Supporting Information

Nickel-Catalyzed Reductive Cross-Coupling of Unactivated Alkyl Halides

Xiaolong Yu, Tao Yang, Shulin Wang, Hailiang Xu, and Hegui Gong*

Department of Chemistry, Shanghai University, 99 Shang-Da Road, Shanghai 200444, China

Hegui_gong@shu.edu.cn

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Experimental Section

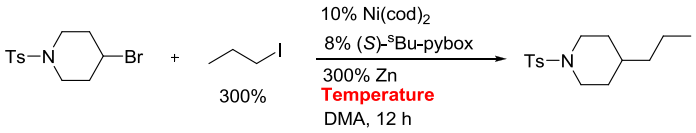
Part 1. General Information

All reagents were reagent grade quality and used as received from Aladdin Co. (China), unless otherwise indicated. All reactions were carried out under an atmosphere of nitrogen unless otherwise indicated. Anhydrous THF was distilled from sodium/benzophenone ketyl prior to use. Andrydrous DCM and MeOH were distilled over CaH_2. All other solvents were technical grade unless noted. The following reagents were purchased, and used as received: anhydrous *N*,*N*-dimethylimidazolidinone (DMI, Aldrich), anhydrous DMF (Acros), DMA (anhydrous and 99.5% extra pure, Acros), $NiCl_2$(Alfa Aesar), $NiBr_2$ (Alfa Aesar), NiI_2 (Alfa Aesar), $Ni(COD)_2$ (Aldrich), zinc powder (Aldrich), I_2 (Aldrich), ^{t}Bu-Terpy (Aldrich) and bathophenanthroline (Alfa Aesar), 1-iodoheptane, 1-iododododecane, and *exo*-2-bromobicyclo[2.2.1]heptane **10a** (Aldrich). The following alkyl halides were purchased and redistilled prior to use: bromocylcohexane, bromocyclopropane, bromocyclopetane, 4-bromobut-1-ene, 2-(2-bromoethyl)-1,3-dioxolane (entry 14, Table 2) and 3-bromopropan-1-ol (entry 9, Table 2), 2-bromopropane and 2-bromobutane. Column chromatography was performed using silica gel 300-400 mesh (purchased from Qingdao-Haiyang Co. China) as the solid support. All NMR spectra were recorded on Bruker Avance 500MHz spectrometer at STP unless otherwise indicated. ^{1}H NMR and ^{13}C NMR chemical shifts are reported in δ units, parts per million (ppm) relative to the chemical shift of residual solvent. Deuterated solvents were used as received from Cambridge Isotope Laboratories, Inc. NMR chemical shifts are reported in δ units, parts per million (ppm) relative to the chemical shift of residual solvent. Reference peaks for chloroform in ^{1}H NMR and ^{13}C NMR spectra were set at 7.28 ppm and 77.0 ppm, respectively. High-resolution mass spectra (HRMS) were obtained using a Bruker APEXIII 7.0 and IonSpec 4.7 TESLA FTMS. Melting point was recorded on a micro melting point apparatus (X-4, YUHUA Co., Ltd, Gongyi, China). Analytical HPLC experiments were performed on a Shimadzu LC-6A HPLC instrument.

Part 2. Details of Optimization and Control experiments

A typical procedure for optimization screens and control reactions: To a flame-dried Schlenk tube equipped with a stir bar was loaded alkyl bromide (R^1-Br, 0.157 mmol, 100 mol%), followed by addition of ligand (0.013 mmol, 8 mol%) and zinc powder (31.0 mg, 0.471 mmol, 300 mol%). The tube was moved to a dry glove box, at which point $Ni(COD)_2$ (4.4 mg, 0.016 mmmol, 10 mol%) was added. The tube was capped with a rubber septum, and it was moved out of the glove box. A second alkyl halide R^2-X (X = I or Br, 0.471 mmol, 300 mol%) and DMA (1 mL) were then added *via* syringe. After the reaction mixture was allowed to stir for 12 h (X = I) or 16 h (X =Br) under N_2 atmosphere at 25 ℃, it was directly loaded onto a silica column without work-up. The residue in the reaction vessel was rinsed with small amount of DCM. Flash column chromatography (SiO_2: ethyl acetate in hexanes) provided the product.

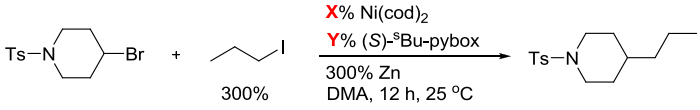
Table S1. Temperature screen.



Entry	T (℃)	Yield (%)[a]
1	0	trace
2	20	67
3	40	48
4	60	trace

[a] Isolated yields.

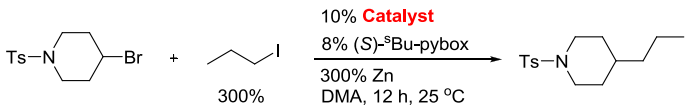
Table S2 Variation of the stoichiometry of catalyst and ligand.



Entry	X mol%	Y mol%	Yield (%)[a]
1	20	15	67
2	10	15	35
3	10	10	57
4	10	8	67
5	10	5	43
6	10	0	ND[b]

[a] Isolated yields. [b] Not detected (with recovered **1**).

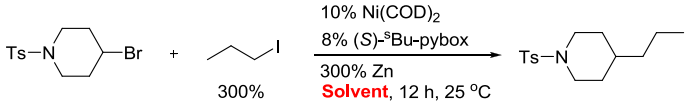
Table S3. Catalyst screen.



Entry	Catalyst	Yield (%)[a]
1	$Ni(COD)_2$	67
2	$NiCl_2$	trace
3	$NiBr_2$	56
4	NiI_2	35
5	None	ND[b]

[a] Isolated yields. [b] Not detected.

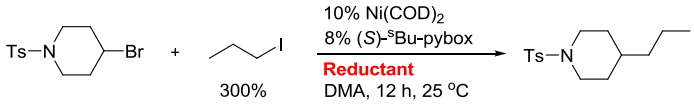
Table S4. Solvent screen.



Entry	Solvent	Yield (%)[a]
1	DMA (extra dry)	63
2	DMA (extra pure)	67
3	DMA (AR Grade)	62
4	DMA (extra pure with 0.5 equiv. H_2O)	67
5	DMF	11
6	NMP	5
7	DMI	8
8	DMPU	55
9	DMA: THF (1:1)	38
10	THF	trace

[a] Isolated yields.

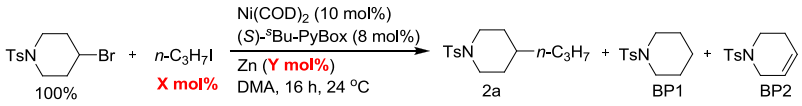
Table S5. Screen of reductants.



Entry	R-X	Reductant	**2**/ Yield (%)[a]	Recovered **1** (%)[a]	R-R (%)[a]
1	*n*-C_3H_7I	Zn	**2a**/ 67	NA[c]	NA
2	*n*-C_3H_7I	Mn	**2a**/ 40	NA	NA
3	*n*-C_3H_7I	TDAE	**2a**/ 33	NA	NA
4	*n*-C_3H_7I	In	**2a**/ trace	NA	NA
5	*n*-C_3H_7I	None	**2a**/ ND[b]	NA	NA
6	*n*-$C_7H_{15}I$	TDAE	**2c**/ 36	63	75
7	$BzO(CH_2)_5I$	Mn	**2i**/ 25	57	79
8	$BzO(CH_2)_5Br$	Mn	**2i**/ 30	NA	NA

[a] Isolated yields. [b] Not detected. [c] Not available

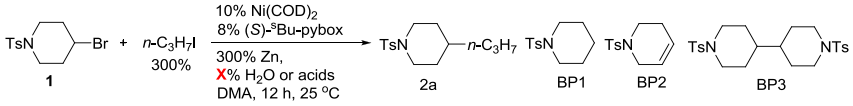
Table S6. Variation of the ratio of *n*-C_3H_7I and Zn.



Entry	X (mol%)	Y (mol%)	Yield (%)[a]		
			2a	BP1	BP2
1	150	150	47	trace	trace
2	200	200	57	trace	trace
3	200	300	59	trace	trace
4	250	300	64	trace	trace
5	300	300	67	trace	trace
6	400	300	61	5	2
7	500	300	49	trace	trace
8	500	500	66	trace	trace

[a] Yields were determined based on NMR analysis of a mixture of 2a, BP1, BP2 after a flash column chromatography.

Table S7. Effects of water and acids.



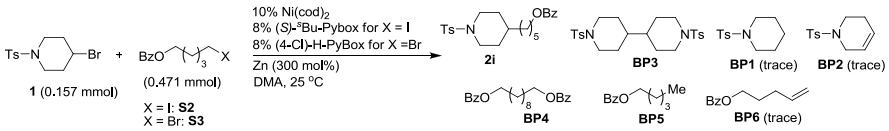
Entry	X (mol%)	Proton Source	Yield (%)				
			2a [a]	BP1 [a]	BP2 [a]	BP3[b]	**1**
1	100	H_2O	62	trace	trace	>30	ND[c]
2	300	H_2O	56	8	trace	>25	ND[c]
3	400	H_2O	31	13	trace	Major	trace
4	800	H_2O	20	23	trace	NA[d]	18
5	1600	H_2O	10	36	trace	NA[d]	45
6	300	4-OMe-Phenol	46	36	trace	>15	trace
7	300	4-Br-Phenol	48	12	trace	NA[d]	18
8	300	Benzoic acid	15	23	trace	NA[d]	55

[a] Yields were estimated based on NMR analysis of a mixture of **2a**, BP1, BP2, and **1** after a flash column chromatography. [b] isolated yields. [c] Not detected based on NMR analysis. [c] Not available.

Part 3. Profiles of Byproducts

(1) Profiles of Byproducts at the Time When One of the Starting Materials Was Consumed.

Table S8. Cross-coupling of **1** with 5-halopentyl benzoate.



		Yield (%)					
Time	**X**	**1**[a]	**2i**[a]	S2 or S3[b]	BP4[b,c]	BP5[b,c]	BP3
1h	I	61	30	0	77	10	trace
4h	Br	trace	60	30	51	4	substantial

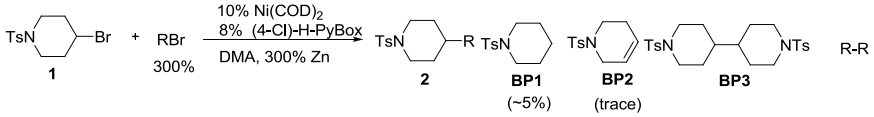
[a] The yields were estimated based on NMR analysis of a mixture containing **2i**, BP1, BP2, BP4 and **1** after a flash column chromatography. [b] The yields were estimated based on NMR analysis of a mixture containing BP4**,** BP6 and S2 or S3 after a flash column chromatography. [c] Yields are based on *n*-$C_7H_{15}X$.

Table S9. Cross-coupling of **1** with *n*-heptyl halides.

		Yield (%)				
Time	X	**1**[a]	**2c**[a]	*n*-$C_7H_{15}X$[b]	*n*-$C_{14}H_{30}$[b,c]	BP3[d]
2 h	I	31	60	trace	75	minor
4 h	Br	0	62	62	9	substantial

[a] The yields were estimated based on NMR analysis of a mixture containing **2c**, BP1, BP2 and **1**. [b] The yields were estimated based on NMR analysis of a mixture containing *n*-$C_7H_{15}X$ and n-$C_{14}H_{30}$ after a flash column chromatography. [c] Yields are based on *n*-$C_7H_{15}X$. [d] BP3 represents the homocoupling byproduct of **1**.

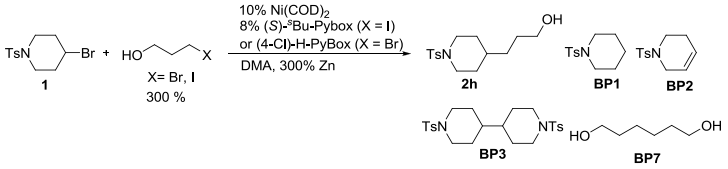
Table S10. Cross-coupling of **1** with phthalimidylpropyl (entry 8, Table 2) and 1-butenyl (entry 13, Table 2) bromides.



		Yield (%)				
Time	R	**1**	**2**[a]	RBr[b]	R-R[b,c]	BP3
3 h	phthalimidylpropyl	0	65 (**2g**)	~20	56	substantial
4.5 h	1-butenyl	0	83 (**2j**)	~20	49	minor

[a] The yields were estimated based on NMR analysis of a mixture containing **2**, BP1, BP2 and **1**. [b] The yields were estimated based on HPLC (for **2j**) or NMR analysis of a mixture containing R-Br and R-R after a flash column chromatography (for **2g**). [c] Yields are based on R-Br.

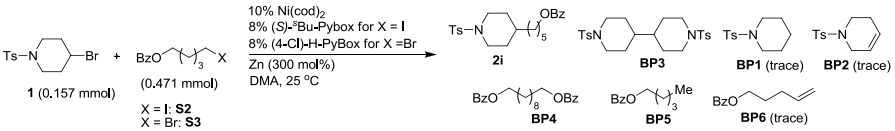
Table S11. Cross-coupling of **1** 3-halopropanol (entries 9-10, Table 2).



		Yield (%)						
Time	**X**	**1**[a]	**2h**[a]	$X(CH_2)_3OH$[b]	BP1[a]	BP2[a]	BP3[c]	BP7[c,d]
12 h	I	10	17	0	10	8	52	85
16 h	Br	0	60	Trace	7	0	28	72

[a] The yields were estimated based on NMR analysis of a mixture containing **2h**, BP1, BP2 and **1** after a flash column chromatography. [b] Based on NMR analysis after a flash column chromatography. [c] Isolated yield. [d]. Yields are based on $X(CH_2)_3OH$

(2) Tracking the reaction progress for the coupling of 1 with 5-iodo and bromopentyl benzoate.



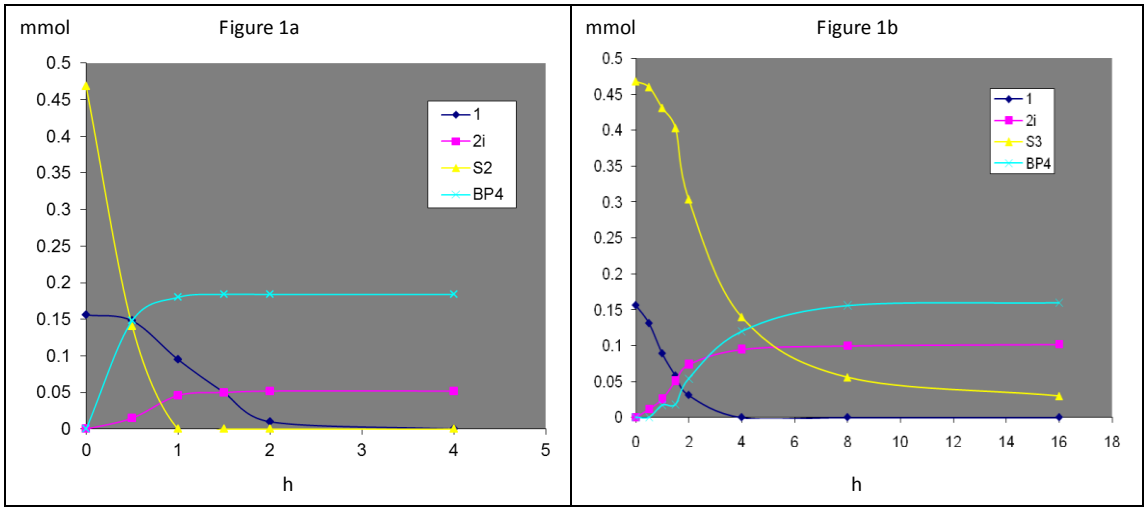
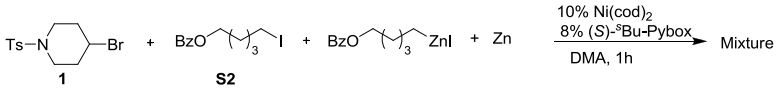


Figure 1a (left). The coupling of **1** with 5-iodopentyl benzoate;
Figure 1b (right). The coupling of **1** with 5-bromopentyl benzoate.

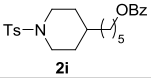
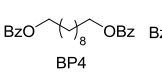
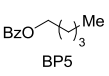
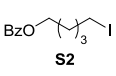
Part 4. Organozinc Formation and Negishi Studies.

(1) Comparison of the Negishi coupling with the Ni(COD)$_2$/Zn coupling chemistry.

Table S12. Comparison of the Negishi coupling with the Ni(COD)$_2$/Zn coupling chemistry.



Method A:	0.16 mmol	0.16 mmol (1 equiv)	0.24 mmol (1.5 equiv)	0 mmol
Method B:	0.16 mmol	0.48 mmol (3 equiv)	0 mmol	0.48 mmol (3 equiv)
Method C:	0.16 mmol	0.24 mmol (1.5 equiv)	0.24 mmol (1.5 equiv)	0 mmol

entry[a]	method	1	 2i	 BP4	 BP5	 S2
1	A	0.15 mmol (95%)	0.01 mmol (6%)	0.08 mmol	0.11 mmol	0.07 mmol (44%)
2	B	0.10 mmol (63%)	0.05 mmol (30%)	0.18 mmol	0.05 mmol	0
3	C	0.15 mmol (94%)	0.01 mmol (6%)	0.10 mmol	0.10 mmol	0.13 mmol (54%)

[a] The yields were estimated based on NMR analysis of a mixture containing **2i**, BP1, BP2 and **1**, and a second mixture containing BP4, BP5 and S2 after a flash column chromatography.

(2). Studies of organozinc formation

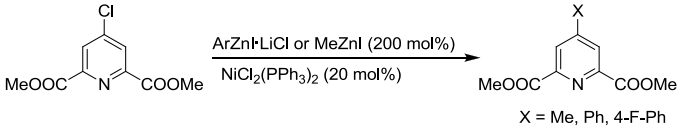
General procedure for the studies of organozinc formation: To a flame-dried Schlenk flask equipped with a magnetic stir bar was added Zn (100 mol% or 300 mol%) and Ni(COD)$_2$ (10 mol%) if applicable in a glove box. After the flask was moved out of the glove box, it was heated at 70 ℃ for 30 min in vacuo. A solution of I_2 in DMA was then added to the flask via syringe (if applicable), followed by the addition of alkyl halides (100 mol%). For the liquid alkyl halides, addition was carried out through a syringe; for the solid aryl halides, addition was performed under N_2 atmosphere. The resultant mixture was allowed to stir for a given time at 25 ℃.

Quenching the reactions was performed using MeOH (or CD_3OD), SiO_2 or I_2. Analysis of the results was carried out using NMR after a flash column chromatography (for **1**, (bromomethyl)cyclopropane and 5-halopentyl benzoate), or HPLC after passing the crude reaction mixture through a silica pad (for 5-halopenyl benzoate).

Part 5. Preparation of PyBox Ligands[1-6]

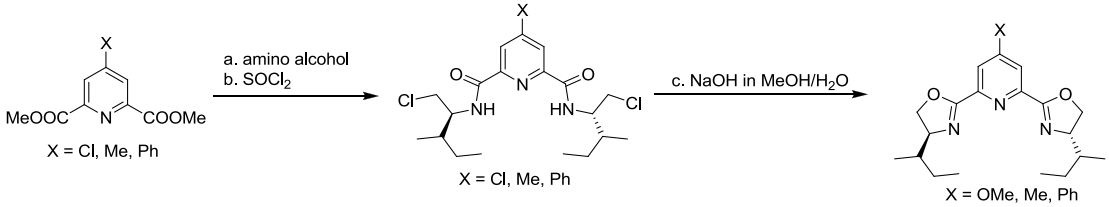
(1) (*S*)-R-PyBox ligands (R = ^{s}Bu (**3a**), Me (**3b**), ^{i}Pr (**3c**), Ph (**3d**), ^{t}Bu (**3e**)),[1] (4-Cl)-H-PyBox (**3n**),[2](4-OMe)-H-PyBox (**3m**)[2] and H-PyBox (**3j**)[1] are literature known compounds.

(2) Synthesis of 4-substituted dimethyl pyridine-2,6-dicarboxylate:



To a flame-dried Schlenk tube equipped with a stir bar was loaded dimethyl 4-chloropyridine-2,6-dicarboxylate[3] (100 mol%) followed by $NiCl_2(PPh_3)_2$ (20 mol%). The flask was capped with a rubber septum, and was evacuated and back-filled N_2 three times. A solution of organozinc reagents[4] (~0.5 M, determined by titration with I_2[5]) in DMF was then added to the flask *via* syringe. The resultant reaction mixture was allowed to stir for 24 h at 25 ℃, at which point the reaction mixture was directly loaded to a silica column without work-up. Flash column chromatography offered the 4-Me pyridinyl dimethyl ester in 76% yield, 4-ph-pyridinyl diemthyl ester in 72 % yield, and (4-(4-F-Ph))-pyridinyl dimethyl ester in 65% yield, respectively.

(2) Preparation of (4-X)-(*S*)-^{s}Bu-PyBox ligands (X = Me, Ph and OMe):[1,6]



Reaction conditions: (a). (*2S*,*3S*)-2-amino-3-methylpentan-1-ol (220 mol%), 120 ℃, neat. (b). $SOCl_2$ (1000 mol%), $CHCl_3$ (~ 0.2 M), 70 ℃ for 2 h. c. NaOH (1000 mol%) in MeOH/ H_2O (v/v, 2:1), 3 d.

(1) Nishiyama, H.; Kondo, M.; Nakamura, T. Itoh, K. *Organometallics* **1991**, *10*, 500–508.

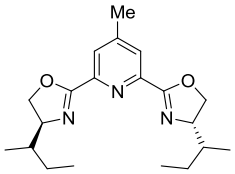
(2) Vermonden, T.; Branowska, D.; Marcelis, A. T. M.; Sudholter, E. J. R. *Tetrahedron*, **2003**, *59*, 5039–5045.

(3) Chavarot, M.; Socquet, S.; Kotera, M.; Lhomme, J. *Tetrahedron*, **1997**, *53*, 13749–13756.

(4) (a) Huo, S. *Org. Lett.* **2003**, *5*, 423–425. (b) Krasovskiy, A.; Malakhov, V.; Gavryushin, A.; Knochel, P. *Angew. Chem. Int. Ed.* **2006**, *45*, 6040–6044.

(5) Krasovskiy, A.; Knochel, P. *Synthesis* **2006**, 890–891.

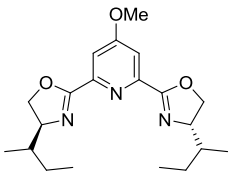
(6) Parsons, A. T.; Johnson, J. S. *J. Am. Chem. Soc*. **2009**, *131*, 3122–3123.



3f

(*S*,4*S*,4′*S*)-2,2'-(4-Methylpyridine-2,6-diyl)bis(4-sec-butyl-4,5-dihydrooxazole)

((4-Me)-(*S*)-^{s}Bu-PyBox (3f)). [1-3,6] Following the literature procedures, this compound was prepared first by heating a mixture of dimethyl 4-methylpyridine-2,6-dicarboxylate (0.20 g, 100 mol%, 0.96 mmol) and (*S*)-^{s}Bu-amino alcohol (0.25 g, 220 mol%, 2.10 mmol) at 120 ℃ for 2 h. After it was cooled to room temperature, the resulting crude material was dissolved in $CHCl_3$ (4.0 mL), followed by addition of $SOCl_2$ (0.70 mL). The reaction mixture was heated at 70 ℃ for 2 h, at which point it was slowly poured into ice water. DCM (10 mL) was added. The organic layer was collected, washed with brine (5.0 mL), aqueous K_2CO_3 (0.1 M, 5.0 mL), and dried over anhydrous $MgSO_4$, After the solvent was removed, the residue was purified by flash column chromatography to give the dichloride intermediate, which was then treated with NaOH (9.6 mmol, 1000 mol%, 1.0 M) in MeOH/ H_2O (v/v, 2:1) for 3 days. The mixture was extracted with CH_2Cl_2(55.0 mL) and the extract was washed with brine. The organic layer was collected and dried, to which silica gel was added. After the solvent was removed under reduced pressure, the residue was loaded onto a silica column. Flash column chromatography (SiO_2: 50% ethyl acetate in hexanes) gave (4-Me)-(*S*)-^{s}Bu-PyBox (**3f**) as colorless oil (0.12 g, 35% yield over 3 steps). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.00 (s, 2H), 4.49 (d, *J* = 7.5 Hz, 1H), 4.48 (d, *J* = 7.5 Hz, 1H), 4.18-4.30 (m, 4H), 2.43 (s, 3H), 1.68-1.76 (m, 2H), 1.59-1.67 (m, 2H), 1.19-1.29 (m, 2H), 0.94 (t, *J* = 7.5 Hz, 6H), 0.86 (d, *J* = 6.5 Hz, 6H).^{13}C NMR (125MHz, $CDCl_3$): δ 162.3, 148.8, 146.5, 126.4, 71.3, 70.4, 39.0, 26.0, 20.8, 14.4, 11.4. HRMS (ESI): m/z $[M]^+$ found 343.2259, calcd 343.2260 for $C_{20}H_{29}N_3O_2$.

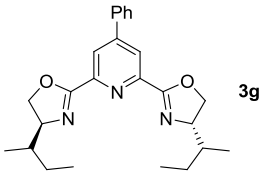


3h

(*S*,4*S*,4′*S*)-2,2'-(4-Methoxypyridine-2,6-diyl)bis(4-sec-butyl-4,5-dihydrooxazole)

((4-MeO)-(*S*)-^{s}Bu-PyBox (3h)). [1-3,6] Following the literature procedures, this compound was prepared first by heating a mixture of dimethyl 4-chloropyridine-2,6-dicarboxylate(0.20 g, 0.87 mmol) and (*S*)-^{s}Bu-amino alcohol (0.22 g, 220 mol%, 1.91 mmol) at 120 ℃ for 2 h. After it was cooled to

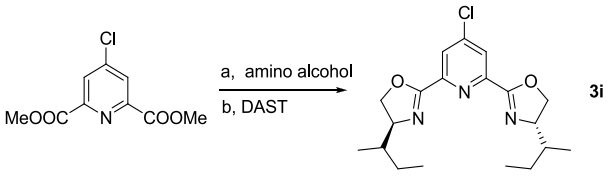
room temperature, the resulting crude material was dissolved in $CHCl_3$ (4.0 mL) followed by addition of $SOCl_2$ (0.60 mL). The reaction mixture was heated at 70 ℃ for 2 h, at which point it was slowly poured into ice water. DCM (10 mL) was added. The organic layer was collected, washed with brine (5.0 mL) and aqueous K_2CO_3 (0.1 M, 5.0 mL), and dried over anhydrous Na_2SO_4. Flash column chromatography gave the dichloride, which was then treated with NaOH (8.7 mmol, 1000 mol%, 1.0 M) in MeOH/ H_2O (v/v, 2:1) for 3 days. The mixture was extracted with CH_2Cl_2 (55.0 mL) and the extract was washed with brine. The organic layer was collected and dried, to which silica gel was added. After the solvent was removed under reduced pressure, the residue was loaded onto a silica column. Flash column chromatography (SiO_2: 50% ethyl acetate in hexanes) gave (4-MeO)-(*S*)-^{s}Bu-PyBox (**3h**) as colorless oil (0.094, 30% yield, over 3 steps). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.70 (s, 2H), 4.52 (d, *J* = 7.5 Hz, 1H), 4.50 (d, *J* = 7.5 Hz, 1H), 4.20-4.30 (m, 4H), 3.96 (s, 3H), 1.70-1.78 (m, 2H), 1.62-1.69 (m, 2H), 1.22-1.31 (m, 2H), 0.97 (t, *J* = 7.5 Hz, 6H), 0.89 (d, *J* = 7.0 Hz, 6H). ^{13}C NMR (125MHz, $CDCl_3$): δ 166.6, 162.2, 148.3, 111.7, 71.3, 70.5, 55.8, 39.1, 26.1, 14.4, 11.5. HRMS (ESI): m/z $[M]^+$ found 359.2214, calcd 359.2209 for $C_{20}H_{29}N_3O_3$.



3g

(*S*,*4S*,*4'S*)-2,2'-(4-Phenylpyridine-2,6-diyl)bis(4-sec-butyl-4,5-dihydrooxazole) ((4-Ph)-(*S*)-^{s}Bu-PyBox (3g)).[1-3,6] Following the literature procedures, this compound was prepared first by heating a mixture of dimethyl 4-phenylpyridine-2,6-dicarboxylate (0.20 g, 0.74 mmol) and (*S*)-^{s}Bu-amino alcohol (0.19 g, 220 mol%, 1.62 mmol) at 120 ℃ for 2 h. After it was cooled to room temperature, the resulting crude material was dissolved in $CHCl_3$ (4.0 mL) followed by addition of $SOCl_2$ (0.70 mL). The reaction mixture was heated at 70 ℃ for 2 h, at which point it was slowly poured into ice water. DCM (10 mL) was added. The organic layer was collected, washed with brine (5.0 mL) and aqueous K_2CO_3 (0.1 M, 5.0 mL), and dried over anhydrous Na_2SO_4. Flash column chromatography gave the dichloride, which was then treated with NaOH (7.4 mmol, 1000 mol%, 1.0 M) in MeOH/ H_2O (v/v, 2:1) for 3 days. The mixture was extracted with CH_2Cl_2 (55.0 mL) and the extract was washed with brine. The organic layer was collected and dried, to which silica gel was added. After the solvent was removed under reduced pressure, the residue was loaded onto a silica column. Flash

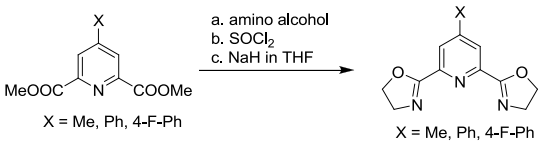
column chromatography (SiO_2: 50% ethyl acetate in hexanes) afforded 0.11 g (37%yield, over 3 steps) of (4-Ph)-(*S*)-^{s}Bu-PyBox (**3g**) as a yellow solid. Analytical data: ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.44 (s, 2H), 7.76-7.80 (m, 2H), 7.46-7.54 (m, 3H), 4.56 (d, *J* = 7.5 Hz, 1H), 4.54 (d, *J* = 7.5 Hz, 1H), 4.25-4.35 (m, 4H), 1.73-1.82 (m, 2H), 1.63-1.73 (m, 2H), 1.24-1.33 (m, 2H), 0.98 (t, *J* = 7.5 Hz, 6H), 0.91 (d, *J* = 6.5 Hz, 6H). ^{13}C NMR (125MHz, $CDCl_3$): δ 162.4, 150.0, 147.4, 136.7, 129.7, 129.2, 127.3, 123.4, 71.4, 70.5, 39.1, 26.2, 14.5, 11.5. M.p. 62-64 ℃; HRMS (ESI): m/z $[M]^+$ found 405.2410, calcd 405.2416 for $C_{25}H_{31}N_3O_2$.



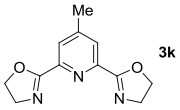
Reaction conditions: a. (*2S*)-2-amino-3-methylpentan-1-ol（220 mol%）, neat, 120 ℃, 2 h. b. Diethylaminosulfur trifluoride (DAST, 300 mol%), CH_2Cl_2, -20 ℃, 24 h.

(*S,4S,4'S*)-2,2'-(4-chloropyridine-2,6-diyl)bis(4-sec-butyl-4,5-dihydrooxazole) ((4-Cl)-(*S*)-^{s}Bu-PyBox (3i)).[3, 6] Following the literature procedures, this compound was prepared first by heating a mixture of dimethyl 4-chloropyridine-2,6-dicarboxylate (0.40 g, 100 mol%, 1.74 mmol) and (*S*)-^{s}Bu-amino alcohol (0.45 g, 220 mol%, 3.83 mmol) at 120 ℃ for 2 h. After it was cooled to room temperature, the resulting crude material was dissolved in DCM (8.0 mL), followed by addition of diethylaminosulfur trifluoride (DAST, 0.89 g, 5.55 mmol, 300 mol%). The reaction mixture was allowed to stir at -20 ℃ for 24 h, at which point it was quenched with aqueous NH_4OH (3.0 M, 2.0 mL) and H_2O (40.0 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 15 mL), and the combined organic extracts were dried and concentrated. Flash column chromatography (SiO_2: 50% ethyl acetate in hexanes) gave (4-Cl)-(*S*)-^{s}Bu-PyBox (**3i**) as colorless oil (0.32 g, 50% yield, over 2 steps). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.20 (s, 2H), 4.53 (d, *J* = 7.5 Hz, 1H), 4.51 (d, *J* = 7.5 Hz, 1H), 4.21-4.30 (m, 4H), 1.68-1.76 (m, 2H), 1.69-1.77 (m, 2H), 1.61-1.69 (m, 2H), 0.96 (t, *J* = 7.5 Hz, 6H), 0.88 (d, *J* = 7.0 Hz, 6H). ^{13}C NMR (125MHz, $CDCl_3$): δ 161.3, 148.0, 145.3, 125.8, 71.5, 70.8, 39.0, 26.0, 14.5, 11.4. HRMS (ESI): m/z $[M]^+$ found 363.1711, calcd 363.1714 for $C_{19}H_{26}ClN_3O_2$.

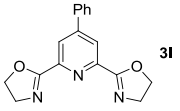
(3) Preparation of **(4-X)-H-PyBox** ligands.[1-3,6]



Reaction conditions: (a) 2-aminoethanol (220 mol%), 120 ℃, neat. (b) $SOCl_2$ (1000 mol%), $CHCl_3$ (~0.2 M), 70 ℃ for 2 h. (c) NaH (300 mol%), THF (~0.1 M), 25 ℃, 20 h.

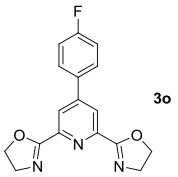


2,2'-(4-methylpyridine-2,6-diyl)bis(4,5-dihydrooxazole) ((4-Me)-H-PyBox (**3k**)**).**[2, 3, 5] Following the literature procedures, this compound was prepared first by heating a mixture of dimethyl 4-methylpyridine-2,6-dicarboxylate (0.40 g, 1.91 mmol) and 2-aminoethanol (0.26 g, 220 mol%, 4.20 mmol) at 120 ℃ for 2 h. After it was cooled to room temperature, the resulting crude material was dissolved in $CHCl_3$ (10.0 mL) followed by addition of $SOCl_2$ (1.40 mL). The reaction mixture was heated at 70 ℃ for 2 h, at which point it was slowly poured into ice water. DCM (20 mL) was added. The organic layer was collected, washed with brine (5.0 mL) and aqueous K_2CO_3(0.1 M, 5.0 mL), and dried over anhydrous Na_2SO_4. Flash column chromatography gave the dichloride, which was dissolved in THF (2.0 mL). The solution was added to a suspension of NaH (5.73 mmol, 300 mol%) in THF (5.0 mL). The reaction mixture was stirred overnight. After filtration and concentration, the residue was extracted with ether. The extract gave a solid upon evaporation of the solvent, which was recrystallised from ethanol afforded 0.11 g (25% yield, not optimized, over 3 steps) of (4-Me)-H-PyBox (**3k**) as a white solid. Analytical data: ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.01（s, 2H）, 4.53 (t, J = 10.0 Hz, 4H), 4.11 (t, J = 9.5 Hz, 4H), 2.46 (s, 3H). ^{13}C NMR (125MHz, $CDCl_3$): δ 163.7, 149.0, 146.5, 126.4, 68.3, 55.0, 20.9. M.p. 166-170 ℃; HRMS (ESI): m/z $[M]^+$ found 231.1006, calcd 231.1008 for $C_{12}H_{13}N_3O_2$.



2,2'-(4-phenylpyridine-2,6-diyl)bis(4,5-dihydrooxazole) ((4-Ph)-H-PyBox (**3l**)**).**[2, 3, 5] Following the literature procedures, this compound was prepared first by heating a mixture of dimethyl 4-phenylpyridine-2,6-dicarboxylate (0.40 g, 1.47 mmol) and 2-aminoethanol (0.20 g, 220 mol%, 3.20 mmol) at 120 ℃ for 2 h. After it was cooled to room temperature, the resulting crude material was dissolved in $CHCl_3$ (7.0 mL) followed by addition of $SOCl_2$ (1.10 mL). The reaction mixture was heated at 70 ℃ for 2 h, at which point it was slowly poured into ice water. DCM (10 mL) was added.

The organic layer was collected, washed with brine (8.0 mL) and aqueous K_2CO_3 (0.1 M, 8.0 mL), and dried over anhydrous Na_2SO_4. Flash column chromatography gave the dichloride, which was dissolved in THF (2 mL). The solution was added to a suspension of NaH (4.41 mmol, 300 mol%) in THF (5 mL). The reaction mixture was stirred overnight. After filtration and concentration, the residue was extracted with ether. The extract gave a solid upon evaporation of the solvent, which was recrystallized from ethanol afforded 0.14 g (32% yield, not optimized, over 3 steps) of (4-Ph)-H-PyBox (**3l**) as a white solid. Analytical data: ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.44 (s, 2H), 7.75-7.80 (m, 2H), 7.47-7.55 (m, 3H), 4.59 (t, *J* = 10.0 Hz, 4H), 4.17 (t, *J* = 10.0 Hz, 4H). ^{13}C NMR (125MHz, $CDCl_3$): δ 163.6, 150.0, 147.3, 136.5, 129.8, 129.2, 127.1, 123.2, 68.4, 55.0. M.p. > 254 ℃; HRMS (ESI): m/z $[M]^+$ found 293.1158, calcd 293.1164 for $C_{17}H_{15}N_3O_2$.



3o

2,2'-(4-(4-fluorophenyl)pyridine-2,6-diyl)bis(4,5-dihydrooxazole) ((4-(4-F-Ph)-H-PyBox (3o)).[2, 3, 6] Following the literature procedures, this compound was prepared first by heating a mixture of dimethyl 4-(4-fluorophenyl)pyridine-2,6-dicarboxylate (0.40 g, 1.38 mmol) and 2-aminoethanol (0.19 g, 220 mol%, 3.04 mmol) at 120 ℃ for 2 h. After it was cooled to room temperature, the resulting crude material was dissolved in $CHCl_3$ (7.0 mL) followed by addition of $SOCl_2$ (1.00 mL). The reaction mixture was heated at 70 ℃ for 2 h, at which point it was slowly poured into ice water. DCM (10 mL) was added. The organic layer was collected, washed with brine (8.0 mL) and aqueous K_2CO_3 (0.1 M, 8.0 mL), and dried over anhydrous Na_2SO_4. Flash column chromatography gave the dichloride, which was dissolved in THF (2.0 mL). The resulting solution was added to a suspension of NaH (4.14 mmol, 300 mol%) in THF (5.0 mL). The reaction mixture was stirred overnight. After filtration and concentration, the residue was extracted with ether. The extract gave a solid upon evaporation of the solvent, which was recrystallized from ethanol afforded (4-(4-F-Ph))-H-PyBox (**3o**) as a white solid (0.13 g, 30% yield, not optimized, over 3 steps). Analytical data: ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.38 (s, 2H), 7.71-7.77 (m, 2H), 7.16-7.22 (m, 2H), 4.57 (t, *J* = 10.0 Hz, 4H), 4.15 (t, *J* = 10.0 Hz, 4H). ^{13}C NMR (125MHz, $CDCl_3$): δ 143.2, 133.0, 129.4, 127.7, 46.4, 45.5, 41.0, 30.5, 30.3, 25.1, 21.4. M.p. 200-213 ℃; HRMS (ESI): m/z $[M]^+$ found 311.1067, calcd

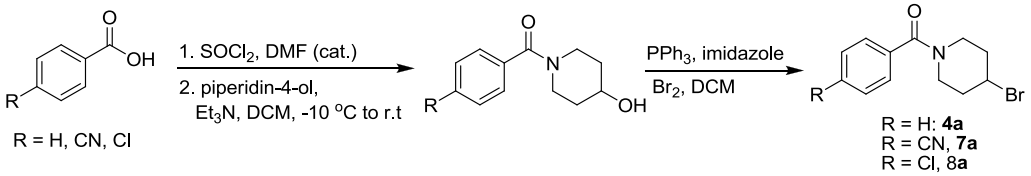
311.1070 for $C_{17}H_{14}FN_3O_2$.

Part 6. Preparation of Alkyl Halides

(1) The following alkyl halides are known compounds in the literature: 4-bromo-1-tosylpiperidine **1**, [7a] 4-iodo-1-tosylpiperidine,[7b] (3-iodopropyl)benzene, [8] ((3-bromopropoxy)methyl)benzene (entry 4, Table 2),[9] ((3-iodopropoxy)methyl)benzene (entry 5, Table 2)[10] ((5-bromopentyloxy)methyl)benzene (entry 3, Table 2),[11] 2-bromo-2,3-dihydro-1H-indene **11a** (entry 9, Table 3),[12] 4-bromocyclohexanone **9a** (entry 6-7, Table 3),[13] and 2-(3-bromopropyl)isoindoline-1,3-dione **17a** (entry 8, Table 2 and entry 17, Table 3). [14] *trans*-2-bromocyclopentanol **13a** (entry 11, Table 3), [15] *trans*-2-bromo-2,3-dihydro-1H-inden-1-ol **12a** (entry 10, Table 3).[15] 3-iodoproan-1-ol was prepared by direct monoiodination.[10]

(2) Preparation of compounds **4a**, **7a**, **8a**, **14a**, **15a**, and 5-bromopentyl benzoate:

A. Preparation of (4-R-phenyl)(4-iodopiperidin-1-yl)methanone **4a**, **7a** and **8a** (entries 1-5, Table 3).



(4-Chlorophenyl)(4-bromopiperidin-1-yl)methanone (entry 5, Table 3) (8a). To a solution of 4-chlorobenzoic acid (2.00 g, 12.8 mmol, 100 mol%) in DCM (40.0 mL) was added DMF (0.30 mL) and $SOCl_2$ (4.7 mL, 500 mol%). The reaction mixture was stirred for 4 h at 25 ℃. After the solvent and excess $SOCl_2$ were removed under reduced pressure, the solid residue was dissolved in DCM (5.0

(7) (a) Gonzalez-Bobes, Francisco; Fu, G. C. *J. Am. Chem. Soc.* **2006**, *128*, 5360-5361. (b) Ollivier, C.; Renaud, P. *J. Am. Chem. Soc.* **2001**, *123*, 4717–4727.

(8) Smith, S. M.; Takacs, J. M. *J. Am. Chem. Soc.* **2010**, *132*, 1740–1741.

(9) Frankowski, K. J.; Jennifer E. Golden, J. E.; Zeng, Y.; Lei, Y.; Aubé, J. *J. Am. Chem. Soc.* **2008**, *130*, 6018–6024.

(10) Barbe, G.; St-Onge, M.; Charette, A. B. *Org. Lett*. **2008**, *105*, 5497–5499.

(11) Engel, P. S.; Kitamura, A.; E. Keys, D. *J. Org. Chem.* **1987**, *52*, 5015–5021.

(12) Prokopowicz, M.; Młynarz, P.; Kafarski. P. *Tetrahedron Lett.* **2009**, *50*, 7314–7317.

(13) Engel, P. S.; Kitamura, A.; E. Keys, D. *J. Org. Chem.* **1987**, *52*, 5015–5021.

(14) Quici, S.; Manfredi, A.; Pozzi, G.; Cavazzini, M.; Rozzoni, A. *Tetrahedron* **1999**, *55*, 10487–10496.

(15) Das, B.; Venkateswarlu, K.; Damodar, K.; Suneel, K. *J. Mol. Catal. A: Chem.* **2007**, *269*, 17–21.

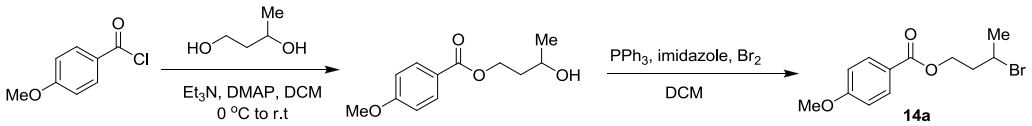
mL). The resulting solution was slowly added to a mixture of 4-hydroxypiperidine (1.29 g, 12.8 mmol, 100 mol%), Et_3N (3.6 mL, 20.0 mmol, 200 mol%) in DCM (40.0 mL) at -10 ℃. The reaction mixture was warmed to room temperature. After it was stirred for 2 h, the reaction mixture was washed with HCl (1 M, 2×20.0 mL) and then brine (30.0 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure to give the alcohol en route to (4-chlorophenyl)(4-hydroxypiperidin-1-yl)methanone as brown oil.

To the solution of the alcohol en route to (4-chlorophenyl)(4-hydroxypiperidin-1-yl)methanone (3.06 g, 12.8 mmol, 100 mol%) in DCM (60.0 mL) was added imidazole (0.87 g, 12.8 mmol, 100 mol%), PPh_3 (3.35 g, 12.8 mmol, 100 mol%) and Br_2 (2.04 g, 12.8 mmol, 100 mol%) at 0 ℃. The reaction mixture was allowed to stir overnight at room temperature. The brown suspension was washed with brine, and $Na_2S_2O_3$ (saturated). The organic phase was dried (over $MgSO_4$) and filtered, at which point silica gel was added. The mixture was concentrated under reduced pressure, and the residue was loaded onto a silica column. Flash chromatography (SiO_2: 30% ethyl acetate in hexanes) afforded **8a** as a white solid (2.71 g, 8.96 mmol, 70% yield over 3 steps). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.73 (dd, *J* = 7.0 and 2.0 Hz, 2H), 7.51 (dd, *J* = 7.0 and 2.0 Hz, 2H), 4.43-4.49 (m, 1H), 3.94 (br s,1H), 3.81 (br s, 1H), 3.60 (br s, 1H), 3.30 (br s, 1H), 2.22 (br s, 1H), 2.01 (br s, 2H), 1.94 (br s, 1H). ^{13}C NMR (125MHz, $CDCl_3$): δ 168.2, 140.0, 132.4, 127.5, 117.9, 113.5, 48.1, 45.4, 40.1, 35.9, 34.9. M.p. = 118-120 ℃.

4-(4-Bromopiperidine-1-carbonyl)benzonitrile (entry 4, Table 3) (7a). Following the procedure for **7a**, this compound was prepared first using 4-cyanobenzoic acid (0.50 g, 3.4 mmol, 100 mol %), DCM (10.0 mL), DMF (0.10 mL) and $SOCl_2$ (1.30 ml, 500 mol %). The resulting crude acid chloride was dissolved in DCM (2.5 mL) and was transferred to a mixture of 4-hydroxypiperidine (0.34 g, 3.40 mmol, 100 mol %), Et_3N (0.98 mL, 6.8 mmol, 200 mol %) in DCM (10.0 mL). Conversion of the alcohol to bromine was carried out using imidazole (0.25 g, 3.40 mmol, 100 mol %), PPh_3 (0.90 g, 3.40 mmol, 100 mol %) and Br_2 (0.18 ml, 3.40 mmol, 100 mol %). Flash column chromatography (SiO_2: 30% ethyl acetate in hexanes) gave **7a** as a white solid (0.40 g, 1.36 mmol, 40 % yield over 3 steps). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.29-7.44 (m , 4H), 4.38-4.48 (m, 1H), 3.93 (br s, 1H), 3.68 (br s, 2H), 3.35 (br s, 1H), 3.17 (br s, 1H), 2.06 (br s, 2H), 1.96 (br s, 1H). ^{13}C NMR (125MHz, $CDCl_3$): δ 169.4, 135.8, 133.9, 128.8, 128.4, 48.6, 45.7, 40.3, 35.9, 35.2. M.p. = 101-103 ℃.

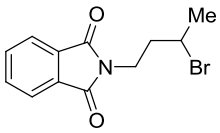
(4-Bromopiperidin-1-yl)(phenyl)methanone (entry 2, Table3) (5a). To a mixture of 4-hydroxypiperidine (0.5 g, 5.0 mmol, 100 mol %), Et_3N (1.43 mL, 9.9 mmol, 200 mol %) in DCM (20.0 mL) was added benzoyl chloride (0.58 ml, 5.0 mmol, 100 mol%) at -10 ℃. The reaction mixture was warmed to room temperature and it was stirred for 2 h, at which point it was washed with HCl (1 M, 2×20.0 mL) and then brine (30.0 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure to give the alcohol en route to (4-chlorophenyl)(4-hydroxypiperidin-1-yl)methanone as brown oil. Conversion of the alcohol to bromine was carried out using imidazole (0.33 g, 4.9 mmol, 100 mol %), PPh_3 (1.30 g, 4.9 mmol, 100 mol %) and Br_2 (0.25 ml, 4.9 mmol, 100 mol %). Flash column chromatography (SiO_2: 20% ethyl acetate in hexanes) gave **5a** as a white solid (0.65g, 2.4 mmol, 50 % yield over 2 steps). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.35-7.43 (m, 5H), 4.38-4.47 (m, 1H), 3.96 (br s, 1H), 3.70 (br s, 1H), 3.65 (br s, 1H), 3.34 (br s, 1H), 2.19 (br s, 1H), 2.05 (br s, 2H), 1.92 (br s, 1H). ^{13}C NMR (125MHz, $CDCl_3$): δ 170.3, 135.5, 129.6, 128.4, 126.7, 48.7, 45.7, 40.2, 35.9, 35.2. M.p. = 69-70 ℃.

B. Preparation of compounds **14a**.



3-Bromobutyl 4-methoxybenzoate (entry 12, Table 3) (14a). To a solution of 3-hydroxybutyl 4-methoxybenzoate (2.24 g, 10.0 mmol), imidazole (0.68 g, 10.0 mmol) and PPh_3 (2.62 g, 10.0 mmol) in CH_2Cl_2 (20.0 mL) was added Br_2 (1.92 g, 12.0 mmol) at 0℃. The reaction mixture was warmed to room temperature, and was allowed to stir overnight. The suspension was washed with brine, saturated $Na_2S_2O_3$ solution. The organic phase was dried (over $MgSO_4$) and filtered, at which point silica gel was added. After the solvent was evaporated, the residual was loaded to a silica column. Flash chromatography (SiO_2: 5% ethyl acetate in hexanes) afforded **14a** as a yellow oil (73% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.01 (d, *J* = 9.0 Hz, 2H), 6.94 (d, *J* = 9.0 Hz, 2H), 4.53-4.50 (m, 1H), 4.37-4.33 (m, 2H), 3.89 (s, 3H), 2.31-2.14 (m, 2H), 2.03 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 166.1, 163.5, 131.6, 122.5, 113.7, 64.4, 55.5, 41.5, 29.0, 24.4. HRMS (ESI): m/z $[M+Na]^+$ found 309.0104, calcd 309.0102 for $C_{12}H_{15}BrNaO_3$.

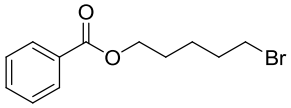
C. Preparation of compounds **15a**.



15a

2-(3-Bromobutyl)isoindoline-1,3-dione (entries 13-15, Table3) (15a). A mixture of 1, 3-dibromobutane (0.50 g, 2.30 mmol, 100 mol%), and potassium 1,3-dioxoisoindolin-2-ide (0.56 g, 3.0 mmol, 130 mol%) in acetone (25.0 mL) was stirred and refluxed for 24 h. After filtering off the precipitate, the solvent and excess dibromobutane was removed under reduced pressure. Flash column chromatography (SiO_2: 15% ethyl acetate in hexanes) gave the title product as a white solid (0.56 g, 2.0 mmol, 67% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.85 (dd, J = 5.4 and 3.1 Hz, 2H), 7.73 (dd, J = 5.4 and 3.1 Hz, 2H), 4.16-4.09 (m, 1H), 3.93-3.87 (m, 1H), 3.85-3.79 (m, 1H), 2.22-2.17 (m, 2H), 1.77 (d, J = 6.6 Hz, 3H).^{13}C NMR (125 MHz, $CDCl_3$): δ 168.2, 133.9, 132.0, 123.3, 47.3, 39.4, 36.6, 26.4.

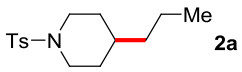
D. Preparation of 5-bromopentyl benzoate.



5-Bromopentyl benzoate (entry 11, Table 2). To a solution of 5-hydroxypentyl benzoate (2.00 g, 9.6 mmol), imidazole (0.65 g, 9.6 mmol) and PPh_3 (2.52 g, 9.6 mmol) in DCM (40.0 mL) was added Br_2 (1.54 g, 9.6 mmol) at -20℃. The reaction mixture was allowed to warm to room temperature and stir overnight. The suspension was washed with brine and a saturated $Na_2S_2O_3$ solution. The organic phase was dried (over $MgSO_4$) and filtered, at which point silica gel was added. After the solvent was removed under reduced pressure, the residual was loaded to a silica column. Flash chromatography (SiO_2: 10% ethyl acetate in hexanes) afforded the title compound as a yellow oil (75% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.04-8.07 (m, 2H), 7.55-7.59 (m, 1H), 7.43-7.48 (m, 2H), 4.35 (t, J = 6.5 Hz, 2H), 3.45 (t, J = 7.0 Hz, 2H), 1.92-1.99 (m, 2H), 1.79-1.85 (m, 2H), 1.59-1.66 (m, 2H). ^{13}C NMR (125MHz, $CDCl_3$): δ 166.5, 132.8, 130.3, 129.5, 128.3, 64.6, 33.4, 32.3, 27.9, 24.7.

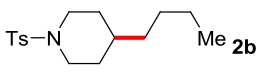
Part 7. Reductive Cross-Coupling of Alkyl Halides

General Procedure. To a flame-dried Schlenk tube equipped with a magnetic stir bar was loaded alkyl bromide (R^1-Br, 0.157 mmol, 100 mol%), followed by addition of (*S*)-^{s}Bu-Pybox (**3a**) (4.2 mg, 0.013 mmol, 8 mol%) or (4-Cl)-H-Pybox (**3n**) (3.2 mg, 0.013 mmol, 8 mol%) and zinc powder (31.0 mg, 0.471 mmol, 300 mol%). The tube was moved into a dry glove box, at which point $Ni(COD)_2$ (4.4 mg, 0.016 mmol, 10 mol%) was added. The tube was capped with a rubber septum, and it was moved out of the glove box. A second alkyl halide R^2-X (X = I or Br, 0.471 mmol, 300 mol %) and DMA (1.0 mL) were then added *via* syringe. After the reaction mixture was allowed to stir for 12 h (X = I) or 16 h (X =Br) under N_2 atmosphere at 25 ℃, it was directly loaded onto a silica column without work-up. The residue in the reaction vessel was rinsed with small amount of DCM. Flash column chromatography (SiO_2: ethyl acetate in hexanes) provided the coupling product.



2a

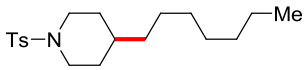
4-Propyl-1-tosylpiperidine (2a). This compound was prepared following the General Procedure using 4-bromo-1-tosylpiperidine **1** (50.0 mg, 0.157 mmol, 100 mol %), 1-iodopropane (45.7 uL, 0.471 mmol, 300 mol%) and (*S*)-^{s}Bu-Pybox (**3a**) (4.2 mg, 0.013 mmol, 8 mol%). Flash column chromatography (SiO_2: 10% ethyl acetate in hexanes) gave the title compound as a white solid (30.0 mg, 0.107 mmol, 67% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.63 (d, *J* = 8.0 Hz, 2H), 7.31 (d, *J* = 8.0 Hz, 2H), 3.74 (d, *J* = 11.5 Hz, 2H), 2.43 (s, 3H), 2.20 (td, *J* = 11.5 and 2.0 Hz, 2H), 1.70 (d, *J* = 13.5 Hz, 2H), 1.25 (m, 4H), 1.15 (m, 3H), 0.84 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 143.2, 133.0, 129.4, 127.6, 46.4, 38.1, 34.6, 31.4, 21.4, 19.5, 14.0. M.p. = 66-68 ℃. HRMS (ESI): m/z $[M]^+$ found 281.1448, calcd 281.1449 for $C_{15}H_{23}NO_2S$.



2b

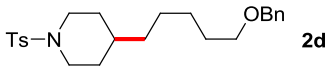
4-Butyl-1-tosylpiperidine (2b) This compound can be prepared according to the General Procedure using 4-bromo-1-tosylpiperidine **1** (50.0 mg, 0.157 mmol, 100 mol %), 1-bromobutane (50.6 uL, 0.471 mmol, 300 mol%) and (4-Cl)-H-Pybox (**3n**) (3.2 mg, 0.013 mmol, 8 mol%). Flash column chromatography (SiO_2: 8% ethyl acetate in hexanes) gave the title product as a white solid (31.1 mg,

0.105 mmol, 67% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.64 (d, *J* = 8.5 Hz, 2H), 7.32 (d, *J* = 8.0 Hz, 2H), 3.75 (d, *J* = 11.5 Hz, 2H), 2.44 (s, 3H), 2.20 (td, *J* = 11.5 and 2.0 Hz, 2H), 1.68-1.74 (m, 2H), 1.18-1.32 (m, 8H), 1.10-1.18 (m, 1H), 0.86 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 143.2, 133.1, 129.5, 127.7, 46.5, 35.7, 35.0, 31.5, 28.7, 22.7, 21.5, 14.0. M.p. = 73-74 ℃. HRMS (ESI): m/z $[M]^+$ found 295.1609, calcd 295.1606 for $C_{16}H_{25}NO_2S$.



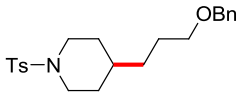
2c

4-Heptyl-1-tosylpiperidine (2c). This compound can be prepared according to the General Procedure using 4-bromo-1-tosylpiperidine **1** (50.0 mg, 0.157 mmol, 100 mol %), 1-iodoheptane (81.3 uL, 0.471 mmol, 300 mol %) and (*S*)-^{s}Bu-Pybox (**3a**) (4.2 mg, 0.013 mmol, 8 mol%). Flash column chromatography (SiO_2: 10% ethyl acetate in hexanes) gave the title product as syrup (32.0 mg, 0.095mmol, 60% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.65 (d, *J* = 7.0 Hz, 2H), 7.33 (d, *J* = 8.0 Hz, 2H), 3.76 (d, *J* = 11.5 Hz, 2H), 2.44 (s, 3H), 2.21 (td, *J* = 12.0 and 2.5 Hz, 2H), 1.68-1.75 (m, 2H), 1.10-1.33 (m, 15H), 0.88 (t, *J* = 6.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 143.3, 133.2, 129.5, 127.7, 46.5, 36.0, 35.1, 31.8, 31.5, 29.6, 29.2, 26.5, 22.6, 21.5, 14.1. HRMS (ESI): m/z $[M]^+$ found 337.2080, calcd 337.2075 for $C_{19}H_{31}NO_2S$.



2d

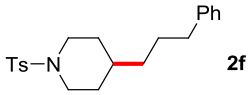
4-(5-(Benzyloxy)pentyl)-1-tosylpiperidine (2d). This compound can be prepared according to the General Procedure using 4-bromo-1-tosylpiperidine **1** (50.0 mg, 0.157 mmol, 100 mol %), ((5-bromopentyloxy)methyl)benzene (121.1 mg, 0.471 mmol, 300 mol%) and (4-Cl)-H-Pybox (**3n**) (3.2 mg, 0.013 mmol, 8 mol%). Flash column chromatography (SiO_2: 8% ethyl acetate in hexanes) gave the title product as a white solid (31.3 mg, 0.075 mmol, 48% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.65 (d, *J* = 7.0 Hz, 2H), 7.28-7.36 (m, 7H), 4.50 (s, 2H), 3.76 (d, *J* = 11.5 Hz, 2H), 3.45 (t, *J* = 6.5 Hz, 2H), 2.45 (s, 3H), 2.21 (td, *J* = 13.0 and 2.5 Hz, 2H), 1.70 (d, *J* = 6.0 Hz, 2H), 1.57-1.62 (m, 2H), 1.20-1.34 (m ,8H), 1.10-1.20 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 143.3, 138.6, 133.2, 129.5, 128.3, 127.7, 127.6, 127.5, 72.9, 70.3, 46.5, 35.9, 35.0, 31.5, 29.7, 26.4, 26.2, 21.5. HRMS (ESI): m/z $[M]^-$ found 416.2271, calcd 415.2181 for $C_{24}H_{33}NO_3S$. M.p. = 73-75 ℃.



2e

4-(3-Phenoxypropyl)-1-tosylpiperidine (2e). This compound can be prepared according to the General Procedure using 4-bromo-1-tosylpiperidine **1** (50.0 mg, 0.157 mmol, 100 mol %), (3-iodopropoxy)methyl)benzene (130.1 mg, 0.471 mmol, 300 mol%) and (*S*)-^{s}Bu-Pybox (**3a**) (3.2 mg, 0.013 mmol, 8 mol%). Flash column chromatography (SiO_2: 8% ethyl acetate in hexanes) gave the title product as syrup (22.5 mg, 0.0581 mmol, 37% yield).

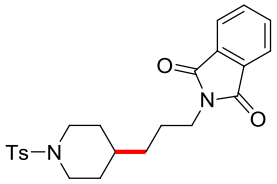
This compound can also be prepared according to the General Procedure using 4-bromo-1-tosylpiperidine **1** (50.0 mg, 0.157 mmol, 100 mol %), (3-bromopropoxy)methyl)benzene (108.0 mg, 0.471 mmol, 300 mol%) and (4-Cl)-H-Pybox (**3n**) (3.2 mg, 0.013 mmol, 8 mol%). Flash column chromatography (SiO_2: 8% ethyl acetate in hexanes) gave the title product as syrup (30.4 mg, 0.0791 mmol, 50% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.65 (d, *J* = 8.0 Hz, 2H), 7.28-7.36 (m, 7 H), 4.49 (S, 2H), 3.76 (d, *J* = 11.5 Hz, 2H), 3.43 (t, *J* = 6.5 Hz, 2H), 2.45 (s, 3H), 2.20 (td, *J* = 12.0 Hz, 2.5 Hz, 2H), 1.72 (d, *J* = 13.0 Hz, 2H), 1.55-1.62 (m, 2H), 1.24-1.35 (m, 4H), 1.11-1.20 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 143.3, 138.5, 133.2, 129.5, 128.3, 127.7, 127.6, 127.5, 72.9, 70.3, 46.6, 35.0, 32.5, 31.5, 26.9, 21.5. HRMS (ESI): m/z $[M]^+$ found 387.1870, calcd 387.1868 for $C_{22}H_{29}NO_3S$.



2f

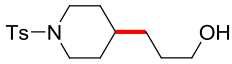
4-(3-Phenylpropyl)-1-tosylpiperidine (2f). This compound can be prepared according to the General Procedure using 4-bromo-1-tosylpiperidine **1** (50.0 mg, 0.157 mmol, 100 mol %), (3-bromopropyl)benzene (94.0 mg, 0.471 mmol, 300 mol%) and (4-Cl)-H-Pybox (**3n**) (3.2 mg, 0.013 mmol, 8 mol%). Flash column chromatography (SiO_2: 8% ethyl acetate in hexanes) gave an inseparable oily mixture of **2f** (37.6 mg, 0.105 mmol, 67 % yield and 1-tosylpiperidinethe arising from simple reduction of **1**. The yield was calculated based on the ^{1}H NMR ratio (10:1) of the product and the byproduct in the mixture. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.67 (d, *J* = 10.0 Hz, 2H), 7.34 (d, *J* = 8.0 Hz,2H), 7.27-7.30(m, 2H), 7.15-7.20 (m, 3H), 3.77 (d, *J* = 6.5 Hz, 2H), 2.57 (t, *J* = 7.5 Hz, 2H), 2.45 (s, 3H), 2.22 (td, *J* = 11.0 and 2.5 Hz, 2H), 1.70-1.75 (m, 2H), 1.55-1.64 (m, 2H), 1.25-1.34 (m, 4H), 1.15-1.23 (m, 1H).^{13}C NMR (125MHz, $CDCl_3$): δ 143.3, 142.3, 133.2, 129.5, 128.3, 128.2, 127.7, 125.7, 46.9, 46.4, 35.9, 35.6, 35.0, 31.4, 28.4, 25.1, 23.5, 21.5. HRMS (ESI): m/z $[M]^+$ found 357.1759,

calcd 357.1762 for $C_{21}H_{27}NO_2S$.



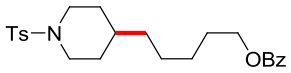
2g

2-(3-(1-Tosylpiperidin-4-yl)propyl)isoindoline-1,3-dione (2g). This compound can be prepared according to the General Procedure using 4-bromo-1-tosylpiperidine **1** (50.0 mg, 0.157 mmol, 100 mol%), 2-(3-bromopropyl)isoindoline-1,3-dione (126.0 mg, 0.471 mmol, 300 mol%) and (4-Cl)-H-Pybox (**3n**) (3.2 mg, 0.013 mmol, 8 mol%). Flash column chromatography (SiO_2: 8% ethyl acetate in hexanes) gave an inseparable white solid mixture of **2g** (43.5 mg, 0.102 mmol, 65% yield) and the homocoupling byproduct of 2-(3-bromopropyl)isoindoline-1,3-dione). The yield was calculated based on the ^{1}H NMR ratio (1:1.5) of the product and the byproduct in the mixture. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.81-7.83 (m, 2H), 7.70-7.77 (m, 2H), 7.63 (d, *J* = 8.0 Hz, 2H), 7.31 (d, *J* = 8.0 Hz, 2H), 3.75 (d, *J* = 10.5 Hz, 2H), 3.63 (t, *J* = 7.0 Hz, 3H), 2.43 (s, 3H), 2.9 (t, *J* = 10.0 Hz, 2H), 1.61-1.74 (m, 4H), 1.20-1.32 (m, 4H). ^{13}C NMR (125MHz, $CDCl_3$): δ 168.1, 143.3, 133.9, 133.1, 132.0, 129.5, 127.7, 123.2, 46.4, 37.8, 34.6, 32.9, 31.3, 25.6, 21.5. HRMS (ESI): m/z $[M+Na]^+$ found 449.1526, calcd 449.1511 for $C_{23}H_{26}N_2NaO_4S$.



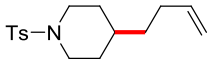
2h

3-(1-Tosylpiperidin-4-yl)propan-1-ol (2h). This compound can be prepared according to the General Procedure using 4-bromo-1-tosylpiperidine **1** (50.0 mg, 0.157 mmol, 100 mol%), 3-bromopropan-1-ol (42.6 uL, 0.471 mmol, 300 mol%) and (4-Cl)-H-Pybox (**3n**) (3.2 mg, 0.013 mmol, 8 mol%). Flash column chromatography (SiO_2: 40% ethyl acetate in hexanes) gave the title product as colorless oil (28.0 mg, 0.094 mmol, 60% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.64 (d, *J* = 8.5 Hz, 2H), 7.33 (d, *J* = 8.0 Hz, 2H), 3.76 (d, *J* = 11.5 Hz, 2H), 3.61 (t, *J* = 6.5 Hz, 2H), 2.44 (s, 3H), 2.22 (td, *J* = 12.0 and 2.0 Hz, 2H), 1.70-1.77 (m, 2H), 1.50-1.56 (m, 2H), 1.27-1.34 (m, 4H), 1.14-1.22 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 143.3, 133.1, 129.5, 127.7, 62.9, 46.4, 35.0, 32.1, 31.5, 29.7, 21.5. HRMS (ESI): m/z $[M]^+$ found 297.1387, calcd 297.1339 for $C_{15}H_{23}NO_3S$.



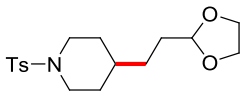
2i

5-(1-Tosylpiperidin-4-yl)pentyl benzoate (2i). This compound can be prepared according to the General Procedure using 4-bromo-1-tosylpiperidine **1** (50.0 mg, 0.157 mmol, 100 mol%), 5-bromopentylbenzoate (113.0 mg, 0.471 mmol, 300 mol%) and (4-Cl)-H-Pybox (**3n**) (3.2 mg, 0.013 mmol, 8 mol%). Flash column chromatography (SiO_2: 15% ethyl acetate in hexanes) gave the title product as colorless oil (43.7 mg, 0.102 mmol, 65% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.04 (m, 2H), 7.65 (d, *J* = 8.0 Hz, 2H), 7.53-7.60 (m, 1H), 7.41-7.48 (m, 2H), 7.33 (d, *J* = 8.0 Hz, 2H), 4.30 (t, *J* = 6.5 Hz, 2H), 3.76 (d, *J* = 12.0 Hz, 2H), 2.44 (s, 3H), 2.20 (td, *J* = 12.0 and 2.5 Hz, 2H), 1.67-1.80 (m, 4H), 1.20-1.44 (m, 8H), 1.10-1.18 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 166.6, 143.3, 133.2, 132.9, 130.4, 129.5, 128.3, 127.7, 64.9, 46.5, 35.9, 35.0, 31.5, 28.6, 26.2, 26.1, 21.5. HRMS (ESI): m/z $[M]^+$ found 429.1974, calcd 429.1974 for $C_{24}H_{31}NO_4S$.



2j

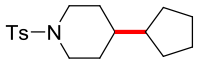
4-(But-3-enyl)-1-tosylpiperidine (2j) This compound can be prepared according to the General Procedure using 4-bromo-1-tosylpiperidine **1** (50.0 mg, 0.157 mmol, 100 mol%), 2-(2-bromoethyl)-1,3-dioxolane (47.5 uL, 0.471 mmol, 300 mol%) and (4-Cl)-H-Pybox (**3n**) (3.2 mg, 0.013 mmol, 8 mol%). Flash column chromatography (SiO_2: 8% ethyl acetate in hexanes) gave the title product as a white solid (38.2 mg, 0.130 mmol, 83% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.64 (d, *J* = 8.5 Hz, 2H), 7.32 (d, *J* = 8.0 Hz, 2H), 5.74 (ddt, *J* = 17.0, 10.0 and 7.0 Hz, 1H), 4.97 (ddd, *J* = 17.5, 2.0 and 1.5 Hz, 1H), 4.92 (ddt, *J* = 10.5, 2.0 and 1.5 Hz, 1H), 3.76 (d, *J* = 12.0 Hz, 2H), 2.44 (s, 3H), 2.20 (td, *J* = 12.0 and 2.5 Hz, 2H), 2.03 (q, *J* = 7.5Hz, 2H), 1.70-1.76 (m, 2H), 1.25-1.35 (m, 4H), 1.13-1.23 (m, 1H).^{13}C NMR (125 MHz, $CDCl_3$): δ 143.3, 138.4, 133.1, 129.5, 127.7, 114.6, 46.4, 35.0, 34.4, 31.1, 30.6, 21.5. HRMS (ESI): m/z $[M]^+$ found 293.1452, calcd 293.1449 for $C_{16}H_{23}NO_2S$. M.p. = 58-60 ℃.



2k

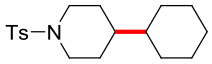
4-(2-(1,3-Dioxolan-2-yl)ethyl)-1-tosylpiperidine (2k). This compound can be prepared according to the General Procedure using 4-bromo-1-tosylpiperidine **1** (50.0 mg, 0.157 mmol, 100 mol %), 2-(2-bromoethyl)-1,3-dioxolane (55.6 uL, 0.471 mmol, 300 mol%) and (4-Cl)-H-Pybox (**3n**) (3.2 mg, 0.013 mmol, 8 mol%). Flash column chromatography (SiO_2: 10% ethyl acetate in hexanes) gave the title product as a white solid (37.9 mg, 0.111 mmol, 71% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.63 (d,

J = 8.5 Hz, 2H),7.62 (d, *J* = 8.0 Hz, 2H), 4.80 (d, *J* = 4.5 Hz, 1H), 3.90-3.98 (m, 2H), 3.79-3.87 (m, 2H), 3.76 (d, *J* = 12.0 Hz, 2H), 2,44 (s, 3H), 2.21 (td, *J* = 12.0 and 2.5 Hz ,2H), 1.68-1.76 (m, 2H), 1.58-1.66 (m, 2H), 1.24-1.38 (m, 4H), 1.13-1.24 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 143.3, 133.1, 129.5, 127.7, 104.4, 64.8, 46.4, 35.0, 31.4, 30.9, 30.1, 21.5. HRMS (ESI): m/z $[M]^+$ found 339.1508, calcd 339.1504 for $C_{17}H_{25}NO_4S$. M.p. = 142-143 ℃.



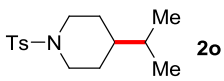
2m

4-Cyclopentyl-1-tosylpiperidine (2m). This compound can be prepared according to the General Procedure using 4-bromo-1-tosylpiperidine **1** (50.0 mg, 0.157 mmol, 100 mol%), bromocyclopentane (50.7 uL, 0.471 mmol, 300 mol%) and (4-Cl)-H-Pybox (**3n**) (3.2 mg, 0.013 mmol, 8 mol%). Flash column chromatography (SiO_2: 8% ethyl acetate in hexanes) gave the title product as a white solid (31.4 mg, 0.102 mmol, 65% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.64 (d, *J* = 8.5 Hz, 2H), 7.32 (d, *J* = 8.0 Hz, 2H), 3.76 (d, *J* = 11.5 Hz, 2H), 2.44 (s, 3H), 2.19 (td, *J* = 12.0 and 2.5 Hz, 2H), 1.68-1.80 (m, 4H), 1.53-1.61 (m, 2H), 1.44-1.53 (m, 3H),1.33 (qt, *J* = 16.5 and 4.0 Hz, 2H), 0.98-1.07 (m, 2H), 089-0.98 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 143.2, 133.1, 129.5, 127.7, 46.6, 45.5, 41.0, 30.5, 30.3, 25.1, 21. 5. HRMS (ESI): m/z $[M]^+$ found 307.1601, calcd 307.1606 for $C_{17}H_{25}NO_2S$. M.p. = 149-151 ℃.



2n

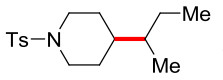
4-Cyclohexyl-1-tosylpiperidine (2n) This compound can be prepared according to the General Procedure using 4-bromo-1-tosylpiperidine **1** (50.0 mg, 0.157 mmol, 100 mol %), bromocyclohexane (55.0 uL, 0.471 mmol, 300 mol%) and (4-Cl)-H-Pybox (**3n**) (3.2 mg, 0.013 mmol, 8 mol%). Flash column chromatography (SiO_2: 8% ethyl acetate in hexanes) gave the title product as a white solid (20.0 mg, 0.062 mmol, 40% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.65 (d, *J* = 8.0 Hz, 2H), 7.32 (d, *J* = 8.5 Hz, 2H), 3.81 (dd, *J* = 9.0 and 2.0 Hz, 2H), 2.44 (s, 3H), 2.15 (td, *J* = 12.5 and 2.5 Hz, 2H), 1.68-1.74 (m, 4H), 1.61-1.68 (m, 3H), 1.35 (m, 2H), 1.04-1.25 (m, 4H), 0.84-1.00 (m, 3H). ^{13}C NMR (125MHz, $CDCl_3$): δ 143.3, 133.1, 129.5, 127.7, 46.9, 42.1, 40.9, 30.0, 28.6, 26.6, 26.5, 21.5. HRMS (ESI): m/z $[M]^+$ found 321.1760, calcd 321.1762 for $C_{18}H_{27}NO_2S$. Mp = 165-167 ℃.



2o

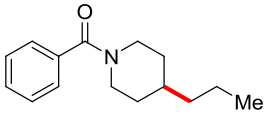
4-Isopropyl-1-tosylpiperidine (2o). This compound can be prepared according to the General

Procedure using 4-bromo-1-tosylpiperidine **1** (50.0 mg, 0.157 mmol, 100 mol %), 2-bromopropane (44.1 uL, 0.471 mmol, 300 mol%) and (4-Cl)-H-Pybox (**3n**) (3.2 mg, 0.013 mmol, 8 mol%). Flash column chromatography (SiO_2: 8% ethyl acetate in hexanes) gave the title product as a white solid (31.8 mg, 0.113mmol, 72% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.65 (d, *J* = 8.5 Hz, 2H), 7.32 (d, *J* = 8.0 Hz, 2H), 3.81 (d, *J* = 11.5 Hz, 2H), 2.44 (s, 3H), 2.17 (td, *J* = 12.0 and 2.5 Hz, 2H), 1.66-1.73 (m, 2H), 1.30-1.47 (m, 3H), 0.88-0.92 (m, 1H), 0.85 (s, 3H), 0.83 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 143.5, 133.1, 129.5, 127.7, 46.8, 41.7, 32.0, 28.5, 21.5, 19.6. HRMS (ESI): m/z $[M]^+$ found 281.1451, calcd 281.1449 for $C_{15}H_{23}NO_2S$. M.p. = 106-107 ℃.



2p

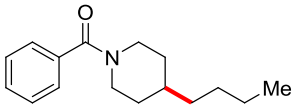
4-*sec*-Butyl-1-tosylpiperidine (2p). This compound can be prepared according to the General Procedure using 4-bromo-1-tosylpiperidine **1** (50.0 mg, 0.157 mmol, 100 mol%), 2-bromobutane (51.2 uL, 0.471 mmol, 300 mol%) and (4-Cl)-H-Pybox (**3n**) (3.2 mg, 0.013 mmol, 8 mol%). Flash column chromatography (SiO_2: 8% ethyl acetate in hexanes) gave the product as syrup (26.5 mg, 0.090 mmol, 57% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.65 (d, *J* = 8.0 Hz, 2H), 7.32 (d, *J* = 8.0 Hz, 2H), 3.78-3.86 (m, 2H), 2.44 (s, 3H), 2.13-2.20 (m, 2H), 1.63 (d, *J* = 13.5 Hz, 2H), 1.30-1.47 (m, 3H), 1.18-1.25 (m, 1H), 1.04-1.14 (m, 2H), 0.83 (t, *J* = 7.5 Hz, 3H), 0.80 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 143.3, 133.1, 129.5, 127.7, 46.9, 46.8, 39.8, 38.6, 29.0, 27.4, 26.3, 21.5, 15.5, 11.5. HRMS (ESI): m/z $[M]^+$ found 295.1610, calcd 295.1606 for $C_{16}H_{25}NO_2S$.



4b

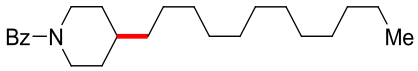
Phenyl(4-propylpiperidin-1-yl)methanone (4b) This compound can be prepared according to the General Procedure using (4-bromopiperidin-1-yl)(phenyl)methanone **4a** (50.0 mg, 0.186 mmol, 100 mol%), 1-iodopropane (54.0 uL, 0.558 mmol, 300 mol%), zinc powder (38.0 mg, 0.558 mmol, 300 mol%), $Ni(COD)_2$ (5.2 mg, 0.019 mmol, 10 mol%) and (*S*)-^{s}Bu-Pybox (**3a**) (4.9 mg, 0.0149 mmol, 8 mol%). Flash column chromatography (SiO_2: 8% ethyl acetate in hexanes) gave the title product as a colorless oil (31.0 mg, 0.134 mmol, 72% yield). ^{1}HNMR (500 MHz, $CDCl_3$): δ 7.38-7.40 (m, 5H), 4.70 (br d, *J* = 10.0 Hz, 1H), 3.72 (br d, *J* = 9.5 Hz, 1H), 2.70-3.04 (m, 2H), 1.81 (br d, *J* = 11.5 Hz, 1H),

1.62 (br d, *J* = 10.0 Hz 1H), 1.46-1.56 (m, 1H), 1.30-1.37 (m, 2H), 1.20-1.27 (m, 3H), 1.06-1.14 (m, 1H), 0.90 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (125MHz, $CDCl_3$): δ 170.2, 136.5, 129.3, 128.3, 126.7, 48.1, 42.5, 38.6, 35.8, 32.9, 31.9, 19.6, 14.2. HRMS (ESI): m/z $[M]^+$ found 231.1624, calcd 231.1623 for $C_{15}H_{21}NO$.



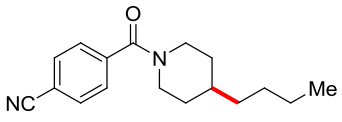
5b

(4-Butylpiperidin-1-yl)(phenyl)methanone (5b). This compound can be prepared according to the General Procedure using (4-bromopiperidin-1-yl)(phenyl)methanone **5a** (**5a = 4a**) (42.0 mg, 0.157mmol, 100%), 1-bromobutane(50.6 uL, 0.471 mmol, 300 mol%) and (4-Cl)-H-Pybox (**3n**) (3.2 mg, 0.013 mmol, 8 mol%). Flash column chromatography (SiO_2: 10% ethyl acetate in hexanes) gave the title product as a colorless oil (27.7 mg, 0.113 mmol, 72% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.38-7.46 (m, 5H), 4.71 (br d, *J* = 9.0 Hz, 1H), 3.74 (br d, *J* = 10.5 Hz, 1H), 2.69-3.05 (m, 2H), 1.82 (br s, 1H), 1.64 (br d, *J* = 9.5 Hz, 1H), 1.46-1.58 (m, 1H), 1.05-1.36 (m, 8H), 0.91 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.2, 136.5, 129.3, 128.3, 126.8, 48.1, 42.5, 36.1, 36.0, 33.0, 32.0, 28.8, 22.8, 14.0. HRMS (ESI): m/z $[M]^+$ found 245.1779, calcd 245.1780 for $C_{16}H_{23}NO$.



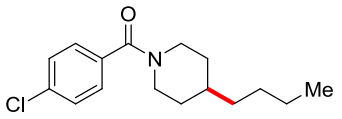
6b

(4-Dodecylpiperidin-1-yl)(phenyl)methanone (6b). This compound can be prepared according to the General Procedure using (4-bromopiperidin-1-yl)(phenyl)methanone **6a** (**6a = 4a**) (50.0 mg, 0.186 mmol, 100 mol%), zinc powder (38.0 mg, 0.558 mmol, 300 mol%), $Ni(COD)_2$ (5.2 mg, 0.019 mmol, 10 mol%), 1-iodododecane (137.0 uL, 0.471 mmol, 300 mol%), (*S*)-^{s}Bu-Pybox (**3a**) (4.9 mg, 0.015 mmol, 8 mol%) and DMA (1.0 mL). Flash column chromatography (SiO_2: 8% ethyl acetate in hexanes) gave the title product as a colorless oil (40.0 mg, 0.112 mmol, 60% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.38-7.42 (m, 5H), 4.70 (br d, *J* = 9.0 Hz, 1H), 3.73 (br d, *J* = 9.0 Hz, 1H), 2.97 (br s, 1H), 2.76 (br s, 1H), 1.83 (br s, 1H), 1.65 (br s, 1H), 1.45-1.57 (m, 1H), 1.19-1.36 (m, 23H), 1.05-1.17 (m, 1H), 0.89 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.2, 136.5, 129.3, 128.3, 126.8, 48.1, 42.5, 36.4, 36.1, 33.0, 32.0, 31.9, 29.8, 29.64, 29.61, 29.3, 26.6, 22.7, 14.1. HRMS (ESI): m/z $[M]^+$ found 357.3026, calcd 357.3032 for $C_{24}H_{39}NO$.



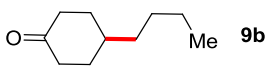
7b

4-(4-Butylpiperidine-1-carbonyl)benzonitrile (7b). This compound can be prepared according to the General Procedure using 4-(4-bromopiperidine-1-carbonyl)benzonitrile **7a** (46.0 mg, 0.157 mmol, 100%), 1-bromobutane (50.6 uL, 0.471 mmol, 300 mol%) and (4-Cl)-H-Pybox (**3n**) (3.2 mg, 0.013 mmol, 8 mol%). Flash column chromatography (SiO_2: 20% ethyl acetate in hexanes) gave the title product as a colorless oil (23.3 mg, 0.0861 mmol, 55% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.71 (d, *J* = 8.0 Hz, 2H), 7.50 (d, *J* = 8.5 Hz, 2H), 4.68 (d, *J* = 12.0 Hz, 1H), 3.58 (d, *J* = 13.0 Hz, 1H), 3.10 (t, *J* = 12.5 Hz, 1H), 2.78 (t, *J* = 12.5 Hz, 1H), 1.85 (d, *J* = 13.0 Hz, 1H), 1.68 (t, *J* = 14.0 Hz, 2H), 1.47-1.50 (m, 1H), 1.16-1.37 (m, 6H), 1.02-1.16 (m, 1H), 0.91 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (125MHz, $CDCl_3$): δ 168.1, 140.9, 132.3, 127.5, 118.2, 113.2, 48.0, 42.6, 36.0, 35.9, 32.9, 31.9, 28.8, 22.8, 14.0. HRMS (ESI): m/z $[M]^+$ found 270.1736, calcd 270.1732 for $C_{17}H_{22}N_2O$.



8b

(4-Butylpiperidin-1-yl)(4-chlorophenyl)methanone (8b). This compound can be prepared according to the General Procedure using (4-bromopiperidin-1-yl)(4-chlorophenyl)methanone **8a** (47.5 mg, 0.157mmol，100% mol), 1-iodobutane (53.6 uL, 0.471 mmol, 300 mol%) and (*S*)-^{s}Bu-Pybox (**3a**) (4.2 mg, 0.013 mmol, 8 mol%). Flash column chromatography (SiO_2: 15% ethyl acetate in hexanes) gave the title product (26.4 mg, 0.0943mmol, 60% yield). ^{1}H NMR (500MHz, $CDCl_3$): δ 7.33-7.41 (m, 4H), 4.67 (br s, 1H), 3.70 (br d, *J* = 5.0 Hz, 1H), 2.99 (br s, 1H), 2.76 (br s, 1H), 1.82 (br s, 1H), 1.66 (br s, 1H), 1.42-1.52 (m, 1H), 1.02 -1.37 (m, 8H), 0.91 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (125MHz, $CDCl_3$): δ 169.2, 135.4, 134.8, 128.6, 128.4, 48.2, 43.0, 36.1, 36.0, 32.0, 31.9, 28.8, 22.8, 14.0. HRMS (ESI): m/z $[M]^+$ found 279.1388, calcd 279.1390 for $C_{16}H_{22}ClNO$. M.p. = 76-78 ℃.

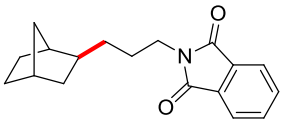


9b

4-Butylcyclohexanone (9b). This compound can be prepared according to the General Procedure using 4-bromocyclohexanone **9a** (50.0 mg, 0.282mol, 100%), 1-bromobutane (91.0 uL, 0.847 mmol, 300 mol%), zinc powder (50.1 mg, 0.847 mmol, 300 mol%) and (4-Cl)-H-Pybox (**3n**) (5.5 mg, 0.022

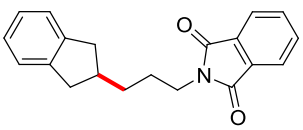
mmol, 8 mol%), $Ni(COD)_2$(7.7 mg, 0.0282 mmol, 10 mol%) in DMA (1.8 mL). Flash column chromatography (SiO_2: 6% ethyl acetate in hexanes) gave the title product as a colorless oil (24.8 mg, 0.161 mmol, 57% yield).

This compound can also be prepared according to the General Procedure using 4-bromocyclohexanone **9a** (50.0 mg, 0.282 mmol, 100 mol %), 1-iodobutane (96.0 uL, 0.847 mmol, 300 mol %) and (*S*)-^{s}Bu-Pybox (**3a**) (7.1 mg, 0.022 mmol, 8 mol %). Flash column chromatography (SiO_2: 8% ethyl acetate in hexanes) gave the title product as a colorless oil (28.3 mg, 0.184 mmol, 65% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.29-2.41 (m, 4H), 2.03-2.10 (m, 2H), 1.68-1.74 (m, 1H), 1.33-1.44 (m, 2H), 1.28-1.36 (m, 6H), 0.92 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (125MHz, $CDCl_3$): δ 212.7, 40.9, 36.0, 35.3, 32.8, 29.6, 22.9, 14.1. HRMS (ESI): m/z $[M]^+$ found 154.1357, calcd 154.1358 for $C_{10}H_{18}O$.



10b

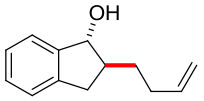
***exo*-Bicyclo[2.2.1]heptan-2-yl)propyl)isoindoline (10b).** This compound can be prepared according to the General Procedure using *exo*-2-bromobicyclo[2.2.1]heptane **10a** (27.5 mg, 0.157 mmol, 100 mol%), 2-(3-bromopropyl)isoindoline (126.3 mg, 0.471 mmol, 300 mol%) and (4-Cl)-H-Pybox (**3n**) (3.2 mg, 0.013 mmol, 8 mol%). Flash column chromatography (SiO_2: 8% ethyl acetate in hexanes) gave the title product (exo:endo > 20:1) as syrup (22.2 mg, 0.079 mmol, 50% yield). The dr was determined based on ^{1}H NMR analysis of a mixture by collecting all fractions in one flask using a flash column chromatography. ^{1}H NMR (500MHz, $CDCl_3$): δ 8.50 (dd, *J* = 5.5 and 3.0 Hz, 2H), 7.71 (dd, *J* = 5.5 and 3.0 Hz, 2H), 3.66 (t, *J* = 7.5 Hz, 2H), 2.17 (s, 1H), 1.94 (s, 1H), 1.60-1.70 (m, 2H), 1.24-1.51 (m, 6H), 0.96-1.16 (m, 5H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 168.5, 133.8, 132.2, 123.1, 41.9, 41.0, 38.2, 38.1, 36.5, 35.2, 33.9, 30.1, 28.7, 27.0. HRMS (ESI): m/z $[M]^+$ found 283.1577, calcd 283.1572 for $C_{18}H_{21}NO_2$.



11b

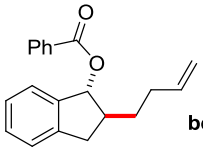
2-(3-(2,3-Dihydro-1H-inden-2-yl)propyl)isoindoline-1,3-dione (11b). This compound can be prepared according to the General Procedure using 2-bromo-2,3-dihydro-1H-indene **11a** (31.0 mg, 0.157 mmol, 100 mol%), 2-(2-bromoethyl)-1,3-dioxolane (126.0 mg, 0.471 mmol, 300 mol%) and

(4-Cl)-H-Pybox (**3n**) (3.2 mg, 0.013 mmol, 8 mol%). Flash column chromatography (SiO_2: 10% ethyl acetate in hexanes) gave an inseparable white solid mixture of **11b** (22.0 mg, 0.0720 mmol, 45% yield) and 2-propylisoindoline-1,3-dione derived from simple reduction of the C-Br bond. The yield was calculated based on the ^{1}H NMR ratio (10:1) of the product and the byproduct in the mixture. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.86-7.88 (m, 2H), 7.72-7.74 (m, 2H), 7.17-7.19 (m, 2H), 7.11-7.14 (m, 2H), 3.74 (t, *J* = 7.0 Hz, 2H), 3.05 (q, *J* = 15.0 Hz, 2H), 2.60 (q, *J* = 15.0 Hz, 2H), 2.43- 2.53 (m, 1H), 1.75-1.83 (m, 2H), 1.56-1.61 (m, 2H). ^{13}C NMR (125MHz, $CDCl_3$): δ 168.5, 143.3, 133.9, 132.2, 126.1, 124.4, 123.2, 39.8, 39.2, 38.1, 32.8, 27.5. HRMS (ESI): m/z $[M]^+$ found 305.1414, calcd 305.1416 for $C_{20}H_{19}NO_2$. M.p. = 103-106 ℃.



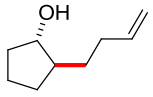
12b (dr 4:1)

***trans*-2-(But-3-enyl)-2,3-dihydro-1H-inden-1-ol (12b).** This compound can be prepared according to the General Procedure using *trans*-2-bromo-2,3-dihydro-1H-inden-1-ol **12a** (33.5 mg, 0.157 mmol, 100 mol%), 4-bromobut-1-ene (47.8 uL, 0.471 mmol, 300 mol%) and (4-Cl)-H-Pybox (**3n**) (3.2 mg, 0.013 mmol, 8 mol%). Flash column chromatography (SiO_2: 8% ethyl acetate in hexanes) gave a mixture of *cis* (minor) and *trans* (major) products (dr 4:1) as a colorless oil (19.2 mg, 0.102 mmol, 65% yield). The dr was determined based on ^{1}H NMR analysis of the characteristic O-CH peaks of the two diastereomers at 4.86 ppm (*trans*) and 4.91 ppm (*cis*). The *trans*-isomer was confirmed by NOESY spectra of **12b** and **benzoylated-12b** (see below). Correlations between 4.86 ppm (-CH-O) and 2.51 ppm (one of the Benzylic-CH_2 *cis* to CH-O), 4.86 ppm (-CH-O) and 1.90-1.97 ppm (one of the protons on -CH_2-allyl), 4.86 ppm (-CH-O) and 1.58-1.66 ppm (one of the protons on -CH_2-allyl) were observed. ^{1}H NMR (500 MHz, $CDCl_3$) for the *trans*-isomer: δ 7.38-7.44 (m, 1H), 7.21-7.27 (m, 3H), 5.90 (ddt, *J* = 17.0, 10.5 and 6.5 Hz, 1H), 5.09 (ddd, *J* = 17.0, 2.0 and 1.5 Hz ,1H), 5.01(ddt, *J* = 10.0, 2.0 and 1.5 Hz, 1H), 5.07-5.09 (m,1H), 4.86 (d, *J* = 7.0 Hz, 1H), 3.15 (dd, *J* = 8.0Hz and 15.5 Hz, 1H), 2.51 (dd, *J* = 8.5 Hz and 15.5Hz, 1H), 2.17-2.32 (m, 2H), 1.90-1.97 (m, 1H), 1.58-1.66 (m, 2H). ^{13}C NMR (125MHz, $CDCl_3$): δ 144.9, 141.7, 138.7, 128.1, 126.7, 124.7, 123.8, 114.7, 81.6, 50.4, 36.0, 32.6, 32.4. HRMS (ESI): m/z $[M]^+$ found 188.1203, calcd 188.1201 for $C_{13}H_{16}O$.



benzoylated-12b

***trans*-2-(but-3-enyl)-2,3-dihydro-1H-inden-1-yl (benzoylated-12b).** A mixture of benzoic anhydride (104.6 mg, 0.462 mmol, 200 mol%), 2-(but-3-enyl)-2,3-dihydro-1H-inden-1-ol (43.5 mg, 0.231 mmol, 100 mol%), pyridine (37.0 ul, 0.462 mmol, 200 mol%) and catalytic amount of DMAP (1.40 mg, 0.007 mmol, 3 mol%) was stirred in dry CH_2Cl_2 (3.0 mL) at 25 ˚C for 20 h. After the reaction was completed, silica gel was added. The solvent was evaporated. Column chromatography (SiO_2: 2% ethyl acetate in hexanes) afforded the product as syrup (60.8 mg, 0.208 mmol, 90% yield). The *trans*-geometry of **benzoylated-12b** was also confirmed by NOESY spectrum. Correlations between 6.34 ppm (-CH-O) and 1.86-1.98 ppm (one of the protons on -CH_2-allyl), 6.34 ppm (-CH-O) and 1.60-1.71 ppm (the other proton from -CH_2-allyl) were observed. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.13 (dd, J = 8.5 and 1.5 Hz, 2H), 7.53-7.65 (m, 1H), 7.47-7.53 (m, 3H), 7.20-7.47 (m, 3H), 6.34 (d, *J* = 5.0 Hz, 1H), 5.85-5.95 (m, 1H), 5.08 (dd, *J* = 15.5 and 1.5 Hz, 1 H), 5.01 (d, *J* = 10.0 Hz, 1H), 3.30-3.40 (m, 1H), 2.65-2.75 (m, 2H), 2.15-2.33 (m, 2H), 1.86-1.98 (m, 1H), 1.60-1.71 (m, 1H). ^{13}C NMR (125MHz, $CDCl_3$): δ 166.6, 142.9, 141.0, 138.2, 132.9, 130.3, 129.7, 128.7, 128.3, 126.8, 125.4, 124.8, 114.8, 83.2, 45.7, 36.3, 32.6, 32.0.

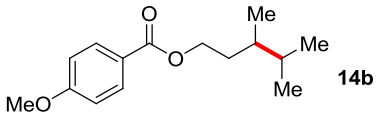


13b (dr 6:1)

***trans*-2-(but-3-enyl)cyclopentanol (13b).**[16] This compound can be prepared according to the General Procedure using *trans*-2-bromocyclopentanol (52.0 mg, 0.314 mmol, 100 mol%), 4-bromobut-1-ene (126.0 mg, 0.942 mmol, 300 mol%), zinc powder (62.0 mg, 0.942 mmol, 300 mol%), $Ni(COD)_2$ (8.8 mg, 0.032 mmol, 10 mol%), (4-Cl)-H-Pybox (**3n**) (6.4 mg, 0.025 mmol, 8 mol%) and DMA (1.0 ml). Flash column chromatography (SiO_2: 8% ethyl acetate in hexanes) gave a mixture of *cis* (minor) and *trans* (major) isomers as a colorless oil (27.7 mg, 0.198 mmol, 63% yield). The dr for the *trans* and *cis* isomers was determined to be 6:1 based on ^{1}H NMR analysis of the characteristic peaks of the CH_2 adjacent to OH for the two isomers at 3.84 (*trans*) and 4.15 ppm (*cis*), respectively. The *trans*-isomer was confirmed by NOESY spectrum based on a correlation between 3.84 ppm (-CH_2OH) and 1.25-1.28 ppm (one of the protons on -CH_2-allyl). ^{1}H NMR (500 MHz, $CDCl_3$) for the *trans*-isomer: δ 5.84 (ddt, *J* = 17.0, 10.0 and 7.0 Hz, 1H), 5.03 (ddd, *J* = 17.0, 2.0 and 1.5 Hz, 1H), 4.96 (ddt, *J* = 10.0, 2.0 and 1.5 Hz, 1H), 3.84 (dd, *J* = 11.5 and 5.5 Hz 1H), 2.04-2.20 (m, 2H), 1.87-1.97 (m,

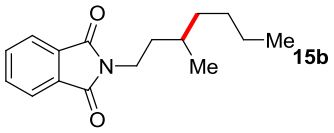
(16) (a) Clive, D. L. J.; Pham, M. P.; Subedi, R. *J. Am. Chem. Soc.* **2007**, *129*, 2713–2717. (b) Wolff, S.; Agosta, W. C. *J. Chem. Res. (S)* **1981**, 78-79.

2H), 1.66-1.75 (m, 2H), 1.52-1.65 (m, 4H), 1.25-1.28 (m, 1H), 1.14-1.22 (m, 1H). ^{13}C NMR (125MHz, $CDCl_3$): δ 138.9, 114.4, 47.8, 34.7, 33.1, 32.5, 30.0, 21.8.



14b

3,4-dimethylpentyl 4-methoxybenzoate (14b) This compound can be prepared according to the General Procedure using 3-bromobutyl 4-methoxybenzoate **14a** (50.0 mg, 0.174 mmol, 100 mol%), 2-bromopropane (49.0 uL, 0.522 mmol, 300 mol%), zinc powder (34.5 mg, 0.522 mmol, 300 mol%), $Ni(COD)_2$ (3.5 mg, 0.017 mmol, 10 mol%), (4-Cl)-H-Pybox (**3n**) (3.5 mg, 0.014 mmol, 8 mol%) and DMA (1.0 ml). Flash column chromatography (SiO_2: 8% ethyl acetate in hexanes) gave the title product as a colorless oil (24.0 mg, 0.0957 mmol, 55% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.00-8.02 (m, 2H), 6.92-6.94 (m, 2H), 4.27-4.38 (m, 2H), 3.88 (s, 3H), 1.82-1.88 (m, 1H), 1.62-1.66 (m, 1H), 1.47-1.58 (m, 2H), 0.91 (d, *J* = 7.0 Hz, 6H), 0.87 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (125MHz, $CDCl_3$): δ 166.5, 163.2 131.5, 123.0 113.5, 63.7, 55.4, 35.5, 32.8, 32.1, 19.9, 18.1, 15.4. HRMS (ESI): m/z $[M]^+$ found 250.1567, calcd 250.1569 for $C_{15}H_{22}O_3$.

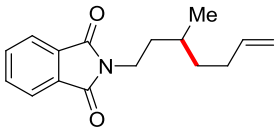


15b

2-(3-methylheptyl)isoindoline-1,3-dione (15b) This compound can be prepared according to the General Procedure using 2-(3-bromobutyl)isoindoline-1,3-dione **15a** (44.3 mg, 0.157 mmol, 100 mol%), 1-bromobutane (50.6 mg, 0.471 mmol, 300 mol%) and (4-Cl)-H-Pybox (**3n**) (3.2 mg, 0.013 mmol, 8 mol%). Flash column chromatography (SiO_2: 8% ethyl acetate in hexanes) gave the product as a colorless oil (19.0 mg, 0.0722 mmol, 46% yield).

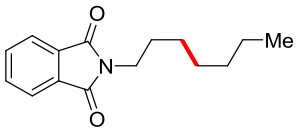
This compound can also be prepared according to the General Procedure using 2-(3-bromobutyl)isoindoline-1,3-dione (44.3 mg, 0.157 mmol, 100 mol%), 1-iodobutane (53.6 mg, 0.471 mmol, 300 mol%) and (*S*)-^{s}Bu-Pybox (**3a**) (4.2 mg, 0.013 mmol, 8 mol%). Flash column chromatography (SiO_2: 8% ethyl acetate in hexanes) gave the title product as a colorless oil (20.6 mg, 0.0785 mmol, 50% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.84 (dd, *J* = 5.5 and 3.0 Hz, 2H), 7.71 (dd, *J* = 5.5 and 3.0 Hz, 2H), 3.67-3.74 (m, 2H), 1.65-1.74 (m, 1H), 1.43-1.52 (m, 2H), 1.14-1.40 (m, 6H),

0.97 (d, J = 6.0 Hz, 3H), 0.88 (d, J = 7.0 Hz, 3H). ^{13}C NMR (125MHz, $CDCl_3$): δ 168.4, 133.8, 132.2, 123.1, 36.4, 36.3, 35.5, 30.7, 29.0, 22.9, 19.4, 14.1. HRMS (ESI): m/z $[M]^+$ found 259.1573, calcd 259.1572 for $C_{16}H_{21}NO_2$.



16b

2-(3-methylhept-6-enyl)isoindoline-1,3-dione (16b). This compound can be prepared according to the General Procedure using 2-(3-bromobutyl)isoindoline-1,3-dione **16a** (**16a = 15a**) (44.3 mg, 0.157 mmol, 100 mol%), 4-bromobut-1-ene (63.6 mg, 0.471 mmol, 300 mol%) and (4-Cl)-H-Pybox (**3n**) (3.2 mg, 0.013 mmol, 8 mol%). Flash column chromatography (SiO_2: 8% ethyl acetate in hexanes) gave the title product as a colorless oil (26.3 mg, 0.102 mmol, 65% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.55 (dd, J = 5.5 and 3.0 Hz, 2H), 7.20 (dd, J = 5.5 and 3.0 Hz, 2H), 5.80 (ddt, J = 17.0, 10.5 and 6.5 Hz, 1H), 5.00 (ddd, J = 17.0, 2.0 and 1.5 Hz, 1H), 4.92 (ddt, J = 10.0, 2.0 and 1.0 Hz, 1H), 3.70-3.75 (m, 2H), 1.99-2.16 (m, 2H), 1.69-1.78 (m, 1H), 1.44-1.56 (m, 3H), 1.24-1.33 (m, 1H), 1.00 (d, J = 6.5 Hz, 3H) . ^{13}C NMR (125MHz, $CDCl_3$): δ 168.4, 138.9, 133.8, 132.2, 123.1, 114.3, 36.2, 35.8, 35.3, 31.1, 30.1, 19.2. HRMS (ESI): m/z $[M]^+$ found 257.1420, calcd 257.1416 for $C_{16}H_{19}NO_2$.



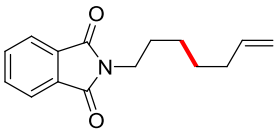
17b

2-heptylisoindoline-1,3-dione (17b).[17] This compound can be prepared according to the General Procedure using 2-(3-bromopropyl)isoindoline-1,3-dione **17a** (42.1 mg, 0.157 mmol, 100%), 1-iodobutane (53.4 uL, 0.471 mmol, 300 mol%) and (*S*)-^{s}Bu-Pybox (**3a**) (4.2 mg, 0.013 mmol, 8 mol%). Flash column chromatography (SiO_2: 8% ethyl acetate in hexanes) gave the title product as a yellow oil (25.0 mg, 0.102 mmol, 65% yield).

This compound can also be prepared according to the General Procedure using 2-(3-bromopropyl)isoindoline-1,3-dione **17a** (42.1 mg, 0.157 mmol, 100%), 1-bromobutane (50.6 uL, 0.471 mmol, 300 mol%) and (4-Cl)-H-Pybox (**3n**) (3.2 mg, 0.013 mmol, 8 mol%). Flash column chromatography (SiO_2: 8% ethyl acetate in hexanes) gave the title product as a yellow oil (27.7 mg, 0.113 mmol, 72% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.82-7.86 (m, 2H), 7.71-7.73 (m, 2H), 3.69 (t,

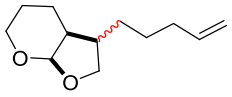
(17) Zhou, J.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 12527–12530.

J = 7.5 Hz, 2H), 1.63-1.70 (m, 2H), 1.26-1.35 (m, 8H), 0.89 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): 168.5, 133.8, 132.1, 38.1, 31.7, 28.9, 28.6, 26.8, 22.6, 14.0.



18b

2-(hept-6-enyl)isoindoline-1,3-dione (18b).[18] This compound can be prepared according to the General Procedure using 2-(3-bromopropyl)isoindoline-1,3-dione **18a** (**18a = 17a**) (42.1 mg, 0.157mmol, 100%), 4-bromobut-1-ene (48.0 uL, 0.471 mmol, 300 mol%) and (4-Cl)-H-Pybox (**3n**) (3.2 mg, 0.013 mmol, 8 mol%). Flash column chromatography (SiO_2: 8% ethyl acetate in hexanes) gave the product as colorless oil (35.0 mg, 0.144 mmol, 92% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.84-7.86(m, 2H), 7.71-7.73(m, 2H), 5.76-5.84 (ddt, *J*= 17.0, 10.5 and 6.5 Hz, 1H), 4.97-5.02 (ddd, *J* = 17.0, 2.0 and 1.5Hz, 1H), 4.92-4.95 (ddt, *J* = 10.0, 2.0 and 1.0 Hz, 1H), 3.69 (t, *J* = 7.5 Hz, 2H), 2.03-2.08 (m, 2H), 1.66-1.73 (m, 2H), 1.42-1.46 (m, 2H), 1.35-1.40(m, 2H). (125MHz, $CDCl_3$): 168.4, 138.7, 133.8, 132.1, 123.1, 114.5, 37.9, 33.5, 28.4, 26.3.



19b (endo:exo > 20:1)

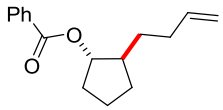
3-(pent-4-enyl)hexahydro-2H-furo[2,3-b]pyran (19b). This compound can be prepared according to the General Procedure using *trans*-2-(allyloxy)-3-bromotetrahydro-2H-pyran **19a**[19] (34.7 mg, 0.157 mmol, 100 mol%), 2-(2-bromoethyl)-1,3-dioxolane (46.1 uL, 0.471 mmol, 300 mol%) and (4-Cl)-H-Pybox (**3n**) (3.2 mg, 0.013 mmol, 8 mol%). Flash column chromatography (SiO_2: 5% ethyl acetate in hexanes) gave the title product (endo:exo > 20:1) as a colorless oil (21.0 mg, 0.107mmol, 68% yield). The dr was determined based on ^{1}H NMR analysis of a mixture by collecting all fractions in one flask using a flash column chromatography. ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.79 (ddt, *J* = 17.5, 10.5 and 6.5 Hz, 1H), 5.28 (d, *J* = 4.0 Hz, 1H), 5.01 (ddd, *J* = 17.0, 2.0 and 1.5 Hz, 1H), 4.97 (ddt, *J* = 10.0, 2.0 and 1.5 Hz, 1H), 3.96 (t, *J* = 8.0 Hz ,1H), 3.71-3.80 (m,1H), 3.61-3.69 (m, 2H), 2.28-2.39 (m, 1H), 2.06 (q, *J* = 13.0 Hz, 2H), 1.90-2.00 (m, 1H), 1.62-1.69 (m, 1H), 1.55-1.62 (m, 2H), 1.26-1.46 (m, 5H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 138.4, 114.7, 102.0, 70.1, 61.0, 40.9, 36.4, 33.9, 27.5, 26.4, 23.2, 19.2. HRMS (ESI): m/z $[M]^+$ found 196.1458, calcd 196.1463 for $C_{12}H_{20}O_2$.

(18) Yang, H.; Carter, R. G. *Org. Lett*. **2010**, *12*, 3108–3111.

(19) Beckwith, A. L. J.; Page, D. M. *Tetrahedron* **1999**, *55*, 3245–3254.

Part 8. Determination of the Enantioselectivities for 12b and 13b.

(1) Determination of the enantioselectivity for **13b** was performed after benzoylation of **13b**.



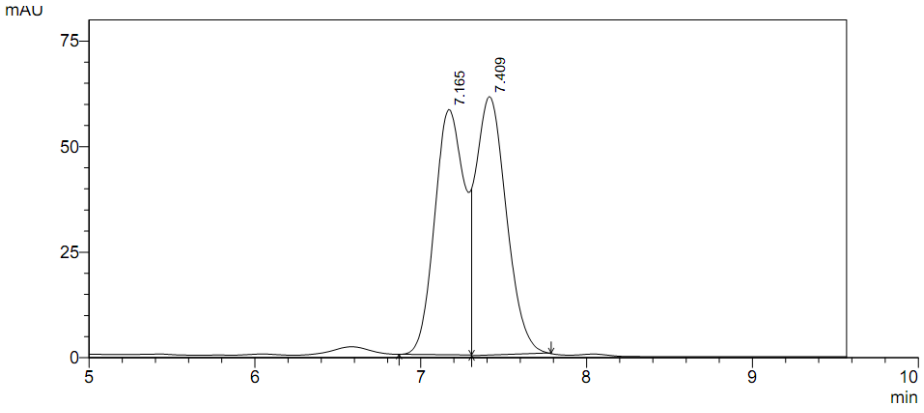
***trans*-2-(but-3-enyl)cyclopentyl benzoate.** A mixture of *trans*-2-(but-3-enyl)cyclopentanol (20.0 mg, 0.143 mmol), benzoic anhydride (64.5 mg, 0.285 mmol), pyridine (23.0 ul, 0.285 mmol) and catalytic amount of DMAP (0.90 mg, 0.00715 mmol) was stirred in dry CH_2Cl_2 (5.0 mL) at 25 ℃ for 20 h. Silca gel was added, and the solvent was evaporated. Column chromatography (SiO_2: 2% ethyl acetate in hexanes) afforded the product as colorless oil (31.0 mg, 0.129 mmol, 90% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.00-8.10 (m, 2H), 7.53-7.63 (m, 1H), 7.40-7.50 (m, 2H), 5.75-5.90 (m, 1H), 4.90-5.10 (m, 3H), 1.95-2.20 (m, 5H), 1.60-1.85 (m, 4H), 1.30-1.45 (m, 2H). ^{13}C NMR (125MHz, $CDCl_3$): δ 166.4, 138.6, 132.7, 130.8, 129.5, 128.3, 114.5, 82.0, 45.0, 32.9, 32.2, 32.0, 30.2, 22.8.

HPLC Conditions for benzoylated-*trans*-**13b**.

Column: Phenomenex Chiralpak amylose-2; Column Size: 250 x 4.6 mm analytical; Detection wavelength: 254nm.

Time (min)	Mobile phase	Flow rate
0	99.0/1.0 Hexane: IPA	0.8 mL/min
10	99.0/1.0 Hexane: IPA	0.8 mL/min

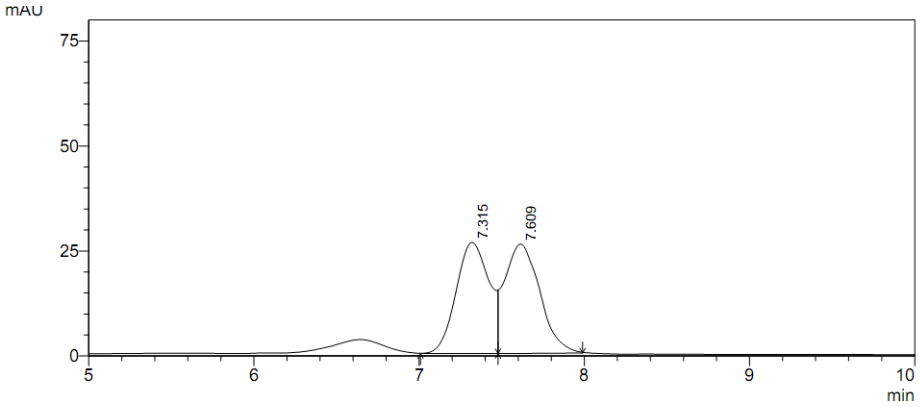
(4-Cl)-H-PyBox (**3n**):



PDA Ch1 254nm 4nm

peak No.	Ret.time(min)	Area	Height	Area%	Height%
1	7.165	746255	58095	49.539	48.684
2	7.409	760140	61236	50.461	51.316
Totals		1506395	119330	100.000	100.000

(*S*)-^{s}Bu-PyBox (**3a**)：



PDA Ch1 254nm 4nm

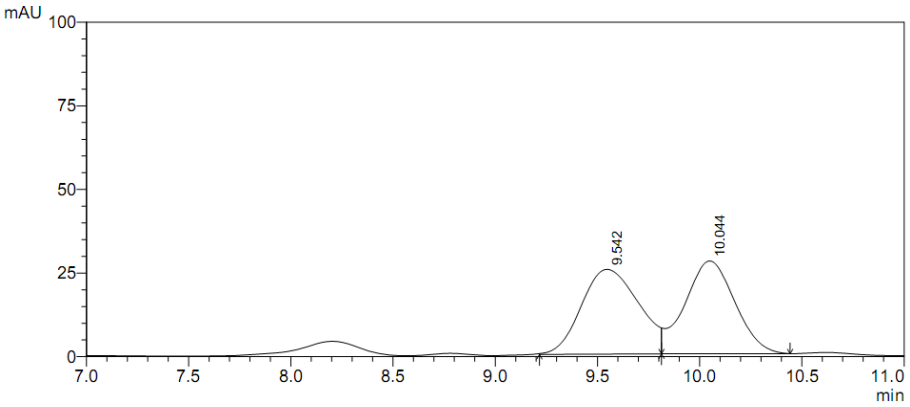
Peak No.	Ret.time(min)	Area	Height	Area%	Height%
1	7.315	373648	26471	49.646	50.432
2	7.609	378983	26017	50.354	49.568
Totals		752631	52488	100.000	100.000

(2) HPLC data for **12b**.

Column: Phenomenex Chiralpak amylose-2; Column Size: 250 x 4.6 mm analytical; Detection wavelength: 254nm.

Time (min)	Mobile phase	Flow rate
0	95.0/5.0 Hexane: IPA	0.8 mL/min
11	95.0/5.0 Hexane: IPA	0.8 mL/min

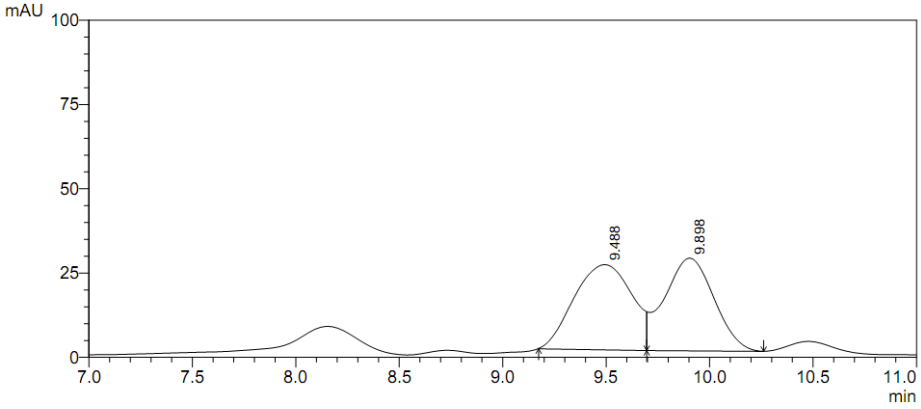
(4-Cl)-H-PyBox (**3n**):



PDA Ch1 254nm 4nm

Peak No.	Ret. time(min)	Area	Height	Area%	Height%
1	9.542	493320	25359	51.082	47.712
2	10.044	472426	27791	48.918	52.288
Totals		965746	53150	100.000	100.000

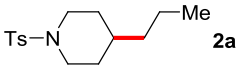
(*S*)-^{s}Bu-PyBox (**3a**)：



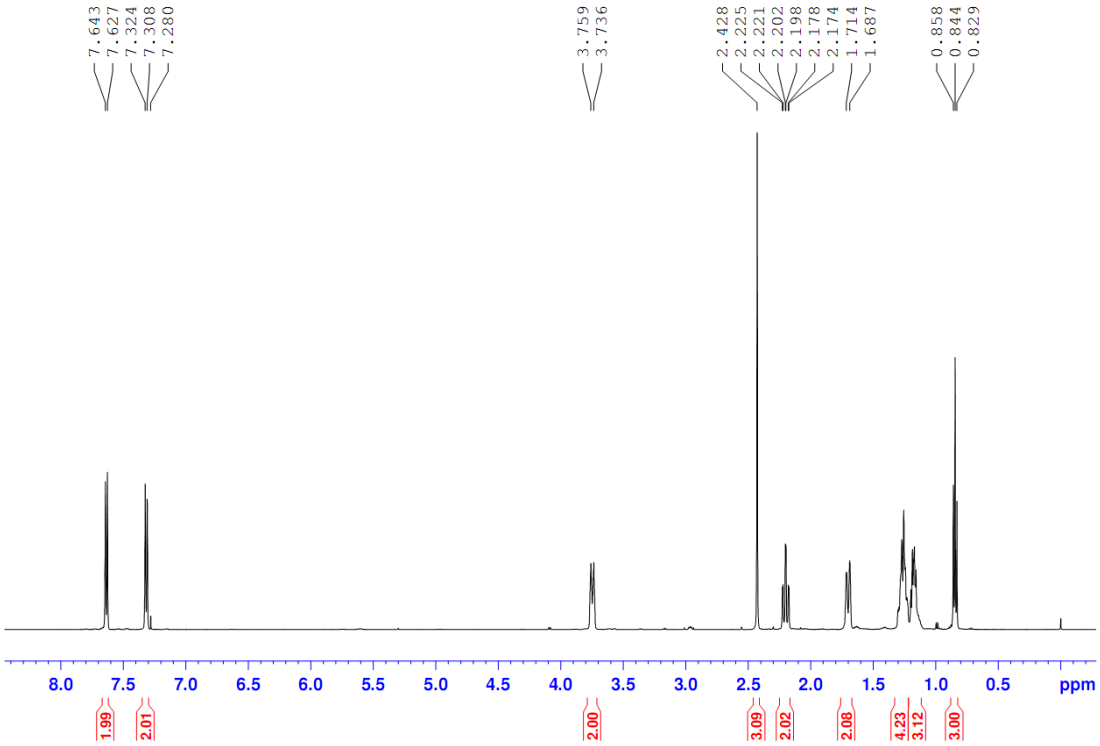
PDA Ch1 254nm 4nm

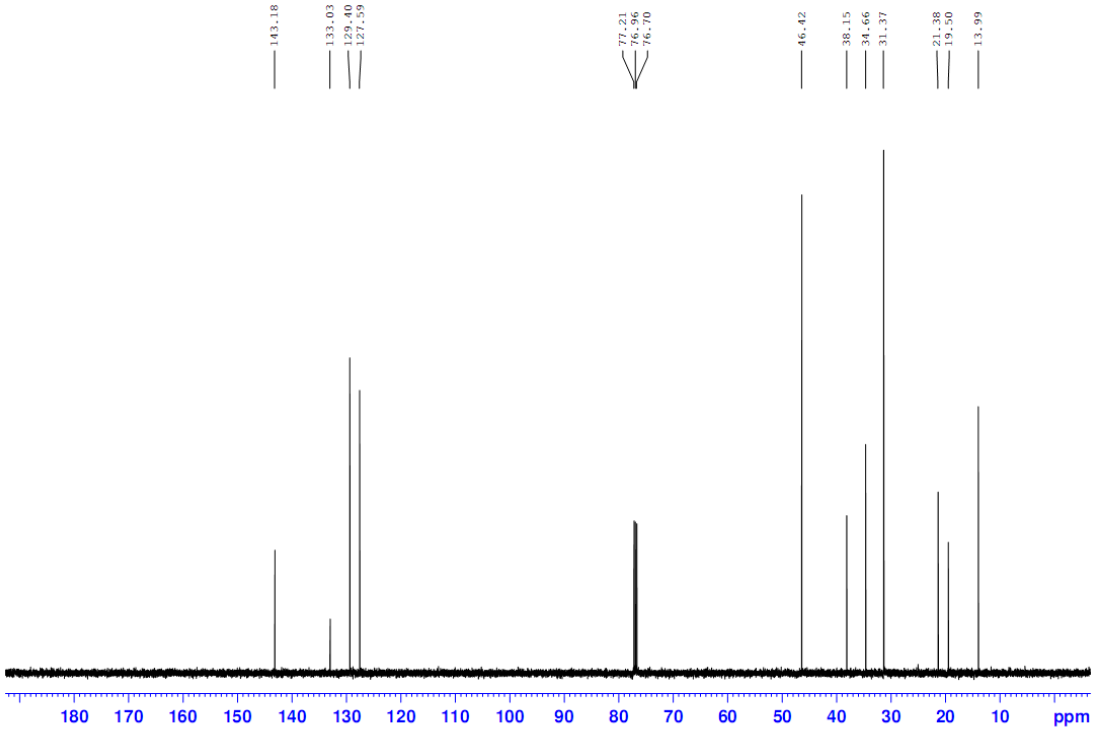
Peak No	Ret. time(min)	Area	Height	Area%	Height%
1	9.488	493547	25283	51.975	47.916
2	9.898	456044	27482	48.025	52.084
Totals		949591	52765	100.000	100.000

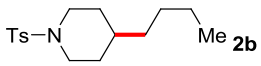
II. NMR Spectra for New Compounds



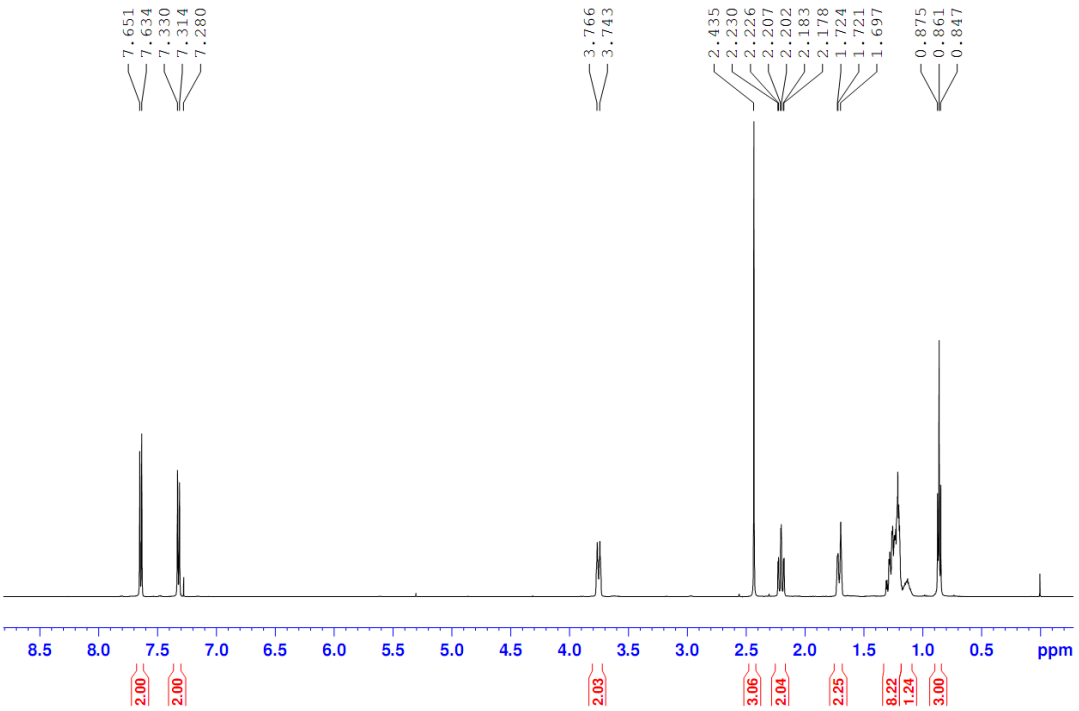
2a

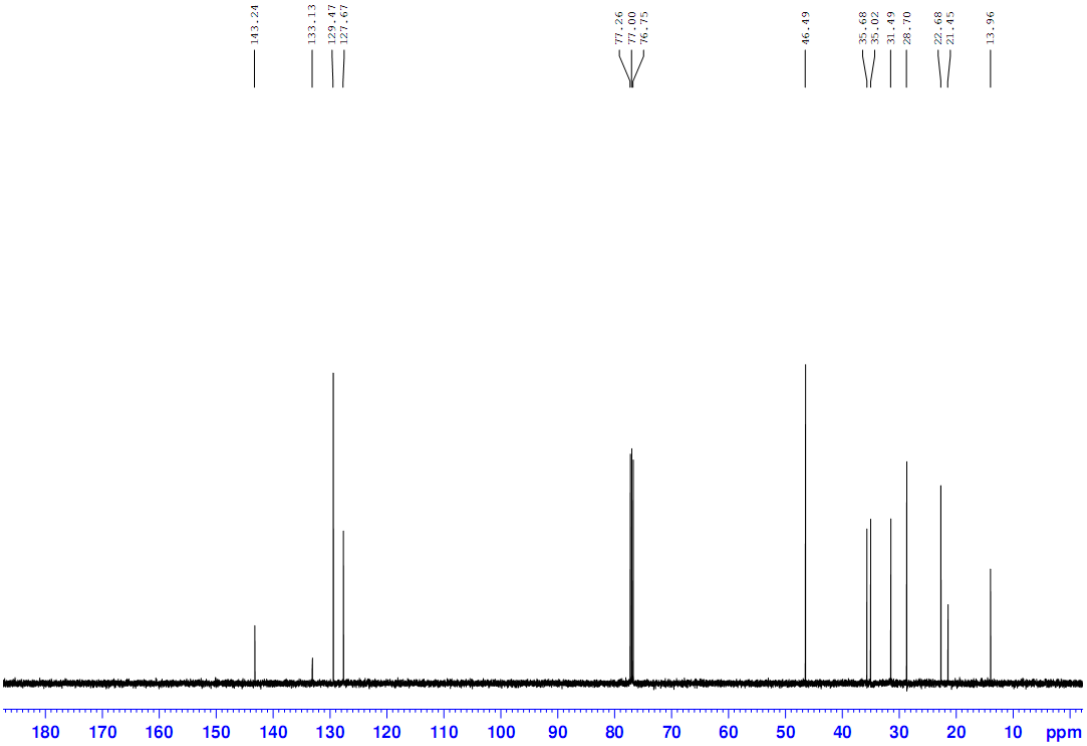


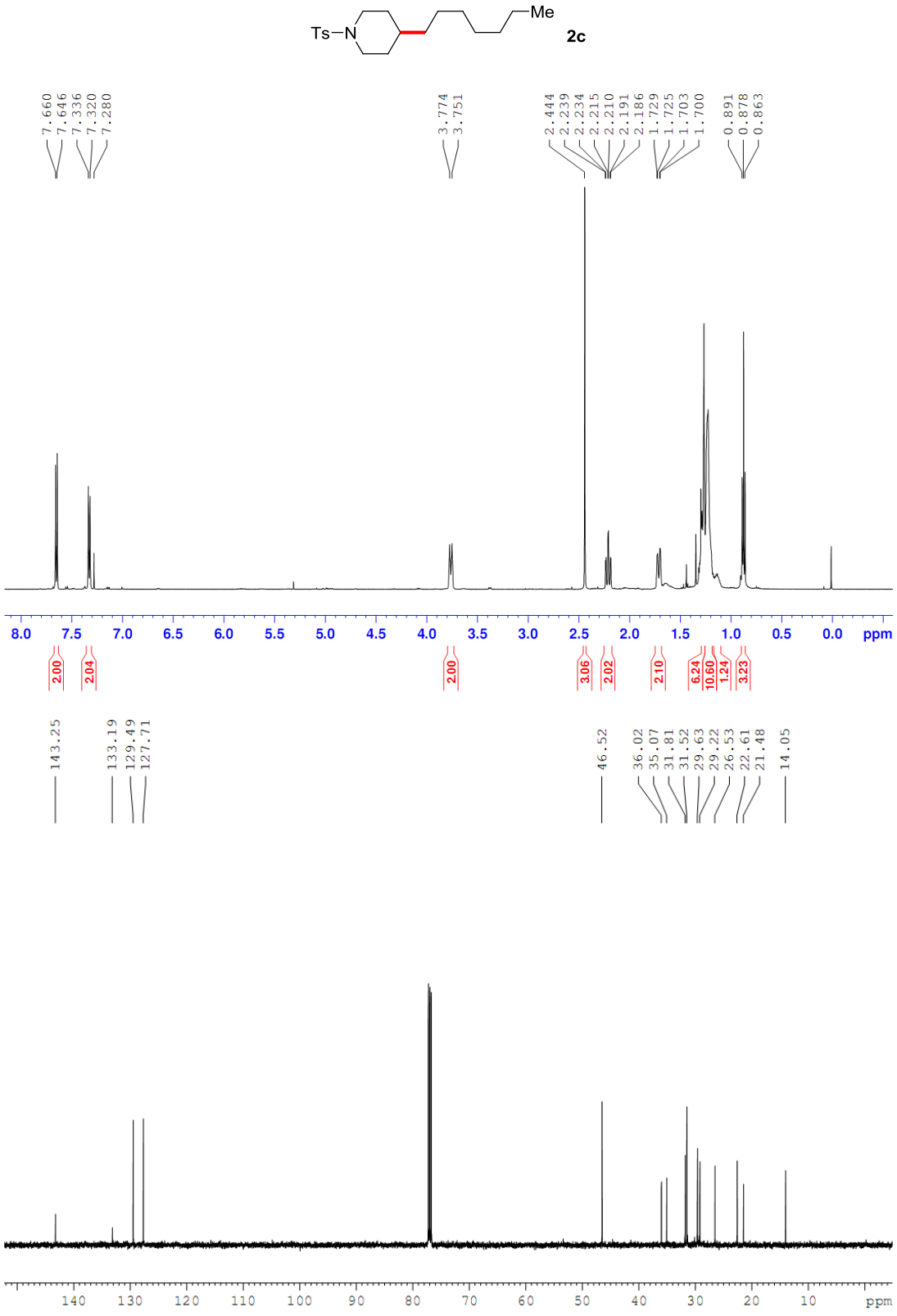


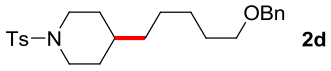

Ts—N
Me

2b

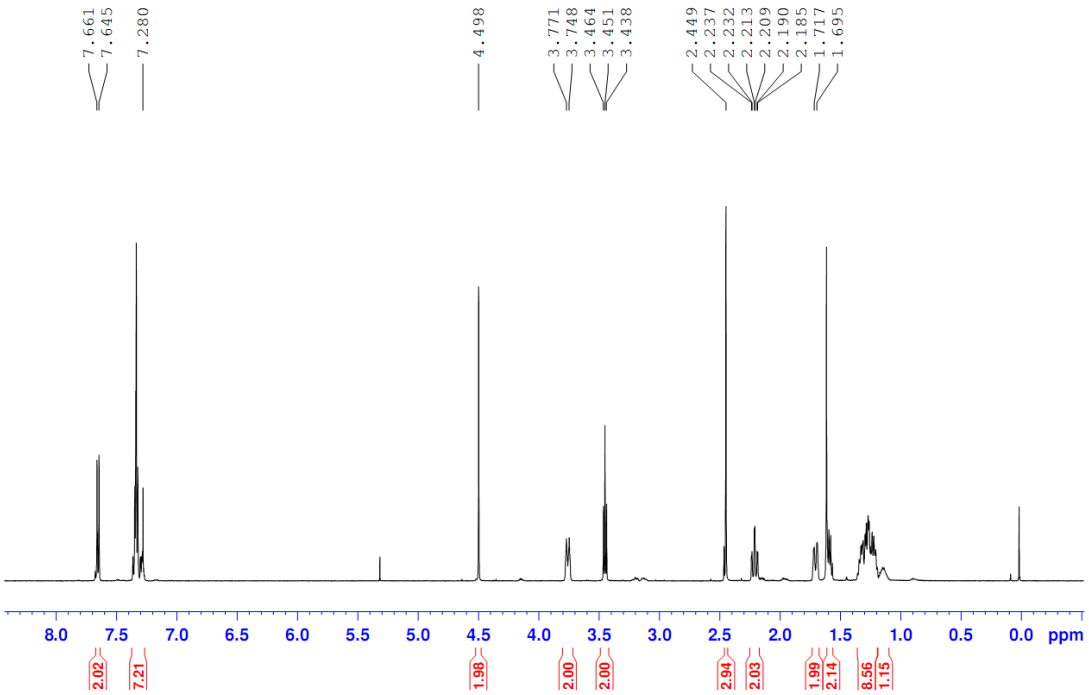

7.651
7.634
7.330
7.314
7.280
3.766
3.743
2.435
2.230
2.226
2.207
2.202
2.183
2.178
1.724
1.721
1.697
0.875
0.861
0.847
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
2.00
2.00
2.03
3.06
2.04
2.25
8.22
1.24
3.00

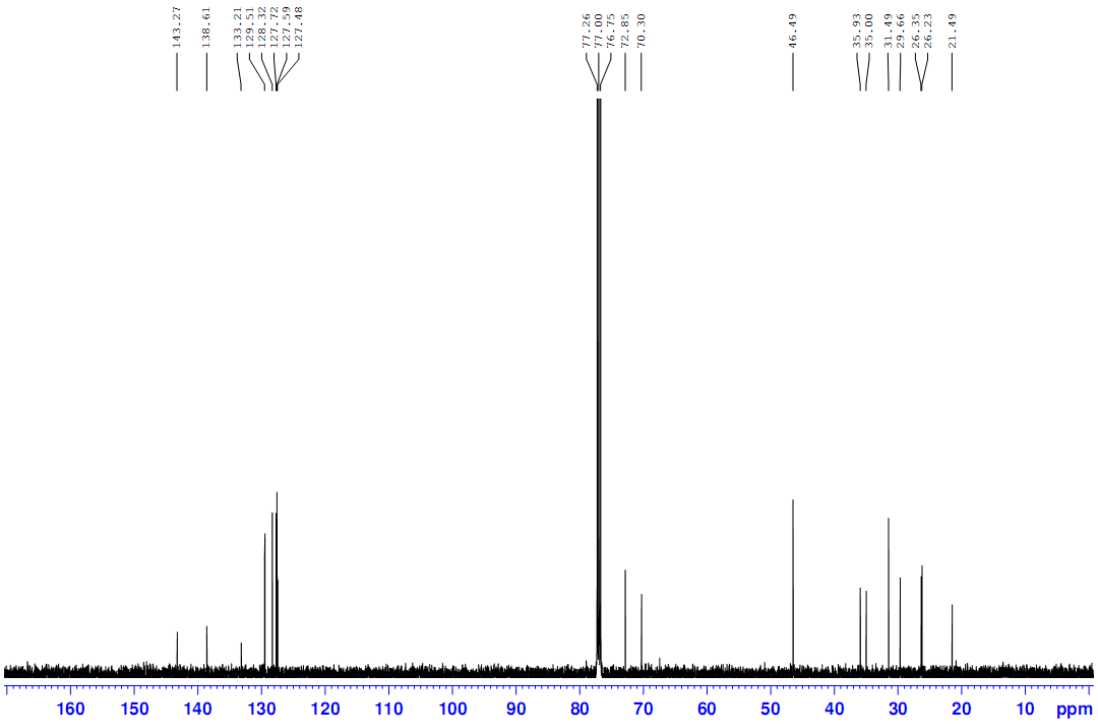

143.24
133.13
129.47
127.67
77.26
77.00
76.75
46.49
35.68
35.02
31.49
28.70
22.68
21.45
13.96
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

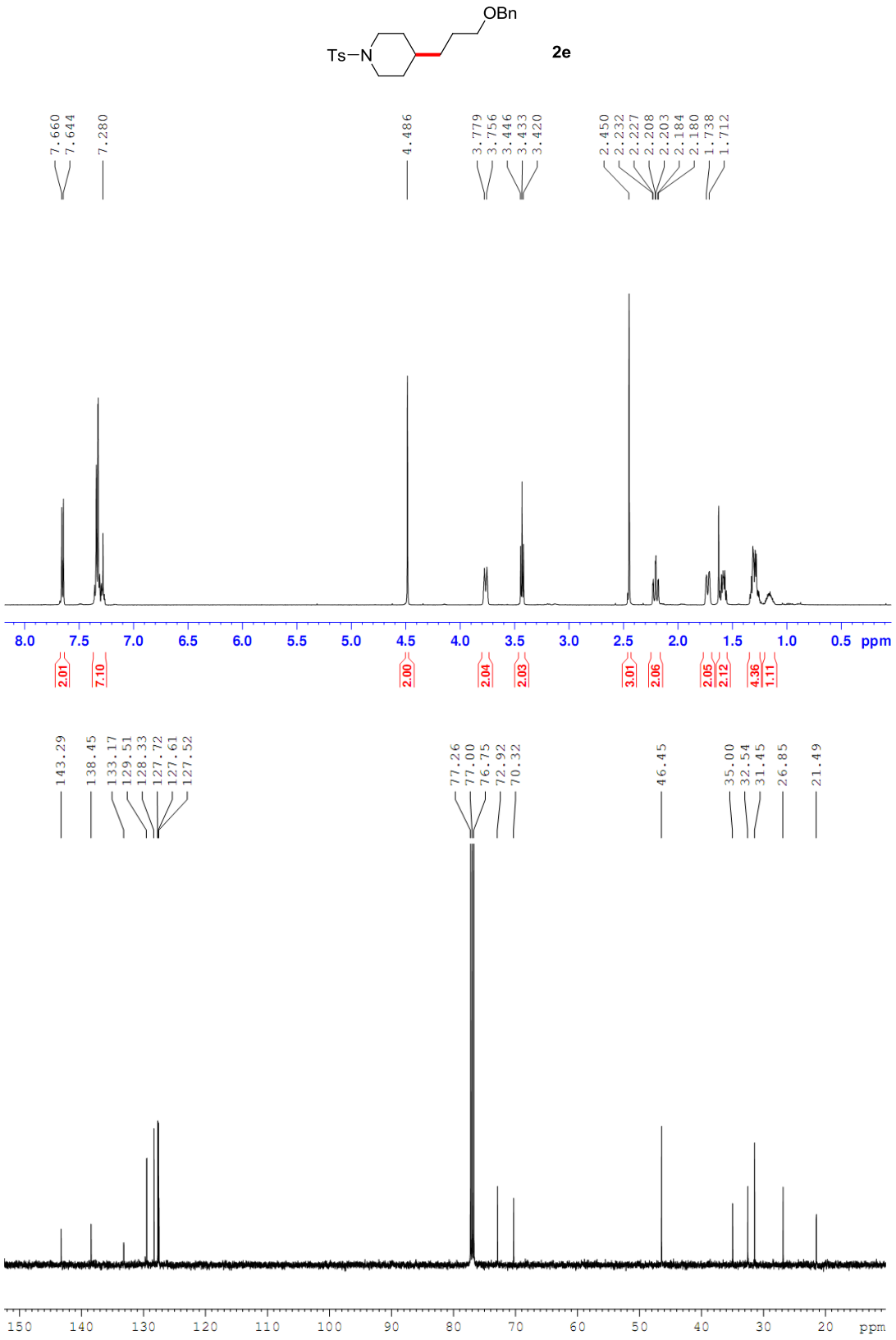

Ts—N
Me
2c
7.660
7.646
7.336
7.320
7.280
3.774
3.751
2.444
2.239
2.234
2.215
2.210
2.191
2.186
1.729
1.725
1.703
1.700
0.891
0.878
0.863
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm
2.00
2.04
2.00
3.06
2.02
2.10
6.24
10.60
1.24
3.23
143.25
133.19
129.49
127.71
46.52
36.02
35.07
31.81
31.52
29.63
29.22
26.53
22.61
21.48
14.05
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

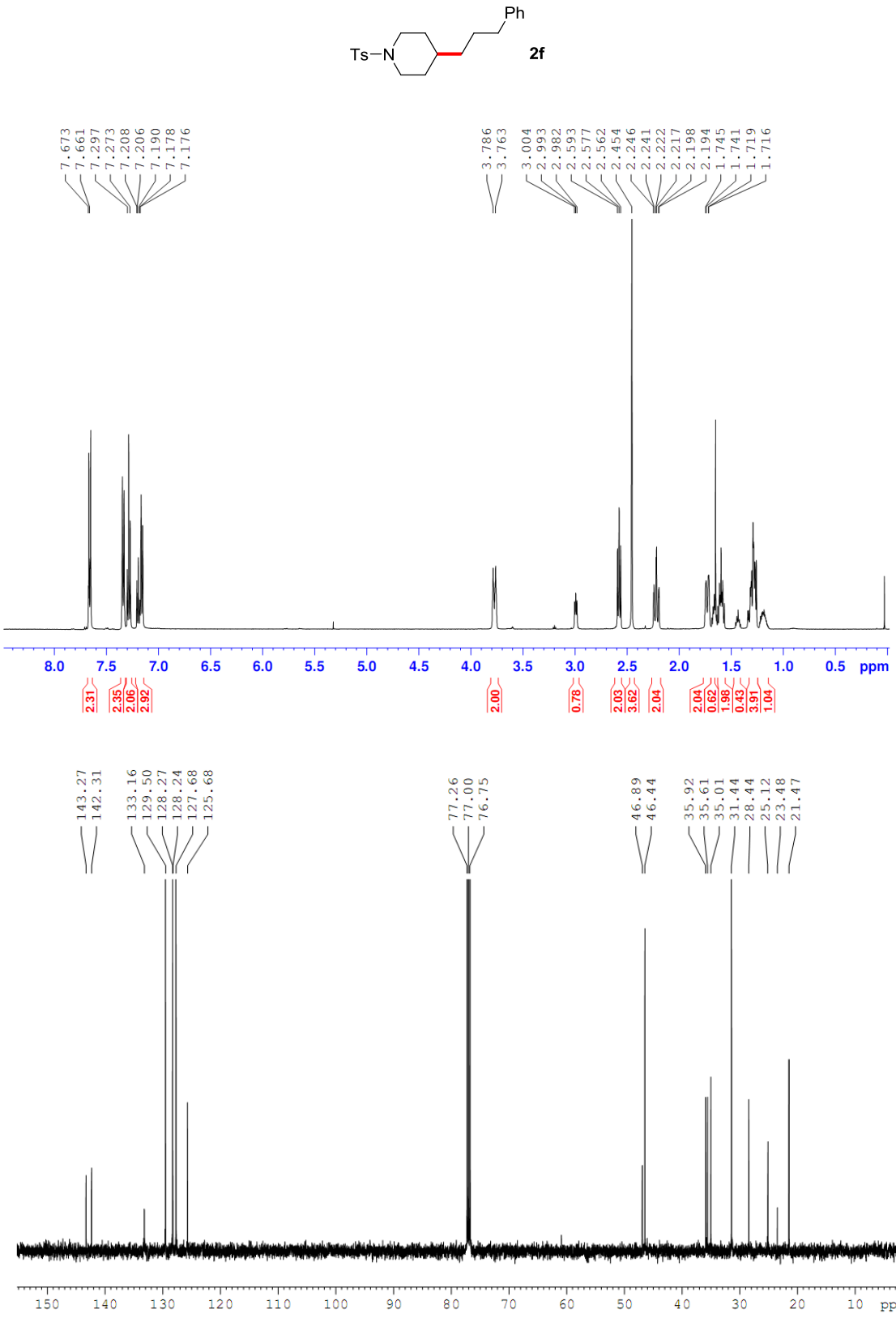

Ts–N
OBn

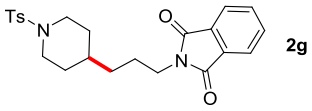
2d


7.661
7.645
7.280
4.498
3.771
3.748
3.464
3.451
3.438
2.449
2.237
2.232
2.213
2.209
2.190
2.185
1.717
1.695
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 ppm
2.02
7.21
1.98
2.00
2.00
2.94
2.03
1.99
2.14
8.56
1.15

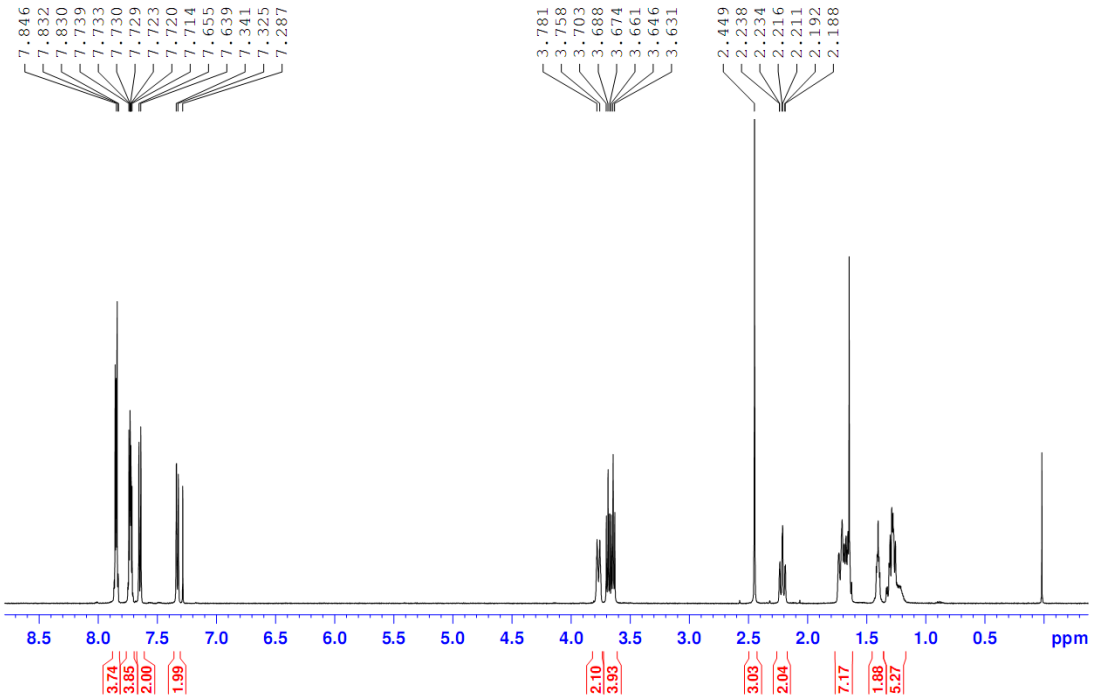

143.27
138.61
133.21
129.51
128.32
127.72
127.59
127.48
77.26
77.00
76.75
72.85
70.30
46.49
35.93
35.00
31.49
29.66
26.35
26.23
21.49
160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

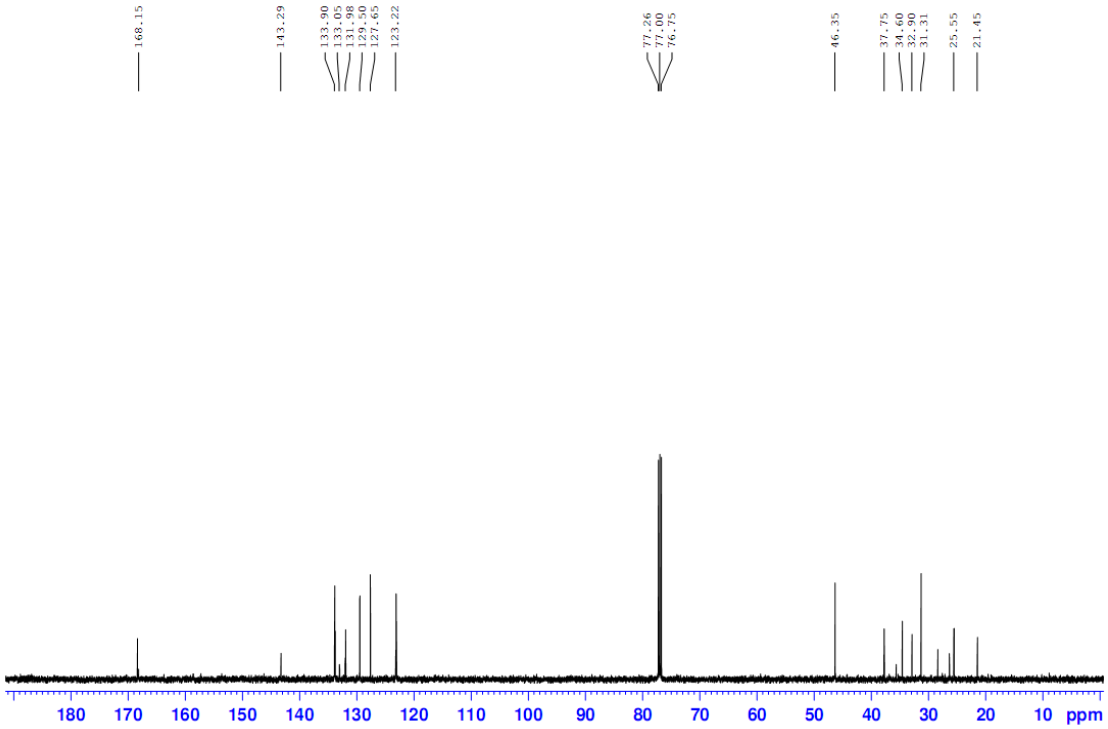

OBn
Ts—N
2e
7.660
7.644
7.280
4.486
3.779
3.756
3.446
3.433
3.420
2.450
2.232
2.227
2.208
2.203
2.184
2.180
1.738
1.712
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
2.01
7.10
2.00
2.04
2.03
3.01
2.06
2.05
2.12
4.36
1.11
143.29
138.45
133.17
129.51
128.33
127.72
127.61
127.52
77.26
77.00
76.75
72.92
70.32
46.45
35.00
32.54
31.45
26.85
21.49
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

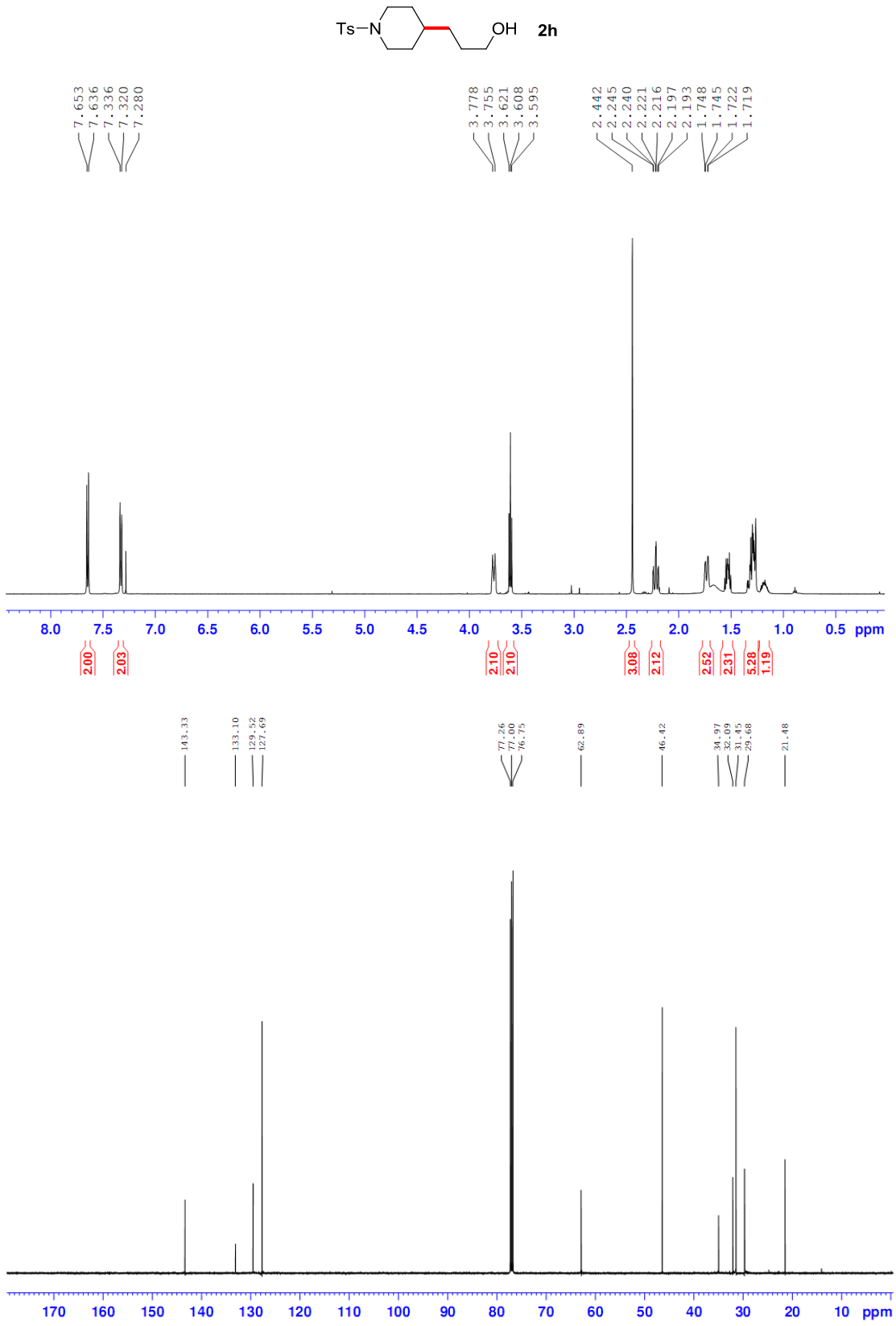

Ph
Ts—N
2f
7.673
7.661
7.297
7.273
7.208
7.206
7.190
7.178
7.176
3.786
3.763
3.004
2.993
2.982
2.593
2.577
2.562
2.454
2.246
2.241
2.222
2.217
2.198
2.194
1.745
1.741
1.719
1.716
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
2.31
2.35
2.06
2.92
2.00
0.78
2.03
3.62
2.04
2.04
0.62
1.98
0.43
3.91
1.04
143.27
142.31
133.16
129.50
128.27
128.24
127.68
125.68
77.26
77.00
76.75
46.89
46.44
35.92
35.61
35.01
31.44
28.44
25.12
23.48
21.47
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

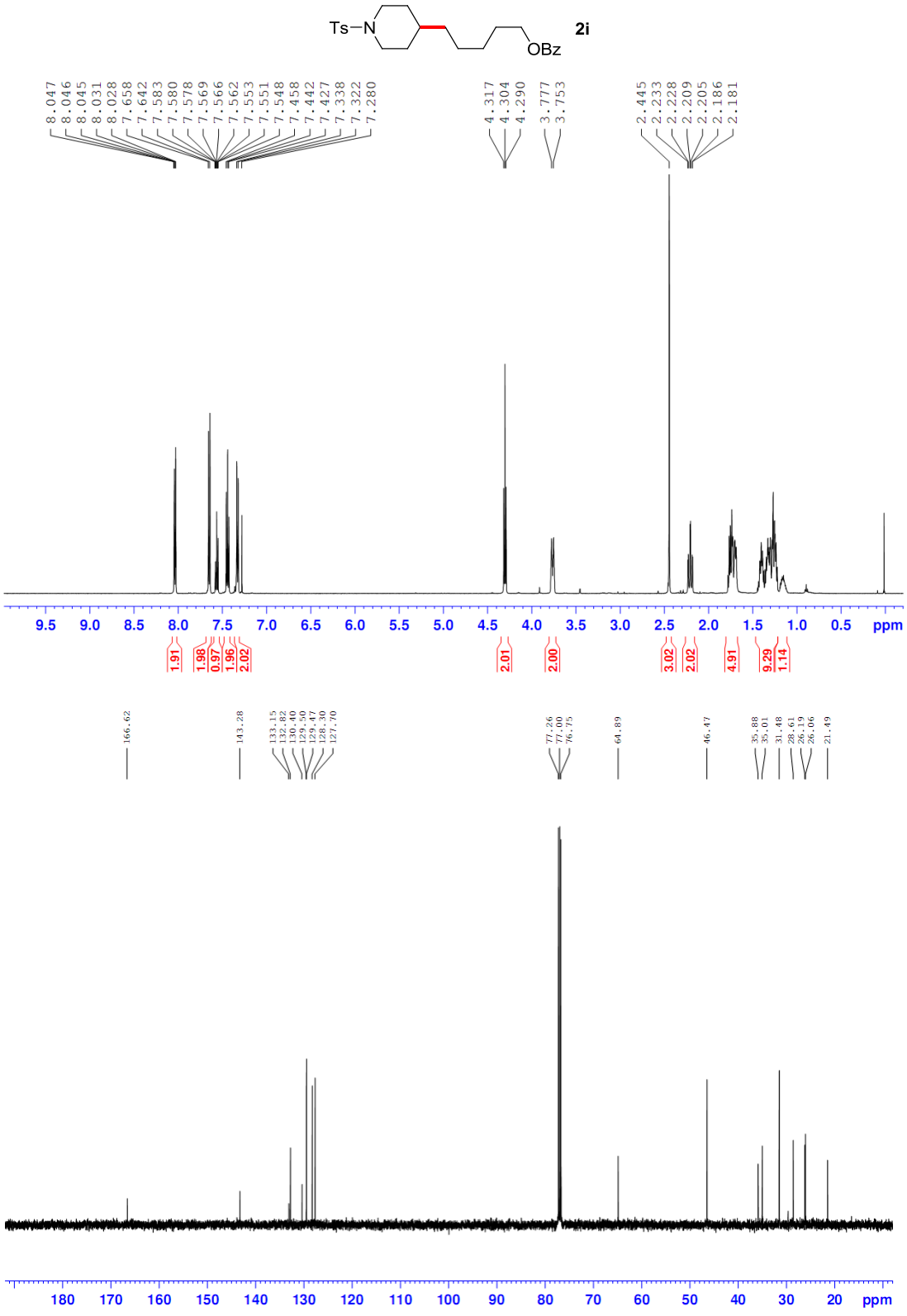

Ts
N
O
N
O

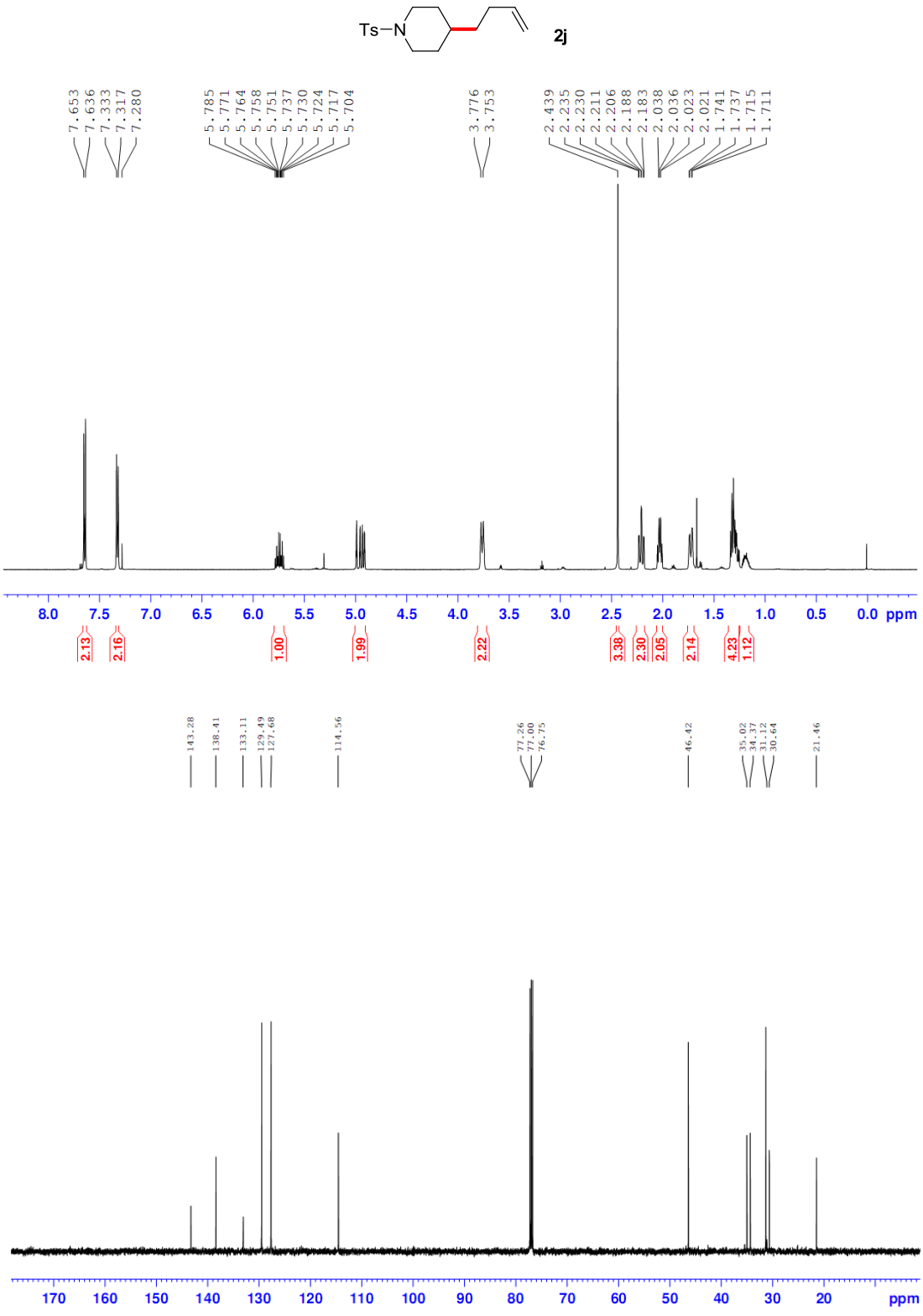
2g

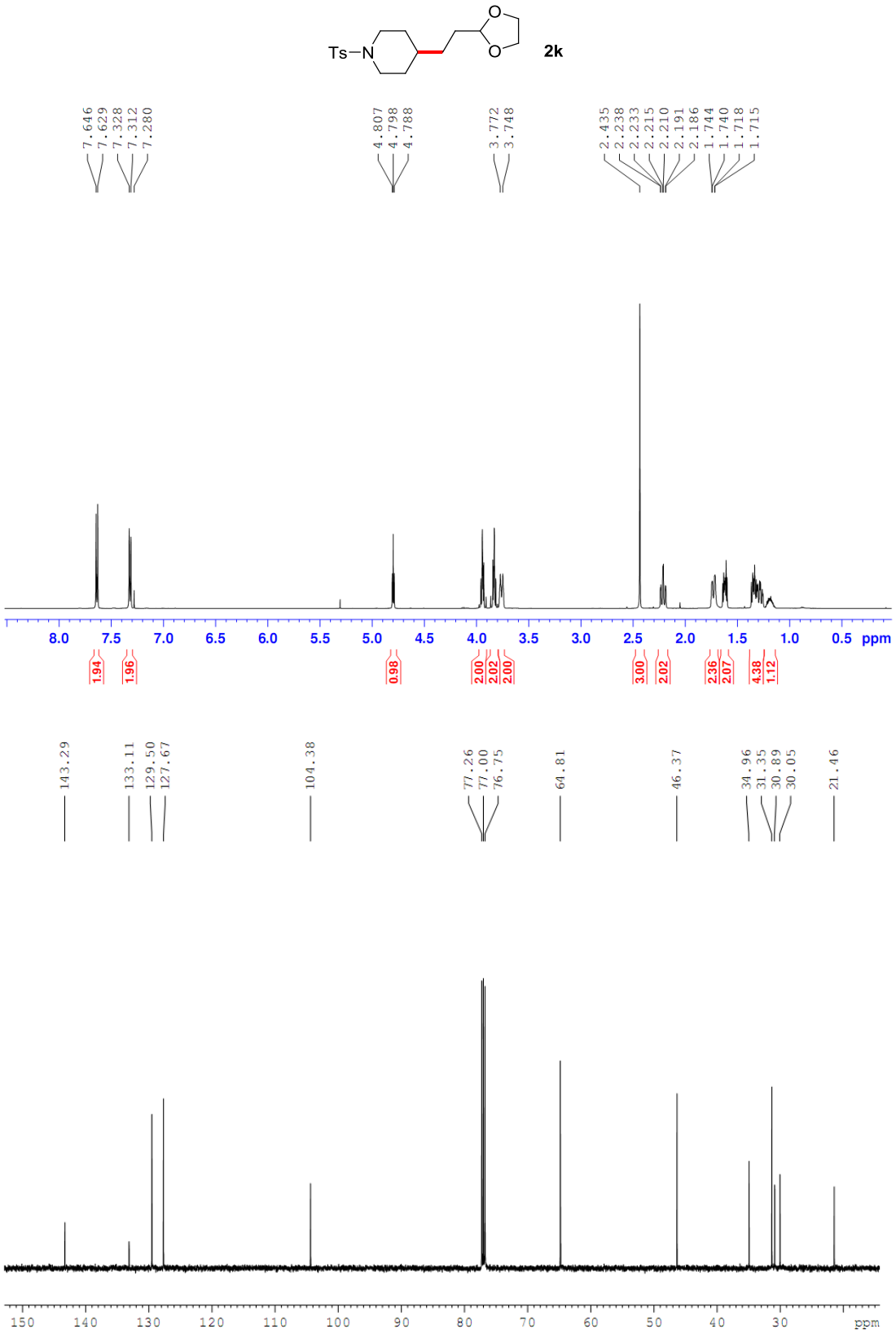

7.846
7.832
7.830
7.739
7.733
7.730
7.729
7.723
7.720
7.714
7.655
7.639
7.341
7.325
7.287
3.781
3.758
3.703
3.688
3.674
3.661
3.646
3.631
2.449
2.238
2.234
2.216
2.211
2.192
2.188
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
3.74
3.85
2.00
1.99
2.10
3.93
3.03
2.04
7.17
1.88
5.27

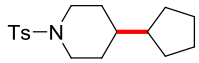

168.15
143.29
133.90
133.05
131.98
129.50
127.65
123.22
77.26
77.00
76.75
46.35
37.75
34.60
32.90
31.31
25.55
21.45
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


Ts–N
OH
2h
7.653
7.636
7.336
7.320
7.280
3.778
3.755
3.621
3.608
3.595
2.442
2.245
2.240
2.221
2.216
2.197
2.193
1.748
1.745
1.722
1.719
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 ppm
2.00
2.03
2.10
2.10
3.08
2.12
2.52
2.31
5.28
1.19
143.33
133.10
129.52
127.69
77.26
77.00
76.75
62.89
46.42
34.97
32.09
31.45
29.68
21.48
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

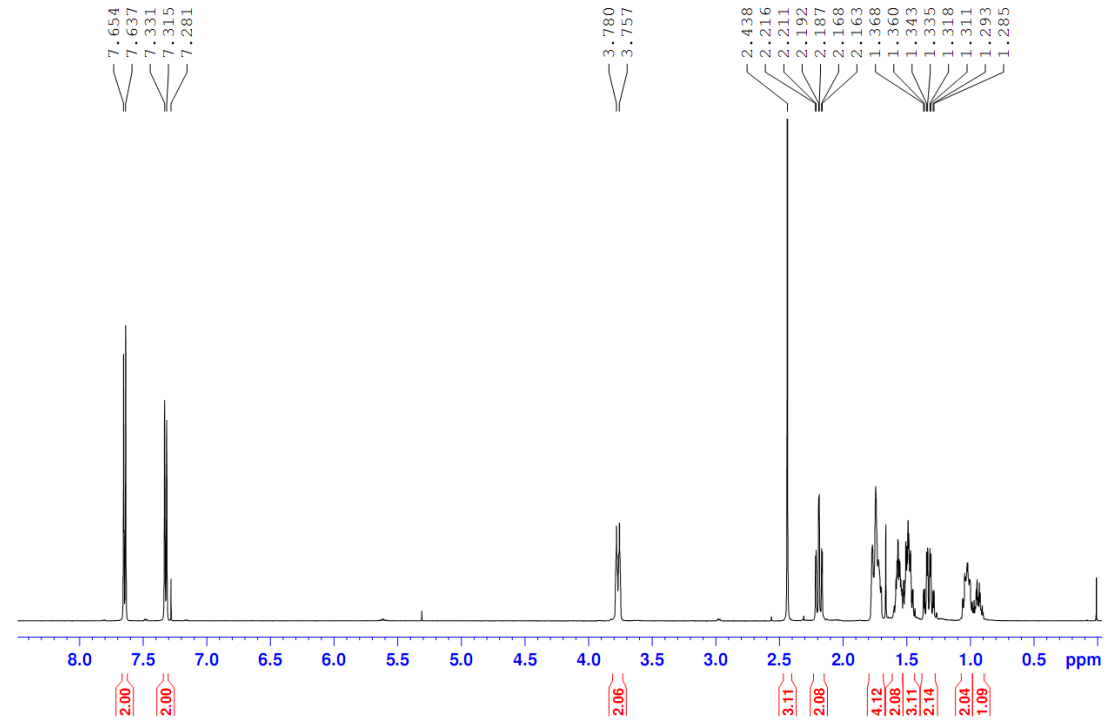

Ts—N
OBz
2i
8.047
8.046
8.045
8.031
8.028
7.658
7.642
7.583
7.580
7.578
7.569
7.566
7.562
7.553
7.551
7.548
7.458
7.442
7.427
7.338
7.322
7.280
4.317
4.304
4.290
3.777
3.753
2.445
2.233
2.228
2.209
2.205
2.186
2.181
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
1.91
1.98
0.97
1.96
2.02
2.01
2.00
3.02
2.02
4.91
9.29
1.14
166.62
143.28
133.15
132.82
130.40
129.50
129.47
128.30
127.70
77.26
77.00
76.75
64.89
46.47
35.88
35.01
31.48
28.61
26.19
26.06
21.49
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

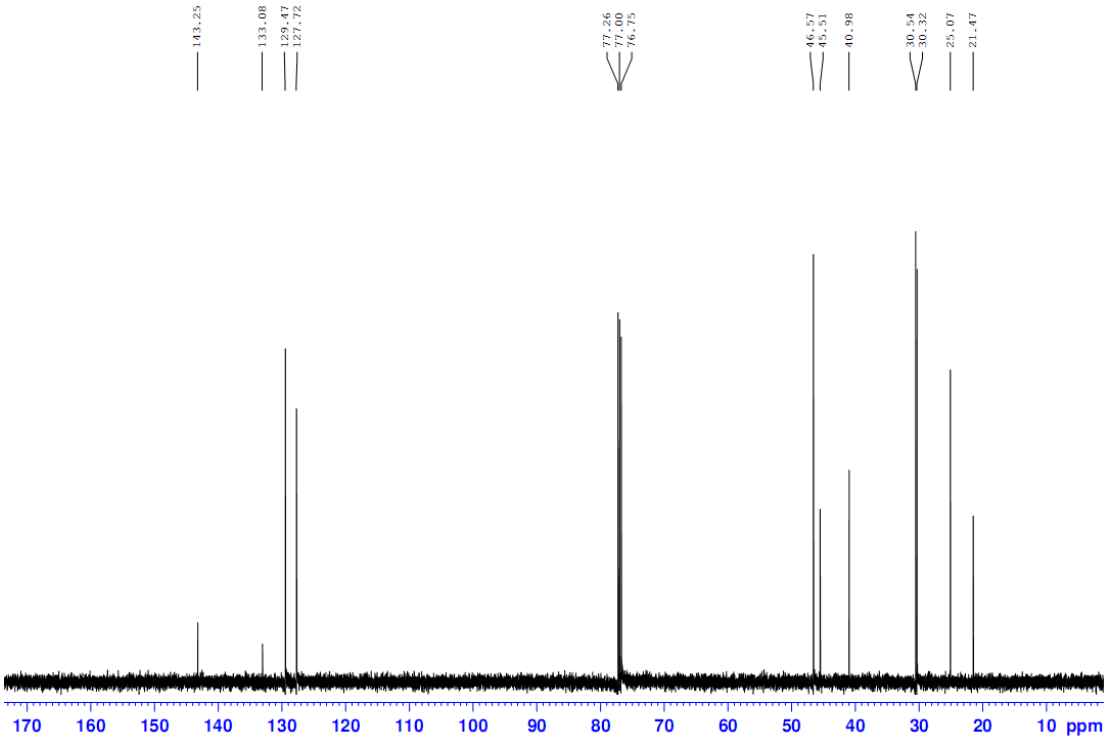

Ts–N
2j
7.653
7.636
7.333
7.317
7.280
5.785
5.771
5.764
5.758
5.751
5.737
5.730
5.724
5.717
5.704
3.776
3.753
2.439
2.235
2.230
2.211
2.206
2.188
2.183
2.038
2.036
2.023
2.021
1.741
1.737
1.715
1.711
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm
2.13
2.16
1.00
1.99
2.22
3.38
2.30
2.05
2.14
4.23
1.12
143.28
138.41
133.11
129.49
127.68
114.56
77.26
77.00
76.75
46.42
35.02
34.37
31.12
30.64
21.46
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

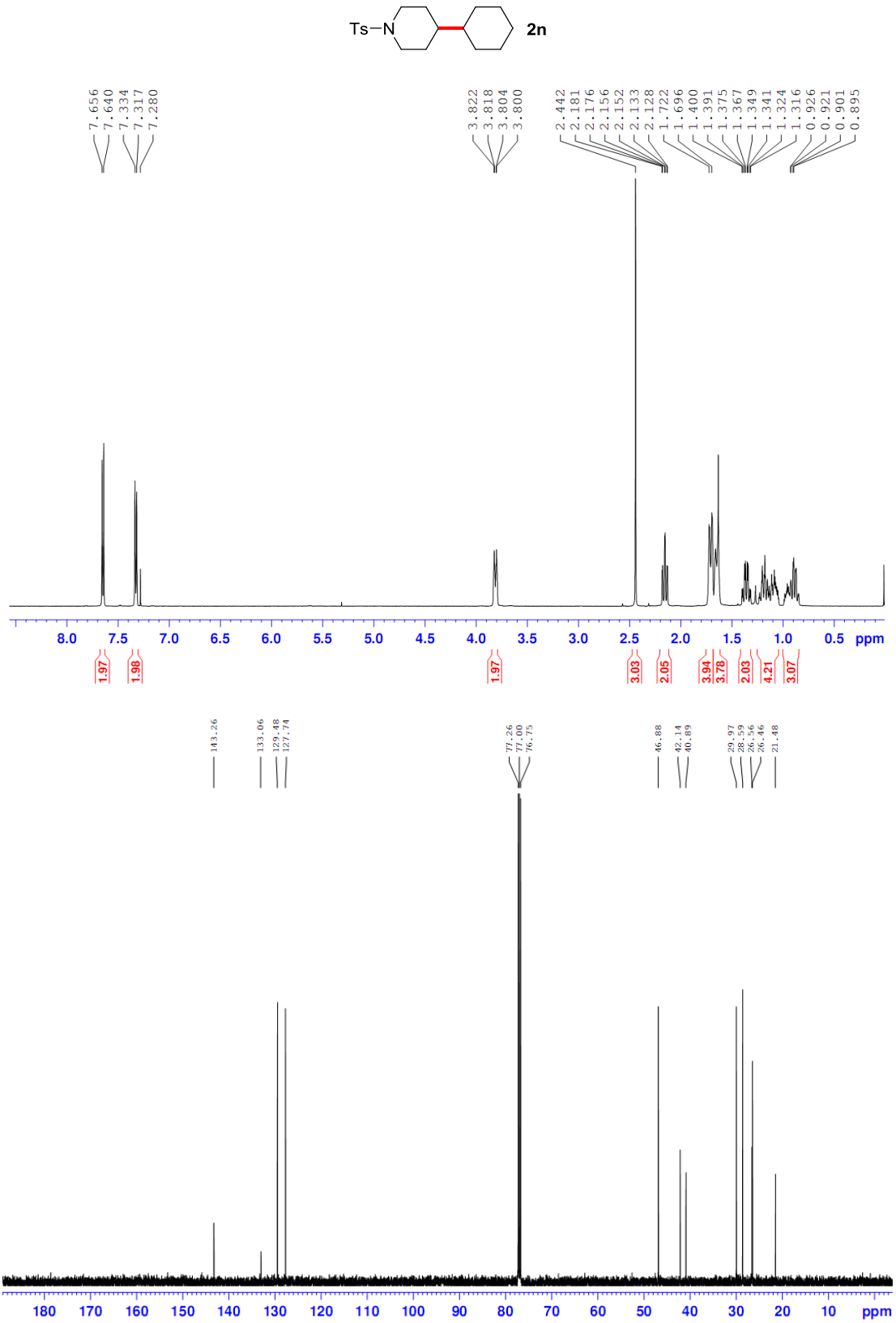

Ts—N
O
O
2k
7.646
7.629
7.328
7.312
7.280
4.807
4.798
4.788
3.772
3.748
2.435
2.238
2.233
2.215
2.210
2.191
2.186
1.744
1.740
1.718
1.715
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
1.94
1.96
0.98
2.00
2.02
2.00
3.00
2.02
2.36
2.07
4.38
1.12
143.29
133.11
129.50
127.67
104.38
77.26
77.00
76.75
64.81
46.37
34.96
31.35
30.89
30.05
21.46
150
140
130
120
110
100
90
80
70
60
50
40
30
ppm

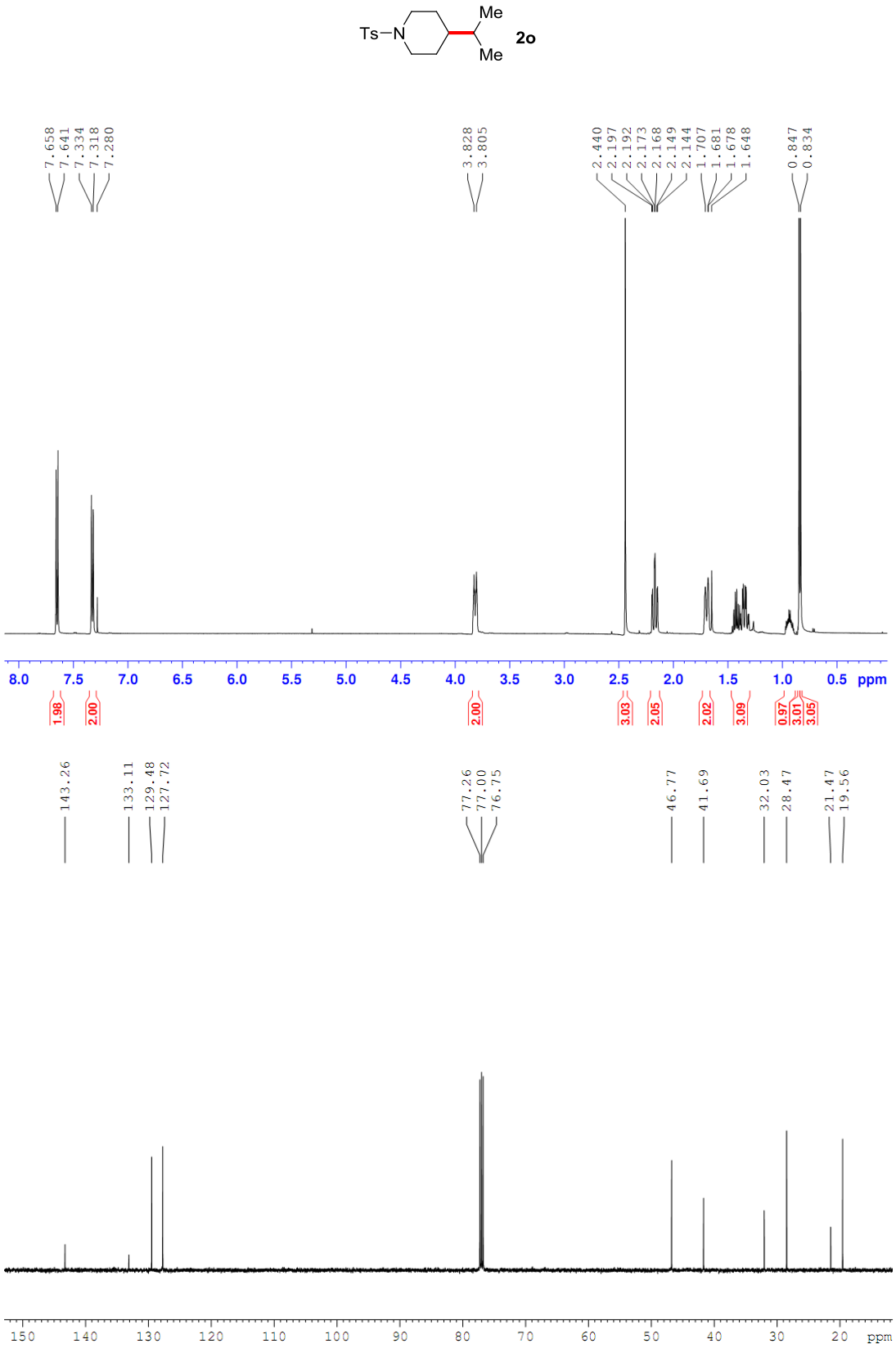

Ts—N

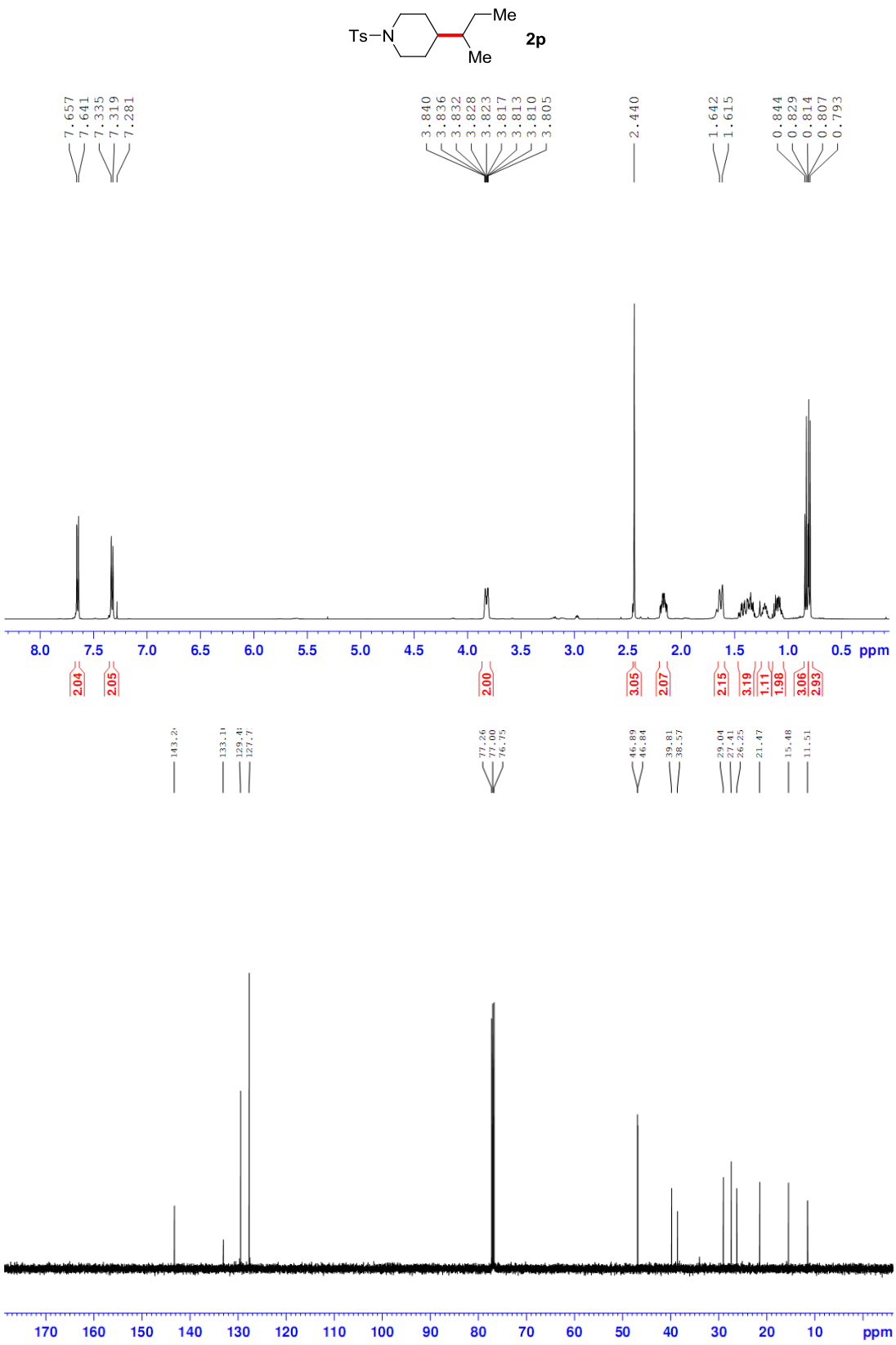
2m

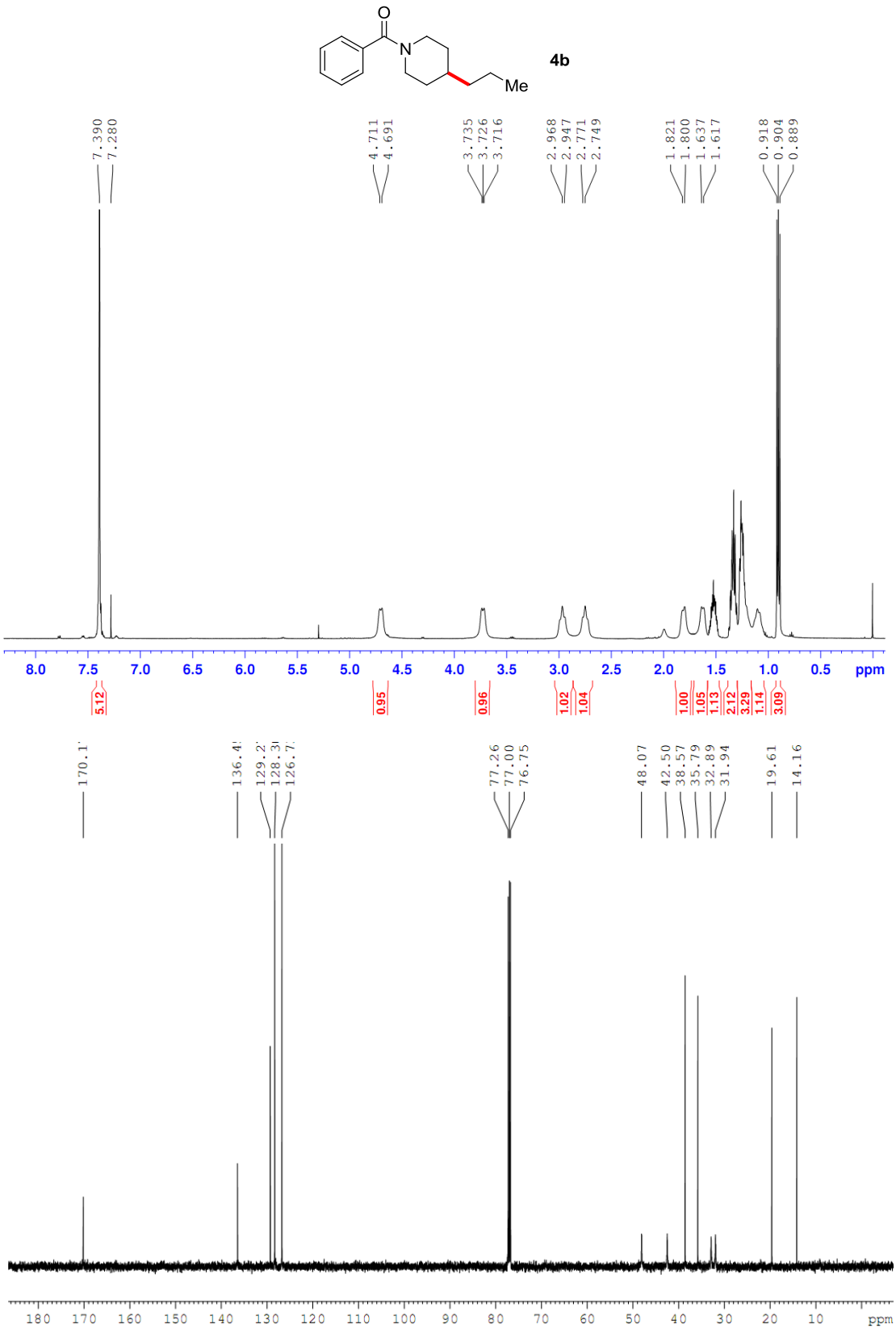

7.654
7.637
7.331
7.315
7.281
3.780
3.757
2.438
2.216
2.211
2.192
2.187
2.168
2.163
1.368
1.360
1.343
1.335
1.318
1.311
1.293
1.285
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
2.00
2.00
2.06
3.11
2.08
4.12
2.08
3.11
2.14
2.04
1.09

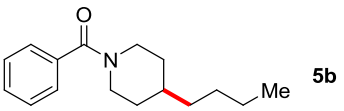

143.25
133.08
129.47
127.72
77.26
77.00
76.75
46.57
45.51
40.98
30.54
30.32
25.07
21.47
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


Ts—N
2n
7.656
7.640
7.334
7.317
7.280
3.822
3.818
3.804
3.800
2.442
2.181
2.176
2.156
2.152
2.133
2.128
1.722
1.696
1.400
1.391
1.375
1.367
1.349
1.341
1.324
1.316
0.926
0.921
0.901
0.895
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 ppm
1.97
1.98
1.97
3.03
2.05
3.94
3.78
2.03
4.21
3.07
143.26
133.06
129.48
127.74
77.26
77.00
76.75
46.88
42.14
40.89
29.97
28.59
26.56
26.46
21.48
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

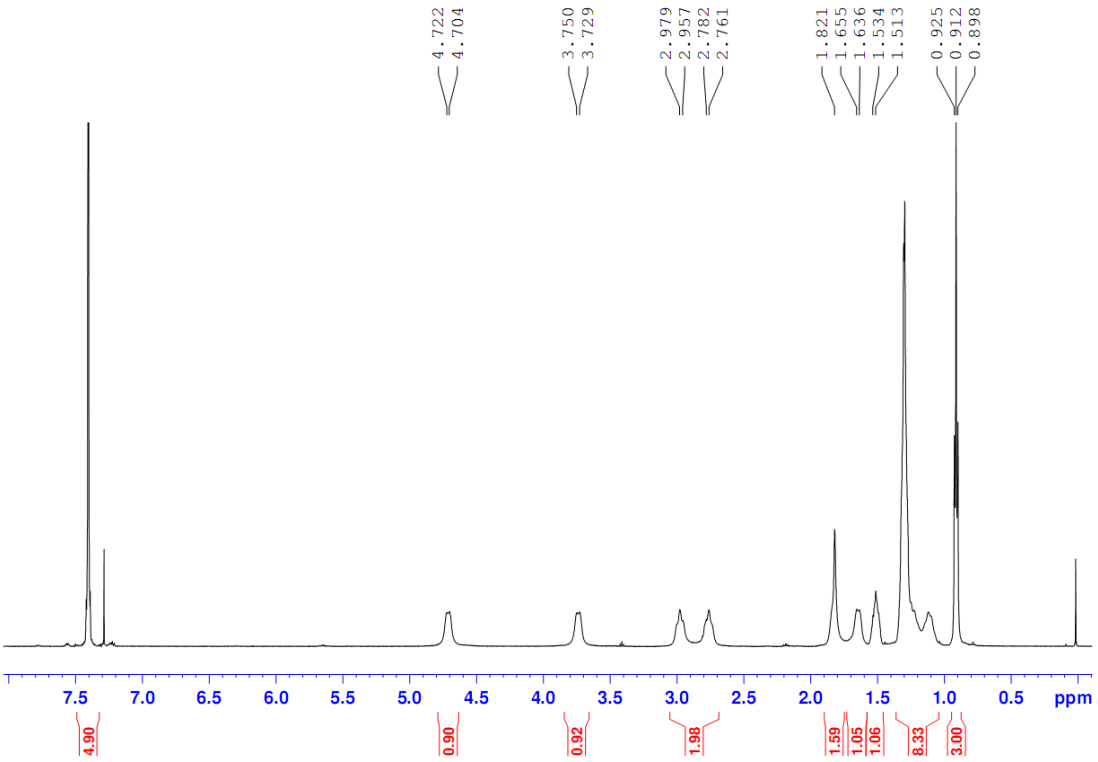

Ts–N
Me
Me
2o
7.658
7.641
7.334
7.318
7.280
3.828
3.805
2.440
2.197
2.192
2.173
2.168
2.149
2.144
1.707
1.681
1.678
1.648
0.847
0.834
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
1.98
2.00
2.00
3.03
2.05
2.02
3.09
0.97
3.01
3.05
143.26
133.11
129.48
127.72
77.26
77.00
76.75
46.77
41.69
32.03
28.47
21.47
19.56
150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

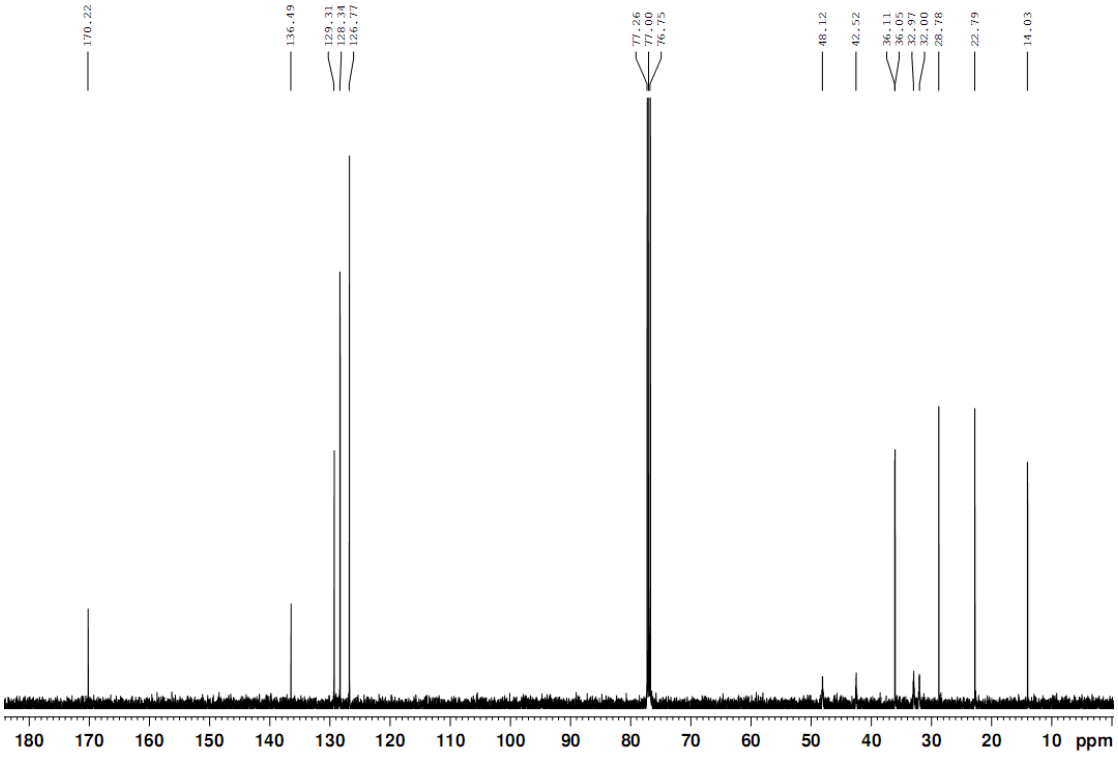

Ts–N
Me
Me
2p
7.657
7.641
7.335
7.319
7.281
3.840
3.836
3.832
3.828
3.823
3.817
3.813
3.810
3.805
2.440
1.642
1.615
0.844
0.829
0.814
0.807
0.793
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
2.04
2.05
2.00
3.05
2.07
2.15
3.19
1.11
1.98
3.06
2.93
143.2
133.1
129.4
127.7
77.26
77.00
76.75
46.89
46.84
39.81
38.57
29.04
27.41
26.25
21.47
15.48
11.51
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

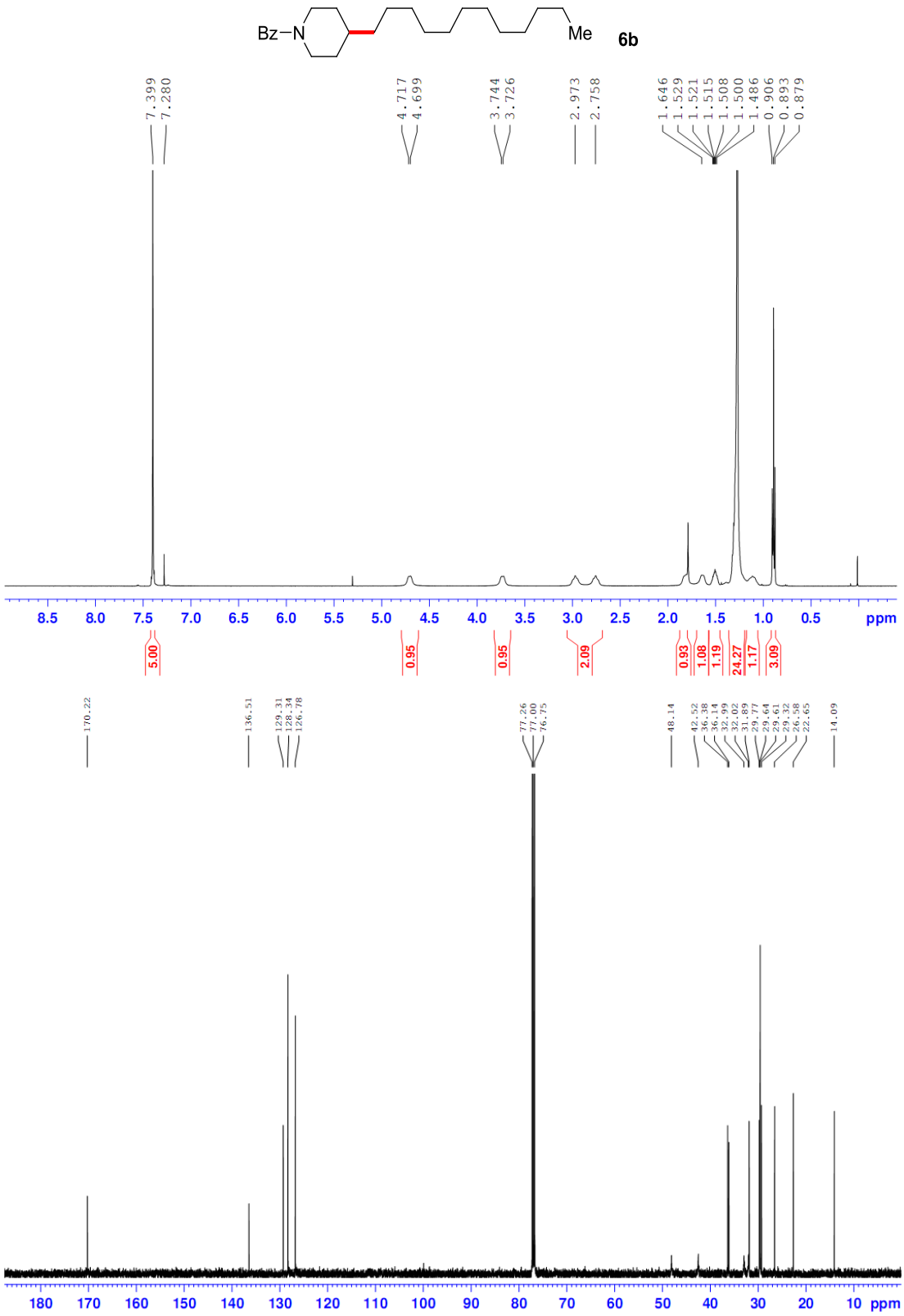

O
N
Me
4b
7.390
7.280
4.711
4.691
3.735
3.726
3.716
2.968
2.947
2.771
2.749
1.821
1.800
1.637
1.617
0.918
0.904
0.889
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
5.12
0.95
0.96
1.02
1.04
1.00
1.05
1.13
2.12
3.29
1.14
3.09
170.1
136.4
129.2
128.3
126.7
77.26
77.00
76.75
48.07
42.50
38.57
35.79
32.89
31.94
19.61
14.16
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

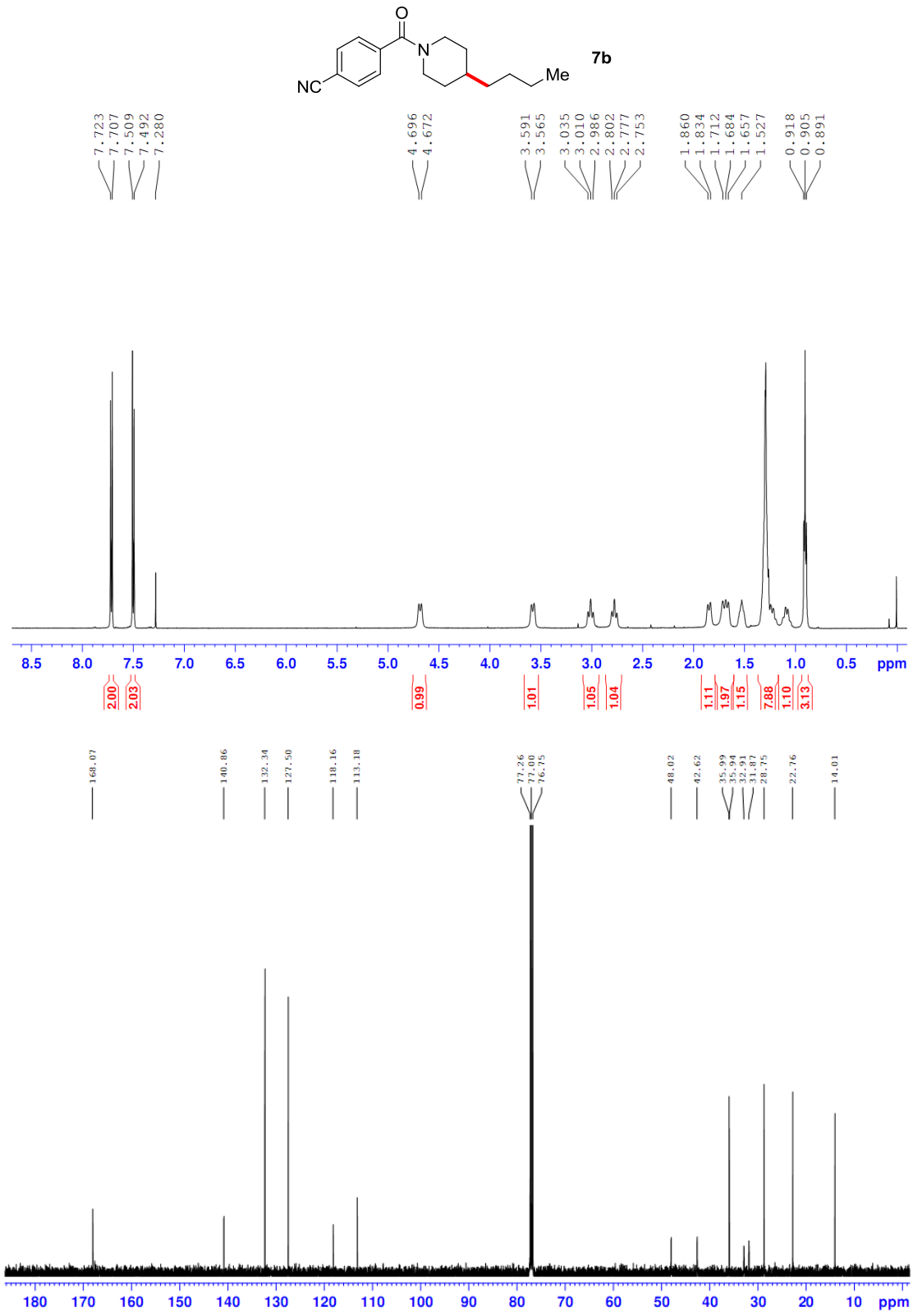

O
N
Me

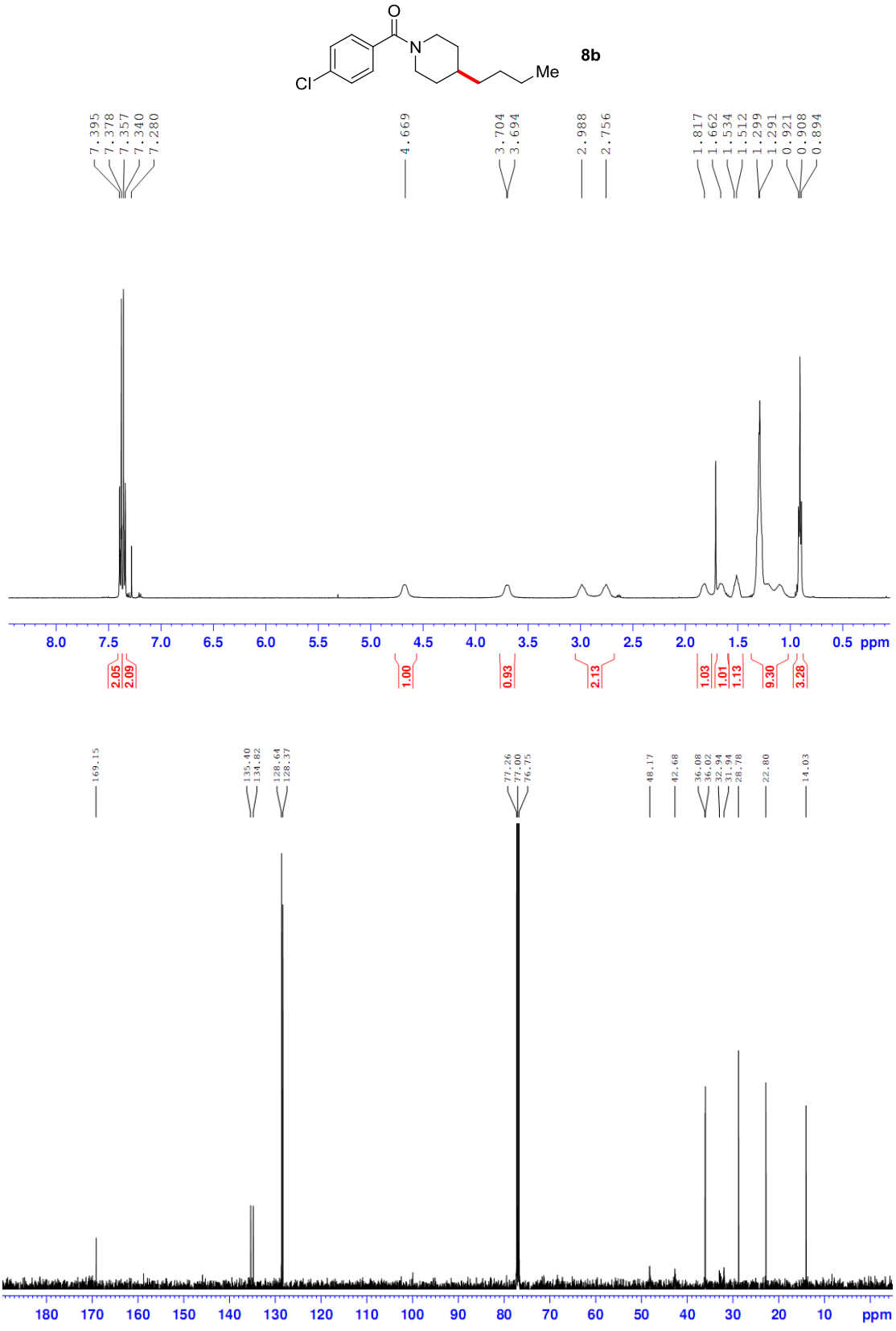
5b

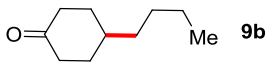

4.722
4.704
3.750
3.729
2.979
2.957
2.782
2.761
1.821
1.655
1.636
1.534
1.513
0.925
0.912
0.898
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
4.90
0.90
0.92
1.98
1.59
1.05
1.06
8.33
3.00


170.22
136.49
129.31
128.34
126.77
77.26
77.00
76.75
48.12
42.52
36.11
32.97
32.00
28.78
22.79
14.03
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

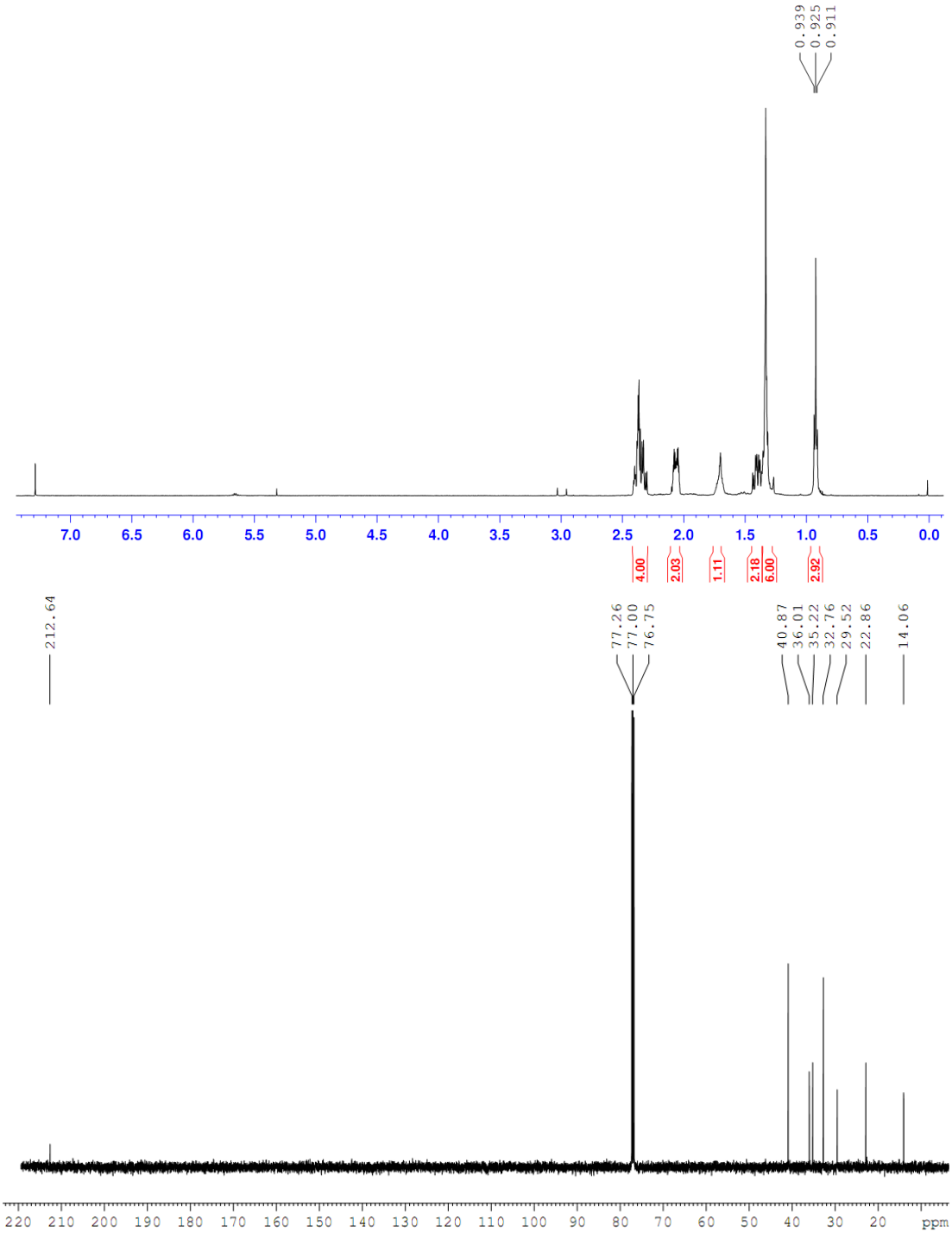

Bz–N
Me
6b
7.399
7.280
4.717
4.699
3.744
3.726
2.973
2.758
1.646
1.529
1.521
1.515
1.508
1.500
1.486
0.906
0.893
0.879
ppm
5.00
0.95
0.95
2.09
0.93
1.08
1.19
24.27
1.17
3.09
170.22
136.51
129.31
128.34
126.78
77.26
77.00
76.75
48.14
42.52
36.38
34.14
32.99
32.02
31.89
29.77
29.64
29.61
29.32
26.58
22.65
14.09
ppm

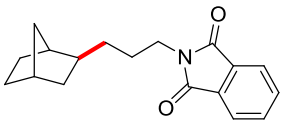

O
N
NC
Me
7b
7.723
7.707
7.509
7.492
7.280
4.696
4.672
3.591
3.565
3.035
3.010
2.986
2.802
2.777
2.753
1.860
1.834
1.712
1.684
1.657
1.527
0.918
0.905
0.891
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
2.00
2.03
0.99
1.01
1.05
1.04
1.11
1.97
1.15
7.88
1.10
3.13
168.07
140.86
132.34
127.50
118.16
113.18
77.26
77.00
76.75
48.02
42.62
35.99
35.94
32.91
31.87
28.75
22.76
14.01
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


O
N
Cl
Me
8b
7.395
7.378
7.357
7.340
7.280
4.669
3.704
3.694
2.988
2.756
1.817
1.662
1.534
1.512
1.299
1.291
0.921
0.908
0.894
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 ppm
2.05
2.09
1.00
0.93
2.13
1.03
1.01
1.13
9.30
3.28
169.15
135.40
134.82
128.64
128.37
77.26
77.00
76.75
48.17
42.68
36.08
36.02
32.94
31.94
28.78
22.80
14.03
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

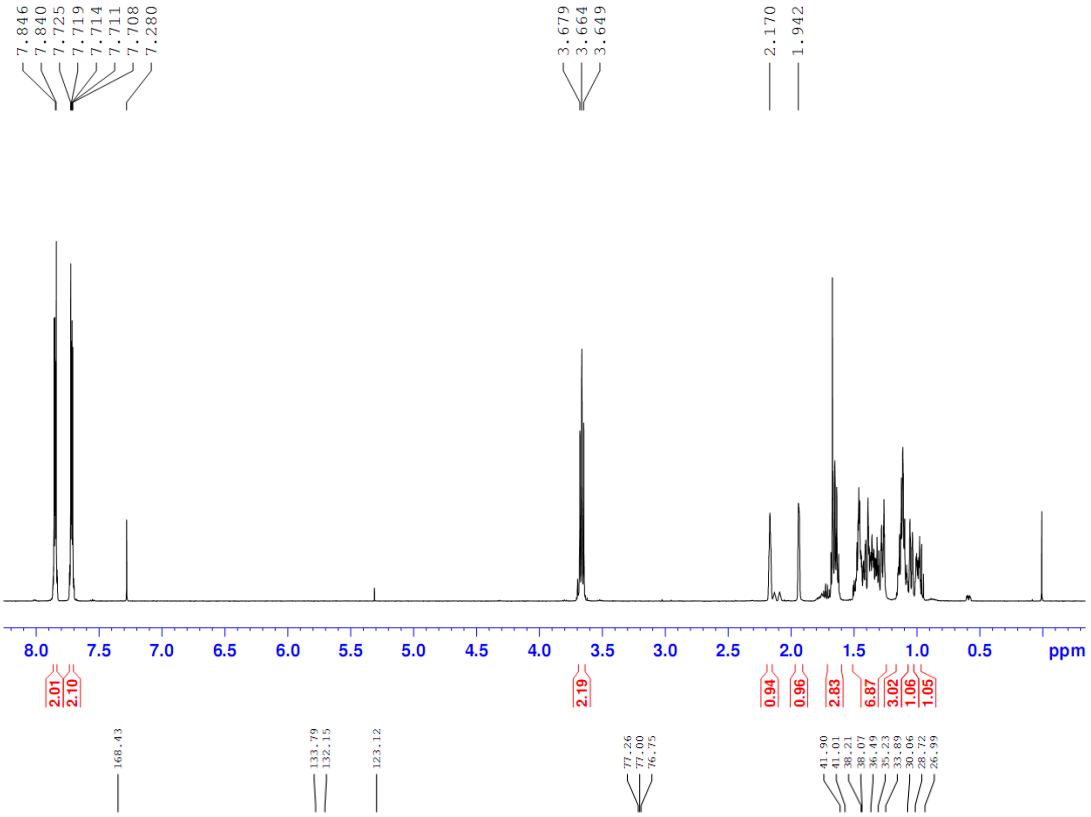

O
Me

9b

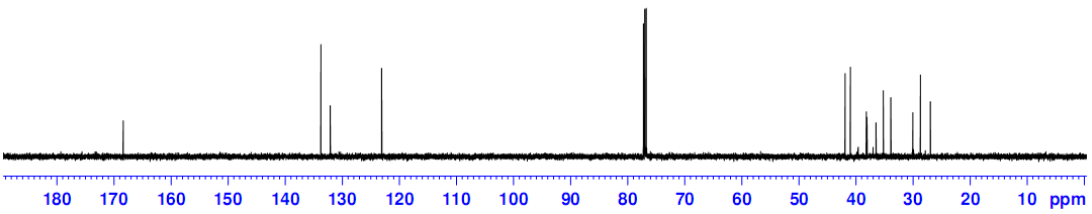

0.939
0.925
0.911
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
4.00
2.03
1.11
2.18
6.00
2.92
212.64
77.26
77.00
76.75
40.87
36.01
35.22
32.76
29.52
22.86
14.06
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

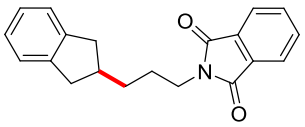

O
N
O

10b


7.846
7.840
7.725
7.719
7.714
7.711
7.708
7.280
3.679
3.664
3.649
2.170
1.942
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
ppm
2.01
2.10
2.19
0.94
0.96
2.83
6.87
3.02
1.06
1.05

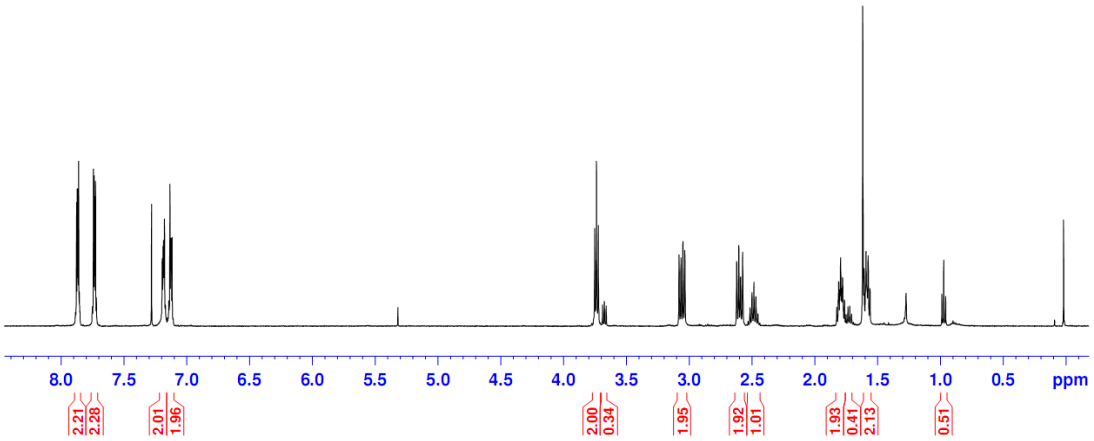
168.43
133.79
132.15
123.12
77.26
77.00
76.75
41.90
41.01
38.21
38.07
36.49
35.23
33.89
30.06
28.72
26.99

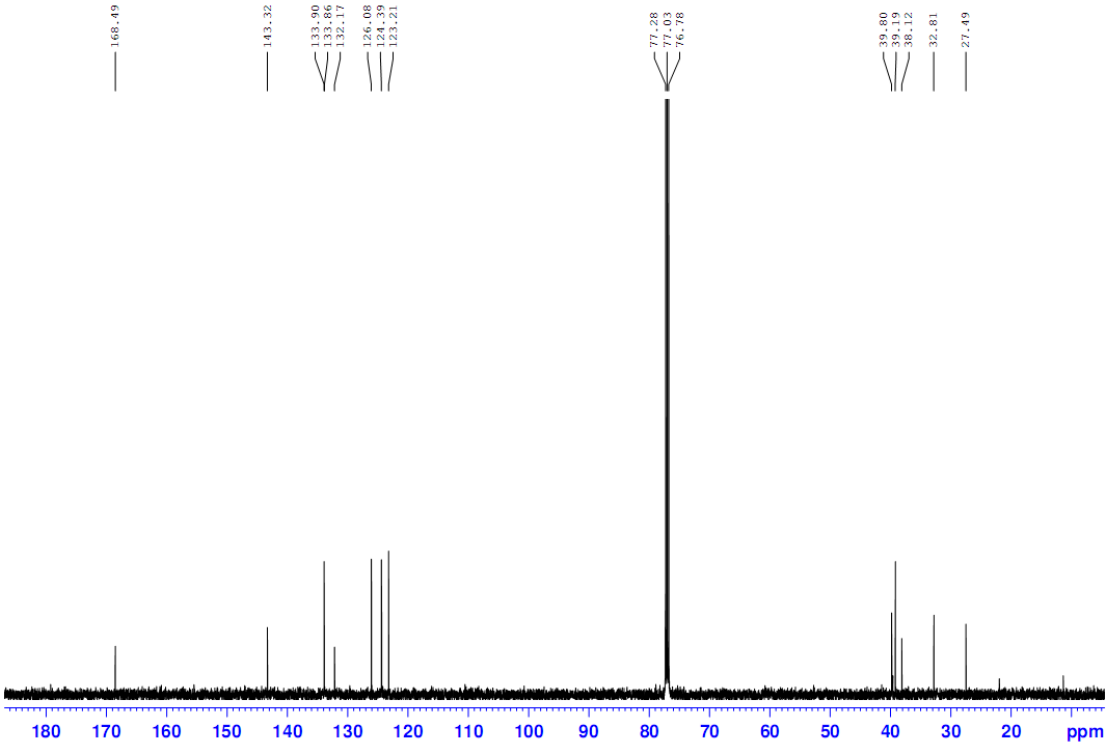

180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

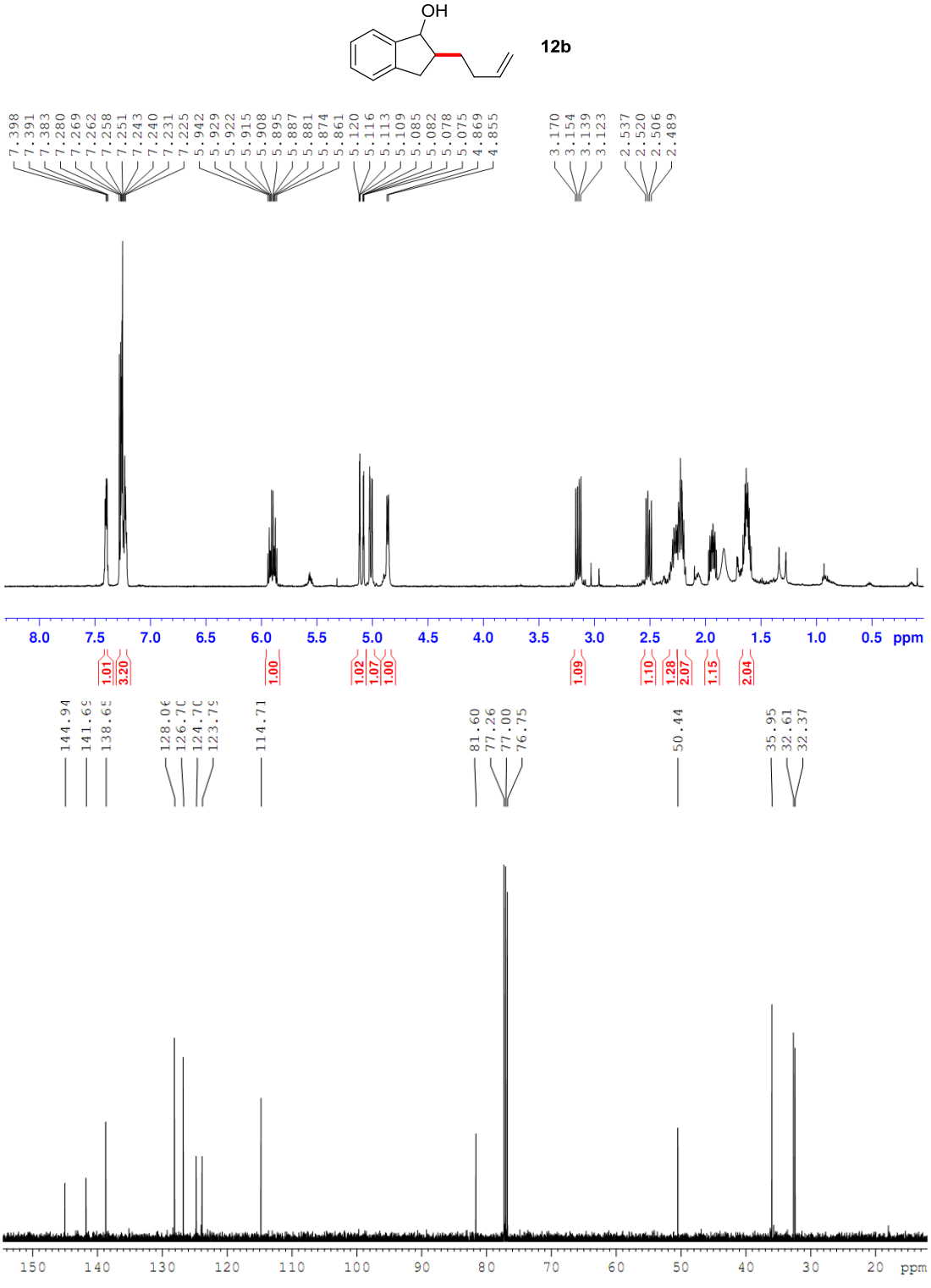

O
N
O

11b

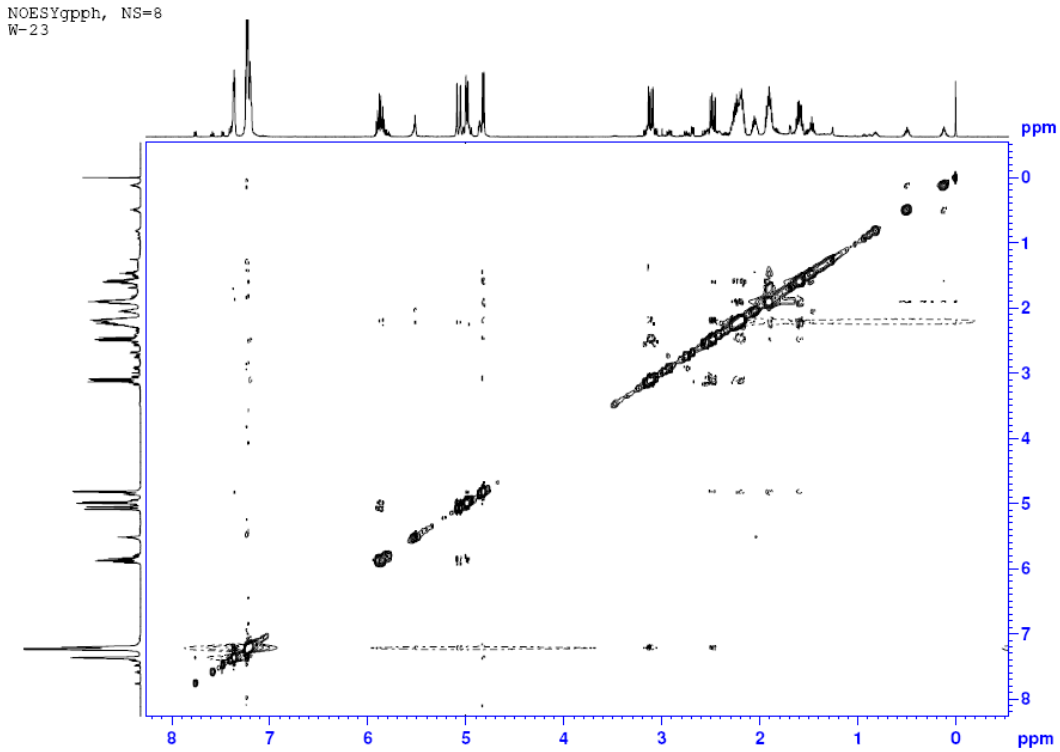

7.855
7.743
7.737
7.732
7.726
7.720
7.280
7.195
7.188
7.184
7.177
7.142
7.134
7.127
7.123
7.116
3.752
3.738
3.723
3.081
3.065
3.050
3.035
2.621
2.605
2.591
2.574
2.530
2.515
2.500
2.484
2.469
2.453
2.438

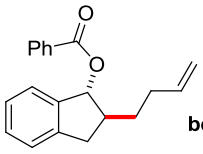

8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
2.21
2.28
2.01
1.96
2.00
0.34
1.95
1.92
1.01
1.93
0.41
2.13
0.51


168.49
143.32
133.90
133.86
132.17
126.08
124.39
123.21
77.28
77.03
76.78
39.80
39.59
39.38
38.12
32.81
27.49
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

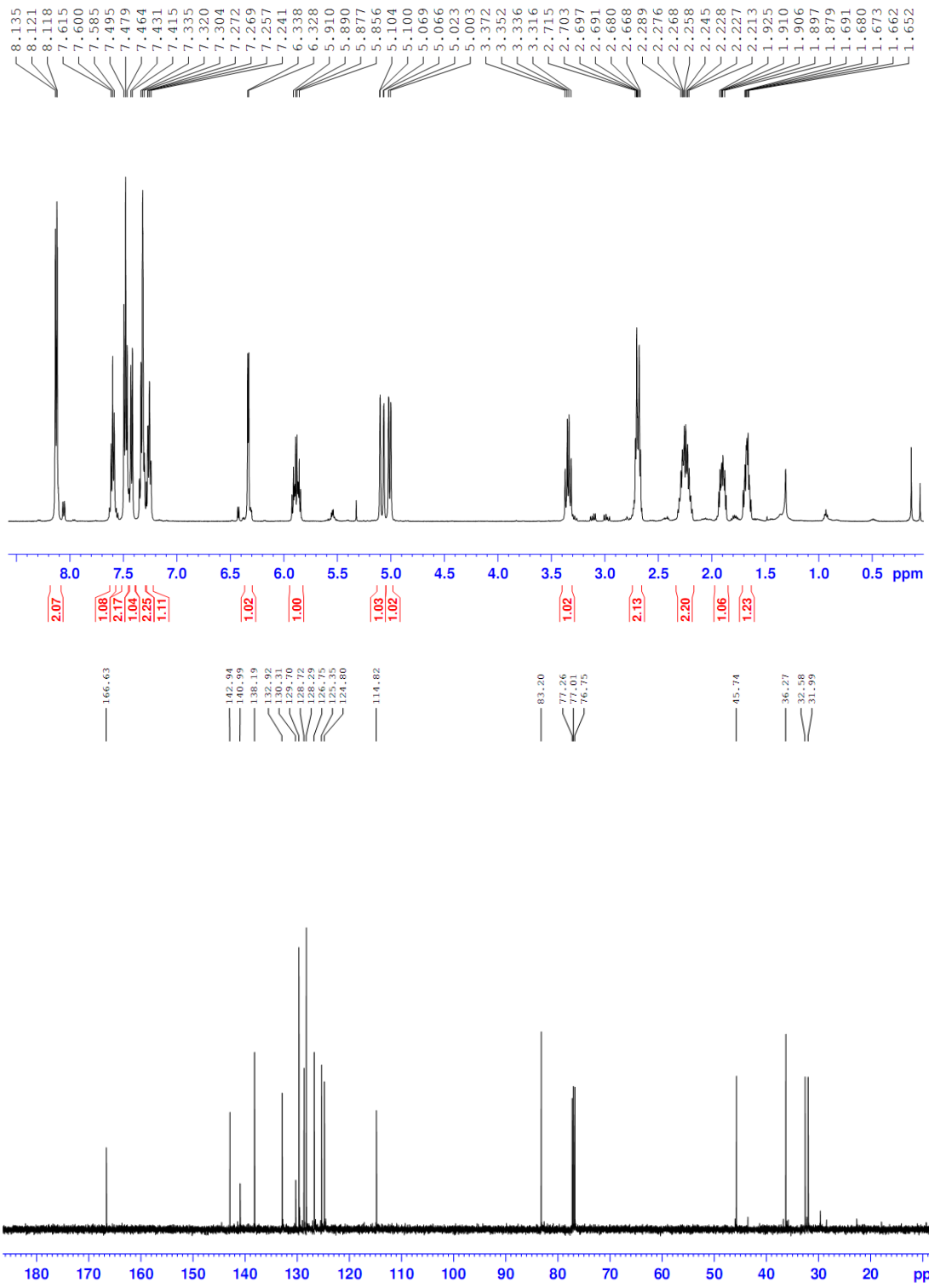

OH
12b
7.398
7.391
7.383
7.280
7.269
7.262
7.258
7.251
7.243
7.240
7.231
7.225
5.942
5.929
5.922
5.915
5.908
5.895
5.887
5.881
5.874
5.861
5.120
5.116
5.113
5.109
5.085
5.082
5.078
5.075
4.869
4.855
3.170
3.154
3.139
3.123
2.537
2.520
2.506
2.489
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
1.01
3.20
1.00
1.02
1.07
1.00
1.09
1.10
1.28
2.07
1.15
2.04
144.94
141.69
138.65
128.06
126.70
124.70
123.79
114.71
81.60
77.26
77.00
76.75
50.44
35.95
32.61
32.37
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

NOESY for **12b**:

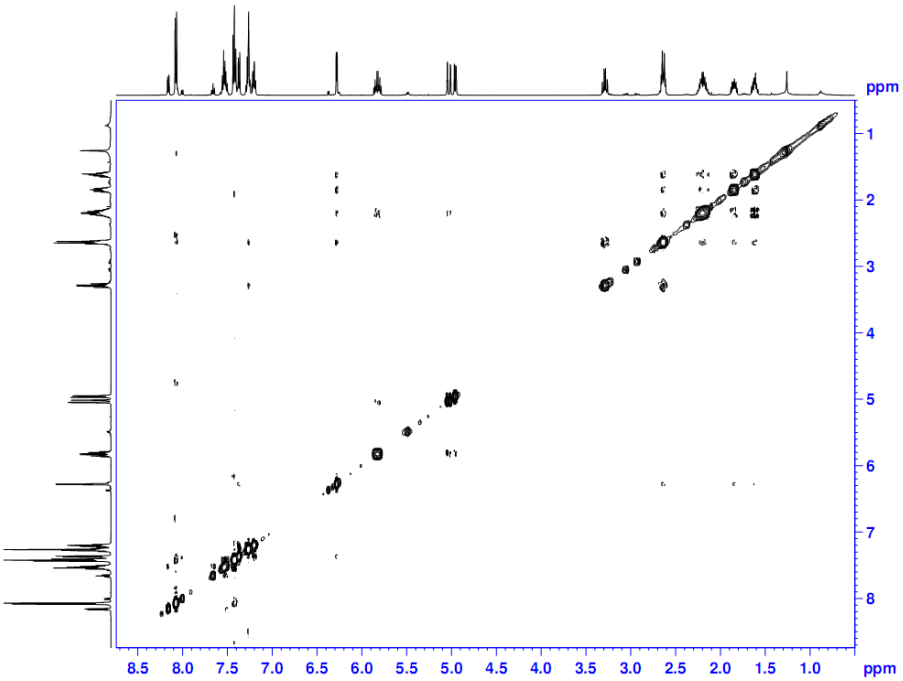




benzoylated 12b

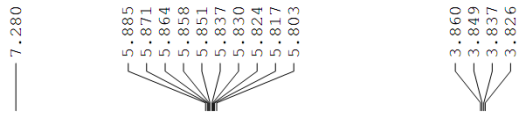


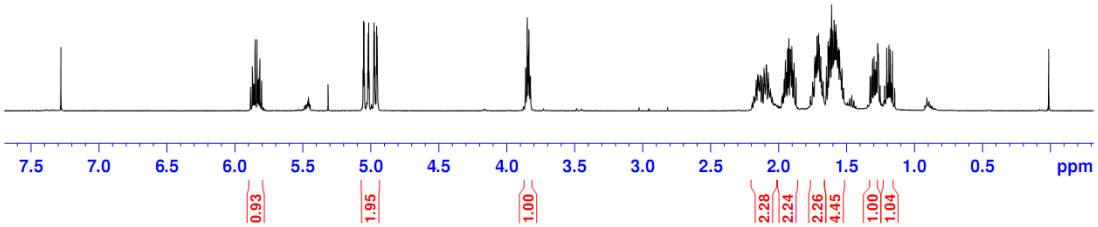
NOESY for **benzoylated-12b**.



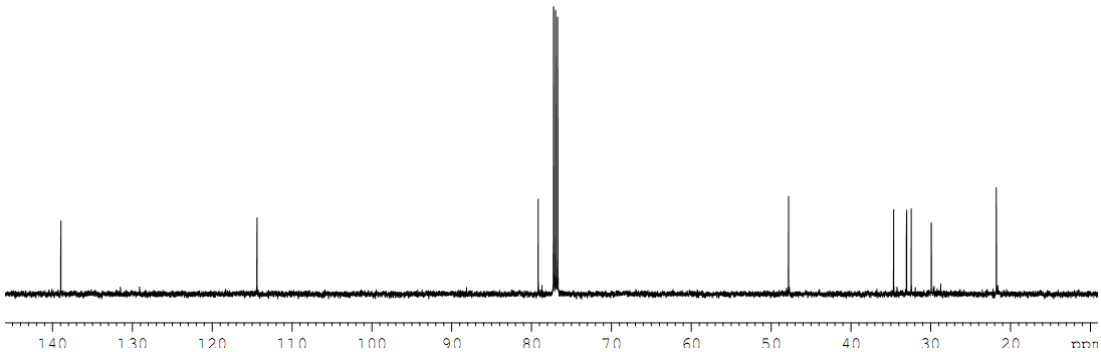

HO

13b

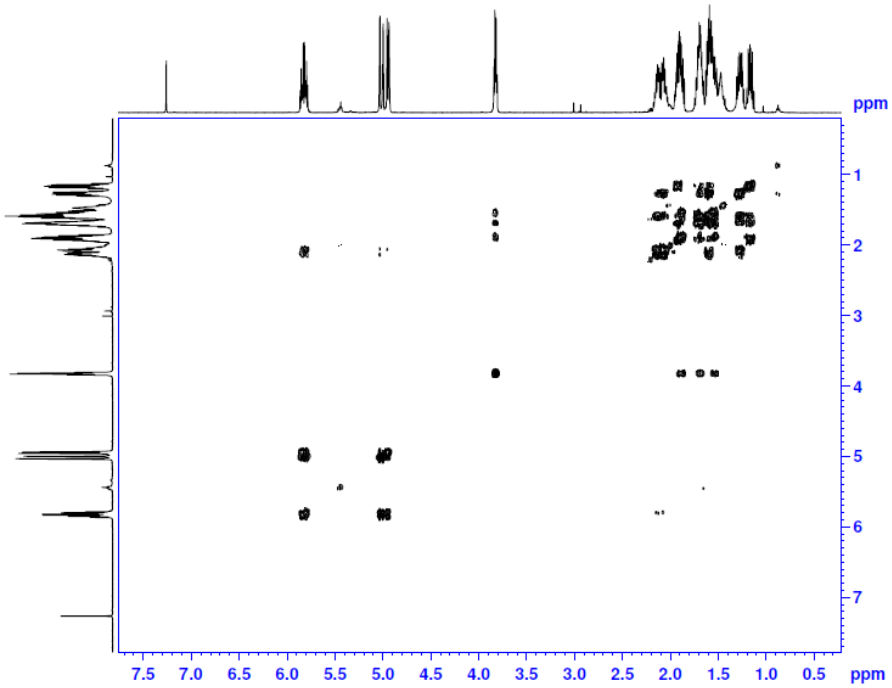

7.280
5.885
5.871
5.864
5.858
5.851
5.837
5.830
5.824
5.817
5.803
3.860
3.849
3.837
3.826


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
ppm
0.93
1.95
1.00
2.28
2.24
2.26
4.45
1.00
1.04

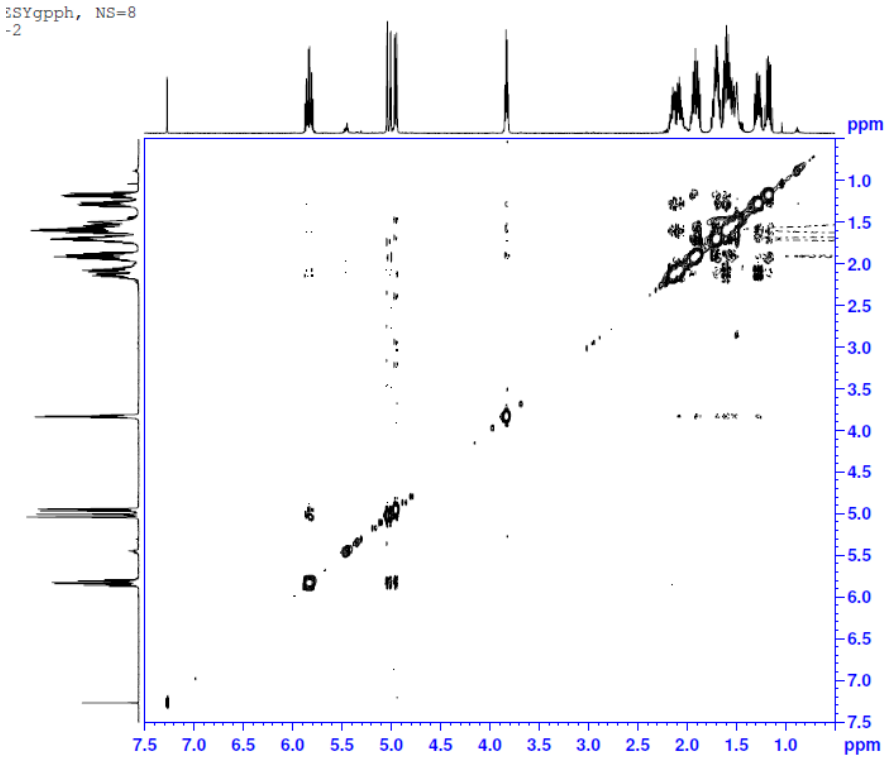

138.95
114.38
79.18
77.26
77.00
76.75
47.83
34.66
33.05
32.45
29.96
21.80

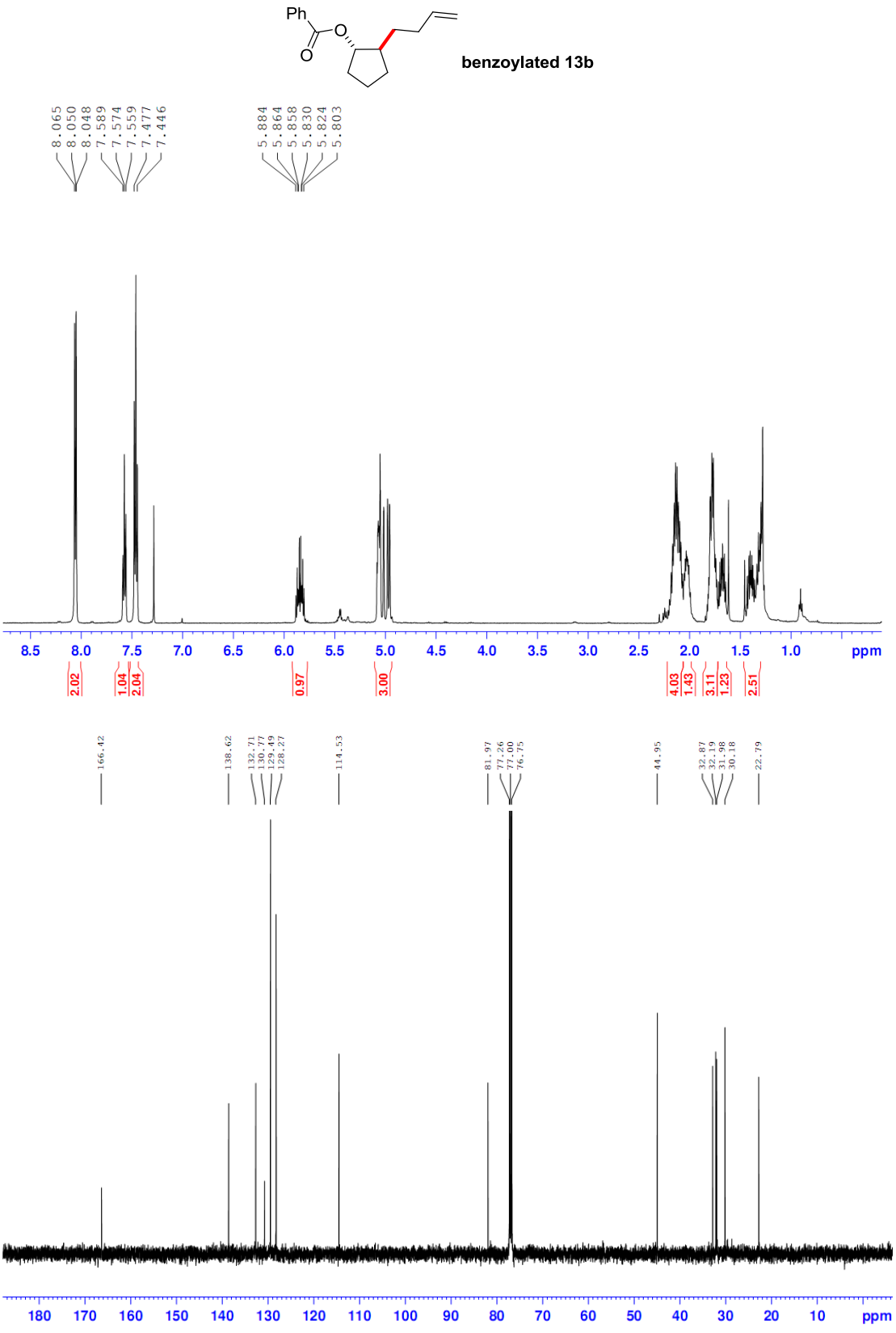

140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

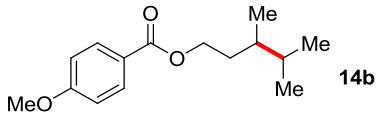
^{1}H-^{1}H COSY:



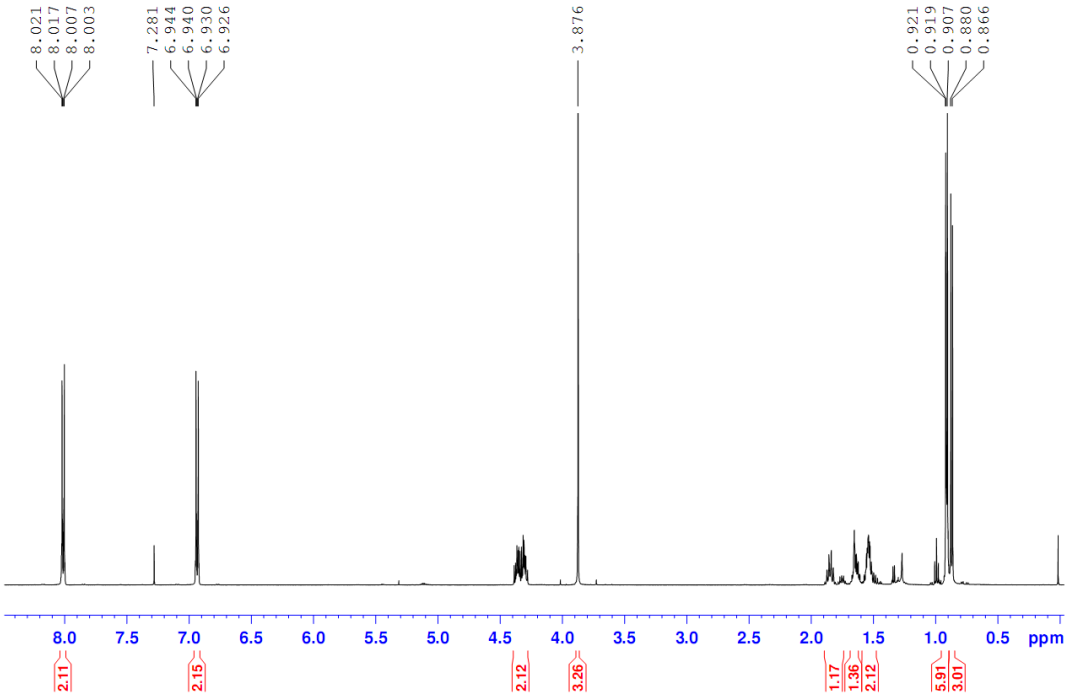
NOESY:

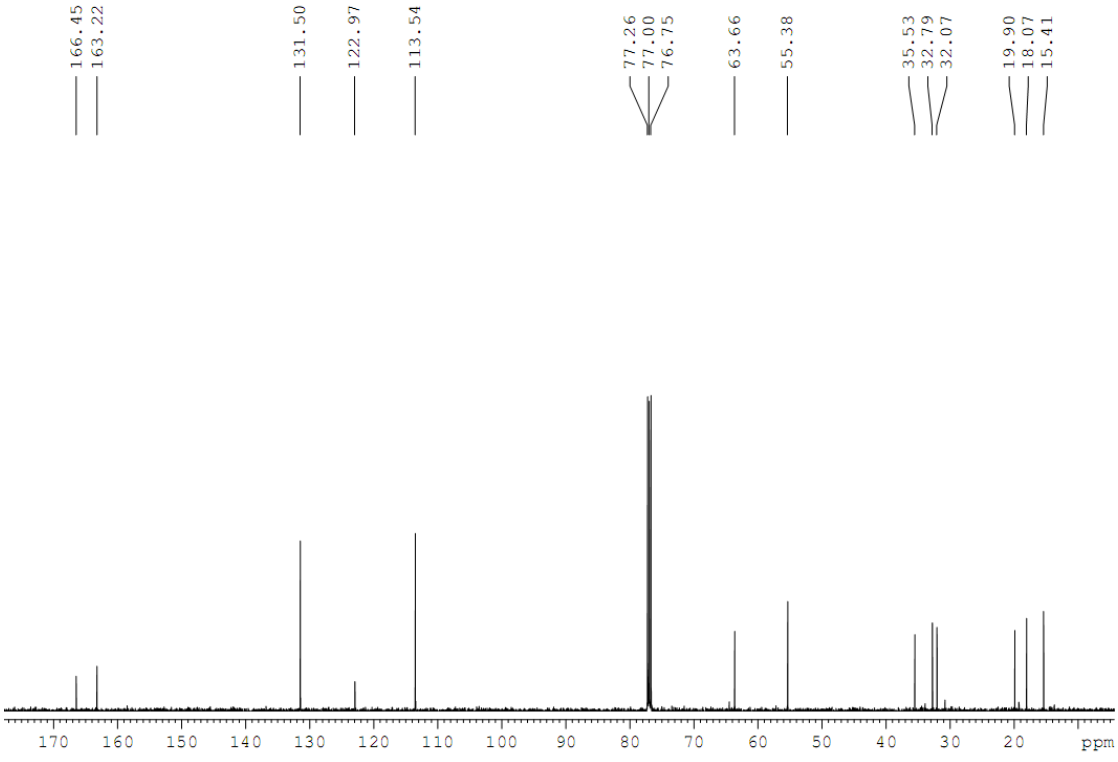



Ph
O
O
benzoylated 13b
8.065
8.050
8.048
7.589
7.574
7.559
7.477
7.446
5.884
5.864
5.858
5.830
5.824
5.803
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm
2.02
1.04
2.04
0.97
3.00
4.03
1.43
3.11
1.23
2.51
166.42
138.62
132.71
130.77
129.49
128.27
114.53
81.97
77.26
77.00
76.75
44.95
32.87
32.19
31.98
30.18
22.79
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


O
Me
Me
O
Me
MeO

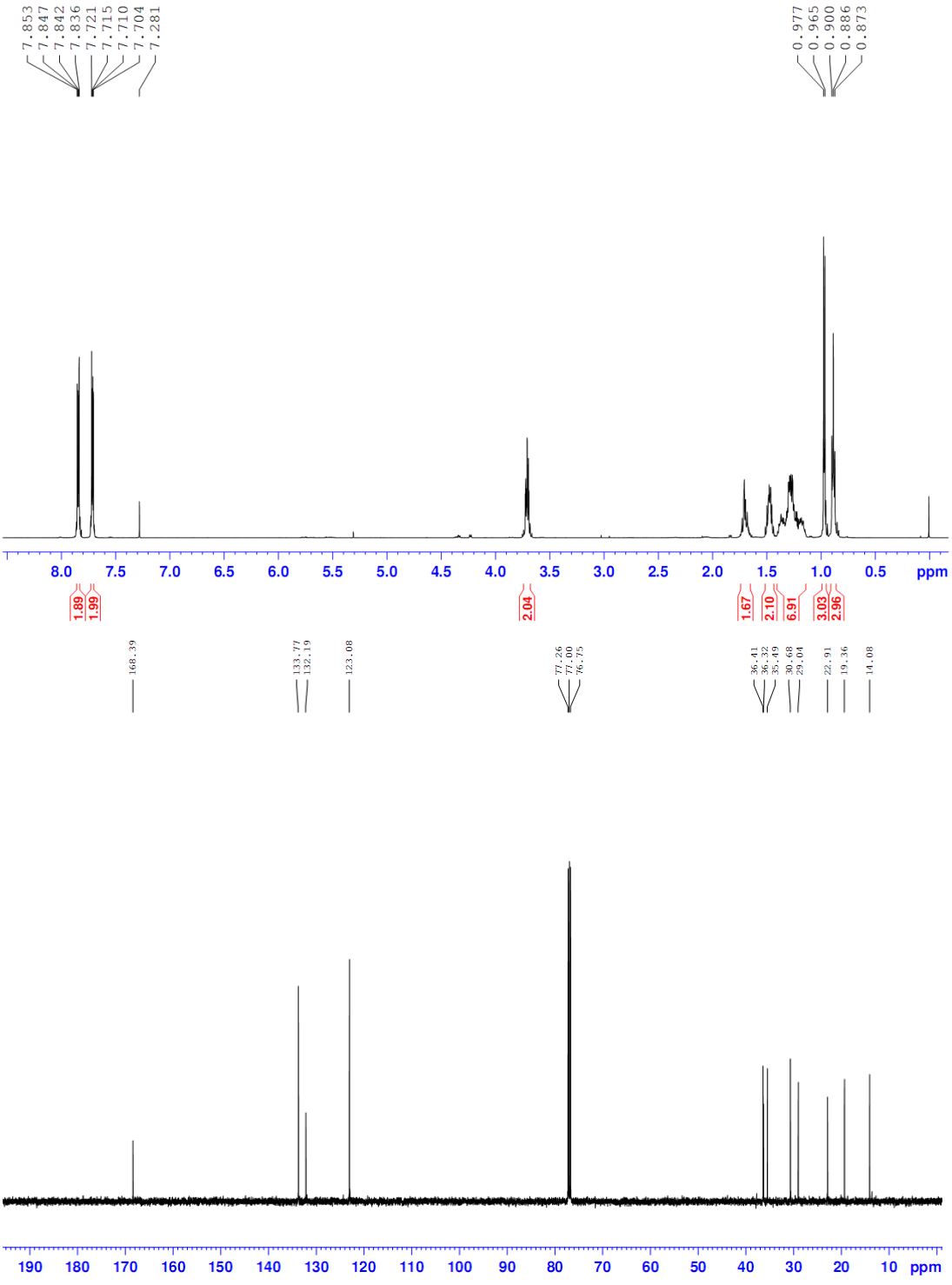
14b

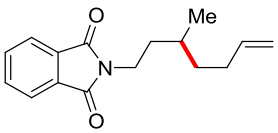

8.021
8.017
8.007
8.003
7.281
6.944
6.940
6.930
6.926
3.876
0.921
0.919
0.907
0.880
0.866
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
2.11
2.15
2.12
3.26
1.17
1.36
2.12
5.91
3.01


166.45
163.22
131.50
122.97
113.54
77.26
77.00
76.75
63.66
55.38
35.53
32.79
32.07
19.90
18.07
15.41
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

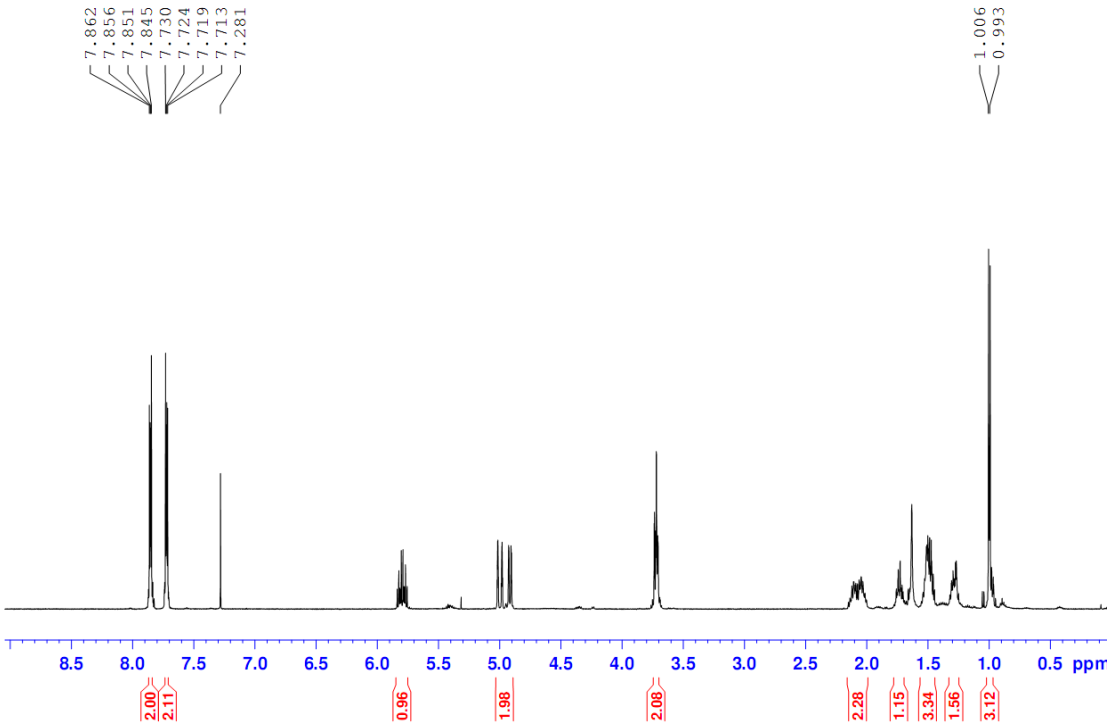

O
N
O
Me
Me

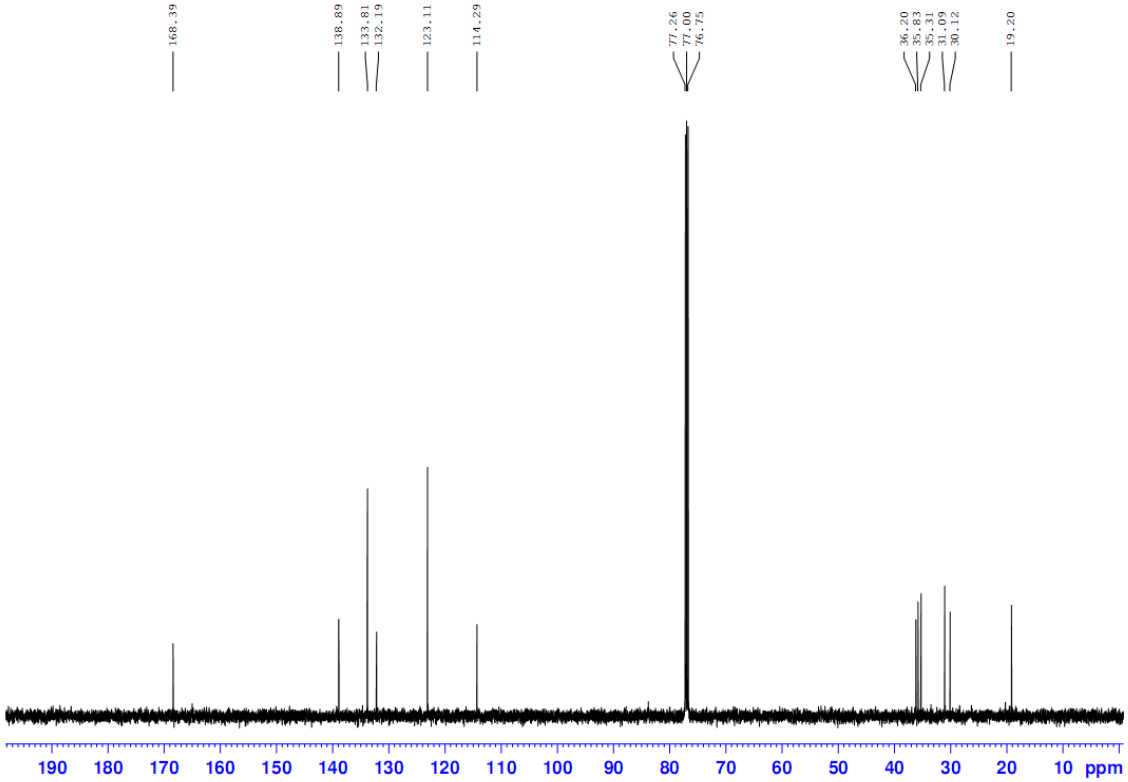
15b

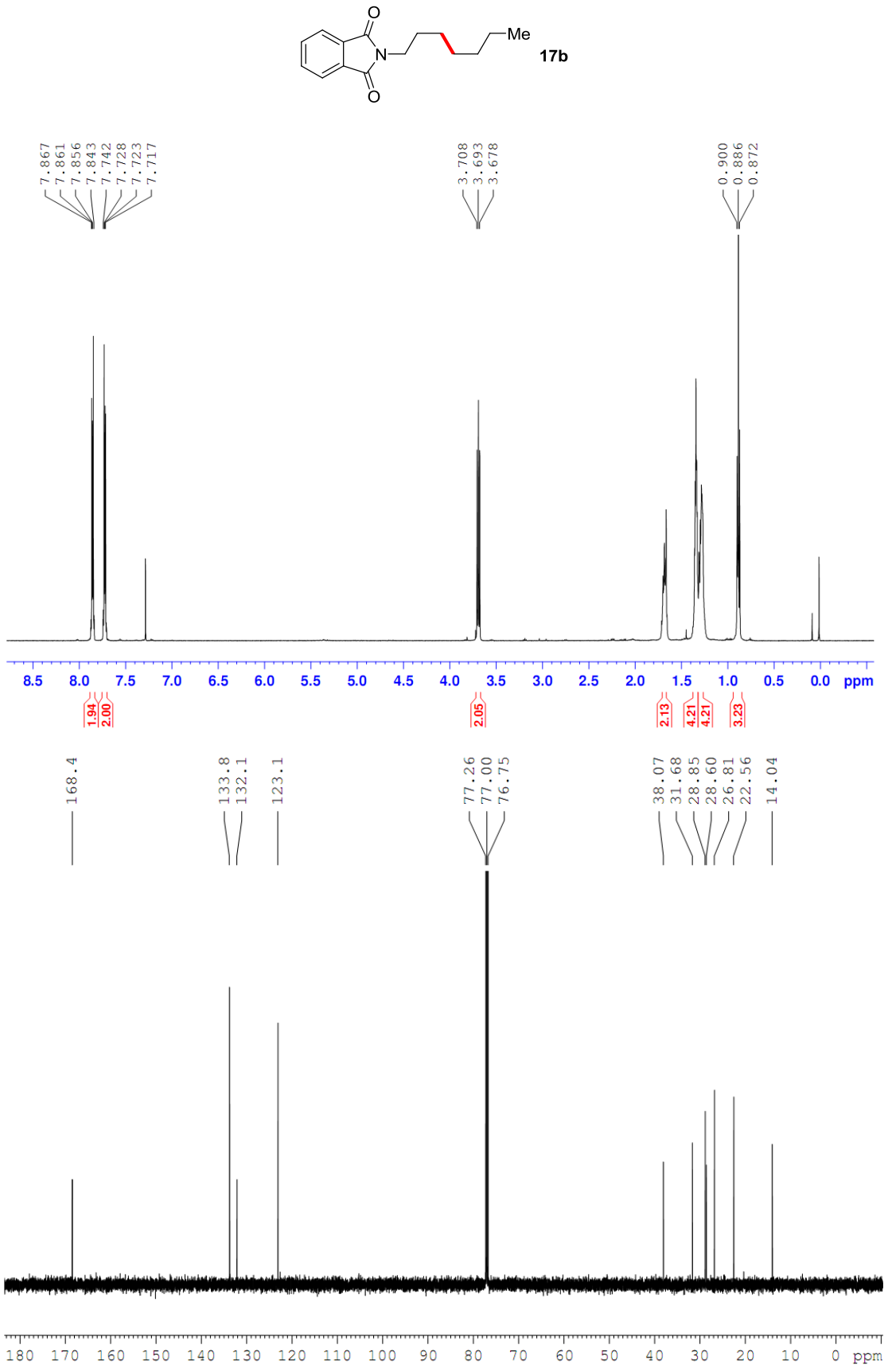

7.853
7.847
7.842
7.836
7.721
7.715
7.710
7.704
7.281
0.977
0.965
0.900
0.886
0.873
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
1.89
1.99
2.04
1.67
2.10
6.91
3.03
2.96
168.39
133.77
132.19
123.08
77.26
77.00
76.75
36.41
36.32
35.49
30.68
29.04
22.91
19.36
14.08
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

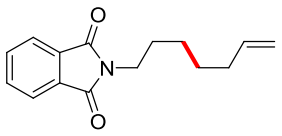

O
Me
N
O

16b

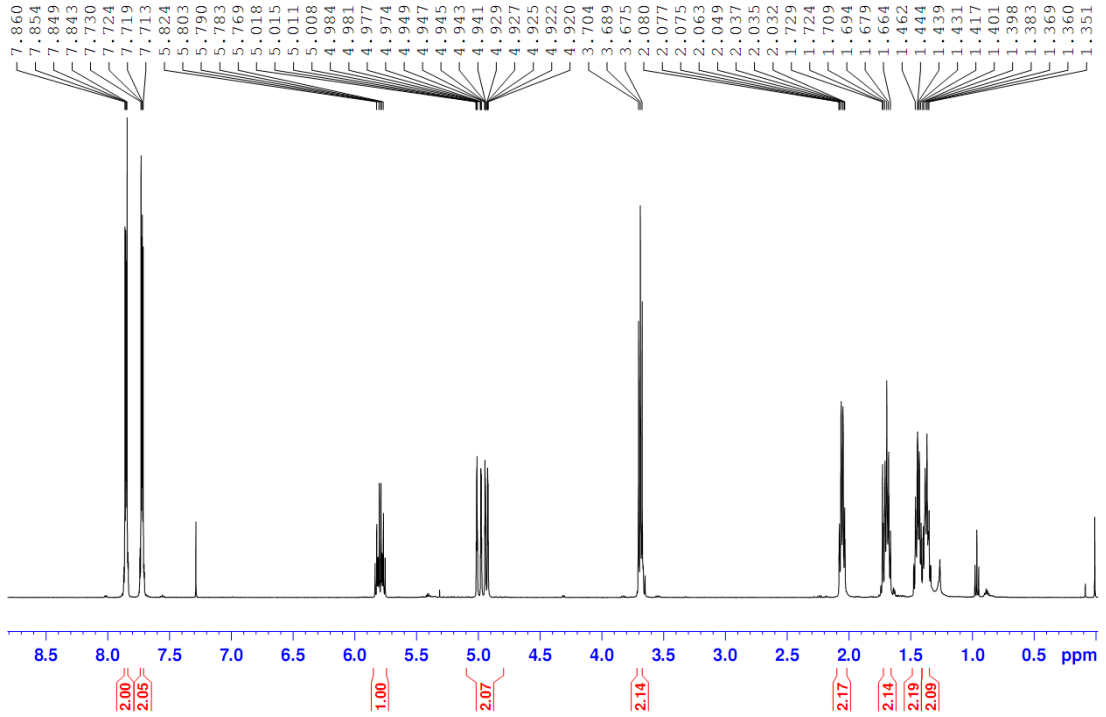

7.862
7.856
7.851
7.845
7.730
7.724
7.719
7.713
7.281
1.006
0.993
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
2.00
2.11
0.96
1.98
2.08
2.28
1.15
3.34
1.56
3.12

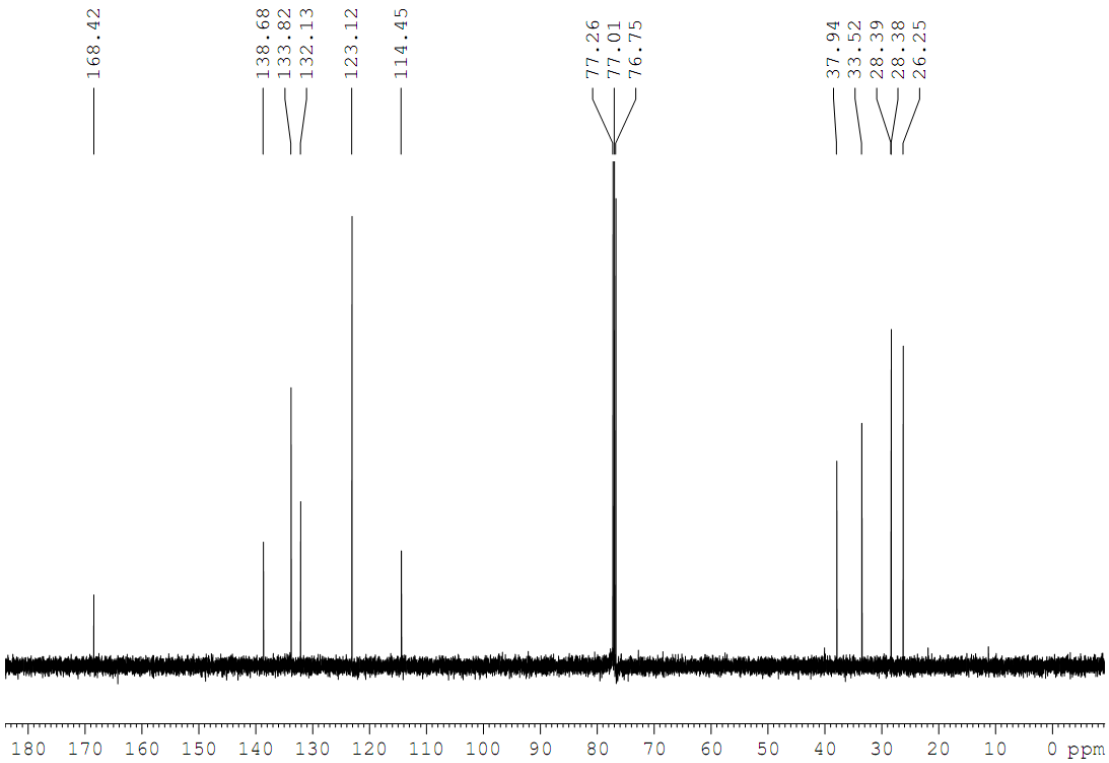

168.39
138.89
133.81
132.19
123.11
114.29
77.26
77.00
76.75
36.20
35.83
35.31
31.09
30.12
19.20
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

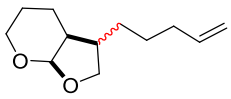

O
N
O
Me
17b
7.867
7.861
7.856
7.843
7.742
7.728
7.723
7.717
3.708
3.693
3.678
0.900
0.886
0.872
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm
1.94
2.00
2.05
2.13
4.21
4.21
3.23
168.4
133.8
132.1
123.1
77.26
77.00
76.75
38.07
31.68
28.85
28.60
26.81
22.56
14.04
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm


O
N
O

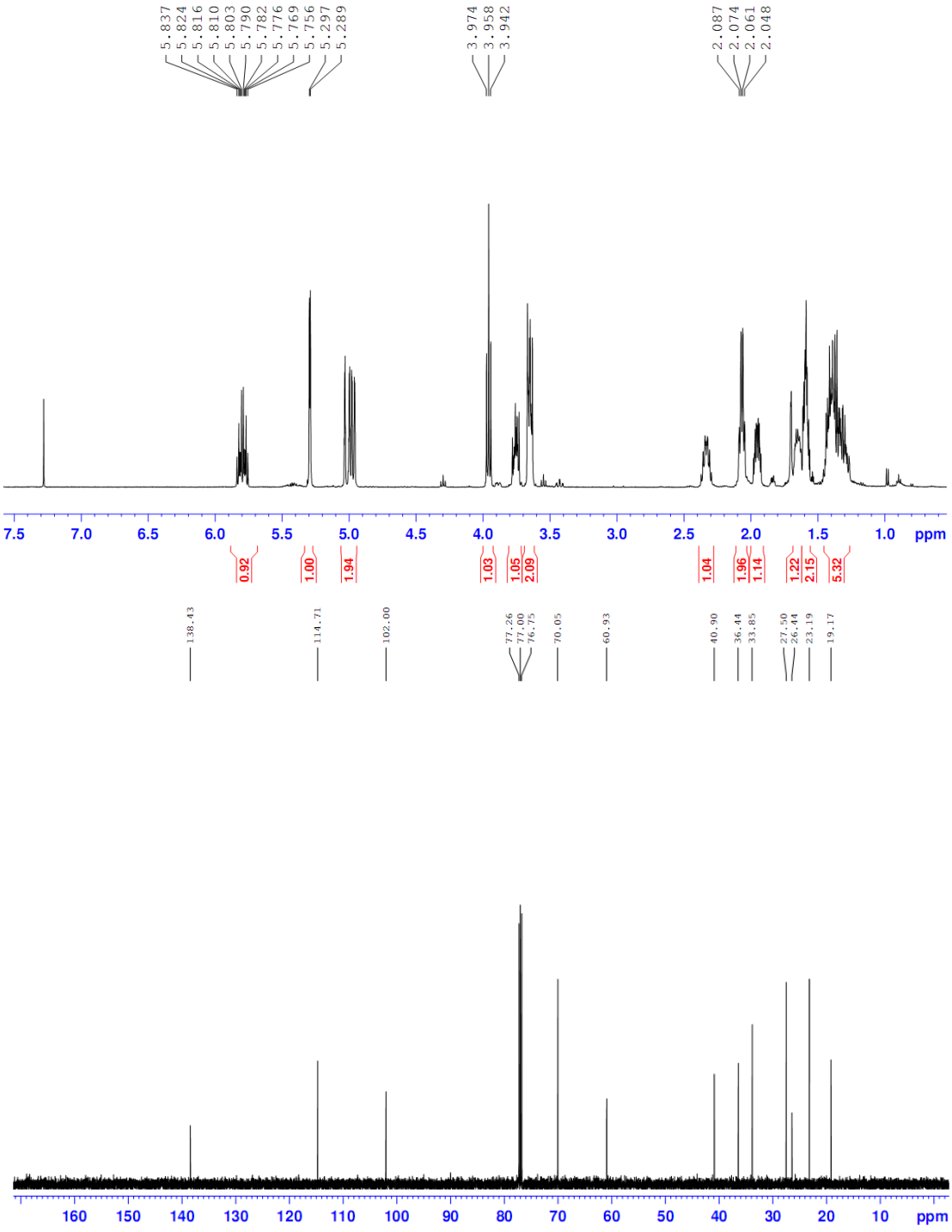
18b

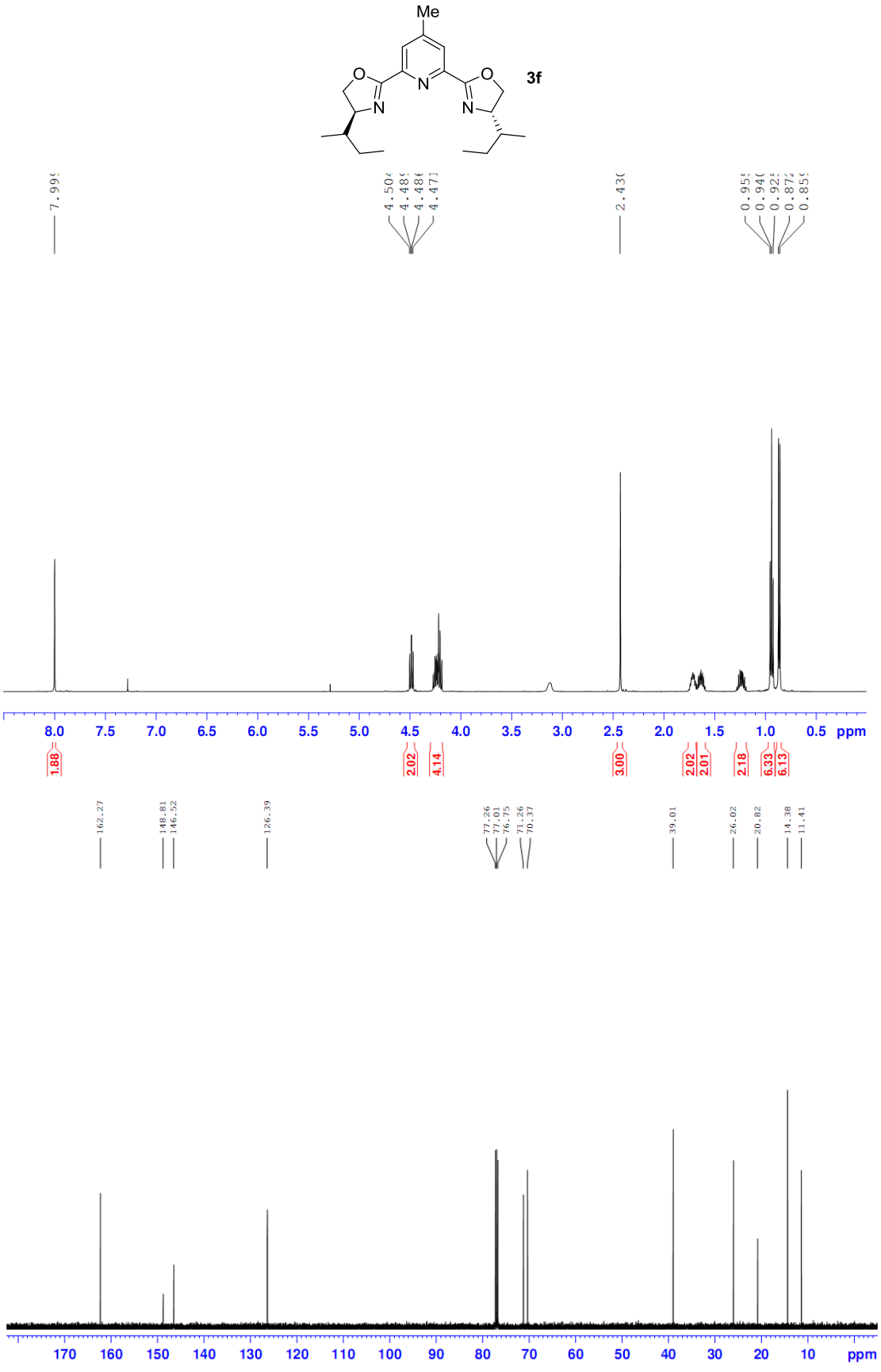

7.860
7.854
7.849
7.843
7.730
7.724
7.719
7.713
5.824
5.803
5.790
5.783
5.769
5.018
5.015
5.011
5.008
4.984
4.981
4.977
4.974
4.949
4.947
4.945
4.943
4.941
4.929
4.927
4.925
4.922
4.920
3.704
3.689
3.675
2.080
2.077
2.075
2.063
2.049
2.037
2.035
2.032
1.729
1.724
1.709
1.694
1.679
1.664
1.462
1.444
1.439
1.431
1.417
1.401
1.398
1.383
1.369
1.360
1.351
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 ppm
2.00
2.05
1.00
2.07
2.14
2.17
2.14
2.19
2.09

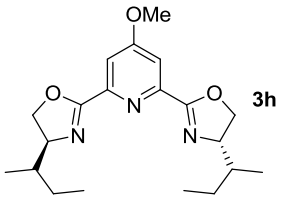

168.42
138.68
133.82
132.13
123.12
114.45
77.26
77.01
76.75
37.94
33.52
28.39
28.38
26.25
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

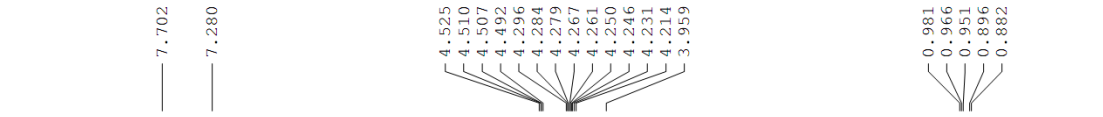


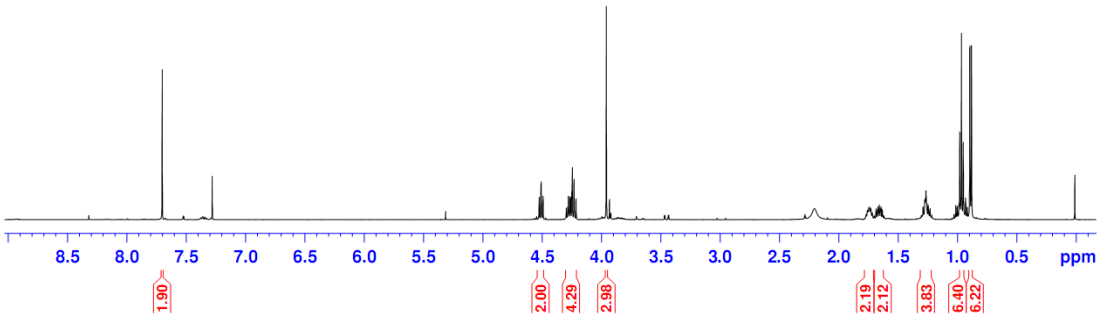
19b

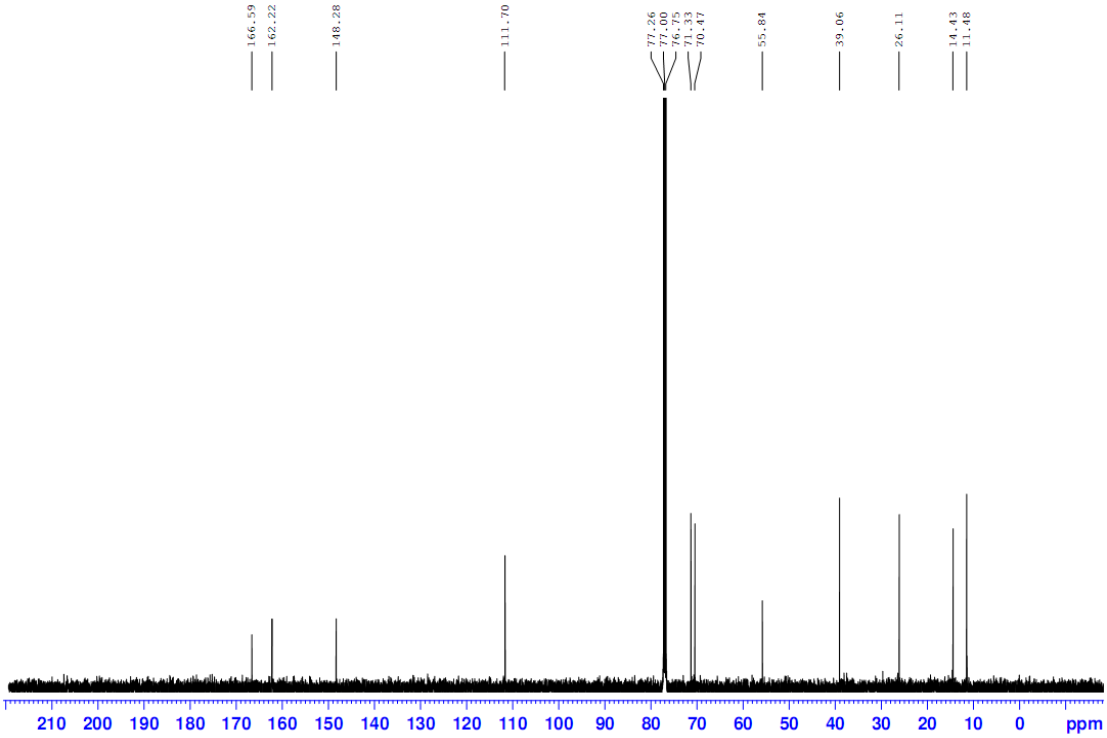

5.837
5.824
5.816
5.810
5.803
5.790
5.782
5.776
5.769
5.756
5.297
5.289
3.974
3.958
3.942
2.087
2.074
2.061
2.048
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
0.92
1.00
1.94
1.03
1.05
2.09
1.04
1.96
1.14
1.22
2.15
5.32
138.43
114.71
102.00
77.26
77.00
76.75
70.05
60.93
40.90
36.44
33.85
27.50
26.44
23.19
19.17
160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

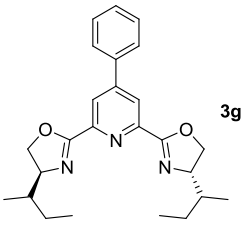

Me
O
N
O
N
N
3f
7.99
4.50
4.48
4.48
4.47
2.43
0.95
0.94
0.92
0.87
0.85
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
1.88
2.02
4.14
3.00
2.02
2.01
2.18
6.33
6.13
162.27
148.81
146.52
126.39
77.26
77.01
76.75
71.26
70.37
39.01
26.02
20.82
14.38
11.41
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


OMe
O
N
O
N
N
3h

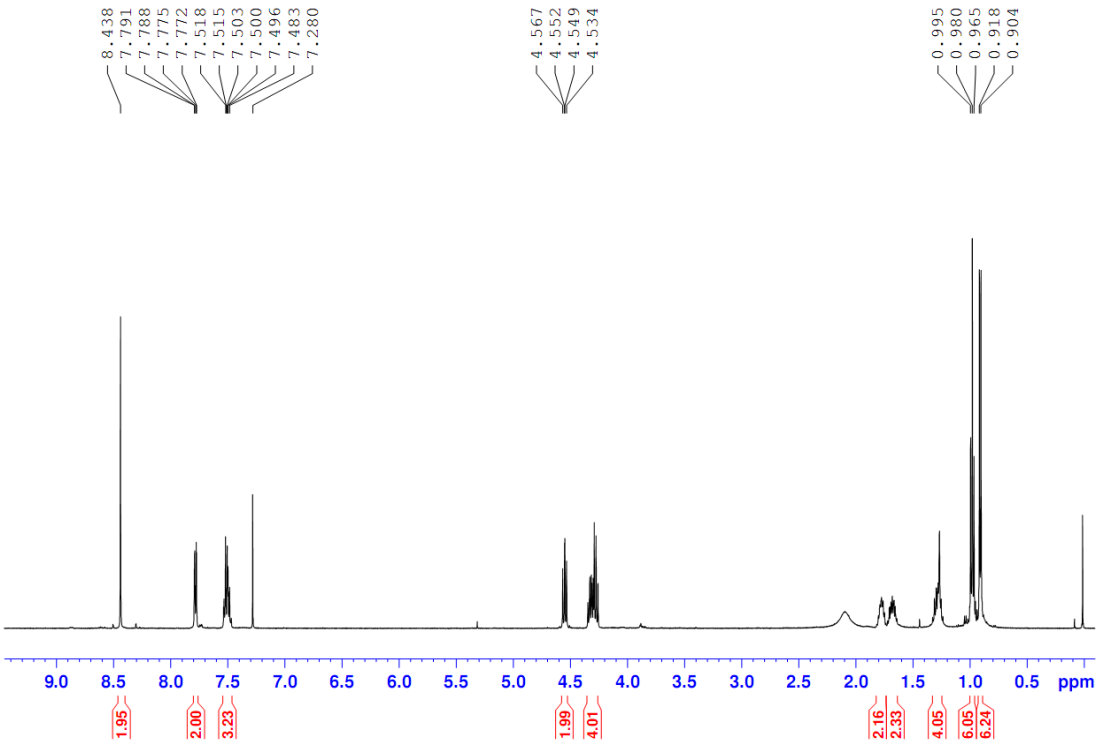

7.702
7.280
4.525
4.510
4.507
4.492
4.296
4.284
4.279
4.267
4.261
4.250
4.246
4.231
4.214
3.959
0.981
0.966
0.951
0.896
0.882

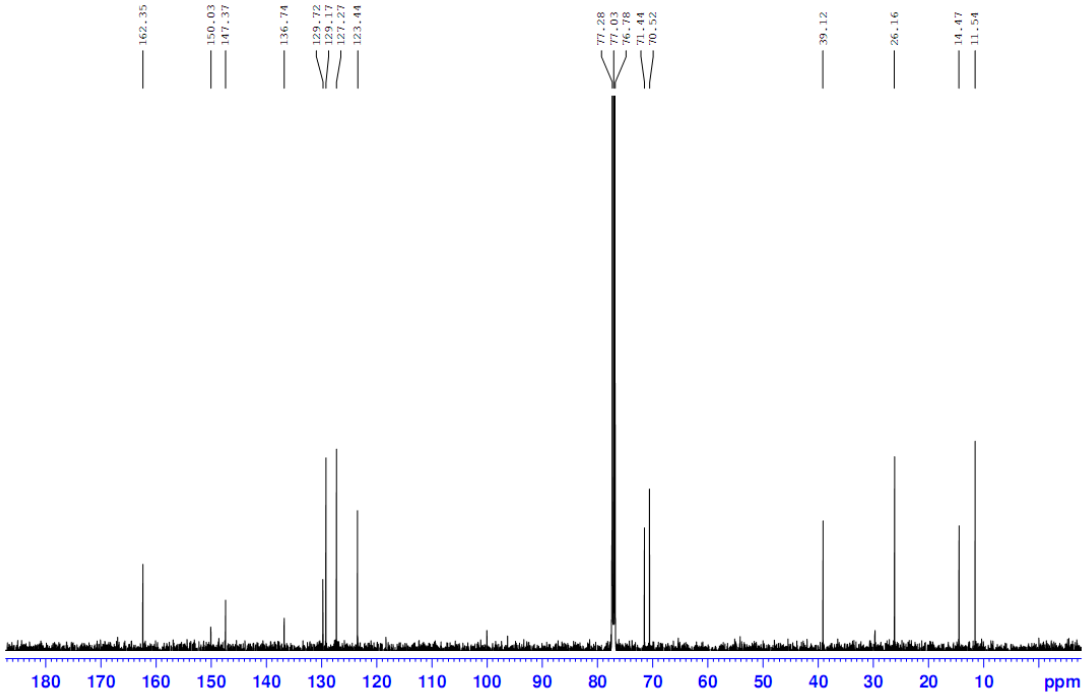

8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
1.90
2.00
4.29
2.98
2.19
2.12
3.83
6.40
6.22

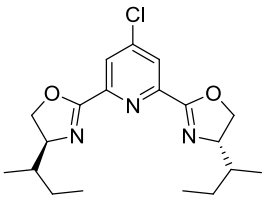

166.59
162.22
148.28
111.70
77.26
77.00
76.75
71.33
70.47
55.84
39.06
26.11
14.43
11.48
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm



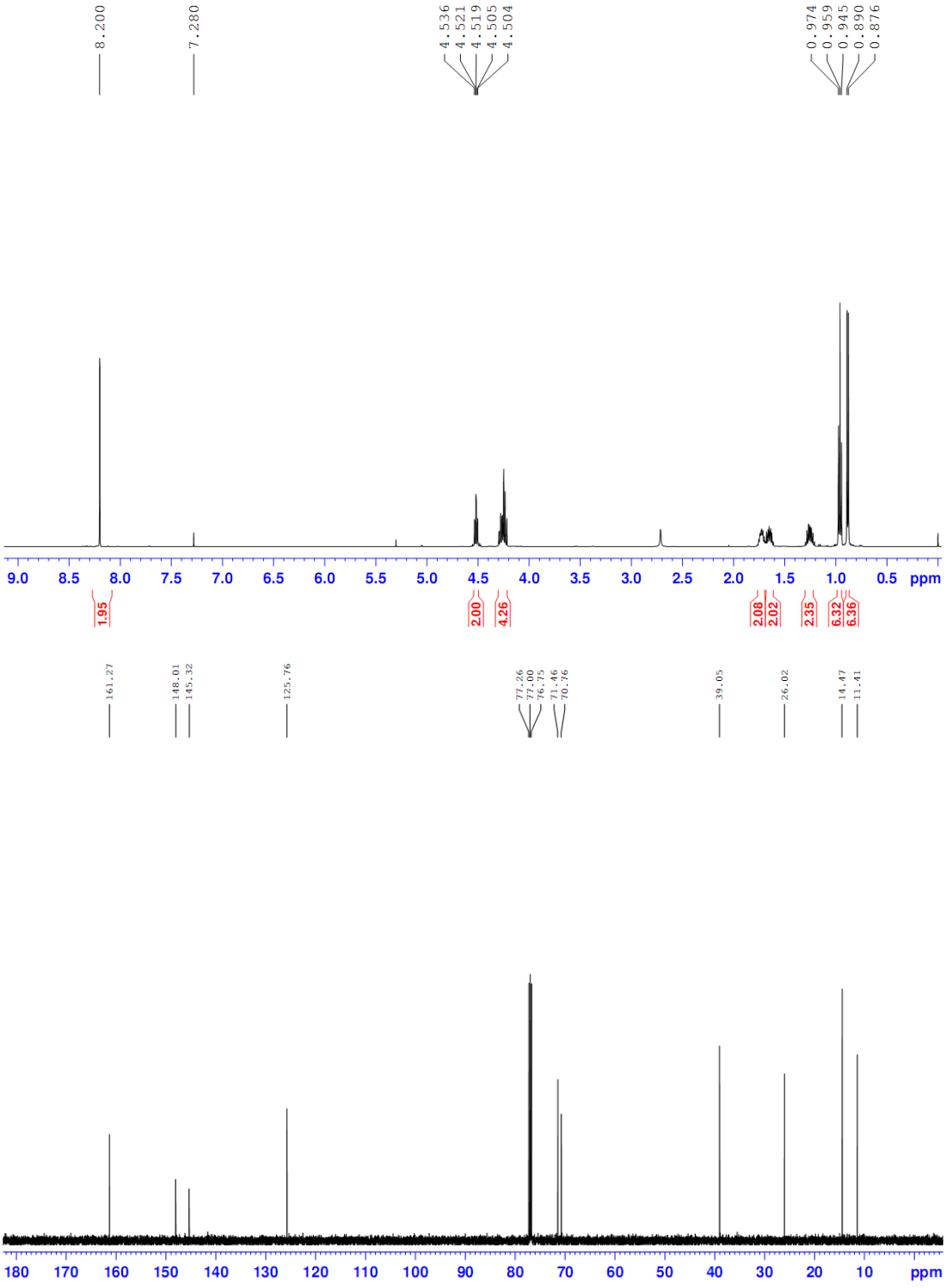
3g

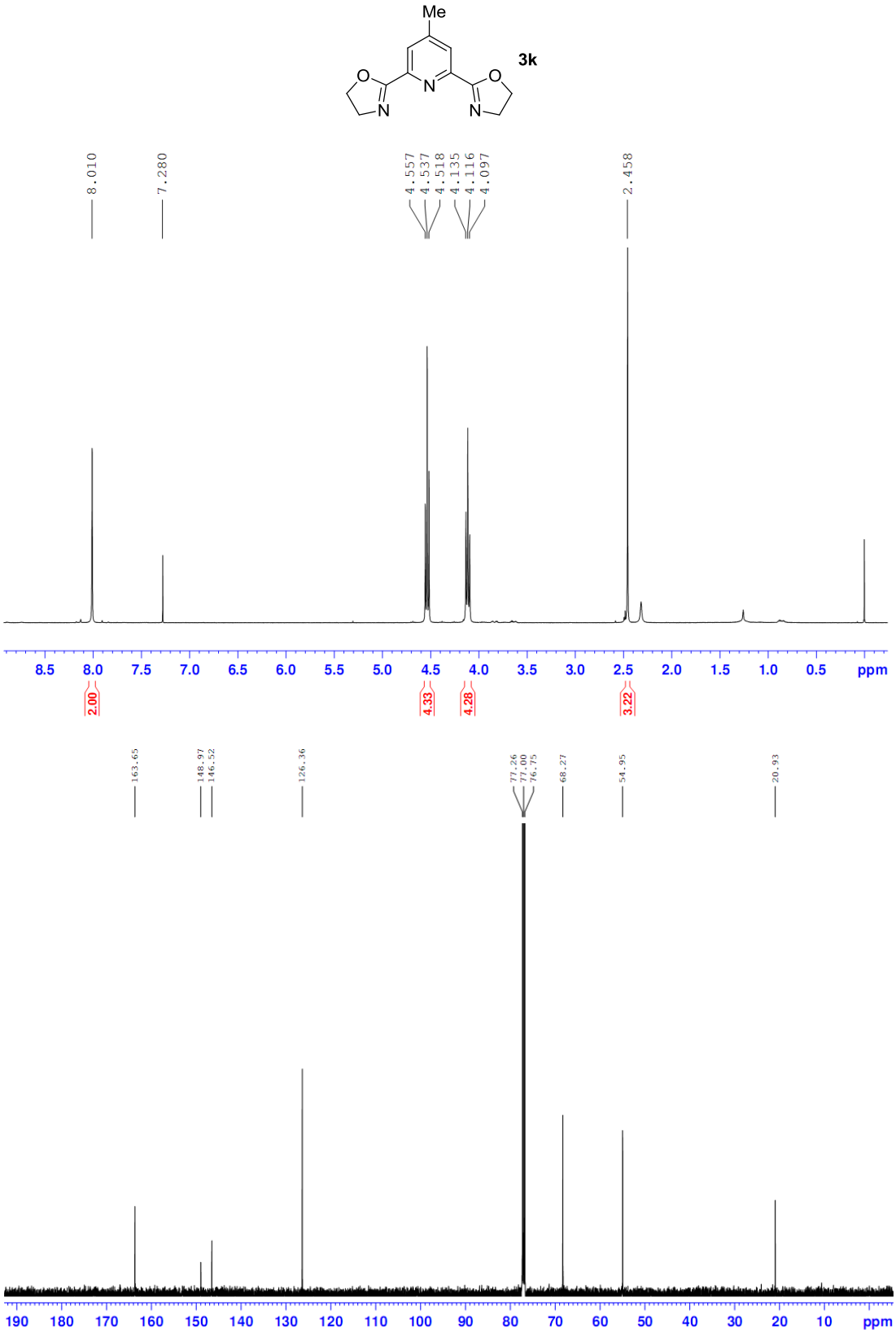

8.438
7.791
7.788
7.775
7.772
7.518
7.515
7.503
7.500
7.496
7.483
7.280
4.567
4.552
4.549
4.534
0.995
0.980
0.965
0.918
0.904
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
1.95
2.00
3.23
1.99
4.01
2.16
2.33
4.05
6.05
6.24

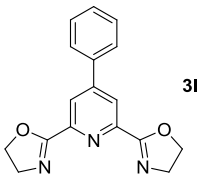

162.35
150.03
147.37
136.74
129.72
129.17
127.27
123.44
77.28
77.03
76.78
71.44
70.52
39.12
26.16
14.47
11.54
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

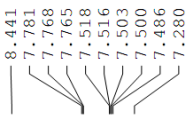

Cl
O
N
O
N
N

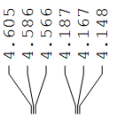
3i

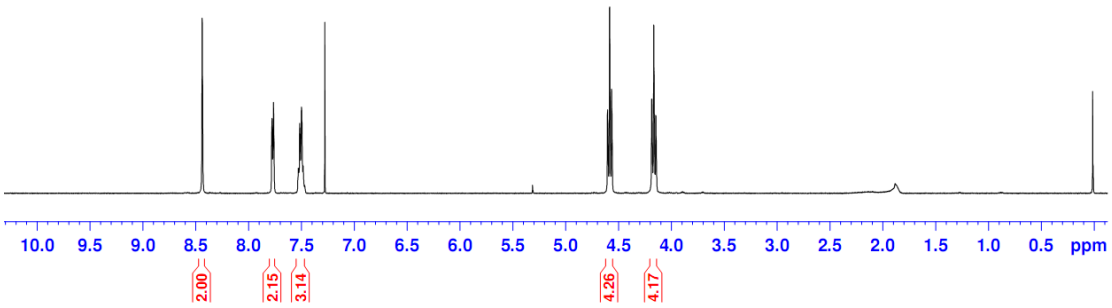

8.200
7.280
4.536
4.521
4.519
4.505
4.504
0.974
0.959
0.945
0.890
0.876
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
1.95
2.00
4.26
2.08
2.02
2.35
6.32
6.36
161.27
148.01
145.32
125.76
77.26
77.00
76.75
71.46
70.76
39.05
26.02
14.47
11.41
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

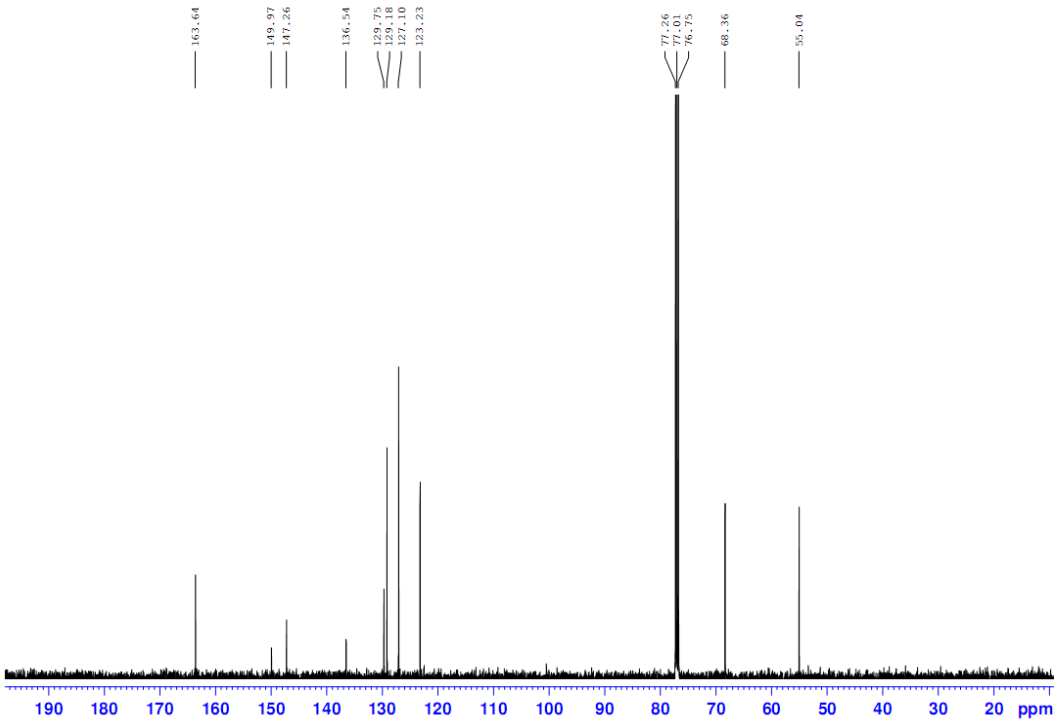

Me
3k
O
N
O
N
N
8.010
7.280
4.557
4.537
4.518
4.135
4.116
4.097
2.458
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
2.00
4.33
4.28
3.22
163.65
148.97
146.52
126.36
77.26
77.00
76.75
68.27
54.95
20.93
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

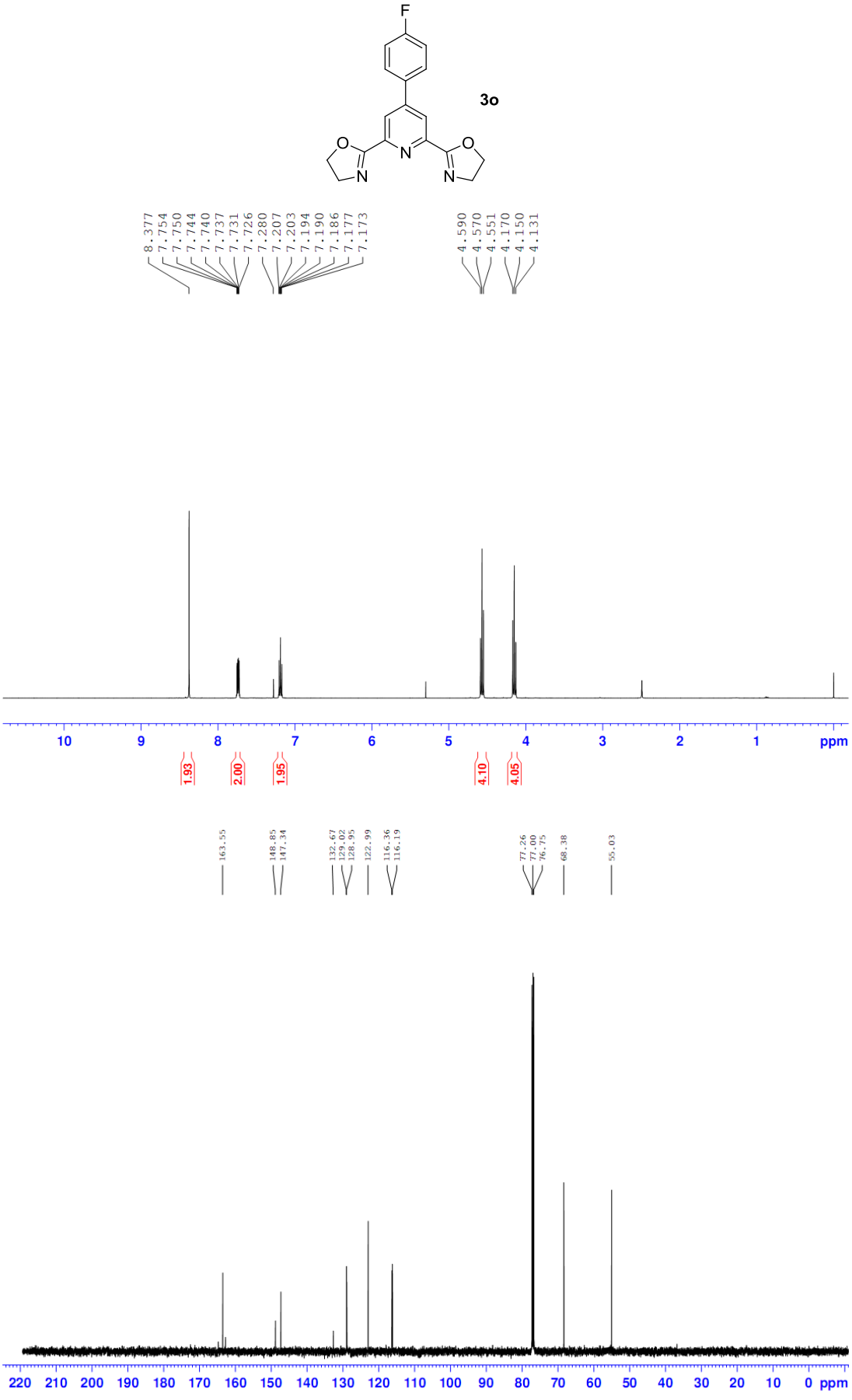

3l
O
N
O
N
N

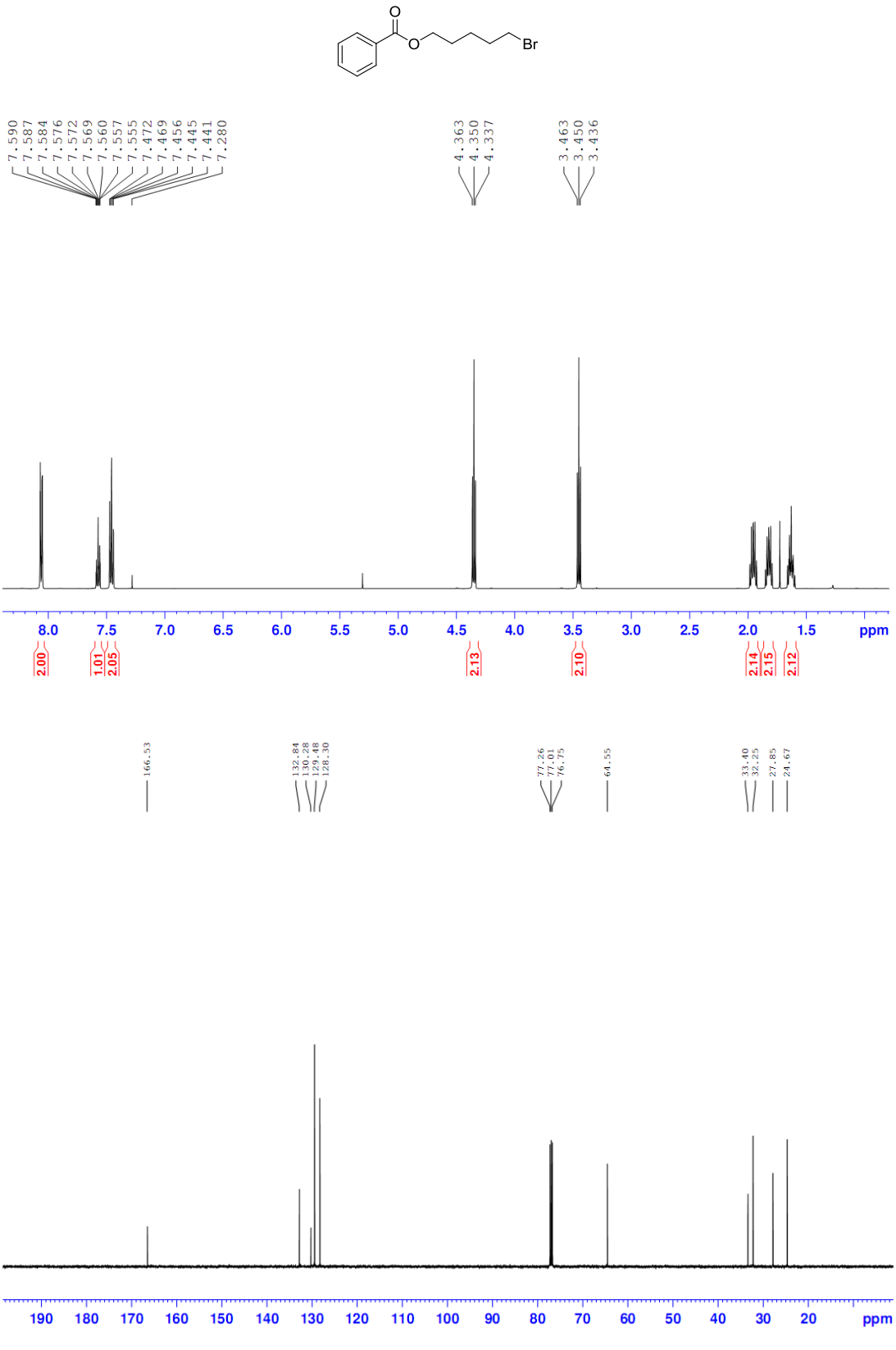

8.441
7.781
7.768
7.765
7.518
7.516
7.503
7.500
7.486
7.280


4.605
4.586
4.566
4.187
4.167
4.148


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 ppm
2.00
2.15
3.14
4.26
4.17


163.64
149.97
147.26
136.54
129.75
129.18
127.10
123.23
77.26
77.01
76.75
68.36
55.04
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm


F
3o
O
N
O
N
N
8.377
7.754
7.750
7.744
7.740
7.737
7.731
7.726
7.280
7.207
7.203
7.194
7.190
7.186
7.177
7.173
4.590
4.570
4.551
4.170
4.150
4.131
10
9
8
7
6
5
4
3
2
1
ppm
1.93
2.00
1.95
4.10
4.05
163.55
148.85
147.34
132.67
129.02
128.95
122.99
116.36
116.19
77.26
77.00
76.75
68.38
55.03
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0 ppm


O
O
Br
7.590
7.587
7.584
7.576
7.572
7.569
7.560
7.557
7.555
7.472
7.469
7.456
7.445
7.441
7.280
4.363
4.350
4.337
3.463
3.450
3.436
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
ppm
2.00
1.01
2.05
2.13
2.10
2.14
2.15
2.12
166.53
132.84
130.28
129.48
128.30
77.26
77.01
76.75
64.55
33.40
32.25
27.85
24.67
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20
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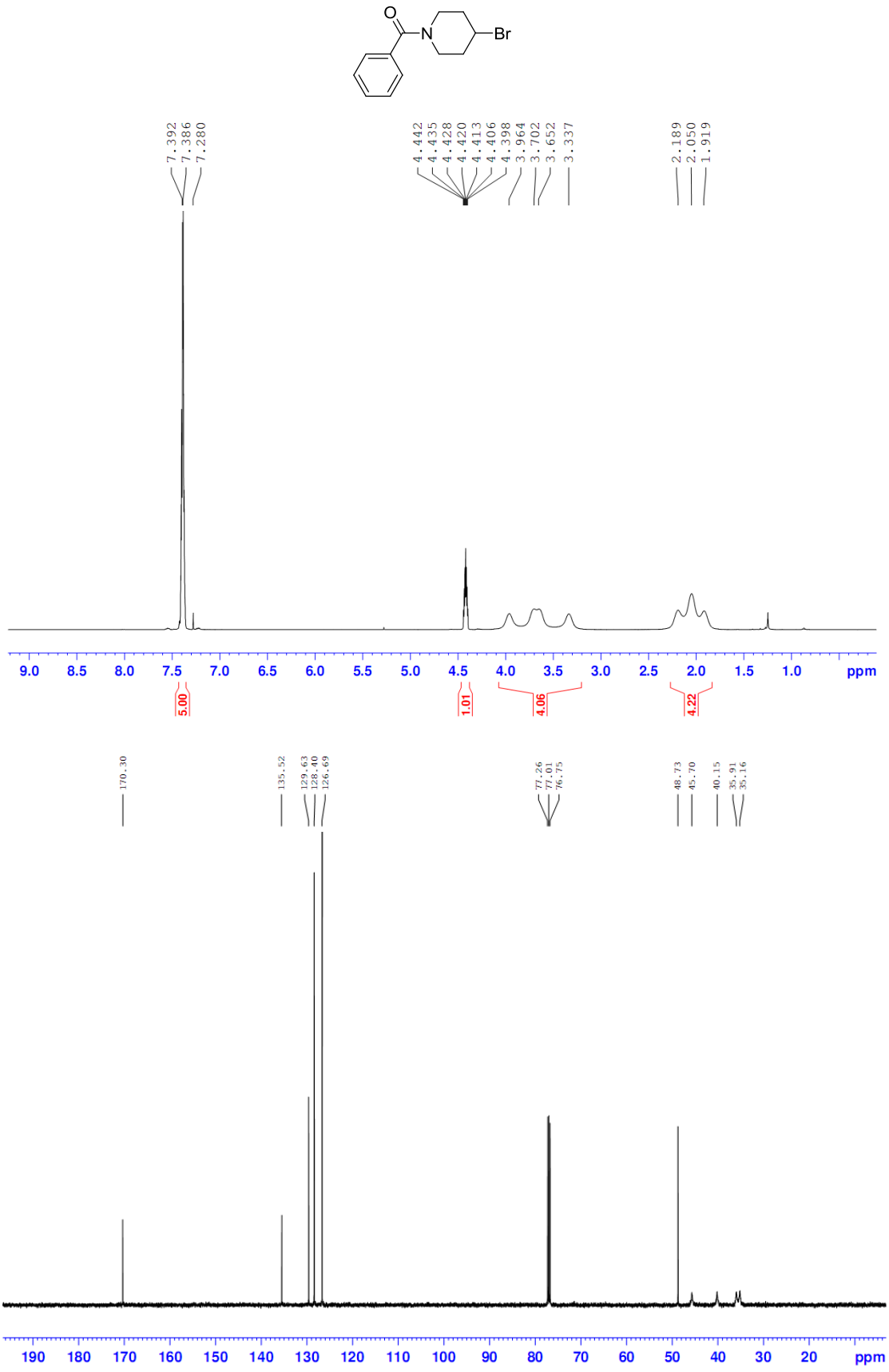
O
N
Br
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4.406
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3.702
3.652
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2.189
2.050
1.919
9.0
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6.0
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2.0
1.5
1.0
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1.01
4.06
4.22
170.30
135.52
129.63
128.40
126.69
77.26
77.01
76.75
48.73
45.70
40.15
35.91
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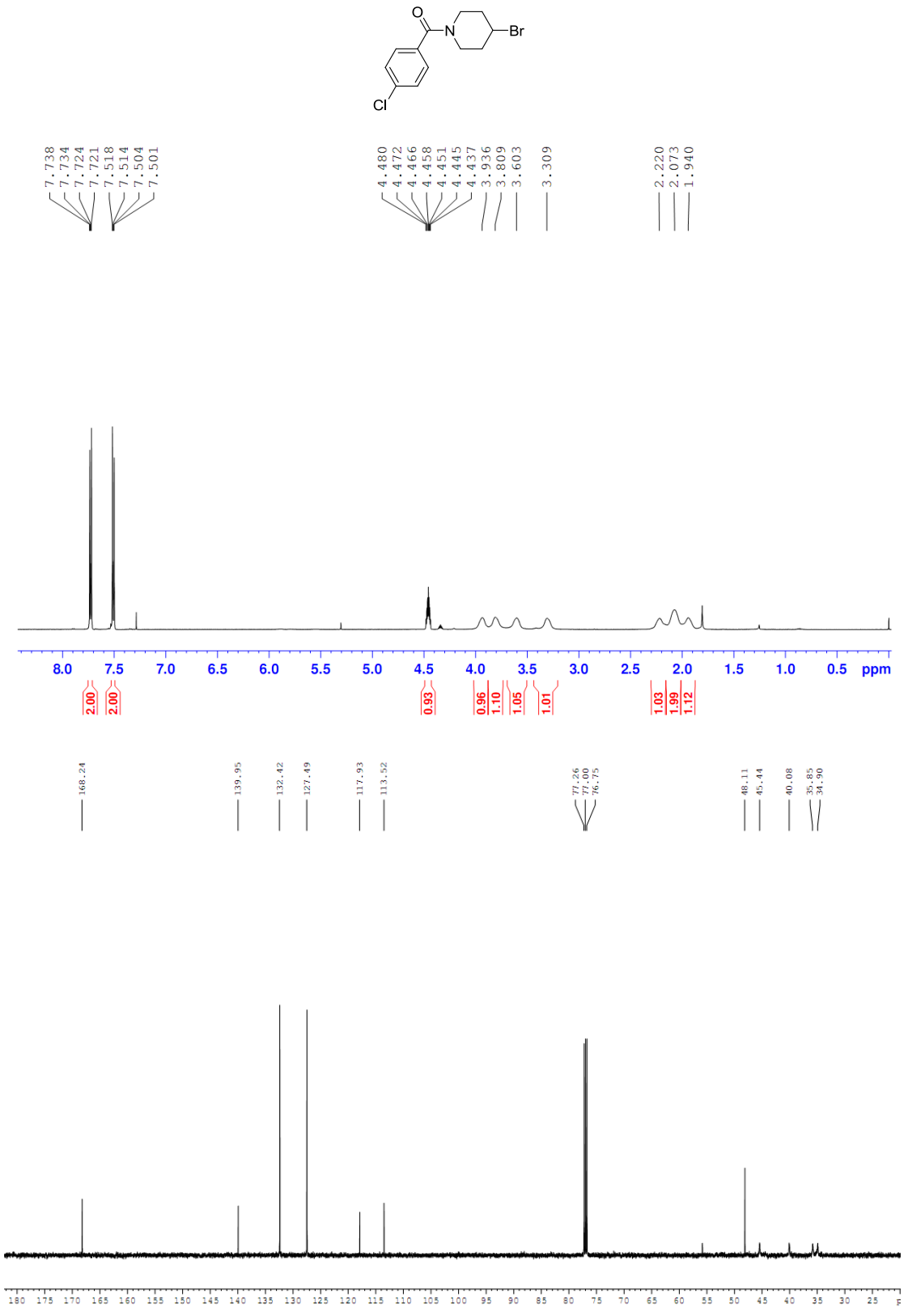
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Br
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7.501
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4.466
4.458
4.451
4.445
4.437
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3.809
3.603
3.309
2.220
2.073
1.940
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4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
2.00
2.00
0.93
0.96
1.10
1.05
1.01
1.03
1.99
1.12
168.24
139.95
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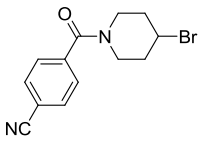
117.93
113.52
77.26
77.00
76.75
48.11
45.44
40.08
35.85
34.90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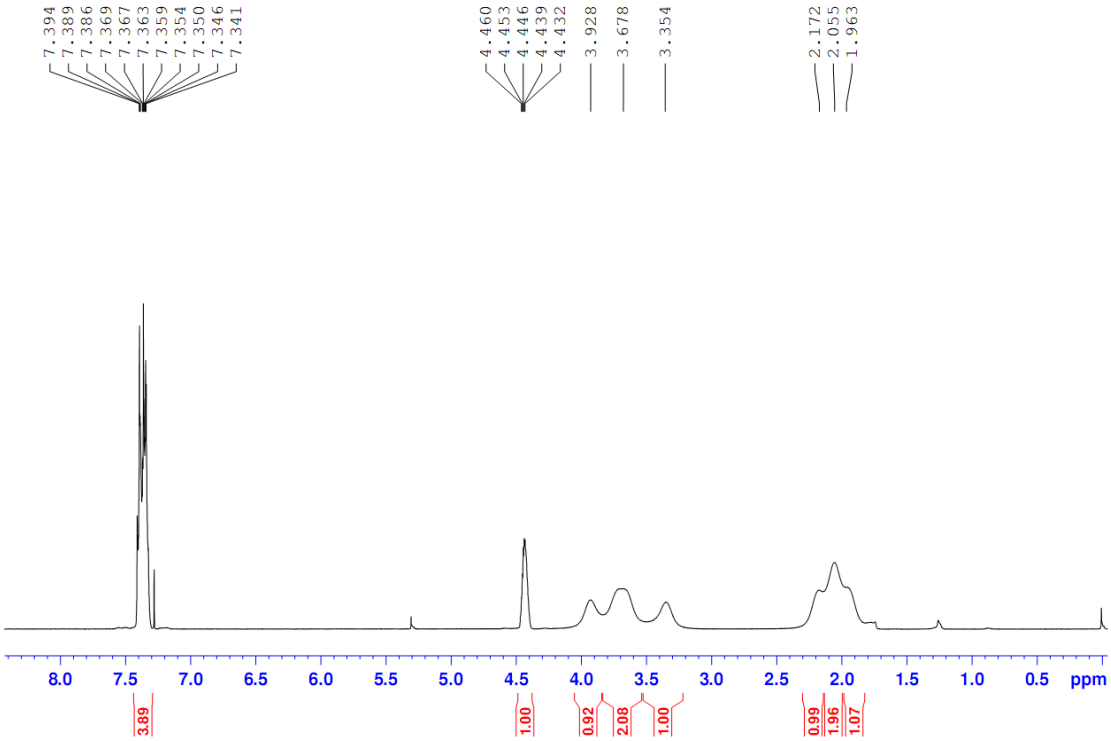
N
Br
NC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4.453
4.446
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3.928
3.678
3.354
2.172
2.055
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6.0
5.5
5.0
4.5
4.0
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3.0
2.5
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ppm
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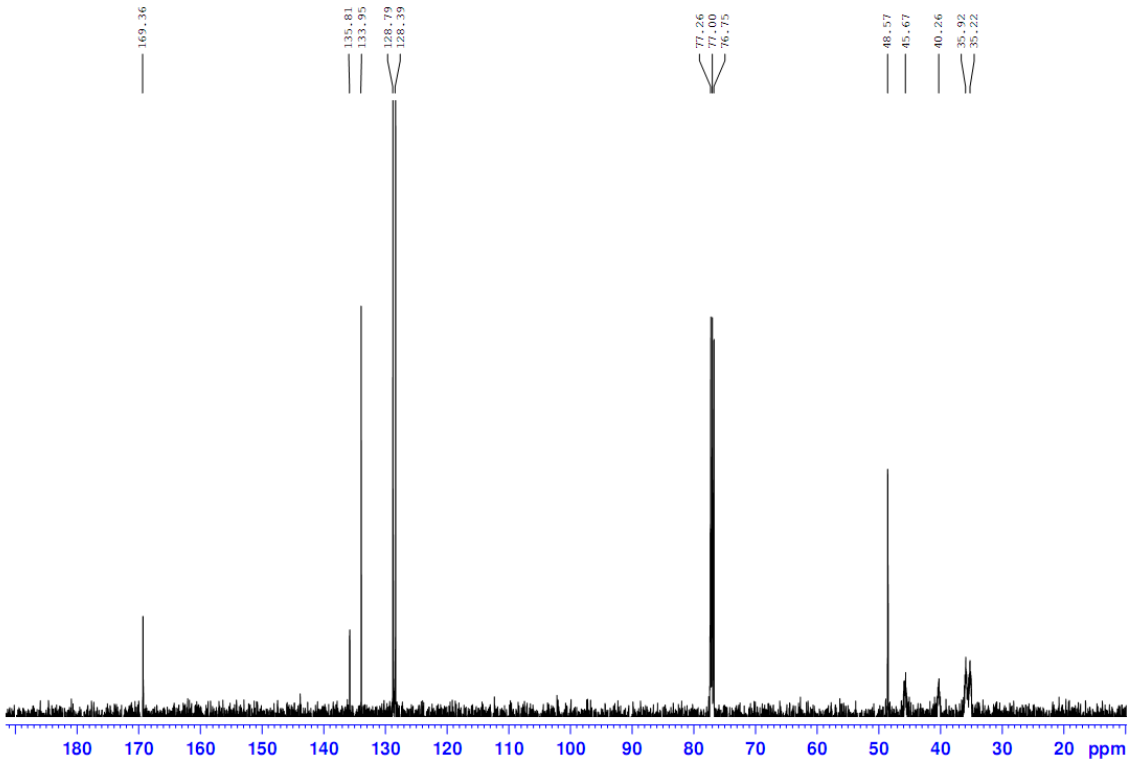
0.92
2.08
1.00
0.99
1.96
1.07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76.75
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40.26
35.92
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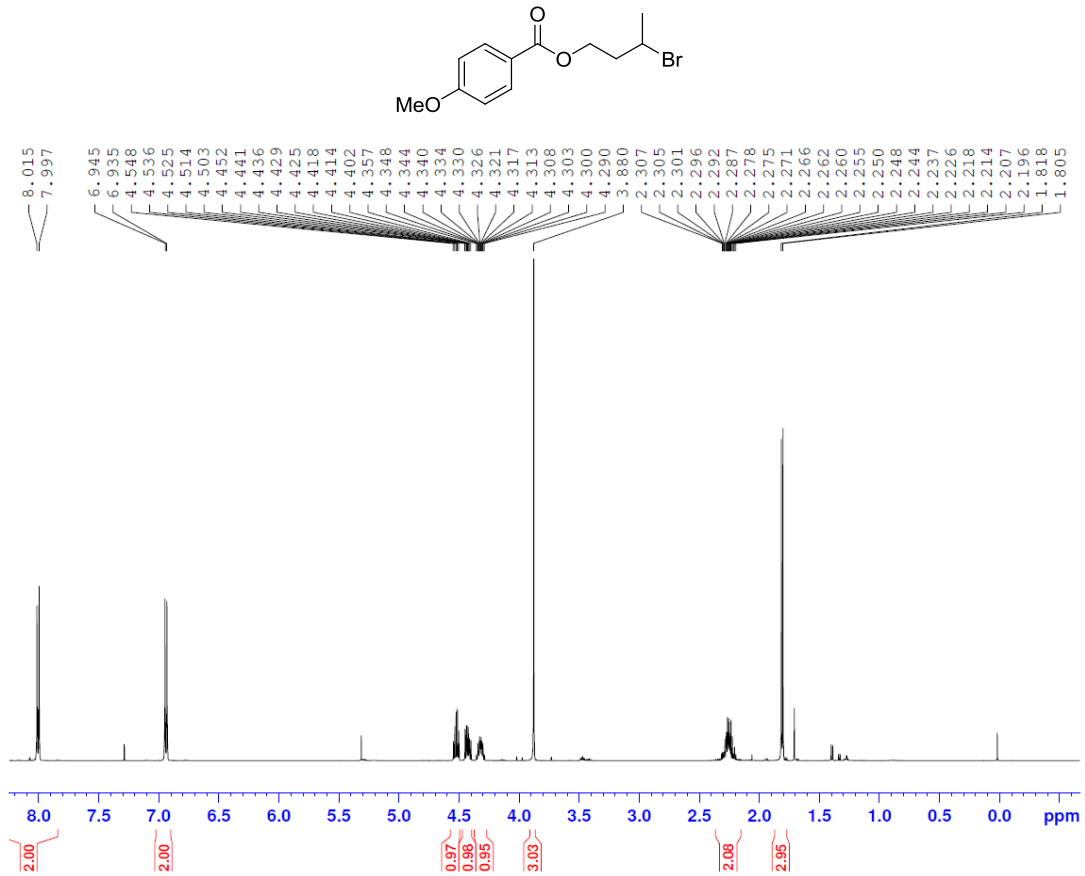
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm


O
O
Br
MeO
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4.452
4.441
4.436
4.429
4.425
4.418
4.414
4.402
4.357
4.348
4.344
4.340
4.334
4.330
4.326
4.321
4.317
4.313
4.308
4.303
4.300
4.290
3.880
2.307
2.305
2.301
2.296
2.292
2.287
2.278
2.275
2.271
2.266
2.262
2.260
2.255
2.250
2.248
2.244
2.237
2.226
2.218
2.214
2.207
2.196
1.818
1.805
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7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
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0.0
ppm
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2.00
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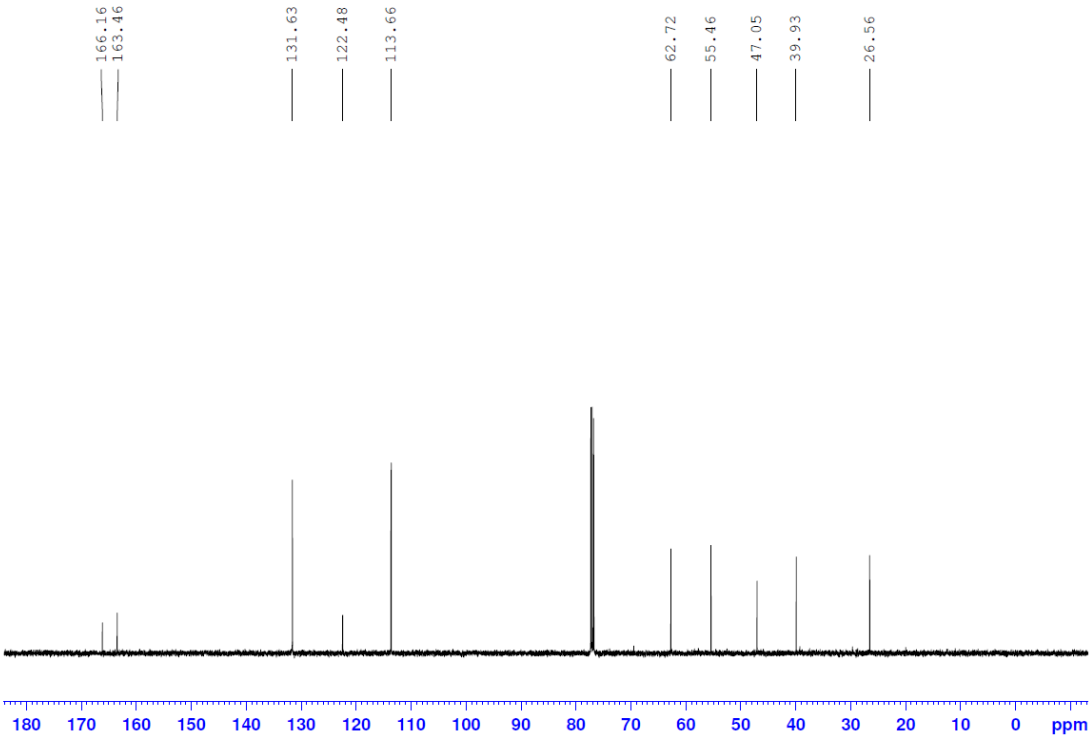
0.98
0.95
3.03
2.08
2.95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62.72
55.46
47.05
39.93
26.56
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm