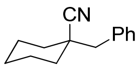
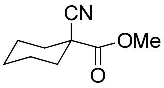
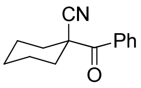
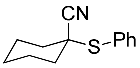
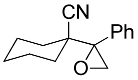
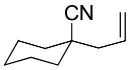
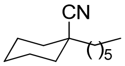
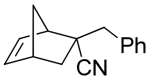
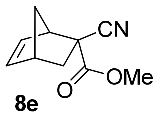
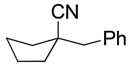
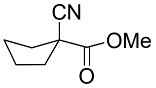
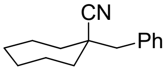
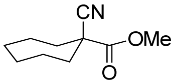
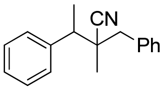
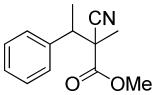
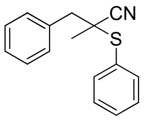
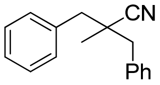
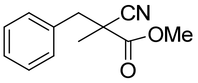
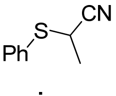
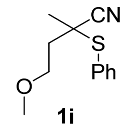
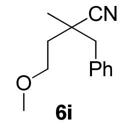
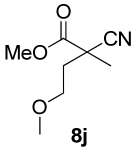
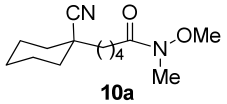
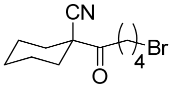
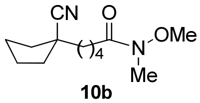
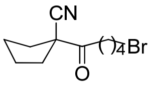
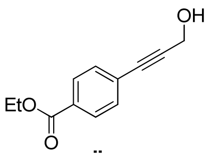
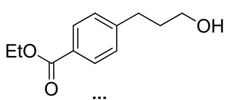
Chemoselective Alkylations with *N*- and *C*-Metalated Nitriles

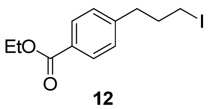
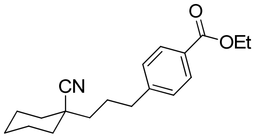
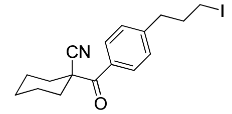
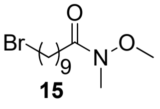
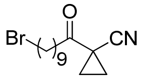
*Xun Yang, Dinesh Nath, Fraser F. Fleming,**

Department of Chemistry and Biochemistry, Duquesne University, Pittsburgh, Pennsylvania 15282-1530
flemingf@duq.edu

	Compound	Procedure	^{1}H NMR	^{13}C NMR
1	 **6a**	S5	S27	S27
2	 **8a**	S6	S28	S28
3	 **8b**	S7	S29	S29
4	 **8c**	S8	S30	S30
5	 **8d**	S8	S31	S31
6	 **6b**	S8	S32	S32
7	 **6c**	S9	S33	S33
8	 **6d**	S9	S34	S34
9	 **8e**	S10	S35	S35

10	 **6e**	S10	S36	S36
11	 **8f**	S11	S37	S37
12	 **6f**	S11	S38	S38
13	 **8g**	S12	S39	S39
14	 **6g**	S13	S40	S40
15	 **8h**	S13	S41	S41
16	 **1h**	S14	S42	S42
17	 **6h**	S14	S43	S43
18	 **8i**	S15	S44	S44
19	 **i**	S15	S45	S45

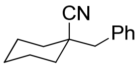
20	 **1i**	S16	S46	S46
21	 **6i**	S16	S47	S47
22	 **8j**	S17	S48	S48
23	 **10a**	S17	S49	S49
24	 **11a**	S18	S50	S50
25	 **10b**	S19	S51	S51
26	 **11b**	S19	S52	S52
27	 **ii**	S20	S53	S53
28	 **iii**	S20	S54	S54

29	 **12**	S21	S55	S55
30	 **10c**	S21	S56	S56
31	 **11c**	S22	S57	S57
32	 **15**	S23	S58	S58
33	 **8k**	S23	S59	S59

General Procedure for Preparing *N*-Lithiated Nitriles: (A) LDA Deprotonation Method: A THF solution of the nitrile (1 equiv.) was added to a -78 °C, THF solution of LDA (1.05 equiv.). After 45 min, the reaction was allowed to warm to room temperature for 15 min. The resulting *N*-lithiated nitrile solution was then cooled to -78 °C and used in the subsequent alkylation.

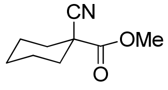
General Procedure for Preparing *C*-Magnesiated Nitriles: (A) Transmetalation with $MgBr_2$: A freshly prepared THF solution of anhydrous $MgBr_2$ (1.05 equiv) was added to a THF solution of the lithiated nitrile. After 15 min, the solution of *C*-magnesiated nitrile was used in the alkylation. **(B) Transmetalation with RMgX:** A THF solution of *i*-PrMgCl (1.05 equiv) was added to a THF, -78 °C solution of the lithiated nitrile. After 15 min, the *C*-magnesiated nitrile solution was used in the subsequent alkylation.

General Chemoselective-Alkylation Procedure: A THF solution containing two electrophiles (1.0 equiv each) was added to a -78 ºC THF solution of the metalated nitrile. In the case of bis-electrophiles, the neat electrophile (1.0 equiv) was added to the metalated nitrile, and then the reaction was allowed to warm to room temperature. After 2 h, saturated, aqueous NH_4Cl was added, the crude reaction mixture was then extracted with EtOAc, dried ($MgSO_4$), concentrated, and was then purified by radial chromatography to afford analytically pure material.



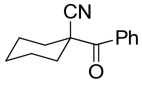
6a

1-Benzylcyclohexanecarbonitrile (6a): (A) LDA Deprotonation Method: A THF solution of lithiated cyclohexanecarbonitrile (0.20 mmol, 1 equiv.) was allowed to react with a THF solution (2 mL) containing methyl cyanoformate (19 mg, 0.22 mmol) and benzyl bromide (38 mg, 0.22 mmol). The reaction mixture was allowed to warm slowly to room temperature. After 2 h saturated, aqueous NH_4Cl was added, the crude reaction mixture was extracted with EtOAc, dried ($MgSO_4$), concentrated, and then purified by radial chromatography (1:10 EtOAc/hexanes) to afford 43 mg (98%) of analytically pure nitrile **6a** as an oil exhibiting spectra data identical to that previously reported.[1] (B) Sulfinyl-Lithium Exchange: A hexanes solution of BuLi (0.21 mmol, 1.05 equiv) was added to a stirred, -78 °C, THF solution of the sulfinylnitrile (0.20 mmol, 1 equiv). After 5 min, a THF solution (2 mL) of methyl cyanoformate (19 mg, 0.22 mmol) and benzyl bromide (38 mg, 0.22 mmol) was added to the reaction mixture and the reaction mixture was then allowed to warm slowly to room temperature. After 2 h saturated, aqueous NH_4Cl was added, the crude reaction mixture was then extracted with EtOAc, dried ($MgSO_4$), concentrated, and purified by radial chromatography (1:10 EtOAc/hexanes), to afford 39 mg (92%) of analytically pure **6a** isolated as an oil exhibiting spectra data identical to that previously reported.[1] (C) Sulfinyl-Lithium Exchange: A hexanes solution of BuLi (0.55 mmol, 1.1 equiv) was added to a -78 °C, THF solution of the sulfinylnitrile (0.50 mmol, 1 equiv). A THF solution (5 mL) of diphenyl disulfide (120 mg, 0.55 mmol) and benzyl bromide (94 mg, 0.55 mmol) was added to the reaction mixture and then the reaction mixture was allowed to warm slowly to room temperature. After 2 h saturated, aqueous NH_4Cl was added, the crude reaction mixture was then extracted with EtOAc, dried ($MgSO_4$), concentrated, and purified by radial chromatography (1:10 EtOAc/hexanes), to afford 54 mg (54%) of analytically pure **6a**[2] and 20 mg (18%) of **8c**[2] both exhibiting spectra data identical to that previously reported.



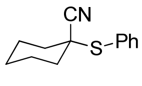
8a

Methyl 1-cyanocyclohexanecarboxylate (8a): (A) Prepared by Transmetalation with $MgBr_2$: A THF solution of bromo magnesiated cyclohexanecarbonitrile (0.20 mmol, 1 equiv.) was prepared by the $MgBr_2$ transmetallation method. A THF solution (2 mL) of methyl cyanoformate (19 mg, 0.22 mmol) and benzyl bromide (38 mg, 0.22 mmol) was added and then the reaction mixture was allowed to warm slowly to room temperature. After 2 h saturated, aqueous NH_4Cl was added, the crude reaction mixture was then extracted with EtOAc, dried ($MgSO_4$), concentrated, and purified by radial chromatography (1:10 EtOAc/hexanes) to afford 40 mg (96%) of analytically pure **8a** as an oil exhibiting spectra data identical to that previously reported.[1] (B) Prepared by Transmetalation with RMgX: A THF solution of chloromagnesium cyclohexanecarbonitrile (0.20 mmol, 1 equiv.) was prepared from *i*-PrMgCl (1.05 equiv) following the general method. A THF solution (2 mL) of methyl cyanoformate (19 mg, 0.22 mmol) and benzyl bromide (38 mg, 0.22 mmol) was then added and the reaction mixture was allowed to warm slowly to room temperature. After 2 h saturated, aqueous NH_4Cl was added, the crude reaction mixture was then extracted with EtOAc, dried ($MgSO_4$), concentrated, and purified by radial chromatography (1:10 EtOAc/hexanes) to afford 39 mg (94%) of analytically pure **8a** as an oil exhibiting spectra data identical to that previously reported.[1] (C) Sulfinyl-Magnesium Exchange: A THF solution of *i*-PrMgCl (0.21 mmol, 1.05 equiv) was added to a -78 °C, THF solution of the sulfinylnitrile (0.20 mmol, 1 equiv). After 5 min, a THF solution (2 mL) of methyl cyanoformate (19 mg, 0.22 mmol) and benzyl bromide (38 mg, 0.22 mmol) was added and the reaction mixture was then allowed to warm slowly to room temperature. After 2 h saturated, aqueous NH_4Cl was added, the crude reaction mixture was then extracted with EtOAc, dried ($MgSO_4$), concentrated, and purified by radial chromatography (1:10 EtOAc/hexanes) to afford 40 mg (96%) of analytically pure **8a** isolated as an oil exhibiting spectra data identical to that previously reported.[1]



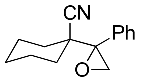
8b

1- benzoylcyclohexanecarbonitrile (8b): Prepared by sulfinyl-magnesium exchange and alkylation with BzCl: A THF solution of *i*-PrMgCl (1.05 equiv.) was added to a -78 °C, THF solution (10 mL) of the sulfinylnitrile (0.50 mmol, 1equiv.). After 5 min, a THF solution (5 mL) of benzoyl chloride (78 mg, 0.55 mmol) and benzyl bromide (94 mg, 0.55 mmol) was added, and then the reaction mixture was allowed to warm slowly to rt. After 2 h, saturated aqueous NH_4Cl was added, the crude reaction mixture was extracted with EtOAc, dried (Na_2SO_4), concentrated, and was then purified by radial chromatography (1:10 EtOAc/hexanes), to afford 77 mg (72%) of **8b** as an oil exhibiting spectra data identical to that previously reported.[3] (B) Prepared by sulfinyl-magnesium exchange and alkylation with $PhCO_2Et$: A THF solution of *i*-PrMgCl (1.05 equiv.) was added to a -78 °C, THF solution (10mL) of the sulfinylnitrile (0.50 mmol, 1equiv.). After 5 min, a THF solution (5 mL) of ethyl benzoate (83 mg, 0.55 mmol) and 1-iodohexane (117 mg, 0.55 mmol) was added, and the reaction mixture was allowed to warm slowly to rt. After 12 h, aqueous NH_4Cl was added, the crude reaction mixture was extracted with EtOAc, dried (Na_2SO_4), concentrated, and then purified by radial chromatography (1:10 EtOAc/hexanes), to afford 79 mg (74%) of **8b** as an oil exhibiting spectra data identical to that previously reported.[3]



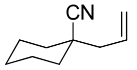
8c

1-(phenylthio)cyclohexanecarbonitrile (8c): Prepared by Sulfinyl-Magnesium Exchange: A THF solution of diphenyl disulfide (120 mg, 0.55 mmol) and benzyl bromide (94 mg, 0.55 mmol) was added to a THF solution of chloromagnesiated cyclohexanecarbonitrile (0.5 mmol, 1 equiv.) prepared at -78 °C with *i*-PrMgCl (1.05 equiv.). The reaction mixture was allowed to warm slowly to room temperature. After 2 h, saturated aqueous NH_4Cl was added, the crude reaction mixture was extracted with EtOAc, dried (Na_2SO_4), concentrated, and then purified by radial chromatography (1:10 EtOAc/hexanes), to afford 87 mg (80%) of **8c**[2] and 8 mg (4%) of **8a**[1] as an oil both exhibiting spectra data identical to that previously reported.



8d

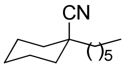
1-(2-Phenyloxiran-2-yl)cyclohexanecarbonitrile (8d): Prepared by Sulfinyl-Magnesium Exchange: A THF solution of *i*-PrMgCl (1.05 equiv.) was added to a -78 °C, THF solution (10 mL) of the sulfinylnitrile (0.50 mmol, 1equiv.). After 5min, a THF solution (5 mL) of allyl bromide (67 mg, 0.55 mmol) and 2-bromoacetophenone (109 mg, 0.55 mmol) was added to the resulting solution and then the reaction mixture was allowed to warm slowly to rt. After 2 h, saturated aqueous NH_4Cl was added, the crude reaction mixture was extracted with EtOAc, dried (Na_2SO_4), concentrated, and was then purified by radial chromatography (1:10 EtOAc/hexanes), to afford 92 mg (81%) of **8d** as an oil exhibiting spectra data identical to that previously reported.[2]



6b

1-Allylcyclohexanecarbonitrile (6b): A hexanes solution of BuLi (1.05 equiv.) was added to a -78 °C, THF solution (10 mL) of the sulfinylnitrile (0.50 mmol, 1equiv.). After 5 min, a THF solution (5 mL) of allyl bromide (67 mg, 0.55 mmol) and 2-

bromoacetophenone (109 mg, 0.55 mmol) was added, and then the reaction mixture was allowed to warm slowly to room temperature. After 2 h, aqueous NH_4Cl was added, the crude reaction mixture was then extracted with EtOAc, dried (Na_2SO_4), concentrated, and purified by radial chromatography (1:10 EtOAc/hexanes), to afford 50 mg (67%) of **6b**[2] and 12mg (11%) of **8d**[2] as an oil both exhibiting spectra data identical to that previously reported.

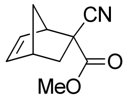


6c

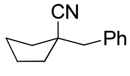
1-Hexylcyclohexanecarbonitrile (6c): A hexanes solution of BuLi (1.05 equiv.) was added to a -78 ºC, THF solution (10 mL) of the sulfinylnitrile (0.50 mmol, 1equiv.). After 5 min, a THF solution (5 mL) of ethyl benzoate (83 mg, 0.55 mmol) and 1-iodohexane (117 mg, 0.55 mmol) was added to the resulting solution and the reaction mixture was allowed to warm slowly to rt. After 12 h, aqueous NH_4Cl was added, the crude reaction mixture was extracted with EtOAc, dried (Na_2SO_4), concentrated, and was then purified by radial chromatography (1:10 EtOAc/hexanes), to afford 53 mg (55%) of **6c** as an oil: IR (film) 2931, 2859, 2230 cm^{-1}; ^{1}H NMR (500 MHz, Chloroform-d) δ 1.92 (d, *J* = 13.0 Hz, 2H), 1.69-1.66 (m, 3H), 1.63 – 1.51 (m, 2H), 1.45-1.44 (m, 4H), 1.28-1.24 (m, 6H), 1.18-1.15 (m, 3H), 0.86 – 0.83 (m, 3H). ^{13}C NMR (126 MHz, CDCl3) δ 123.82, 40.61, 39.02, 35.73, 31.61, 29.38, 25.49, 24.34, 23.10, 22.56, 14.03. HRMS (ESI) calcd for (M+Na$^+$), $C_{13}H_{23}N+Na^+$ 216.1723, found 216.1723.

6d

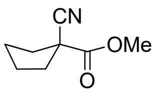
2-benzylbicyclo[2.2.1]hept-5-ene-2-carbonitrile (6d): A hexanes solution of BuLi (0.53 mmol, 1.05 equiv) was added to a -78 °C, THF solution (10 mL) of the sulfinylnitrile (0.50 mmol, 1 equiv). After 5 min, a THF solution (5 mL) of methyl cyanoformate (47 mg, 0.55 mmol) and benzyl bromide (94 mg, 0.55 mmol) was added to the reaction mixture and then the reaction mixture was allowed to warm slowly to rt. After 2 h, saturated, aqueous NH_4Cl was added, the crude reaction mixture was extracted with EtOAc, dried (Na_2SO_4), concentrated, and was then purified by radial chromatography (1:10 EtOAc/hexanes), to afford 73 mg (70%) of analytically pure **6d** isolated as an oil exhibiting spectra data identical to that previously reported.[2]


8e

Methyl (1R,2R,4R)-2-cyanobicyclo[2.2.1]hept-5-ene-2-carboxylate (8e): A THF solution of *i*-PrMgCl (1.05 equiv.) was added to a -78 ºC, THF solution (10 mL) of the sulfinylnitrile (0.50 mmol, 1 equiv.). After 5 min, a THF solution (5 mL) of methyl cyanoformate (47 mg, 0.55 mmol) and benzyl bromide (94 mg, 0.55 mmol) was added to the reaction mixture and then the reaction mixture was allowed to warm slowly to rt. After 2 h, saturated aqueous NH_4Cl was added, the crude reaction mixture was extracted with EtOAc, dried (Na_2SO_4), concentrated, and then purified by radial chromatography (1:10 EtOAc/hexanes), to afford 71 mg (82%) of analytically pure **8e** isolated as an oil: IR (film) 2987, 2957, 2238, 1741 cm^{-1}; Endo isomer: ^{1}H NMR (400 MHz, Chloroform-d) δ 6.45 – 6.43 (m, 1H), 6.33 – 6.31 (m, 1H), 3.84 (s, 3H), 3.39 – 3.37 (m, 1H), 3.10 – 3.08 (m, 1H), 2.55 (dd, *J* = 12.3, 3.4 Hz, 1H), 1.81 – 1.49 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.84, 141.08, 134.17, 121.01, 53.85, 52.45, 47.04, 46.83, 42.75, 39.26. Exo isomer: ^{1}H NMR (400 MHz, Chloroform-d) 6.20 – 6.18 (m, 1H), 5.87 – 5.85 (m, 1H), 3.76 (s, 3H), 3.57 – 3.55 (m, 1H), 3.23 (s, 1H), 3.03 (d, *J* = 6.3 Hz, 1H), 2.25 (dd, *J* = 12.5, 3.7 Hz, 1H), 2.05 (dd, *J* = 12.5, 2.9 Hz, 1H), 1.81 – 1.49 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) 169.84, 140.33, 131.09, 121.01, 53.70, 53.55, 49.23, 42.98, 37.36. HRMS (ESI) calcd for (M+Na$^+$), $C_{10}H_{11}NO_2$+Na$^+$ 200.0682, found 200.0674.

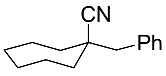

6e

Benzylcyclopentane-1-carbonitrile (6e): Prepared by the LDA deprotonation method: A THF solution (5 mL) of methyl cyanoformate (94 mg, 1.1 mmol) and benzyl bromide (188 mg, 1.1 mmol) was added to a -78 ºC THF solution of lithiated cyclopentanecarbonitrile (1.0 mmol) prepared by the LDA deporonation method. After the addition, the reaction mixture was allowed to warm slowly to rt. After 2 h, saturated aqueous NH_4Cl was added, the crude reaction mixture was extracted with EtOAc, dried (Na_2SO_4), concentrated, and was then purified by radial chromatography (1:10 EtOAc/hexanes) to afford 111 mg (60%) of **6e**, which exhibited spectral data identical to that previously reported,[2] and 18 mg (12%) of **8f** as oil. For **8f**: IR (film) 2959, 2879, 2242, 1742 cm^{-1}; ^{1}H NMR (400 MHz, Chloroform-d) δ 3.82 (s, 3H), 2.29 – 2.25 (m, 4H), 1.89 – 1.86 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.36, 121.11, 53.71, 47.54, 37.94, 25.27. HRMS (ESI) calcd for (M+Na$^+$), $C_{18}H_{11}NO_2$+Na$^+$ 176.0682, found 176.0677.



8f

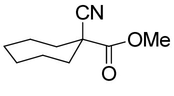
Methyl 1-cyanocyclohexanecarboxylate (8f): A THF solution of chloromagnesium cyclopentanecarbonitrile (1 mmol) was prepared by the transmetallation method with a THF solution of *i*-PrMgCl (1.05 equiv). After 15 min, a THF solution (5 mL) of methyl cyanoformate (94 mg, 1.1 mmol) and benzyl bromide (188 mg, 1.1 mmol) was added and the reaction mixture was allowed to warm slowly to rt. After 2 h saturated, aqueous NH_4Cl was added, the crude reaction mixture was extracted with EtOAc, dried (Na_2SO_4), concentrated, and was then purified by radial chromatography (1:10 EtOAc/hexanes) to afford 88 mg (57%) of analytically pure **8f** and 8 mg (5%) of **6e**[2] as oils both exhibiting spectra data identical to that previously reported.



6f

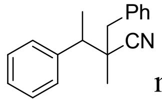
1-Benzylcycloheptane-1-carbonitrile (6f): A THF solution (5 mL) containing methyl cyanoformate (94 mg, 1.1 mmol) and benzyl bromide (188 mg, 1.1 mmol) was added to a THF solution of lithiated cycloheptanecarbonitrile (1.0 mmol) prepared by the

LDA deprotonation method. The reaction mixture was allowed to warm slowly to rt. After 2 h saturated, aqueous NH_4Cl was added, the crude reaction mixture was extracted with EtOAc, dried (Na_2SO_4), concentrated, and was then purified by radial chromatography (1:10 EtOAc/hexanes) to afford 87 mg (41%) of **6f** and 62 mg (34%) of **8g** as oils. For **6f**: IR: 2927, 2858, 2230 cm^{-1}; ^{1}H NMR (400 MHz, Chloroform-d) δ 7.35 – 7.25 (m, 5H), 2.82 (s, 2H), 1.95 (ddd, J = 14.3, 5.4, 2.9 Hz, 2H), 1.70 – 1.51 (m, 10H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.90, 130.53, 128.38, 127.29, 124.45, 46.64, 42.73, 37.99, 27.94, 23.30. HRMS (ESI) calcd for (M+K$^+$), $C_{15}H_{19}N+K^+$ 252.1149, found 252.1151. For **8g**: IR (film) 2932, 2862, 2240, 1741 cm^{-1}; ^{1}H NMR (400 MHz, Chloroform-d) δ 3.78 (s, 3H), 2.17 – 2.09 (m, 2H), 2.03 (ddd, J = 14.5, 9.7, 3.0 Hz, 2H), 1.75 – 1.64 (m, 6H), 1.57 – 1.54 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.60, 120.38, 53.51, 47.94, 36.05, 27.95, 23.57. HRMS (ESI) calcd for (M+K$^+$), $C_{10}H_{15}NO_2+K^+$ 220.0734, found 220.0732.



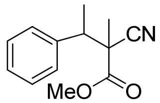
8g

Methyl 1-cyanocyclohexanecarboxylate (8g): Prepared by Transmetalation with *i*-PrMgCl: A THF solution of chloromagnesium cycloheptanecarbonitrile (1.0 mmol) was prepared from a THF solution of *i*-PrMgCl (1.05 equiv) following the transmetallation method. After 15 min, a THF solution (5 mL) of methyl cyanoformate (94 mg, 1.1 mmol) and benzyl bromide (188 mg, 1.1 mmol) was added and the reaction mixture was allowed to warm slowly to rt. After 2 h saturated, aqueous NH_4Cl was added, the crude reaction mixture was extracted with EtOAc, dried (Na_2SO_4), concentrated, and was then purified by radial chromatography (1:10 EtOAc/hexanes) to afford 162 mg (76%) of analytically pure **8g** and 4 mg (2%) of **6f** as oils that both exhibited spectra identical to that of material previously isolated.



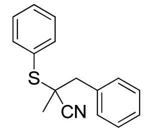
6g

2-Benzyl-2-methyl-3-phenylbutanenitrile (**6g**): A THF solution (5 mL) containing methyl cyanoformate (47 mg, 0.55 mmol) and benzyl bromide (94 mg, 0.55 mmol) was added to a THF solution of lithiated 2-methyl-3-phenylbutanenitrile [6] (0.5 mmol, 1 equiv.), prepared by the LDA (0.55 mmol) deprotonation method. The reaction was then allowed to warm slowly to rt. After 2 h saturated, aqueous NH_4Cl was added, the crude reaction mixture was separated, the aqueous phase was extracted with EtOAc, and the combined organic phase was dried (Na_2SO_4), concentrated, and then purified by radial chromatography (1:10 EtOAc/hexanes) to afford 44 mg (35 %) of **6g** as a white crystalline solid (mp 71- 72 °C) and 38 mg (35 %) of **8h**[6] as an oil exhibiting spectra data identical to that previously reported. For **6g**: IR (film): 3030, 2979, 2231 cm^{-1}. ^1H NMR (500 MHz, Chloroform-d) δ 7.37 – 7.24 (m, 10H), 3.18 (d, J = 13.4 Hz, 1H), 2.84 (q, J = 7.1 Hz, 1H), 2.59 (d, J = 13.4 Hz, 1H), 1.61 (d, J = 7.1 Hz, 3H), 0.99 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 141.40, 135.61, 130.54, 128.72, 128.47, 128.41, 127.44, 127.35, 123.37, 47.43, 44.13, 42.67, 21.66, 17.56. HRMS (ESI) calcd for ($M+Na^+$), $C_{18}H_{19}N+Na^+$ 272.1410, found 272.1410.



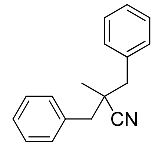
8h

Methyl 2-cyano-2-methyl-3-phenylbutanoate (8h): A THF solution (5 mL) containing methyl cyanoformate (47 mg, 0.55 mmol) and benzyl bromide (94 mg, 0.55 mmol) was added to a THF solution of chloromagnesium 2-methyl-3-phenylbutanenitrile[6] (0.50 mmol) prepared from LDA (0.55 mmol) and *i*-PrMgCl (0.55 mmol) by the transmetallation method. The reaction mixture was allowed to warm slowly to rt. After 2 h, saturated, aqueous NH_4Cl was added, the phases were separated, the aqueous phase extracted with EtOAc, and the combined extract was dried (Na_2SO_4), concentrated, and purified by radial chromatography (1:10 EtOAc/hexanes) to afford, 60 mg (55 %) of analytically pure **8h** as an oil exhibiting spectra data identical to that previously reported.[6]



1h

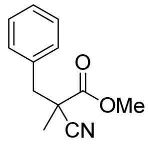
2-Methyl-3-phenyl-2-(phenylthio)propanenitrile (1h): A THF solution (10 mL) of lithiated 3-phenyl-2-(phenylthio)propanenitrile[2] (300mg, 1.26 mmol) was prepared by the LDA (1.4 mmol) method. Neat iodomethane (1.4 mmol) was added to the reaction mixture, that was then allowed to warm slowly to rt. After 12 h, saturated, aqueous NH_4Cl was added. The mixture was extracted with EtOAc, the combined extracts were washed with brine and water, dried (Na_2SO_4), and then concentrated. The residue was purified by radial chromatography to afford 350 mg (83%) of **1h** as a white crystalline solid (mp 63-64 °C): IR (film) 3062, 3028, 2235 cm^{-1} ; ^1H NMR (400 MHz, Chloroform-d) δ 7.74 – 7.71 (m, 2H), 7.50 – 7.41 (m, 3H), 7.37-7.28 (m, 5H), 3.17 (d, *J* = 13.6 Hz, 1H), 2.96 (d, *J* = 13.6 Hz, 1H), 1.47 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.23, 134.43, 130.53, 129.53, 129.46, 128.67, 127.94, 121.50, 45.83, 45.10, 25.00; HRMS (ESI) calcd for ($M+Na^+$), $C_{16}H_{15}NS+Na^+$ 276.0817, found 276.0818.



6h

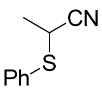
2-Benzyl-2-methyl-3-phenylpropanenitrile (6h): A hexanes solution of BuLi (0.55 mmol) was added to a -78 °C, THF solution (10 mL) of 2-methyl-3-phenyl-2-(phenylthio)propanenitrile (0.5 mmol). After 5 min, a THF solution (5 mL) of methyl cyanoformate (47 mg, 0.55 mmol) and benzyl bromide (94 mg, 0.55 mmol) was added to the reaction mixture, and the reaction was allowed to warm slowly to rt. After 2 h, saturated, aqueous NH_4Cl was added. The phases were separated and the aqueous phase was extracted with EtOAc. The combined organic phase was sequentially washed with brine and water, dried

(Na_2SO_4), and was then concentrated. The residue was purified by radial chromatography to afford, after purification by radial chromatography (1:10 EtOAc/hexanes), 25 mg (25 %) of **8i** and 59 mg (50 %) of **6h**[5] both exhibiting spectral data identical to that previously reported.



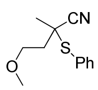
8i

Methyl 2-cyano-2-methyl-3-phenylpropanoate (8i): A THF solution (5 mL) of methyl cyanoformate (47 mg, 0.55 mmol) and benzyl bromide (94 mg, 0.55 mmol) was added to chloromagnesium 2-methyl-3-phenylpropanenitrile (0.50 mmol) prepared by transmetallation with *i*-PrMgCl (0.55 mmol). The reaction mixture was allowed to warm slowly to rt. After 2 h, saturated, aqueous NH_4Cl was added. The phases were separated and the aqueous phase was extracted with EtOAc. The combined orgniac phase was sequentially washed with brine and water, dried (Na_2SO_4), and was then concentrated. The residue was purified by radial chromatography to afford, after purification by radial chromatography (1:10 EtOAc/hexanes), 11mg (9%) of **6g** that exhibited spectral data identical to that of material previously isolated[7] and 64 mg (63 %) of **8i** as an oil. For **8i**: IR (film) 3033, 2956, 2245, 1743 cm^{-1}; ^1H NMR (400 MHz, Chloroform-d) δ 7.35 – 7.25 (m, 5H), 3.73 (s, 3H), 3.23 (d, *J* = 13.5 Hz, 1H), 3.04 (d, *J* = 13.5 Hz, 1H), 1.62 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.56, 134.17, 130.00, 128.67, 128.00, 119.67, 53.53, 45.44, 43.79, 23.24; HRMS (ESI) calcd for ($M+Na^+$), $C_{12}H_{13}NO_2+Na^+$ 226.0839, found 226.0839.



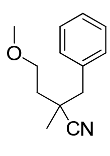
i

2-(Phenylthio)propanenitrile (i): A THF solution (5 mL) of diphenyl disulfide (5.5 mmol) was added to a THF solution (40 mL) of lithiated propiononitrile (5.0 mmol), prepared by LDA deprotonation. The solution was allowed to warm slowly to rt. After 2h, saturated aquesous NH_4Cl was added, the crude reaction mixture was extracted with EtOAc, dried (Na_2SO_4), concentrated, and was then purified by radial chromatography (1:10 EtOAc/hexanes) to afford 525 mg (64%) of **i** as an oil exhibiting spectra data identical to that previously reported.[4]



1i

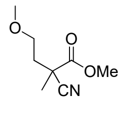
4-Methoxy-2-methyl-2-(phenylthio)butanenitrile (1i): Neat 2-bromoethyl methyl ether (2.0 mmol) was added to THF solution (10 mL) of lithiated 2-(phenylthio)propanenitrile (1.8 mmol) prepared by LDA deprotonation. The reaction mixture was allowed to warm slowly to rt. After 12 h, saturated aqueous NH_4Cl was added, the crude reaction extracted with EtOAc, washed with brine and water, dried (Na_2SO_4), concentrated, and then the residue was purified by radial chromatography (1:10 EtOAc/hexanes) to afford 350 mg (89%) of **1i** as an oil: IR (film) 2929, 2232 cm^{-1} ; ^{1}H NMR (400 MHz, Chloroform-d) δ 7.70 – 7.67 (m, 2H), 7.49 – 7.39 (m, 3H), 3.64 (t, *J* = 6.5 Hz, 2H), 3.35 (s, 3H), 2.13 – 2.01 (m, 2H), 1.60 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.20, 130.52, 129.43, 121.60, 69.01, 58.97, 43.06, 39.14, 25.97; HRMS (ESI) calcd for (M+Na$^+$), $C_{12}H_{15}NOS+Na^+$ 244.0767, found 244.0767.



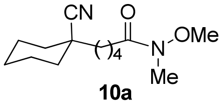
6i

2-Benzyl-4-methoxy-2-methylbutanenitrile (6i): A hexanes solution of BuLi (0.55 mmol, 1.1 equiv.) was added to a -78 °C, THF solution (10 mL) of 4-methoxy-2-methyl-2-(phenylthio)butanenitrile (111 mg, 0.5 mmol). After 5 min, a THF solution (5 mL) of methyl cyanoformate (47 mg, 0.55 mmol) and benzyl bromide (94 mg, 0.55 mmol) was added, and the reaction was allowed to warm slowly to rt. After 2 h, saturated aqueous NH_4Cl was added, the mixture was extracted with EtOAc, washed with brine and water, dried (Na_2SO_4), and concentrated. The residue was then purified by radial chromatography (1:10 EtOAc/hexanes) to afford, 61 mg (60%) of **6i** and 14 mg (15%) of **8j** as oils. For **6i**: IR (film) 3032, 2875, 2928, 2233 cm^{-1}; ^{1}H NMR (400 MHz, Chloroform-d) δ 7.34 – 7.26 (m, 5H), 3.62

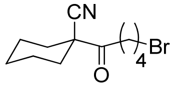
(t, *J* = 6.6 Hz, 2H), 3.36 (s, 3H), 2.95 (d, *J* = 13.5 Hz, 1H), 2.80 (d, *J* = 13.5 Hz, 1H), 1.95-1.90 (m, 1H), 1.81-1.76 (m, 1H), 1.33 (s, 3H); ^{13}C NMR (101 MHz, CDCl$_3$) δ 135.37, 130.54, 128.51, 127.49, 123.76, 69.38, 58.95, 45.96, 38.52, 36.70, 24.48; HRMS (ESI) calcd for (M+Na$^+$), $C_{13}H_{17}NO$+Na$^+$ 226.1202, found 226.1203. For **8j**: IR (film) 2934, 2241, 1746 cm^{-1}; ^{1}H NMR (400 MHz, Chloroform-d) δ 3.77 (s, 3H), 3.56 – 3.53 (m, 2H), 3.27 (s, 3H), 2.32-2.25 (m, 1H), 1.97-1.91 (m, 1H), 1.60 (S, 3H); ^{13}C NMR (101 MHz, CDCl$_3$) δ 169.92, 119.68, 68.60, 58.95, 53.46, 42.17, 38.03, 24.13. HRMS (ESI) calcd for (M+Na$^+$), $C_8H_{13}NO_3$+Na$^+$ 194.0788, found 194.0788.


8j

Methyl 2-cyano-4-methoxy-2-methylbutanoate (8j): A THF solution (5 mL) of methyl cyanoformate (47 mg, 0.55 mmol) and benzyl bromide (94 mg, 0.55 mmol) was added to a -78 °C, THF solution (10 mL) of chloromagnesiated 4-methoxy-2-methylbutanenitrile (0.50 mmol) prepared by transmetallation with a THF solution of *i*-PrMgCl (0.55 mmol). The reaction mixture was allowed to warm slowly to rt. After 2 h, saturated, aqueous NH$_4$Cl was added. The mixture was extracted with EtOAc, and the combined extracts were washed with brine and water, dried (Na$_2$SO$_4$), and then concentrated. The residue was purified by radial chromatography (1:10 EtOAc/hexanes) to afford, 73 mg (85%) of **8j** and 6 mg (6%) of **6i** as oils that both exhibited spectral data identical to that of material previously isolated.

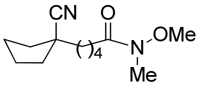

10a

5-(1-cyanocyclohexyl)-*N*-methoxy-*N*-methylpentanamide (10a): A THF solution (5 mL) of 5-bromo-*N*-methoxy-*N*-methylpentanamide[7] (246 mg, 1.1 mmol) was added to a THF solution of lithiated cyclohexanecarbonitrile (1.0 mmol) prepared by the LDA (1.1 mmol) deprotonation method. The reaction was allowed to warm slowly to rt. After 12 h, saturated, aqueous NH_4Cl was added, the phases were separated and the aqueous phase was extracted with EtOAc. The combined organic extracts were dried (Na_2SO_4), concentrated, and then purified by radial chromatography (15:85 EtOAc/hexanes) to afford, 179 mg (71%) of **10** as an oil: IR (film) 2934, 2859, 2230, 1660 cm^{-1}; ^{1}H NMR (400 MHz, Chloroform-d) δ 3.66 (s, 3H), 3.15 (s, 3H), 2.43 (t, *J* = 7.3 Hz, 2H), 1.94 (d, *J* = 12.7 Hz, 2H), 1.72 – 1.50 (m, 11H), 1.23 – 1.13 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.27, 123.84, 61.31, 40.44, 39.06, 35.77, 32.23, 31.67, 25.50, 24.69, 24.37, 23.14; HRMS (ESI) calcd for (M+Na$^+$), $C_{14}H_{24}N_2O_2$+Na$^+$ 275.1730, found 275.1734.



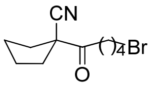
11a

1-(5-bromopentanoyl)cyclohexane-1-carbonitrile (11a): A THF solution (5 mL) of 5-bromo-*N*-methoxy-*N*-methylpentanamide[7] (123 mg, 0.55 mmol) was added to a -78 ºC, THF solution (10 mL) of chloromagnesiated cyclohexanecarbonitrile (0.50 mmol, 1 equiv.) prepared by the magnesium exchange method with *i*-PrMgCl (0.55 mmol). The reaction was allowed to warm slowly to rt. After 12 h saturated, aqueous NH_4Cl was added, the phases were separated and the aqueous phase was extracted with EtOAc. The combined organic extracts were dried (Na_2SO_4), concentrated, and then purified by radial chromatography (15:85 EtOAc/hexanes) to afford, 110 mg (81%) of **11** as an oil: IR (film) 2937, 2861, 2232,1720 cm^{-1}; ^{1}H NMR (400 MHz, Chloroform-d) δ 3.40 (t, *J* = 6.5 Hz, 2H), 2.82 (t, *J* = 6.9 Hz, 2H), 1.97 (d, *J* = 8.3 Hz, 2H), 1.89 – 1.75 (m, 8H), 1.68 – 1.61 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 203.95, 120.61, 51.33, 38.21, 33.12, 32.24, 31.87, 24.79, 22.46, 22.22; HRMS (ESI) calcd for (M+K$^+$), $C_{12}H_{18}BrNO$+K$^+$ 310.0203, found 310.0203.



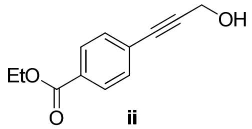
10b

5-(1-cyanocyclohexyl)-*N*-methoxy-*N*-methylpentanamide (10b):: A THF solution (5 mL) of 5-bromo-*N*-methoxy-*N*-methylpentanamide[7] (246 mg, 1.1mmol) was added to a -78 °C, THF solution of the lithiated cyclopentanecarbonitrile (1.0 mmol) prepared by the LDA deprotonation method. The reaction mixture was allowed to slowly warm to room temperature over 12 h, and then saturated, aqueous NH_4Cl was added. The mixture was diluted with ethyl acetate, the phases were separated and the aqueous phase was washed sequentially with brine and water, and then dried (Na_2SO_4). The solvent was evaporated under vacuum and then the residue was purified by radial chromatography to afford, after purification by radial chromatography (15:85 EtOAc/hexanes), 179 mg (78%) of **10b** as an oil: IR (film) 2941, 2871, 2230, 1660 cm^{-1}; ^{1}H NMR (400 MHz, Chloroform-d) δ 3.58 (s, 3H), 3.06 (s, 3H), 2.34 (t, *J* = 7.4 Hz, 2H), 2.02-1.99 (m, 2H), 1.76 – 1.40 (m, 12H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.94, 125.18, 61.06, 42.94, 38.21, 37.95, 31.88, 31.38, 26.09, 24.35, 24.02; HRMS (ESI) calcd for (M+Na$^+$), $C_{13}H_{22}N_2O_2$+Na$^+$ 261.1573, found 261.1573.

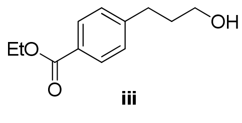


11b

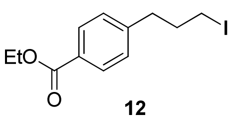
1-(5-Bromopentanoyl)cyclopentane-1-carbonitrile (11b): A THF solution (5 mL) of 5-bromo-*N*-methoxy-*N*-methylpentanamide[7] (246 mg, 1.1mmol) was added to a -78 °C, THF solution of the chloromagnesium cyclopentanecarbonitrile prepared with *i*-PrMgCl (1.1 mmol) by the RMgX transmetalation method. The reaction mixture was allowed to slowly warm to room temperature over 12 h, and then saturated, aqueous NH_4Cl was added. The mixture was diluted with ethyl acetate, the phases were separated, and the aqueous phase was washed sequentially with brine and water, and then dried (Na_2SO_4). The solvent was evaporated under vacuum and then the residue was purified by radial chromatography (1:10 EtOAc/hexanes) to afford, 167 mg (65%) of **11b** as an oil: IR (film) 2958, 2874, 2234, 1723 cm^{-1}; ^{1}H NMR (400 MHz, Chloroform-d) δ 3.39 (t, *J* = 6.4 Hz, 2H), 2.84 (t, *J* = 6.9 Hz, 2H), 2.16 – 2.12 (m, 4H), 1.91 – 1.72 (m, 8H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 202.97, 122.46, 53.14, 39.04, 36.67, 33.10, 31.79, 25.49, 22.27; HRMS (ESI) calcd for (M+Na$^+$), $C_{11}H_{16}BrNO+Na^+$ 280.0307, found 280.0308.


ii

Ethyl 4-(3-hydroxyprop-1-yn-1-yl)benzoate (ii): Alkynol **ii** was prepared by a modification of the literature method developed for the corresponding methyl ester[8]: A Et_2NH solution (75 mL) of ethyl 4-iodobenzoate (4.14 g, 15.0 mmol), propargyl alcohol (3.02g, 56.0 mmol), palladium chloride (53 mg, 0.30 mmol), copper (I) iodide (114 mg, 0.60 mmol), and triphenylphosphine (197 mg, 0.75 mmol) was stirred at room temperature. After 48 h, saturated, aqueous NH_4Cl was added, the phases were separated and the aqueous phase was extracted with EtOAc. The combined organic extracts were dried (Na_2SO_4), concentrated, and then the crude reaction mixture was purified by silica gel column chromatography (20: 80 EtOAc/Hexanes) to afford 2.86 g (93 %) of **ii** as a white crystalline solid (mp 61- 62 °C) : IR (film) 3452, 2987, 2941, 1700, 1607 cm^{-1}; ^{1}H NMR (400 MHz, Chloroform-d) δ 7.95 (d, *J* = 8.4 Hz, 2H), 7.43 (d, *J* = 8.4 Hz, 2H), 4.53 (s, 2H), 4.37 (q, *J* = 7.1 Hz, 2H), 3.30 (s, 1H), 1.38 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, CDCl3) δ 166.25, 131.51, 129.84, 129.40, 127.29, 90.53, 84.58, 61.32, 51.29, 14.25; HRMS (ESI) calcd for (M+Na$^+$), $C_{12}H_{12}O_3+Na^+$ 227.0679, found 227.0679.

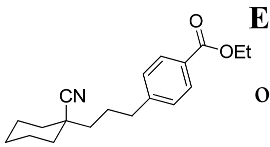

iii

Ethyl 4-(3-hydroxypropyl)benzoate (iii): A modification of the literature method was employed[8]: A suspension of ethyl 4-(3-hydroxyprop-1-yn-1-yl)benzoate (2.86 g, 14 mmol) and 10% palladium on carbon (150 mg) in MeOH (75 mL) was treated with hydrogen gas at 50 psi in a Parr shaker. After 10 h, the reaction mixture was filtered through Celite, and then evaporated under vacuum. The crude reaction mixture was purified by silica gel column chromatography (30: 70 EtOAc/Hexanes) to afford 2.82g (97 %) of **iii** as an oil: IR (film) 3422, 2981, 2939, 1713, 1610 cm^{-1}; ^1H NMR (400 MHz, Chloroform-d) δ 7.95 (d, *J* = 8.3 Hz, 2H), 7.25 (d, *J* = 8.3 Hz, 2H), 4.35 (q, *J* = 7.1 Hz, 2H), 3.64 (t, *J* = 6.4 Hz, 2H), 3.05 (s, 1H), 2.79 – 2.70 (m, 2H), 1.92 – 1.85 (m, 2H), 1.37 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.76, 147.50, 129.60, 128.37, 127.94, 61.60, 60.82, 33.78, 32.04, 14.25. HRMS (ESI) calcd for ($M+Na^+$), $C_{12}H_{16}O_3+Na^+$ 231.0992, found 231.0992.



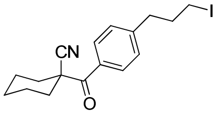
12

Ethyl 4-(3-iodopropyl)benzoate (12): A modification of the literature method was employed[9]: A CH_2Cl_2 solution (50 mL) of ethyl 4-(3-hydroxypropyl)benzoate (1.04 g, 5 mmol), iodine (1.905g, 7.5 mmol), triphenylphosphine (1.965 g, 7.5 mmol) and imidazole (850 mg, 12.5 mmol) was stirred at room temperature. After 12 h, the solvent was removed under vacuum and then the crude reaction mixture was purified by silica gel column chromatography (3: 97 EtOAc/Hexanes) to afford 1.12 g (70 %) of **12** as an oil: IR (film) 2980, 2935, 1712, 1610 cm^{-1}; ^1H NMR (400 MHz, Chloroform-d) δ 7.98 (d, *J* = 8.2 Hz, 2H), 7.27 (d, *J* = 6.7 Hz, 2H), 4.37 (q, *J* = 7.1 Hz, 2H), 3.16 (t, *J* = 6.8 Hz, 2H), 2.79 (t, *J* = 7.4 Hz, 2H), 2.14 (p, *J* = 6.9 Hz, 2H), 1.39 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.69, 145.88, 129.95, 128.69, 61.01, 36.35, 34.56, 14.50, 6.03; HRMS (ESI) calcd for ($M+Na^+$), $C_{12}H_{15}IO_3+Na^+$ 341.0009, found 341.0009.



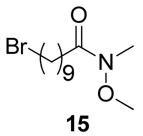
10c

Ethyl 4-(3-(1-cyanocyclohexyl)propyl)benzoate (10c): A hexanes solution of BuLi (1.05 equiv.) was added to a -78 ºC, THF solution (10 mL) of the sulfinylnitrile (0.50 mmol, 1equiv.). After 5 min, a THF solution (5 mL) of ethyl 4-(3-iodopropyl)benzoate (175 mg, 0.55 mmol) was added to the resulting solution and the reaction mixture was allowed to slowly warm to room temperature over 12 h, and then saturated, aqueous NH_4Cl was added. The mixture was diluted with ethyl acetate, the phases were separated and the combined organic phase was washed sequentially with brine and water, and was then dried (Na_2SO_4). The solvent was evaporated and then the residue was purified by silica gel column chromatography (10:90 EtOAc/hexanes) to afford, 107 mg (72%) of **10c** as an oil: IR (film) 2935, 2860, 2230, 1714, 1611 cm^{-1}; ^{1}H NMR (400 MHz, Chloroform-d) δ 7.97 (d, *J* = 8.2 Hz, 2H), 7.25 (d, *J* = 8.2 Hz, 2H), 4.37 (q, *J* = 7.1 Hz, 2H), 2.71 (t, *J* = 7.5 Hz, 2H), 1.95 (d, *J* = 12.8 Hz, 2H), 1.87 – 1.83 (m, 2H), 1.73 – 1.50 (m, 7H), 1.39 (t, *J* = 7.1 Hz, 3H), 1.22 – 1.14 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.65, 146.97, 129.79, 128.41, 123.65, 60.88, 39.95, 38.94, 35.78, 35.72, 25.80, 25.45, 23.10, 14.42; HRMS (ESI) calcd for (M+Na$^+$), $C_{19}H_{25}NO_2+Na^+$ 322.1778, found 322.1776.

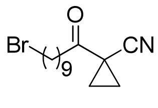


11c

1-(4-(3-iodopropyl)benzoyl)cyclohexanecarbonitrile (11c): A THF solution (5 mL) of ethyl 4-(3-iodopropyl)benzoate (105 mg, 0.33 mmol) was added to a -78 °C, THF solution of chloromagnesium cyclohexanecarbonitrile (0.3 mmol, 1 equiv.) prepared by the magnesium exchange method with *i*-PrMgCl (0.33 mmol). The reaction mixture was allowed to slowly warm to room temperature over 12 h, and then saturated, aqueous NH_4Cl was added. The mixture was diluted with ethyl acetate, the phases were separated, and the combined organic phase was washed sequentially with brine and water, and was then dried (Na_2SO_4). The solvent was evaporated and the resulting crude nitrile was purified by silica gel column chromatography (1:10 EtOAc/hexanes) to afford 87 mg (76%) of **11c** as an oil: IR (film) 2934, 2859, 2229, 1683, 1606 cm^{-1}; ^{1}H NMR (400 MHz, Chloroform-d) δ 8.09 (d, *J* = 8.4 Hz, 2H), 7.32 (d, *J* = 8.4 Hz, 2H), 3.17 (t, *J* = 6.7 Hz, 2H), 2.81 (t, *J* = 7.4 Hz, 2H), 2.26 (d, *J* = 5.9 Hz, 2H), 2.15 (p, *J* = 6.8 Hz, 2H), 1.87 – 1.79 (m, 7H), 1.30 – 1.24 (m, 1H); ^{13}C NMR (101 MHz, CDCl$_3$) δ 193.93, 147.03, 132.33, 129.80, 128.95, 121.11, 48.09, 36.31, 34.32, 33.82, 24.97, 22.51, 5.89; HRMS (ESI) calcd for (M+Na$^+$), $C_{17}H_{20}INO$+Na$^+$ 404.0482, found 404.0483.


15

10-Bromo-*N*-methoxy-*N*-methyldecanamide (15): Following a modification of the literature method,[7] anhydrous pyridine (0.45 mL) was added dropwise to a rt, CH$_2$Cl$_2$ solution (15 mL) of 10-bromodecanoic acid (1.2 g, 5 mmol), tetrabromomethane (1.83 mg, 5.5 mmol), triphenylphosphine (1.4 g, 5.5 mmol) and *N*, *O*-dimethylhydroxylamine hydrochloride (567 mg, 5.5 mmol). After 6 h, the solvent was removed under vacuum, and then the crude reaction mixture was purified by silica gel column chromatography (15: 85 EtOAc/Hexanes) to afford 1.27 g (87%) of **15** as an oil: IR (film) 2927, 2854, 1663 cm^{-1}; ^{1}H NMR (400 MHz, Chloroform-d) δ 3.56 (s, 3H), 3.27 (t, *J* = 6.8 Hz, 2H), 3.05 (s, 3H), 2.28 (t, *J* = 7.4 Hz, 2H), 1.72 (p, *J* = 7.0 Hz, 2H), 1.51-1.47 (m, 2H), 1.29 (t, *J* = 7.4 Hz, 2H), 1.20-1.19 (m, 8H); ^{13}C NMR (101 MHz, CDCl$_3$) δ 174.52, 61.03, 33.82, 32.61, 31.93, 31.63, 29.16, 29.10, 29.07, 28.50, 27.94, 24.39; HRMS (ESI) calcd for (M+H$^+$), $C_{12}H_{24}BrNO_2$+H$^+$ 294.1063, found 294.1063.


8k

1-(10-Bromodecanoyl)cyclopropane-1-carbonitrile (8k): (A): A THF solution (5 mL) of 10-bromo-*N*-methoxy-*N*-methyldecanamide (323 mg, 1.1mmol) was added to a THF solution of lithiated cyclopropanecarbonitrile (1.0 mmol) prepared by the LDA (1.1 mmol) deprotonation method. The reaction mixture was allowed to warm slowly to rt. After 12 h, saturated, aqueous NH$_4$Cl was added. The mixture was diluted with ethyl acetate, the phases were separated and the aqueous phase was extracted with EtOAc. The combined organic extract was washed sequentially with brine and water, and was then dried (Na_2SO_4). The solvent was evaporated under vacuum, and then the residue was purified by radial chromatography to afford, after purification by radial chromatography (1:10 EtOAc/hexanes), 182 mg (61%) of **8k** as an oil. (B) Prepared by the *i*-PrMgCl transmetalation method: A THF solution (5 mL) of 10-bromo-*N*-methoxy-*N*-methyldecanamide (323mg, 1.1mmol) was added to a -78 ºC, THF solution (10 mL) of chloromagnesium cyclopropanecarbonitrile (1.0 mmol) prepared by transmetallation with *i*-PrMgCl (0.55 mmol). The reaction mixture was allowed to slowly warm to rt. After 12 h, saturated aqueous NH_4Cl was added. The mixture was diluted with ethyl acetate, the phases were separated and the aqueous phase was sequentially washed with brine and water, and was then dried (Na_2SO_4). The solvent was evaporated under vacuum and then the residue was purified by radial chromatography (1:10 EtOAc/hexanes) to afford, 213 mg (71%) of **8k** as an oil: IR (film) 2927, 2855, 2242, 1713 cm^{-1}; ^1H NMR (400 MHz, Chloroform-d) δ 3.32 (t, *J* = 6.9 Hz, 2H), 2.82 (t, *J* = 7.3 Hz, 2H), 1.77 (p, *J* = 6.9 Hz, 2H), 1.58 – 1.49 (m, 6H), 1.35-1.32 (m, 2H), 1.24 – 1.21 (m, 8H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 201.34, 120.29, 41.63, 33.86, 32.63, 29.03, 28.69, 28.50, 27.96, 23.27, 20.86, 19.36; HRMS (ESI) calcd for ($M+Na^+$), $C_{14}H_{22}BrNO+Na^+$ 322.0777, found 322.0777.

Cross-Over Experiment

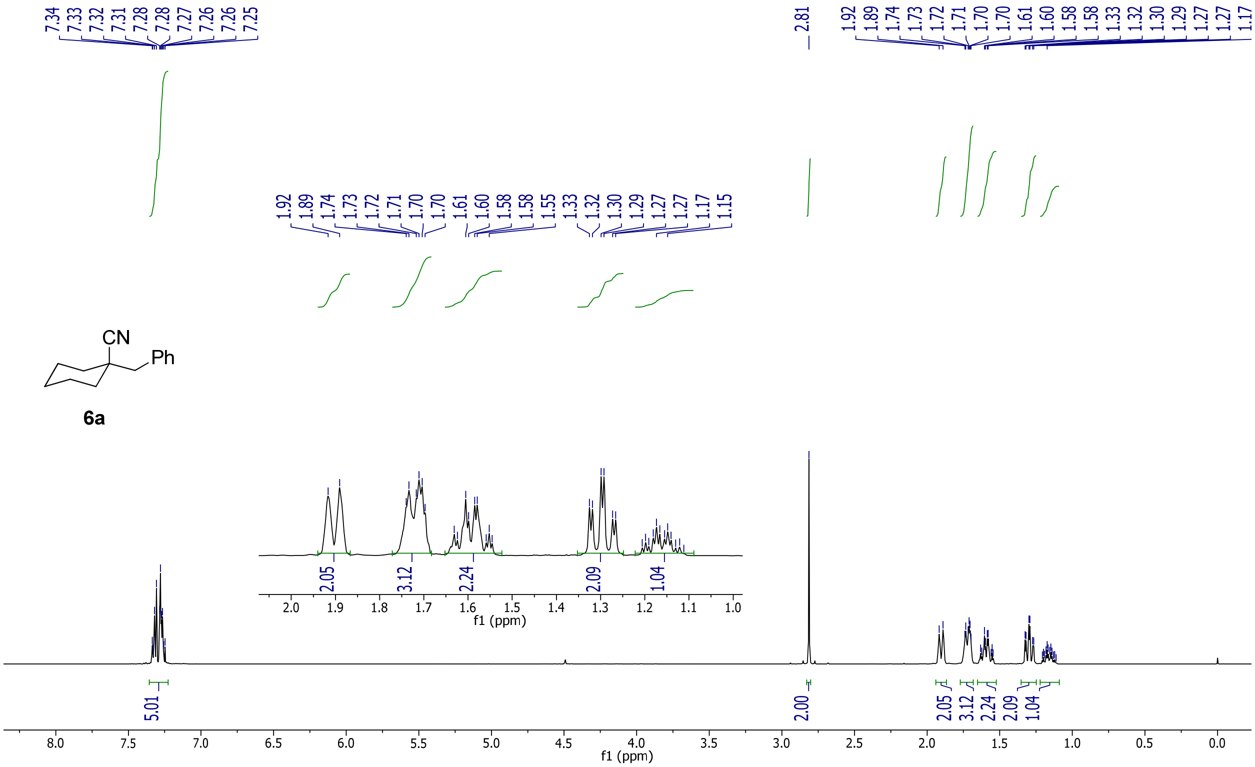
A THF solution (5 mL) of lithiated cyclohexanecarbonitrile (0.5 mmol) was prepared by treating sulfinylnitrile (**1c**, 0.5 mmol) with a hexanes solution of BuLi (0.55 mmol). After 5 min, a THF solution (5 mL) of chloromagnesium cyclohexanecarbonitrile (0.5 mmol) prepared by treating sulfinylnitrile with a THF solution of *i*-PrMgCl (0.55 mmol) was added. After 5 min, a THF solution (5 mL) of methyl cyanoformate (94 mg, 1.1 mmol) and benzyl bromide (188 mg, 1.1

mmol) was added and then the reaction mixture was allowed to warm slowly to room temperature. After 2 h saturated, aqueous NH_4Cl was added, the phases were separated and the aqueous phase was extracted with EtOAc. The combined organic phase was dried (Na_2SO_4), concentrated, and then purified by silica gel column chromatography (5:95 EtOAc/hexanes) to afford 10 mg (10 %) of **8a** and 109 mg (65 %) of **6a** that exhibited spectral data identical to that of material previously isolated.

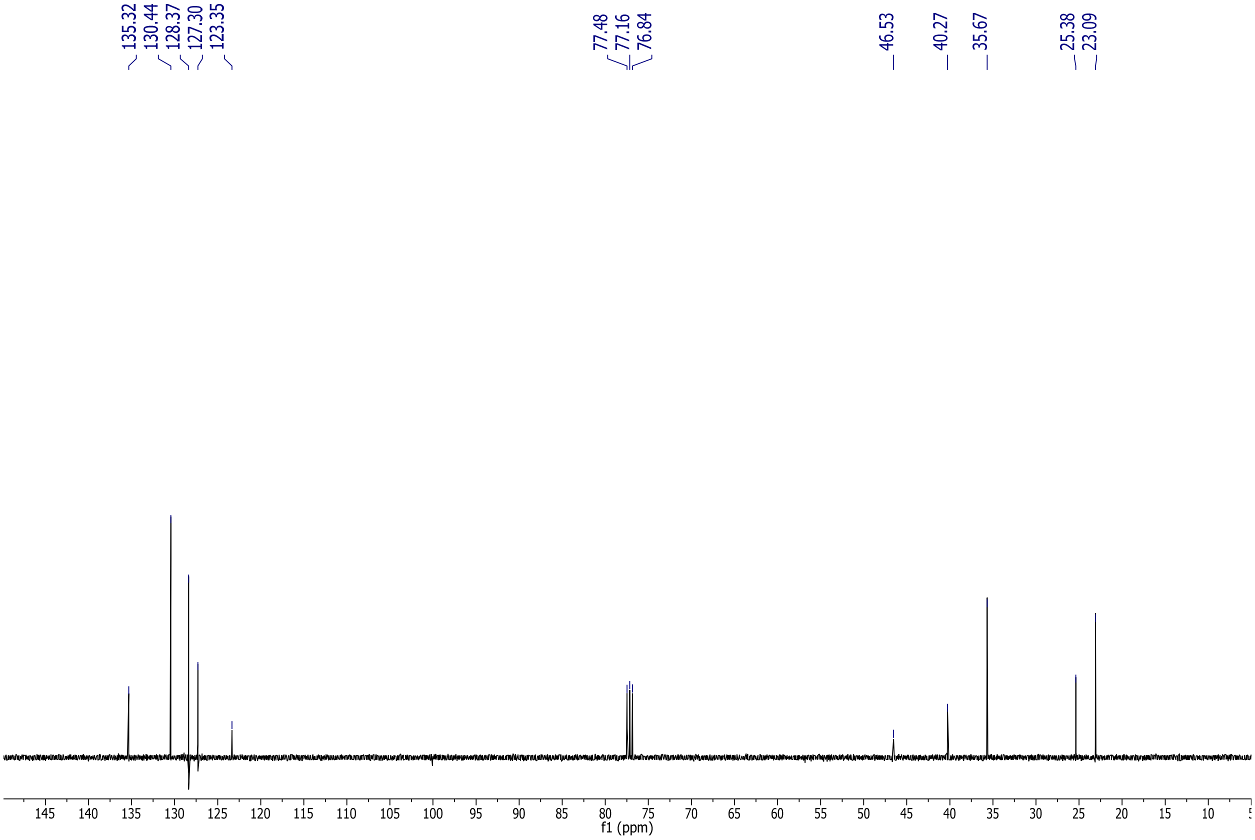
Alkylations of Lithiated Cyclohexanecarbonitrile with Mixtures of BnBr and MeOC(O)CN. A. 2:1 Ratio of MeOC(O)CN: BnBr. A THF solution (5 mL) containing methyl cyanoformate (94 mg, 1.1 mmol) and benzyl bromide (94 mg, 0.55 mmol) was added to a THF solution of lithiated cyclohexanecarbonitrile (0.50 mmol) prepared by the LDA deprotonation method. The reaction mixture was allowed to warm slowly to room temperature. After 2 h saturated, aqueous NH_4Cl was added, the phases were separated, the aqueous phase was extracted with EtOAc, and the combined phase was dried (Na_2SO_4), concentrated, and then purified by silica gel column chromatography (5:95 EtOAc/hexanes) to afford 22 mg (22 %) of **8a** and 52 mg (62 %) of **6a** that exhibited spectral data identical to that of material previously isolated. B. 5:1 Ratio of MeOC(O)CN: BnBr. A THF solution (5 mL) containing methyl cyanoformate (234 mg, 2.75 mmol) and benzyl bromide (94 mg, 0.55 mmol) was added to a THF solution of lithiated cyclohexanecarbonitrile (0.50 mmol) prepared by the LDA deprotonation method. The reaction mixture was allowed to warm slowly to room temperature. After 2 h saturated, aqueous NH_4Cl was added, the phases were separated, the aqueous phase was extracted with EtOAc, and the combined phase was dried (Na_2SO_4), concentrated, and then purified by silica gel column chromatography (5:95 EtOAc/hexanes) to afford 13 mg (13 %) of **8a** and 54 mg (65 %) of **6a** that exhibited spectral data identical to that of material previously isolated. C. 10:1 Ratio of MeOC(O)CN: BnBr. A THF solution (5 mL) containing methyl cyanoformate (468 mg, 5.5 mmol) and benzyl bromide (94 mg, 0.55 mmol) was added to a THF solution of lithiated cyclohexanecarbonitrile (0.50 mmol) prepared by the LDA deprotonation method. The reaction mixture was allowed to warm slowly to room temperature. After 2 h saturated, aqueous NH_4Cl was added, the phases were separated, the aqueous phase was extracted with EtOAc, and the combined phase was dried (Na_2SO_4), concentrated, and then purified by silica gel column chromatography (5:95 EtOAc/hexanes) to afford 7 mg (7 %) of **8a** and 64 mg (77 %) of **6a** that exhibited spectral data identical to that of material previously isolated.

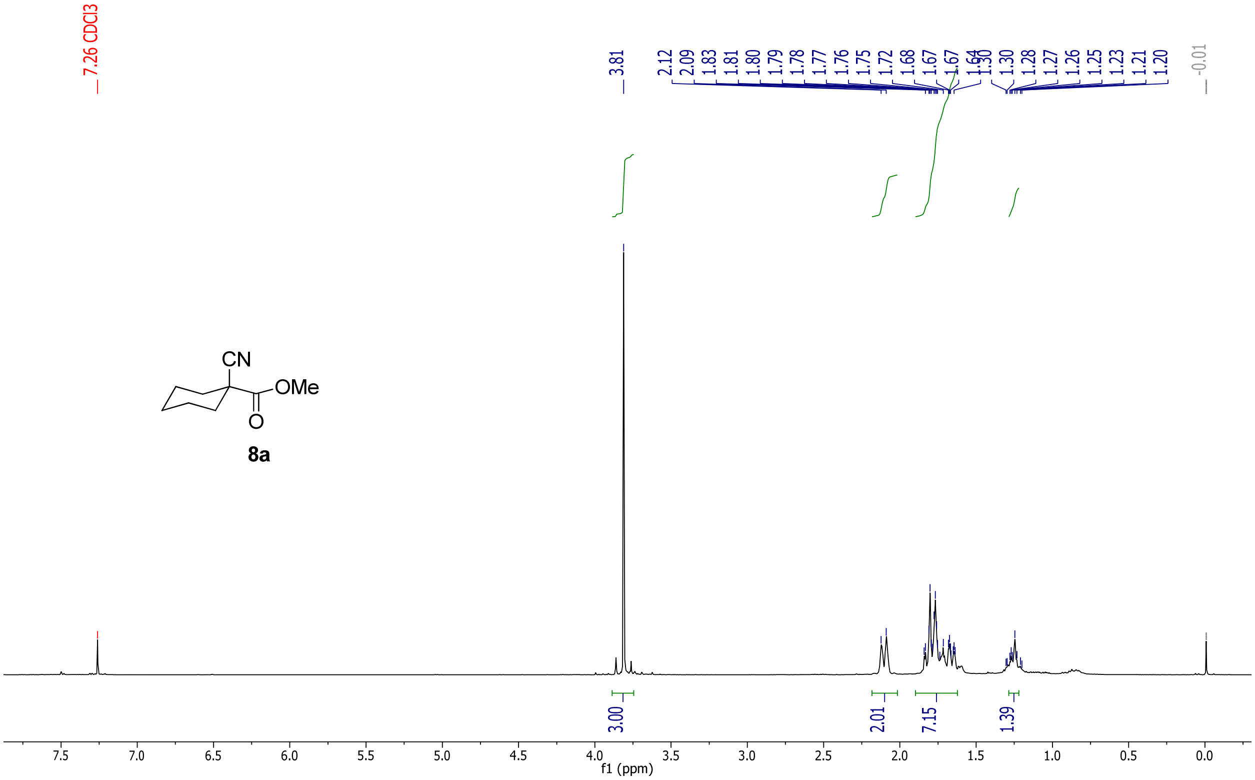
References

1. Fleming, F.; Zhang, Z.; Liu, W; Knochel, P. *J. Org. Chem.* **2005**, *70*, 2200-2205.
2. Nath, D and Fleming, F. *Chem. Eur. J.* **2013**, *19*, 2023 – 2029.
3. Chiba, T; Okimoto, M. *J. Org. Chem.* **1991***, 56,* 6163–6166.
4. Friend, C; Simpkins, N; Anson, M; Polywka, M. *Tetrahedron.* **1998**, 54, 2801-2808.
5. Rojas, G; Baughman, T; Wagener, K.: *Synth. Commum.* **2007**, *37*, 3923–3931.
6. Fleming, F; Liu, W, Ghosh, S; Steward, W. *J. Org. Chem.* **2008**, *73*, 2803-2810.
7. Einhorn, J; Einhorn, C; Luche, J.-L. *Synth. Commum.* **1990**, *20*, 1105–1112.
8. Taylor, E.; Gillespie, P. *J. Org. Chem*. **1992**, *57*, 5757–5761.
9. Kumamoto, H; Deguchi, K; Wagata, T; Furuya, Y; Odanaka, Y; Kitade, Y; Tanaka, H. . *Tetrahedron*. **2009**, *65*, 8007–8013.

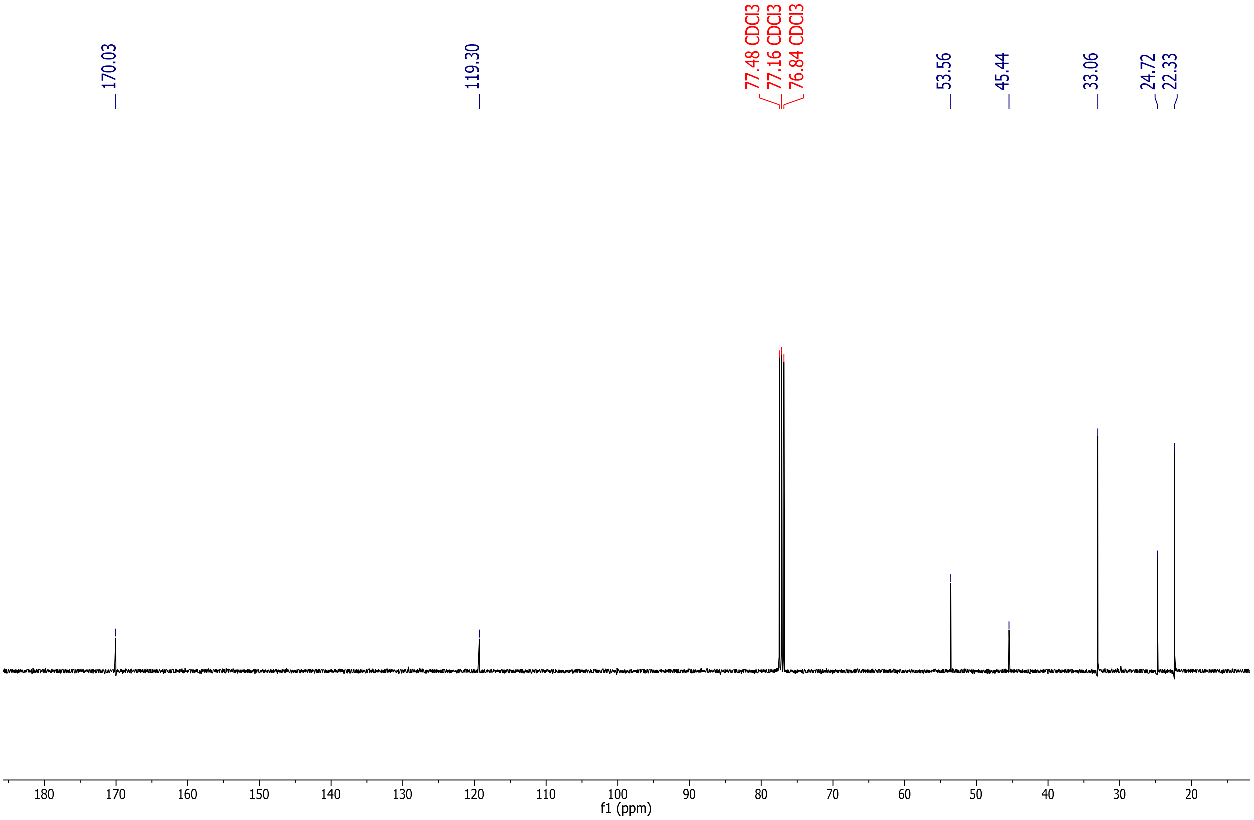

7.34 7.33 7.32 7.31 7.28 7.28 7.27 7.26 7.26 7.25
2.81
1.92 1.89 1.74 1.73 1.72 1.71 1.70 1.70 1.61 1.60 1.58 1.58 1.33 1.32 1.30 1.29 1.27 1.27 1.17
1.92 1.89 1.74 1.73 1.72 1.71 1.70 1.70 1.61 1.60 1.58 1.58 1.55 1.33 1.32 1.30 1.29 1.27 1.27 1.17 1.15
CN
Ph
2.05 3.12 2.24 2.09 1.04
2.0 1.9 1.8 1.7 1.6 1.5 1.4 1.3 1.2 1.1 1.0
f1 (ppm)
5.01 2.00 2.05 3.12 2.24 2.09 1.04
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

6a


135.32 130.44 128.37 127.30 123.35
77.48 77.16 76.84
46.53 40.27 35.67 25.38 23.09
145 140 135 130 125 120 115 110 105 100 95 90 85 80 75 70 65 60 55 50 45 40 35 30 25 20 15 10 5
f1 (ppm)

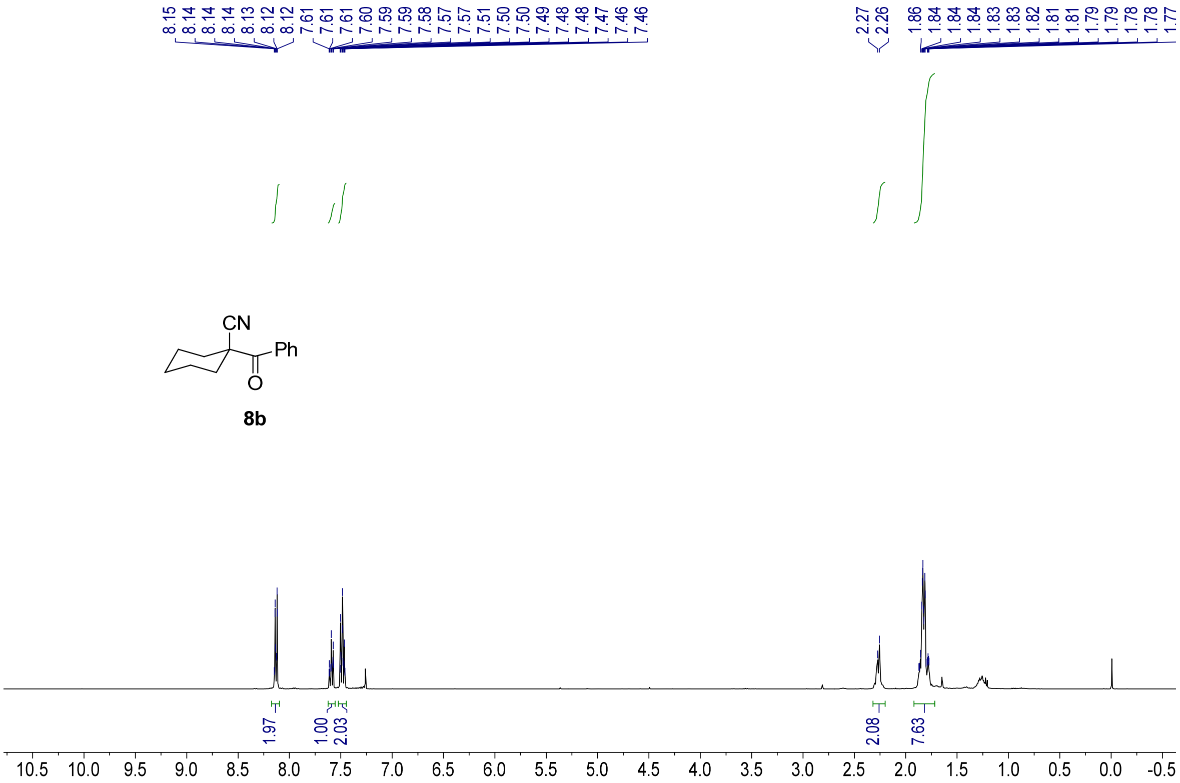

7.26 CDCl3
3.81
2.12
2.09
1.83
1.81
1.80
1.79
1.78
1.77
1.76
1.75
1.72
1.68
1.67
1.67
1.64
1.30
1.30
1.28
1.27
1.26
1.25
1.23
1.21
1.20
-0.01
CN
OMe
O
3.00
2.01
7.15
1.39
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

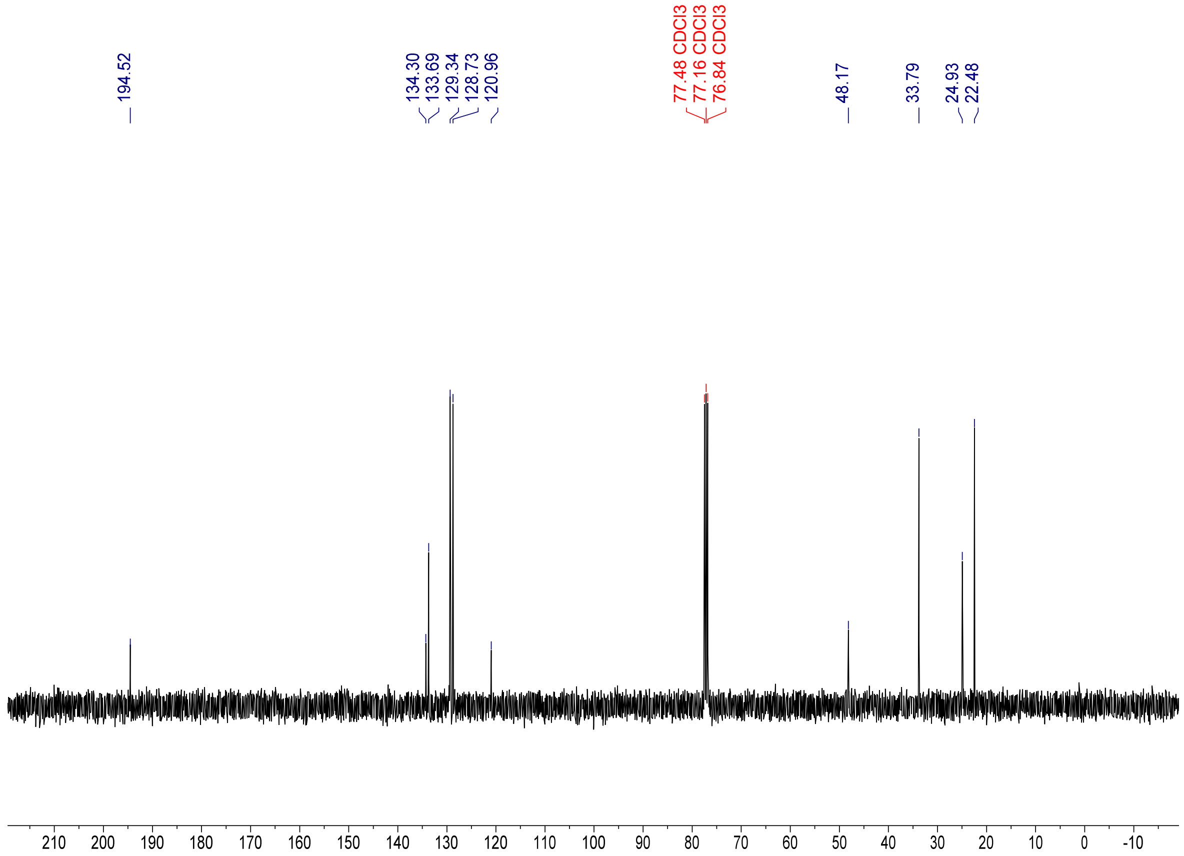
8a

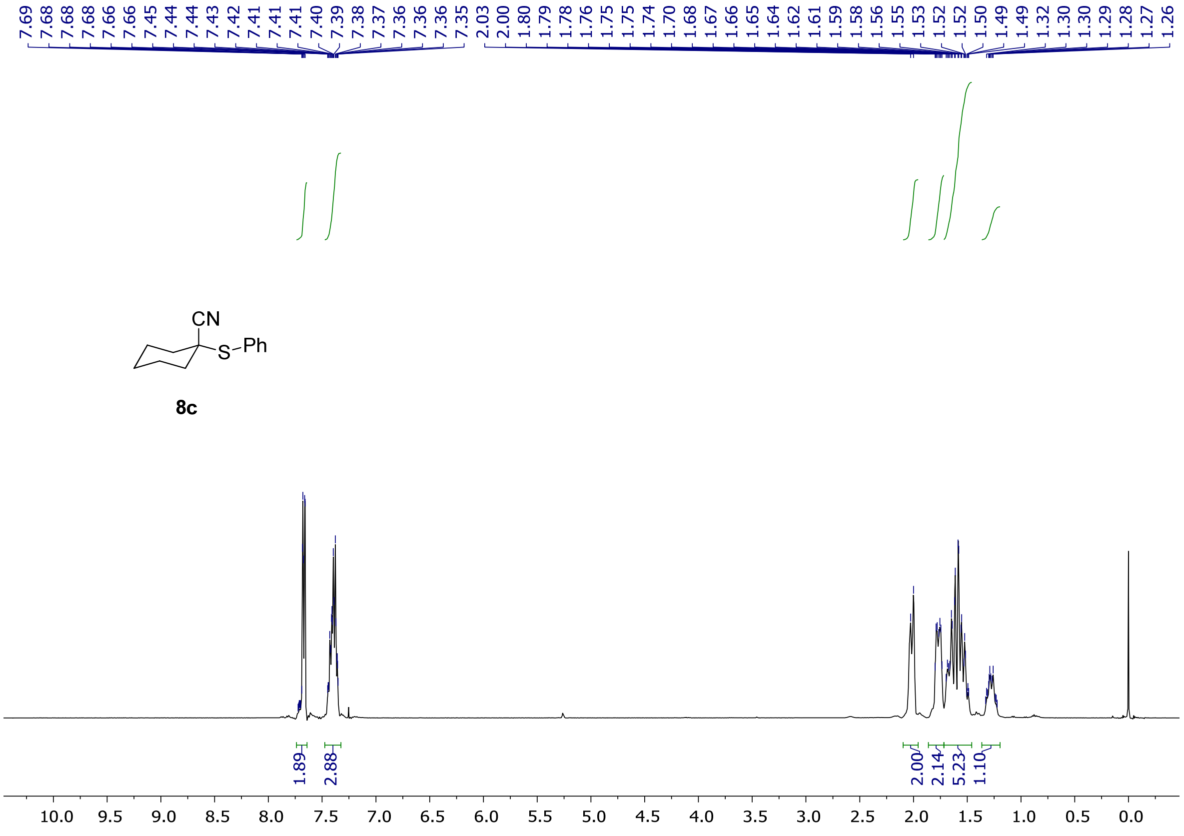

170.03
119.30
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
53.56
45.44
33.06
24.72
22.33
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
f1 (ppm)

CN
Ph
O

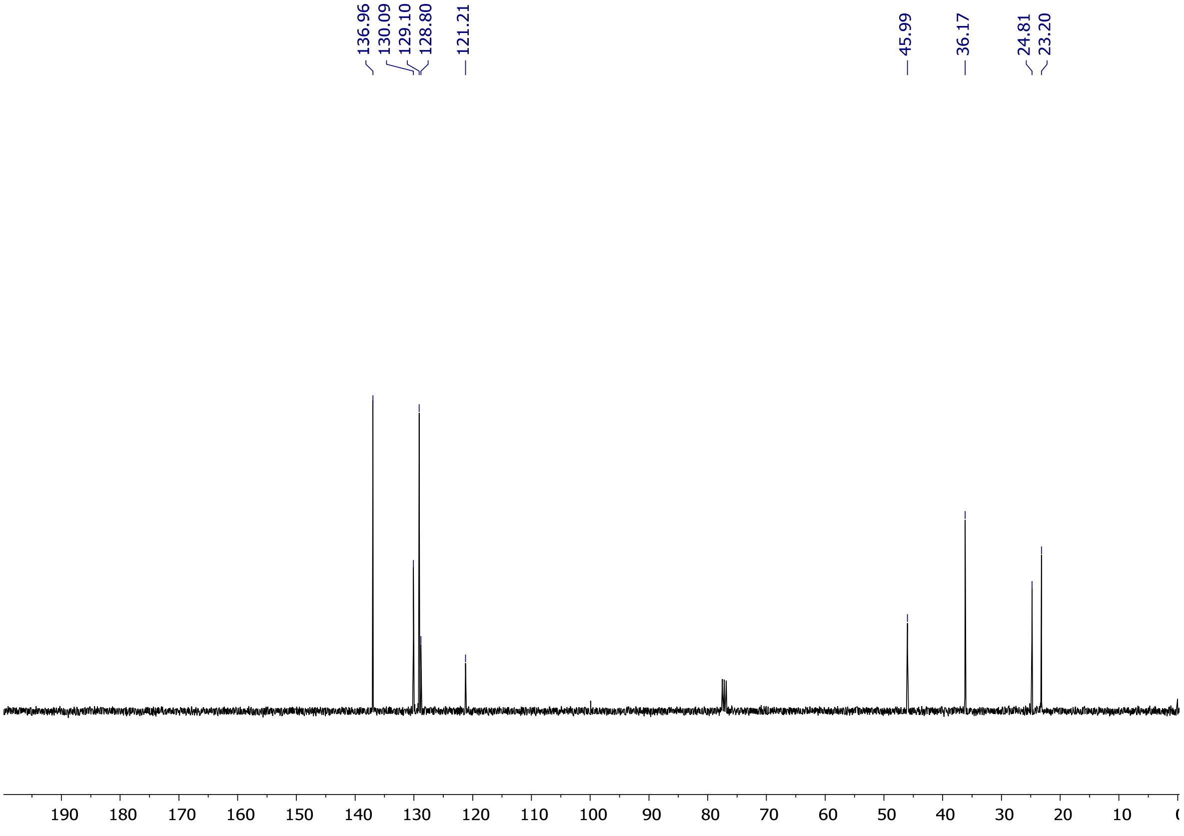
8b

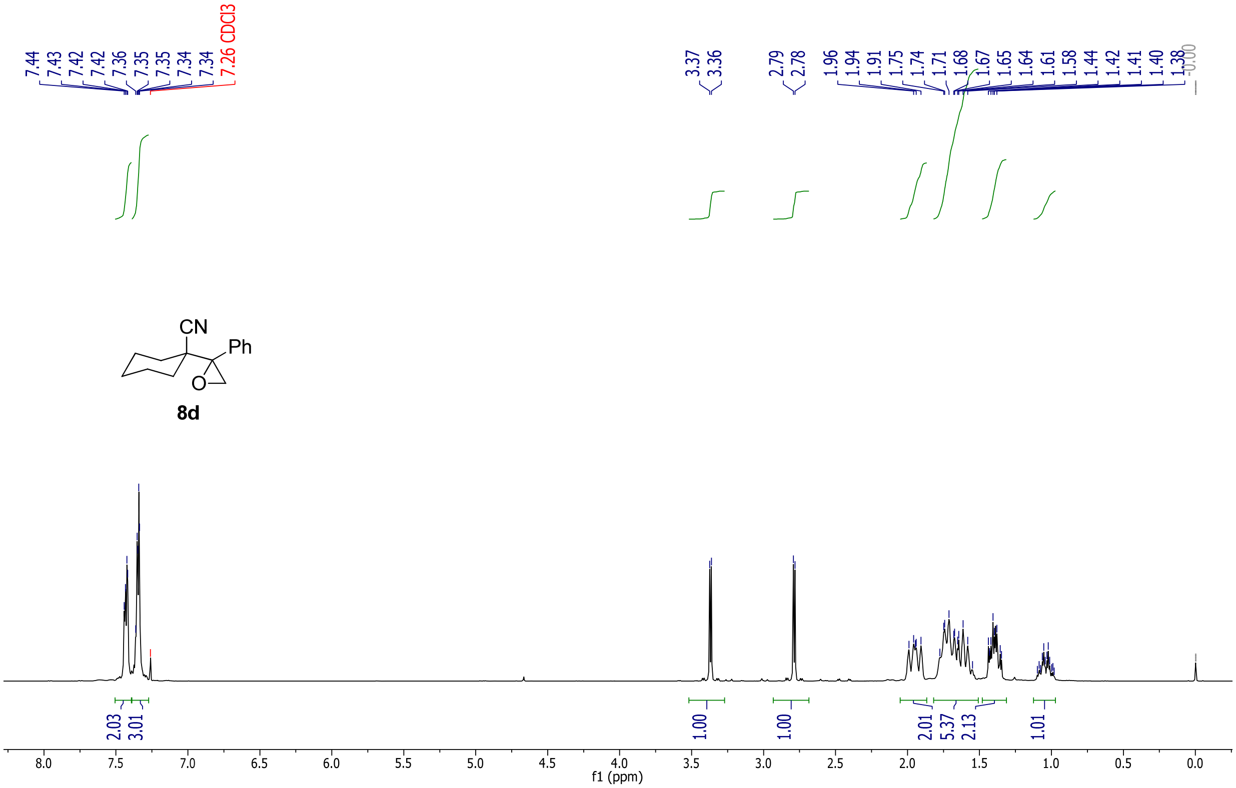

8.15
8.14
8.14
8.14
8.13
8.12
8.12
7.61
7.61
7.61
7.60
7.59
7.58
7.57
7.57
7.51
7.50
7.50
7.49
7.48
7.48
7.47
7.46
7.46
2.27
2.26
1.86
1.84
1.84
1.84
1.83
1.83
1.82
1.81
1.81
1.79
1.79
1.78
1.78
1.77
1.97
1.00
2.03
2.08
7.63
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5

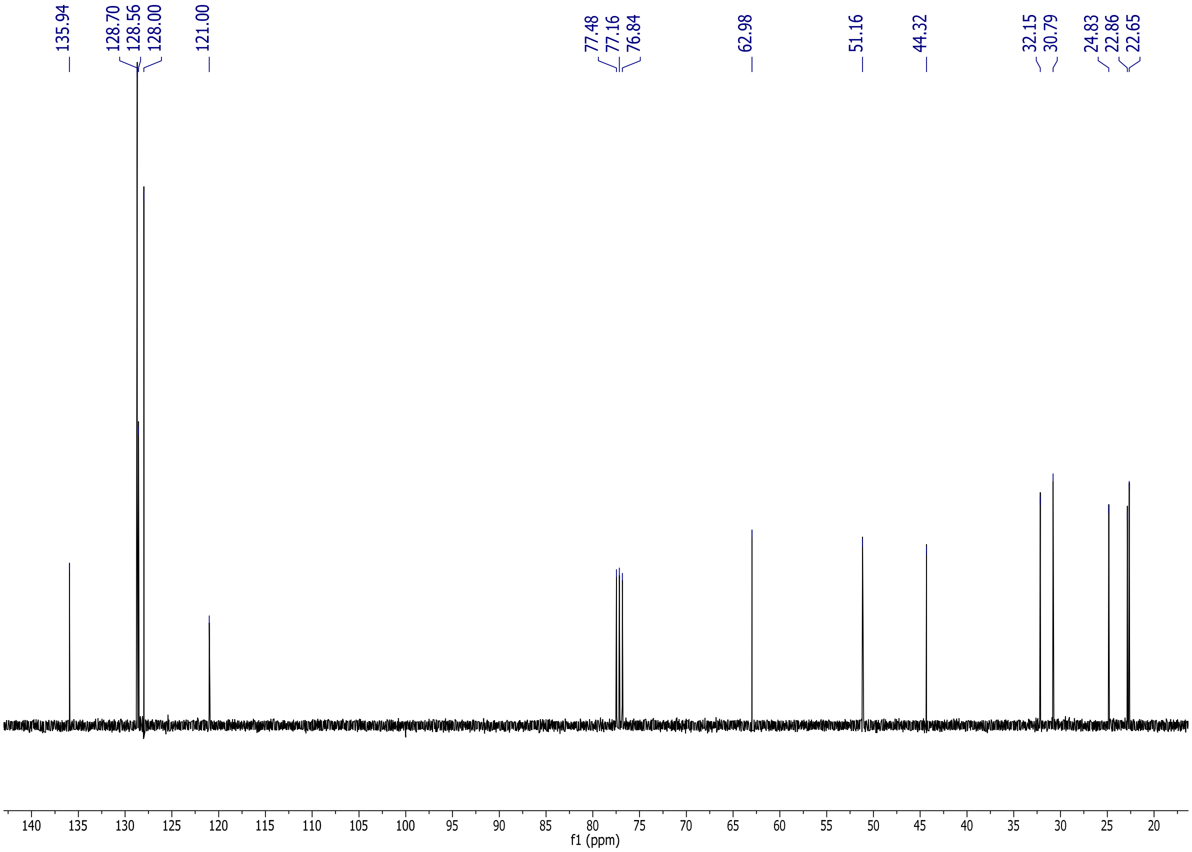

194.52
134.30
133.69
129.34
128.73
120.96
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
48.17
33.79
24.93
22.48
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

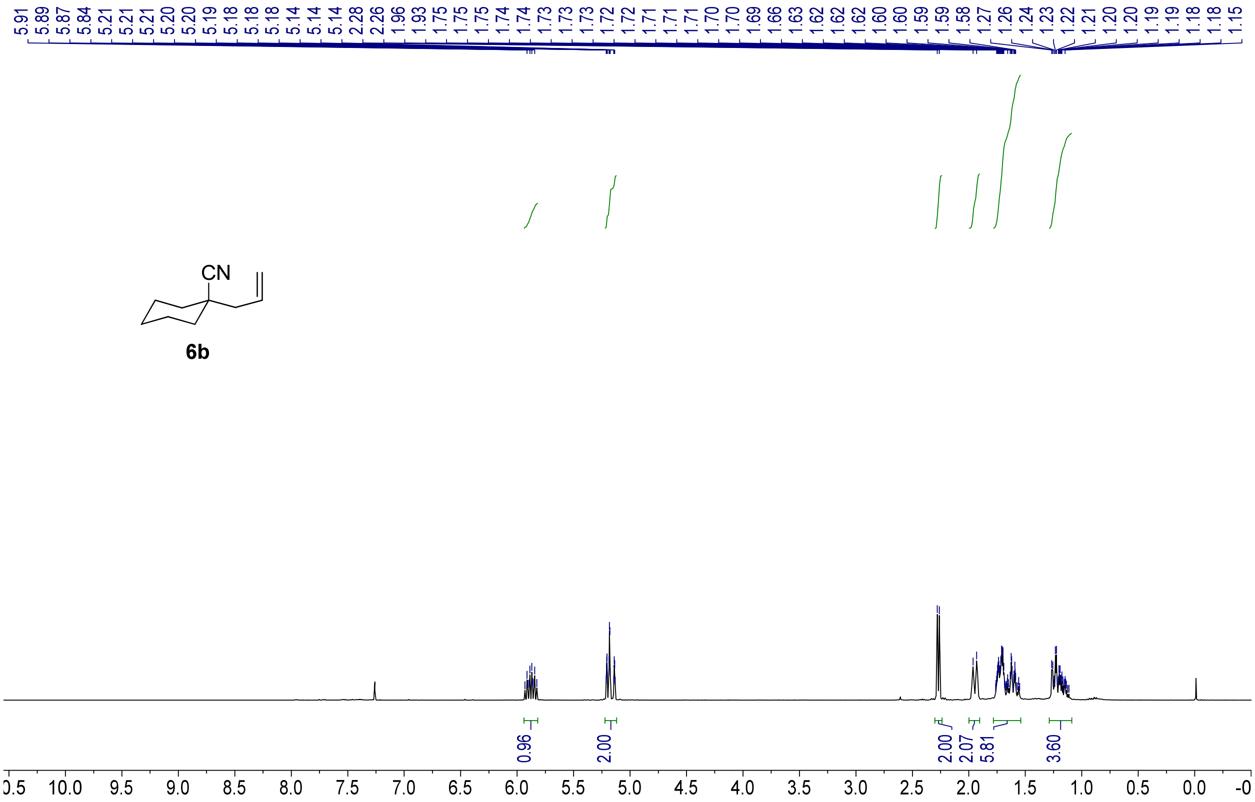

7.69
7.68
7.68
7.66
7.66
7.45
7.44
7.44
7.43
7.42
7.41
7.41
7.40
7.39
7.38
7.37
7.36
7.36
7.35
2.03
2.00
1.80
1.79
1.78
1.76
1.75
1.75
1.74
1.70
1.68
1.67
1.66
1.65
1.64
1.62
1.61
1.59
1.58
1.56
1.55
1.53
1.52
1.52
1.50
1.49
1.32
1.30
1.30
1.29
1.28
1.27
1.26
CN
S
Ph
1.89
2.88
2.00
2.14
5.23
1.10
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

8c

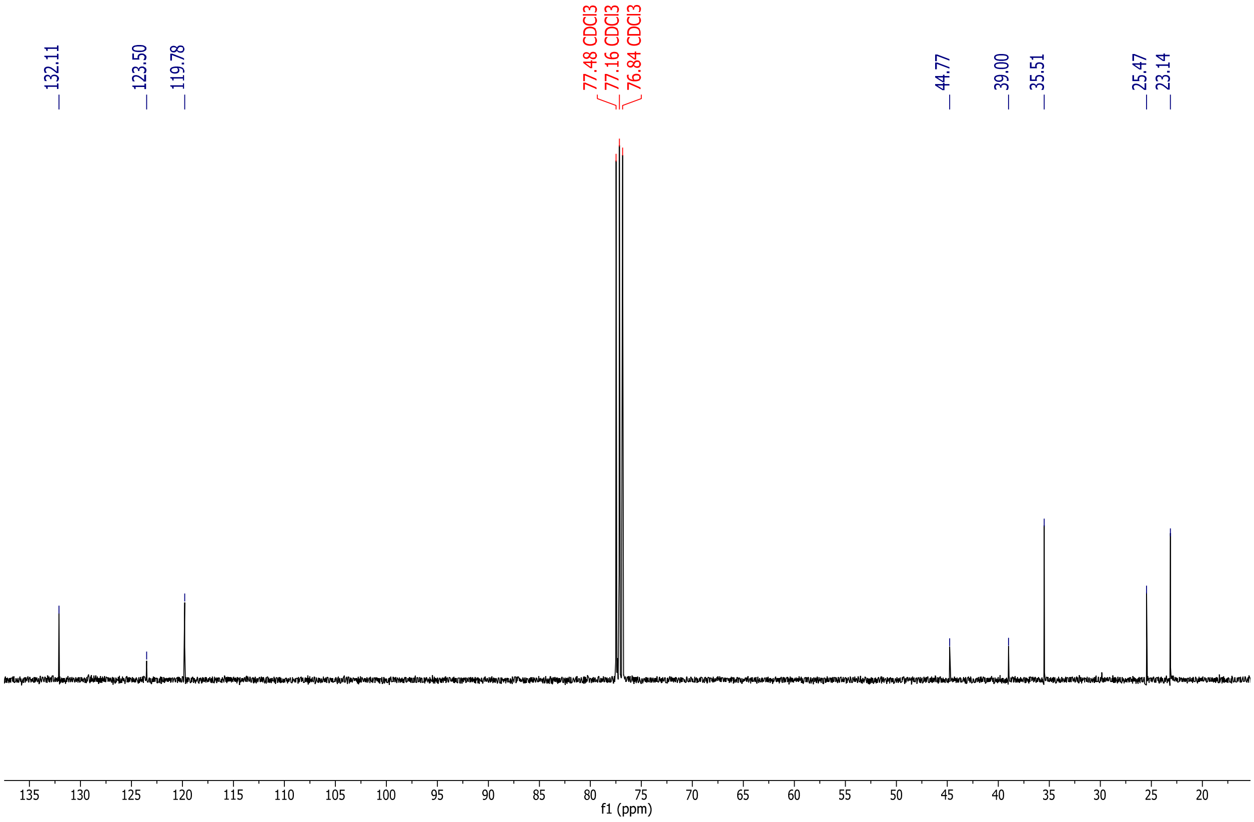

136.96
130.09
129.10
128.80
121.21
45.99
36.17
24.81
23.20
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10

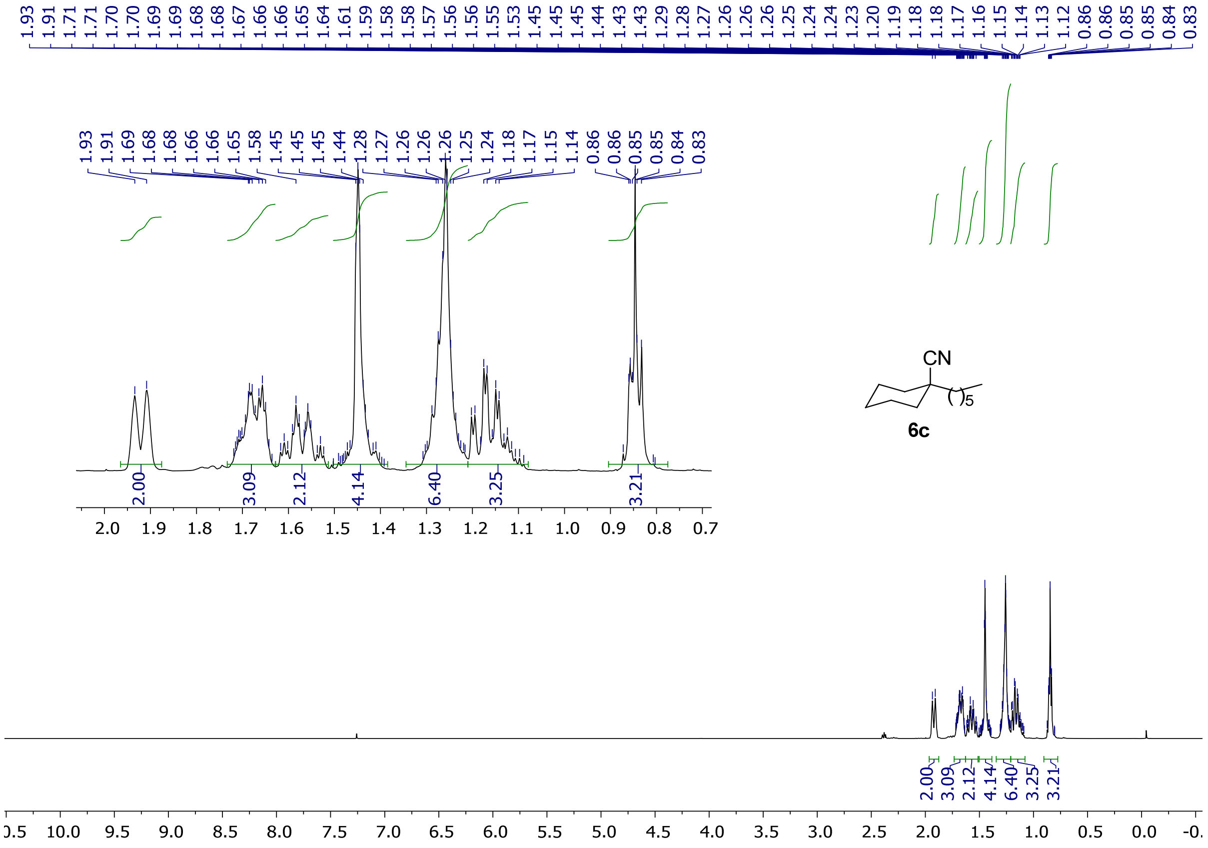

7.44
7.43
7.42
7.42
7.36
7.35
7.35
7.34
7.34
7.26 CDCl3
3.37
3.36
2.79
2.78
1.96
1.94
1.91
1.75
1.74
1.71
1.68
1.67
1.65
1.64
1.61
1.58
1.44
1.42
1.41
1.40
1.38
0.00
CN
Ph
O
8d
2.03
3.01
1.00
1.00
2.01
5.37
2.13
1.01
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


135.94
128.70
128.56
128.00
121.00
77.48
77.16
76.84
62.98
51.16
44.32
32.15
30.79
24.83
22.86
22.65
140
135
130
125
120
115
110
105
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
f1 (ppm)

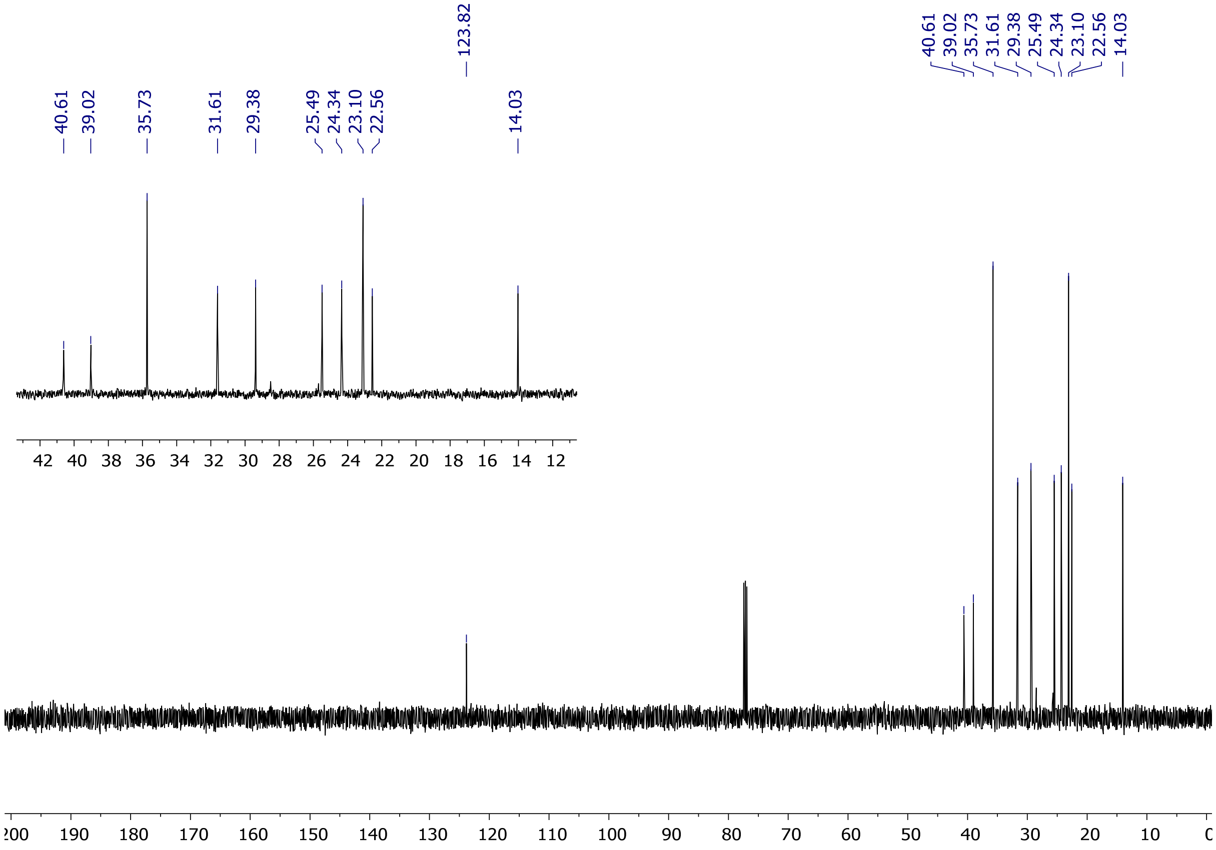

5.91
5.89
5.87
5.84
5.21
5.21
5.21
5.20
5.20
5.19
5.18
5.18
5.18
5.14
5.14
5.14
2.28
2.26
1.96
1.93
1.75
1.75
1.75
1.74
1.74
1.73
1.73
1.73
1.72
1.72
1.71
1.71
1.71
1.70
1.70
1.69
1.66
1.63
1.62
1.62
1.62
1.60
1.60
1.59
1.59
1.58
1.27
1.26
1.24
1.23
1.22
1.21
1.20
1.20
1.19
1.19
1.18
1.15
CN
0.96
2.00
2.00
2.07
5.81
3.60
0.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0

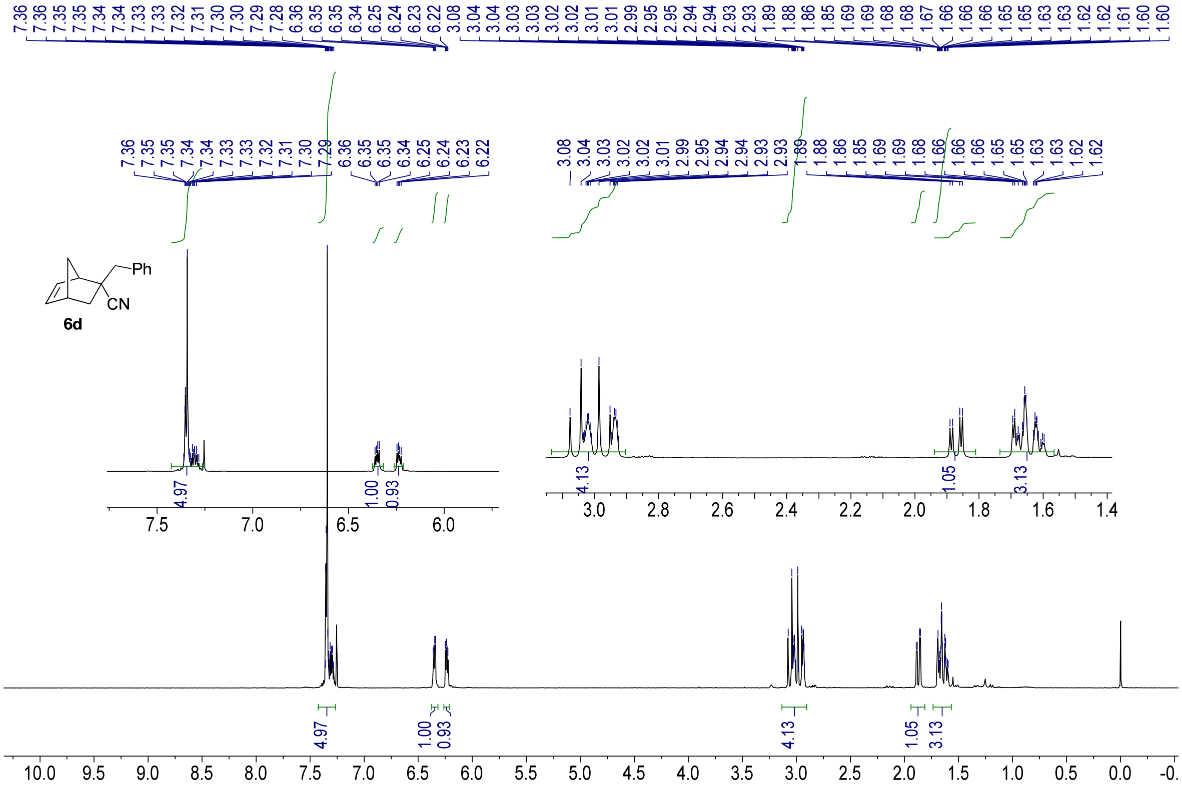
6b

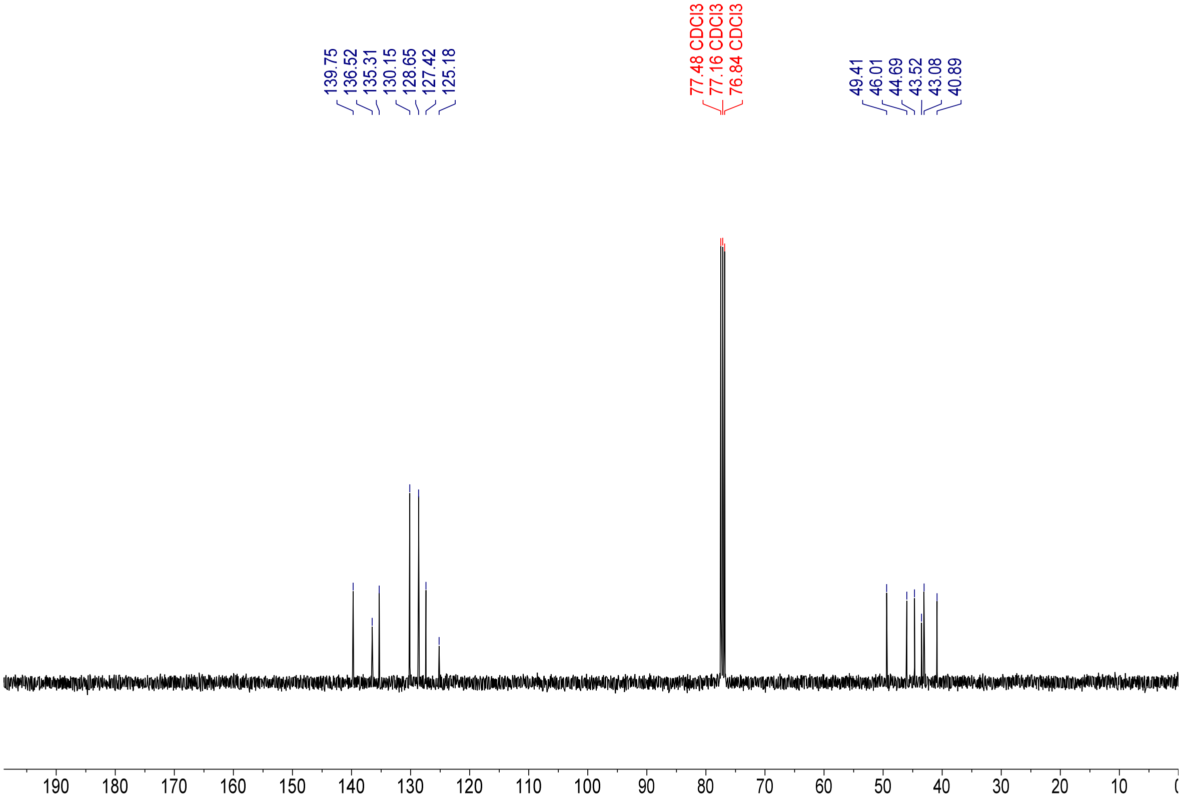

132.11
123.50
119.78
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
44.77
39.00
35.51
25.47
23.14
135
130
125
120
115
110
105
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
f1 (ppm)

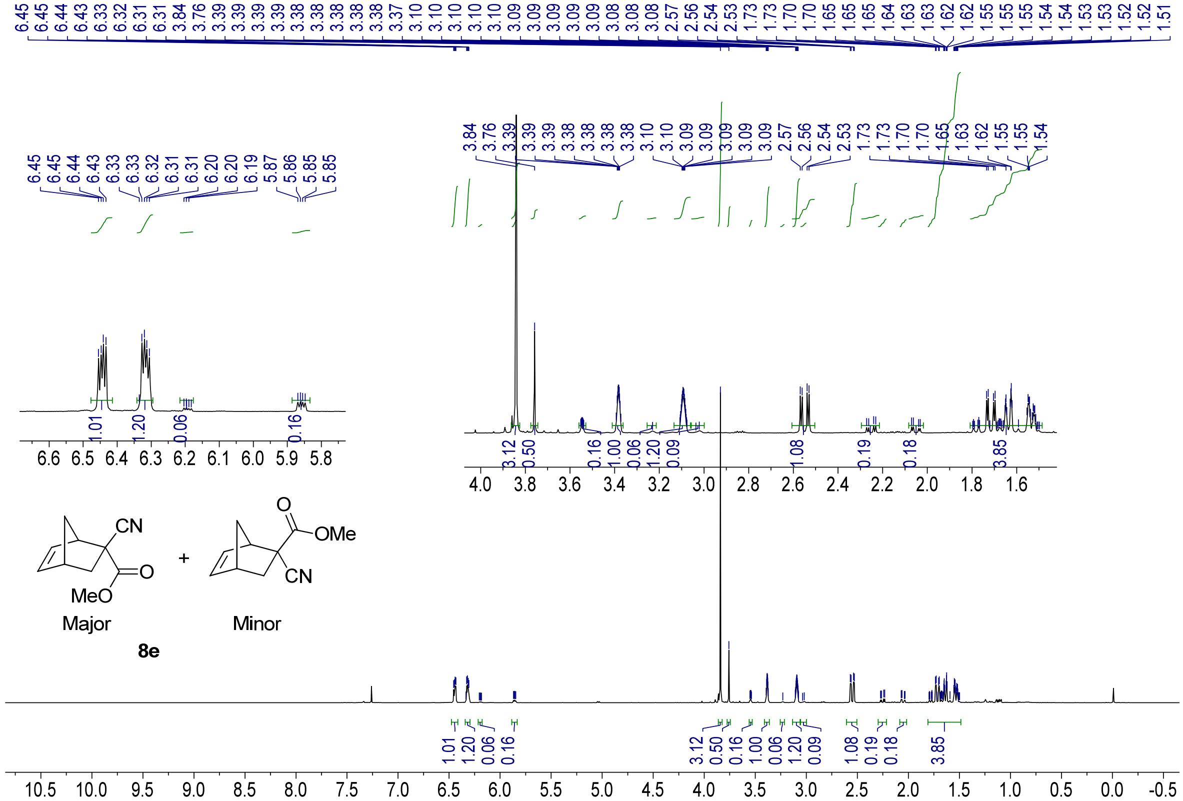

1.93 1.91 1.71 1.71 1.70 1.69 1.69 1.68 1.68 1.67 1.66 1.66 1.65 1.64 1.61 1.59 1.58 1.58 1.57 1.56 1.56 1.55 1.53 1.45 1.45 1.45 1.44 1.43 1.43 1.29 1.28 1.27 1.26 1.26 1.26 1.25 1.24 1.24 1.23 1.20 1.19 1.18 1.18 1.17 1.16 1.15 1.14 1.13 1.12 0.86 0.86 0.85 0.85 0.84 0.83
1.93 1.91 1.69 1.68 1.68 1.66 1.66 1.65 1.58 1.45 1.45 1.45 1.44 1.28 1.27 1.26 1.26 1.26 1.25 1.24 1.18 1.17 1.15 1.14 0.86 0.86 0.85 0.85 0.84 0.83
2.00
3.09
2.12
4.14
6.40
3.25
3.21
2.0 1.9 1.8 1.7 1.6 1.5 1.4 1.3 1.2 1.1 1.0 0.9 0.8 0.7
CN
5
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5

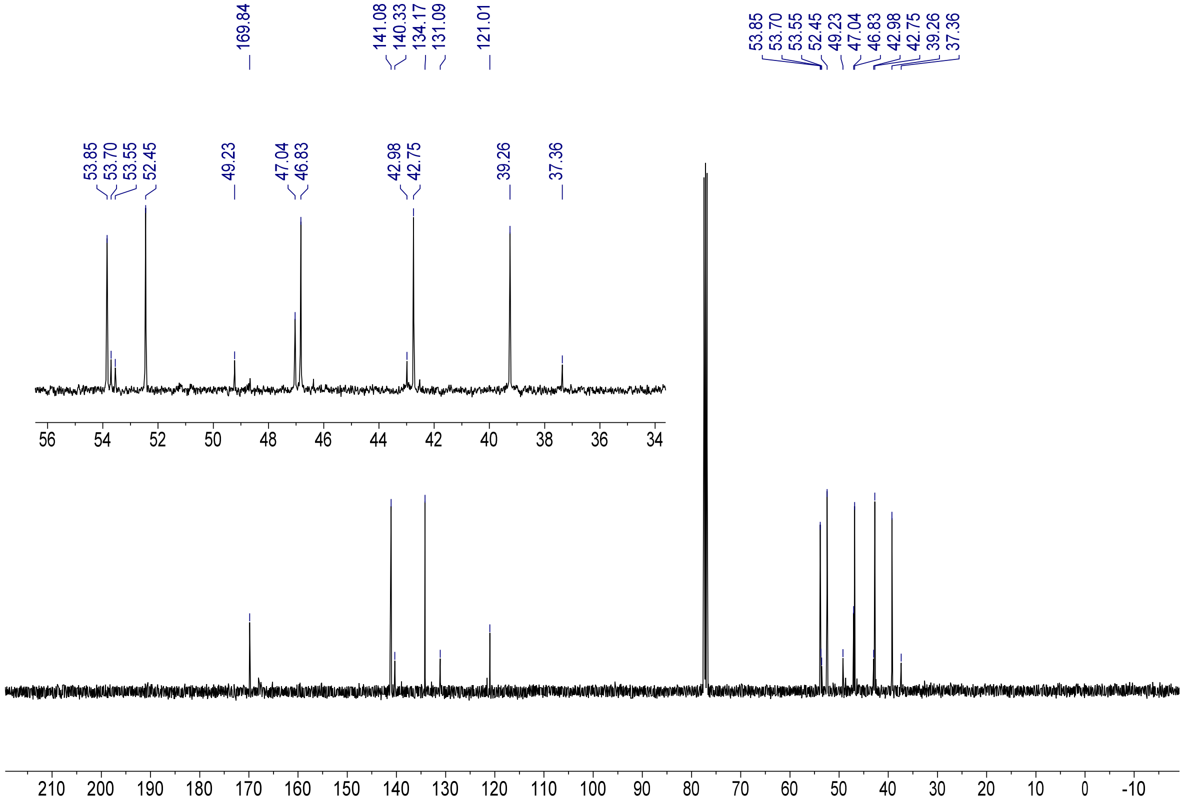
6c

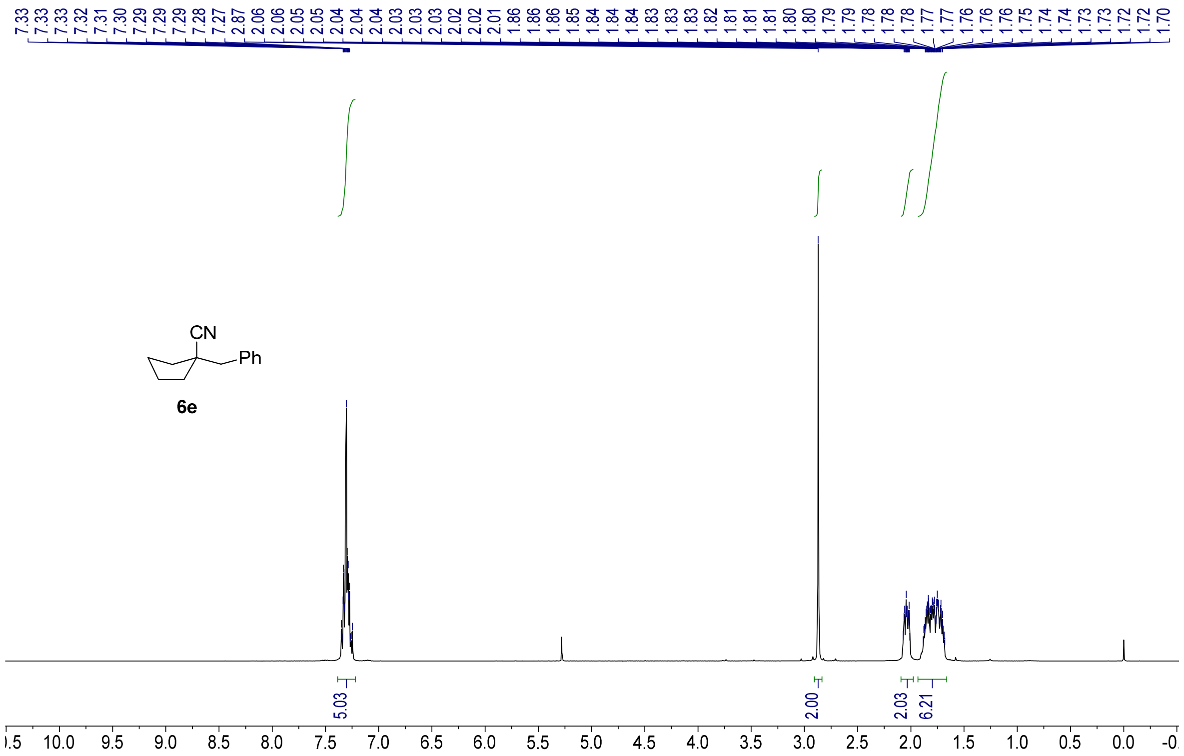

123.82
40.61 39.02 35.73 31.61 29.38 25.49 24.34 23.10 22.56 14.03
40.61 39.02 35.73 31.61 29.38 25.49 24.34 23.10 22.56 14.03
42 40 38 36 34 32 30 28 26 24 22 20 18 16 14 12
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

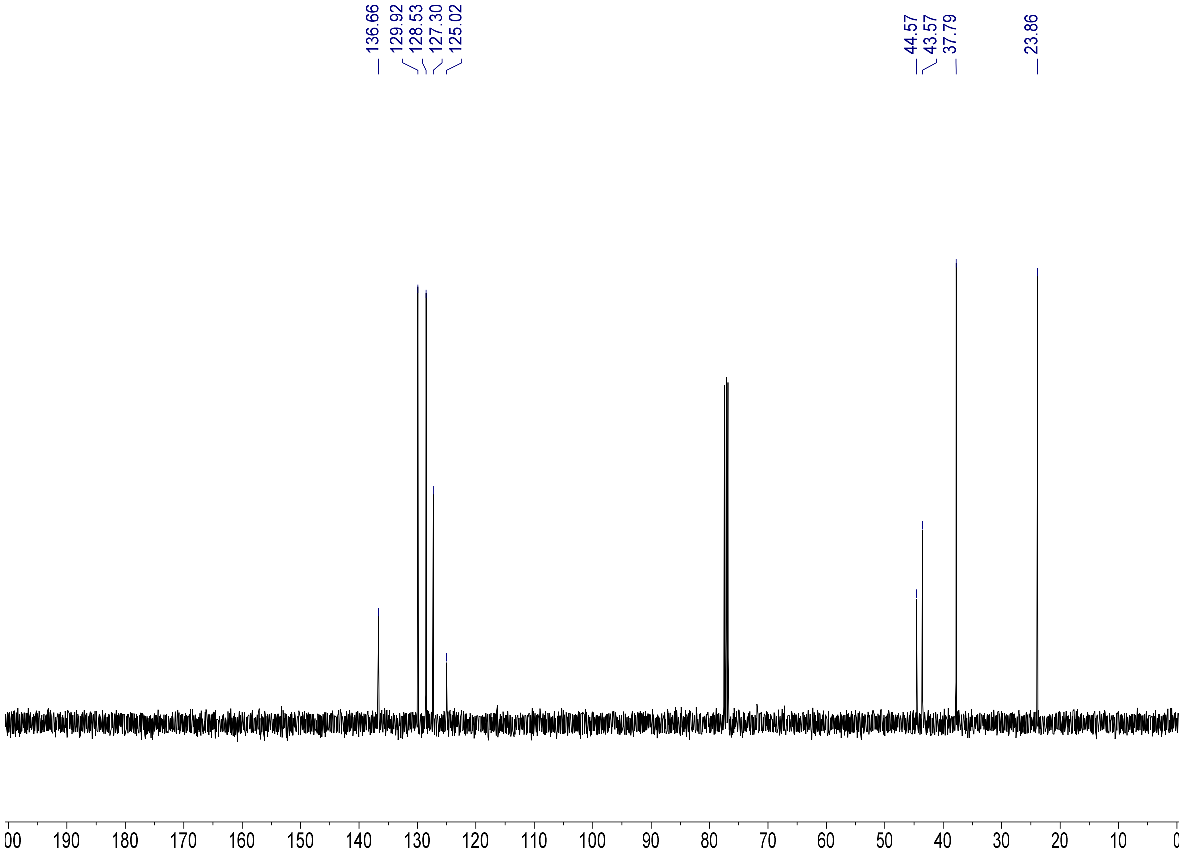

7.36 7.36 7.35 7.35 7.34 7.34 7.34 7.33 7.33 7.32 7.31 7.30 7.30 7.29 7.28 6.36 6.35 6.35 6.34 6.25 6.24 6.23 6.22 3.08 3.04 3.04 3.03 3.03 3.02 3.02 3.01 3.01 2.99 2.95 2.95 2.94 2.94 2.93 2.93 1.89 1.88 1.86 1.85 1.69 1.69 1.68 1.68 1.67 1.66 1.66 1.66 1.65 1.65 1.63 1.63 1.62 1.62 1.61 1.60 1.60
7.36 7.35 7.35 7.34 7.34 7.33 7.33 7.32 7.31 7.30 7.29 6.36 6.35 6.35 6.34 6.25 6.24 6.23 6.22
3.08 3.04 3.03 3.02 3.02 3.01 2.99 2.95 2.94 2.94 2.93 2.93 1.89 1.88 1.86 1.85 1.69 1.69 1.68 1.66 1.66 1.65 1.65 1.63 1.63 1.62 1.62
Ph
CN
6d
4.97
1.00
0.93
7.5 7.0 6.5 6.0
4.13
1.05
3.13
3.0 2.8 2.6 2.4 2.2 2.0 1.8 1.6 1.4
4.97 1.00 0.93 4.13 1.05 3.13
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.

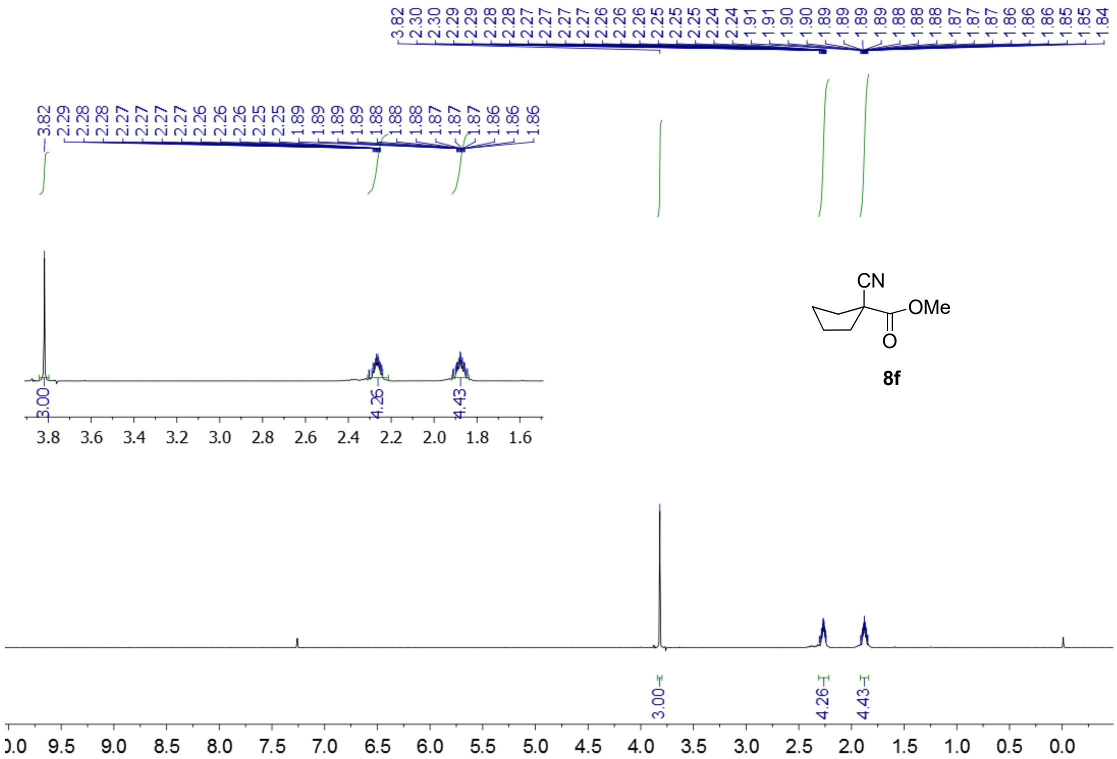

139.75
136.52
135.31
130.15
128.65
127.42
125.18
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
49.41
46.01
44.69
43.52
43.08
40.89
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0


6.45 6.45 6.44 6.33 6.32 6.31 6.31 3.84 3.76 3.39 3.39 3.39 3.39 3.38 3.38 3.38 3.38 3.38 3.37 3.10 3.10 3.10 3.10 3.10 3.09 3.09 3.09 3.09 3.09 3.08 3.08 3.08 2.57 2.56 2.54 2.53 1.73 1.73 1.70 1.70 1.65 1.65 1.65 1.64 1.63 1.63 1.62 1.55 1.55 1.55 1.54 1.54 1.53 1.53 1.52 1.52 1.51
6.45 6.45 6.44 6.43 6.33 6.33 6.32 6.31 6.31 6.20 6.20 6.19 5.87 5.86 5.85 5.85
1.01 1.20 0.06 0.16
6.6 6.5 6.4 6.3 6.2 6.1 6.0 5.9 5.8
3.84 3.76 3.39 3.39 3.39 3.38 3.38 3.38 3.38 3.10 3.10 3.09 3.09 3.09 3.09 3.09 2.57 2.56 2.54 2.53 1.73 1.73 1.70 1.70 1.65 1.63 1.62 1.55 1.55 1.54
3.12 0.50 0.16 1.00 0.06 1.20 0.09 1.08 0.19 0.18 3.85
4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0 1.8 1.6
CN
MeO
O
Major
+
O
OMe
CN
Minor
8e
1.01 1.20 0.06 0.16 3.12 0.50 0.16 1.00 0.06 1.20 0.09 1.08 0.19 0.18 3.85
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5

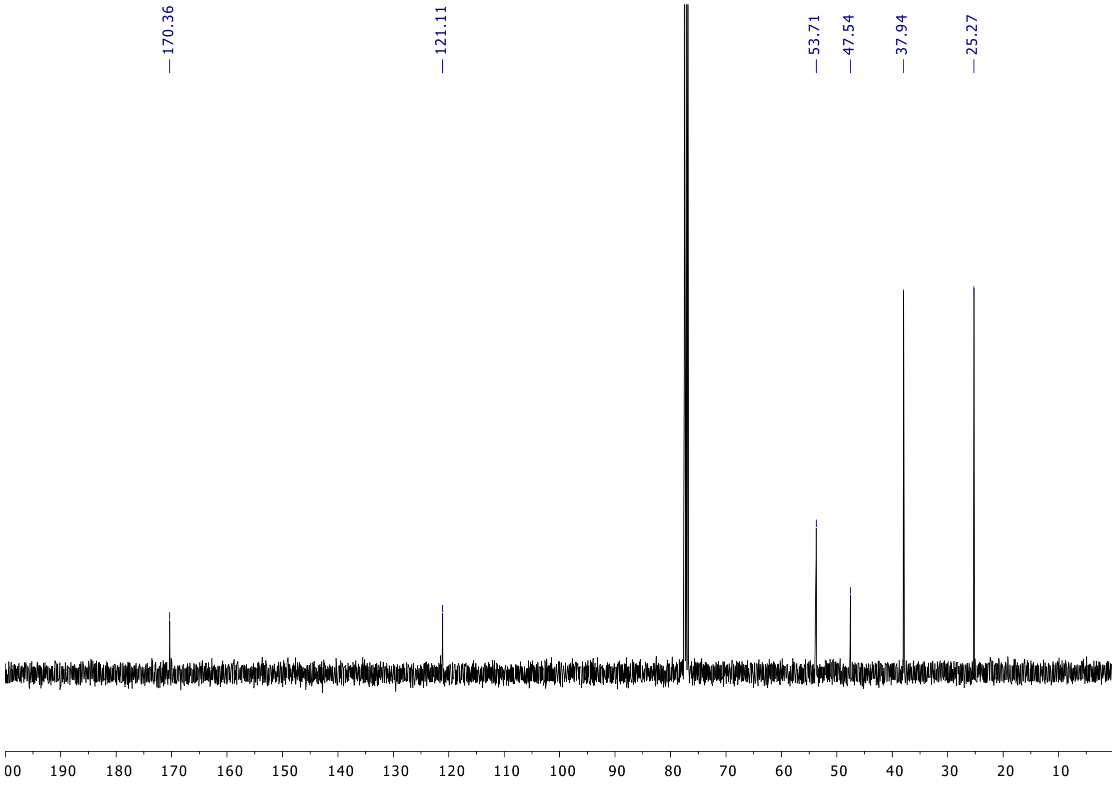

169.84
141.08 140.33 134.17 131.09
121.01
53.85 53.70 53.55 52.45 49.23 47.04 46.83 42.98 42.75 39.26 37.36
53.85 53.70 53.55 52.45
49.23
47.04 46.83
42.98 42.75
39.26
37.36
56 54 52 50 48 46 44 42 40 38 36 34
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10

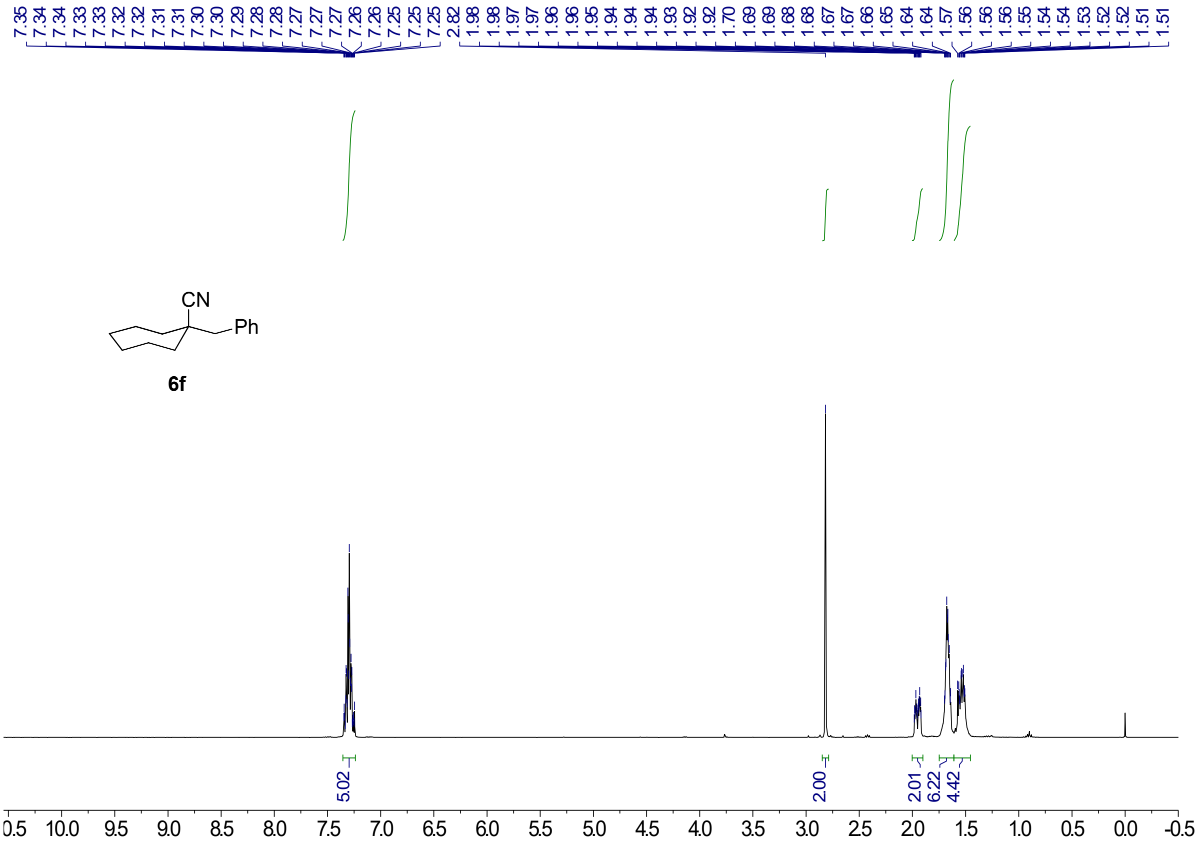

7.33
7.33
7.33
7.32
7.31
7.30
7.29
7.29
7.29
7.28
7.27
2.87
2.06
2.06
2.05
2.05
2.04
2.04
2.04
2.03
2.03
2.03
2.02
2.02
2.01
1.86
1.86
1.86
1.85
1.84
1.84
1.84
1.83
1.83
1.83
1.82
1.81
1.81
1.81
1.80
1.80
1.79
1.79
1.78
1.78
1.78
1.77
1.77
1.76
1.76
1.75
1.74
1.74
1.73
1.72
1.72
1.70
CN
Ph
6e
5.03
2.00
2.03
6.21
.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.


136.66
129.92
128.53
127.30
125.02
44.57
43.57
37.79
23.86
00
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

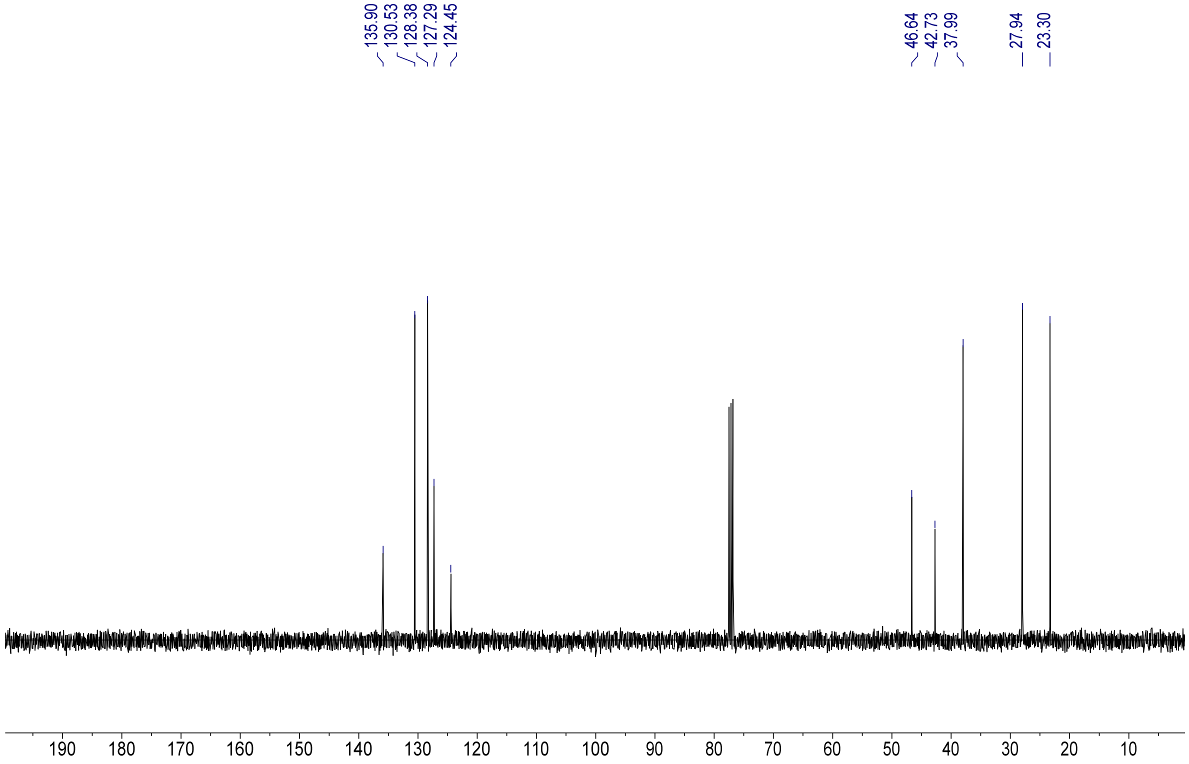

3.82
2.30
2.30
2.29
2.29
2.28
2.28
2.27
2.27
2.27
2.27
2.26
2.26
2.26
2.25
2.25
2.25
2.24
2.24
1.91
1.91
1.90
1.90
1.89
1.89
1.89
1.89
1.88
1.88
1.88
1.87
1.87
1.87
1.86
1.86
1.86
1.85
1.85
1.84
3.82
2.29
2.28
2.28
2.27
2.27
2.27
2.27
2.26
2.26
2.26
2.25
2.25
1.89
1.89
1.89
1.89
1.88
1.88
1.88
1.87
1.87
1.87
1.86
1.86
1.86
3.00
4.26
4.43
3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0 1.8 1.6
CN
OMe
O
3.00
4.26
4.43
.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0

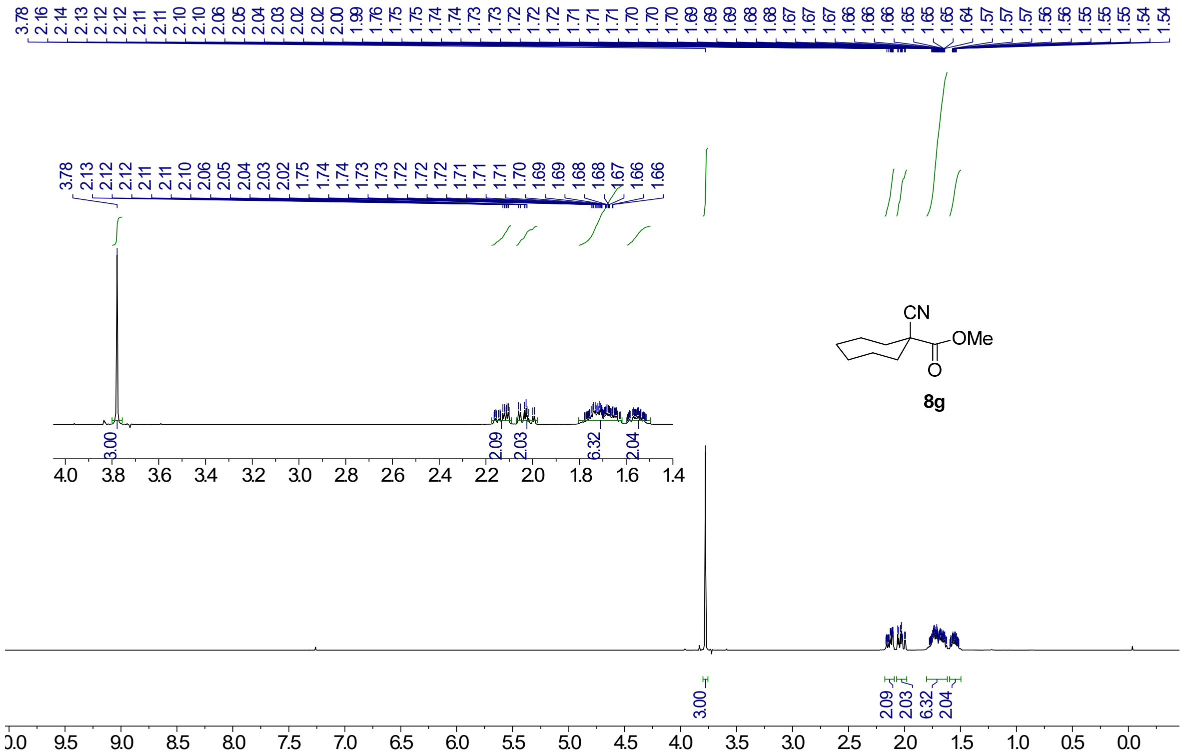
8f


170.36
121.11
53.71
47.54
37.94
25.27
00 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10

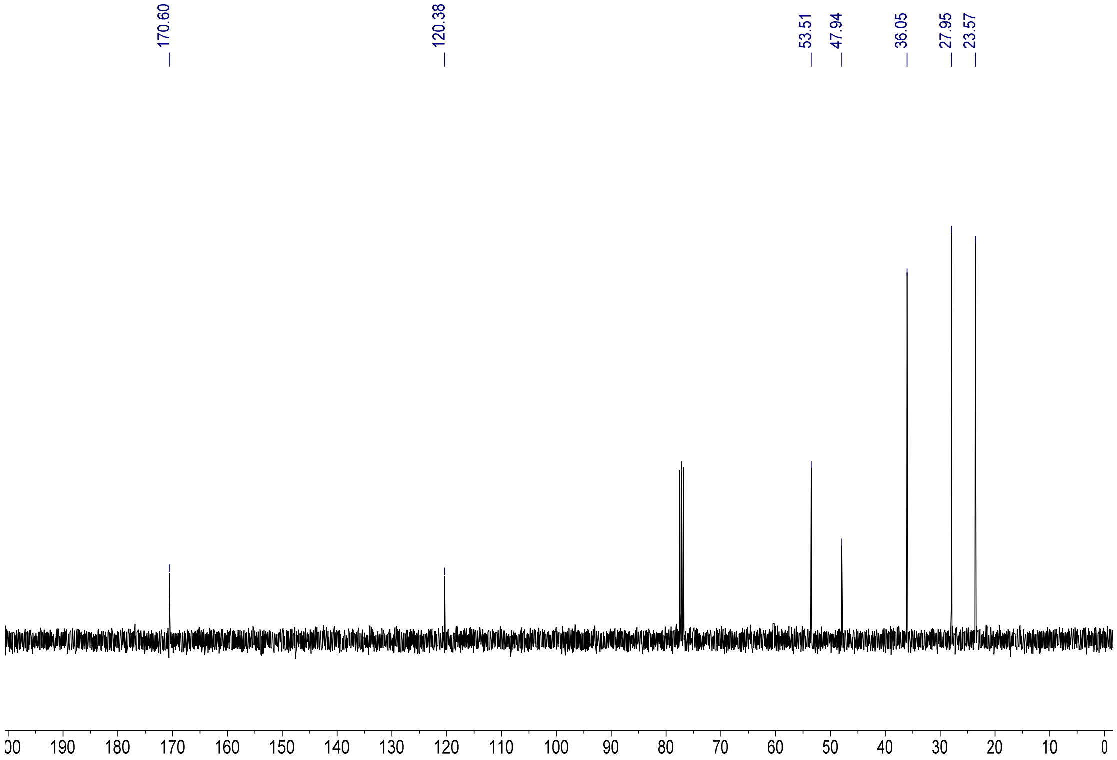

7.35 7.34 7.34 7.33 7.33 7.32 7.32 7.31 7.31 7.30 7.30 7.29 7.28 7.28 7.27 7.27 7.27 7.26 7.26 7.25 7.25 7.25
2.82
1.98 1.98 1.97 1.97 1.96 1.96 1.95 1.94 1.94 1.94 1.93 1.92 1.92 1.92 1.70 1.69 1.69 1.68 1.68 1.67 1.67 1.66 1.65 1.64 1.64 1.57 1.56 1.56 1.56 1.55 1.54 1.54 1.53 1.52 1.52 1.51 1.51
CN
Ph
5.02
2.00
2.01
6.22
4.42
0.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5

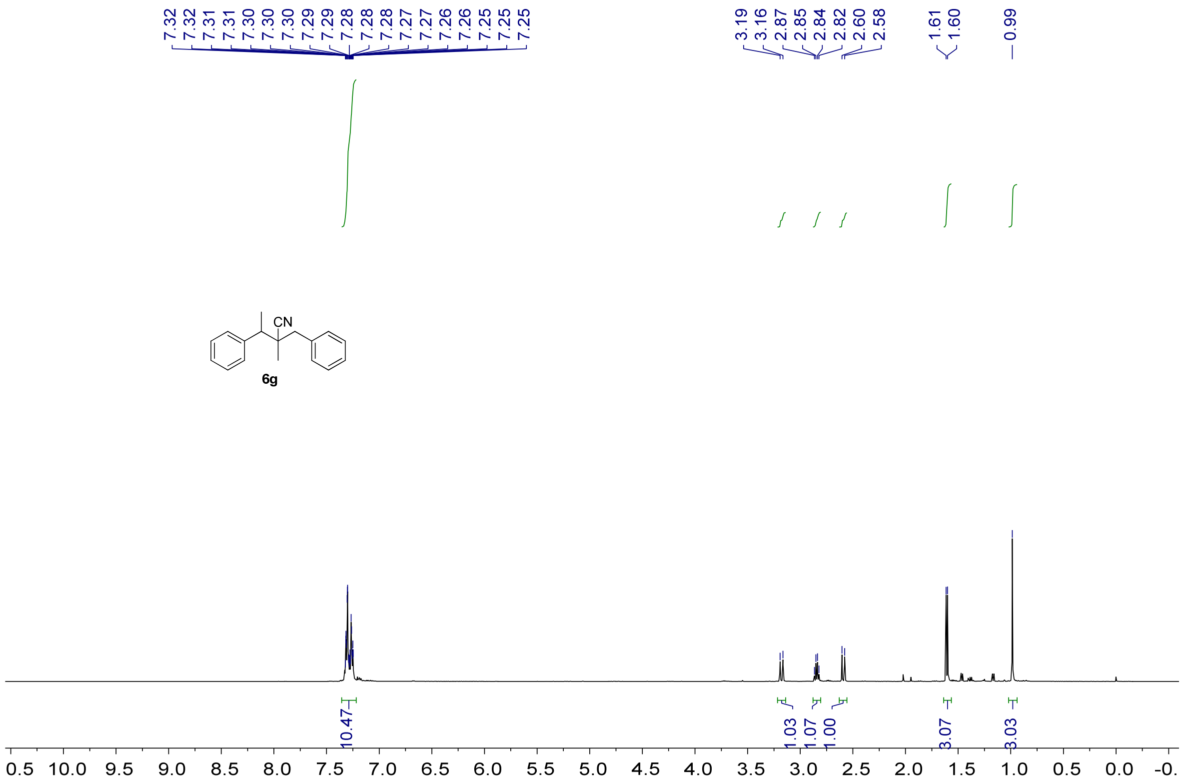
6f

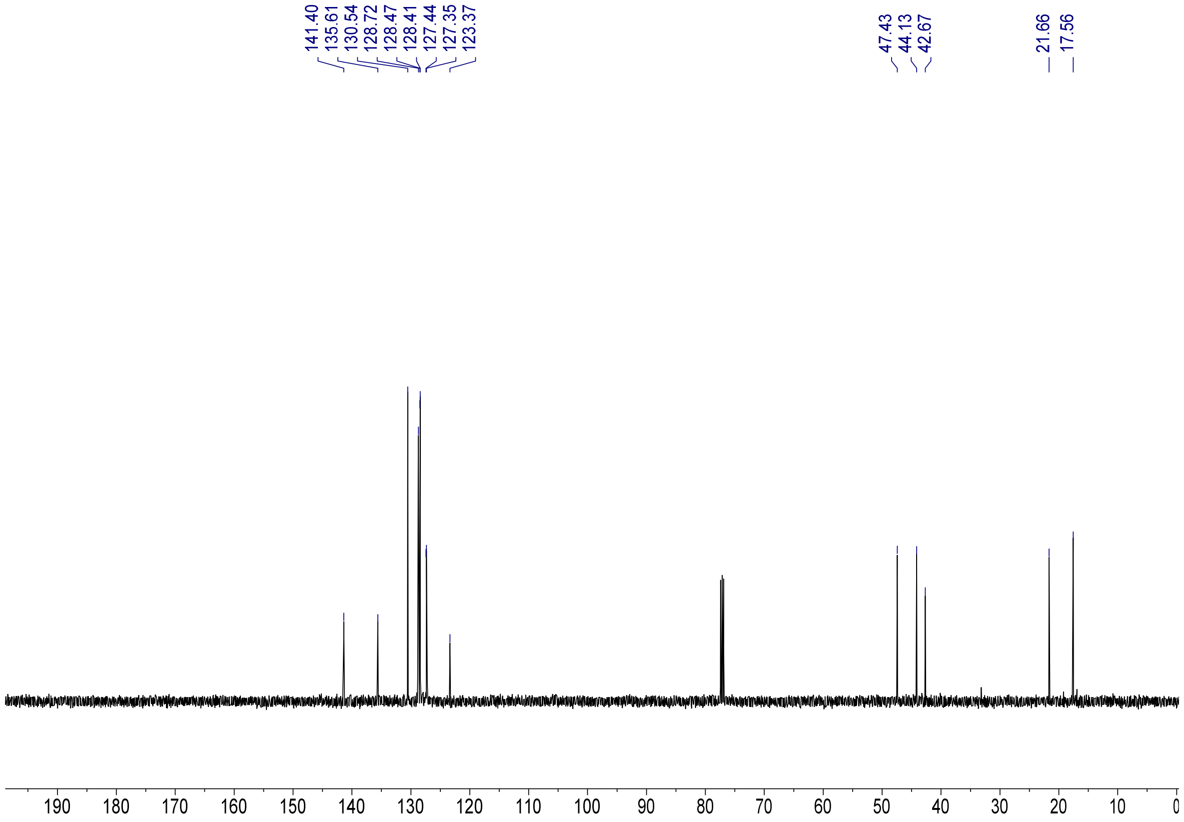

135.90
130.53
128.38
127.29
124.45
46.64
42.73
37.99
27.94
23.30
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10

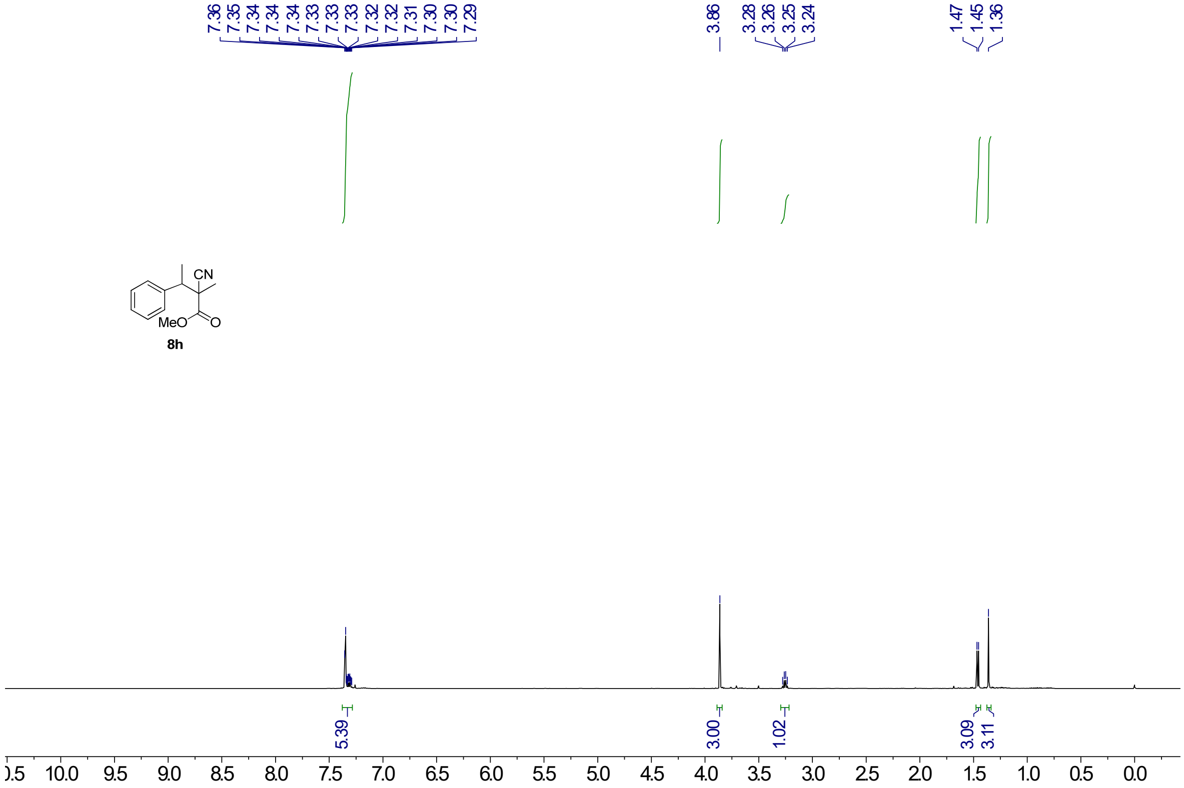

3.78 2.16 2.14 2.13 2.12 2.12 2.11 2.11 2.10 2.10 2.06 2.05 2.04 2.03 2.02 2.02 2.00 1.99 1.76 1.75 1.75 1.74 1.74 1.73 1.73 1.72 1.72 1.72 1.71 1.71 1.71 1.70 1.70 1.69 1.69 1.69 1.68 1.68 1.67 1.67 1.66 1.66 1.66 1.65 1.65 1.65 1.64 1.57 1.57 1.57 1.56 1.56 1.55 1.55 1.55 1.54 1.54
3.78 2.13 2.12 2.12 2.11 2.11 2.10 2.06 2.05 2.04 2.03 2.02 1.75 1.74 1.74 1.73 1.73 1.72 1.72 1.72 1.71 1.71 1.71 1.70 1.69 1.69 1.68 1.68 1.67 1.66 1.66
3.00
2.09
2.03
6.32
2.04
4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0 1.8 1.6 1.4
CN
OMe
O
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0

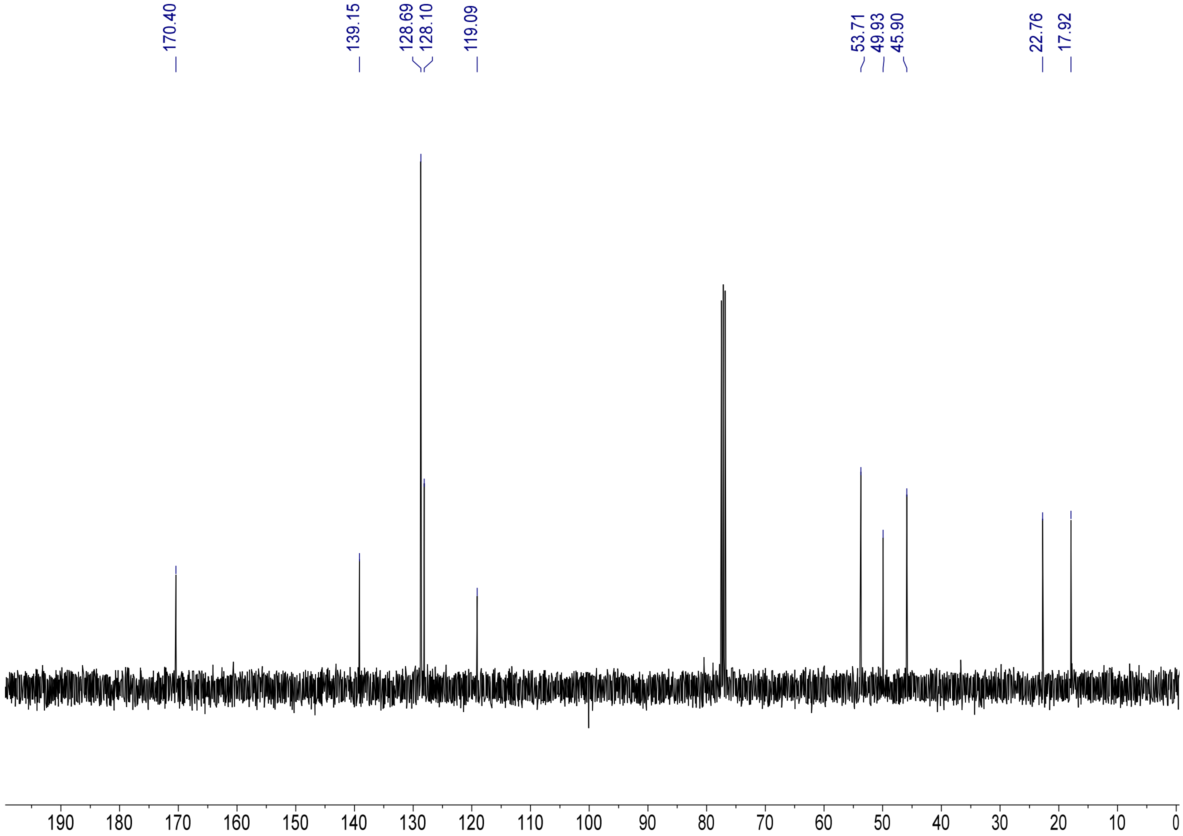
8g

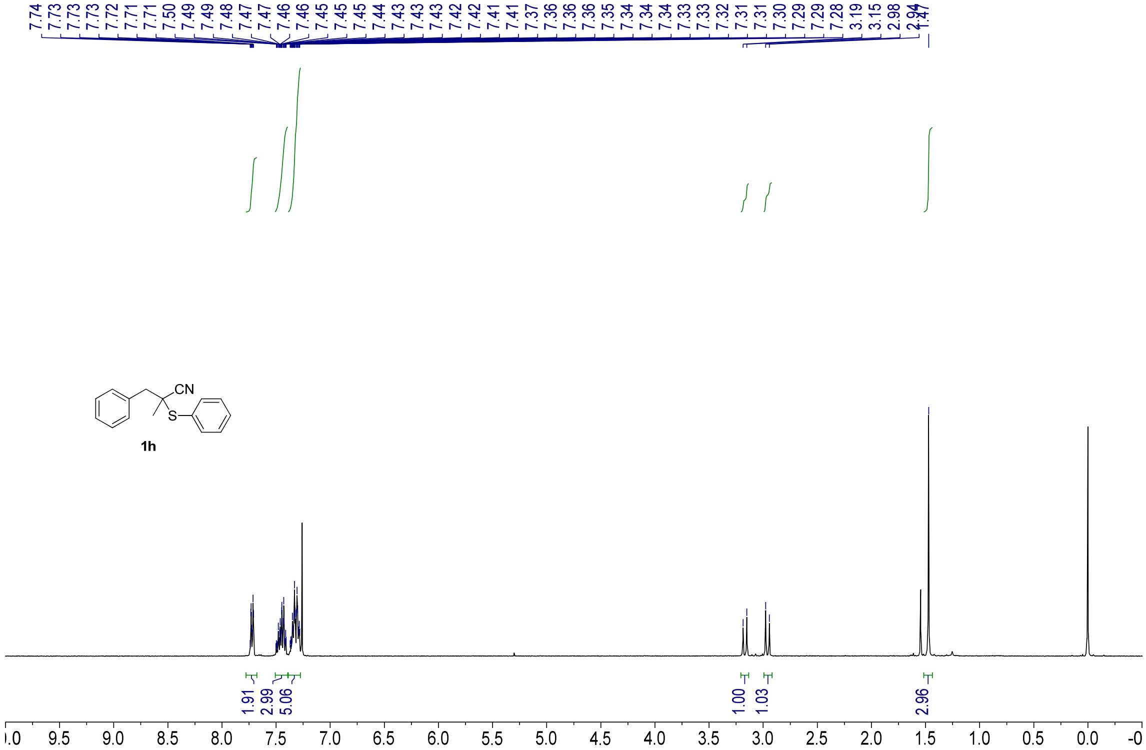

170.60
120.38
53.51
47.94
36.05
27.95
23.57
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

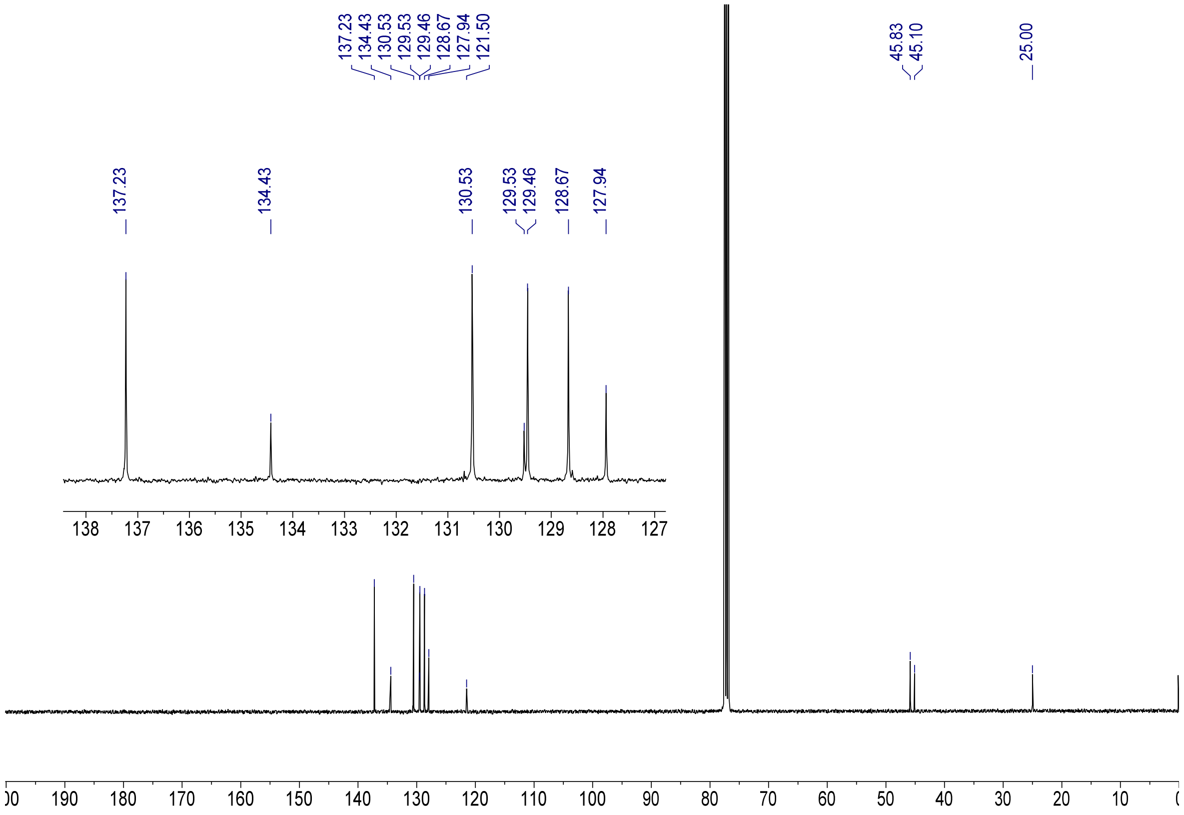

7.32
7.32
7.31
7.31
7.30
7.30
7.30
7.29
7.29
7.28
7.28
7.28
7.27
7.27
7.26
7.26
7.25
7.25
7.25
3.19
3.16
2.87
2.85
2.84
2.82
2.60
2.58
1.61
1.60
0.99
CN
6g
10.47
1.03
1.07
1.00
3.07
3.03
0.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.

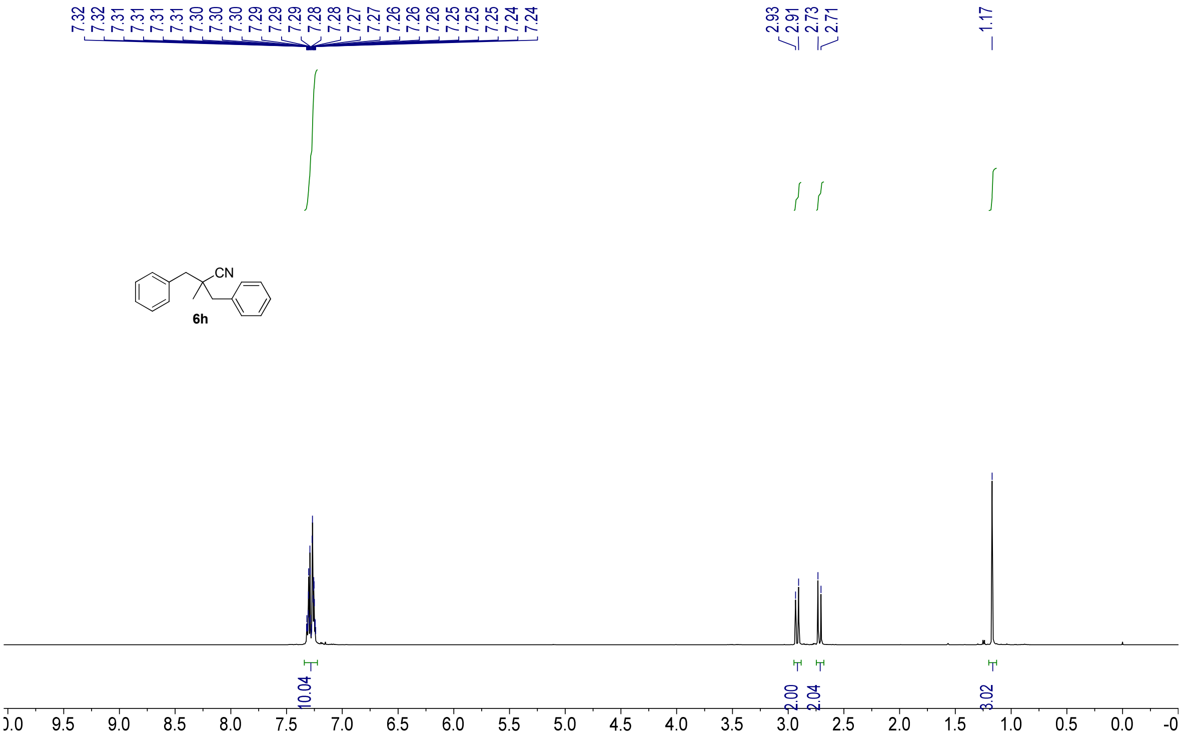

141.40
135.61
130.54
128.72
128.47
128.41
127.44
127.35
123.37
47.43
44.13
42.67
21.66
17.56
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

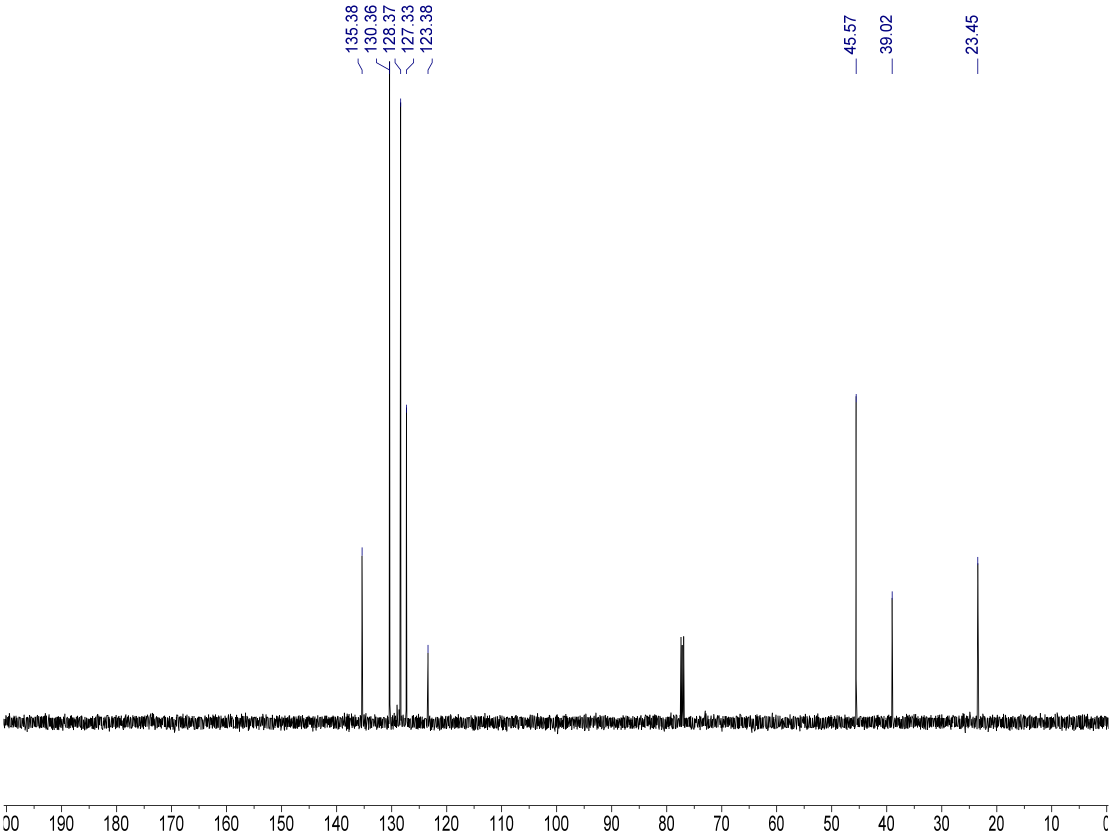

7.36
7.35
7.34
7.34
7.34
7.33
7.33
7.33
7.32
7.32
7.31
7.30
7.30
7.29
3.86
3.28
3.26
3.25
3.24
1.47
1.45
1.36
CN
MeO
O
8h
5.39
3.00
1.02
3.09
3.11
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

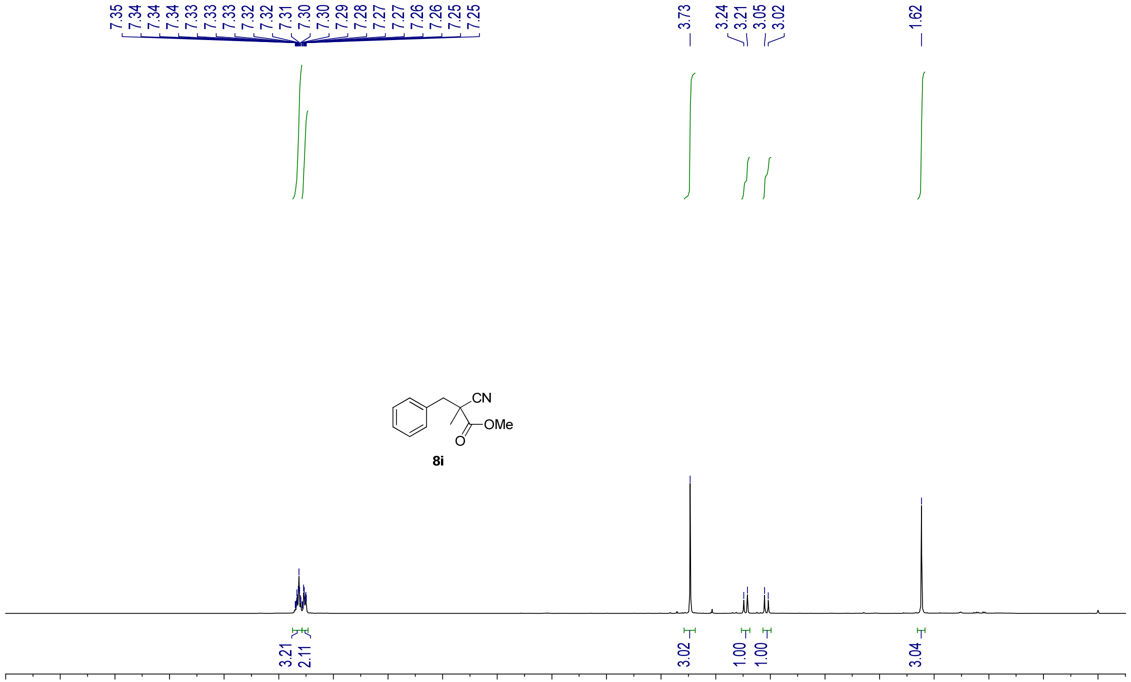

170.40
139.15
128.69
128.10
119.09
53.71
49.93
45.90
22.76
17.92
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

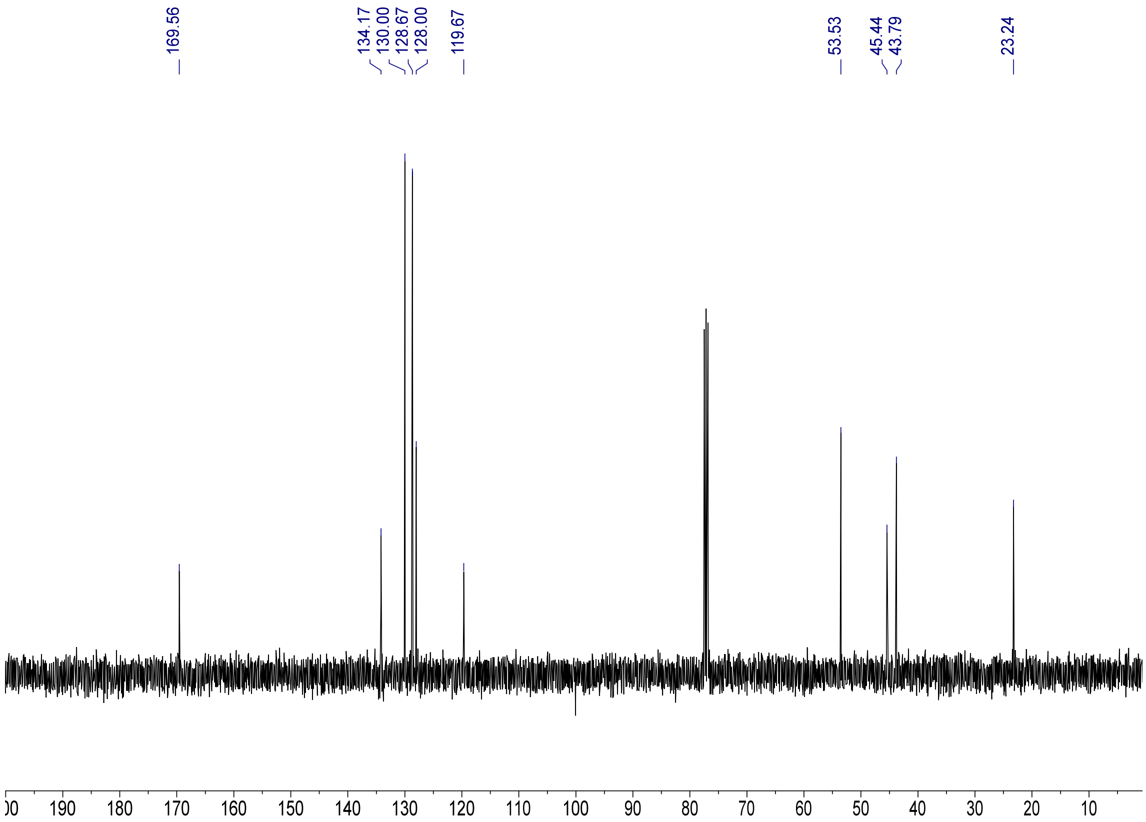

7.74
7.73
7.73
7.73
7.72
7.71
7.71
7.50
7.49
7.49
7.48
7.47
7.47
7.46
7.46
7.45
7.45
7.44
7.43
7.43
7.43
7.42
7.42
7.41
7.41
7.37
7.36
7.36
7.36
7.35
7.34
7.34
7.34
7.33
7.33
7.32
7.31
7.31
7.30
7.29
7.29
7.28
3.19
3.15
2.98
2.94
1.47
CN
S
1h
1.91
2.99
5.06
1.00
1.03
2.96
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0

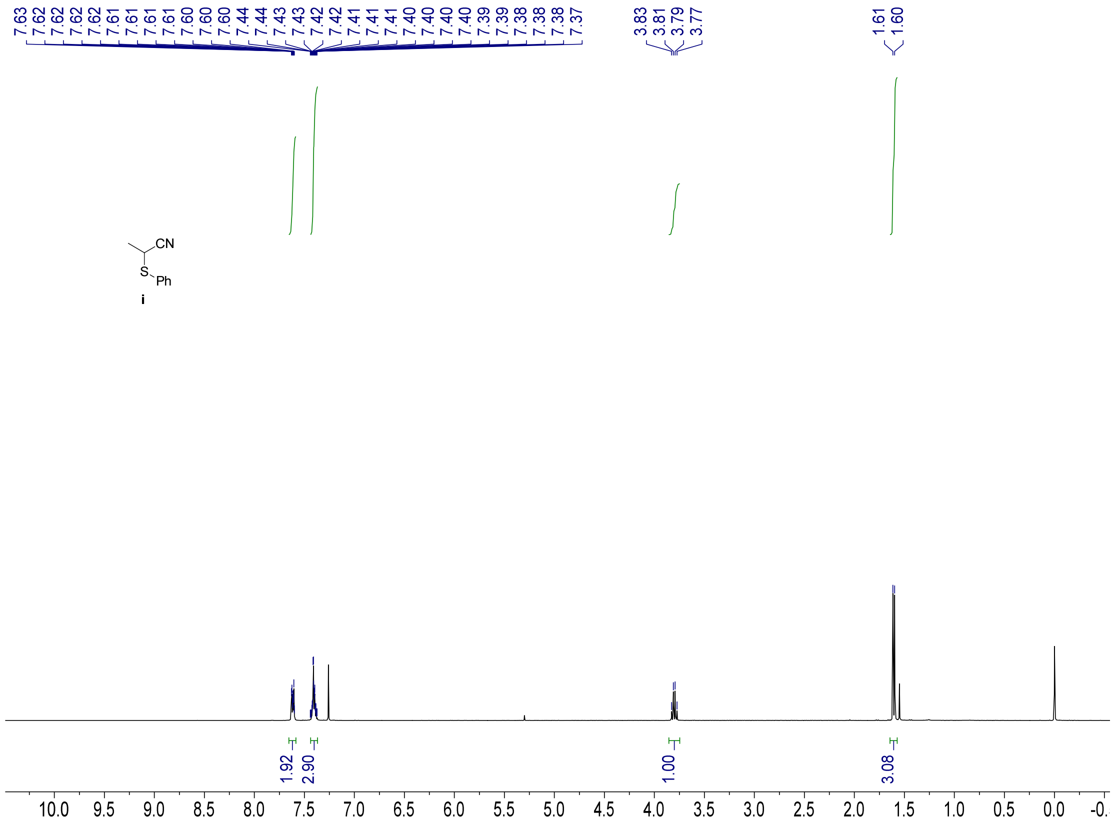

137.23
134.43
130.53
129.53
129.46
128.67
127.94
121.50
45.83
45.10
25.00
137.23
134.43
130.53
129.53
129.46
128.67
127.94
138
137
136
135
134
133
132
131
130
129
128
127
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

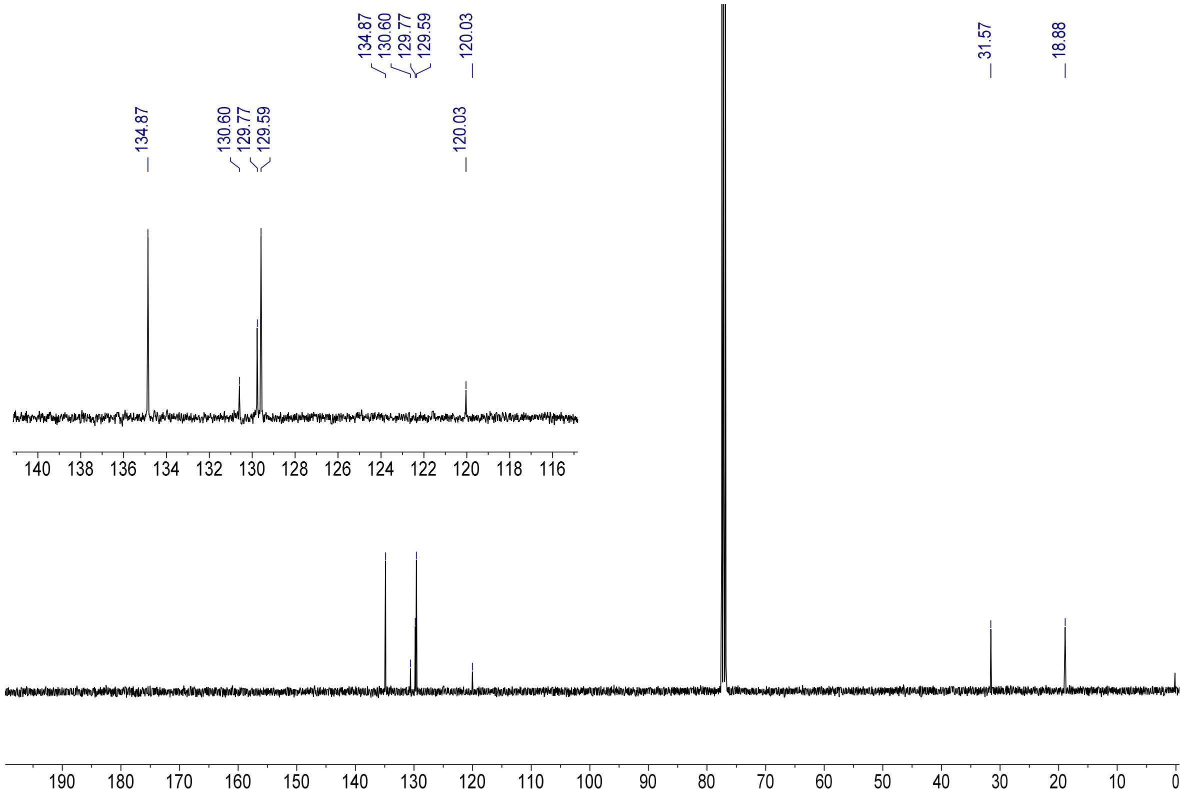

7.32
7.32
7.31
7.31
7.31
7.30
7.30
7.30
7.29
7.29
7.29
7.28
7.28
7.27
7.27
7.26
7.26
7.26
7.25
7.25
7.25
7.24
7.24
2.93
2.91
2.73
2.71
1.17
CN
6h
10.04
2.00
2.04
3.02
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0

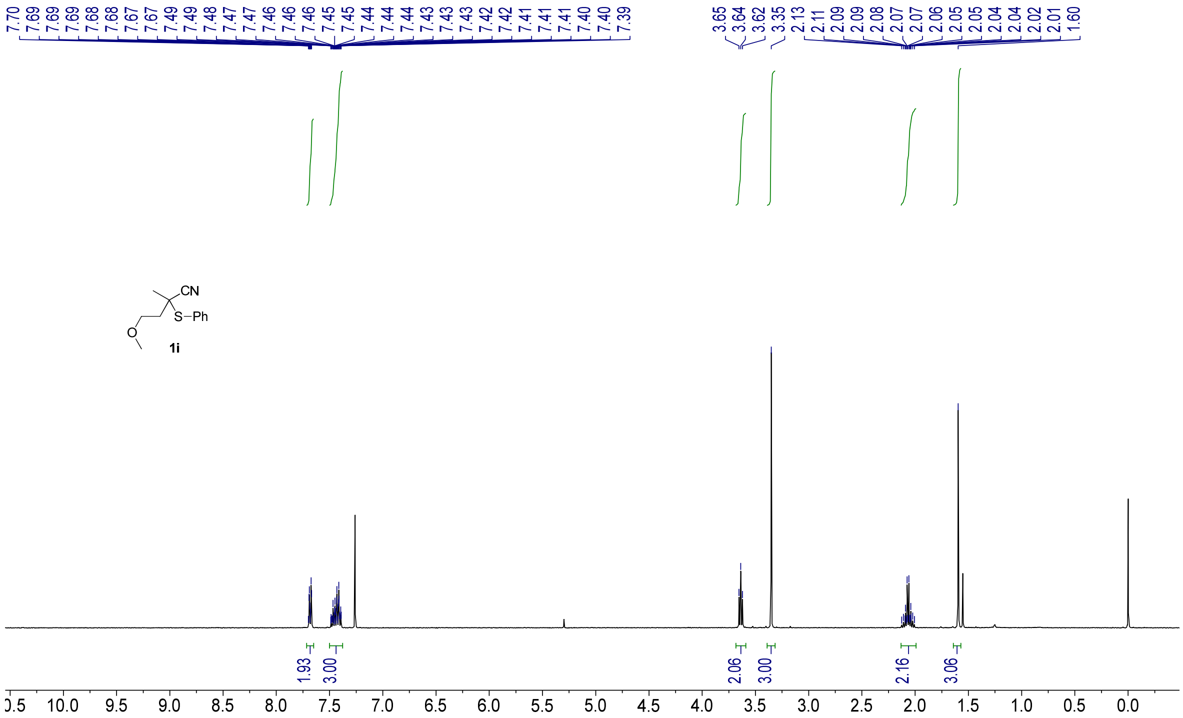

135.38
130.36
128.37
127.33
123.38
45.57
39.02
23.45
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

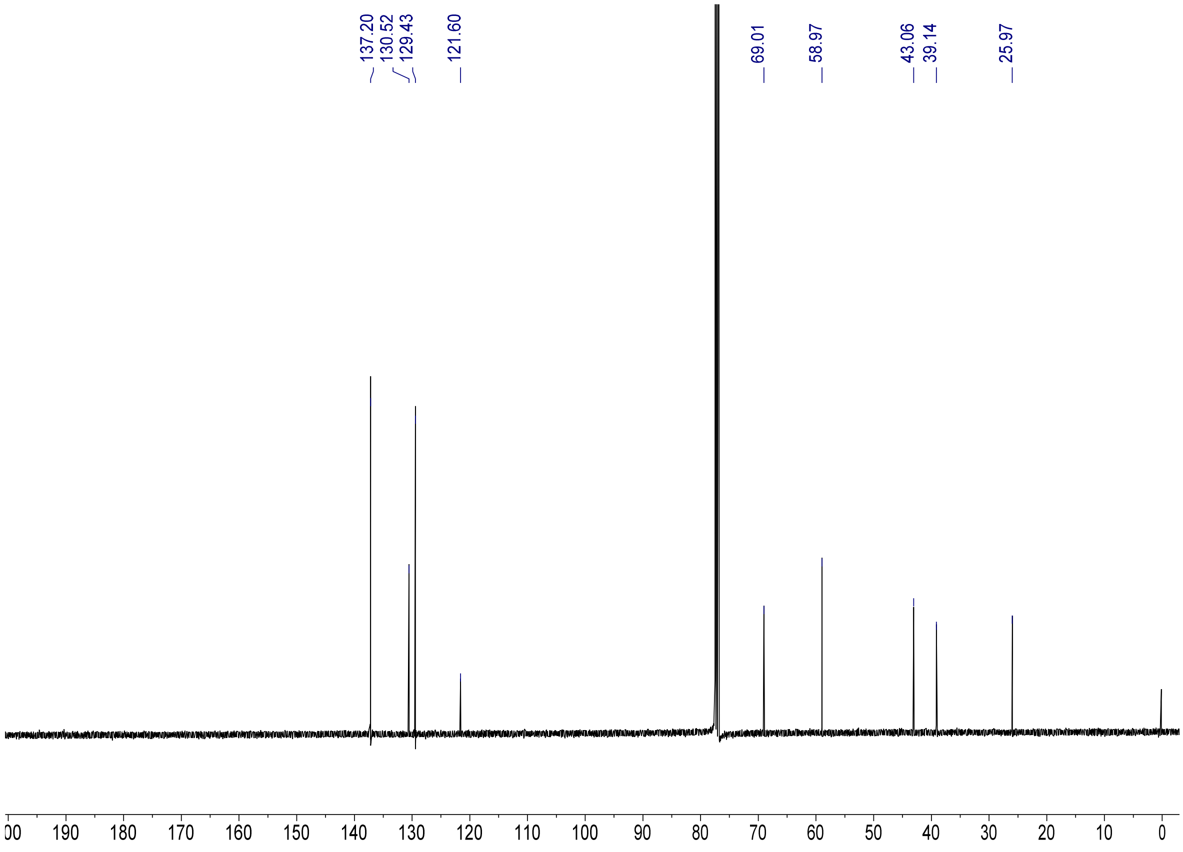

7.35
7.34
7.34
7.34
7.33
7.33
7.33
7.32
7.32
7.31
7.30
7.30
7.29
7.28
7.27
7.27
7.26
7.26
7.25
7.25
3.73
3.24
3.21
3.05
3.02
1.62
CN
OMe
O
8i
3.21
2.11
3.02
1.00
1.00
3.04
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

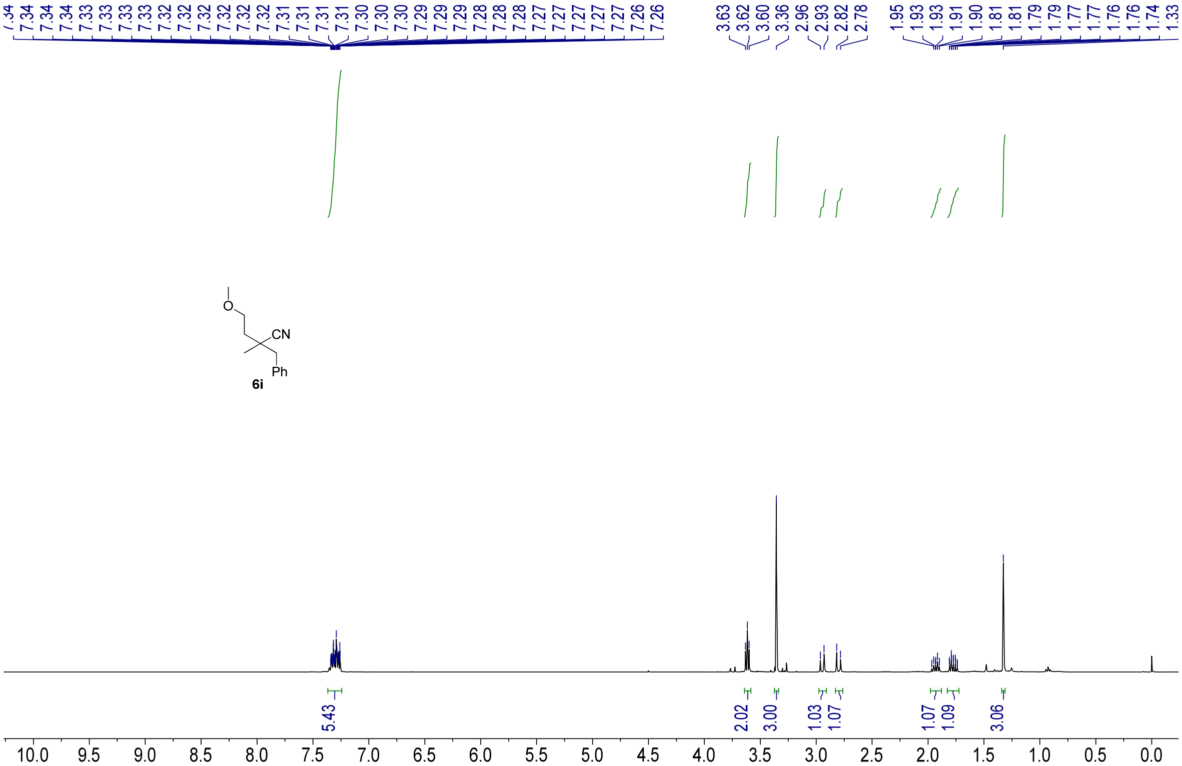

169.56
134.17
130.00
128.67
128.00
119.67
53.53
45.44
43.79
23.24
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10


7.63
7.62
7.62
7.62
7.61
7.61
7.61
7.60
7.60
7.44
7.44
7.43
7.43
7.42
7.42
7.41
7.41
7.40
7.40
7.40
7.39
7.39
7.38
7.38
7.37
3.83
3.81
3.79
3.77
1.61
1.60
CN
S
Ph
i
1.92
2.90
1.00
3.08
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.

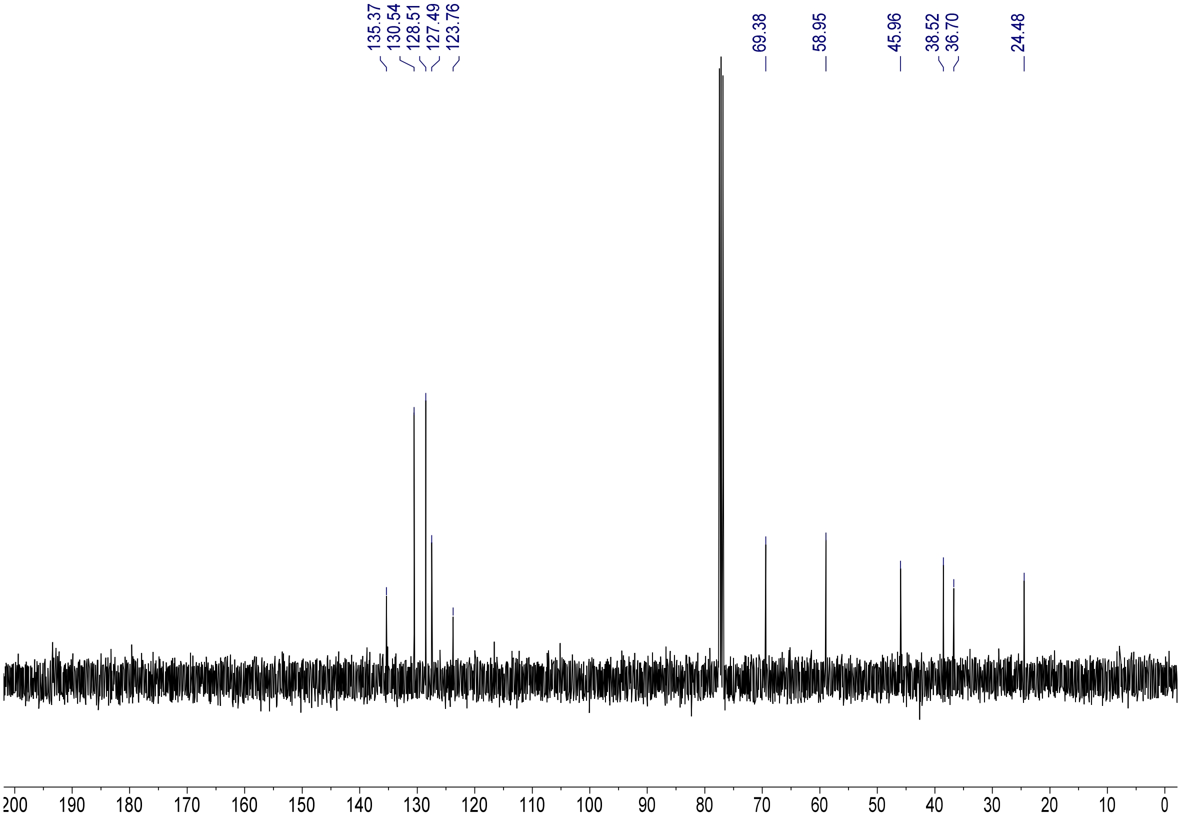

134.87
130.60
129.77
129.59
120.03
31.57
18.88
134.87
130.60
129.77
129.59
120.03
140
138
136
134
132
130
128
126
124
122
120
118
116
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0


7.70
7.69
7.69
7.68
7.68
7.67
7.67
7.49
7.49
7.48
7.47
7.47
7.46
7.46
7.45
7.45
7.44
7.44
7.44
7.43
7.43
7.43
7.42
7.42
7.41
7.41
7.41
7.40
7.40
7.39
3.65
3.64
3.62
3.35
2.13
2.11
2.09
2.09
2.08
2.07
2.07
2.06
2.05
2.05
2.04
2.04
2.02
2.01
1.60
CN
S–Ph
O
1i
1.93
3.00
2.06
3.00
2.16
3.06
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

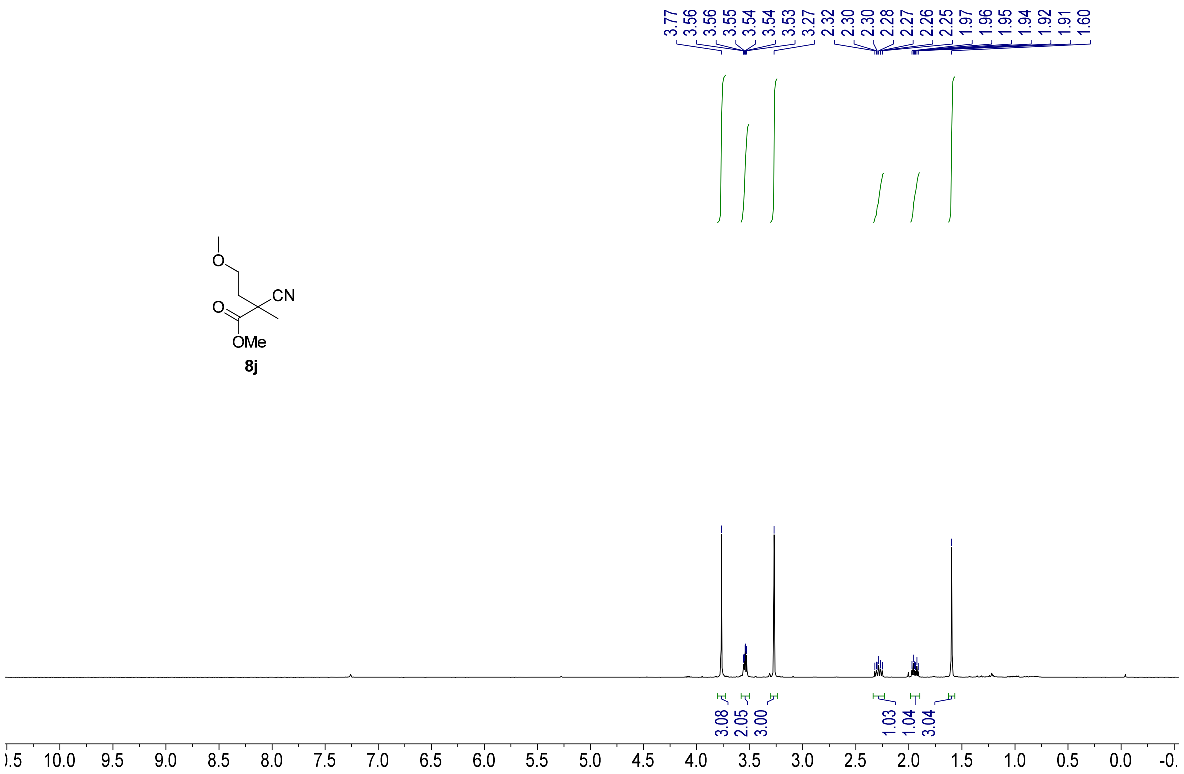

137.20
130.52
129.43
121.60
69.01
58.97
43.06
39.14
25.97
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

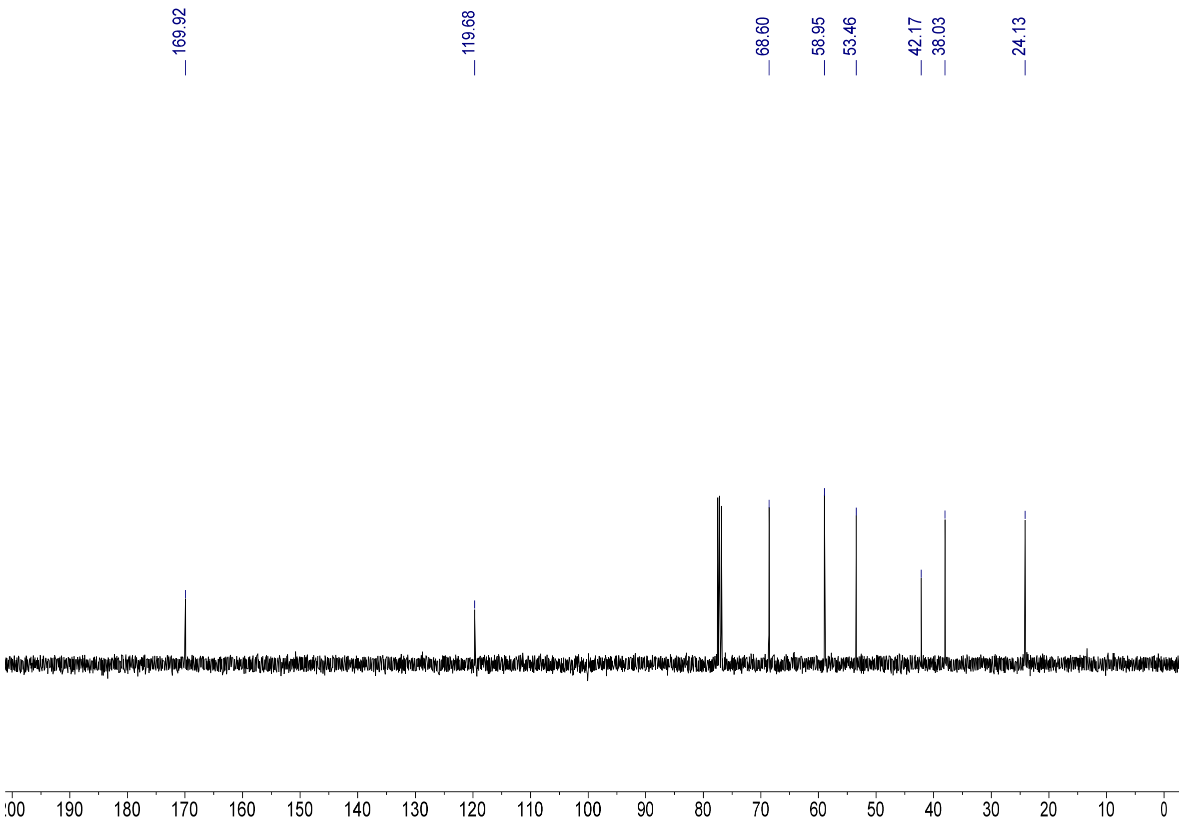


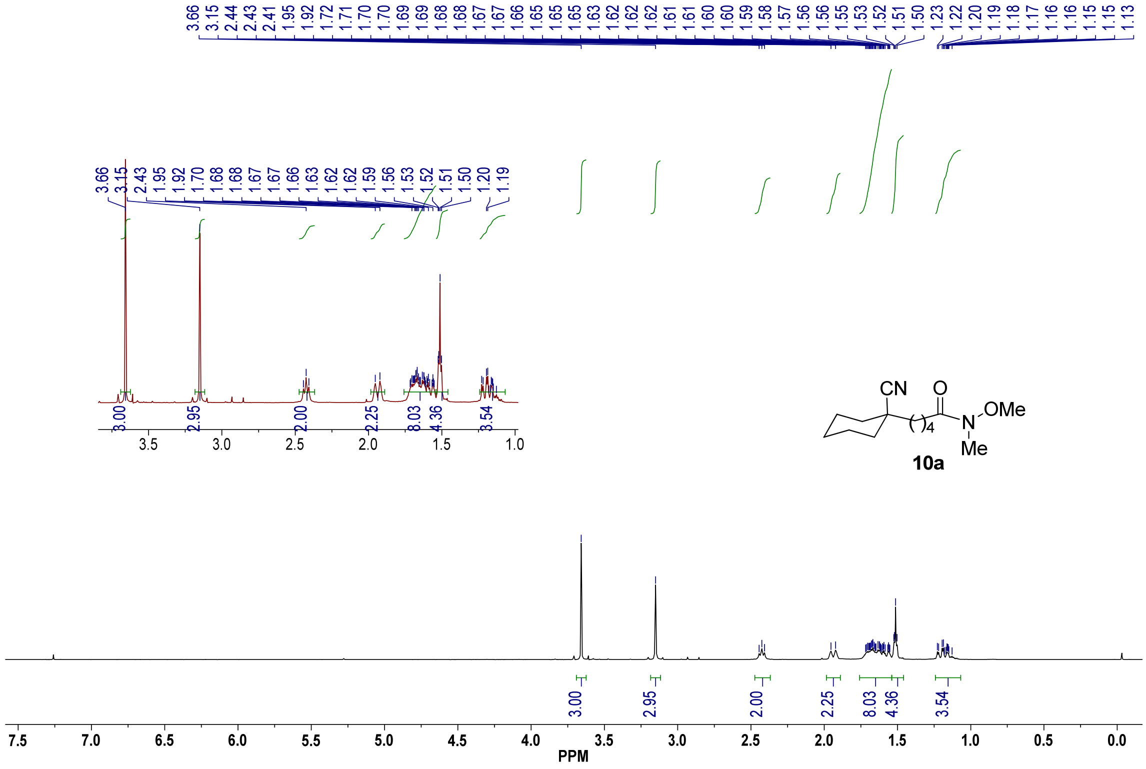
7.34
7.34
7.34
7.33
7.33
7.33
7.32
7.32
7.32
7.32
7.31
7.31
7.31
7.30
7.30
7.29
7.29
7.28
7.28
7.28
7.27
7.27
7.27
7.27
7.26
7.26
3.63
3.62
3.60
3.36
2.96
2.93
2.82
2.78
1.95
1.93
1.93
1.91
1.90
1.81
1.81
1.79
1.77
1.77
1.76
1.74
1.33
O
CN
Ph
6i
5.43
2.02
3.00
1.03
1.07
1.07
1.09
3.06
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0



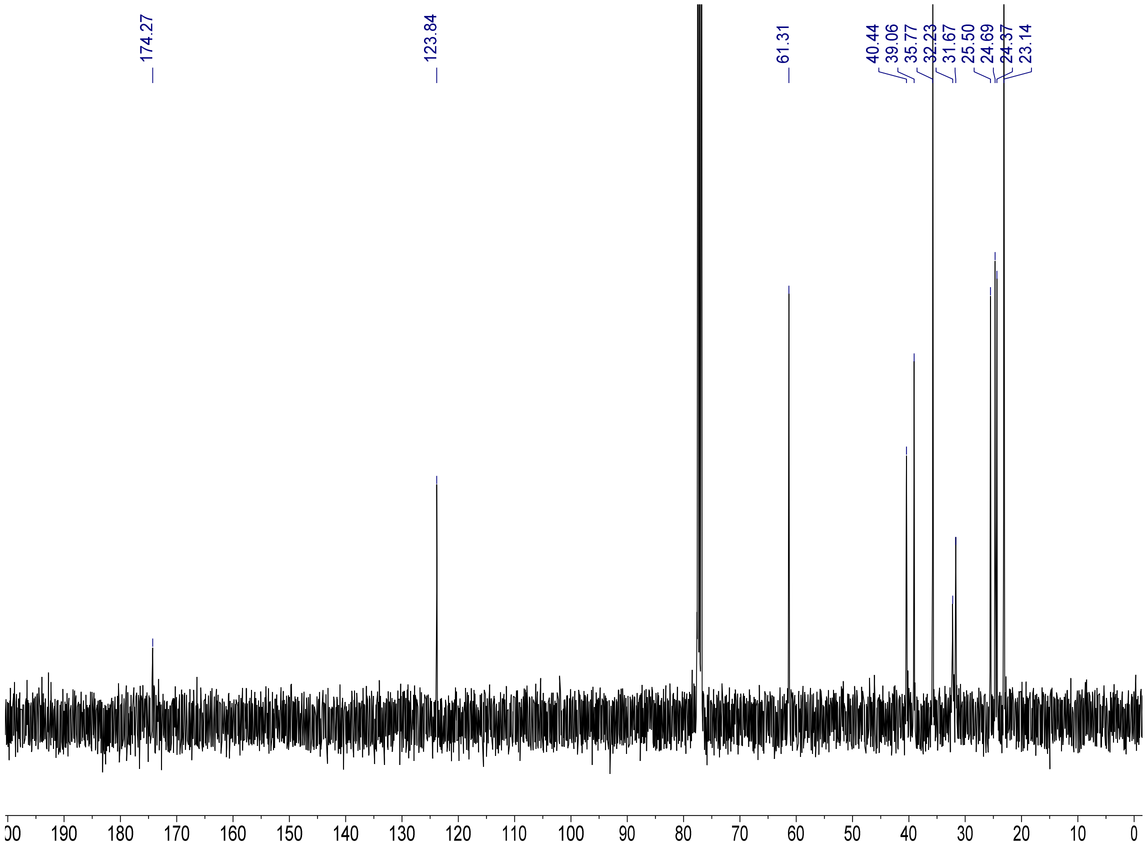
135.37
130.54
128.51
127.49
123.76
69.38
58.95
45.96
38.52
36.70
24.48
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

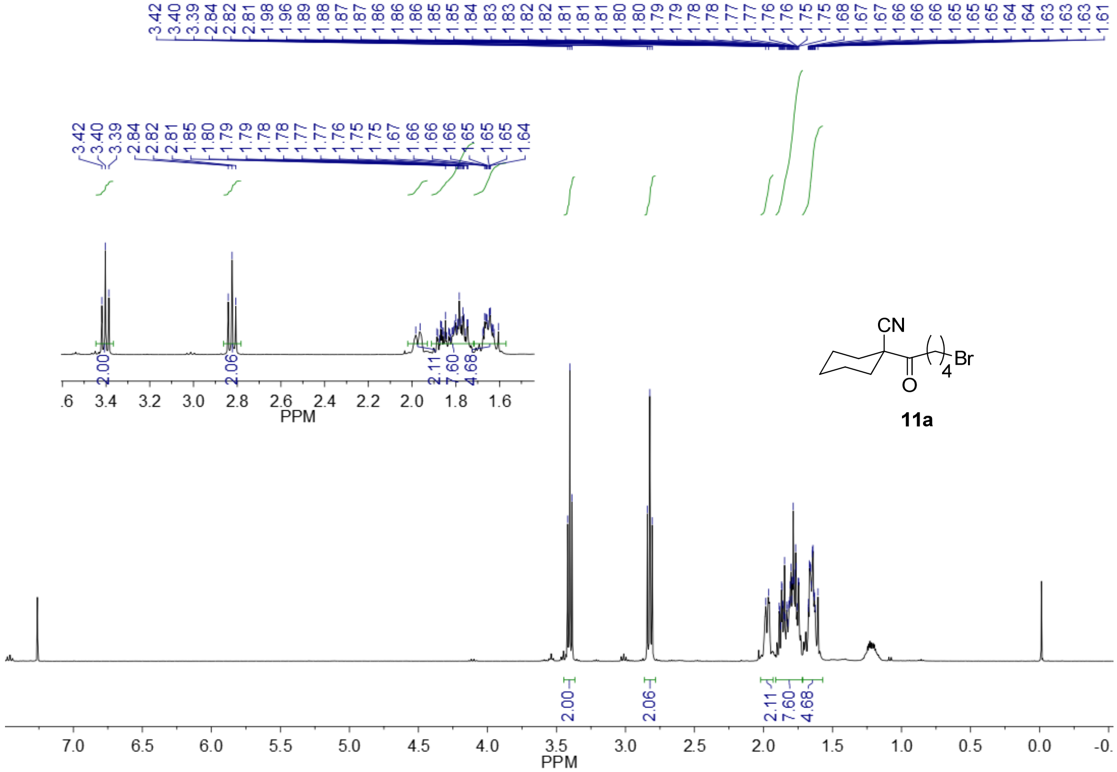

3.77
3.56
3.55
3.54
3.54
3.53
3.27
2.32
2.30
2.30
2.28
2.27
2.26
2.25
1.97
1.96
1.95
1.94
1.92
1.91
1.60
CN
O
O
OMe
8j
3.08
2.05
3.00
1.03
1.04
3.04
.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.

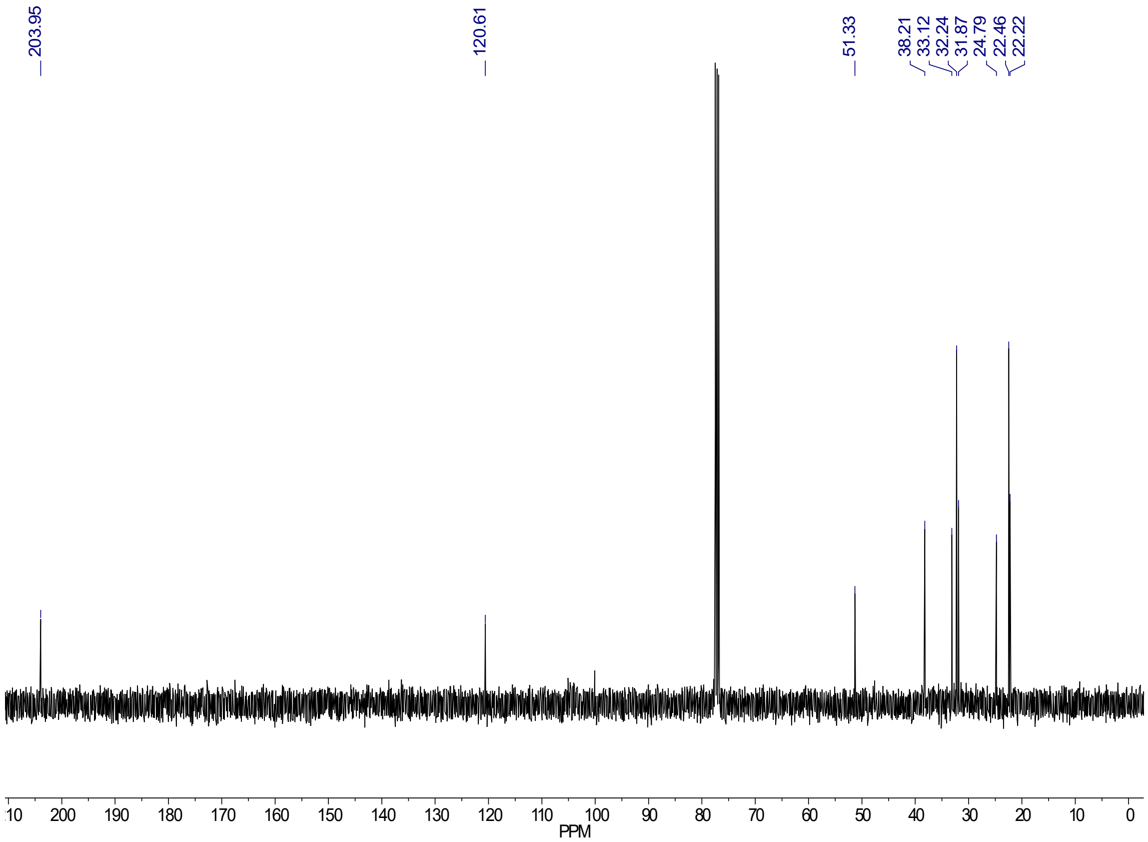

169.92
119.68
68.60
58.95
53.46
42.17
38.03
24.13
00
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

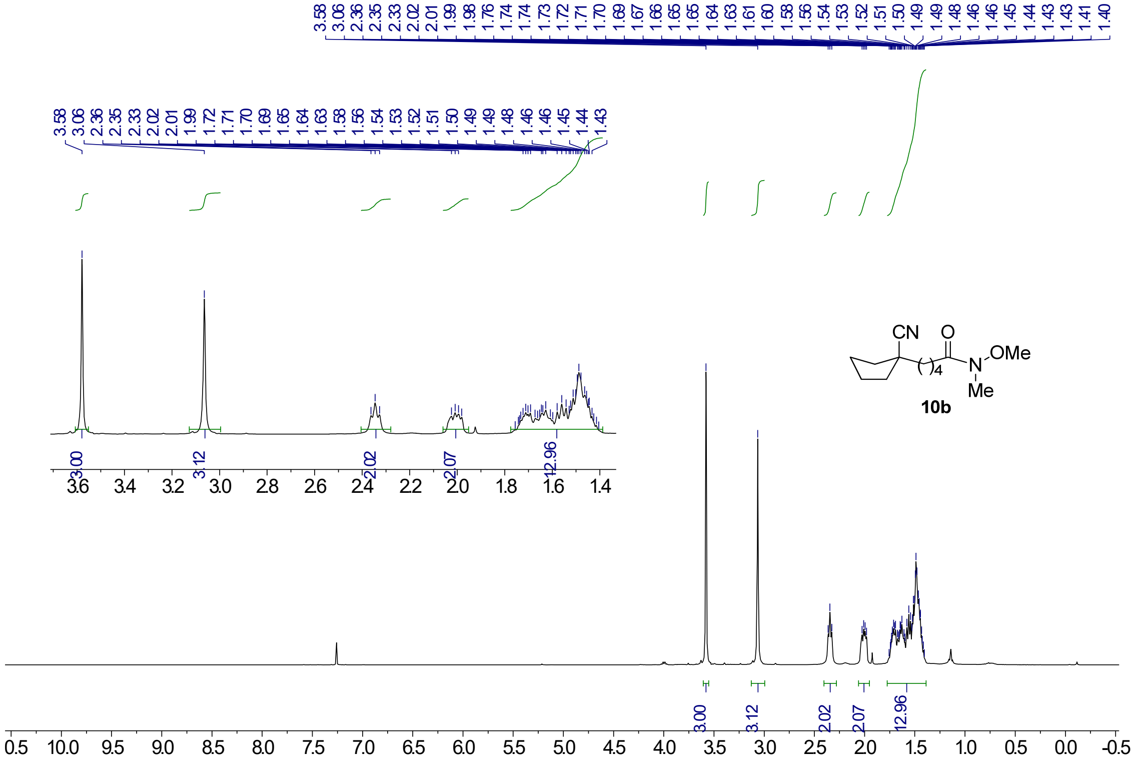

3.66
3.15
2.44
2.43
2.41
1.95
1.92
1.72
1.71
1.70
1.70
1.69
1.69
1.68
1.68
1.67
1.67
1.66
1.65
1.65
1.63
1.62
1.62
1.62
1.61
1.61
1.60
1.59
1.58
1.57
1.56
1.56
1.55
1.53
1.52
1.51
1.50
1.23
1.22
1.20
1.19
1.18
1.17
1.16
1.16
1.15
1.15
1.13
3.66
3.15
2.43
1.95
1.92
1.70
1.68
1.68
1.67
1.67
1.66
1.63
1.62
1.62
1.59
1.56
1.53
1.52
1.51
1.50
1.20
1.19
3.00
2.95
2.00
2.25
8.03
4.36
3.54
3.5
3.0
2.5
2.0
1.5
1.0
CN
O
( )4
N
OMe
Me
3.00
2.95
2.00
2.25
8.03
4.36
3.54
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
PPM

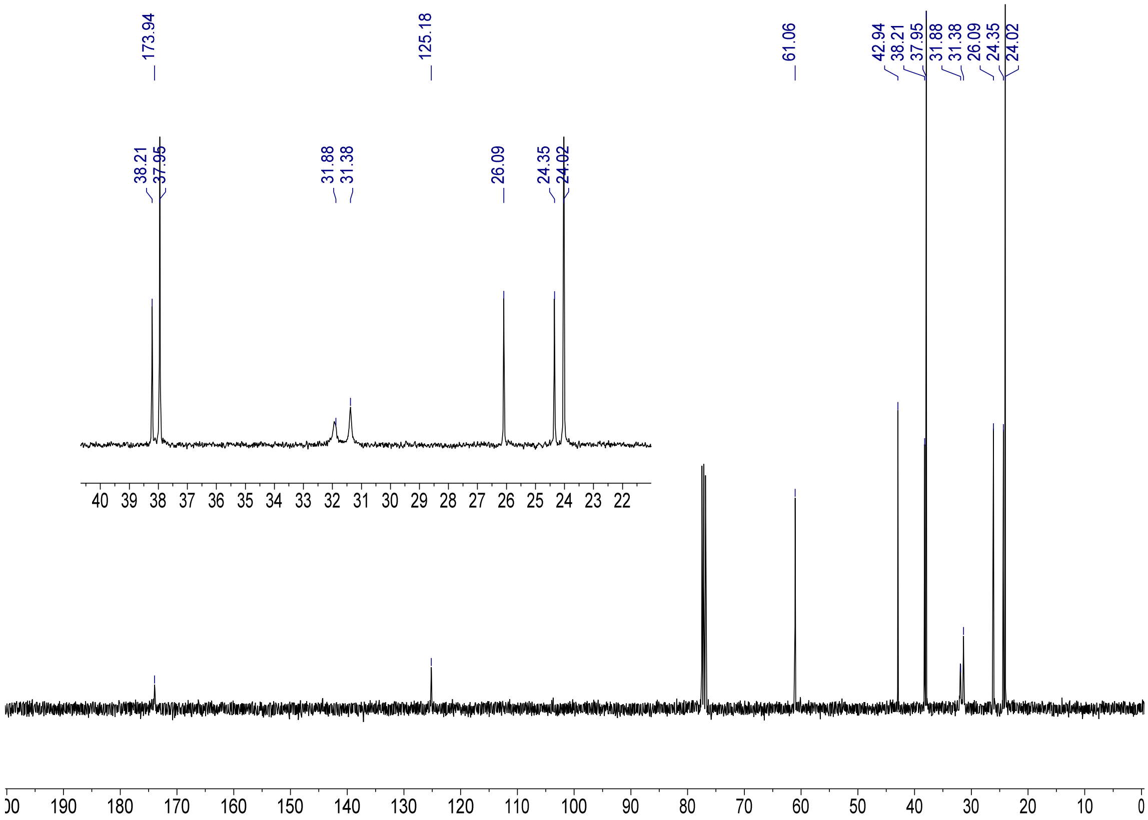
10a

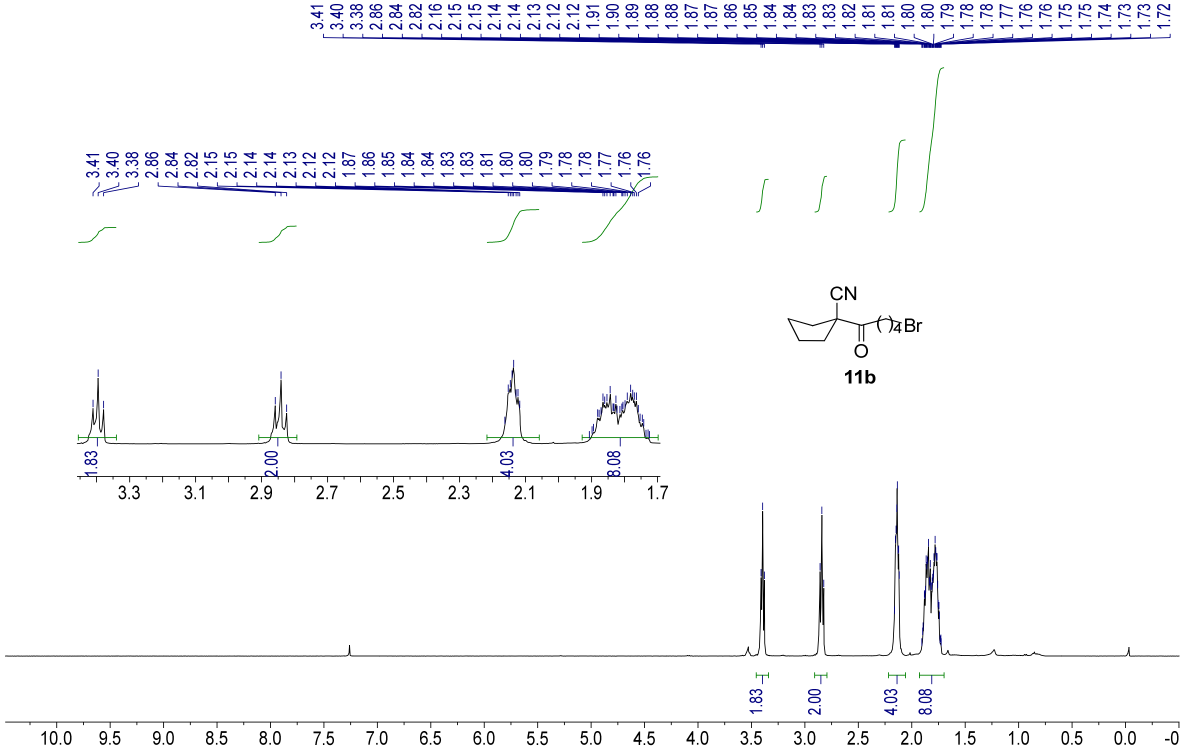

174.27
123.84
61.31
40.44
39.06
35.77
32.23
31.67
25.50
24.69
24.37
23.14
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

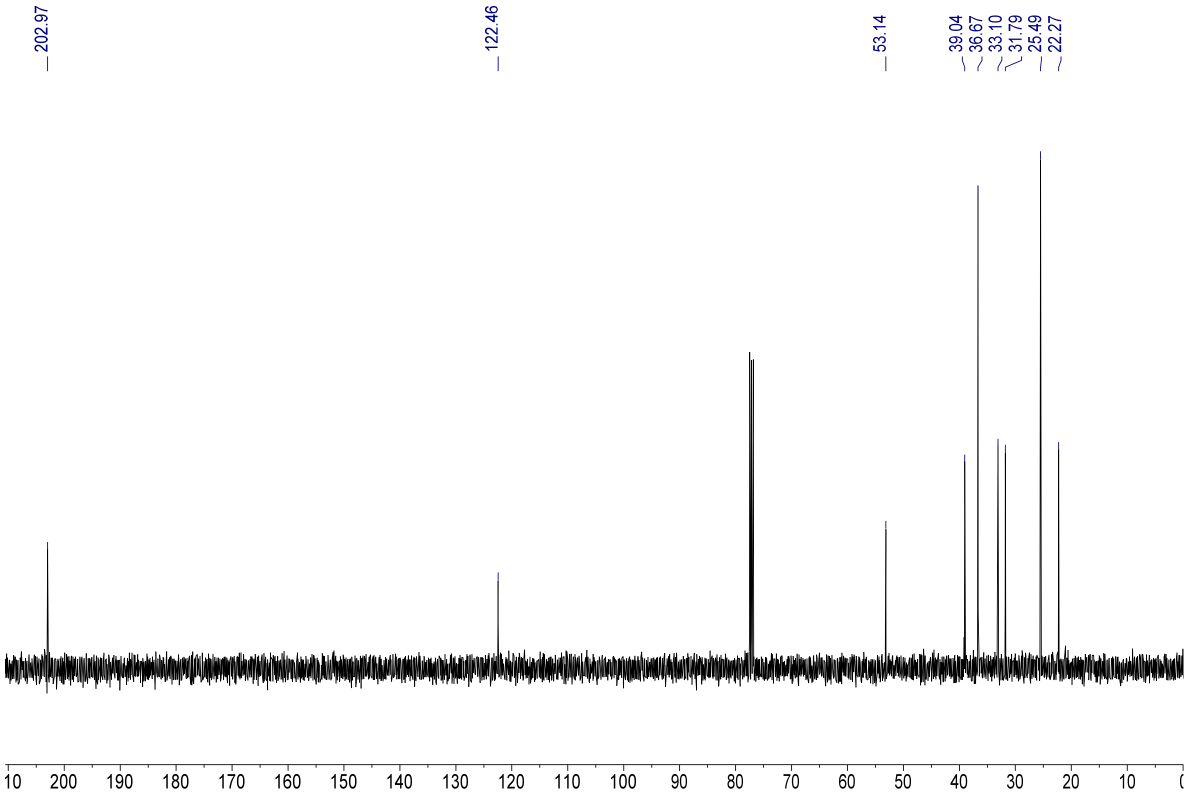

3.42 3.40 3.39 2.84 2.82 2.81 1.98 1.96 1.89 1.88 1.87 1.87 1.86 1.86 1.86 1.85 1.85 1.84 1.83 1.83 1.82 1.81 1.81 1.80 1.80 1.79 1.78 1.78 1.77 1.76 1.76 1.75 1.75 1.68 1.67 1.67 1.66 1.66 1.65 1.65 1.65 1.64 1.64 1.63 1.63 1.63 1.61
3.42 3.40 3.39 2.84 2.82 2.81 1.85 1.80 1.79 1.79 1.78 1.78 1.77 1.77 1.76 1.75 1.75 1.67 1.66 1.66 1.66 1.65 1.65 1.65 1.64
2.00
2.06
2.11
7.60
4.68
.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0 1.8 1.6
PPM
CN
4
Br
O
11a
7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.
PPM

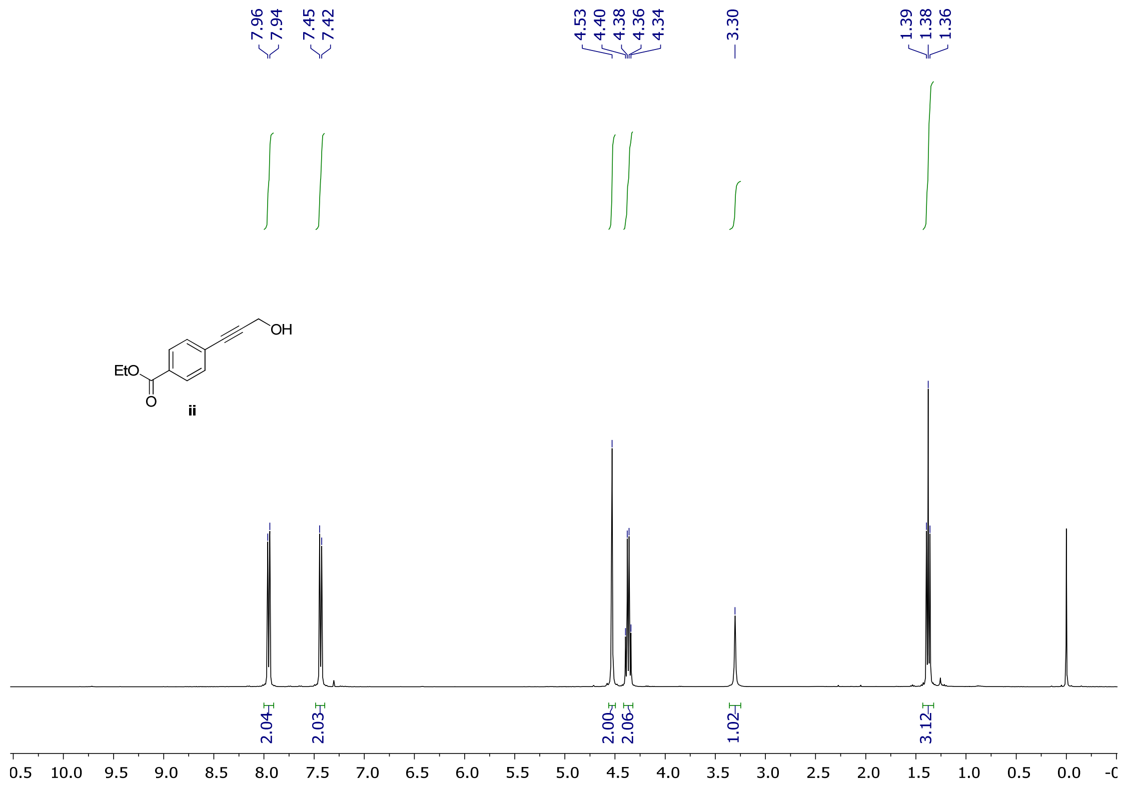

203.95
120.61
51.33
38.21
33.12
32.24
31.87
24.79
22.46
22.22
10 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
PPM


3.58 3.06 2.36 2.35 2.33 2.02 2.01 1.99 1.98 1.76 1.74 1.74 1.73 1.72 1.71 1.70 1.69 1.67 1.66 1.65 1.65 1.64 1.63 1.61 1.60 1.58 1.56 1.54 1.53 1.52 1.51 1.50 1.49 1.49 1.48 1.46 1.46 1.45 1.44 1.43 1.43 1.41 1.40
3.58 3.06 2.36 2.35 2.33 2.02 2.01 1.99 1.72 1.71 1.70 1.69 1.65 1.64 1.63 1.58 1.56 1.54 1.53 1.52 1.51 1.50 1.49 1.48 1.46 1.46 1.45 1.44 1.43
3.00 3.12 2.02 2.07 12.96
3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0 1.8 1.6 1.4
CN
O
OMe
N
Me
4
10b
3.00 3.12 2.02 2.07 12.96
0.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5

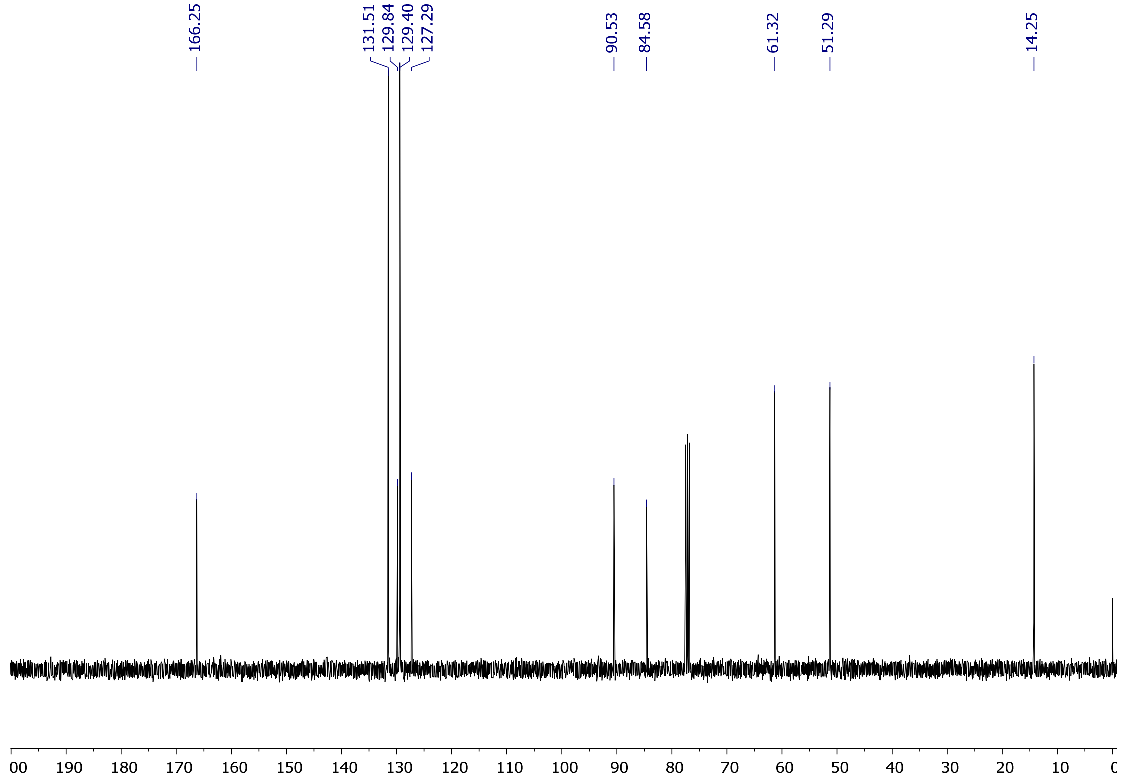

173.94
125.18
61.06
42.94 38.21 37.95 31.88 31.38 26.09 24.35 24.02
38.21 37.95
31.88 31.38
26.09
24.35 24.02
40 39 38 37 36 35 34 33 32 31 30 29 28 27 26 25 24 23 22
00 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

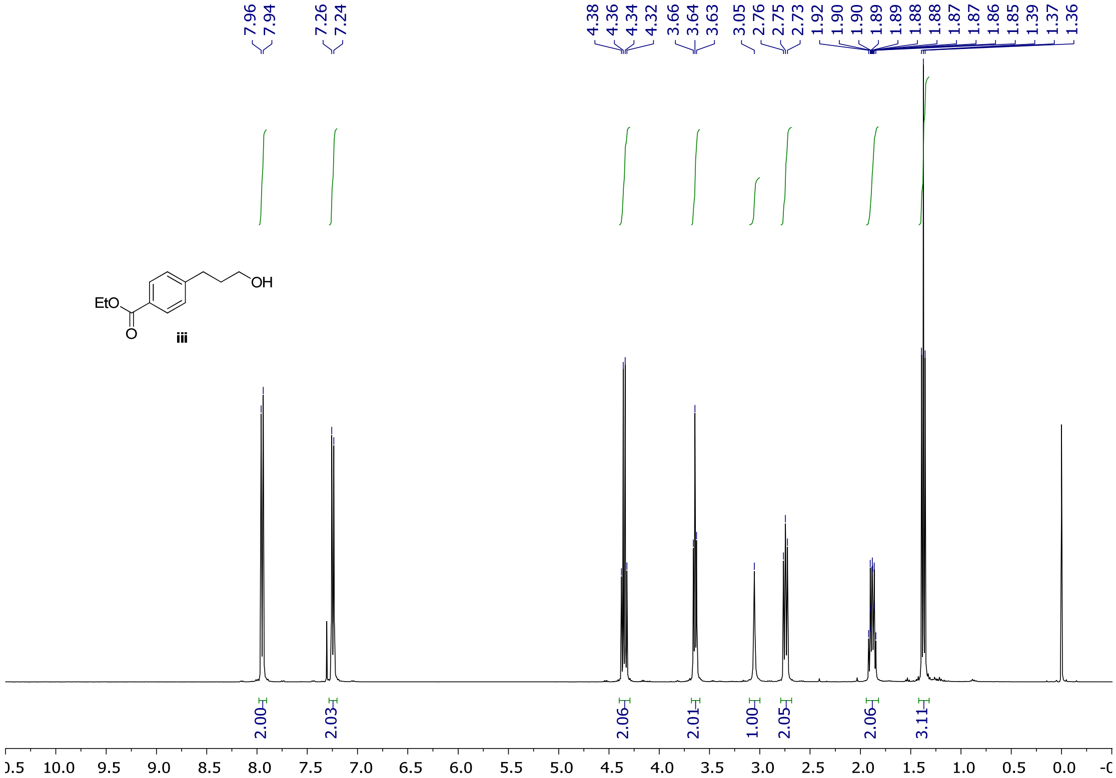

3.41 3.40 3.38 2.86 2.84 2.82 2.16 2.15 2.15 2.14 2.14 2.13 2.12 2.12 1.91 1.90 1.89 1.88 1.88 1.87 1.87 1.86 1.85 1.84 1.84 1.83 1.83 1.82 1.81 1.81 1.80 1.80 1.79 1.78 1.78 1.77 1.76 1.76 1.75 1.74 1.73 1.73 1.72
3.41 3.40 3.38 2.86 2.84 2.82 2.15 2.15 2.14 2.14 2.13 2.12 2.12 1.87 1.86 1.85 1.84 1.84 1.83 1.83 1.81 1.80 1.80 1.79 1.78 1.78 1.77 1.76 1.76
1.83
2.00
4.03
8.08
3.3 3.1 2.9 2.7 2.5 2.3 2.1 1.9 1.7
CN
O
4Br
11b
1.83
2.00
4.03
8.08
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0

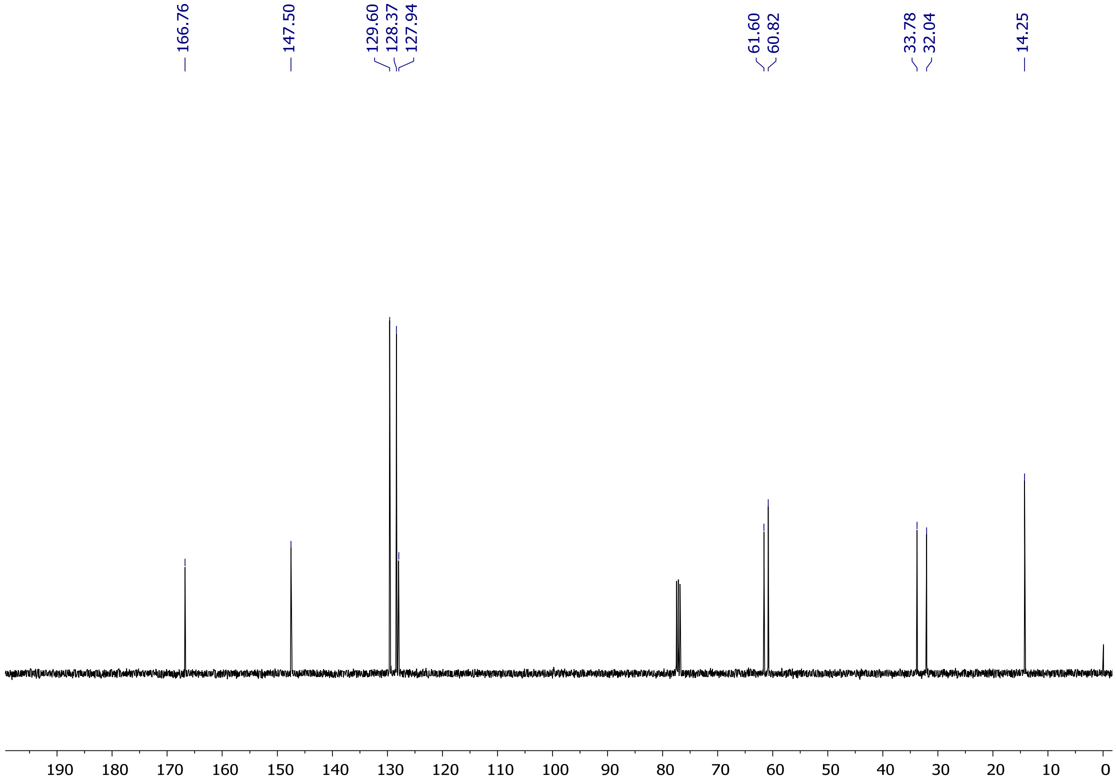

202.97
122.46
53.14
39.04
36.67
33.10
31.79
25.49
22.27
10 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10

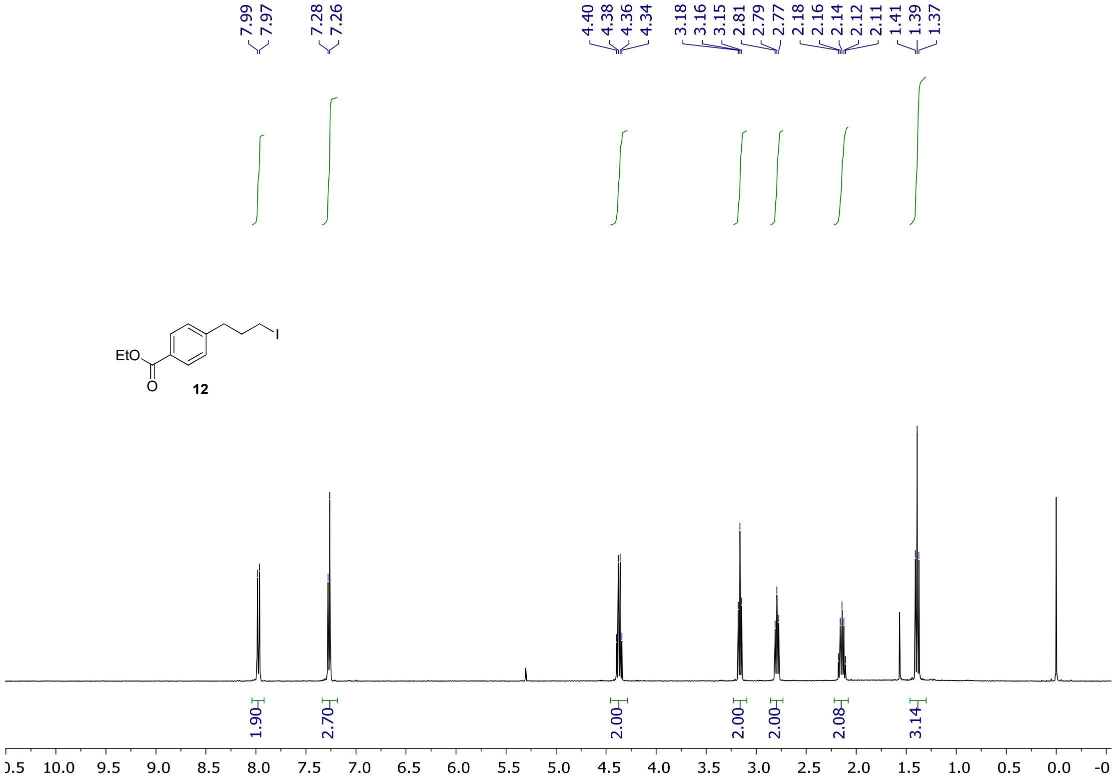

7.96
7.94
7.45
7.42
4.53
4.40
4.38
4.36
4.34
3.30
1.39
1.38
1.36
OH
EtO
O
2.04
2.03
2.00
2.06
1.02
3.12
0.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0

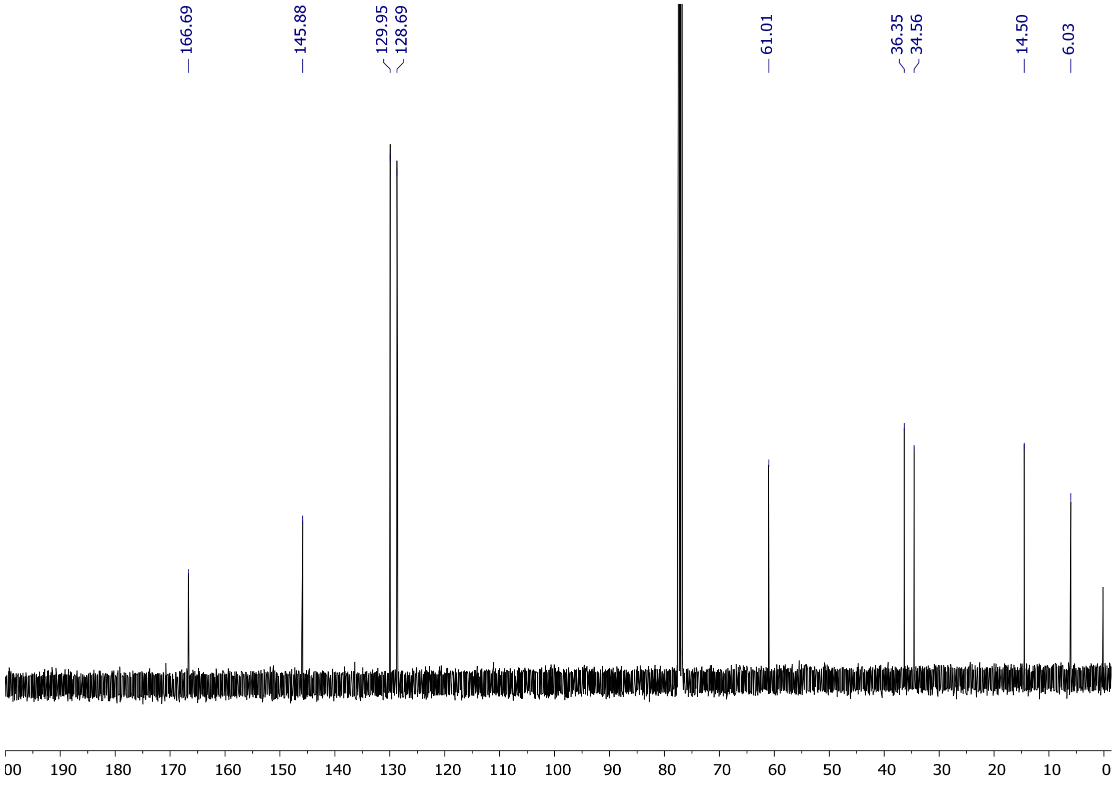
ii

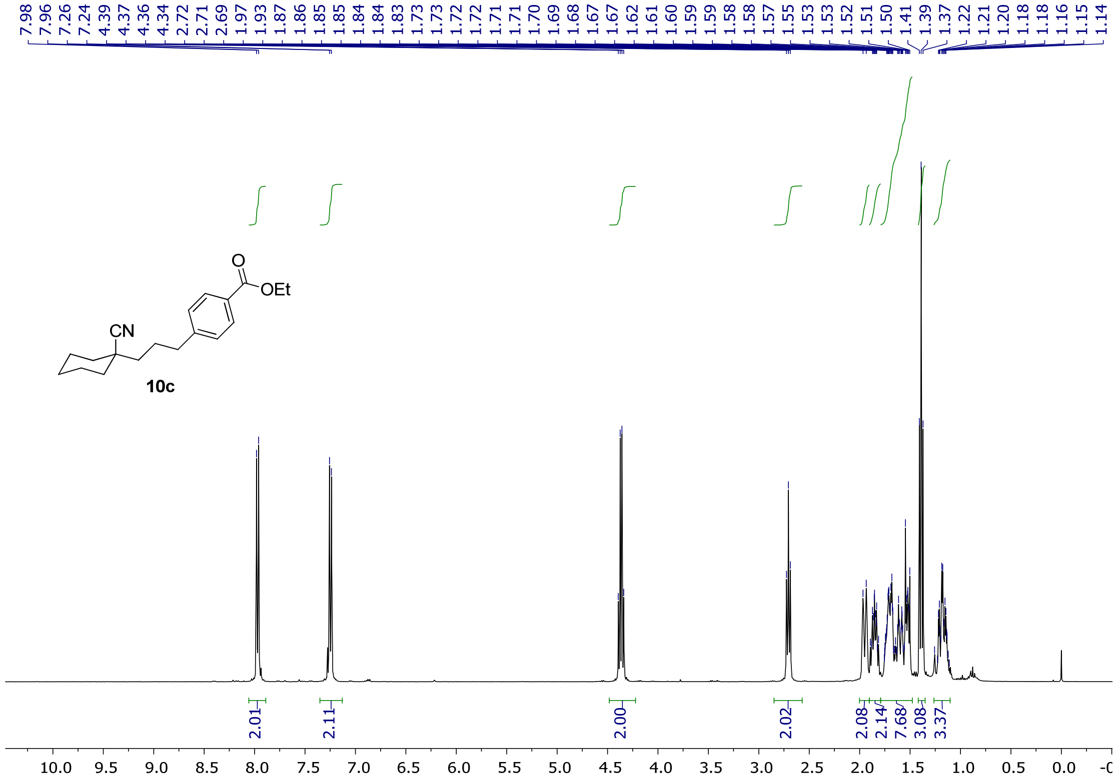

166.25
131.51
129.84
129.40
127.29
90.53
84.58
61.32
51.29
14.25
00 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10

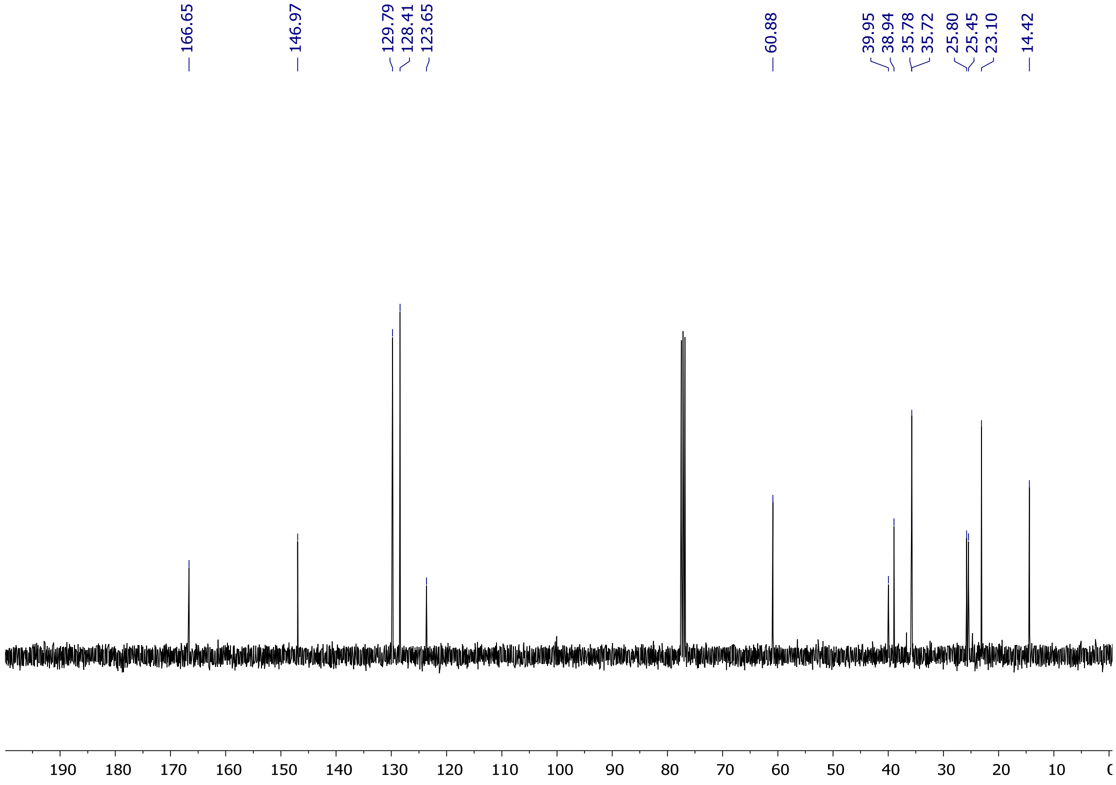

7.96
7.94
7.26
7.24
4.38
4.36
4.34
4.32
3.66
3.64
3.63
3.05
2.76
2.75
2.73
1.92
1.90
1.90
1.89
1.89
1.88
1.88
1.87
1.87
1.86
1.85
1.39
1.37
1.36
EtO
OH
O
iii
2.00
2.03
2.06
2.01
1.00
2.05
2.06
3.11
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0


166.76
147.50
129.60
128.37
127.94
61.60
60.82
33.78
32.04
14.25
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

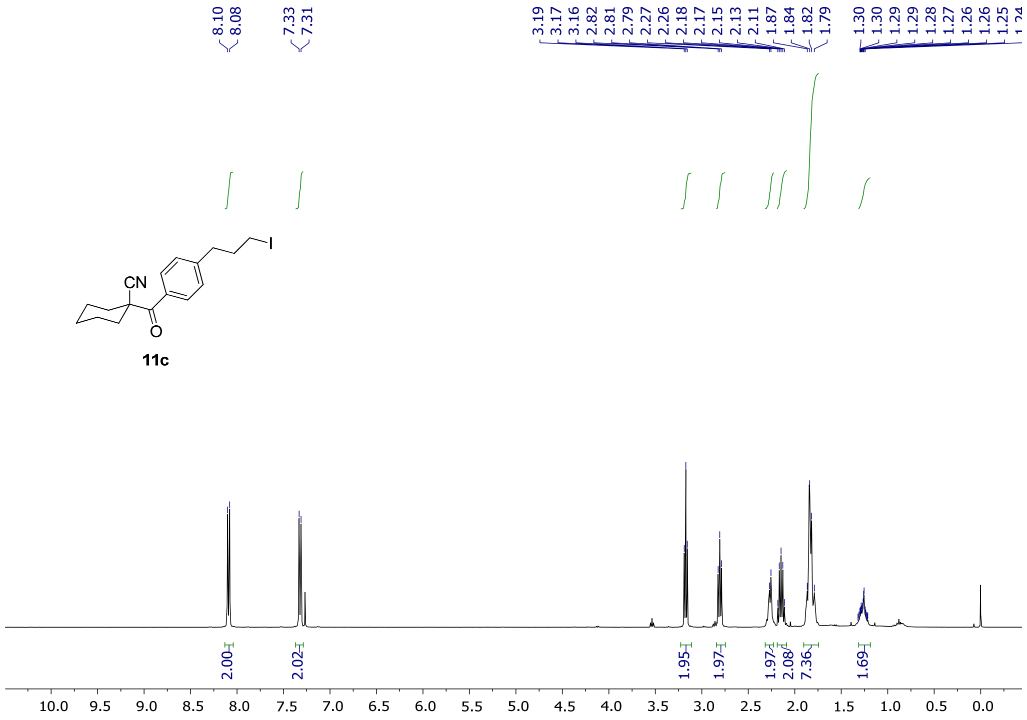

7.99
7.97
7.28
7.26
4.40
4.38
4.36
4.34
3.18
3.16
3.15
2.81
2.79
2.77
2.18
2.16
2.14
2.12
2.11
1.41
1.39
1.37
EtO
O
I
12
1.90
2.70
2.00
2.00
2.00
2.08
3.14
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

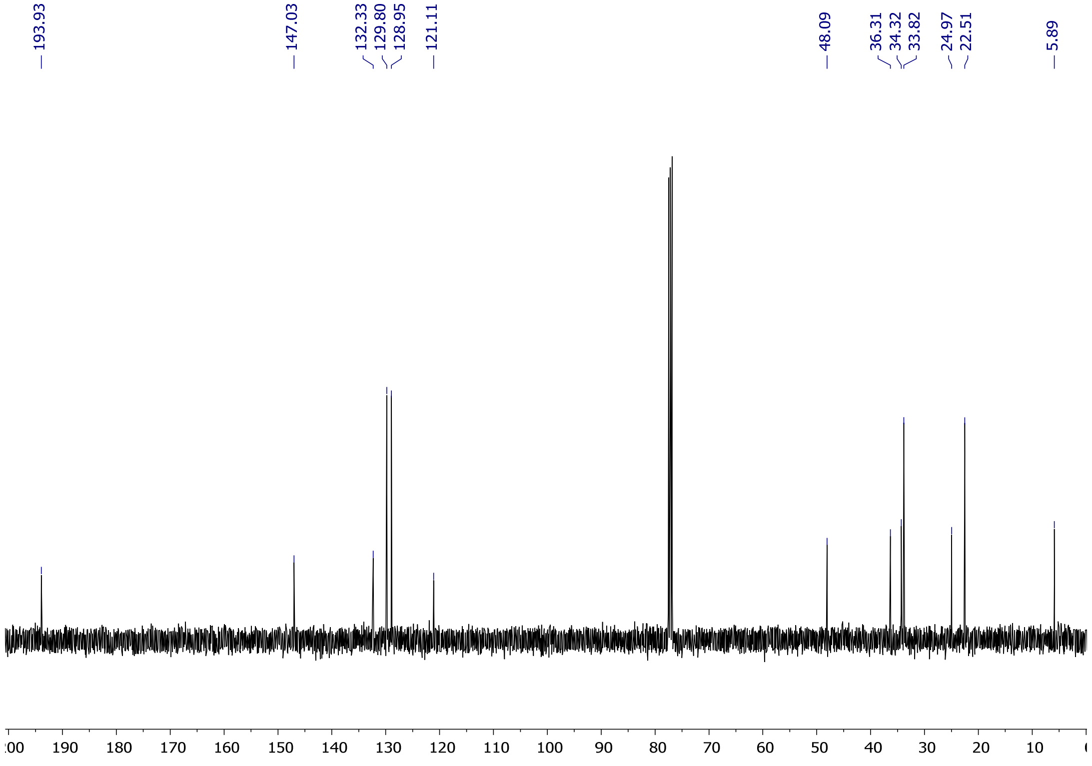

166.69
145.88
129.95
128.69
61.01
36.35
34.56
14.50
6.03
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

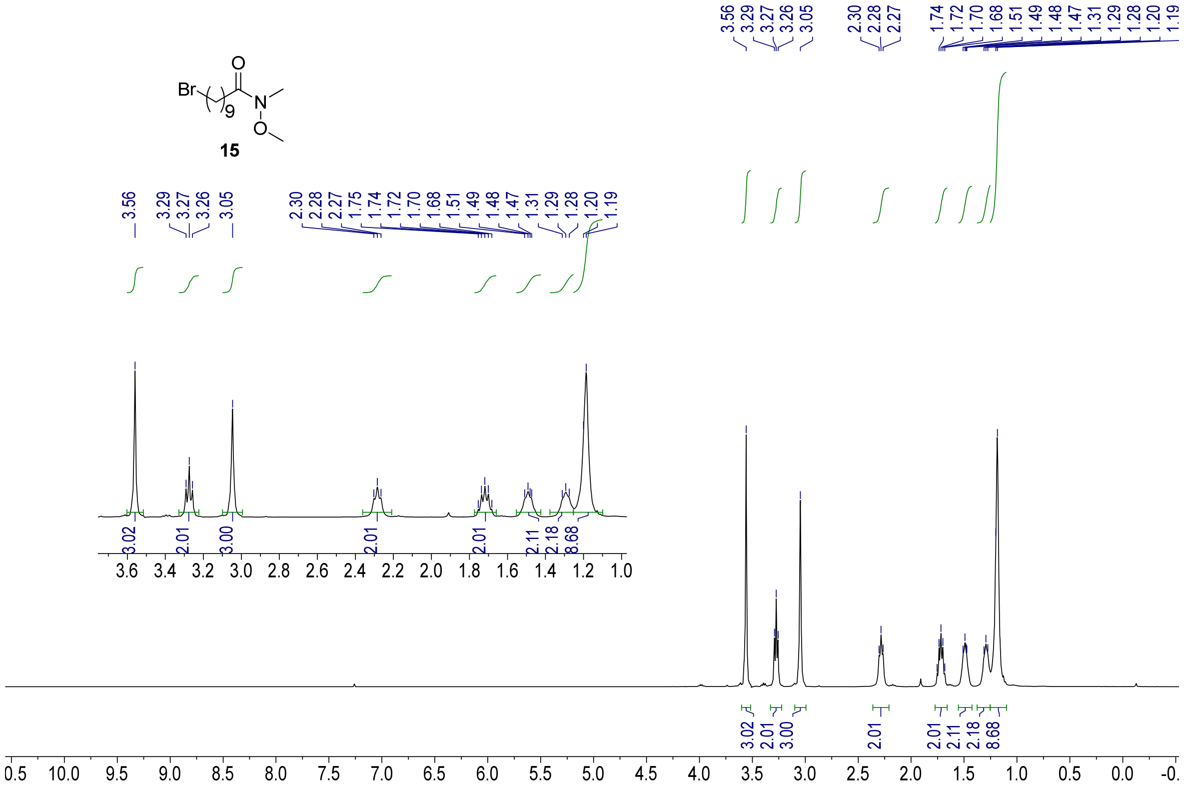

7.98
7.96
7.26
7.24
4.39
4.37
4.36
4.34
2.72
2.71
2.69
1.97
1.93
1.87
1.86
1.85
1.85
1.84
1.84
1.83
1.73
1.73
1.72
1.72
1.71
1.71
1.70
1.69
1.68
1.67
1.67
1.62
1.61
1.60
1.59
1.59
1.58
1.58
1.57
1.55
1.53
1.53
1.52
1.51
1.50
1.41
1.39
1.37
1.22
1.21
1.20
1.18
1.18
1.16
1.15
1.14
O
OEt
CN
10c
2.01
2.11
2.00
2.02
2.08
2.14
7.68
3.08
3.37
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0


166.65
146.97
129.79
128.41
123.65
60.88
39.95
38.94
35.78
35.72
25.80
25.45
23.10
14.42
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10

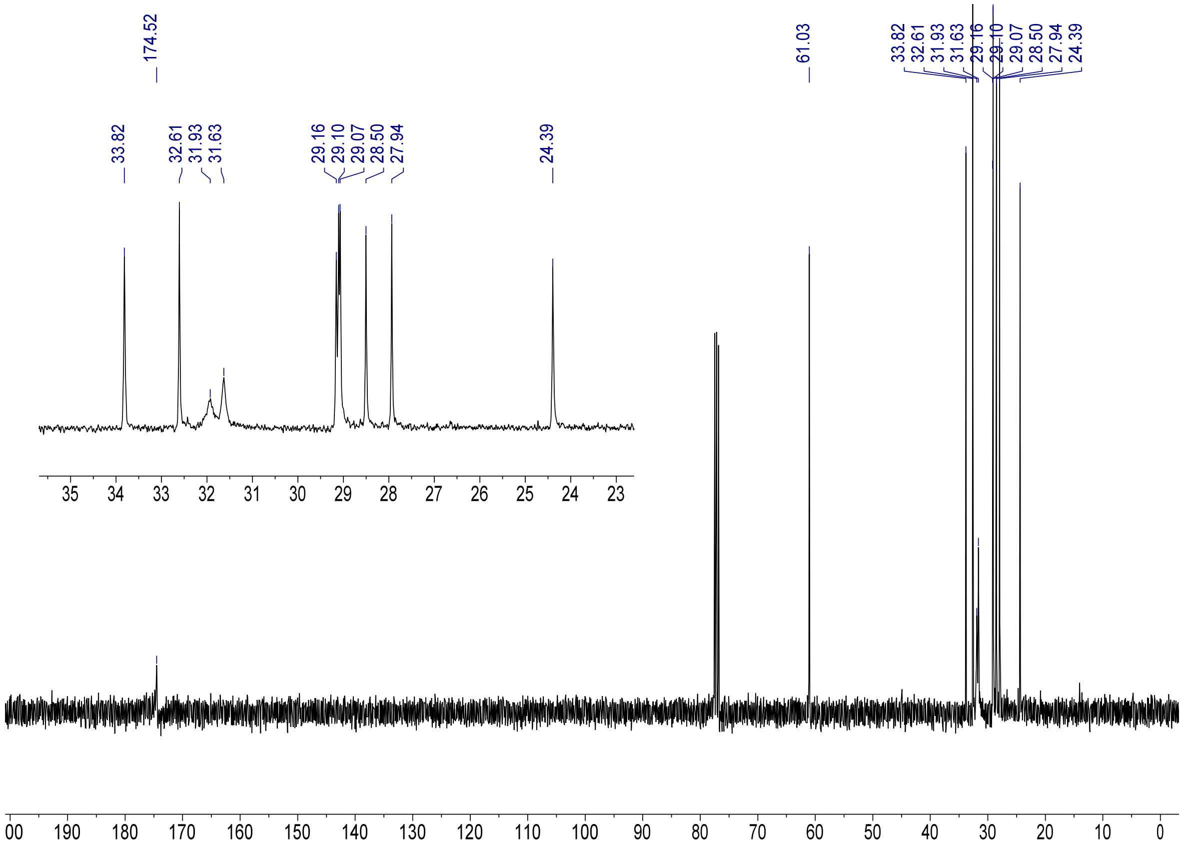
11c

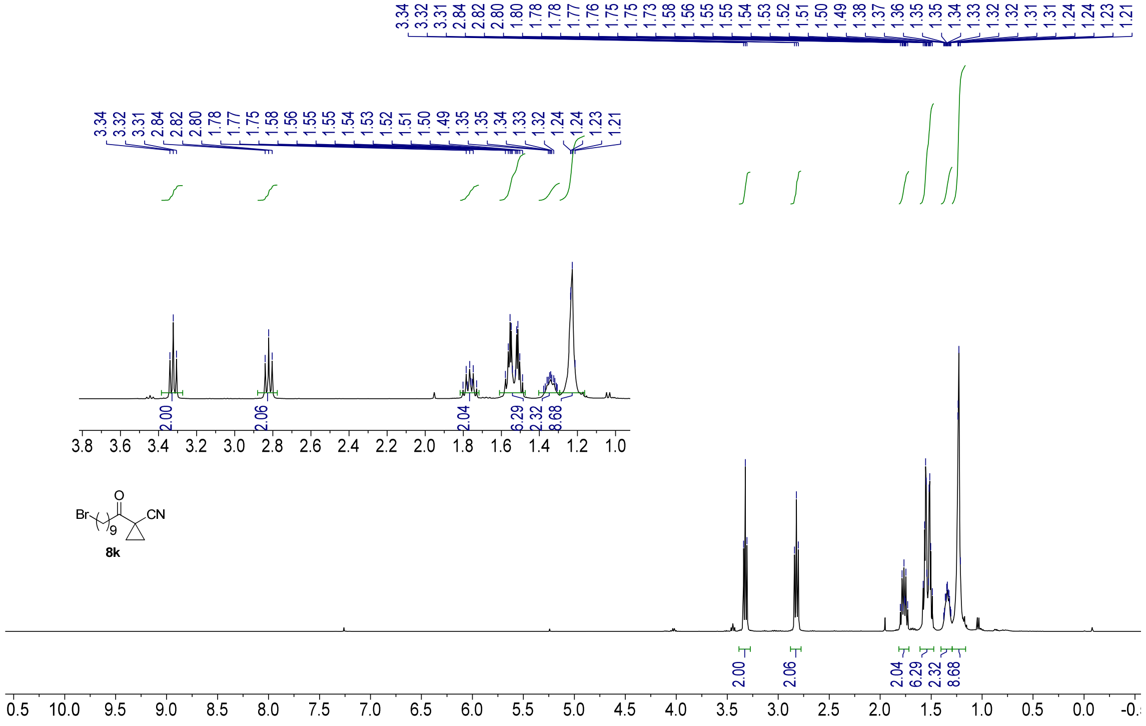

8.10
8.08
7.33
7.31
3.19
3.17
3.16
2.82
2.81
2.79
2.27
2.26
2.18
2.17
2.15
2.13
2.11
1.87
1.84
1.82
1.79
1.30
1.30
1.29
1.29
1.28
1.27
1.26
1.26
1.25
2.00
2.02
1.95
1.97
1.97
2.08
7.36
1.69
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

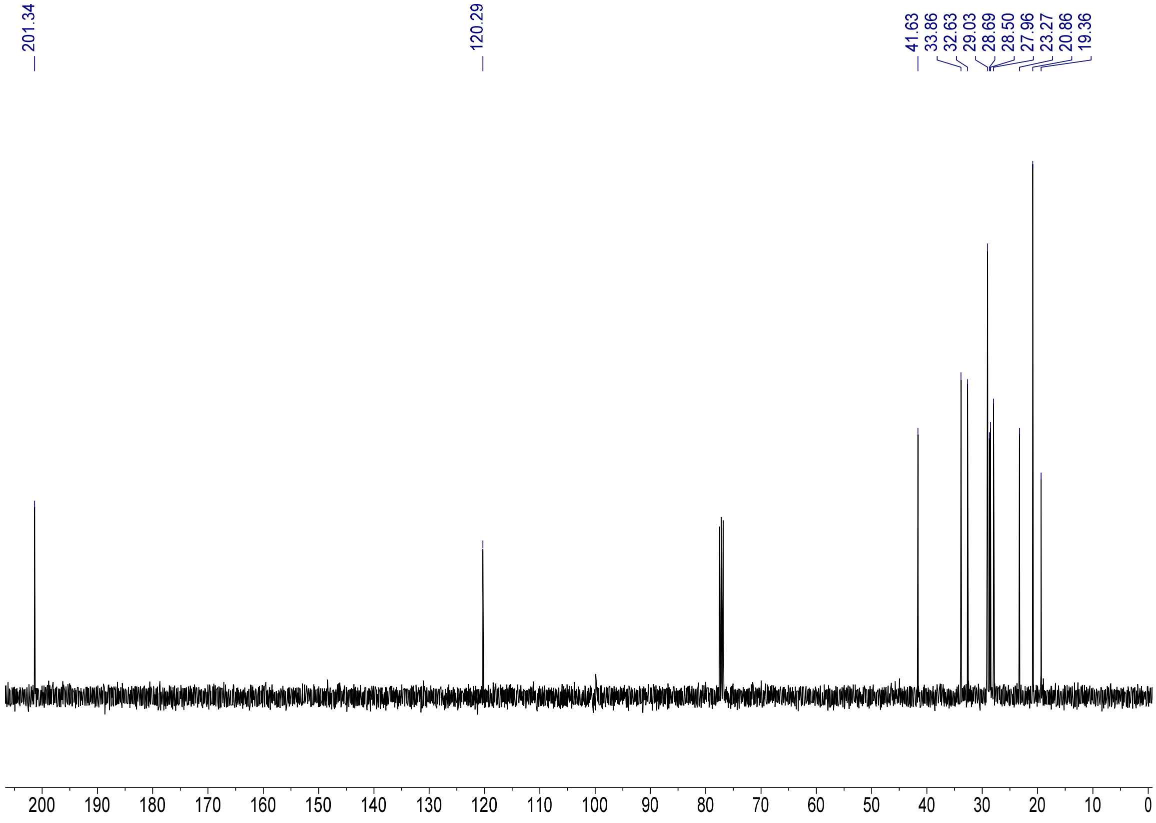

193.93
147.03
132.33
129.80
128.95
121.11
48.09
36.31
34.32
33.82
24.97
22.51
5.89
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10

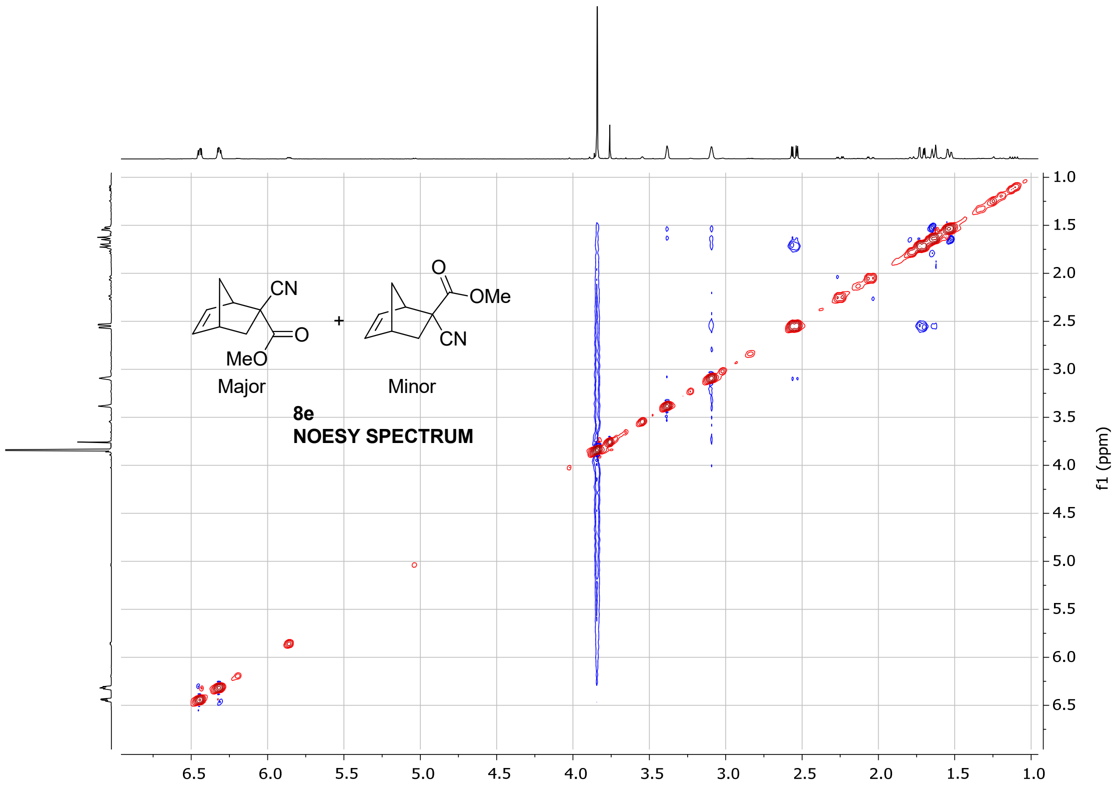

Br
O
N
O
9
3.56
3.29
3.27
3.26
3.05
2.30
2.28
2.27
1.75
1.74
1.72
1.70
1.68
1.51
1.49
1.48
1.47
1.31
1.29
1.28
1.20
1.19
3.02
2.01
3.00
2.01
2.01
2.11
2.18
8.68
3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0 1.8 1.6 1.4 1.2 1.0
0.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.

15

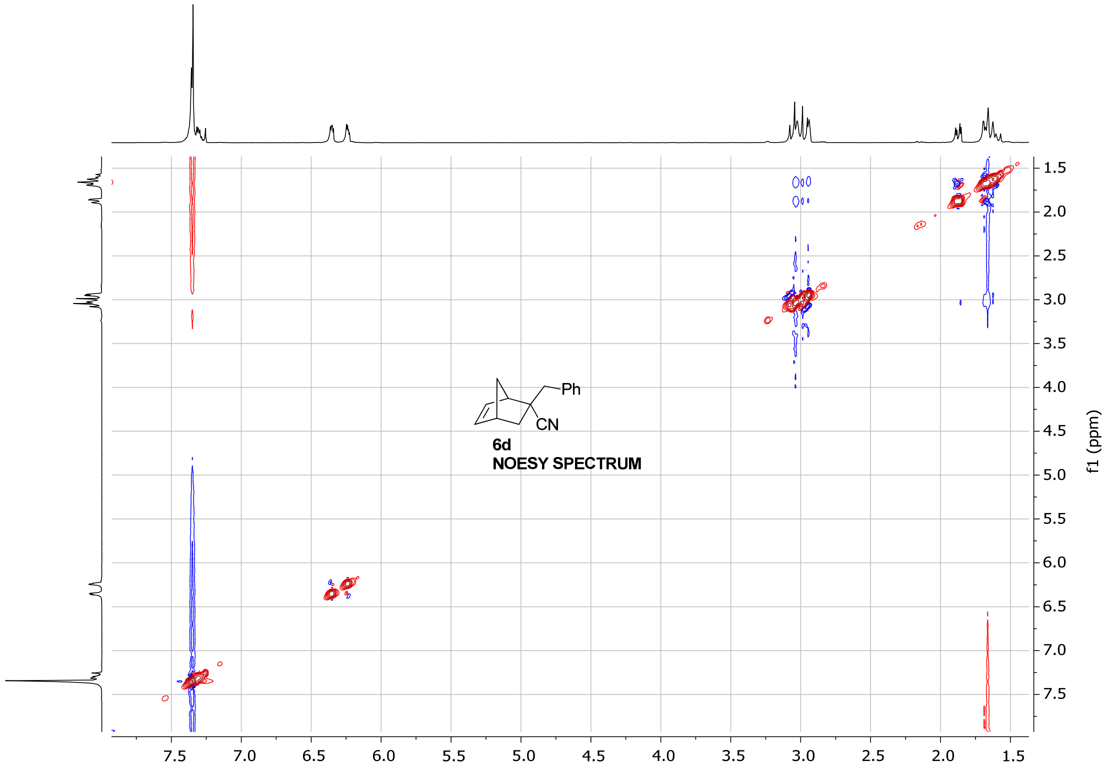

174.52
61.03
33.82
32.61
31.93
31.63
29.16
29.10
29.07
28.50
27.94
24.39
35 34 33 32 31 30 29 28 27 26 25 24 23
00 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0


3.34
3.32
3.31
2.84
2.82
2.80
1.80
1.78
1.78
1.77
1.76
1.75
1.75
1.73
1.58
1.56
1.55
1.55
1.54
1.53
1.52
1.51
1.50
1.49
1.38
1.37
1.36
1.35
1.35
1.34
1.33
1.32
1.32
1.31
1.24
1.24
1.23
1.21
3.34
3.32
3.31
2.84
2.82
2.80
1.78
1.77
1.75
1.58
1.56
1.55
1.55
1.54
1.53
1.52
1.51
1.50
1.49
1.35
1.35
1.34
1.33
1.32
1.24
1.24
1.23
1.21
2.00
2.06
2.04
6.29
2.32
8.68
3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0 1.8 1.6 1.4 1.2 1.0
Br
O
9
CN
8k
2.00
2.06
2.04
6.29
2.32
8.68
0.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.


201.34
120.29
41.63
33.86
32.63
29.03
28.69
28.50
27.96
23.27
20.86
19.36
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0



CN
O
MeO
Major
+
O
OMe
CN
Minor
8e
NOESY SPECTRUM
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
f1 (ppm)



Ph
CN
6d
NOESY SPECTRUM
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
f1 (ppm)