Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry


# Supplementary Information

## Redesign of enzyme for improving catalytic activity and enantioselectivity toward poor substrates: manipulation of the transition state

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**[A] Methods.**

All the DNA manipulations and bacterial transformation were carried out according to the standard protocols[1] or manufacturers' instructions unless otherwise stated. The computational design, overexpression, refolding, purification, and immobilization of the recombinant lipases were done as reported previously.[2,3] The method for the determination of kinetic constants has been reported.[3] Racemic alcohols **1a–d** were synthesized as described previously,[3] while **1n–q** were purchased.

**[B] Site-directed mutagenesis.**

The mutations were introduced by the overlap-extension PCR method as reported previously.[2,3] The mutagenic oligonucleotides used as primers and the plasmids used as templates are shown in Table S1.

**Table S1** Primers and templates used for site-directed mutagenesis

| Mutant | Primer | Sequence | Template |
|---|---|---|---|
| I287F | BC-I287F-1F | 5'-CTACAAGTGGAACCATTTCGACGAG-3' | pELIP |
| | BC-I287F-2R | 5'-CTCGTCGAAATGGTTCCACTTGTAG-3' | |
| I287A | BC-I287A-1F | 5'-CTACAAGTGGAACCATGCCGACGAG-3' | pELIP |
| | BC-I287A-2R | 5'-CTCGTCGGCATGGTTCCACTTGTAG-3' | |
| I287W | BC-I287W-1F | 5'-CTACAAGTGGAACCATTGGGACGAG-3' | pELIP |
| | BC-I287W-2R | 5'-CTCGTCCCAATGGTTCCACTTGTAG-3' | |
| I287Y | BC-I287Y-1F | 5'-GTGGAACCATTACGACGAG-3' | pELIP |
| | BC-I287Y-3R | 5'-CTCGTCGTAATGGTTCCACTTGTAG-3' | |
| I290A | BC-I290A-1F | 5'-GACGAGGCCAACCAGTTGC-3' | pELIP |
| | BC-I290A-3R | 5'-CAACTGGTTGGCCTCGTCG-3' | |
| I287F/I290A | BC-I290A-1F | 5'-GACGAGGCCAACCAGTTGC-3' | pELIP(I287F) |
| | BC-I290A-3R | 5'-CAACTGGTTGGCCTCGTCG-3' | |
| I287F/I290F | BC-I290F-1F | 5'-CGACGAGTTCAACCAGTTGC-3' | pELIP(I287F) |
| | BC-I290F-2R | 5'-GCAACTGGTTGAACTCGTCG-3' | |
| I287F/I290A/ Q292A | BC-Q292A-1F | 5'-CAACGCGTTGCTTGG-3' | pELIP(I287F/ I290A) |
| | BC-Q292A-3R | 5'-AAGCAACGCGTTGGCCTC-3' | |

**[C] Synthesis of racemic alcohols.**

**2-Methoxymethoxy-1-phenylethanol (1e).**[4] To a solution of 2-methoxymethoxy-1-phenylethanone [5] (1.68 g, 9.32 mmol) in dry EtOH (20 mL) was added $NaBH_4$ (177 mg, 4.67 mmol) in an ice bath. The mixture was stirred at room temperature overnight. The solution was adjusted to pH 6. After EtOH had been removed under reduced pressure, brine (9 mL) was added. The solution was neutralized, and the product was extracted with EtOAc (15 mL × 3). The mixture was dried over $MgSO_4$, and concentrated. The product was purified by silica gel column chromatography (hexane/EtOAc (3:1)) to afford **1e** as a colorless oil (1.23 g, 72%): $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 3.04 (d, $J$ = 2.6 Hz, 1H), 3.39 (s, 3H), 3.59 (dd, $J$ = 8.7, 10.7 Hz, 1H), 3.79 (dd, $J$ = 3.1, 10.6 Hz, 1H), 4.70 (d, $J$ = 6.6 Hz, 1H), 4.72 (d, $J$ = 6.6 Hz, 1H), 4.89–4.92 (m, 1H), 7.28–7.41 (m, 5H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 55.4, 72.9, 74.1, 96.8, 126.1, 127.7, 128.3, 140.3; IR (neat) 3433, 3063, 3032, 2932, 2889, 2824, 2781, 1605, 1493, 1454, 1404, 1327, 1211, 1034, 918, 829, 760, 702 cm$^{-1}$;

HRMS (EI) calcd for $C_{10}H_{14}O_3$ 182.0943, found 182.0943 ($M^+$).

**1-Phenyl-5-hexen-1-ol (1f).**[6] To a mixture of Mg (260 mg, 10.7 mmol) in dry THF (3 mL) under Ar was added dropwise a solution of 5-bromo-1-pentene (1.1 mL, 9.5 mmol) and $Br(CH_2)_2Br$ (a few drops) in dry THF (7 mL) over 30 min at room temperature. The mixture was stirred for 2 h. To the slurry was added dropwise a solution of benzaldehyde (0.91 mL, 9.0 mmol) in dry THF (5 mL) over 8 min in an ice bath, and the mixture was stirred at room temperature overnight. The reaction was quenched with saturated aqueous $NH_4Cl$, and the solution was adjusted to pH 4. The mixture was extracted with EtOAc (10 mL × 4), dried over $MgSO_4$, and concentrated. The product was purified by silica gel column chromatography (hexane/EtOAc (5:1)) to afford **1f** as a colorless oil (1.39 g, 88%): $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 1.36–1.42 (m, 1H), 1.50–1.57 (m, 1H), 1.70–1.83 (m, 3H), 2.05–2.11 (m, 2H), 4.66–4.71 (m, 1H), 4.93–5.02 (m, 2H), 5.73–5.83 (m, 1H), 7.28–7.35 (m, 5H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 25.0, 33.5, 38.4, 74.4, 114.6, 125.8, 127.5, 128.4, 138.5, 144.8; IR (neat) 3348, 3063, 3028, 2977, 2936, 2858, 1639, 1605, 1493, 1454, 1416, 1277, 1200, 995, 910, 760, 702 cm$^{-1}$; HRMS (EI) calcd for $C_{12}H_{16}O$ 176.1201, found 176.1186 ($M^+$).

**5-Methoxymethoxy-1-phenyl-1-pentanol (1g).** To a mixture of Mg (205 mg, 8.43 mmol) in dry THF (3 mL) under Ar was added dropwise a solution of 1-bromo-4-methoxymethoxybutane[7] (1.54 g, 7.81 mmol) and $Br(CH_2)_2Br$ (a few drops) in dry THF (7 mL) over 20 min at room temperature. The mixture was stirred for 2 h. To the slurry was added dropwise a solution of benzaldehyde (0.81 mL, 8.0 mmol) in dry THF (5 mL) over 10 min in an ice bath, and the mixture was stirred at room temperature for 3 h. The reaction was quenched with saturated aqueous $NH_4Cl$, and the solution was adjusted to pH 7. The mixture was extracted with EtOAc (15 mL × 4), dried over $MgSO_4$, and concentrated. The product was purified by silica gel column chromatography ($CH_2Cl_2$/THF (20:1)) to afford **1g** as a colorless oil (1.14 g, 65%): $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 1.35–1.43 (m, 1H), 1.48–1.57 (m, 1H), 1.60–1.67 (m, 2H), 1.70–1.86 (m, 3H), 3.34 (s, 3H), 3.51 (t, $J$ = 6.5 Hz, 2H), 4.60 (s, 2H), 4.67–4.71 (m, 1H), 7.27–7.35 (m, 5H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 22.4, 29.4, 38.7, 55.0, 67.5, 74.3, 96.2, 125.8, 127.4, 128.3, 144.8; IR (neat) 3433, 3063, 3028, 2939, 2870, 1493, 1454, 1389, 1308, 1211, 1146, 1111, 1042, 918, 760, 702 cm$^{-1}$; HRMS (EI) calcd for $C_{13}H_{20}O_3$ 224.1412, found 224.1399 ($M^+$).

**1,6-Diphenyl-1-hexanol (1h).** To a mixture of Mg (256 mg, 10.5 mmol) in dry THF (3 mL) under Ar was added dropwise a solution of (5-bromopentyl)benzene (1.9 mL, 10 mmol) and $Br(CH_2)_2Br$ (a few drops) in dry THF (7 mL) over 30 min at room temperature. The mixture was stirred for 2 h. To the slurry was added dropwise a solution of benzaldehyde (0.92 mL, 9.1 mmol) in dry THF (5 mL) over 12 min in an ice bath, and the mixture was stirred at room temperature for 2.5 h. The reaction was quenched with saturated aqueous $NH_4Cl$, and the solution was adjusted to pH 4. The mixture was extracted with EtOAc (15 mL × 4), dried over $MgSO_4$, and concentrated. The product was purified by silica gel column chromatography (hexane/EtOAc/$CH_2Cl_2$ (20:1:5) to (10:1:5)) to afford **1h** as a colorless oil (1.24 g, 54%): $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 1.31–1.48 (m, 4H), 1.57–1.65 (m, 2H), 1.67–1.82 (m, 3H), 2.58 (t, $J$ = 7.6 Hz, 2H), 4.64–4.68 (m, 1H), 7.14–7.18 (m, 3H) 7.25–7.37 (m, 7H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 25.6, 29.1, 31.3, 35.8, 38.9, 74.5, 125.5, 125.8, 127.4, 128.2, 128.3, 128.4, 142.6, 144.8; IR (neat) 3352, 3063, 3028, 2932, 2855, 1948, 1605,

1493, 1454, 1312, 1200, 1030, 910, 748, 698 $cm^{-1}$; HRMS (EI) calcd for $C_{18}H_{22}O$ 254.1671, found 254.1680 ($M^+$).

**5-Methyl-1-phenyl-1-hexanol (1i).**[8] To a mixture of Mg (269 mg, 11.1 mmol) in dry THF (3 mL) under Ar was added dropwise a solution of 1-bromo-4-methylpentane (1.6 mL, 11 mmol) and $Br(CH_2)_2Br$ (a few drops) in dry THF (7 mL) over 30 min at room temperature. The mixture was stirred for 2.5 h. To the slurry was added dropwise a solution of benzaldehyde (1.1 mL, 10 mmol) in dry THF (5 mL) over 15 min in an ice bath, and the mixture was stirred at room temperature for 3 h. The reaction was quenched with saturated aqueous $NH_4Cl$, and the solution was adjusted to pH 4. The mixture was extracted with EtOAc (20 mL × 3), dried over $MgSO_4$, and concentrated. The product was purified by silica gel column chromatography (hexane/EtOAc (7:1)) to afford **1i** as a colorless oil (1.06 g, 53%): $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 0.85 (d, $J$ = 6.6 Hz, 6H), 1.16–1.22 (m, 2H), 1.24–1.31 (m, 1H), 1.39–1.47 (m, 1H), 1.49–1.54 (m, 1H), 1.64–1.82 (m, 3H), 4.66–4.69 (m, 1H), 7.27–7.35 (m, 5H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 22.5, 22.6, 23.6, 27.8, 38.8, 39.3, 74.6, 125.8, 127.4, 128.4, 144.9; IR (neat) 3348, 3028, 2870, 1605, 1493, 1454, 1385, 1366, 1200, 1126, 1045, 760, 702, 552 $cm^{-1}$; HRMS (EI) calcd for $C_{13}H_{20}O$ 192.1514, found 192.1513 ($M^+$).

**1-(4-Trifluoromethylphenyl)-1-hexanol (1j).**[9] To a mixture of Mg (243 mg, 10.0 mmol) in dry THF (3 mL) under Ar was added dropwise a solution of 1-bromopentane (1.2 mL, 9.7 mmol) and $Br(CH_2)_2Br$ (a few drops) in dry THF (7 mL) over 20 min at room temperature. The mixture was stirred for 2.5 h. To the slurry was added dropwise a solution of 4-trifluoromethylbenzaldehyde (1.3 mL, 9.7 mmol) in dry THF (5 mL) over 10 min in an ice bath, and the mixture was stirred at room temperature for 5 h. The reaction was quenched with saturated aqueous $NH_4Cl$, and the solution was adjusted to pH 4. The mixture was extracted with EtOAc (15 mL × 3), dried over $MgSO_4$, and concentrated. The product was purified by silica gel column chromatography (hexane/EtOAc (5:1)) to afford **1j** as a colorless oil (1.22 g, 51%): $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 0.86–0.89 (m, 3H), 1.29–1.46 (m, 6H), 1.65–1.80 (m, 2H), 1.89 (d, $J$ = 3.4 Hz, 1H), 4.73–4.77 (m, 1H), 7.46 (d, $J$ = 8.1 Hz, 2H), 7.60 (d, $J$ = 8.1 Hz, 2H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 13.9, 22.5, 25.3, 31.6, 39.1, 74.0, 124.2 (q, $J_{CF}$ = 270.2 Hz), 125.3 (q, $J_{CF}$ = 3.8 Hz), 126.1, 129.5 (q, $J_{CF}$ = 34.1 Hz), 148.8; $^{19}$F NMR ($CDCl_3$, 376 MHz) $\delta$ –63.6 (s, 3F); IR (neat) 3341, 2959, 2932, 2862, 1921, 1682, 1620, 1466, 1420, 1327, 1126, 1069, 1018, 840 $cm^{-1}$; HRMS (EI) calcd for $C_{13}H_{17}F_3O$ 246.1231, found 246.1227 ($M^+$).

**1-(4-Methoxylphenyl)-1-hexanol (1k).**[10] To a mixture of Mg (294 mg, 12.1 mmol) in dry THF (3 mL) under Ar was added dropwise a solution of 1-bromopentane (1.5 mL, 12 mmol) and $Br(CH_2)_2Br$ (a few drops) in dry THF (7 mL) over 20 min at room temperature. The mixture was stirred for 2 h. To the slurry was added dropwise a solution of 4-methoxybenzaldehyde (1.3 mL, 11 mmol) in dry THF (5 mL) over 10 min in an ice bath, and the mixture was stirred at room temperature overnight. The reaction was quenched with saturated aqueous $NH_4Cl$, and the solution was adjusted to pH 4. The mixture was extracted with EtOAc (15 mL × 3), dried over $MgSO_4$, and concentrated. The product was purified by silica gel column chromatography (hexane/EtOAc (5:1)) to afford **1k** as a colorless oil (1.88 g, 85%): $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 0.87 (t, $J$ = 7.0 Hz, 3H), 1.28–1.42 (m, 6H), 1.66–1.70 (m, 1H), 1.72 (d, $J$ = 3.2 Hz, 1H), 1.75–1.84 (m, 1H), 3.81 (s, 3H), 4.59–4.63 (m, 1H), 6.86–6.90 (m, 2H), 7.25–7.29 (m, 2H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 14.0,

22.5, 25.5, 31.7, 38.9, 55.2, 74.2, 113.7, 127.1, 137.1, 158.9; IR (neat) 3368, 2997, 2955, 2932, 2858, 1612, 1585, 1512, 1462, 1300, 1250, 1177, 1115, 1038, 926, 833, 733 $cm^{-1}$; HRMS (EI) calcd for $C_{13}H_{20}O_2$ 208.1463, found 208.1452 ($M^+$).

**1-(3-Methoxymethoxyphenyl)-1-hexanol (1l).**[11] To a mixture of Mg (258 mg, 10.6 mmol) in dry THF (3 mL) under Ar was added dropwise a solution of 1-bromopentane (1.3 mL, 11 mmol) and $Br(CH_2)_2Br$ (a few drops) in dry THF (7 mL) over 20 min at room temperature. The mixture was stirred for 2.5 h. To the slurry was added dropwise a solution of 3-methoxymethoxybenzaldehyde (1.51 g, 9.09 mmol) in dry THF (5 mL) over 10 min in an ice bath, and the mixture was stirred at room temperature for 4 h. The reaction was quenched with saturated aqueous $NH_4Cl$, and the solution was adjusted to pH 7. The mixture was extracted with EtOAc (15 mL × 4), dried over $MgSO_4$, and concentrated. The product was purified by silica gel column chromatography (hexane/EtOAc (3:1)) to afford **1l** as a colorless oil (1.50 g, 70%): $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 0.86–0.89 (m, 3H), 1.29–1.47 (m, 6H), 1.66–1.81 (m, 3H), 3.48 (s, 3H), 4.62–4.66 (m, 1H), 5.18 (s, 2H), 6.94–7.03 (m, 3H), 7.24–7.28 (m, 1H); $^{13}C$ NMR ($CDCl_3$, 100 MHz) $\delta$ 14.0, 22.5, 25.4, 31.6, 38.9, 55.9, 74.3, 94.3, 113.8, 115.0, 119.4, 129.3, 146.8, 157.2; IR (neat) 3410, 2955, 2932, 2858, 1589, 1485, 1454, 1246, 1153, 1080, 1018, 926, 791, 702 $cm^{-1}$; HRMS (EI) calcd for $C_{14}H_{22}O_3$ 238.1569, found 238.1556 ($M^+$).

**1-(2-Naphthyl)-1-hexanol (1m).**[10] To a mixture of Mg (244 mg, 10.0 mmol) in dry THF (3 mL) under Ar was added dropwise a solution of 1-bromopentane (1.2 mL, 9.7 mmol) and $Br(CH_2)_2Br$ (a few drops) in dry THF (7 mL) over 25 min at room temperature. The mixture was stirred for 2.5 h. To the slurry was added dropwise a solution of 2-naphthaldehyde (1.40 g, 8.96 mmol) in dry THF (5 mL) over 10 min in an ice bath, and the mixture was stirred at room temperature for 4 h. The reaction was quenched with saturated aqueous $NH_4Cl$, and the solution was adjusted to pH 4. The mixture was extracted with EtOAc (15 mL × 4), dried over $MgSO_4$, and concentrated. The product was purified by silica gel column chromatography (hexane/EtOAc (4:1)) to afford **1m** as a white solid (1.65 g, 82%): mp 57–58 °C; $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 0.85–0.89 (m, 3H), 1.27–1.35 (m, 5H), 1.40–1.49 (m, 1H), 1.76–1.92 (m, 3H), 4.82–4.86 (m, 1H), 7.44–7.50 (m, 3H), 7.78–7.85 (m, 4H); $^{13}C$ NMR ($CDCl_3$, 100 MHz) $\delta$ 14.0, 22.6, 25.5, 31.7, 38.9, 74.8, 124.1, 124.6, 125.7, 126.1, 127.6, 127.9, 128.2, 132.9, 133.2, 142.2; IR (KBr) 3271, 3055, 3020, 2955, 2928, 2855, 1601, 1466, 1369, 1315, 1173, 1103, 1034, 895, 860, 826, 748 $cm^{-1}$; Anal. Calcd for $C_{16}H_{20}O$: C, 84.16; H, 8.83. Found: C, 84.40; H, 8.97; HRMS (EI) calcd for $C_{16}H_{20}O$ 228.1514, found 228.1514 ($M^+$).

**[D] Determination of enantiomeric purities and absolute configurations.**

The enantiomeric purities of **1a–f**, **1h–p**, and **2e–p** were determined by HPLC using chiral columns (Daicel Chemical Industries), and those of **2a–d** and **1g** were determined after conversion to the corresponding alcohols and acetate, respectively. Those of **1q** and **2q** were determined by chiral GC. HPLC for **1a**: Chiralcel OB-H, hexane/*i*-PrOH = 9:1, 0.5 mL/min, 254 nm, (*S*) 10.6 min, (*R*) 12.2 min. HPLC for **1b**: Chiralcel OD-H, hexane/*i*-PrOH = 98:2, 0.5 mL/min, 254 nm, (*R*) 29.3 min, (*S*) 35.3 min. HPLC for **1c**: Chiralcel OB-H, hexane/*i*-PrOH = 9:1, 0.5 mL/min, 254 nm, (*S*) 12.2 min, (*R*) 14.3 min. HPLC for **1d**: Chiralcel OB-H, hexane/*i*-PrOH = 98:2, 0.5 mL/min, 254 nm, (*S*) 15.1 min, (*R*) 29.9 min. HPLC for **1e**: Chiralpak IC, hexane/*i*-PrOH = 9:1, 0.5 mL/min, 254 nm, (*R*) 17.6 min, (*S*) 22.8 min. HPLC for **2e**: Chiralpak IC, hexane/*i*-PrOH = 20:1, 0.5 mL/min, 254 nm, (*S*) 19.7 min, (*R*) 21.7 min. HPLC for **1f**: Chiralpak IC, hexane/*i*-PrOH = 100:1, 0.5 mL/min, 254 nm, (*R*) 29.7 min, (*S*) 31.3 min. HPLC for **2f**: Chiralpak IC, hexane/*i*-PrOH = 100:1, 0.5 mL/min, 254 nm, (*R*) 13.8 min, (*S*) 17.2 min. HPLC for **2g**: Chiralpak IA, hexane/*i*-PrOH = 200:1, 0.5 mL/min, 254 nm, (*S*) 27.5 min, (*R*) 30.4 min. HPLC for **1h**: Chiralpak IA, hexane/*i*-PrOH = 98:2, 0.5 mL/min, 254 nm, (*S*) 47.3 min, (*R*) 49.1 min. HPLC for **2h**: Chiralpak IC, hexane/*i*-PrOH = 98:2, 0.5 mL/min, 254 nm, (*R*) 16.5 min, (*S*) 21.7 min. HPLC for **1i**: Chiralpak IC, hexane/*i*-PrOH = 200:1, 0.5 mL/min, 254 nm, (*R*) 42.2 min, (*S*) 45.4 min. HPLC for **2i**: Chiralpak IC, hexane/*i*-PrOH = 100:1, 0.5 mL/min, 254 nm, (*R*) 14.5 min, (*S*) 17.4 min. HPLC for **1j**: Chiralpak IC, hexane/*i*-PrOH = 100:1, 0.5 mL/min, 254 nm, (*R*) 24.1 min, (*S*) 29.3 min. HPLC for **2j**: Chiralpak IA, hexane/*i*-PrOH = 30:1, 0.5 mL/min, 254 nm, (*R*) 9.1 min, (*S*) 10.2 min. HPLC for **1k**: Chiralcel OB-H, hexane/*i*-PrOH = 9:1, 0.5 mL/min, 254 nm, (*S*) 24.6 min, (*R*) 28.2 min. HPLC for **2k**: Chiralpak IA, hexane/*i*-PrOH = 30:1, 0.5 mL/min, 254 nm, (*R*) 10.5 min, (*S*) 12.1 min. HPLC for **1l**: Chiralpak IC, hexane/*i*-PrOH = 98:2, 0.5 mL/min, 254 nm, (*S*) 45.1 min, (*R*) 47.9 min. HPLC for **2l**: Chiralpak IC, hexane/*i*-PrOH = 9:1, 0.5 mL/min, 254 nm, (*R*) 11.1 min, (*S*) 12.3 min. HPLC for **1m**: Chiralpak IB, hexane/*i*-PrOH = 20:1, 0.5 mL/min, 254 nm, (*S*) 23.5 min, (*R*) 25.3 min. HPLC for **2m**: Chiralpak IB, hexane/*i*-PrOH = 98:2, 0.5 mL/min, 254 nm, (*R*) 10.0 min, (*S*) 11.2 min. HPLC for **1n**: Chiralcel OD-H, hexane/*i*-PrOH = 98:2, 1.0 mL/min, 254 nm, (*R*) 11.8 min, (*S*) 13.7 min. HPLC for **2n**: Chiralcel OB-H, hexane/*i*-PrOH = 97:3, 0.5 mL/min, 254 nm, (*S*) 10.0 min, (*R*) 12.3 min. HPLC for **1o**: Chiralpak IC, hexane/*i*-PrOH = 100:1, 0.5 mL/min, 254 nm, (*R*) 25.4 min, (*S*) 27.0 min. HPLC for **2o**: Chiralpak IC, hexane/*i*-PrOH = 20:1, 0.5 mL/min, 254 nm, (*R*) 9.7 min, (*S*) 10.5 min. HPLC for **1p**: Chiralcel OD-H, hexane/*i*-PrOH = 99:1, 0.5 mL/min, 254 nm, (*R*) 45.8 min, (*S*) 59.5 min. HPLC for **2p**: Chiralcel OD-H, hexane/*i*-PrOH = 99:1, 0.5 mL/min, 254 nm, (*R*) 11.2 min, (*S*) 12.2 min. GC for **1q**: Inj. 250 °C, Col. 95 °C, Det. 220 °C, (*R*) 29.3 min, (*S*) 32.0 min. GC for **2q**: Inj. 250 °C, Col. 95 °C, Det. 220 °C, (*S*) 24.9 min, (*R*) 27.7 min. The absolute configurations of **1a**, **1b**, **1e**, **1f**, **1k**, and **1m–q** were determined by comparison with the signs of the reported optical rotation, and those of **1c**, **1d**, **1g–j**, and **1l** were determined by the Mosher method with MTPA.[12]

**[E] Lipase-catalyzed kinetic resolution.**

**General procedure.** A mixture of alcohol **1** (0.50 mmol), immobilized lipase (700 mg for **1a–e** and 200 mg for **1f–q**, 0.5% (w/w) enzyme/Toyonite-200M), and molecular sieves 3A (three pieces) in dry *i*-$Pr_2O$ (5.0 mL) in a test tube with a rubber septum was stirred at 30 °C for 30 min. The reaction was started by addition of vinyl acetate (93 μL, 1.0 mmol) via a syringe. The progress of the reaction was monitored by TLC. The reaction was stopped by filtration at an appropriate conversion, and the filtrate was concentrated under reduced pressure. Alcohol **1** and ester **2** were separated by silica gel column chromatography.

**Kinetic resolution of 1-phenyl-1-hexanol (1a).** (*S*)-**1a**: Colorless oil; $[\alpha]^{35}_{D}$ –6.4 (*c* 1.18, $CHCl_3$), 18.2% ee, lit.[13] $[\alpha]^{28}_{D}$ +35.3 (*c* 1.04, $CHCl_3$) for (*R*)-**1a** with 94% ee. (*R*)-**2a**:[14] Colorless oil; $[\alpha]^{34}_{D}$ +44.1 (*c* 0.673, $CHCl_3$), 61.3% ee; $^1$H NMR ($CDCl_3$, 600 MHz) $\delta$ 0.86 (t, $J$ = 7.1 Hz, 3H), 1.22–1.32 (m, 6H), 1.73–1.78 (m, 1H), 1.86–1.91 (m, 1H), 2.07 (s, 3H), 5.72 (dd, $J$ = 6.5, 7.6 Hz, 1H), 7.27–7.35 (m, 5H).

**Kinetic resolution of 1-phenyl-1-heptanol (1b).** (*S*)-**1b**: Colorless oil; $[\alpha]^{23}_{D}$ –16.1 (*c* 1.05, $CHCl_3$), 44.9% ee, lit.[13] $[\alpha]^{30}_{D}$ +32.0 (*c* 1.02, $CHCl_3$) for (*R*)-**1b** with 93% ee. (*R*)-**2b**:[14] Colorless oil; $[\alpha]^{23}_{D}$ +48.1 (*c* 1.19, $CHCl_3$), 70.8% ee; $^1$H NMR ($CDCl_3$, 600 MHz) $\delta$ 0.86 (t, $J$ = 7.0 Hz, 3H), 1.21–1.31 (m, 8H), 1.74–1.78 (m, 1H), 1.87–1.91 (m, 1H), 2.07 (s, 3H), 5.72 (dd, $J$ = 6.5, 7.5 Hz, 1H), 7.27–7.35 (m, 5H).

**Kinetic resolution of 6,6,6-trifluoro-1-phenyl-1-hexanol (1c).** (*S*)-**1c**: Colorless oil; $[\alpha]^{35}_{D}$ –17.0 (*c* 1.07, $CHCl_3$), 41.5% ee. (*R*)-**2c**: Colorless oil; $[\alpha]^{34}_{D}$ +48.2 (*c* 1.22, $CHCl_3$), 80.8% ee; $^1$H NMR ($CDCl_3$, 600 MHz) $\delta$ 1.29–1.33 (m, 1H), 1.39–1.43 (m, 1H), 1.54–1.59 (m, 2H), 1.76–1.82 (m, 1H), 1.90–1.96 (m, 1H), 2.00–2.06 (m, 2H), 2.07 (s, 3H), 5.73 (dd, $J$ = 6.4, 7.4 Hz, 1H), 7.28–7.36 (m, 5H); $^{13}$C NMR ($CDCl_3$, 150 MHz) $\delta$ 21.2, 21.6 (q, $J_{CF}$ = 3.1 Hz), 24.6, 33.5 (q, $J_{CF}$ = 28.3 Hz), 35.9, 75.7, 126.4, 127.0 (q, $J_{CF}$ = 275.0 Hz), 128.0, 128.5, 140.3, 170.3; $^{19}$F NMR ($CDCl_3$, 565 MHz) $\delta$ –67.5 (t, $J_{FH}$ = 11.0 Hz, 3F); IR (neat) 3034, 2949, 2874, 1736, 1497, 1437, 1375, 1240, 1140, 1040, 837, 761, 700 $cm^{-1}$; HRMS (EI) calcd for $C_{14}H_{17}F_3O_2$ 274.1181, found 274.1179 ($M^+$).

**Kinetic resolution of 4,4,5,5,6,6,6-heptafluoro-1-phenyl-1-hexanol (1d).** (*S*)-**1d**: White solid; $[\alpha]^{27}_{D}$ –4.5 (*c* 0.97, $CHCl_3$), 18.6% ee. (*R*)-**2d**: Colorless oil; $^1$H NMR ($CDCl_3$, 600 MHz) $\delta$ 2.04–2.21 (m, 4H), 2.12 (s, 3H), 5.79 (dd, $J$ = 4.8, 7.8 Hz, 1H), 7.31–7.39 (m, 5H); $^{13}$C NMR ($CDCl_3$, 150 MHz) $\delta$ 21.0, 27.02 (t, $J_{CF}$ = 21.8 Hz), 27.04 (t, $J_{CF}$ = 3.5 Hz), 74.4 (t, $J_{CF}$ = 10.9 Hz), 108.7 (t of sextet, $J_{CF}$ = 36.5, 262.1 Hz), 117.4 (tt, $J_{CF}$ = 31.2, 251.8 Hz), 117.8 (qt, $J_{CF}$ = 33.7, 285.7 Hz), 126.2, 128.4, 128.7, 139.2, 170.1; $^{19}$F NMR ($CDCl_3$, 565 MHz) $\delta$ –128.8 (s, 2F), –116.4 (m, 2F), –81.8 (t, $J$ = 9.3 Hz, 3F); IR (neat) 3068, 3037, 2951, 1747, 1454, 1354, 1227, 1173, 1115, 1026, 702 $cm^{-1}$; HRMS (EI) calcd for $C_{14}H_{13}F_7O_2$ 346.0804, found 346.0810 ($M^+$).

**Kinetic resolution of 2-methoxymethoxy-1-phenylethanol (1e).** (*R*)-**1e**: Colorless oil; $[\alpha]^{25}_{D}$ –37.3 (*c* 1.03, $CHCl_3$), 73.7% ee, lit.[15] $[\alpha]^{22}_{D}$ +24.9 (*c* 4.25, cyclohexane) for (*S*)-**1e** with 70% ee. (*S*)-**2e**:[4] Colorless oil; $[\alpha]^{25}_{D}$ +74.8 (*c* 1.05, $CHCl_3$), 99.2% ee; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 2.12 (s, 3H), 3.30 (s, 3H), 3.75 (dd, $J$ = 4.0, 11.0 Hz, 1H), 3.85 (dd, $J$ = 7.9, 11.0 Hz, 1H), 4.62 (d, $J$ = 6.7

Hz, 1H), 4.64 (d, $J$ = 6.7 Hz, 1H), 5.96 (dd, $J$ = 4.0, 7.9 Hz, 1H), 7.30–7.38 (m, 5H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 21.1, 55.2, 69.9, 74.5, 96.3, 126.7, 128.3, 128.4, 137.4, 170.1; IR (neat) 3036, 2939, 2889, 1739, 1497, 1454, 1373, 1234, 1153, 1111, 1042, 949, 918, 860, 760, 702 cm$^{-1}$; HRMS (EI) calcd for $C_{12}H_{17}O_4$ 225.1127, found 225.1111 ($[M + H]^+$).

**Kinetic resolution of 1-phenyl-5-hexen-1-ol (1f).** (*S*)-**1f**: Colorless oil; $[\alpha]^{30}_D$ –28.0 (*c* 0.976, $CHCl_3$), 64.0% ee, lit.[16] $[\alpha]_D$ –35.1 (*c* 1.74, $CHCl_3$) for (*S*)-**1f** with 92% ee. (*R*)-**2f**: Colorless oil; $[\alpha]^{30}_D$ +69.8 (*c* 0.979, $CHCl_3$), 98.9% ee; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 1.31–1.37 (m, 1H), 1.38–1.48 (m, 1H), 1.73–1.82 (m, 1H), 1.87–1.96 (m, 1H), 2.06 (q, $J$ = 7.2 Hz, 2H), 2.07 (s, 3H), 4.93–5.01 (m, 2H), 5.70–5.80 (m, 2H), 7.28–7.36 (m, 5H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 21.2, 24.7, 33.3, 35.7, 75.9, 114.8, 126.4, 127.8, 128.4, 138.2, 140.7, 170.3; IR (neat) 3067, 3036, 2939, 2862, 1736, 1373, 1238, 1022, 910, 760, 698 cm$^{-1}$; HRMS (EI) calcd for $C_{14}H_{18}O_2$ 218.1307, found 218.1298 ($M^+$).

**Kinetic resolution of 5-methoxymethoxy-1-phenyl-1-pentanol (1g).** (*S*)-**1g**: Colorless oil; $[\alpha]^{29}_D$ –28.6 (*c* 1.07, $CHCl_3$), 83.2% ee. (*R*)-**2g**: Colorless oil; $[\alpha]^{35}_D$ +58.1 (*c* 1.05, $CHCl_3$), 96.4% ee; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 1.29–1.34 (m, 1H), 1.39–1.45 (m, 1H), 1.57–1.64 (m, 2H), 1.77–1.83 (m, 1H), 1.89–1.95 (m, 1H), 2.07 (s, 3H), 3.33 (s, 3H), 3.49 (t, $J$ = 6.6 Hz, 2H), 4.59 (s, 2H), 5.73 (dd, $J$ = 6.3, 7.6 Hz, 1H), 7.28–7.36 (m, 5H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 21.2, 22.2, 29.3, 36.0, 55.0, 67.3, 75.9, 96.3, 126.4, 127.8, 128.3, 140.6, 170.3; IR (neat) 3065, 3034, 2941, 2870, 1738, 1456, 1373, 1240, 1150, 1111, 1047, 918, 762, 700 cm$^{-1}$; HRMS (EI) calcd for $C_{15}H_{22}O_4$ 266.1518, found 266.1505 ($M^+$).

**Kinetic resolution of 1,6-diphenyl-1-hexanol (1h).** (*S*)-**1h**: Colorless oil; $[\alpha]^{20}_D$ –15.7 (*c* 1.03, $CHCl_3$), 69.1% ee. (*R*)-**2h**: Colorless oil; $[\alpha]^{19}_D$ +51.8 (*c* 1.04, $CHCl_3$), >99.5% ee; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 1.25–1.36 (m, 4H), 1.57–1.60 (m, 2H), 1.74–1.78 (m, 1H), 1.85–1.90 (m, 1H), 2.06 (s, 3H), 2.57 (t, $J$ = 7.8 Hz, 2H), 5.71 (t, $J$ = 6.8 Hz, 1H), 7.13–7.18 (m, 3H), 7.24–7.35 (m, 7H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 21.2, 25.3, 28.9, 31.2, 35.7, 36.1, 76.0, 125.6, 126.4, 127.8, 128.1, 128.30, 128.33, 140.7, 142.5, 170.3; IR (neat) 3086, 3063, 3028, 2934, 2856, 1736, 1603, 1495, 1454, 1371, 1236, 1022, 964, 750, 700 cm$^{-1}$; HRMS (EI) calcd for $C_{18}H_{21}$ 237.1643, found 237.1575 ($[M – OAc]^+$).

**Kinetic resolution of 5-methyl-1-phenyl-1-hexanol (1i).** (*S*)-**1i**: White solid; $[\alpha]^{30}_D$ –15.5 (*c* 1.15, $CHCl_3$), 53.4% ee. (*R*)-**2i**: Colorless oil; $[\alpha]^{30}_D$ +66.8 (*c* 1.14, $CHCl_3$), 97.7% ee; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 0.83 (d, $J$ = 6.8 Hz, 3H), 0.84 (d, $J$ = 6.8 Hz, 3H), 1.14–1.35 (m, 4H), 1.46–1.53 (m, 1H), 1.69–1.77 (m, 1H), 1.84–1.91 (m, 1H), 2.07 (s, 3H), 5.72 (t, $J$ = 7.0 Hz, 1H), 7.28–7.36 (m, 5H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 21.2, 22.46, 22.48, 23.2, 27.7, 36.4, 38.5, 76.1, 126.5, 127.7, 128.3, 140.8, 170.3; IR (neat) 3067, 3032, 2955, 2870, 1740, 1493, 1458, 1369, 1242, 1123, 1022, 961, 899, 760, 698, 552 cm$^{-1}$; HRMS (EI) calcd for $C_{15}H_{22}O_2$ 234.1620, found 234.1609 ($M^+$).

**Kinetic resolution of 1-(4-trifluoromethylphenyl)-1-hexanol (1j).** (*S*)-**1j**: Colorless oil; $[\alpha]^{25}_D$ –20.9 (*c* 1.07, $CHCl_3$), 80.7% ee. (*R*)-**2j**: Colorless oil; $[\alpha]^{24}_D$ +48.9 (*c* 0.991, $CHCl_3$), 97.8% ee; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 0.85–0.88 (m, 3H), 1.27–1.29 (m, 6H), 1.73–1.77 (m, 1H), 1.86–1.90

(m, 1H), 2.08 (s, 3H), 5.74 (t, $J$ = 6.4 Hz, 1H), 7.43 (d, $J$ = 8.2 Hz, 2H), 7.60 (d, $J$ = 8.2 Hz, 2H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 13.9, 21.1, 22.4, 25.0, 31.4, 36.2, 75.4, 124.0 (q, $J_{CF}$ = 270.6 Hz), 125.4 (q, $J_{CF}$ = 3.7 Hz), 126.7, 129.9 (q, $J_{CF}$ = 32.2 Hz), 144.9, 170.2; $^{19}$F NMR ($CDCl_3$, 376 MHz) $\delta$ –63.6 (s, 3F); IR (neat) 2959, 2934, 2862, 1742, 1622, 1373, 1327, 1238, 1167, 1128, 1069, 1018, 837 cm$^{-1}$; HRMS (EI) calcd for $C_{15}H_{19}F_3O_2$ 288.1337, found 288.1323 ($M^+$).

**Kinetic resolution of 1-(4-methoxylphenyl)-1-hexanol (1k).** (*S*)-**1k**: Colorless oil; $[\alpha]^{26}_D$ –18.1 (*c* 0.818, $CHCl_3$), 69.1% ee, lit.[10] $[\alpha]^{23}_D$ –17.8 (*c* 1.13, MeOH) for (*S*)-**1k** with 88% ee. (*R*)-**2k**:[17] Colorless oil; $[\alpha]^{26}_D$ +85.4 (*c* 1.11, $CHCl_3$), 99.3% ee; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 0.84–0.87 (m, 3H), 1.19–1.28 (m, 6H), 1.69–1.76 (m, 1H), 1.82–1.91 (m, 1H), 2.04 (s, 3H), 3.80 (s, 3H), 5.67 (t, $J$ = 7.1 Hz, 1H), 6.87 (d, $J$ = 8.7 Hz, 2H), 7.26 (d, $J$ = 8.7 Hz, 2H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 13.9, 21.2, 22.4, 25.2, 31.4, 35.9, 55.1, 75.8, 113.7, 127.9, 132.8, 159.1, 170.3; IR (neat) 3001, 2955, 2932, 2858, 1732, 1612, 1585, 1516, 1462, 1373, 1242, 1177, 1107, 1034, 949, 829 cm$^{-1}$; HRMS (EI) calcd for $C_{15}H_{22}O_3$ 250.1569, found 250.1567 ($M^+$).

**Kinetic resolution of 1-(3-methoxymethoxyphenyl)-1-hexanol (1l).** (*S*)-**1l**: Colorless oil; $[\alpha]^{24}_D$ –19.1 (*c* 1.01, $CHCl_3$), 73.2% ee. (*R*)-**2l**: Colorless oil; $[\alpha]^{24}_D$ +61.1 (*c* 1.02, $CHCl_3$), 99.2% ee; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 0.84–0.88 (m, 3H), 1.27–1.29 (m, 6H), 1.73–1.78 (m, 1H), 1.82–1.89 (m, 1H), 2.07 (s, 3H), 3.48 (s, 3H), 5.16 (d, $J$ = 6.9 Hz, 1H), 5.18 (d, $J$ = 6.9 Hz, 1H), 5.69 (dd, $J$ = 6.4, 7.5 Hz, 1H), 6.95–6.98 (m, 3H), 7.23–7.26 (m, 1H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 13.9, 21.2, 22.4, 25.1, 31.4, 36.2, 56.0, 75.9, 94.5, 114.5, 115.2, 119.9, 129.4, 142.6, 157.3, 170.3; IR (neat) 2955, 2934, 2860, 2827, 1736, 1587, 1489, 1456, 1371, 1236, 1151, 1080, 1018, 995, 924, 876, 789, 700 cm$^{-1}$; HRMS (EI) calcd for $C_{16}H_{24}O_4$ 280.1675, found 280.1664 ($M^+$).

**Kinetic resolution of 1-(2-naphthyl)-1-hexanol (1m).** (*S*)-**1m**: White solid; $[\alpha]^{35}_D$ –25.4 (*c* 1.00, $CHCl_3$), 68.0% ee, lit.[10] $[\alpha]^{23}_D$ –18 (*c* 1, MeOH) for (*S*)-**1m** with 82% ee. (*R*)-**2m**: Colorless oil; $[\alpha]^{33}_D$ +76.5 (*c* 1.10, $CHCl_3$), >99.5% ee; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 0.86 (t, $J$ = 7.0 Hz, 3H), 1.28–1.30 (m, 6H), 1.84–1.88 (m, 1H), 1.95–2.00 (m, 1H), 2.09 (s, 3H), 5.89 (t, $J$ = 7.0 Hz, 1H), 7.44–7.49 (m, 3H), 7.78–7.84 (m, 4H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 13.9, 21.3, 22.4, 25.2, 31.5, 36.1, 76.2, 124.3, 125.7, 125.9, 126.1, 127.6, 127.9, 128.2, 133.0, 133.1, 138.1, 170.3; IR (neat) 3055, 2955, 2932, 2858, 1736, 1601, 1508, 1458, 1369, 1238, 1126, 1022, 945, 895, 856, 818, 748 cm$^{-1}$; HRMS (EI) calcd for $C_{18}H_{22}O_2$ 270.1620, found 270.1618 ($M^+$).

**Kinetic resolution of 1-phenyl-1-pentanol (1n).** (*S*)-**1n**: Colorless oil; $[\alpha]^{31}_D$ –25.9 (*c* 1.05, $CHCl_3$), 66.9% ee, lit.[18] $[\alpha]^{24}_D$ –39.3 (*c* 0.57, $CHCl_3$) for (*S*)-**1n** with 92% ee. (*R*)-**2n**: Colorless oil; $[\alpha]^{30}_D$ +79.3 (*c* 1.04, $CHCl_3$), 98.0% ee, lit.[19] $[\alpha]^{23}_D$ +76.7 (*c* 1.01, $CHCl_3$) for (*R*)-**2n** with 90.1% ee; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 0.85–0.89 (m, 3H), 1.18–1.35 (m, 4H), 1.72–1.81 (m, 1H), 1.86–1.95 (m, 1H), 2.07 (s, 3H), 5.70–5.74 (m, 1H), 7.28–7.36 (m, 5H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 13.9, 21.2, 22.4, 27.6, 36.0, 76.1, 126.5, 127.7, 128.3, 140.8, 170.4; IR (neat) 3088, 3065, 3034, 2957, 2936, 2862, 1738, 1605, 1587, 1495, 1456, 1371, 1240, 1109, 1074, 1020, 964, 760, 700, 550 cm$^{-1}$; HRMS (EI) calcd for $C_{13}H_{18}O_2$ 206.1307, found 206.1286 ($M^+$).

**Kinetic resolution of 1-phenyl-1-butanol (1o).** (*S*)-**1o**: White solid; $[\alpha]^{31}_{D}$ –34.4 (*c* 1.06, $CHCl_3$), 72.0% ee, lit.[18] $[\alpha]^{24}_{D}$ –44.9 (*c* 0.45, $CHCl_3$) for (*S*)-**1o** with 92% ee. (*R*)-**2o**: Colorless oil; $[\alpha]^{31}_{D}$ +86.6 (*c* 1.04, $CHCl_3$), 98.6% ee, lit.[20] $[\alpha]^{22}_{D}$ +78.2 (*c* 0.9, $CHCl_3$) for (*R*)-**2o** with 93% ee; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 0.91 (t, *J* = 7.4 Hz, 3H), 1.23–1.39 (m, 2H), 1.69–1.78 (m, 1H), 1.85–1.94 (m, 1H), 2.07 (s, 3H), 5.74 (dd, *J* = 6.3, 7.7 Hz, 1H), 7.27–7.36 (m, 5H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 13.7, 18.7, 21.2, 38.4, 75.9, 126.5, 127.7, 128.3, 140.8, 170.4; IR (neat) 3088, 3065, 3034, 2961, 2936, 2874, 1728, 1605, 1587, 1495, 1456, 1371, 1236, 1180, 1103, 1055, 1024, 957, 845, 762, 700, 544 $cm^{-1}$; HRMS (EI) calcd for $C_{12}H_{16}O_2$ 192.1150, found 192.1145 ($M^+$).

**Kinetic resolution of 1-phenyl-1-propanol (1p).** (*S*)-**1p**: Colorless oil; $[\alpha]^{28}_{D}$ –27.3 (*c* 0.973, $CHCl_3$), 56.6% ee, lit.[18] $[\alpha]^{24}_{D}$ –44.4 (*c* 0.63, $CHCl_3$) for (*S*)-**1p** with 80% ee. (*R*)-**2p**: Colorless oil; $[\alpha]^{26}_{D}$ +100.3 (*c* 1.10, $CHCl_3$), >99.5% ee, lit.[21] $[\alpha]^{20}_{D}$ +98.2 (*c* 1.308, $CHCl_3$) for (*R*)-**2p** with 99% ee; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 0.88 (t, *J* = 7.4 Hz, 3H), 1.76–1.85 (m, 1H), 1.87–1.98 (m, 1H), 2.08 (s, 3H), 5.66 (t, *J* = 7.0 Hz, 1H), 7.27–7.36 (m, 5H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 9.9, 21.2, 29.2, 77.3, 126.5, 127.8, 128.3, 140.5, 170.4; IR (neat) 3090, 3065, 3034, 2970, 2937, 2880, 1736, 1495, 1454, 1371, 1236, 1086, 1042, 1020, 966, 893, 839, 754, 700, 548 $cm^{-1}$; HRMS (EI) calcd for $C_{11}H_{14}O_2$ 178.0994, found 178.0968 ($M^+$).

**Kinetic resolution of 1-phenylethanol (1q).** (*S*)-**1q**: Colorless oil; $[\alpha]^{25}_{D}$ –56.9 (*c* 0.686, $CHCl_3$), 99.8% ee, lit.[18] $[\alpha]^{23}_{D}$ –43.7 (*c* 0.90, $CHCl_3$) for (*S*)-**1q** with 69% ee. (*R*)-**2q**: Colorless oil; $[\alpha]^{26}_{D}$ +110.6 (*c* 1.02, $CHCl_3$), 99.1% ee, lit.[19] $[\alpha]^{25}_{D}$ +112 (*c* 1.00, $CHCl_3$) for (*R*)-**2q** with 99.9% ee; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 1.54 (d, *J* = 6.6 Hz, 3H), 2.07 (s, 3H), 5.88 (q, *J* = 6.6 Hz, 1H), 7.28–7.36 (m, 5H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 21.2, 22.1, 72.2, 126.0, 127.8, 128.4, 141.6, 170.2; IR (neat) 3088, 3065, 3034, 2982, 2934, 2872, 1732, 1605, 1585, 1495, 1454, 1371, 1209, 1242, 1067, 1030, 943, 854, 762, 700, 621, 540 $cm^{-1}$.

**Table S2** Kinetic resolution of **1** with wild-type and mutant enzymes[a]

| Entry | **1** | Lipase | Time (h) | *c* (%)[b] | % Yield[c] (% ee) (*R*)-**2** | (*S*)-**1** | *E*[d] |
|---|---|---|---|---|---|---|---|
| 1 | **1a** | wild-type | 41 | 23 | 21 (61.3) | 73 (18.2) | 5 |
| 2 | **1a** | I287F | 41 | 46 | 49 (87.1) | 44 (72.8) | 32 |
| 3 | **1a** | I287A | 41 | 20 | 13 (13.5) | 78 (3.4) | 1.4 |
| 4 | **1a** | I287W | 41 | 17 | 11 (62.1) | 62 (12.4) | 5 |
| 5 | **1a** | I287Y | 41 | 10 | 10 (84.3) | 87 (9.5) | 13 |
| 6 | **1a** | I287F/I290A | 2.5 | 50 | 43 (98.9) | 50 (98.4) | >200 |
| 7 | **1a** | I287F/I290F | 41 | 10 | 18 (56.4) | 80 (6.4) | 4 |
| 8 | **1a** | I290A | 41 | 41 | 35 (95.1) | 51 (65.3) | 79 |
| 9 | **1a** | I287F/I290A/Q292A | 6 | 45 | 37 (91.8) | 51 (73.7) | 52 |
| 10 | **1b** | wild-type | 41 | 39 | 35 (70.8) | 58 (44.9) | 9 |
| 11 | **1b** | I287F | 22 | 47 | 39 (92.8) | 43 (83.9) | 71 |
| 12 | **1b** | I287F/I290A | 4 | 47 | 40 (98.7) | 46 (86.6) | >200 |
| 13 | **1c** | wild-type | 41 | 34 | 35 (80.8) | 61 (41.5) | 14 |
| 14 | **1c** | I287F | 22 | 47 | 40 (91.4) | 38 (80.2) | 55 |
| 15 | **1c** | I287F/I290A | 4 | 50 | 41 (98.4) | 46 (96.5) | >200 |
| 16 | **1d** | I287F/I290A | 75 | 19 | 9 (78.9) | 44 (18.6) | 10 |
| 17 | **1e** | wild-type | 41 | 45 | 41 (53.3) | 49 (43.0) | 5[e] |
| 18 | **1e** | I287F | 41 | 42 | 41 (79.5) | 45 (58.3) | 16[e] |
| 19 | **1e** | I287F/I290A | 3 | 43 | 40 (99.2) | 54 (73.7) | >200[e] |

[a] Conditions: immobilized lipase (700 mg, 0.5% (w/w) enzyme/Toyonite-200M), **1** (0.50 mmol), vinyl acetate (1.0 mmol), molecular sieves 3A (three pieces), dry *i*-$Pr_2O$ (5 mL), 30 °C. [b] Conversion calculated from $c$ = ee(**1**)/(ee(**1**) + ee(**2**)). [c] Isolated yield. [d] Calculated from $E = \ln[1 - c(1 + \text{ee}(\mathbf{2}))]/\ln[1 - c(1 - \text{ee}(\mathbf{2}))]$. [e] (*S*)-**2e** and (*R*)-**1e** were obtained.

**Table S3** Substrate scope of I287F/I290A double mutant[a]

| | | | | % Yield[c] (% ee) | | | Wild-type | |
|---|---|---|---|---|---|---|---|---|
| Entry | **1** | Time (h) | *c* (%)[b] | (*R*)-**2** | (*S*)-**1** | *E*[d] | *c* (%)[e] | *E*[d] |
| 1 | **1f** | 7 | 39 | 35 (98.9) | 56 (64.0) | >200 | 0 | – |
| 2 | **1g** | 22 | 46 | 44 (96.4) | 46 (83.2) | 143 | 6 | – |
| 3 | **1h** | 6.5 | 41 | 38 (>99.5) | 56 (69.1) | >200 | 3 | – |
| 4 | **1i** | 9 | 35 | 34 (97.7) | 62 (53.4) | 147 | 0 | – |
| 5 | **1j** | 54 | 45 | 42 (97.8) | 46 (80.7) | >200 | 4 | – |
| 6 | **1k** | 7 | 41 | 35 (99.3) | 57 (69.1) | >200 | 2 | – |
| 7 | **1l** | 7 | 42 | 40 (99.2) | 56 (73.2) | >200 | 3 | – |
| 8 | **1m** | 7 | 41 | 42 (>99.5) | 56 (68.0) | >200 | 0 | – |
| 9 | **1n** | 24 | 41 | 36 (98.0) | 53 (66.9) | 199 | 5 | – |
| 10 | **1o** | 50 | 42 | 32 (98.6) | 44 (72.0) | >200 | 18[b] | 19 |
| 11 | **1p** | 50 | 36 | 33 (>99.5) | 61 (56.6) | >200 | 38[b] | 113 |
| 12 | **1q** | 3 | 50 | 47 (99.1) | 40 (99.8) | >200 | 45[b] | 68 |

[a] Conditions: immobilized lipase (200 mg, 0.5% (w/w) enzyme/Toyonite-200M), **1** (0.50 mmol), vinyl acetate (1.0 mmol), molecular sieves 3A (three pieces), dry *i*-$Pr_2O$ (5 mL), 30 °C. [b] Conversion calculated from $c$ = ee(**1**)/(ee(**1**) + ee(**2**)). [c] Isolated yield. [d] Calculated from $E = \ln[1 - c(1 + \text{ee}(\mathbf{2}))]/\ln[1 - c(1 - \text{ee}(\mathbf{2}))]$. [e] Conversion calculated from $^1$H NMR.

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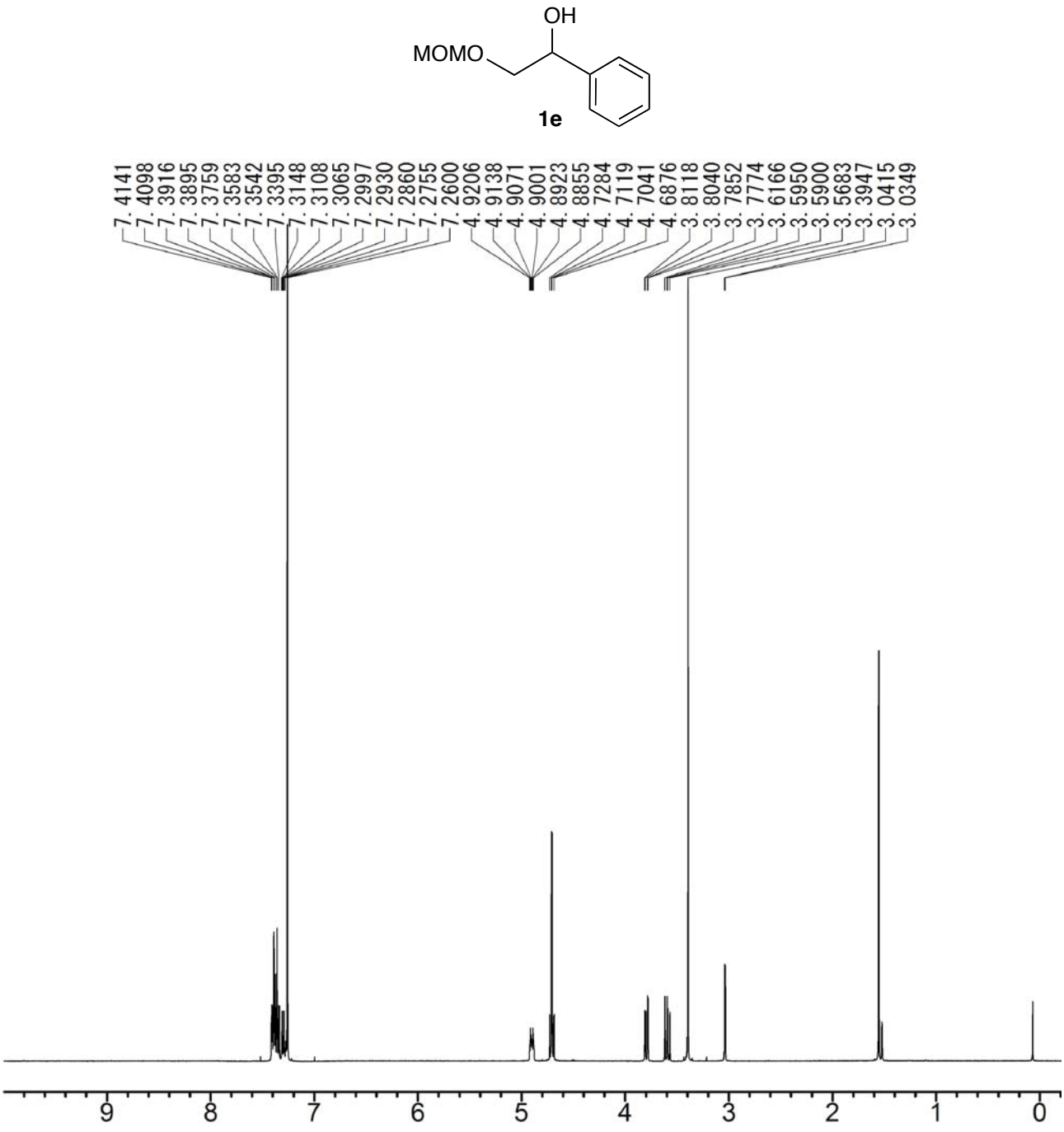
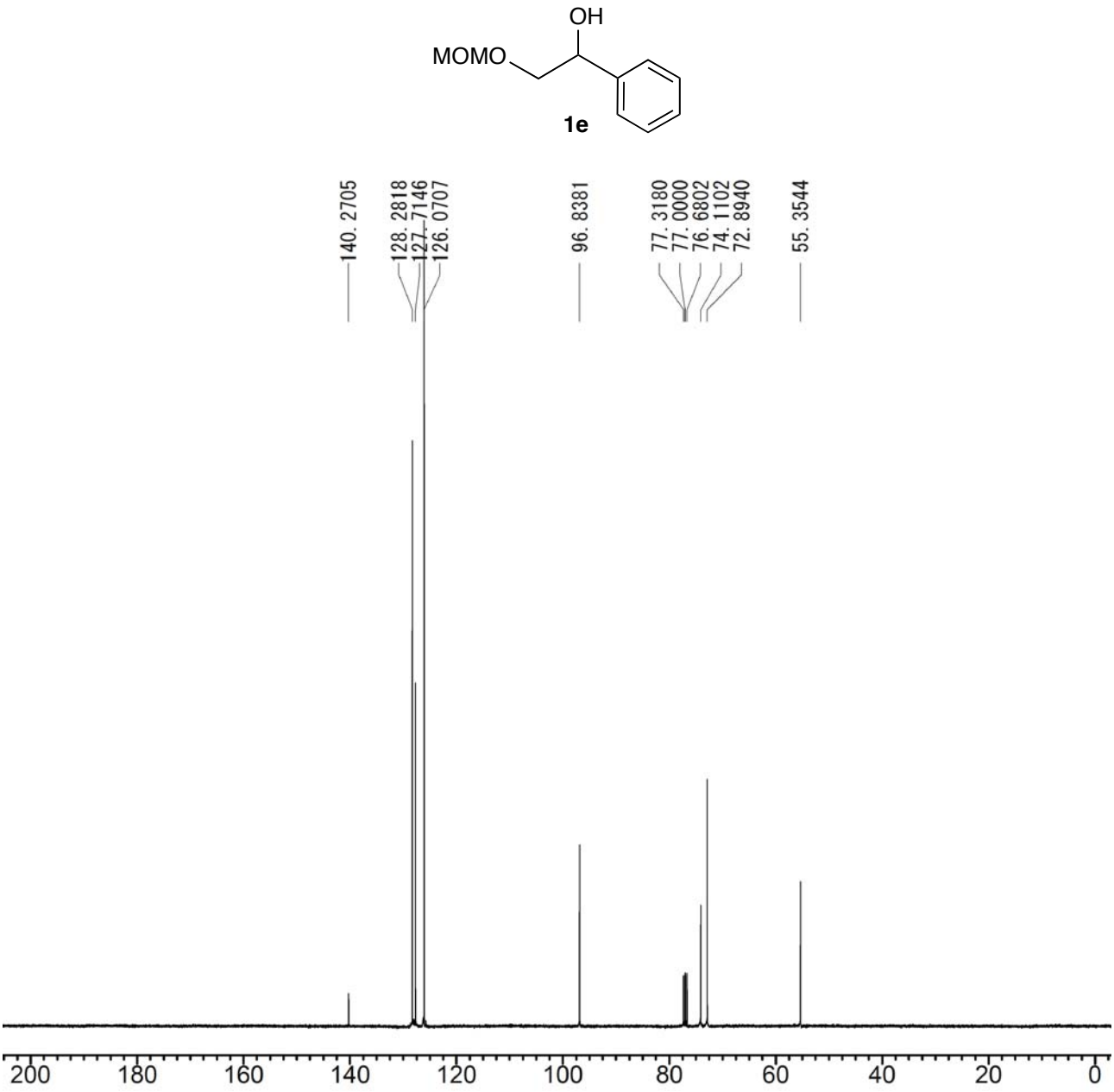
**[F] NMR spectra.**




400 MHz $^{1}$H NMR of **1e** in $CDCl_3$.

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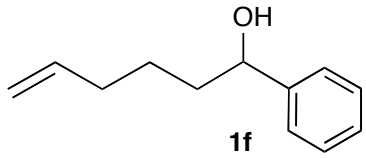


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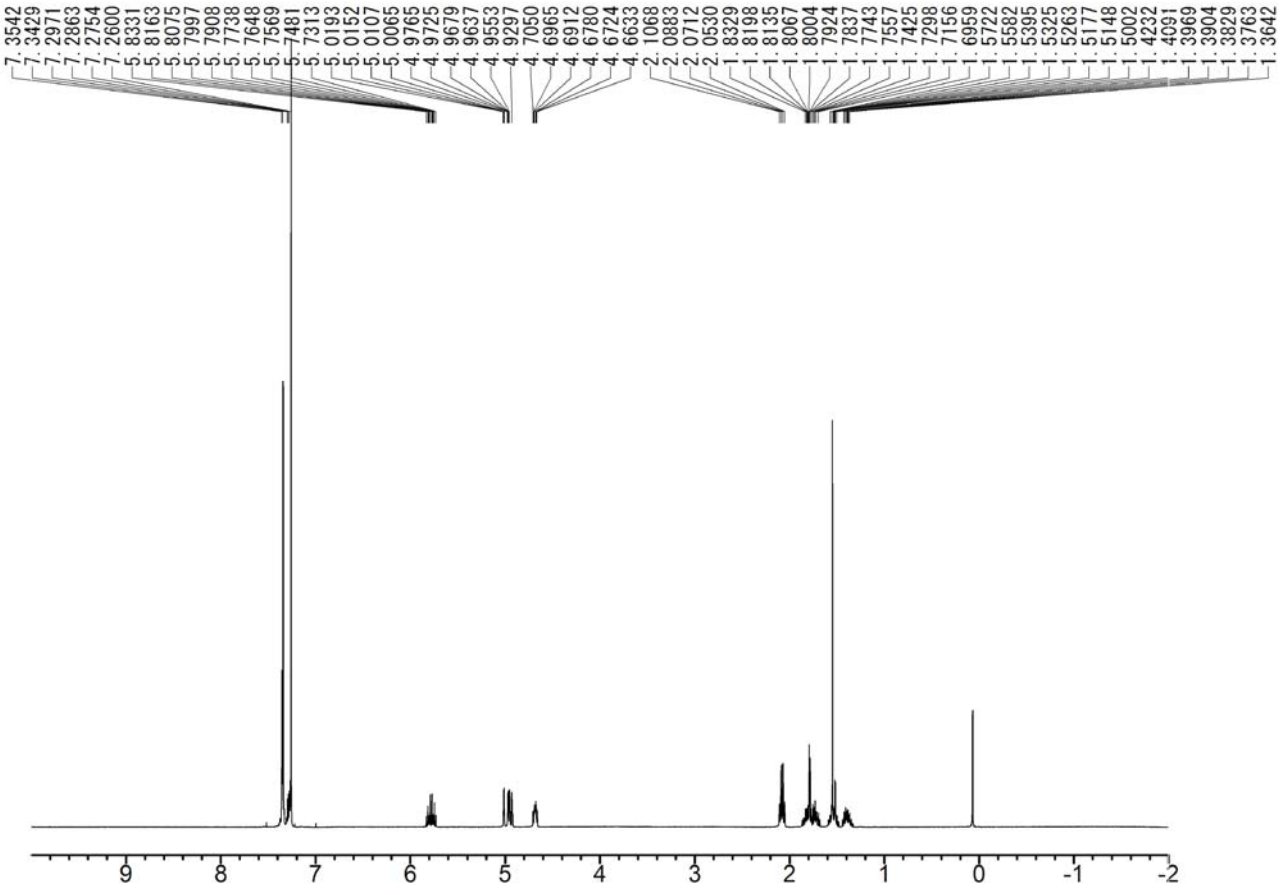


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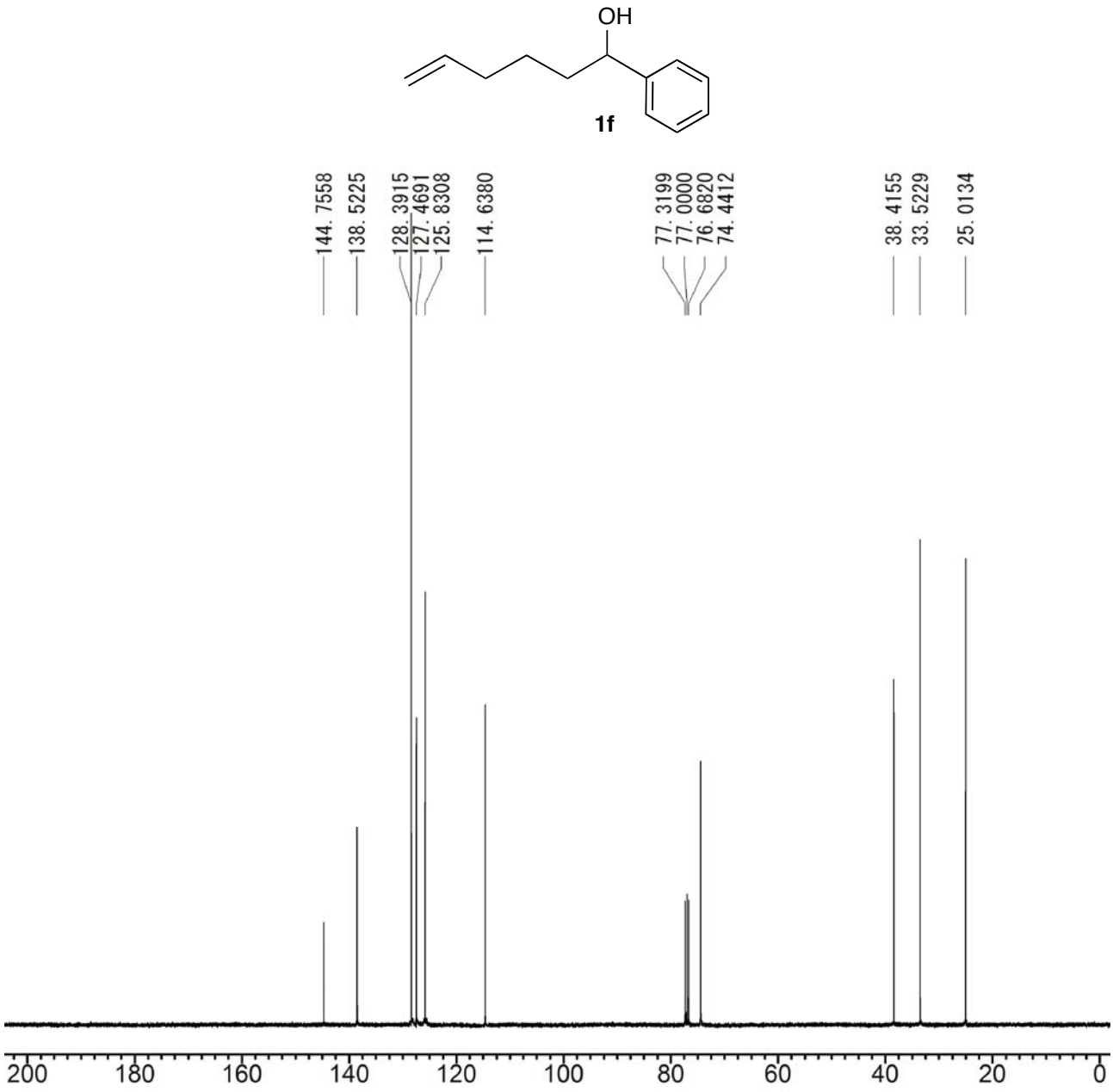


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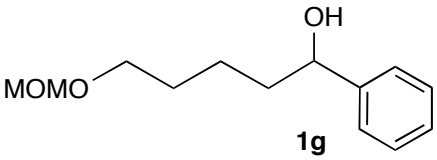
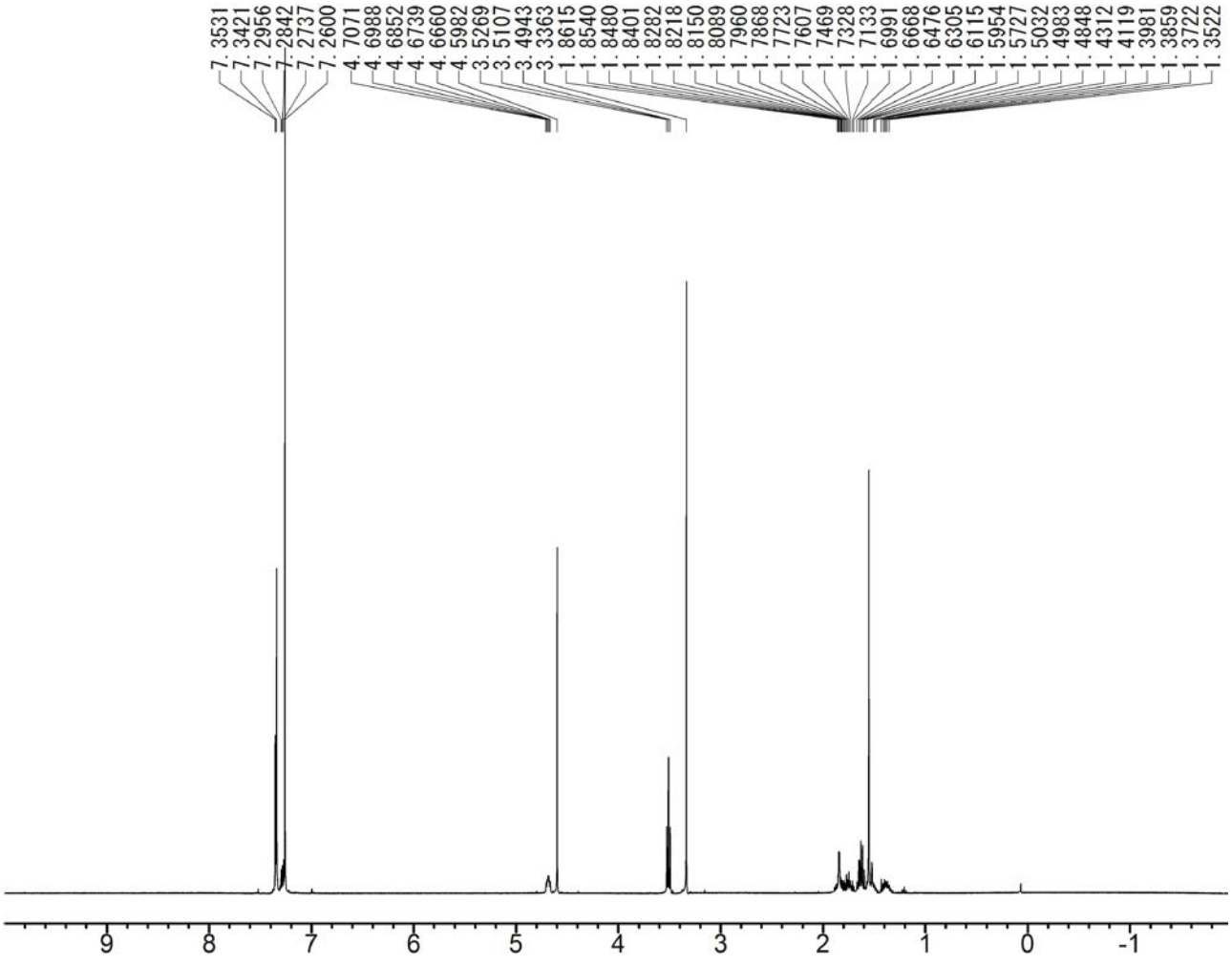



**1g**

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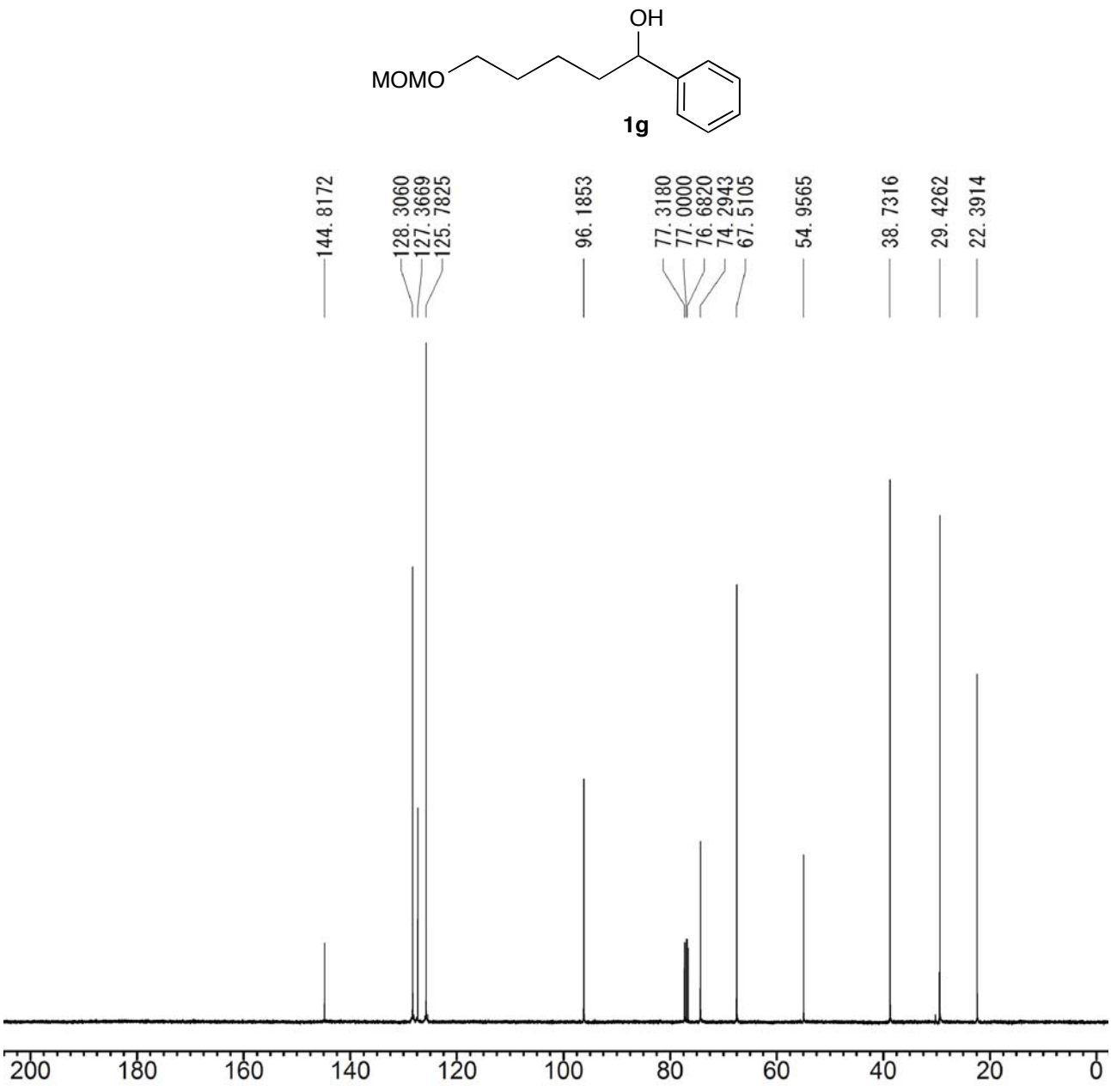


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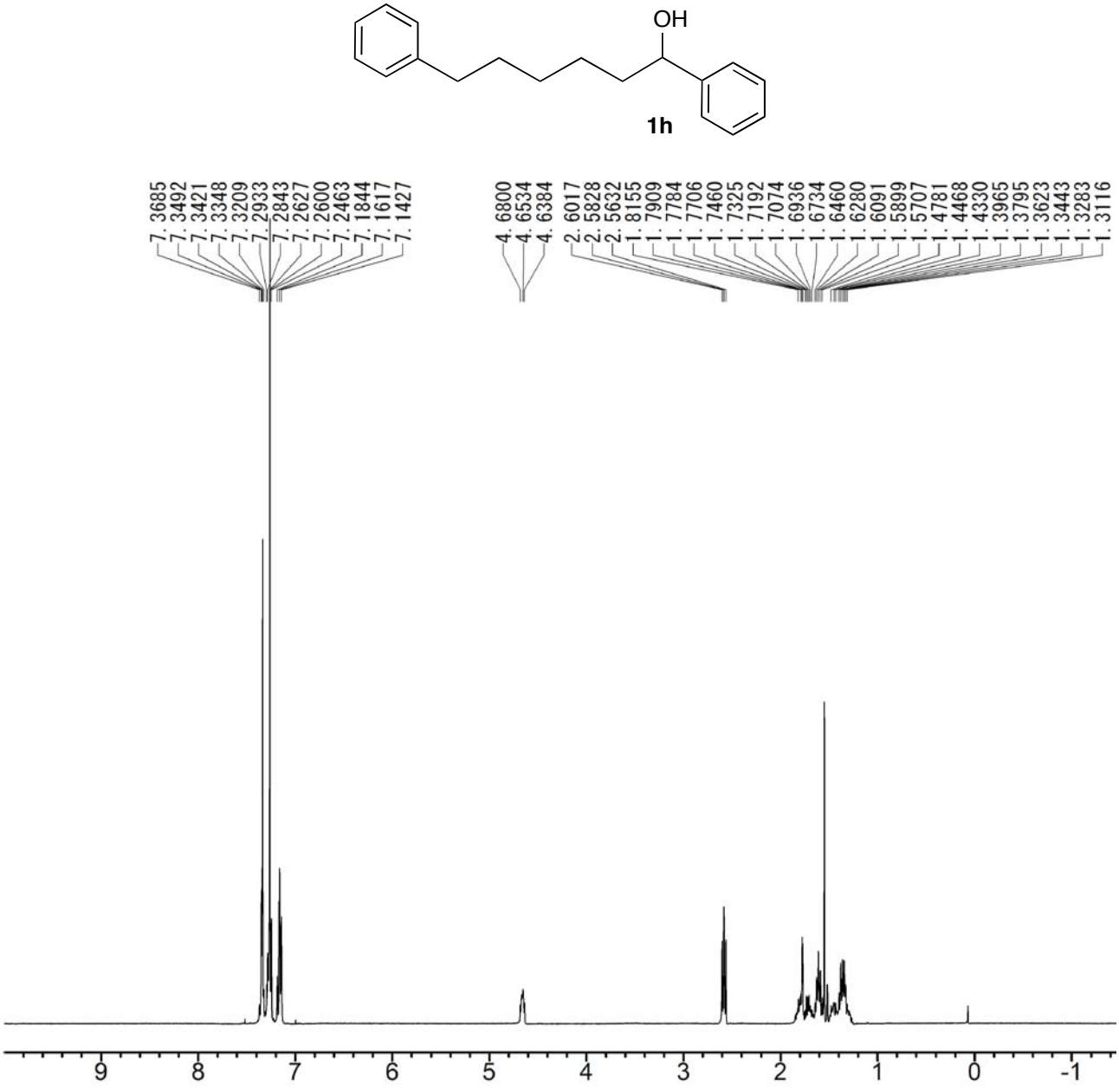


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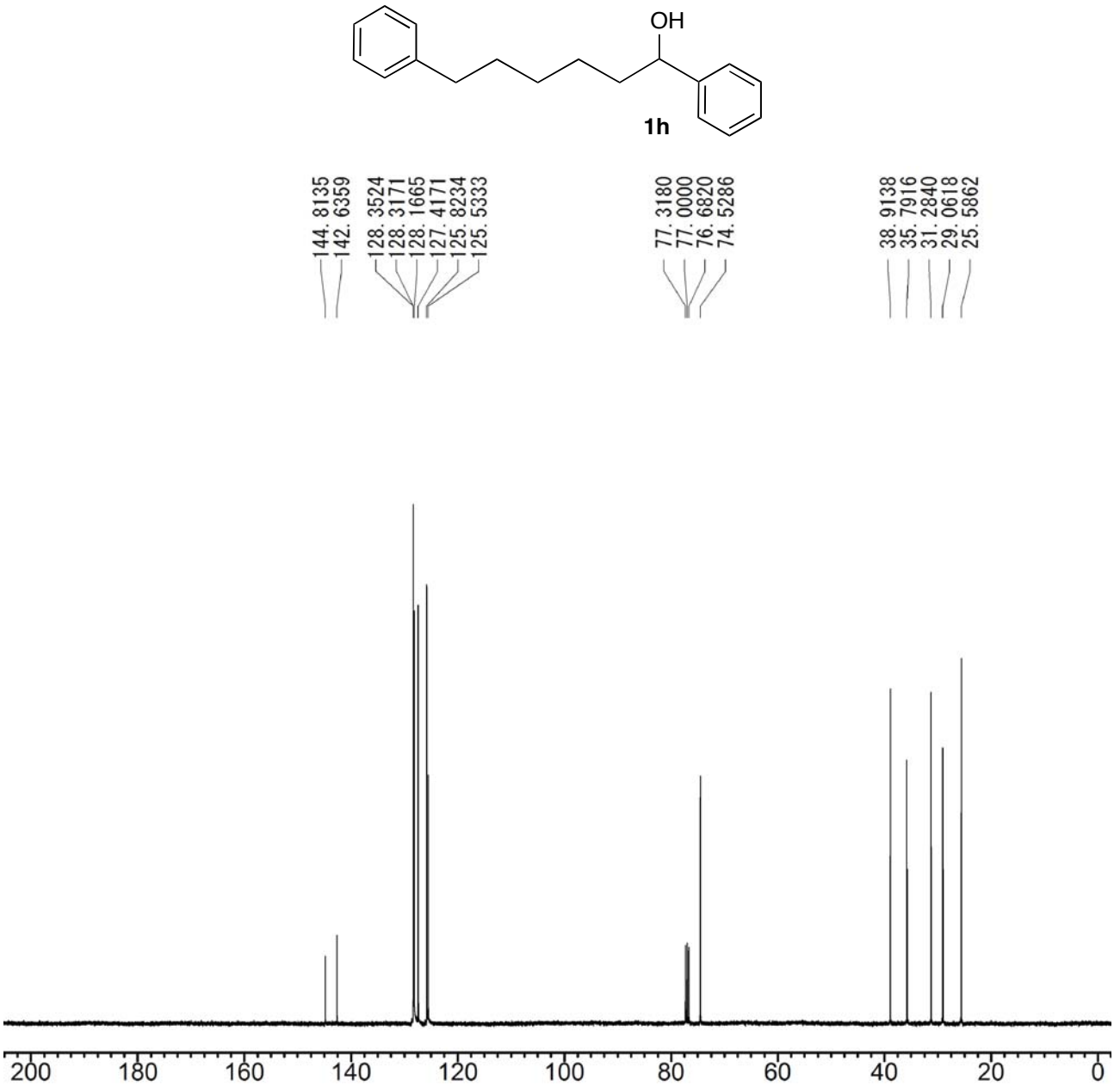


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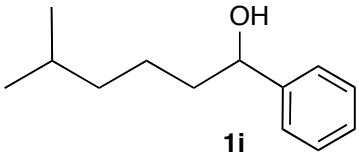
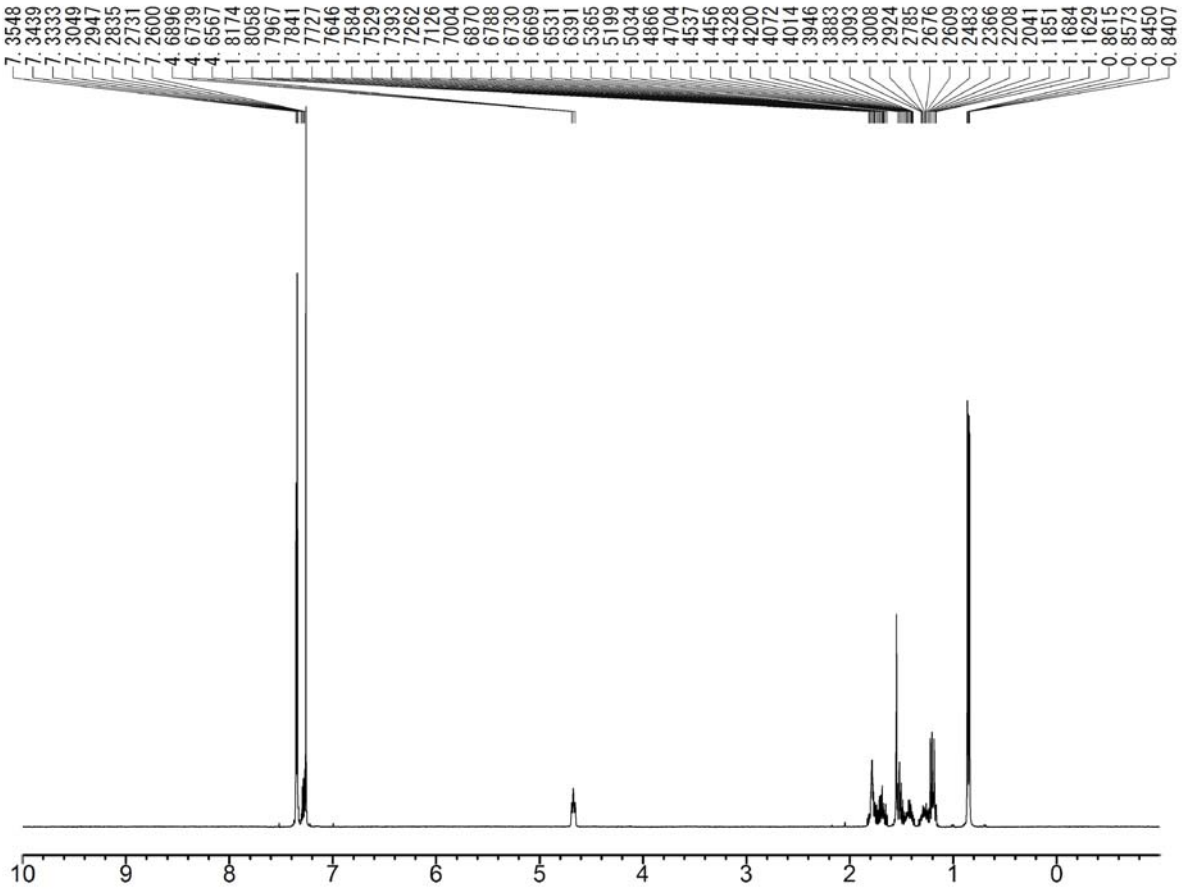



**1i**

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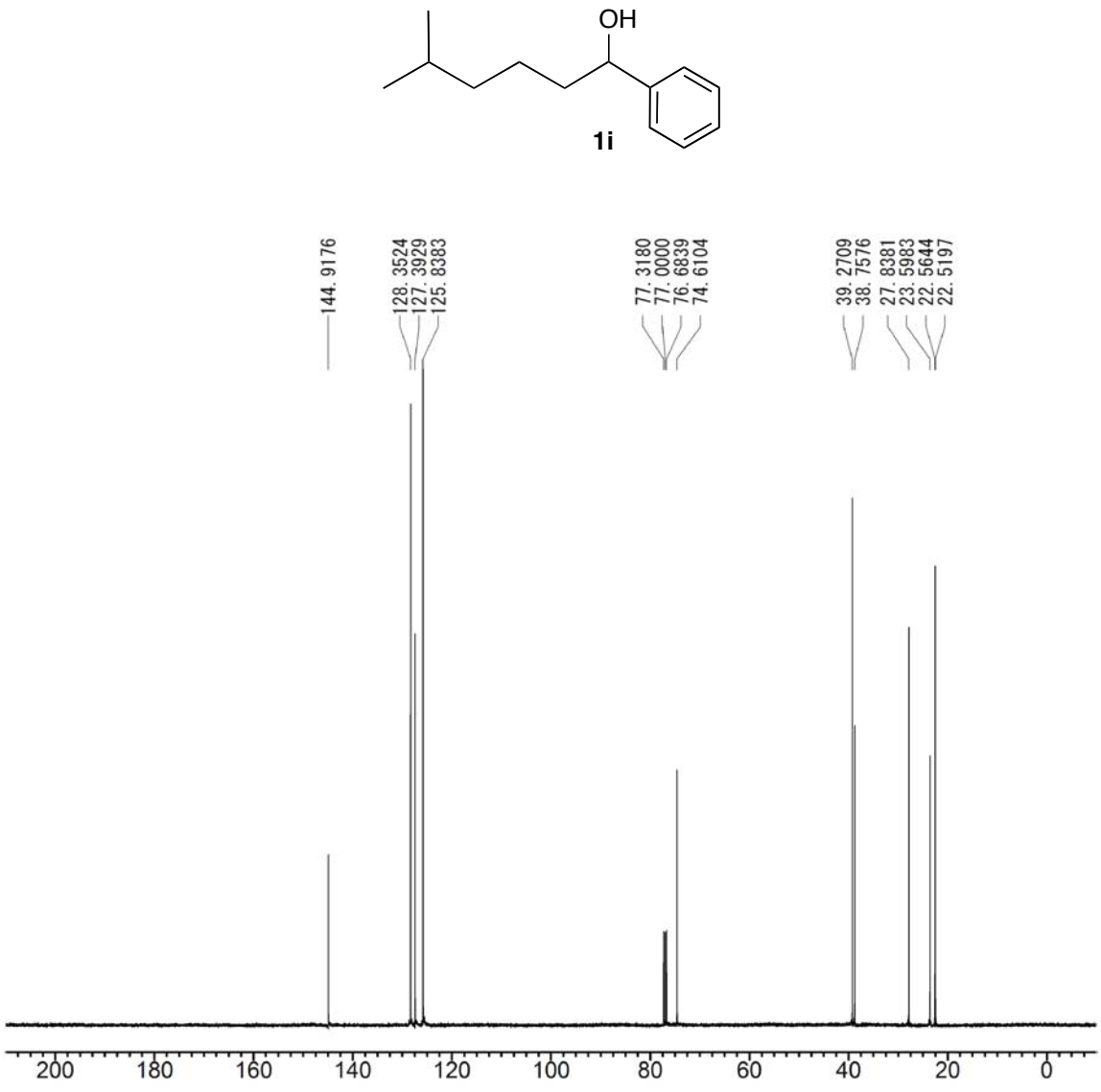


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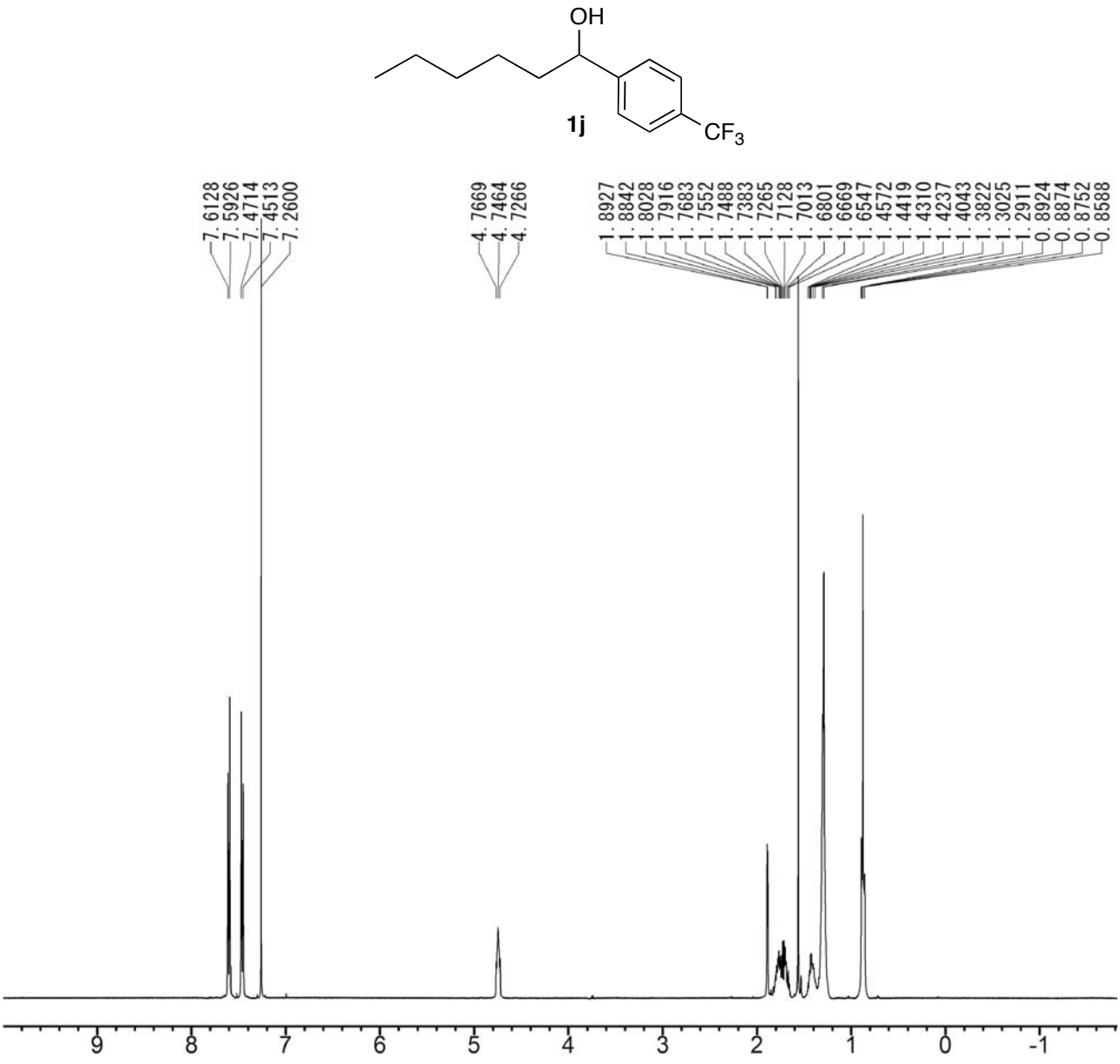


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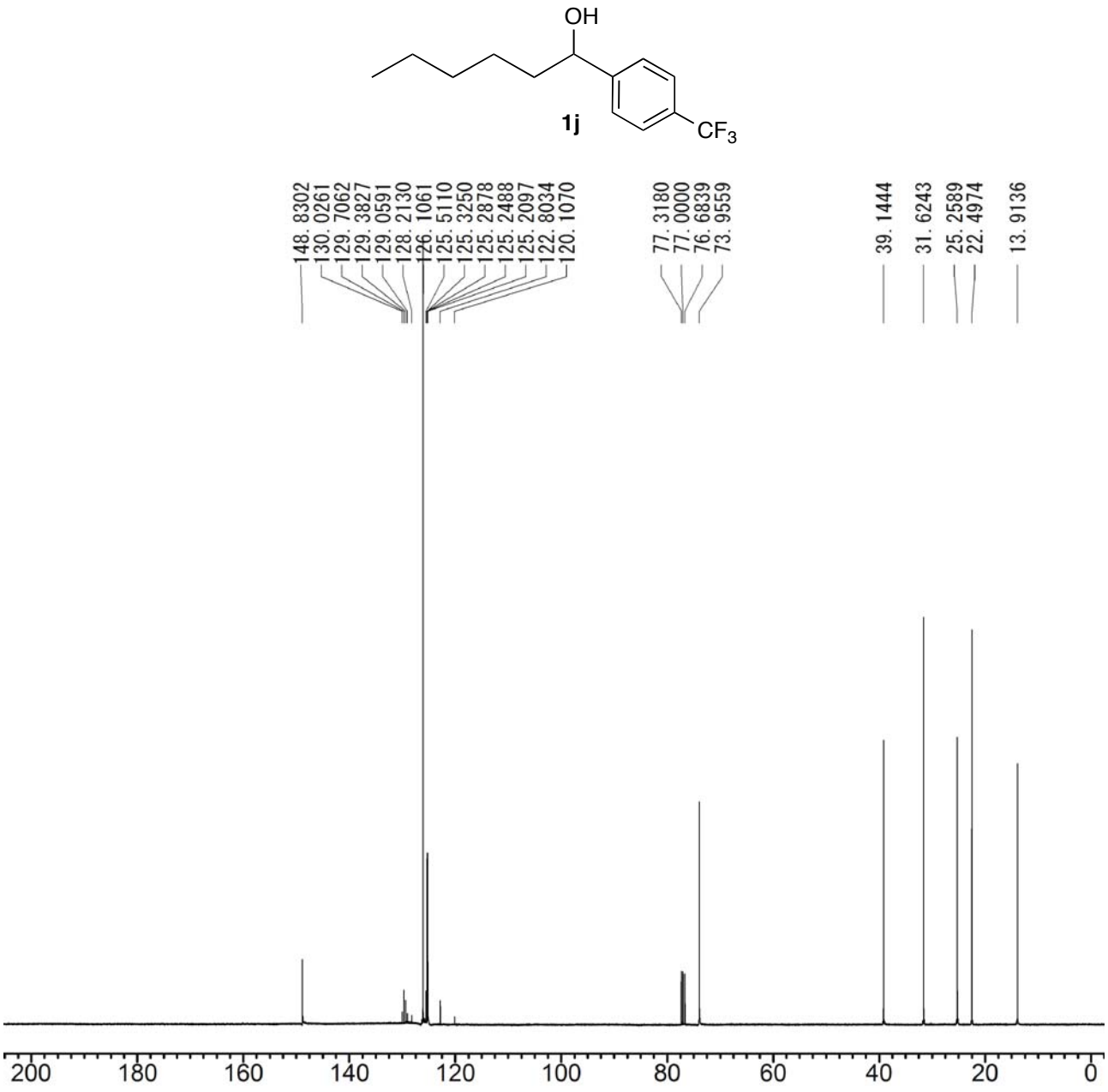


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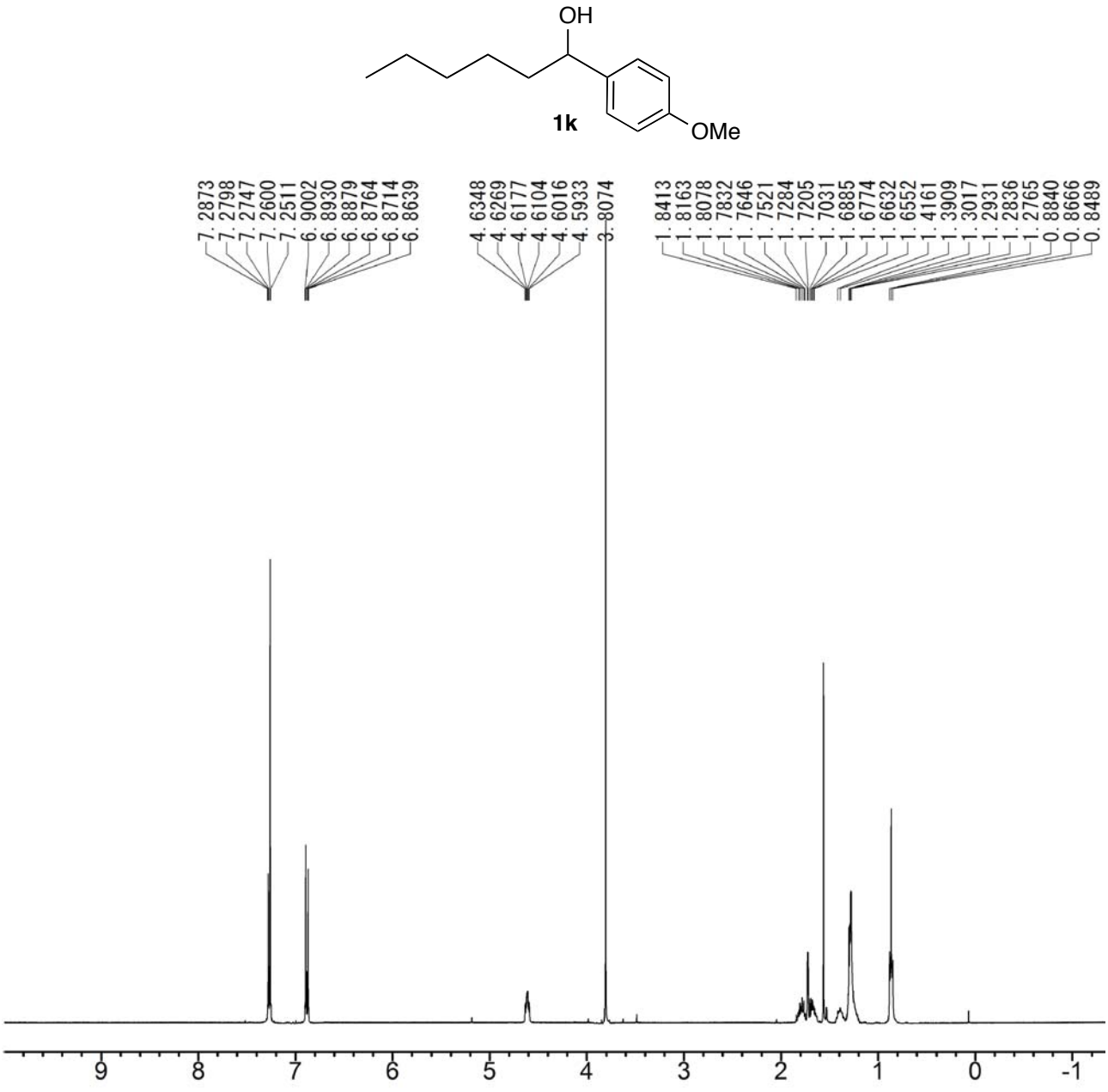


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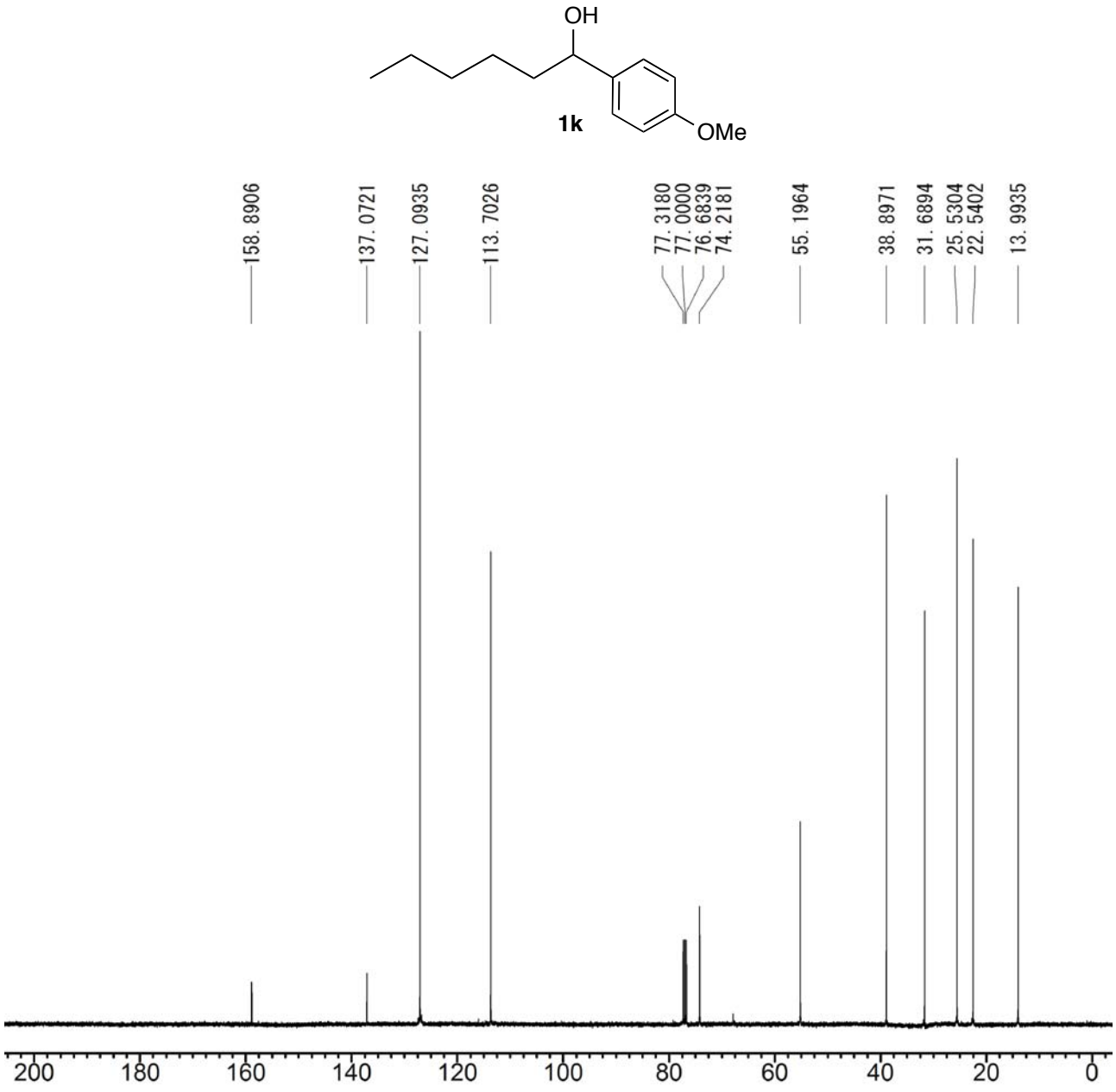


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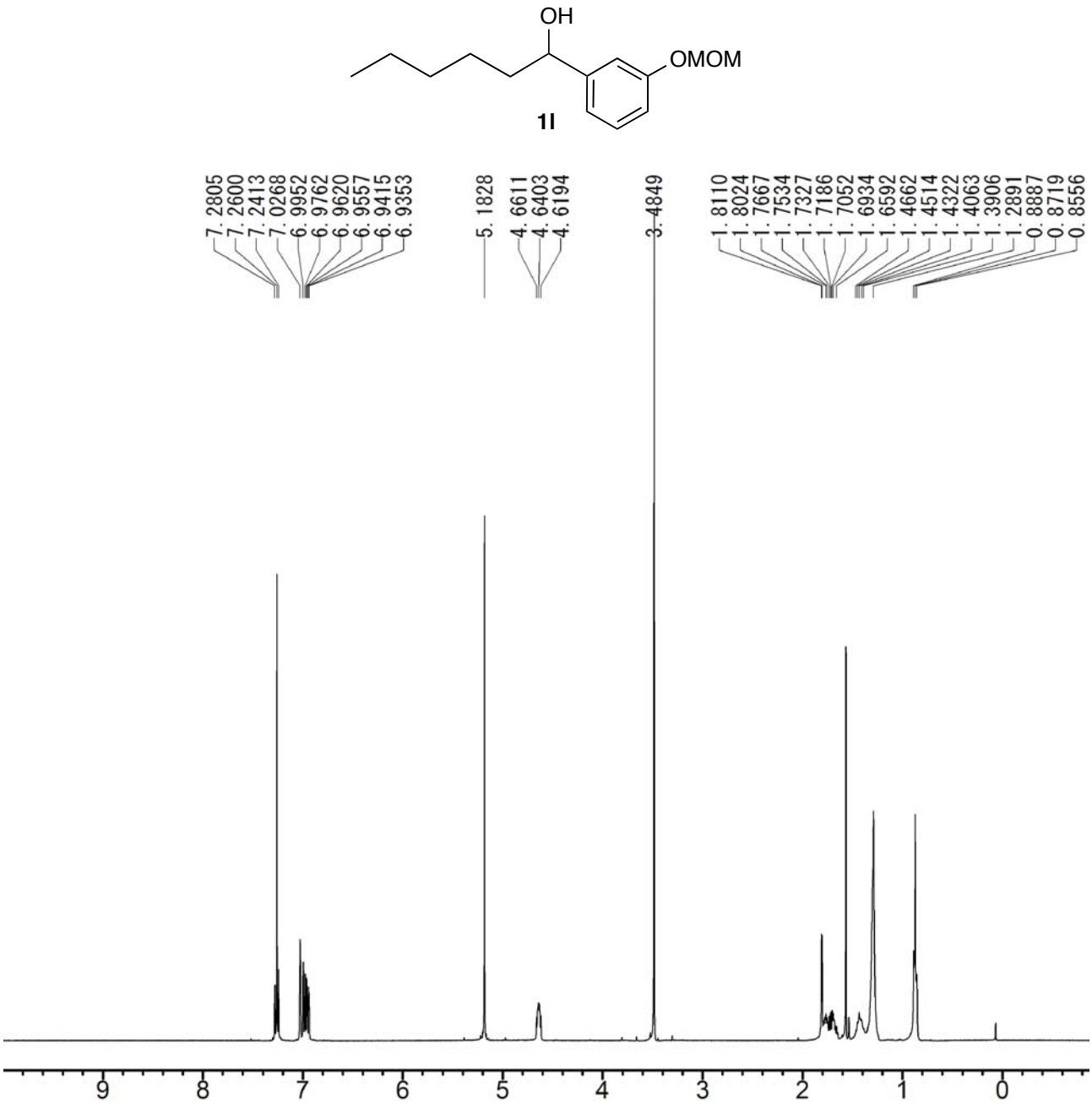


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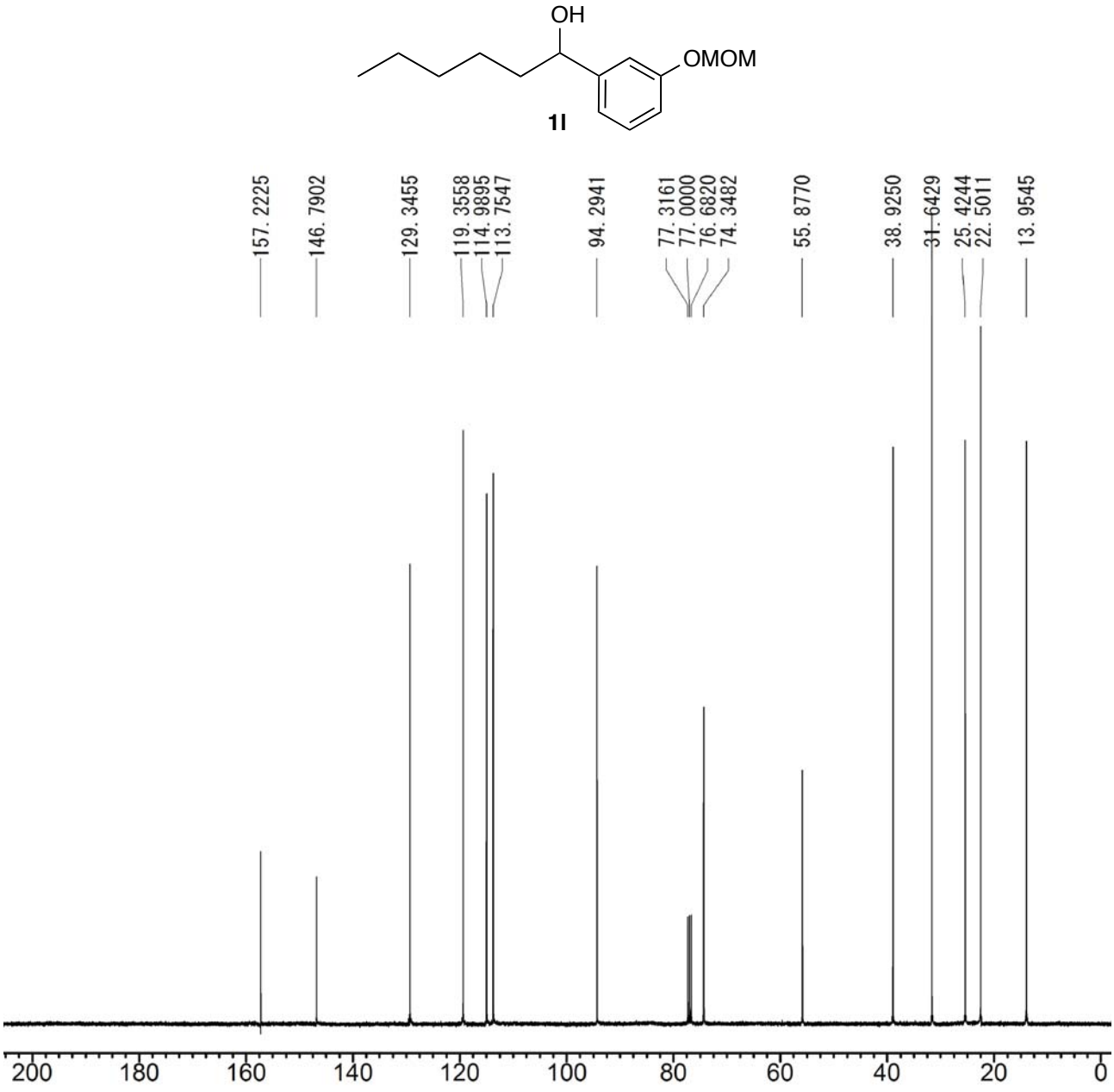


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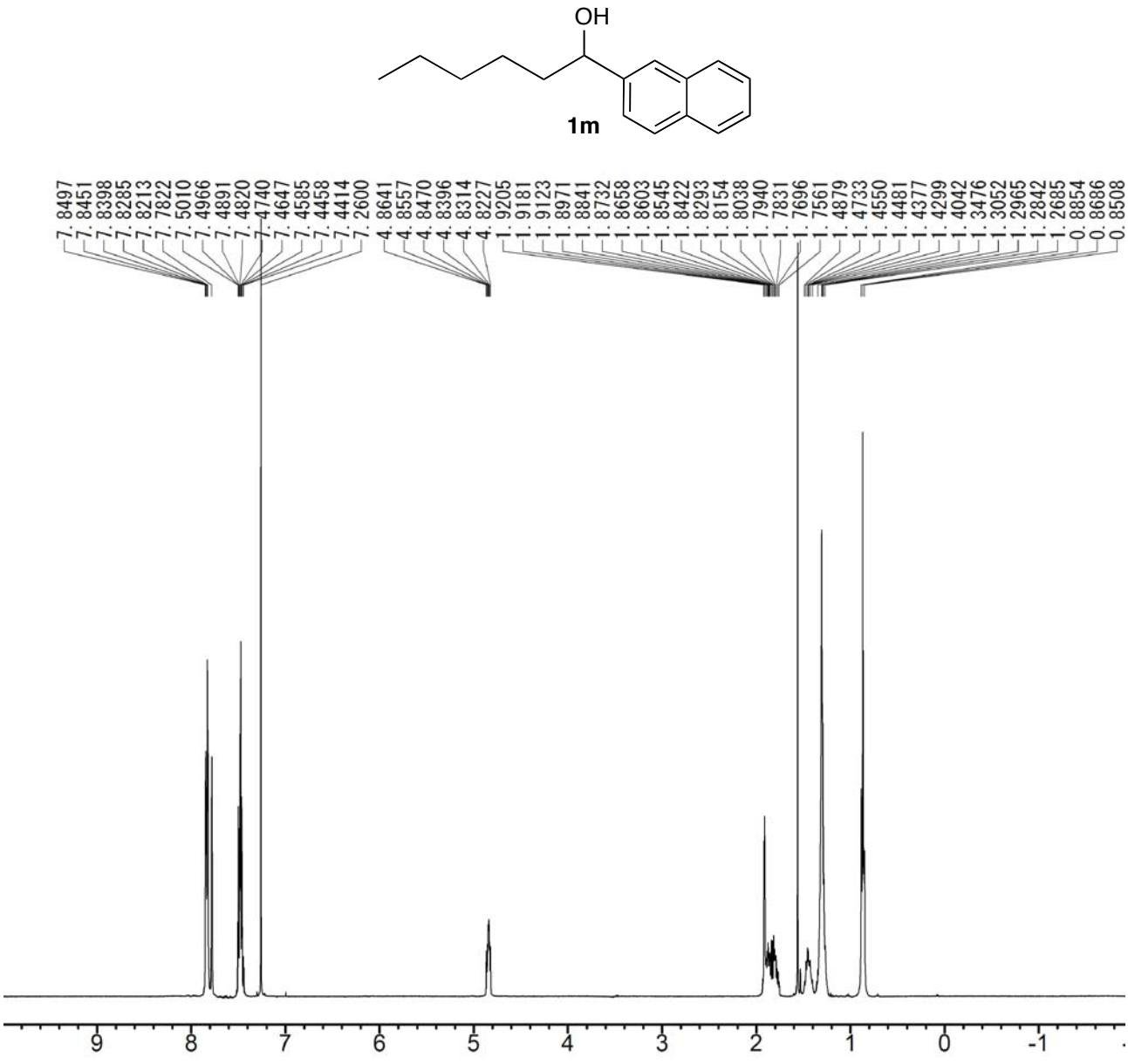


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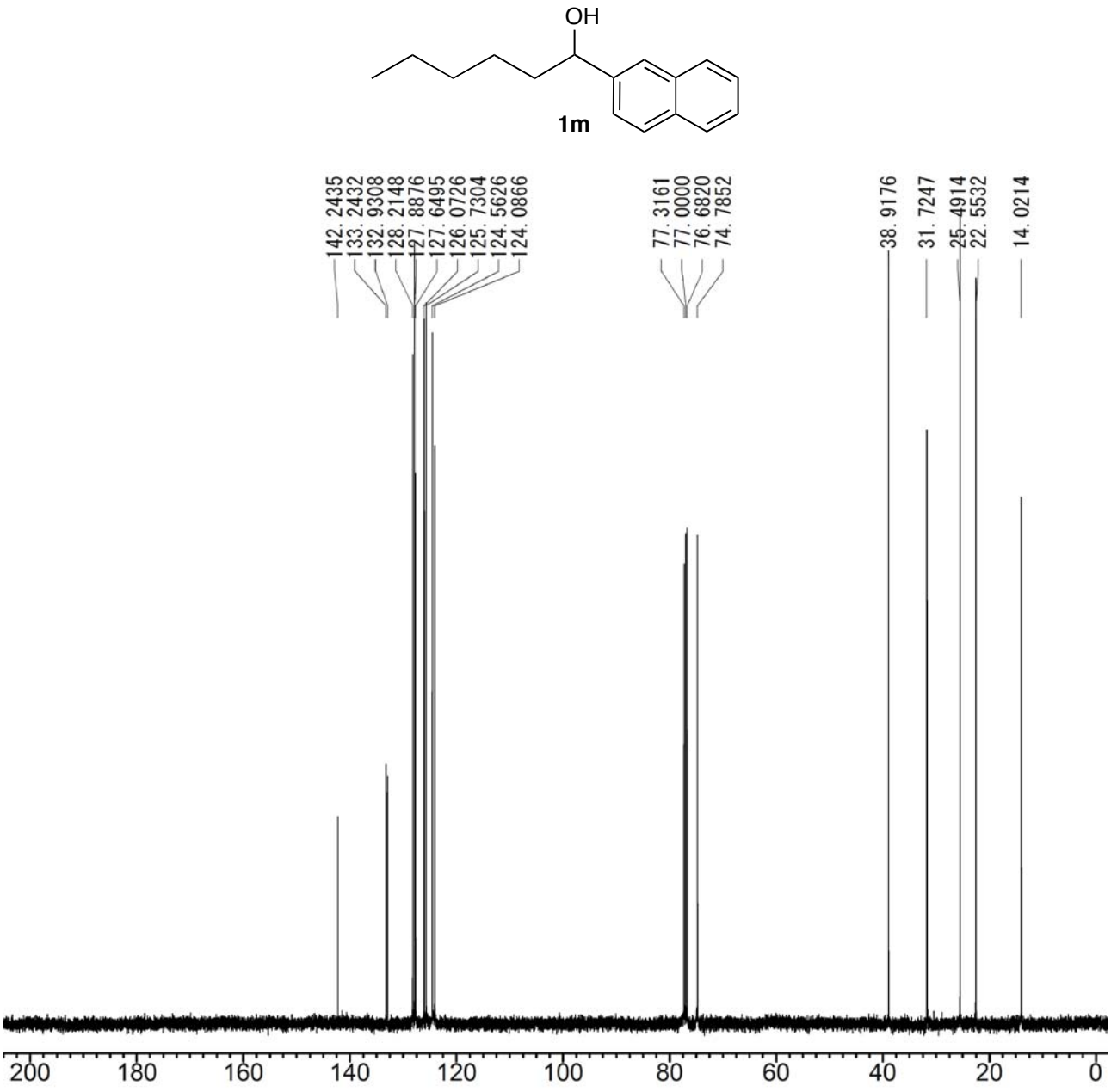


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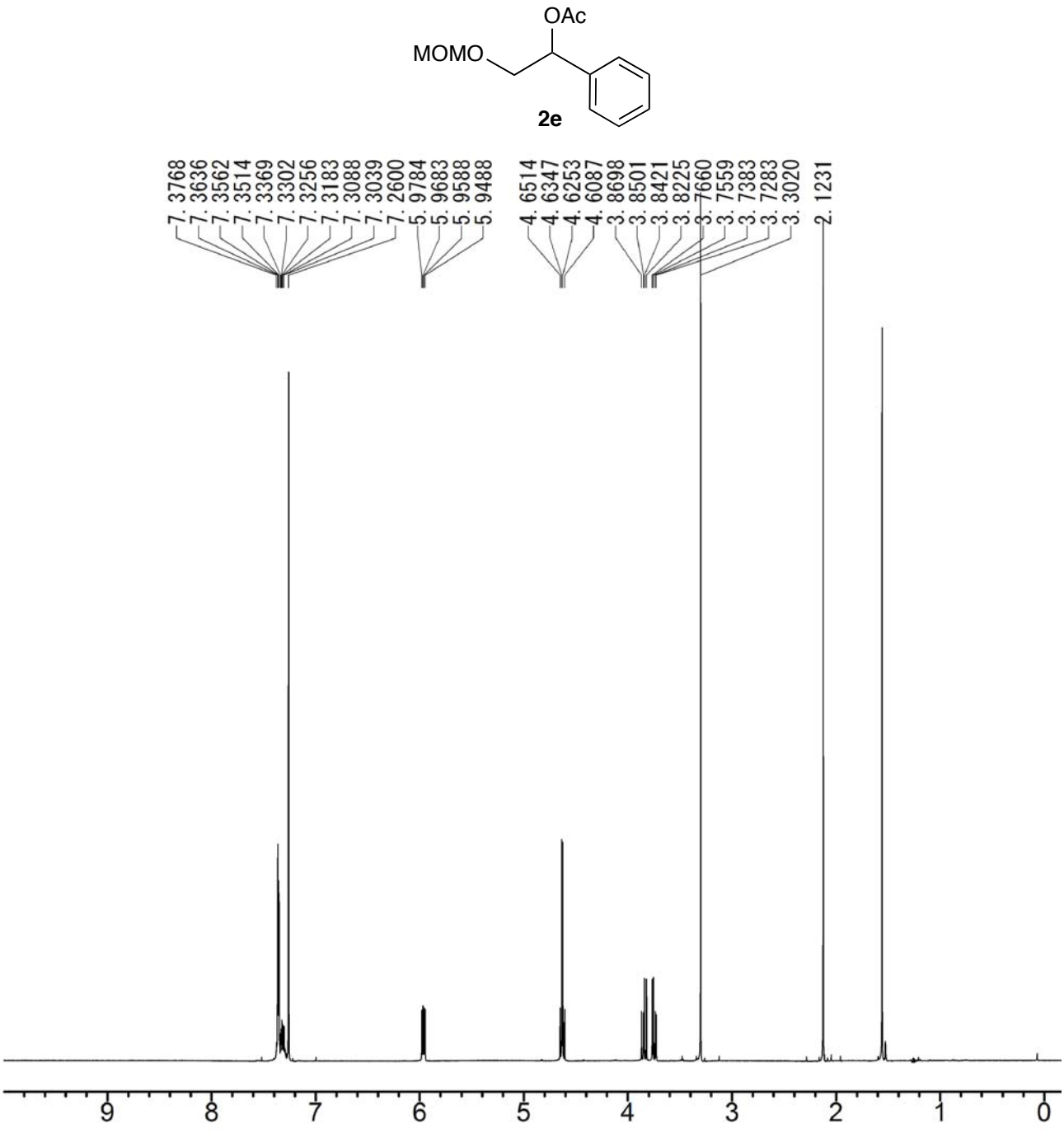


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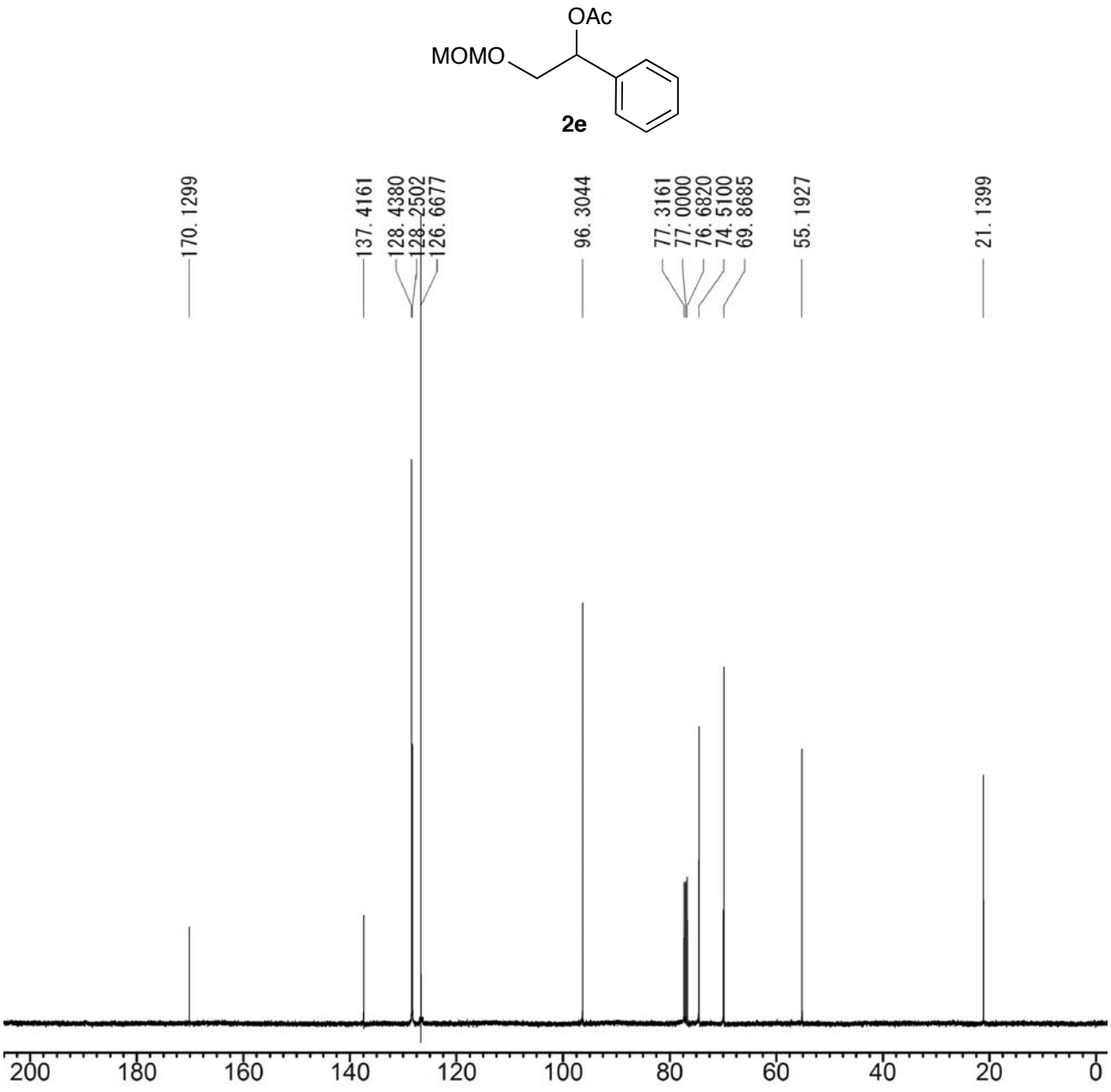


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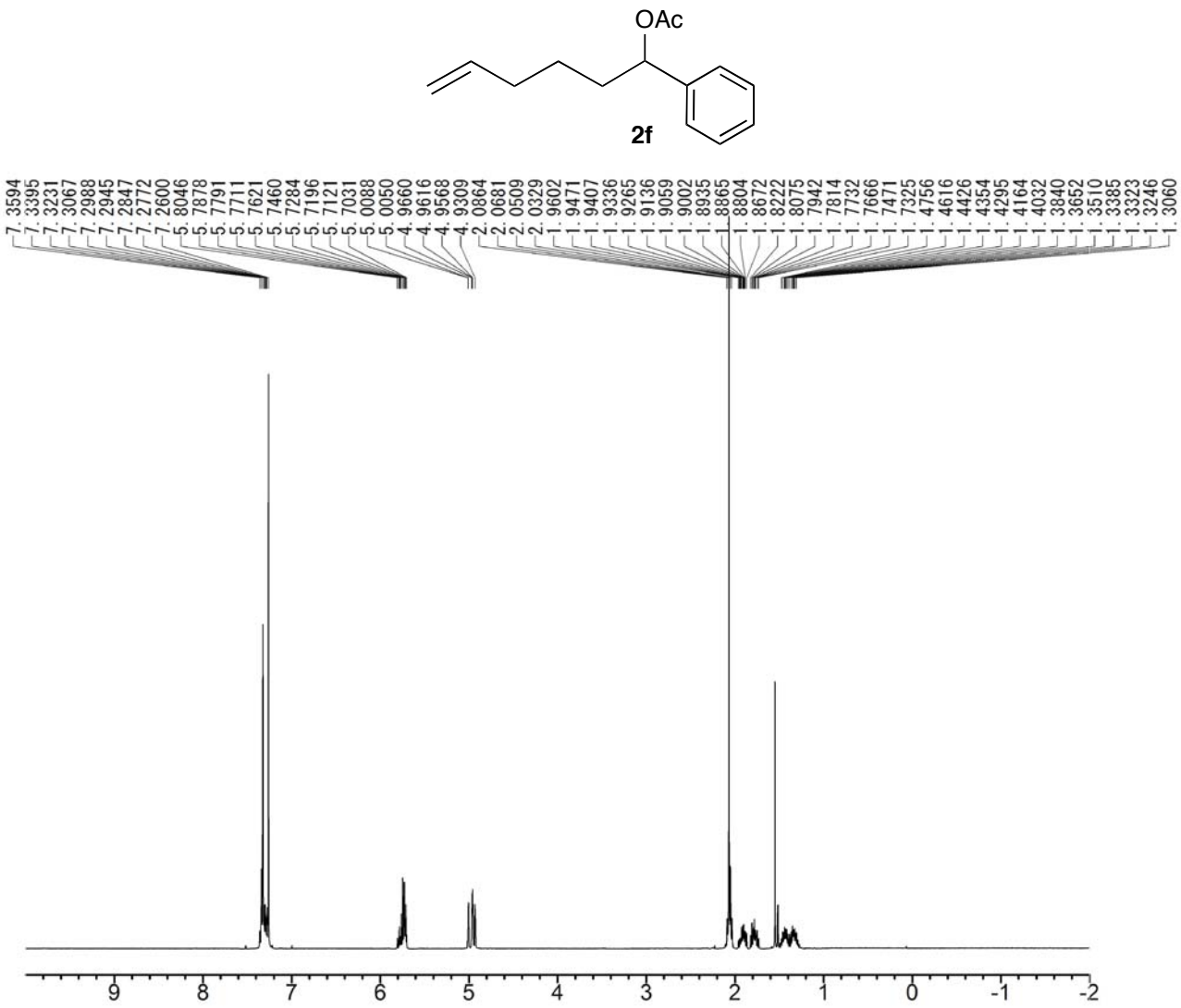


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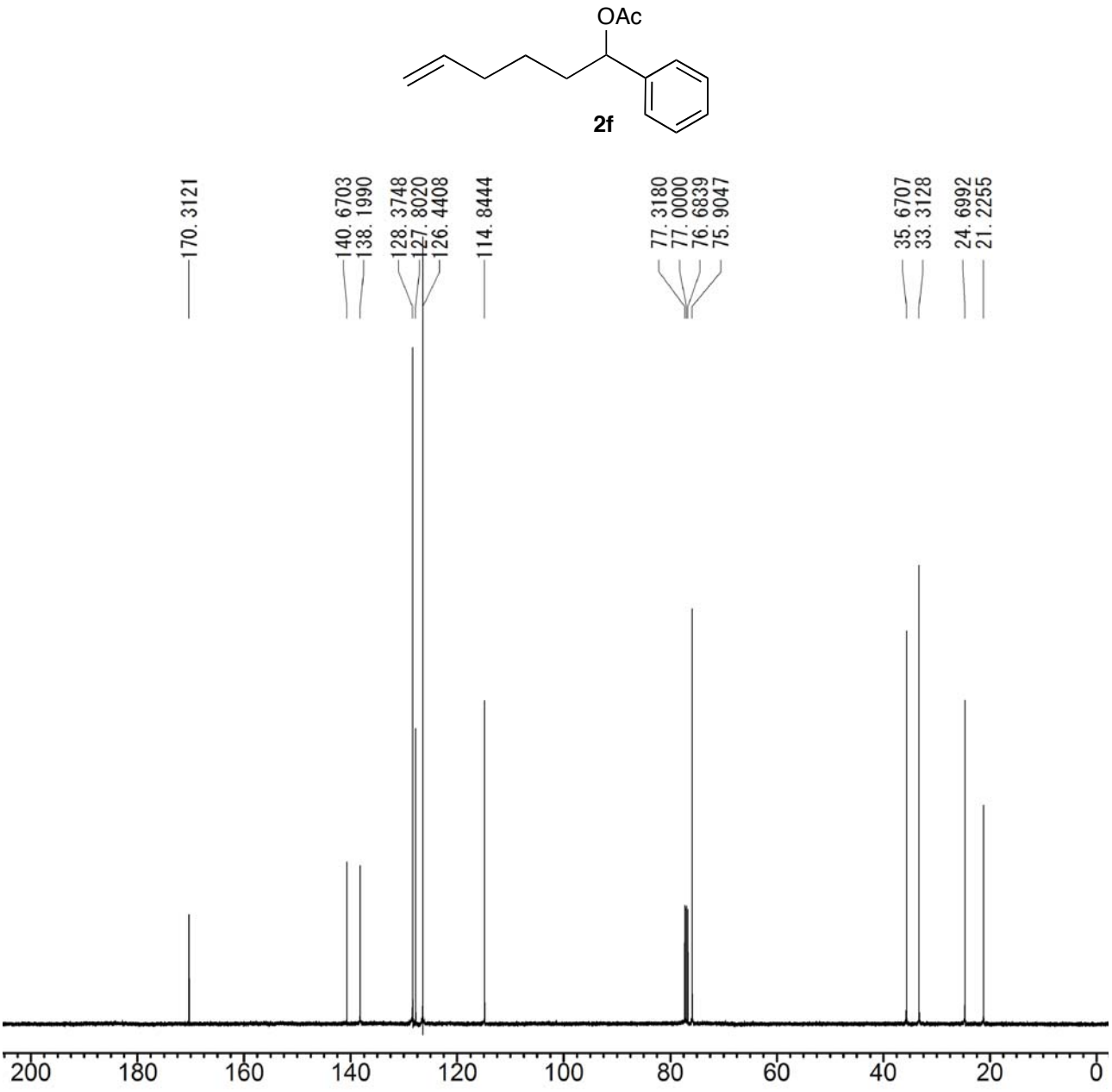


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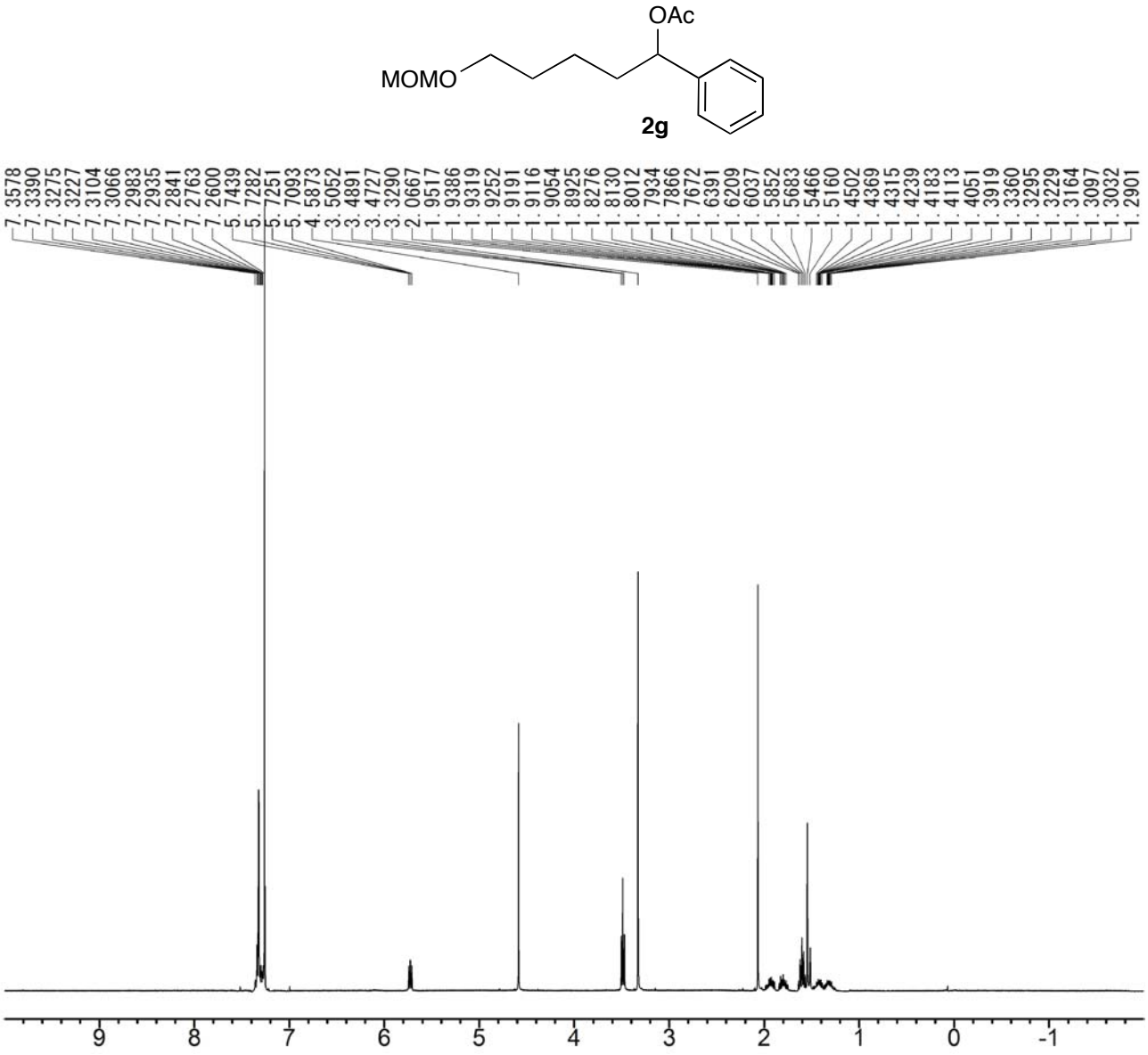


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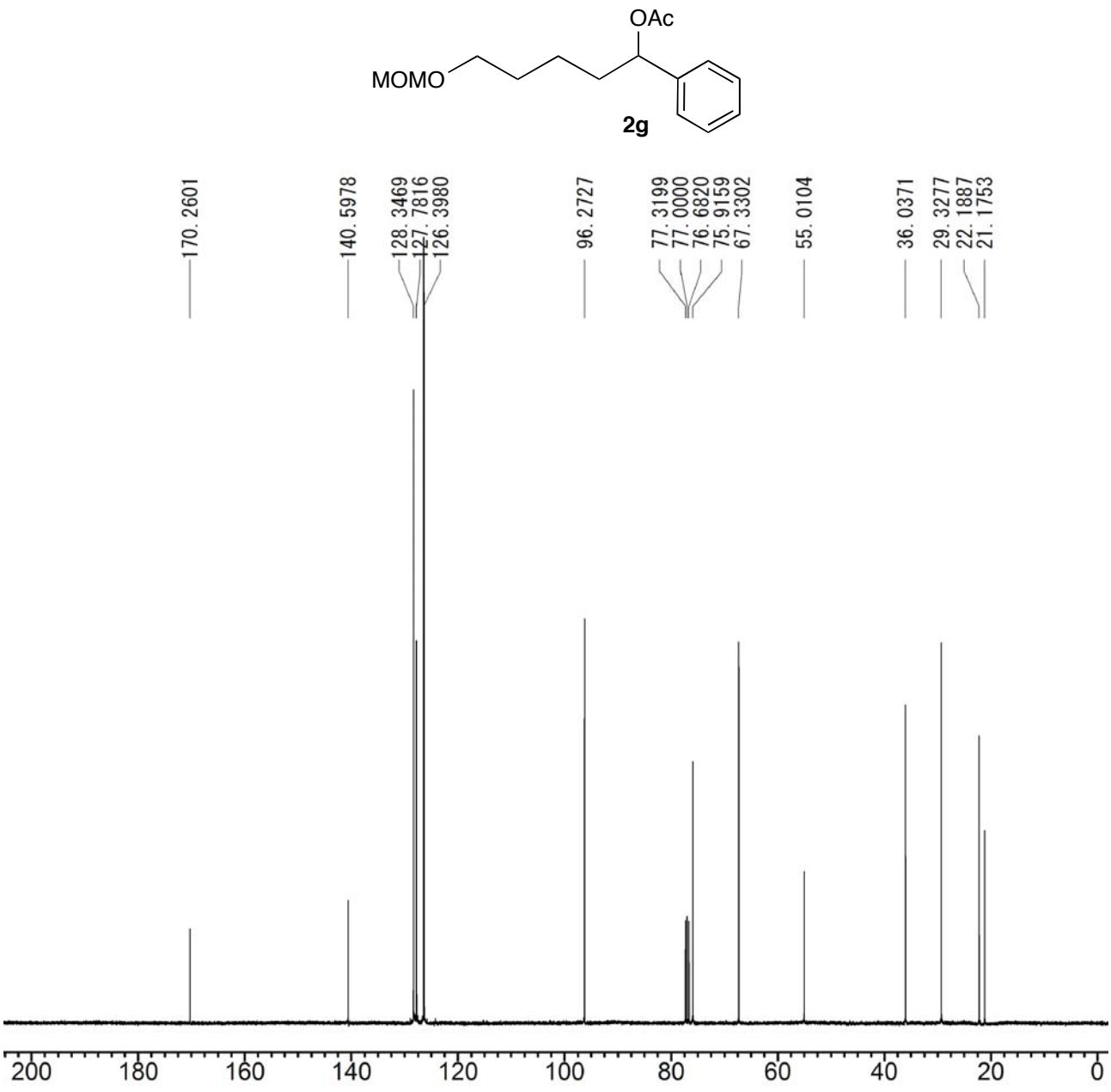


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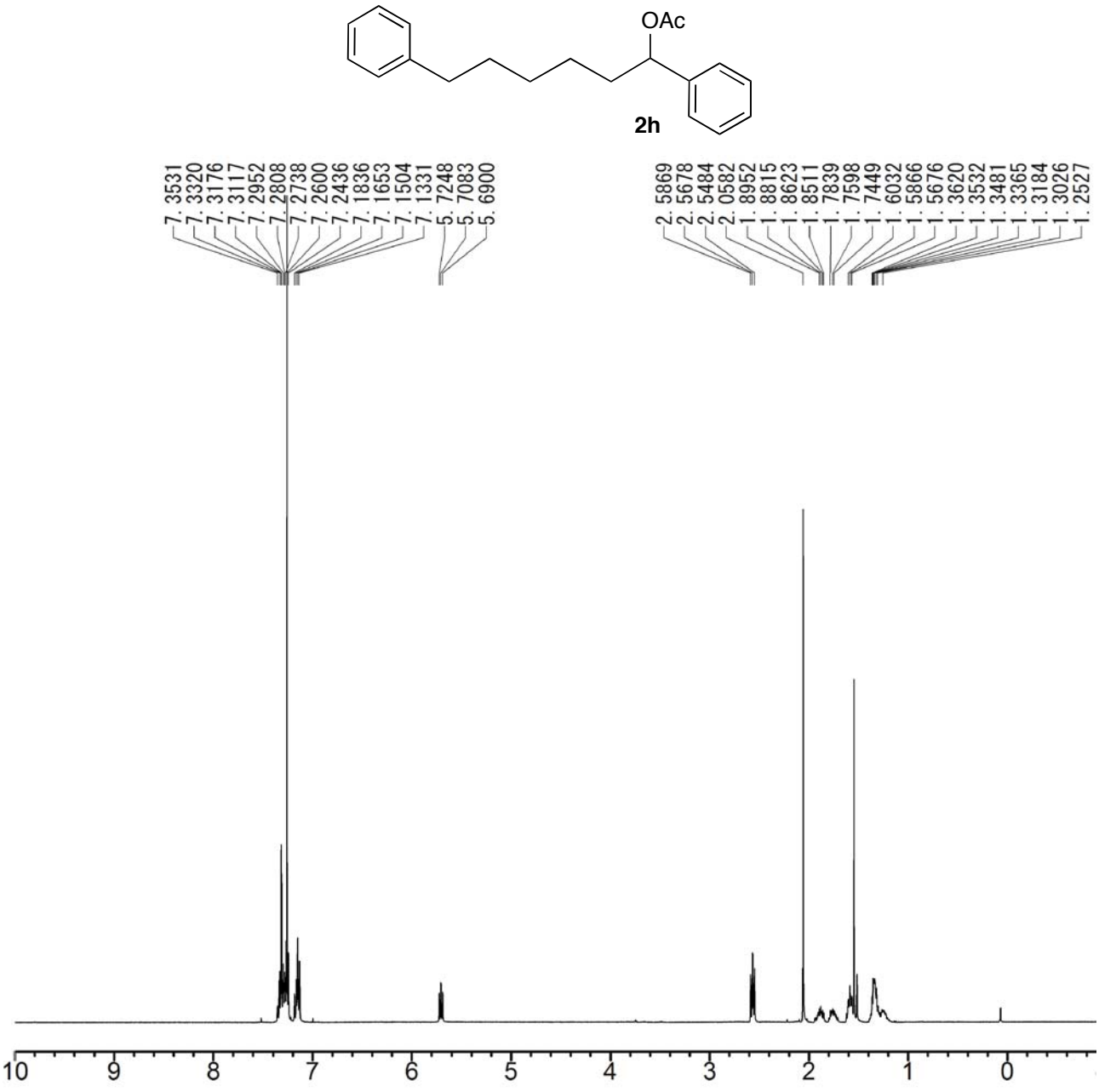


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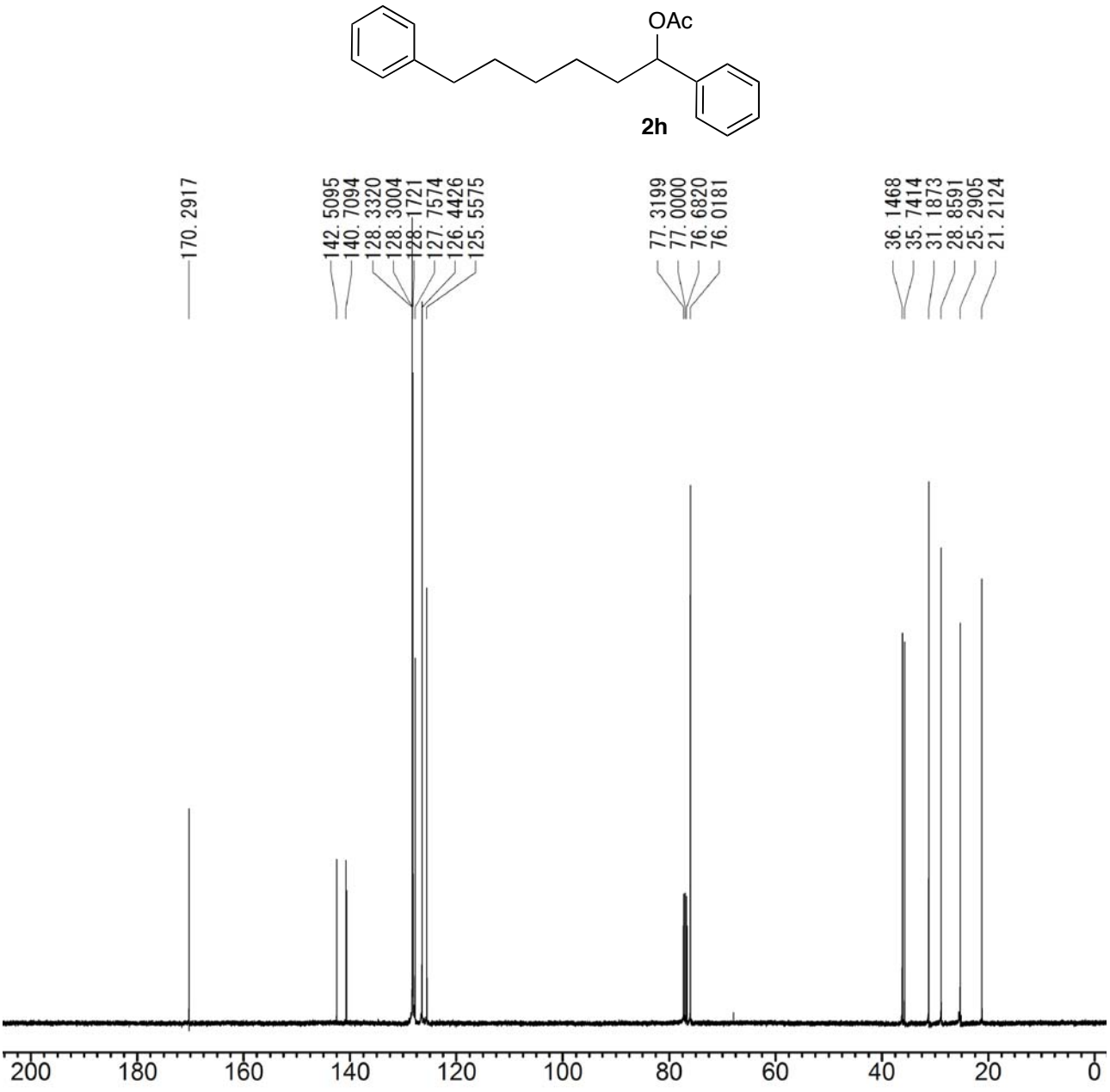


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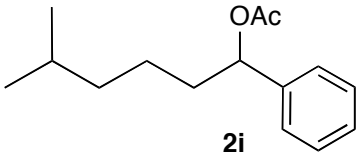
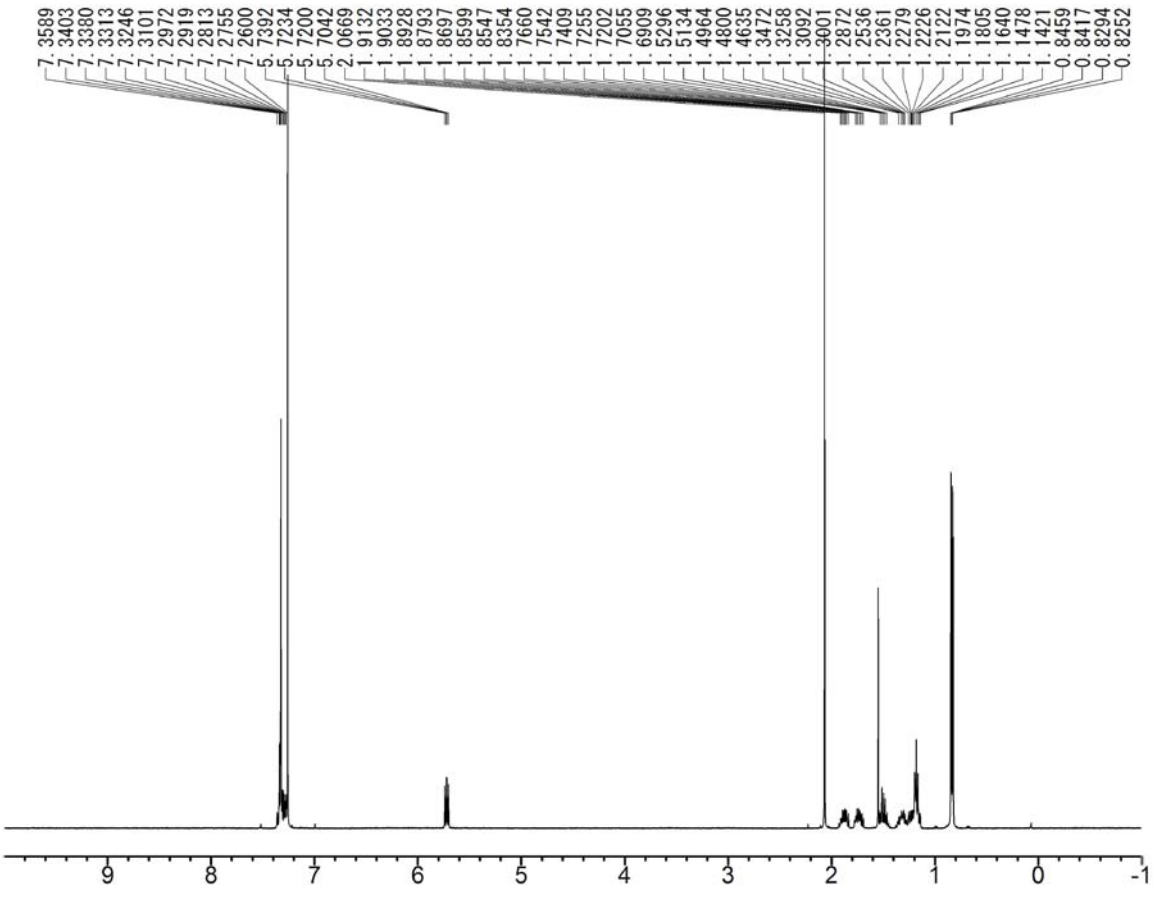



**2i**

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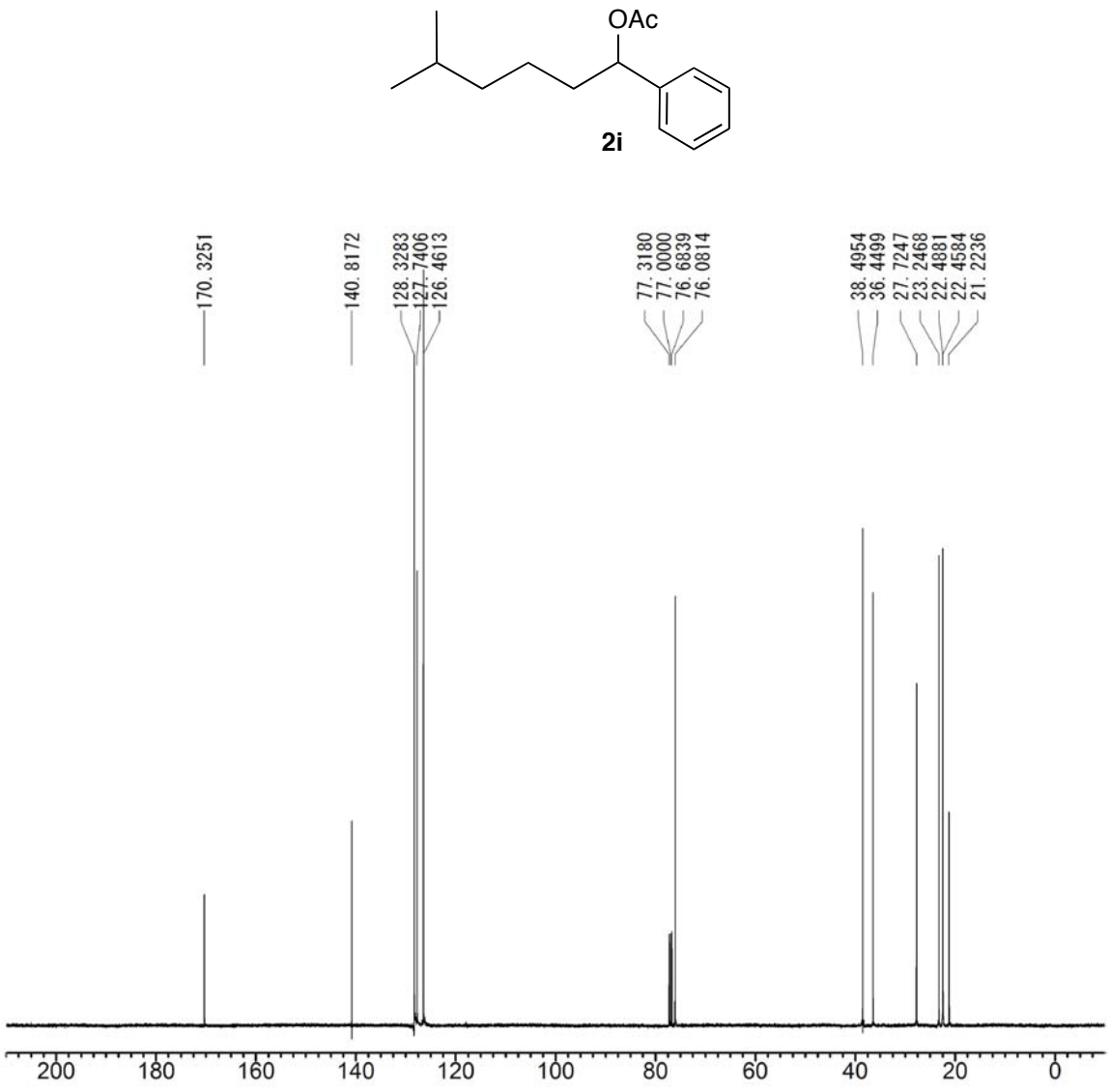


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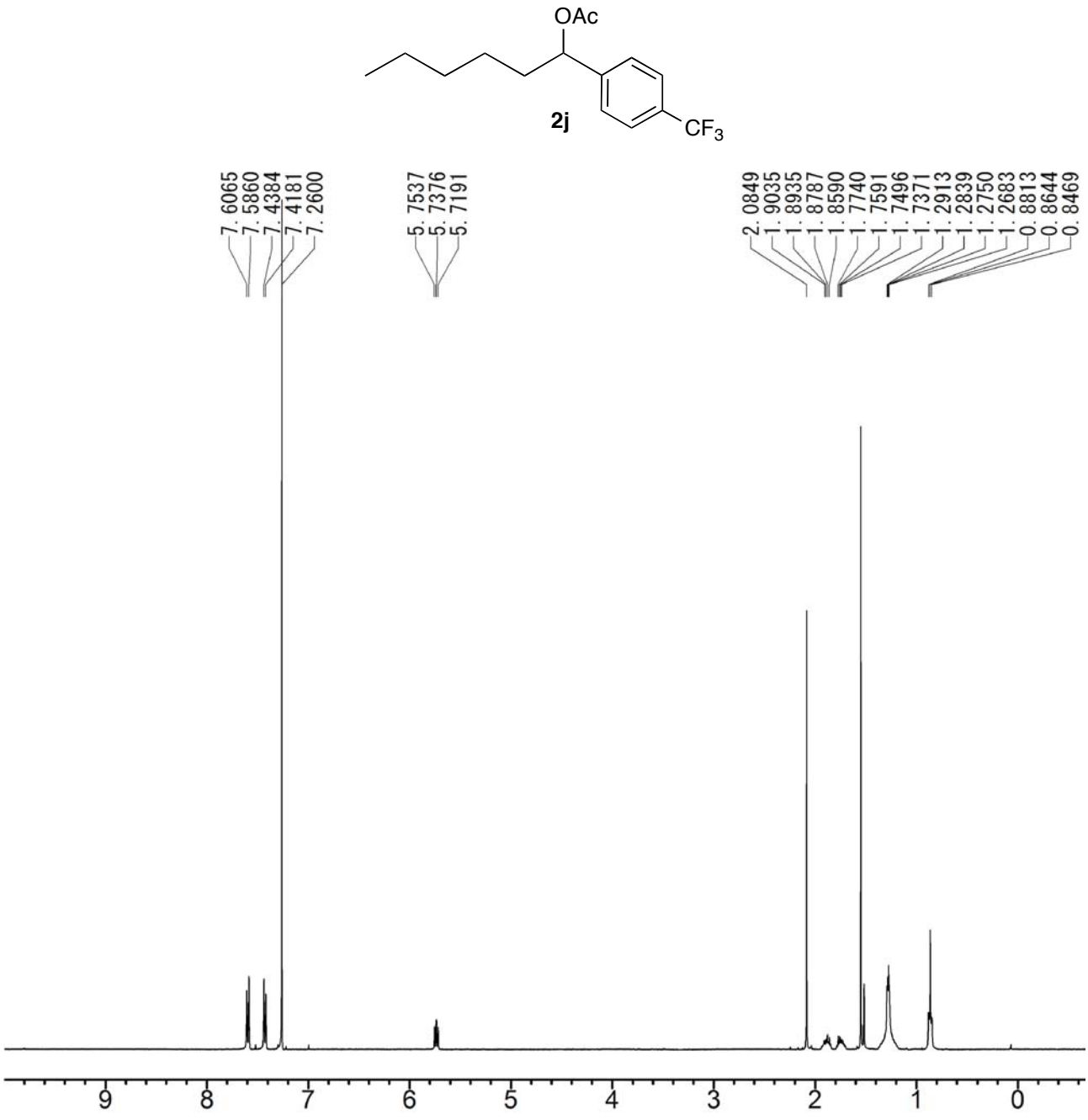


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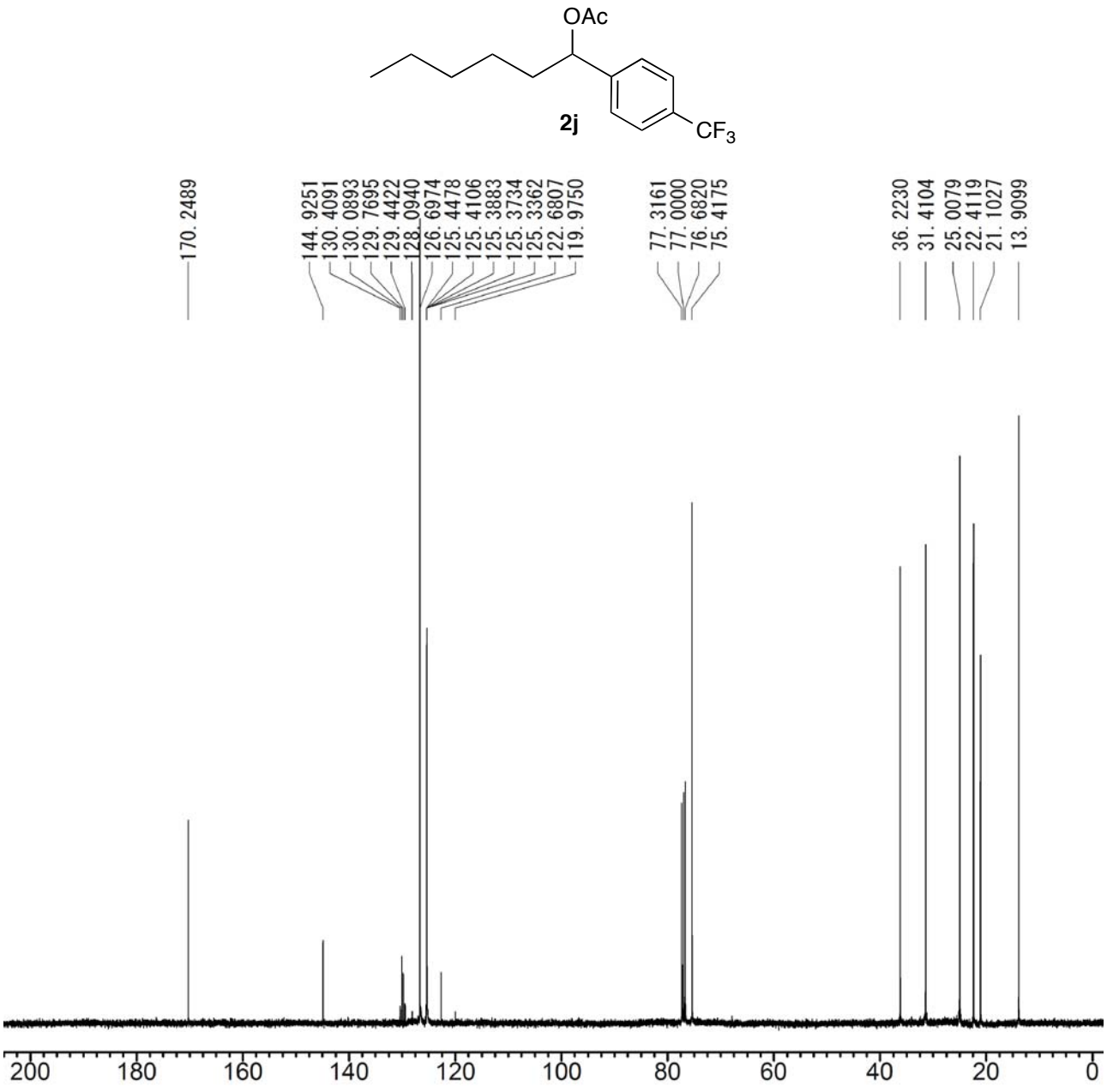


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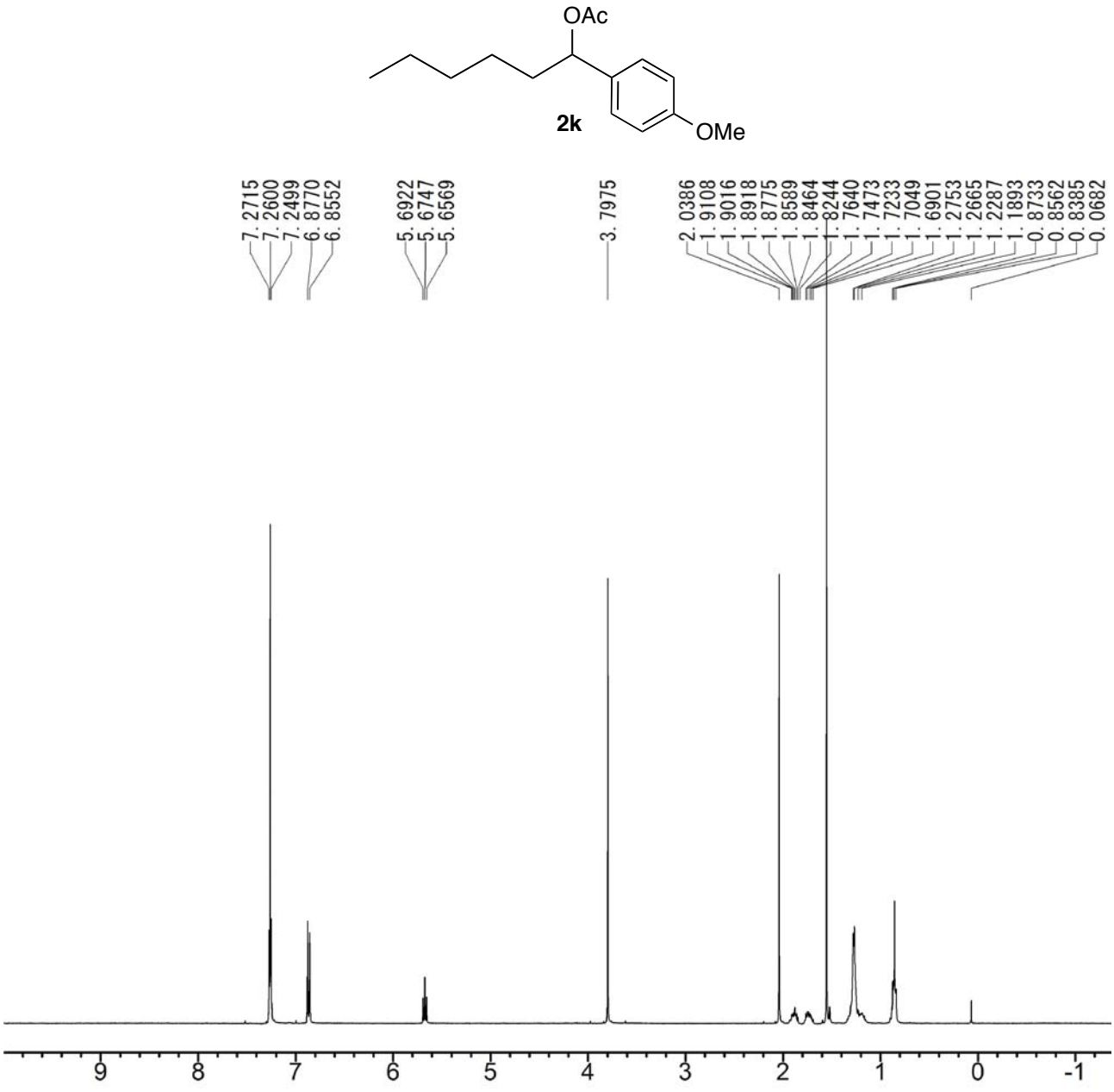


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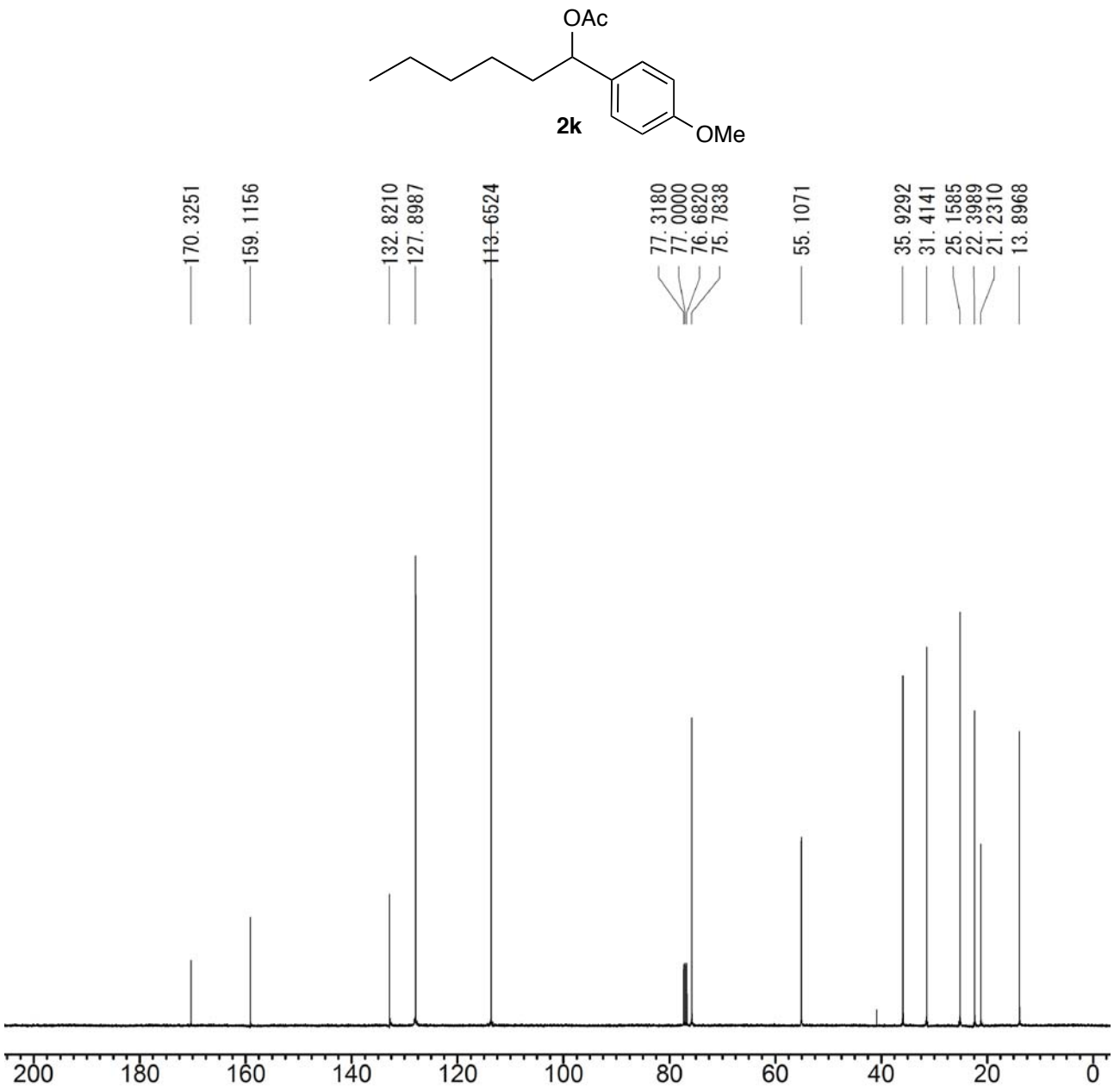


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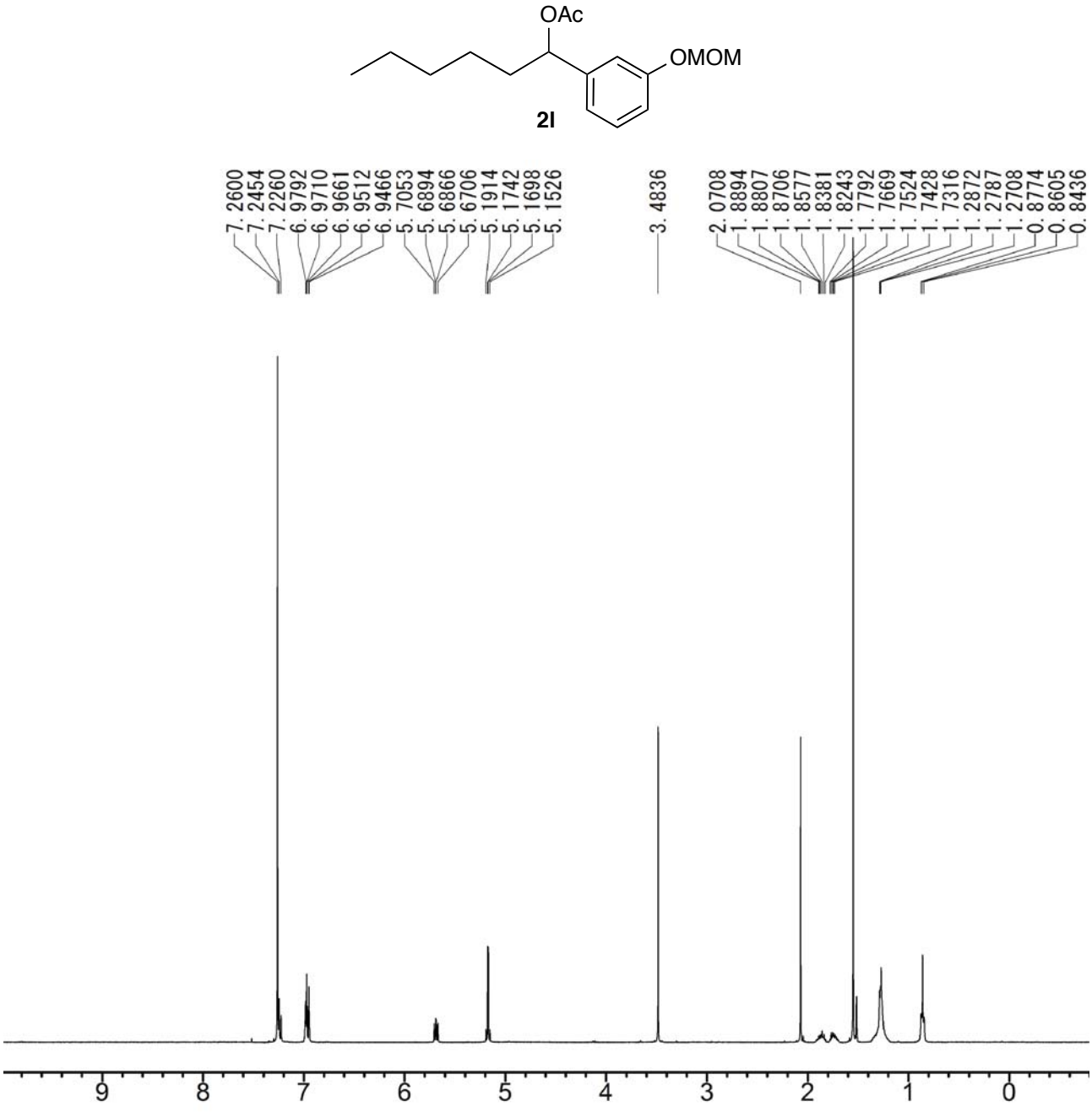


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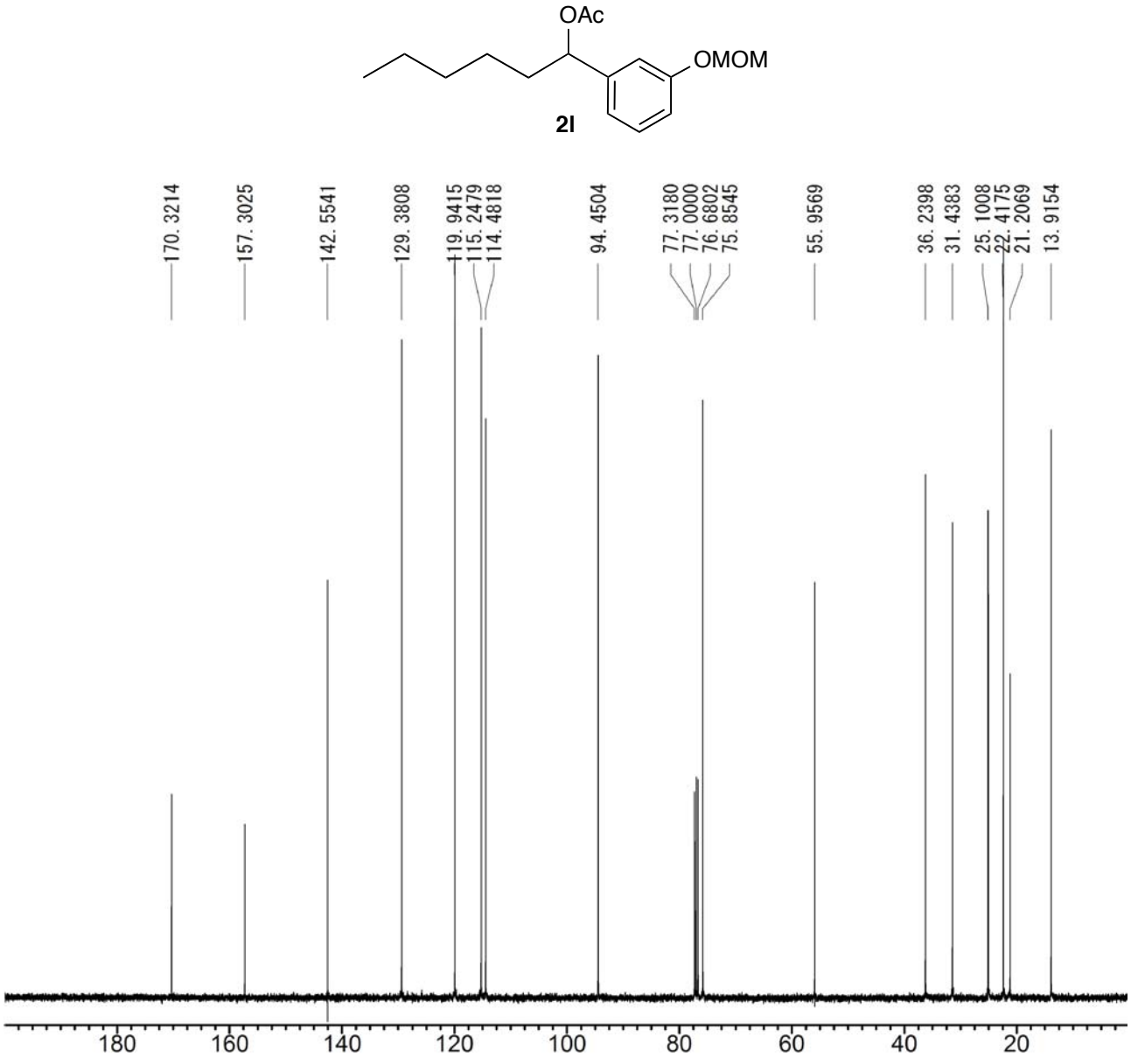


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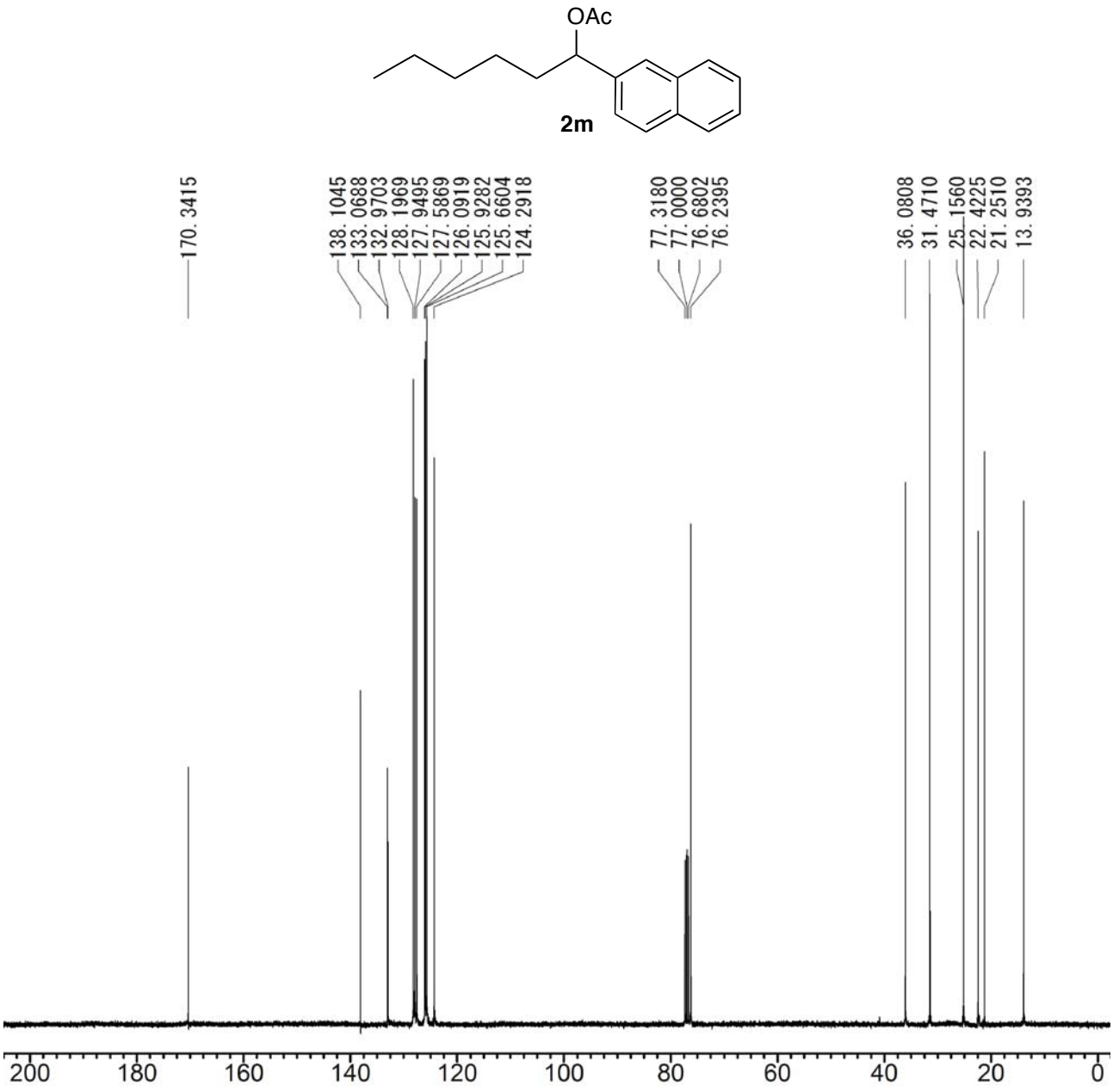
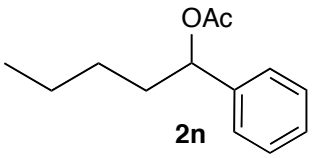
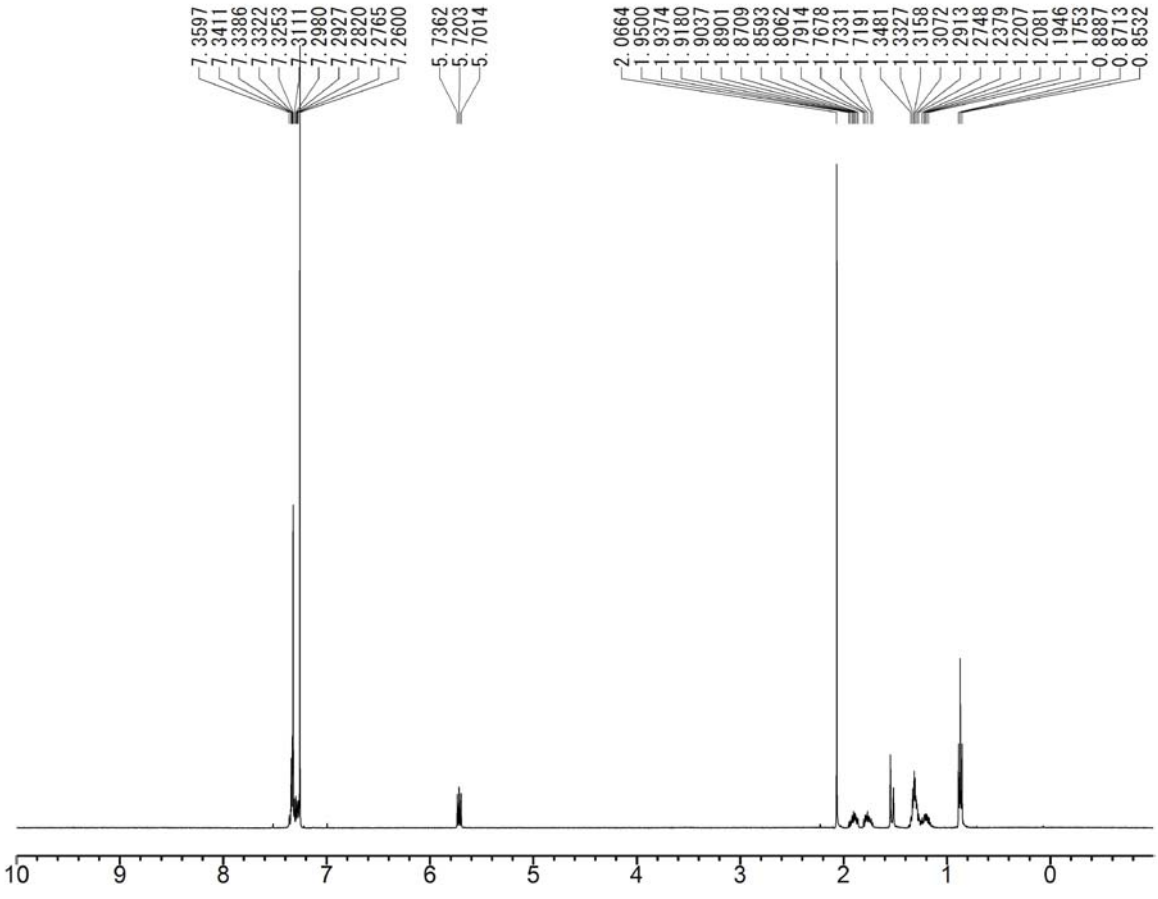
400 MHz $^{1}$H NMR of **2m** in $CDCl_3$.



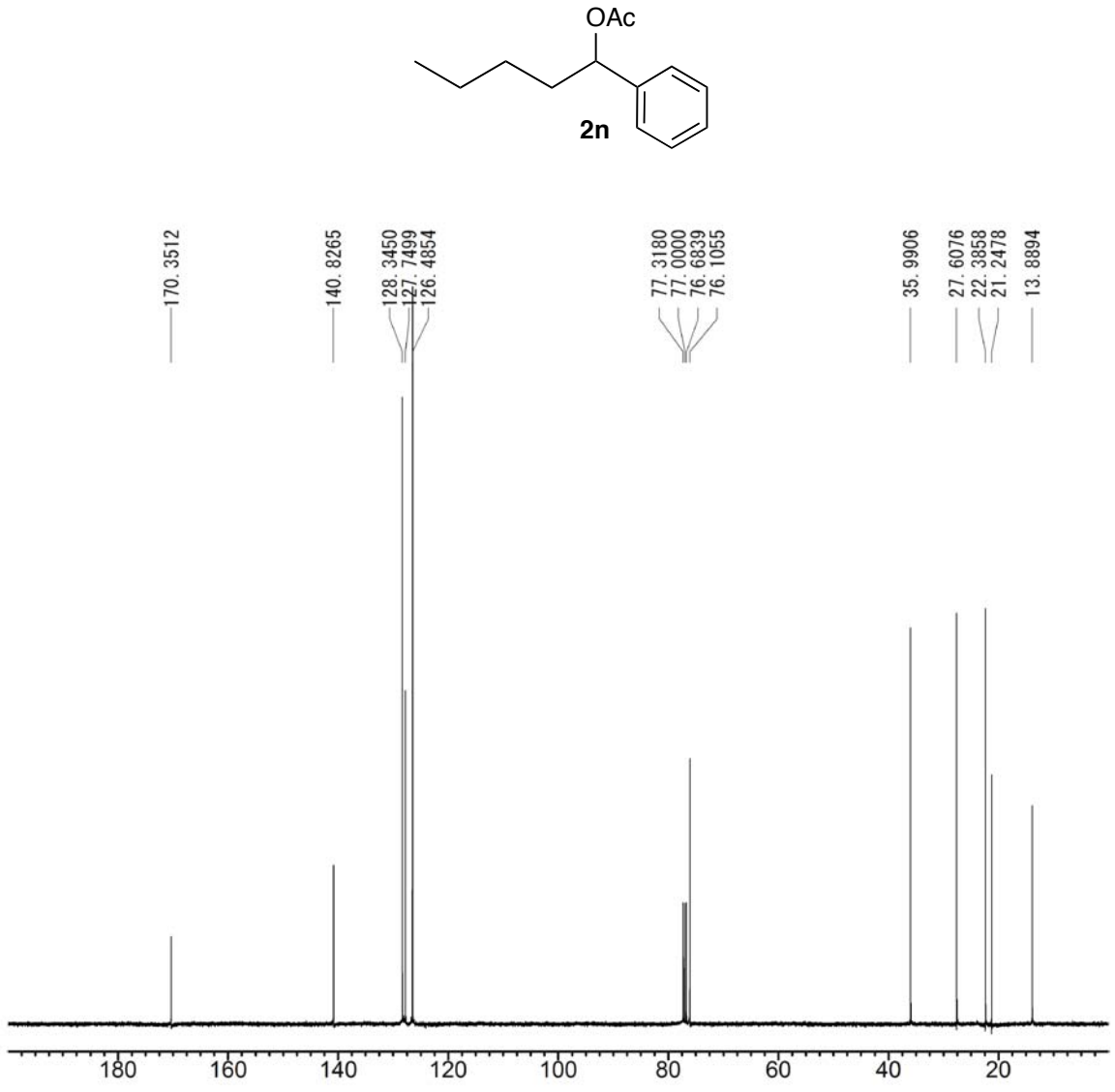

100 MHz $^{13}C$ NMR of **2m** in $CDCl_3$.



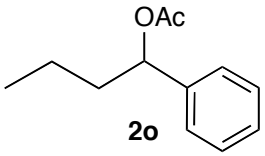

**2n**



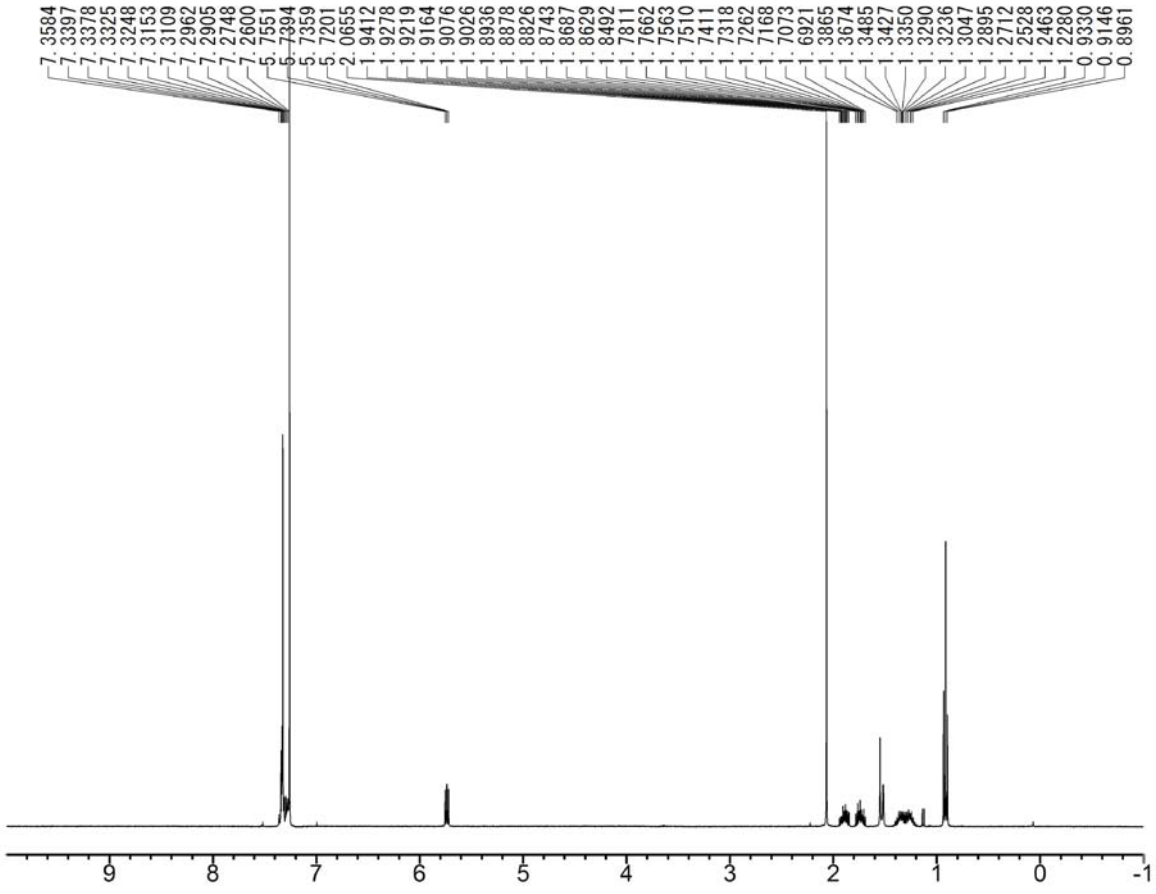

400 MHz $^{1}$H NMR of **2n** in $CDCl_3$.



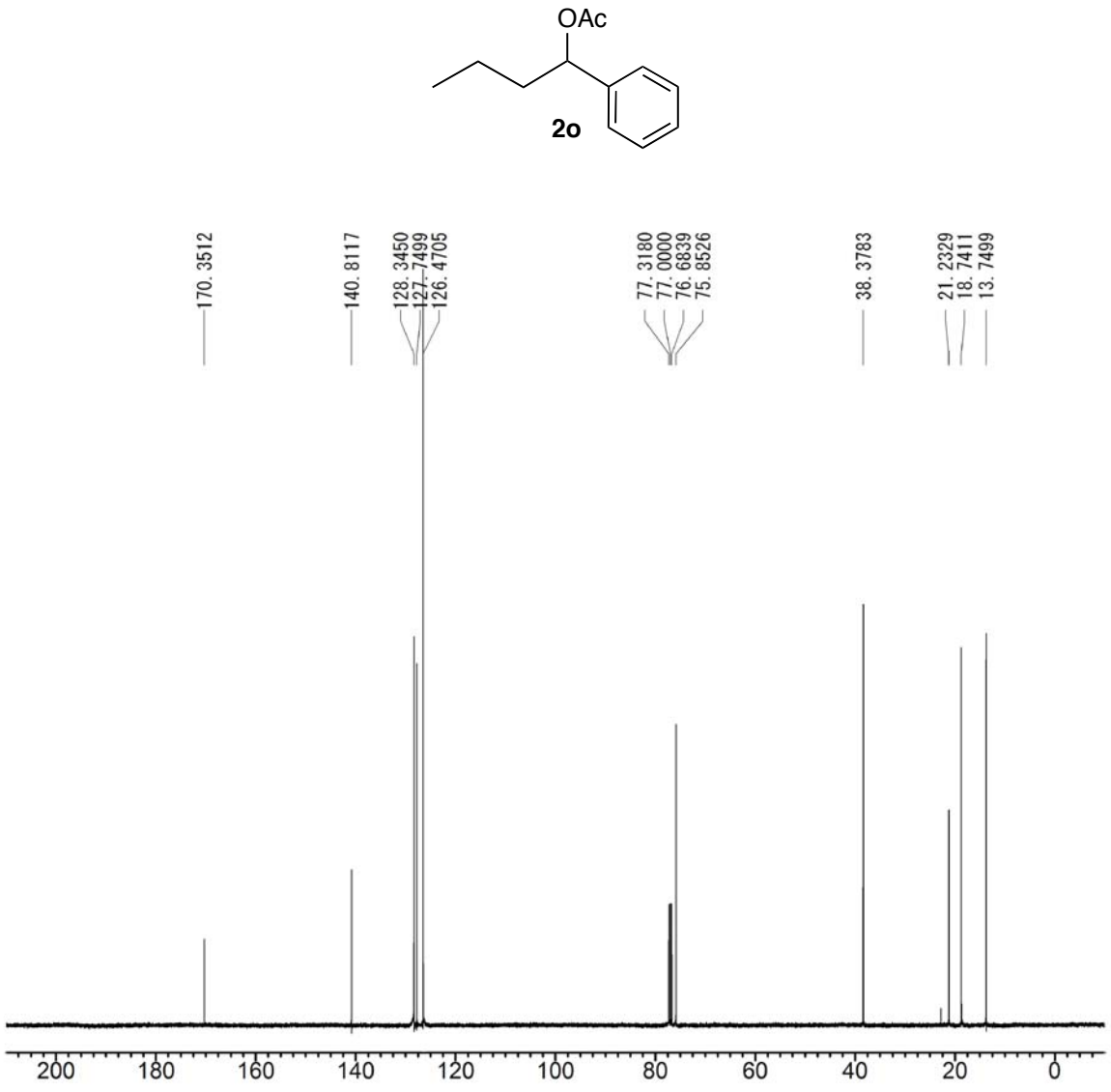

100 MHz $^{13}C$ NMR of **2n** in $CDCl_3$.



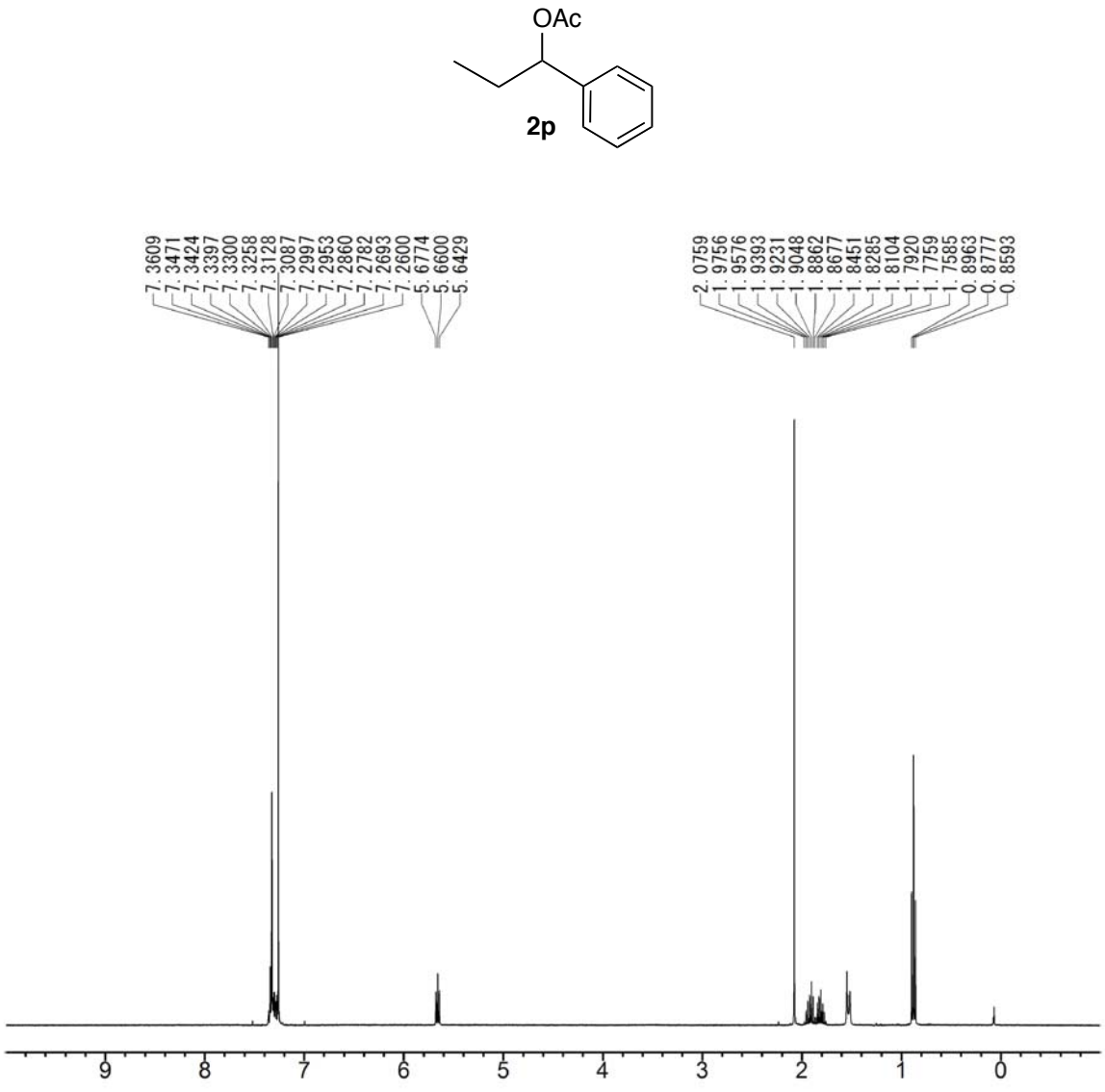

**2o**



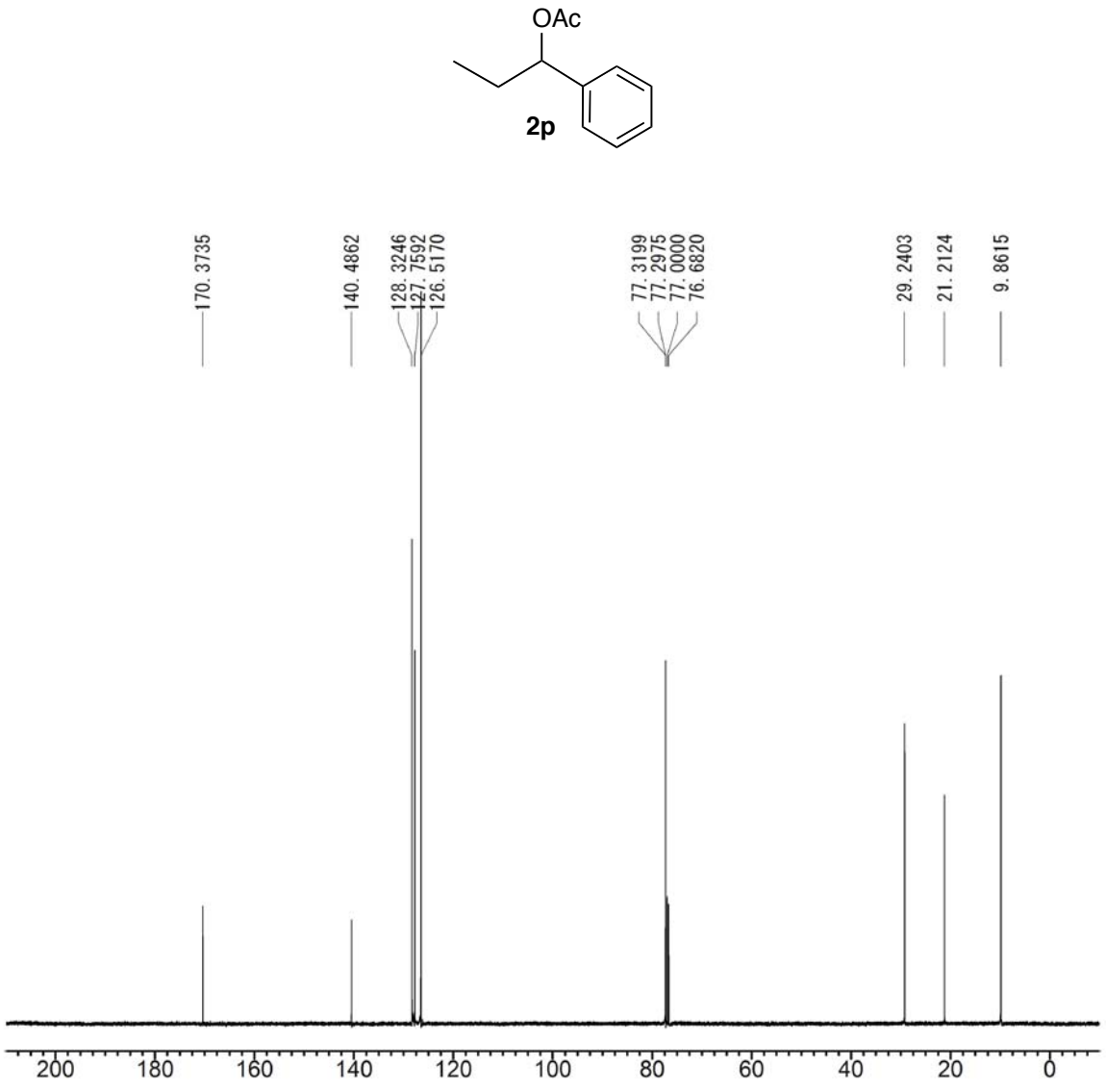

400 MHz $^{1}$H NMR of **2o** in $CDCl_3$.



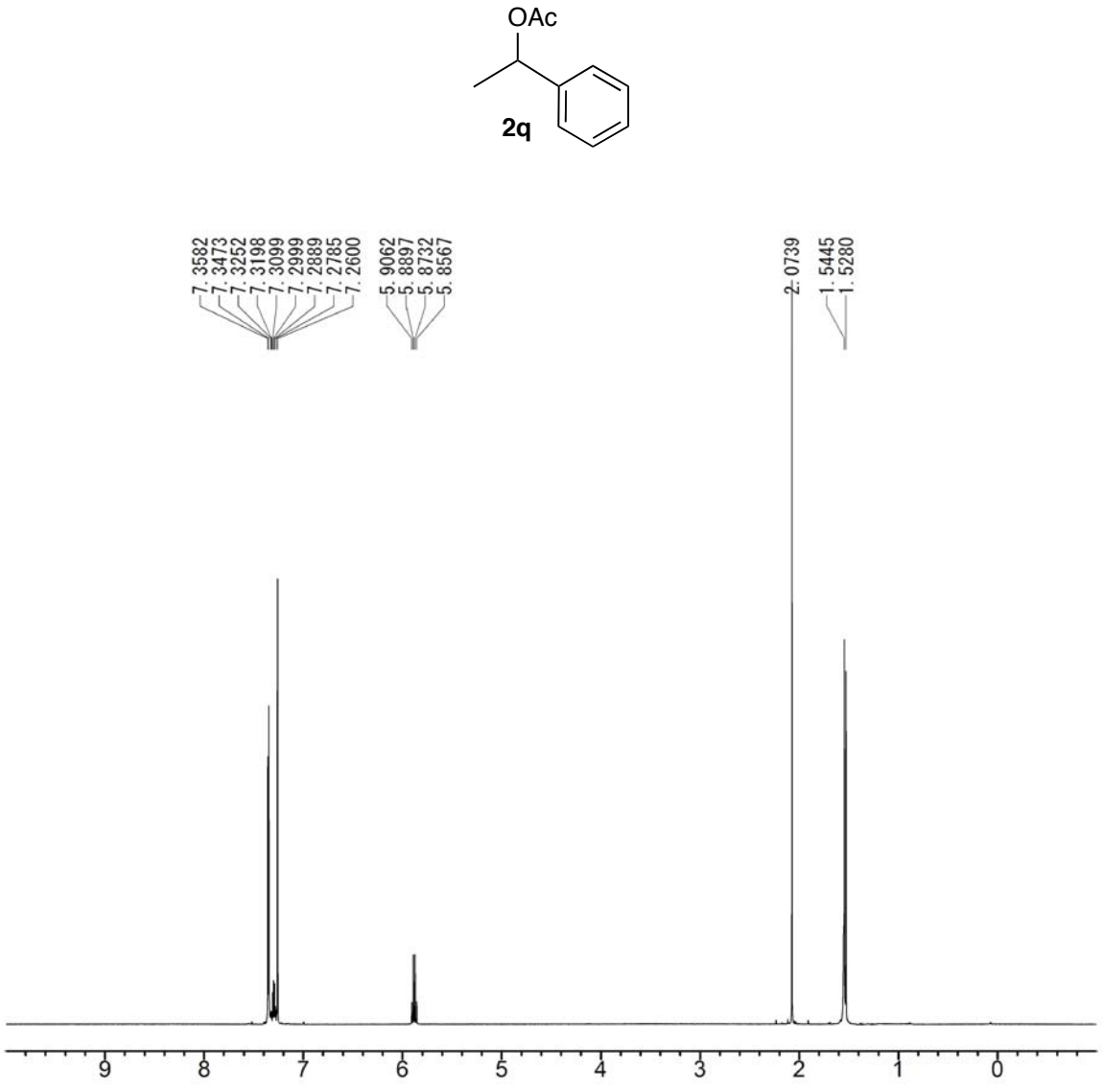

100 MHz $^{13}C$ NMR of **2o** in $CDCl_3$.



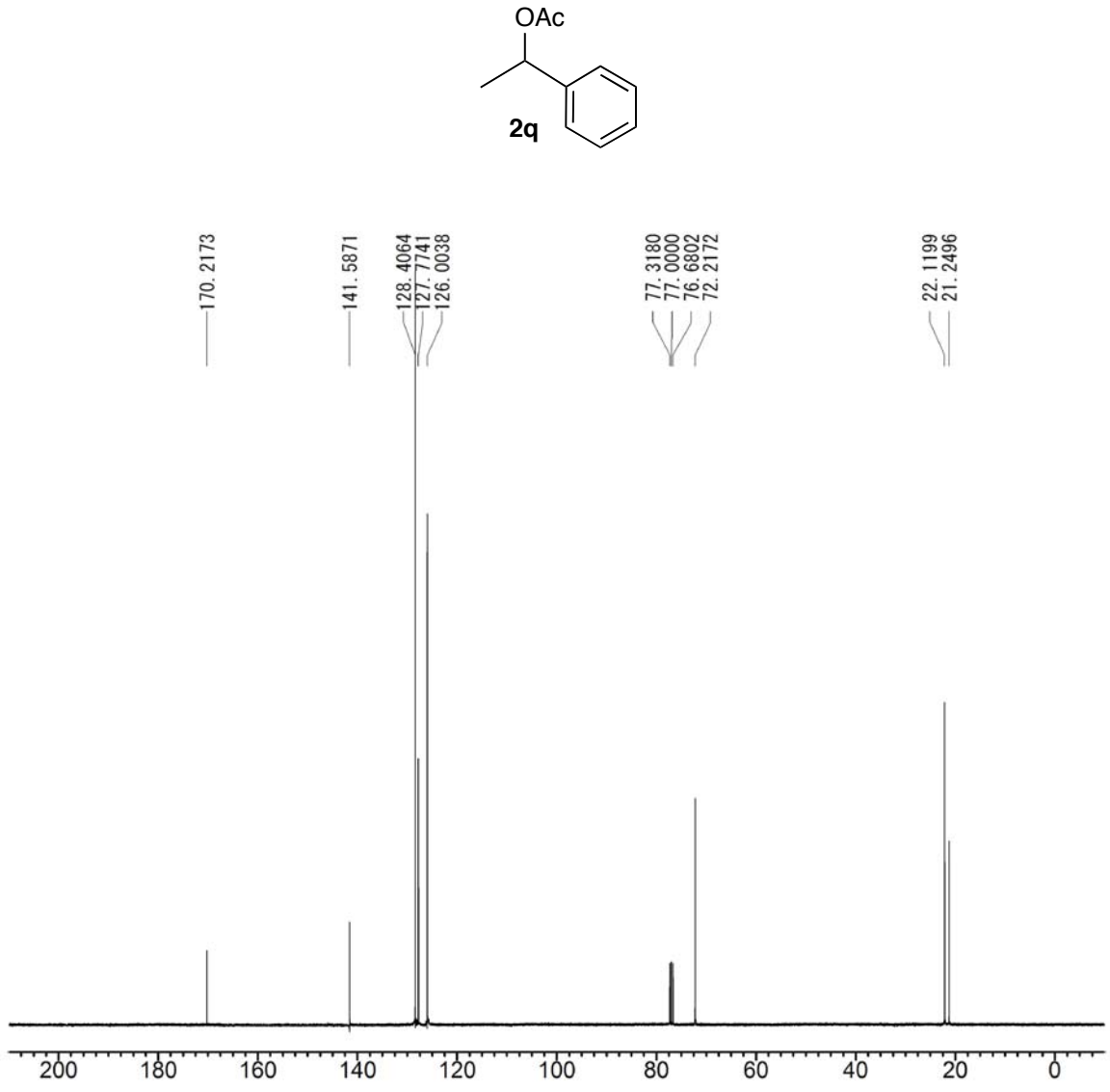

400 MHz $^{1}$H NMR of **2p** in $CDCl_3$.




100 MHz $^{13}C$ NMR of **2p** in $CDCl_3$.




400 MHz $^{1}$H NMR of **2q** in $CDCl_3$.




100 MHz $^{13}C$ NMR of **2q** in $CDCl_3$.