Electronic Supplementary Material (ESI) for Catalysis Science & Technology

Non-enzymatic Dynamic Kinetic Resolution of Racemic α-Arylalkanoic Acids: An Advanced Asymmetric Synthesis of Chiral Nonsteroidal Anti-inflammatory Drugs (NSAIDs)

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Supporting Information

General Information. All melting points are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded with chloroform (in chloroform-*d*) as internal standard. Thin layer chromatography was performed on Wakogel B5F.
All reactions were carried out under argon atmosphere in dried glassware.

Typical Procedure (A) for Dynamic Kinetic Resolution of Racemic Carboxylic Acids [Table 1, Entry 10]: To a solution of racemic ibuprofen ((±)-**1**) (41.3 mg, 0.200 mmol), pivalic anhydride (97.4 μL, 0.480 mmol), and bis(α-naphtyl)methanol (**3**) (68.2 mg, 0.240 mmol) in *N*,*N*-dimethylformamide (1.0 mL) at room temperature were successively added diisopropylethylamine (167 μL, 0.959 mmol) and (*R*)-BTM (2.5 mg, 9.9 μmol). The reaction mixture was stirred for 48 h at room temperature, and then quenched with 1 M hydrochloric acid at 0 °C. After stirring for 10 min at room temperature, the reaction mixture was diluted with ethyl acetate and the organic layer was separated, and then the aqueous layer was extracted with ethyl acetate. The combined organic layer was dried over sodium sulfate. After filtration of the mixture and evaporation of the solvent, the crude product was purified by preparative thin layer chromatography on silica (benzene/hexane = 3/1) to afford the corresponding ester (*R*)-**2** (87.7 mg, 93% yield, 91% ee) as a colorless oil and semi-purified recovered optically active carboxylic acid. The product was re-purified by preparative thin layer chromatography on silica (formic acid/ethyl acetate/hexane = 1/10/30) to afford the recovered optically active carboxylic acid (*S*)-**1** (1.7 mg, 4% yield, 12% ee) as a colorless oil.

Typical Procedure (B) for Dynamic Kinetic Resolution of Racemic 2-(4-Methoxyphenyl)propanoic acid ((±)-1d) [Scheme 2]: To a solution of racemic 2-(4-methoxyphenyl)propanoic acid ((±)-**1d**) (36.0 mg, 0.200 mmol), pivalic anhydride (194 μL, 0.956 mmol), and bis(α-naphtyl)methanol (**3**) (68.2 mg, 0.240 mmol) in *N*,*N*-dimethylformamide (1.0 mL) at room temperature were successively added diisopropylethylamine (167 μL, 0.959 mmol) and (*R*)-BTM (2.5 mg, 9.9 μmol). The reaction mixture was stirred for 72 h at room temperature, and then quenched with 1 M hydrochloric acid at 0 °C. After stirring for 10 min at room temperature, the reaction mixture was diluted with ethyl acetate and the organic layer was separated, and then the aqueous layer was extracted with ethyl acetate. The combined organic layer was dried over sodium sulfate. After filtration of the mixture and evaporation of the solvent, the crude product was purified by preparative thin layer chromatography on silica (benzene) to afford the corresponding ester (*R*)-**2d** (83.8 mg, 94% yield, 87% ee) as a colorless oil.

Typical Procedure (C) for Dynamic Kinetic Resolution of Racemic 2-(4-Chlorophenyl)propanoic acid ((±)-1g) [Scheme 2]: To a solution of racemic 2-(4-chlorophenyl)propanoic acid ((±)-**1g**) (36.9 mg, 0.200 mmol), pivalic anhydride

(97.4 μL, 0.480 mmol), and bis(α-naphtyl)methanol (**3**) (68.2 mg, 0.240 mmol) in *N*,*N*-dimethylformamide (1.0 mL) at 0 °C were successively added diisopropylethylamine (167 μL, 0.959 mmol) and (*R*)-BTM (2.5 mg, 9.9 μmol). The reaction mixture was stirred for 48 h at 0 °C, and then quenched with 1 M hydrochloric acid. After stirring for 10 min at room temperature, the reaction mixture was diluted with ethyl acetate and the organic layer was separated, and then the aqueous layer was extracted with ethyl acetate. The combined organic layer was dried over sodium sulfate. After filtration of the mixture and evaporation of the solvent, the crude product was purified by preparative thin layer chromatography on silica (benzene/hexane = 3/1) to afford the corresponding ester (*R*)-**2g** (89.2 mg, 99% yield, 87% ee) as a colorless oil.

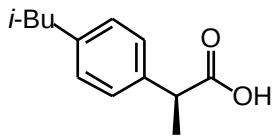
Production of (*S*)-Ibuprofen by the DKR/KR Combined Method [Scheme 4]: To a solution of racemic ibuprofen ((±)-**1**) (2.06 g, 10.0 mmol), pivalic anhydride (4.87 mL, 24.0 mmol), and bis(α-naphtyl)methanol (**3**) (3.41 g, 12.0 mmol) in *N*,*N*-dimethylformamide (50 mL) at room temperature were successively added diisopropylethylamine (8.36 mL, 48.1 mmol) and (*S*)-BTM (126 mg, 0.499 mmol). The reaction mixture was stirred for 48 h at room temperature, and then quenched with 1 M hydrochloric acid at 0 °C. After stirring for 10 min at room temperature, the reaction mixture was diluted with ethyl acetate and the organic layer was separated, and then the aqueous layer was extracted with ethyl acetate. The combined organic layer was dried over sodium sulfate. After filtration of the mixture and evaporation of the solvent, the crude product was purified by column chromatography on silica (toluene/hexane = 1/3) to afford the corresponding ester (*S*)-**2** (4.58 g, 97% yield, 92% ee) as a colorless oil.

To a solution of the above (*S*)-ibuprofen bis(α-naphthyl)methyl ester ((*S*)-**2**) (4.58 g, 9.69 mmol, 92% ee) in THF (49 mL) at room temperature under argon atmosphere was added palladium on carbon (10% loading, 50 wt.%, 4.13 g, 1.94 mmol). The mixture was stirred for 24 h at room temperature under hydrogen atmosphere (1.0 atm), and then it was replaced by argon atmosphere. After filtration of the mixture through Celite with ethyl acetate and evaporation of the solvent, the crude product was purified by column chromatography on silica (ethyl acetate/hexane = 1/9 to 1/1) to afford (*S*)-ibuprofen ((*S*)-**1**) (1.96 g, 98% yield, 92% ee) as a white solid.

To a solution of the above (*S*)-ibuprofen ((*S*)-**1**) (1.96 g, 9.50 mmol, 92% ee), pivalic anhydride (4.60 mL, 22.7 mmol), and bis(α-naphtyl)methanol (**3**) (2.58 g, 9.08 mmol) in toluene (48 mL) at room temperature were successively added diisopropylethylamine (6.00 mL, 34.4 mmol) and (*S*)-BTM (120 mg, 0.476 mmol). The reaction mixture was stirred for 12 h at room temperature, and then quenched with 1 M hydrochloric acid at 0 °C. After stirring for 10 min at room temperature, the organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layer was dried over sodium sulfate. After filtration of the mixture and evaporation of the solvent, the crude product was purified by column chromatography on silica (toluene/hexane = 1/3 to 1/1) to afford the corresponding ester (*S*)-**2** (4.02 g, 90% yield, 99% ee) as a colorless oil.

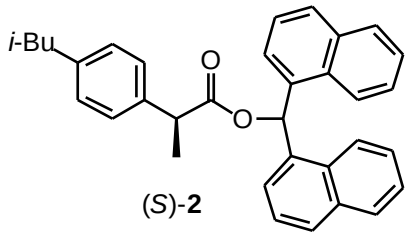
To a solution of the above (*S*)-ibuprofen bis(α-naphthyl)methyl ester ((*S*)-**2**) (4.02 g, 8.51 mmol, 99% ee) in THF (43 mL) and EtOH (43 mL) at room temperature under

argon atmosphere was added palladium on carbon (10% loading, 50 wt.%, 3.62 g, 1.70 mmol). The mixture was stirred for 24 h at room temperature under hydrogen atmosphere (1.0 atm), and then it was replaced by argon atmosphere. After filtration of the mixture through Celite with ethyl acetate and evaporation of the solvent, the crude product was purified by column chromatography on silica (ethyl acetate/hexane = 1/9 to 1/1) to afford (*S*)-ibuprofen ((*S*)-**1**) (1.58 g, 90% yield, 99% ee) as a white solid.



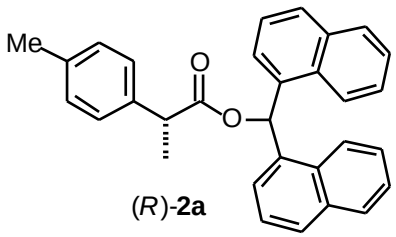
(*S*)-**1**

(*S*)-Ibuprofen ((*S*)-1) [**Scheme 4**, 99% ee]: HPLC (CHIRALPAK AD-H, *i*-PrOH/hexane/TFA = 1/100/0.1, flow rate = 1.0 mL/min); t_R = 25.2 min (99.3%), t_R = 28.1 min (0.7%); $[\alpha]_D^{23}$ = +56.8 (c 2.00, EtOH); Mp: 47–48 °C; IR (KBr): 2954, 2638, 1705, 1281, 949 cm^{-1}; ^1H NMR ($CDCl_3$): δ 10.3 (br s, 1H, COOH), 7.14 (d, *J* = 7.9 Hz, 2H), 7.02 (d, *J* = 7.9 Hz, 2H), 3.63 (q, *J* = 7.3 Hz, 1H), 2.37 (q, *J* = 7.3 Hz, 2H), 1.77 (tqq, *J* = 7.3, 6.5, 6.5 Hz, 1H), 1.42 (d, *J* = 7.3 Hz, 3H), 0.82 (d, *J* = 6.5 Hz, 6H); ^{13}C NMR ($CDCl_3$): δ 181.0, 140.8, 136.9, 129.4, 127.3, 45.0, 44.9, 30.2, 22.4, 18.1.



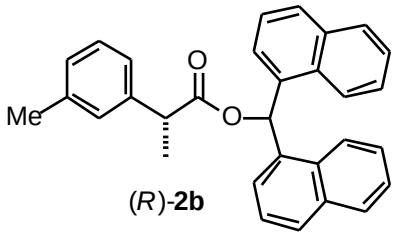
(*S*)-**2**

(*S*)-Ibuprofen di(1-naphthyl)methyl ester ((*S*)-2) [**Scheme 4**, 99% ee]: HPLC (CHIRALPAK AD-H, *i*-PrOH/hexane = 1/9, flow rate = 0.5 mL/min); t_R = 12.5 min (99.3%), t_R = 24.2 min (0.7%); IR (neat): 3034, 1733, 1604, 1508, 782, 679 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.29 (s, 1H), 8.00–7.90 (m, 1H), 7.82–6.96 (m, 17H), 6.95–6.81 (m, 2H), 3.86 (q, *J* = 7.0 Hz, 1H), 3.79 (s, 3H), 1.49 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 173.6, 157.6, 135.1, 134.7, 134.5, 133.8, 133.7, 133.6, 131.2, 130.8, 129.3, 129.1, 128.9, 128.8, 128.7, 128.6, 128.3, 127.1, 126.7, 126.5, 126.3, 126.2, 125.8, 125.6, 125.3, 125.2, 125.0, 123.4, 123.3, 118.9, 105.5, 71.2, 55.2, 45.5, 18.3; HR MS: calcd for $C_{35}H_{28}O_3Na$ ($M+Na^+$) 519.1931, found 519.1932.



(*R*)-**2a**

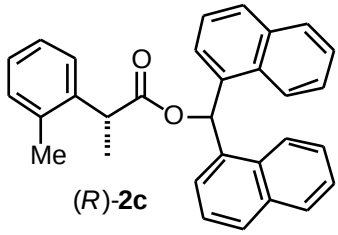
Di(1-naphthyl)methyl (*R*)-2-(4-methylphenyl)propanoate ((*R*)-2a) [**Scheme 2**, 84% ee]: HPLC (CHIRALPAK AD-H, *i*-PrOH/hexane = 1/9, flow rate = 0.5 mL/min); t_R = 14.1 min (8.2%), t_R = 19.7 min (91.8%); IR (neat): 3051, 1733, 1598, 1512, 801, 777, 732 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.27 (s, 1H), 7.98–7.91 (m, 1H), 7.83–7.76 (m, 1H), 7.72 (t, *J* = 8.2 Hz, 2H), 7.66 (d, *J* = 8.2 Hz, 1H), 7.62 (d, *J* = 8.6 Hz, 1H), 7.44–7.36 (m, 1H), 7.31 (t, *J* = 7.5 Hz, 1H), 7.22–7.14 (m, 2H), 7.13–7.01 (m, 4H), 6.97 (d, *J* = 7.9 Hz, 2H), 6.92 (d, *J* = 7.5 Hz, 1H), 3.72 (q, *J* = 7.0 Hz, 1H), 2.25 (s, 3H), 1.42 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 173.7, 137.0, 136.7, 134.9, 134.6, 133.8, 133.7, 131.2, 130.9, 129.2, 129.1, 128.8, 128.7, 128.6, 128.3, 127.6, 126.7, 126.3, 126.2, 125.8, 125.6, 125.3, 125.2, 125.0, 123.5, 123.3, 71.1, 45.2, 21.0, 18.2; HR MS: calcd for $C_{31}H_{26}O_2Na$ ($M+Na^+$) 453.1825, found 453.1816.



(*R*)-**2b**

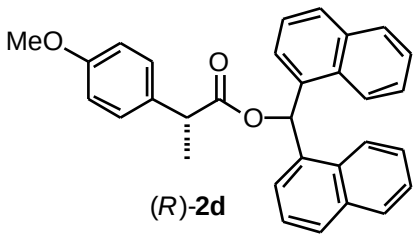
Di(1-naphthyl)methyl (*R*)-2-(3-methylphenyl)propanoate ((*R*)-2b) [**Scheme 2**, 91% ee]: HPLC (CHIRALPAK AD-H, *i*-PrOH/hexane = 1/9, flow rate = 0.5 mL/min); t_R = 14.4 min (4.6%), t_R = 18.0 min (95.4%); ^1H NMR ($CDCl_3$): δ 8.38 (s, 1H), 8.09–8.00 (m, 1H), 7.92–7.82 (m, 1H), 7.86–7.75 (m, 2H), 7.73 (dd, *J* = 8.4, 8.4 Hz, 2H), 7.54–7.34 (m, 3H), 7.32–7.11 (m, 5H), 7.09–6.98 (m, 4H), 3.80 (qd, *J* = 6.9, 1.8 Hz, 1H), 2.22 (s, 3H), 1.51 (dd, *J* = 6.9, 1.8 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 173.6, 139.9, 138.2, 134.8, 134.5, 133.8, 133.6, 131.2, 130.8, 129.1, 128.8, 128.7, 128.6, 128.4, 128.3, 127.9, 126.7, 126.33, 126.27, 125.8, 125.6, 125.3, 125.2, 125.0, 124.8, 123.5, 123.3, 71.0, 45.5, 21.3, 18.2; HR MS: calcd for $C_{31}H_{26}O_2Na$ ($M+Na^+$) 453.1825, found 453.1817.

Analytical data on racemic compound: Mp: 120–121 °C (hexane); IR (KBr): 3055, 2970, 2931, 1728, 1597, 1242, 1157, 779, 741, 710 cm^{-1}.



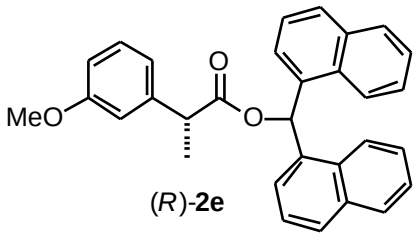
(*R*)-**2c**

Di(1-naphthyl)methyl (*R*)-2-(2-methylphenyl)propanoate ((*R*)-2c) [**Scheme 2**, 90% ee]: HPLC (CHIRALPAK AD-H, *i*-PrOH/hexane = 1/50, flow rate = 0.5 mL/min); t_R = 21.6 min (5.1%), t_R = 34.0 min (94.9%); IR (neat): 3057, 1599, 1510, 752, 730 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.31 (s, 1H), 8.02–7.96 (m, 1H), 7.83–7.78 (m, 1H), 7.73 (t, *J* = 8.0 Hz, 2H), 7.69–7.62 (m, 2H), 7.45–7.39 (m, 2H), 7.34–7.30 (m, 1H), 7.23–7.17 (m, 2H), 7.14–7.00 (m, 6H), 6.88 (d, *J* = 8.0 Hz, 1H), 4.00 (q, *J* = 7.0 Hz, 1H), 2.16 (s, 3H), 1.43 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 173.7, 138.5, 135.9, 134.9, 134.6, 133.8, 133.7, 131.2, 130.9, 130.5, 129.1, 128.9, 128.7, 128.6, 127.0, 126.9, 126.7, 126.34, 126.30, 126.28, 125.8, 125.6, 125.3, 125.2, 125.0, 123.5, 123.4, 71.0, 41.4, 19.7, 17.6; HR MS: calcd for $C_{31}H_{26}O_2Na$ ($M+Na^+$) 453.1825, found 453.1813.



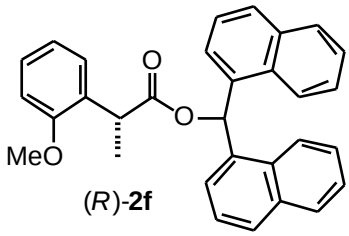
(*R*)-**2d**

Di(1-naphthyl)methyl (*R*)-2-(4-methoxyphenyl)propanoate ((*R*)-2d) [**Scheme 2**, 87% ee]: HPLC (CHIRALPAK AD-H, *i*-PrOH/hexane = 1/9, flow rate = 0.5 mL/min); t_R = 22.7 min (6.4%), t_R = 28.8 min (93.6%); IR (neat): 3059, 1733, 1608, 1512, 783, 733 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.26 (s, 1H), 7.97–7.89 (m, 1H), 7.85–7.58 (m, 5H), 7.46–7.04 (m, 9H), 6.93 (d, *J* = 6.9 Hz, 1H), 6.75–6.67 (m, 2H), 3.78–3.68 (m, 4H), 1.42 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 173.7, 158.7, 134.8, 134.6, 133.8, 133.6, 132.1, 131.2, 130.9, 129.1, 128.83, 128.76, 128.71, 128.6, 128.3, 126.7, 126.3, 126.2, 125.8, 125.6, 125.3, 125.2, 125.0, 123.5, 123.3, 113.9, 71.0, 55.3, 44.8, 18.2; HR MS: calcd for $C_{31}H_{26}O_3Na$ ($M+Na^+$) 469.1774, found 469.1754.



(*R*)-**2e**

Di(1-naphthyl)methyl (*R*)-2-(3-methoxyphenyl)propanoate ((*R*)-2e) [**Scheme 2**, 91% ee]: HPLC (CHIRALPAK AD-H, *i*-PrOH/hexane = 1/9, flow rate = 0.5 mL/min); t_R = 21.3 min (4.5%), t_R = 35.6 min (95.5%); IR (neat): 3055, 2978, 1736, 1597, 1250, 1157, 779, 764, 702 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.36 (s, 1H), 8.08–7.98 (m, 1H), 7.92–7.84 (m, 1H), 7.81 (d, *J* = 7.5 Hz, 1H), 7.79 (d, *J* = 8.1 Hz, 1H), 7.75 (d, *J* = 8.1 Hz, 1H), 7.72 (d, *J* = 8.7 Hz, 1H), 7.53–7.43 (m, 2H), 7.40 (dd, *J* = 7.5, 7.5 Hz, 1H), 7.32–7.12 (m, 5H), 7.01 (d, *J* = 6.9 Hz, 1H), 6.87–6.71 (m, 3H), 3.82 (q, *J* = 7.2 Hz, 1H), 3.62 (s, 3H), 1.52 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 173.4, 159.7, 141.4, 134.7, 134.5, 133.8, 133.6, 131.2, 130.8, 129.5, 129.1, 128.8, 128.7, 128.6, 126.7, 126.4, 126.3, 125.8, 125.6, 125.3, 125.2, 125.0, 123.4, 123.3, 120.1, 113.1, 112.9, 71.1, 55.1, 45.6, 18.1; HR MS: calcd for $C_{31}H_{26}O_3Na$ ($M+Na^+$) 469.1774, found 469.1766.

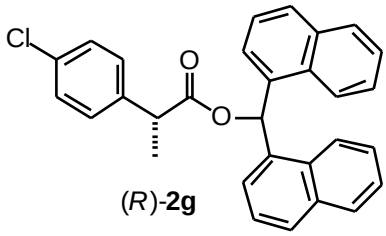


(*R*)-**2f**

Di(1-naphthyl)methyl (*R*)-2-(2-methoxyphenyl)propanoate ((*R*)-2f) [**Scheme 2**, 97% ee]: HPLC (CHIRALPAK AD-H, *i*-PrOH/hexane = 1/9, flow rate = 0.5 mL/min); t_R = 17.8 min (1.5%), t_R = 30.0 min (98.5%); ^1H NMR ($CDCl_3$): δ 8.35 (s, 1H), 8.13–7.95 (m, 1H), 7.82–7.53 (m, 5H), 7.46–7.32 (m, 3H), 7.30–7.07 (m, 7H), 6.79 (td, *J* = 7.3, 1.2 Hz, 1H), 6.68 (dd, *J* = 8.1, 1.2 Hz, 1H), 4.08 (q, *J* = 7.2 Hz, 1H), 3.39 (s, 3H), 1.42 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 174.1, 156.8, 135.2, 135.0, 133.8, 133.7, 131.2, 131.0, 128.9, 128.8, 128.74, 128.67, 128.61, 128.3, 128.1, 126.6, 126.4, 126.2, 125.8, 125.7, 125.6, 125.14, 125.06, 123.7, 123.6, 120.5, 110.3, 70.8, 55.0, 39.6, 16.8; HR MS: calcd for $C_{31}H_{26}O_3Na$ ($M+Na^+$) 469.1774, found 469.1770.

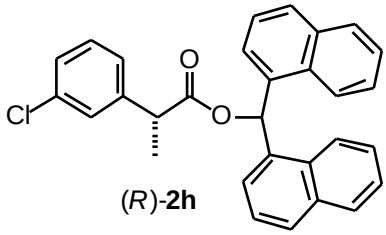
Analytical data on racemic compound: Mp: 160–161 °C ($CHCl_3$/petroleum ether); IR

(KBr): 3060, 1730, 1600, 1494, 778, 758 cm^{-1}.



(*R*)-**2g**

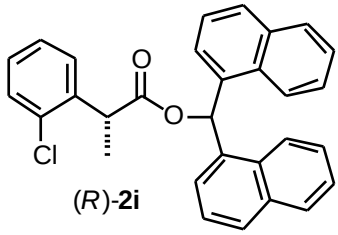
Di(1-naphthyl)methyl (*R*)-2-(4-chlorophenyl)propanoate ((*R*)-2g) [**Scheme 2**, 87% ee]: HPLC (CHIRALPAK AD-H, *i*-PrOH/hexane = 1/9, flow rate = 0.5 mL/min); t_R = 17.9 min (6.6%), t_R = 20.3 min (93.4%); IR (neat): 3052, 1737, 1599, 1510, 837, 777 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 8.26 (d, *J* = 3.0 Hz, 1H), 7.90 (dd, *J* = 7.5, 3.0 Hz, 1H), 7.81 (d, *J* = 7.5 Hz, 1H), 7.75 (t, *J* = 8.5 Hz, 2H), 7.70 (d, *J* = 8.0 Hz, 1H), 7.62 (dd, *J* = 8.5, 3.0 Hz, 1H), 7.45–7.32 (m, 3H), 7.26–7.04 (m, 8H), 6.93 (dd, *J* = 7.0, 3.0 Hz, 1H), 3.73 (qd, *J* = 8.5, 1.5 Hz, 1H), 1.45–1.41 (m, 3H); ^{13}C NMR ($CDCl_3$): δ 173.1, 138.4, 134.5, 134.4, 133.8, 133.7, 133.0, 131.1, 130.8, 129.2, 129.1, 128.9, 128.7, 128.6, 128.3, 126.7, 126.4, 126.1, 125.9, 125.7, 125.3, 125.2, 124.5, 123.3, 123.2, 71.4, 45.0, 18.0; HR MS: calcd for $C_{30}H_{23}O_2ClNa$ ($M+Na^+$) 473.1279, found 473.1284.



(*R*)-**2h**

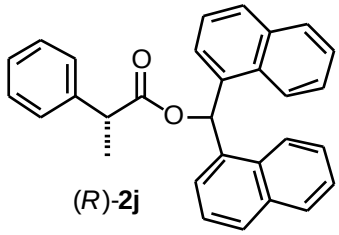
Di(1-naphthyl)methyl (*R*)-2-(3-chlorophenyl)propanoate ((*R*)-2h) [**Scheme 2**, 87% ee]: HPLC (CHIRALPAK AD-H, *i*-PrOH/hexane = 1/9, flow rate = 0.5 mL/min); t_R = 12.7 min (6.3%), t_R = 16.9 min (93.7%); IR (neat): 3055, 2978, 1728, 1604, 1257, 1157, 1072, 779, 756 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 8.37 (s, 1H), 8.00 (d, *J* = 8.5 Hz, 1H), 7.91–7.87 (m, 1H), 7.82 (dd, *J* = 7.5, 7.5 Hz, 2H), 7.77 (d, *J* = 8.0 Hz, 1H), 7.73 (d, *J* = 8.5 Hz, 1H), 7.52–7.45 (m, 2H), 7.42 (dd, *J* = 7.5, 7.5 Hz, 1H), 7.33–7.27 (m, 2H), 7.26–7.17 (m, 4H), 7.14 (dd, *J* = 7.5, 7.5 Hz, 1H), 7.09 (d, *J* = 7.5 Hz, 1H), 7.04 (d, *J* = 8.0 Hz, 1H), 3.81 (q, *J* = 7.0 Hz, 1H), 1.51 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 172.9, 141.9, 134.6, 134.38, 134.38, 133.8, 133.7, 131.2, 130.9, 129.8, 129.2, 128.90, 128.90, 128.7, 127.9, 127.4, 126.8, 126.4,

126.2, 126.0, 125.9, 125.7, 125.4, 125.2, 125.0, 123.34, 123.25, 71.4, 45.3, 18.1; HR MS: calcd for $C_{30}H_{23}O_2ClNa$ ($M+Na^+$) 473.1279, found 473.1298.



(*R*)-**2i**

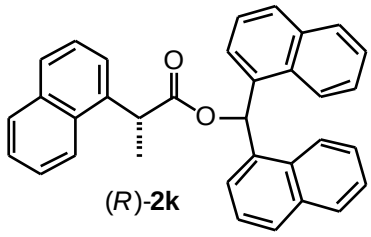
Di(1-naphthyl)methyl (*R*)-2-(2-chlorophenyl)propanoate ((*R*)-2i) [**Scheme 2**, 88% ee]: HPLC (CHIRALPAK IC, *i*-PrOH/hexane = 1/50, flow rate = 1.0 mL/min); t_R = 8.7 min (6.0%), t_R = 10.8 min (94.0%); ^{1}H NMR ($CDCl_3$): δ 8.35 (s, 1H), 8.12–7.96 (m, 1H), 7.83–7.65 (m, 5H), 7.42–7.38 (m, 2H), 7.34 (t, *J* = 7.5 Hz, 1H), 7.30–7.21 (m, 3H), 7.19–7.12 (m, 3H), 7.10–6.98 (m, 3H), 4.29 (q, *J* = 7.5 Hz, 1H), 1.43 (d, *J* = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 173.1, 137.8, 134.8, 134.5, 133.83, 133.81, 133.7, 131.2, 130.9, 129.5, 129.1, 128.9, 128.8, 128.7, 128.5, 128.3, 127.0, 126.7, 126.4, 126.3, 125.8, 125.7, 125.6, 125.2, 125.0, 123.6, 123.4, 71.4, 42.1, 17.4; HR MS: calcd for $C_{30}H_{23}O_2ClNa$ ($M+Na^+$) 473.1279, found 473.1261.
Analytical data on racemic compound: Mp: 143–144 °C (petroleum ether); IR (KBr): 3067, 1718, 1598, 1509, 795, 764 cm^{-1}.



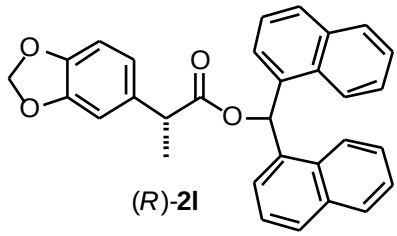
(*R*)-**2j**

Di(1-naphthyl)methyl (*R*)-2-phenylpropanoate ((*R*)-2j) [**Scheme 3**, 92% ee]: HPLC (CHIRALPAK AD-H, *i*-PrOH/hexane = 1/50, flow rate = 1.0 mL/min); t_R = 14.8 min (4.1%), t_R = 19.8 min (95.9%); ^{1}H NMR ($CDCl_3$): δ 8.29 (s, 1H), 7.99–7.94 (m, 1H), 7.84–7.79 (m, 1H), 7.74 (t, *J* = 7.0 Hz, 2H), 7.68 (d, *J* = 8.0 Hz, 1H), 7.63 (d, *J* = 8.5 Hz, 1H), 7.45–7.38 (m, 2H), 7.35–7.31 (m, 1H), 7.23–7.14 (m, 7H), 7.11 (t, *J* = 7.5 Hz, 1H), 7.06 (d, *J* = 7.5 Hz, 1H), 6.90 (d, *J* = 7.0 Hz, 1H), 3.77 (q, *J* = 7.0 Hz, 1H), 1.45 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 173.5, 140.0, 134.8, 134.6, 133.8, 133.7, 131.2, 130.8, 129.1, 128.9, 128.7, 128.64, 128.57, 127.8, 127.2, 126.7, 126.4, 126.3, 125.9, 125.6, 125.2, 125.0, 123.5, 123.3, 71.1, 45.6, 18.2; HR

MS: calcd for $C_{30}H_{24}O_2Na$ ($M+Na^+$) 439.1669, found 439.1668.
Analytical data on racemic compound: Mp: 128 °C (*i*-PrOH/hexane); IR (KBr): 3067, 1728, 1600, 1509, 776, 699 cm^{-1}.

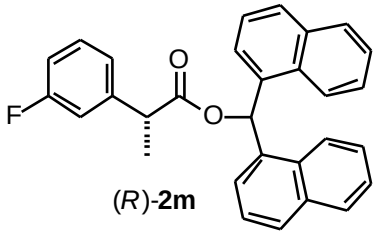

(*R*)-**2k**

Di(1-naphthyl)methyl (*R*)-2-(1-naphthyl)propanoate ((*R*)-2k) [**Scheme 3**, 91% ee]: HPLC (CHIRALPAK AD-H, *i*-PrOH/hexane = 1/9, flow rate = 0.5 mL/min); t_R = 19.0 min (4.3%), t_R = 32.7 min (95.7%); ^{1}H NMR ($CDCl_3$): δ 8.33 (s, 1H), 7.97–7.83 (m, 2H), 7.83–7.56 (m, 7H), 7.46–6.92 (m, 11H), 6.85 (d, *J* = 7.2 Hz, 1H), 4.54 (q, *J* = 6.9 Hz, 1H), 1.60 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 174.0, 136.0, 134.7, 134.4, 133.9, 133.8, 133.7, 131.4, 131.2, 130.9, 129.0, 128.82, 128.80, 128.7, 128.6, 128.3, 127.8, 126.7, 126.4, 126.22, 126.16, 125.8, 125.7, 125.6, 125.4, 125.1, 124.9, 124.8, 123.5, 123.4, 123.3, 71.3, 41.6, 17.9; HR MS: calcd for $C_{34}H_{26}O_2Na$ ($M+Na^+$) 489.1825, found 489.1809.
Analytical data on racemic compound: Mp: 152–153 °C ($CHCl_3$/petroleum ether); IR (KBr): 3055, 1735, 1599, 1509, 778 cm^{-1}.


(*R*)-**2l**

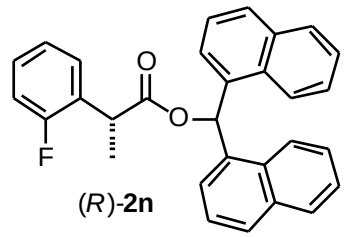
Di(1-naphthyl)methyl (*R*)-2-(3,4-methylenedioxyphenyl)propanoate ((*R*)-2l) [**Scheme 3**, 87% ee]: HPLC (CHIRALPAK AD-H, *i*-PrOH/hexane = 1/9, flow rate = 1.0 mL/min); t_R = 15.1 min (6.4%), t_R = 31.1 min (93.6%); IR (neat): 3055, 2978, 1728, 1604, 1242, 1157, 1041, 787, 733 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 8.34 (s, 1H), 8.00 (d, *J* = 8.5 Hz, 1H), 7.91–7.86 (m, 1H), 7.82 (dd, *J* = 8.0, 8.0 Hz, 2H), 7.77 (d, *J* = 8.0 Hz, 1H), 7.72 (d, *J* = 9.0 Hz, 1H), 7.48 (dddd, *J* = 15.0, 7.5, 7.5, 2.0 Hz, 2H), 7.44–7.38 (m, 1H), 7.33–7.27 (m, 2H), 7.25 (dd, *J* = 8.0, 8.0 Hz, 2H), 7.19 (d, *J* = 7.5 Hz, 1H), 7.08 (d, *J* = 7.5 Hz, 1H), 6.74–6.72 (m, 1H), 6.69–6.67 (m, 1H), 5.90

(s, 2H), 3.75 (q, *J* = 7.0 Hz, 1H), 1.48 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 173.5, 147.7, 146.7, 134.7, 134.5, 133.8, 133.74, 133.69, 131.2, 130.9, 129.1, 128.84, 128.81, 128.6, 126.7, 126.3, 126.2, 125.8, 125.6, 125.4, 125.2, 125.0, 123.5, 123.3, 121.0, 108.20, 108.16, 100.9, 71.2, 45.2, 18.2; HR MS: calcd for $C_{31}H_{24}O_4Na$ (M+Na$^+$) 483.1567, found 483.1574.



(*R*)-**2m**

Di(1-naphthyl)methyl (*R*)-2-(3-fluorophenyl)propanoate ((*R*)-2m) [**Scheme 3**, 89% ee]: HPLC (CHIRALPAK AD-H, *i*-PrOH/hexane = 1/9, flow rate = 0.5 mL/min); t_R = 12.3 min (5.4%), t_R = 15.2 min (94.6%); IR (neat): 3055, 2978, 1736, 1589, 1242, 1165, 787, 725, 694 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 8.37 (s, 1H), 8.01 (d, *J* = 8.0 Hz, 1H), 7.89 (d, *J* = 8.0 Hz, 1H), 7.83 (dd, *J* = 8.0, 8.0 Hz, 2H), 7.77 (d, *J* = 8.5 Hz, 1H), 7.73 (d, *J* = 8.5 Hz, 1H), 7.53–7.45 (m, 2H), 7.44–7.39 (m, 1H), 7.32 (d, *J* = 7.5 Hz, 1H), 7.29 (d, *J* = 7.5 Hz, 1H), 7.25–7.16 (m, 3H), 7.05–6.99 (m, 2H), 6.98–6.91 (m, 2H), 3.84 (q, *J* = 7.0 Hz, 1H), 1.52 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 172.9, 162.8 (d, *J* = 246.3 Hz), 142.3 (d, *J* = 7.5 Hz), 134.6, 134.4, 133.8, 133.7, 131.1, 130.8, 130.0 (d, *J* = 8.1 Hz), 129.2, 128.87, 128.87, 128.7, 126.7, 126.4, 126.1, 125.9, 125.7, 125.3, 125.2, 125.0, 123.50, 123.47, 123.3 (d, *J* = 7.5 Hz), 114.7 (d, *J* = 21.8 Hz), 114.1 (d, *J* = 21.2 Hz), 71.3, 45.3 (d, *J* = 1.2 Hz), 18.0; HR MS: calcd for $C_{30}H_{23}O_2FNa$ (M+Na$^+$) 457.1574, found 457.1581.

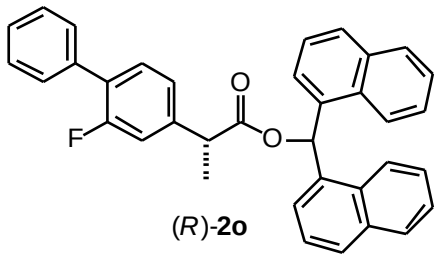


(*R*)-**2n**

Di(1-naphthyl)methyl (*R*)-2-(2-fluorophenyl)propanoate ((*R*)-2n) [**Scheme 3**, 93% ee]: HPLC (CHIRALPAK AD-H, *i*-PrOH/hexane = 1/9, flow rate = 0.5 mL/min); t_R = 14.7 min (3.7%), t_R = 18.5 min (96.3%); ^{1}H NMR ($CDCl_3$): δ 8.42 (s, 1H), 8.09–8.04 (m, 1H), 7.91–7.86 (m, 1H), 7.85–7.79 (m, 3H), 7.77 (d, *J* = 8.5 Hz,

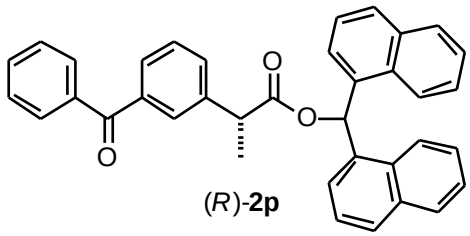
1H), 7.52–7.47 (m, 2H), 7.42 (dd, *J* = 8.0, 8.0 Hz, 1H), 7.33 (dd, *J* = 8.0, 8.0 Hz, 1H), 7.31 (dd, *J* = 8.0, 8.0 Hz, 1H), 7.27–7.16 (m, 4H), 7.13 (d, *J* = 7.0 Hz, 1H), 7.03–6.96 (m, 2H), 4.18 (q, *J* = 7.5 Hz, 1H), 1.52 (d, *J* = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 173.0, 160.4 (d, *J* = 246.0 Hz), 134.8, 134.6, 133.8, 133.7, 131.2, 130.9, 129.1, 128.84 (d, *J* = 7.3 Hz), 128.81, 128.78, 128.70 (d, *J* = 6.3 Hz), 128.67, 127.3 (d, *J* = 14.4 Hz), 126.7, 126.4, 126.2, 125.9, 125.7, 125.4, 125.2, 125.0, 124.2 (d, *J* = 3.1 Hz), 123.5, 123.4, 115.4 (d, *J* = 22.7 Hz), 71.3, 38.4 (d, *J* = 3.0 Hz), 17.3; HR MS: calcd for $C_{30}H_{23}O_2FNa$ (M+Na$^+$) 457.1574, found 457.1555.

Analytical data on racemic compound: Mp: 127–128 °C (hexane); IR (KBr): 3062, 1736, 1188, 1157, 779 cm^{-1}.



(*R*)-**2o**

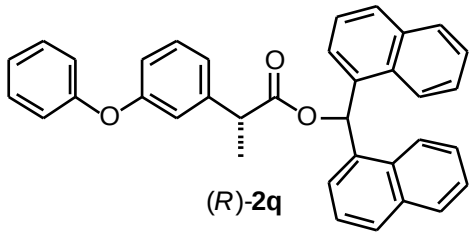
(*R*)-Flurbiprofen di(1-naphthyl)methyl ester ((*R*)-2o) [**Scheme 3**, 81% ee]: HPLC (CHIRALPAK AD-H, *i*-PrOH/hexane = 1/9, flow rate = 0.75 mL/min); t_R = 10.8 min (9.5%), t_R = 17.7 min (90.5%); IR (neat): 3035, 1734, 1599, 1513, 783, 679 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 8.29 (s, 1H), 7.95–7.86 (m, 1H), 7.80–7.72 (m, 1H), 7.70 (d, *J* = 8.1 Hz, 2H), 7.64 (d, *J* = 8.1 Hz, 2H), 7.46–7.04 (m, 13H), 7.01–6.90 (m, 3H), 3.74 (q, *J* = 7.0 Hz, 1H), 1.44 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 172.9, 159.6 (d, *J* = 248.2 Hz), 141.3, 141.2, 135.5, 134.6, 134.4, 133.8, 133.7, 131.1, 130.9, 130.7 (d, *J* = 3.7 Hz), 129.2, 128.9 (d, *J* = 3.2 Hz), 128.7, 128.5, 128.3, 127.8 (d, *J* = 13.7 Hz), 127.7, 126.7, 126.4, 126.1, 125.9, 125.7, 125.4, 125.2, 125.0, 123.8 (d, *J* = 3.1 Hz), 123.4, 123.3, 115.4 (d, *J* = 23.6 Hz), 71.5, 45.1, 17.9; HR MS: calcd for $C_{36}H_{27}O_2FNa$ (M+Na$^+$) 533.1887, found 533.1865.



(*R*)-**2p**

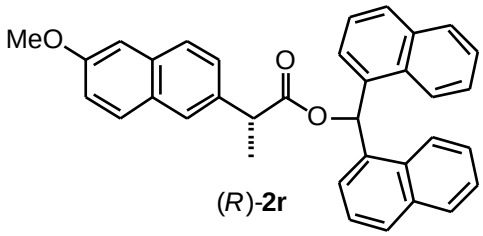
(*R*)-Ketoprofen di(1-naphthyl)methyl ester ((*R*)-2p) [**Scheme 3**, 86% ee]:

HPLC (CHIRALPAK AD-H, *i*-PrOH/hexane = 1/4, flow rate = 1.0 mL/min); t_R = 13.9 min (6.9%), t_R = 35.8 min (93.1%); IR (neat): 3035, 1735, 1660, 1599, 1511, 780, 680 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.28 (s, 1H), 7.93–7.85 (m, 1H), 7.82–7.54 (m, 6H), 7.52–7.44 (m, 2H), 7.44–7.06 (m, 13H), 6.95 (d, *J* = 7.1 Hz, 1H), 3.81 (q, *J* = 7.1 Hz, 1H), 1.46 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 196.3, 173.0, 140.1, 137.8, 137.3, 134.5, 134.4, 133.8, 133.7, 132.4, 131.6, 131.1, 130.8, 129.9, 129.5, 129.2, 128.93, 128.91, 128.86, 128.7, 128.6, 128.3, 128.2, 126.7, 126.4, 126.1, 125.9, 125.7, 125.4, 125.2, 125.0, 123.2, 71.4, 45.5, 17.9; HR MS: calcd for $C_{37}H_{28}O_3Na$ ($M+Na^+$) 543.1931, found 543.1910.



(*R*)-**2q**

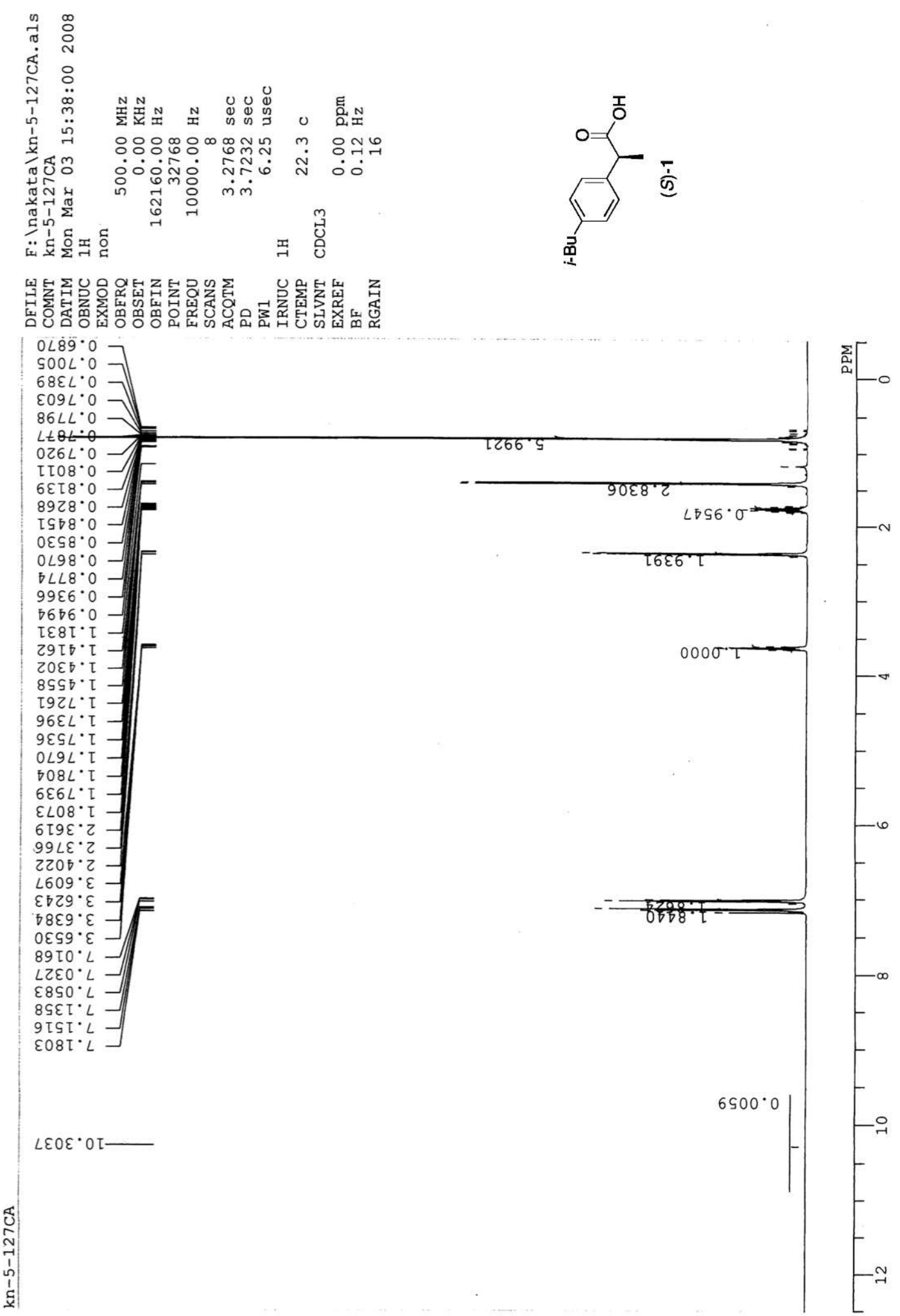
(*R*)-Fenoprofen di(1-naphthyl)methyl ester ((*R*)-2q) [**Scheme 3**, 87% ee]: HPLC (CHIRALPAK AD-H, *i*-PrOH/hexane = 1/50, flow rate = 1.0 mL/min); t_R = 21.0 min (6.7%), t_R = 25.2 min (93.3%); IR (neat): 3036, 1735, 1585, 1485, 781, 679 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.28 (s, 1H), 7.92 (d, *J* = 8.0 Hz, 1H), 7.82–7.62 (m, 5H), 7.43–7.30 (m, 3H), 7.27–7.09 (m, 7H), 6.98–6.91 (m, 3H), 6.86–6.83 (m, 1H), 6.82–6.73 (m, 3H), 3.72 (q, *J* = 7.0 Hz, 1H), 1.42 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 173.1, 157.3, 157.0, 141.9, 134.7, 134.6, 133.8, 133.7, 131.2, 130.9, 129.8, 129.7, 129.1, 128.9, 128.8, 128.7, 128.3, 126.7, 126.4, 126.1, 125.9, 125.7, 125.3, 125.2, 125.1, 123.4, 123.3, 123.1, 122.6, 118.7, 118.4, 117.6, 71.2, 45.5, 17.9; HR MS: calcd for $C_{36}H_{28}O_3Na$ ($M+Na^+$) 531.1931, found 531.1948.

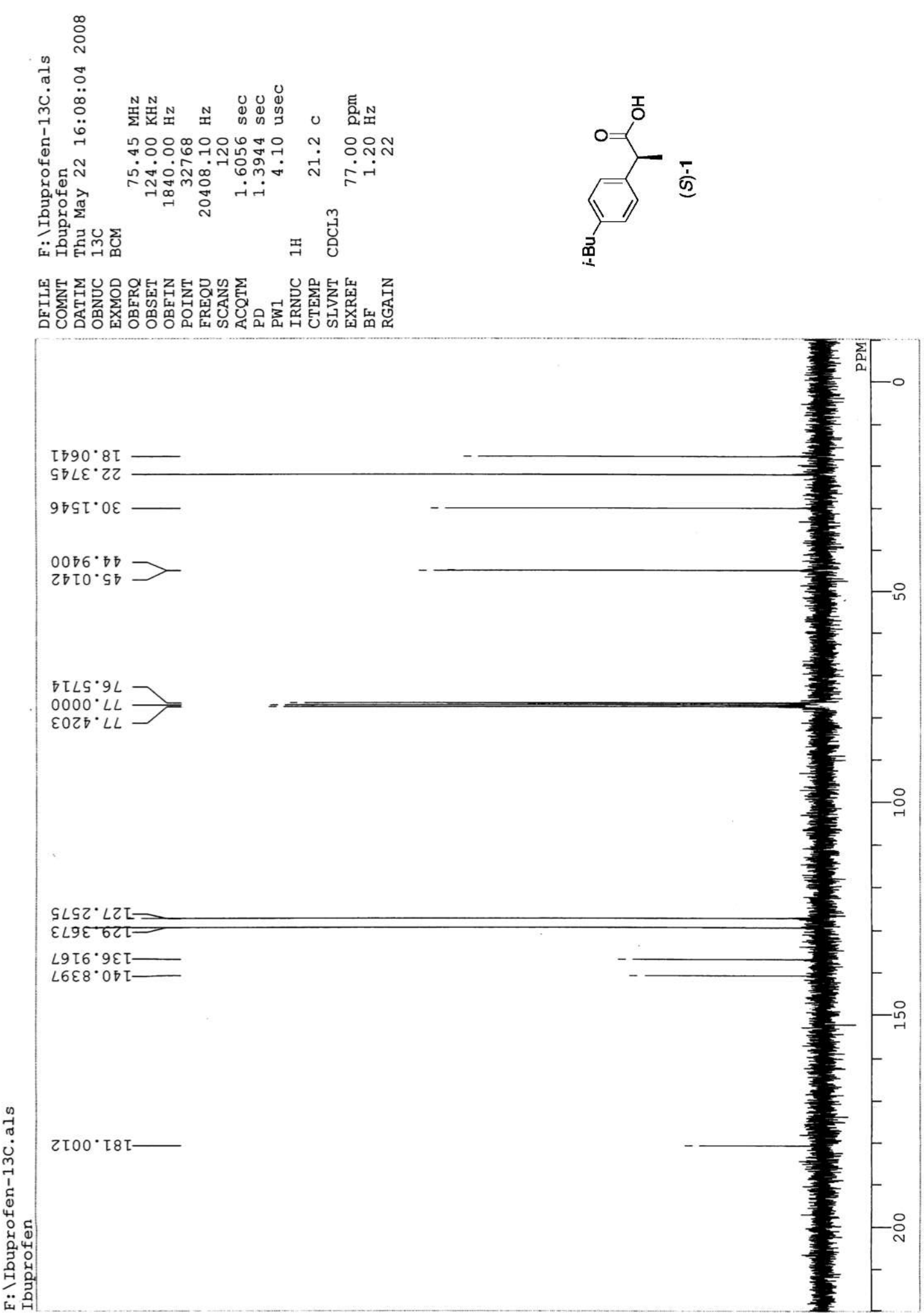


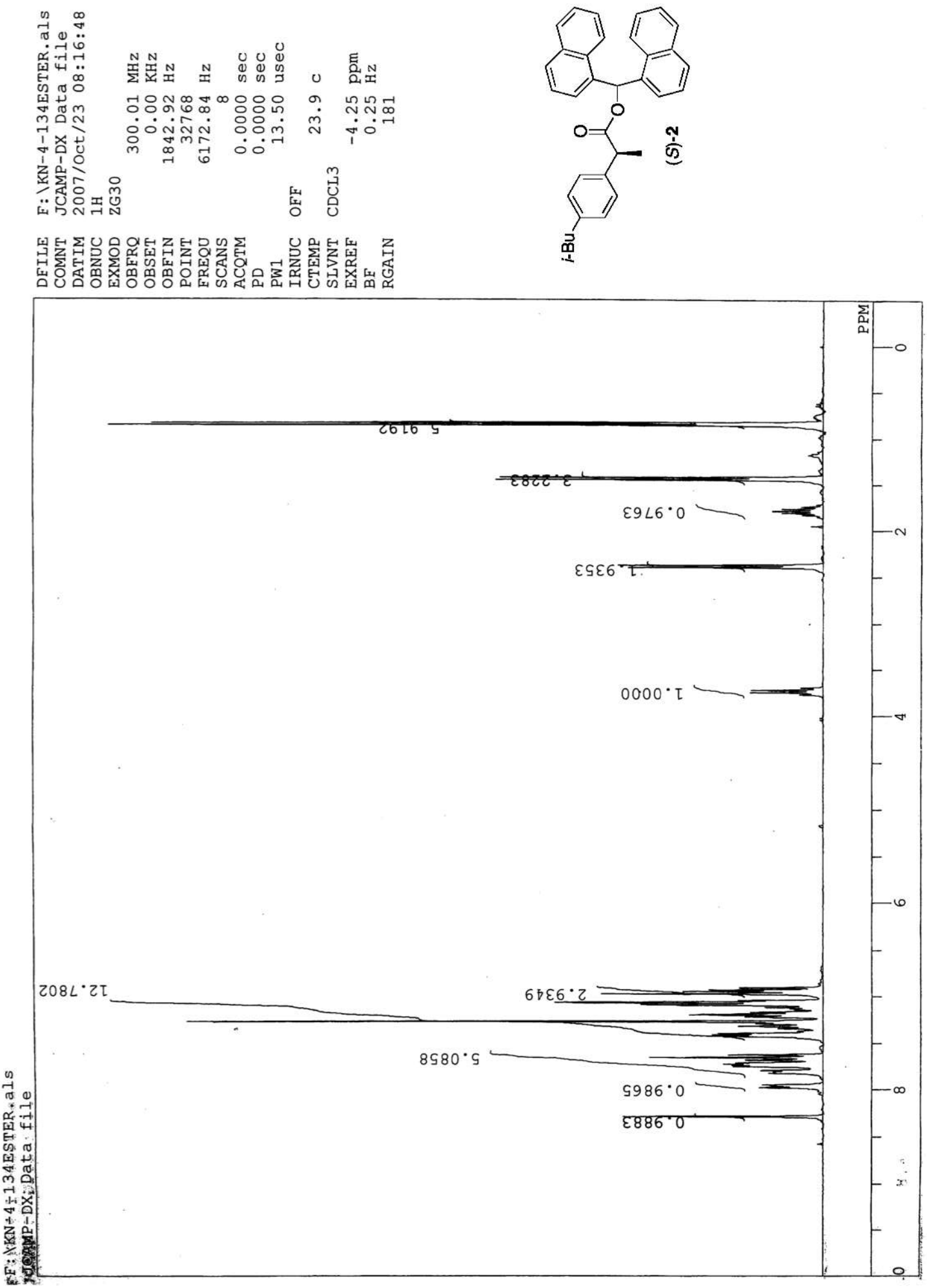
(*R*)-**2r**

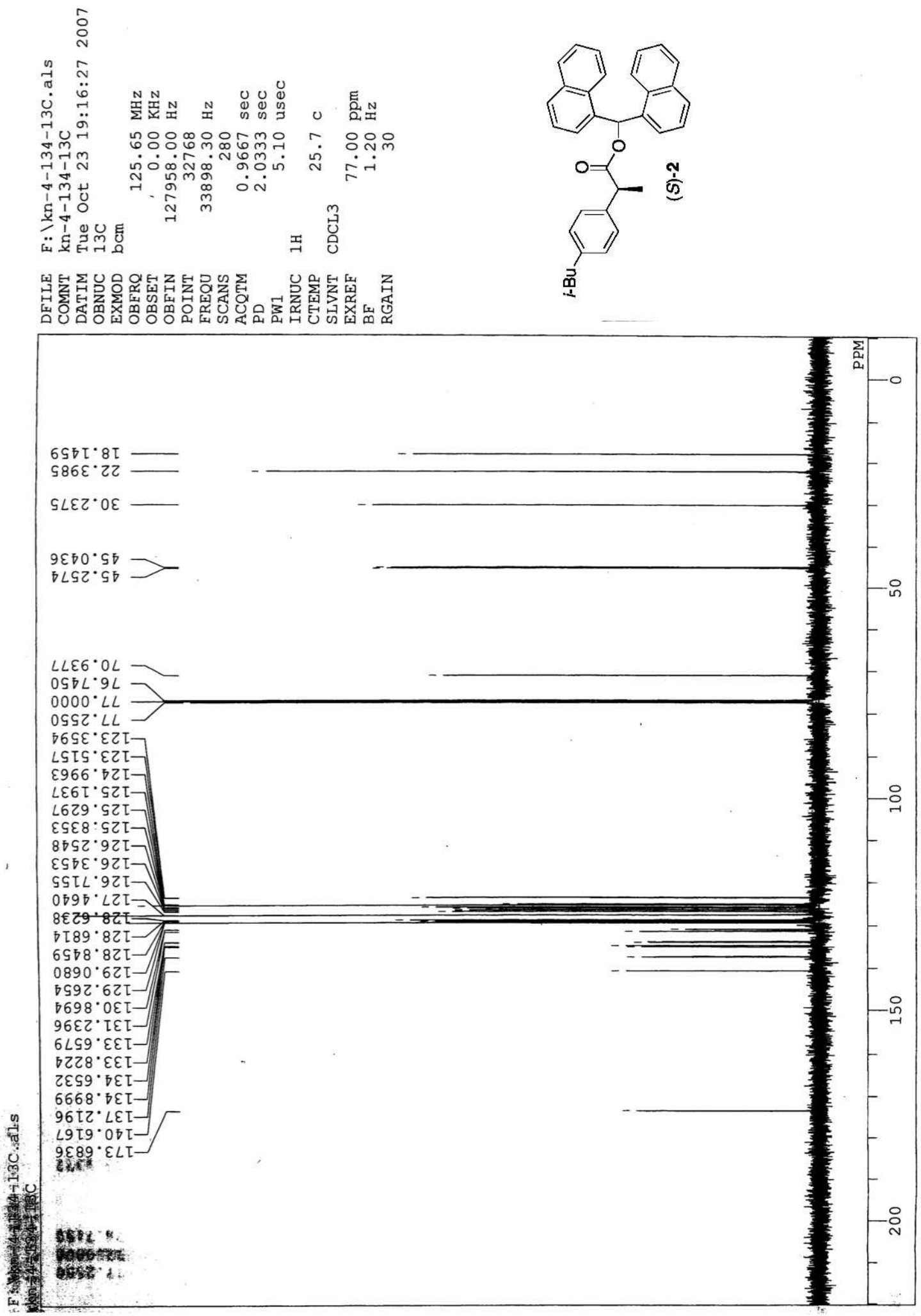
(*R*)-Naproxen di(1-naphthyl)methyl ester ((*R*)-2r) [**Scheme 3**, 90% ee]: HPLC (CHIRALPAK AD-H, *i*-PrOH/hexane = 1/9, flow rate = 1.0 mL/min); t_R = 13.1 min (5.1%), t_R = 16.5 min (94.9%); IR (neat): 3034, 1733, 1604, 1508, 782, 679 cm^{-1};

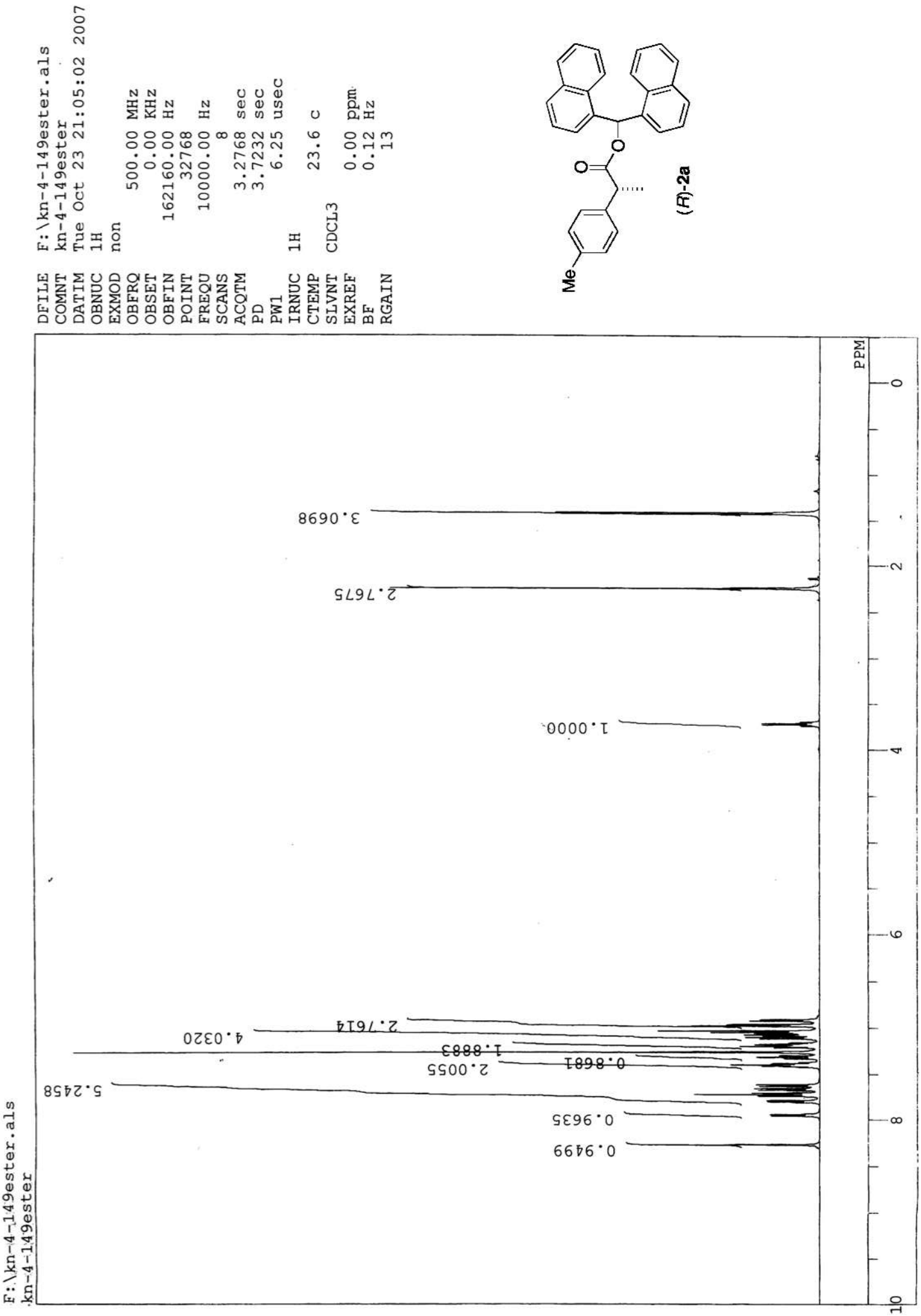
^{1}H NMR ($CDCl_3$): δ 8.29 (s, 1H), 8.00–7.90 (m, 1H), 7.82–6.96 (m, 17H), 6.95–6.81 (m, 2H), 3.86 (q, *J* = 7.0 Hz, 1H), 3.79 (s, 3H), 1.49 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 173.6, 157.6, 135.1, 134.7, 134.5, 133.8, 133.7, 133.6, 131.2, 130.8, 129.3, 129.1, 128.9, 128.8, 128.7, 128.6, 128.3, 127.1, 126.7, 126.5, 126.3, 126.2, 125.8, 125.6, 125.3, 125.2, 125.0, 123.4, 123.3, 118.9, 105.5, 71.2, 55.2, 45.5, 18.3; HR MS: calcd for $C_{35}H_{28}O_3Na$ ($M+Na^+$) 519.1931, found 519.1932.

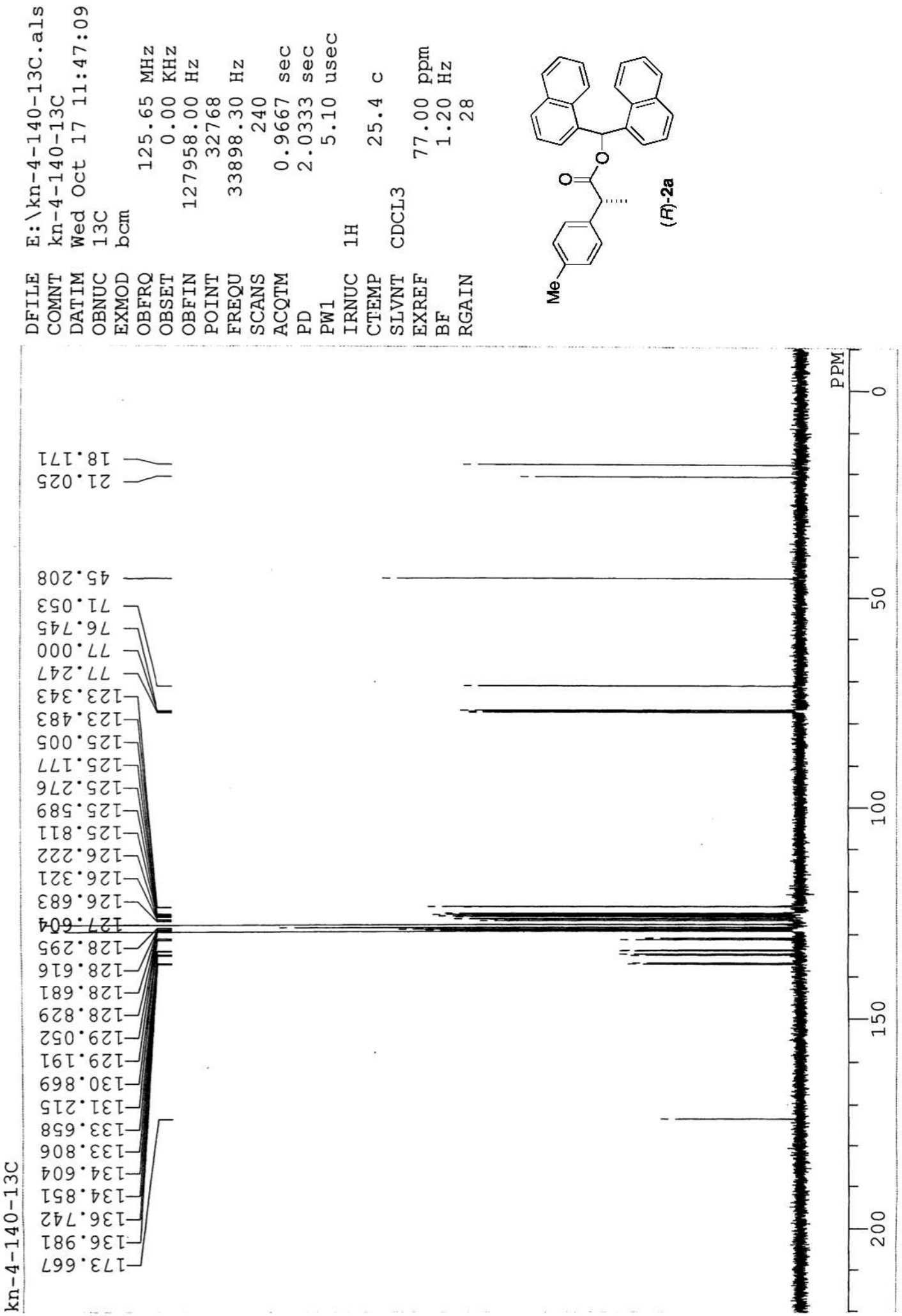


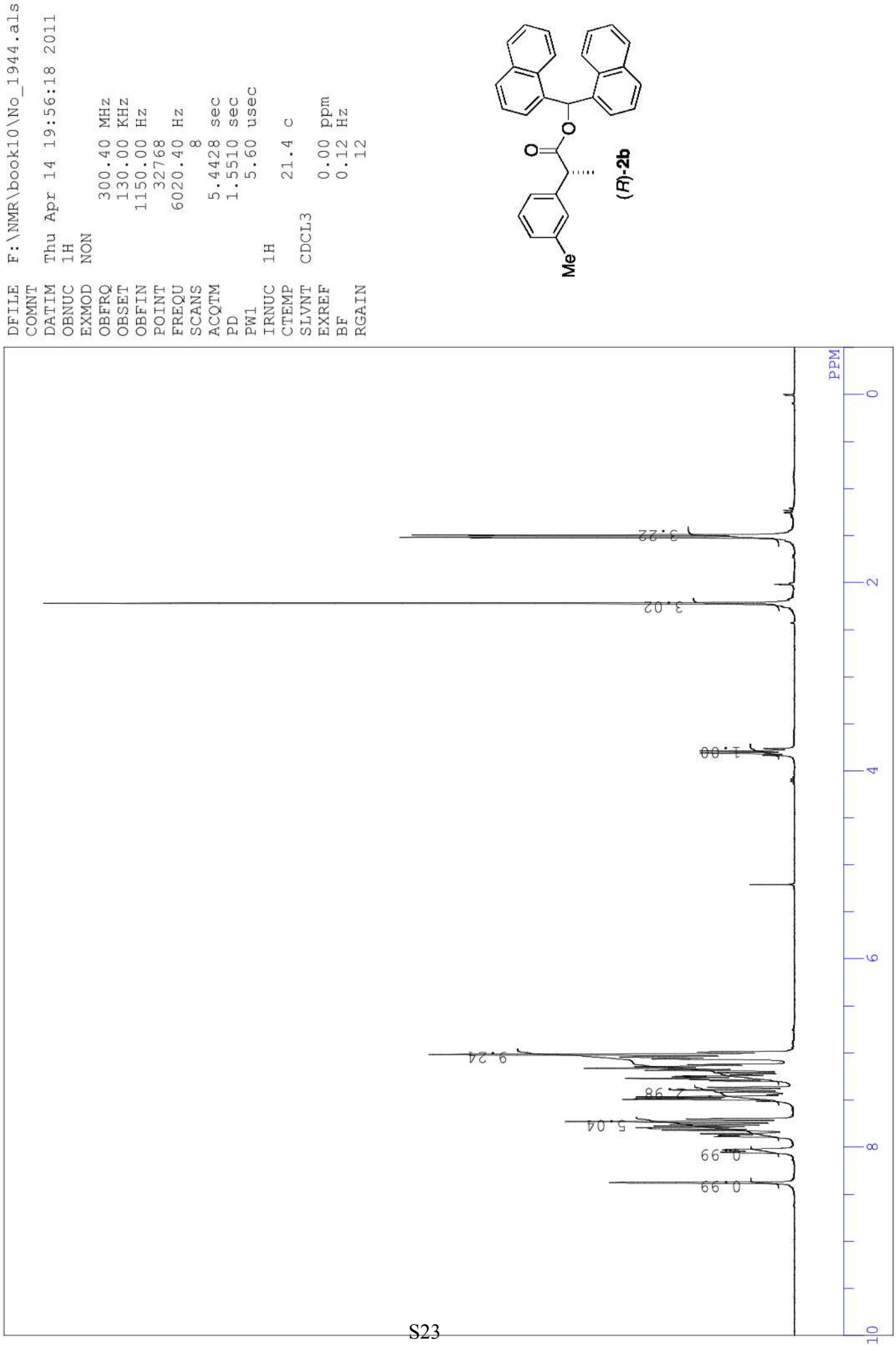


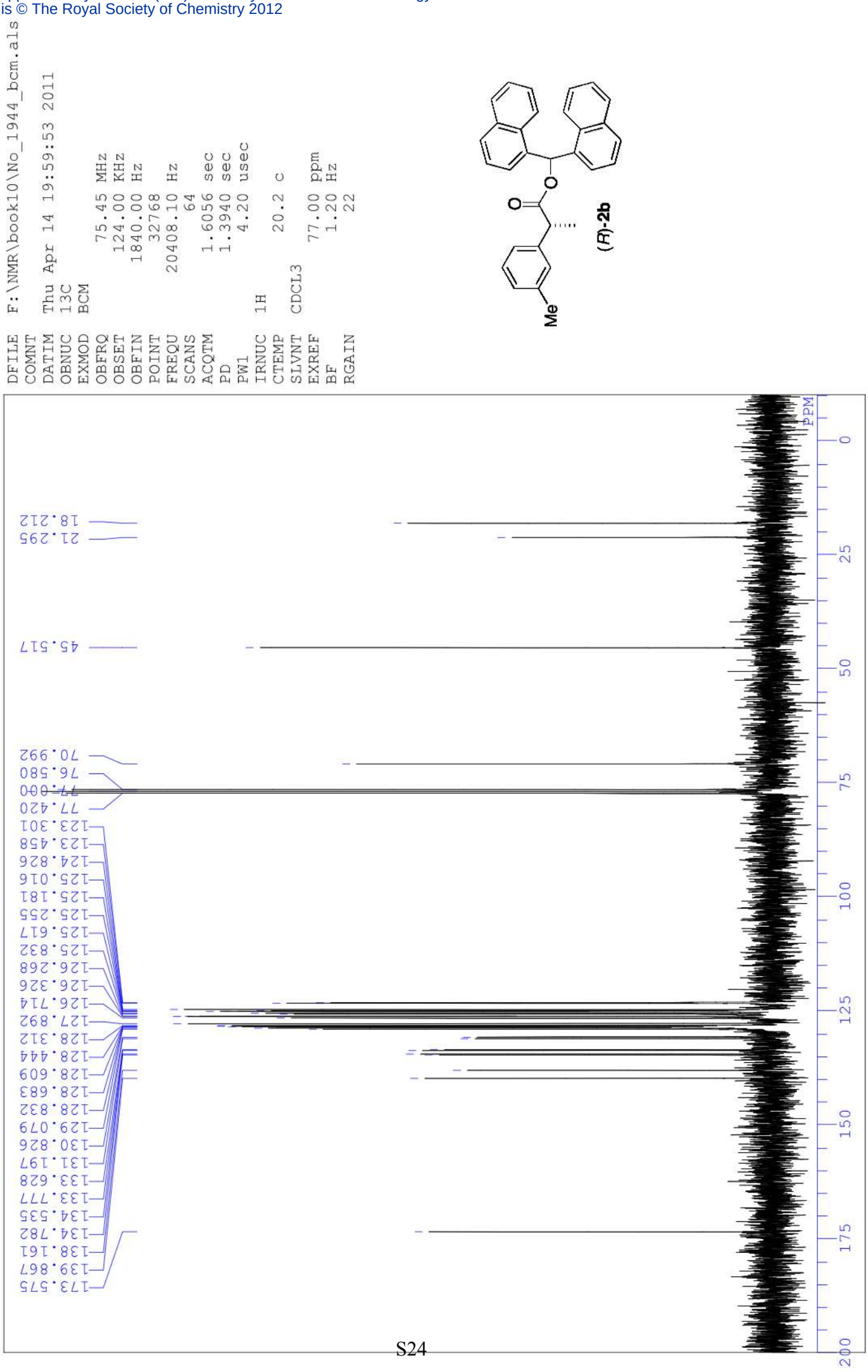


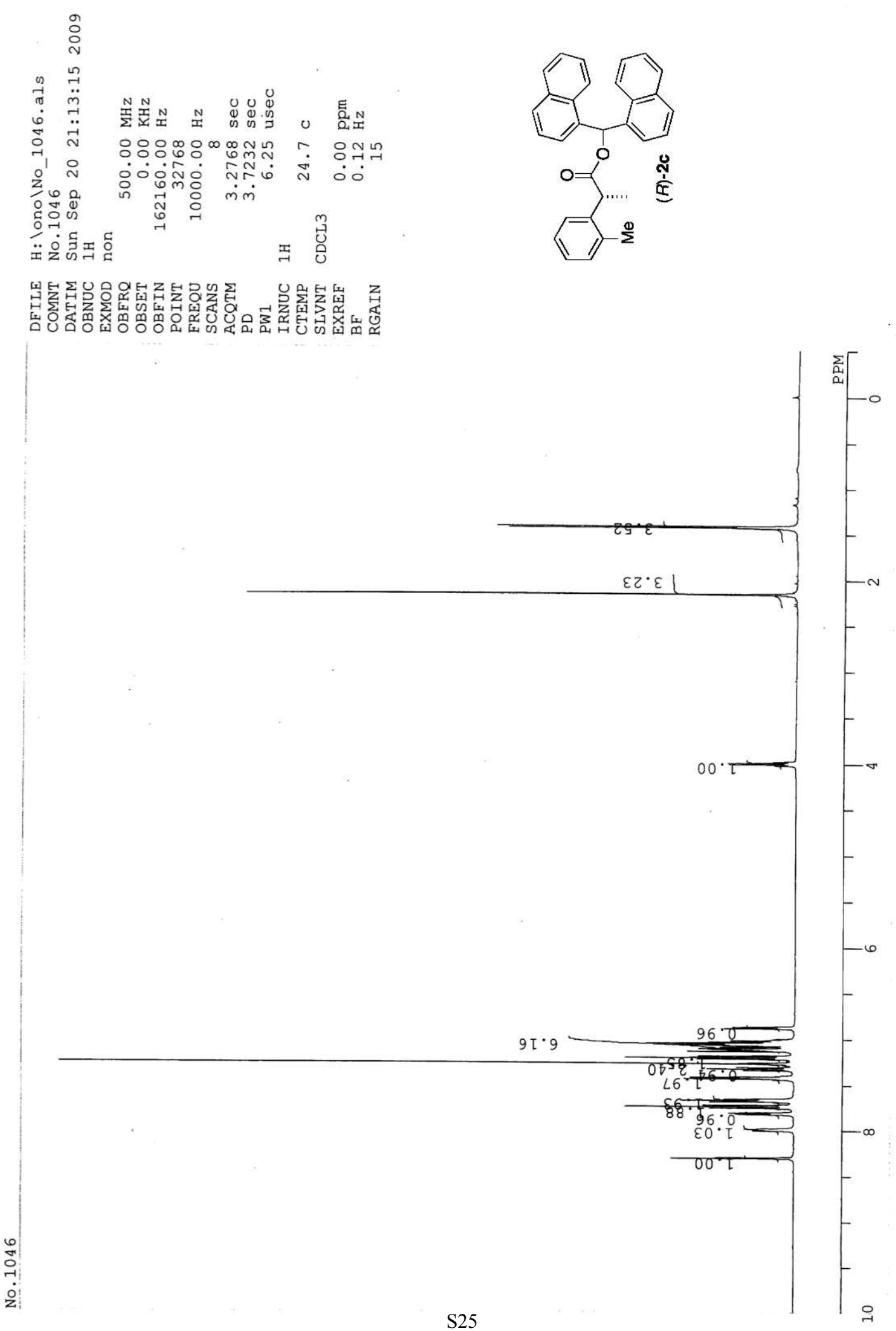


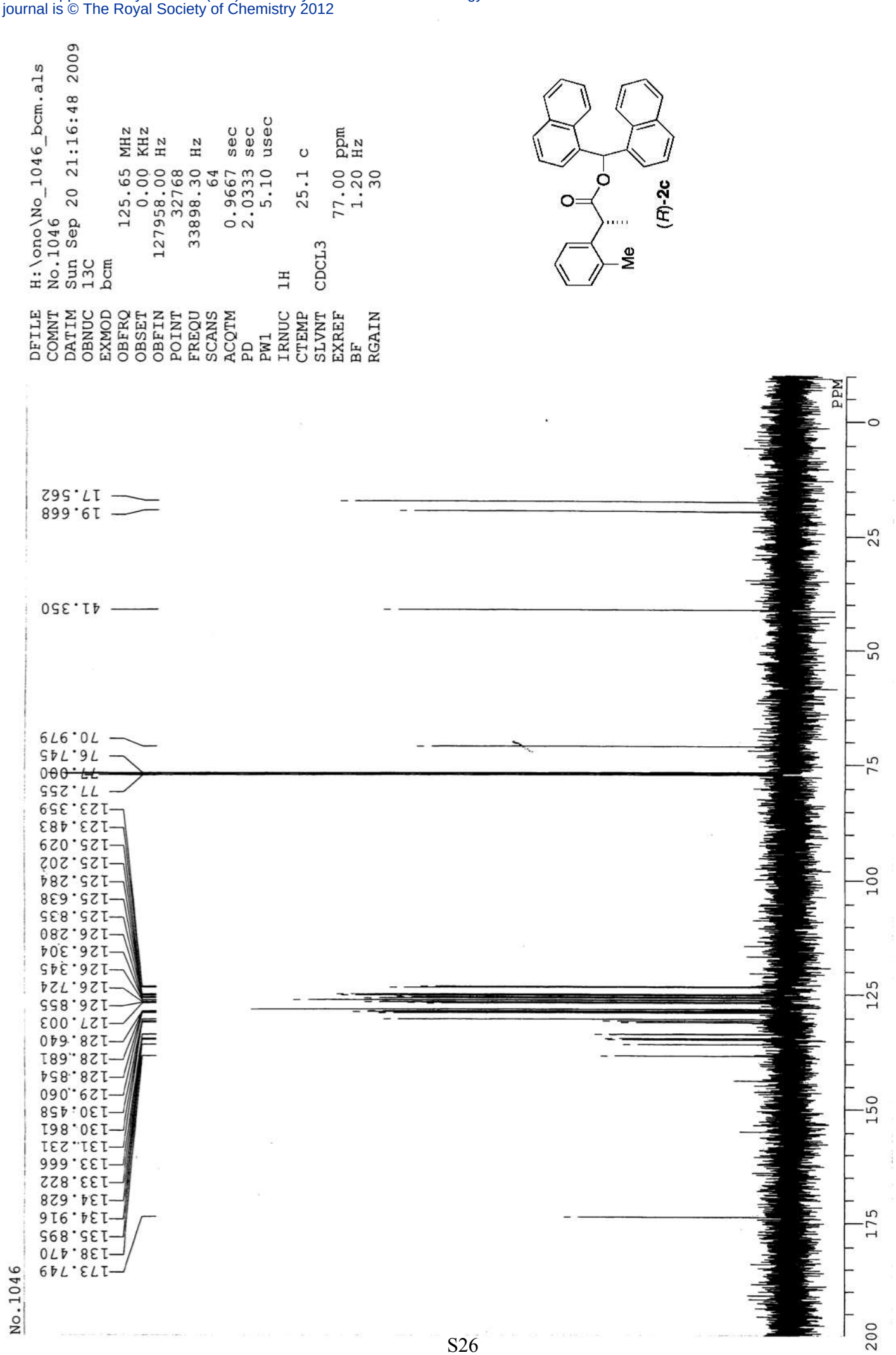


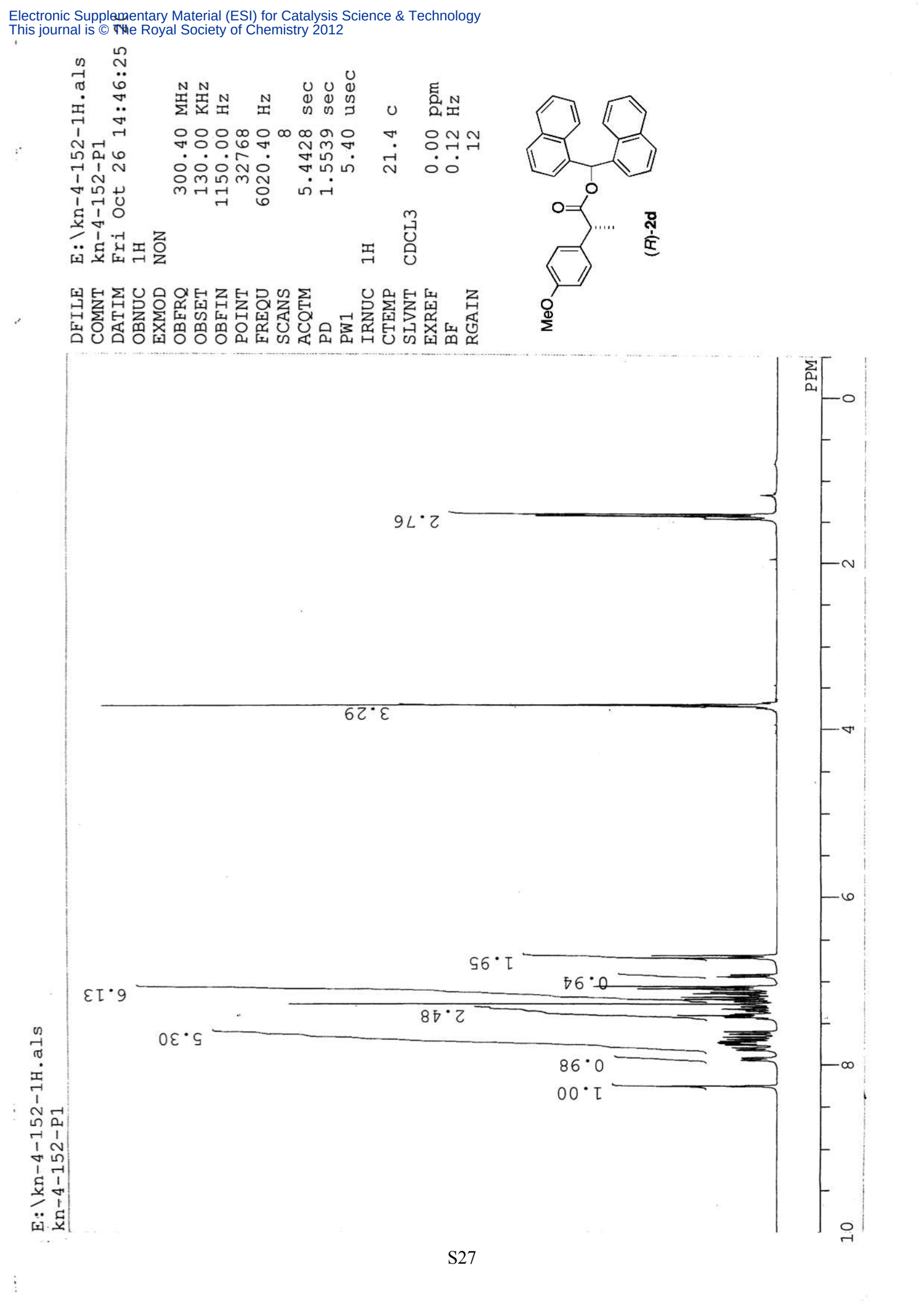


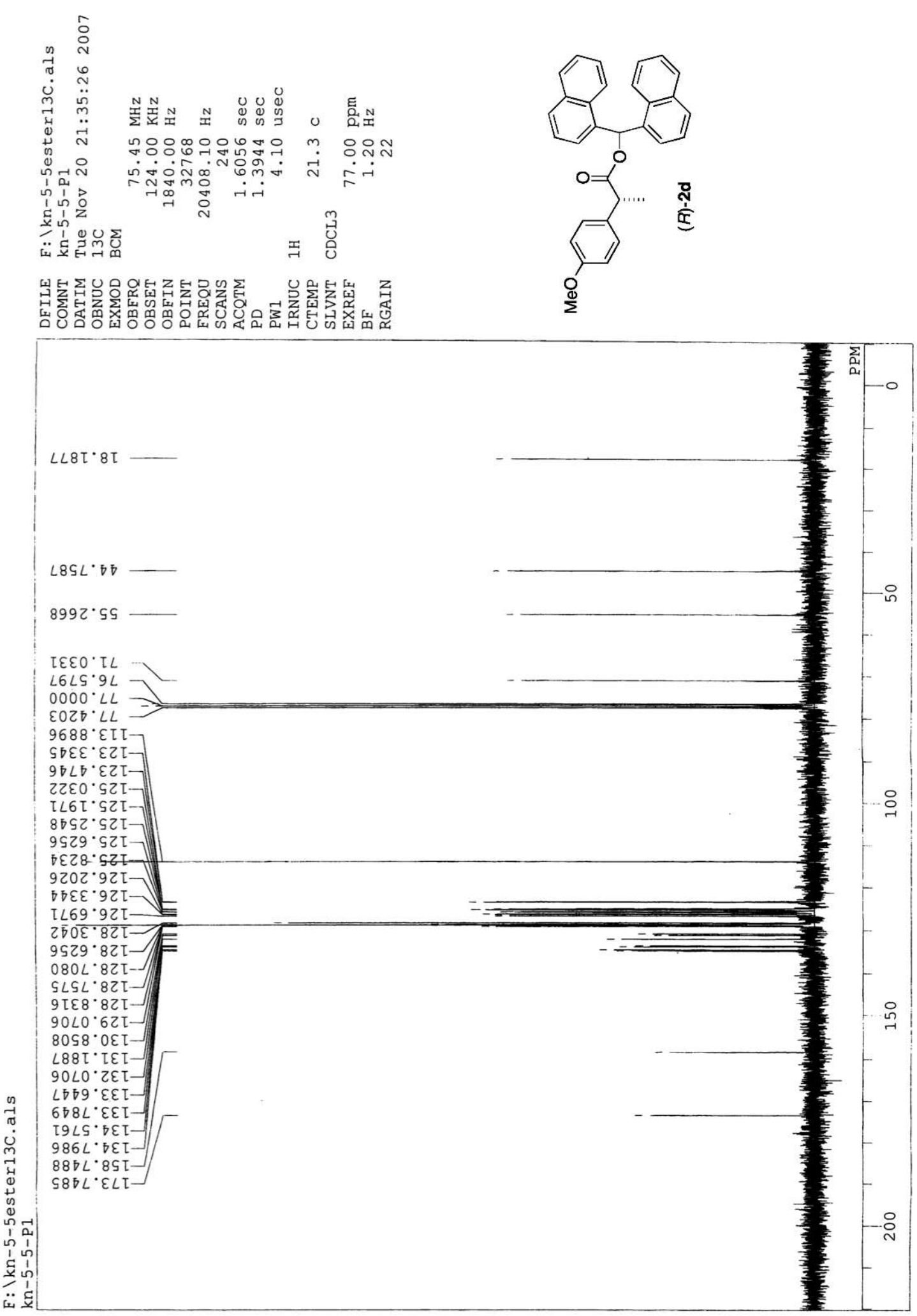


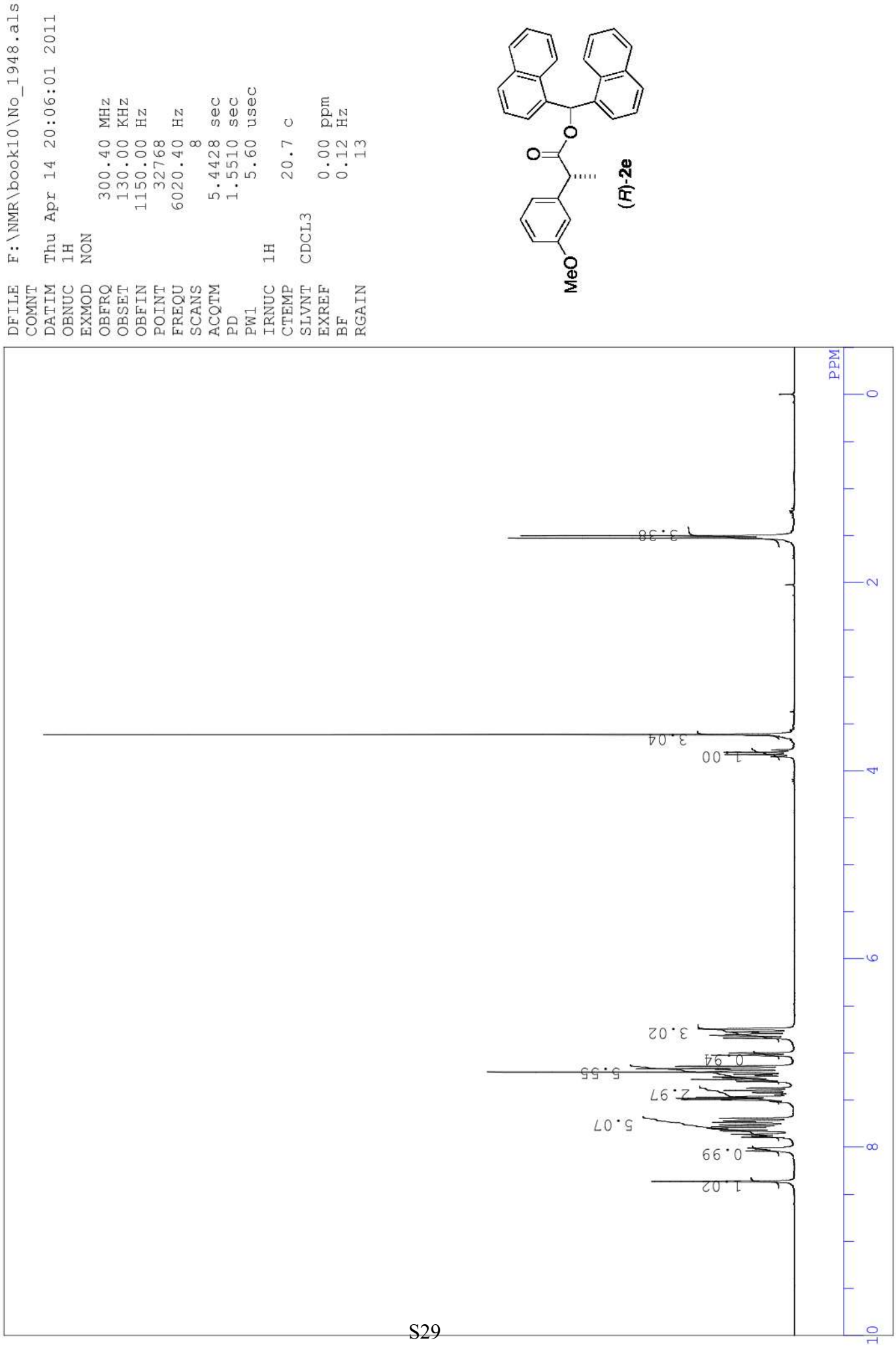


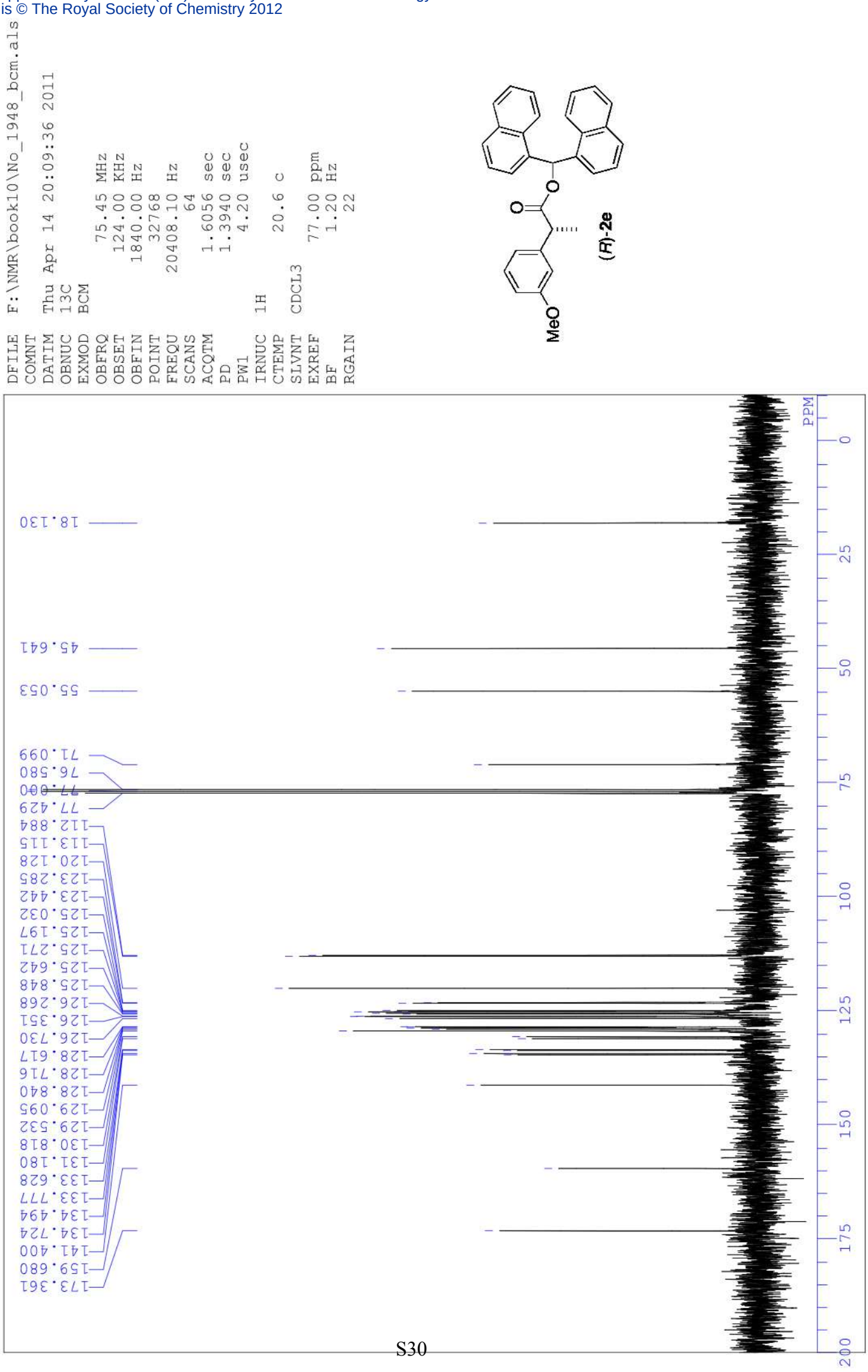


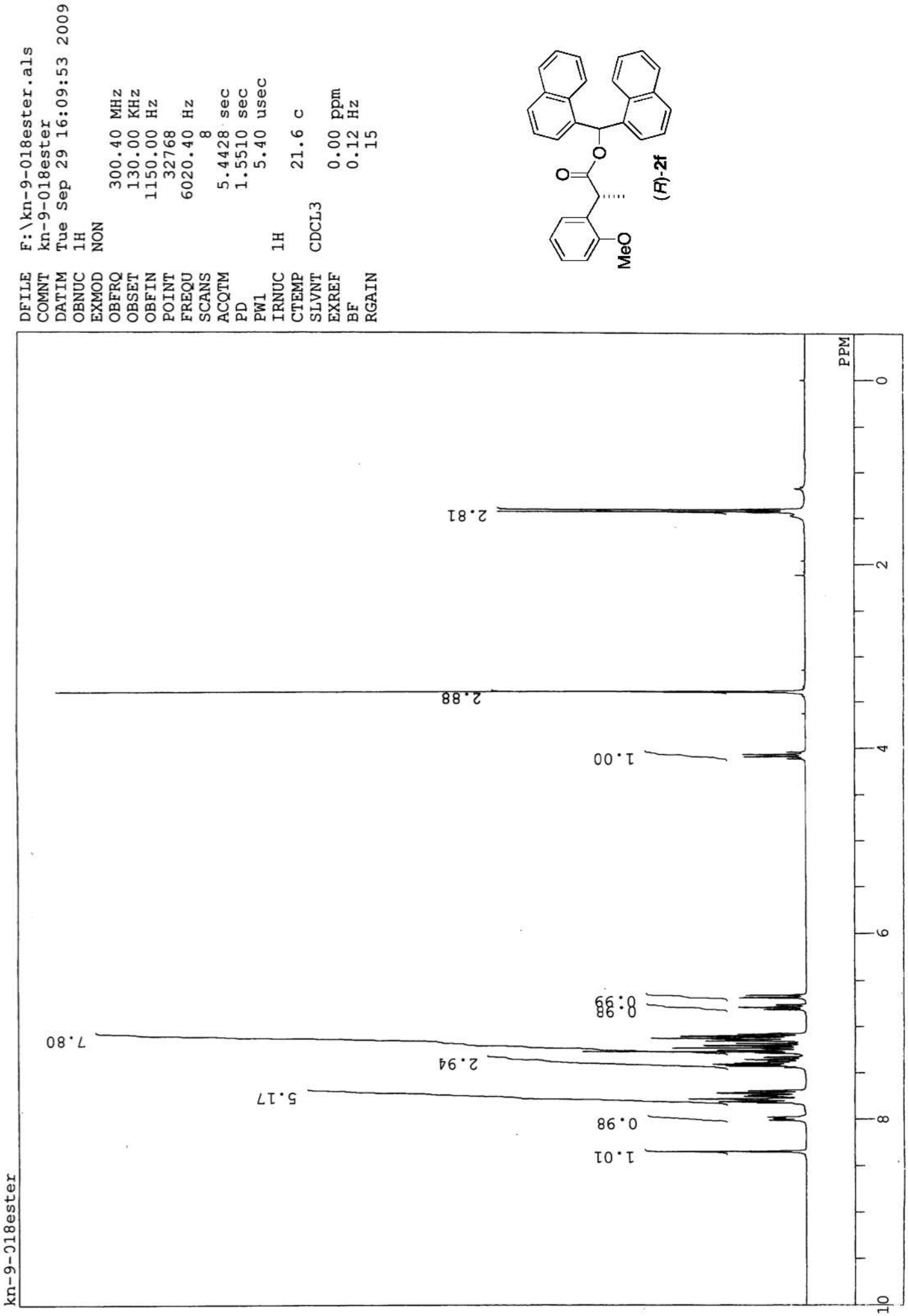


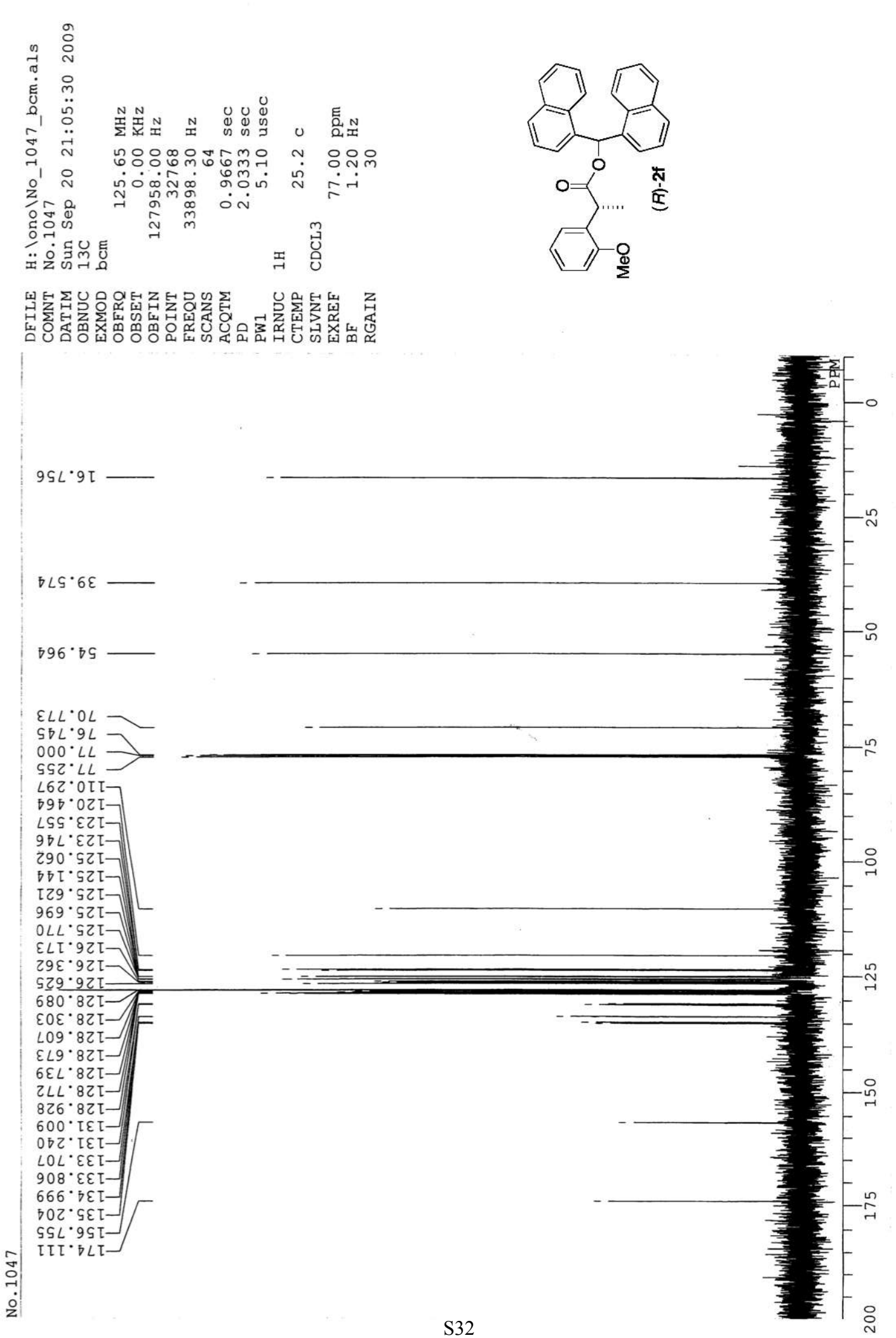


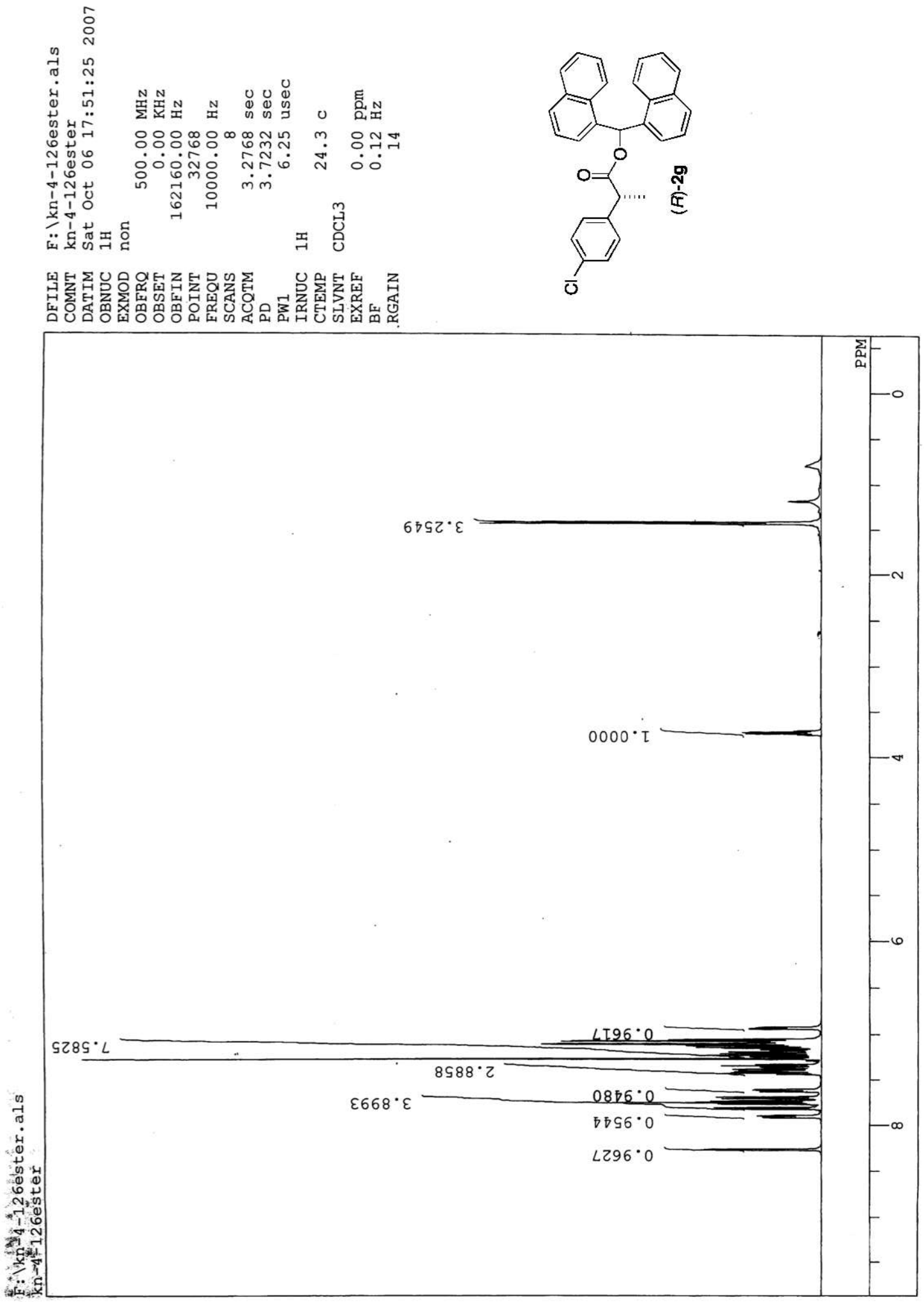


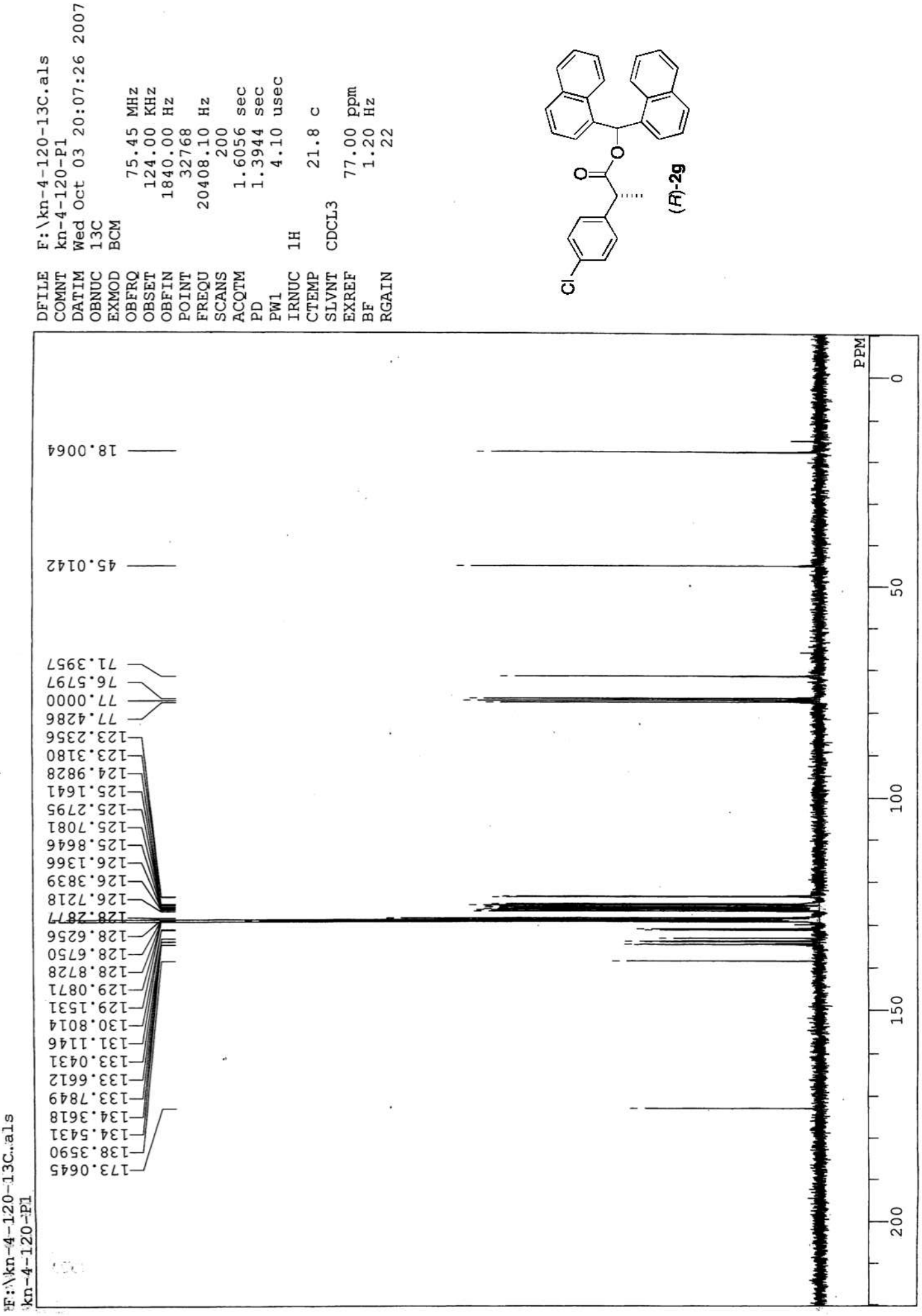


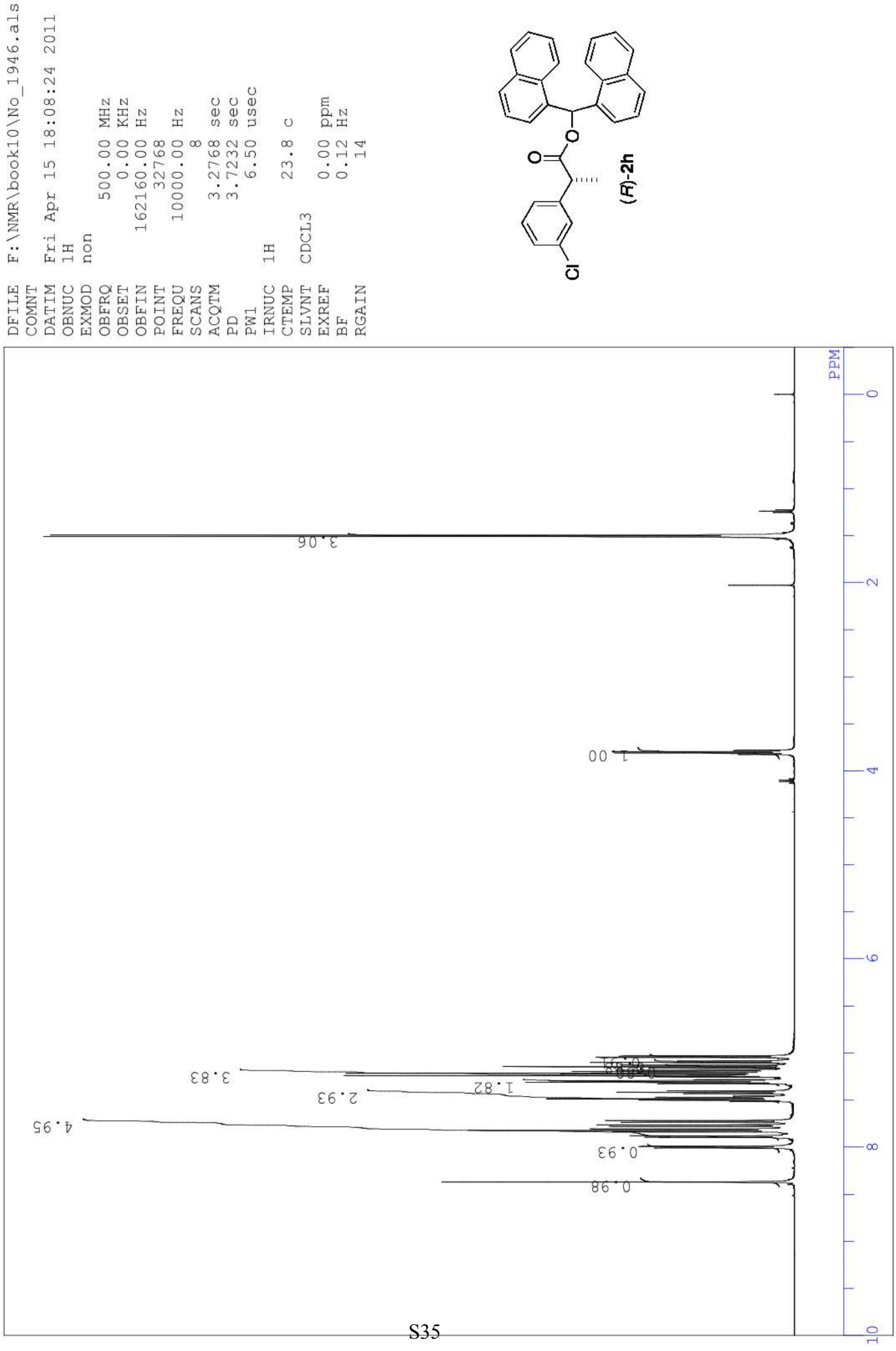


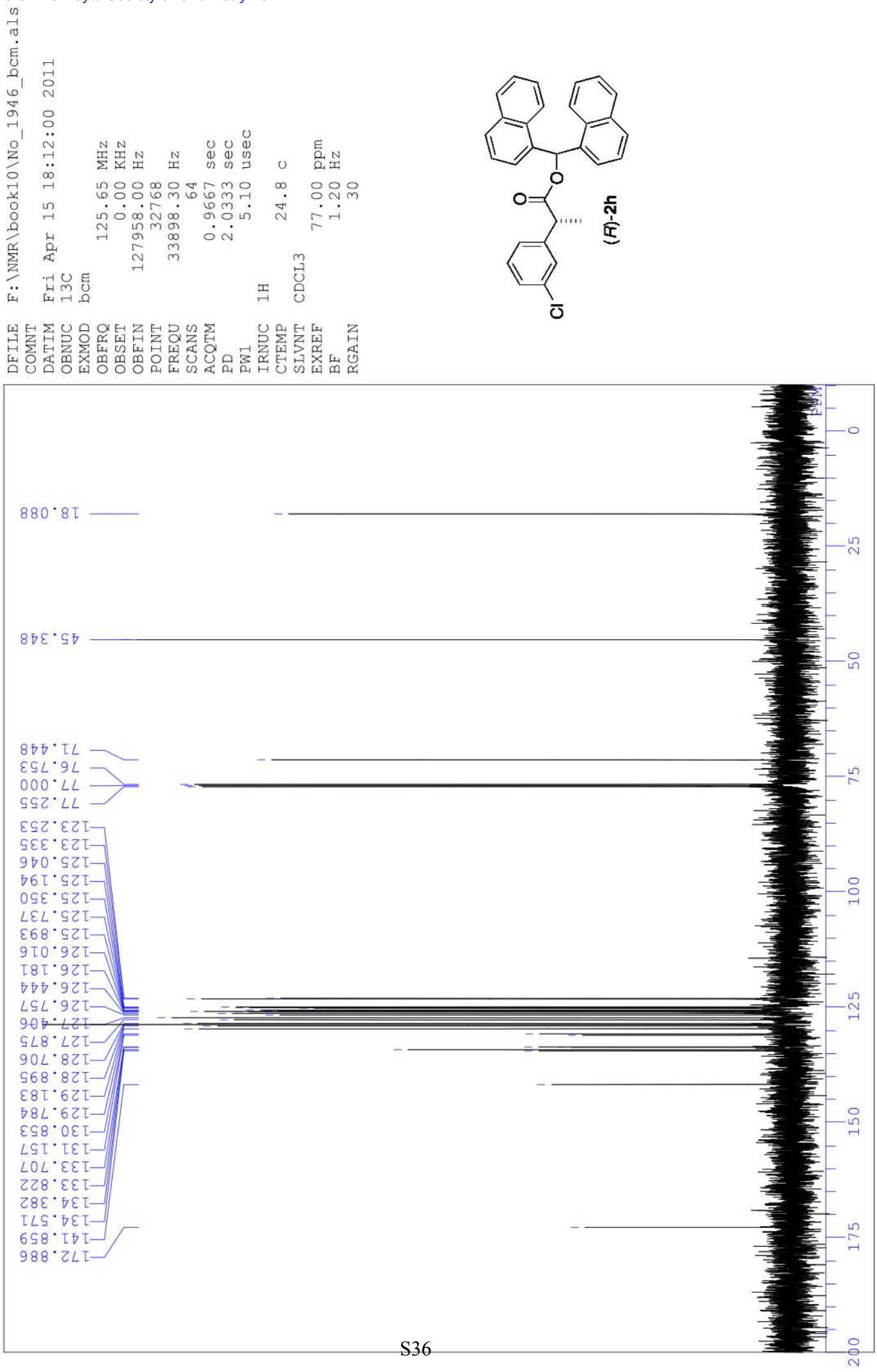


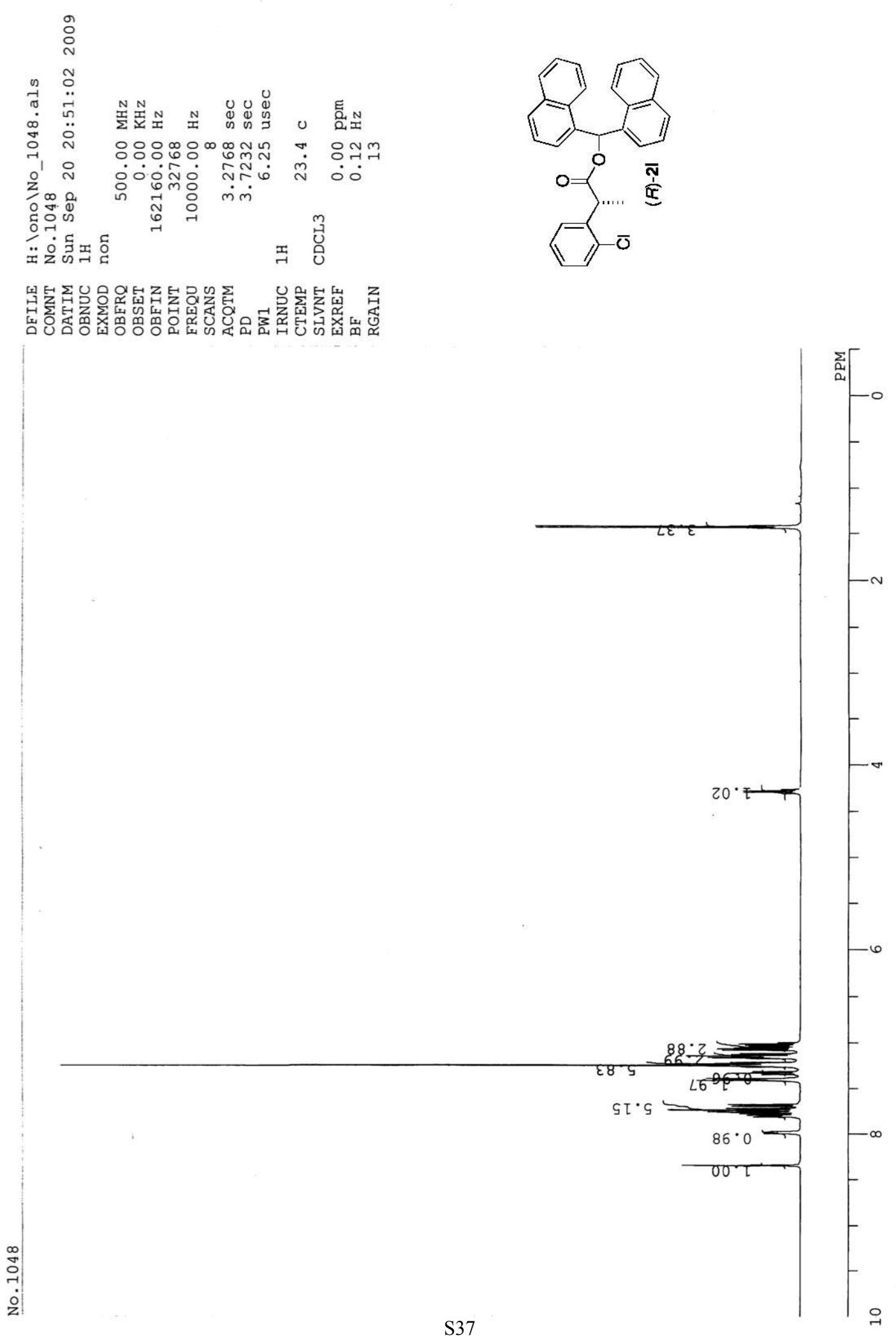


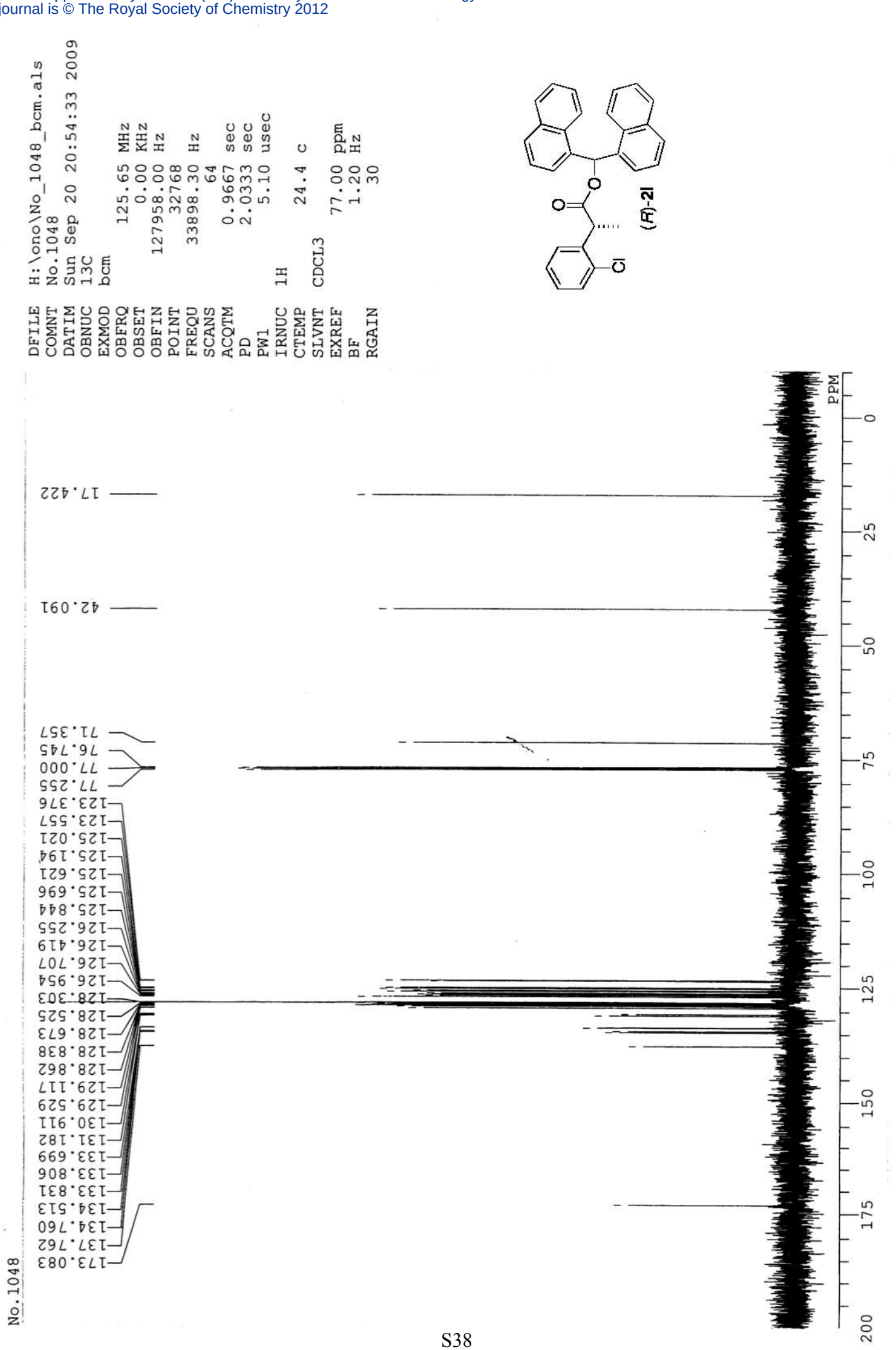


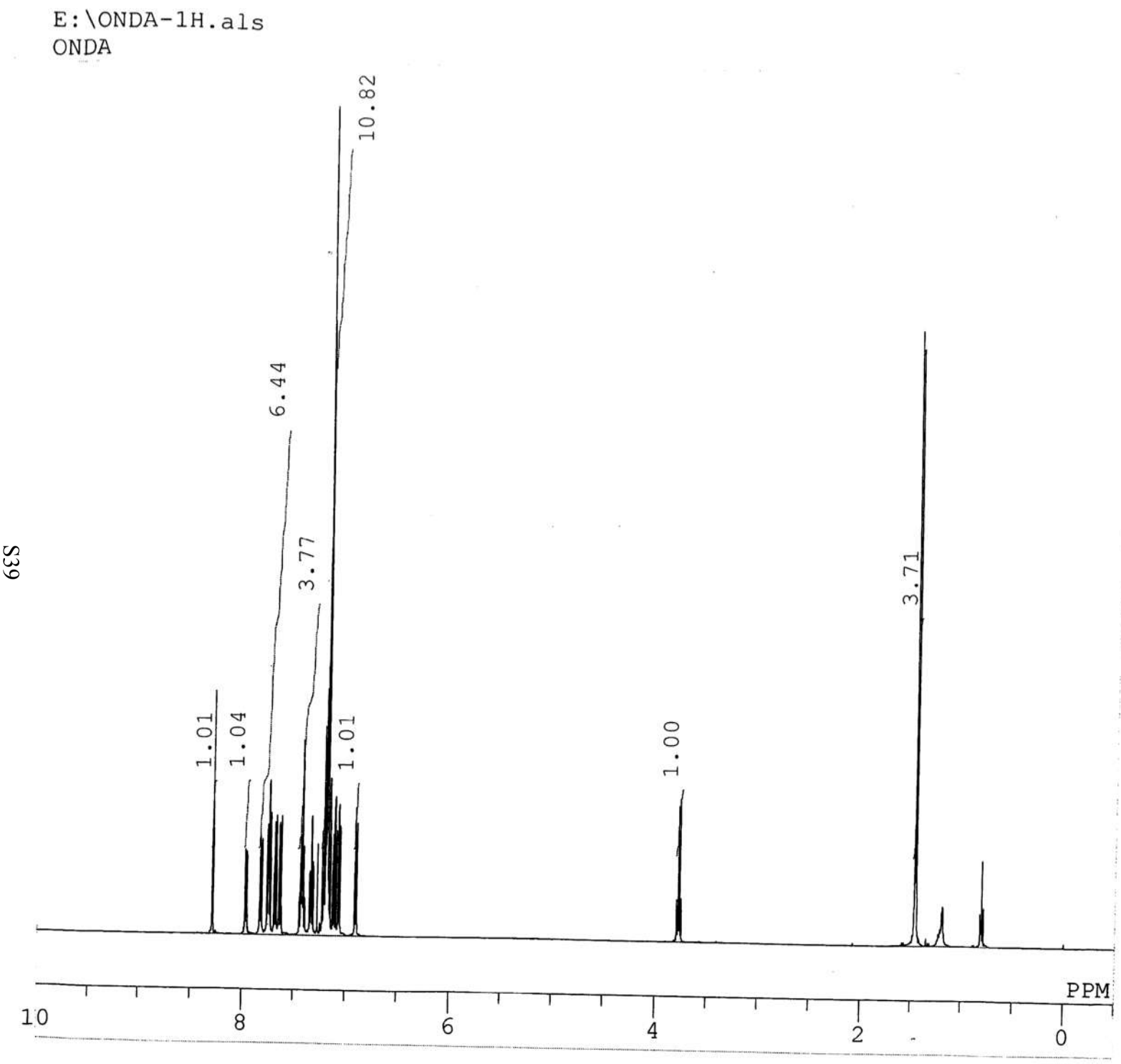












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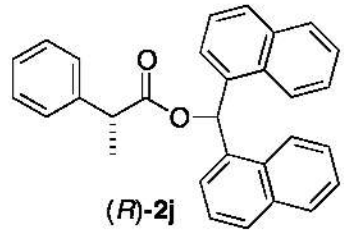

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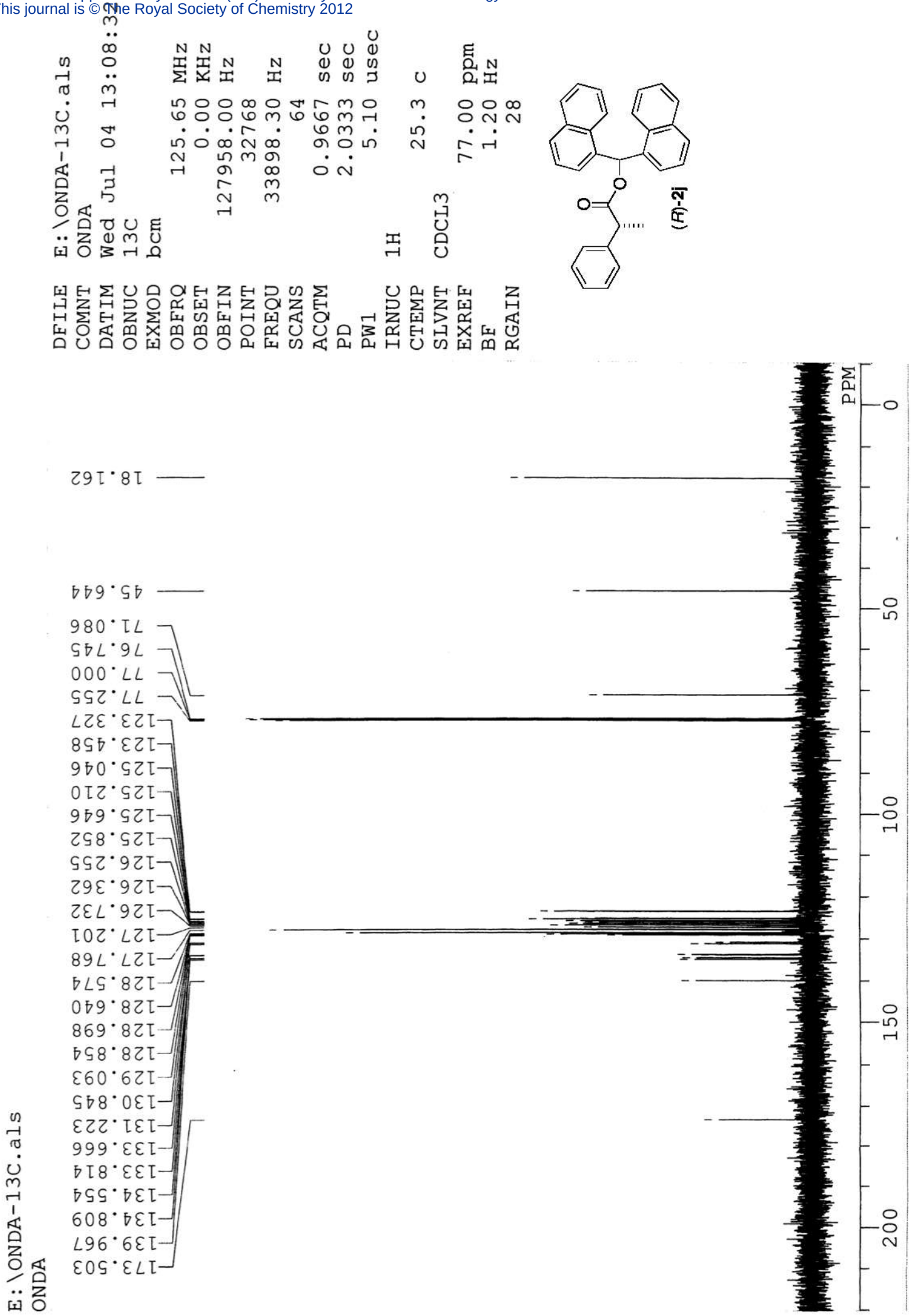

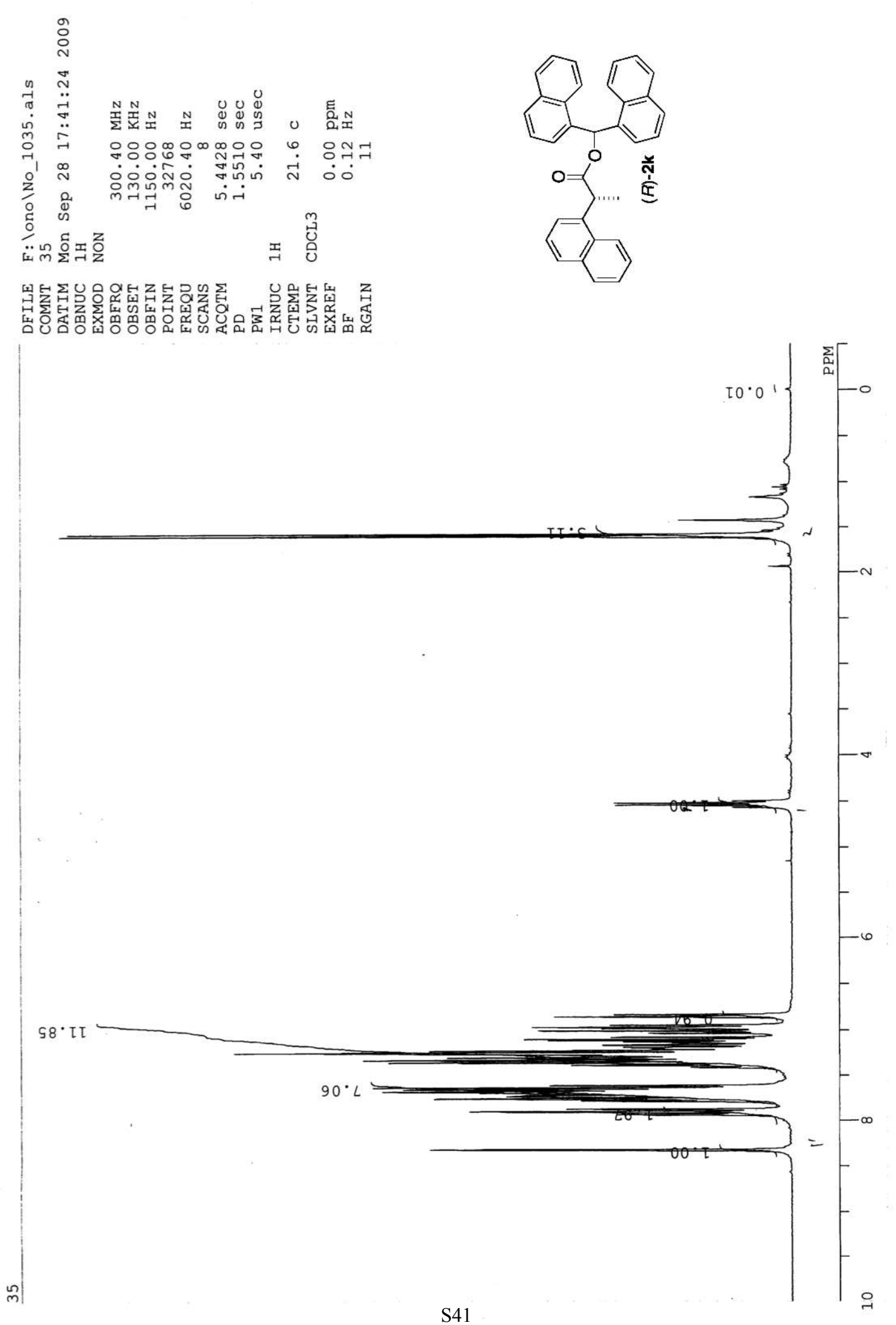

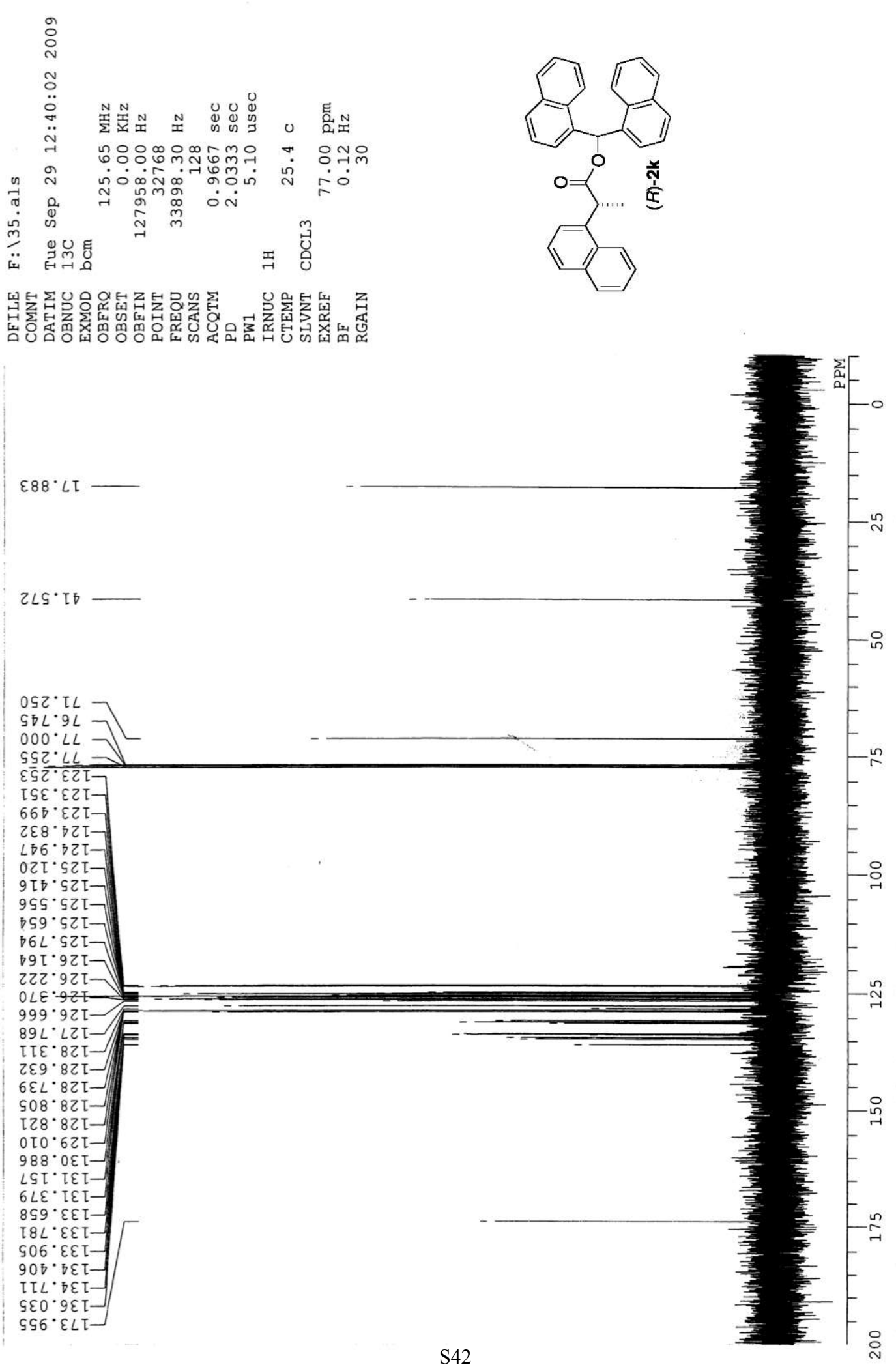

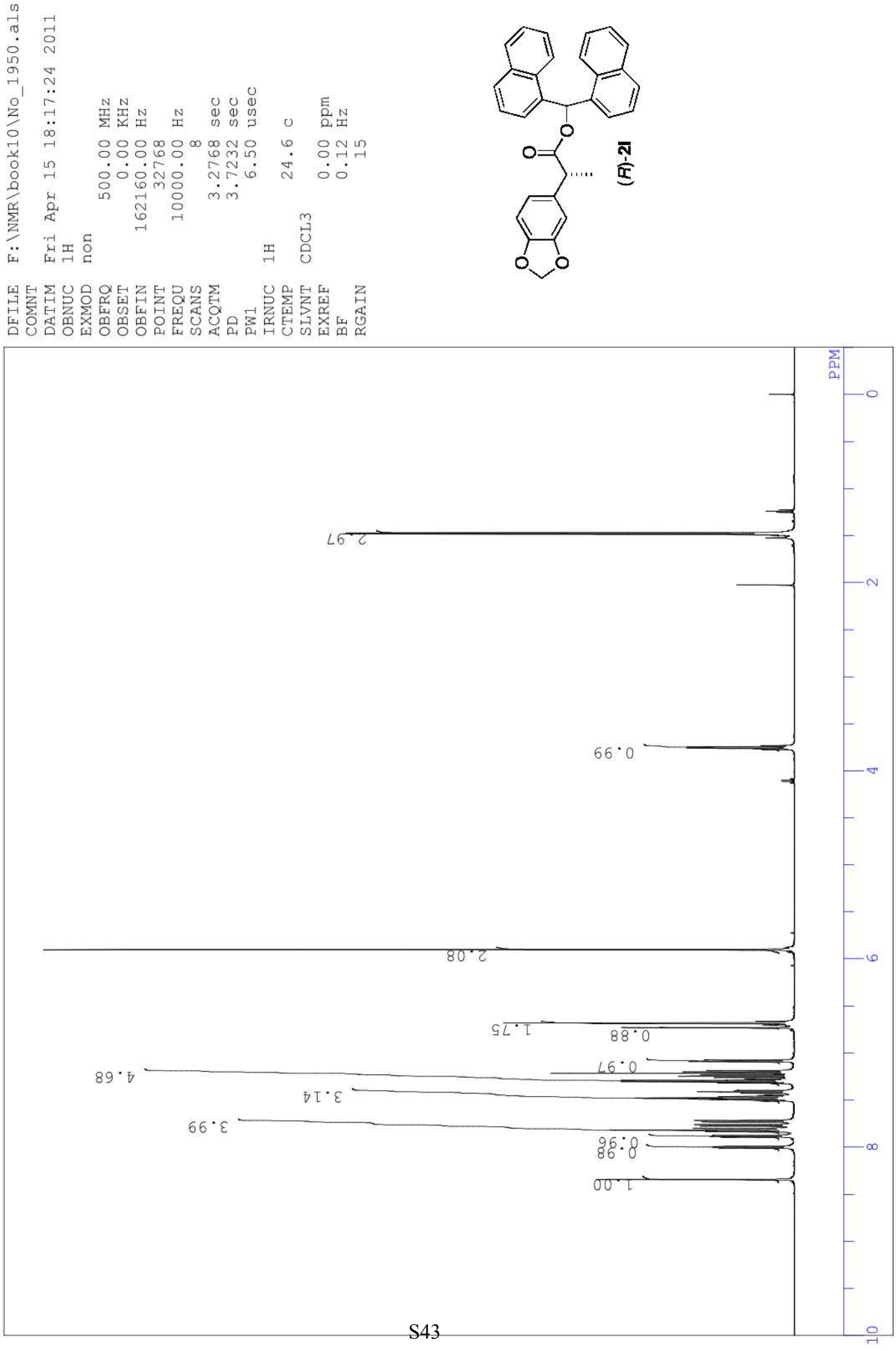
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