Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry

The acid-mediated ring-opening reactions of α-aryl lactams.

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Supplementary Notes

General procedure for the TfOH-mediate phenylation reaction.

Triflic acid (10 mmol) was added to a stirred solution of the lactam or cinnamamide (1 mmol) in dry benzene (20 ml) and the reaction mixture was heated under gentle reflux for the stated time. The reaction mixture was cooled to room temperature, water (20 ml) was added and the mixture basified with an excess of solid K_2CO_3. The product was extracted into DCM (2 x 50 ml), dried ($MgSO_4$), concentrated *in vacuo* and the product purified by column chromatography on SiO_2.

General procedure for the $AlCl_3$-mediate phenylation reaction.

Aluminium chloride (3mmol) was added to a stirred solution of the lactam or cinnamamide (1mmol) in dry benzene and the reaction mixture stirred at room temperature for the stated time. Water (10 ml) and DCM (20 ml) was added and the reaction stirred until all solids had dissolved. The product was extracted with DCM (2 x 50 ml), dried ($MgSO_4$), concentrated *in vacuo* and the product purified by column chromatography on SiO_2.

6-Phenyl-piperidin-2-one 1c

A solution of 4-benzoylbutyric acid (3.9g, 20mmol) and ammonium acetate (45g) in MeOH (120 ml) was stirred with the $NaBH_3CN$ (1.3g, 20 mmol) at rt for 2 days. Conc. HCl (270 ml) was and the solvent removed by rotary evaporation. The residue was extracted with IPA (2 x 200 ml), filtered and the solvent removed by rotary evaporation. The residue was heated to 210°C (block temp) for 1h. On cooling, the product was extracted into $CHCl_3$ (100 ml), the solvent was removed by rotary evaporation and the residue purified by column chromatography on silica, eluting with 2% MeOH/DCM to give **1c** (2.9g 82% yield), mp 139-40°C (EtOAc/ petroleum ether) (lit. 137°C: T. A. Ondrus, E. E. Knaus, C. S. Giam Can. J. Chem, 1979, **57**, 2342).

6,6-Diphenylhexanoic acid amide 2d

Prepared using TfOH (1.9 ml, 19mmol) in benzene (15 ml), reflux for 1h in 88% yield (0.45g) from **1d** (0.36g, 1.9mmol) and purified on silica by elution with 2% MeOH/DCM ; mp 88-9°C ($CHCl_3$/petroleum ether) lit. 94°C. (G. Cauquil, J, Rouzaud, R.E. Lyle, H.L. Fielding and G.G. Lyle, *Bull. Soc. Chim. Fr.* 1955, 513.). ^{1}H-NMR (500 MHz) δ = 1.27 – 1.36 (2H, m), 1.66 (2H, quintet, *J* = 7.6 Hz), 2.07 (2H, quartet, *J* = 7.8 Hz), 2.14 (2H, t, *J* = 7.5 Hz), 3.90 (1H, t, *J* = 7.8 Hz), 5.50 (1H, brs), 5.98 (1H, brs), 7.13 – 7.35 (10H, m), ^{13}C-NMR + DEPT (125 MHz) δ = 25.2 (CH_2), 27.7 (CH_2), 35.5 (CH_2), 35.9 (CH_2), 51.3 (CH), 126.2 (CH), 128.0 (CH), 128.5 (CH), 145.1 (C), 175.9 (C).

7,7-Diphenylheptanoic acid amide 2e

Prepared using TfOH (2 ml, 20 mmol) in benzene (15 ml), reflux for 1h in 94% yield (0.52g) from **1d** (0.4g, 2mmol) and purified on silica by elution with 2% MeOH/DCM ; mp 95-6°C (EtOAc/petroleum ether) lit. 105-6°C (benzene/petroleum ether) (G. Cauquil, J, Rouzaud, R.E. Lyle, H.L. Fielding and G.G. Lyle, *Bull. Soc. Chim. Fr.* 1955, 513). ^{1}H-NMR (500 MHz) δ = 1.23-1.42 (4H, m), 1.60 (2H, quintet, J = 7.6 Hz), 2.04 (2H, quartet, *J* = 7.6 Hz), 2.16 (2H, t, *J* = 7.5 Hz), 3.87 (1H, t, *J* = 7.8 Hz), 5.41 (1H, brs), 5.52 (1H, brs), 7.16 (2H, t, J = 7.1 Hz), 7.20 – 7.29 (8H, m); ^{13}C-NMR + DEPT (125 MHz) δ = 25.4 (CH_2), 27.8 (CH_2), 29.2 (CH_2), 35.6 (CH_2), 35.8 (CH_2), 51.4 (CH), 126.1 (CH), 128.2 (CH), 128.5 (CH), 145.2 (C), 175.4 (C). LRMS (EI) 281, 167; HRMS calcd for $C_{19}H_{23}NO$, 281.1774 found 281.1778. FT IR (neat) 3409, 3171, 2935, 2852, 1650, 1624, 1495, 1401, 1308, 1135, 801, 752, 738, 698, 676 cm^{-1}.

4-(3-Methyl-phenyl)-azetidin-2-one 3b

A solution of 3-methylstryrene (1.2g, 10mmol) and chlorosulphonyl isocyanate (1.1ml, 10mmol) in toluene (40 ml) was allowed to stand at room temperature for 7 days. The reaction mixture was treated with a solution of sodium sulfite (2.4g) and potassium carbonate (12g) in water (100 ml) and stirred for 1h. The product was extracted into Et_2O (100 ml), the organic layer separated and dried ($MgSO_4$). Evaporation and purification on silica, eluting initially with DCM, then 2% MeOH/DCM gave **3b** (1.37g, 84% yield) mp 83-4oC (EtOAc/petroleum ether). ^{1}H-NMR (500 MHz) δ = 2.36 (3H, s), 2.86 (1H, ddd, *J* = 1.0, 2.5, 14.9 Hz), 3.42 (1H, ddd, *J* = 2.4, 5.3, 14.9 Hz), 4.68 (1H, dd, *J* = 2.5, 5.3 Hz), 7.11 – 7.19 (3H, m), 7.26 (1H, t, *J* = 7.7 Hz). ^{13}C-NMR + DEPT (125 MHz) δ = 21.4 (CH3), 48.0 (CH2), 50.4 (CH), 122.8 (CH), 126.3 (CH), 128.8 (CH), 129.0

(CH), 138.7 (C), 140.3 (C), 168.2 (C). LRMS (EI) 161, 118, 117, 91; HRMS calcd for $C_{10}H_{11}NO$, 161.0835 found 161.0832. FT IR (neat) 3161, 3096, 1772, 1707, 1609, 1352, 1277, 1189, 1161, 989, 967, 935, 781, 713, 698 cm^{-1}.

TfOH-mediated ring opening of 1f

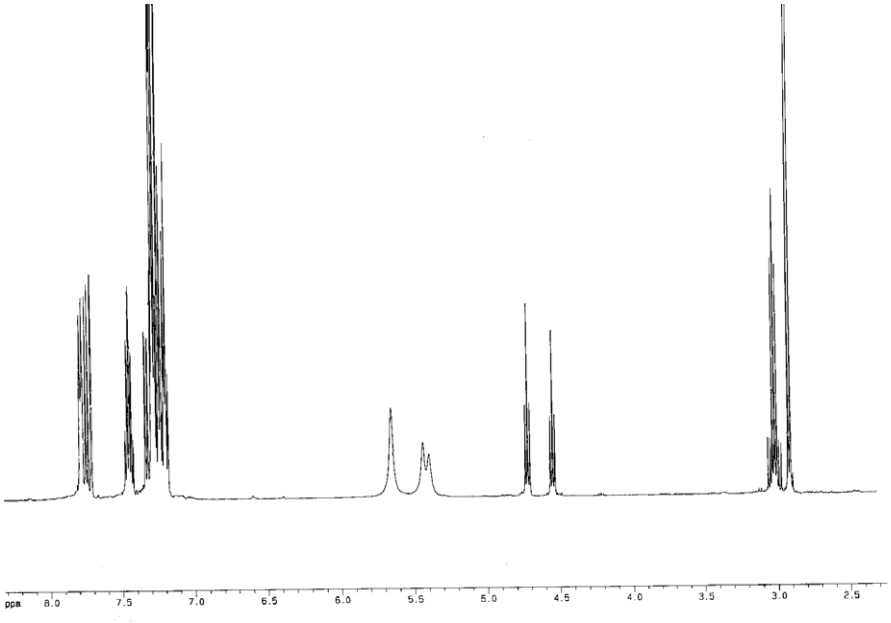
The reaction used TfOH (2 ml, 20 mmol) in benzene (15 ml), reflux for 1h, from **1d** (0.44g, 2mmol) and purified on silica by elution with 2% MeOH/DCM 0.5g of product was obtained. NMR was consistent with a mixture of $Ph_2CH(CH_2)_6CONH_2$, $Ph(CH_2)_7CONH_2$ and other unidentified products: ^{1}H-NMR (500 MHz) (integration relative to NH) δ = 1.10 – 1.42 (6H, m), 1.50 – 1.75 (2H, m), 2.00 – 2,25 (4H, m), 2.60 (0.5H, t, *J* = 7.9Hz), 2.75 – 2.82 (0.25Hm m), 2.87 (0.25H, d, *J* = 7.3 Hz), 3.88 (0.5H, t, *J* = 7.8 Hz), 5.51 (1H, brs), 5.90 (1H, brs), 7.10 – 7.40 (~9H, m), ^{13}C-NMR + DEPT (125 MHz) (major product) δ = 25.4 (CH_2), 27.9 (CH_2), 29.1 (CH_2), 29.4 (CH_2), 35.7 (CH_2), 35.9 (CH_2), 51.4 (CH), 126.1 (CH), 127.9 (CH), 128.5 (CH), 145.3 (C), 175.8 (C).

Preparation of E-3-(4-methylphenyl)-acrylamide 5a from 3a

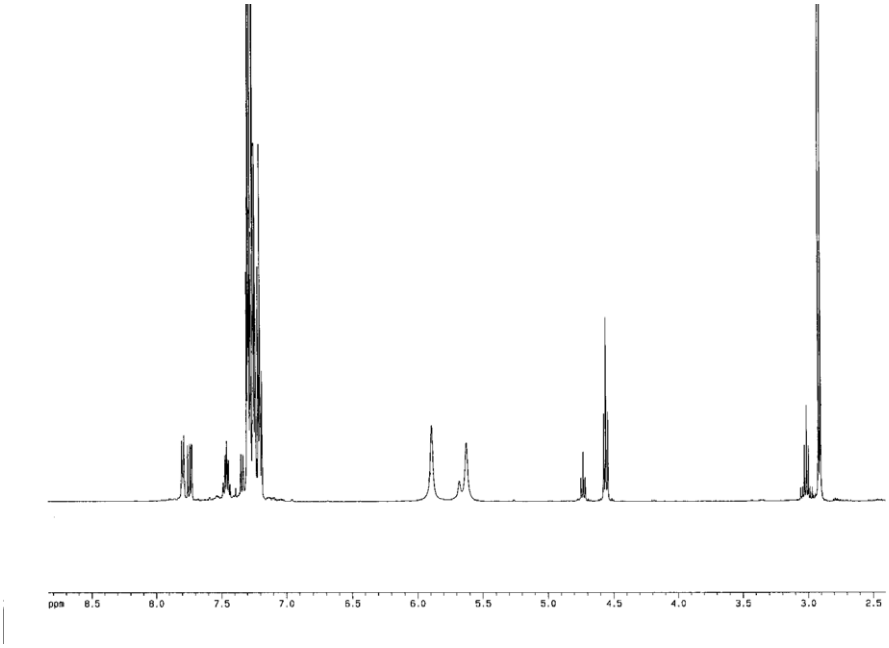
A stirred solution of **3a** (0.32g, 2mmol) in $CHCl_3$ (20 ml) was heated under reflux with TfOH (2 ml, 20 mmol) for 0.5h. The reaction mixture was cooled, water (20 ml) was added and the aqueous layer basified with solid K_2CO_3. The $CHCl_3$ was removed by rotary evaporation, water (20 ml) added and the solid collected, washed with water (20 ml) and dried to give 0.32g of **5a** (100% yield), mp 187-9°C ($CHCl_3$/petroleum ether) Lit. 189-90°C (Y. Ito, H. Hosomi and S. Ohba *Tetrahedron,* 2000 , **56**, 6833).

Ring opening of 3i

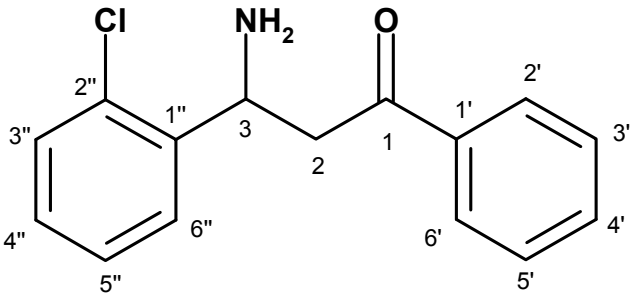
The reaction used TfOH (2 ml, 20 mmol) in benzene (15 ml), reflux for 0.5h, from **3i** (0.4g, 2mmol) and purified on silica by elution with 1% MeOH/DCM 0.33g of product was obtained, NMR consistent with a 1:1 mixture of **4i** and **2a**. ^{1}H-NMR (500 MHz) (integration relative to NH = 1) δ = 2.92 (1H, d, *J* = 7.8 Hz), 2.98 (0.5H, dd, *J* = 7.8, 14.6 Hz), 3.03 (0.5H, dd, *J* = 7.8, 14.6 Hz), 4.55 (0.5H, t, *J* = 7.8 Hz), 4.72 (0.5H, t, *J* = 7.7 Hz), 5.40 (0.5H, brs), 5.45 (0.5H, brs), 5.65 (1H, brs), 7.17 – 7.30 (7.5H, m), 7.33 (0.5H, dd, *J* = 1.8, 8.5 Hz), 7.43 (0.5H, dt, J = 1.5, 6.9Hz), 7.47 (0.5H, dt, J = 1.5, 6.9Hz), 7.70 – 7.80 (2H, m).



Repeating the reaction, but heating for 1.5h also gave 0.33g of product, NMR consistent with a 1:5 mixture of **4i** and **2a**. ^{1}H-NMR (500 MHz):



3-Amino-3-(2-chlorophenyl)-1-phenyl-propan-1-one 6



Following the general procedure, **3e** (0.36g, 2mmol) was heated under reflux in benzene (15 ml) with TfOH (1ml, 10mmol) for 1.5h. Purification by column chromatography on SiO_2, eluting initially with 3:1 petroleum ether/Et_2O to 1:1 petroleum ether/Et_2O gave **6** as an oil (0.29g, 55% yield). ^{1}H-NMR (500 MHz) δ = 1.89 (2H, brs, NH_2), 3.19 (1H, dd, *J* = 9.5, 17.3 Hz C2-H), 3.41 (1H, dd, *J* = 2.9, 17.3 Hz C2-H), 5.05 (1H, dd, *J* = 2.9, 9.5 Hz C3-H), 7.20 (1H, dt, *J* = 1.7, 7.7 Hz C4"-H), 7.30 (1H, dt, *J* = 1.2, 7.6 Hz C5"-H), 7.35 (1H, dd, *J* = 1.2, 7.9 Hz C3"-H), 7.44 (2H, t, *J* = 7.5 Hz C3'-H), 7.55 (1H, t, *J* = 7.4 Hz C4'-H), 7.67 (1H, dd, *J* = 1.6, 7.8 Hz C6"-H), 7.96 (2H, d, *J* = 7.4 Hz C2'-H). ^{13}C-NMR (125Hz) δ = 46.8 (CH_2), 48.8 (CH), 127.3 (5"-CH), 127.6 (6"-CH), 128.2 (2'-CH), 128.3 (4"-CH), 128.7 (3'-CH), 129.8 (3"-CH), 132.9 (2"-C), 133.4 (4'-CH), 137.2 (1'-C), 142.7 (1"-C), 199.2 (1-C). LRMS (EI) 260, 258(M-H), 207 ($C_{15}H_{13}N$), 140 ($C_7H_7ClN^+$), 105 ($PhCO^+$), 77(Ph^+). HRMS calcd. for M-H $C_{15}H_{13}ClNO$ 258.0680, found 258.0678. FT IR (neat) 3062, 1679, 1596, 1447, 1207, 1034, 980, 908, 751, 731, 689.

8-(4-Bromophenyl)-azocan-2-one 8

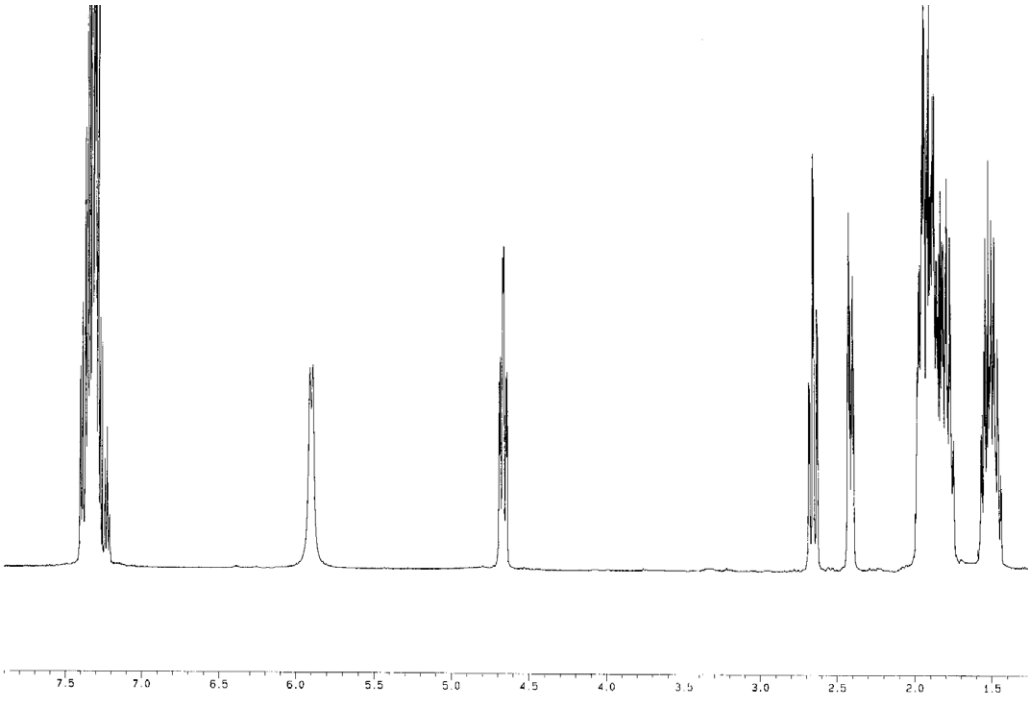
Following the procedures described for **7**, p-bromobenzaldehyde tosylhydrazide (G.W. Kabalka, J.T. Maddox, E. Bogas and S.W. Kelley, *J. Org. Chem*. 1997, **62**, 3688) (6.8g, 20mmol) was converted to 2-(4-bromophenyl)cycloheptanone (3.0g, 55% yield), mpt. 41-3°C (MeOH/H_2O). ^{1}H-NMR (500 MHz) δ = 1.40 – 1.52 (2H, m), 1.60 – 1.73 (1H, m), 1.86 – 2.13 (5H, m), 2.49 – 2.55 (1H, m), 2.63 (1H, dt, *J* = 3.4, 10.7 Hz), 3.70 (1H, dd, *J* = 3.9, 11.4 Hz), 7.09 (2H, d, *J* = 8.4 Hz), 7.43 (2H, d, *J* = 8.4 Hz); ^{13}C-NMR + DEPT (125 MHz) δ = 25.0 (CH_2), 28.8 (CH_2), 29.8 (CH_2), 32.2 (CH_2), 43.0 (CH_2), 58.0 (CH), 120.9 (C), 129.8 (CH), 131.6 (CH), 139.5 (C), 212.8 (C). LRMS (EI) 268, 266, 197, 195, 184, 182, 171, 169, 116; HRMS calcd for $C_{13}H_{15}BrO$, 266.0301, found 266.0298; FT IR (neat) 2929, 281, 1691, 1488, 1441, 1323, 1161, 1133, 1071, 1008, 937, 830, 792, 746, 704.
The ketone (2.8 g, 10.4 mmol) was converted to its oxime (3.0 g, 95% yield) mpt 139-40°C (toluene/petrol).

The oxime (2.3g, 8 mmol) was converted into **8**, (1.2g, 52% yield), mp 130-1°C (EtOAc/petroleum ether). ^{1}H-NMR (500 MHz) δ = 1.40 – 1.55 (2H, m), 1.71 – 2.02 (6H, m), 2.42 (1H, dt, *J* = 3.5, 12.5 Hz), 2.63 (1H, dt, *J* = 2.6, 12.8 Hz), 4.63 (1H, dt, *J* = 2.9, 11.1 Hz), 5.80 (1H, brd, *J* = 9.6 Hz), 7.21 (2H, d, *J* = 8.4 Hz), 7.48 (2H, d, J = 8.4 Hz); ^{13}C-NMR + DEPT (125 MHz) δ = 24.5 (CH_2), 26.1 (CH_2), 28.4 (CH_2), 33.6 (CH_2), 38.4 (CH_2), 55.2 (CH), 121.7 (C), 128.1 (CH), 132.0 (CH), 140.4 (C), 176.7 (C). LRMS (EI) 283, 281, 240, 238, 186, 184, 123; HRMS calcd for $C_{13}H_{16}BrNO$, 281.0410 found 281.0413. FT IR (neat) 3173, 3051, 2923, 1642, 1452, 1404, 1151, 1076, 1010, 818, 780, 751, 712, 678 cm^{-1}.

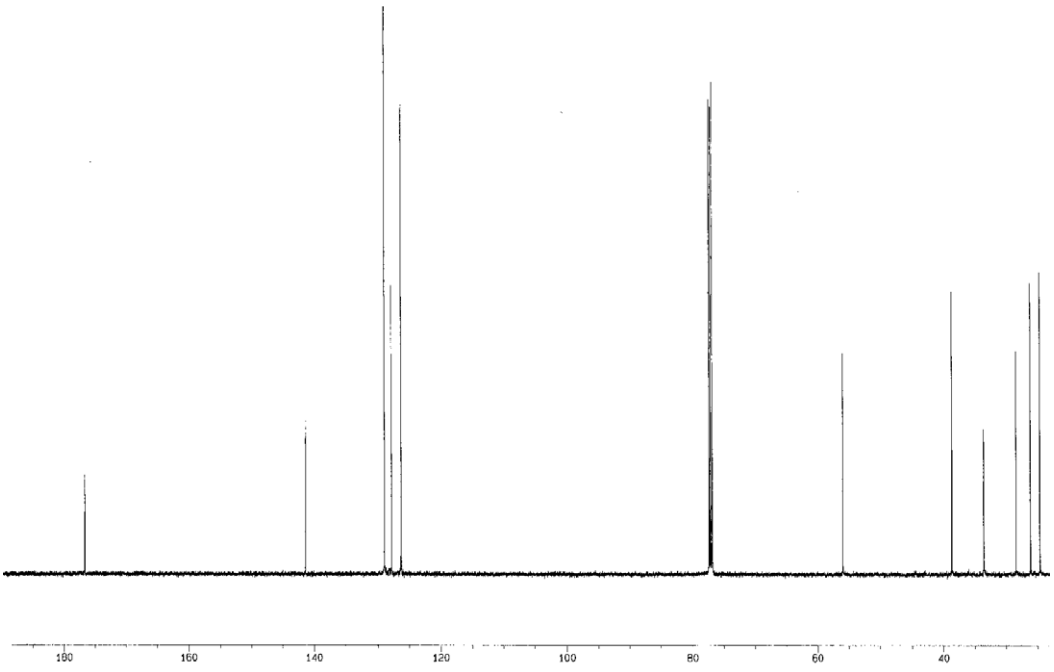
8-(2-Naphthyl)-azocan-2-one 9

Following the procedures described for **7**, 2-naphthaldehyde tosylhydrazide (1.6g, 5 mmol) (P.R. West, A.M. Mooring, R.J. McMahon and O.L. Chapman *J. Org. Chem*. 1986, **51**, 1316) was converted to the 2-(2-naphthyl)-cycloheptanone (1.1g, 88% yield), mpt 58-60°C (Et_2O/petrol). ^{1}H-NMR (500 MHz) δ = 1.49 – 1.55 (2H, m), 1.66 – 1.73 (1H, m), 1.96 – 2.13 (4H, m), 2.19 – 2.26 (1H, m), 2.54 – 2.60 (1H, m), 2.75 (1H, ddd, *J* = 3.2, 12.2, 13.4 Hz), 3.91 (1H, dd, *J* = 4.2, 11.4 Hz), 7.39 (1H, dd, *J* = 1.8, 8.5 Hz), 7.43 – 7.50 (2H, m), 7.68 (1H, d, *J* = 0.8 Hz), 7.79 – 7.68 (3H, m). ^{13}C-NMR + DEPT (125 MHz) δ = 25.4 (CH_2), 28.7 (CH_2), 30.1 (CH_2), 32.0 (CH_2), 42.9 (CH_2), 58.9 (CH), 125.8 (CH), 126.1 (CH), 126.3 (CH), 126.6 (CH), 127.7 (CH), 127.9 (CH), 128.2 (CH), 132.6 (C), 133.6 (C), 138.0 (C), 213.5 (C). LRMS (EI) 238, 172, 141; HRMS calcd for $C_{17}H_{18}O$ 238.152, found 238.1355; FT IR (neat) 2927, 2849, 1689, 1442, 1322, 1155, 1129, 937, 854, 826, 799, 741 cm^{-1}.
The ketone (1.0g, 4.2mmol) was converted to its oxime (1.1g, ~100%), mpt 105-6°C (EtOAc/petrol). ^{13}C-NMR + DEPT (125 MHz) (major tautomer) δ = 25.8 (CH_2), 26.5 (CH_2), 26.7 (CH2), 31.2 (CH_2), 32.6 (CH_2), 49.3 (CH), 125.5 (CH), 125.6 (CH), 126.1 (CH), 126.6 (CH), 127.7 (CH), 128.0 (CH), 128.1 (CH), 132.4 (C), 133.6 (C), 140.3 (C), 164.7 (C).
The oxime (1.3g, 5.2 mmol) was converted into **9**, (0.7g, 54% yield), purified by column chromatography on silica, eluting with 9:1 DCM/EtOAc, mp 140-1°C (EtOAc/petroleum ether), ^{1}H-NMR (500 MHz) δ = 1.40 – 1.55 (2H, m), 1.71 – 2.02 (6H, m), 2.43 (1H, dt, *J* = 4.8, 12.8 Hz), 2.67 (1H, dt, *J* = 3.4, 12.8 Hz), 4.78 (dt, *J* = 5.5, 10.2 Hz), 6.87 (1H, brd, *J* = 10.1 Hz), 7.40 – 7.50 (3H, m), 7.75 – 7.83 (4H, m); ^{13}C-NMR + DEPT (125 MHz) δ = 25.8 (CH_2), 26.5 (CH_2), 26.7 (CH_2), 31.2 (CH_2), 33.2 (CH_2), 49.3 (CH), 125.5 (CH), 125.6 (CH), 126.0 (CH), 126.6 (CH), 127.7 (CH), 128.0 (CH), 128.1 (CH), 132.4 (C), 133.8 (C), 140.3 (C), 164.7 (C). LRMS (EI) 253, 210, 156, 155, 154; HRMS calcd for $C_{17}H_{19}NO$, 253.1461 found 253.1460. FT IR (neat) 3187, 3060, 2921, 1641, 1454, 1447, 1409, 824, 799, 748 cm^{-1}.

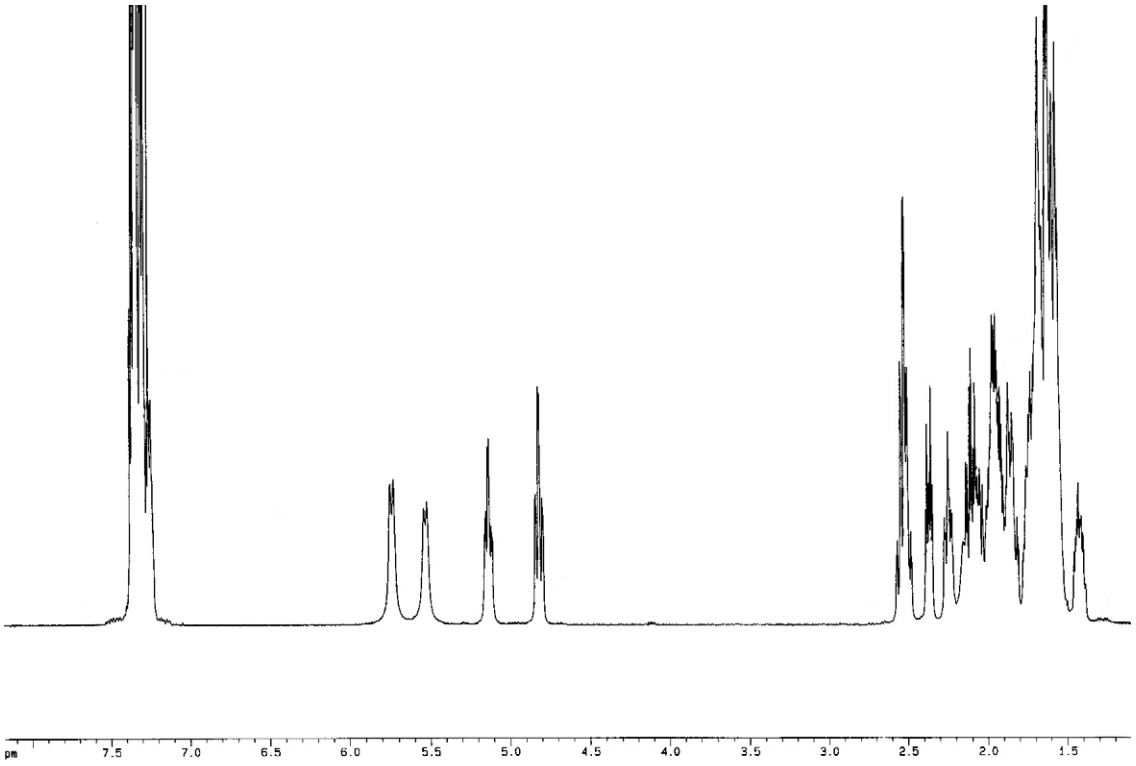
^{1}H-NMR spectrum of 1e



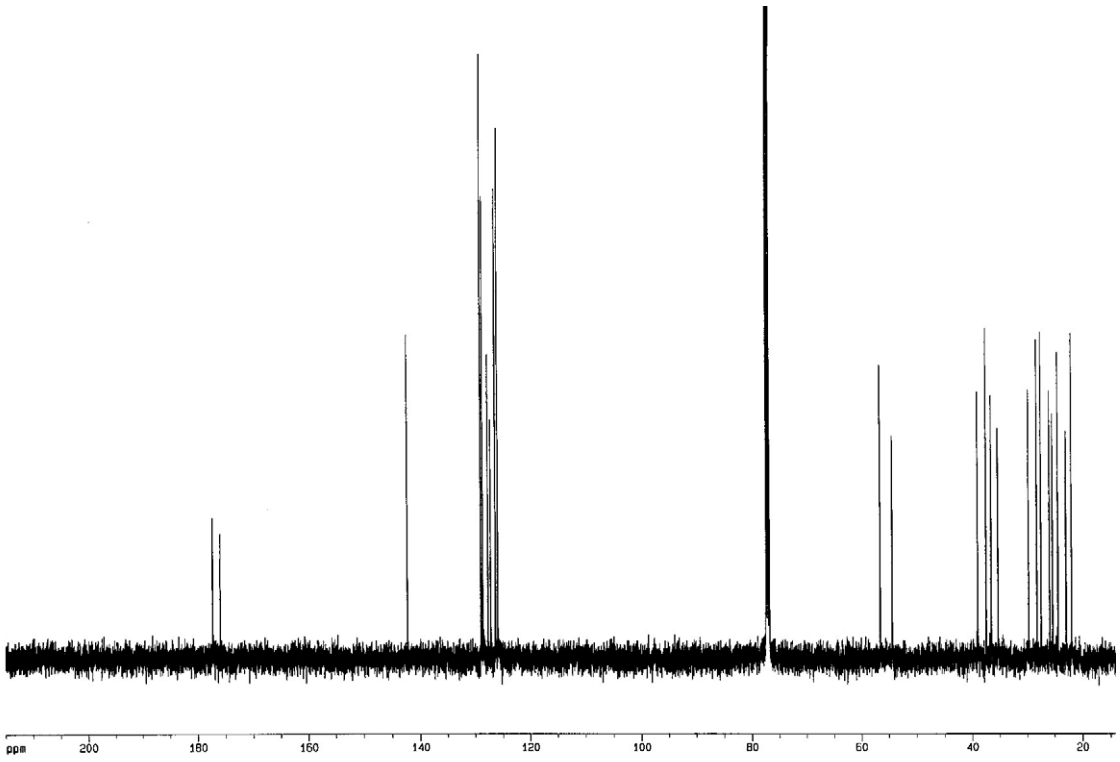
^{13}C-NMR spectrum of 1e



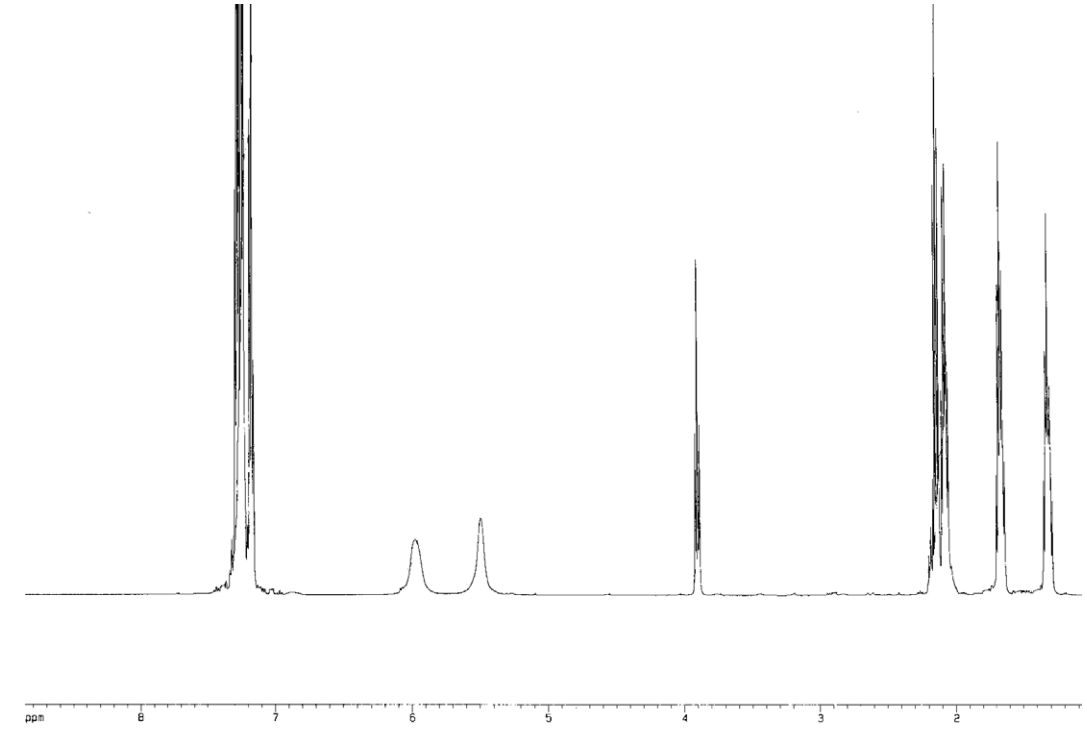
^{1}H-NMR spectrum of 1f



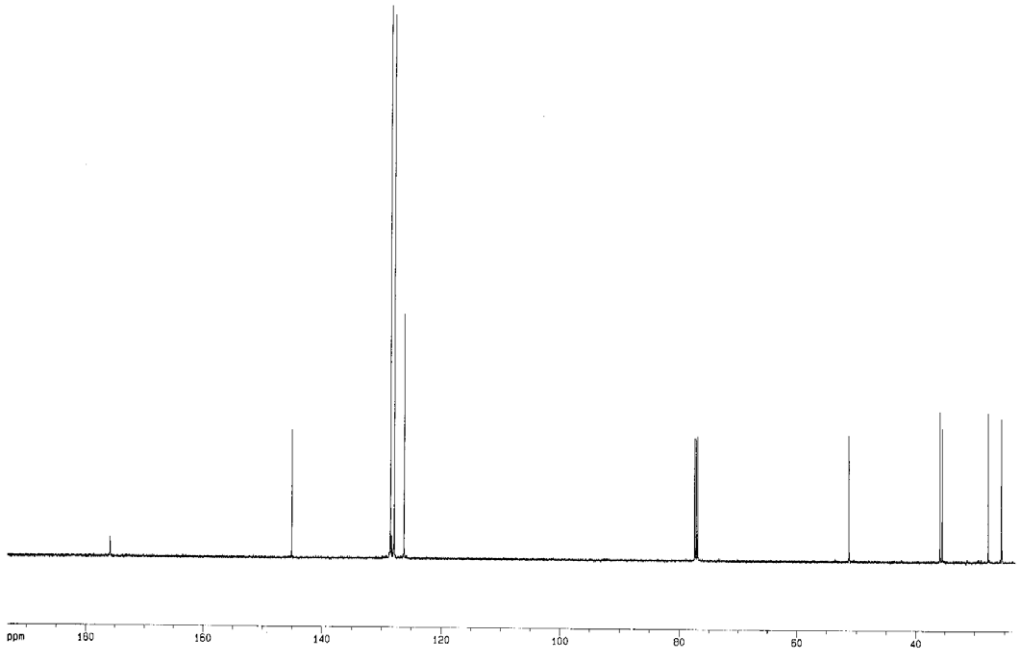
^{13}C-NMR spectrum of 1f



^{1}H-NMR spectrum of 2d



^{13}C-NMR spectrum of 2d



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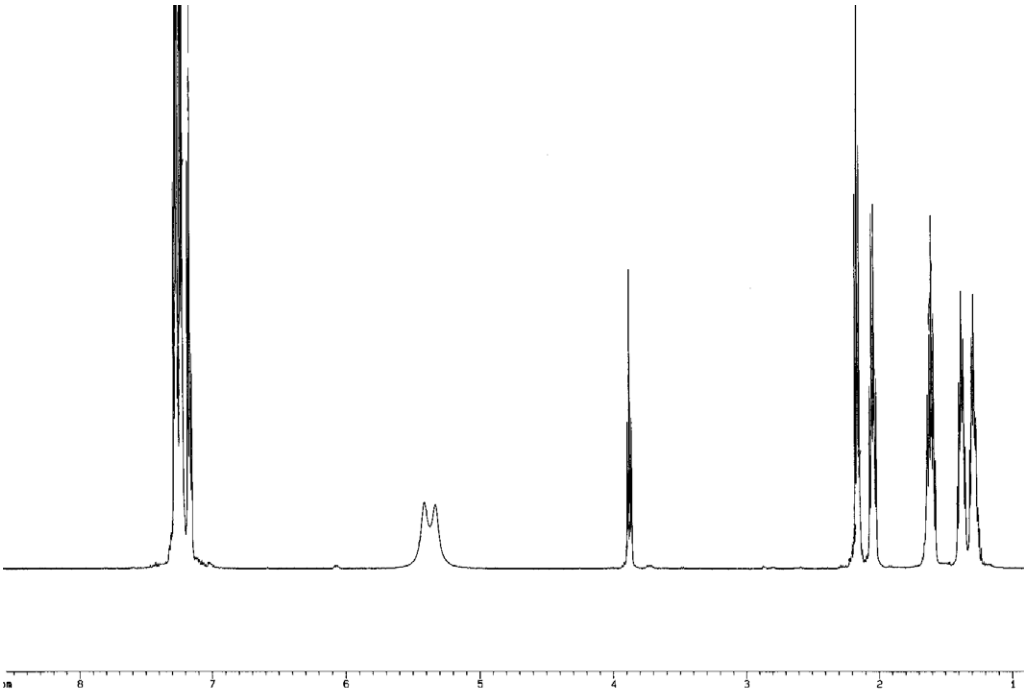
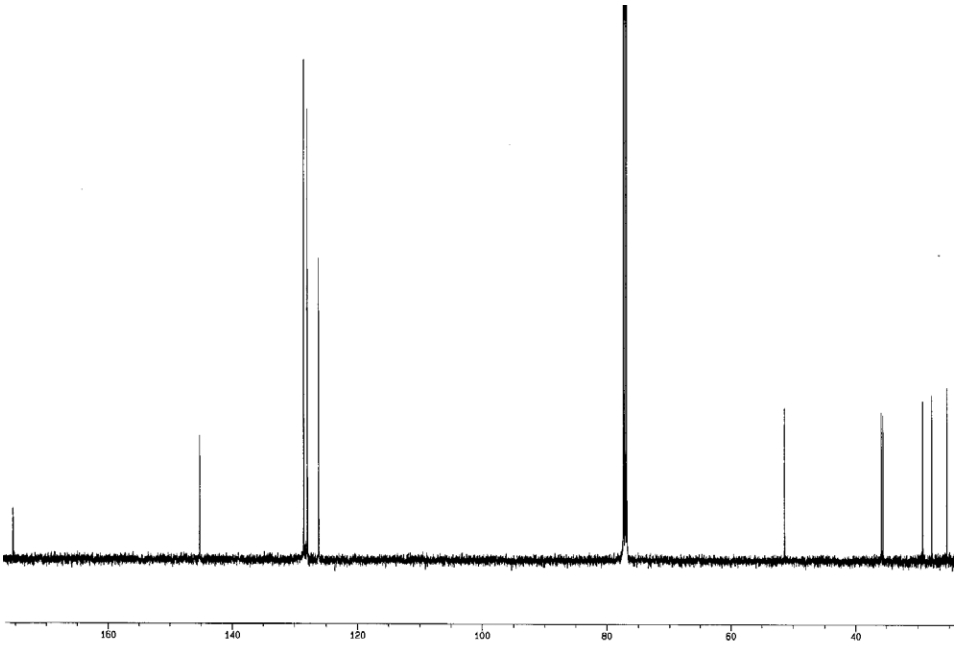
1H-NMR spectrum of 2e

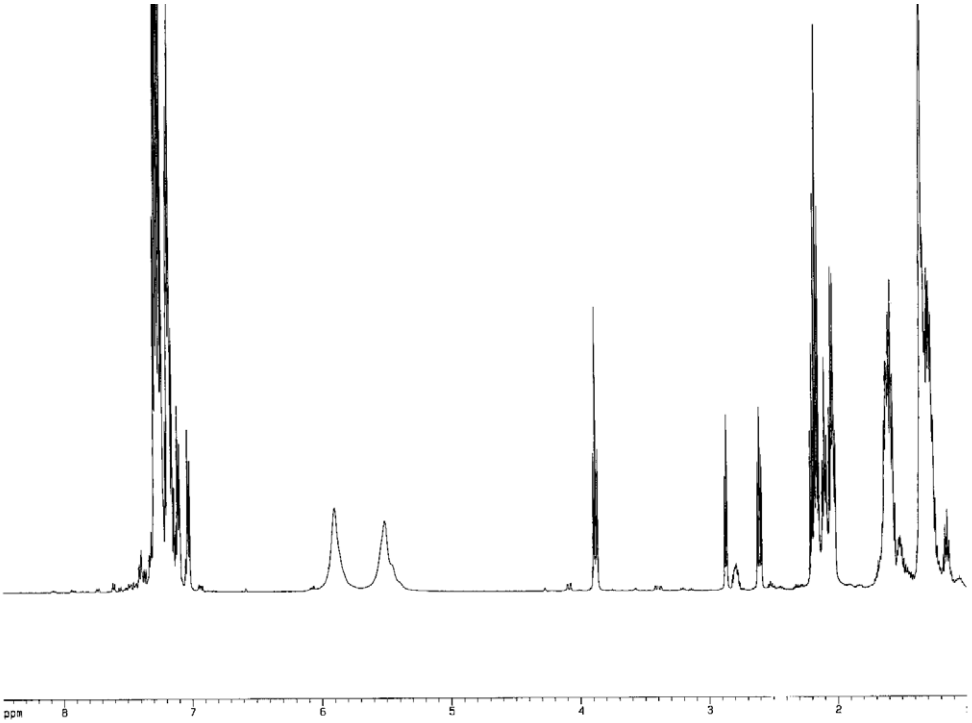


13C-NMR spectrum of 2e

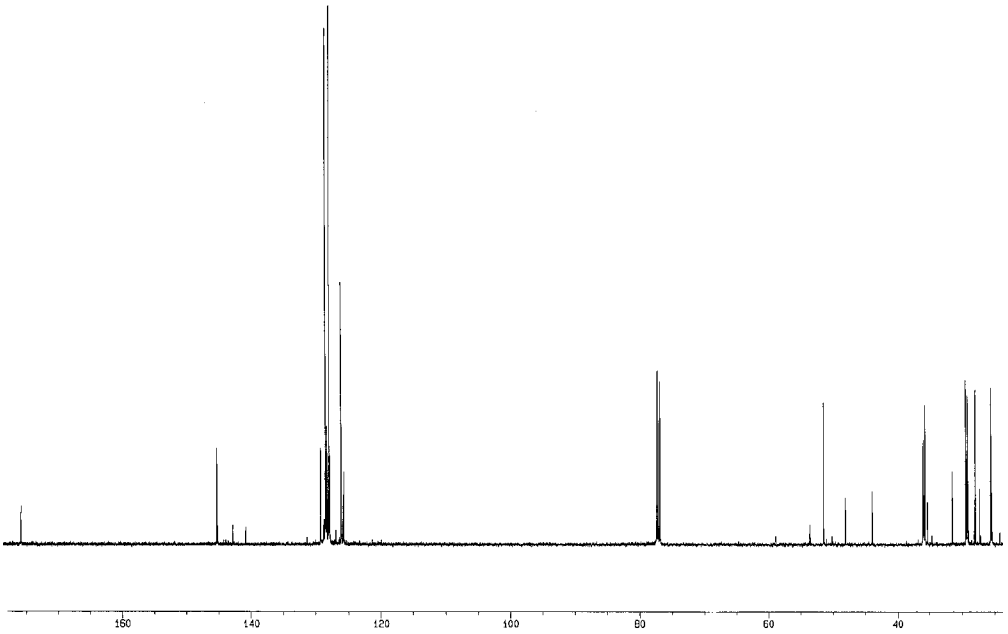


Product from ring-opening of 1f

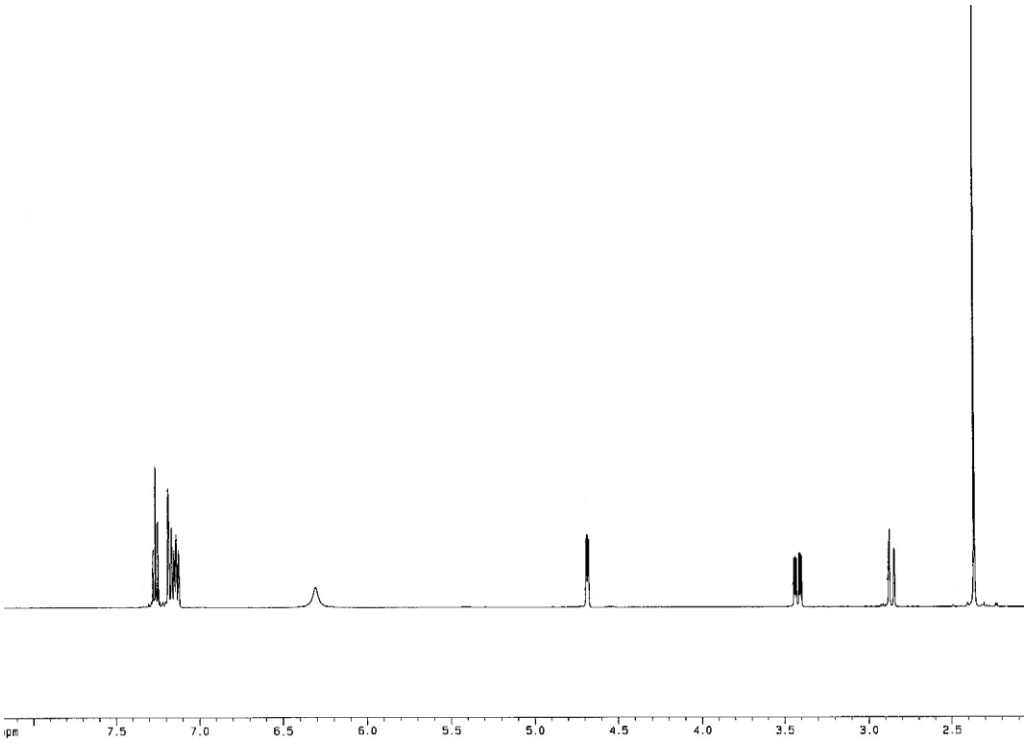
^{1}H-NMR spectrum



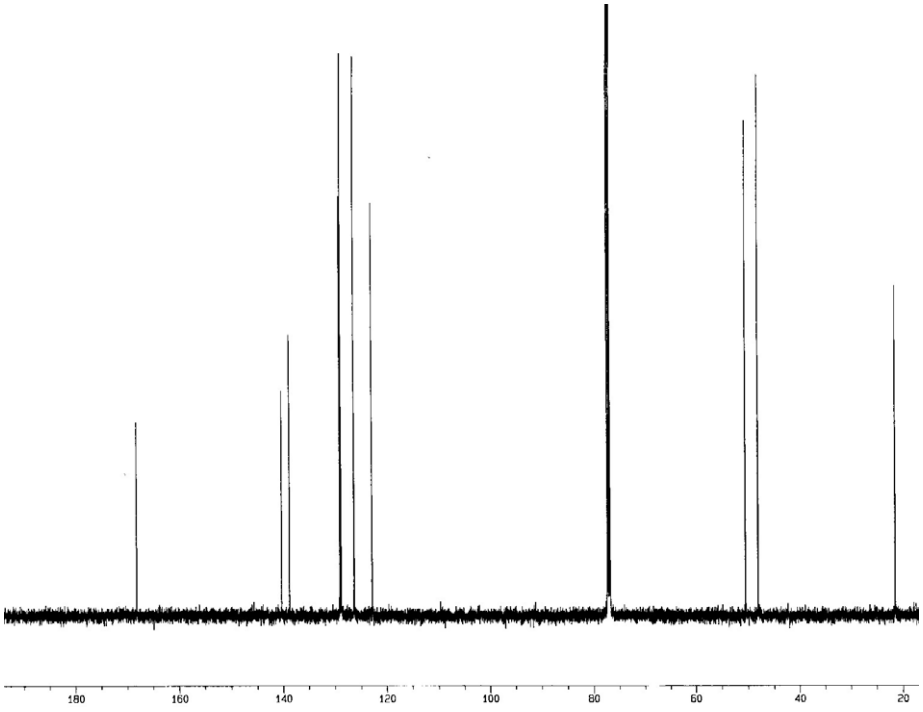
^{13}C-NMR spectrum



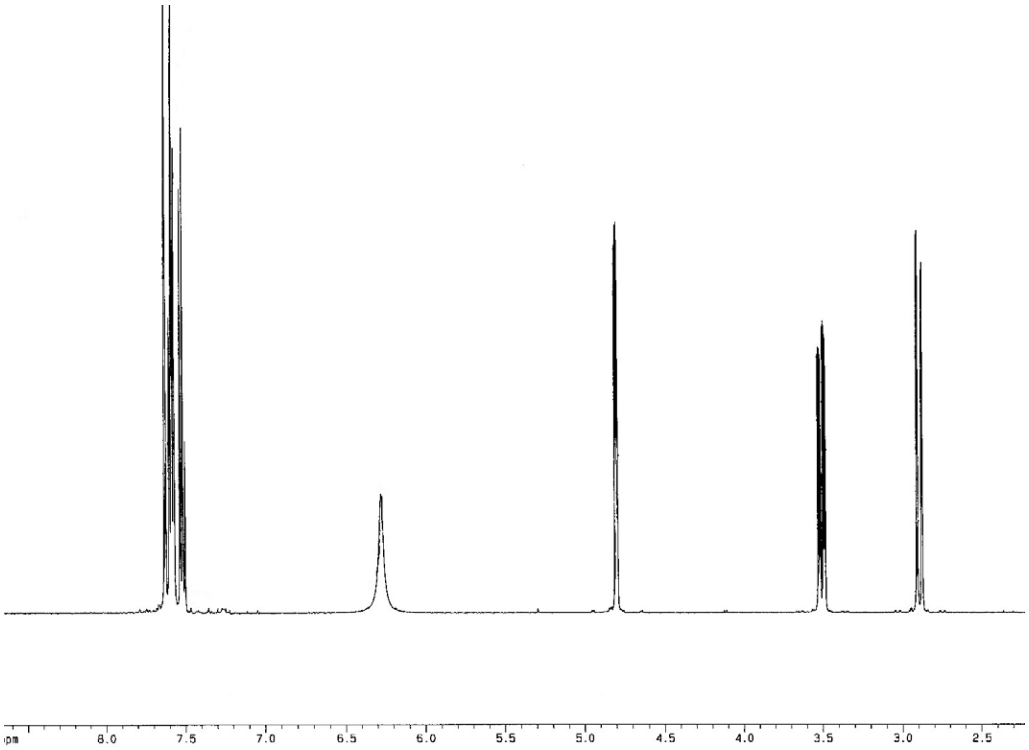
^{1}H-NMR spectrum of 3b



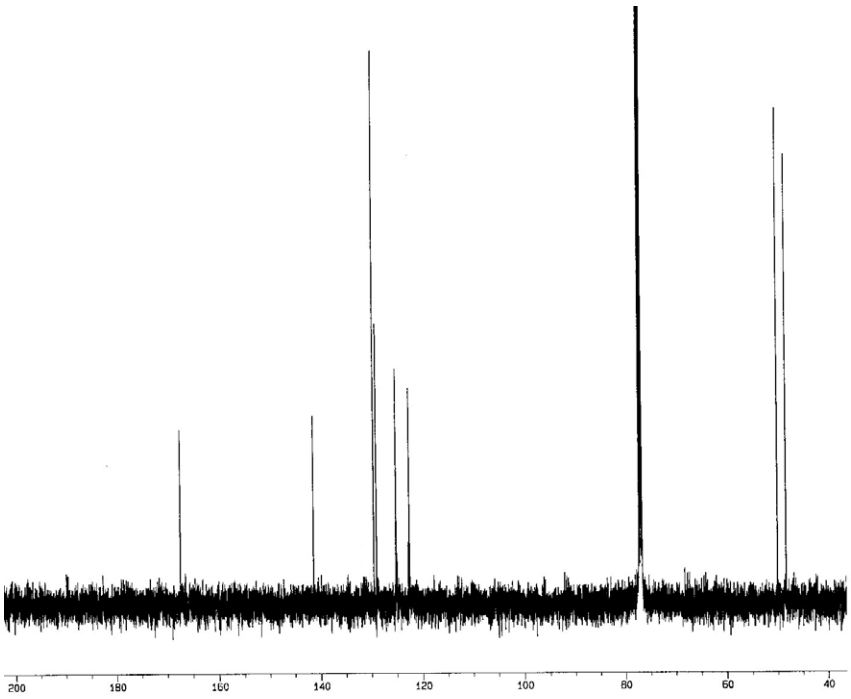
^{13}C-NMR spectrum of 3b



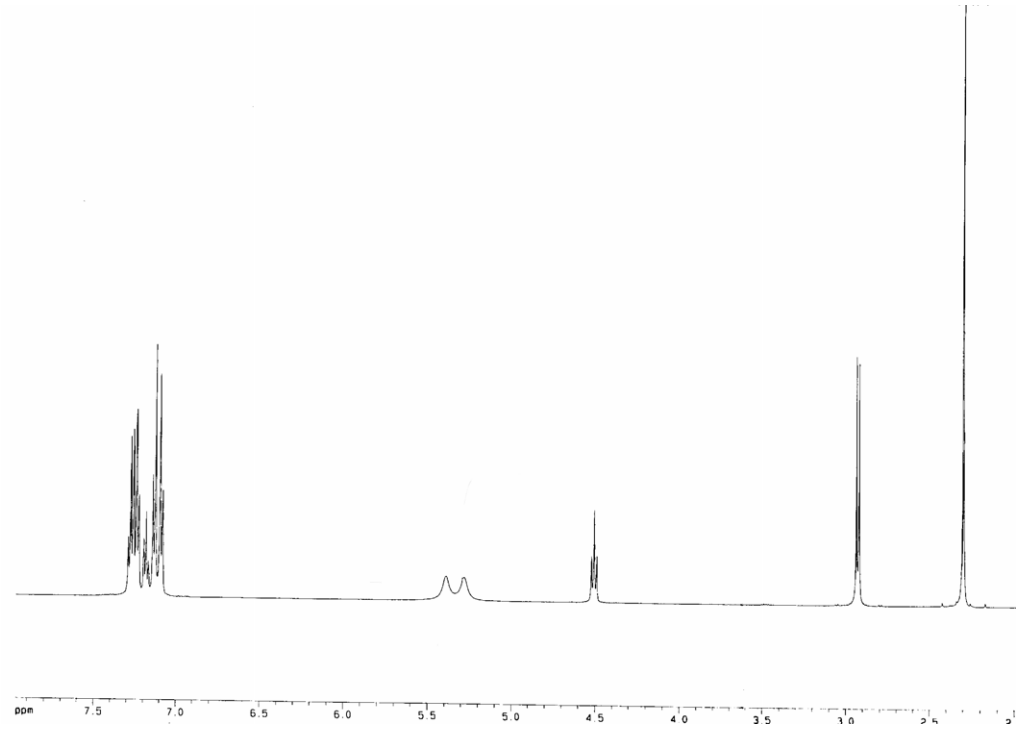
^{1}H-NMR spectrum of 3h



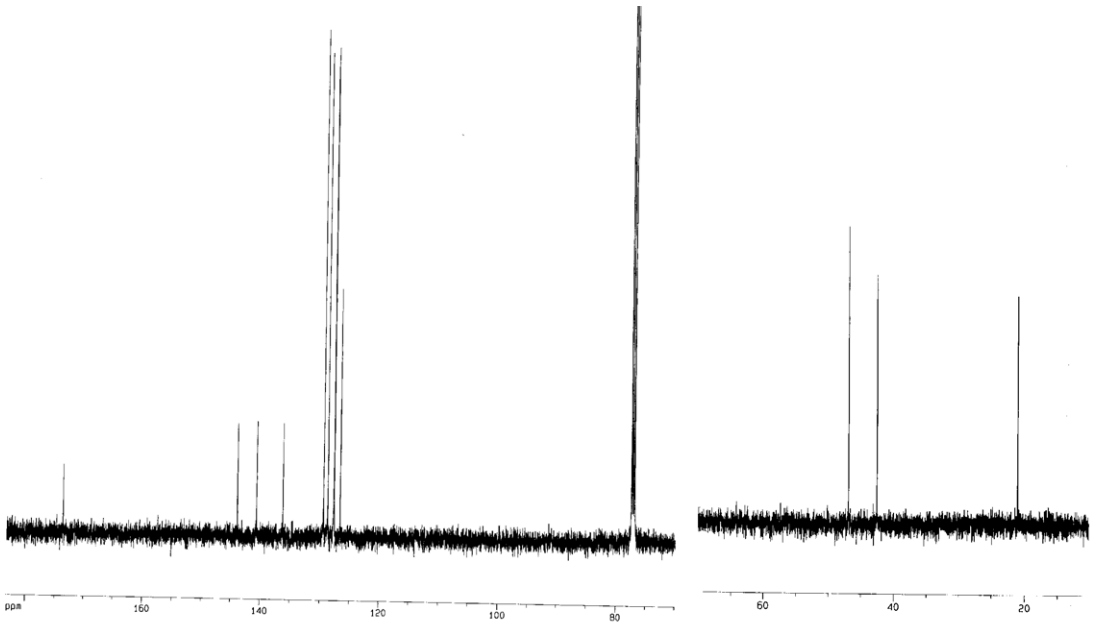
^{13}C-NMR spectrum of 3h



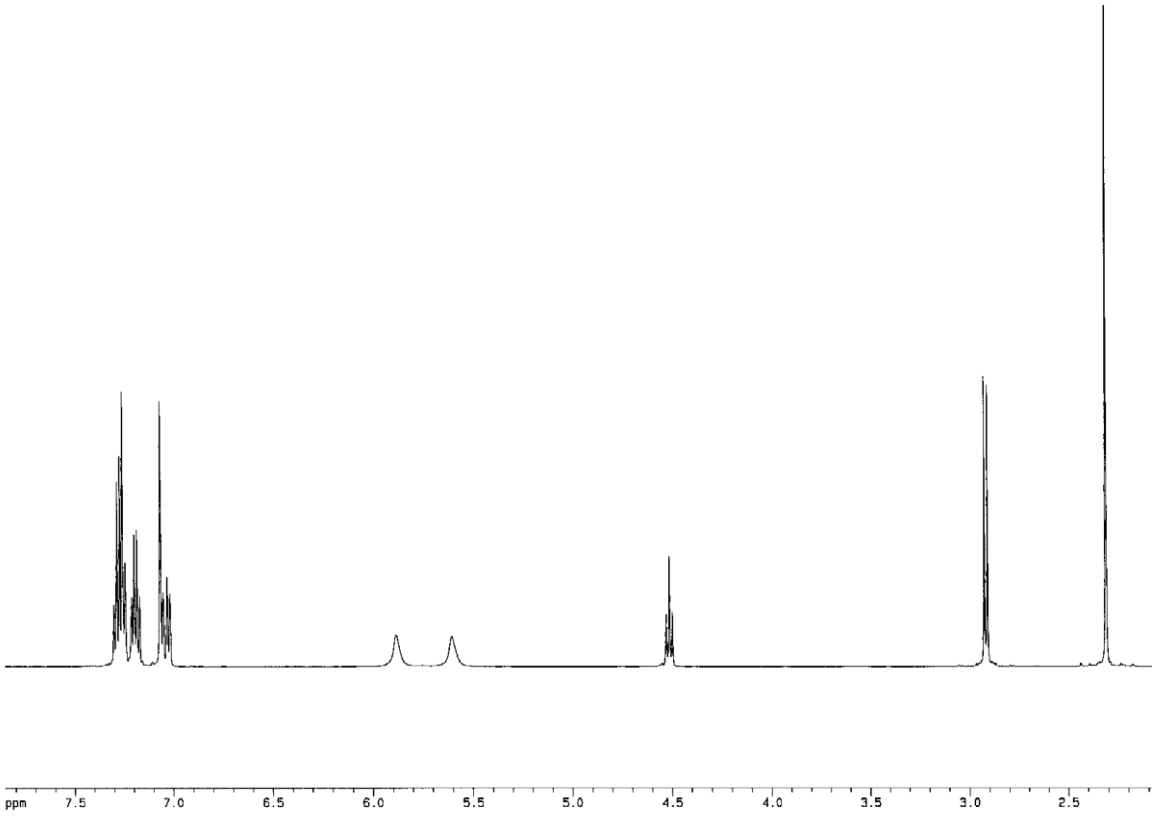
^{1}H-NMR spectrum of 4a



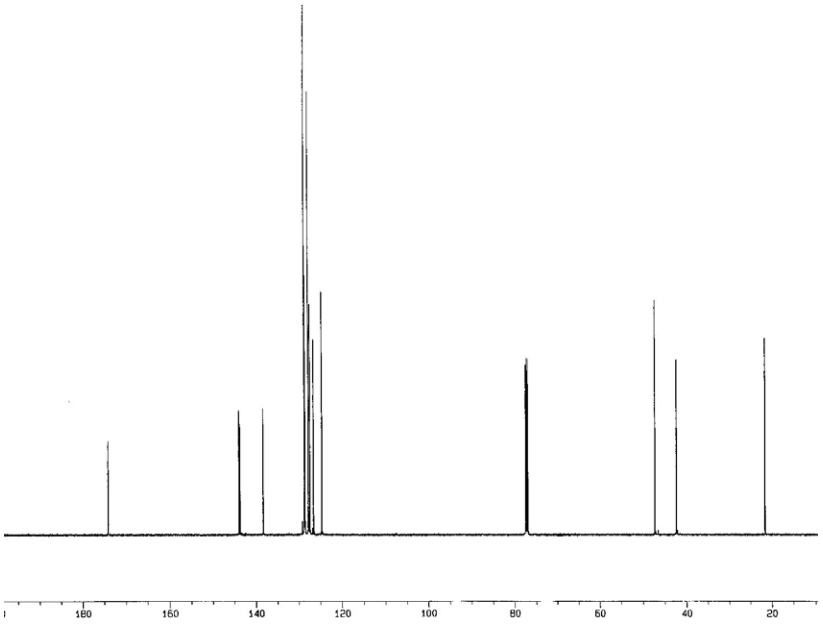
^{13}C-NMR spectrum of 4a



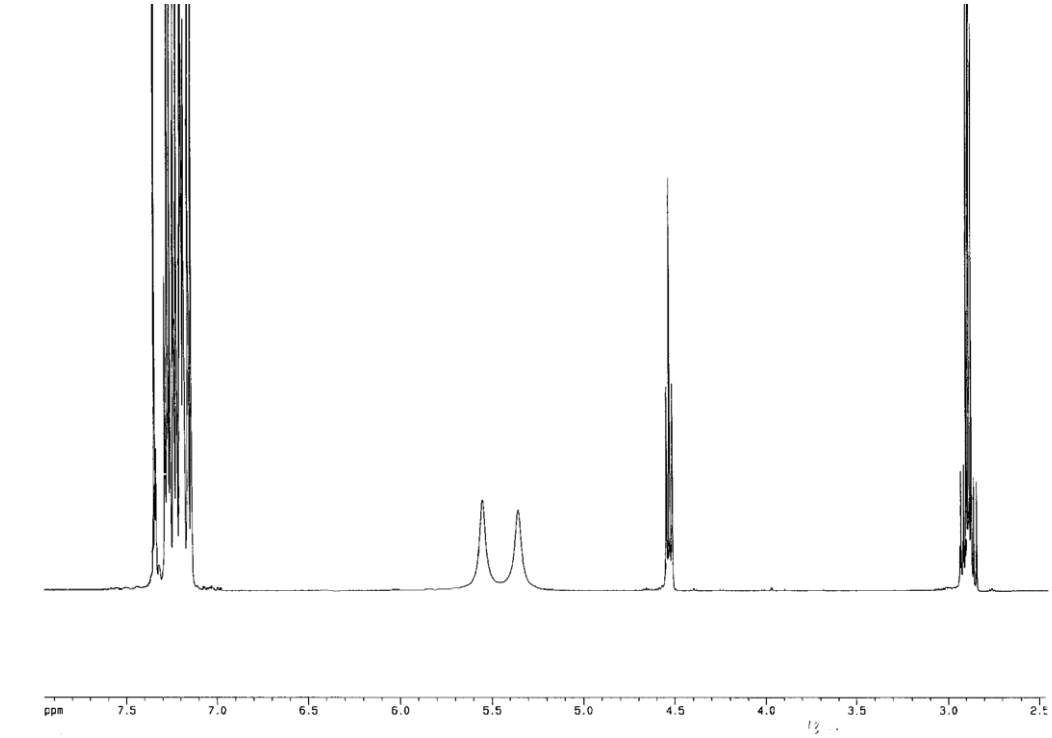
^{1}H-NMR spectrum of 4b



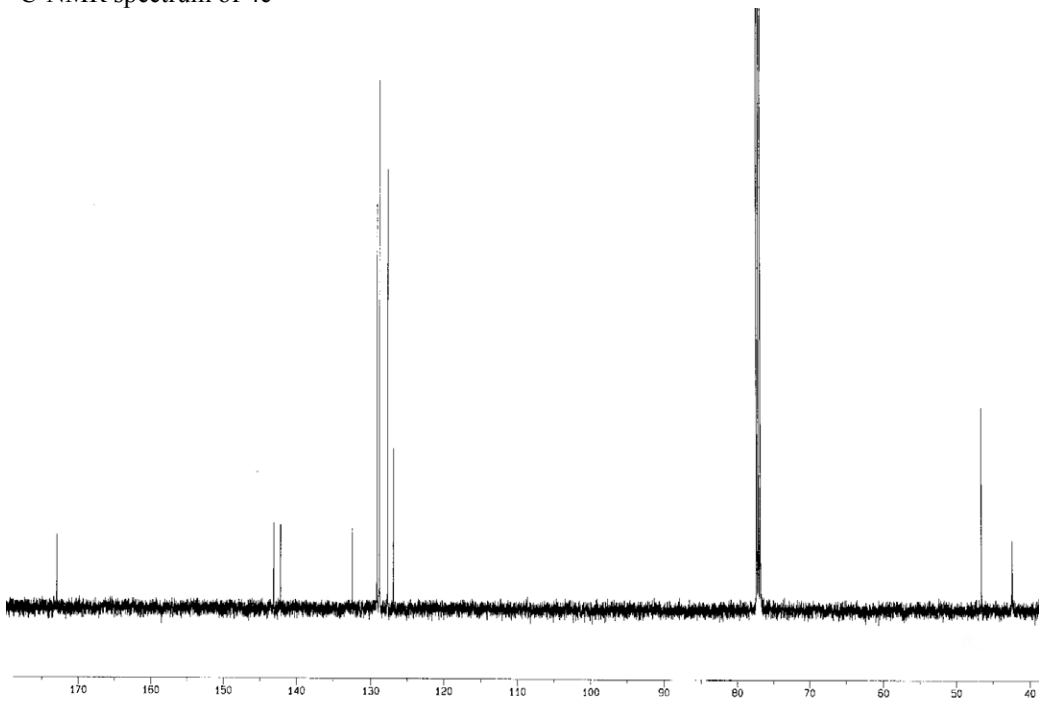
^{13}C-NMR spectrum of 4b



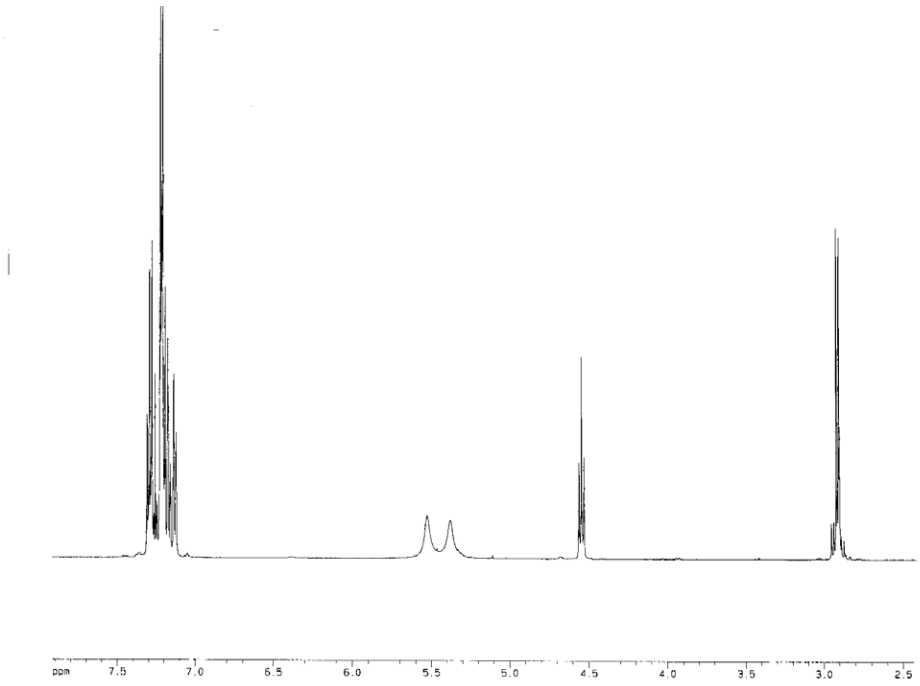
^{1}H-NMR spectrum of 4c



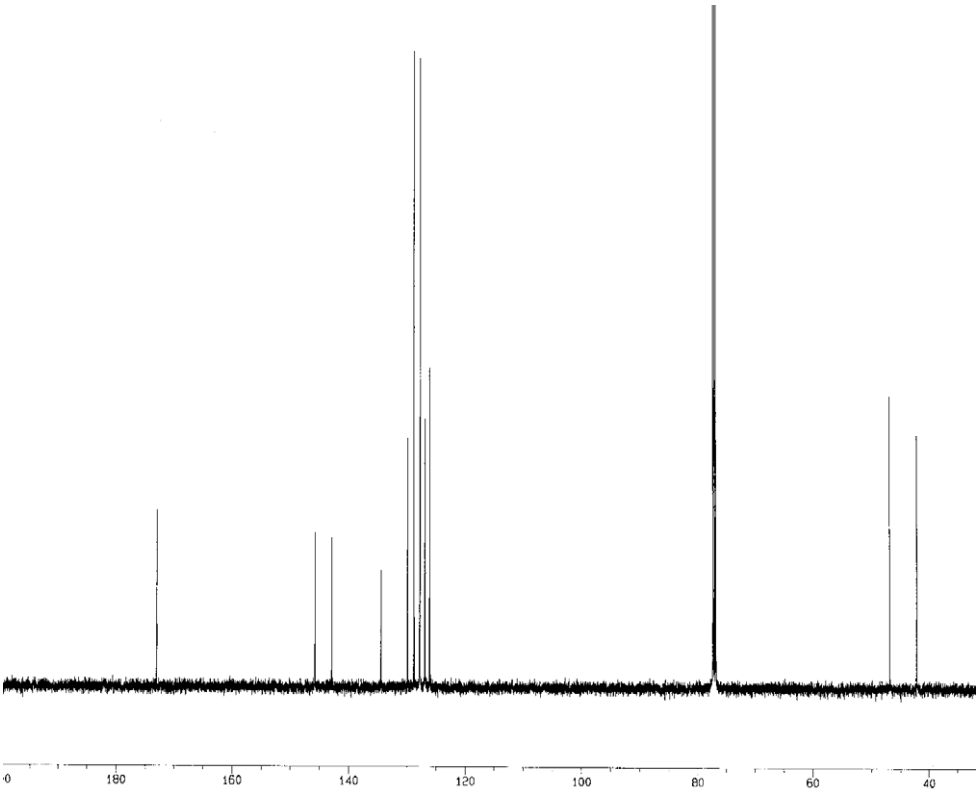
^{13}C-NMR spectrum of 4c



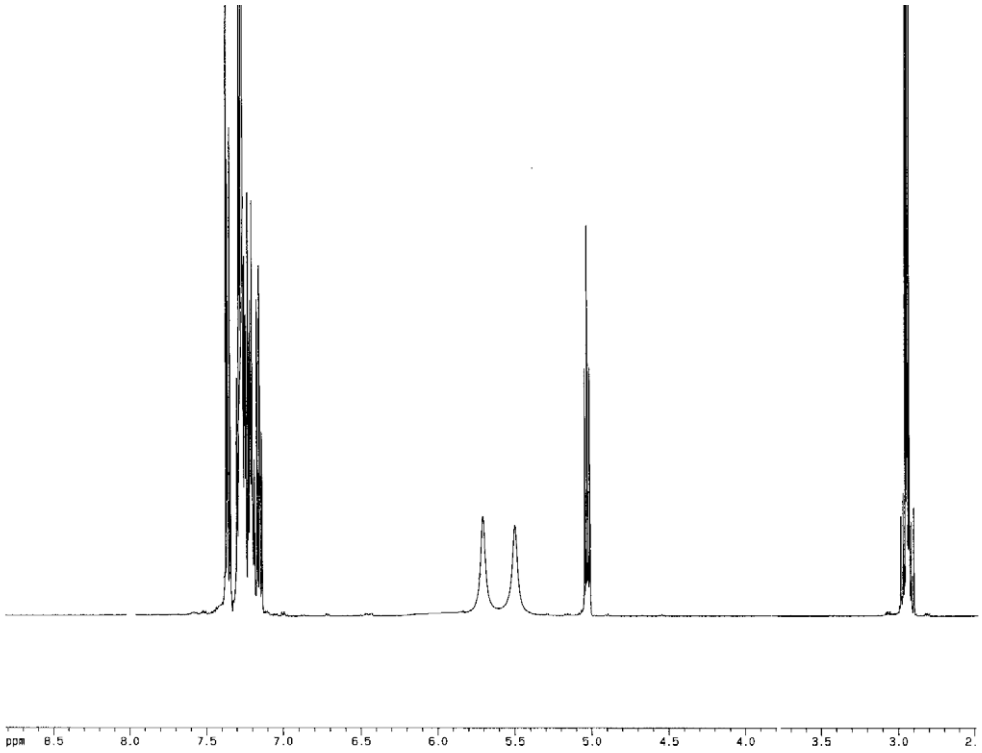
^{1}H-NMR spectrum of 4d



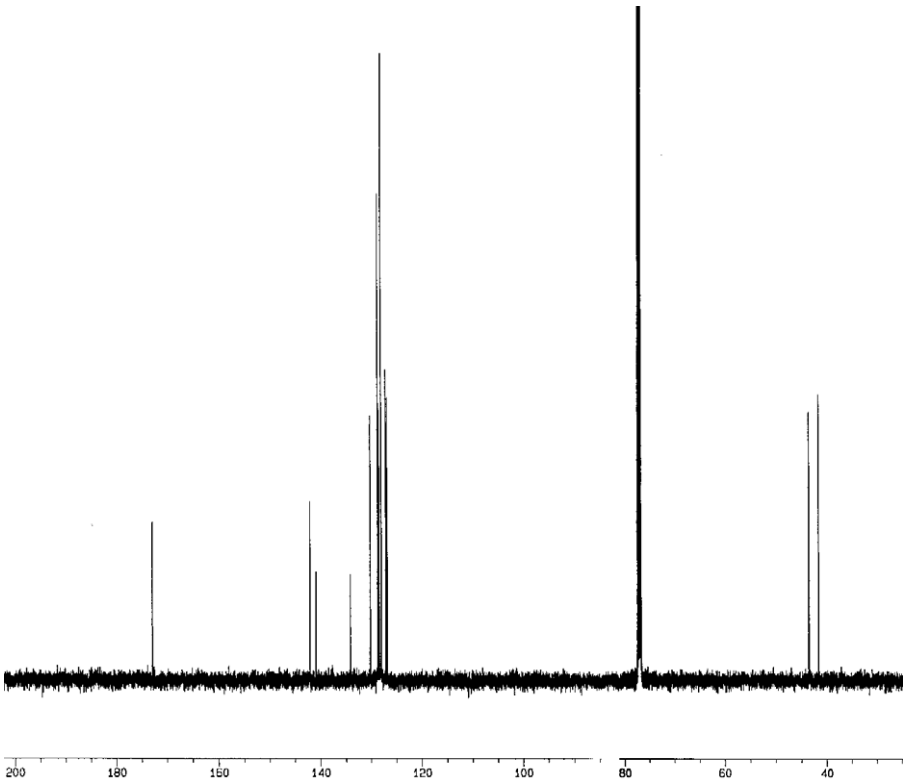
^{13}C-NMR spectrum of 4d



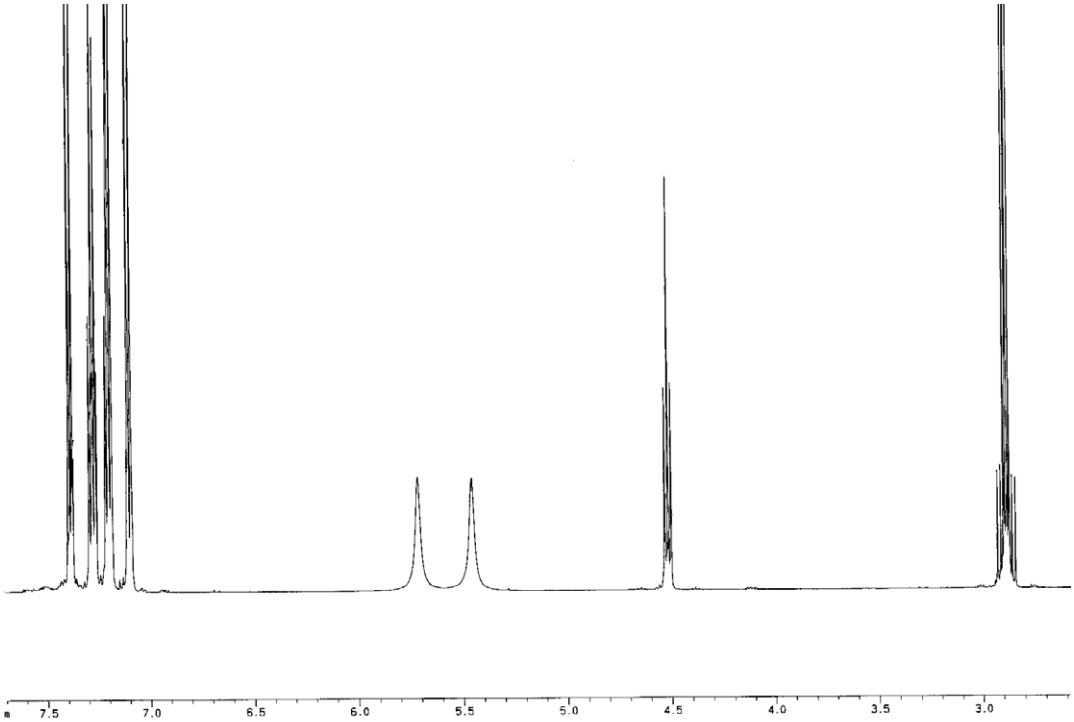
^{1}H-NMR spectrum of 4e



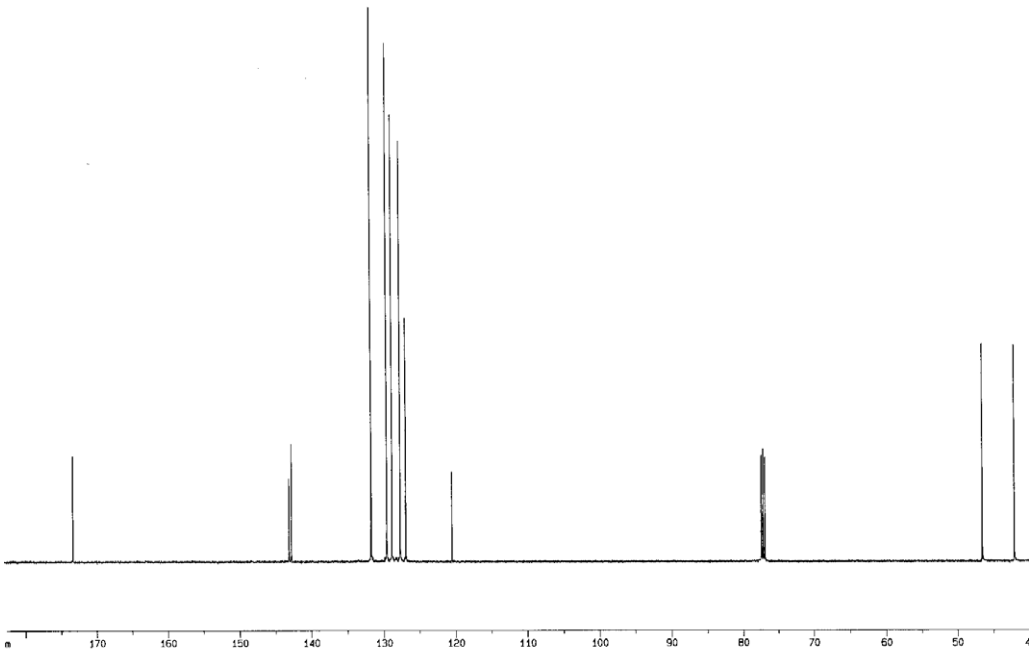
^{13}C-NMR spectrum of 4



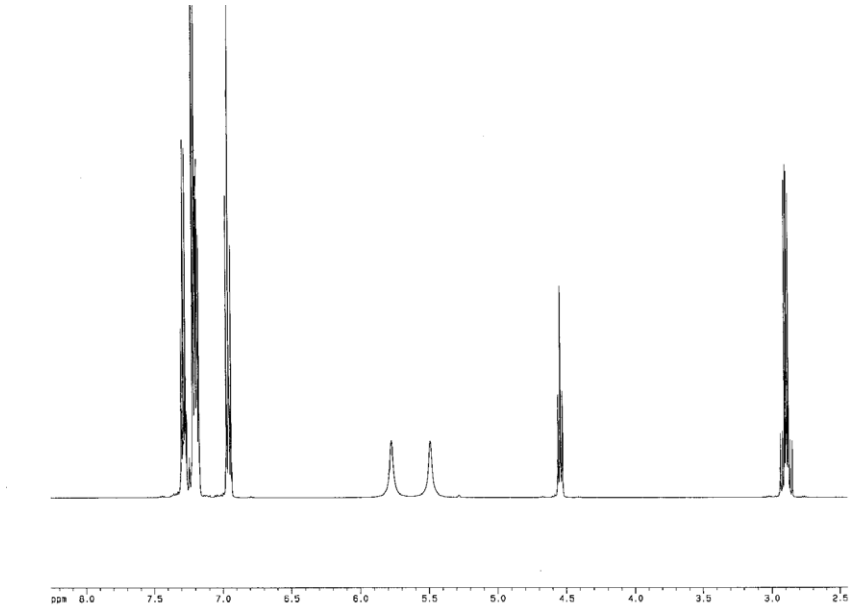
^{1}H-NMR spectrum of 4f



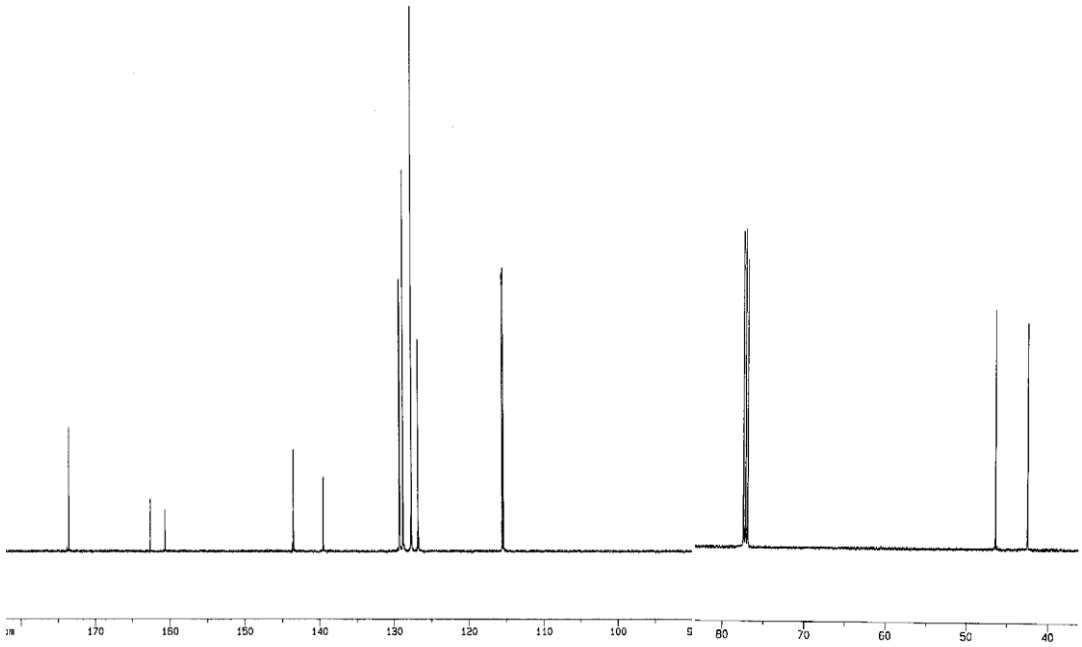
^{13}C-NMR spectrum of 4f



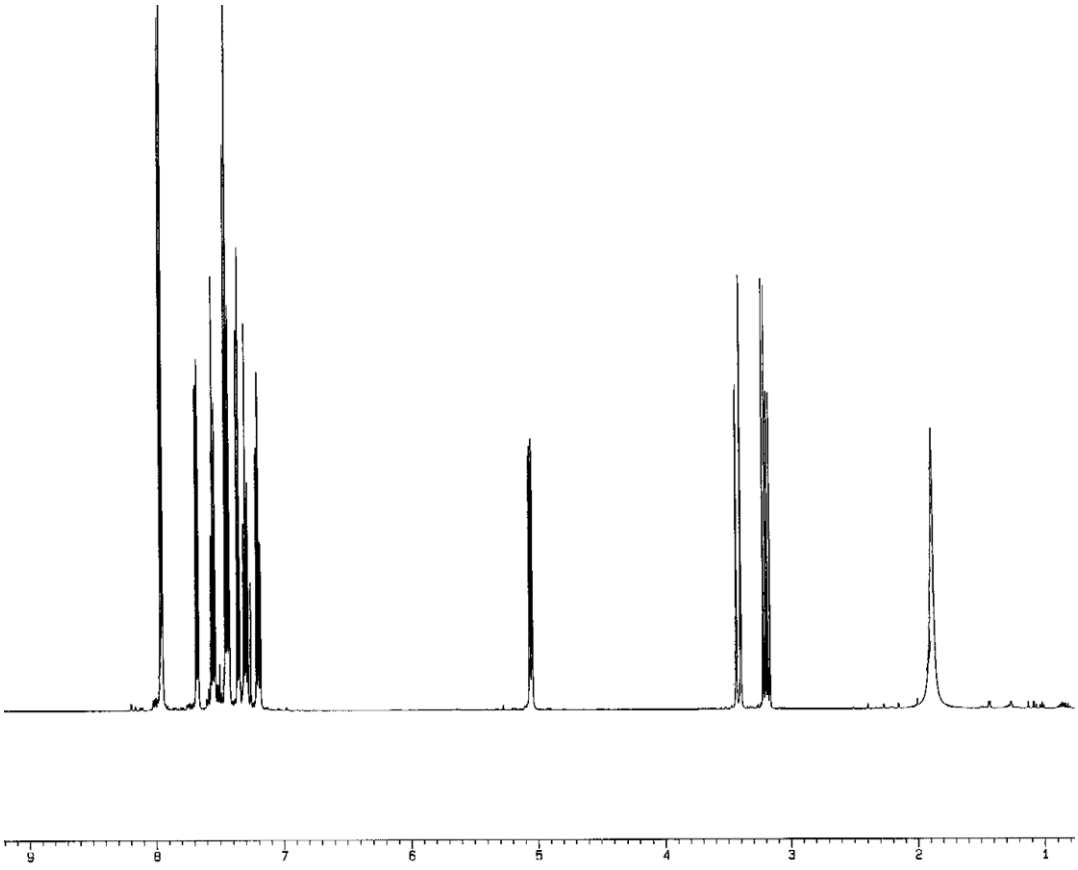
^{1}H-NMR spectrum of 4g



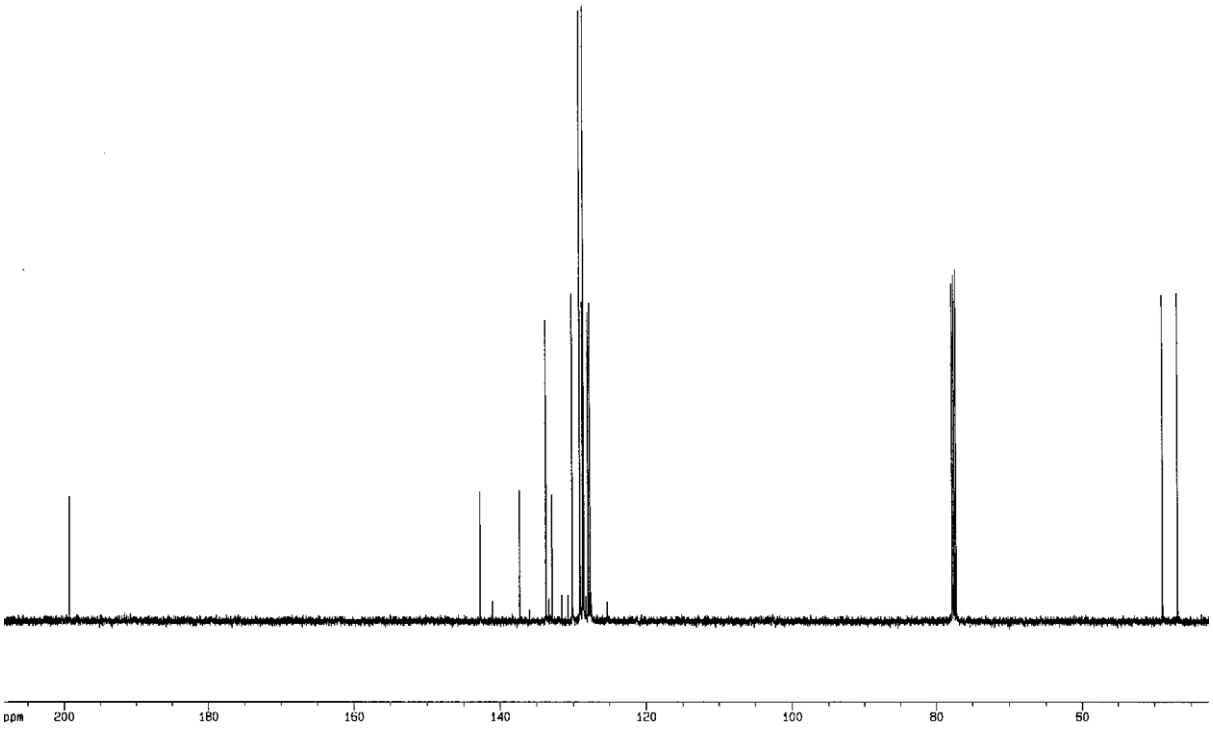
^{13}C-NMR spectrum of 4g



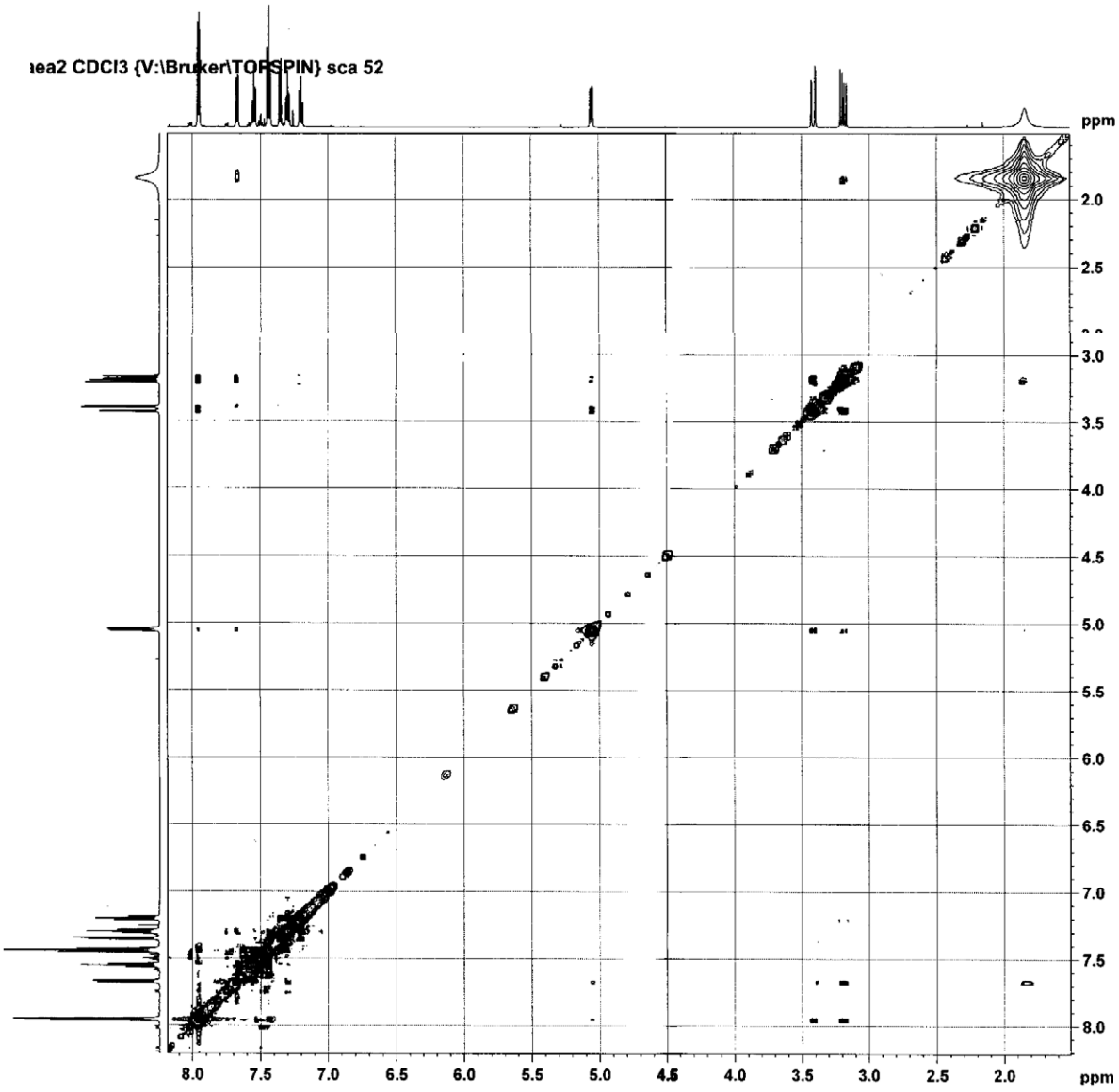
^{1}H-NMR spectrum of 6



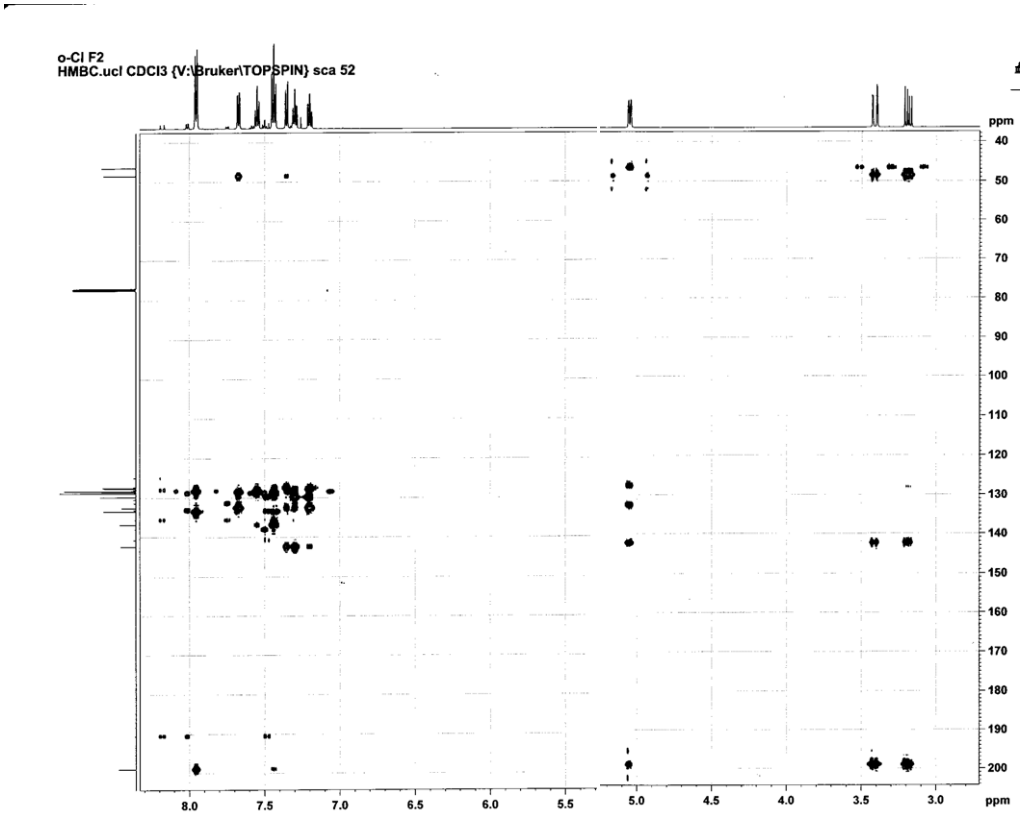
^{13}C-NMR spectrum of 6



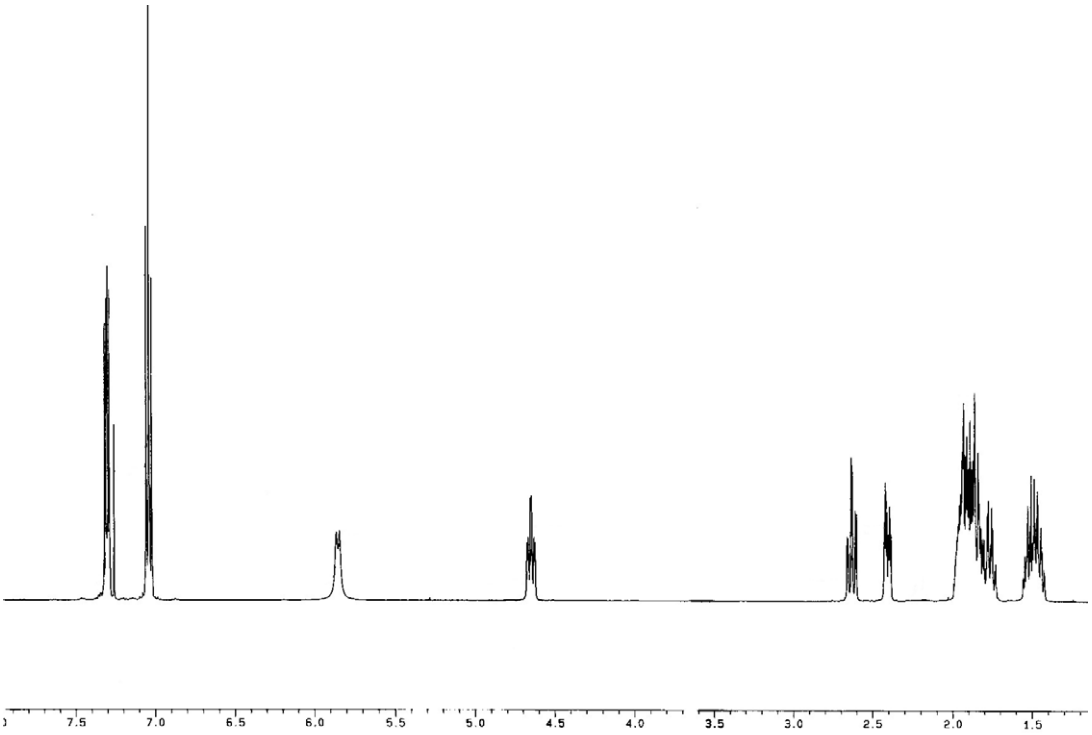
NOESY spectrum of 6



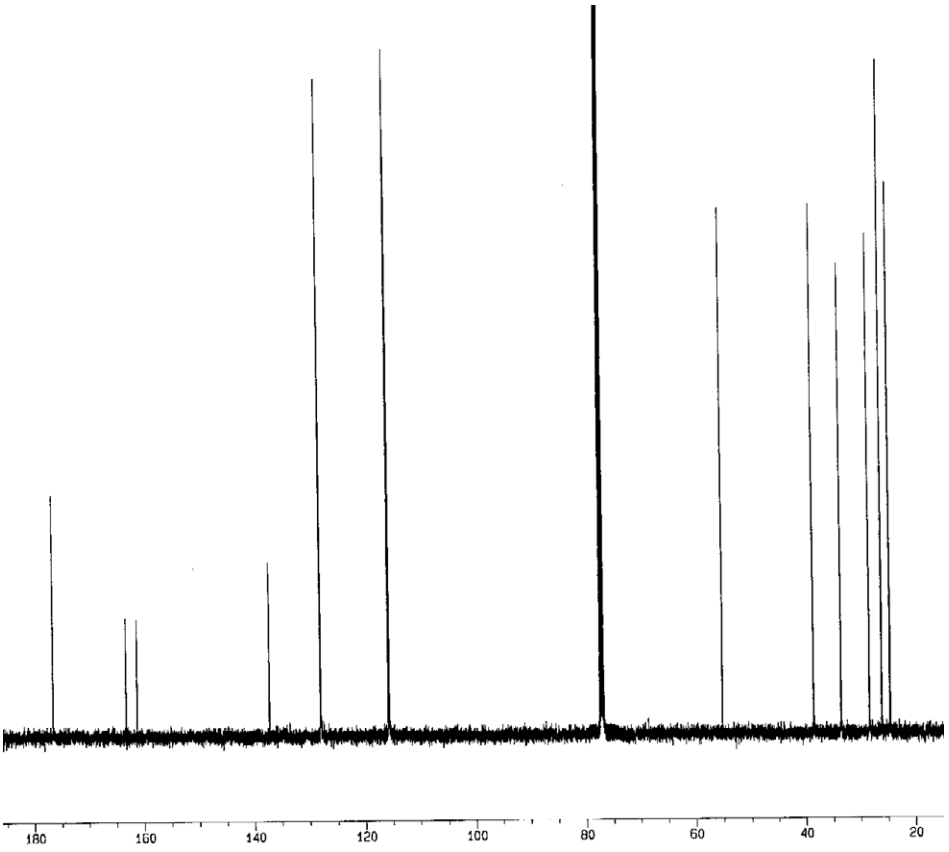
HMBC spectrum of 6



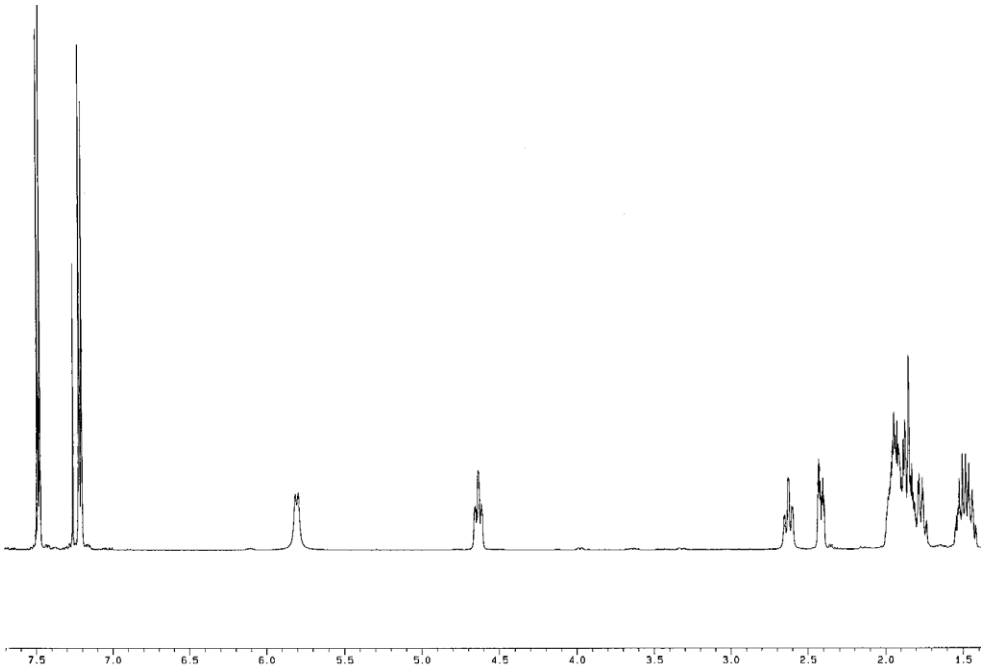
^{1}H-NMR spectrum of 7



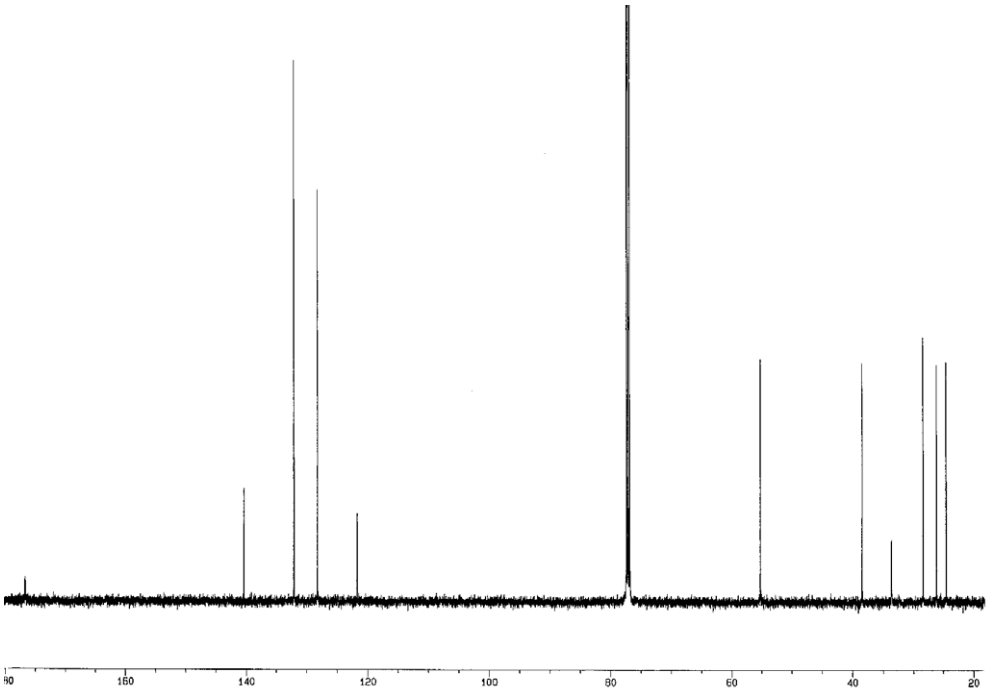
^{13}C-NMR spectrum of 7



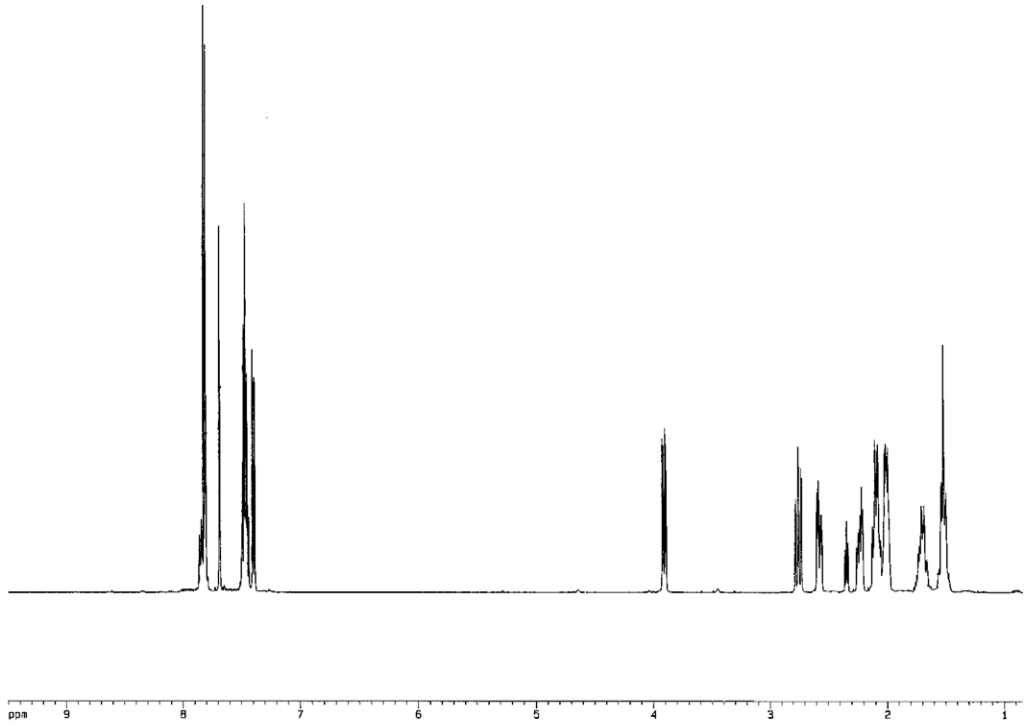
^{1}H-NMR spectrum of 8



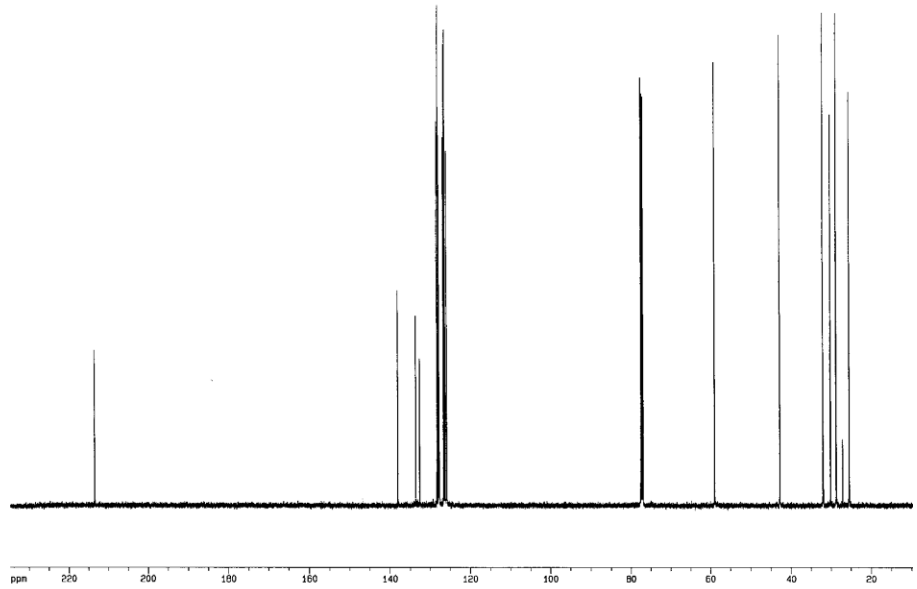
^{13}C-NMR spectrum of 8



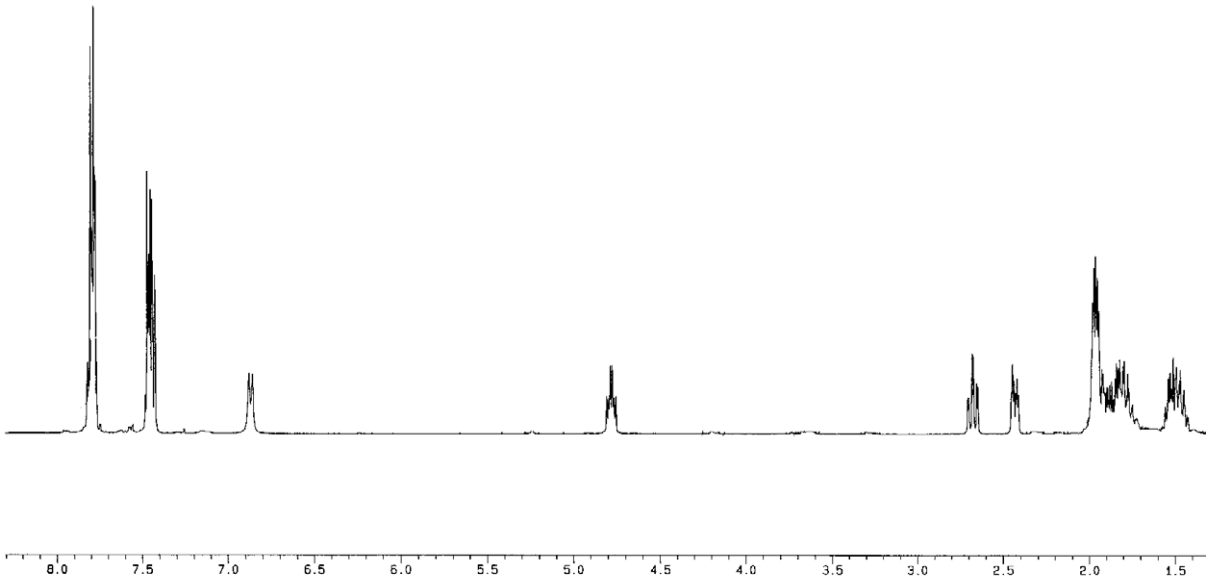
^{1}H-NMR spectrum of 2-(2-naphthyl)cyloheptanone



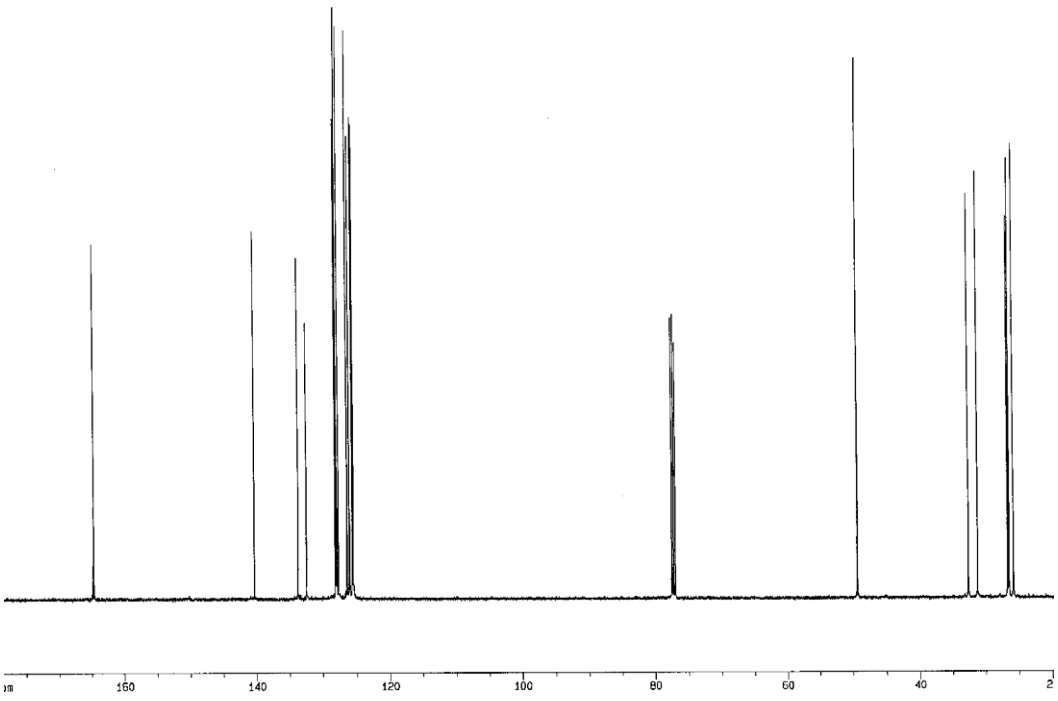
^{13}C-NMR spectrum of 2-(2-naphthyl)cyloheptanone



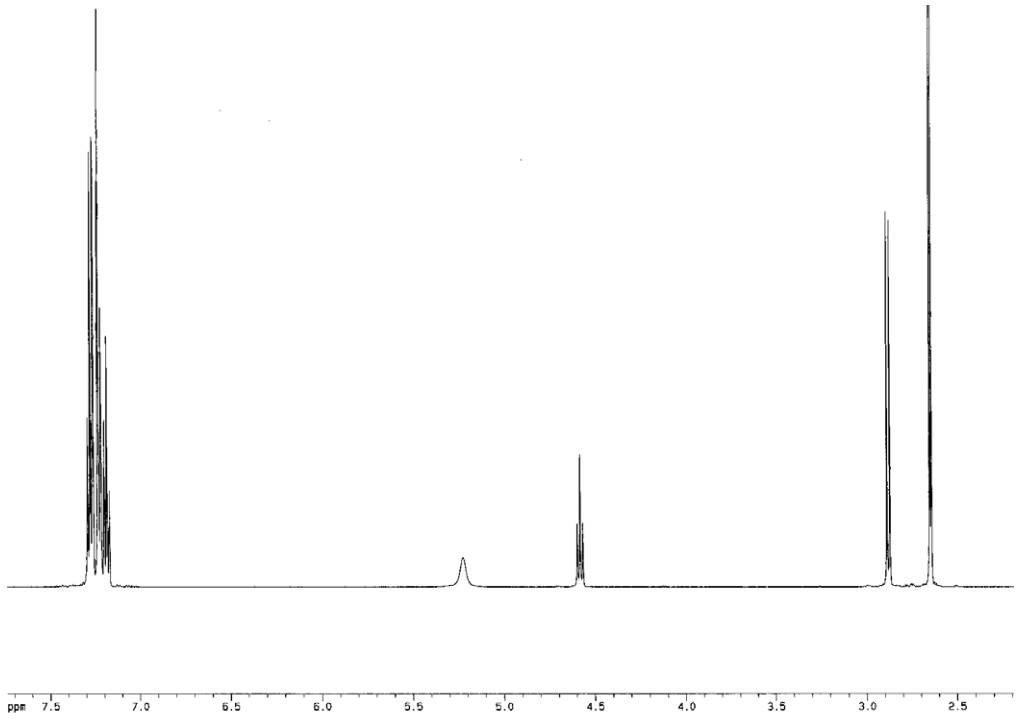
^{1}H-NMR spectrum of 9



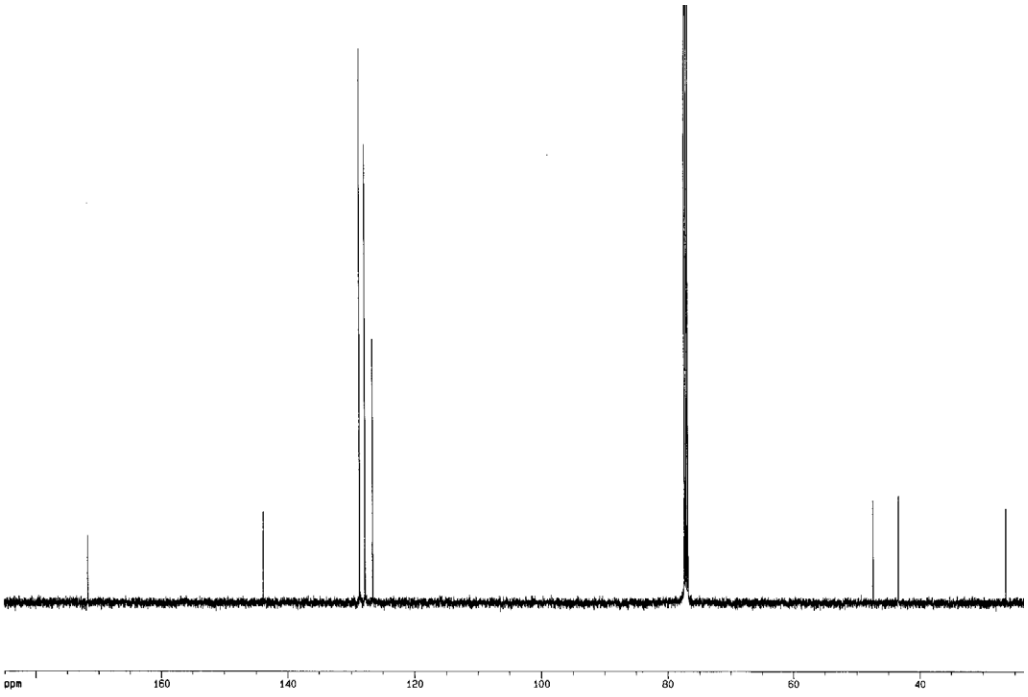
^{13}C-NMR spectrum of 9



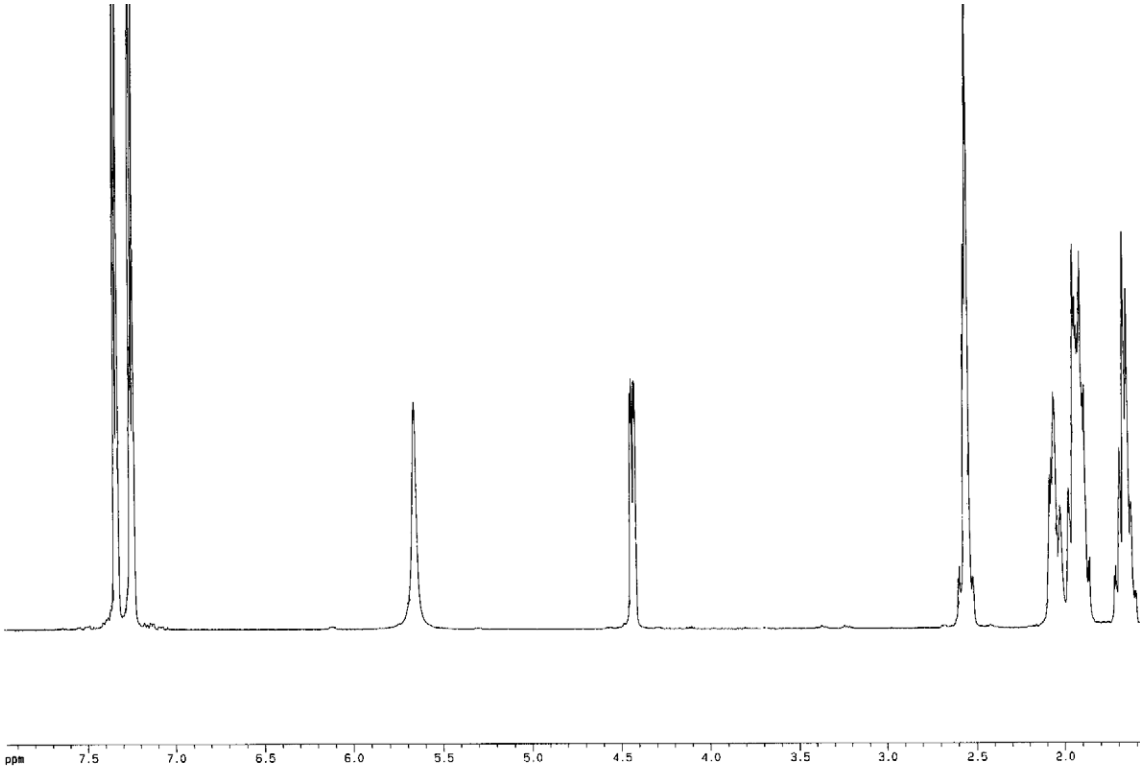
1H-NMR spectrum of 11



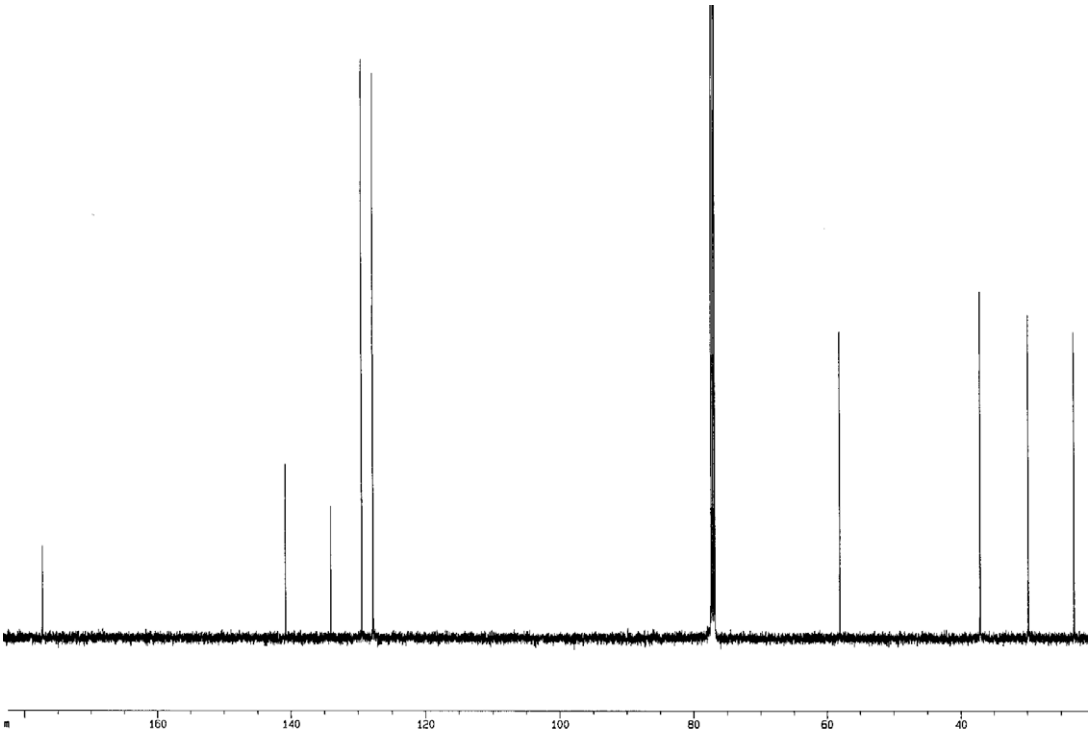
^{13}C-NMR spectrum of 11



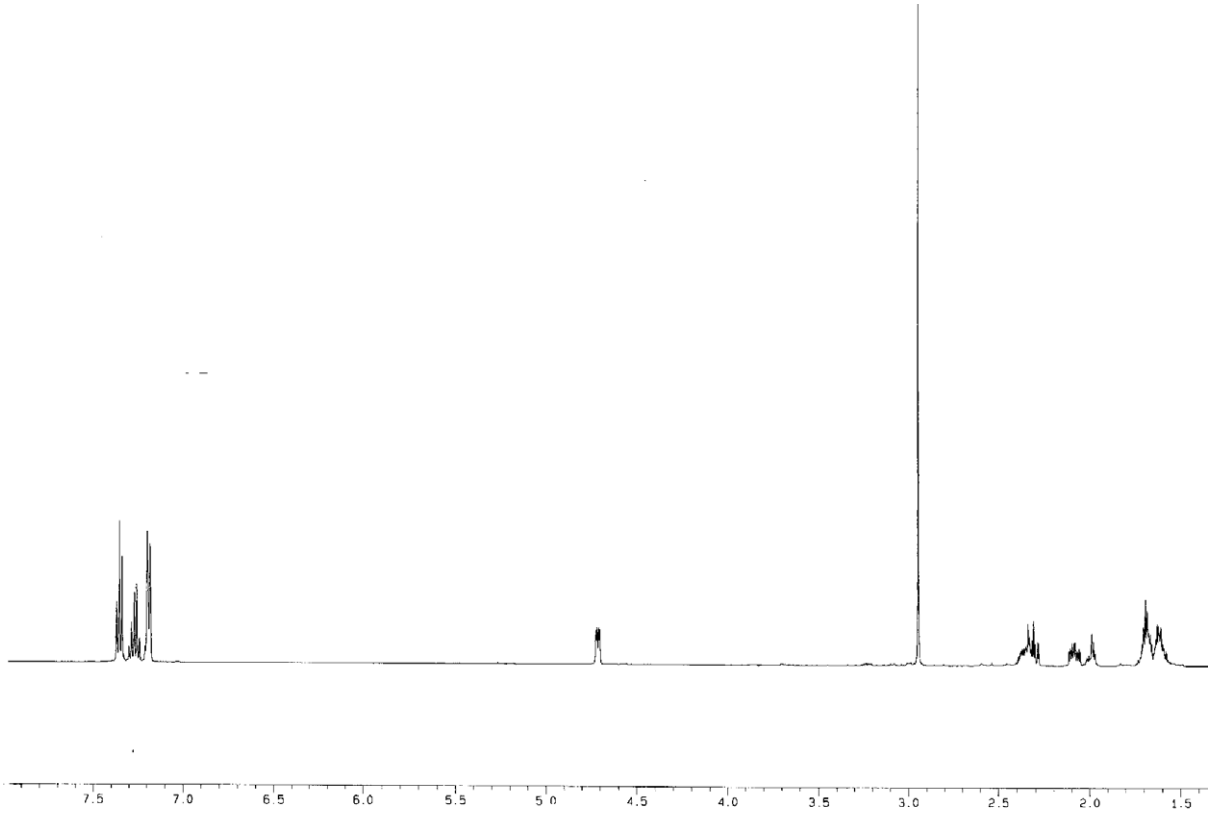
^{1}H-NMR spectrum of 12



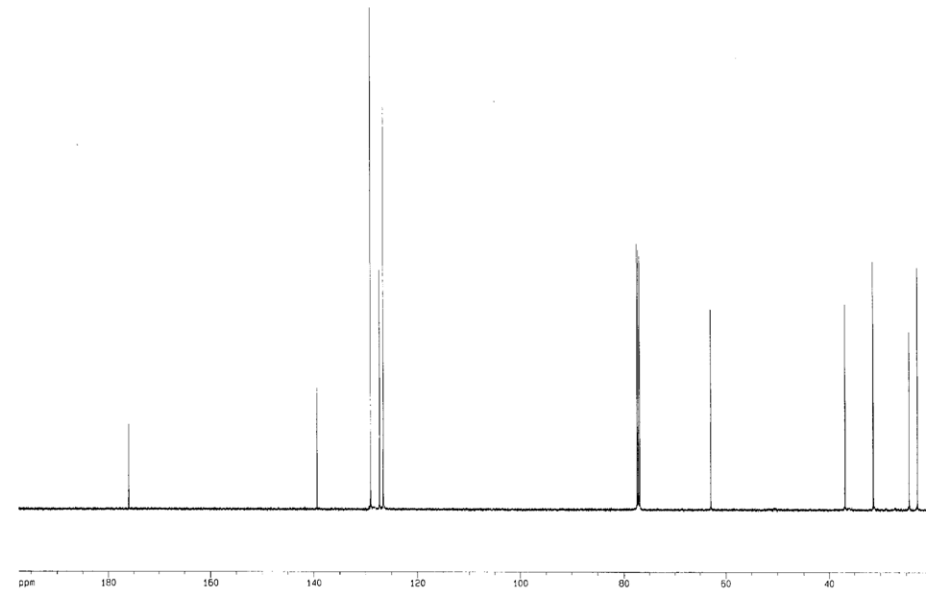
^{13}C-NMR spectrum of 12



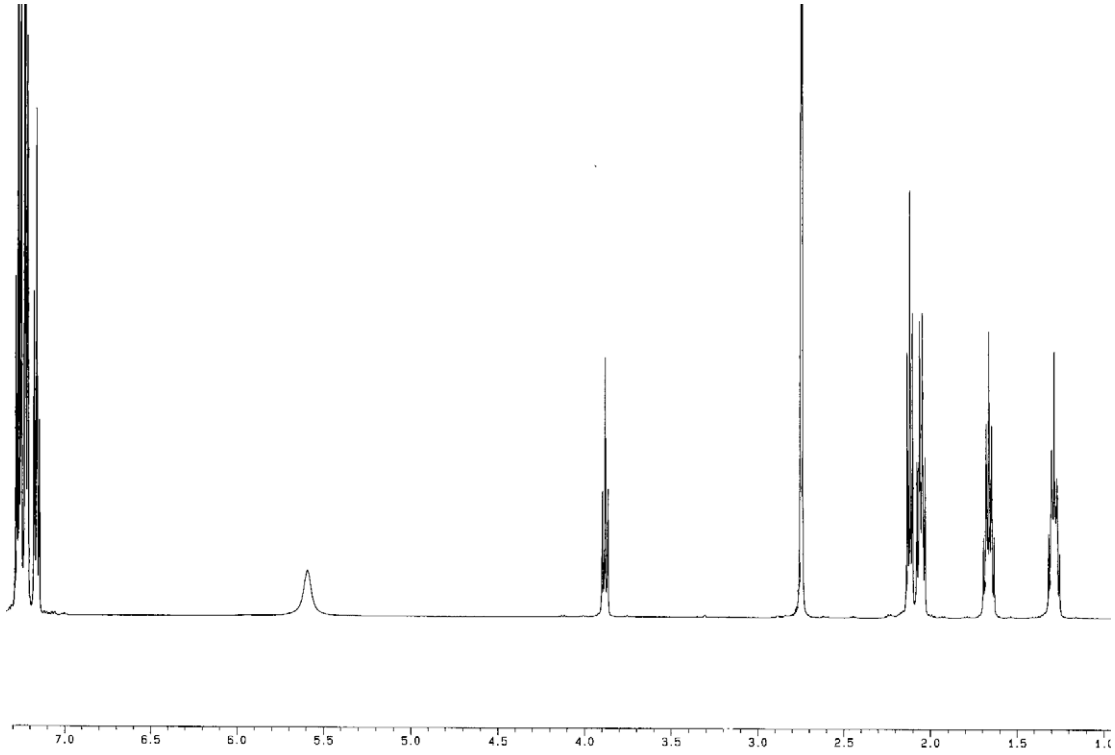
^{1}H-NMR spectrum of 13



^{13}C-NMR spectrum of 13



1H-NMR spectrum of 14



^{13}C-Spectrum of 14