

Rh-Catalyzed Asymmetric Hydroformylation of Functionalized 1,1-Disubstituted Olefins

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Supporting Information

1. General reagent information.....	S2
2. General analytical information.....	S2
3. General procedures.....	S3
4. Specific experimental procedure and compound data.....	S4
5. NMR, GC and HPLC spectra.....	S19

General Reagent Information.

Hydroformylation reactions were set up in a CAT24 autoclave from HEL Inc. and were stirred with a teflon-coated magnetic stir bar. Rh(CO)₂acac and ligands were purchased from Strem Chemical Co. Lithium bis(trimethylsilyl)amide (LHMDS, 1.0 M in THF), methyl methacrylate, ethyl 2-ethylacrylate, ethyl 2-propylacrylate, ethyl acetoacetate, ethyl 2-benzylacetoacetate, ethyl 2-cyclohexylacetate, ethyl 2-isopropylacetoacetate and paraformaldehyde were purchased from Aldrich Chemical Co. Methyl 2-cyclopentyl-3-oxobutanoate was purchased from ASDI. Anhydrous dodecane was purchased from Aldrich in Sure/Seal™ bottles. All reagents from commercial sources were used as received. Flash chromatography was performed with silica gel from American International Chemical, Inc. (40-63 Micron). DCM, THF, Et₂O and toluene were dried by activated alumina according to Pangborn, A.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics*, **1996**, *15*, 1518.

General Analytical Information.

All new compounds were characterized by ¹H NMR, ¹³C NMR, IR spectroscopy and high resolution mass spectroscopy. Copies of NMR spectra are included for all new compounds. ¹H and ¹³C NMR spectra were recorded on Bruker models Avance DPX 400 (400 MHz) spectrometers. ¹H NMR spectra are reported in parts per million (ppm) downfield of TMS and were measured relative to the signals for CHCl₃ (7.26 ppm). All ¹³C NMR spectra were reported in ppm relative to residual CHCl₃ (77.0 ppm) and were obtained with ¹H decoupling. In reporting spectral data the format (δ) chemical shift (multiplicity, *J* values in Hz, integration) was used with the following abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, quint = quintuplet, m = multiplet. Infrared spectra were recorded on a Perkin-Elmer Model 2000 FTIR

using KBr plates (thin film). Peaks are reported in wavenumbers (cm^{-1}). High resolution mass spectra were reported in units of m/z , and were obtained on a Bruker Daltonics APEXIV 4.7 Tesla Fourier Transform Ion Cyclotron Resonance Mass Spectrometer (FT-ICR-MS). Optical rotations were measured using Jasco P-1010 polarimeter using Na lamp (589 nm). The concentration of the samples is given in g/100 mL. GC analyses were performed on an Agilent 6890 gas chromatograph with an FID detector using a J&W DB-1 column (10 m \times 0.1 mm). Chiral GC analyses were performed on an Agilent 6850 Series system with a Chrompack capillary column (CP Chirasil-Dex CD, 25 m \times 0.25 mm \times 0.25 mm) or Astec G-TA column (30 m \times 0.25 mm). HPLC analyses were carried out on an Agilent 1100 Series system with Daicel Chiralcel[®] (OD-H) or Chiralpak[®] (AS-H) columns (4.6 mm \times 250 mm) in hexanes/^{*i*}PrOH mixtures. The yields reported are isolated yields and represent an average of at least two independent runs. The pure compounds are estimated to be $\geq 95\%$ pure as determined by ¹H NMR and GC analysis.

General procedure 1: the preparation of α -alkylacrylate.¹

To the solution of ethyl 2-alkylacetoacetate (1.0 equiv) in THF (0.3 M) was slowly added LHMDS (1.1 equiv, 1.0 M solution in THF) at $-78\text{ }^{\circ}\text{C}$. The solution was stirred for 30 min, and paraformaldehyde (excess) was added in one portion. The orange suspension was warmed to room temperature and stirred for 12 h. The reaction was followed by TLC. The mixture was filtered through a pad of celite to remove the excess paraformaldehyde. The filtrate was concentrated, and the residue was purified by flash chromatography to afford the corresponding α -alkylacrylate.

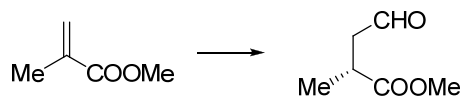
¹ Lee, H.-S.; Park, J.-S.; Kim, B. M.; Gellman, S. H. *J. Org. Chem.* **2003**, *68*, 1575.

General procedure 2: the asymmetric hydroformylation of 1,1-disubstituted olefins.

(Caution: Reactions employing elevated pressure should be carried out in suitable equipment behind a blast shield and with all appropriate precautions.)

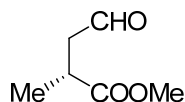
Each asymmetric hydroformylation reaction was conducted in the HEL-CAT24 reactor system. In a reaction tube, olefin (0.50 mmol), Rh(CO)₂acac (1.3 mg, 0.005 mmol) and (*R,R*)-BenzP* (1.7 mg, 0.006 mmol) were dissolved in anhydrous dodecane (0.4 mL). The reaction tube was placed in the reactor which was pressurized with 10 bar of CO and H₂ (1:5), and heated to 100 °C while stirring at 700 rpm. The reaction was stopped after 4 to 8 h by immersing the reactor in an ice bath for 15 min followed by venting the system. The mixture was analyzed by chiral GC, chiral HPLC or NMR.

Specific experimental procedure and compound data.



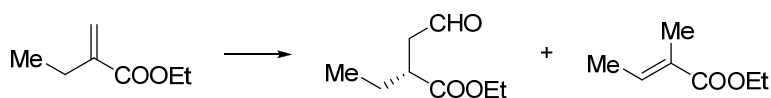
(Table 3, entry 1)

General procedure 2 was followed by employing methyl methacrylate (53 μ L, 0.50 mmol). Purification by flash chromatography eluting with pentane/Et₂O (100:1 to 5:1) afforded the linear aldehyde (35 mg, 54%, colorless oil):



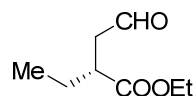
(*R*)-methyl 2-methyl-4-oxobutanoate: Enantiomeric excess (83%) was determined by chiral GC analysis [CP Chirasil-Dex CD, 25 m \times 0.25 mm \times 0.25 mm, flow rate 3.5 mL/min, method:

ramp from 50 °C to 130 °C at 2.0 °C/min, 130 °C for 5 min: (*R*) t_r = 12.8 min, (*S*) t_r = 13.3 min)]; $[\alpha]_D^{25} +21$ (c 0.39, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 9.77 (quasi-s, 1H), 3.70 (s, 3H), 2.99 (qdd, J = 7.6, 7.2, 5.6 Hz, 1H), 2.91 (dd, J = 18.0, 8.0 Hz, 1H), 2.54 (dd, J = 18.0, 5.2 Hz, 1H), 1.23 (d, J = 7.2 Hz, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 200.1, 175.6, 52.0, 46.9, 33.5, 17.0; IR (thin film) 2984, 1733, 1718, 1559, 1457, 1388, 1232, 1096 cm⁻¹; HRMS (ESI) m/z [M + Na]⁺ calcd for C₆H₁₀NaO₃: 153.0528, found 153.0537.



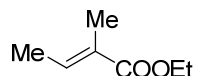
(Table 3, entry 2)

General procedure 2 was followed by employing ethyl 2-ethylacrylate (71 μL, 0.50 mmol). Purification by flash chromatography eluting with pentane/Et₂O (100:1 to 5:1) afforded the linear aldehyde (54 mg, 68%, colorless oil) and the olefin isomer (7 mg, 11%, colorless oil):

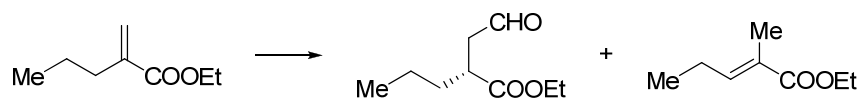


(*R*)-Ethyl 2-ethyl-4-oxobutanoate: Enantiomeric excess (87%) was determined by chiral GC analysis [Astec G-TA column 30 m × 0.25 mm, flow rate 1.5 mL/min, method: ramp from 50 °C to 150 °C at 2.0 °C/min, (*S*) t_r = 28.1 min, (*R*) t_r = 28.9 min)]; $[\alpha]_D^{25} +0.77$ (c 0.92, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 9.78 (quasi-s, 1H), 4.16 (qd, J = 6.8, 1.2 Hz, 2H), 2.89 (ddd, J = 17.2, 8.8, 1.2 Hz, 1H), 2.84 (ddt, J = 8.8, 6.6, 6.6 Hz, 1H), 2.54 (ddd, J = 16.4, 3.2, 0.9 Hz, 1H), 1.70 (ddq, J = 14.4, 7.6, 7.6 Hz, 1H), 1.60 (dq, J = 14.8, 7.6, 6.4 Hz, 1H), 1.26 (t, J = 7.2 Hz, 3H), 0.93 (t, J = 7.6 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 200.5, 174.8, 60.9, 45.1, 40.6, 25.2, 14.4,

11.5; IR (thin film) 2970, 1733, 1714, 1379, 1179, 1030 cm^{-1} ; HRMS (DART) m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_8\text{H}_{15}\text{O}_3$: 159.1016, found 159.1014.

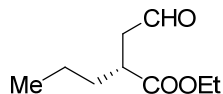


(E)-Ethyl 2-methylbut-2-enoate:² ^1H NMR (400 MHz, CDCl_3) δ 6.85 (qq, $J = 7.2, 1.2$ Hz, 1H), 4.18 (q, $J = 7.2$ Hz, 2H), 1.83 (quasi-quint, $J = 1.2$ Hz, 3H), 1.78 (dq, $J = 7.2, 1.2$ Hz, 3H), 1.29 (t, $J = 7.2$ Hz, 3H); HRMS (DART) m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_7\text{H}_{13}\text{O}_2$: 129.0910, found 129.0915.



(Table 3, entry 3)

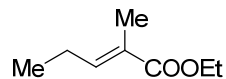
General procedure 2 was followed by employing ethyl 2-propylacrylate (81 μL , 0.50 mmol). Purification by flash chromatography eluting with pentane/ Et_2O (100:1 to 5:1) afforded the linear aldehyde (54 mg, 63%, colorless oil) and the olefin isomer (15 mg, 21%, colorless oil):



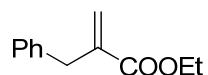
(R)-Ethyl 2-(2-oxoethyl)pentanoate: Enantiomeric excess (89%) was determined by chiral GC analysis [Astec G-TA column 30 m \times 0.25 mm, flow rate 1.5 mL/min, method: ramp from 50 $^\circ\text{C}$ to 150 $^\circ\text{C}$ at 2.0 $^\circ\text{C}/\text{min}$, (*S*) $t_r = 31.3$ min, (*R*) $t_r = 32.1$ min]; $[\alpha]_D^{25} +5.2$ (c 1.3, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 9.77 (quasi-s, 1H), 4.15 (q, $J = 7.2$ Hz, 2H), 2.91 (m, 1H), 2.87 (ddd, $J = 13.2, 9.2, 0.8$ Hz, 1H), 2.54 (ddd, $J = 24.8, 12.4, 0.8$ Hz, 1H), 1.65 (dtd, $J = 19.2, 7.2, 3.6$ Hz,

² Duke, R. K.; Chebib, M.; Hibbs, D. E.; Mewett, K. N.; Johnston, G. A. R. *Tetrahedron: Asymmetry*, **2004**, 15, 1745.

1H), 1.48 (dtd, $J = 21.2, 7.6, 6.0$ Hz, 1H), 1.33 (hex, $J = 8.0$ Hz, 2H), 1.26 (t, $J = 7.2$ Hz, 3H), 0.92 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 200.4, 174.9, 60.7, 45.4, 38.8, 34.0, 20.2, 14.2, 13.8; IR (thin film) 2962, 1734, 1717, 1380, 1179, 1031 cm^{-1} ; HRMS (DART) m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_9\text{H}_{17}\text{O}_3$: 173.1172, found 173.1176.

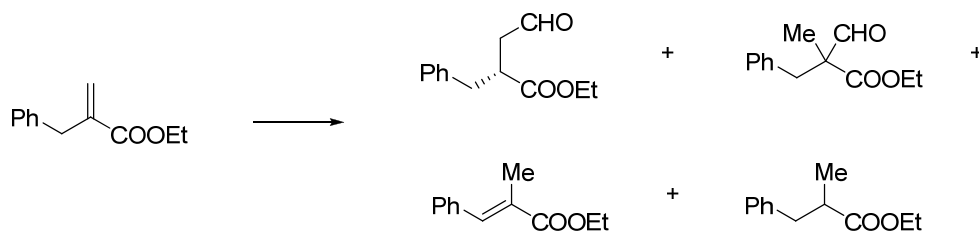


(E)-Ethyl 2-methylpent-2-enoate:³ ^1H NMR (400 MHz, CDCl_3) δ 6.75 (tq, $J = 7.6, 1.2$ Hz, 1H), 4.19 (q, $J = 6.8$ Hz, 2H), 2.18 (dq, $J = 7.6, 7.6, 0.8$ Hz, 2H), 1.83 (quasi-q, $J = 1.2$ Hz, 3H), 1.30 (t, $J = 6.8$ Hz, 3H), 1.05 (t, $J = 7.6$ Hz, 3H); HRMS (DART) m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_8\text{H}_{15}\text{O}_2$: 143.1067, found 143.1066.



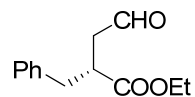
Ethyl 2-benzylacrylate: General procedure 1 was followed by employing ethyl 2-benzylacetoacetate (4.40 g, 20.0 mmol, 1.0 equiv), LHMDS (22.0 mL, 22.0 mmol, 1.1 equiv), paraformaldehyde (2.80 g) and THF (120 mL). Purification by flash chromatography eluting with hexanes/EtOAc (45:1) afforded the title compound (1.86 g, 49%) as a colorless oil: ^1H NMR (400 MHz, CDCl_3) δ 7.30–7.15 (m, 5H), 6.20 (s, 1H), 5.42 (quasi-d, $J = 1.2$ Hz, 1H), 4.15 (q, $J = 7.2$ Hz, 2H), 3.60 (s, 2H), 1.23 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 167.0, 140.4, 138.8, 129.1, 128.4, 126.3, 126.0, 60.8, 38.1, 14.2; IR (thin film) 2983, 1717, 1635, 1558, 1456, 1300, 1198, 1134, 1028 cm^{-1} ; HRMS (DART) m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{12}\text{H}_{15}\text{O}_2$: 191.1067, found 191.1068.

³ Yadav, J. S.; Pratap, T. V.; Rajender, V. *J. Org. Chem.* **2007**, *72*, 5882.

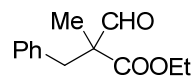


(Table 3, entry 4)

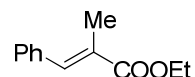
General procedure 2 was followed by employing ethyl 2-benzylacrylate (95 mg, 0.50 mmol). Purification by flash chromatography eluting with pentane/Et₂O (100:1 to 5:1) afforded the linear aldehyde (66 mg, 60%, colorless oil), the branched aldehyde (4 mg, 4%, colorless oil), the olefin isomer and the hydrogenation product as an inseparable mixture (29 mg, 30% total yield, colorless oil):



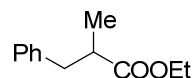
(R)-Ethyl 2-benzyl-4-oxobutanoate: Enantiomeric excess (84%) was determined by chiral GC analysis [CP Chirasil-Dex CD, 25 m × 0.25 mm × 0.25 mm, flow rate 3.5 mL/min, method: ramp from 50 °C to 130 °C at 1.0 °C/min, 130 °C for 10 min: (*S*) *t_r* = 85.8 min, (*R*) *t_r* = 86.4 min)]; [α]_D²⁵ +18 (c 0.91, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 9.70 (quasi-s, 1H), 7.33–7.13 (m, 5H), 4.13 (q, *J* = 7.2 Hz, 2H), 3.17 (tdd, *J* = 17.6, 6.4, 4.8 Hz, 1H), 3.07 (dd, *J* = 13.2, 6.4 Hz, 1H), 2.84 (dd, *J* = 18.0, 8.8 Hz, 1H), 2.76 (dd, *J* = 13.6, 8.8 Hz, 1H), 2.51 (dd, *J* = 18.4, 4.8 Hz, 1H), 1.20 (t, *J* = 7.2 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 200.0, 174.1, 138.1, 129.0, 128.6, 126.8, 60.9, 44.4, 40.9, 37.6, 14.1; IR (thin film) 2983, 1725, 1379, 1185, 1096 cm⁻¹; HRMS (DART) *m/z* [M – H]⁺ calcd for C₁₃H₁₅O₃: 219.1021, found 219.1021.



Ethyl 2-benzyl-2-methyl-3-oxopropanoate: Enantiomeric excess (28%) was determined by chiral GC analysis [CP Chirasil-Dex CD, 25 m × 0.25 mm × 0.25 mm, flow rate 3.5 mL/min, method: ramp from 50 °C to 130 °C at 1.0 °C/min, 130 °C for 10 min: (*minor*) $t_r = 74.4$ min, (*major*) $t_r = 74.9$ min]; $[\alpha]_D^{25} -4.1$ (c 0.13, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 9.77 (s, 1H), 7.30–7.07 (m, 5H), 4.18 (q, $J = 7.2$ Hz, 2H), 3.22 (d, $J = 13.6$ Hz, 1H), 3.08 (d, $J = 13.6$ Hz, 1H), 1.27 (s, 3H), 1.23 (t, $J = 7.2$ Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 199.6, 171.7, 135.5, 130.1, 128.4, 127.1, 61.5, 58.7, 40.3, 17.1, 14.1; IR (thin film) 2983, 1718, 1559, 1456 cm⁻¹; HRMS (DART) m/z [M – H]⁺ calcd for C₁₃H₁₅O₃: 219.1021, found 219.1030.



(E)-Ethyl 2-methyl-3-phenylacrylate:⁴ ¹H NMR (400 MHz, CDCl₃) δ 7.69 (q, $J = 1.2$ Hz, 1H), 7.42–7.35 (m, 5H), 4.28 (q, $J = 7.2$ Hz, 2H), 2.12 (d, $J = 1.6$ Hz, 3H), 1.34 (t, $J = 7.2$ Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 168.7, 138.6, 135.9, 129.6, 128.6, 128.3, 128.2, 60.9, 14.3, 14.0; IR (thin film) 2984, 1701, 1369, 1259, 1204, 1115 cm⁻¹; HRMS (DART) m/z [M + H]⁺ calcd for C₁₂H₁₅O₂: 191.1067, found 191.1071.

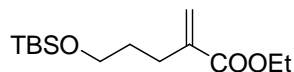


Ethyl 2-methyl-3-phenylpropanoate:⁵ ¹H NMR (400 MHz, CDCl₃) δ 7.38–7.25 (m, 5H), 4.09 (q, $J = 7.2$ Hz, 2H), 3.02 (dd, $J = 12.8, 6.4$ Hz, 1H), 2.72 (hex, $J = 7.2$ Hz, 1H), 2.66 (dd, $J = 12.4,$

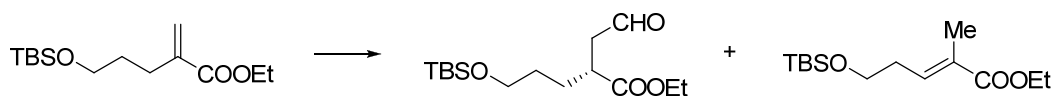
⁴ Green, J. E.; Bender, D. M.; Jackson, S.; O'Donnell, M. J.; McCarthy, J. R. *Org. Lett.* **2009**, *11*, 807.

⁵ Black, P. J.; Edwards, M. G.; Williams, J. M. J. *Eur. J. Org. Chem.* **2006**, 4367.

7.6 Hz, 1H), 1.19 (t, $J = 7.2$ Hz, 3H), 1.15 (d, $J = 6.8$ Hz, 3H); HRMS (DART) m/z $[M - H]^+$ calcd for $C_{12}H_{15}O_2$: 191.1067, found 191.1071.

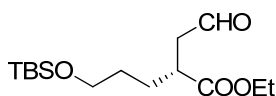


Ethyl 5-((tert-butyldimethylsilyloxy)-2-methylenepentanoate: To a suspension of *t*-BuOK (1.39 g, 12.5 mmol) in THF (30 mL) were added ethyl acetoacetate (1.52 mL, 12.0 mmol) and *t*-BuOH (113 μ L, 1.19 mmol) at 0 °C. The resulting solution was stirred for 30 min, and (3-bromopropoxy)(*tert*-butyl)dimethylsilane (3.00 g, 11.9 mmol) was added. The mixture was stirred at 70 °C for 12 h before concentrated and purified by flash chromatography eluting with hexanes/EtOAc (30:1) to give the crude ethyl 2-acetyl-5-((*tert*-butyldimethylsilyloxy)pentanoate (2.88 g). Then general procedure 1 was followed by employing the crude intermediate (2.88 g, 9.54 mmol, 1.0 equiv), LHMDS (11.4 mL, 11.4 mmol, 1.2 equiv), paraformaldehyde (2.80 g) and THF (50 mL). Purification by flash chromatography eluting with hexanes/EtOAc (60:1 to 15:1) afforded the title compound (1.25 g, 39%, two-step yield) as a colorless oil: ^1H NMR (400 MHz, CDCl_3) δ 6.14 (s, 1H), 5.52 (q, $J = 1.2$ Hz, 1H), 4.19 (q, $J = 7.2$ Hz, 2H), 3.62 (t, $J = 6.4$ Hz, 2H), 2.35 (t, $J = 7.6$ Hz, 2H), 1.68 (tt, $J = 6.4, 4.0$ Hz, 2H), 1.29 (t, $J = 7.2$ Hz, 3H), 0.89 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (100 MHz, CDCl_3) δ 167.3, 140.6, 124.5, 62.4, 60.6, 31.5, 28.3, 25.9, 18.3, 14.2, -5.3 ; IR (thin film) 2956, 2858, 1718, 1653, 1559, 1256, 1103, 836, 776, 668 cm^{-1} ; HRMS (DART) m/z $[M + H]^+$ calcd for $C_{14}H_{29}O_3\text{Si}$: 273.1886, found 273.1883.

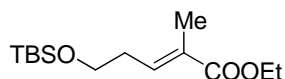


(Table 3, entry 5)

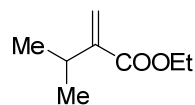
General procedure 2 was followed by employing ethyl 5-(*tert*-butyldimethylsilyloxy)-2-methylenepentanoate (136 mg, 0.50 mmol). Purification by flash chromatography eluting with pentane/Et₂O (100:1 to 5:1) afforded the linear aldehyde (93 mg, 62%, colorless oil) and the olefin isomer (34 mg, 25%, colorless oil):



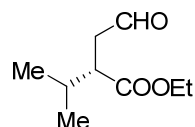
(*R*)-ethyl 5-(*tert*-butyldimethylsilyloxy)-2-(2-oxoethyl)pentanoate: Enantiomeric excess (81%) was determined by chiral GC analysis [CP Chirasil-Dex CD, 25 m × 0.25 mm × 0.25 mm, flow rate 3.5 mL/min, method: ramp from 50 °C to 130 °C at 2.0 °C/min, 130 °C for 40 min: (*S*) *t_r* = 66.0 min, (*R*) *t_r* = 66.8 min]; [α]_D²⁵ +11 (c 0.34, CHCl₃); ¹H NMR (600 MHz, CDCl₃) δ 9.75 (quasi-s, 1H), 4.13 (q, *J* = 7.2 Hz, 2H), 3.59 (t, *J* = 6.0 Hz, 2H), 2.90 (m, 1H), 2.87 (dd, *J* = 16.2, 9.0 Hz, 1H), 2.53 (dd, *J* = 16.2, 3.0 Hz, 1H), 1.69 (m, 1H), 1.59 (m, 1H), 1.51 (m, 2H), 1.24 (t, *J* = 7.2 Hz, 3H), 0.87 (s, 9H), 0.02 (s, 6H); ¹³C NMR (150 MHz, CDCl₃) δ 200.1, 174.6, 62.5, 60.7, 45.4, 38.8, 30.0, 28.3, 25.9, 18.2, 14.1, -5.4; IR (thin film) 2955, 1734, 1716, 1473, 1256, 1179, 1100, 837, 777 cm⁻¹; HRMS (DART) *m/z* [M + H]⁺ calcd for C₁₅H₃₁O₄Si: 303.1992, found 303.1984.



(E)-Ethyl 5-(*tert*-butyldimethylsilyloxy)-2-methylpent-2-enoate: ^1H NMR (600 MHz, CDCl_3) δ 6.77 (td, $J = 7.8, 1.2$ Hz, 1H), 4.18 (q, $J = 7.2$ Hz, 2H), 3.69 (t, $J = 6.6$ Hz, 2H), 2.39 (q, $J = 7.2$ Hz, 2H), 1.83 (s, 3H), 1.27 (t, $J = 7.2$ Hz, 3H), 0.88 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (150 MHz, CDCl_3) δ 168.0, 138.5, 129.3, 61.7, 60.4, 32.4, 25.9, 18.3, 14.2, 12.5, -5.4 ; IR (thin film) 2956, 1714, 1473, 1257, 1101, 837, 776 cm^{-1} ; HRMS (DART) m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{14}\text{H}_{29}\text{O}_3\text{Si}$: 273.1886, found 273.1862.

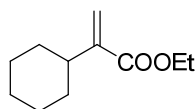


Ethyl 3-methyl-2-methylenebutanoate: General procedure 1 was followed by employing ethyl 2-isopropylacetoacetate (8.60 g, 50.0 mmol, 1.0 equiv), LHMDS (55.0 mL, 55.0 mmol, 1.1 equiv), paraformaldehyde (7.00 g) and THF (200 mL). Purification by flash chromatography eluting with hexanes/EtOAc (20:1) afforded the title compound (4.16 g, 59%) as a colorless oil: ^1H NMR (400 MHz, CDCl_3) δ 6.11 (s, 1H), 5.50 (quasi-s, 1H), 4.21 (q, $J = 7.2$ Hz, 2H), 2.81 (hept-d, $J = 6.8, 0.8$ Hz, 1H), 1.30 (t, $J = 6.8$ Hz, 3H), 1.08 (d, $J = 6.8$ Hz, 6H); ^{13}C NMR (100 MHz, CDCl_3) δ 167.5, 147.4, 121.5, 60.5, 29.3, 21.8, 14.2; IR (thin film) 2965, 1717, 1465, 1370, 1277, 1183 cm^{-1} ; HRMS (DART) m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_8\text{H}_{15}\text{O}_2$: 143.1072, found 143.1073.



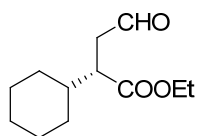
(Table 3, entry 6)

(S)-Ethyl 2-isopropyl-4-oxobutanoate: General procedure 2 was followed by employing ethyl 3-methyl-2-methylenebutanoate (71 mg, 0.50 mmol). Purification by flash chromatography eluting with pentane/Et₂O (100:1 to 5:1) afforded the title compound (78 mg, 91%) as a colorless oil: Enantiomeric excess (92%) was determined by chiral GC analysis [CP Chirasil-Dex CD, 25 m × 0.25 mm × 0.25 mm, flow rate 3.5 mL/min, method: ramp from 60 °C to 75 °C at 0.3 °C/min, 75 °C for 20 min: (*R*) *t_r* = 47.5 min, (*S*) *t_r* = 47.8 min)]; [α]_D²⁵ +3.6 (c 1.9, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 9.77 (quasi-s, 1H), 4.15 (dq, *J* = 10.4, 6.8 Hz, 1H), 4.12 (dq, *J* = 11.2, 7.2 Hz, 1H), 2.87 (ddd, *J* = 18.0, 10.4, 0.8 Hz, 1H), 2.75 (ddd, *J* = 10.4, 5.6, 3.6 Hz, 1H), 2.48 (dd, *J* = 17.6, 3.2 Hz, 1H), 2.01 (oct, *J* = 6.0 Hz, 1H), 1.24 (t, *J* = 7.0 Hz, 3H), 0.92 (d, *J* = 6.8 Hz, 3H), 0.90 (d, *J* = 6.8 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 200.6, 174.1, 60.5, 45.1, 42.3, 29.8, 20.1, 19.4, 14.2; IR (thin film) 2966, 1732, 1467, 1374, 1182, 1039 cm⁻¹; HRMS (DART) *m/z* [M – H]⁺ calcd for C₉H₁₅O₃: 171.1021, found 171.1030.



Ethyl 2-cyclohexylacrylate: To the solution of ethyl 2-cyclohexylacetate (2.36 g, 13.9 mmol, 1.0 equiv) in THF (25 mL) was slowly added LHMDS (1.0 M solution in THF, 16.7 mL, 16.7 mmol, 1.2 equiv) at –78 °C. The solution was stirred for 30 min, and then paraformaldehyde (6.00 g, excess) was added in one portion. The orange suspension was warmed to room temperature and stirred for 12 h. The mixture was filtered through a pad of celite to remove the

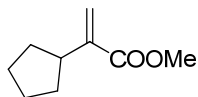
excess paraformaldehyde. The filtrate was concentrated and redissolved in DCM (25 mL). The solution was cooled to 0 °C and DBU (2.07 g, 13.6 mmol) followed by mesyl chloride (1.21 g, 10.5 mmol) was added. The solution was stirred at room temperature for 48 h before cooled to –78 °C and added LHMDS (12.4 mL, 12.4 mmol). The stirring continued for 24 h and the suspension was filtered through celite. The filtrate was concentrated, and the residue was purified by flash chromatography eluting with hexanes/EtOAc (60:1) to afford the title compound (320 mg, 13%) as a colorless oil: ¹H NMR (400 MHz, CDCl₃) δ 6.10 (d, *J* = 0.8 Hz, 1H), 5.46 (t, *J* = 1.2 Hz, 1H), 4.20 (q, *J* = 7.2 Hz, 2H), 2.44 (tt, *J* = 11.6, 2.8, 1.2 Hz, 1H), 1.79 (tt, *J* = 13.6, 3.0 Hz, 4H), 1.70 (m, 1H), 1.41–1.05 (m, 5H), 1.30 (t, *J* = 6.8 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 167.6, 146.6, 121.8, 60.5, 39.1, 32.5 (2C), 26.6 (2C), 26.2, 14.2; IR (thin film) 2926, 1717, 1540, 1457, 1278, 1152 cm⁻¹; HRMS (DART) *m/z* [M + H]⁺ calcd for C₁₁H₁₉O₂: 183.1385, found 183.1388.



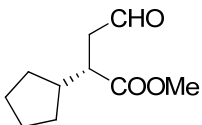
(Table 3, entry 7)

(S)-Ethyl 2-cyclohexyl-4-oxobutanoate: General procedure 2 was followed by employing ethyl 2-cyclohexylacrylate (91 mg, 0.50 mmol). Purification by flash chromatography eluting with pentane/Et₂O (100:1 to 5:1) afforded the title compound (89 mg, 84%) as a colorless oil: Enantiomeric excess (94%) was determined by chiral GC analysis [Astec G-TA column 30 m × 0.25 mm, flow rate 1.5 mL/min, method: ramp from 100 °C to 150 °C at 0.5 °C/min, (*R*) *t_r* = 51.8 min, (*S*) *t_r* = 53.0 min]; [*α*]_D²⁵ +5.8 (c 0.69, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 9.78 (quasi-s, 1H), 4.15 (q, *J* = 7.2 Hz, 2H), 2.90 (ddd, *J* = 18.0, 10.4, 0.8 Hz, 1H), 2.75 (ddd, *J* = 9.2,

5.2, 3.6 Hz, 1H), 2.54 (dd, $J = 18.0, 3.6$ Hz, 1H), 1.74 (m, 2H), 1.64 (m, 4H), 1.26 (t, $J = 7.2$ Hz, 3H), 1.23–0.95 (m, 5H); ^{13}C NMR (100 MHz, CDCl_3) δ 200.1, 174.3, 60.5, 44.8, 42.8, 39.8, 30.7, 30.0, 26.3 (2C), 26.1, 14.2; IR (thin film) 2930, 1733, 1717, 1449, 1177, 1035 cm^{-1} ; HRMS (DART) m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{12}\text{H}_{21}\text{O}_3$: 213.1491, found 213.1478.



Methyl 2-cyclopentylacrylate: General procedure 1 was followed by employing methyl 2-cyclopentyl-3-oxobutanoate (2.00 g, 10.9 mmol, 1.0 equiv), LHMDS (12.1 mL, 12.1 mmol, 1.1 equiv), paraformaldehyde (2.00 g) and THF (20 mL). Purification by flash chromatography eluting with hexanes/EtOAc (30:1 to 15:1) afforded the title compound (1.23 g, 74%) as a colorless oil: ^1H NMR (600 MHz, CDCl_3) δ 6.10 (s, 1H), 5.53 (s, 1H), 3.75 (s, 3H), 2.85 (quint, $J = 8.4$ Hz, 1H), 1.90 (dtd, $J = 10.8, 10.8, 4.2$ Hz, 2H), 1.69 (m, 2H), 1.61 (tdd, $J = 16.8, 9.0, 3.6$ Hz, 2H), 1.39 (ddt, $J = 14.4, 11.4, 8.4$ Hz, 2H); ^{13}C NMR (150 MHz, CDCl_3) δ 168.1, 144.4, 121.8, 51.7, 41.4, 31.9, 24.9; IR (thin film) 2953, 1724, 1437, 1270, 1137, 939 cm^{-1} ; HRMS (DART) m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_9\text{H}_{15}\text{O}_2$: 155.1072, found 155.1074.

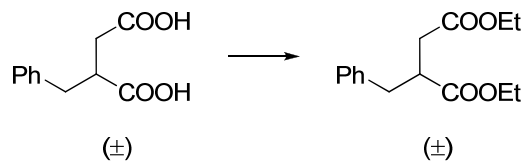


(Table 3, entry 8)

(S)-methyl 2-cyclopentyl-4-oxobutanoate: General procedure 2 was followed by employing methyl 2-cyclopentylacrylate (77 mg, 0.50 mmol). Purification by flash chromatography eluting with pentane/Et₂O (100:1 to 5:1) afforded the title compound (78 mg, 85%) as a colorless oil:

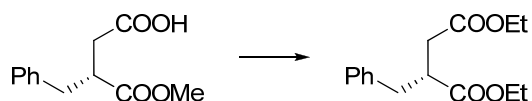
Enantiomeric excess (93%) was determined by chiral GC analysis [CP Chirasil-Dex CD, 25 m × 0.25 mm × 0.25 mm, flow rate 3.5 mL/min, method: ramp from 50 °C to 130 °C at 4.0 °C/min, 130 °C for 25 min: (*R*) t_r = 21.7 min, (*S*) t_r = 21.8 min]; $[\alpha]_D^{25}$ +8.8 (c 0.78, CHCl₃); ¹H NMR (600 MHz, CDCl₃) δ 9.75 (quasi-s, 1H), 3.68 (s, 3H), 2.91 (ddd, J = 18.0, 10.2, 0.6 Hz, 1H), 2.72 (ddd, J = 9.0, 9.0, 4.2 Hz, 1H), 2.62 (dd, J = 18.0, 3.6 Hz, 1H), 1.99 (ttd, J = 9.6, 7.2, 7.2 Hz, 1H), 1.76 (dtd, J = 10.8, 7.2, 3.6 Hz, 1H), 1.68 (dtd, J = 10.8, 7.8, 3.6 Hz, 1H), 1.63 (m, 2H), 1.53 (m, 2H), 1.27 (m, 1H), 1.15 (qdd, J = 9.0, 9.0, 3.6 Hz, 1H); ¹³C NMR (150 MHz, CDCl₃) δ 200.5, 175.2, 51.7, 45.1, 43.8, 42.2, 30.5, 30.4, 24.9, 24.8; IR (thin film) 2953, 1734, 1436, 1170, 1029 cm⁻¹; HRMS (DART) m/z [M + H]⁺ calcd for C₁₀H₁₇O₃: 185.1178, found 185.1175.

Determination of the absolute configuration of the aldehyde products.

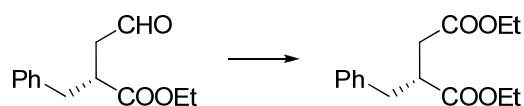


Diethyl 2-benzylsuccinate (racemic): To a solution of 2-benzylsuccinic acid (62 mg, 0.30 mmol) in DCM (2 mL) were added DMAP (15 mg, 0.12 mmol), EDCI (115 mg, 0.60 mmol) and ethanol (70 μ L, 1.2 mmol). The solution was stirred for 30 min and concentrated. Purification by flash chromatography eluting with hexanes/EtOAc (19:1) afforded title diethyl ester (58 mg, 73%) as a colorless oil: Separation of enantiomers was done by chiral HPLC [Chiralcel OD-H, hexanes/*i*-PrOH, 98.5:1.5, 1.0 mL/min: (*R*) t_r = 14.6 min, (*S*) t_r = 19.0 min]; ¹H NMR (400 MHz, CDCl₃) δ 7.32–7.13 (m, 5H), 4.12 (q, J = 7.2 Hz, 2H), 4.09 (q, J = 7.2 Hz, 2H), 3.11 (dddd, J = 9.2, 8.4, 6.4, 5.2 Hz, 1H), 3.04 (dd, J = 13.2, 6.4 Hz, 1H), 2.76 (dd, J = 13.6, 8.4 Hz, 1H), 2.66 (dd, J = 16.8, 9.2 Hz, 1H), 2.39 (dd, J = 16.8, 5.2 Hz, 1H), 1.22 (t, J = 7.2 Hz, 3H), 1.19 (t, J =

7.2 Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 174.2, 171.8, 138.2, 129.0, 128.5, 126.6, 60.7, 60.6, 43.1, 37.8, 35.3, 14.1, 14.0; IR (thin film) 2982, 1734, 1456, 1374, 1178, 1031, 701 cm^{-1} ; HRMS (DART) m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{15}\text{H}_{21}\text{O}_4$: 265.1440, found 265.1441.

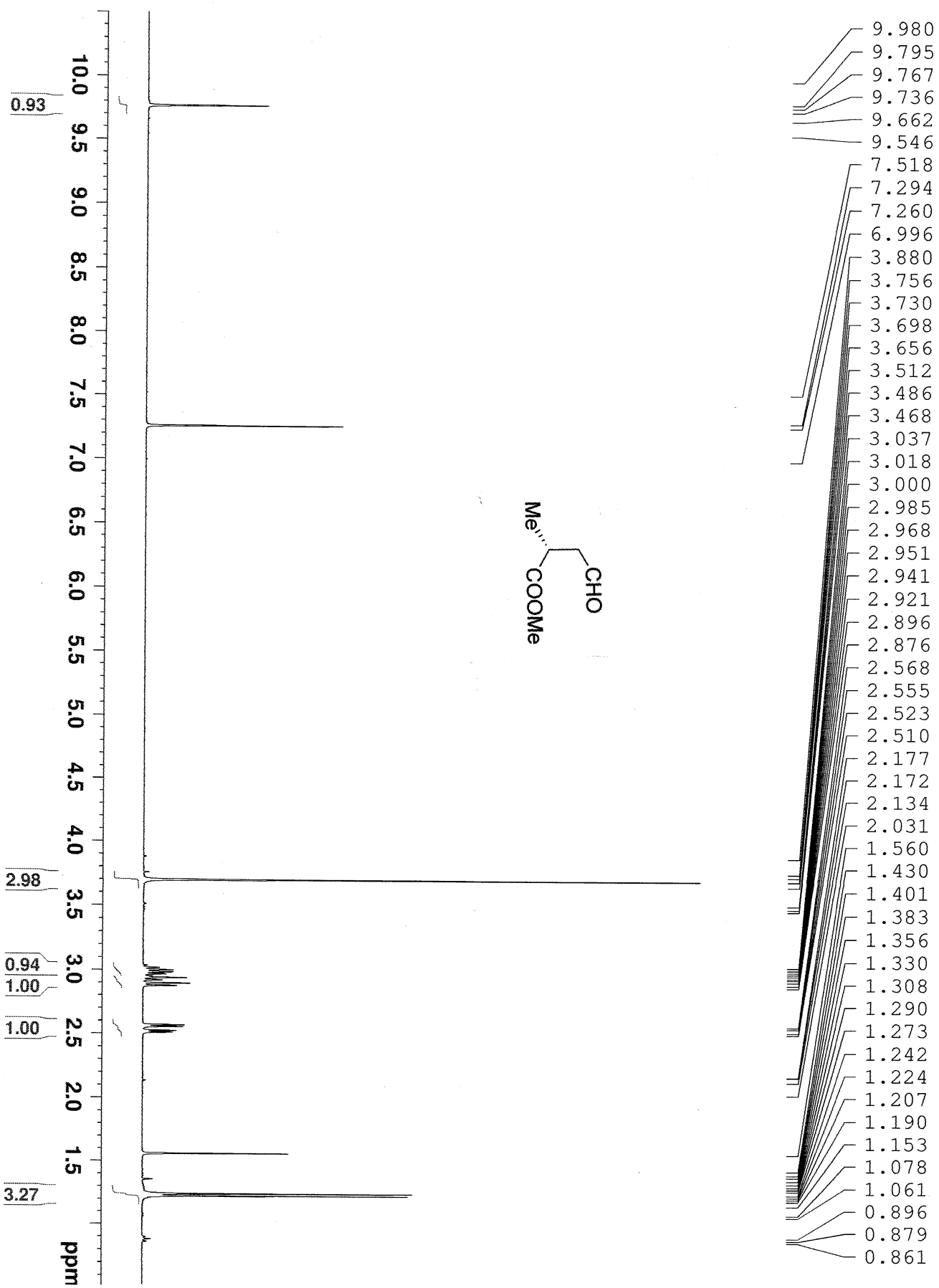


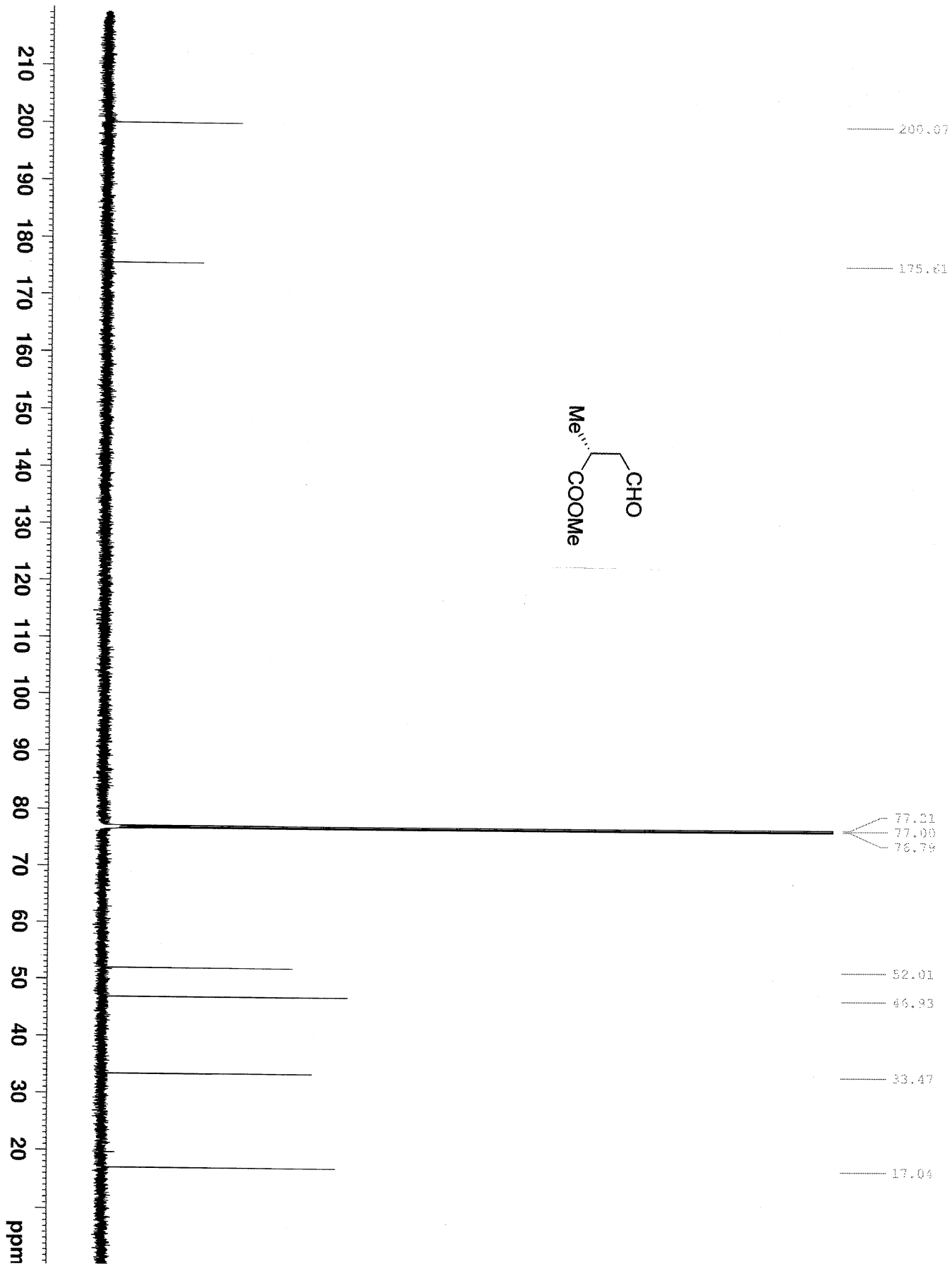
(R)-Diethyl 2-benzylsuccinate (from commercially available, enantiopure monoester): To a solution of (*R*)-3-benzyl-4-methoxy-4-oxobutanoic acid (20 mg, 0.090 mmol) in THF/ H_2O (1:1, 2 mL) was added K_2CO_3 (25 mg, 0.18 mmol) at room temperature. The reaction was followed by TLC and ^1H NMR analysis. After the hydrolysis was complete, the mixture was neutralized by adding aqueous HCl (3 M) to pH = 7, and was passed through a layer of silica gel eluting with EtOAc (15 mL). The solvent was removed under reduced pressure and the residue was dissolved in DCM (2 mL). To the solution were added DMAP (4.4 mg, 0.036 mmol), EDCI (35 mg, 0.18 mmol) and ethanol (21 μL , 0.36 mmol). The solution was stirred at room temperature for 1 h and then concentrated *in vacuo*. Purification by flash chromatography eluting with hexanes/EtOAc (40:1) afforded the diethyl ester (9.0 mg, 38%) as a colorless oil: Spectroscopy data are identical with those of the racemic compound; Separation of enantiomers was done by chiral HPLC [Chiralcel OD-H, hexanes/*i*-PrOH, 98.5:1.5, 1.0 mL/min: (*R*, major) t_r = 14.7 min, (*S*, minor) t_r = 18.9 min].

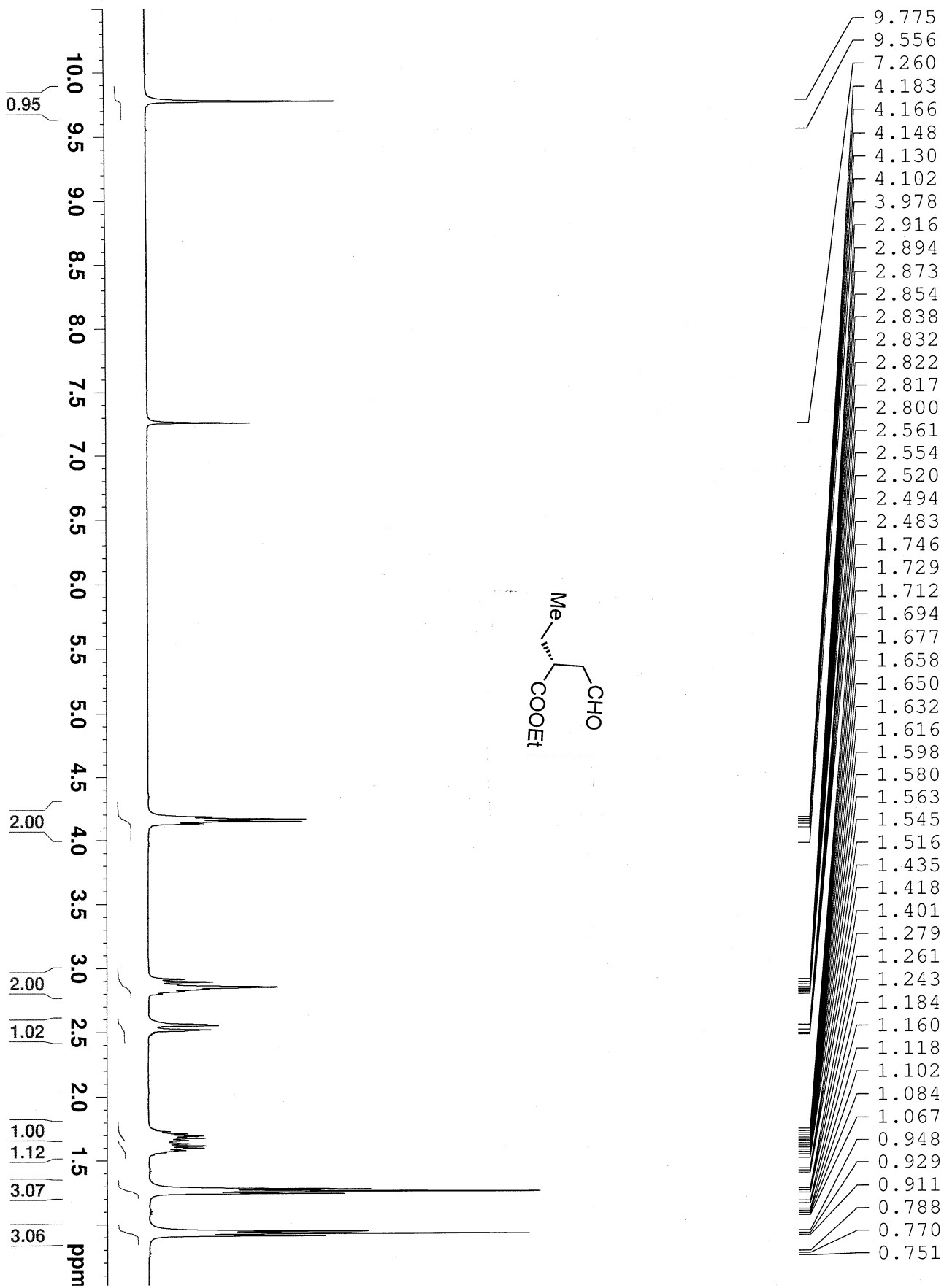


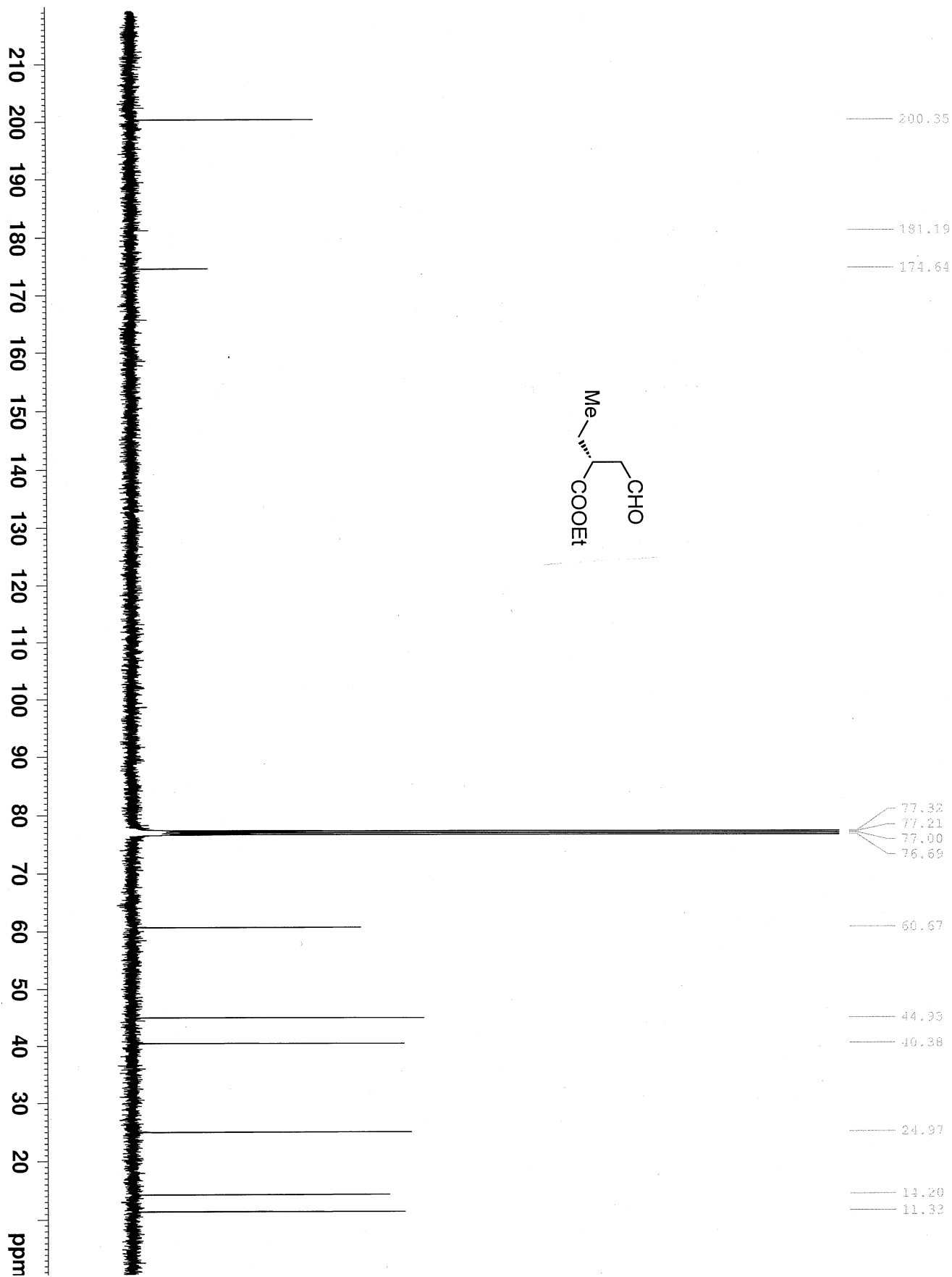
(R)-Diethyl 2-benzylsuccinate (from the hydroformylation product):⁶ A solution of sodium chlorite (13 mg of commercial 80 w%, 0.12 mmol) in pH 3.5 buffer (1 mL) was added dropwise to a solution of (*R*)-ethyl 2-benzyl-4-oxobutanoate (20 mg, 0.091 mmol, with 70% ee isolated from a test run) and 2-methyl-2-butene (2 M in THF, 0.46 mL, 0.91 mmol) in *tert*-butyl alcohol (5 mL) at room temperature. The reaction was followed by TLC. After 10 h, the mixture was passed through a layer of silica gel eluting with EtOAc (15 mL). The solvent was removed under reduced pressure. The residue was dissolved in DCM (2 mL), and to the solution were added DMAP (2.2 mg, 0.018 mmol), EDCI (17.5 mg, 0.091 mmol) and ethanol (11 μ L, 0.18 mmol). The mixture was stirred for 30 min and concentrated. Purification by flash chromatography eluting with hexanes/EtOAc (40:1) afforded the diethyl ester (11 mg, 46%) as a colorless oil: Spectroscopy data are identical with those of the racemic compound; Separation of enantiomers was done by chiral HPLC [Chiralcel OD-H, hexanes/*i*-PrOH, 98.5:1.5, 1.0 mL/min: (*R*, major) t_r = 14.6 min, (*S*, minor) t_r = 19.0 min].

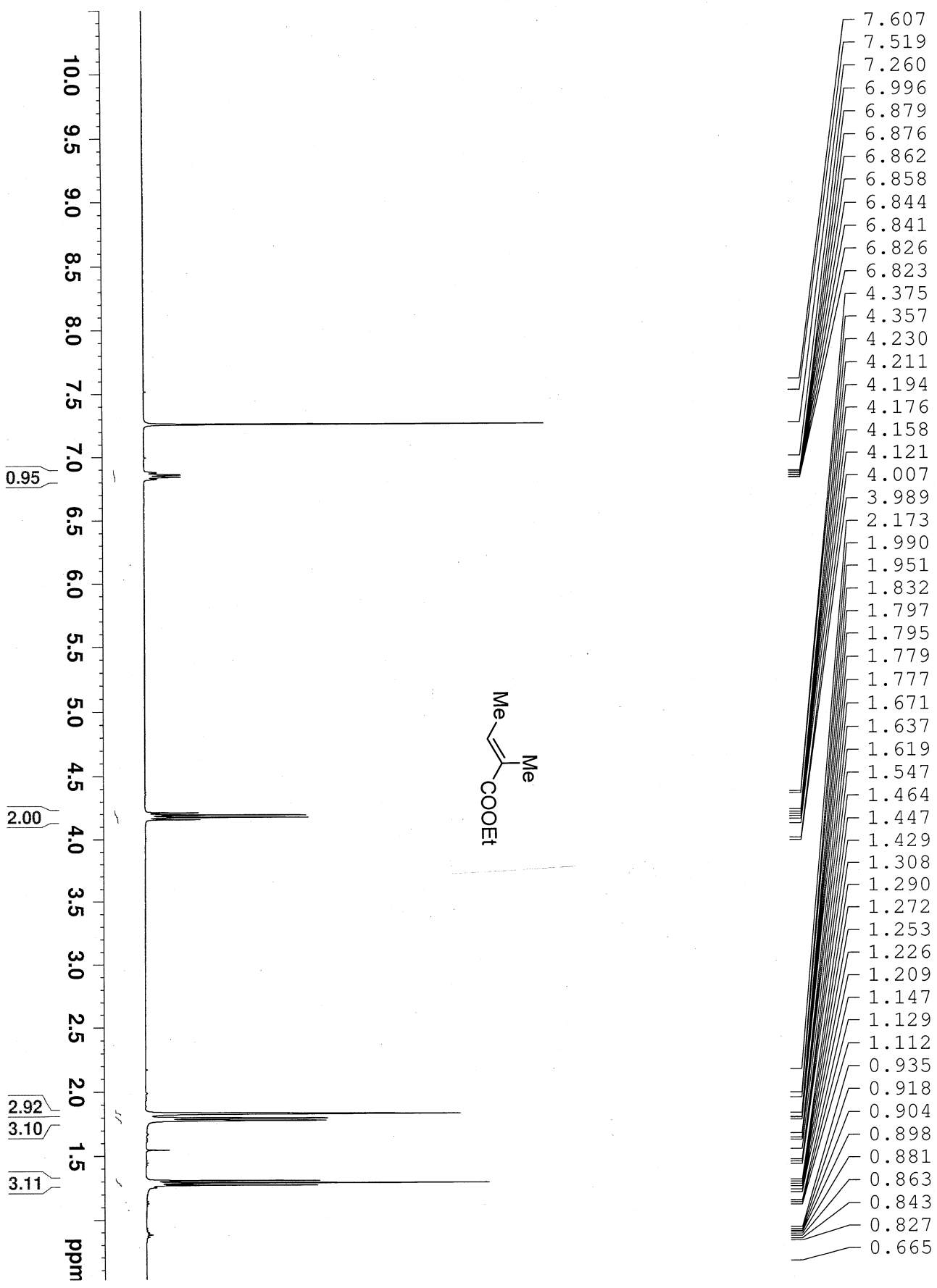
⁶ Kraus, G. A.; Roth, B. *J. Org. Chem.* **1980**, *45*, 4825.

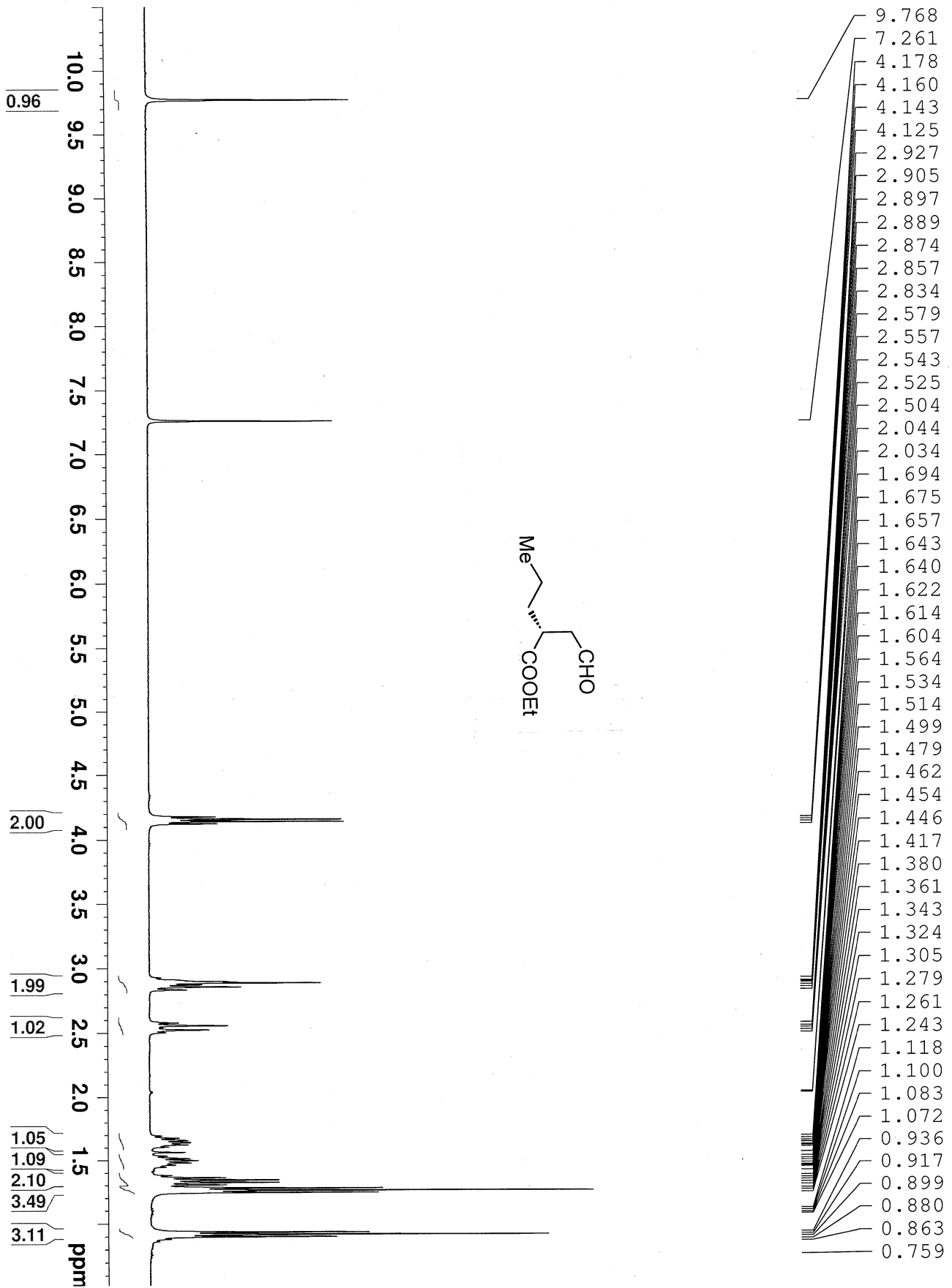


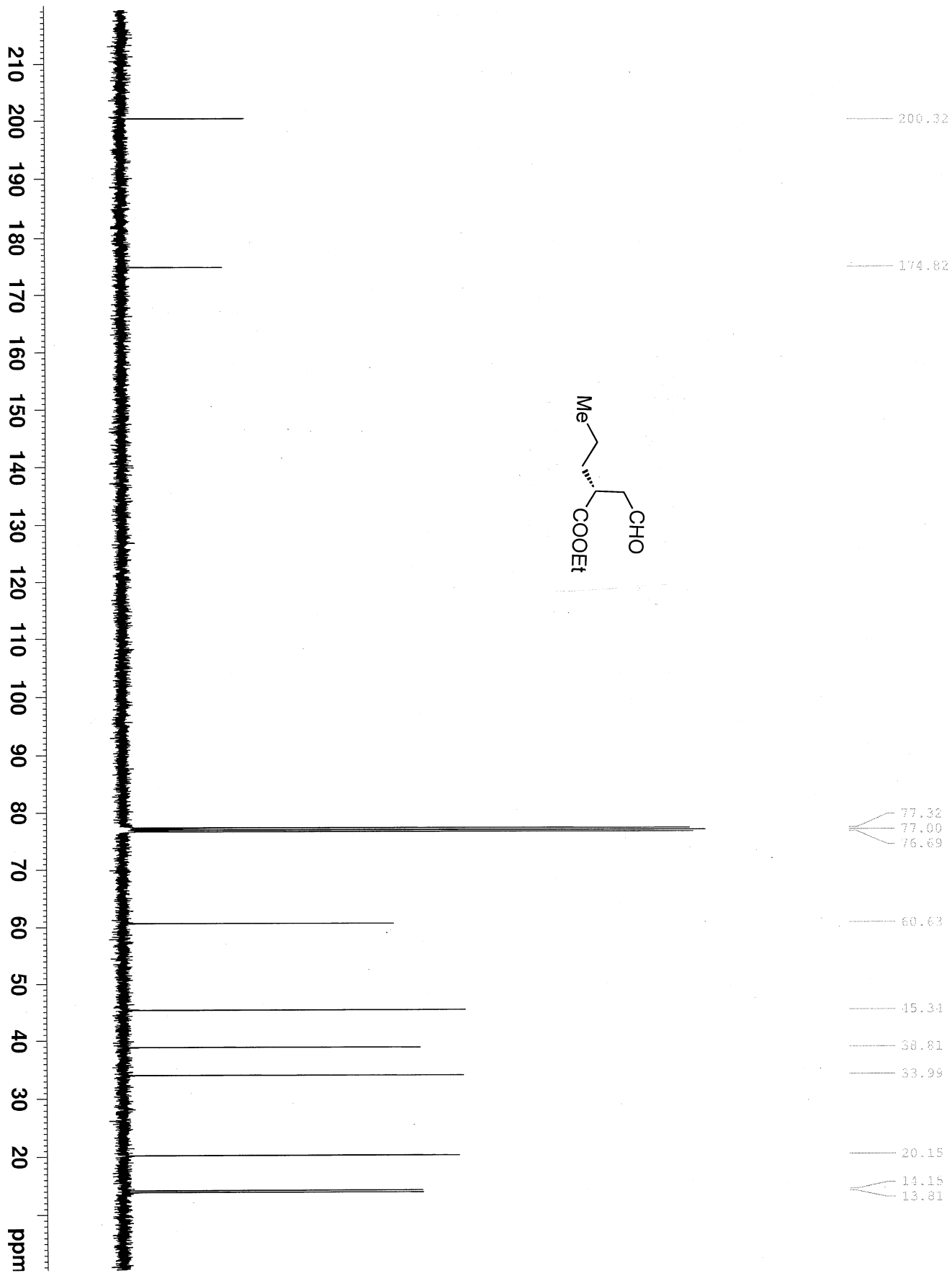


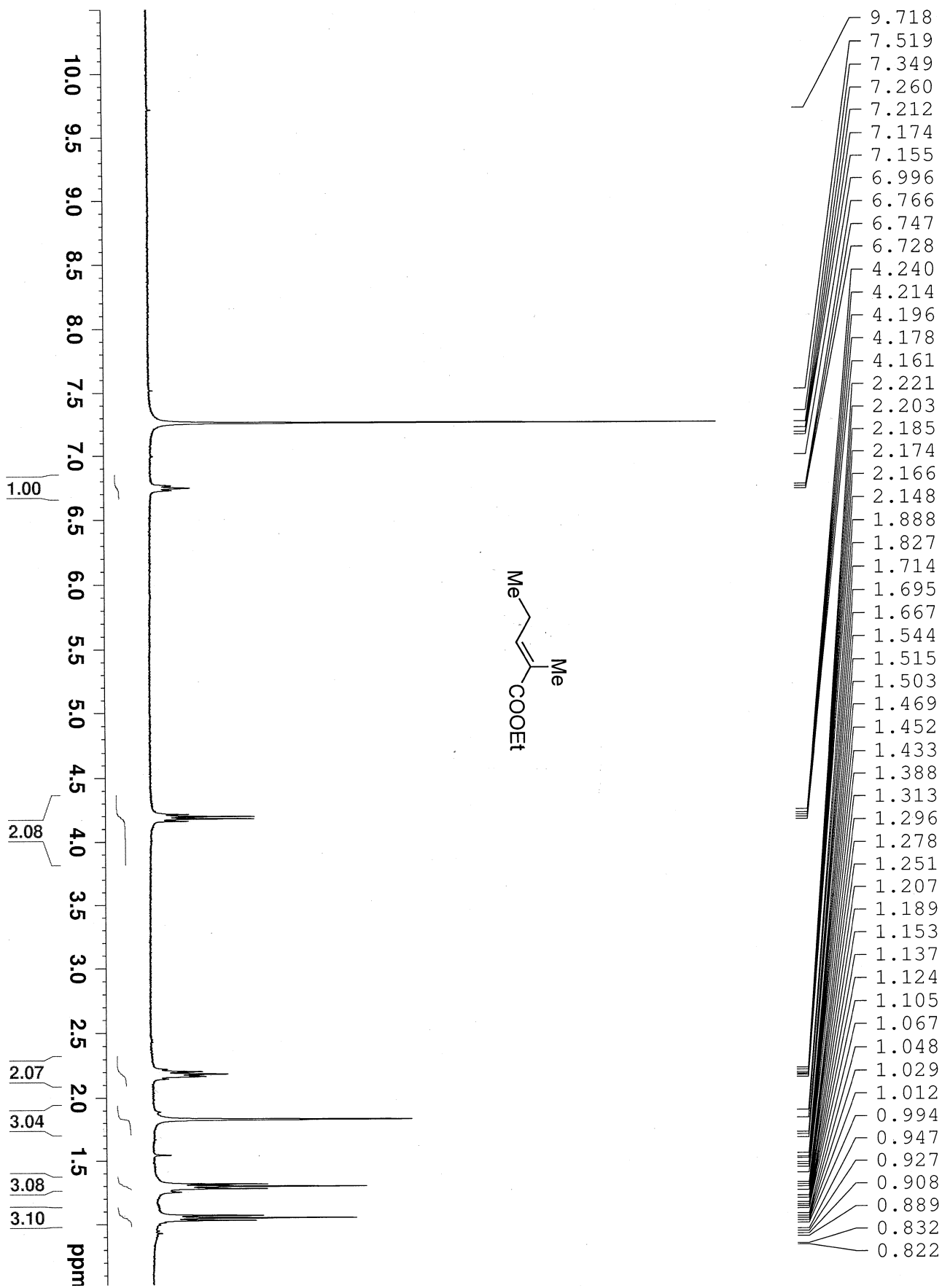


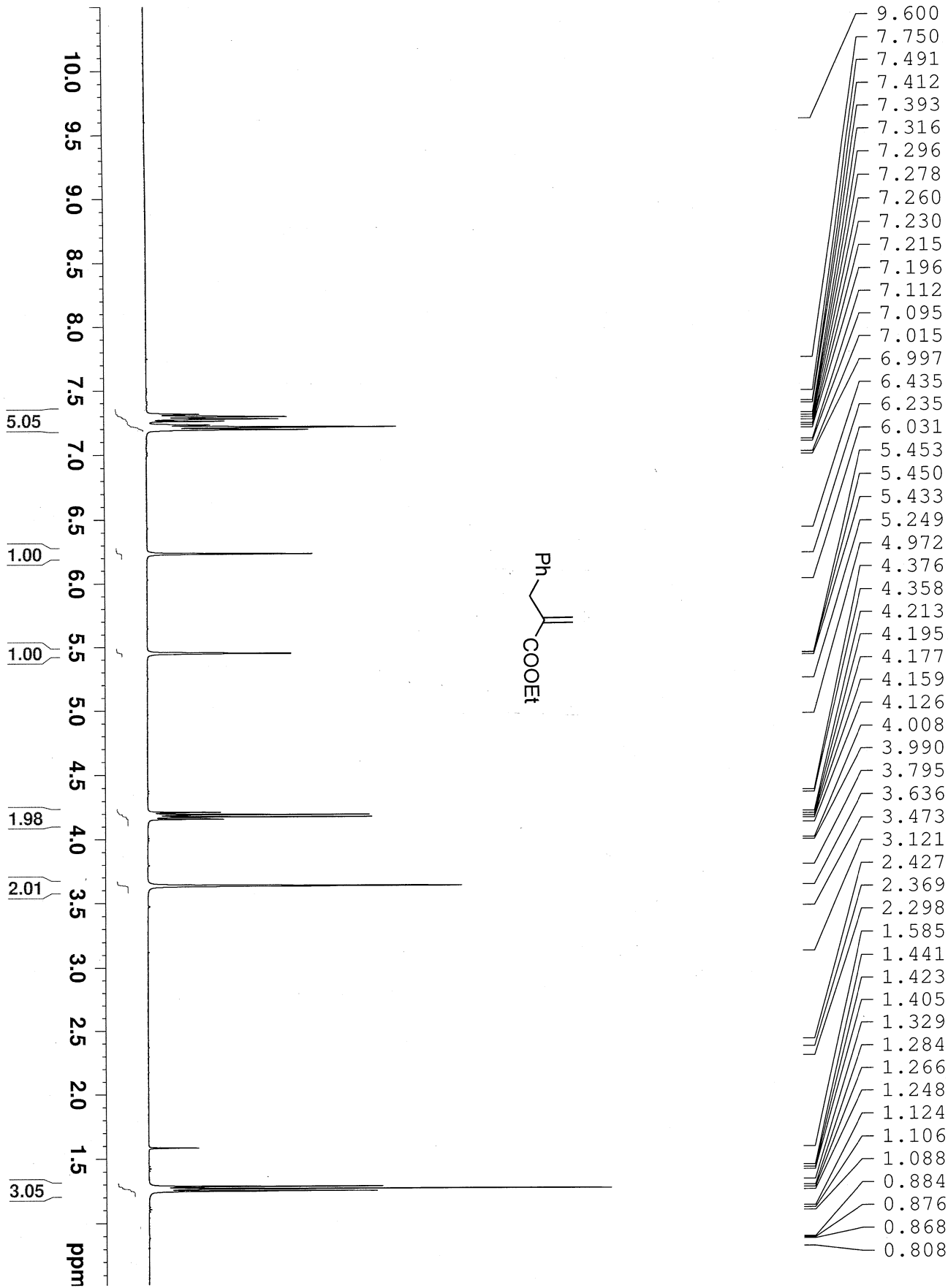


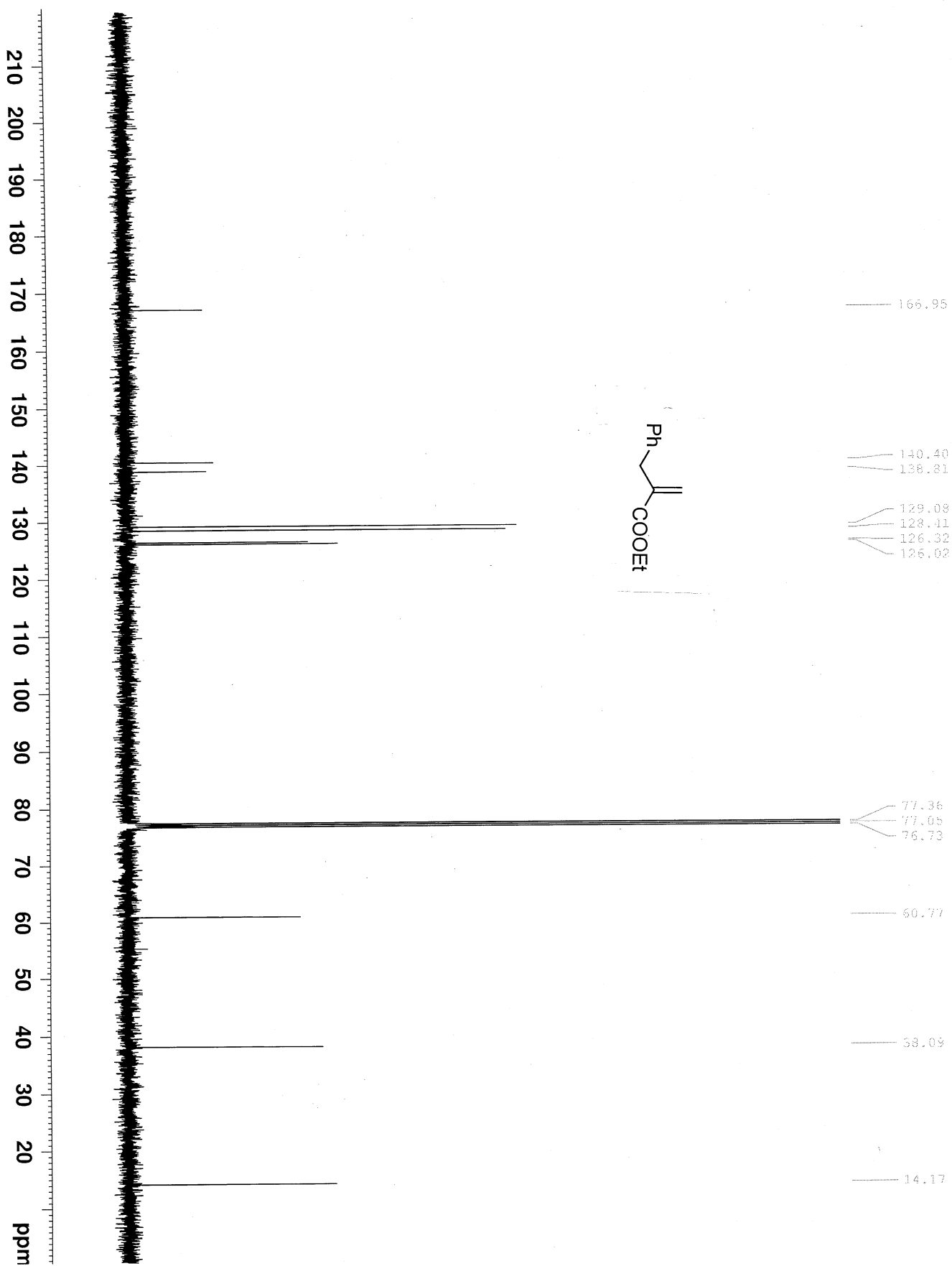
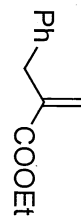


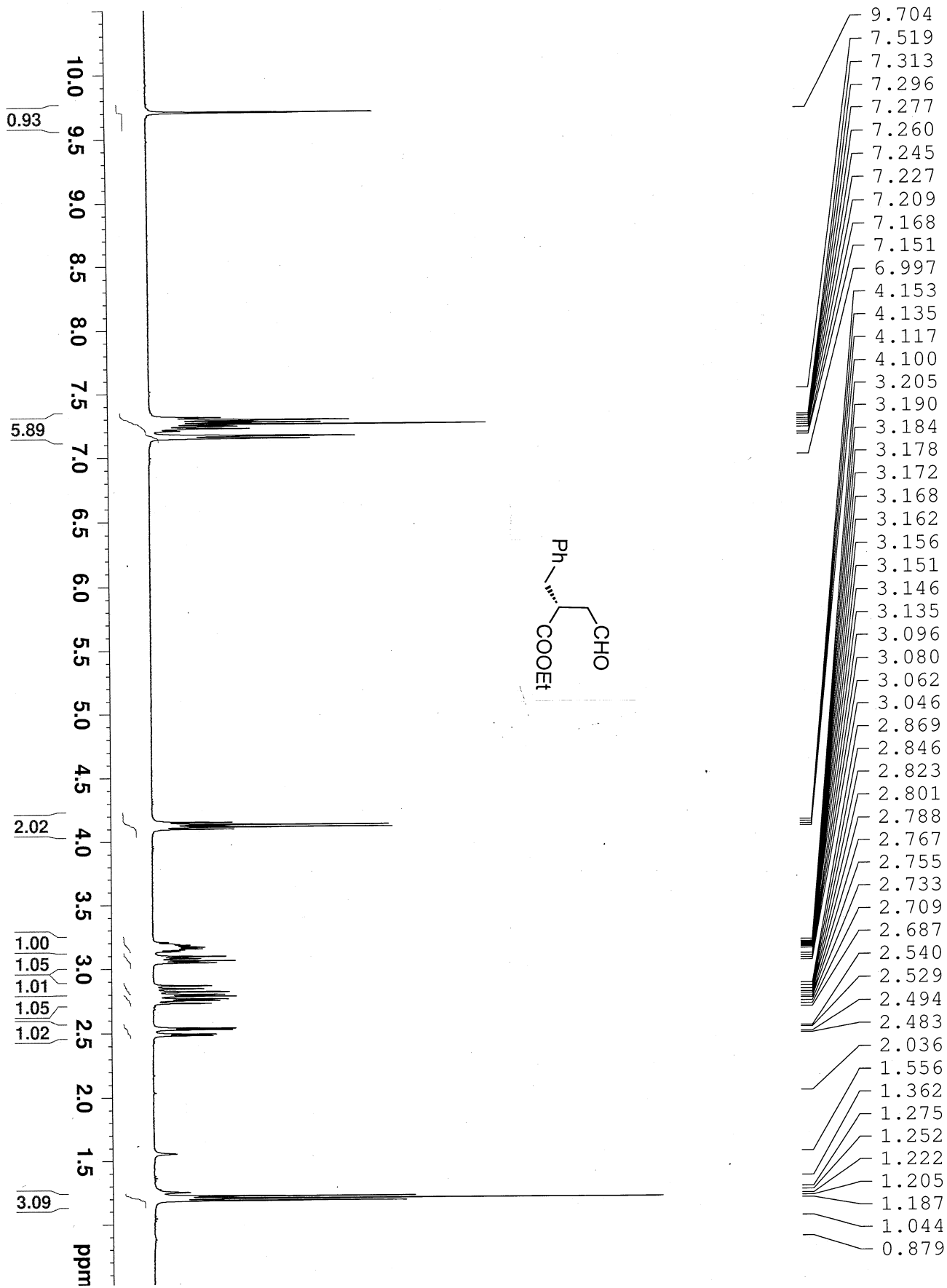


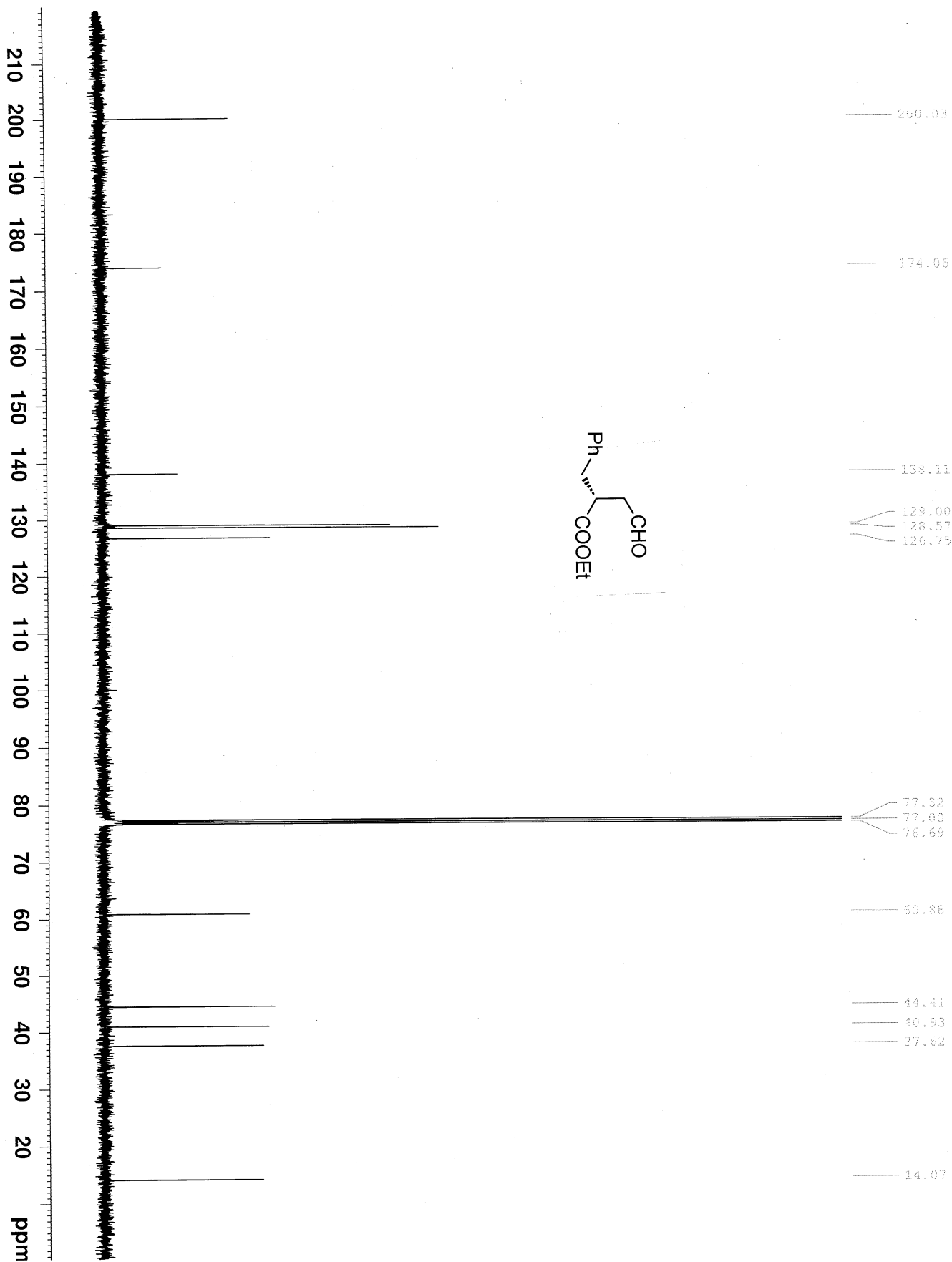


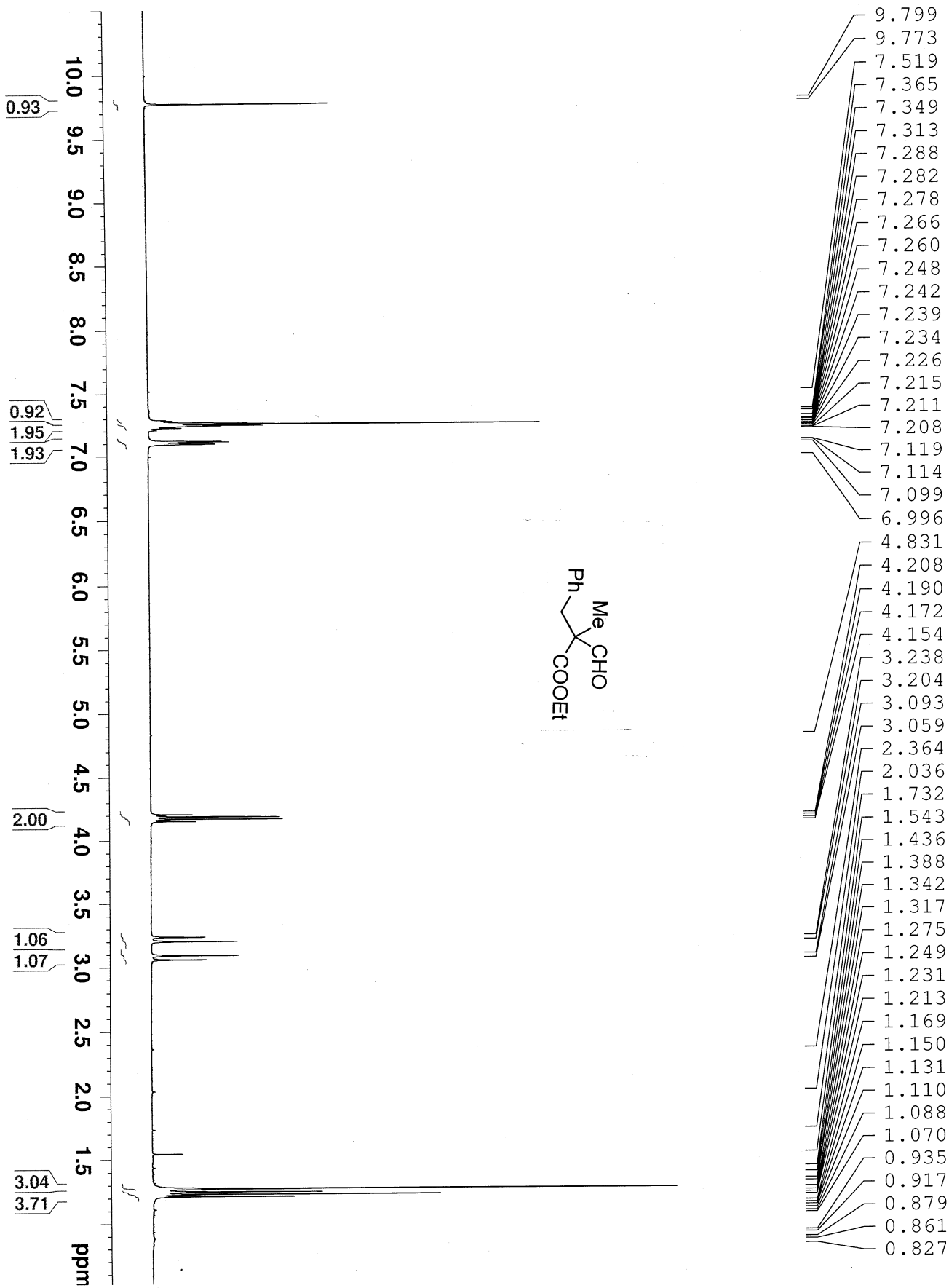


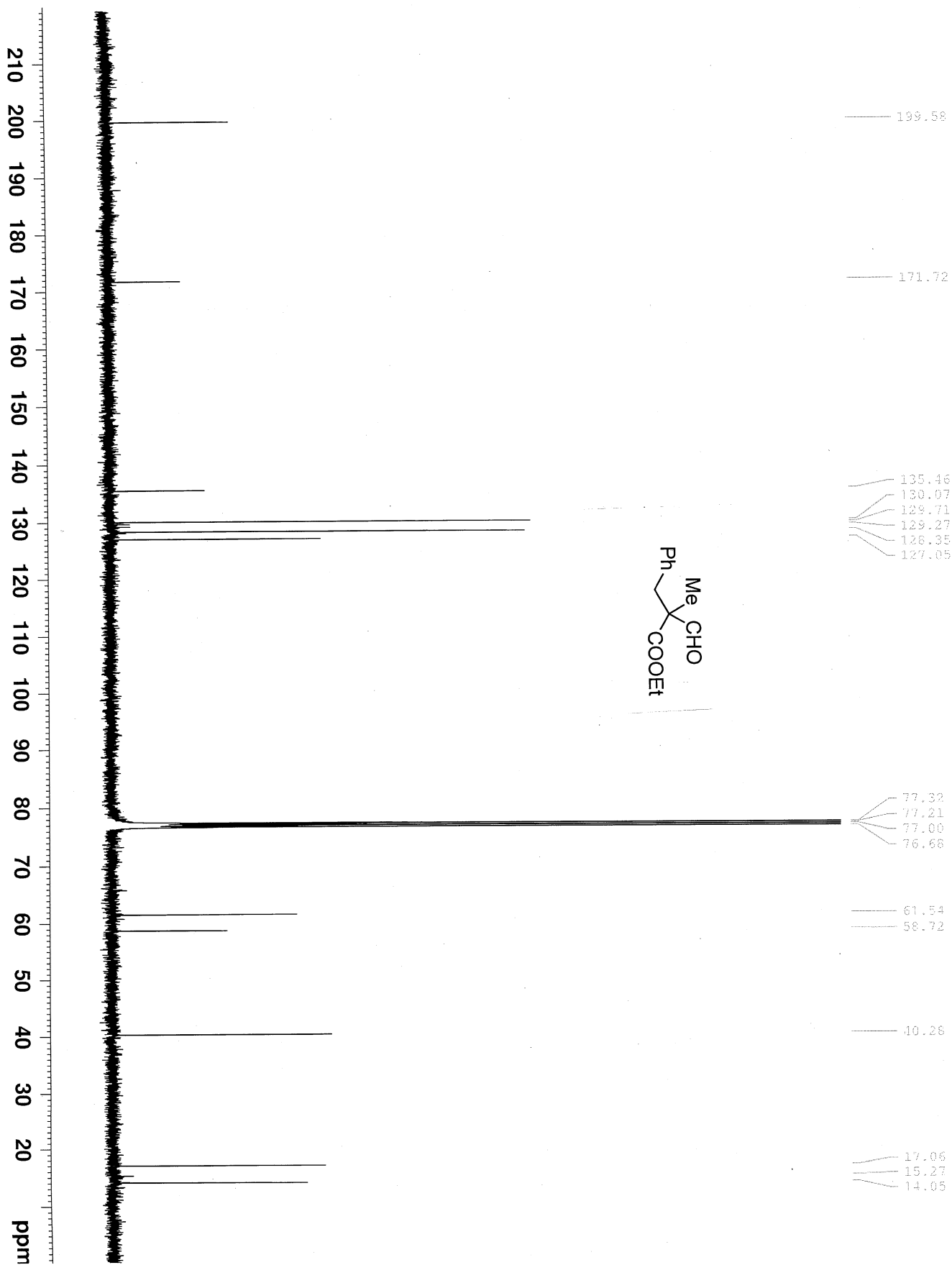


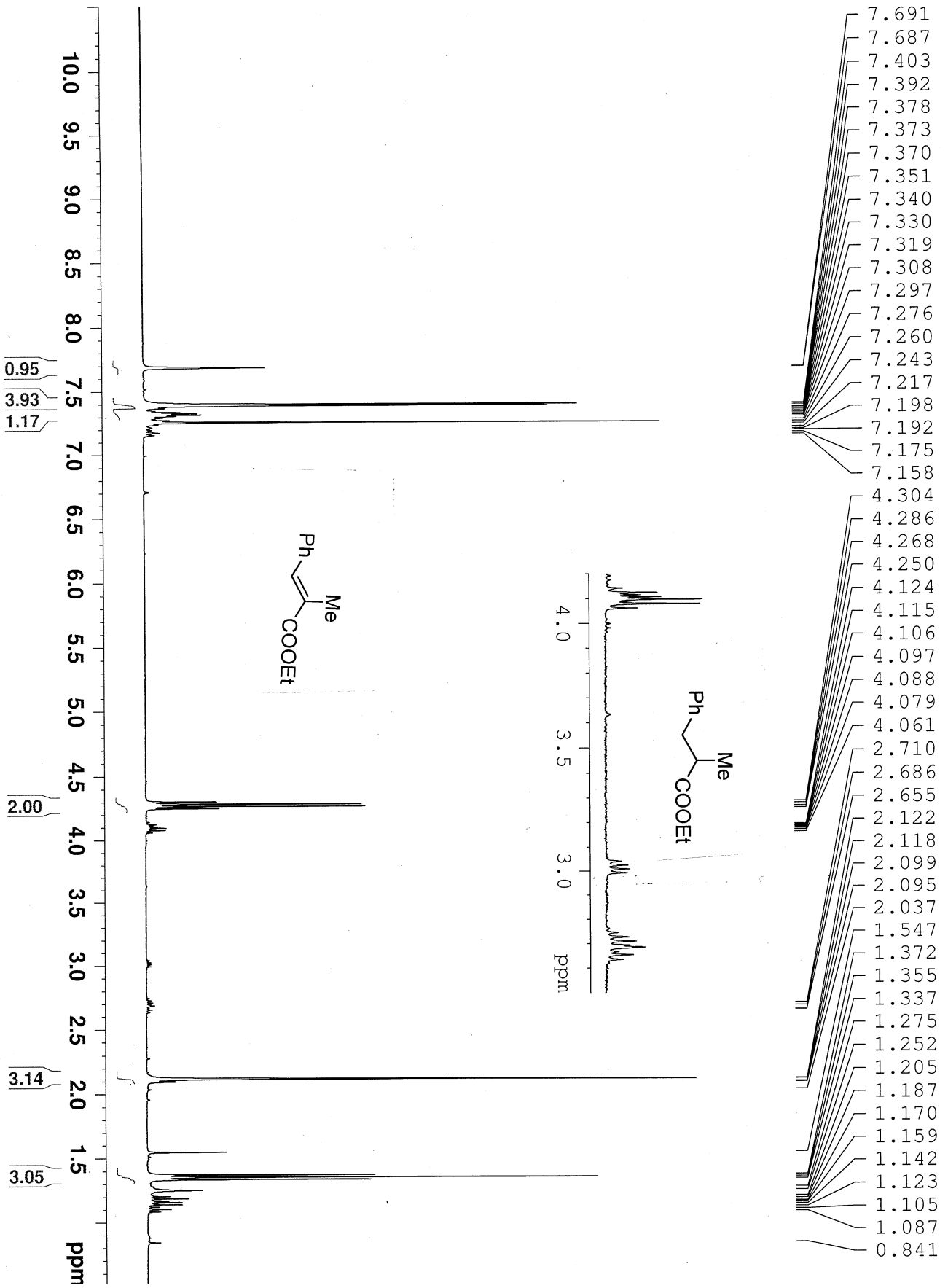


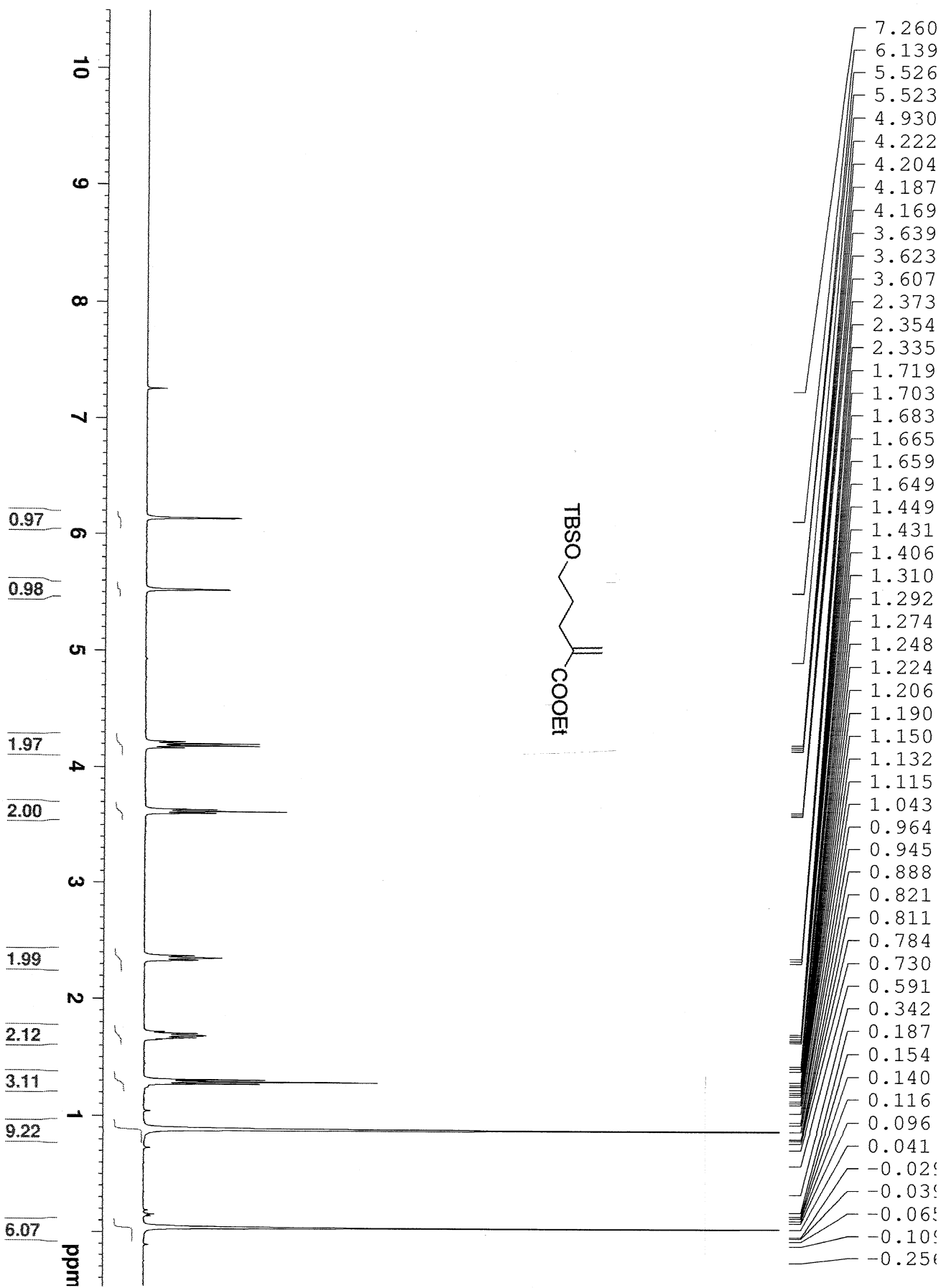


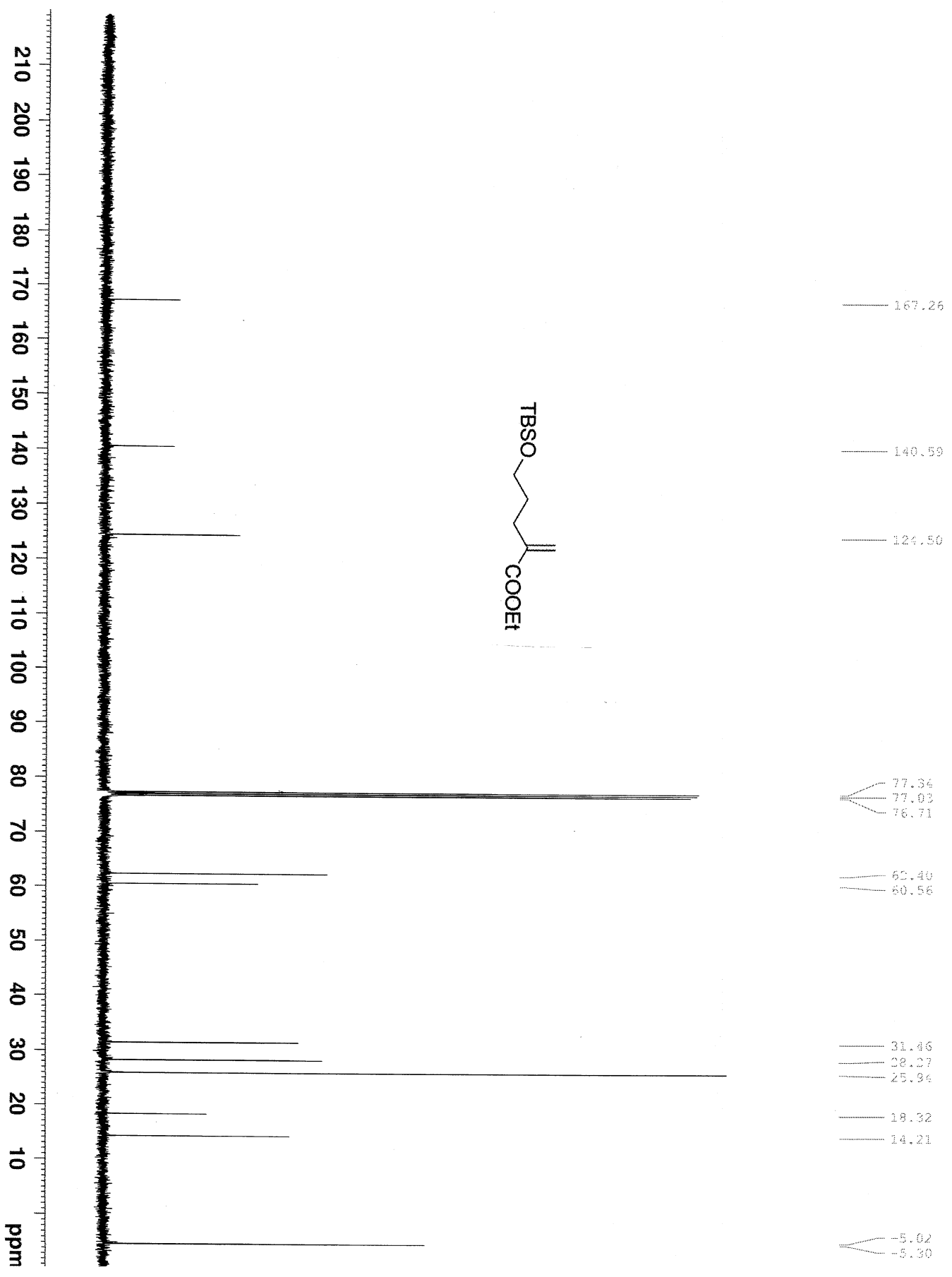


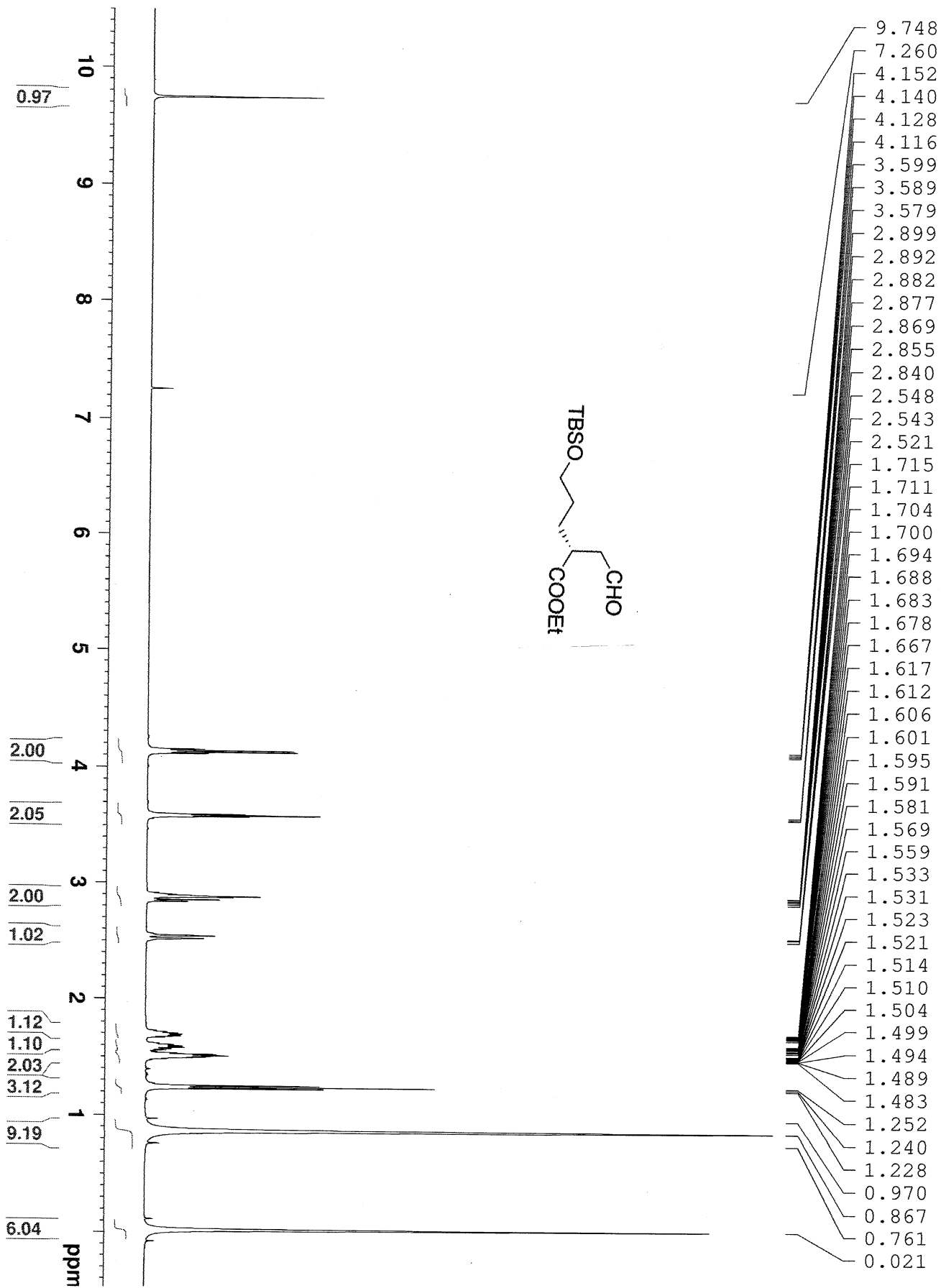


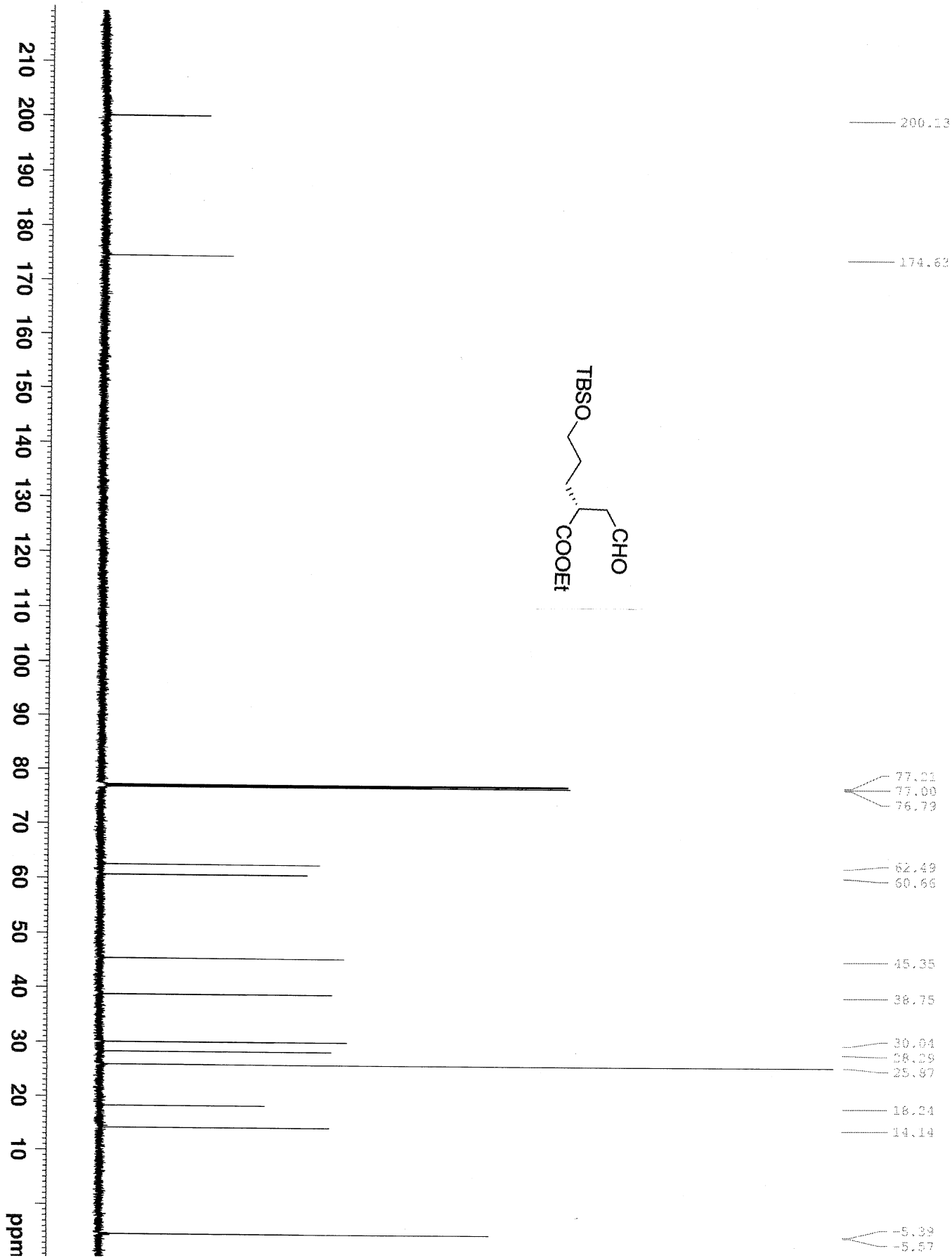


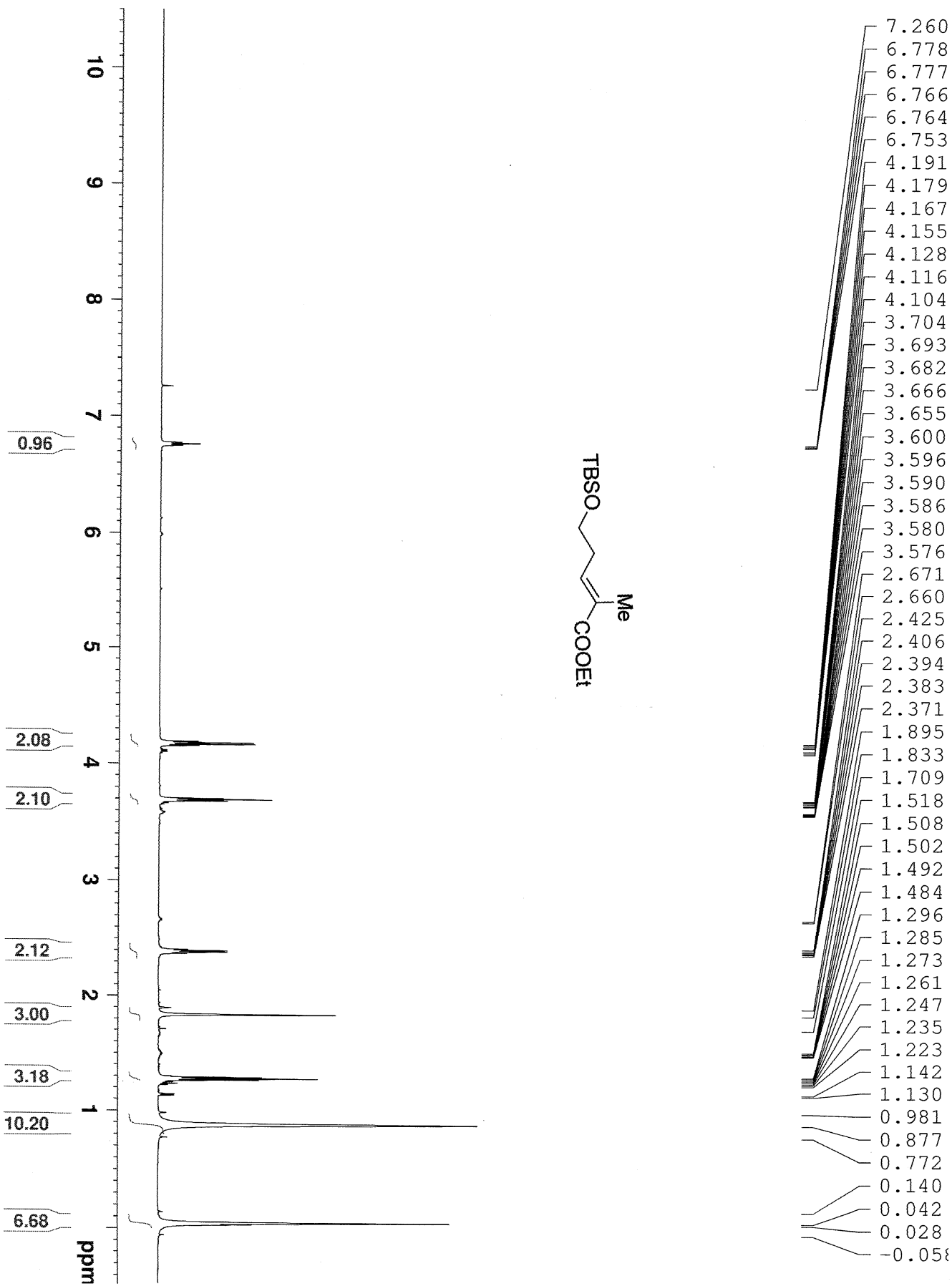


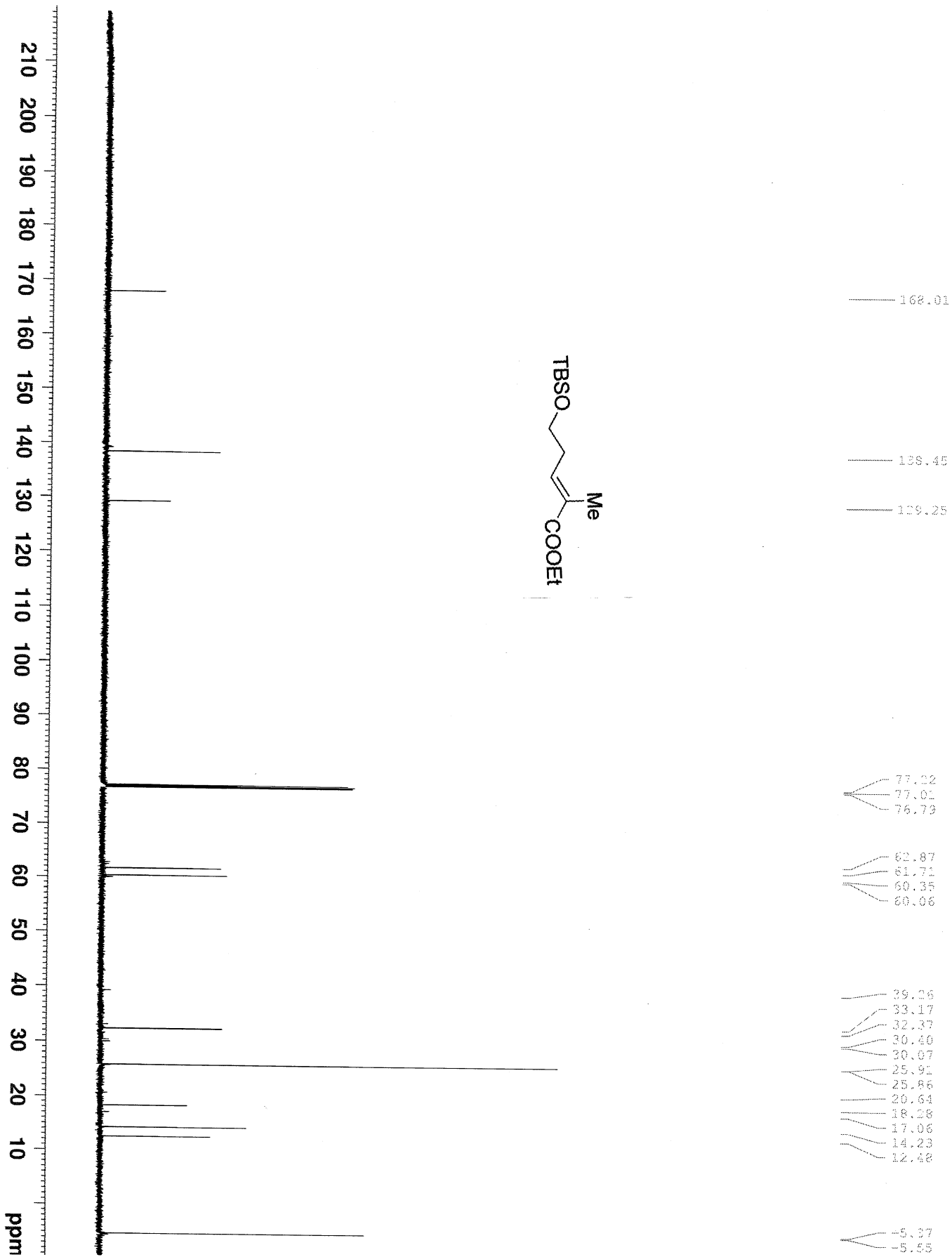


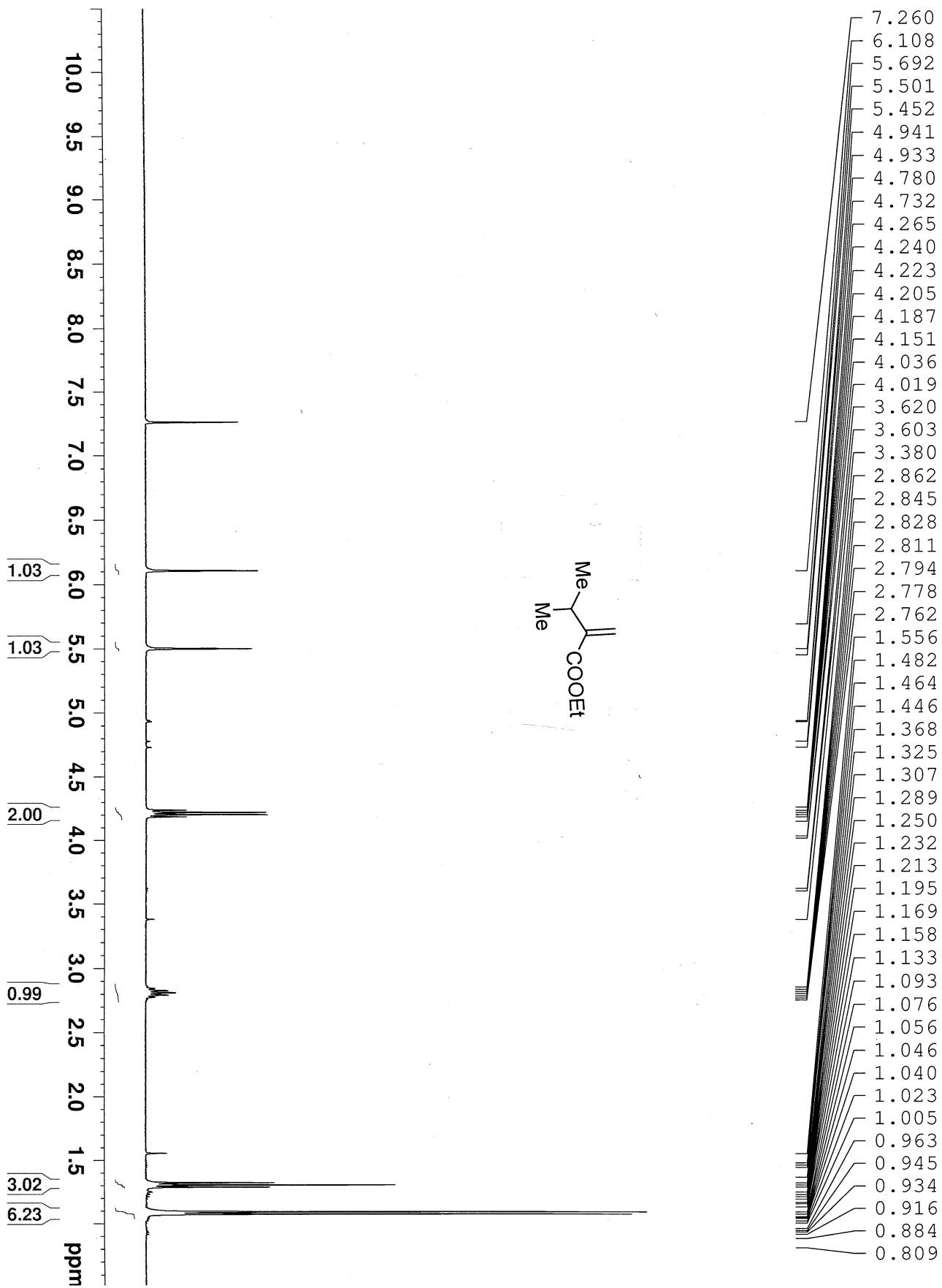


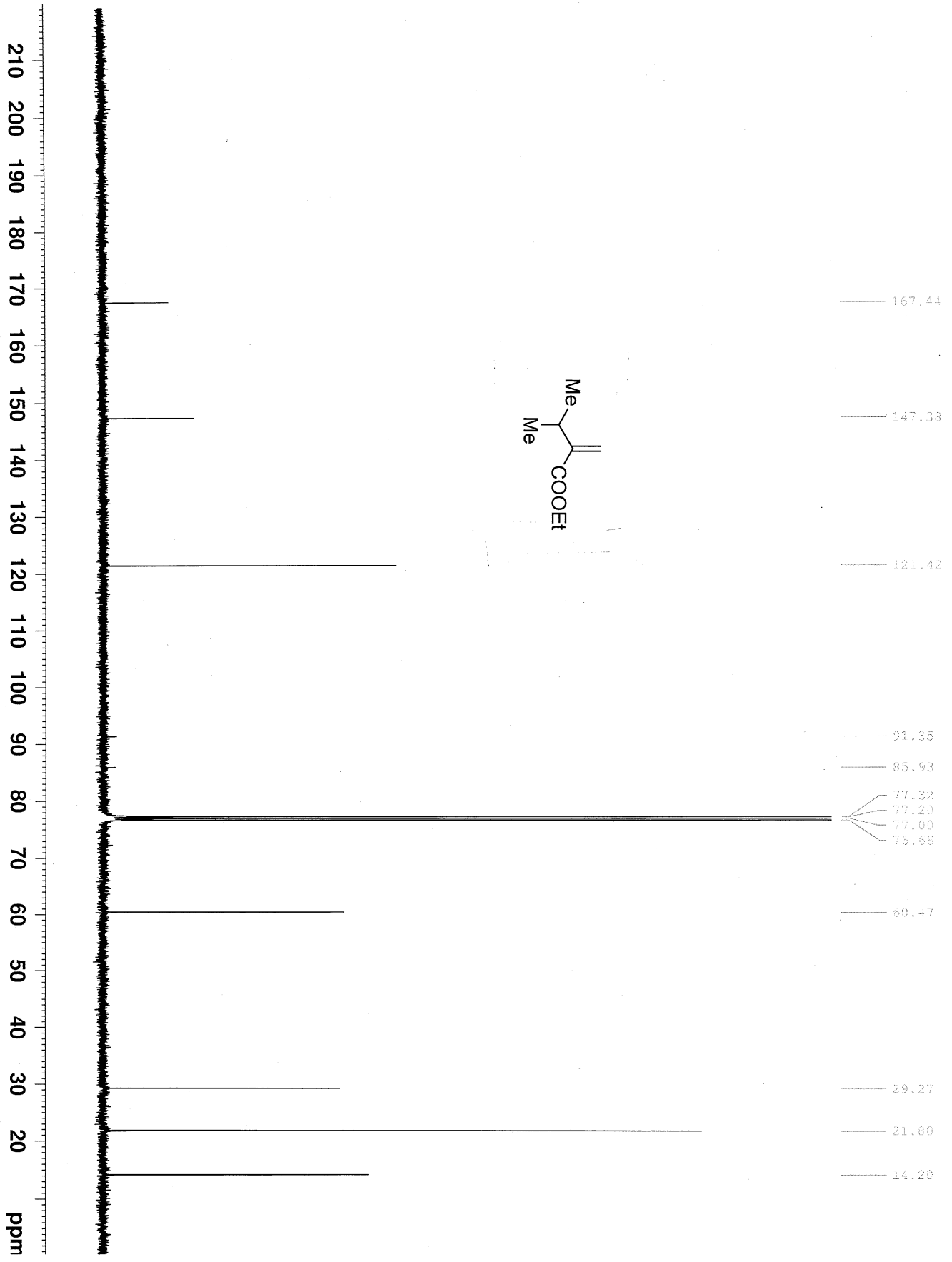


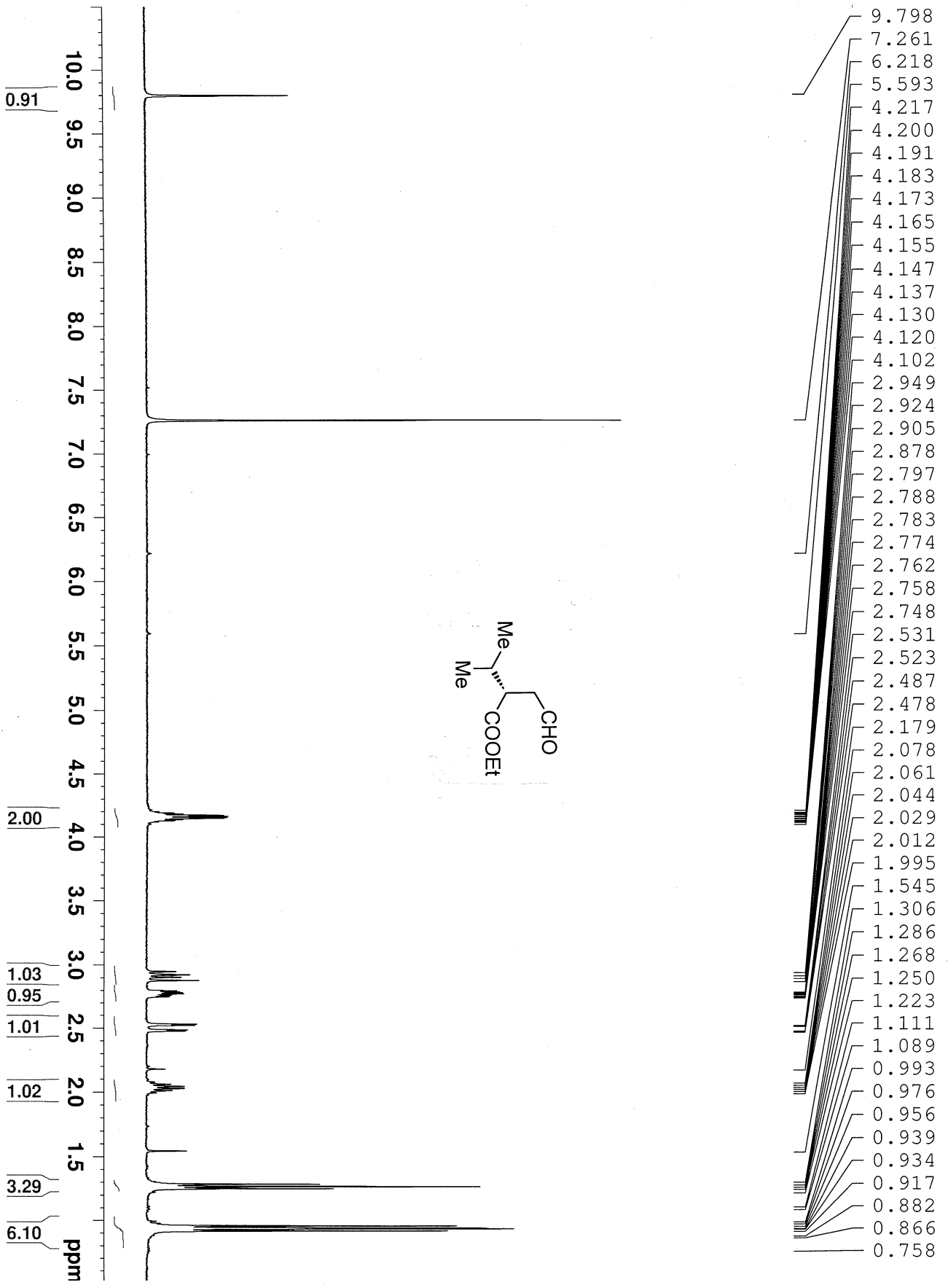


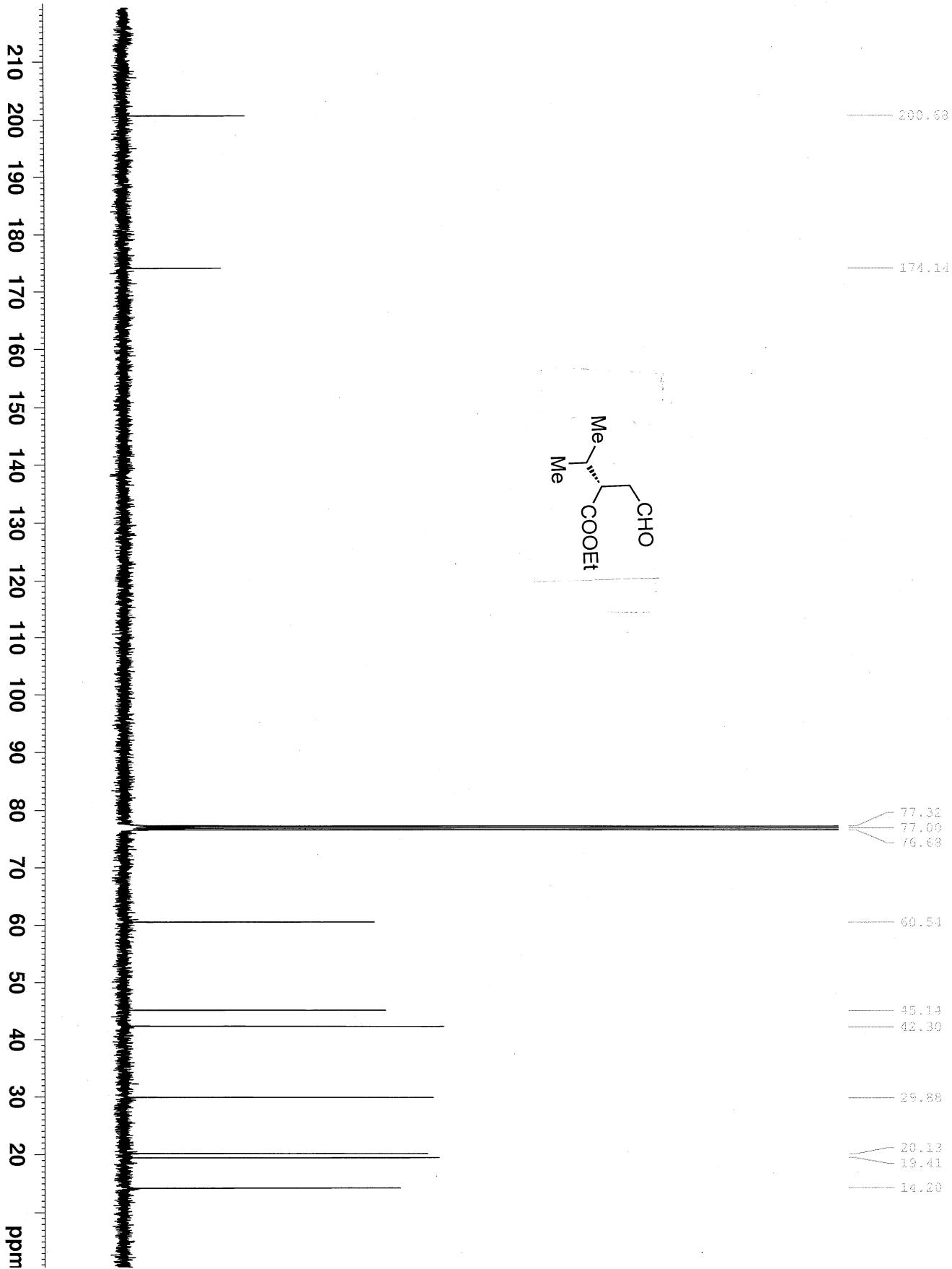


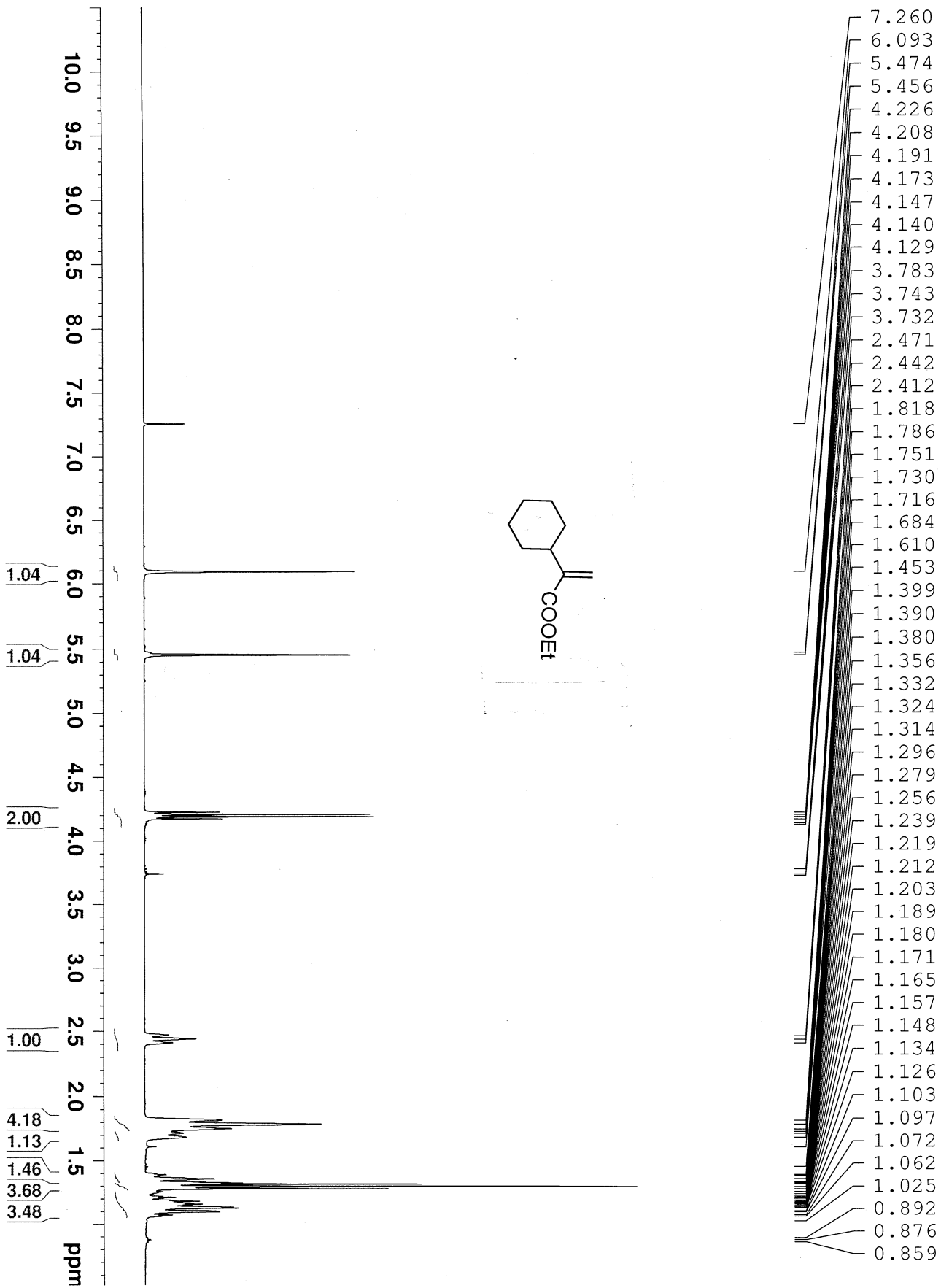


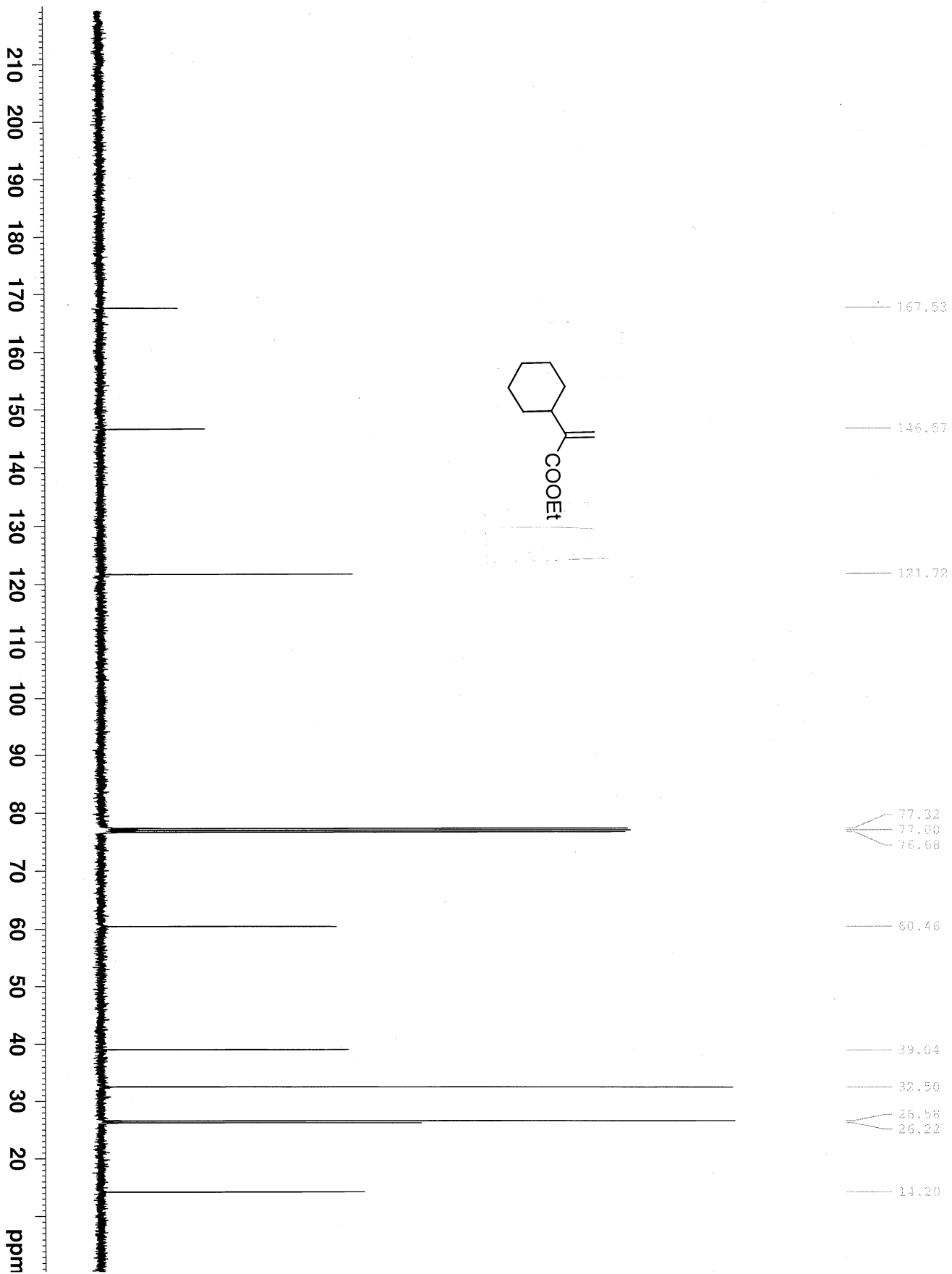


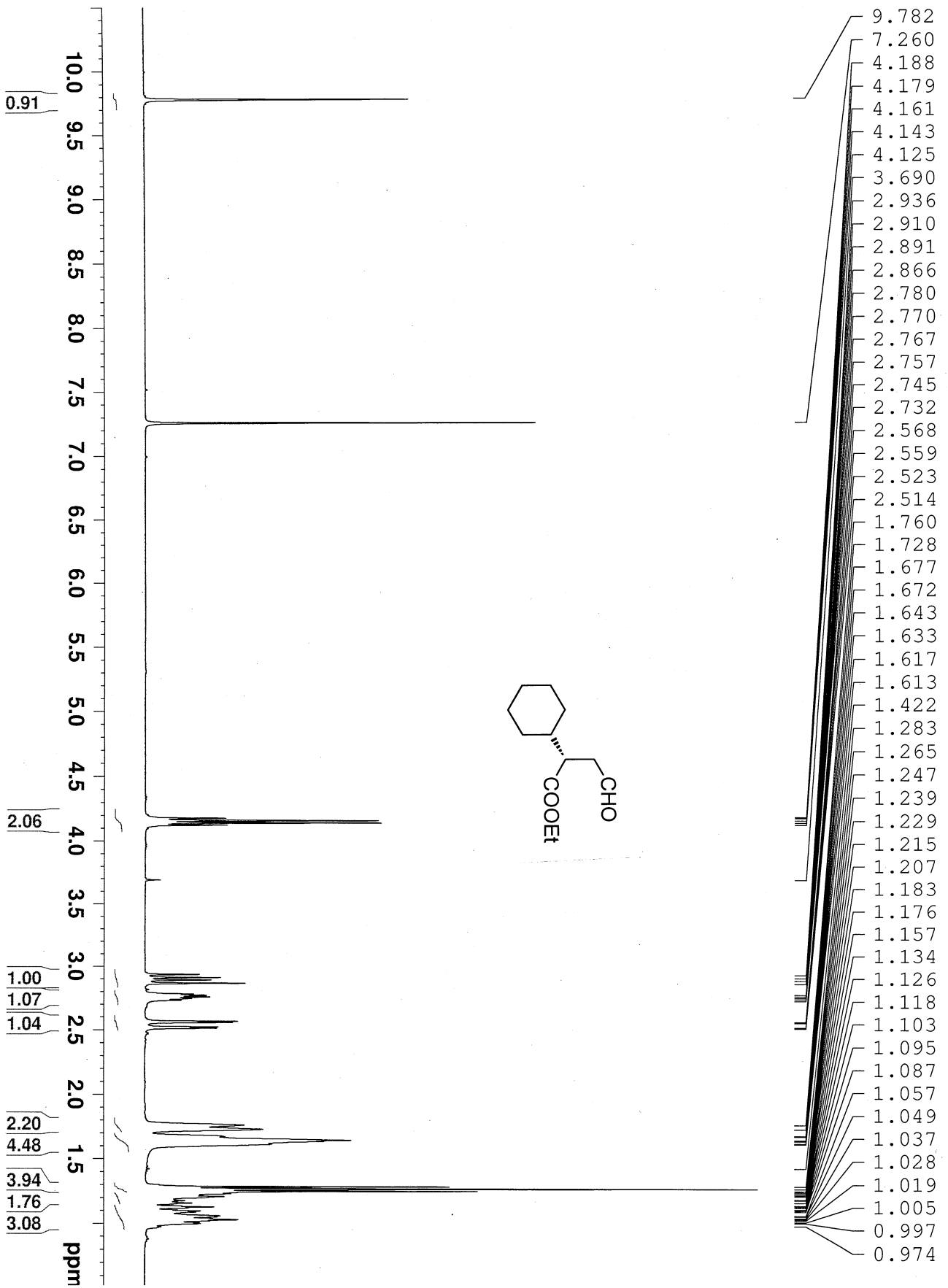


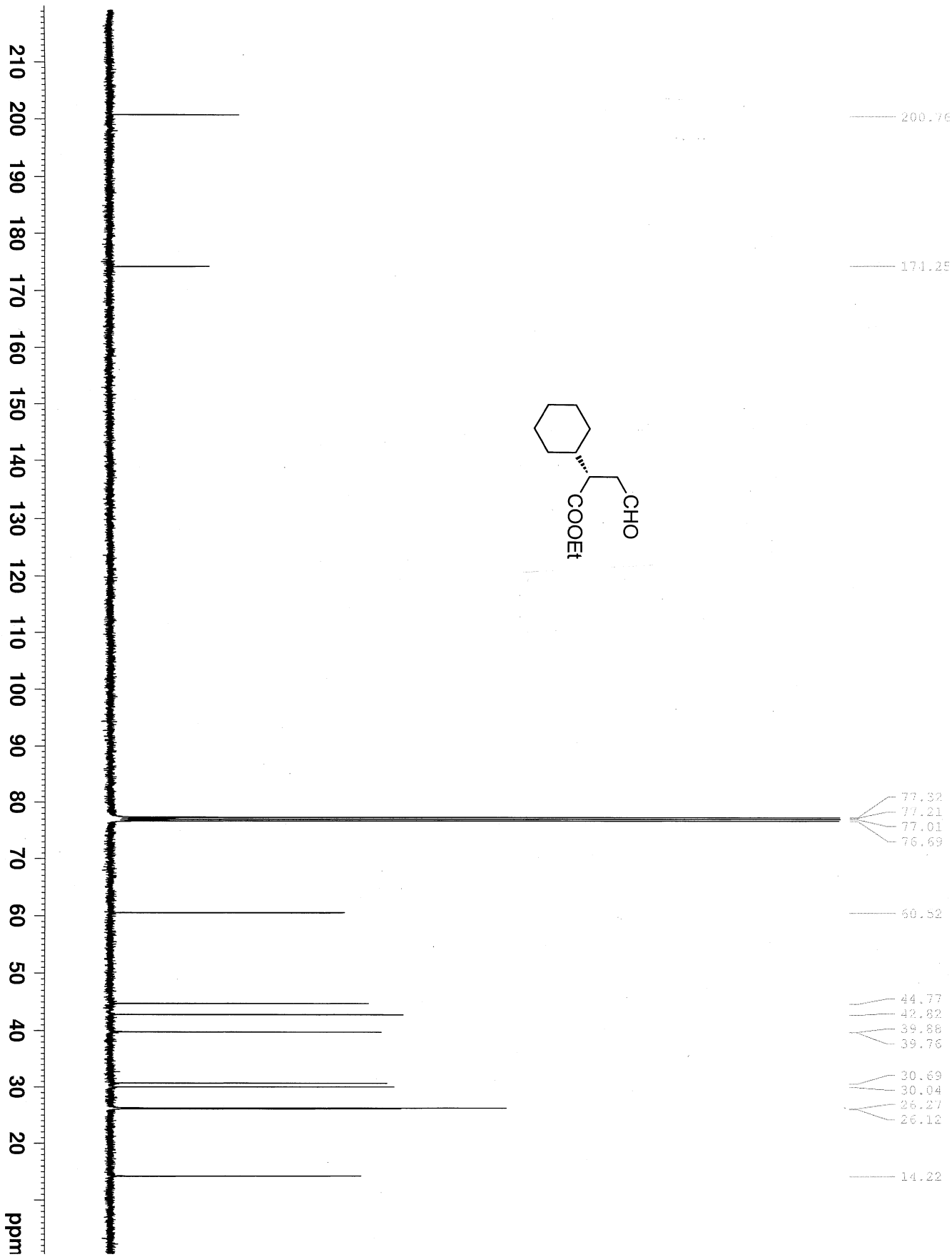


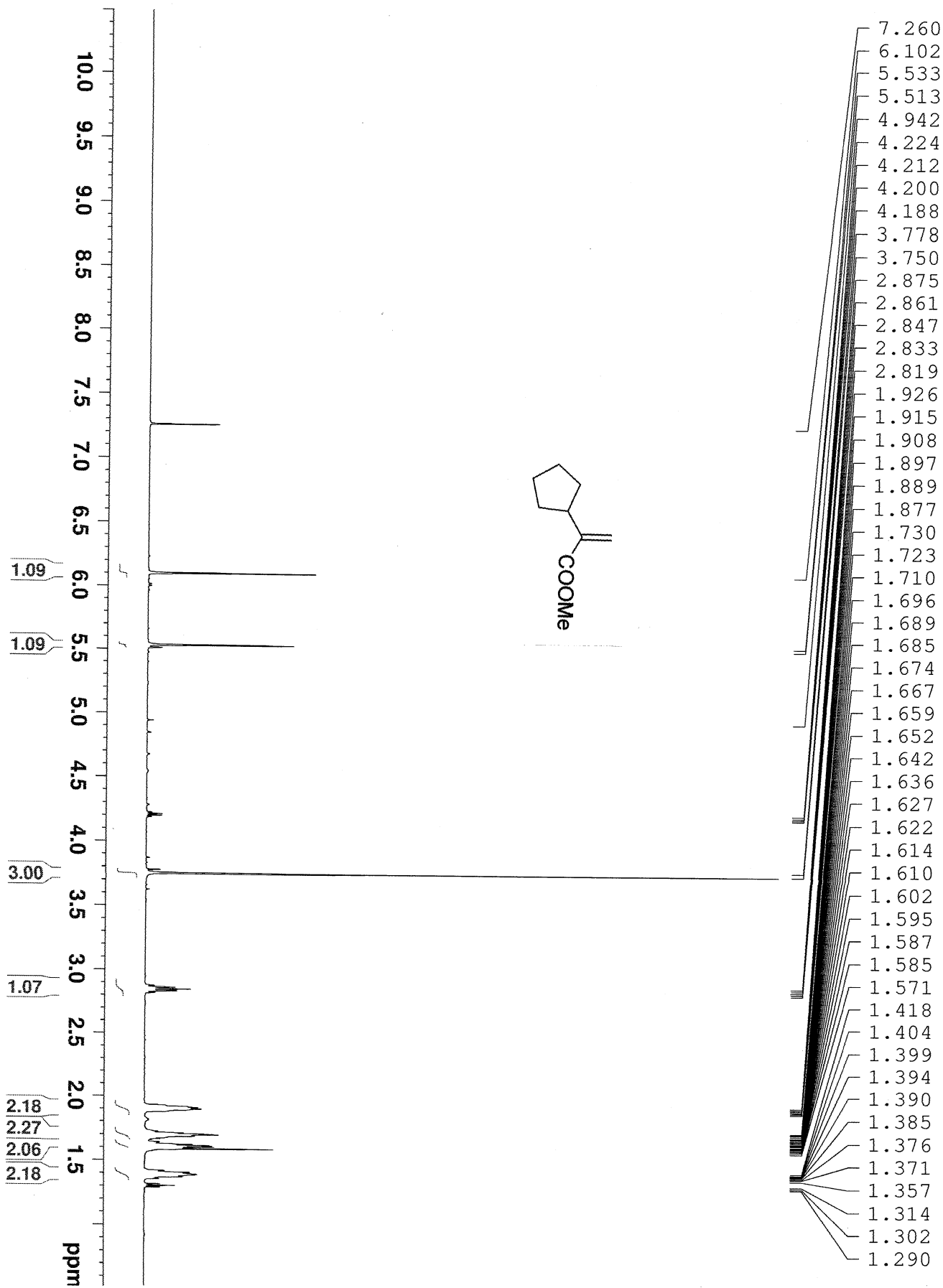


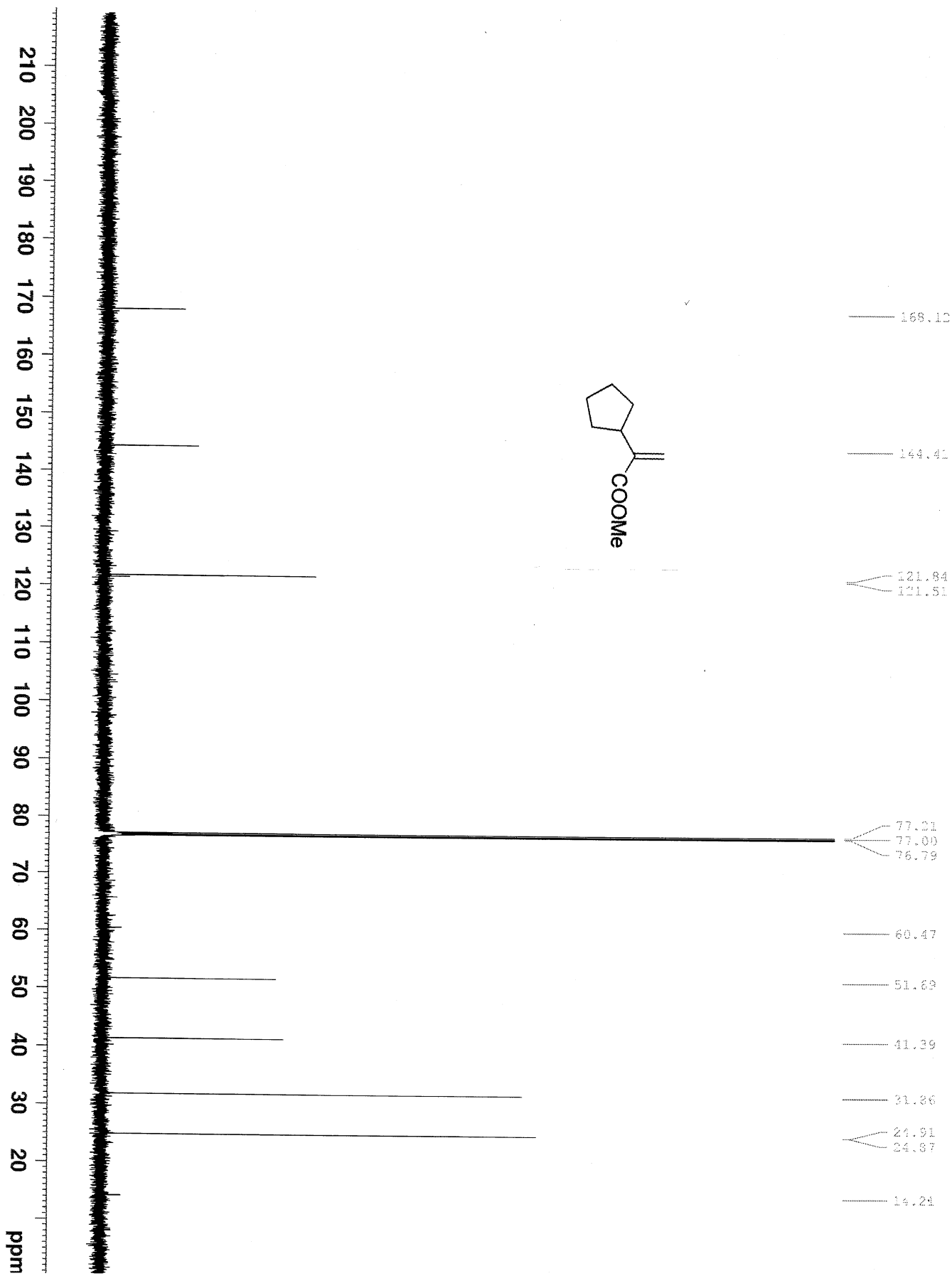


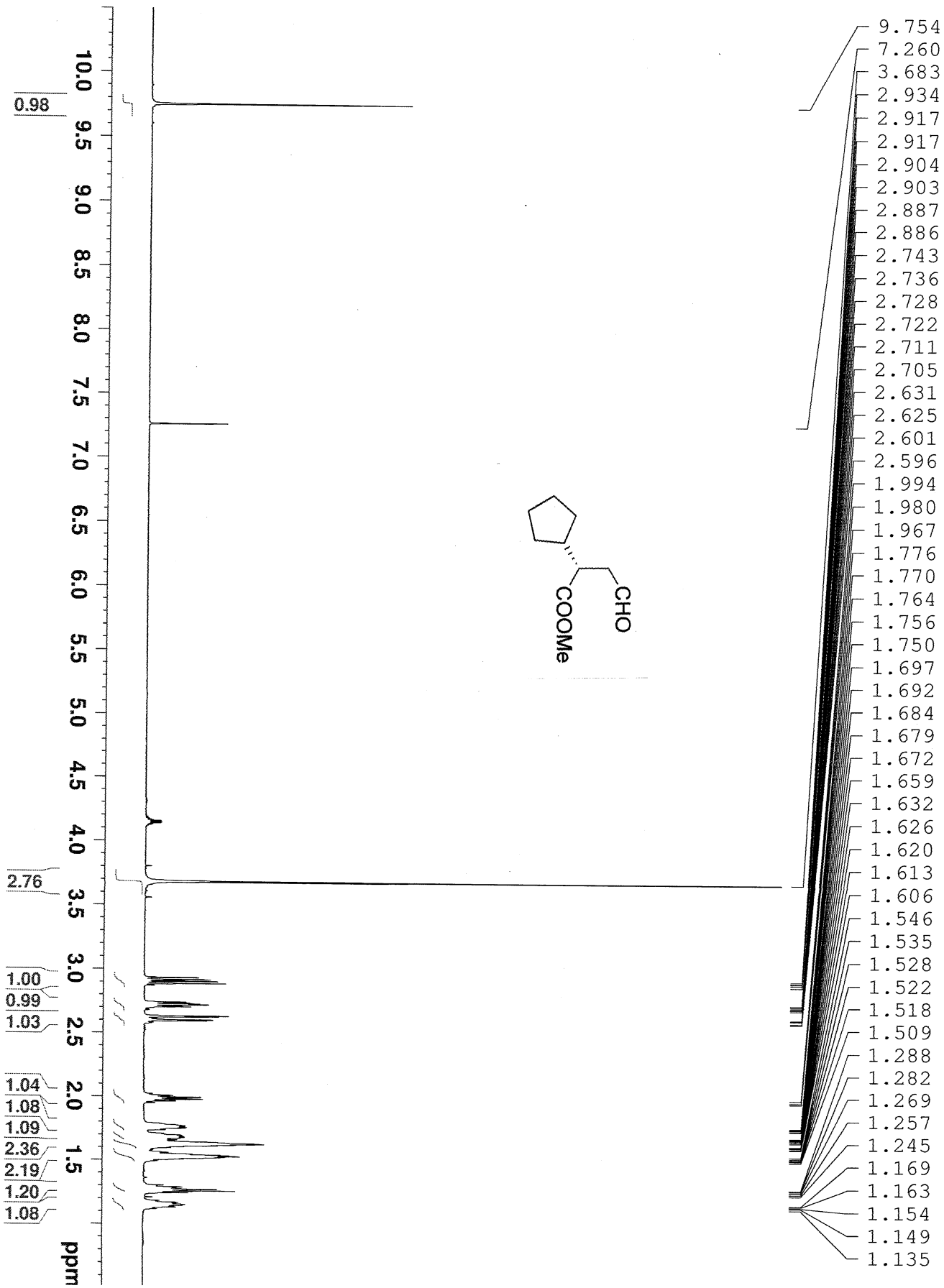


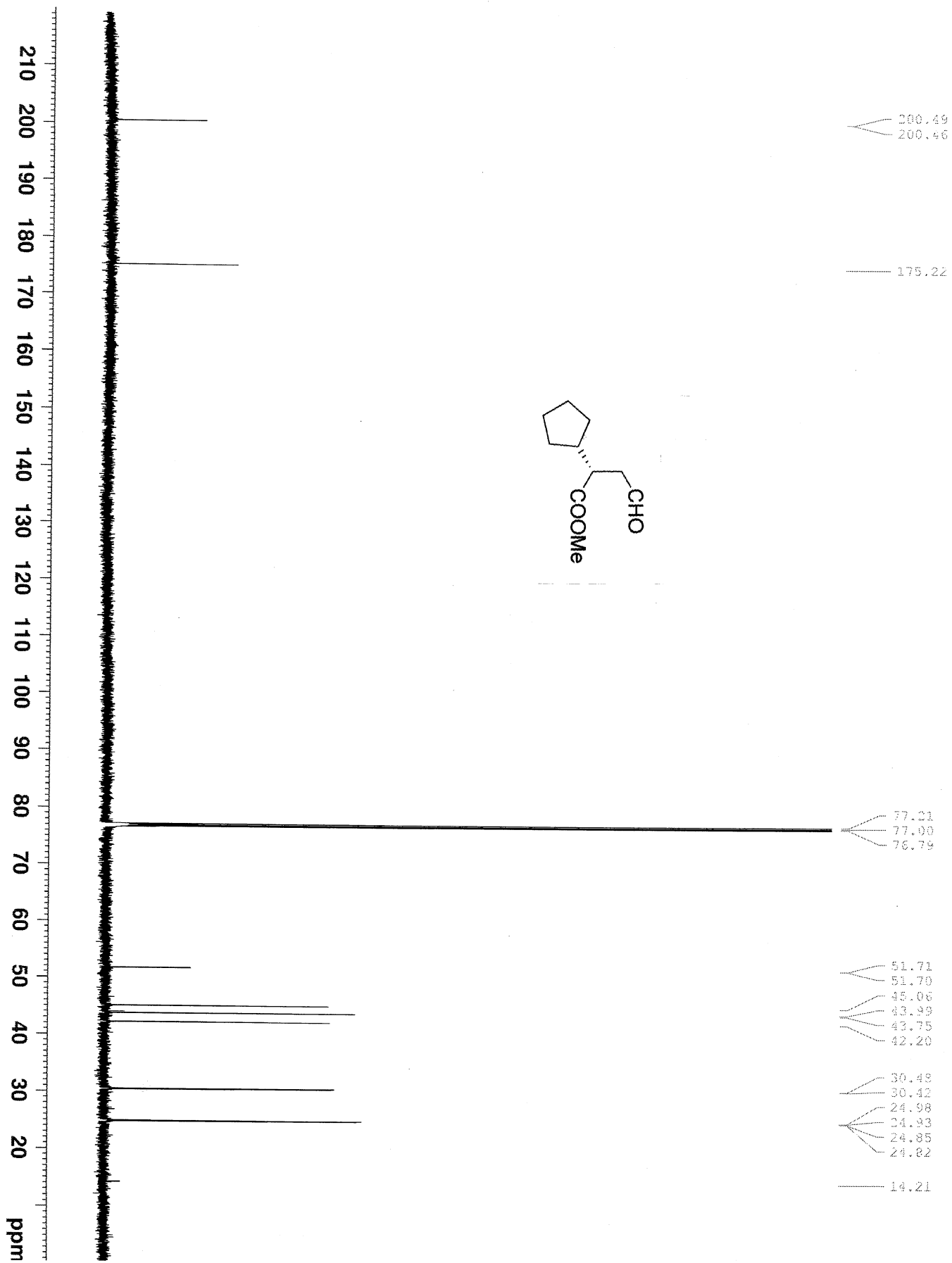


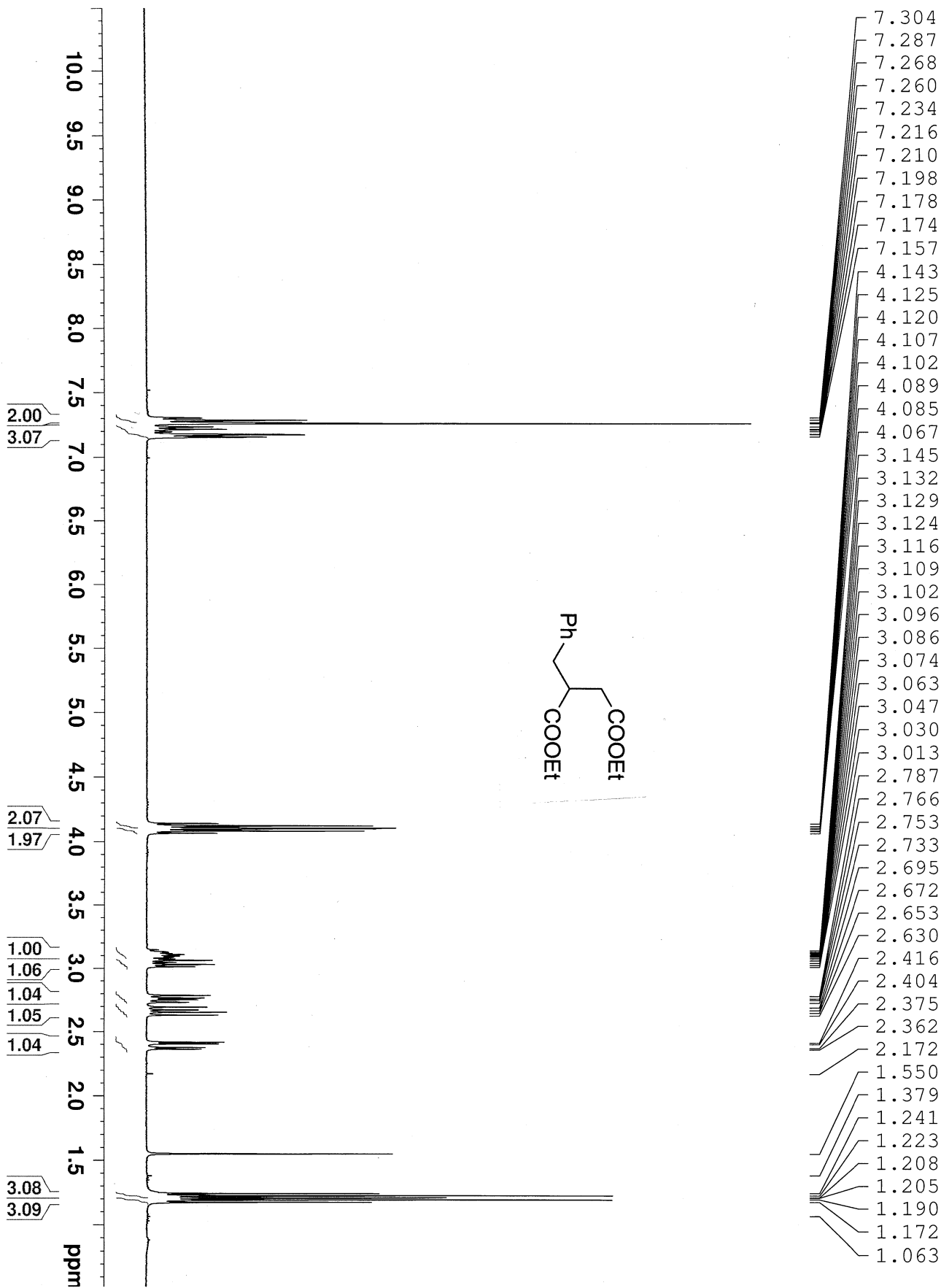


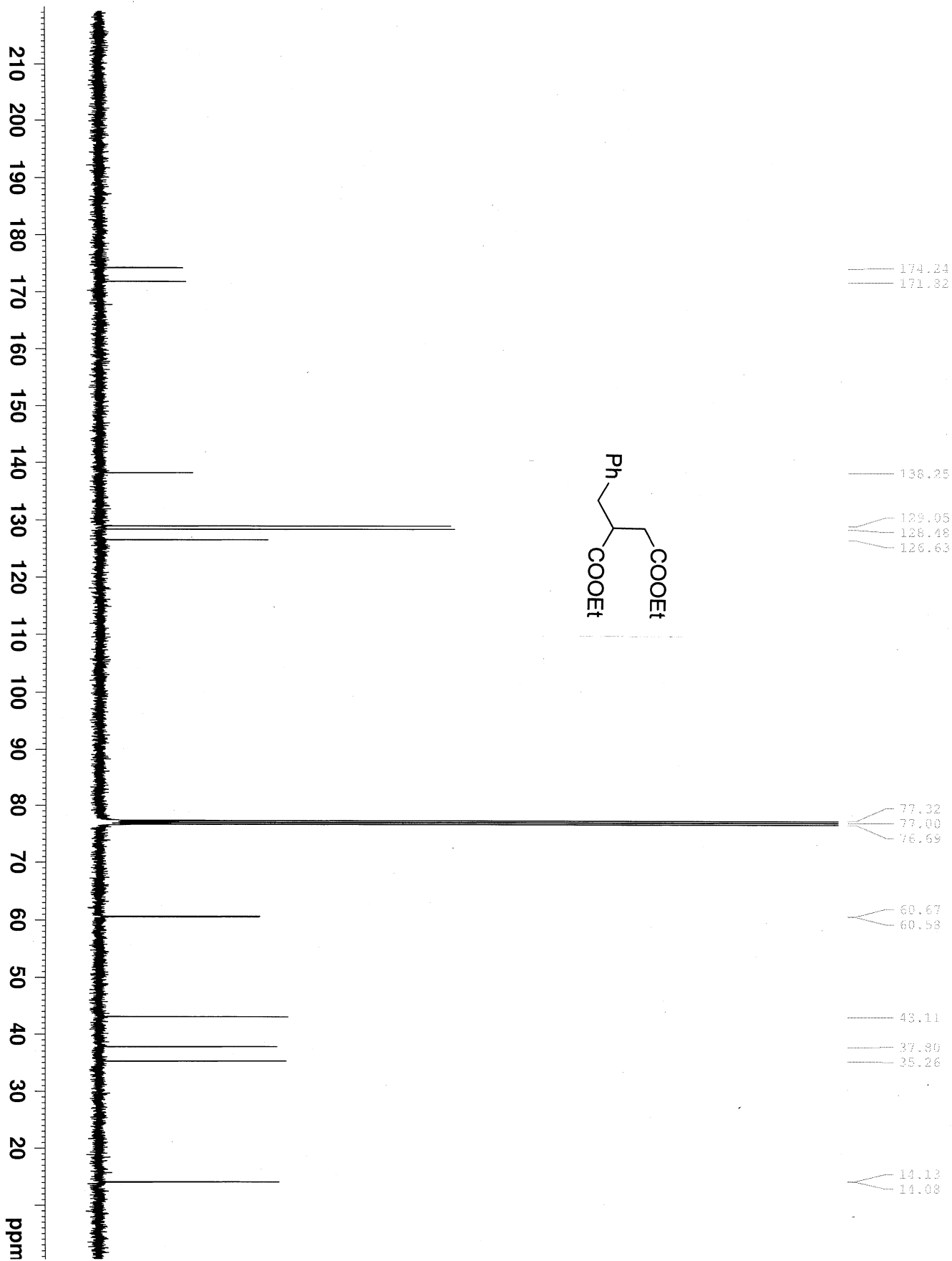




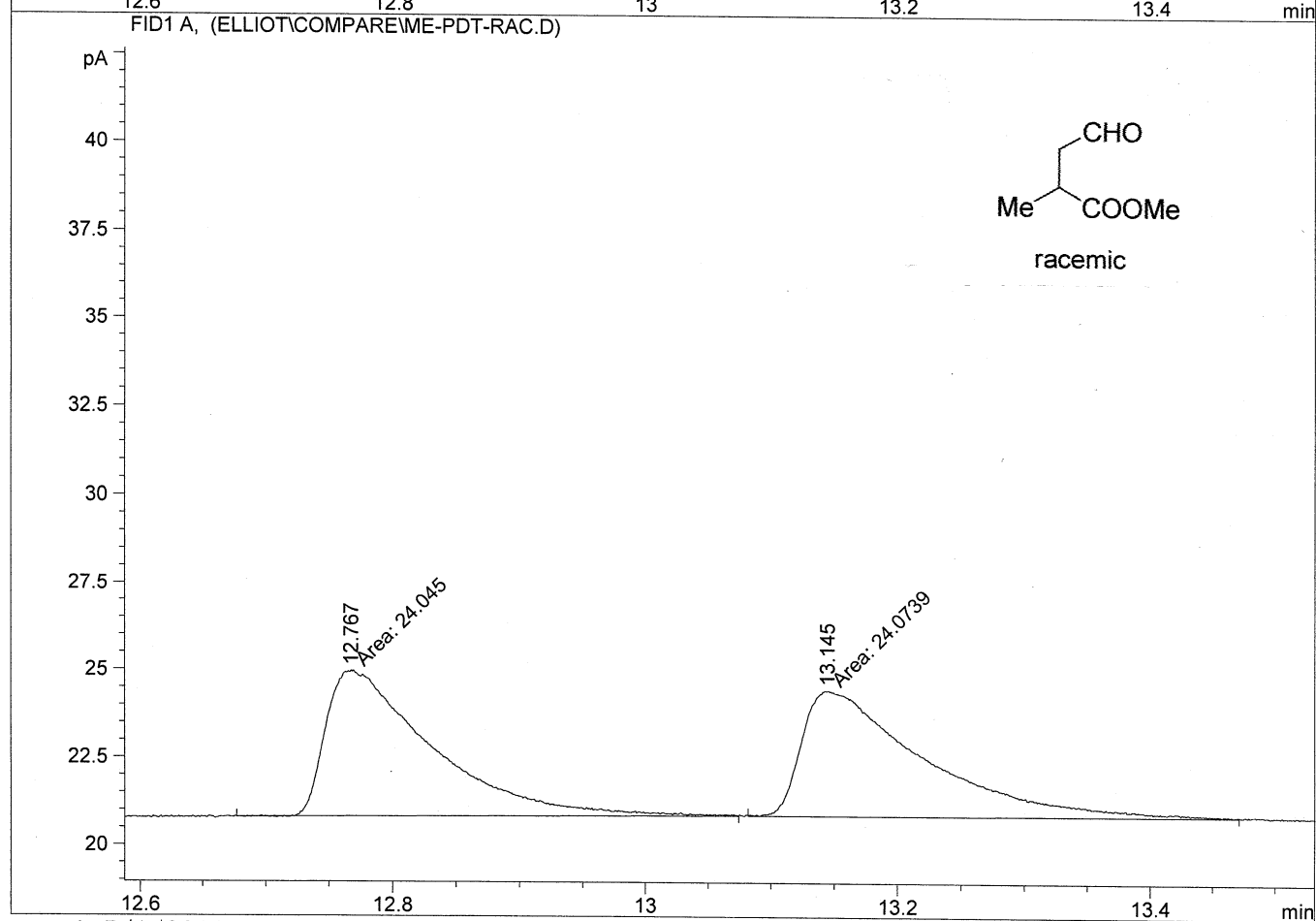
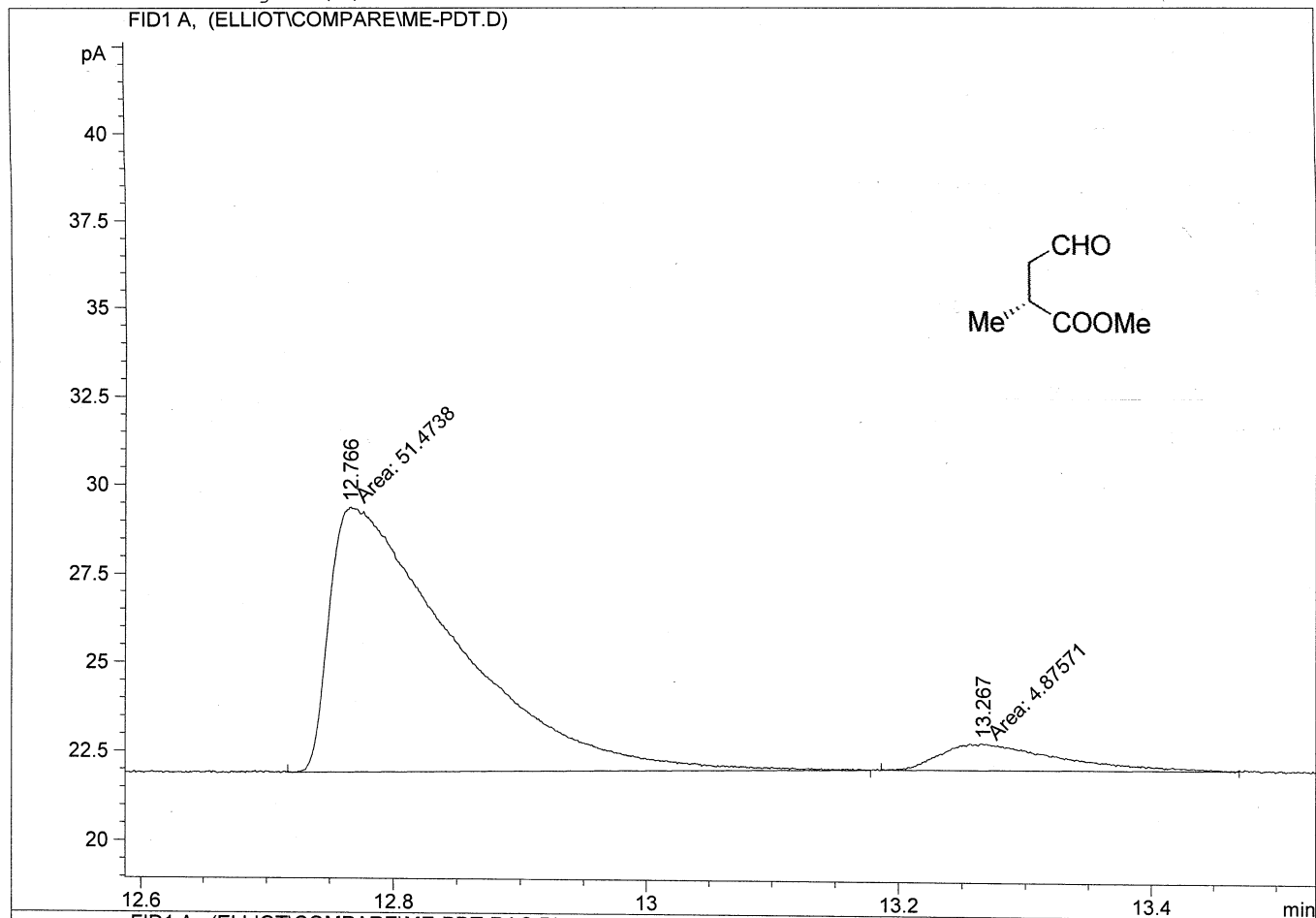




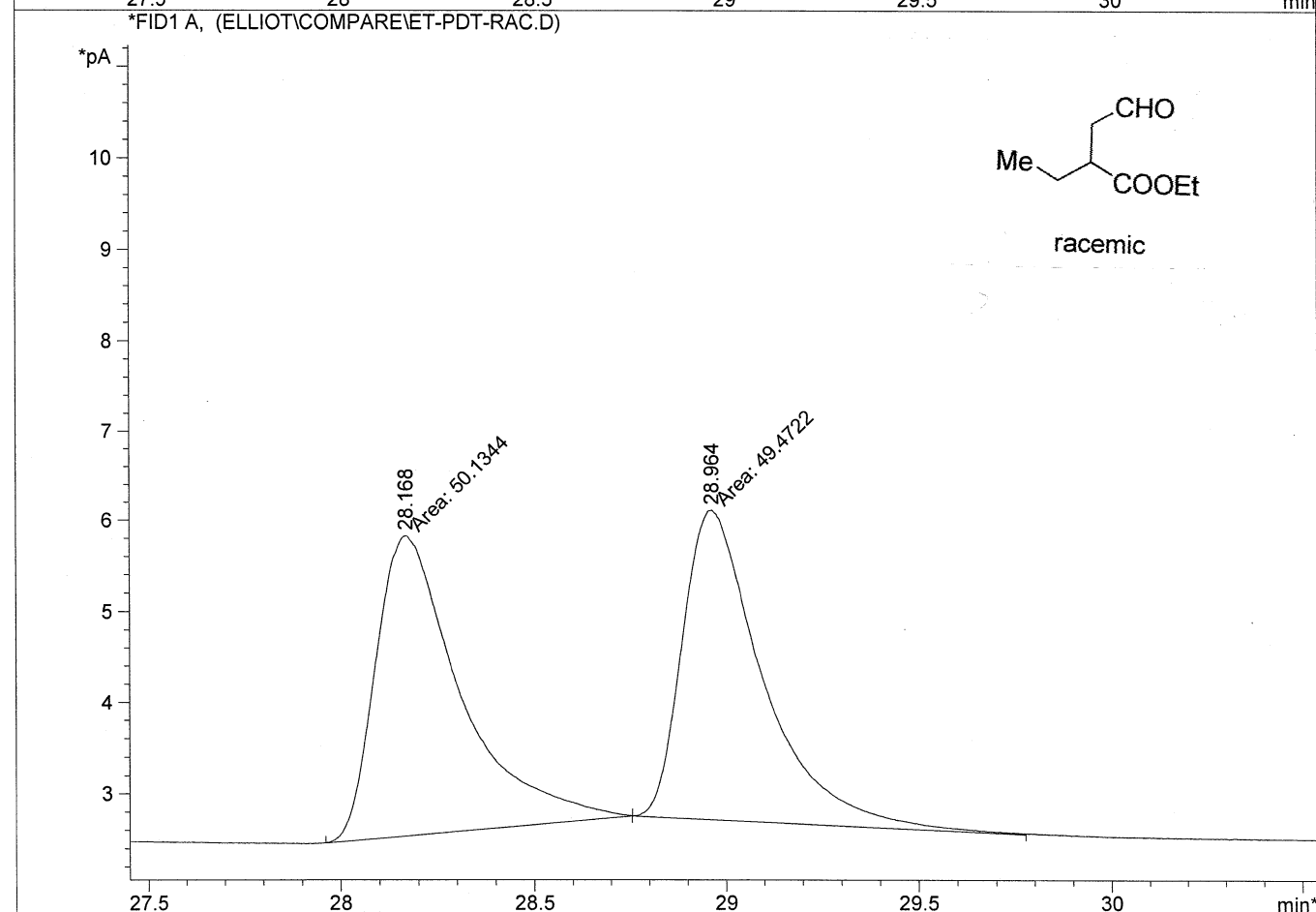
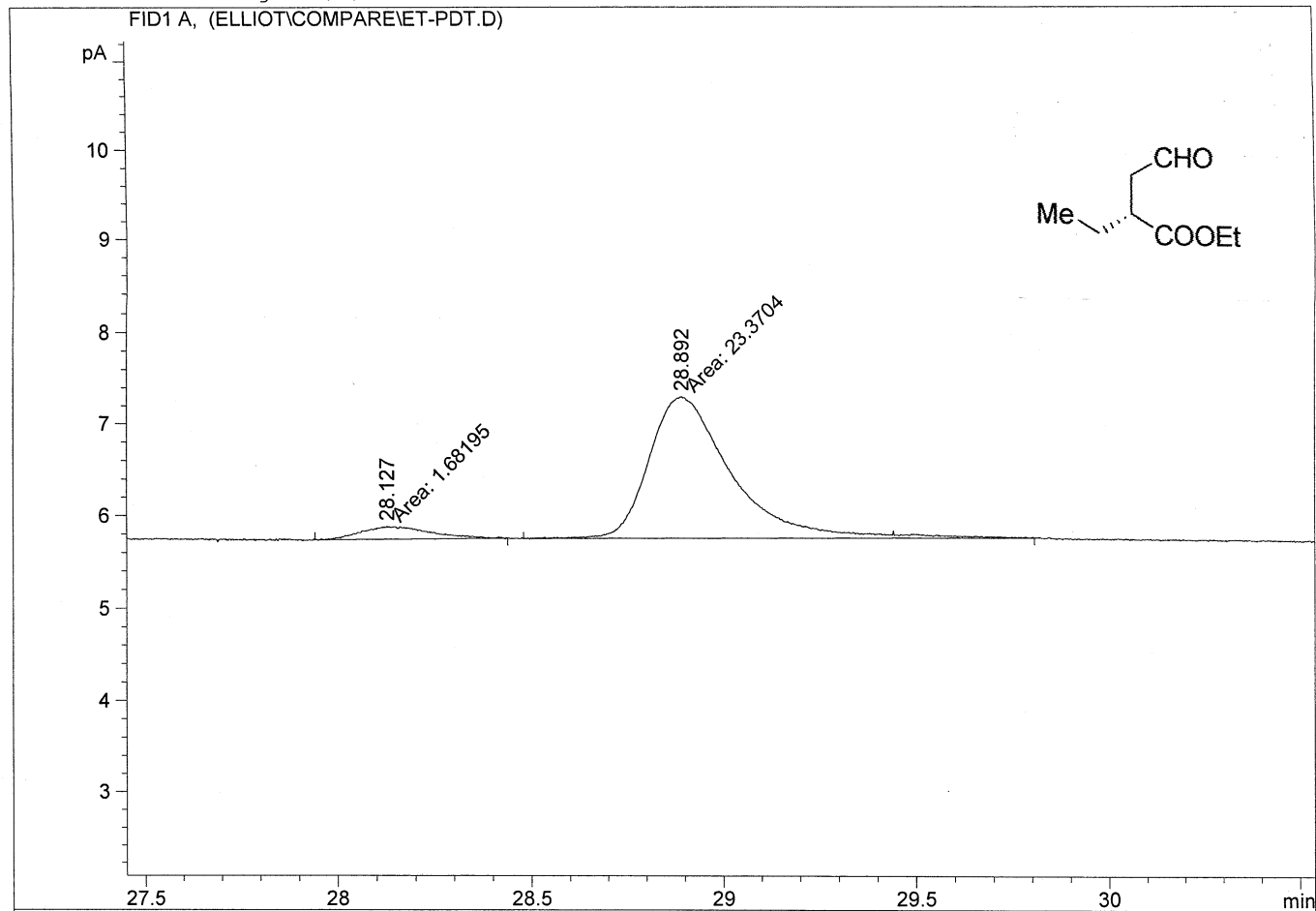




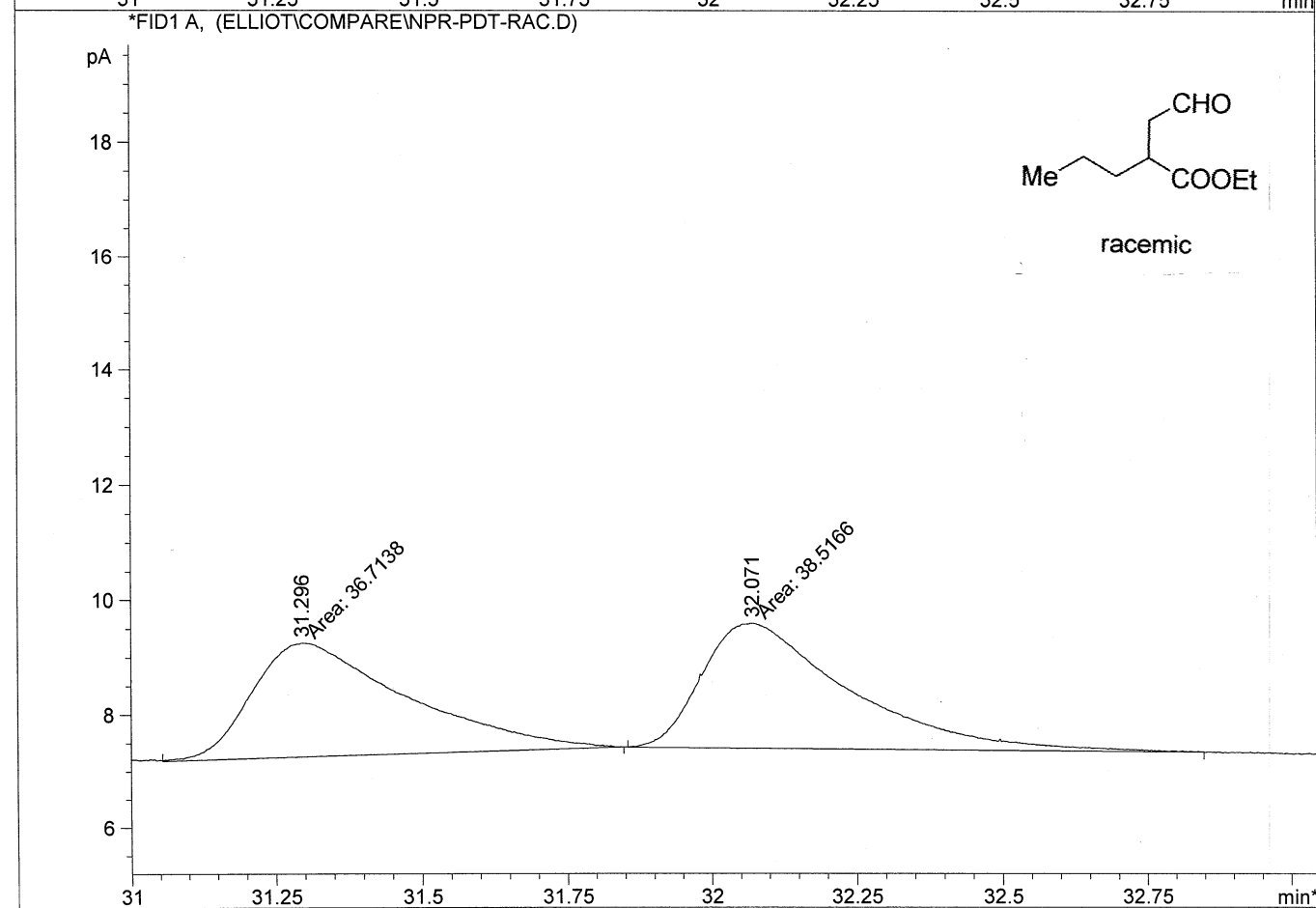
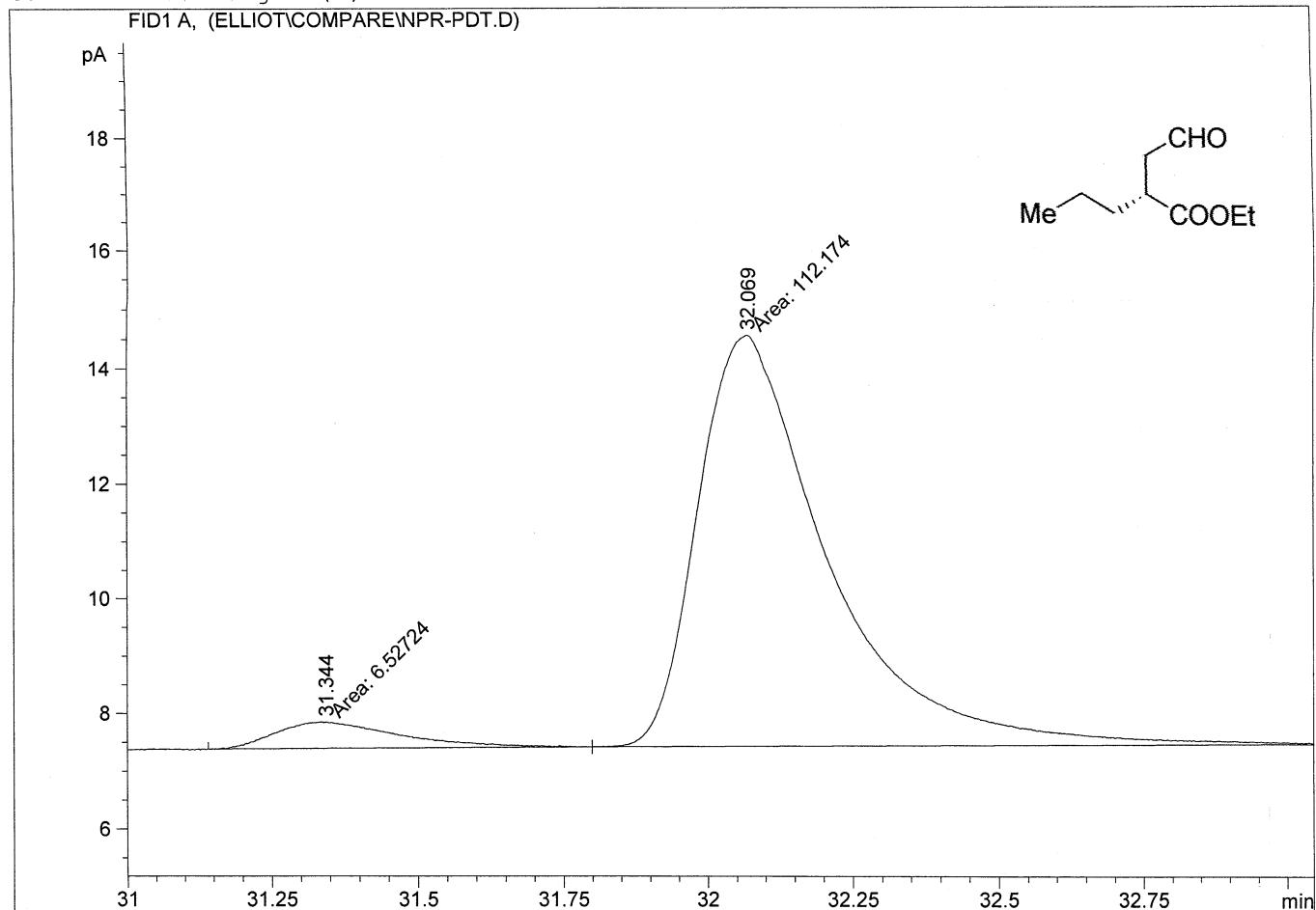
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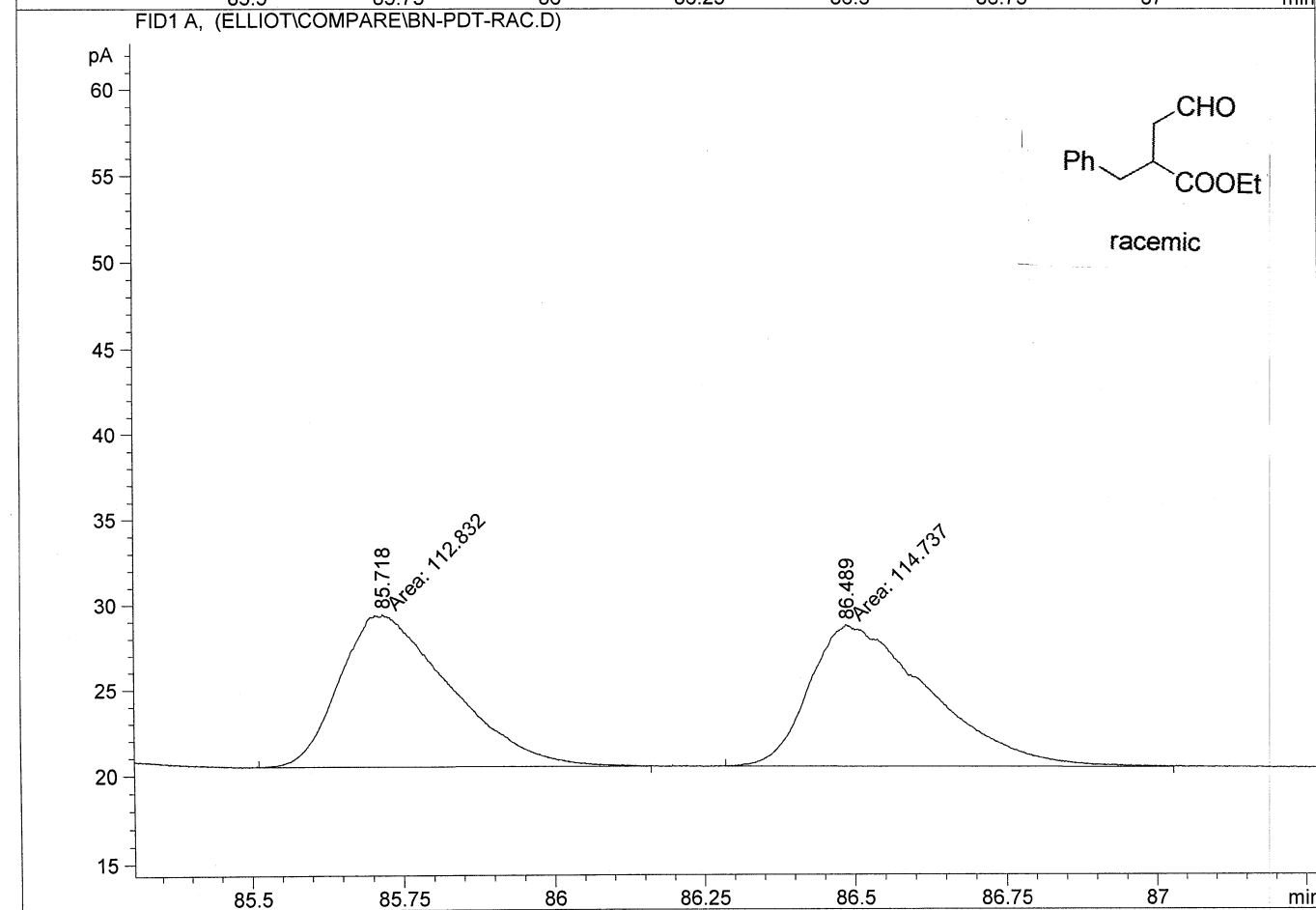
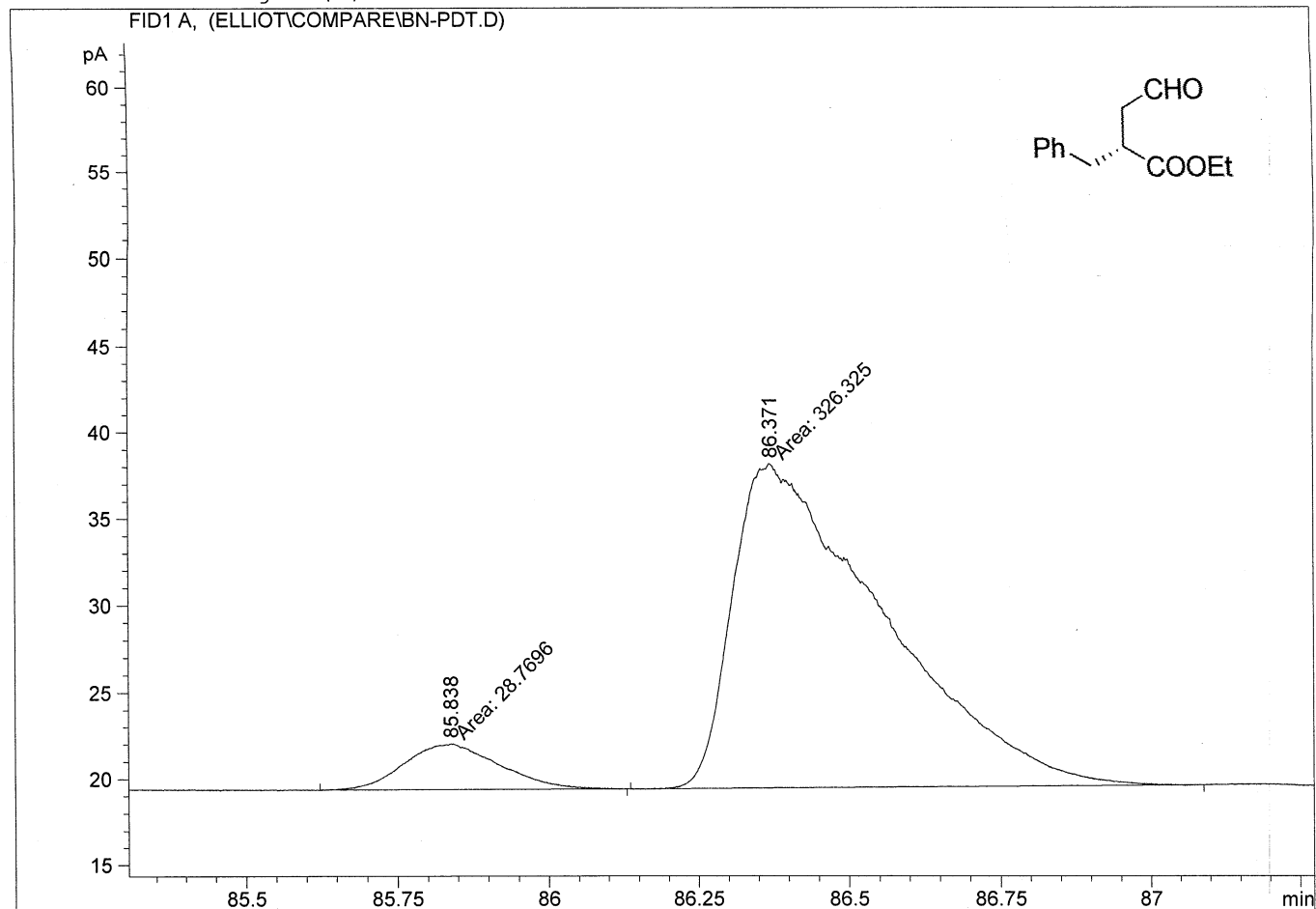
Current Chromatogram(s)



Current Chromatogram(s)

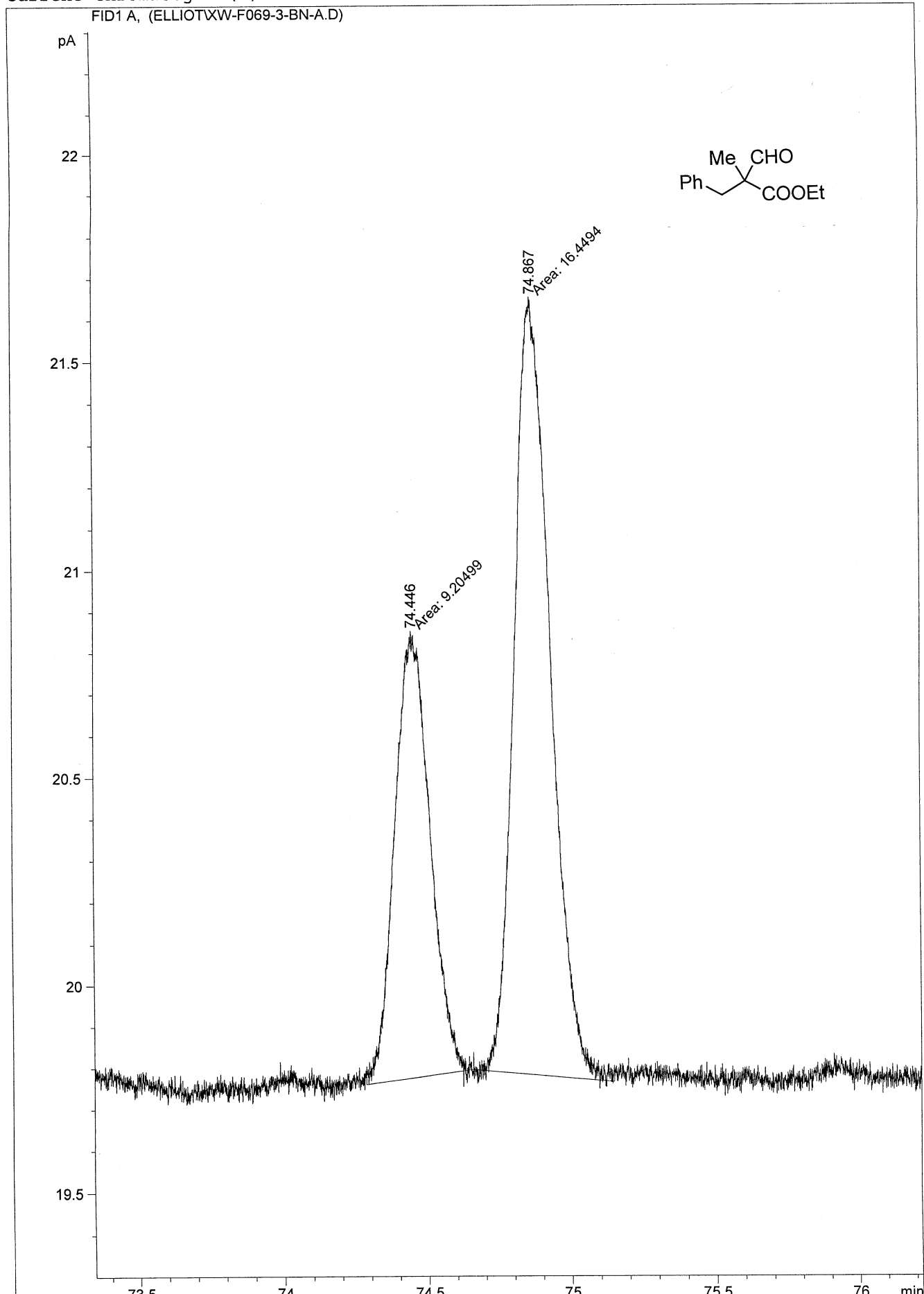
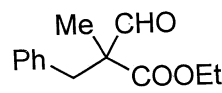


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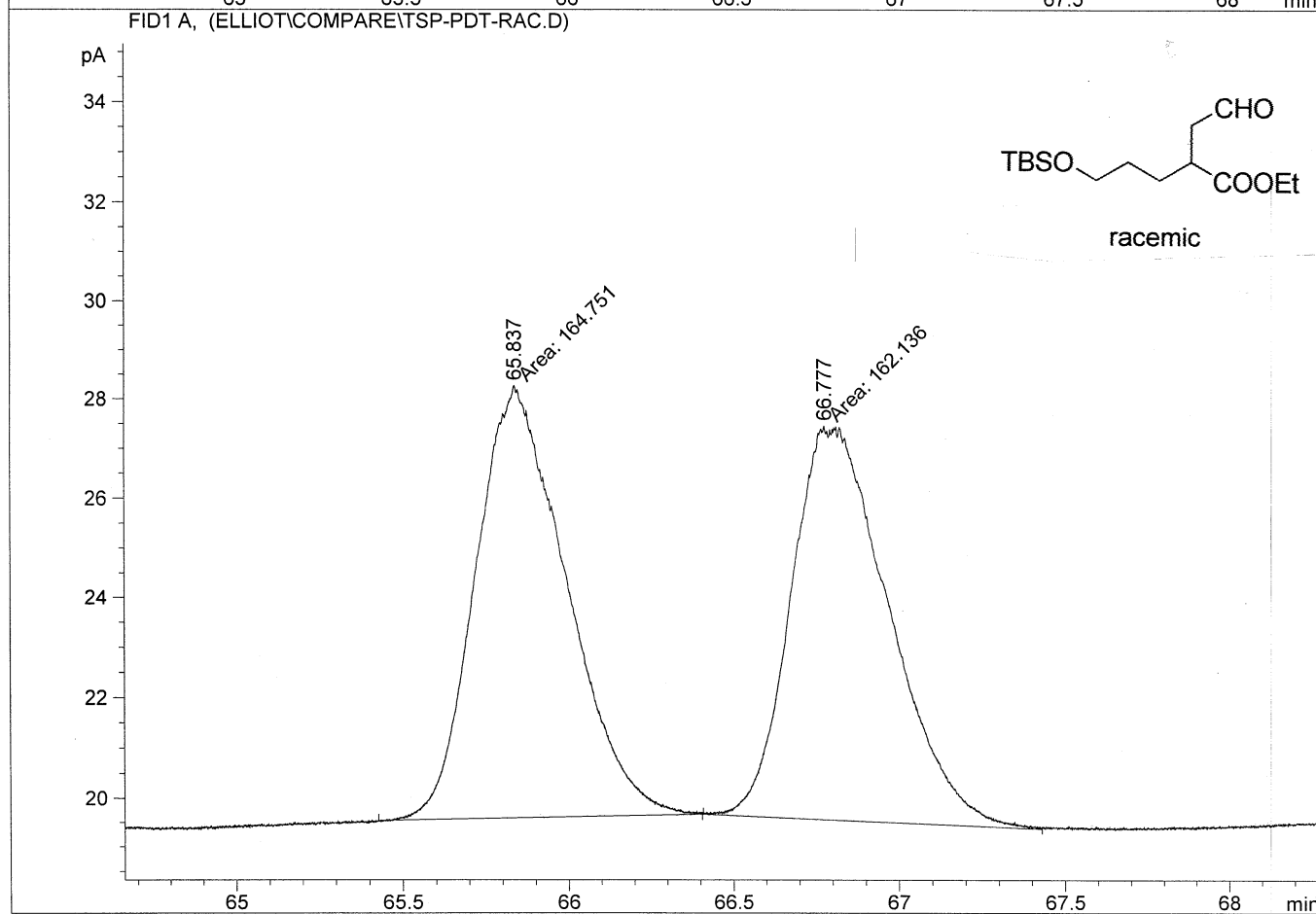
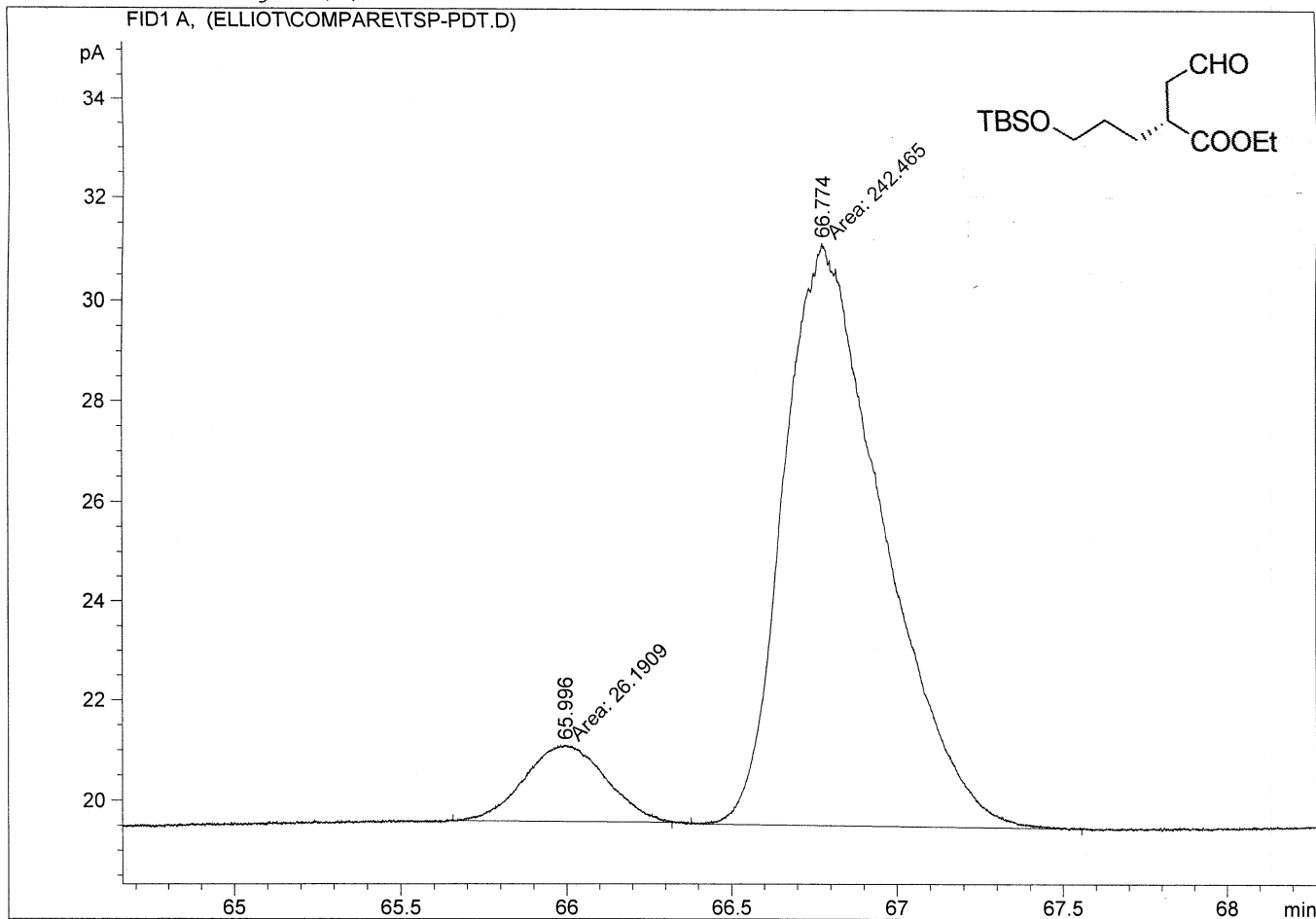


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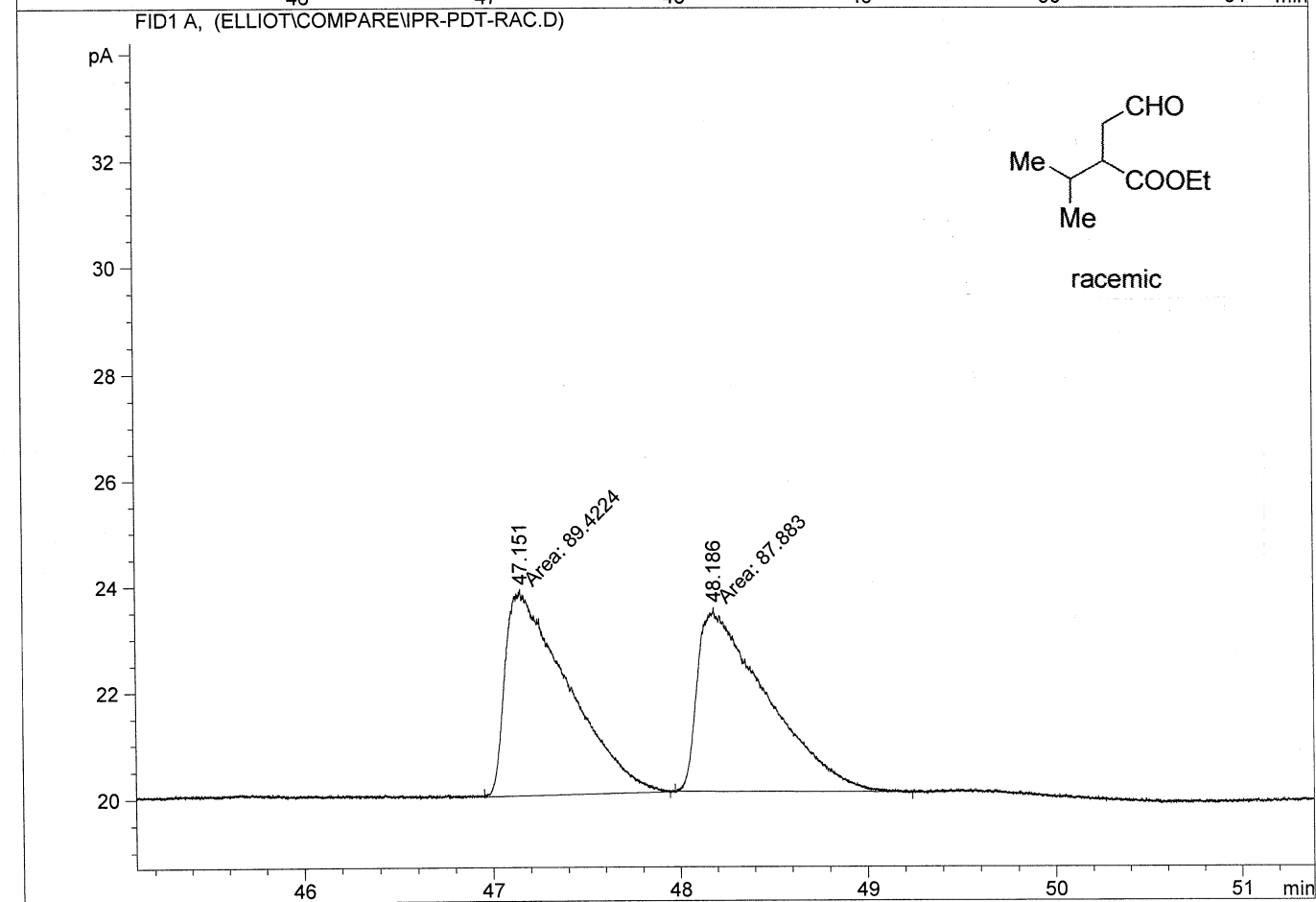
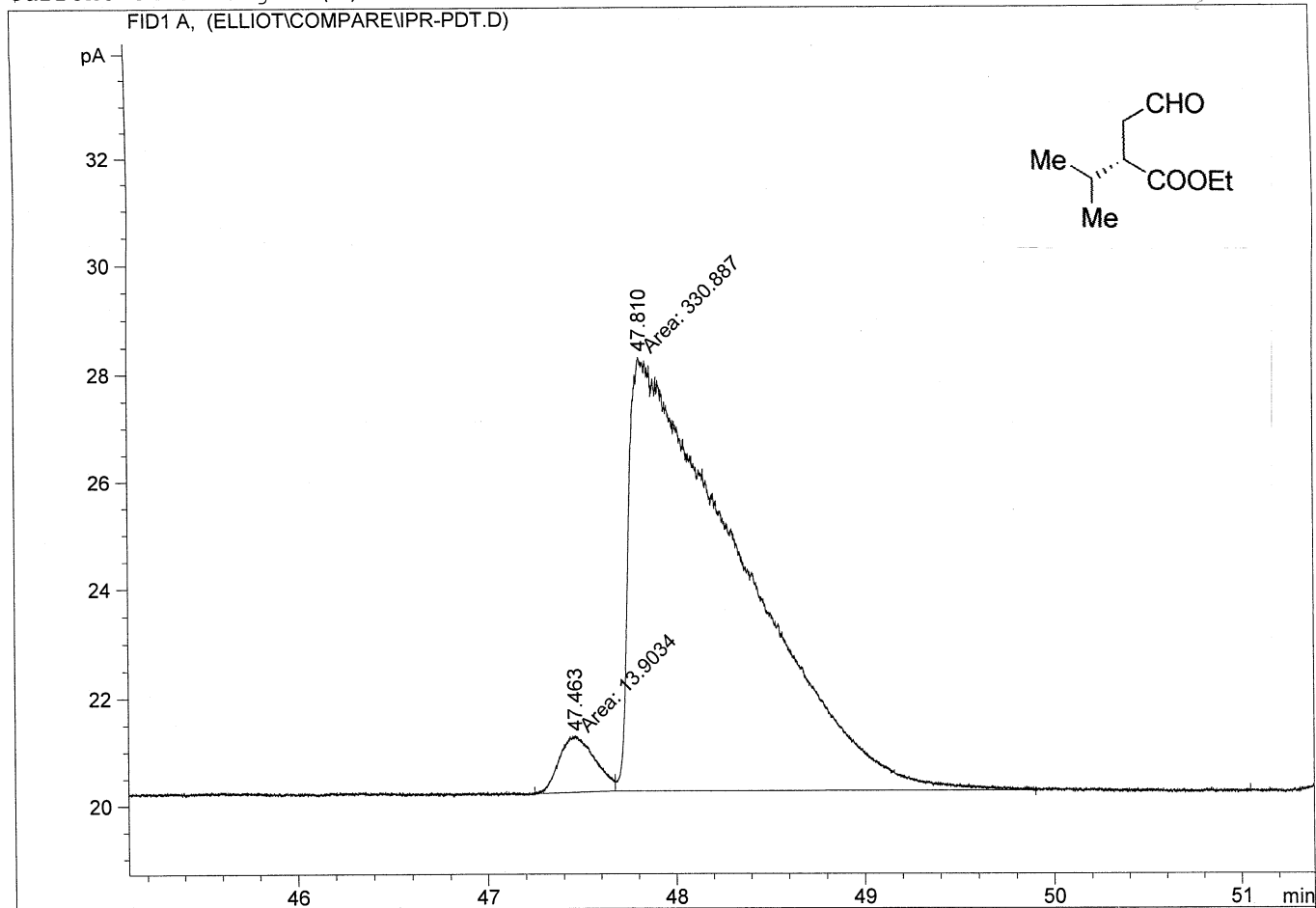
FID1 A, (ELLIOTXW-F069-3-BN-A.D)



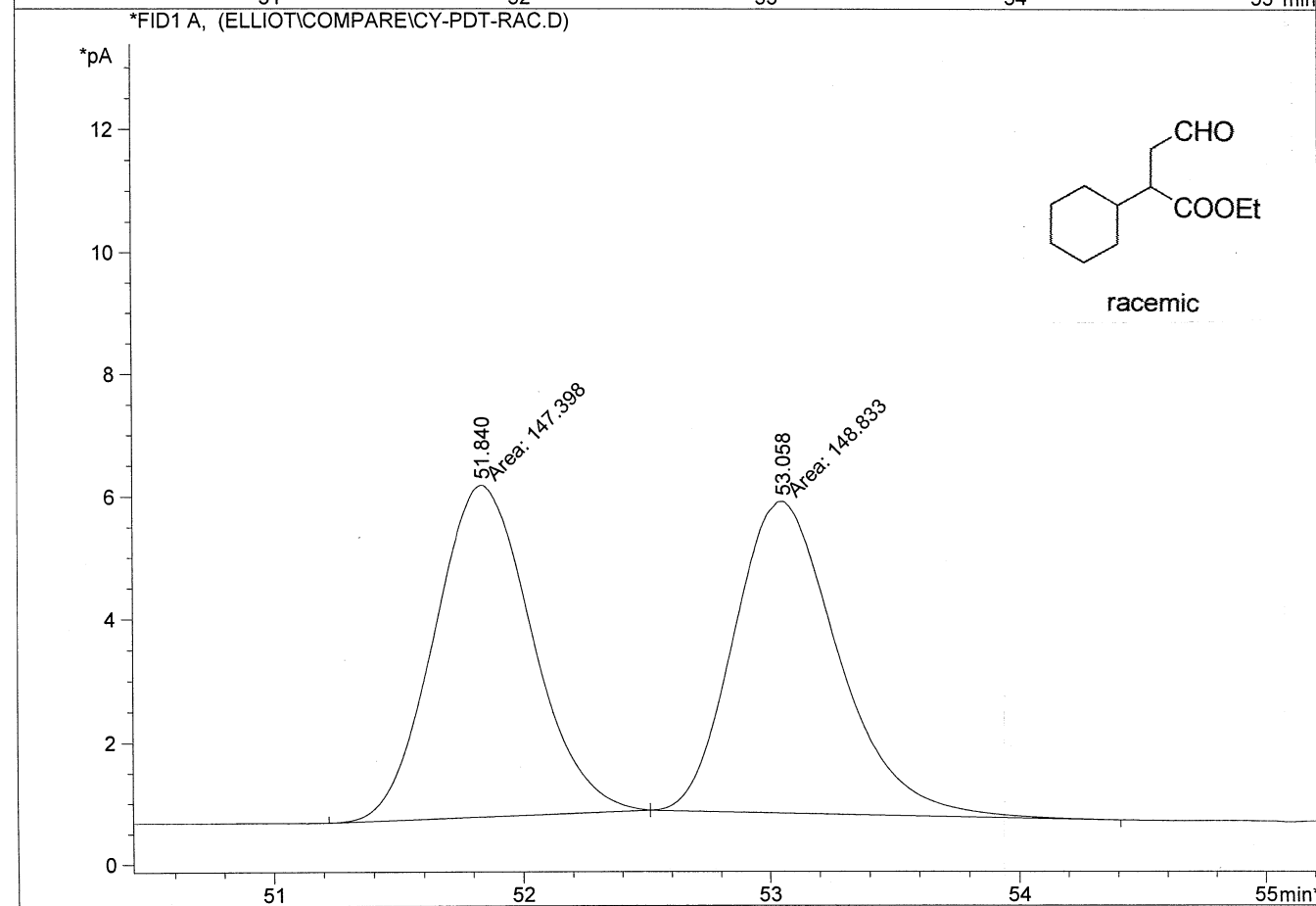
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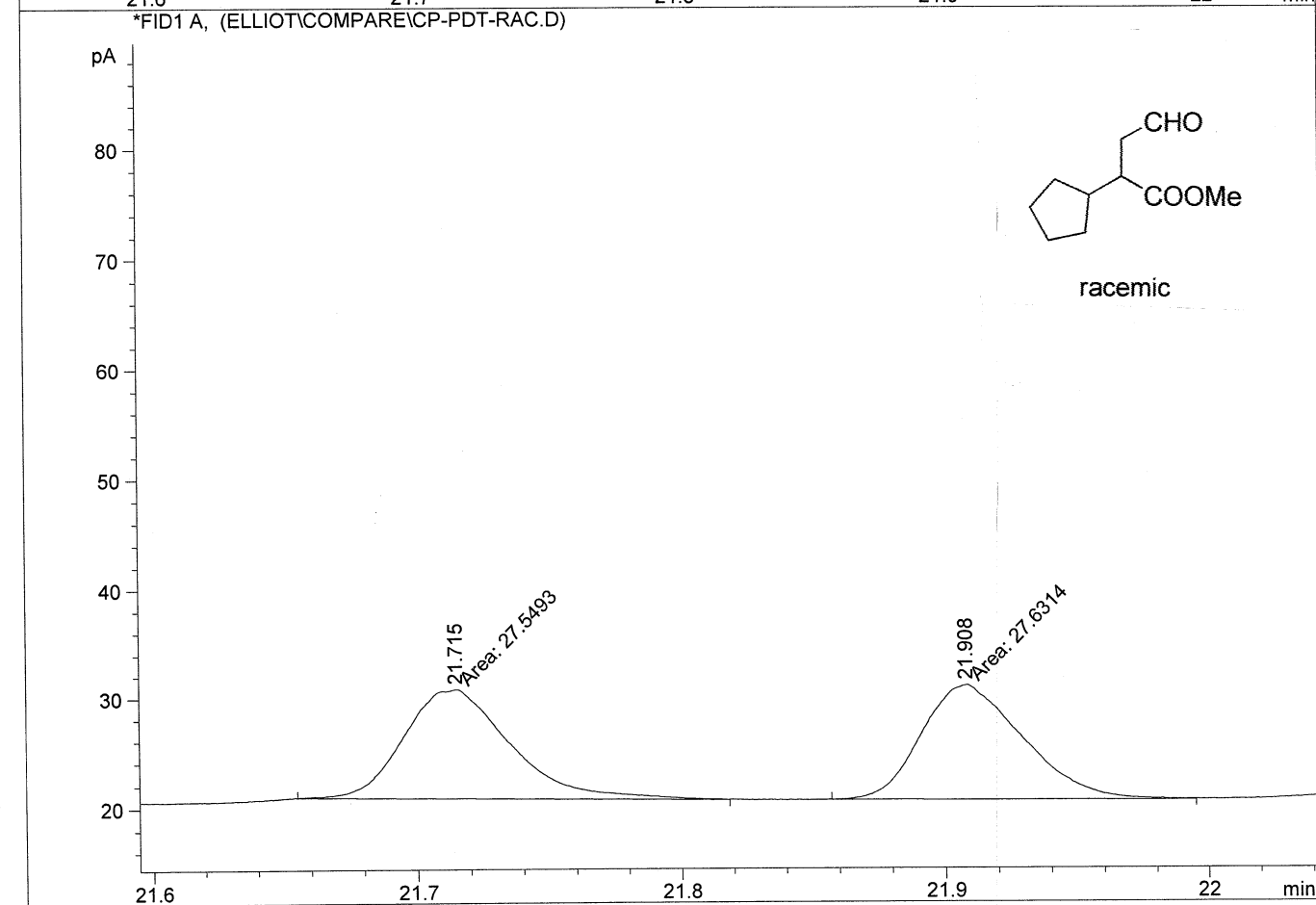
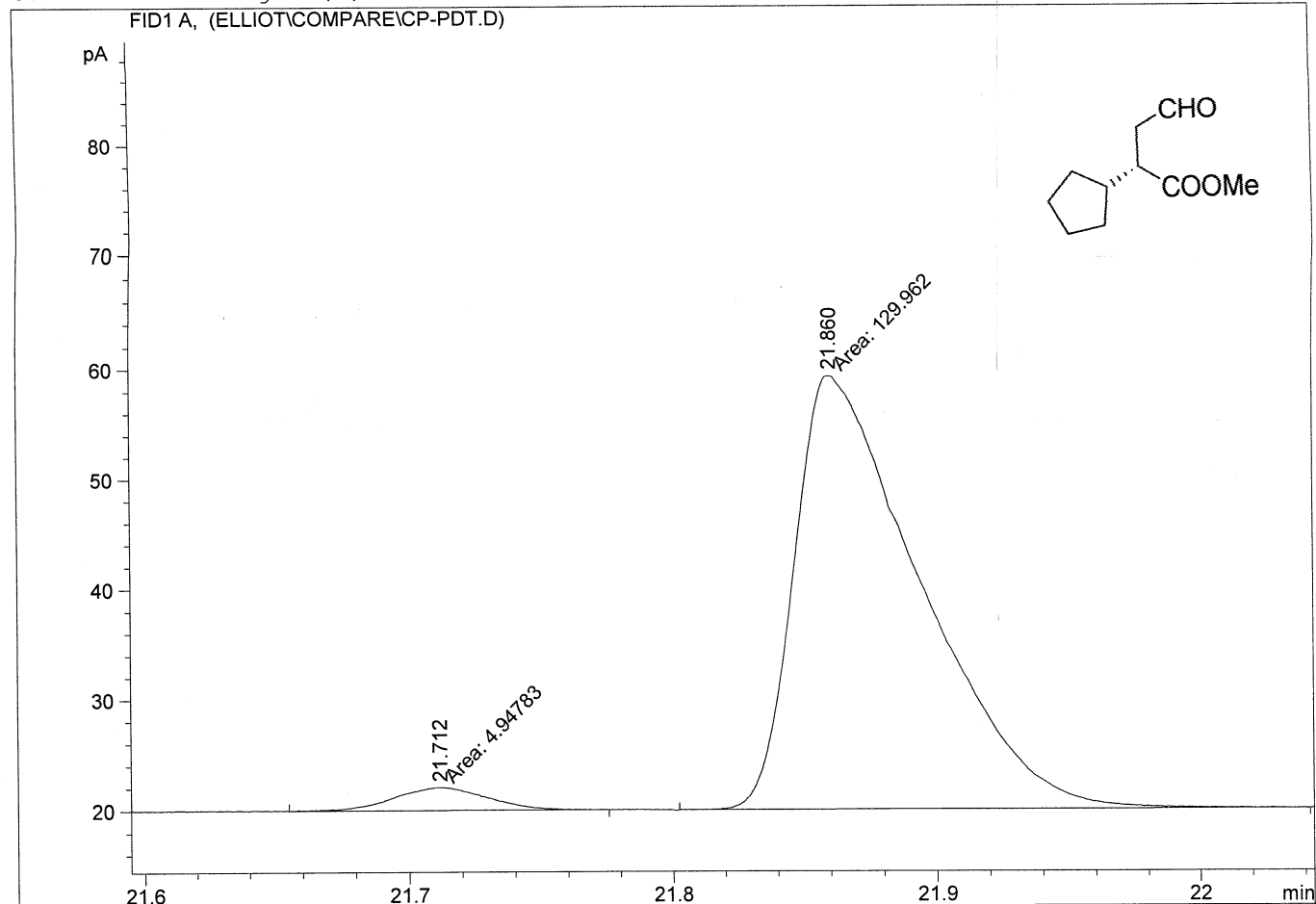
Current Chromatogram(s)



Current Chromatogram(s)



Current Chromatogram(s)



Current Chromatogram(s)

