Supporting Information
Reaction of Metalated Nitriles with Enones

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Contents

Experimental Section

Table S-1. Time and solvent dependence of reaction of **3** with benzylideneacetone at -78 °C (Fig. 3).

Solvent	Time / sec	**4:5**	**4** *dr*	**5** *dr*	% SM[a]	% Recovery
THF[b]	3	95:5	67:33	-	17	99
THF	15	94:6	60:40	-	9	98
THF	120	83:17	60:40	83:17	11	79
THF	630	63:37	57:43	85:15	9	116
THF	2400	41:59	54:46	80:20	4	98
THF	5420	26:74	48:52	87:13	1	95
1:1 THF/Tol	5	85:15			-	88
1:1 THF/Tol	30	83:17			-	92
1:1 THF/Tol	60	81:19			-	88
1:1 THF/Tol	300	71:29			-	79
1:1 THF/Tol	600	66:34			-	96
1:1 THF/Tol	1200	53:47			-	91
3:7 THF/Tol	2	91:9			18	90
3:7 THF/Tol	15	88:12			0	120
3:7 THF/Tol	120	84:16			7	107
3:7 THF/Tol	300	77:23			12	135
3:7 THF/Tol	900	69:31			17	125
3:7 THF/Tol	1800	62:38			7	118
3:7 THF/Tol	3600	48:52			0	113
3:7 THF/Tol	14700	37:63			0	109

[a] Recovered benzylideneacetone. [b] Dilute experiment at 0.001M concentration instead of standard 0.083 M.

Table S-2. Time dependence of reaction of **3** with benzylideneacetone with one eq. of LiOPh in THF at -78 °C (Fig. 3).

Time / sec	**4**:**5**	% Recovery
60	91:9	117
360	93:7	91
1200	93:7	109
2700	83:17	100
1800	87:13	90
3600	78:22	95
5400	68:32	128

Table S-3. Time dependence of reaction of **4** (**9**) in THF at -78 °C rearranging to **5 (10)** (Fig. 3).

Time / sec	**4**:**5**	% SM[a]
15	93:7	34
40	88:12	33
120	73:27	18
300	83:17	18
635	65:35	27
1200	49:51	7
2400	35:65	16
5400	20:80	13

[a] Recovered benzylideneacetone.

3-Hydroxy-2,5-diphenyl-3-methylpent-4-enenitrile (4): ^{1}H NMR (300 MHz, $CDCl_3$): (62:38 diastereomer ratio after 15 sec, major diastereomer marked with *): δ: 7.4-7.2 (m, 10H), 6.62 (d, J = 16.0 Hz, 1H), 6.58 (d, J = 16.0 Hz, 1H)*, 6.28 (d, J = 16.0 Hz, 1H)*, 6.27 (d, J = 16.0 Hz, 1H), 3.95 (s, 1H)*, 3.92 (s, 1H), 2.27 (s, OH)*, 2.25 (s, OH), 1.52 (s, 3H), 1.49 (s, 3H)*. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ: 135.9 (C), 131.7 (C), 131.6 (C), 131.3 (CH), 130.4 (CH), 130.3 (CH), δ 129.5 (CH), δ 128.6 (CH), 128.0 (CH), 126.6 (CH), 119.3 (CN), 119.2 (CN), 74.1 (C), 74.1 (C), 50.1 (CH), 50.0 (CH), 26.1 (CH_3), 25.8 (CH_3). IR (neat): 3605 cm-1 (free OH), 2241 cm-1 (CN). [M^+] = 263.1297, (calc. for $C_{18}H_{17}NO$, 263.1310).

5-Oxo-2,3-diphenylhexanenitrile (5): ^{1}H NMR (300 MHz, $CDCl_3$), (83:17 diastereomer ratio after 90 min, major diastereomer marked with *): δ 7.4-6.9 (m, 10H), 4.34 (d, J = 6.0 Hz, 1H)*, 4.09 (d, J = 6.5 Hz, 1H), 3.71 (ddd, J = 9.0, 6.0, 5.0 Hz, 1H), 3.61 (dt, J = 8.5, 6.0 Hz, 1H)*, 3.17 (dd, J = 17.0, 8.5 Hz, 1H)*, 3.14 (dd, J = 17.0, 9.0 Hz, 1H), 2.97 (dd, J = 17.0, 6.0 Hz, 1H)*, 2.90 (dd, J = 17.0, 5.0 Hz, 1H), 2.15 (s, 3H)*, 2.05 (s, 3H). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 206.1 (C), 205.4 (C), 139.2 (C), 138.0 (C), 133.8 (C), 133.4 (C), 128.7 (CH), 128.5 (CH), 128.3 (CH), 128.2 (CH), 127.9 (CH), 127.8 (CH), 127.6 (CH), 119.4 (CN), 119.2 (CN), 46.3 (CH_2), 45.2 (CH_2), 44.9 (CH), 44.8 (CH), 43.7 (CH), 42.8 (CH), 30.5 (CH_3). IR (neat): 2240 cm-1 (CN), 1720 (C=O). M+ = 263.1313, (calc. for $C_{18}H_{17}NO$, 263.1310).

Table S-4. Diastereomer interconversion of **4A** or **4B** at -78 °C in THF (Fig. 4, measurement of $k_{-1,2}$).

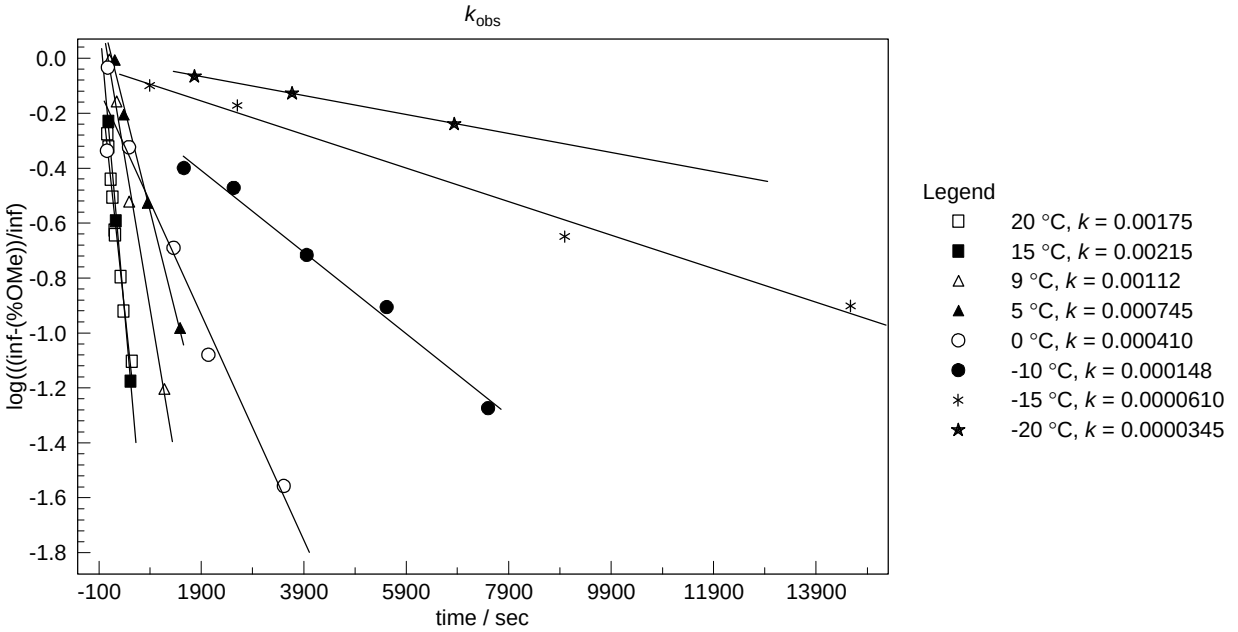
Time / sec	% **4A** in SM	% **4A** after rxn
5	20	37
10	20	46
30	20	46
45	20	48
60	20	54
90	20	56
120	20	54
5	93	83
10	93	60
30	93	74
60	93	67
90	93	68

Table S-5. Time dependence of benzaldehyde trapping of **3** at -78 °C in THF (measurement of $k_{1,2}$).

Time / sec	**4**:**11**	% **4**	% **11** (*anti*:*syn*)	% Benzylideneacetone
4	87:13	76	11 (83:17)	23
5	78:22	74	21 (85:15)	24
5	80:20	74	19 (79:21)	20
5	62:38	48	29 (74:26)	31
5	67:33	62	31 (81:19)	32
6	76:24	73	23 (78:22)	25
10	73:27	77	28 (81:19)	29
10	64:36	56	32 (80:20)	36
10	78:22	78	22 (85:15)	21
12	54:46	44	37 (87:13)	44
13	48:52	35	38 (79:21)	30
20	93:7	93	7 (83:17)	7
20	68:32	60	28 (75:25)	27
20	60:40	66	44 (83:17)	43
30	58:42	33	46 (77:23)	44
40	51:49	51	49 (84:16)	47
40	55:45	38	31 (78:22)	33
40	49:51	52	55 (82:18)	55
60	62:38	50	31(82:18)	31
60	40:60	39	58 (79:21)	55
61	44:56	41	52 (76:24)	50
120	17:83	13	64 (82:18)	65

3-Hydroxy-2,3-diphenylpropionitrile (11). ^{1}H NMR (300 MHz, $CDCl_3$), (79:21 *anti*:*syn* diastereomer ratio after 5 sec, *anti* diastereomer marked with *): δ 7.18-7.35 (m, 10H), 4.99 (d, J = 7 Hz, 1H), 4.96 (d, J = 6 Hz, 1H)*, 4.15 (d, J = 7 Hz, 1H), 4.04 (d, J = 6 Hz, 1H)*, 3.22 (bs, 1H). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 139.4* (C), 138.8 (C), 32.4 *(C), 131.9 (C), 128.80* (CH), 128.76 (CH), 128.7 (CH), 128.6* (CH), 128.5 (CH), 128.43* (CH), 128.41 (CH), 128.39* (CH), 128.37* (CH), 128.32 (CH), 126.6 (CH), 126.20* (CH), 126.19 (CH), 118.8* (CN), 118.7 (CN), 76.2* (CH), 76.0 (CH), 47.3* (CH), 46.5 (CH). HRMS (EI) (m/z):calcd. for $C_{15}H_{11}N$ (M-H_2O^+), 205.0891; found 205.0890.

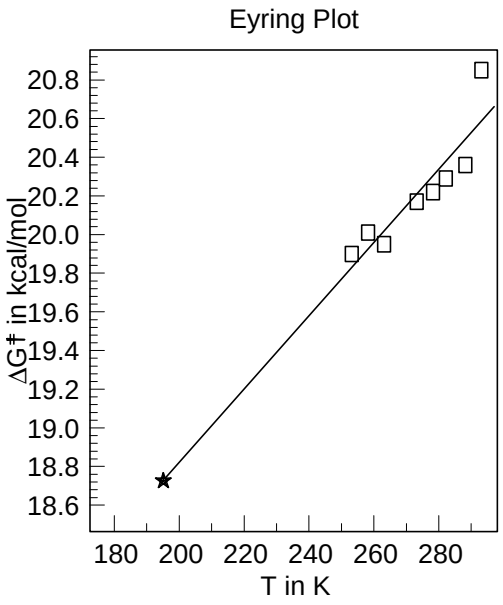
Figure S-1. First order rate plots of incorporation of *m*-methoxyphenylacetonitrile **(12)** into 1,4 adduct (**5**) at various temperatures (Scheme 2, measurement of $k_{-1,4}$).[a]



[a] Points shown were up to 70% conversion (100% conversion corresponds to 66% incorporation of **12).**

Figure S-2: Extrapolation of $\Delta G^{\ddagger}$ vs. T to give $\Delta G^{\ddagger}_{-78}$ = 18.7 kcal/mol, $\Delta H^{\ddagger}$ = 15.0 ± 1.0 kcal/mol, and $\Delta S^{\ddagger}$ = 19 ± 3.7 e.u.

T in °K	k_{obs} in sec $^{-1}$	$\Delta G^{\neq}$ in kcal/mol
293	0.00175	20.85
288	0.00215	20.36
282	0.00112	20.29
278	0.000745	20.22
273	0.000410	20.17
263	0.000148	19.95
258	0.0000610	20.01
253	0.0000345	19.90
195	Extrapolated	18.73



2-(3-Methoxyphenyl)-5-oxo-3-phenylhexanenitrile (keto-13). (73:27 dr after 85 sec at 20 °C, major diastereomer marked with *) ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.4-6.9 (m, 10H), 4.30 (d, J = 6.5 Hz, 1H)*, 4.06 (d, J = 6.5 Hz, 1H), 3.71 (ddd, J = Hz, 1H), 3.61 (dt, J =Hz, 1H)*, 3.17 (dd, J = 17.0, 8.5 Hz, 1H)*, 3.14 (dd, J = 17.0, 9.0 Hz, 1H), 2.97 (dd, J = 17.0, 6.0 Hz, 1H)*, 2.90 (dd, J = 17.0, 5.0 Hz, 1H), 2.15 (s, 3H)*, 2.05 (s, 3H). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 206.1* (C), 205.5 (C), 159.6* (C), 139.3 (C), 138.1* (C), 135.3*(C),

134.9 (C), 129.8 (CH), 129.7* (CH), 128.7 (CH), 128.4* (CH), 128.3, 127.9 (CH), 127.7*(CH), 120.34*(CH), 120.30(CH), 119.4 (CN), 119.2* (CN), 114.1* (CH), 113.9(CH), 113.8 (CH), 113.3 (CH), 55.2* (CH_3), 46.4 (CH_2), 45.2 (CH_2), 45.0* (CH), 44.9 (CH), 43.9 (CH), 42.9* (CH), 30.6* (CH_3). HRMS (EI) (m/z): calcd. for $C_{19}H_{19}NO_2$ (M^+.), 293.1416; found 293.1419.

Preparation of 4-Substituted phenylmethoxyacetonitriles (17-X): Sample Procedure.

Phenylmethoxyacetonitrile (17-H). Prepared according to a standard procedure for making methyl ethers of cyanohydrins[28] from 0.761g (5.0 mmol) of the dimethyl acetal of benzaldehyde,[30] 668 μL (5.0 mmol) of trimethylsilyl cyanide, and a catalytic amount (66 mg, 0.34 mmol) of anhydrous $SnCl_2$, allowed to stir 3 h at 20 °C , taken up in 20 mL of diethyl ether, washed with once with 20 mL of saturated sodium bicarbonate solution, twice with 20 mL of water, once with 20 mL of brine and dried with anhydrous magnesium sulfate and rotary evaporated and run on a silica gel column eluted with 3:4 hexanes:diethyl ether to give 0.283g (38% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.43- 7.41 (m, 5H), 5.19 (s, 1H), 3.53 (s, 3H). ^{13}C (75.4 4 MHz, $CDCl_3$): δ 133.3 (C), 129.8 (CH), 129.0 (CH), 127.2 (CH), 116.9 (C), 72.3 (CH_2), 57.1 (CH_3). HRMS (EI) (m/z): calcd. for C_9H_9NO (M^+), 147.0684; found 147.0689.

(4-Cyanophenyl)methoxyacetonitrile (17-CN). Prepared according to a standard procedure for making methyl ethers of cyanohydrins[28] from 0.605 g (3.33 mmol) of the dimethyl acetal of 4-cyanobenzaldehyde,[30] 445 μL (3.33 mmol) of trimethylsilyl cyanide, and a catalytic amount (44.2 mg, 0.23 mmol) of anhydrous $SnCl_2$, stirred 3 h, to give 0.478 g (83.4% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.76- 7.62 (AA'BB', 4H), 5.26 (s, 1H), 3.60 (s, 3H). ^{13}C (75.4 4 MHz, $CDCl_3$): δ 138.1 (C), 132.8 (CH), 127.7 (CH), 117.9 (C), 116.0 (C), 113.8 (C), 71.4 (CH_2), 57.8 (CH_3). HRMS (EI) (m/z): calcd.for $C_{10}H_8N_2O$ (M^+), 172.0637; found 172.0636.

(4-Dimethylamino-phenyl)methoxyacetonitrile (17-NMe_2). Prepared according to a standard procedure for making methyl ethers of cyanohydrins[28] from 1.405 g (7.2 mmol) of the dimethyl acetal of 4-dimethylaminobenzaldehyde,[30] 962 μL (7.2 mmol) of trimethylsilyl cyanide, and a catalytic amount (96 mg, 0.50 mmol) of anhydrous $SnCl_2$, stirred 12 h, to give 0.650 g (47.4% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.34- 7.31, 6.73-6.71 (AA'BB', 4H), 5.10 (s, 1H), 3.47 (s, 3H), 2.98 (s, 6H). ^{13}C (75.4 4 MHz, $CDCl_3$): δ 151.3 (C), 128.6 (CH), 120.2 (C), 117.4 (CN), 112.0 (CH), 72.0 (CH), 56.4 (CH_3), 40.2 (CH_3). HRMS (ESI) (m/z): calcd. for $C_{11}H_{15}ON_2$ (MH^+), 191.1184; found 191.1184.

(4-Chloro-phenyl)methoxyacetonitrile (17-Cl). Prepared according to a standard procedure for making methyl ethers of cyanohydrins[28] from 0.267 g (1.43 mmol) of the dimethyl acetal of 4-chlorobenzaldehyde,[30] 190 μL (1.43 mmol) of trimethylsilyl cyanide, and a catalytic amount (19 mg, 0.10 mmol) of anhydrous $SnCl_2$, stirred 5 h, to give 0.202 g (78.2% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.43(AA'BB', 4H), 5.18 (s, 1H), 3.55 (s, 3H). ^{13}C (NMR (75.4 MHz, $CDCl_3$): δ 135.9(C), 131.8 (C), 129.2 (CH), 128.6 (CH), 116.6 (CN), 71.5 (CH), 57.3 (CH_3). HRMS (EI) (m/z): calcd. for C_8H_5ClN (M-OMe^+), 150.0111; found 150.0115.

Methoxy-(4-trifluoromethylphenyl)acetonitrile (17-CF_3). Prepared according to a standard procedure for making methyl ethers of cyanohydrins,[28] using 1.865 g (8.47 mmol) of the dimethyl acetal of 4-trifluoromethylbenzaldehyde,[30] 1.13 mL (8.47 mmol) of trimethylsilyl cyanide, and a catalytic amount (112 mg, 0.59 mmol) of anhydrous $SnCl_2$, stirred 3 h, to give 0.704 g (38.6% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.62-7.73 (AA'BB', 4H), 5.26 (s, 1H), 3.59 (s, 3H). ^{13}C (NMR (90.6 MHz, $CDCl_3$): δ 137.0(C), 131.8 C, $^2J_{C-F}$ = 32.5Hz), 127.5 (CH), 126.0 ($^3CF_3$ J_{C-F} = 4 Hz), 123.6 (CF_3 $^1J_{C-F}$ = 273 Hz) 116.3 (CN), 71.53 (CH), 57.6 (CH_3). HRMS(EI) (m/z): calcd. for $C_{10}H_8F_3ON$ (M^+), 215.0558; found 215.0567.

Table S-6. Time dependence of reaction of **17-X** with mesityl oxide (Fig. 6).

Nucleophile	**20-X**:**21-X**	Time / sec	% 1,2	%1,4	%RXN	%recov.	T in °C	Solvent
17-CF_3	50:50	6	5	5	12	86	-78	THF
17-CF_3	24:74	8	11	34	43	105	-78	THF
17-CF_3	12:88	25	5	36	46	90	-78	THF
17-CF_3	7:93	60	6	82	81	108	-78	THF
17-CF_3	85:15	10	17	3	20	101	-120	3:2 THF:Et2O
17-Cl	96:4	5	48	2	60	83	-78	THF
17-Cl	75:25	30	46	15	73	83	-78	THF
17-Cl	40:60	120	25	37	77	81	-78	THF
17-Cl	18:82	900	12	55	85	79	-78	THF
17-Cl	100:0	5	43	0	40	107	-78	DME
17-CN	0:100	40	7	26	35	93.5	-78	THF
17-CN	0:100	360	0	87.2	84	104	-78	THF
17-CN	0:100	1860	0	98	98	100	-78	THF
17-NMe_2	100:0	30	100	0	100	100	-78	THF
17-NMe_2	100:0	600	89	0	100	89	-78	THF
17-NMe_2	100:0	21360	91	0	100	91	-78	THF
17-NMe_2	0:100	25200	0	76	87	87	-78 to 0	THF
17-NMe_2	90:10	1800	46	5	58	88	-42	THF
17-NMe_2	76:24	7200	34	11	67	67	-42	THF
17-NMe_2	37:63	64800	12.5	21	49	68	-42	THF
17-NMe_2	7:93	147600	3	41	50	88	-42	THF
17-H	100:0	20	100	0	100	100	-78	THF
17-H	95:5	30	75	4	93	85	-78	THF
17-H	83:17	300	64	13	86	90	-78	THF
17-H	84:16	600	69	13.5	100	82.5	-78	THF
17-H	64:36	1800	56	31	89	98	-78	THF
17-H	55:45	9030	43.4	36.1	100	79.5	-78	THF
17-H	98:2	12	78	2	100	80	-78	Et_2O

2-Phenyl-3-hydroxy-2-methoxy-3,6-dimethylhex-4-enenitrile (20-H). ^{1}H NMR (300 MHz, $CDCl_3$), (62:38 dr after 20 sec, major diastereomer marked with *): δ 7.37-6.71 (m, 5H), 5.36 (sextet, J =1.5 Hz, 1H), 3.42 (s, 3H), 3.41 (s, 3H)*, 1.71 (d, J= 1.5 Hz, 3H)*, 1.70 (d, J = 1.5 Hz, 3H)*, 1.67 (d, J = 1.5 Hz, 3H), 1.53 (d, J = 1.5 Hz, 3H), 1.46 (s, 3H), 1.35 (s, 3H)*. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 138.0 (C), 132.8 (C), 129.13*, 129.05 (CH), 128.1 (CH), 128.03* (CH), 127.96* (CH), 127.9 (CH), 124.4* (CH), 123.8 (CH), 118.2 (CN), 88.8* (C), 88.6 (C), 78.0 (C), 54.96 (CH_3), 54.98* (CH_3), 27.8 (CH_3), 24.6 (CH_3), 24.2* (CH_3), 18.8* (CH_3), 18.5 (CH_3). HRMS (EI) (m/z): calcd. for $C_{14}H_{18}NO_2$ (M-OH^+), 228.1388; found 228.1383.

2-Phenyl-2-methoxy-3, 3-dimethyl-5-oxohexanenitrile (21-H). ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.43 (m, 5H), 3.36 (s, 3H), 2.75-2.55 (AB quartet, J = 16.0 Hz, 2H), 2.18 (s, 3H), 1.17 (s, 3H), 1.12 (s, 3H). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 207.3 (C), 132.6 (C), 129.1 (CH), 128.1 (CH), 128.0 (CH), 118.1 (CN), 89.2 (C), 54.8 (CH_3), 48.8 (CH_2), 42.8 (C), 32.7 (CH_3), 22.4 (CH_3), 20.6 (CH_3). HRMS (EI) (m/z): calcd. for $C_{15}H_{19}NO_2$ (M^+), 245.1416; found 245.1411.

2-(4-Cyanophenyl)-2-methoxy-3, 3-dimethyl-5-oxo-hexanenitrile (21-CN). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.76-7.57 (AA'BB', 4H), 3.35 (s, 3H), 2.73-2.54 (AB quartet, J = 14.0 Hz, 2H), 2.17 (s, 3H), 1.15 (s, 3H), 1.09 (s, 3H). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 206.4 (C), 138.2 (C), 131.8 (CH), 128.9 (CH), 117.8 (CN), 117.1 (CN), 113.4 (C), 88.8 (C), 55.1 (CH_3), 48.6 (CH_2), 43.0 (C), 32.4 (CH_3), 22.2 (CH_3), 20.3 (CH_3). HRMS (EI) (m/z): calcd. for $C_{16}H_{19}N_2O_2$ (MH^+), 271.1147; found 271.1434.

2-(4-Dimethylaminophenyl)-3-hydroxy-2-methoxy-3,5-dimethylhex-4-enenitrile (20-NMe_2). ^{1}H NMR (300 MHz, $CDCl_3$): (75:25 dr after 30 sec, major diastereomer marked with *) δ 7.37-6.71 (AA'BB', 4H)*, 5.36 (bs, 1H)*, 3.40 (s, 3H)*, 3.00 (s, 6H)*, 2.35 (bs, 1H)*, 1.78 (d, J = 1.5 Hz, 3H)*, 1.73 (d, J = 1.5 Hz, 3H), 1.35 (s, 3H)*. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 150.8 (C), 137.5 (C), 128.9 (CH), 124.9 (CH), 119.5 (C), 111.3 (CH), 88.7 (C), 78.1 (C), 54.5 (CH_3), 40.2 (CH_3), 27.8 (CH_3), 24.0 (CH_3), 18.8(CH_3). HRMS (ESI) (m/z): calcd. for $C_{17}H_{24}O_2N_2Na$ (MNa^+), 311.1735; found 311.1738.

2-(4-Dimethylaminophenyl)-2-methoxy-3, 3-dimethyl-5-oxo-hexanenitrile (21-NMe_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.34-6.38 (AA'BB', 4H), 3.32 (s, 3H), 2.98 (s, 6H), 2.73-2.52 (AB quartet, J = 15.0 Hz, 2H), 2.15 (s, 3H), 1.14 (s, 3H), 1.09 (s, 3H). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 207.7 (C), 150.6 (C), 129.0 (CH), 119.4 (C), 118.5 (CN), 113.4 (C), 89.1 (C), 54.5 (CH_3), 49.1 (CH_2), 43.0 (C), 40.2 (CH_3), 32.7 (CH_3), 22.5 (CH_3), 20.7 (CH_3). HRMS (ESI) (m/z): calcd. for $C_{17}H_{24}O_2N_2Na$ (MNa^+), 311.1735; found 311.1721.

2-(4-Chlorophenyl)-3-hydroxy-2-methoxy-3,5-dimethylhex-4-enenitrile (20-Cl). ^{1}H NMR (300 MHz, $CDCl_3$), (70:30 dr after 5 sec, major diastereomer marked with *): δ 7.38-7.43 (AA'BB', 4H), 5.29 (bs, 1H), 3.42 (s, 3H), (s, 3.40)* 1.72 (d, J=1.5 Hz, 3H)*, 1.70 (d, J=1.5 Hz, 3H)*, 1.68 (d, J = 1.5 Hz, 3H), 1.54 (d, J = 1.5 Hz, 3H), 1.47 (s, 3H) 1.36 (s, 3H)*. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 138.54* (C), 138.47 (C), 135.4 (C), 131.6 (C), 131.5 (C), 129.6 (CH), 129.4* (CH), 128.4* (CH), 128.3 (CH), 124.2* (CH), 123.7 (CH), 117.9 (CN), 88.4* (C), 87.9(C), 78.1 (C), 78.0* (C) 55.0(CH_3), 54.9 (CH_3), 27.8* (CH_3), 27.7 (CH_3), 24.7 (CH_3), 24.4* (CH_3), 18.8* (CH_3), 18.6 (CH_3). HRMS (EI) [MNa^+] (m/z): calcd.for $C_{15}H_{18}ClO_2NNa$ (MNa^+), 302.0924; found 302.1110.

2-(4-Chlorophenyl)-2-methoxy-3, 3-dimethyl-5-oxohexanenitrile (21-Cl). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35-7.44 (AA'BB', 4H), 3.35 (s, 3H), 2.55-2.76 (AB quartet, J = 15.0 Hz, 2H), 2.18 (s, 3H), 1.15 (s, 3H), 1.10 (s, 3H). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 207.0 (C), 135.4 (C), 129.5 (CH), 128.4 (CH), 117.7 (CN), 88.8 (C), 54.9 (CH_3), 48.8 (CH_2), 42.9 (C), 32.7 (CH_3), 22.4 (CH_3), 20.5 (CH_3). HRMS (EI) (m/z): calcd. for $C_{12}H_{13}ClON$ (M-$C_3H_5O^+$), 222.0686; found 222.0683.

2-(4-Trifluoromethylphenyl)-3-hydroxy-2-methoxy-3,5-dimethylhex-4-enenitrile (20-CF_3). We were not able to obtain pure **20-CF_3**, since it did not survive chromatography on silica gel. The NMR spectrum was

obtained from a mixture of **20-CF_3** and **21-CF_3**. ^{1}H NMR (300 MHz, $CDCl_3$), (59:41 dr after 6 sec, major diastereomer marked with *): δ 7.70-7.66 (4H, AA'BB'), 5.31 (1H, bs)*, 3.44 (3H, s), (3.42, s)*, 2.30 (1H, s)*, 1.73 (d, J=1.5 Hz, 3H)*, 1.69 (d, J=1.5 Hz, 3H), 1.66 (d, J = 1.5 Hz, 3H)*, 1.50 (d, J = 1.5 Hz, 3H), * 1.49 (s, 3H), 1.38 (s, 3H)*.^{13}C NMR (75.4 MHz, $CDCl_3$): δ 138.6 (C), 137.2* (C), 137.1 (C), 131.3* (C, $^2J_{C\text{-}F}$ = 33 Hz), 131.2 (C, $^2J_{C\text{-}F}$ = 33 Hz), 129.6 (CH), 129.4* (CH), 128.6 (CH), 124.7 (CH $^3J_{C\text{-}F}$ = 4 Hz), 123.9* (CH), 123.5 (CH), 123.3 (CF_3 $^1J_{C\text{-}F}$ = 272 Hz), 117.4 (CN), 88.4* (C), 87.8(C), 78.1 (C), 78.0* (C) 55.0 (CH_3), 54.9* (CH_3), 27.58* (CH_3), 27.55 (CH_3), 24.6 (CH_3), 24.5* (CH_3), 18.5* (CH_3), 18.3 (CH_3).

2-(4-Trifluoromethylphenyl)-2-methoxy-3, 3-dimethyl-5-oxohexanenitrile (21-CF_3). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.57-7.73(AA'BB', 4H), 3.37 (s, 3H), 2.72-2.58 (AB quartet, J = 15.0 Hz, 2H), 2.20 (s, 3H), 1.17 (s, 3H), 1.11(s, 3H). ^{13}C NMR (90.6 MHz, $CDCl_3$): δ 206.8 (C), 136.9 (C), 131.4 C, ($^2J_{C\text{-}F}$ = 32Hz), 128.6 (CH), 125.1 ($^3CF_3$ $J_{C\text{-}F}$ = 4 Hz), 123.6 (CF_3 $^1J_{C\text{-}F}$ = 272 Hz), 117.5 (CN), 88.8 (C), 55.0 (CH_3), 48.6 (CH_2), 42.9 (C), 32.6 (CH_3), 22.3 (CH_3), 20.4 (CH_3). HRMS (EI) (m/z): calcd. for $C_{32}H_{36}F_6N_2O_4Na$ ($2MNa^+$), 649.2477; found 649.2482.

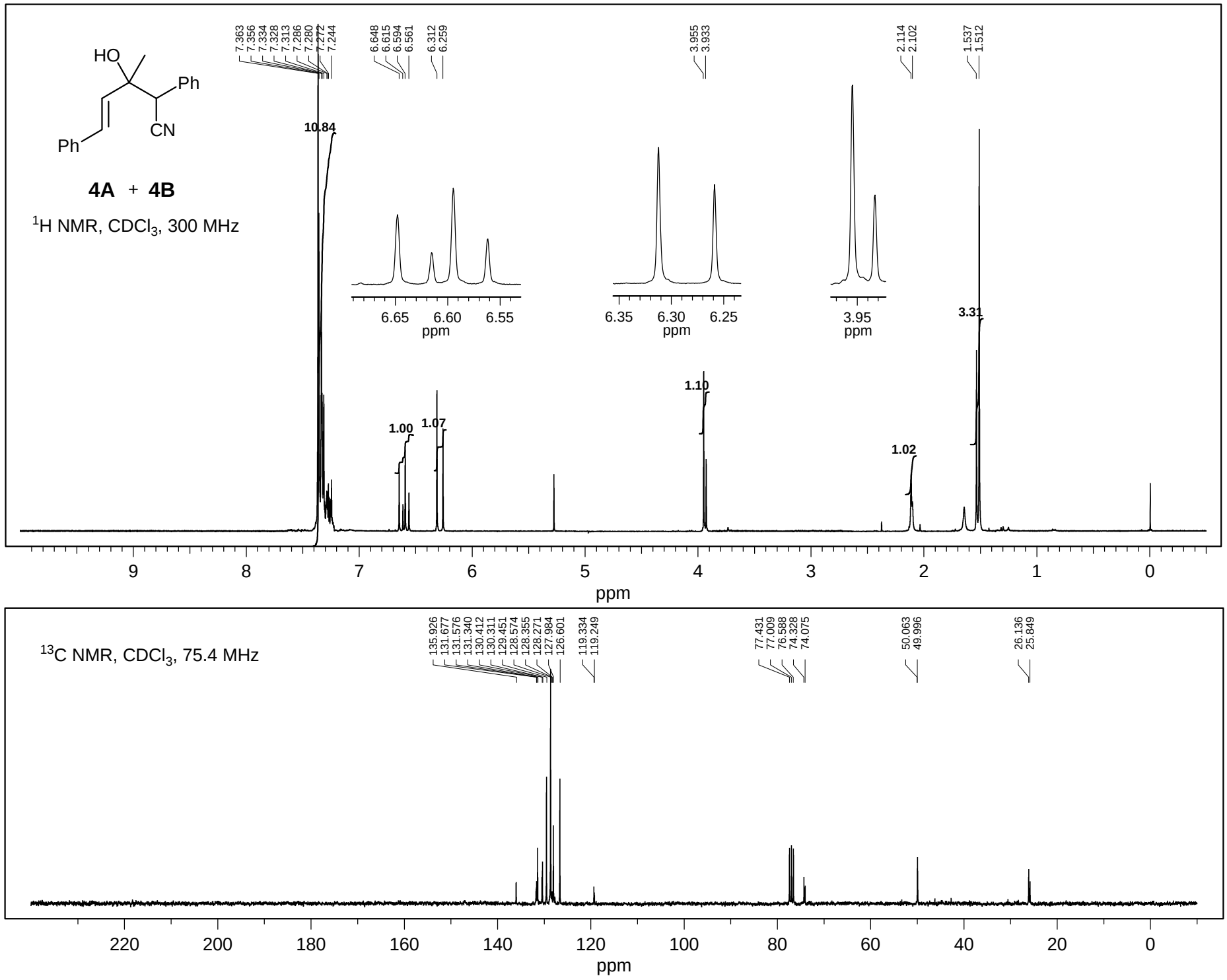
Lithio-(4-methoxyphenyl)acetonitrile with mesityl oxide (4-Methoxyphenyl)acetonitrile (34 μL, 0.25 mmol)was added to a N_2 purged 5mL long neck RBF, 3 mL of dry THF was added, and the system was cooled to -78 °C under positive nitrogen pressure. *n*-BuLi (95 μL of 2.65 M, 0.25 mmol) was added, stirred for 20 min, and 100 μL of 2.5 M mesityl oxide in THF was injected. The solution was stirred for the indicated time, quenched with 200 μL of 3 M propionic acid in diethyl ether and worked up as in reaction of **3** with benzylidene acetone. Data are displayed in **Table S-7**.

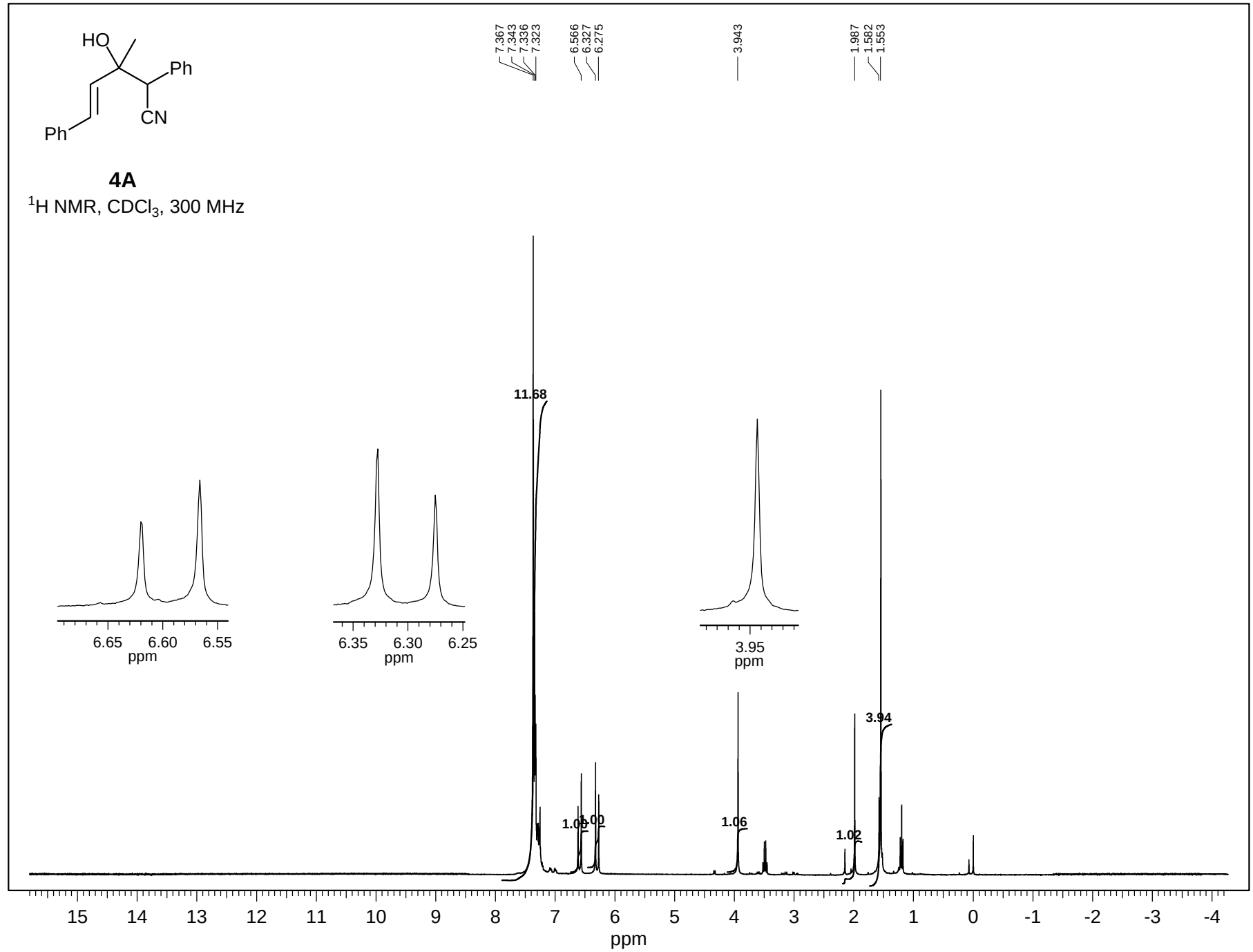
Table S-7. Time dependence of reaction of lithio- 4-methoxyphenylacetonitrile with mesityl oxide at -78 °C in THF.

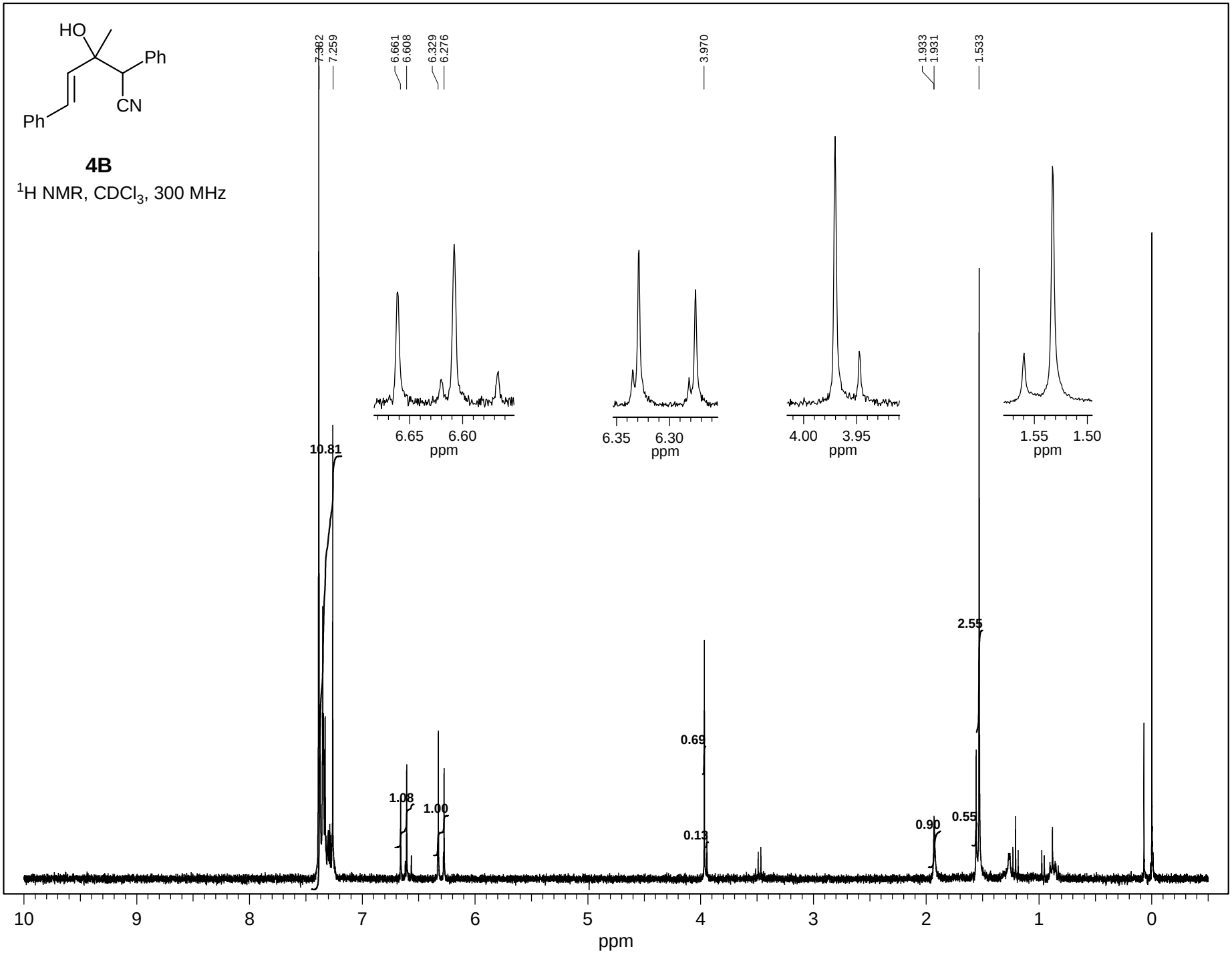
time / sec	1,2:1,4	% recovery
7	100:0	102
120	90:10	105
1140	52:48	103
7200	7:93	105

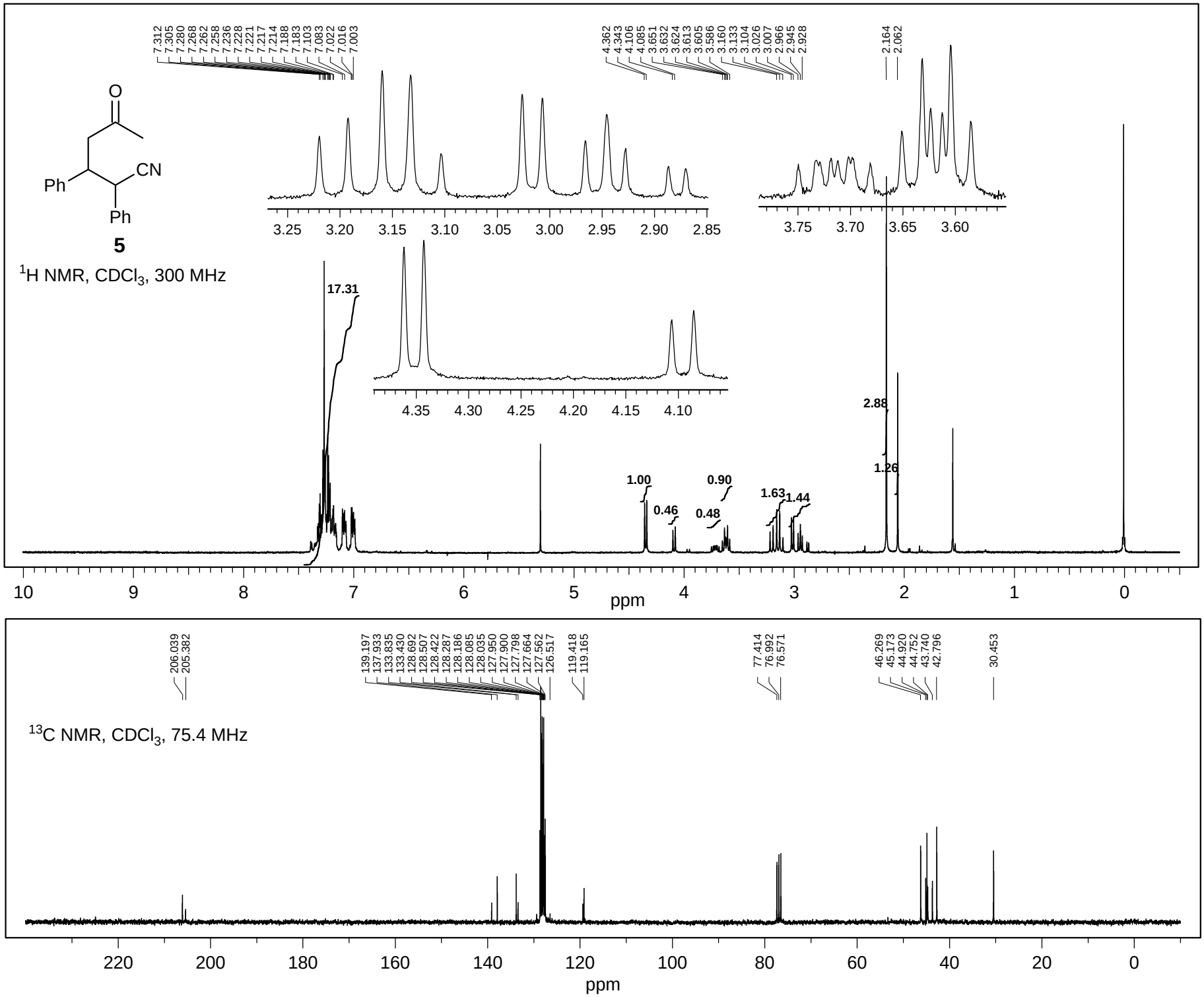
2-(4-Methoxyphenyl)-3-hydroxy-3,5-dimethylhex-4-enenitrile. ^{1}H NMR (300 MHz, $CDCl_3$): (56:44 dr after 7 sec, major diastereomer marked with *) δ 7.23-6.79 (AA'BB', 4H)*, 5.24 (bs, 1H)*, 3.81 (s, 1H), 3.77 (s, 1H)*, 3.72 (s, 3H), 2.07 (bs, 1H)*, 1.70 (d, J = 1 Hz, 3H)*, 1.65 (d, J = 1 Hz, 3H), 1.37 (s, 3H), 1.33 (s, 3H)*. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 159.5 (C), 137.8*, 137.6 (C), 130.6, 130.5* (CH), 126.5, 126.4* (CH), 124.04*, 123.98 (CH), 120.0*, 119.9 (C), 113.9*, 113.7 (CH), 74.4*, 74.1 (C), 55.1 (CH_3), 49.3*, 49.0 (CH), 27.3, 27.2* (CH_3), 26.9*, 26.8 (CH_3), 18.7 (CH_3). HRMS (ESI) (m/z): calcd. for $C_{15}H_{19}O_2N$ (M^+), 245.1416; found 245.1419.

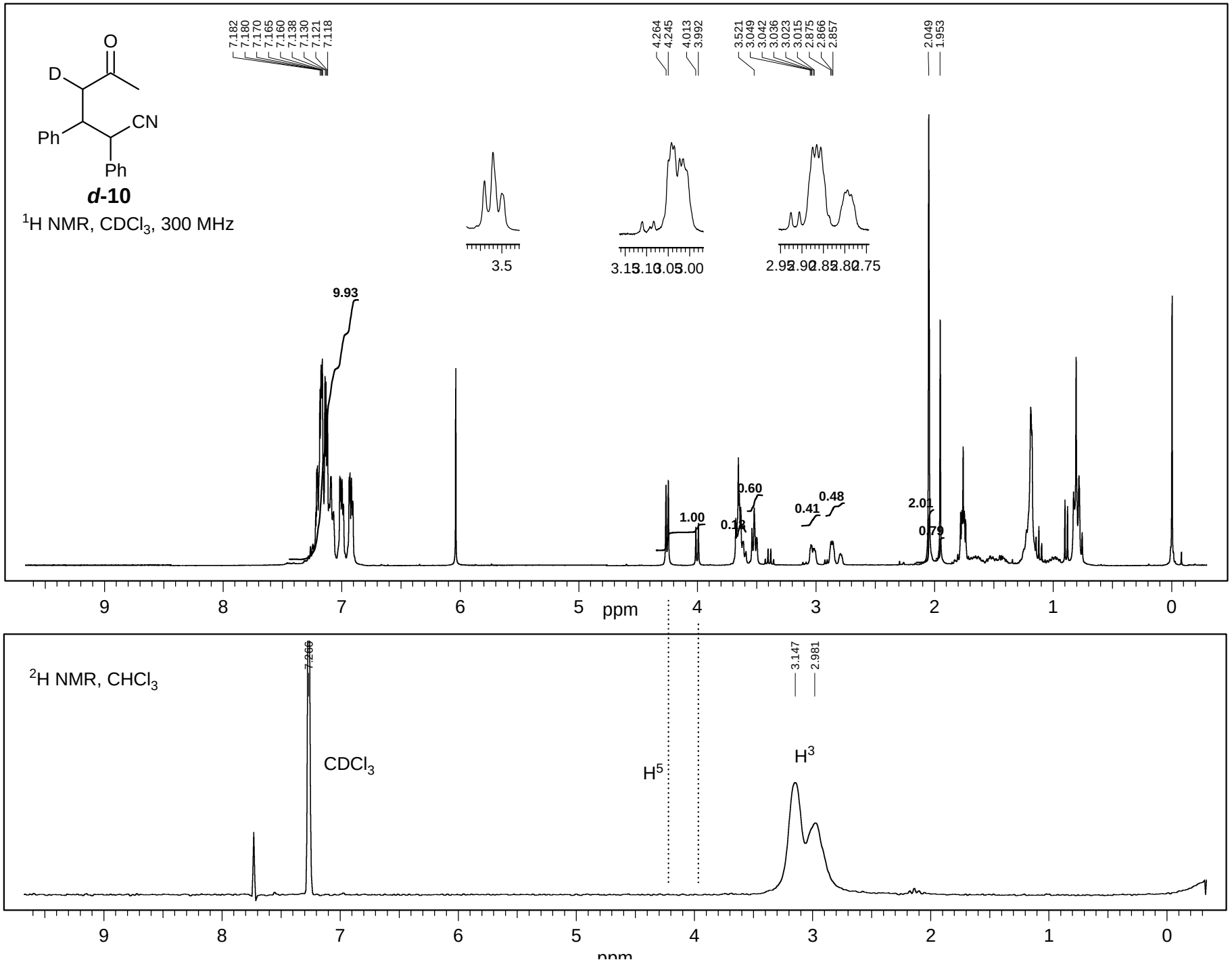
2-(4-Methoxyphenyl)-3, 3-dimethyl-5-oxo-hexanenitrile. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.22-6.87 (AA'BB', 4H), 4.4 (s, 1H), 3.8 (s, 3H), 2.60-2.14 (AB quartet, J = 18.0 Hz, 2H), 2.14 (s, 3H), 1.20 (s, 3H), 1.05 (s, 3H). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 207.8 (C), 159.4 (C), 130.6 (CH), 124.8 (C), 120.5 (C), 113.9 (CH), 55.3 (CH_3), 51.1 (CH_2), 44.7 (CH), 36.9 (C), 31.8 (CH_3), 25.1 (CH_3), 24.4 (CH_3). HRMS (ESI) (m/z): calcd. for $C_{15}H_{19}O_2N$ (M+), 245.1416; found 245.1419.

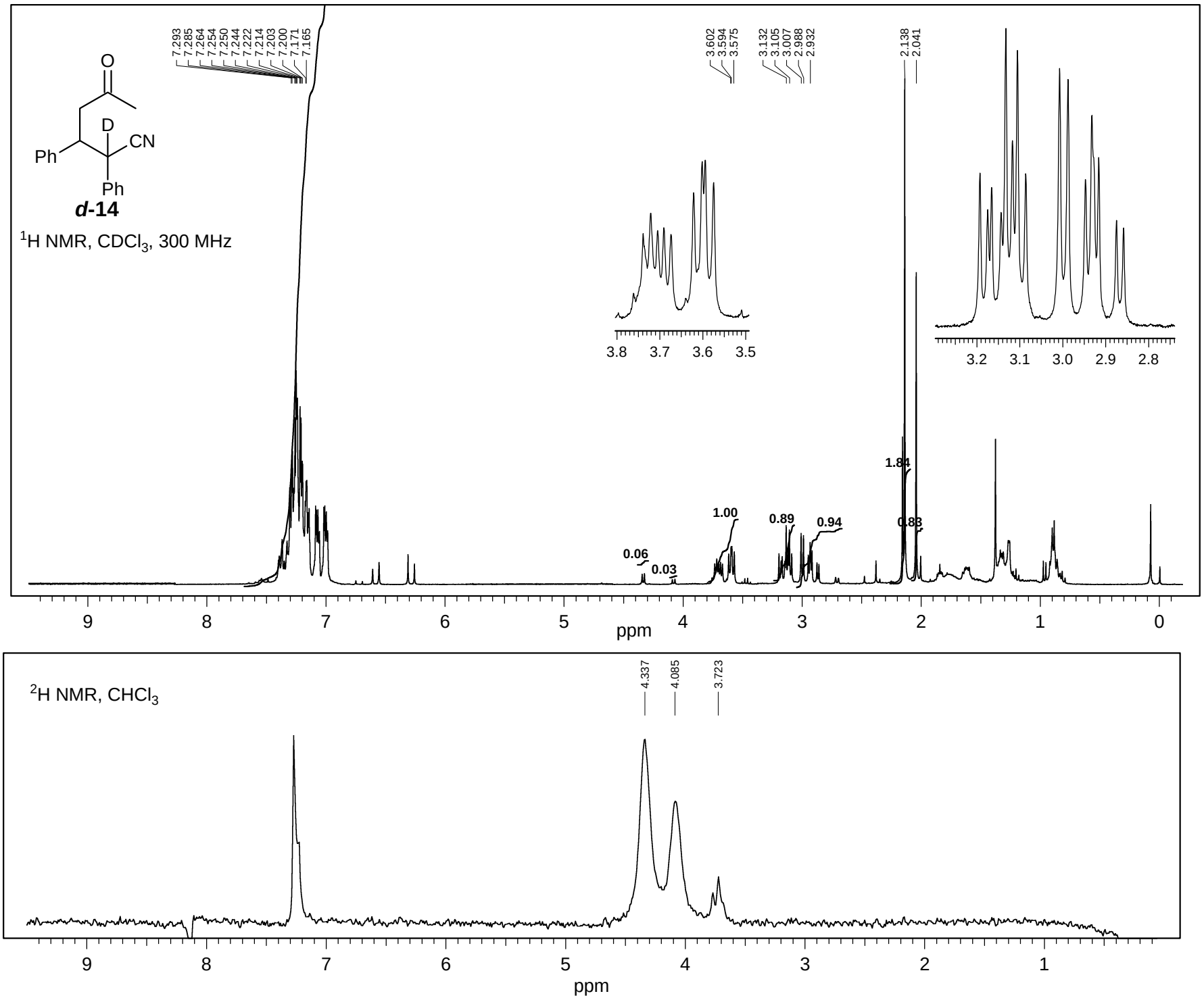

HO
Ph
CN
Ph
4A + 4B
1H NMR, CDCl3, 300 MHz
7.363
7.356
7.334
7.328
7.313
7.286
7.280
7.272
7.244
6.648
6.615
6.594
6.561
6.312
6.259
3.955
3.933
2.114
2.102
1.537
1.512
10.84
1.00
1.07
1.10
1.02
3.31
6.65
6.60
6.55
ppm
6.35
6.30
6.25
ppm
3.95
ppm
9
8
7
6
5
4
3
2
1
0
ppm
13C NMR, CDCl3, 75.4 MHz
135.926
131.677
131.576
131.340
130.412
130.311
129.451
128.574
128.355
128.271
127.984
126.601
119.334
119.249
77.431
77.009
76.588
74.328
74.075
50.063
49.996
26.136
25.849
220
200
180
160
140
120
100
80
60
40
20
0
ppm

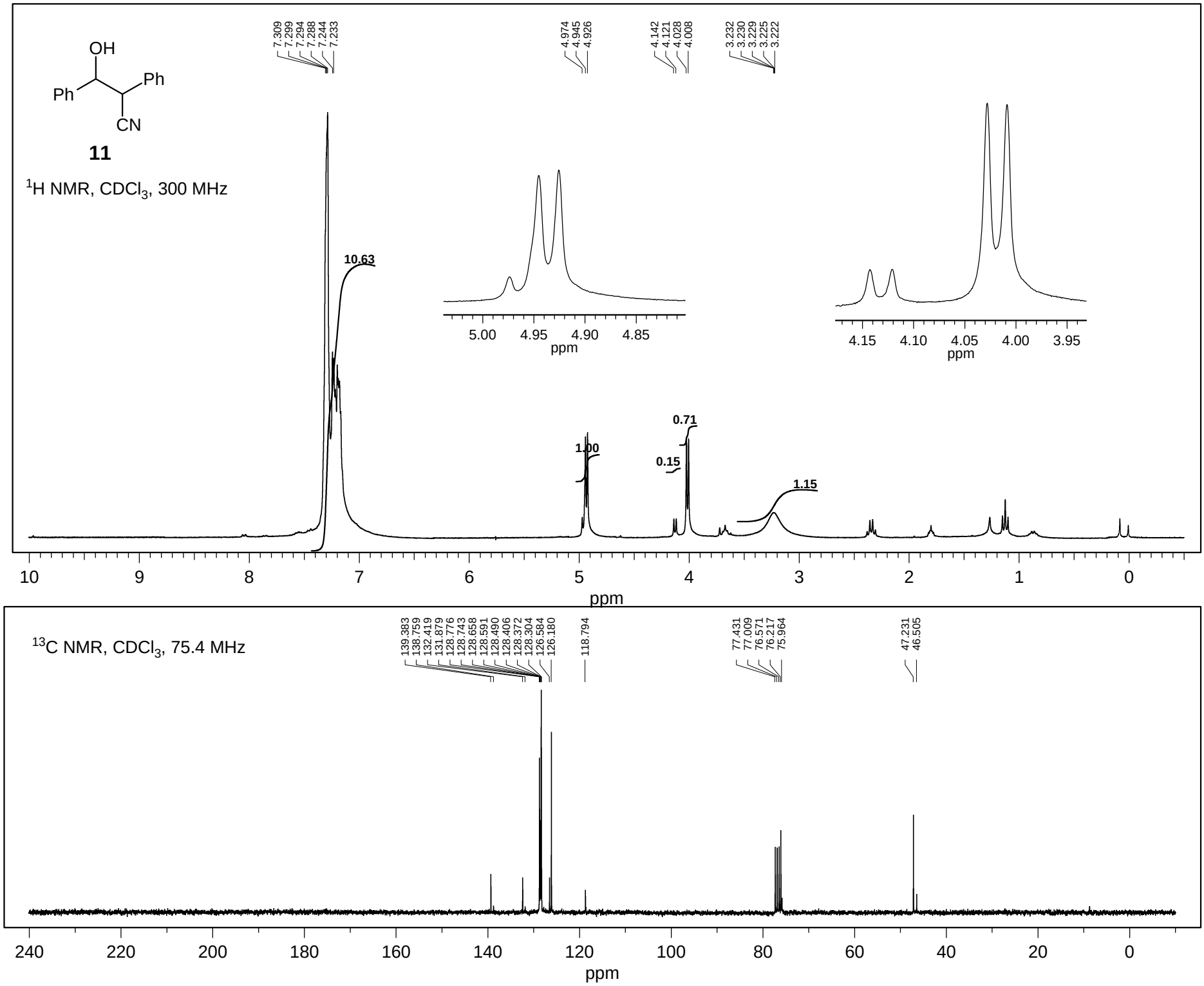

HO
Ph
CN
Ph
4A
1H NMR, CDCl3, 300 MHz
7.367
7.343
7.336
7.323
6.566
6.327
6.275
3.943
1.987
1.582
1.553
11.68
1.00
1.00
1.06
1.02
3.94
6.65 6.60 6.55
ppm
6.35 6.30 6.25
ppm
3.95
ppm
15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1 -2 -3 -4
ppm

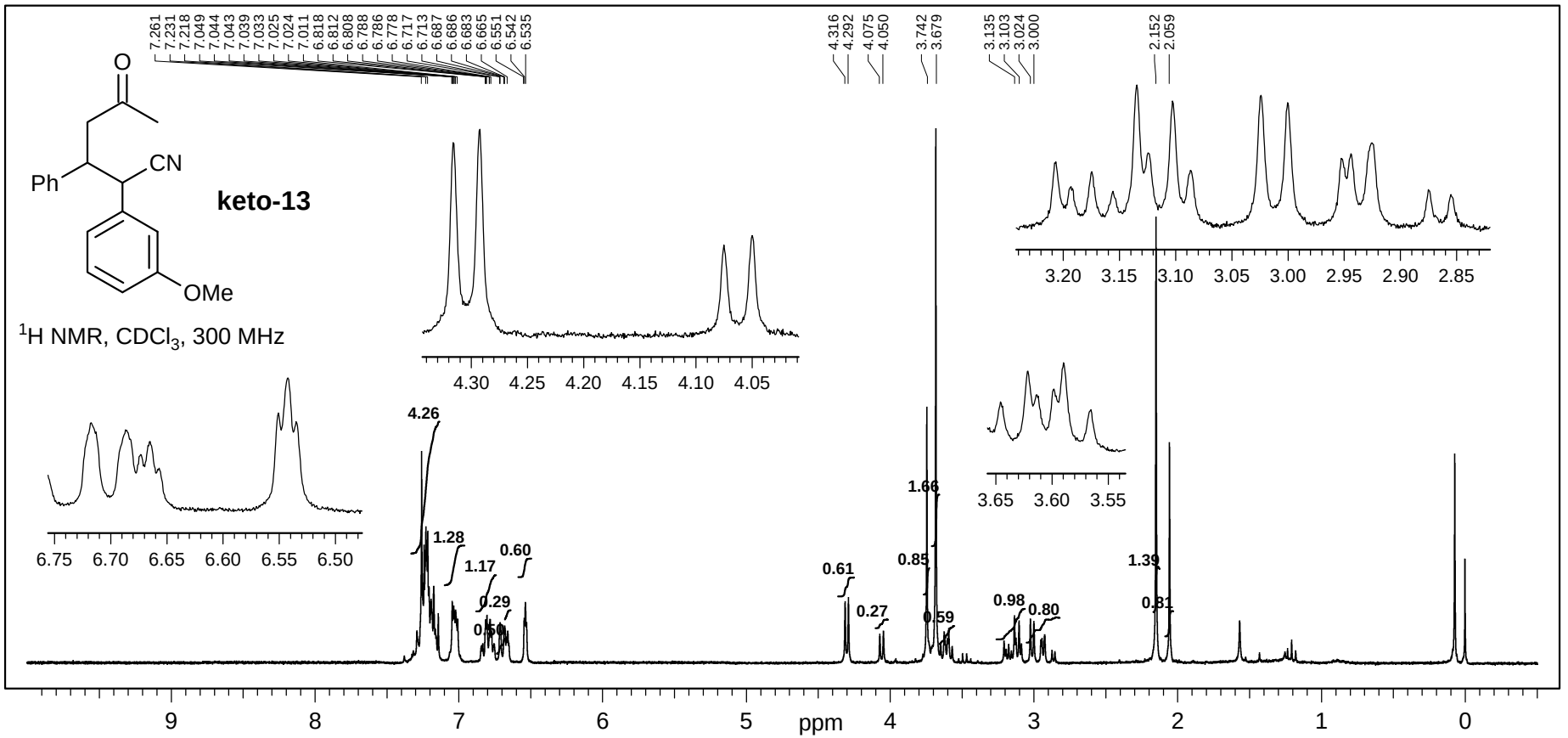

HO
Ph
CN
Ph
4B
1H NMR, CDCl3, 300 MHz
7.382
7.259
6.661
6.608
6.329
6.276
3.970
1.933
1.931
1.533
10.81
1.08
1.00
0.69
0.13
0.90
2.55
0.55
6.65 6.60 ppm
6.35 6.30 ppm
4.00 3.95 ppm
1.55 1.50 ppm
10 9 8 7 6 5 4 3 2 1 0
ppm

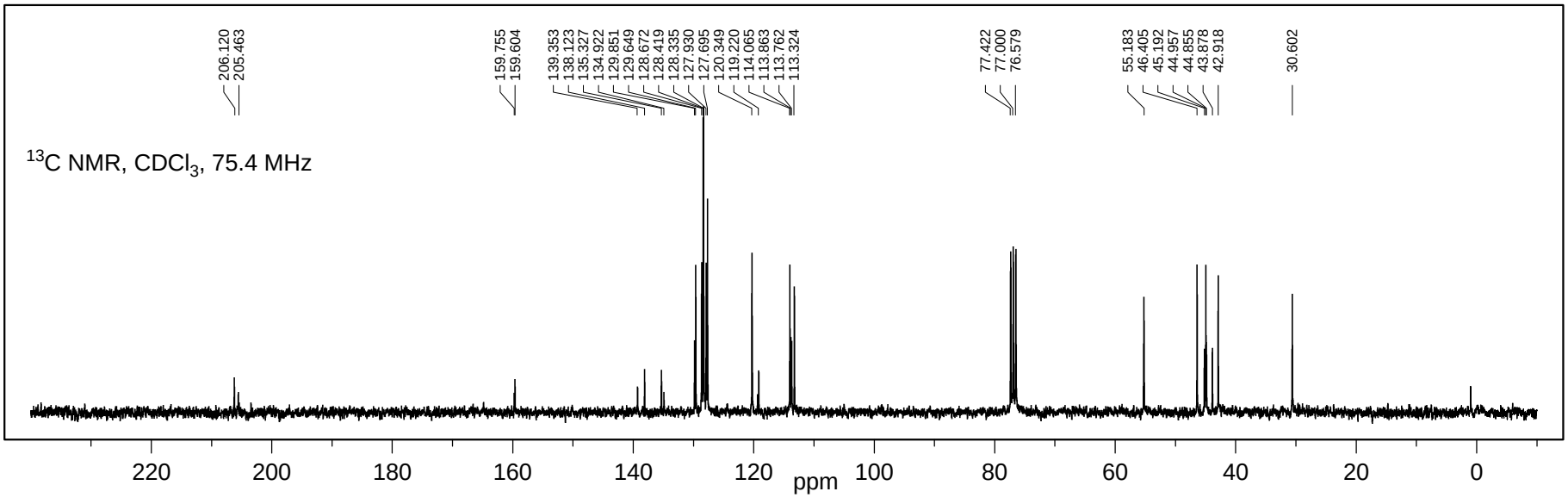

7.312
7.305
7.280
7.268
7.262
7.258
7.236
7.228
7.221
7.217
7.214
7.188
7.183
7.103
7.083
7.022
7.016
7.003
4.362
4.343
4.106
4.085
3.651
3.632
3.624
3.613
3.605
3.586
3.160
3.133
3.104
3.026
3.007
2.966
2.945
2.928
2.164
2.062
O
CN
Ph
Ph
5
1H NMR, CDCl3, 300 MHz
17.31
1.00
0.46
0.48
0.90
1.63
1.44
2.88
1.26
ppm
206.039
205.382
139.197
137.933
133.835
133.430
128.692
128.507
128.422
128.287
128.186
128.085
128.035
127.950
127.900
127.798
127.664
127.562
126.517
119.418
119.165
77.414
76.992
76.571
46.269
45.173
44.920
44.752
43.740
42.796
30.453
13C NMR, CDCl3, 75.4 MHz
ppm

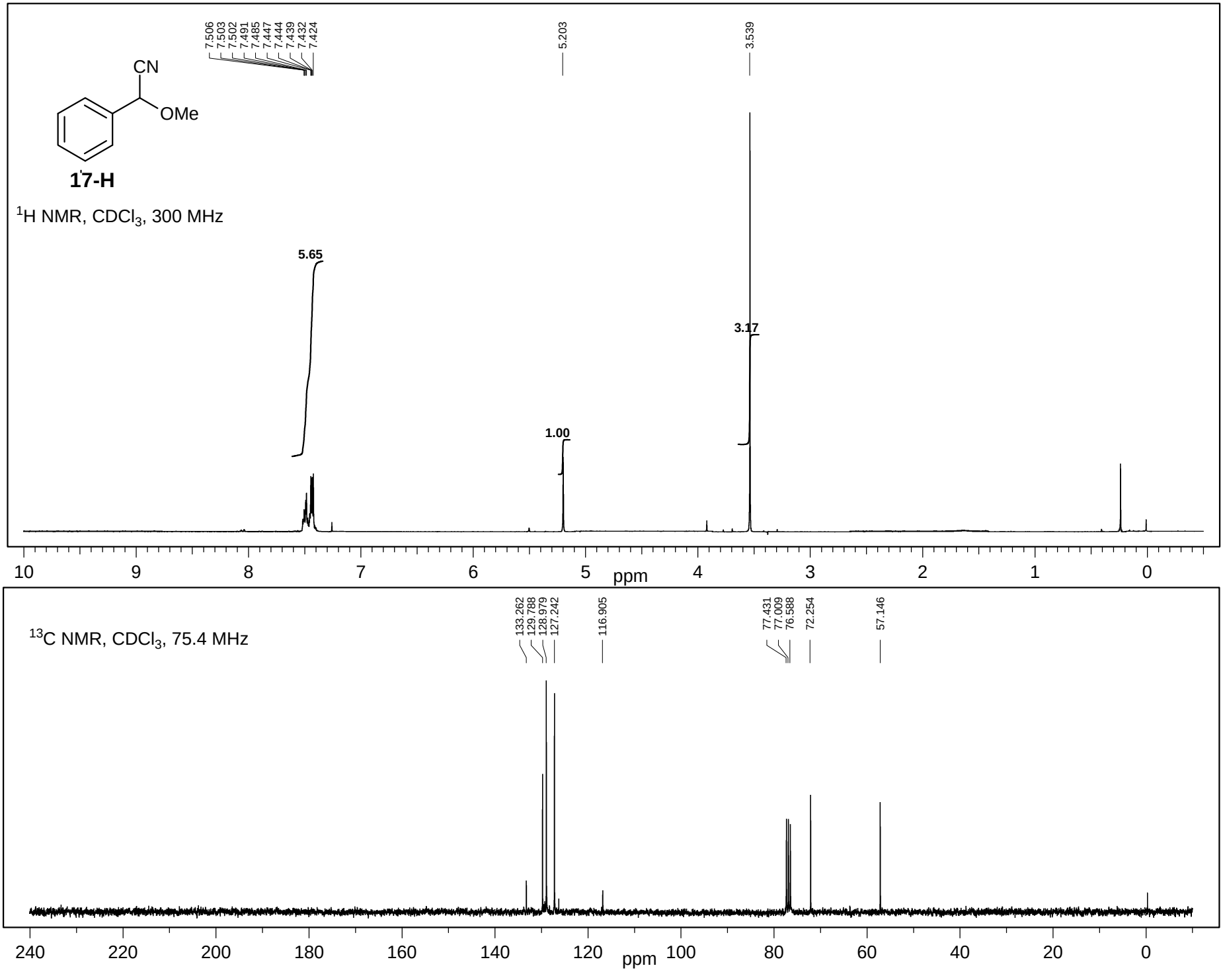

O
D
CN
Ph
Ph
d-10
1H NMR, CDCl3, 300 MHz
7.182
7.180
7.170
7.165
7.160
7.138
7.130
7.121
7.118
4.264
4.245
4.013
3.992
3.521
3.049
3.042
3.036
3.023
3.015
2.875
2.866
2.857
2.049
1.953
9.93
1.00
0.60
0.48
0.41
2.01
0.79
ppm
2H NMR, CHCl3
7.266
CDCl3
H5
H3
3.147
2.981
ppm

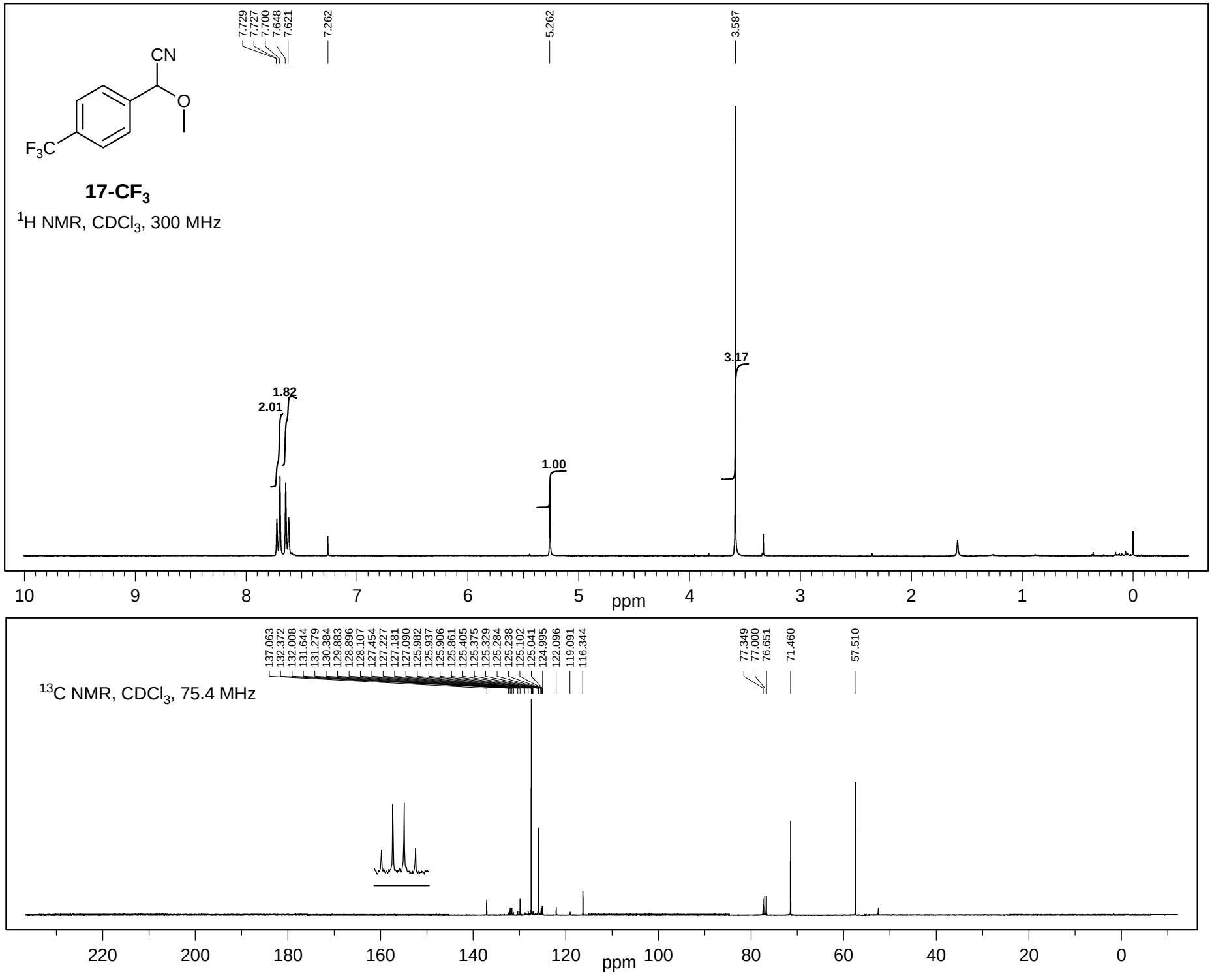

7.293
7.285
7.264
7.254
7.250
7.244
7.222
7.214
7.203
7.200
7.171
7.165
3.602
3.594
3.575
3.132
3.105
3.007
2.988
2.932
2.138
2.041
O
D
CN
Ph
Ph
d-14
1H NMR, CDCl3, 300 MHz
3.8 3.7 3.6 3.5
3.2 3.1 3.0 2.9 2.8
1.84
1.00
0.89
0.94
0.83
0.06
0.03
9 8 7 6 5 4 3 2 1 0
ppm
2H NMR, CHCl3
4.337
4.085
3.723
9 8 7 6 5 4 3 2 1
ppm

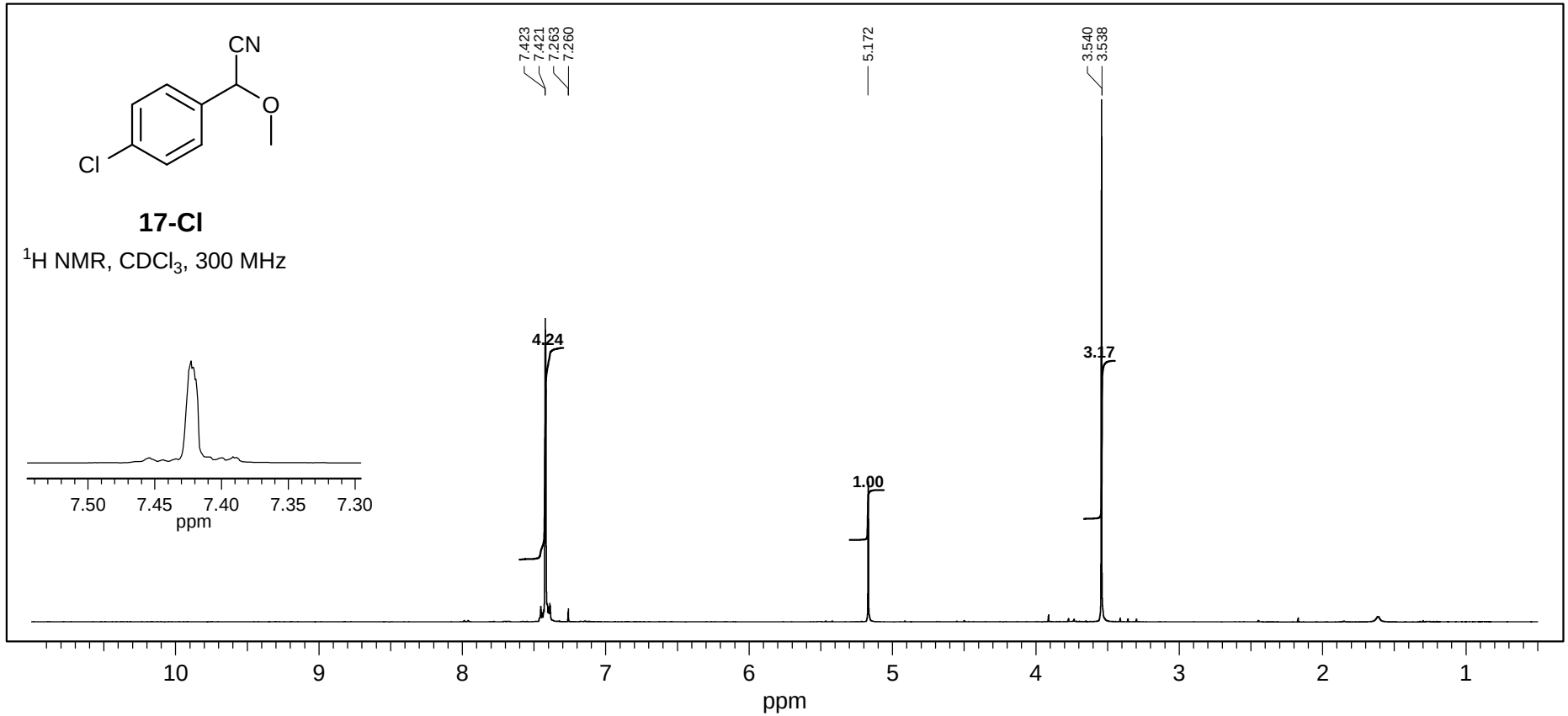

OH
Ph
Ph
CN
11
1H NMR, CDCl3, 300 MHz
7.309
7.299
7.294
7.288
7.244
7.233
4.974
4.945
4.926
4.142
4.121
4.028
4.008
3.232
3.230
3.229
3.225
3.222
10.63
1.00
0.71
0.15
1.15
5.00
4.95
4.90
4.85
ppm
4.15
4.10
4.05
4.00
3.95
ppm
10
9
8
7
6
5
4
3
2
1
0
ppm
13C NMR, CDCl3, 75.4 MHz
139.383
138.759
132.419
131.879
128.776
128.743
128.658
128.591
128.490
128.406
128.372
128.304
126.584
126.180
118.794
77.431
77.009
76.571
76.217
75.964
47.231
46.505
240
220
200
180
160
140
120
100
80
60
40
20
0
ppm

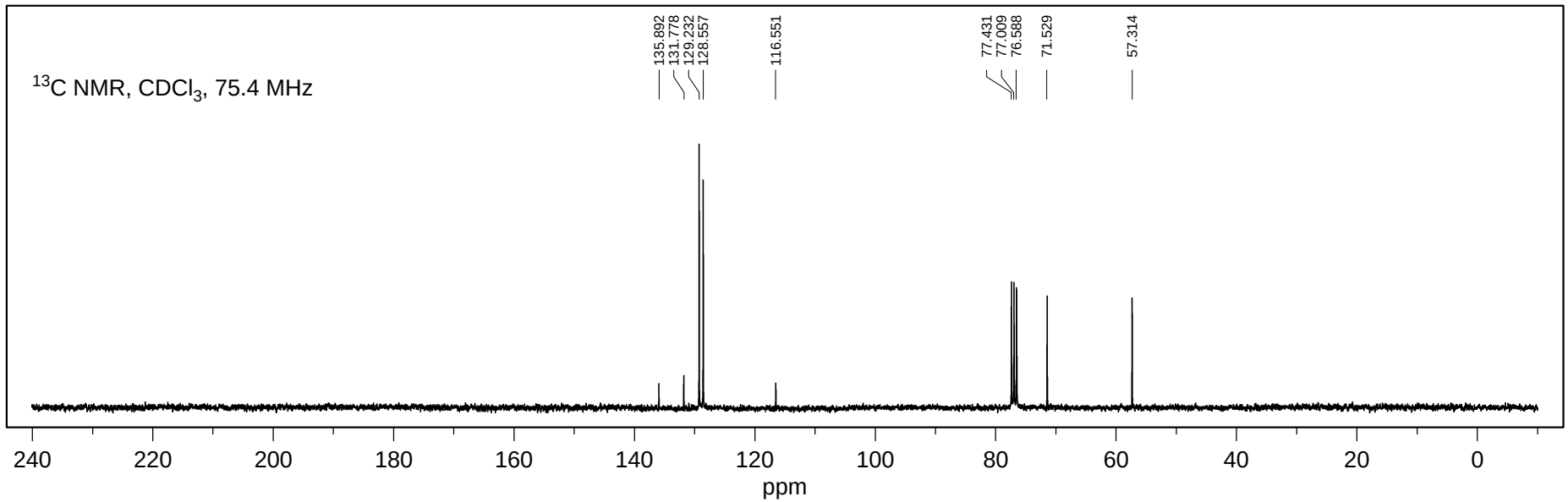

keto-13
^{1}H NMR, CDCl$_3$, 300 MHz
ppm

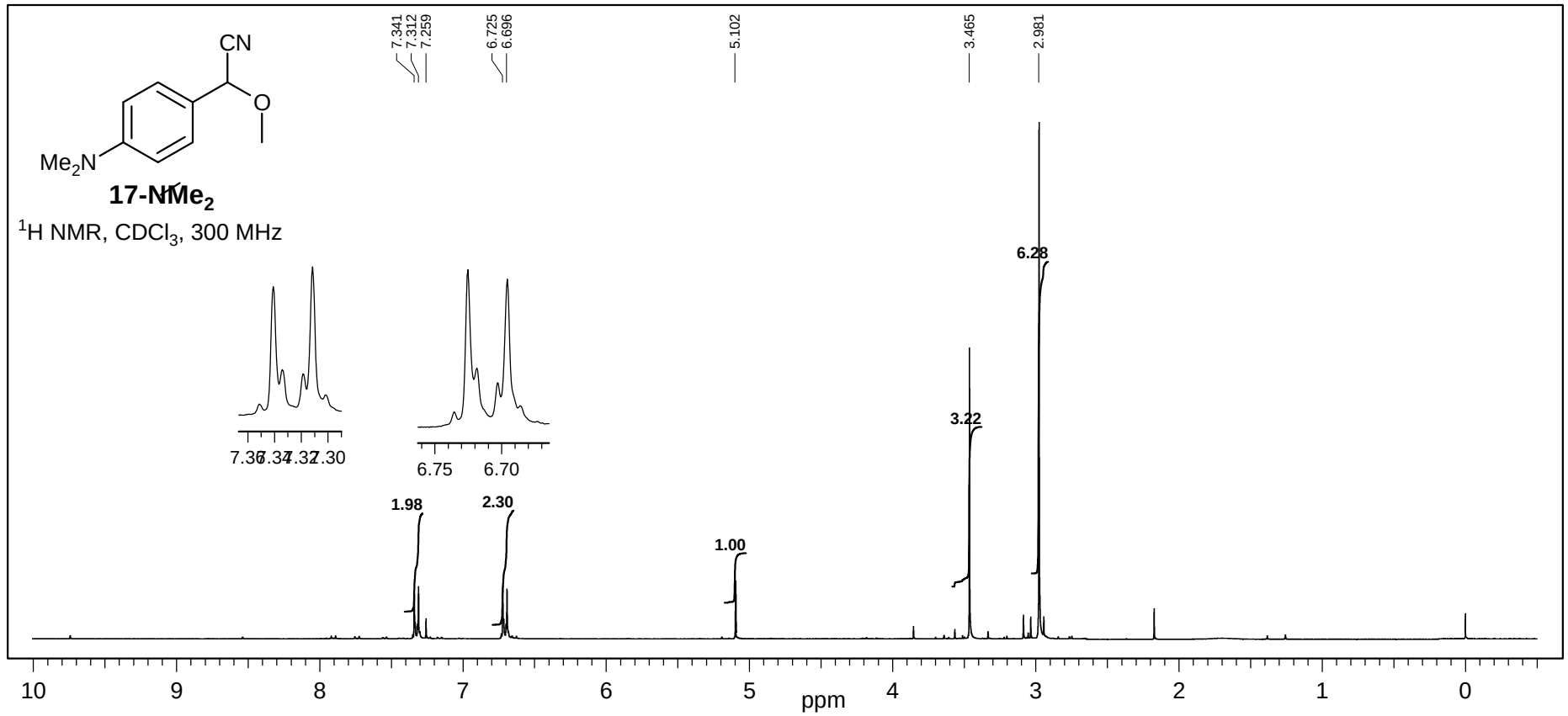

^{13}C NMR, CDCl$_3$, 75.4 MHz
ppm

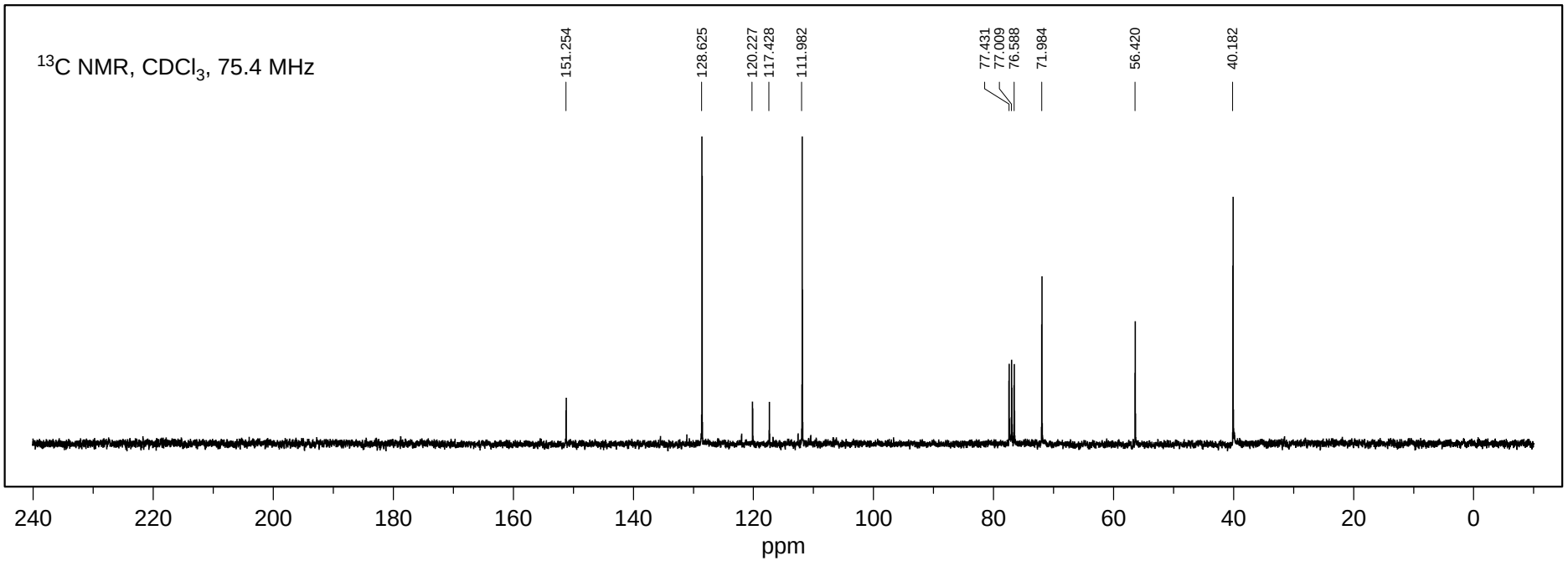

7.506
7.503
7.502
7.491
7.485
7.447
7.444
7.439
7.432
7.424
5.203
3.539
CN
OMe
17-H
1H NMR, CDCl3, 300 MHz
5.65
3.17
1.00
10
9
8
7
6
5
ppm
4
3
2
1
0
13C NMR, CDCl3, 75.4 MHz
133.262
129.788
128.979
127.242
116.905
77.431
77.009
76.588
72.254
57.146
240
220
200
180
160
140
120
ppm
100
80
60
40
20
0

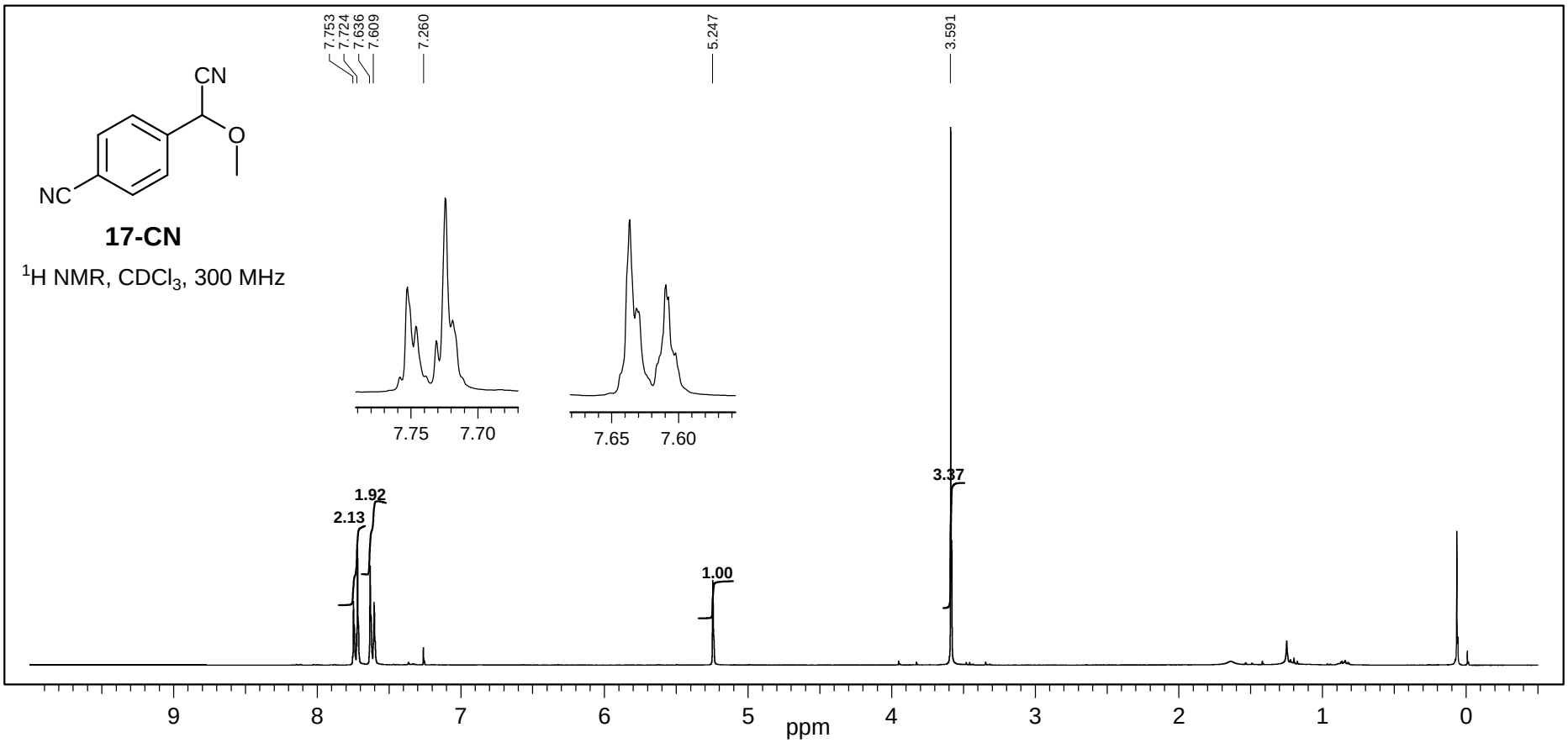

7.729
7.727
7.700
7.648
7.621
7.262
5.262
3.587
CN
O
F3C
17-CF3
1H NMR, CDCl3, 300 MHz
3.17
1.82
2.01
1.00
10
9
8
7
6
5
ppm
4
3
2
1
0
137.063
132.372
132.008
131.644
131.279
130.384
129.883
128.896
128.107
127.454
127.227
127.181
127.090
125.982
125.937
125.906
125.861
125.405
125.375
125.329
125.284
125.238
125.102
125.041
124.995
122.096
119.091
116.344
77.349
77.000
76.651
71.460
57.510
13C NMR, CDCl3, 75.4 MHz
220
200
180
160
140
120
ppm
100
80
60
40
20
0

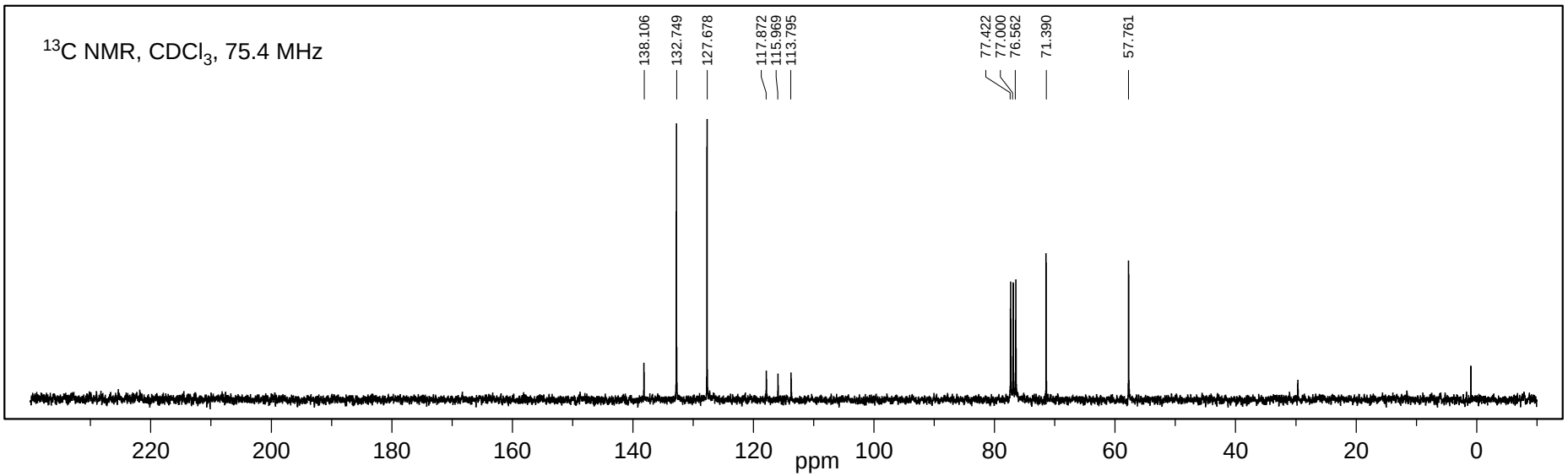

CN
O
Cl
17-Cl
1H NMR, CDCl3, 300 MHz
7.423
7.421
7.263
7.260
5.172
3.540
3.538
4.24
1.00
3.17
7.50
7.45
7.40
7.35
7.30
ppm
10
9
8
7
6
5
4
3
2
1
ppm

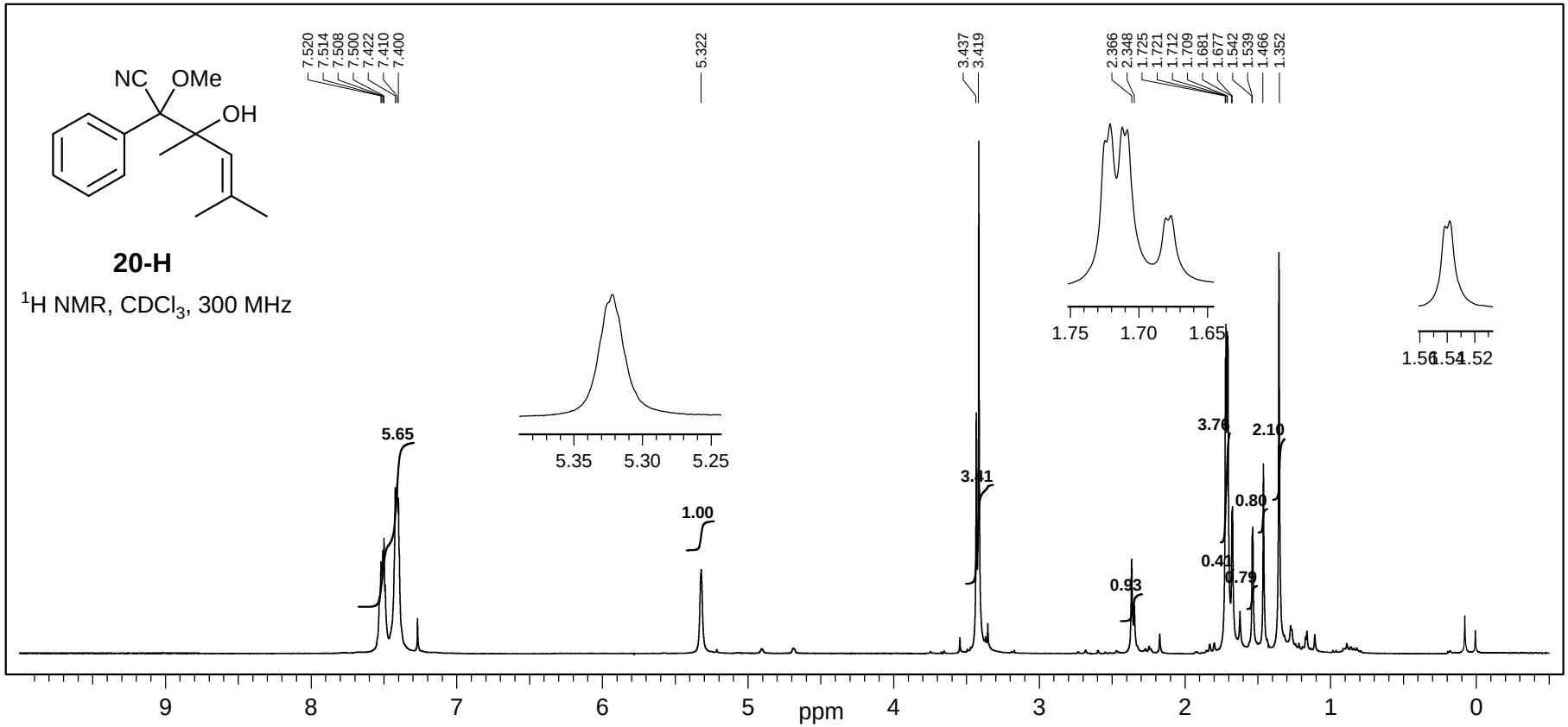

13C NMR, CDCl3, 75.4 MHz
135.892
131.778
129.232
128.557
116.551
77.431
77.009
76.588
71.529
57.314
240
220
200
180
160
140
120
100
80
60
40
20
0
ppm

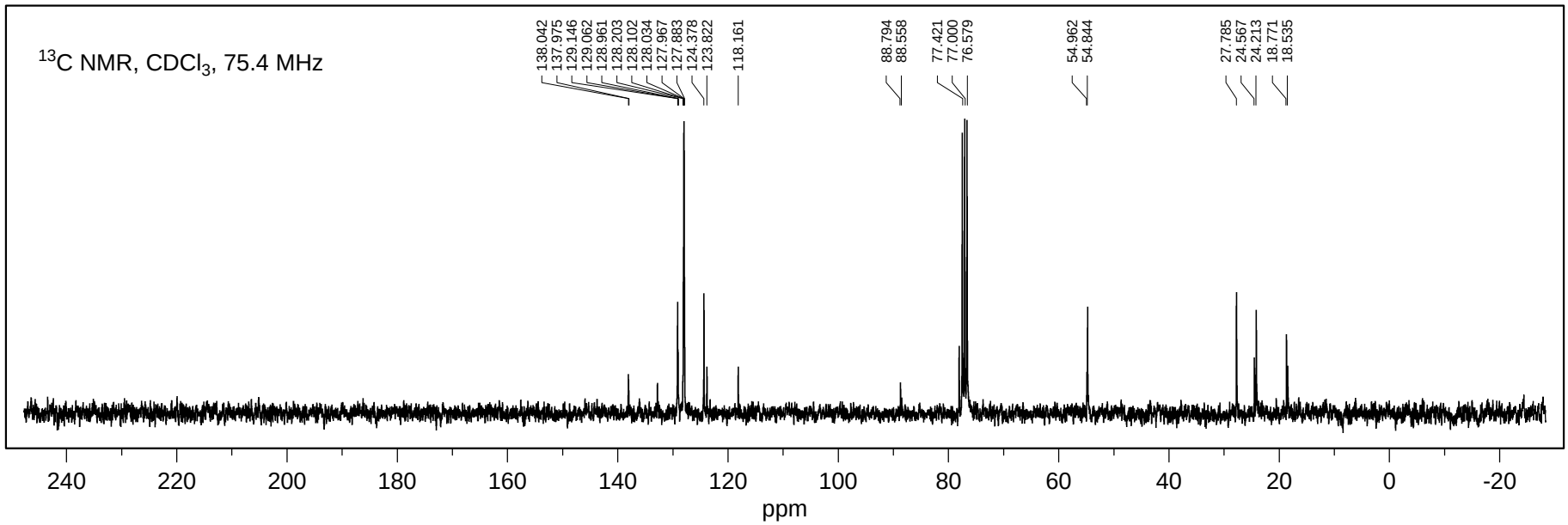

CN
O
Me2N
17-NMe2
1H NMR, CDCl3, 300 MHz
7.341
7.312
7.259
6.725
6.696
5.102
3.465
2.981
6.28
3.22
1.98
2.30
1.00
7.36
7.34
7.32
7.30
6.75
6.70
10
9
8
7
6
5
4
3
2
1
0
ppm

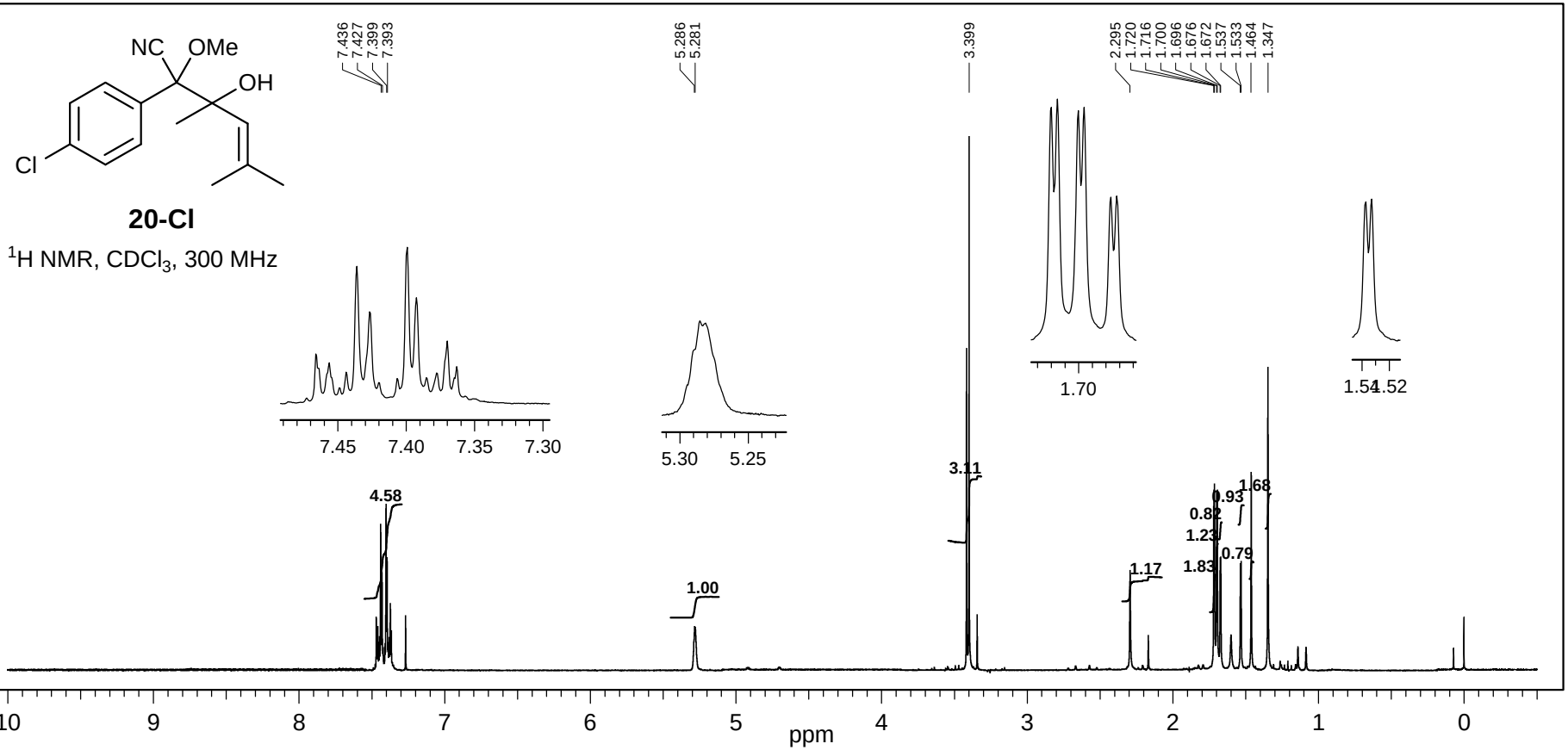

13C NMR, CDCl3, 75.4 MHz
151.254
128.625
120.227
117.428
111.982
77.431
77.009
76.588
71.984
56.420
40.182
240
220
200
180
160
140
120
100
80
60
40
20
0
ppm

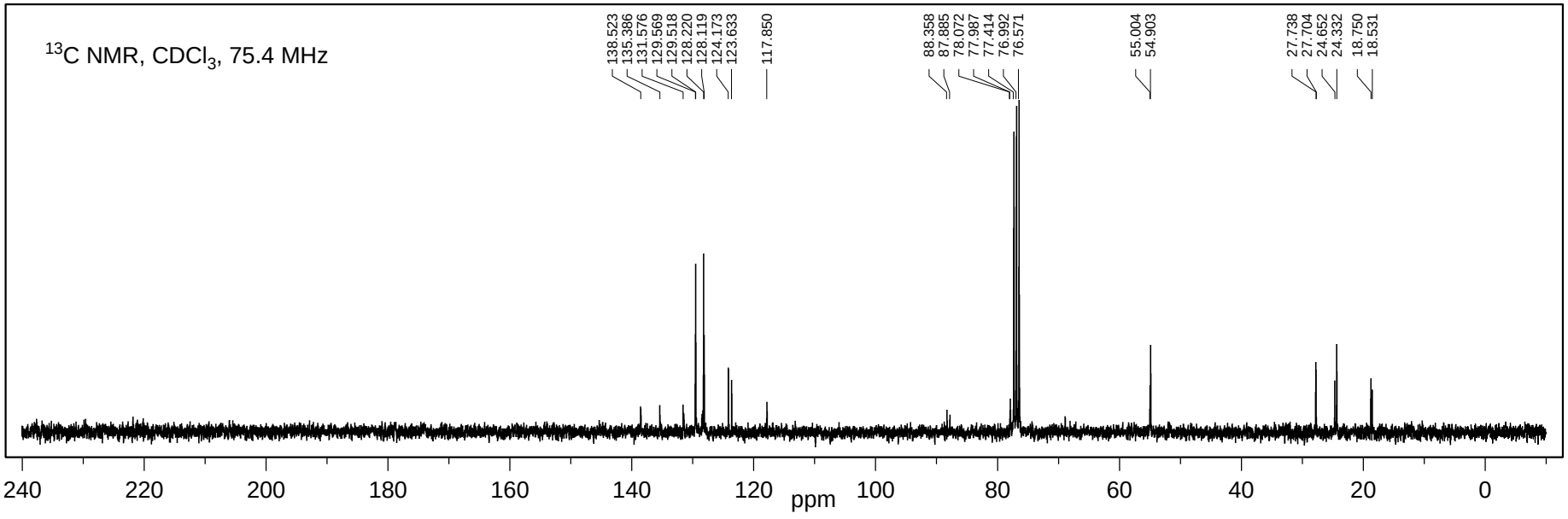

7.753
7.724
7.636
7.609
7.260
5.247
3.591
CN
O
NC
17-CN
1H NMR, CDCl3, 300 MHz
7.75
7.70
7.65
7.60
3.37
1.92
2.13
1.00
9
8
7
6
5
ppm
4
3
2
1
0

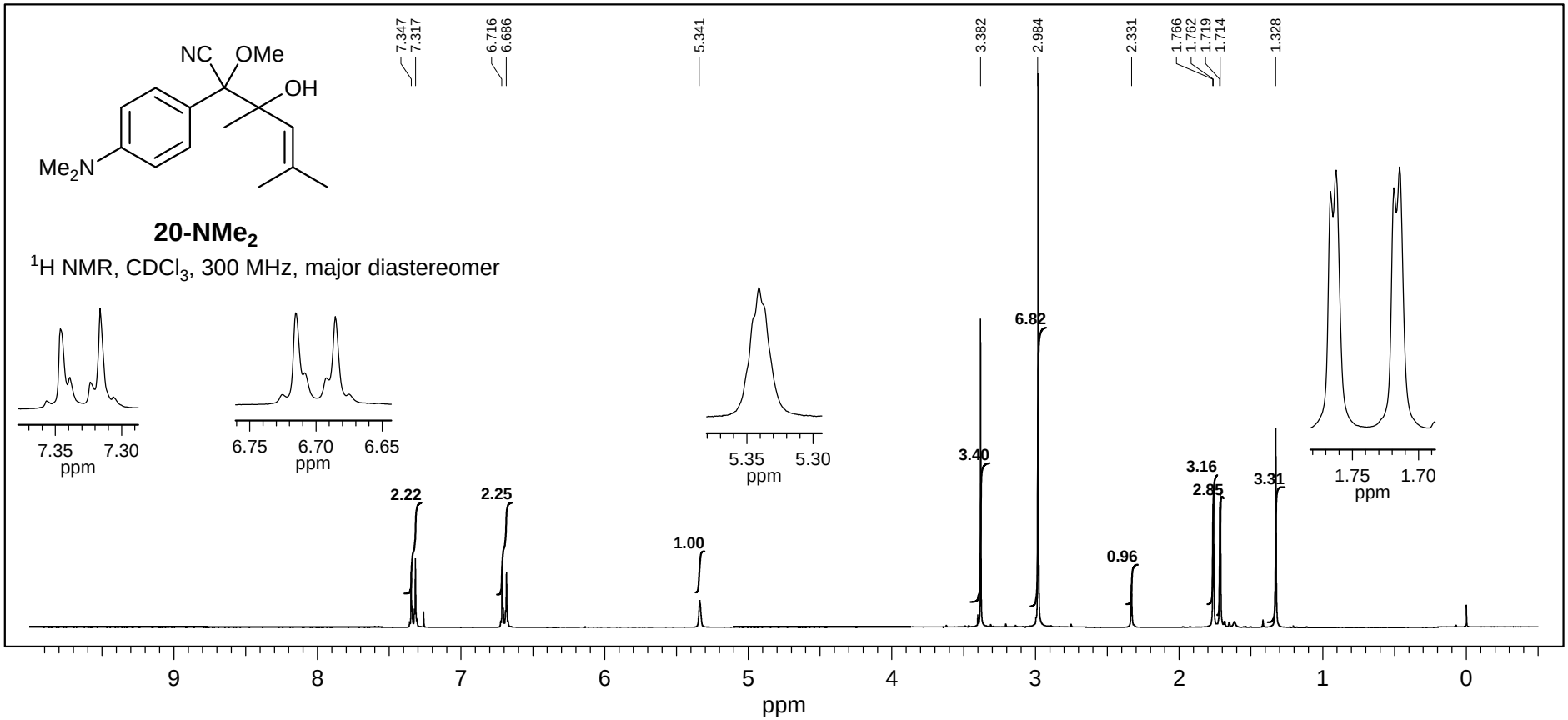

13C NMR, CDCl3, 75.4 MHz
138.106
132.749
127.678
117.872
115.969
113.795
77.422
77.000
76.562
71.390
57.761
220
200
180
160
140
120
ppm
100
80
60
40
20
0

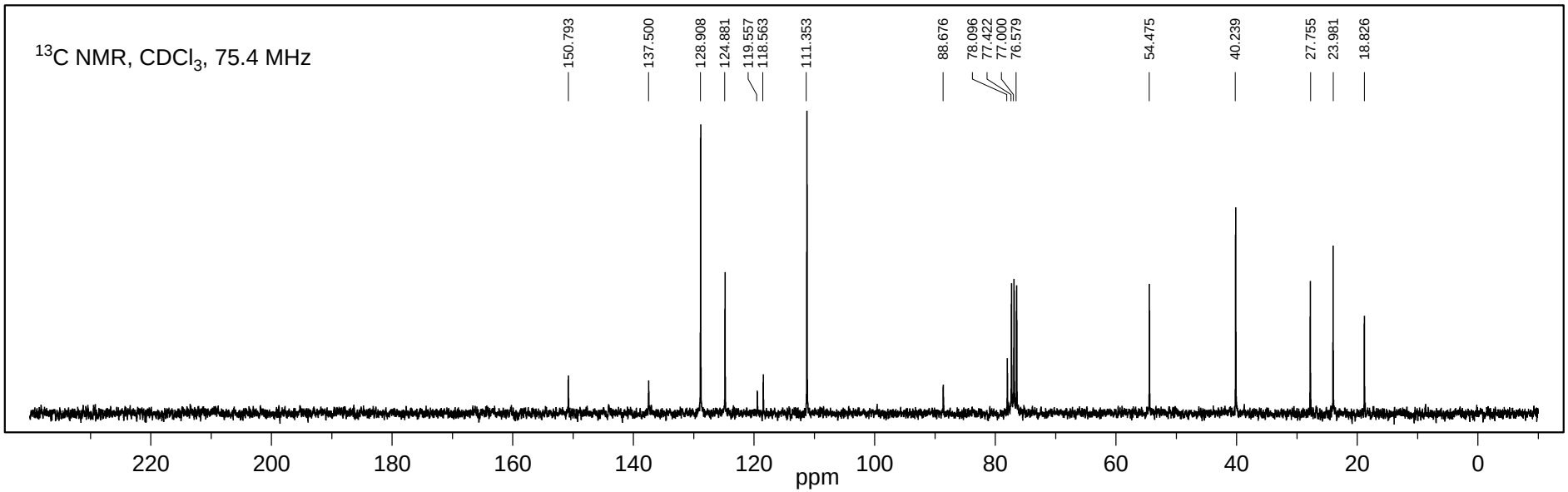

NC
OMe
OH
20-H
1H NMR, CDCl3, 300 MHz
7.520
7.514
7.508
7.500
7.422
7.410
7.400
5.322
3.437
3.419
2.366
2.348
1.725
1.721
1.712
1.709
1.681
1.677
1.542
1.539
1.466
1.352
5.65
1.00
3.41
0.93
3.76
2.10
0.80
0.41
0.79
ppm

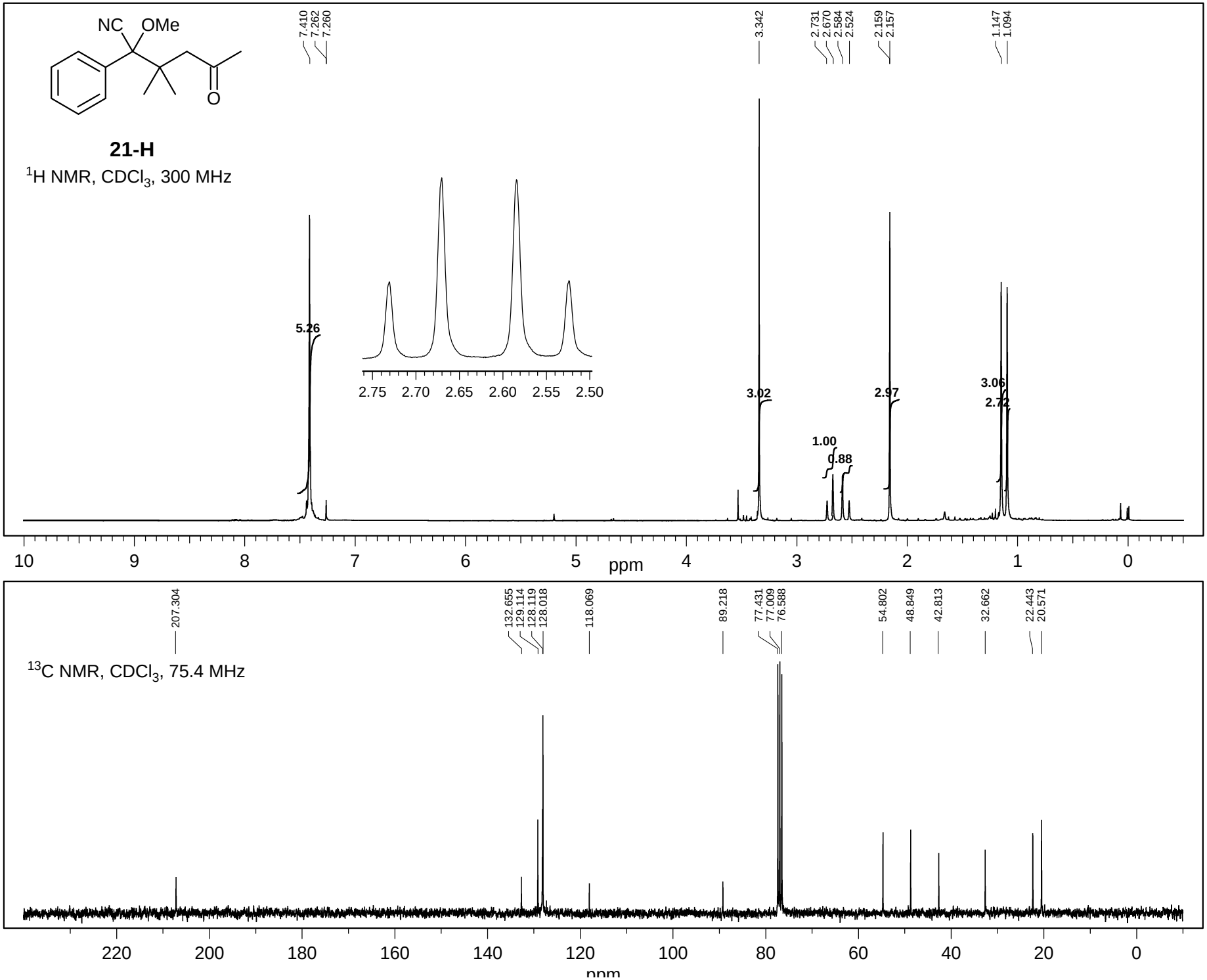

13C NMR, CDCl3, 75.4 MHz
138.042
137.975
129.146
129.062
128.961
128.203
128.102
128.034
127.967
127.883
124.378
123.822
118.161
88.794
88.558
77.421
77.000
76.579
54.962
54.844
27.785
24.567
24.213
18.771
18.535
ppm

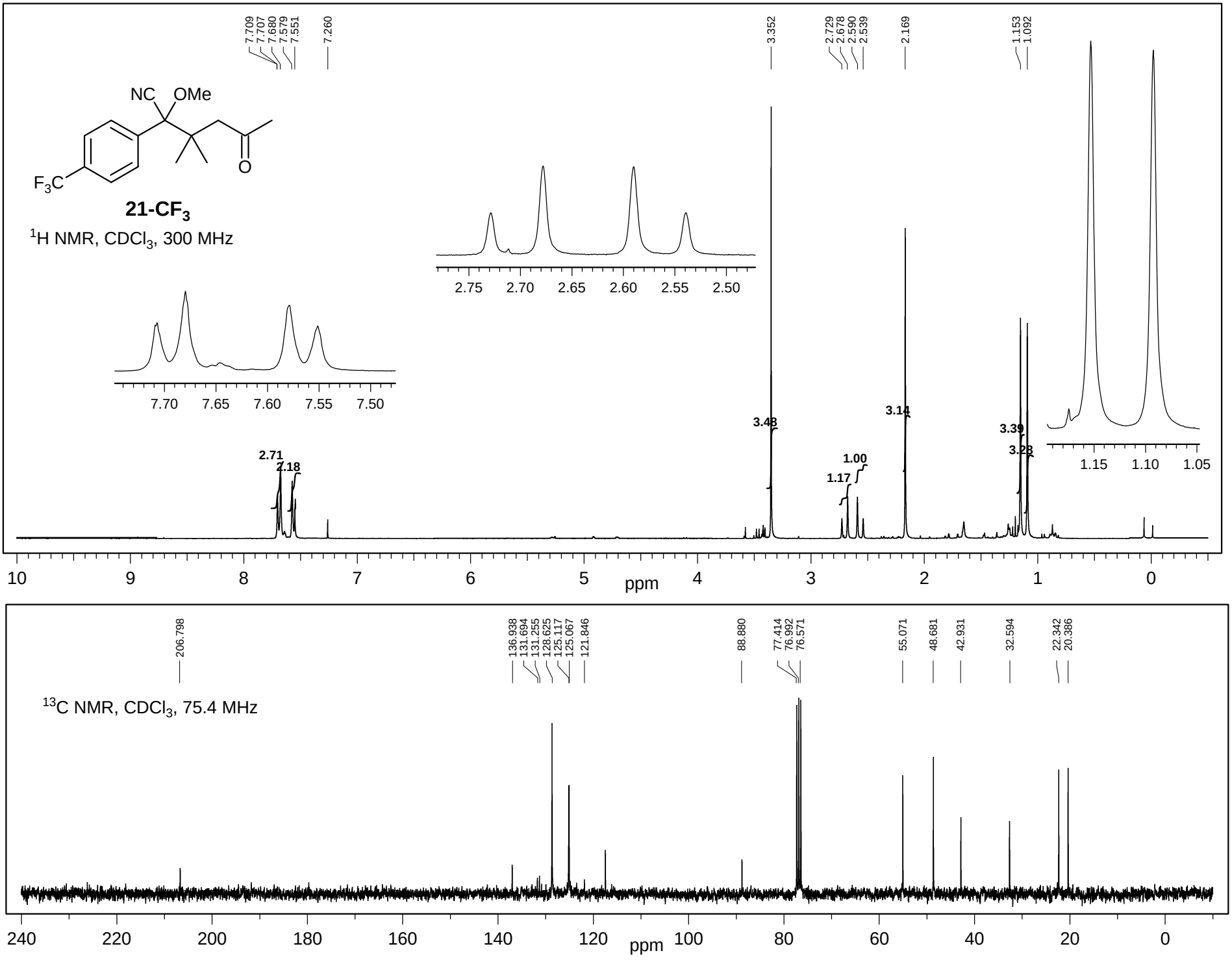

NC
OMe
OH
Cl
20-Cl
1H NMR, CDCl3, 300 MHz
7.436
7.427
7.399
7.393
5.286
5.281
3.399
2.295
1.720
1.716
1.700
1.696
1.676
1.672
1.537
1.533
1.464
1.347
7.45
7.40
7.35
7.30
5.30
5.25
1.70
1.54
1.52
4.58
1.00
3.11
1.17
1.83
1.23
0.82
0.93
0.79
1.68
10
9
8
7
6
5
4
3
2
1
0
ppm

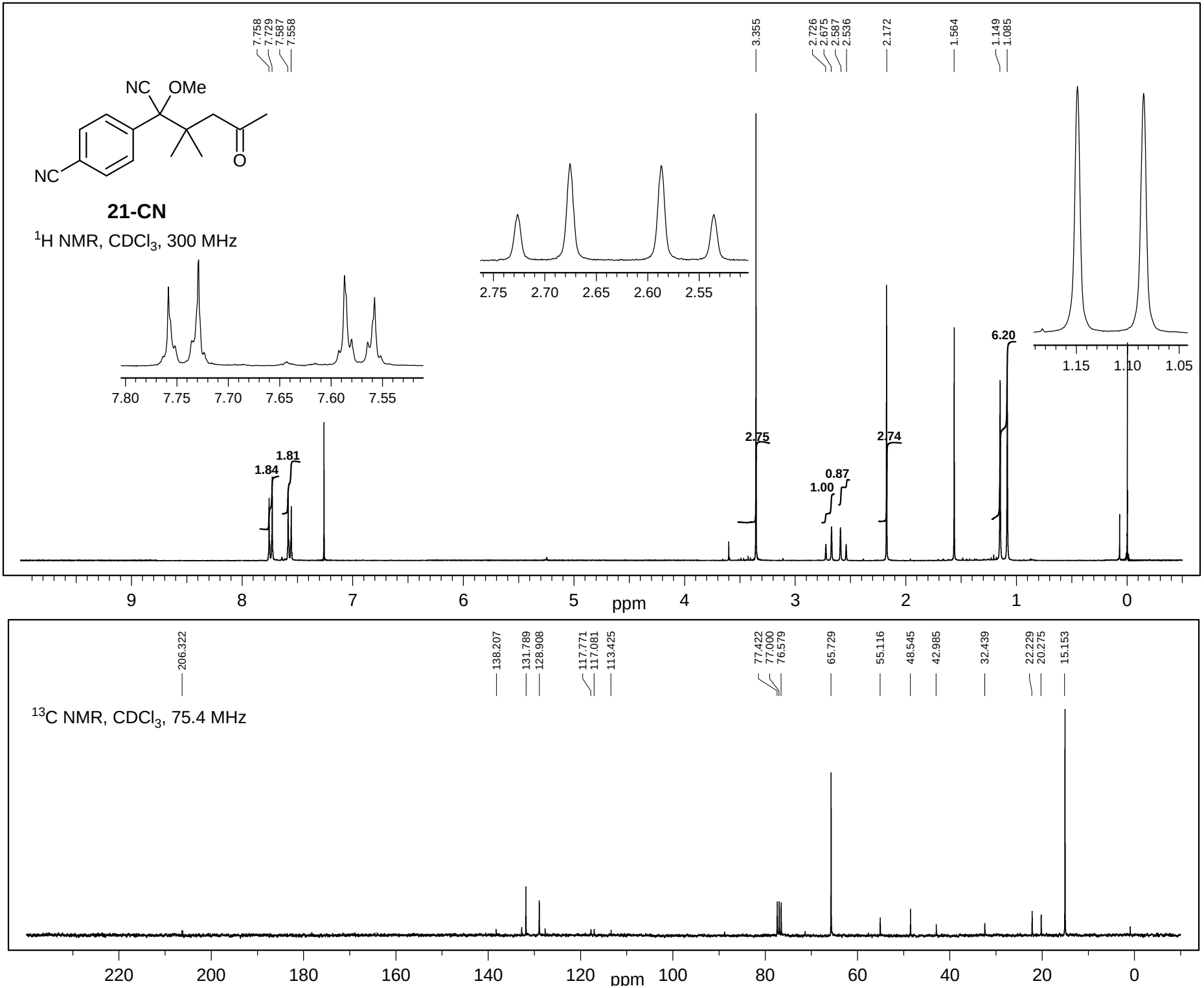

13C NMR, CDCl3, 75.4 MHz
138.523
135.386
131.576
129.569
129.518
128.220
128.119
124.173
123.633
117.850
88.358
87.885
78.072
77.987
77.414
76.992
76.571
55.004
54.903
27.738
27.704
24.652
24.332
18.750
18.531
240
220
200
180
160
140
120
100
80
60
40
20
0
ppm

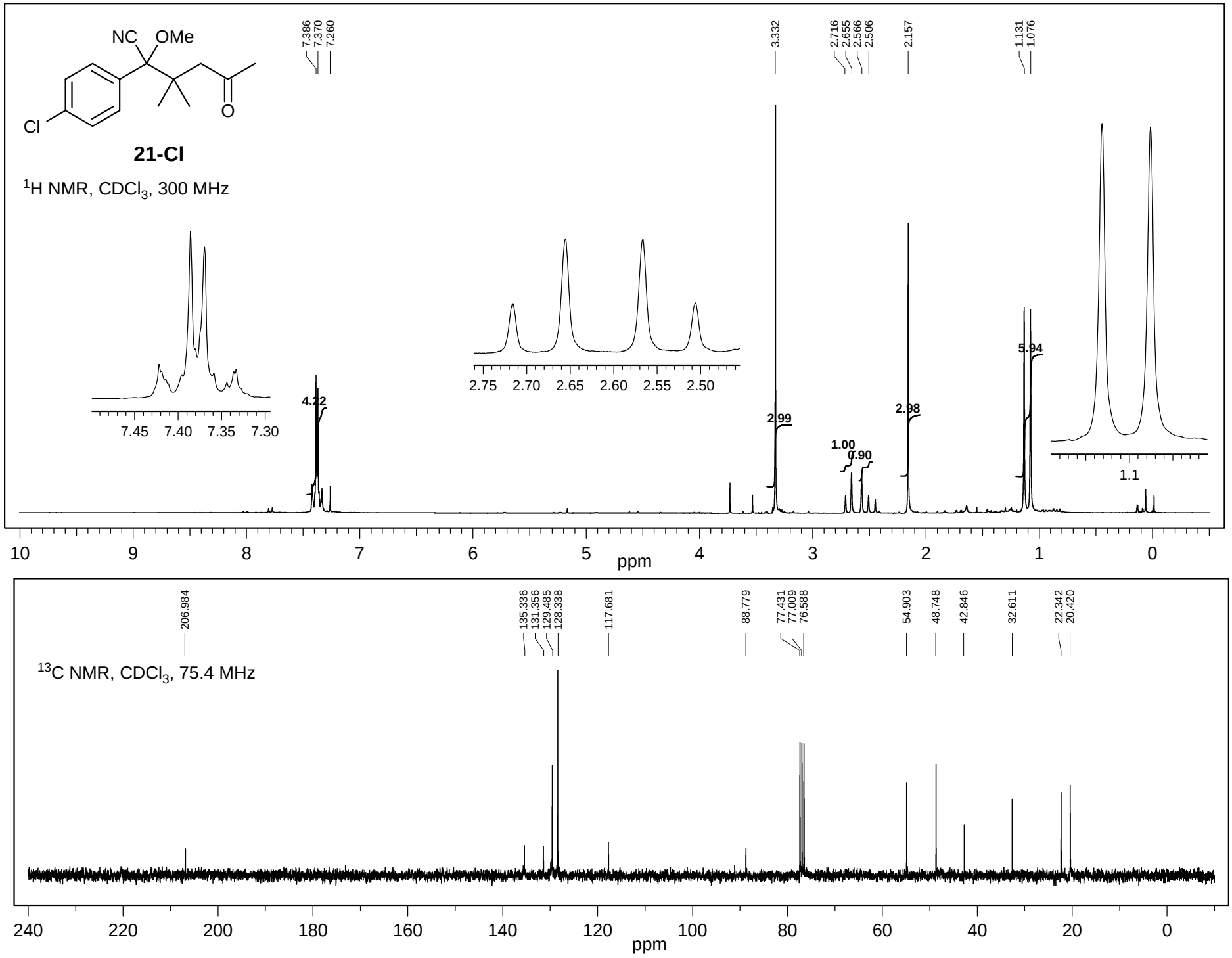

NC
OMe
OH
Me2N
20-NMe2
1H NMR, CDCl3, 300 MHz, major diastereomer
7.347
7.317
6.716
6.686
5.341
3.382
2.984
2.331
1.766
1.762
1.719
1.714
1.328
6.82
3.40
3.16
2.85
3.31
2.22
2.25
1.00
0.96
7.35 7.30 ppm
6.75 6.70 6.65 ppm
5.35 5.30 ppm
1.75 1.70 ppm
9 8 7 6 5 4 3 2 1 0
ppm

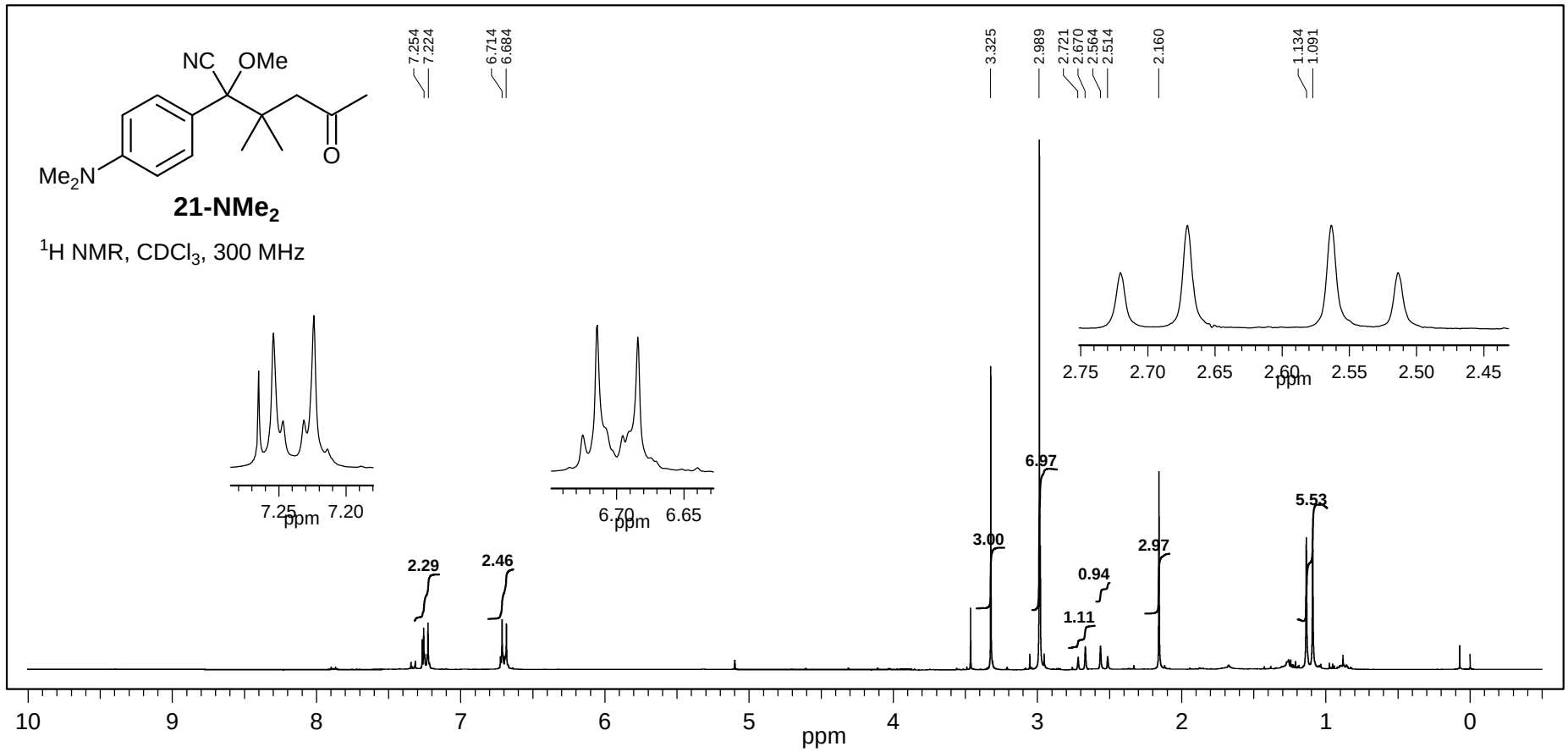

13C NMR, CDCl3, 75.4 MHz
150.793
137.500
128.908
124.881
119.557
118.563
111.353
88.676
78.096
77.422
77.000
76.579
54.475
40.239
27.755
23.981
18.826
220 200 180 160 140 120 100 80 60 40 20 0
ppm

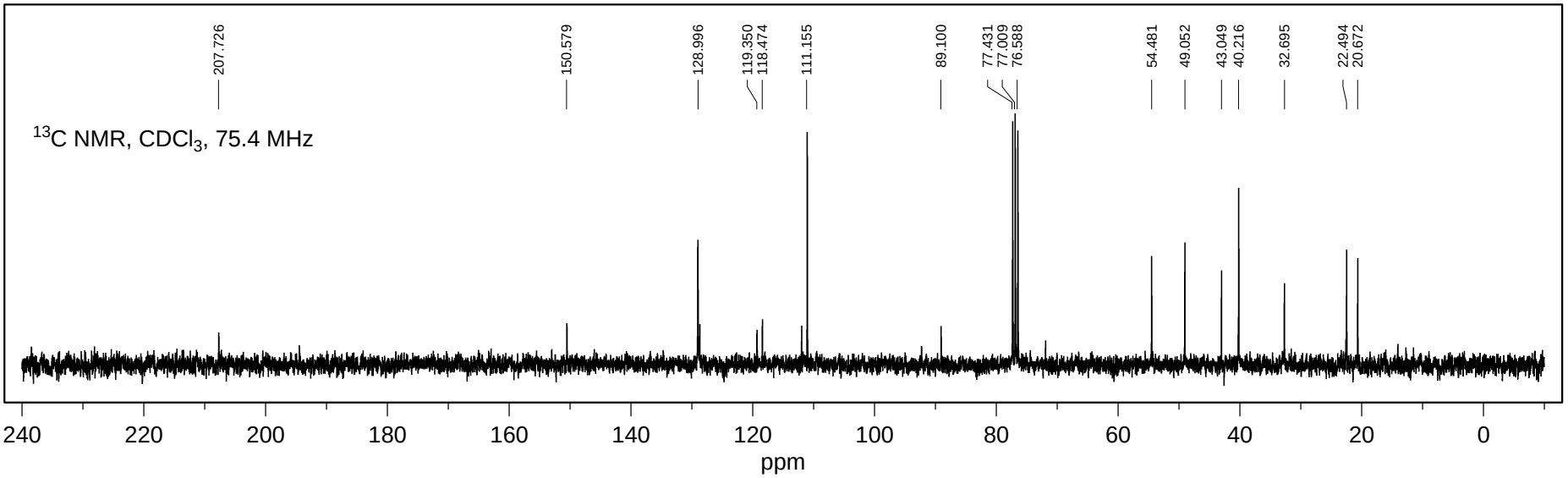

NC
OMe
O
21-H
1H NMR, CDCl3, 300 MHz
7.410
7.262
7.260
3.342
2.731
2.670
2.584
2.524
2.159
2.157
1.147
1.094
5.26
3.02
2.97
3.06
2.72
1.00
0.88
2.75 2.70 2.65 2.60 2.55 2.50
10 9 8 7 6 5 ppm 4 3 2 1 0
13C NMR, CDCl3, 75.4 MHz
207.304
132.655
129.114
128.119
128.018
118.069
89.218
77.431
77.009
76.588
54.802
48.849
42.813
32.662
22.443
20.571
220 200 180 160 140 120 100 80 60 40 20 0
ppm

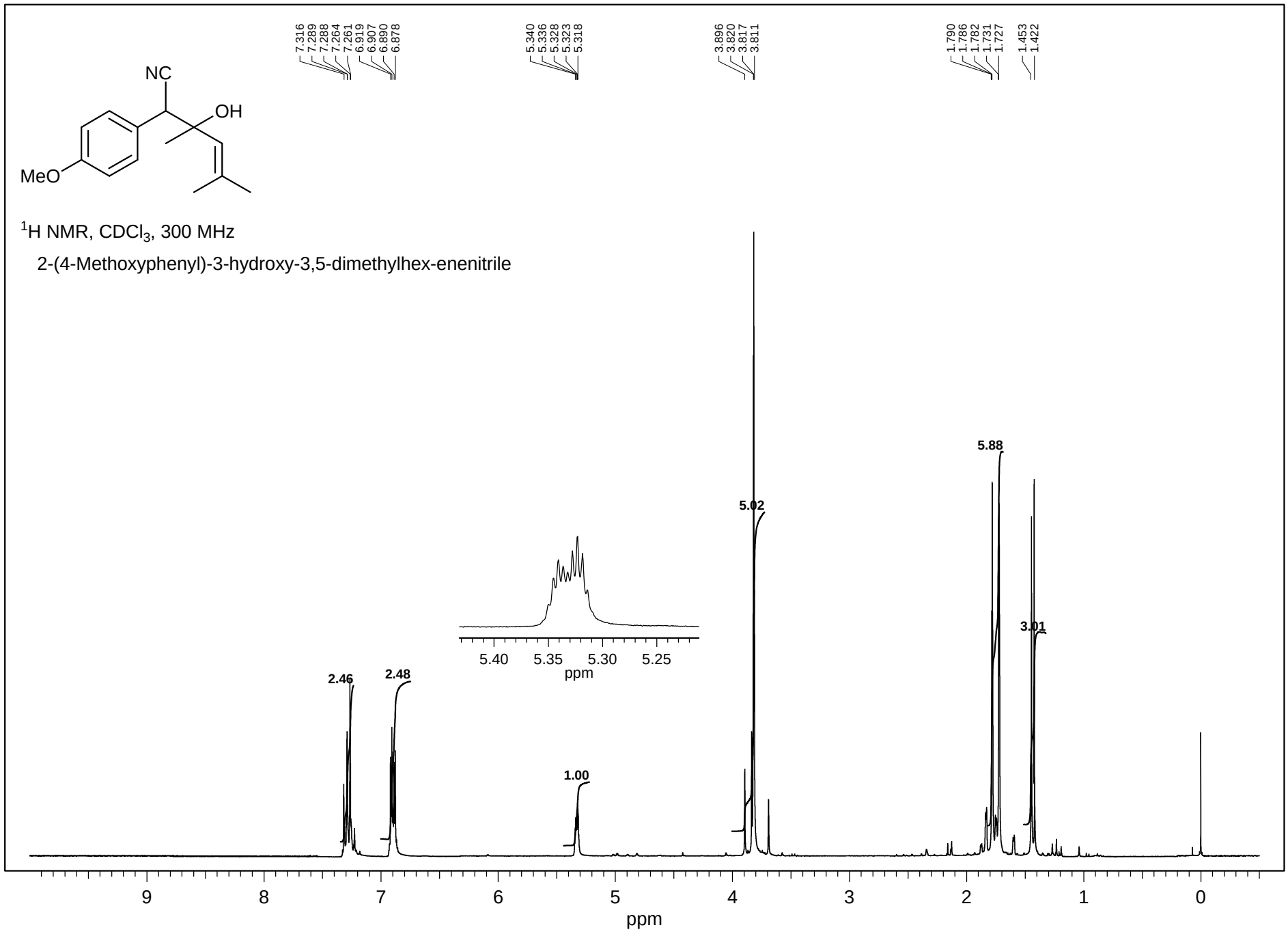

NC
OMe
O
F3C
21-CF3
1H NMR, CDCl3, 300 MHz
7.709
7.707
7.680
7.579
7.551
7.260
3.352
2.729
2.678
2.590
2.539
2.169
1.153
1.092
3.48
3.14
3.39
3.23
2.71
2.18
1.00
1.17
ppm
13C NMR, CDCl3, 75.4 MHz
206.798
136.938
131.694
131.255
128.625
125.117
125.067
121.846
88.880
77.414
76.992
76.571
55.071
48.681
42.931
32.594
22.342
20.386
ppm

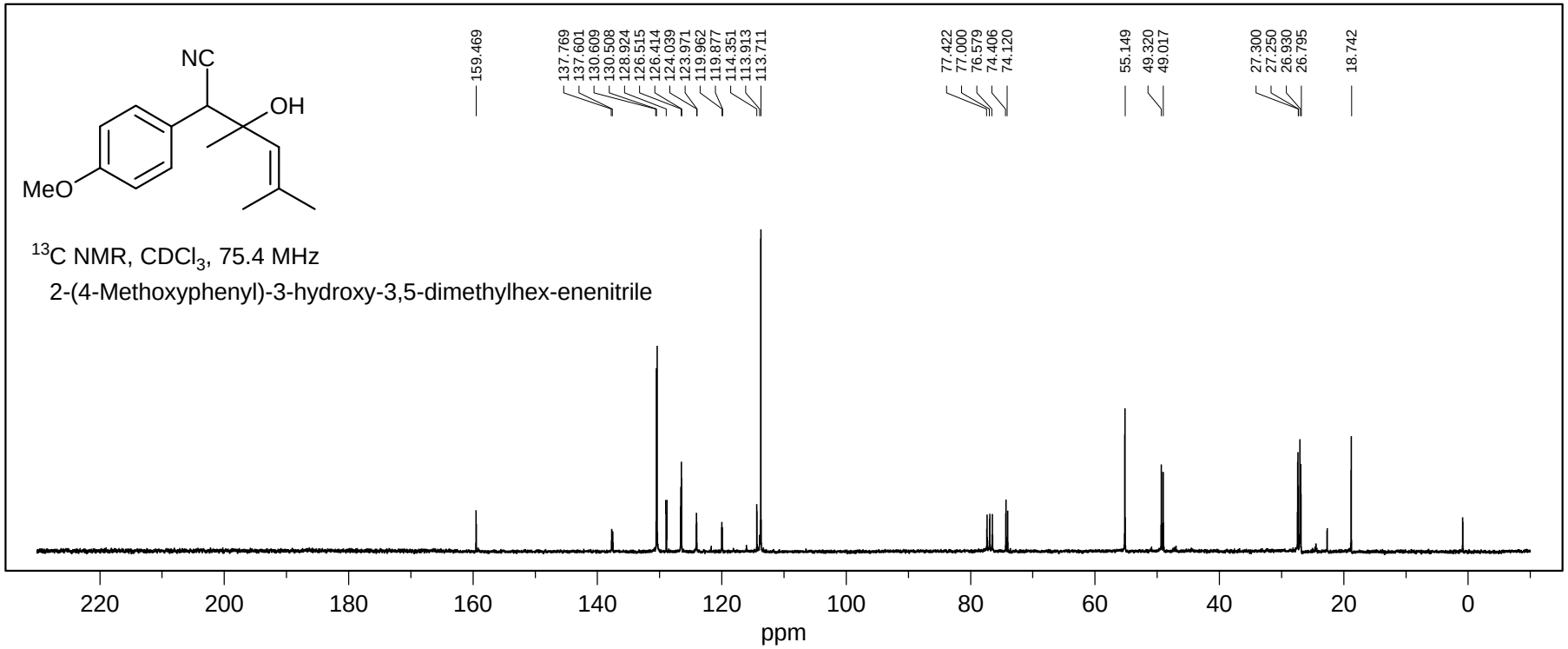

NC
OMe
NC
O
21-CN
1H NMR, CDCl3, 300 MHz
7.758
7.729
7.587
7.558
3.355
2.726
2.675
2.587
2.536
2.172
1.564
1.149
1.085
6.20
2.75
2.74
1.84
1.81
0.87
1.00
ppm
13C NMR, CDCl3, 75.4 MHz
206.322
138.207
131.789
128.908
117.771
117.081
113.425
77.422
77.000
76.579
65.729
55.116
48.545
42.985
32.439
22.229
20.275
15.153
ppm

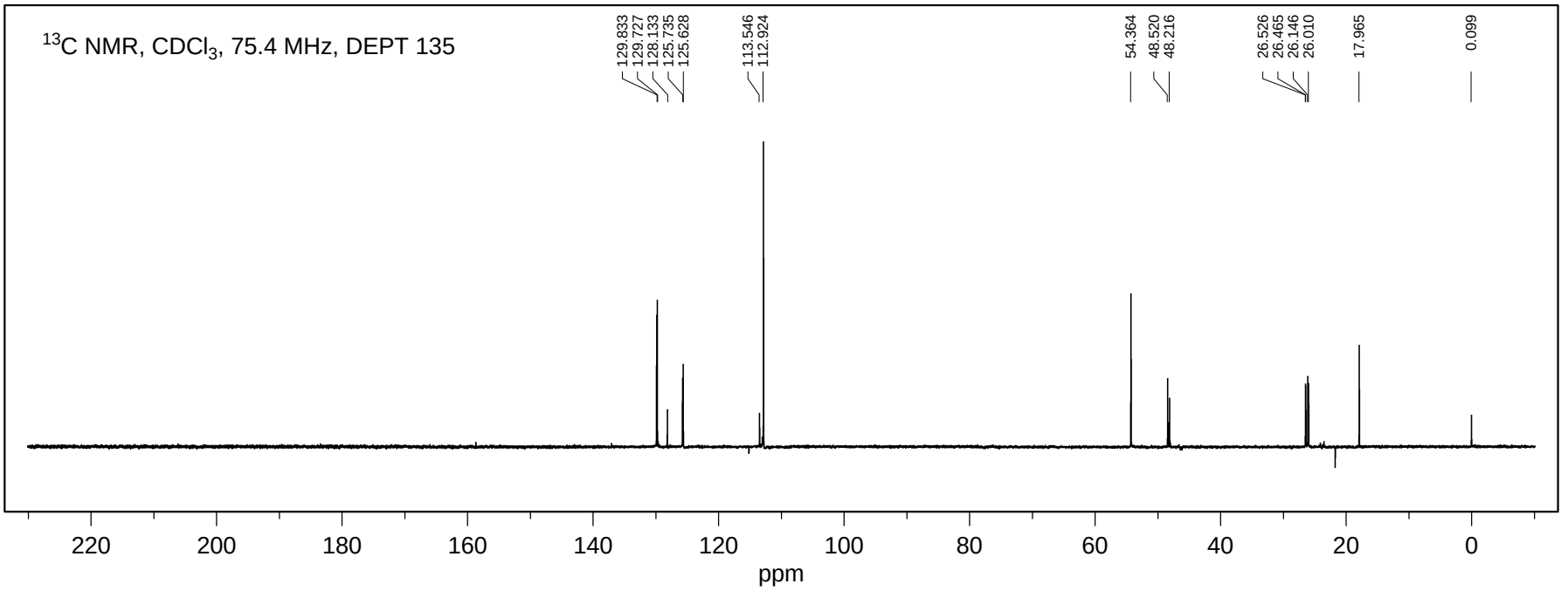

NC
OMe
Cl
O
21-Cl
1H NMR, CDCl3, 300 MHz
7.386
7.370
7.260
3.332
2.716
2.655
2.566
2.506
2.157
1.131
1.076
4.22
2.99
1.00
0.90
2.98
5.94
7.45 7.40 7.35 7.30
2.75 2.70 2.65 2.60 2.55 2.50
1.1
10 9 8 7 6 5 4 3 2 1 0
ppm
206.984
135.336
131.356
129.485
128.338
117.681
88.779
77.431
77.009
76.588
54.903
48.748
42.846
32.611
22.342
20.420
13C NMR, CDCl3, 75.4 MHz
240 220 200 180 160 140 120 100 80 60 40 20 0
ppm

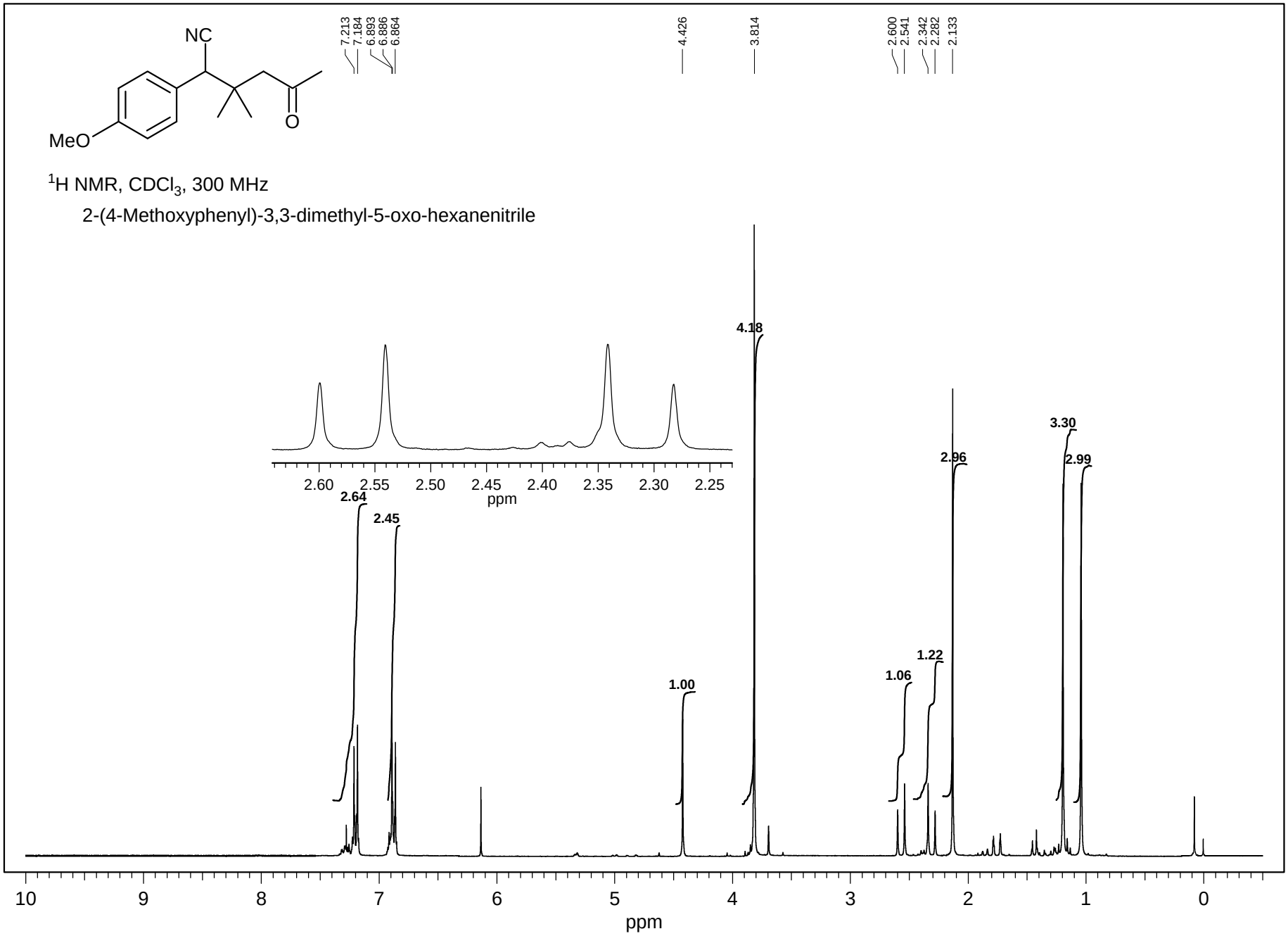

NC OMe
Me2N
O
21-NMe2
1H NMR, CDCl3, 300 MHz
7.254
7.224
6.714
6.684
3.325
2.989
2.721
2.670
2.564
2.514
2.160
1.134
1.091
2.29
2.46
3.00
6.97
0.94
1.11
2.97
5.53
ppm

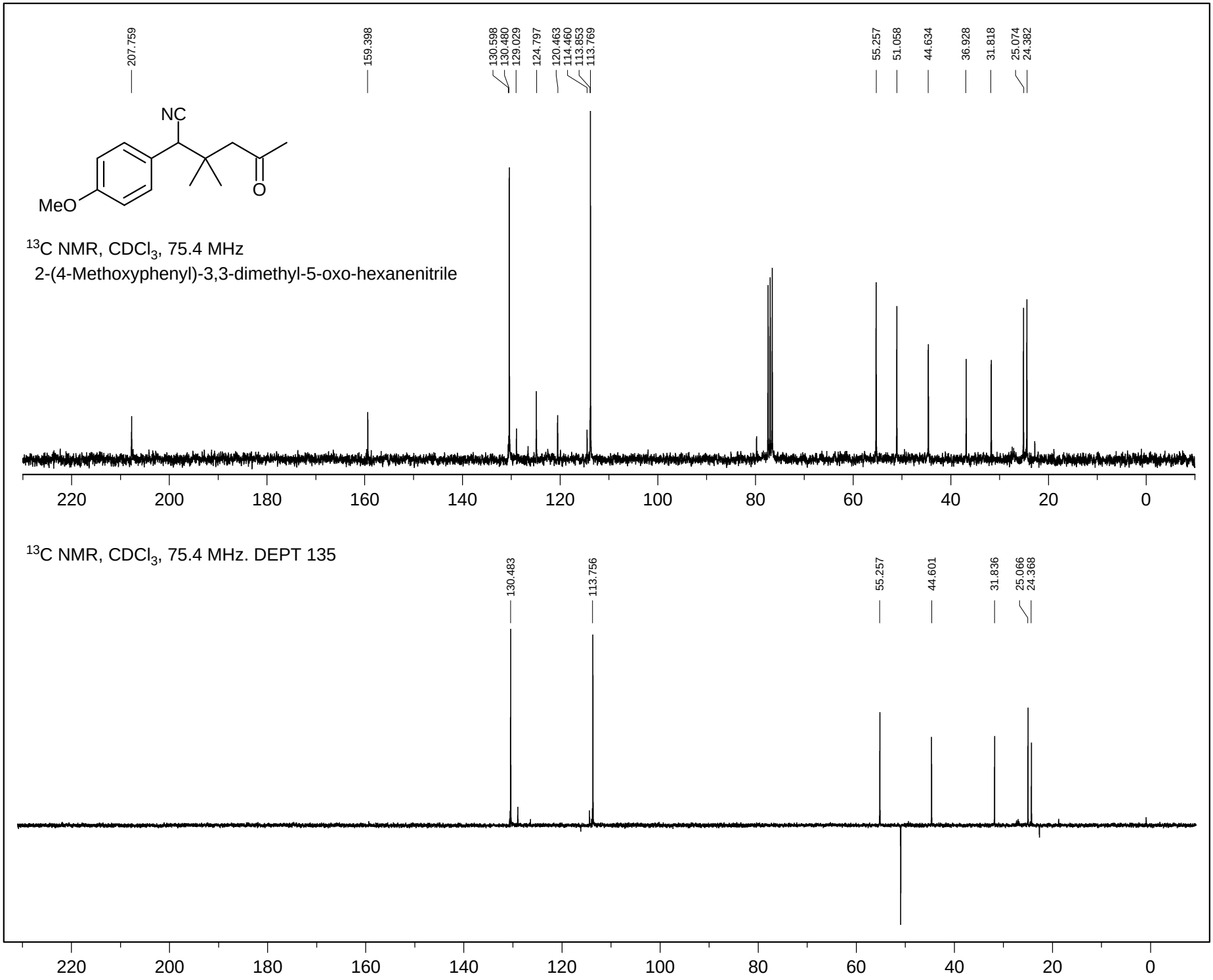

207.726
150.579
128.996
119.350
118.474
111.155
89.100
77.431
77.009
76.588
54.481
49.052
43.049
40.216
32.695
22.494
20.672
13C NMR, CDCl3, 75.4 MHz
ppm


NC
OH
MeO
7.316
7.289
7.288
7.264
7.261
6.919
6.907
6.890
6.878
5.340
5.336
5.328
5.323
5.318
3.896
3.820
3.817
3.811
1.790
1.786
1.782
1.731
1.727
1.453
1.422
^{1}H NMR, $CDCl_3$, 300 MHz
2-(4-Methoxyphenyl)-3-hydroxy-3,5-dimethylhex-enenitrile
2.46
2.48
1.00
5.02
5.88
3.01
5.40
5.35
5.30
5.25
ppm
9
8
7
6
5
4
3
2
1
0
ppm


NC
OH
MeO
159.469
137.769
137.601
130.609
130.508
128.924
126.515
126.414
124.039
123.971
119.962
119.877
114.351
113.913
113.711
77.422
77.000
76.579
74.406
74.120
55.149
49.320
49.017
27.300
27.250
26.930
26.795
18.742
^{13}C NMR, $CDCl_3$, 75.4 MHz
2-(4-Methoxyphenyl)-3-hydroxy-3,5-dimethylhex-enenitrile
220
200
180
160
140
120
100
80
60
40
20
0
ppm


^{13}C NMR, $CDCl_3$, 75.4 MHz, DEPT 135
129.833
129.727
128.133
125.735
125.628
113.546
112.924
54.364
48.520
48.216
26.526
26.465
26.146
26.010
17.965
0.099
220
200
180
160
140
120
100
80
60
40
20
0
ppm


NC
MeO
O
7.213
7.184
6.893
6.886
6.864
4.426
3.814
2.600
2.541
2.342
2.282
2.133
^{1}H NMR, $CDCl_3$, 300 MHz
2-(4-Methoxyphenyl)-3,3-dimethyl-5-oxo-hexanenitrile
4.18
3.30
2.99
2.96
2.64
2.45
1.22
1.06
1.00
2.60 2.55 2.50 2.45 2.40 2.35 2.30 2.25
ppm
10 9 8 7 6 5 4 3 2 1 0
ppm


207.759
159.398
130.598
130.480
129.029
124.797
120.463
114.460
113.853
113.769
55.257
51.058
44.634
36.928
31.818
25.074
24.382
NC
O
MeO
13C NMR, CDCl3, 75.4 MHz
2-(4-Methoxyphenyl)-3,3-dimethyl-5-oxo-hexanenitrile
220
200
180
160
140
120
100
80
60
40
20
0
13C NMR, CDCl3, 75.4 MHz. DEPT 135
130.483
113.756
55.257
44.601
31.836
25.066
24.368
220
200
180
160
140
120
100
80
60
40
20
0