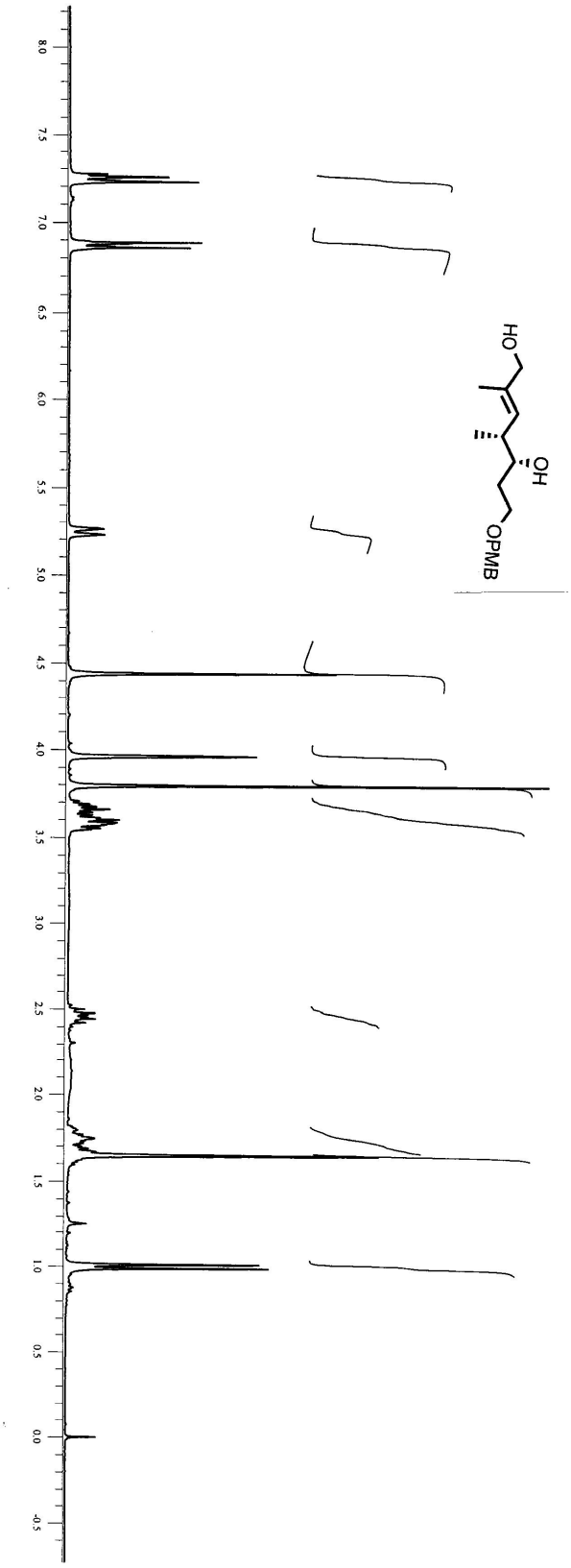
^{13}C NMR of Compound **36** ($CDCl_3$, 75 MHz)



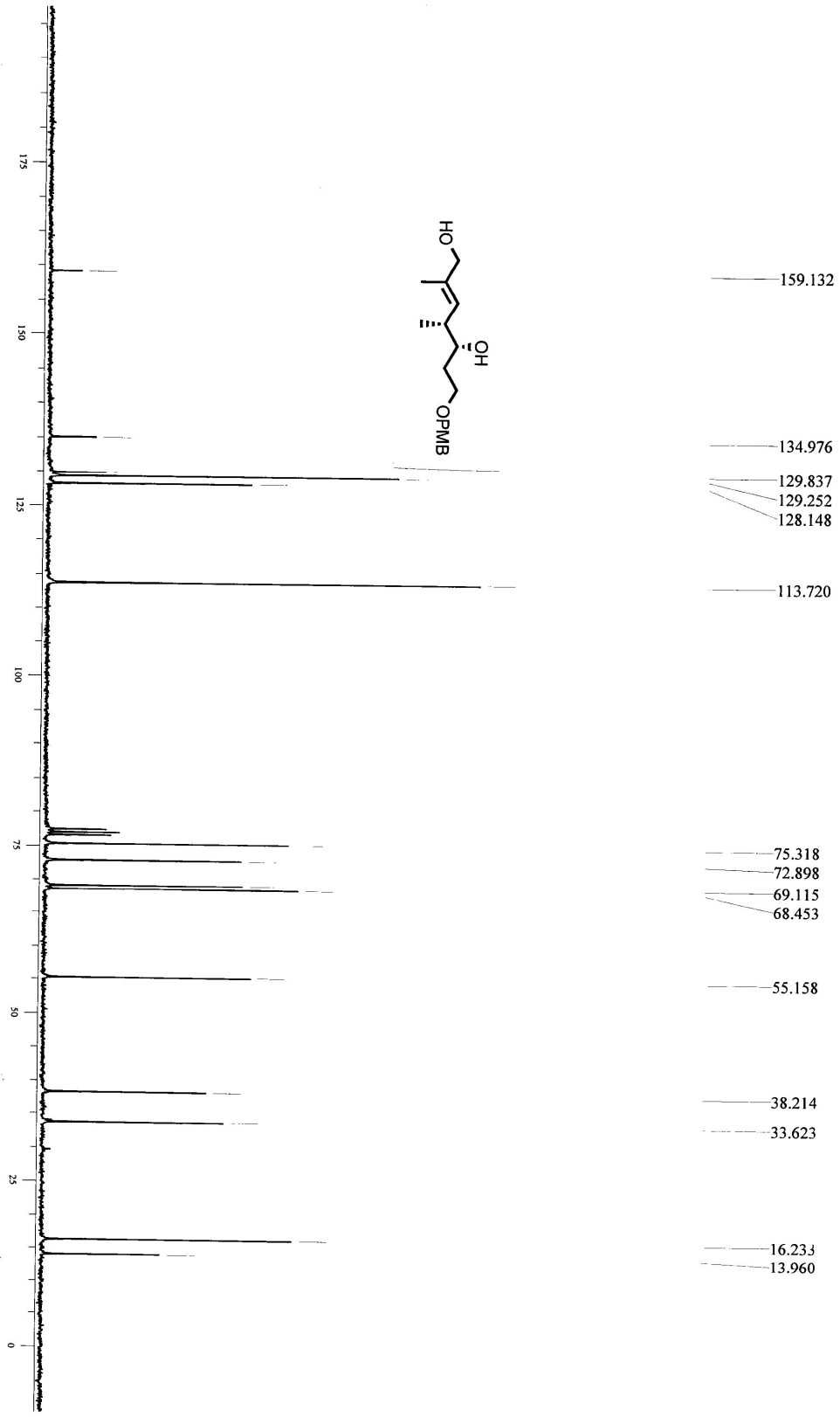
^{1}H NMR of Compound **37** ($CDCl_3$, 300 MHz)



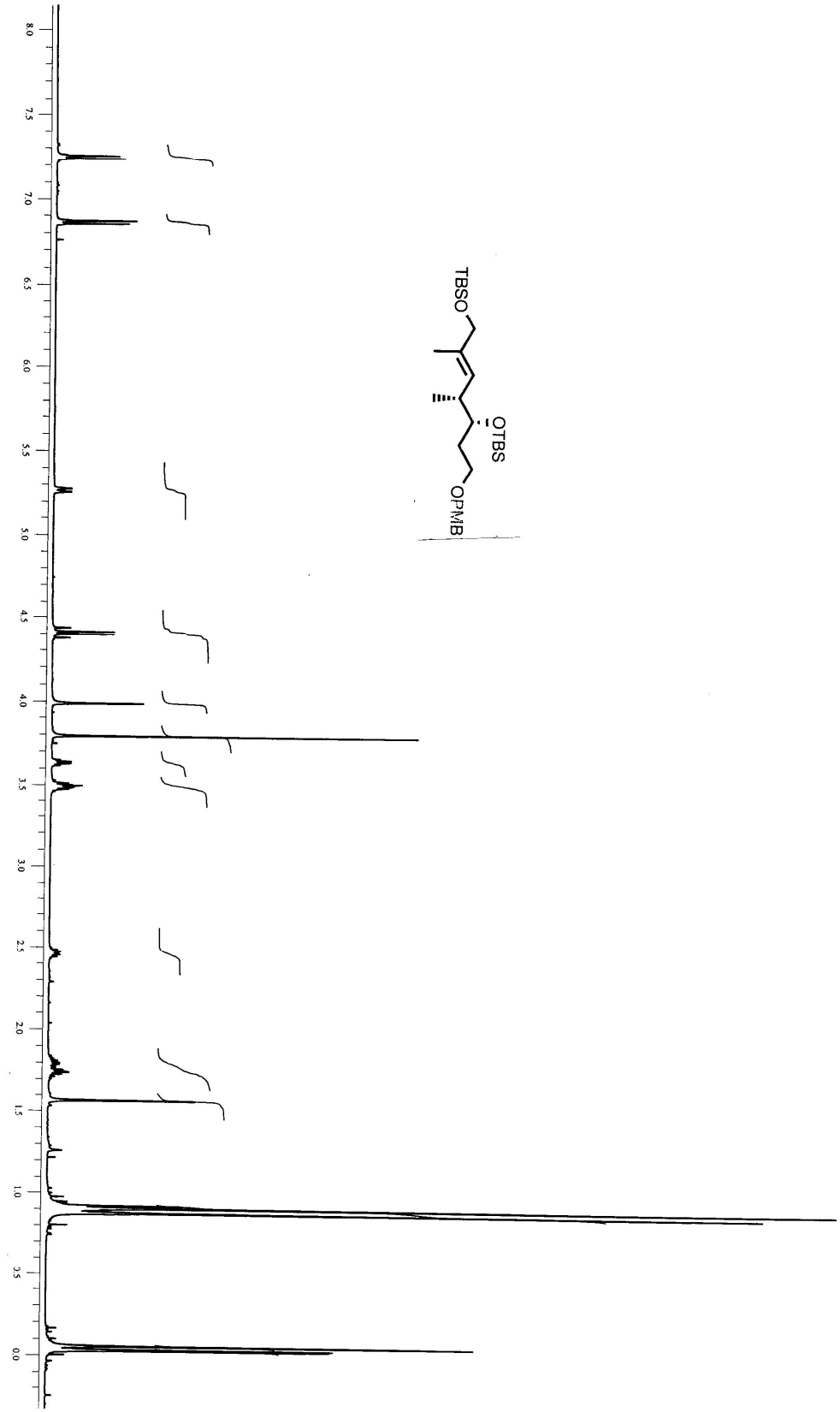
^{13}C NMR of Compound **37** ($CDCl_3$, 75 MHz)



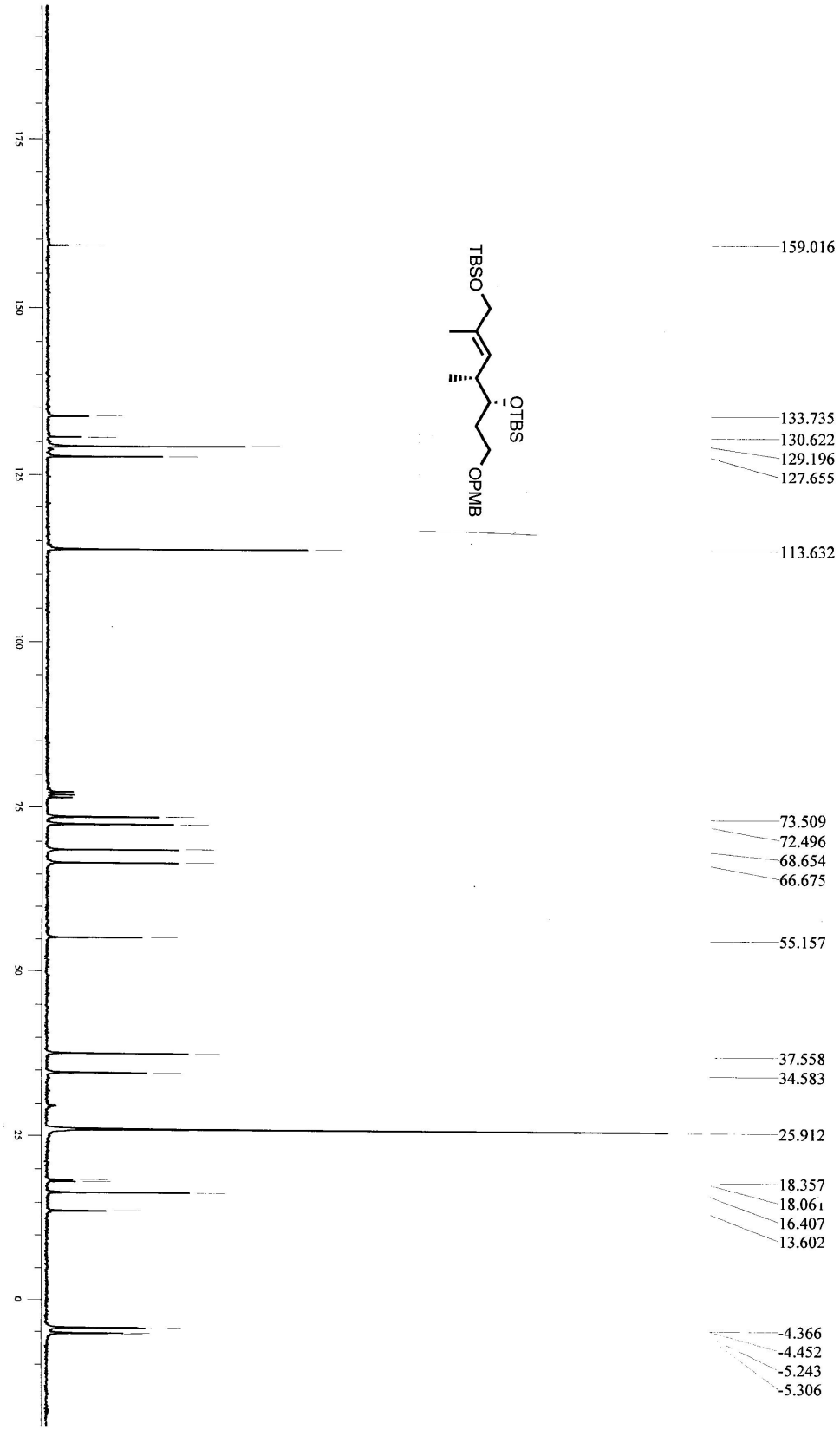
^{1}H NMR of Compound **38** ($CDCl_3$, 300 MHz)



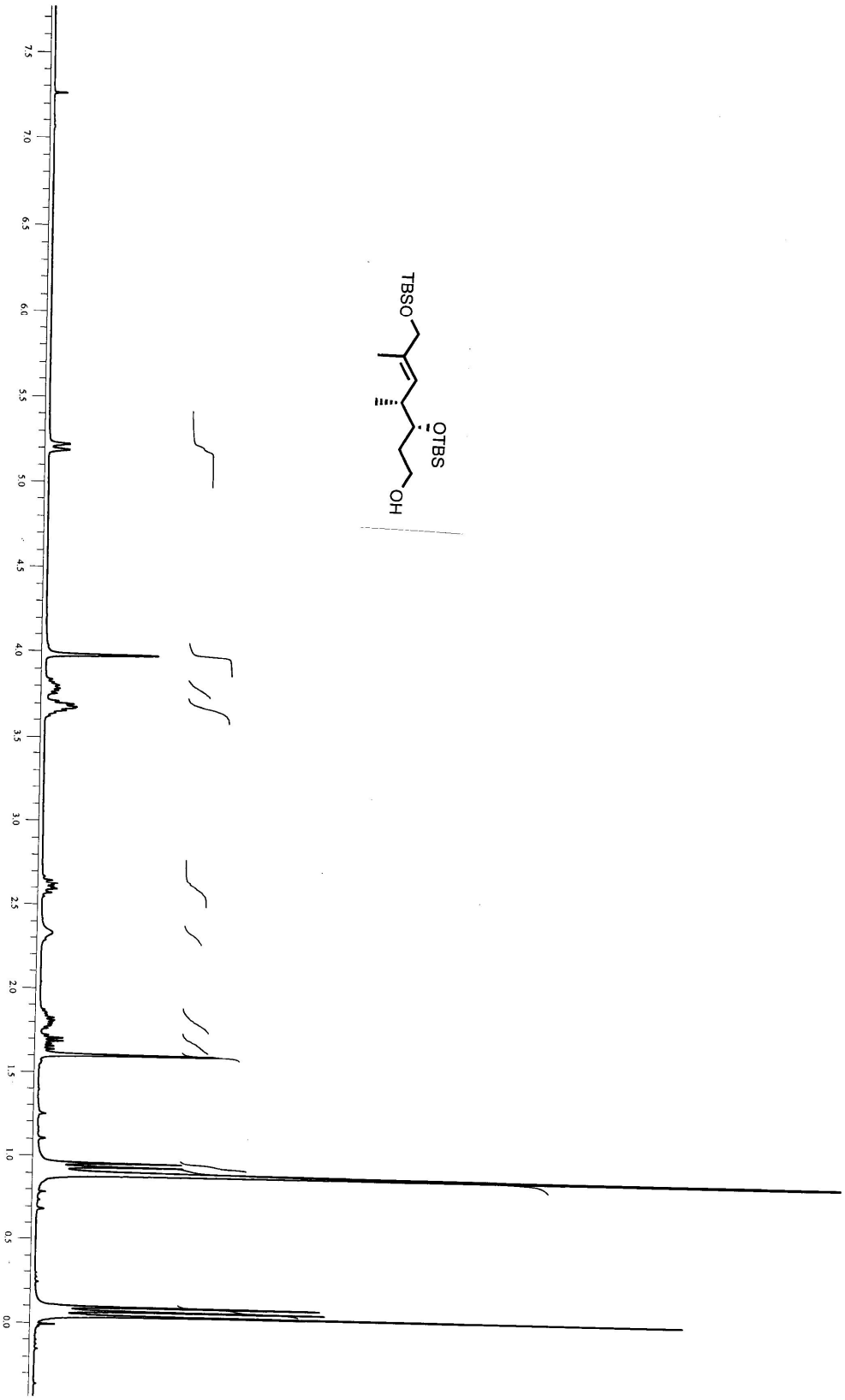
^{13}C NMR of Compound **38** ($CDCl_3$, 75 MHz)



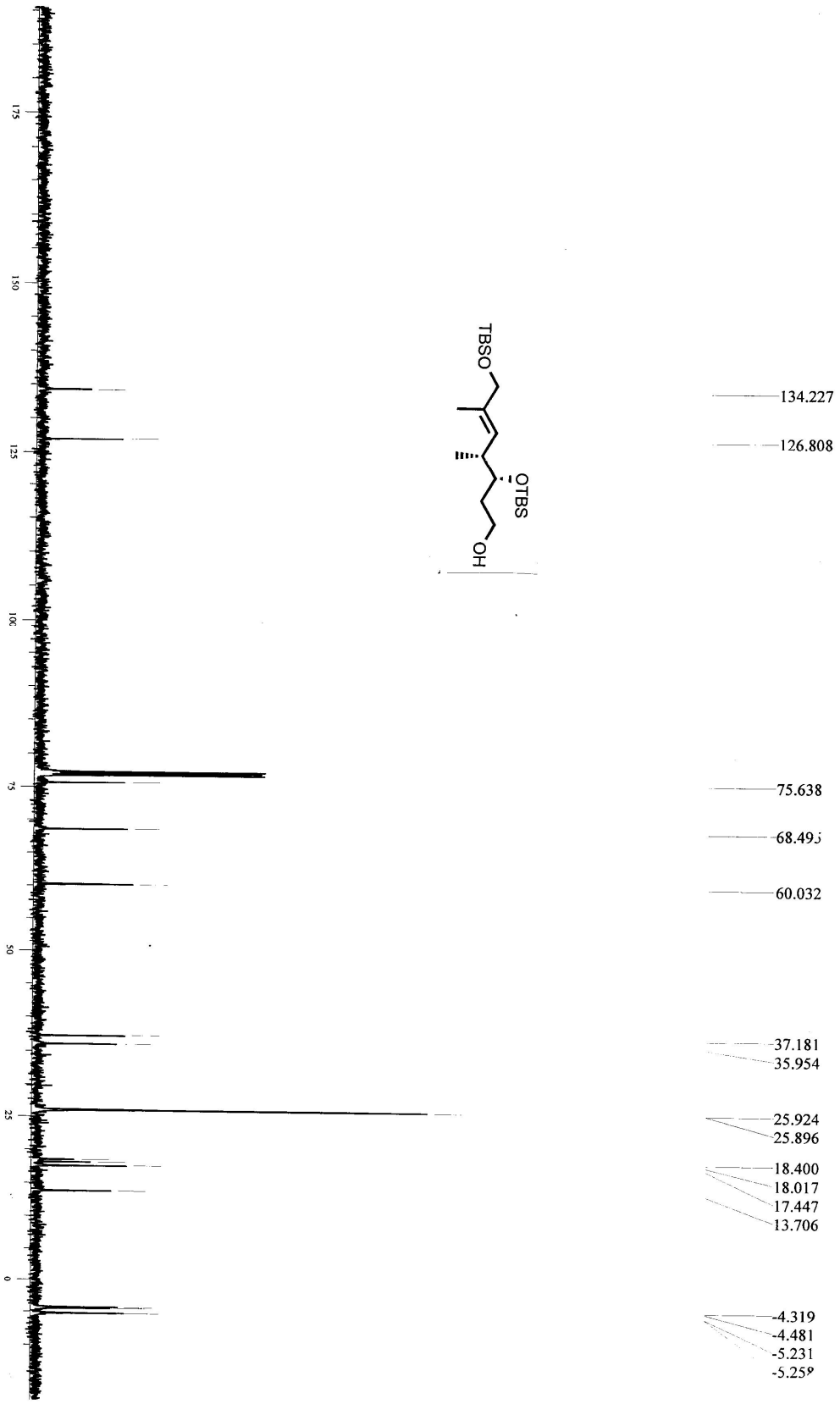
^{1}H NMR of Compound **39** ($CDCl_3$, 300 MHz)



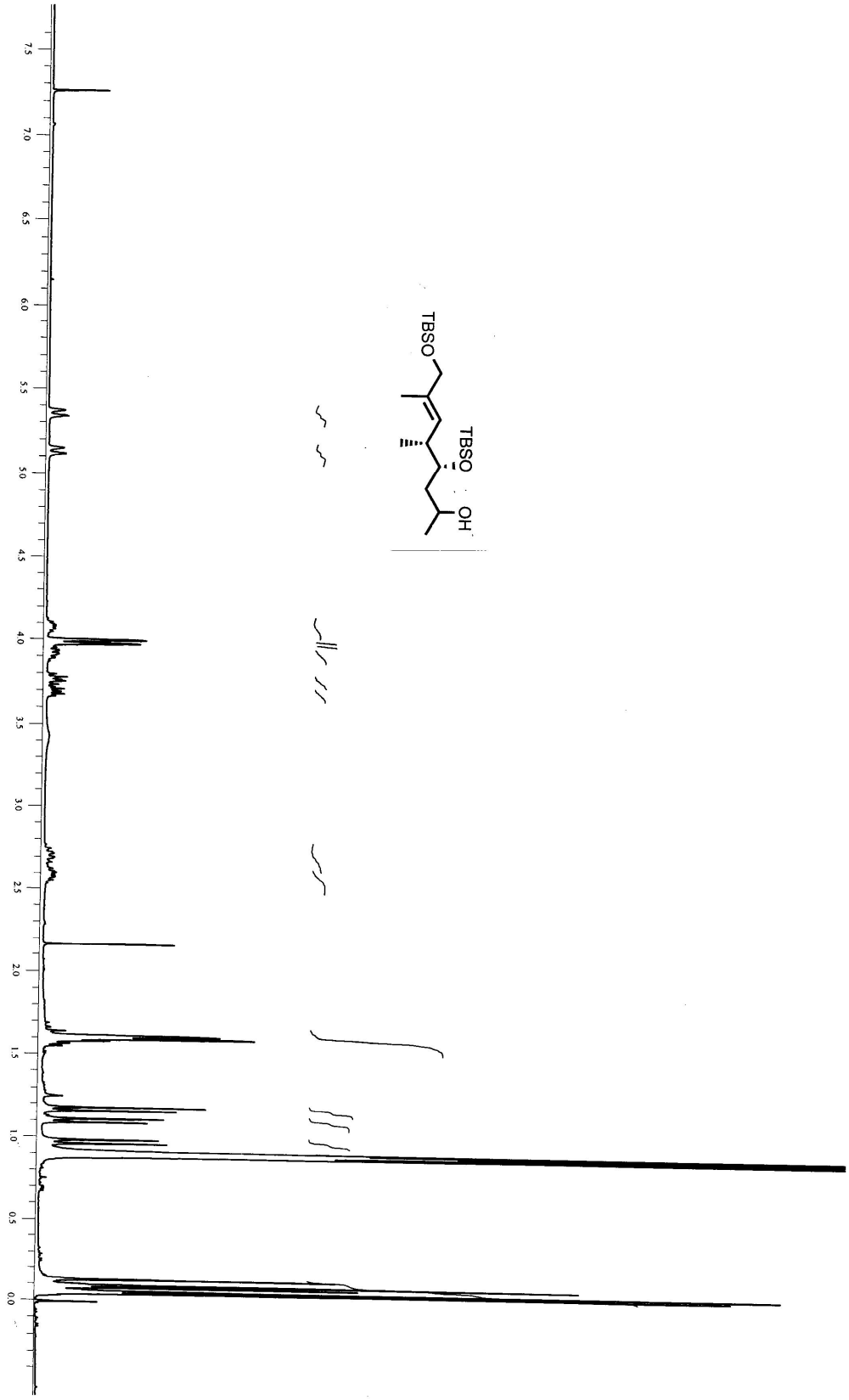
^{13}C NMR of Compound **39** ($CDCl_3$, 75 MHz)



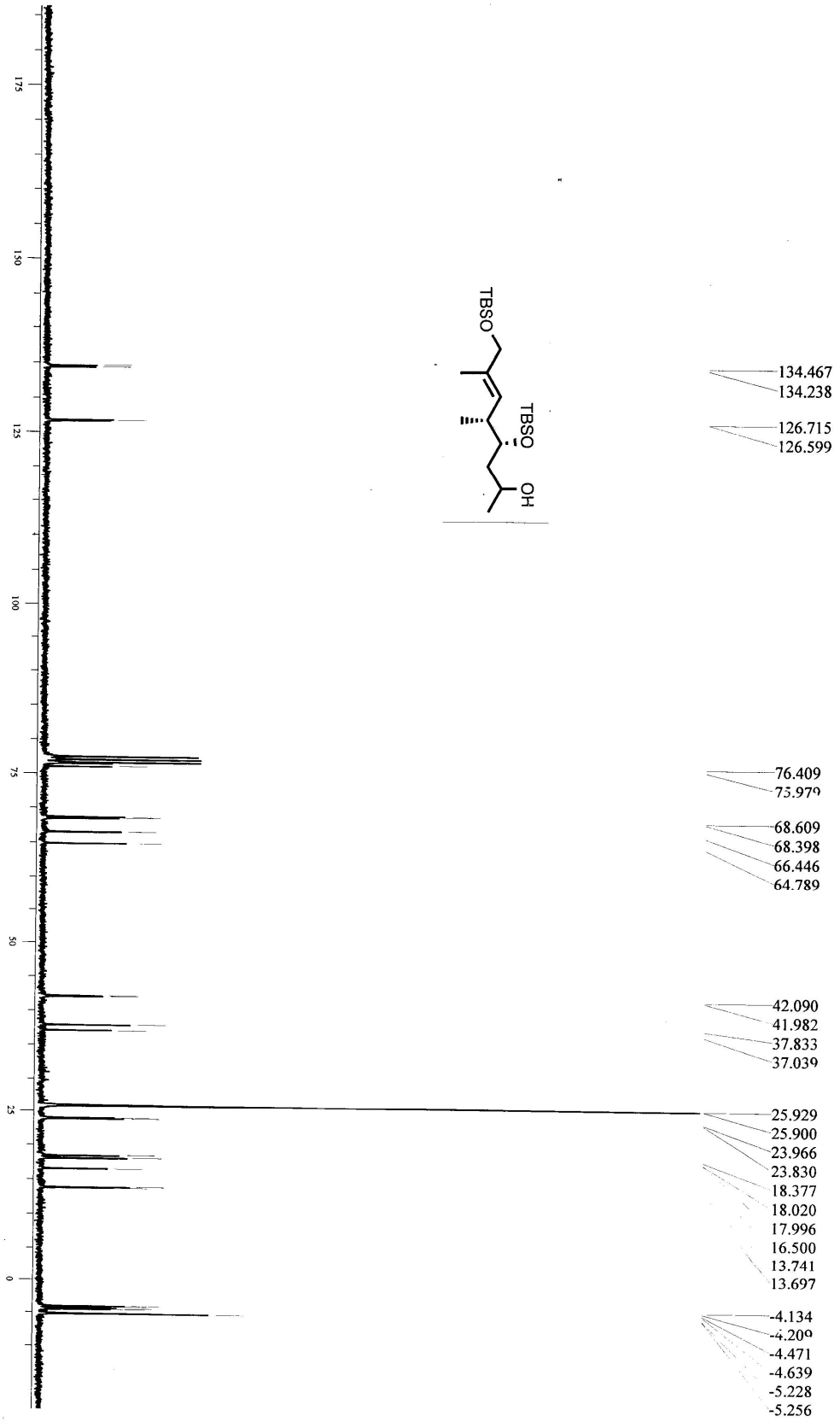
^{1}H NMR of Compound **40** ($CDCl_3$, 300 MHz)



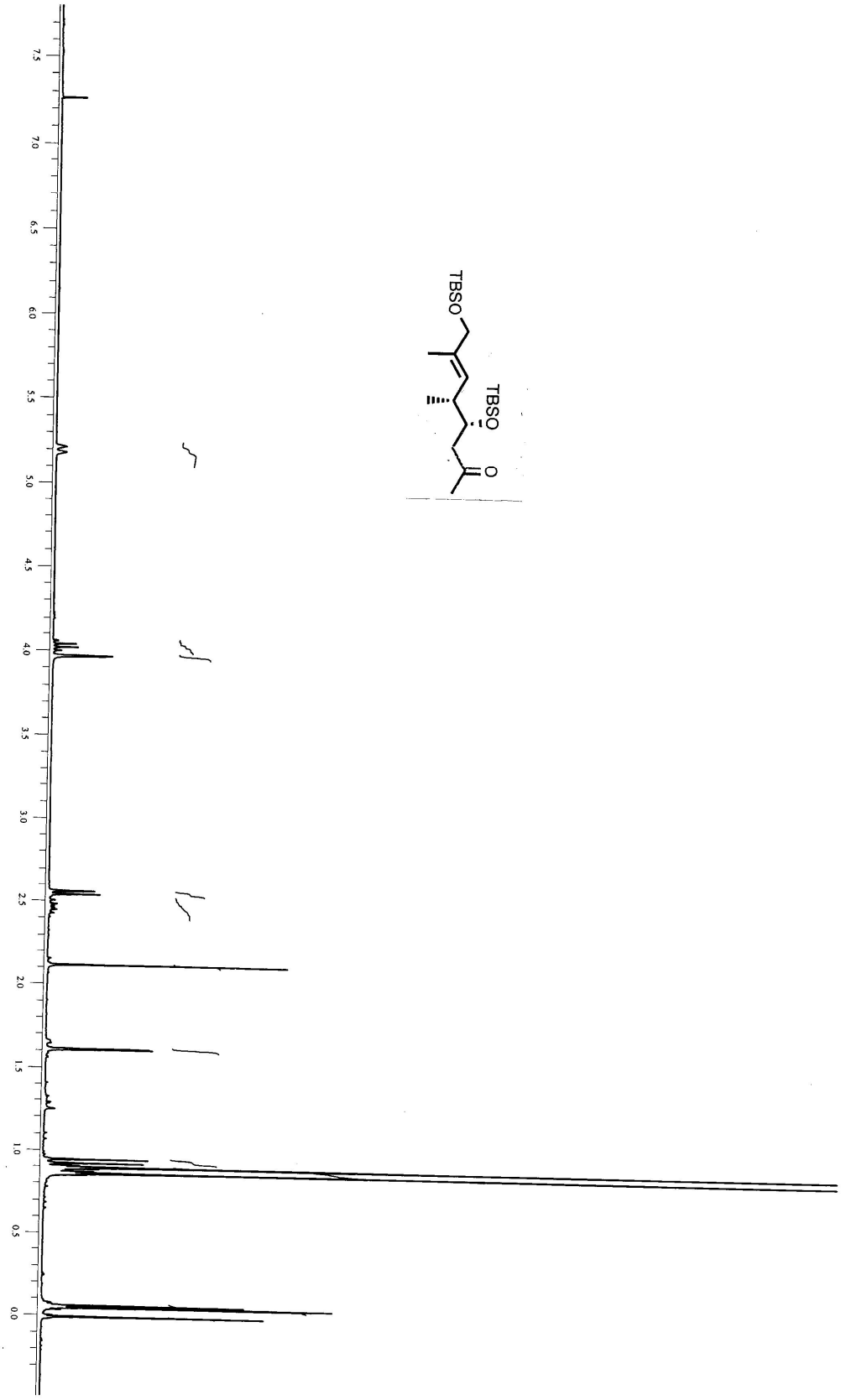
^{13}C NMR of Compound **40** ($CDCl_3$, 75 MHz)



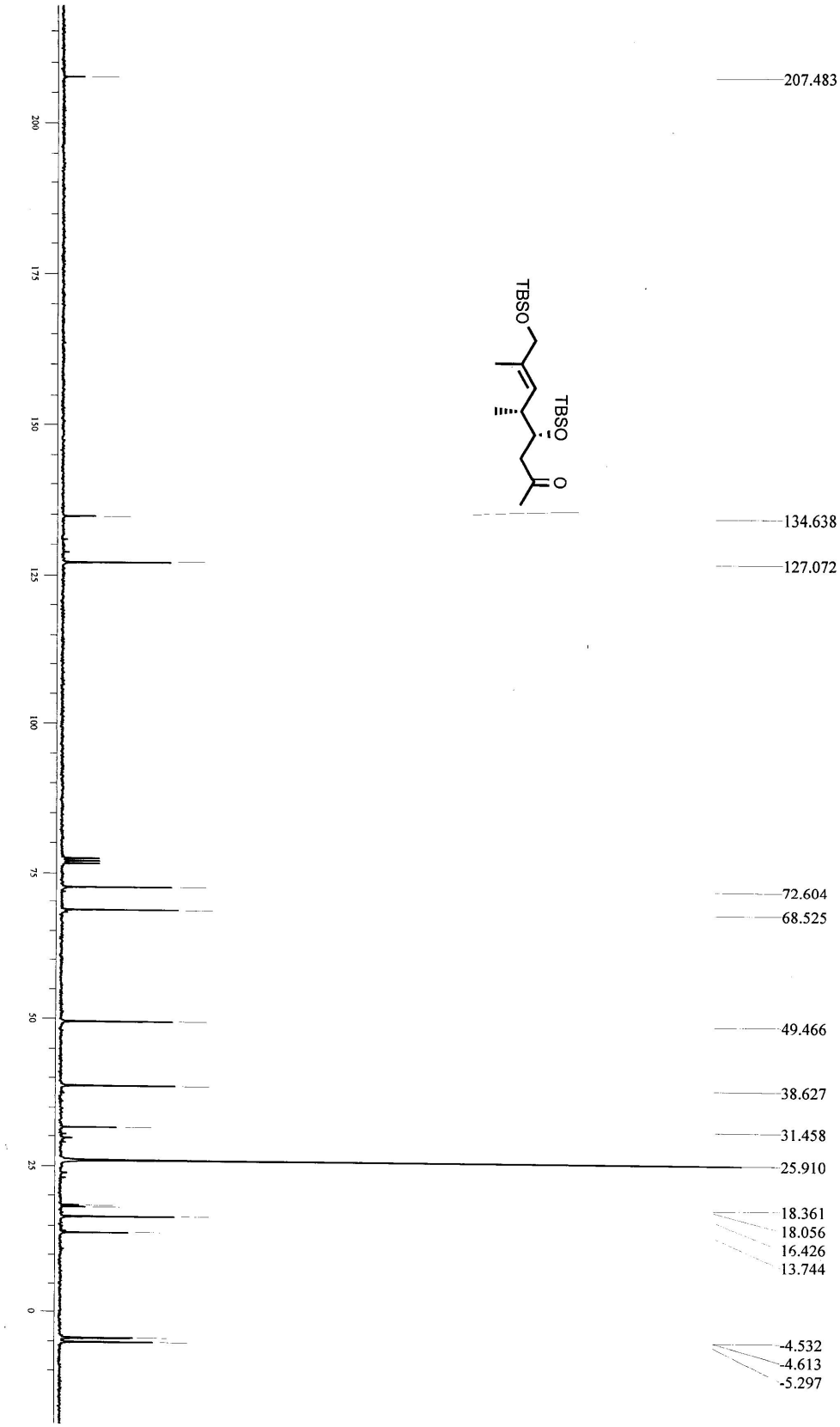
^{1}H NMR of Compound **41** ($CDCl_3$, 300 MHz)



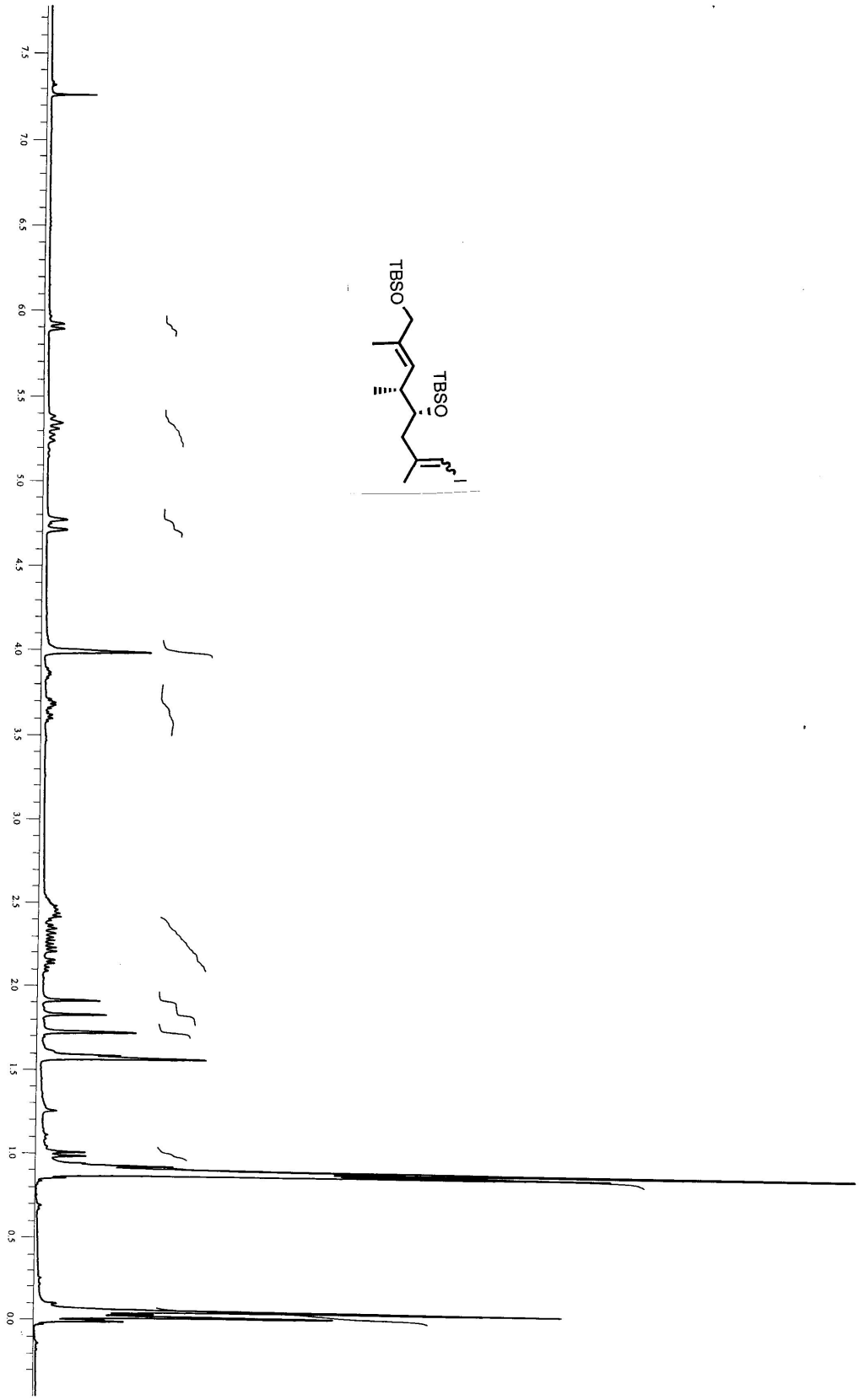
^{13}C NMR of Compound **41** ($CDCl_3$, 75 MHz)



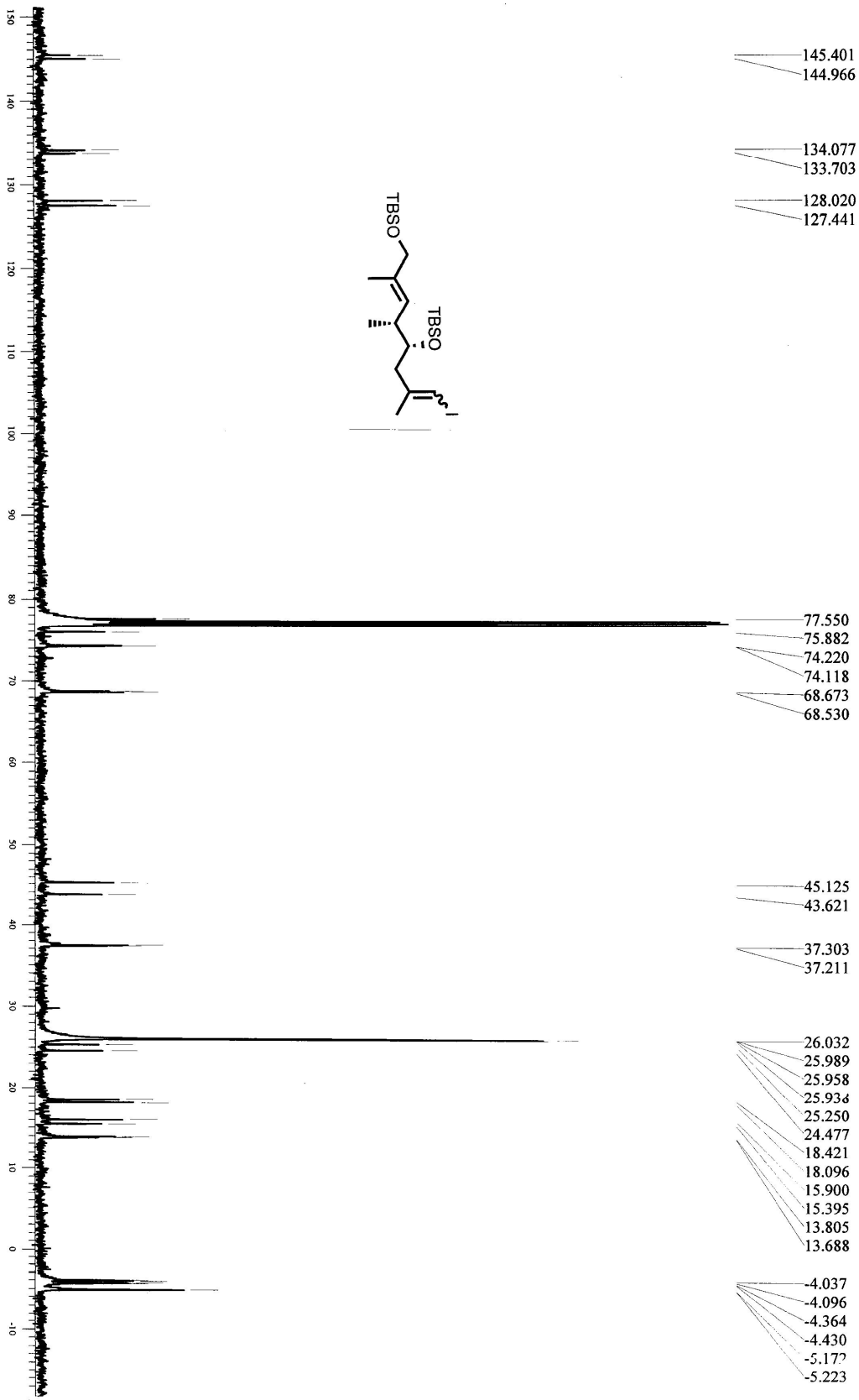
^{1}H NMR of Compound **42** ($CDCl_3$, 300 MHz)



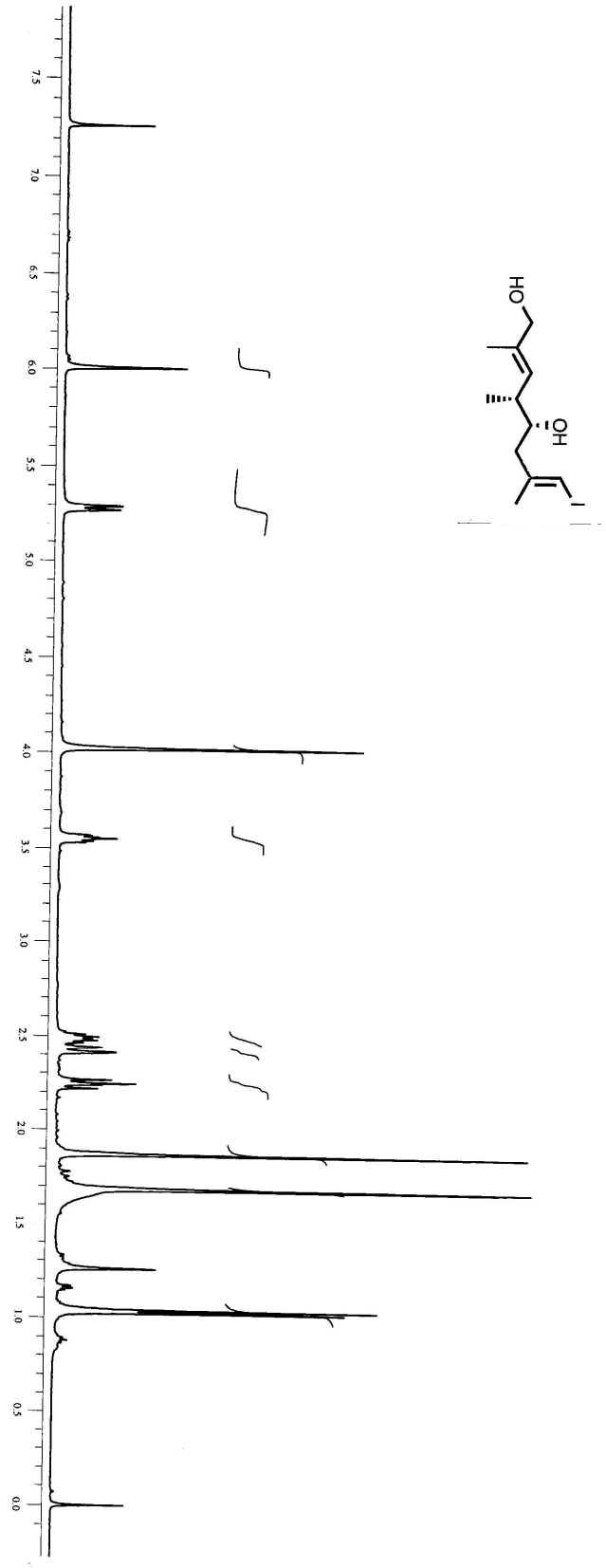
^{13}C NMR of Compound **42** ($CDCl_3$, 75 MHz)



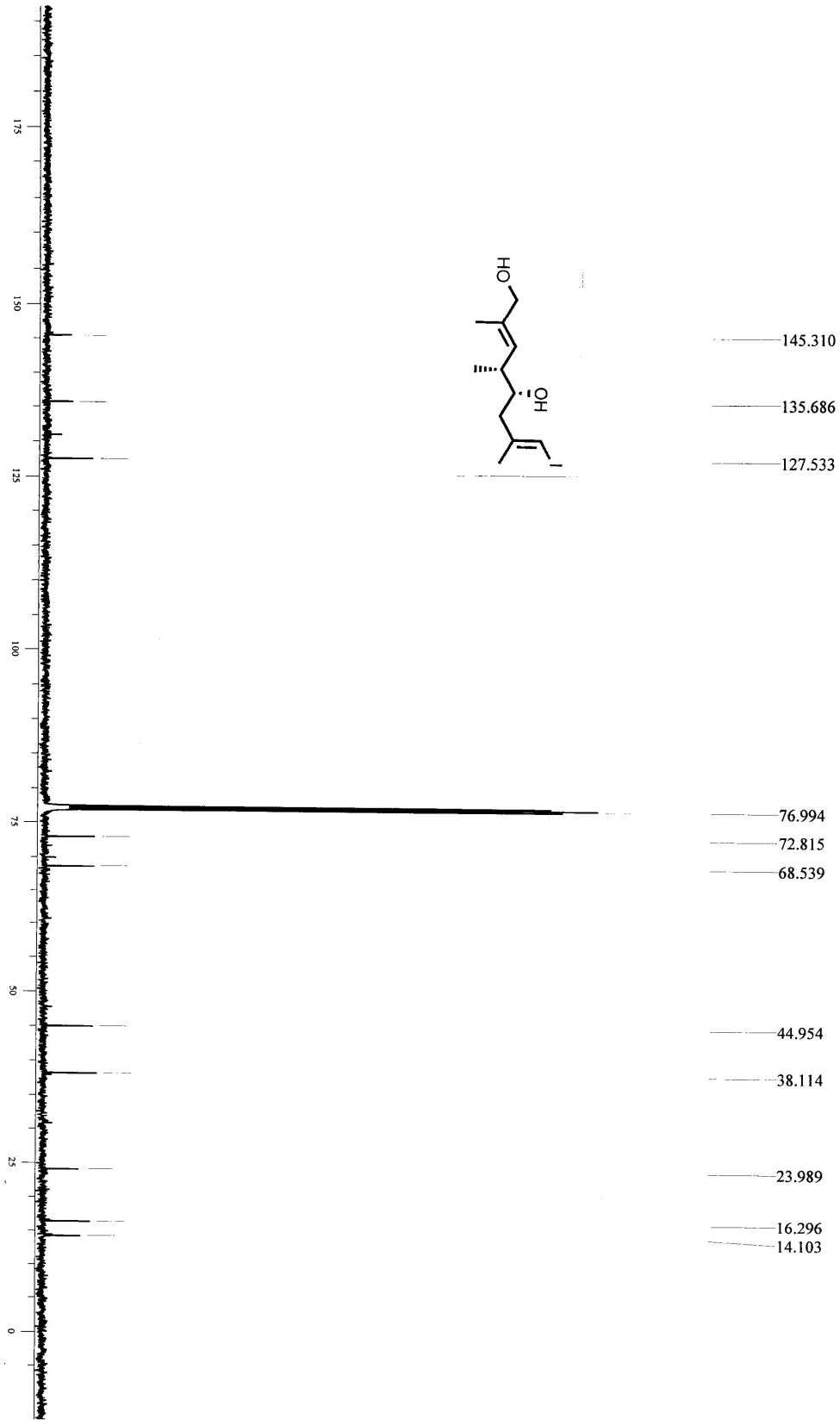
^{1}H NMR of Compound **43** ($CDCl_3$, 300 MHz)



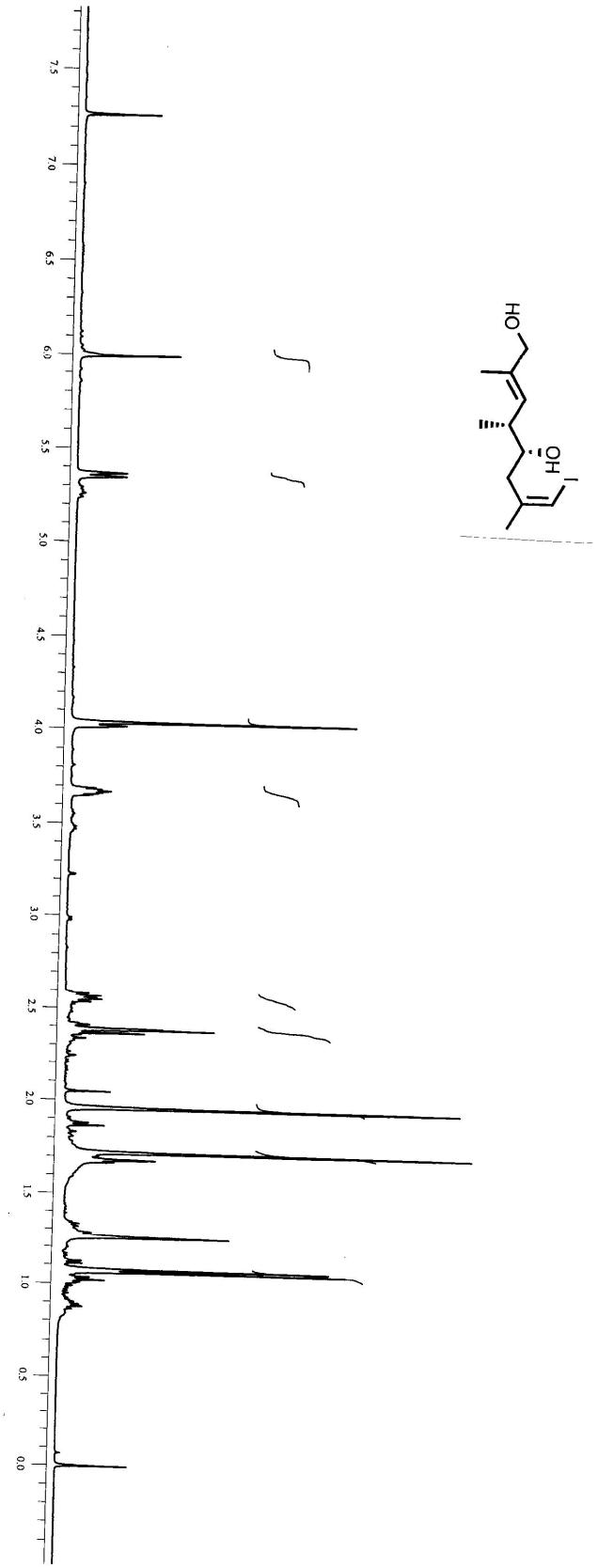
^{13}C NMR of Compound **43** ($CDCl_3$, 75 MHz)



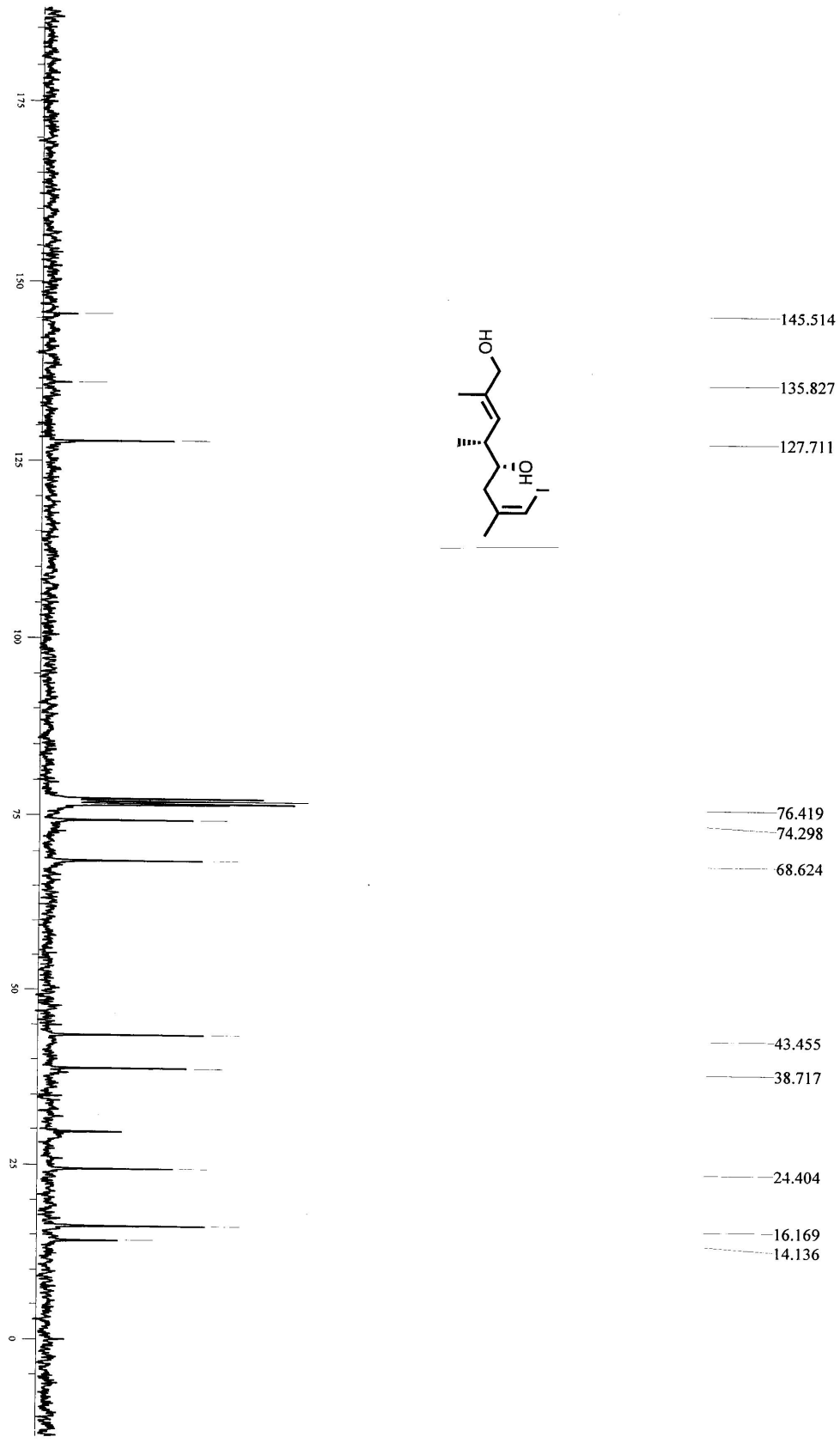
^{1}H NMR of Compound **44** ($CDCl_3$, 500 MHz)



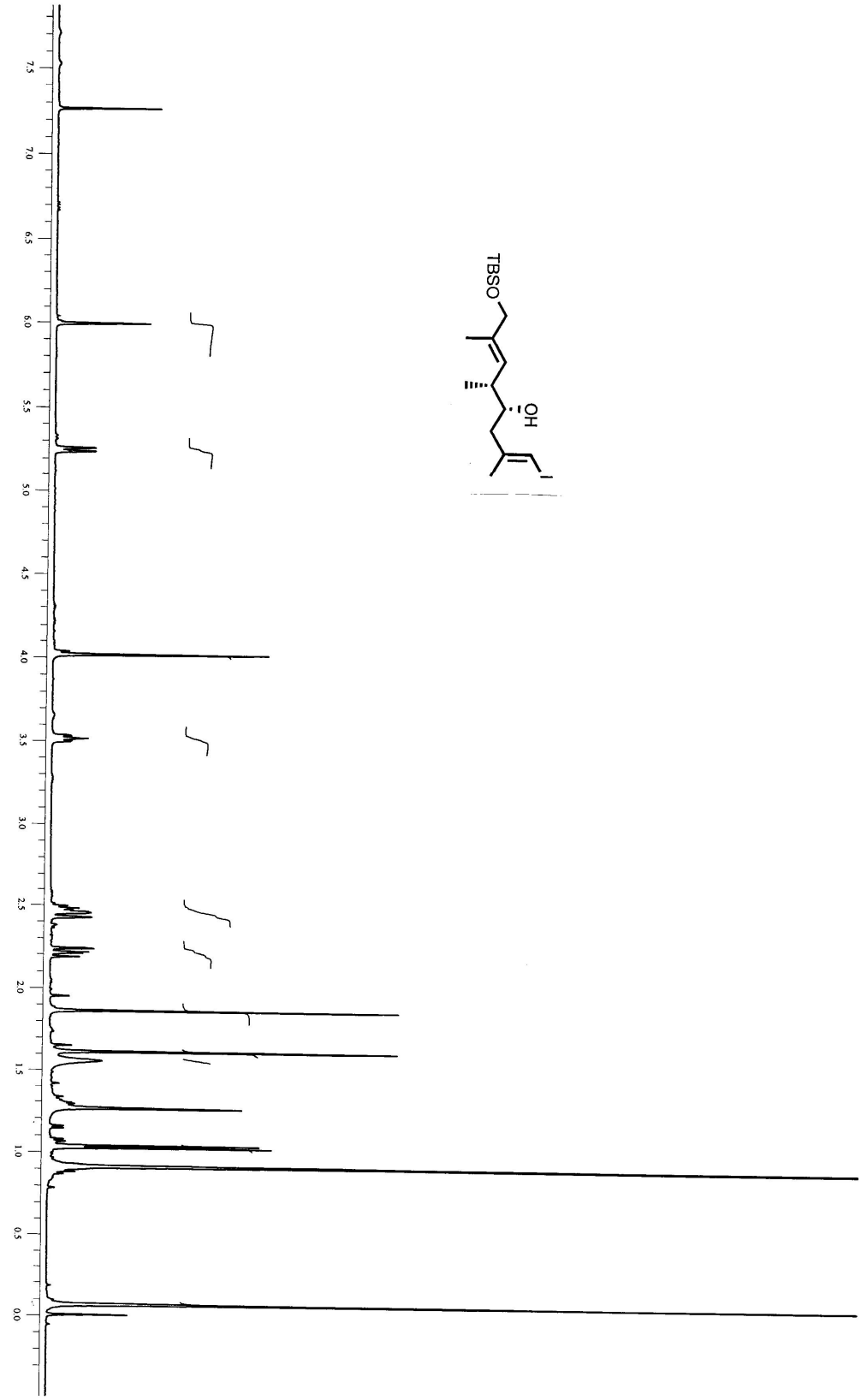
^{13}C NMR of Compound **44** ($CDCl_3$, 75 MHz)



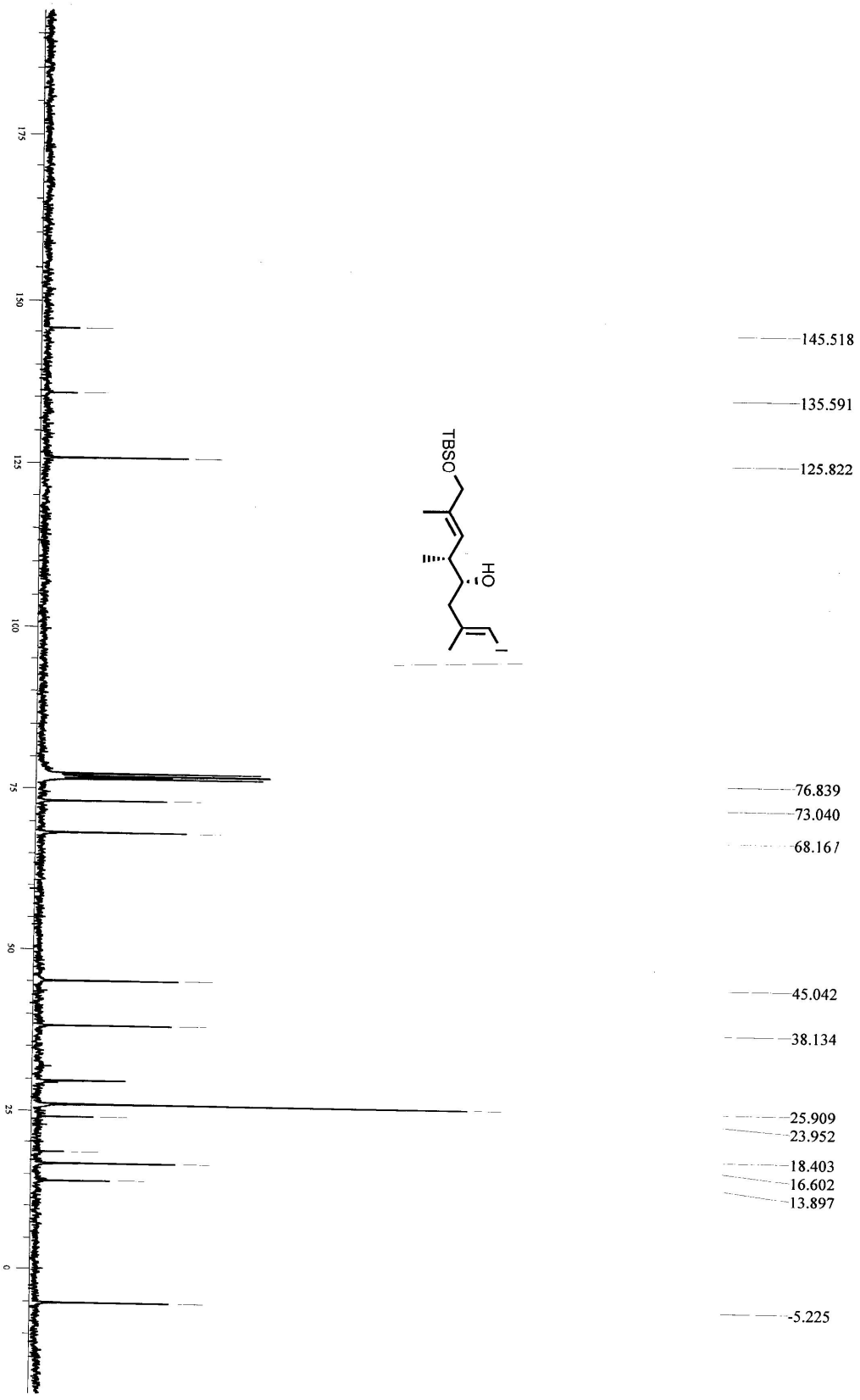
^{1}H NMR of Compound **44a** ($CDCl_3$, 500 MHz)



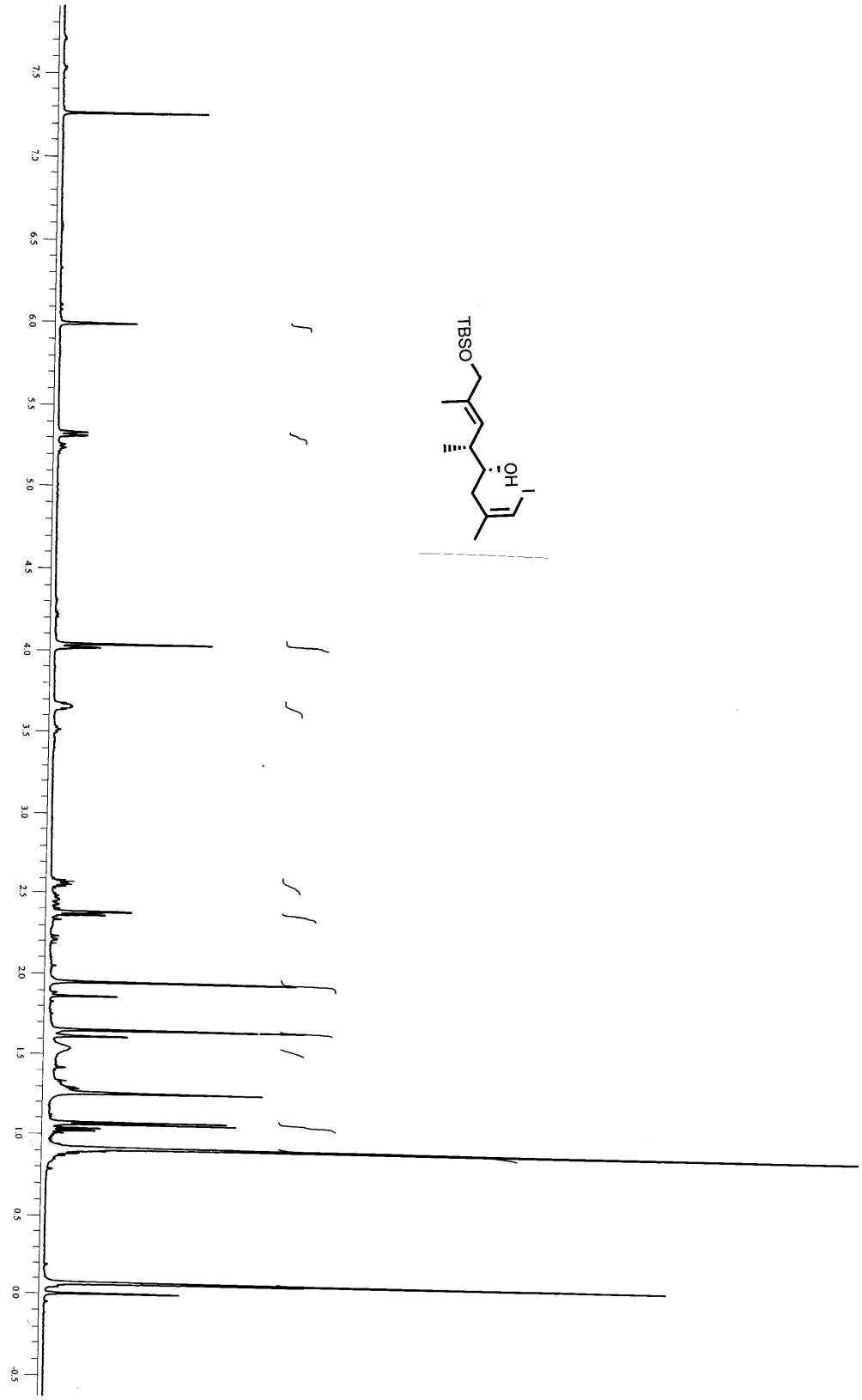
^{13}C NMR of Compound **44a** ($CDCl_3$, 75 MHz)



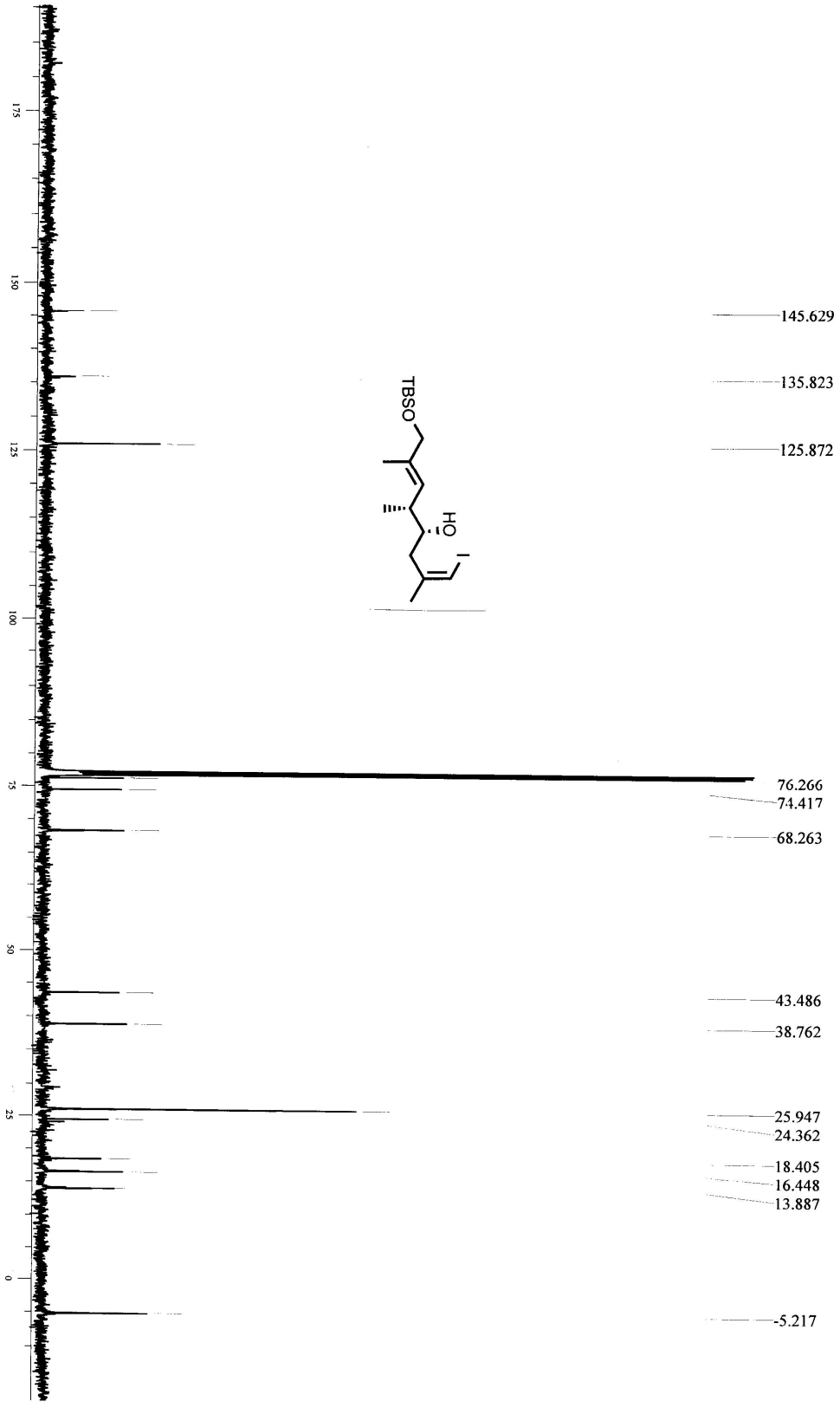
^{1}H NMR of Compound **4** ($CDCl_3$, 500 MHz)



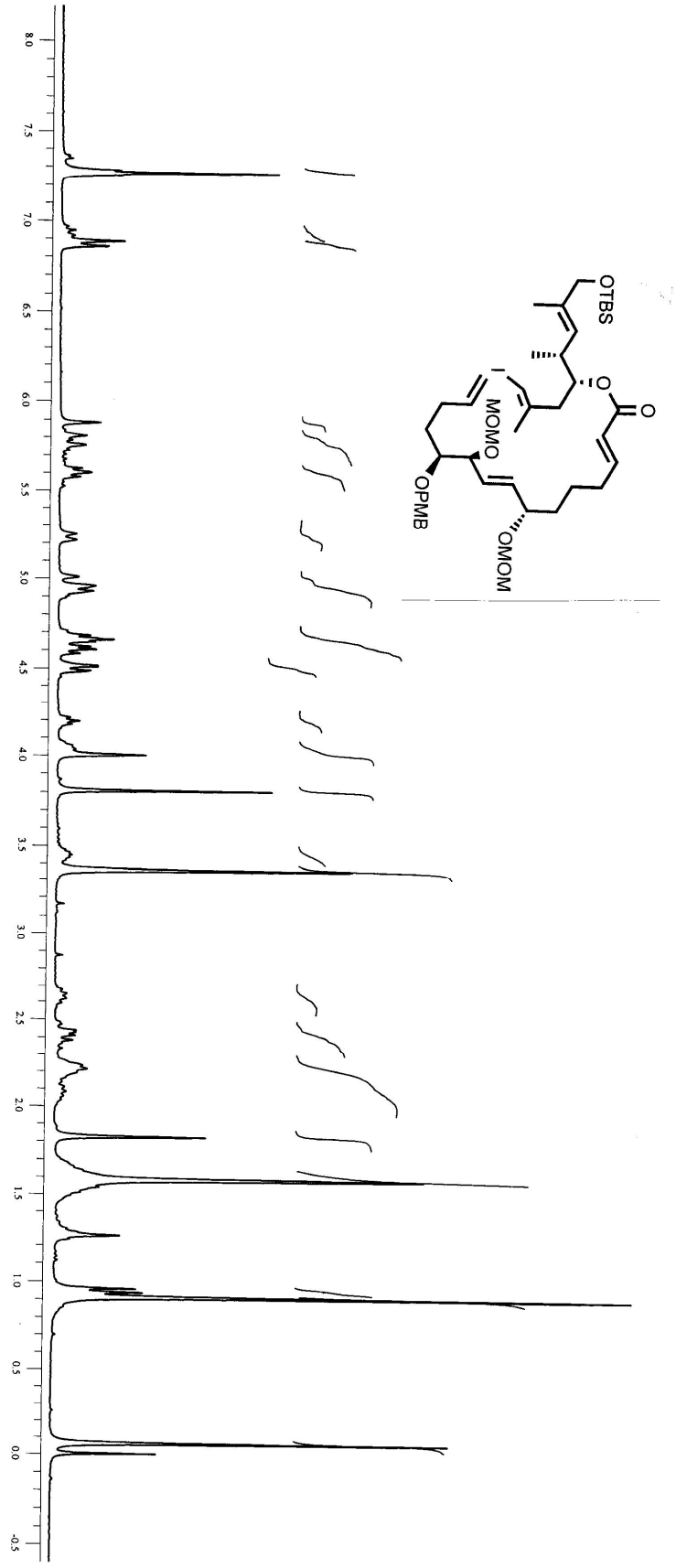
^{13}C NMR of Compound **4** ($CDCl_3$, 75 MHz)



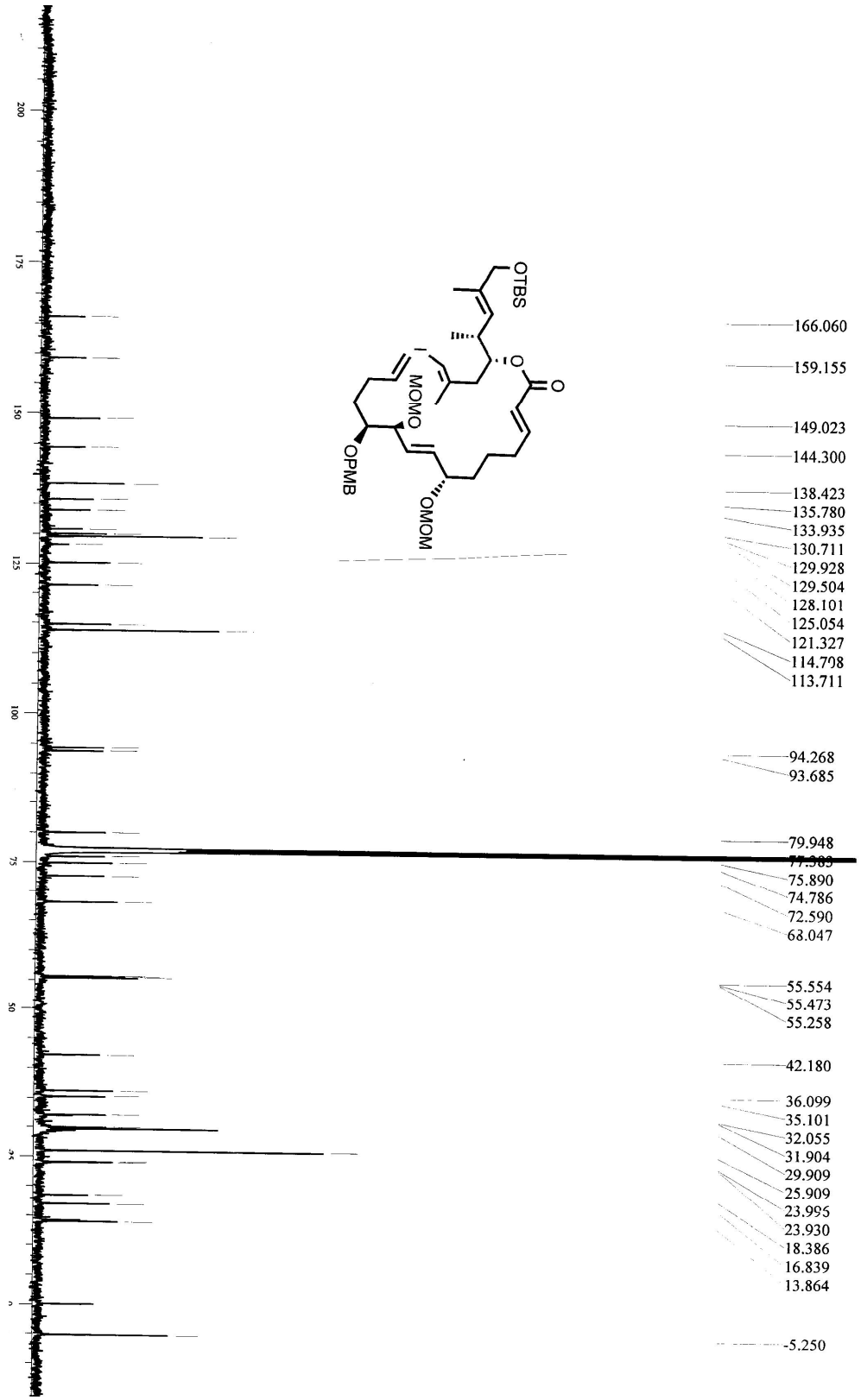
^{1}H NMR of Compound **4a** ($CDCl_3$, 500 MHz)



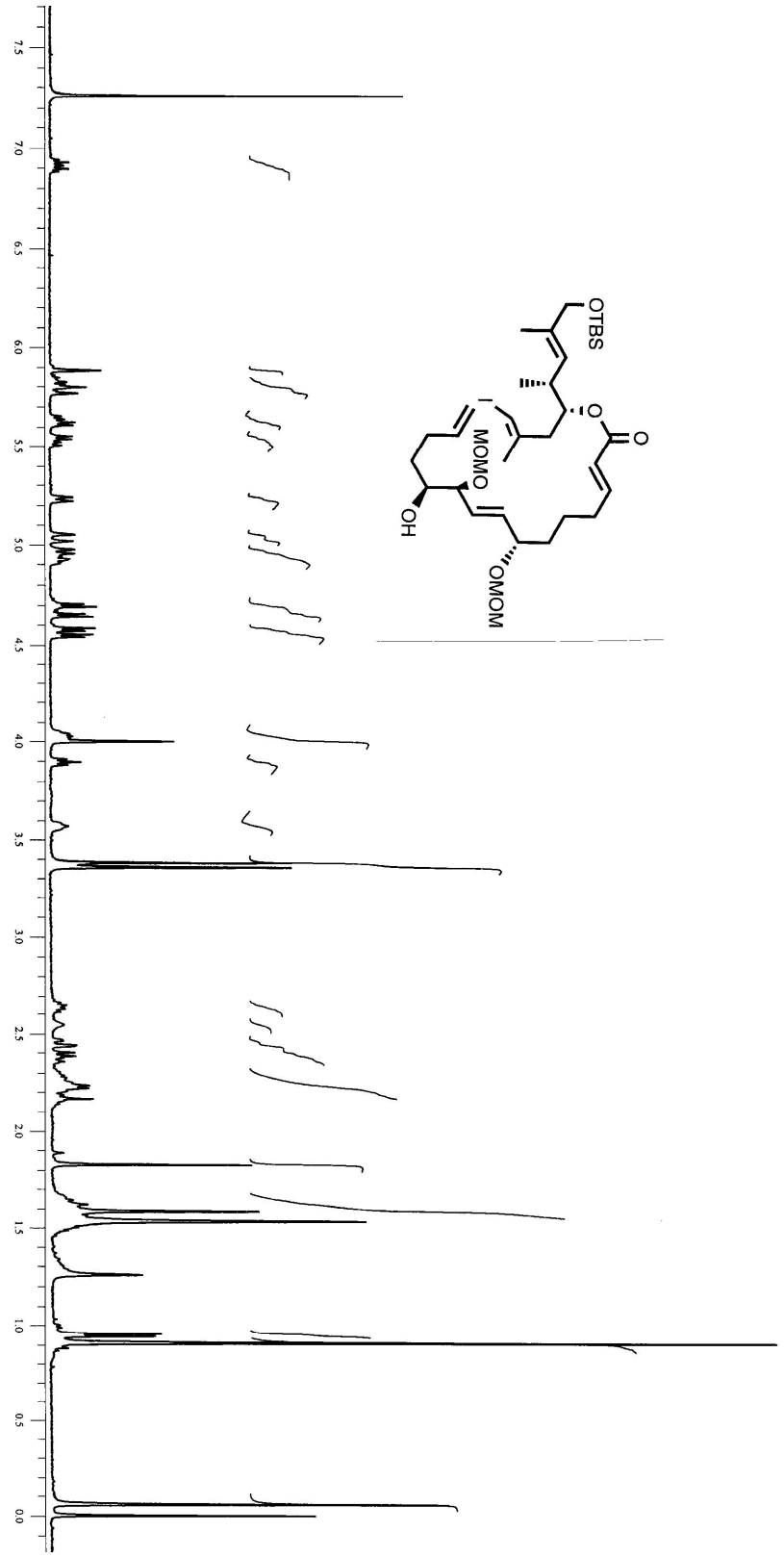
^{13}C NMR of Compound **4a** ($CDCl_3$, 75 MHz)



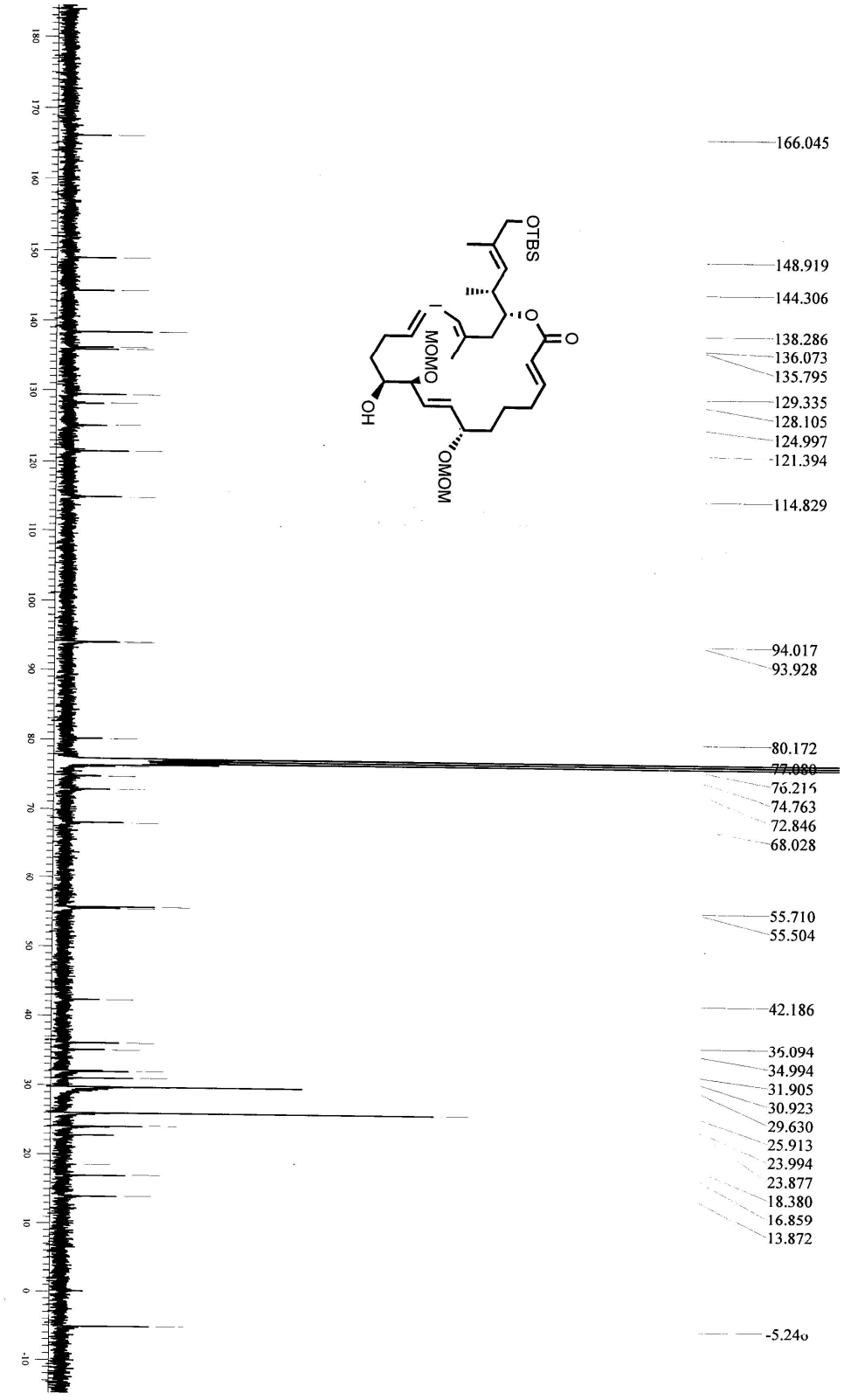
^{1}H NMR of Compound **45** ($CDCl_3$, 300 MHz)



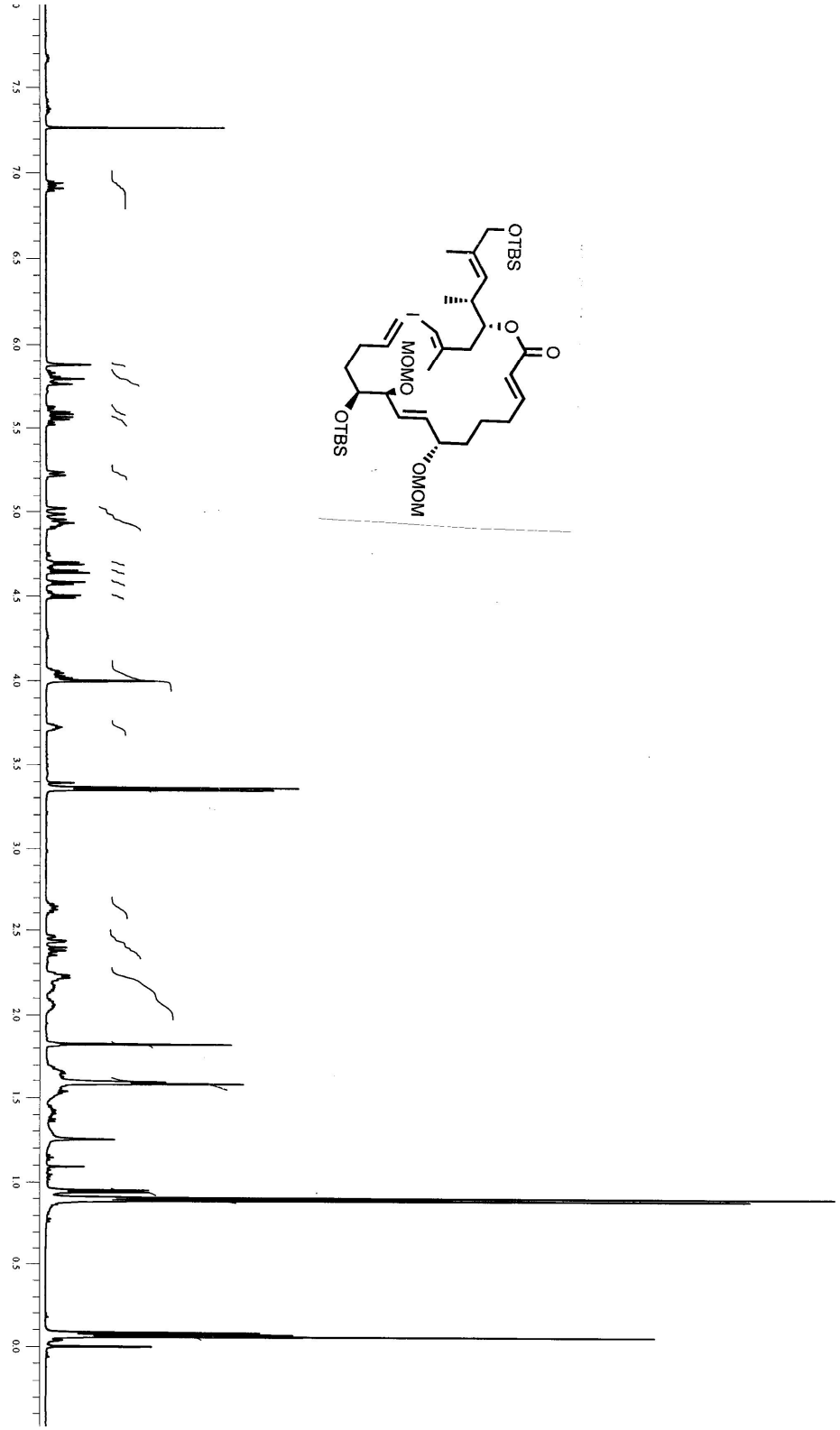
^{13}C NMR of Compound **45** ($CDCl_3$, 125 MHz)



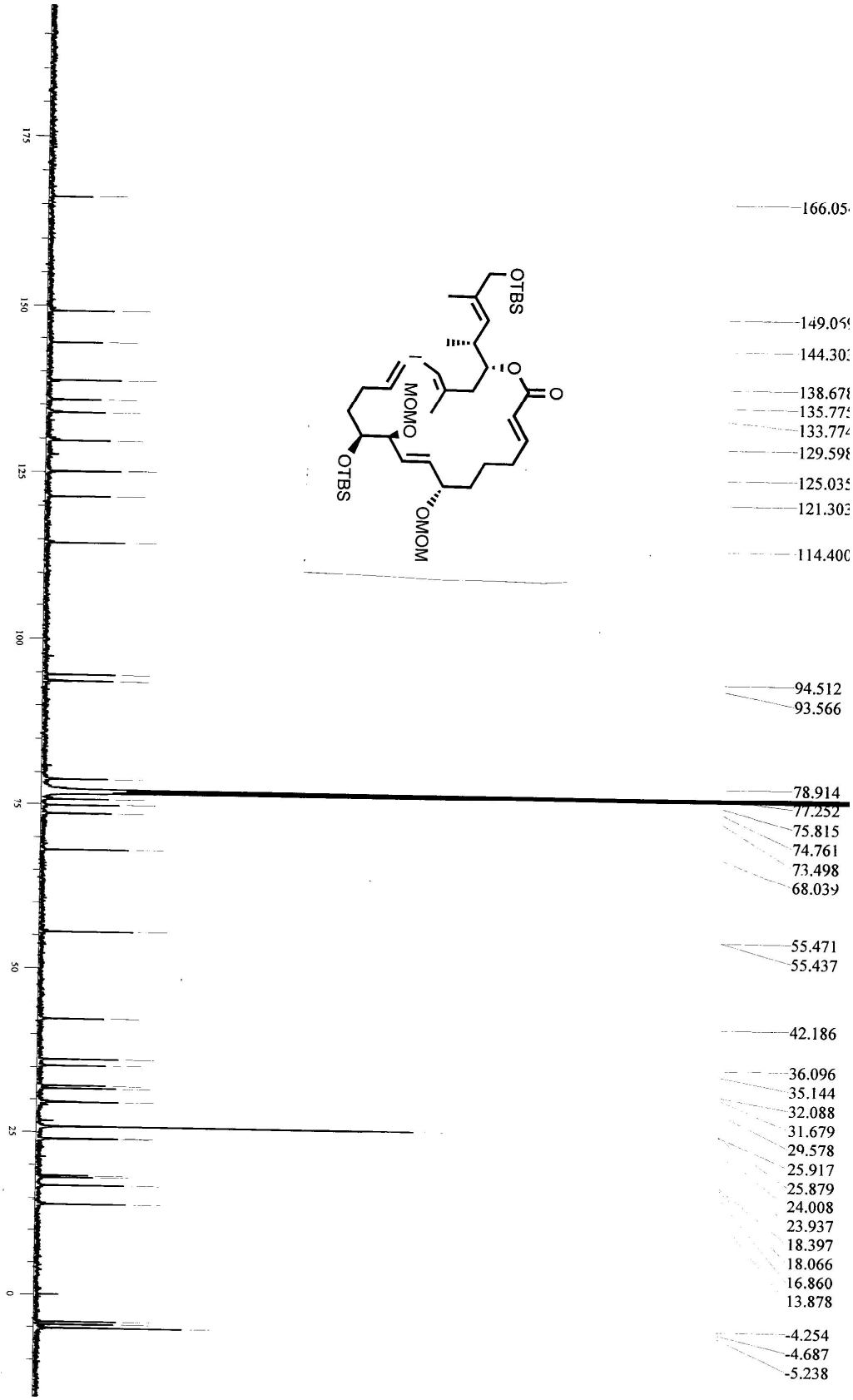
^{1}H NMR of Compound **46** ($CDCl_3$, 500 MHz)



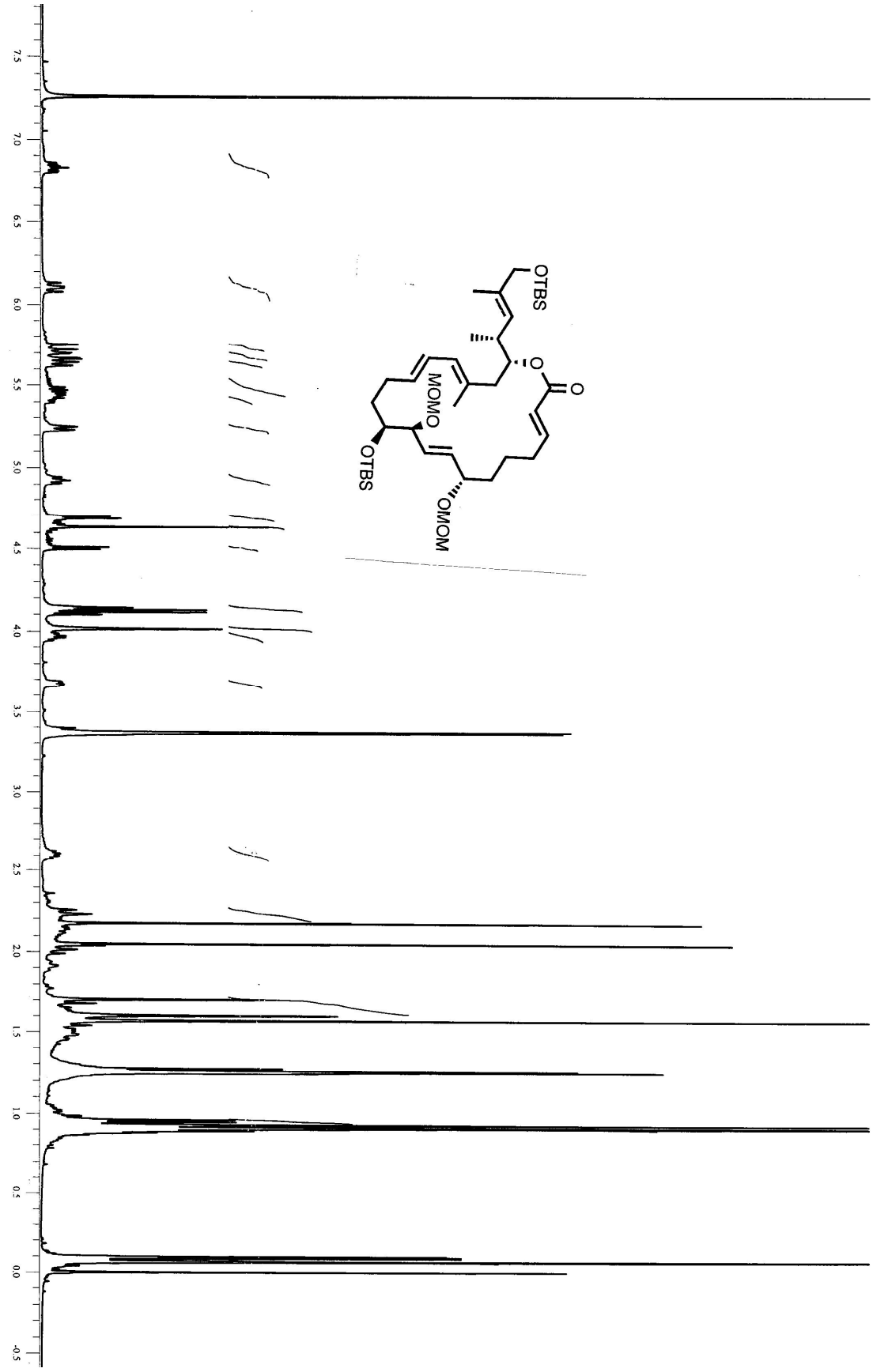
^{13}C NMR of Compound **46** ($CDCl_3$, 100 MHz)



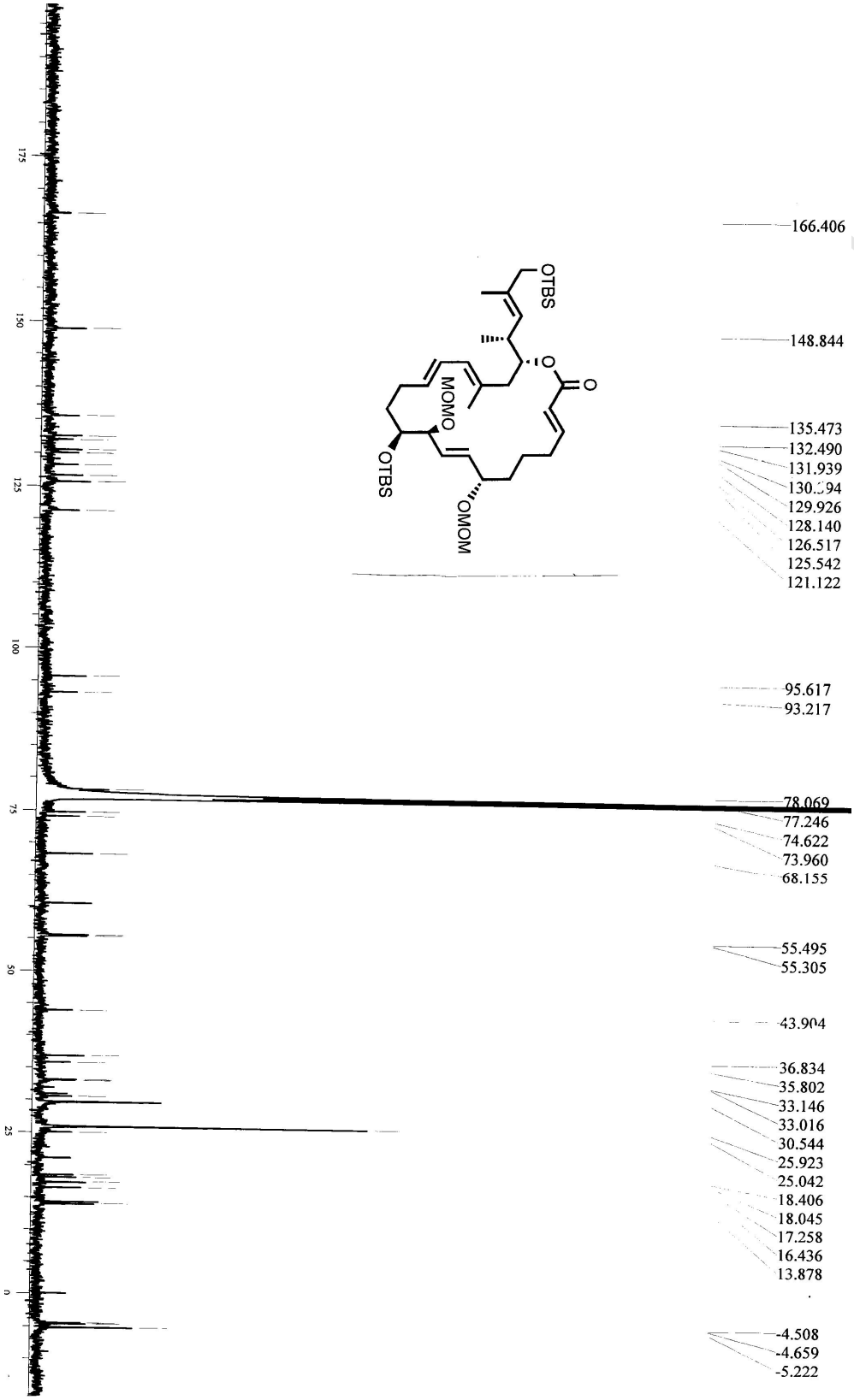
^{1}H NMR of Compound **47** ($CDCl_3$, 500 MHz)



^{13}C NMR of Compound **47** ($CDCl_3$, 125 MHz)



^{1}H NMR of Compound **2** ($CDCl_3$, 500 MHz)



^{13}C NMR of Compound **2** ($CDCl_3$, 125 MHz)