

Synergistic effect of additives on cyclopropanation of olefins

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Supporting Information

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General Methods. All commercially available reagents were used without further purification. 1,2-Dimethoxyethane was distilled from sodium-benzophenone. Dichloromethane was distilled from CaH₂. Column chromatography was performed on silica gel (200-300 mesh). ¹H NMR spectra were recorded on a 400 MHz NMR spectrometer and ¹³C NMR spectra were recorded on a 100 MHz NMR spectrometer. IR spectra were recorded on a FT-IR spectrometer. Melting points were uncorrected.

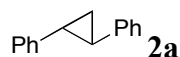
Representative procedure for cyclopropanation of *trans*-stilbene with Zn(CH₂I)₂ (2.0 equiv), CCl₃CO₂H (0.2 equiv), and DME (1.0 equiv) (Figure 1, curve E). To a flame-dried schlenk tube equipped with a stir bar, septum stopper, and nitrogen inlet was added freshly distilled CH₂Cl₂ (1.0 mL), followed by ZnEt₂ (1.0 mL, 1.0 mmol) (1.0 M in *n*-hexane) at rt. After cooling at -40 °C for 5 min, a solution of CH₂I₂ (0.540 g, 2.0 mmol) in CH₂Cl₂ (0.5 mL) was added dropwise. After the reaction mixture was stirred at -40 °C for 1 h, a solution of CCl₃CO₂H (0.0163 g, 0.10 mmol) and DME (0.045 g, 0.50 mmol) in freshly distilled CH₂Cl₂ (0.5 mL) was added. The reaction mixture was warmed to -15 °C and stirred at this temperature for 1 h. A solution of *trans*-stilbene (0.092 g, 0.50 mmol) in CH₂Cl₂ (0.5 mL) was then added dropwise at -15 °C. The resulting mixture was moved to a 30 °C oil bath and stirred at this temperature for 24 h. Small aliquots (0.1 mL) of the reaction mixture were taken with a syringe successively at 2 h, 4 h, 6 h, 16 h, 18 h, and 24 h. The crude sample mixture was diluted with CH₂Cl₂ (1.5 mL) and passed through a pad of silica gel. The conversion was analyzed on a GC instrument with an FID detector using a capillary B-DM column (T = 150 °C, P = 30 psi); Retention time: 10.42 min for the product, 11.48 min for the starting material.

Representative procedure for cyclopropanation of olefins (Table 2, entry 4). To a flame-dried schlenk tube equipped with a stir bar, septum stopper, and nitrogen inlet was added freshly distilled CH₂Cl₂ (1.0 mL), followed by ZnEt₂ (1.0 mL, 1.0 mmol) (1.0 M in *n*-hexane) at rt. After cooling at -40 °C for 5 min, a solution of CH₂I₂ (0.540 g, 2.0 mmol) in CH₂Cl₂ (0.5 mL) was added dropwise. After the reaction mixture was

stirred at -40 °C for 1 h, a solution of $\text{CCl}_3\text{CO}_2\text{H}$ (0.0163 g, 0.10 mmol) and DME (0.045 g, 0.50 mmol) in freshly distilled CH_2Cl_2 (0.5 mL) was added. The reaction mixture was warmed to -15 °C and stirred at this temperature for 1 h. A solution of olefin **1d** (0.124 g, 0.50 mmol) in CH_2Cl_2 (0.5 mL) was then added dropwise at -15 °C. Upon moving to a 25 °C oil bath and stirring at this temperature for 18 h, the reaction mixture was quenched with saturated aqueous NH_4Cl (10 mL) [or aqueous 0.1N HCl (5 mL)], extracted with CH_2Cl_2 (10 mL x 3), washed with brine, dried over Na_2SO_4 , filtered, concentrated, and purified by flash chromatography (silica gel, eluent: pentane/ CH_2Cl_2 = 10/1) to give cyclopropane **2d** as colorless oil (0.1251 g, 95%).

For acid-sensitive products such as **2c**, **2j**, **2t**, **2u**, **2v** and **2w**, the reaction mixture was quenched with saturated aqueous NaHCO_3 (5 mL). Upon stirring at rt for 20 min, the reaction mixture was diluted with H_2O (10 mL), extracted with CH_2Cl_2 (15 mL x 2), washed with saturated aqueous NH_4Cl (10 mL), saturated aqueous Na_2SO_3 (10 mL), saturated aqueous NaHCO_3 (10 mL x 2), and brine. The organic layer was dried over Na_2SO_4 , filtered, concentrated, and purified by flash chromatography.

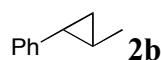
Table 2, entry 1



Colorless oil; IR (film) 3028, 1603, 1498, 696 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.31-7.26 (m, 4H), 7.18 (t, J = 7.2 Hz, 2H), 7.14 (d, J = 7.2 Hz, 4H), 2.17 (dd, J = 7.6, 7.2 Hz, 2H), 1.45 (dd, J = 7.6, 7.2 Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 142.7, 128.6, 125.9, 28.3, 18.5.

1) S.-M. Zhou, M.-Z. Deng, L.-J. Xia and M.-H. Tang, *Angew. Chem., Int. Ed.*, 1998, **37**, 2845; 2) J. C. Lorenz, J. Long, Z. Yang, S. Xue, Y. Xie and Y. Shi, *J. Org. Chem.*, 2004, **69**, 327.

Table 2, entry 2

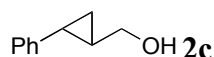


Colorless oil; IR (film) 2924, 1459 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.27-7.19 (m, 2H), 7.11 (t, J = 7.2 Hz, 1H), 7.02 (d, J = 7.2 Hz, 2H), 1.56 (dt, J = 8.8, 4.8 Hz, 1H),

1.17 (d, $J = 6.0$ Hz, 3H), 1.10-0.99 (m, 1H), 0.91-0.82 (m, 1H), 0.76-0.69 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 144.3, 128.4, 125.6, 125.3, 24.5, 19.3, 18.2, 17.8.

1) H. E. Simmons and R. D. Smith, *J. Am. Chem. Soc.*, 1959, **81**, 4256; 2) S. E. Denmark and J. P. Edwards, *J. Org. Chem.*, 1991, **56**, 6974; 3) J. C. Lorenz, J. Long, Z. Yang, S. Xue, Y. Xie and Y. Shi, *J. Org. Chem.*, 2004, **69**, 327.

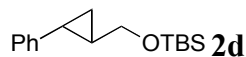
Table 2, entry 3



Colorless oil; IR (film) 3331, 1604, 1020, 697 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.25 (t, $J = 7.2$ Hz, 2H), 7.15 (t, $J = 7.2$ Hz, 1H), 7.06 (d, $J = 7.2$ Hz, 2H), 3.66-3.53 (m, 2H), 1.81 (dt, $J = 9.2, 4.8$ Hz, 1H), 1.74 (br s, 1H), 1.50-1.39 (m, 1H), 1.01-0.86 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 142.6, 128.5, 126.0, 125.8, 66.7, 25.5, 21.5, 14.1.

1) S. E. Denmark and S. P. O'Connor, *J. Org. Chem.*, 1997, **62**, 584; 2) J. C. Lorenz, J. Long, Z. Yang, S. Xue, Y. Xie and Y. Shi, *J. Org. Chem.*, 2004, **69**, 327.

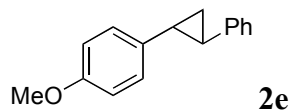
Table 2, entry 4



Colorless oil; IR (film) 2929, 1462, 1097 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.32-7.21 (m, 2H), 7.14 (t, $J = 7.2$ Hz, 1H), 7.07 (d, $J = 7.2$ Hz, 2H), 3.72 (dd, $J = 10.8, 5.6$ Hz, 1H), 3.62 (dd, $J = 10.8, 6.0$ Hz, 1H), 1.80 (dt, $J = 8.4, 4.0$ Hz, 1H), 1.41-1.31 (m, 1H), 0.97-0.88 (m, 2H), 0.90 (s, 9H), 0.07 (s, 6H); ^{13}C NMR (100 MHz, CDCl_3) δ 143.3, 128.5, 126.1, 125.6, 66.1, 26.2, 25.5, 21.0, 18.7, 13.9, -4.9.

J. C. Lorenz, J. Long, Z. Yang, S. Xue, Y. Xie and Y. Shi, *J. Org. Chem.*, 2004, **69**, 327.

Table 2, entry 5

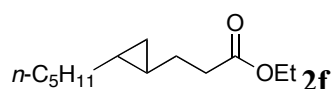


White solid; mp. 70-71 $^{\circ}\text{C}$; IR (film) 1515, 1247 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.28 (t, $J = 7.6$ Hz, 2H), 7.17 (t, $J = 7.2$ Hz, 1H), 7.13 (d, $J = 7.2$ Hz, 2H), 7.08

(d, $J = 8.4$ Hz, 2H), 6.84 (d, $J = 8.8$ Hz, 2H), 3.79 (s, 3H), 2.17-2.04 (m, 2H), 1.39 (dd, $J = 7.6, 6.8$ Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 158.0, 142.9, 134.7, 128.6, 127.1, 125.9, 125.8, 114.0, 55.5, 27.7, 27.6, 18.1; HRMS Calcd for $\text{C}_{16}\text{H}_{17}\text{O}$ ($\text{M}+\text{H}$): 225.1274; Found: 225.1270.

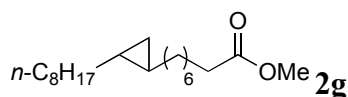
1) M. Yasuda, R. Kojima, H. Tsutsui, D. Utsunomiya, K. Ishii, K. Jinnouchi and T. Shiragami, *J. Org. Chem.*, 2003, **68**, 7618; 2) C. R. Solorio-Alvarado and A. Echavarren, *J. Am. Chem. Soc.*, 2010, **132**, 11881.

Table 2, entry 6



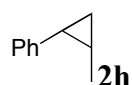
Colorless oil; IR (film) 1739 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 4.12 (q, $J = 7.2$ Hz, 2H), 2.36 (t, $J = 7.6$ Hz, 2H), 1.61-1.42 (m, 2H), 1.38-1.16 (m, 10H), 1.15-1.05 (m, 1H), 0.87 (dd, $J = 7.2, 6.4$ Hz, 3H), 0.47-0.37 (m, 2H), 0.23-0.15 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 174.0, 60.4, 34.7, 34.3, 31.9, 29.9, 29.5, 22.9, 19.0, 18.4, 14.5, 14.3, 12.0; HRMS Calcd for $\text{C}_{13}\text{H}_{25}\text{O}_2$ ($\text{M}+\text{H}$): 213.1849; Found: 213.1853.

Table 2, entry 7



Colorless oil; IR (film) 1744 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 3.66 (s, 3H), 2.30 (t, $J = 7.6$ Hz, 2H), 1.64-1.57 (m, 2H), 1.42-1.04 (m, 24H), 0.87 (t, $J = 6.8$ Hz, 3H), 0.40-0.30 (m, 2H), 0.16-0.09 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 174.6, 51.7, 34.6, 34.5, 34.3, 32.1, 29.9, 29.82, 29.75, 29.6, 29.5, 29.4, 25.2, 22.9, 19.0, 18.9, 14.4, 12.0; HRMS Calcd for $\text{C}_{20}\text{H}_{39}\text{O}_2$ ($\text{M}+\text{H}$): 311.2945; Found: 311.2946.

Table 2, entry 8

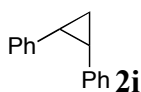


Colorless oil; IR (film) 3063, 1497, 698 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ

7.28-7.22 (m, 2H), 7.20-7.12 (m, 3H), 2.06 (td, $J = 8.8, 6.0$ Hz, 1H), 1.18-1.06 (m, 1H), 0.95 (td, $J = 8.4, 5.2$ Hz, 1H), 0.77 (d, $J = 6.4$ Hz, 3H), 0.56 (q, $J = 5.6$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 139.7, 129.5, 128.0, 125.7, 21.3, 13.8, 12.9, 11.0.

1) C. P. Casey, S. W. Polichnowski, A. J. Shusterman and C. R. Jones, *J. Am. Chem. Soc.*, 1979, **101**, 7282; 2) J. C. Lorenz, J. Long, Z. Yang, S. Xue, Y. Xie and Y. Shi, *J. Org. Chem.*, 2004, **69**, 327.

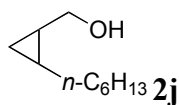
Table 2, entry 9



Colorless oil; IR (film) 3026, 1603, 1497, 696 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.17-7.04 (m, 6H), 6.98 (d, $J = 7.6$ Hz, 4H), 2.52 (dd, $J = 8.4, 6.4$ Hz, 2H), 1.50 (td, $J = 8.8, 5.6$ Hz, 1H), 1.41 (td, $J = 6.4, 5.6$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 138.6, 129.2, 127.8, 125.8, 24.5, 11.6.

1) N. Kawabata, I. Kamemura and M. Naka, *J. Am. Chem. Soc.*, 1979, **101**, 2139; 2) J. C. Lorenz, J. Long, Z. Yang, S. Xue, Y. Xie and Y. Shi, *J. Org. Chem.*, 2004, **69**, 327.

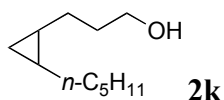
Table 2, entry 10



Colorless oil; IR (film) 3330, 1467, 1032 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 3.63 (dd, $J = 10.8, 7.2$ Hz, 1H), 3.57 (dd, $J = 10.8, 8.4$ Hz, 1H), 1.49-1.15 (m, 11H), 1.15-1.03 (m, 1H), 0.90-0.80 (m, 1H), 0.87 (t, $J = 6.8$ Hz, 3H), 0.69 (td, $J = 8.4, 4.8$ Hz, 1H), -0.05 (q, $J = 5.2$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 63.5, 32.1, 30.3, 29.4, 28.8, 22.9, 18.3, 16.4, 14.3, 9.7.

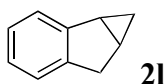
G. D. Coxon, J. R. Al-Dulayymi, M. S. Baird, S. Knobl, E. Roberts and D. E. Minnikin, *Tetrahedron: Asymmetry*, 2003, **14**, 1211.

Table 2, entry 11



Colorless oil; IR (film) 3330, 1457, 1059 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 3.68 (t, *J* = 6.8 Hz, 2H), 1.68 (quintet, *J* = 6.8 Hz, 2H), 1.53-1.10 (m, 11H), 0.88 (t, *J* = 6.8 Hz, 3H), 0.73-0.55 (m, 3H), -0.30 (td, *J* = 5.2, 4.4 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 63.2, 33.5, 32.1, 30.1, 28.8, 25.1, 22.9, 16.1, 15.6, 14.3, 11.2; HRMS Calcd for C₁₁H₂₃O (M+H): 171.1743; Found: 171.1740.

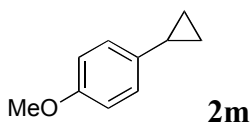
Table 2, entry 12



Colorless oil; IR (film) 2925, 1492, 739 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.33-7.28 (m, 1H), 7.18-7.05 (m, 3H), 3.19 (dd, *J* = 16.8, 6.8 Hz, 1H), 2.94 (d, *J* = 16.8 Hz, 1H), 2.40-2.33 (m, 1H), 1.90-1.81 (m, 1H), 1.06 (td, *J* = 8.0, 4.4 Hz, 1H), 0.07 (td, *J* = 4.4, 3.6 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 147.3, 142.2, 126.1, 125.7, 125.5, 123.6, 35.7, 24.1, 16.9, 16.2.

J. C. Lorenz, J. Long, Z. Yang, S. Xue, Y. Xie and Y. Shi, *J. Org. Chem.*, 2004, **69**, 327.

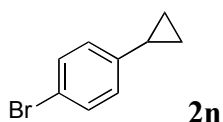
Table 2, entry 13



Colorless oil; IR (film) 3002, 1515, 1247 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.04 (d, *J* = 8.4 Hz, 2H), 6.84 (d, *J* = 8.4 Hz, 2H), 3.80 (s, 3H), 1.93-1.83 (m, 1H), 0.96-0.89 (m, 2H), 0.68-0.61 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 157.7, 136.0, 127.0, 113.9, 55.5, 14.8, 8.7.

1) L. Ackermann, A. R. Kapdi and C. Schulzke, *Org. Lett.*, 2010, **12**, 2298; 2) M. Arndt, G. Hilt, A. F. Khlebnikov, S. I. Kozhushkov and A. de Meijere, *Eur. J. Org. Chem.*, 2012, 3112.

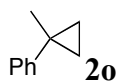
Table 2, entry 14



Colorless oil; IR (film) 3081, 1490, 813 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.36 (d, $J = 8.4$ Hz, 2H), 6.94 (d, $J = 8.4$ Hz, 2H), 1.90-1.81 (m, 1H), 1.10-0.94 (m, 2H), 0.70-0.63 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 143.3, 131.4, 127.6, 119.0, 15.2, 9.6.

1) M. Salamone, M. Bietti, A. Calcagni and G. Gente, *Org. Lett.*, 2009, **11**, 2453; 2) O. B. Bondarenko, A. Y. Gavrilova, M. A. Kazantseva, V. N. Tikhanushkina, E. E. Nifantev, L. G. Saginova and N. V. Zyk, *Russ. J. Org. Chem.*, 2006, **42**, 249.

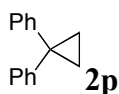
Table 2, entry 15



Colorless oil; IR (film) 3076, 1497, 698 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.31-7.22 (m, 4H), 7.18-7.12 (m, 1H), 1.40 (s, 3H), 0.88-0.84 (m, 2H), 0.75-0.70 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 147.3, 128.4, 126.9, 125.6, 25.9, 19.9, 15.9.

A. B. Charette, S. Francoeur, J. Martel and N. Wilb, *Angew. Chem., Int. Ed.*, 2000, **39**, 4539.

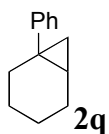
Table 2, entry 16



Colorless oil; IR (film) 3082, 1496, 699 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.31-7.13 (m, 10H), 1.30 (s, 4H); ^{13}C NMR (100 MHz, CDCl_3) δ 145.9, 128.6, 128.5, 126.1, 30.1, 16.7.

1) S. S. Hixson and L. A. Franke, *J. Org. Chem.*, 1988, **53**, 2706; 2) A. Oku, Y. Ose, T. Kamada and T. Yoshida, *Chem. Lett.*, 1993, **22**, 573.

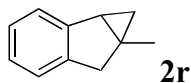
Table 2, entry 17



Colorless oil; IR (film) 2927, 1601, 698 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.31-7.22 (m, 4H), 7.18-7.11 (m, 1H), 2.14-2.00 (m, 2H), 1.98-1.89 (m, 1H), 1.73-1.61 (m, 1H), 1.52-1.17 (m, 5H), 0.94 (dd, $J = 9.2, 4.4$ Hz, 1H), 0.63 (t, $J = 5.2$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 149.8, 128.4, 127.6, 125.6, 31.7, 24.7, 24.2, 21.88, 21.87, 19.2, 18.5.

1) A. Balsamo, C. Battistini, P. Crotti, B. Macchia and F. Macchia, *J. Org. Chem.*, 1975, **40**, 3233; 2) J. C. Lorenz, J. Long, Z. Yang, S. Xue, Y. Xie and Y. Shi, *J. Org. Chem.*, 2004, **69**, 327.

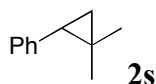
Table 2, entry 18



Colorless oil; IR (film) 3022, 1477, 753 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.26-7.20 (m, 1H), 7.14-7.01 (m, 3H), 3.02 (d, $J = 16.8$ Hz, 1H), 2.95 (d, $J = 16.8$ Hz, 1H), 2.11-2.05 (m, 1H), 1.39 (s, 3H), 0.96 (dd, $J = 7.6, 4.0$ Hz, 1H), 0.24 (dd, $J = 4.0, 3.2$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 148.1, 142.8, 126.0, 125.4, 125.2, 123.2, 41.8, 31.1, 24.1, 24.0, 21.9.

1) M. A. O'Leary and D. Wege, *Tetrahedron*, 1981, **37**, 801; 2) J. C. Lorenz, J. Long, Z. Yang, S. Xue, Y. Xie and Y. Shi, *J. Org. Chem.*, 2004, **69**, 327.

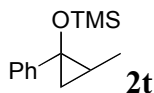
Table 2, entry 19



Colorless oil; IR (film) 2924, 1450, 699 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.30-7.23 (m, 2H), 7.19-7.12 (m, 3H), 1.88 (dd, $J = 8.4, 6.0$ Hz, 1H), 1.22 (s, 3H), 0.83-0.74 (m, 2H), 0.79 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 140.5, 129.1, 128.0, 125.7, 29.9, 27.7, 20.5, 19.2, 18.5.

1) I. Fleming and C. J. Urch, *J. Organomet. Chem.*, 1985, **285**, 173; 2) J. E. Argüello, A. B. Peñeñory and R. A. Rossi, *J. Org. Chem.*, 1999, **64**, 6115.

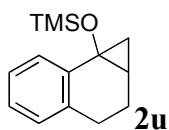
Table 2, entry 20



Colorless oil; IR (film) 3062, 1450 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.37-7.25 (m, 4H), 7.25-7.17 (m, 1H), 1.38 (dd, $J = 9.6, 6.0$ Hz, 1H), 1.29 (d, $J = 6.0$ Hz, 3H), 1.08-0.97 (m, 1H), 0.80 (t, $J = 6.4$ Hz, 1H), 0.14 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ 146.1, 128.2, 126.0, 124.8, 61.1, 23.1, 22.4, 13.1, 1.3.

J. C. Lorenz, J. Long, Z. Yang, S. Xue, Y. Xie and Y. Shi, *J. Org. Chem.*, 2004, **69**, 327.

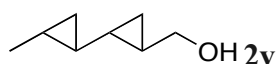
Table 2, entry 21



Colorless oil; IR (film) 2957, 1488, 1275, 750 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.65 (d, $J = 7.6$ Hz, 1H), 7.24 (t, $J = 7.2$ Hz, 1H), 7.09 (t, $J = 7.6$ Hz, 1H), 7.04 (d, $J = 7.2$ Hz, 1H), 2.62 (dd, $J = 16.4, 4.8$ Hz, 1H), 2.45-2.30 (m, 1H), 2.08-1.96 (m, 1H), 1.85-1.72 (m, 2H), 1.18 (dd, $J = 10.0, 6.0$ Hz, 1H), 1.01 (t, $J = 6.0$ Hz, 1H), 0.15 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ 141.3, 132.5, 128.3, 126.3, 125.4, 125.2, 56.2, 26.3, 23.9, 18.6, 16.4, 1.4.

H. Du, J. Long and Y. Shi, *Org. Lett.*, 2006, **8**, 2827.

Scheme 3

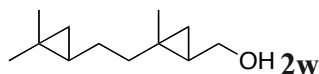


Colorless oil; IR (film) 3331, 3065, 1507, 1018 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 3.44-3.32 (m, 2H), 1.75 (br s, 1H), 0.96 (d, $J = 5.6$ Hz, 3H), 0.89-0.75 (m, 1H), 0.73-0.64 (m, 1H), 0.53-0.38 (m, 2H), 0.33-0.22 (m, 2H), 0.21-0.13 (m, 1H), 0.11-0.02 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) (major isomer) δ 67.1, 20.9, 19.7, 19.0, 18.8,

11.7, 11.3, 8.7. HRMS Calcd for C_8H_{13} (M-OH): 109.1012; Found: 109.1013.

A. G. M. Barrett, W. W. Doubleday and G. J. Tustin, *Tetrahedron*, 1996, **52**, 15325.

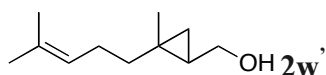
Scheme 4



Colorless oil; IR (film) 3345, 3055, 1455, 1025 cm^{-1} ; 1H NMR (400 MHz, $CDCl_3$) δ 3.73-3.64 (m, 1H), 3.56-3.46 (m, 1H), 1.44-1.14 (m, 5H), 1.07 (s, 3H), 1.02 (s, 3H), 1.00 (s, 3H), 0.94-0.83 (m, 1H), 0.53-0.47 (m, 1H), 0.46-0.38 (m, 1H), 0.36-0.30 (m, 1H), 0.11 (t, $J = 4.8$ Hz, 1H), -0.16 (t, $J = 4.8$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 64.2, 41.81, 41.79, 27.8, 27.3, 26.4, 26.3, 24.81, 24.78, 20.3, 20.2, 20.0, 19.91, 19.87, 18.00, 17.95, 17.34, 17.32, 15.6. HRMS Calcd for $C_{12}H_{22}NaO$ (M+Na): 205.1563; Found: 205.1567.

1) H. Sakauchi, H. Asao, T. Hasaba, S. Kuwahara and H. Kiyota, *Chemistry & Biodiversity*, 2006, **3**, 544; 2) G. Brunner, L. Eberhard, J. Oetiker and F. Schröder, *J. Org. Chem.*, 2008, **73**, 7543.

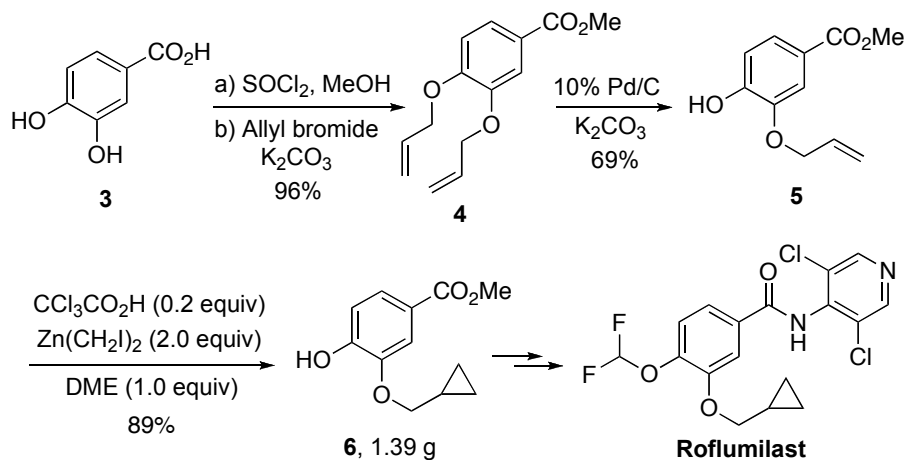
Scheme 4



Colorless oil; IR (film) 3331, 3056, 1452, 1028 cm^{-1} ; 1H NMR (400 MHz, $CDCl_3$) δ 5.13-5.05 (m, 1H), 3.70 (dd, $J = 11.2, 6.4$ Hz, 1H), 3.48 (dd, $J = 11.2, 8.8$ Hz, 1H), 2.11-1.99 (m, 2H), 1.67 (s, 3H), 1.60 (s, 3H), 1.43-1.31 (m, 2H), 1.18-1.10 (m, 1H), 1.08 (s, 3H), 0.95-0.83 (m, 1H), 0.49 (dd, $J = 8.8, 4.4$ Hz, 1H), 0.11 (t, $J = 4.8$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 131.5, 124.8, 64.1, 41.3, 26.4, 25.9, 25.7, 20.1, 17.84, 17.78, 17.2. HRMS Calcd for $C_{11}H_{20}NaO$ (M+Na): 191.1406; Found: 191.1405.

1) H. Sakauchi, H. Asao, T. Hasaba, S. Kuwahara and H. Kiyota, *Chemistry & Biodiversity*, 2006, **3**, 544; 2) G. Brunner, L. Eberhard, J. Oetiker and F. Schröder, *J. Org. Chem.*, 2008, **73**, 7543.

Preparation of a key intermediate for Roflumilast (Scheme 5)



To a stirred solution of 3,4-dihydroxybenzoic acid (3.08 g, 20.0 mmol) in MeOH (50 mL) was added SOCl_2 (9.52 g, 80.0 mmol) dropwise at 0 °C over 30 min. Upon stirring at 50 °C for 8 h, the reaction mixture was cooled to rt, concentrated, and dissolved in dry acetone (30 mL), followed by the addition of K_2CO_3 (13.80 g, 100.0 mmol). After stirring at rt for 10 min, allyl bromide (7.26 g, 60.0 mmol) was added. The reaction mixture was stirred at rt overnight, concentrated, brought to pH = 7 with aqueous 1N HCl, extracted with EtOAc (30 mL x 3), washed with brine, dried over Na_2SO_4 , filtered, concentrated, and purified by flash column chromatography (silica gel, eluent: Petroleum ether/EtOAc = 20/1) to give compound **4** as colorless oil (4.76 g, 96%). IR (film) 3083, 1717, 1294 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.64 (dd, J = 8.8, 2.0 Hz, 1H), 7.56 (d, J = 2.0 Hz, 1H), 6.89 (d, J = 8.8 Hz, 1H), 6.15-6.01 (m, 2H), 5.48-5.39 (m, 2H), 5.34-5.27 (m, 2H), 4.69-4.63 (m, 4H), 3.88 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 167.0, 152.6, 148.1, 133.1, 132.9, 123.9, 122.9, 118.3, 118.2, 114.7, 112.5, 70.0, 69.8, 52.2; HRMS Calcd for $\text{C}_{14}\text{H}_{17}\text{O}_4$ ($\text{M}+\text{H}$): 249.1121; Found: 249.1123.

F. L. Monte, T. Kramer, J. Gu, U. R. Anumala, L. Marinelli, V. L. Pietra, E. Novellino, B. Franco, D. Demedts, F. V. Leuven, A. Fuertes, J. M. Dominguez, B. Plotkin, H. Eldar-Finkelman and B. Schmidt, *J. Med. Chem.*, 2012, **55**, 4407.

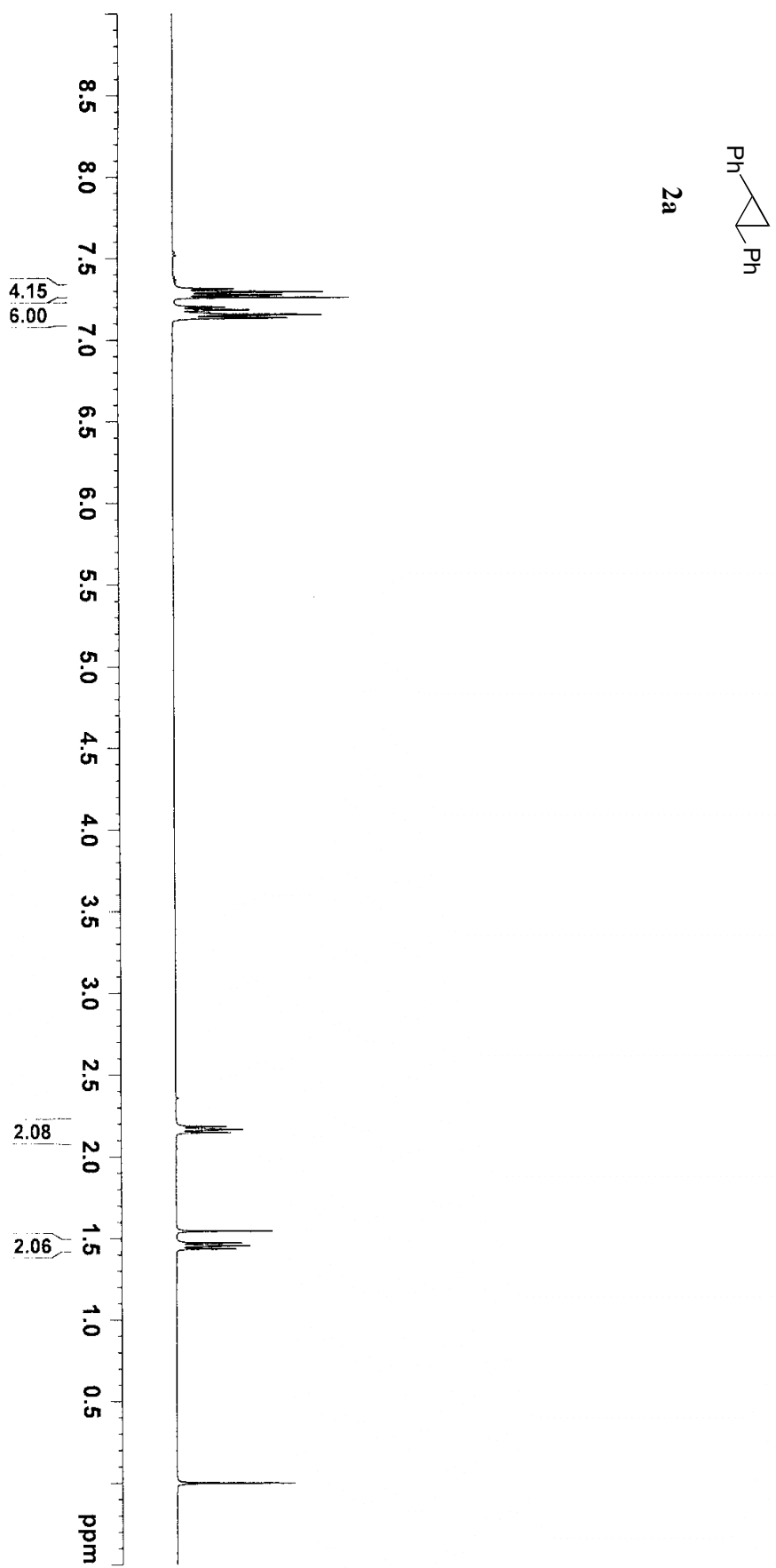
A mixture of compound **4** (4.60 g, 18.5 mmol), 10% Pd/C (0.64 g), and K₂CO₃ (20.0 g) in MeOH (228 mL) was stirred at 50 °C for 5 h, filtered through a Celite pad, washed with DCM (20 mL), concentrated to remove MeOH, brought to pH = 7 with aqueous 1N HCl (~150 mL), extracted with DCM (30 mL x 2), washed with water and brine, dried over Na₂SO₄, filtered, concentrated, and purified by flash column chromatography (silica gel, eluent: Petroleum ether/EtOAc = 20/1) to give compound **5** as white solid (2.64 g, 69%). mp. 36-38 °C; IR (film) 3399, 1713, 1285 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.62 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.54 (d, *J* = 1.6 Hz, 1H), 6.94 (d, *J* = 8.4 Hz, 1H), 6.25 (s, 1H), 6.10-5.97 (m, 1H), 5.47-5.39 (m, 1H), 5.32 (d, *J* = 10.4 Hz, 1H), 4.63 (d, *J* = 5.2 Hz, 2H), 3.87 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 167.0, 150.4, 145.3, 132.5, 124.5, 122.4, 119.0, 114.5, 113.3, 70.1, 52.2; HRMS Calcd for C₁₁H₁₃O₄ (M+H): 209.0808; Found: 209.0803.

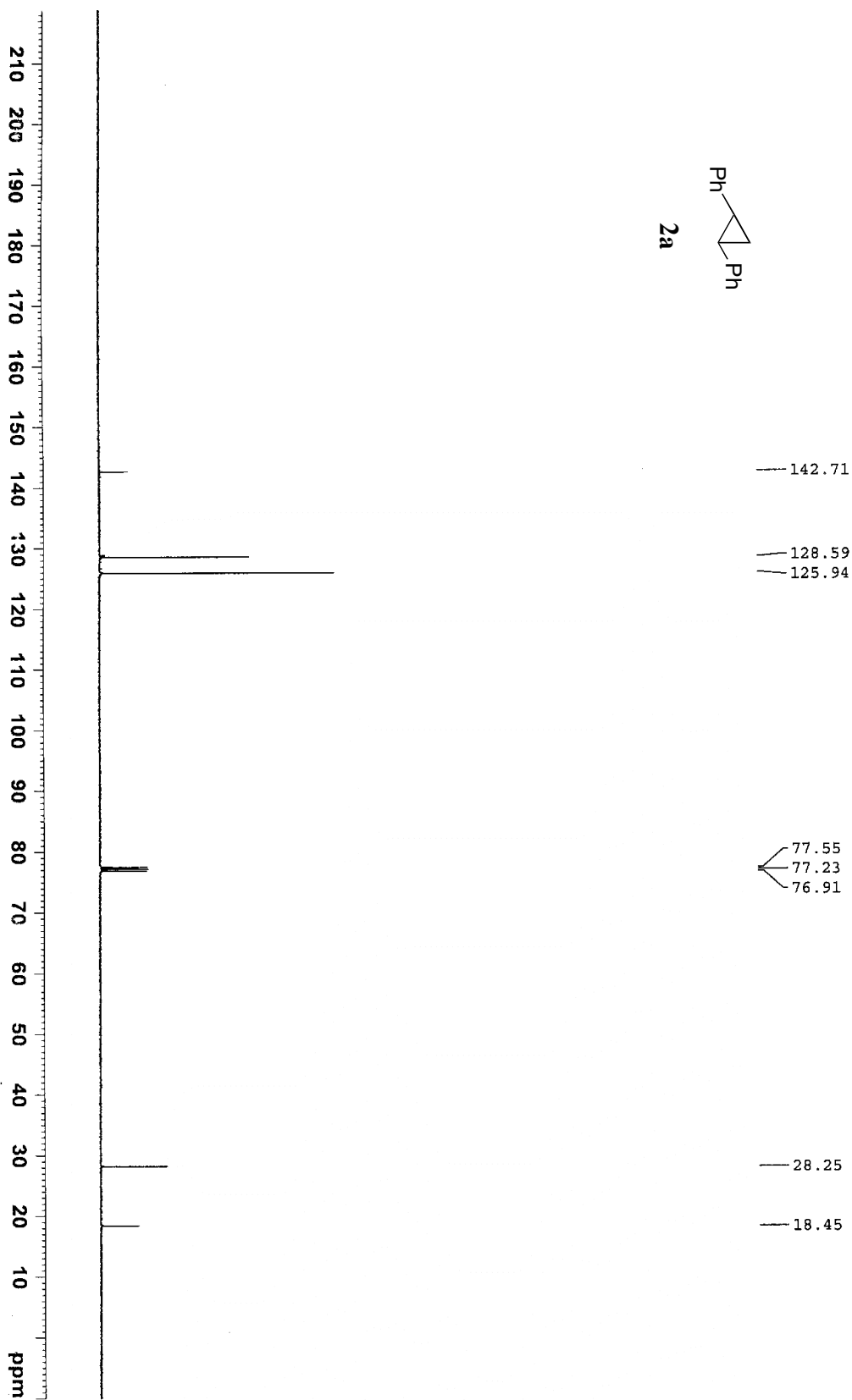
J. Li, D. Zhang, X. Zhu, Z. He, S. Liu, M. Li, J. Pang and Y. Lin, *Mar. Drugs*, 2011, **9**, 1887.

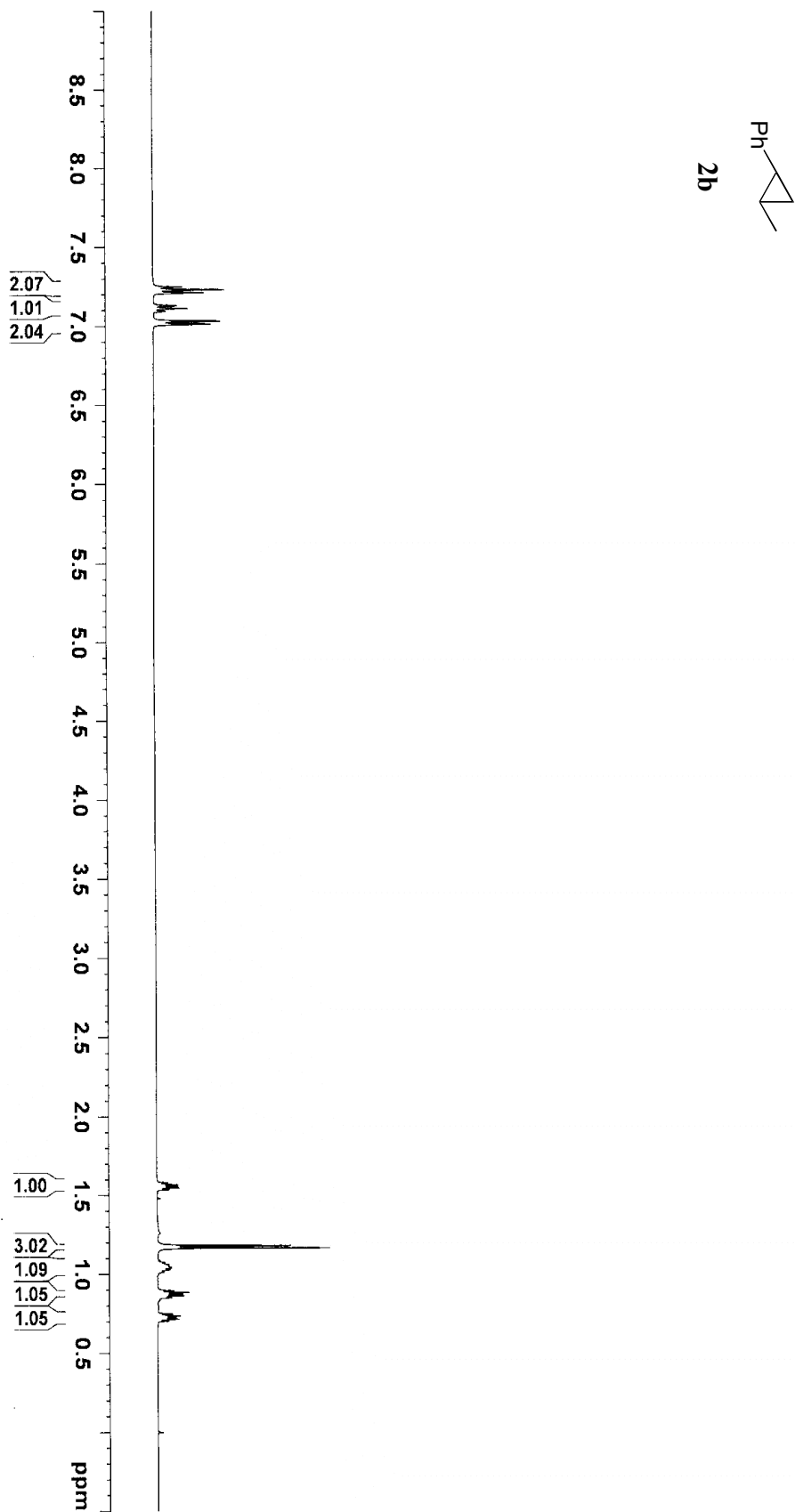
To a flame-dried flask equipped with a stir bar, septum stopper, and nitrogen inlet was added freshly distilled CH₂Cl₂ (14.0 mL), followed by ZnEt₂ (14.0 mL, 14.0 mmol) (1.0 M in *n*-hexane) at rt. After cooling at -40 °C for 10 min, a solution of CH₂I₂ (7.50 g, 28.0 mmol) in CH₂Cl₂ (7.0 mL) was added dropwise. After the reaction mixture was stirred at -40 °C for 1 h, a solution of CCl₃CO₂H (0.228 g, 1.4 mmol) and DME (0.631 g, 7.0 mmol) in freshly distilled CH₂Cl₂ (7.0 mL) was added. The reaction mixture was warmed to -15 °C and stirred at this temperature for 1 h. A solution of olefin **5** (1.46 g, 7.0 mmol) in CH₂Cl₂ (7.0 mL) was then added dropwise at -15 °C. Upon moving to a 25 °C oil bath and stirring at this temperature for 24 h, the reaction mixture was quenched with aqueous 0.1N HCl (100 mL), extracted with CH₂Cl₂ (20 mL x 4), washed with brine, dried over Na₂SO₄, filtered, concentrated, and purified by flash chromatography (silica gel, eluent: Petroleum ether/EtOAc = 20/1) to give compound **6** as white solid (1.39 g, 89%). mp. 50 °C; IR (film) 3400, 1713, 1287 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.62 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.50 (d, *J* = 1.6 Hz, 1H), 6.94 (d, *J* = 8.4 Hz, 1H), 6.16 (s, 1H), 3.92 (d, *J* = 6.8 Hz, 2H), 3.87 (s, 3H), 1.35-1.22 (m,

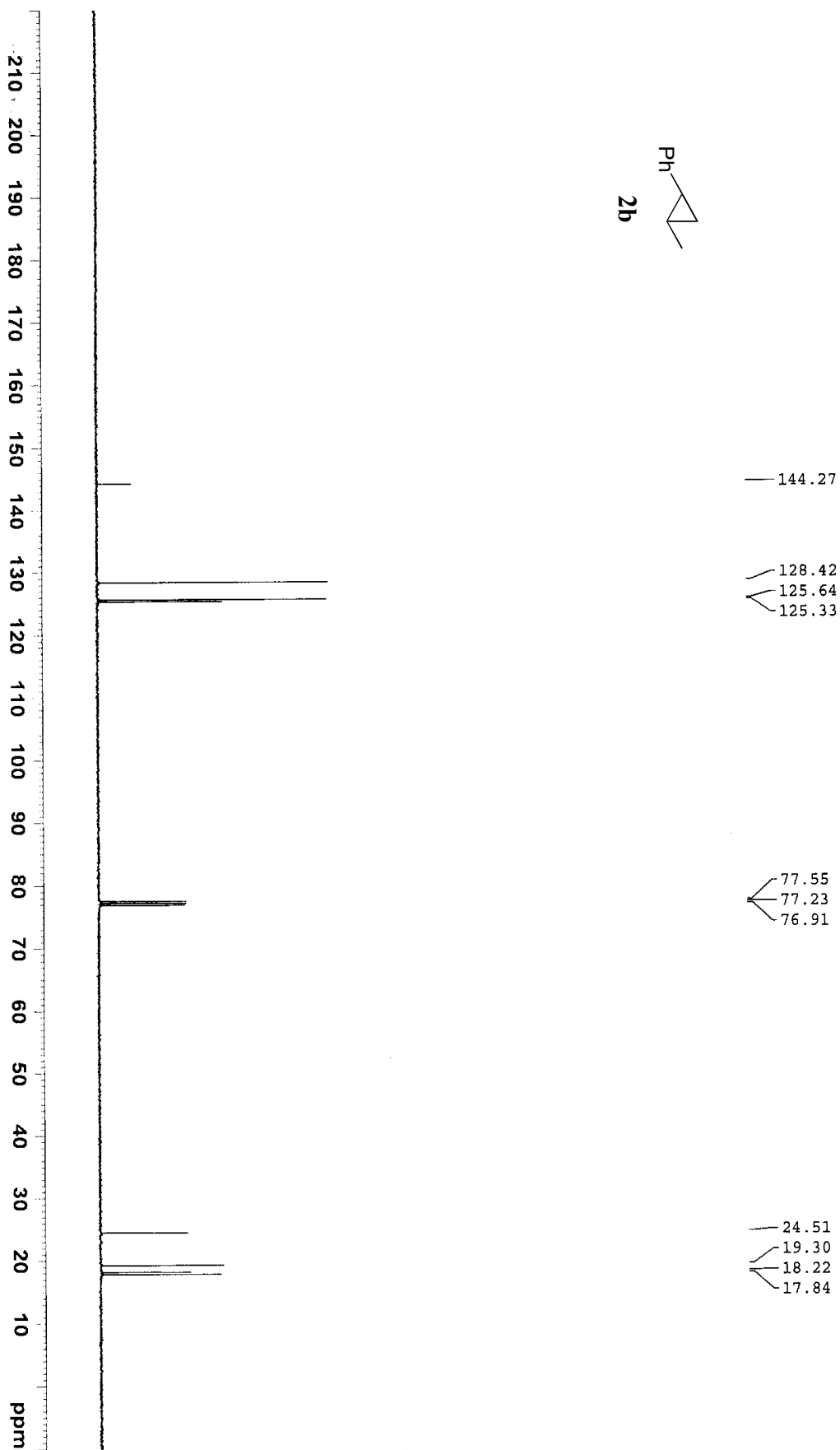
1H), 0.71-0.61 (m, 2H), 0.40-0.31 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 167.1, 150.4, 145.7, 124.2, 122.2, 114.2, 113.0, 74.3, 52.1, 10.3, 3.5; HRMS Calcd for C₁₂H₁₅O₄ (M+H): 223.0965; Found: 223.0962.

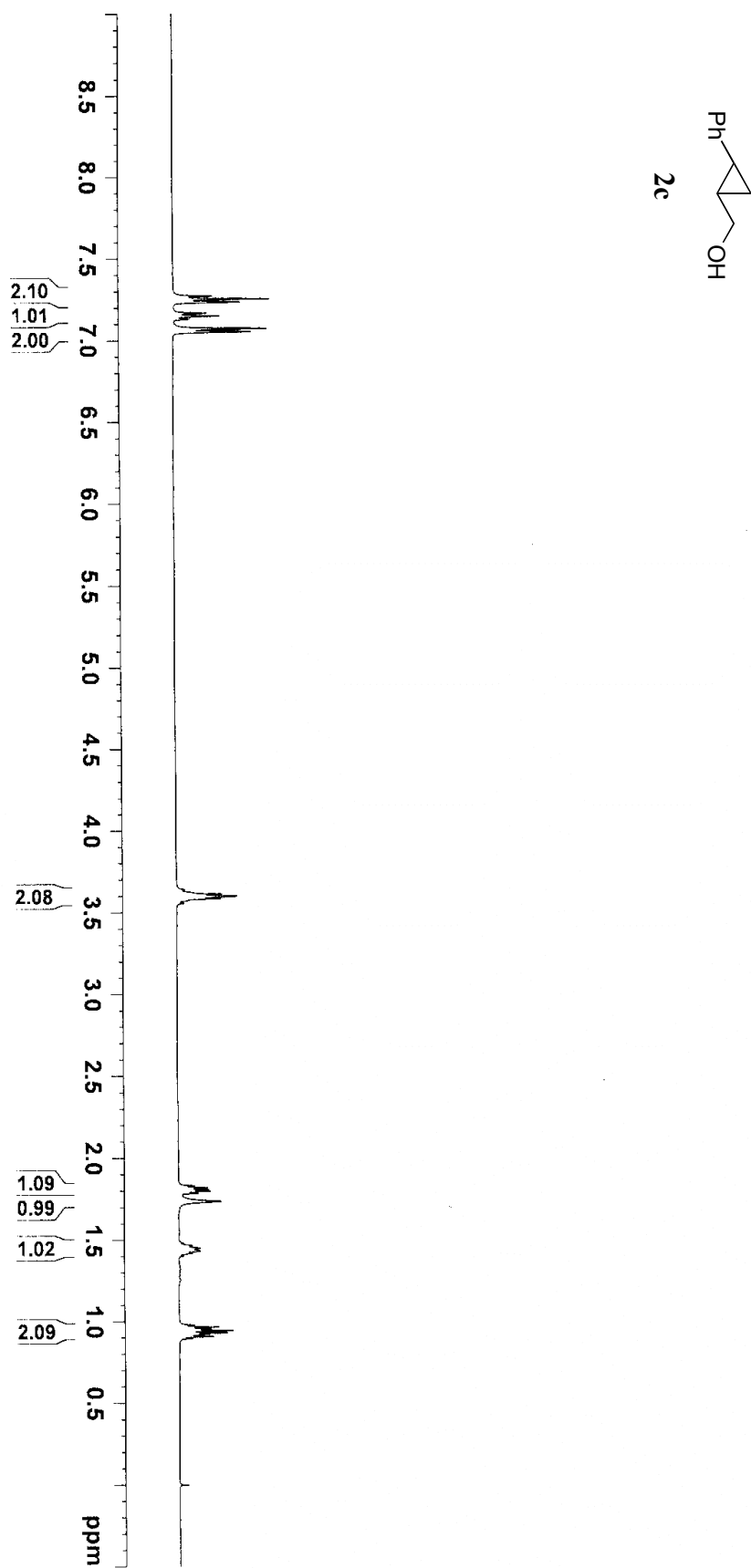
1) P. Bose, Y. P. Sachdeva, R. S. Rathore and Y. Kumar, PCT Int. Appl. WO 2005026095, 2005; 2) F. Ni and J. Li, *Synthesis*, 2012, **44**, 3598.

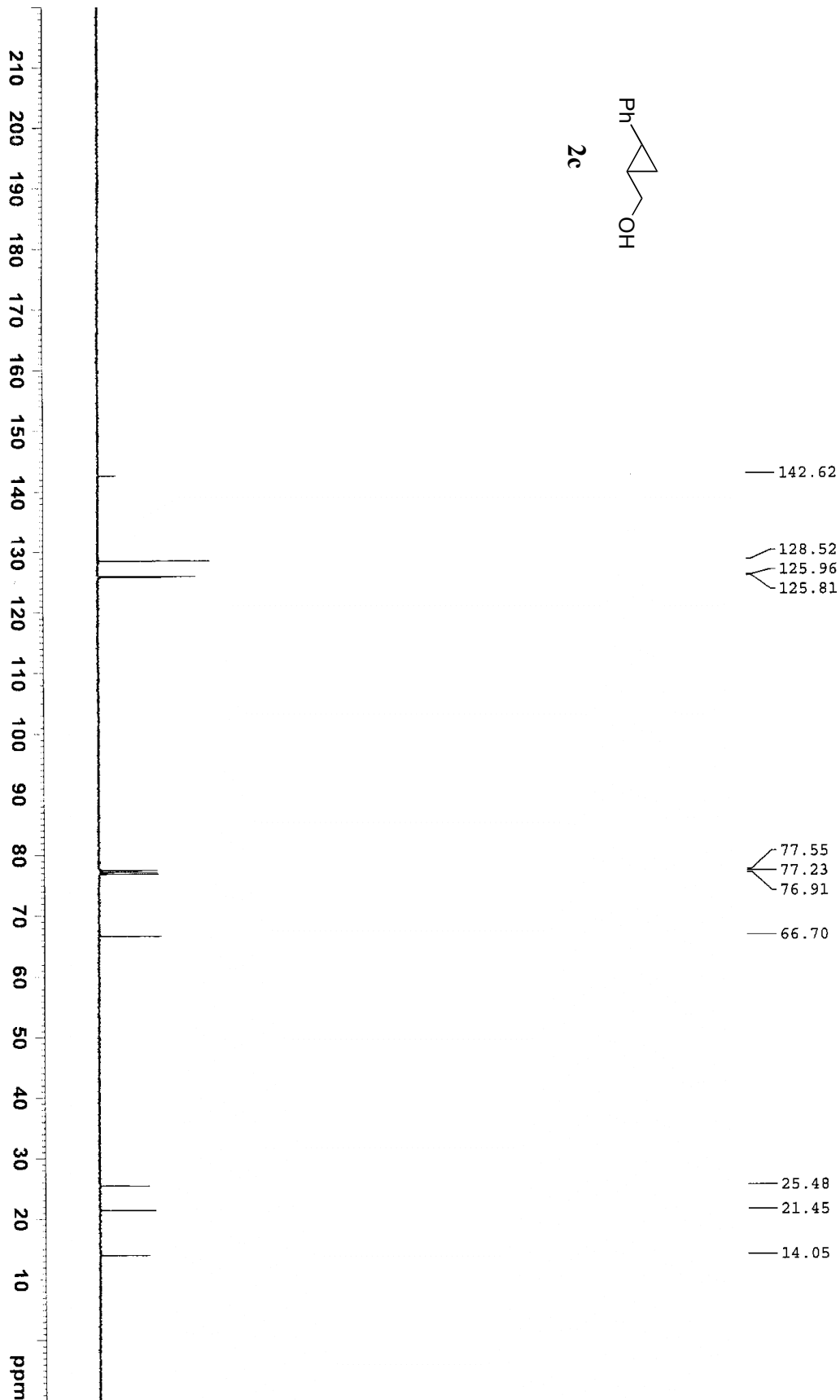


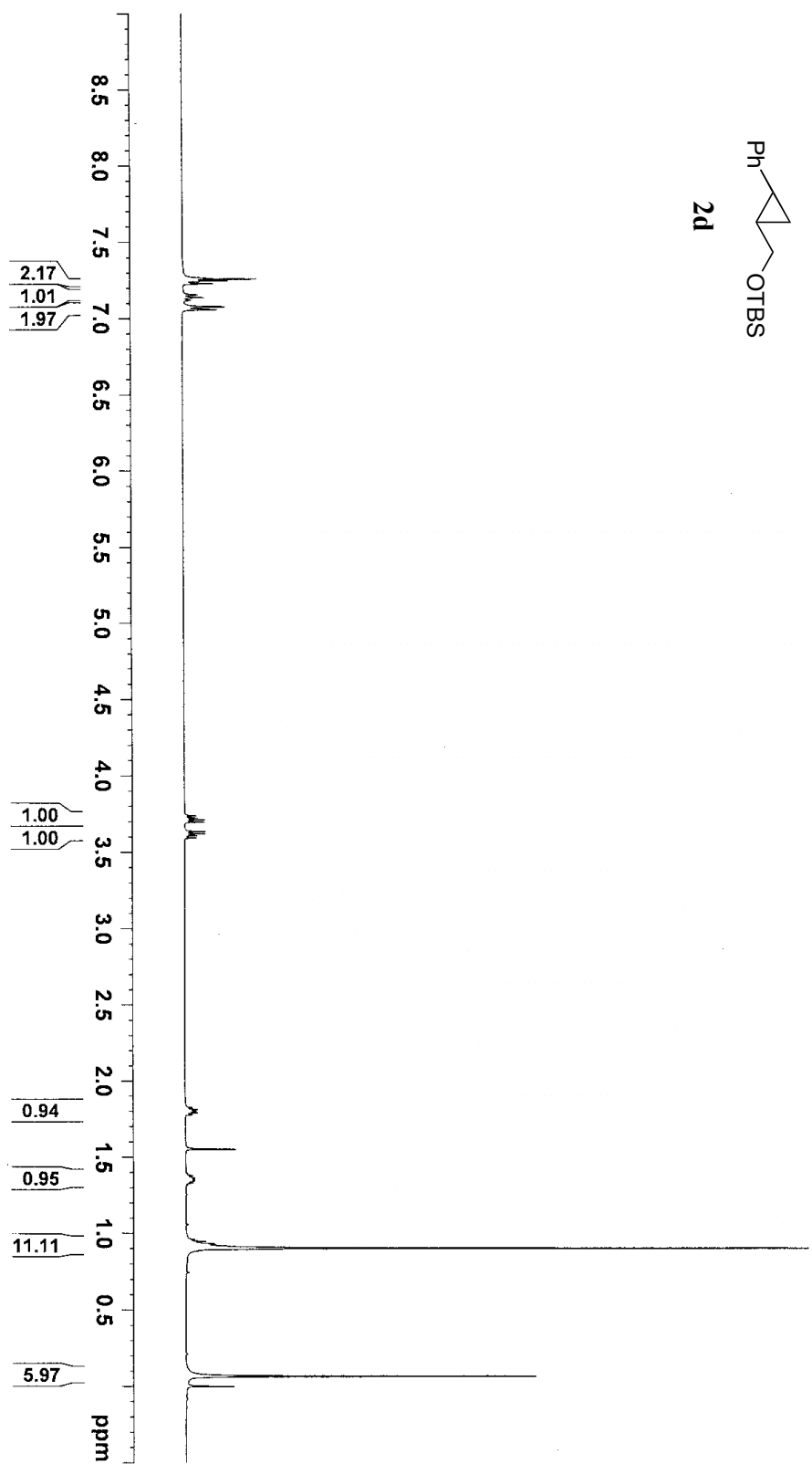


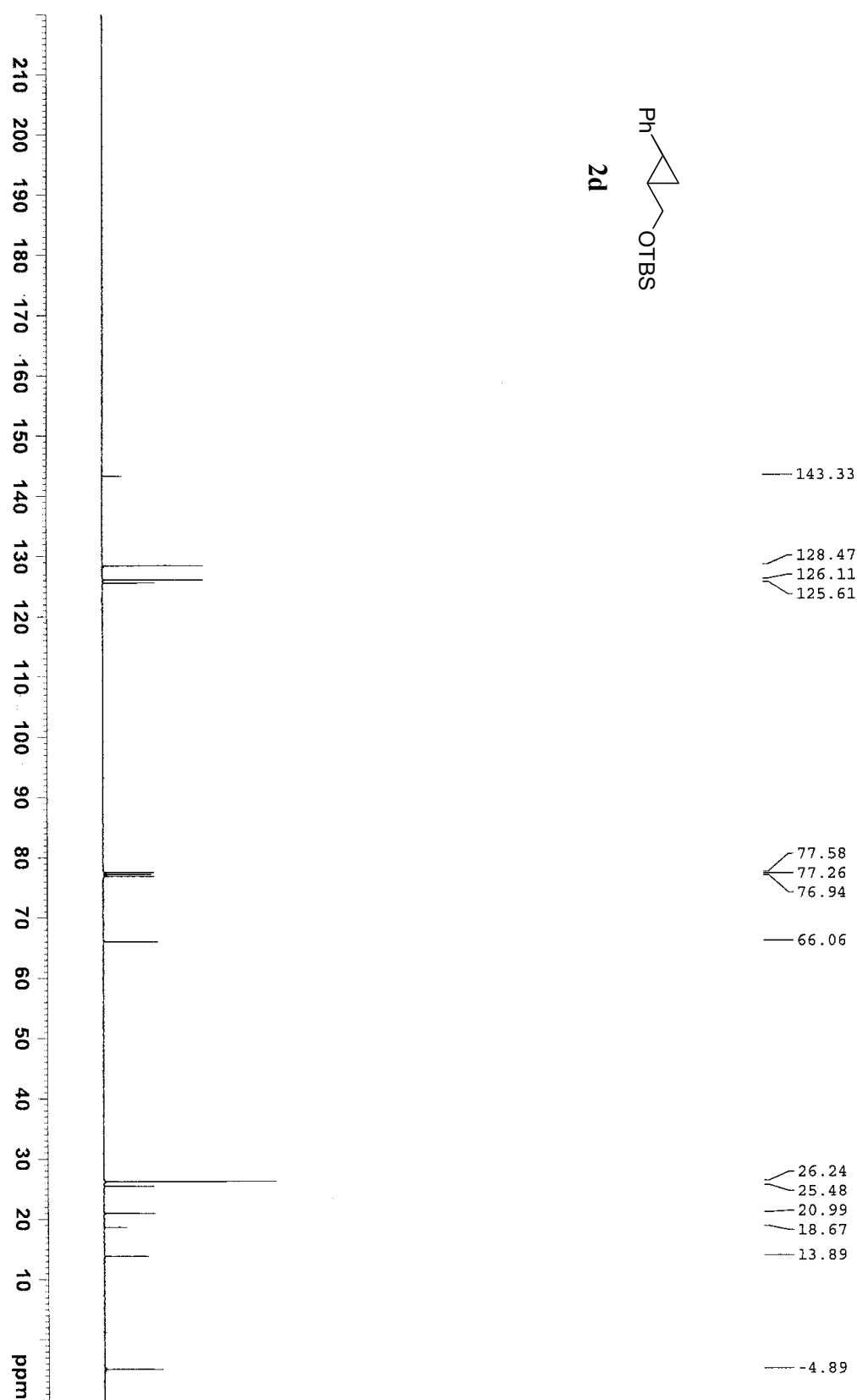


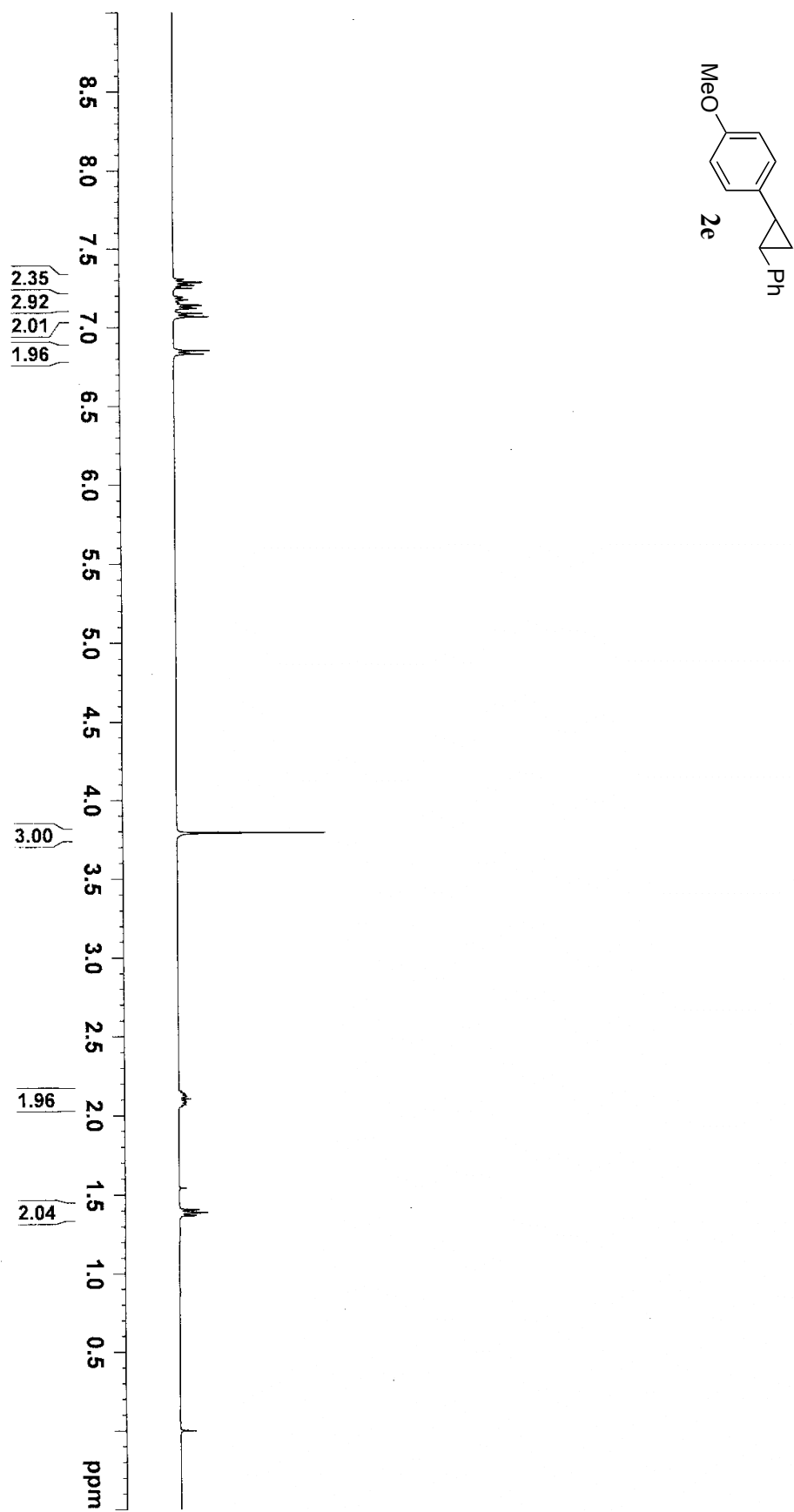


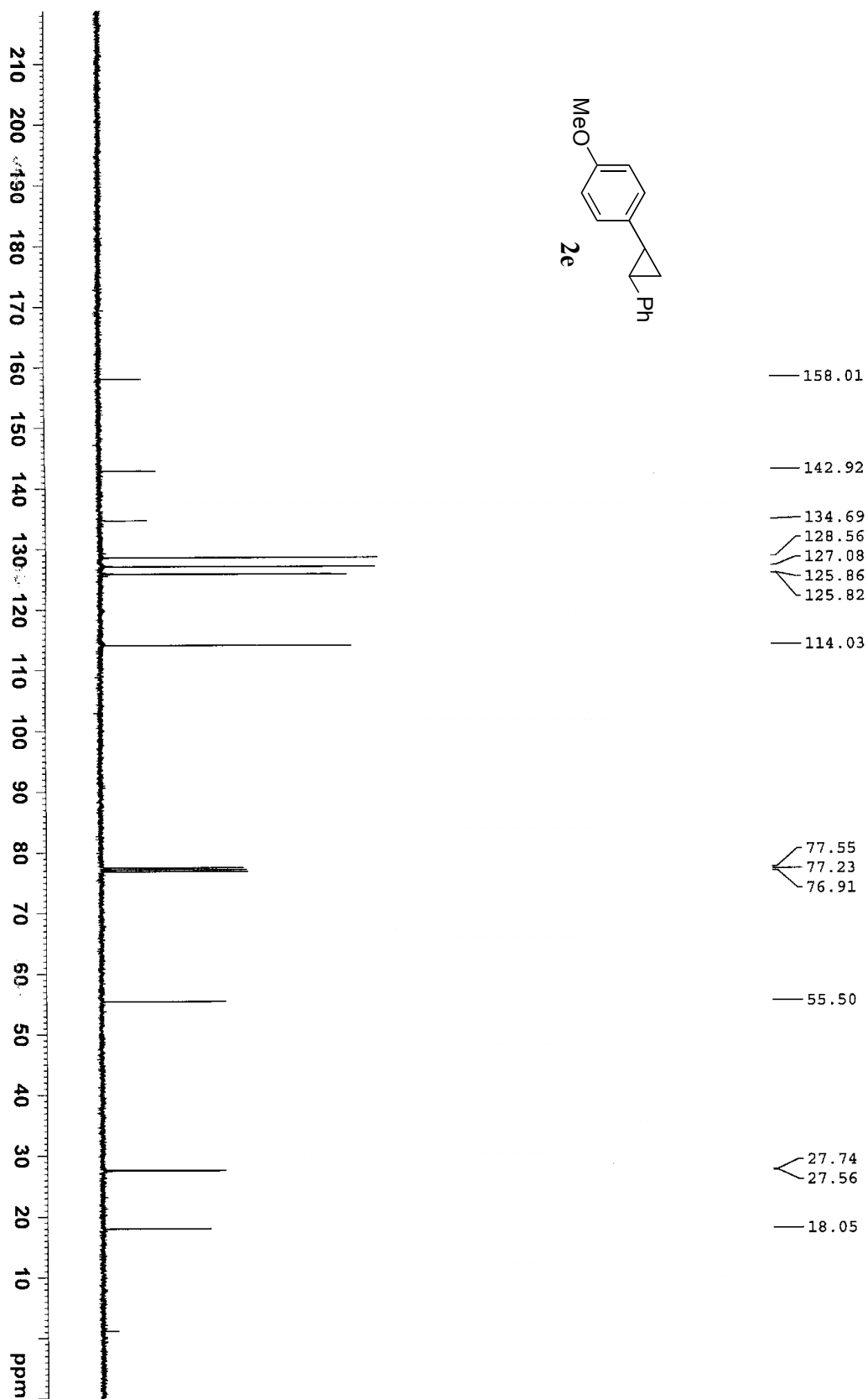


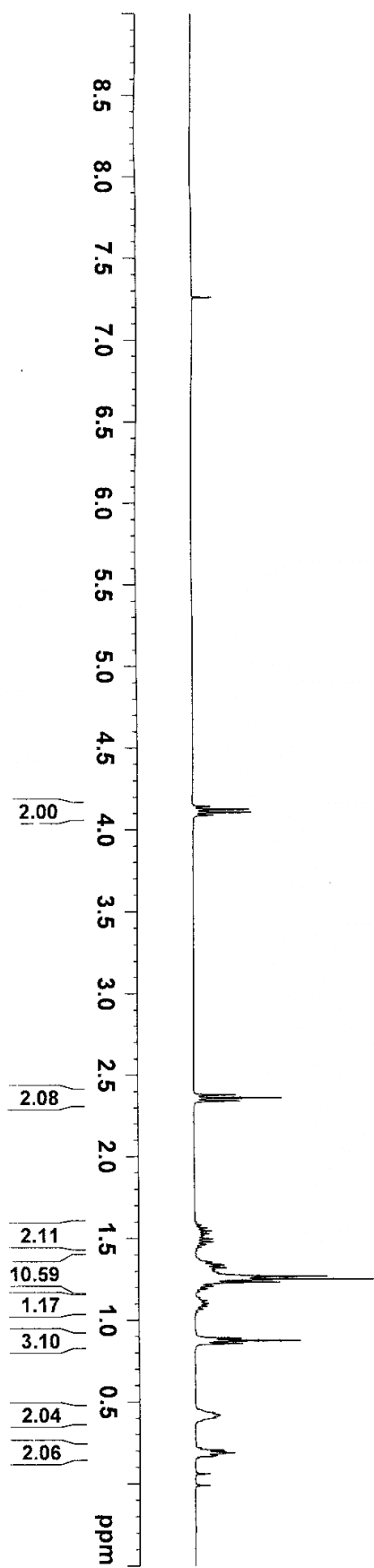
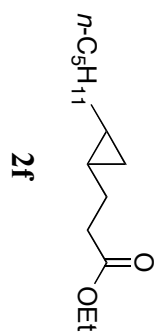


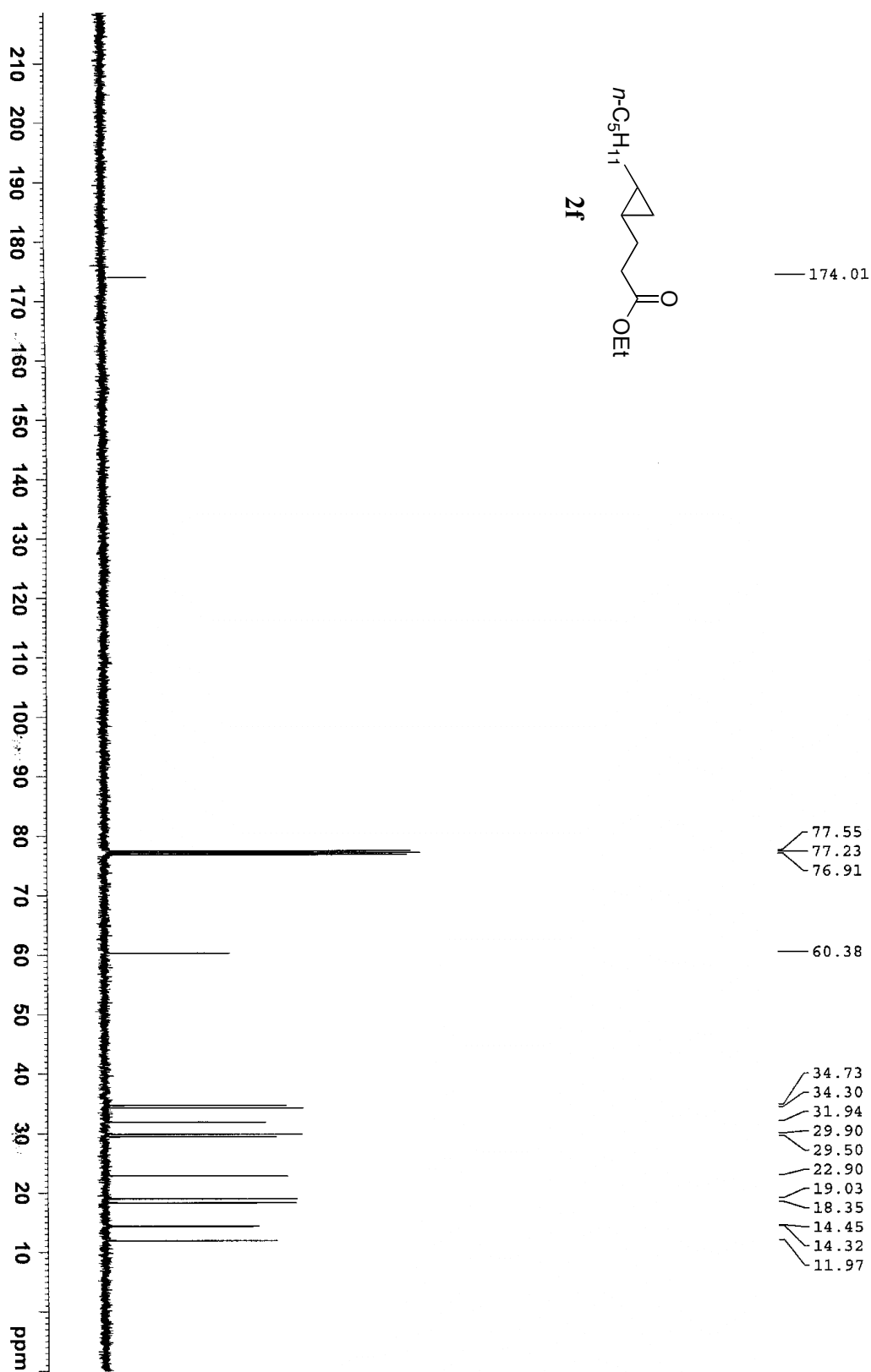


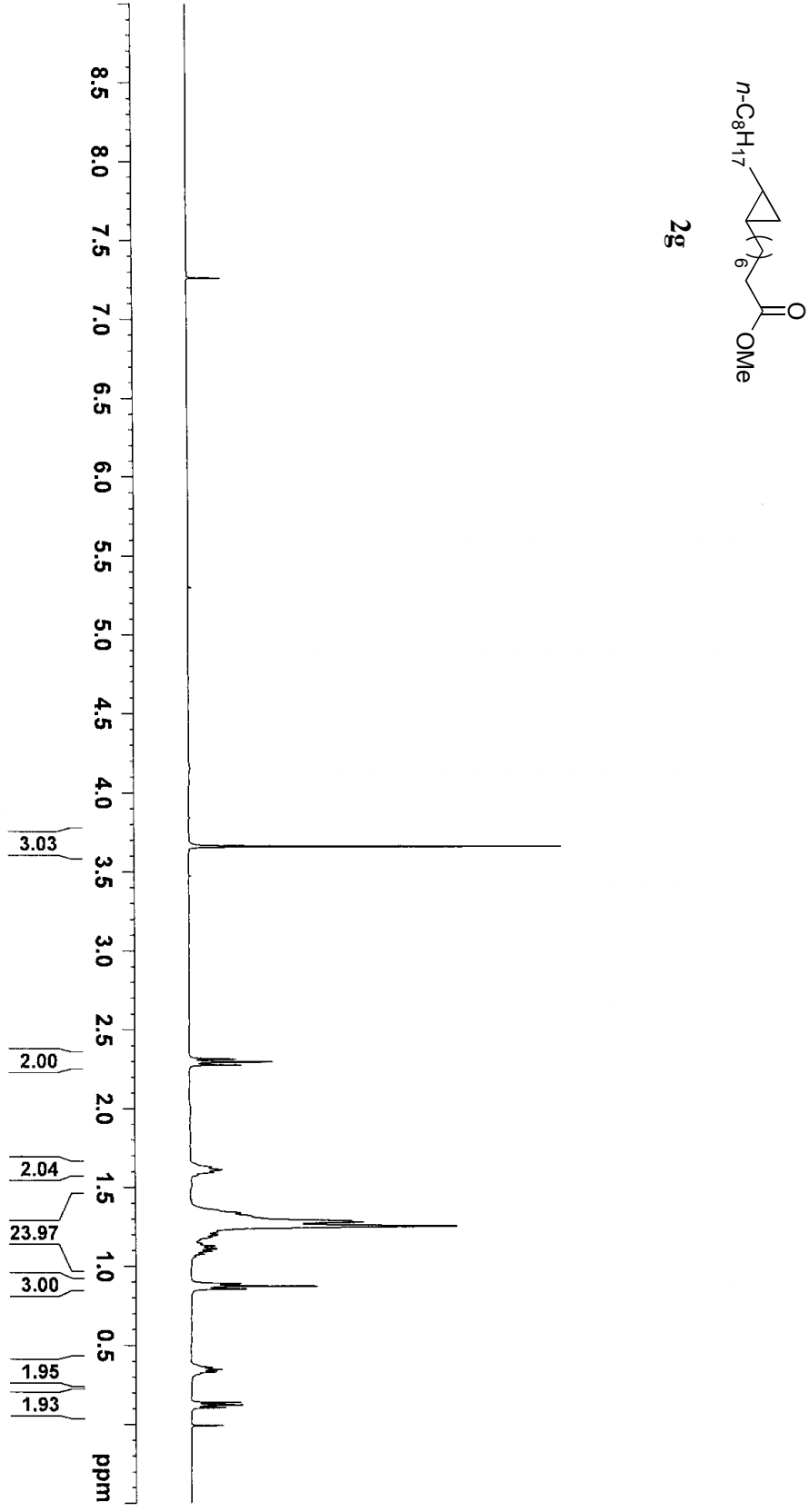


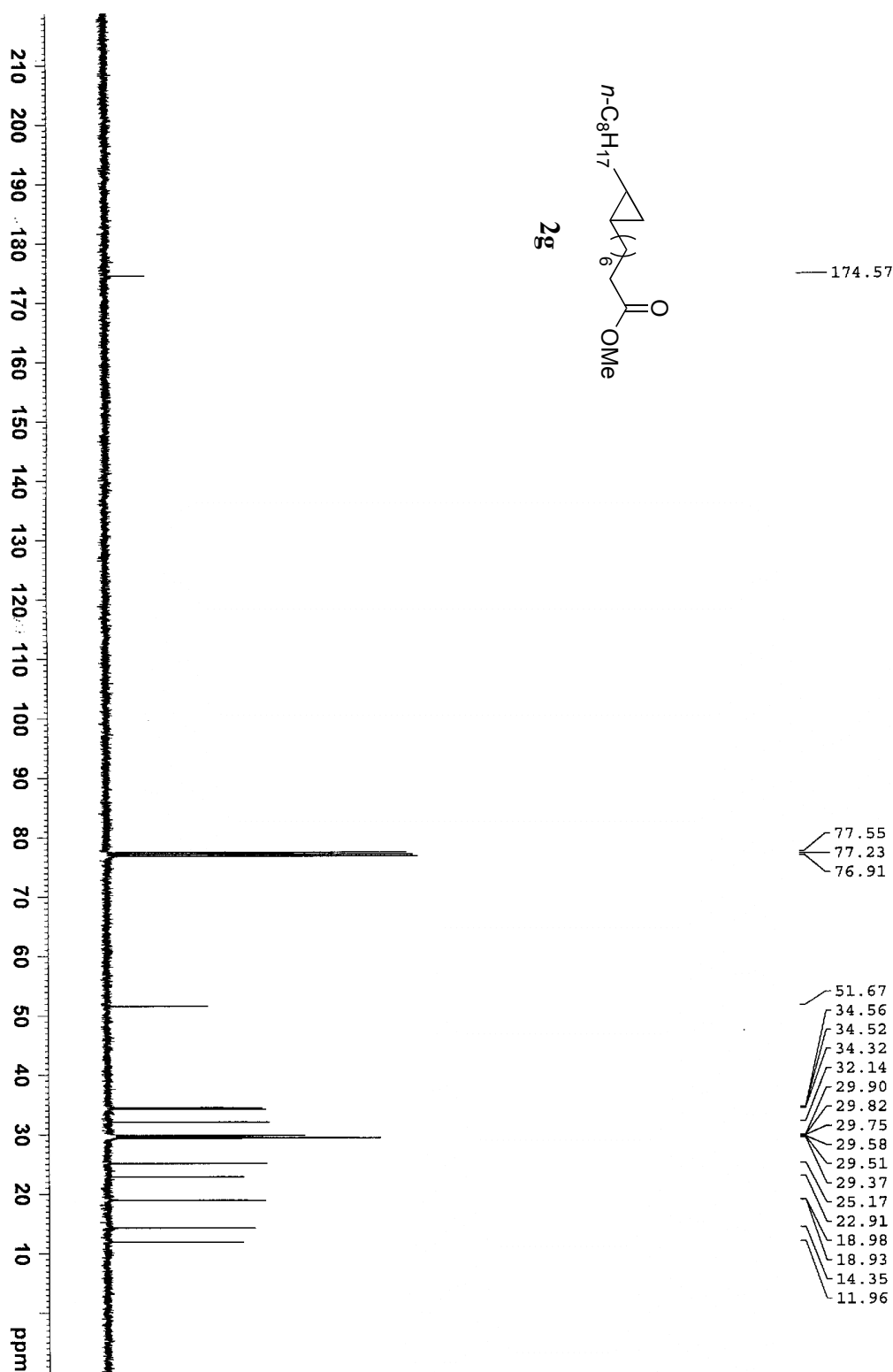


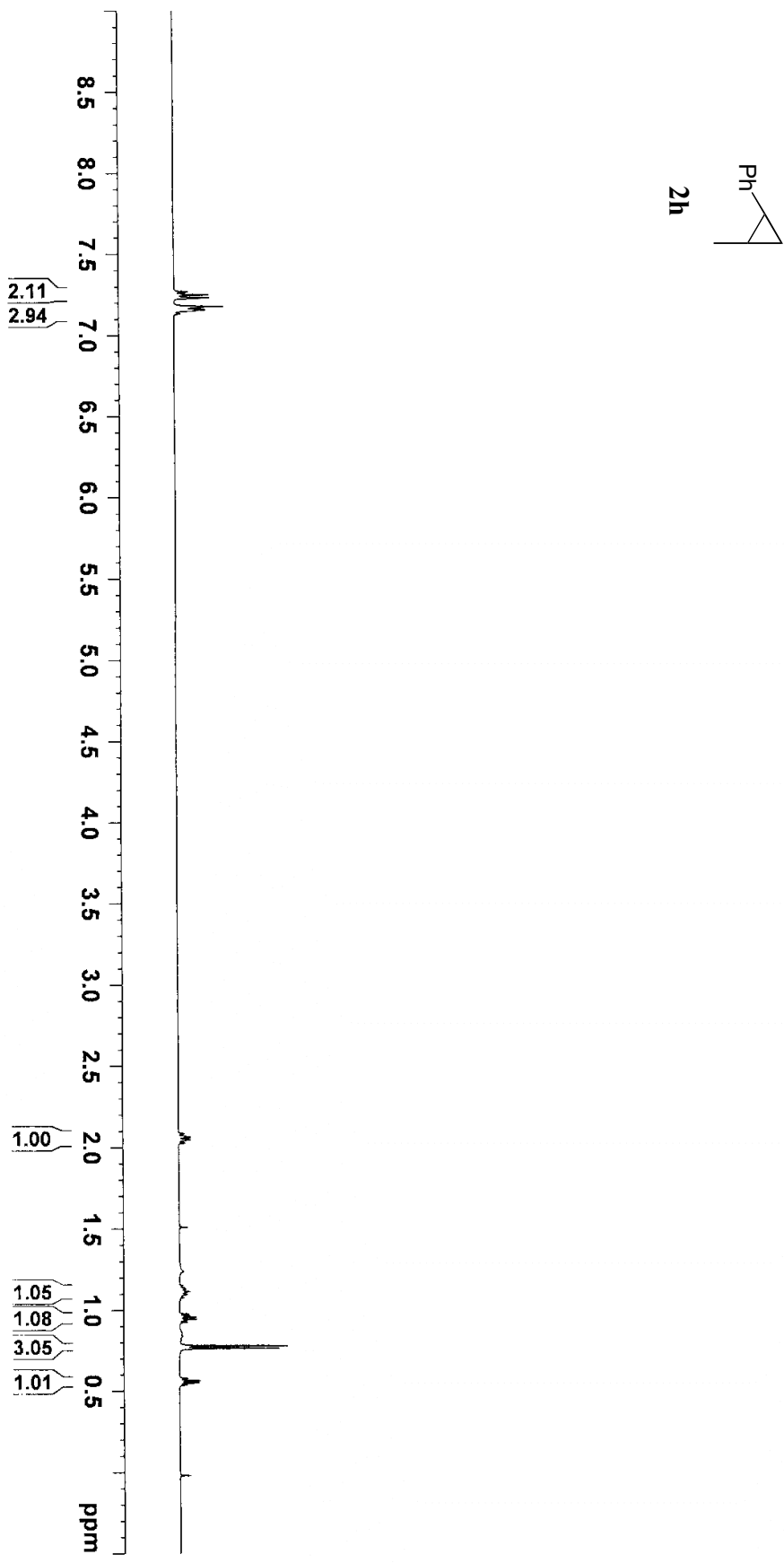


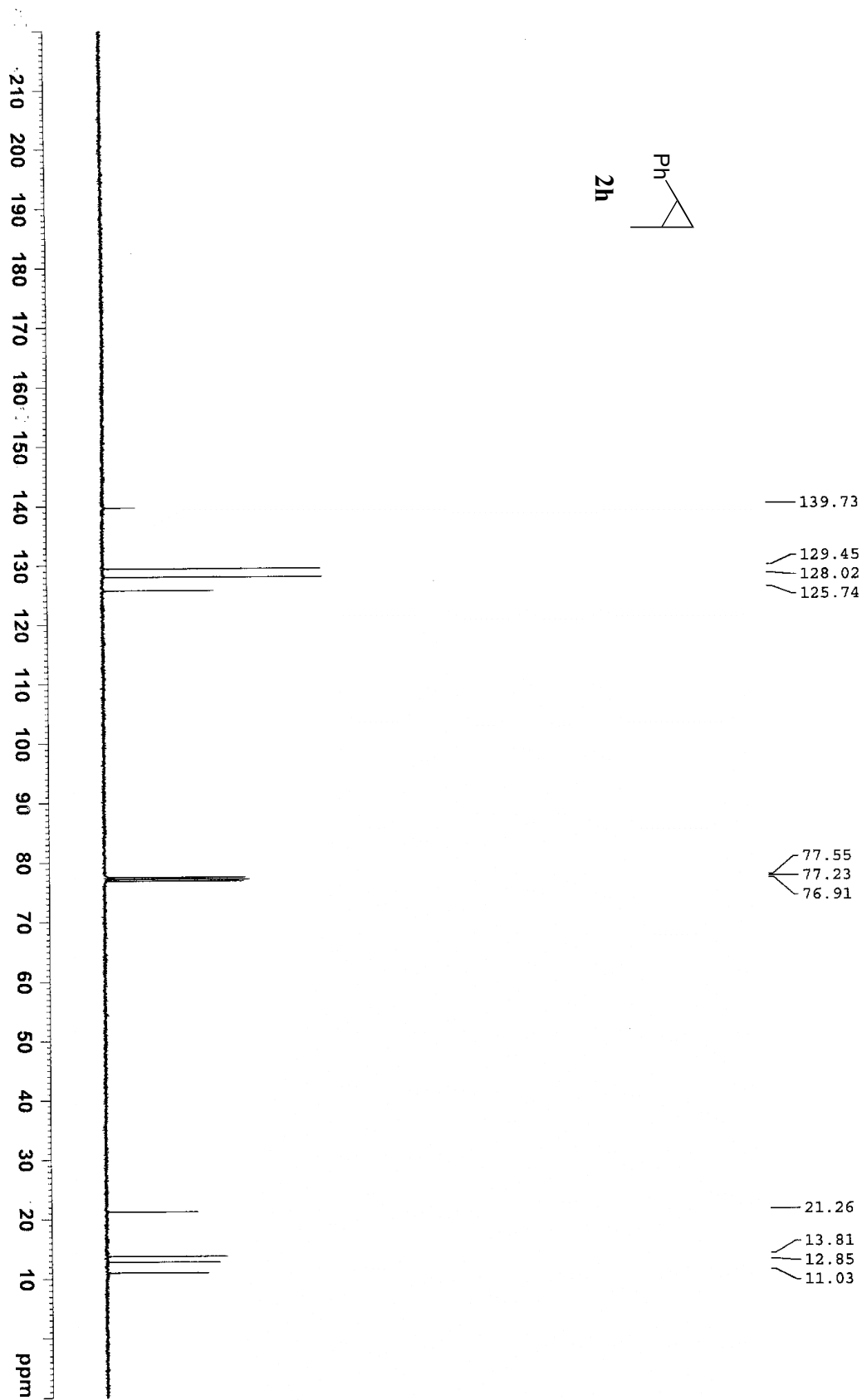


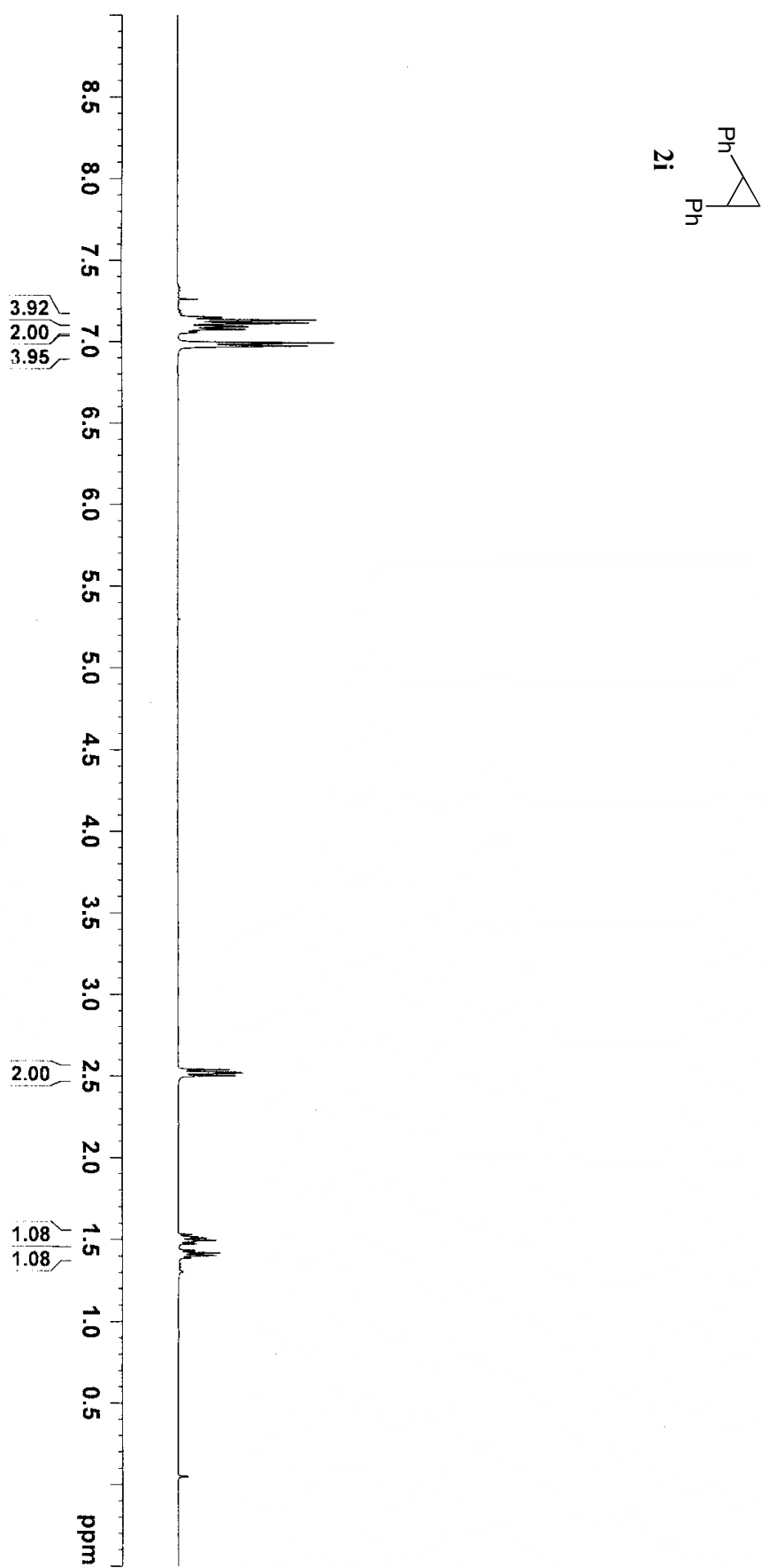


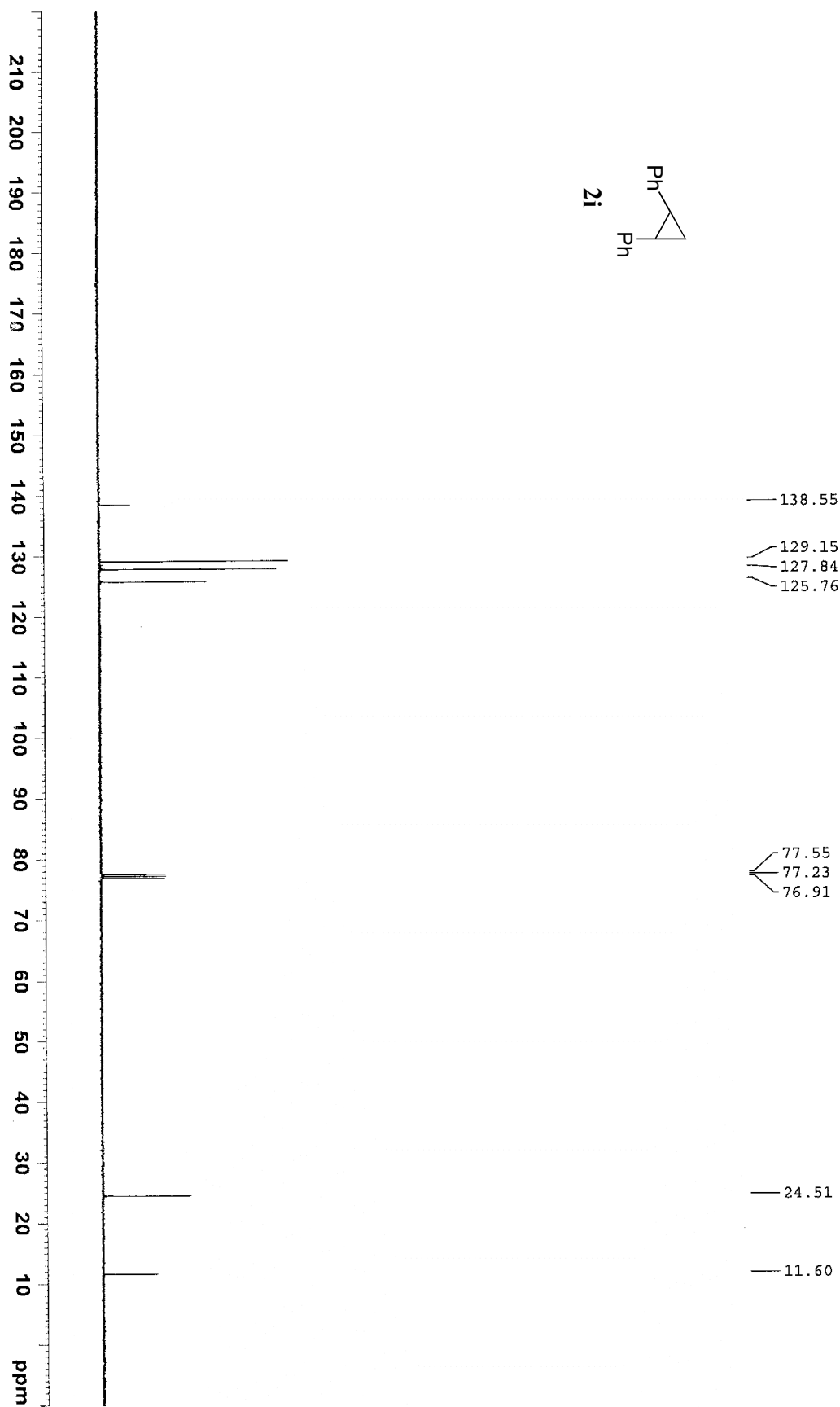


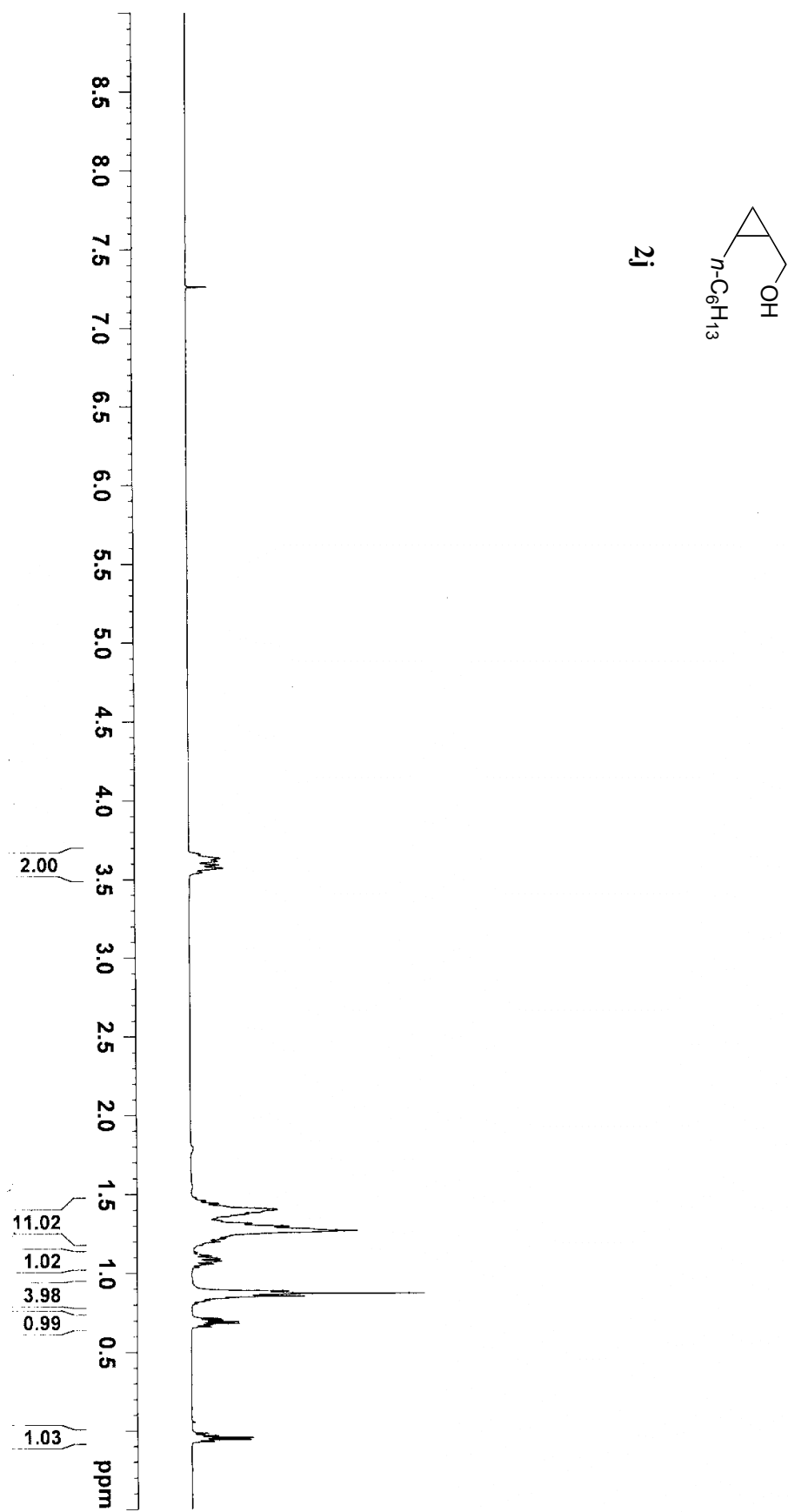


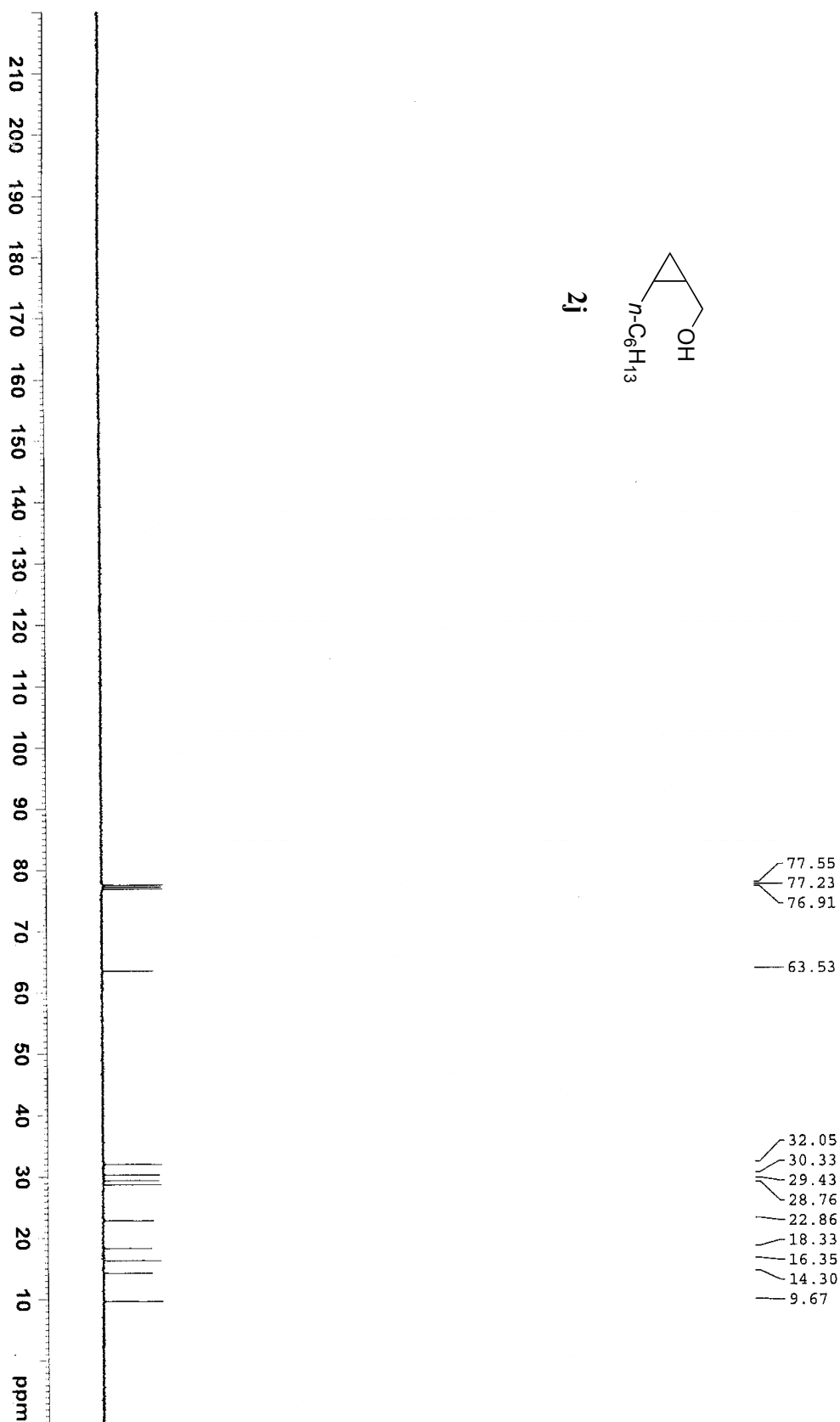


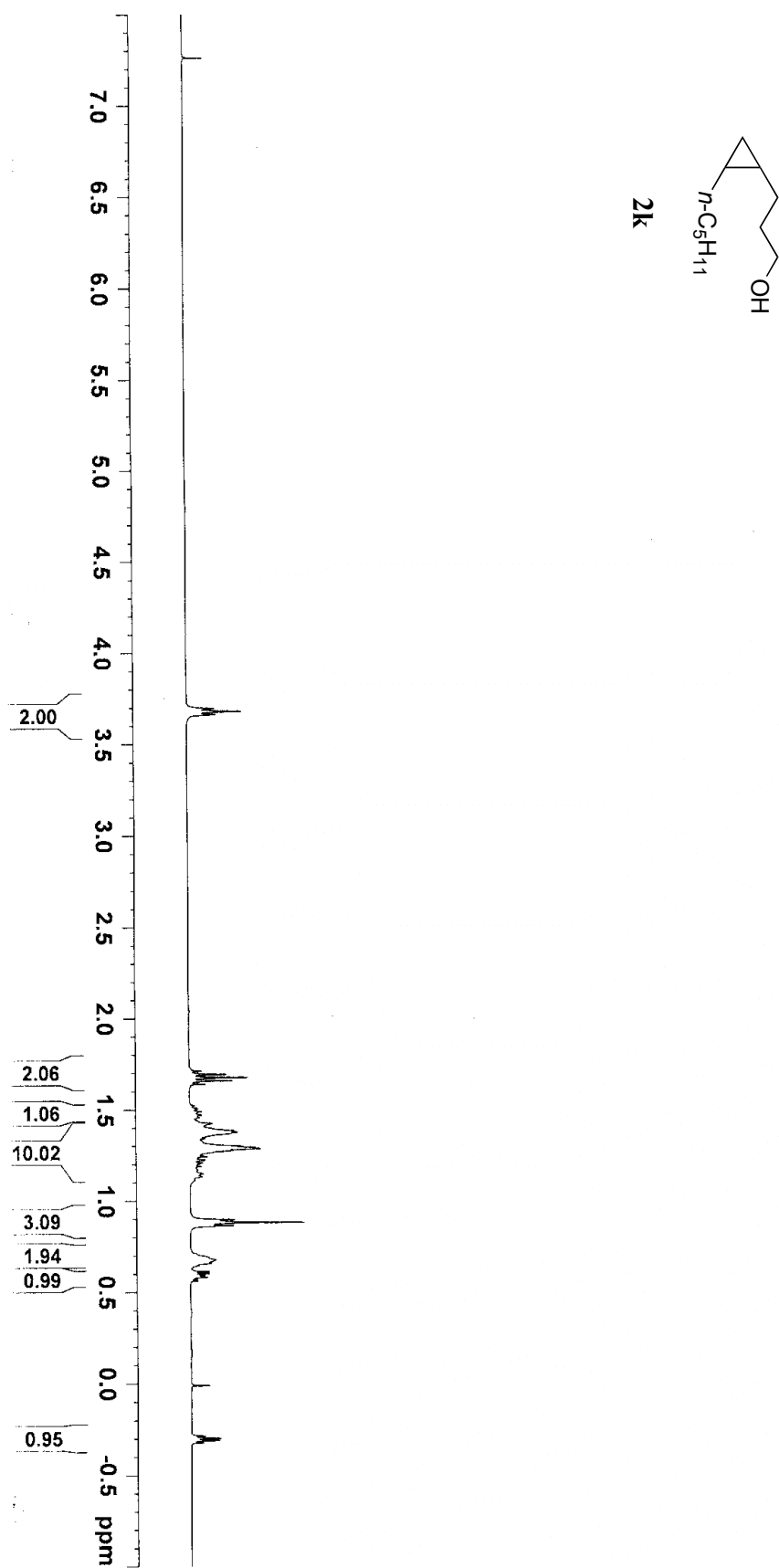


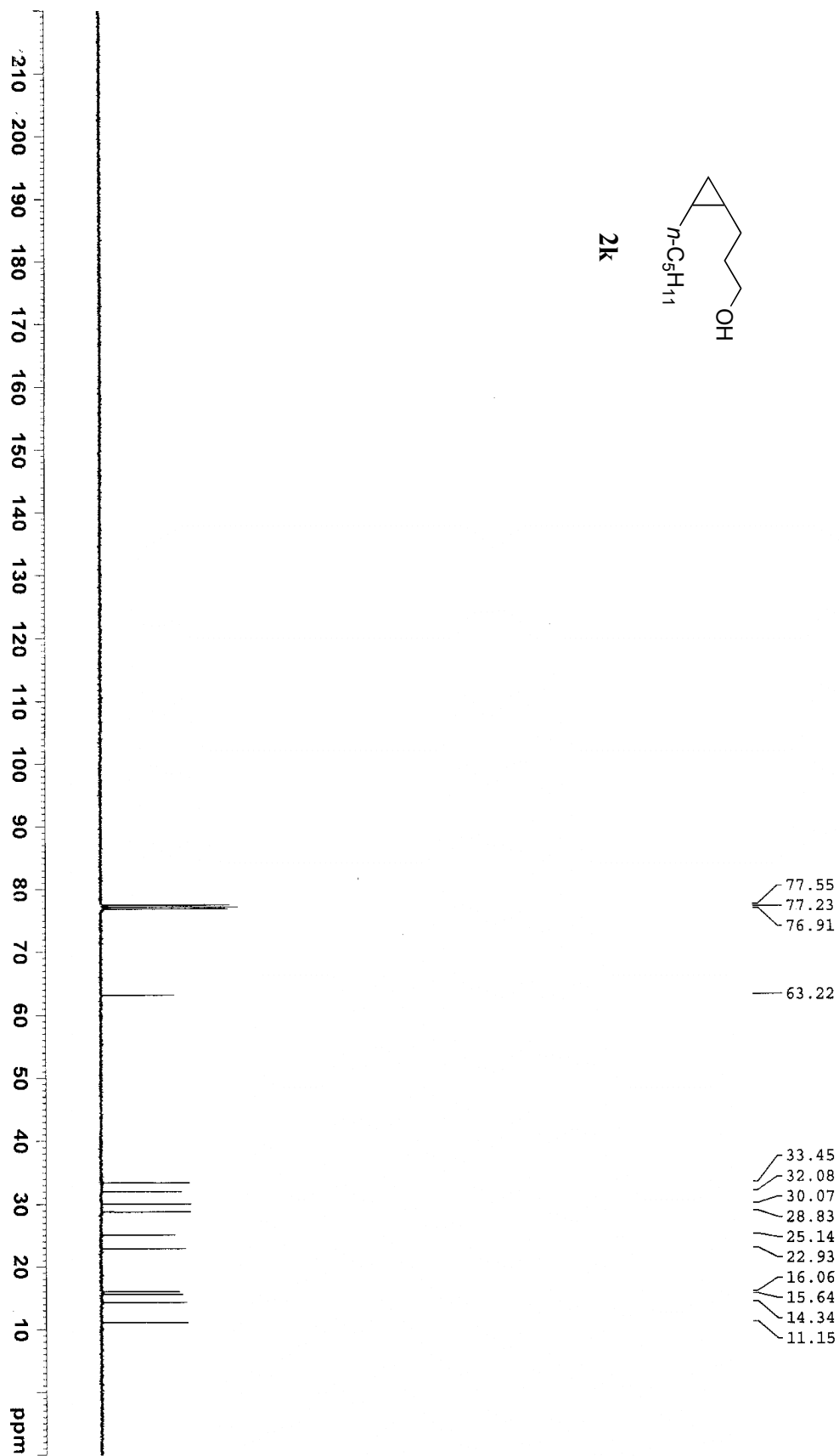


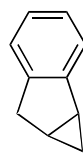












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