SUPPORTING INFORMATION

Fe-Catalysed Kumada-type Alkyl-Alkyl Cross-Coupling. Evidence for the intermediacy of Fe(I) complexes

Manuel Guisán-Ceinos, Francisco Tato, Elena Buñuel, Paloma Calle, Diego J. Cárdenas

Departamento de Química Orgánica, Universidad Autónoma de Madrid, Cantoblanco, 28049-Madrid, Spain

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1. Materials and Methods

All reactions were carried out under argon in anhydrous THF dried using a Solvent Purification System (SPS) and/or distillation over Na/benzophenone. Thin layer chromatography was carried out using pre-coated TLC-aluminum sheets with 0.20 mm of silica gel and fluorescent indicator UV_{254} (ALUGRAM® Xtra SIL G/UV_{254}) and visualized with UV light and/or phosphomolybdic acid ethanol solution and potassium permanganate aqueous solution. Chromatography purifications were carried out using flash grade silica gel (Chromatogel 60 ACC, 40-60 μm). NMR spectra were recorded at 23 ºC on a Bruker Avance 300 MHz. The ^{1}H and the $^{13}C\{1H\}$ NMR chemical shifts are given in parts per million (ppm) relative to the residual signals of the deuterated solvents.[1] Carbon types were determined from DEPT - ^{13}C NMR. The following abbreviations are used to indicate the multiplicity: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; bs, broad signal. Mass spectra were recorded on a Waters VG AutoSpec and gas chromatography was recorded on a Varian 3800 GC. EPR spectra were recorded on a Varian E-12 ((modulation frequency 100 kHz; modulation amplitude 5 G; power 6.32 kW).

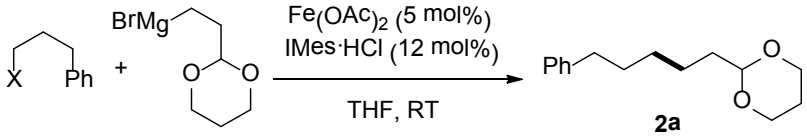
Starting iodides such as (3-iodopropyl)benzene **1**,[2] 1-(3-iodopropyl)-4-methoxybenzene,[3] methyl 5-iodopentanoate,[4] ethyl 4-iodocyclohexanecarboxylate,[5] 2-(iodomethyl)tetrahydro-*2H*-pyran,[6] 4-iodo-2,2-dimethyltetrahydro-*2H*-pyran,[7] 2-(3-iodopropoxy)tetrahydro-2H-pyran,[8] tert-butyl 4-iodopiperidine-1-carboxylate,[9] 1-benzyl-4-iodopiperidine,[10] 2-(2-iodoethyl)-*N*-tosylindol,[11] and cholesteryl iodide[12] have been synthesized following the procedures reported in the literature and using starting materials commercially available. Other chemicals were used as received without further purifications. Iron(II) acetate was purchased from Aldrich and Strem Chemicals with 99.99% and 97% purity respectively and no change was observed concerning the reactivity. However the catalytic effectiveness diminished over time. All other commercially available compounds were used as received.

2. Optimization of Reaction Parameters

Electrophiles:

Various alkyl halides and tosylate were tested in the alkyl-alkyl cross-coupling. As we can see in Table S1, the more reactive alkyl iodide (Table S1, entry 1), gave the higher yield (55%). With the bromide derivative, the yield dropped to 39% (Table S1, entry 2) and with the alkyl chloride (Table S1, entry 3), the reaction did not take place. On the other hand, when the alkyl tosylate was used as starting electrophile the reaction afforded a 20% yield (Table S1, entry 4).

Table S1. Alkyl electrophile investigations of the alkyl-alkyl cross-coupling reaction.



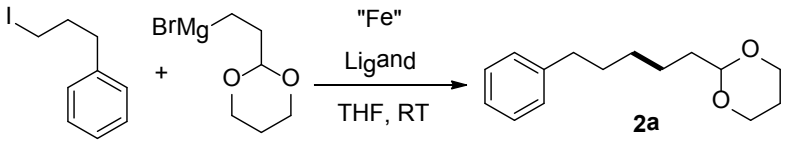
Entry[a]	Alkyl-X	Yield[b]
1	X = I	55%
2	X = Br	39%
3	X = Cl	NR
4	X = OTs	20%

[a] Reaction was carried out by the slow addition of Grignard reagent (2 equiv) to a THF solution of alkyl halide or tosylate (1 equiv), $Fe(OAc)_2$ (5 mol%) and IMes·HCl (12 mol%) under Argon at RT. [b] Yield of isolated product.

Iron Source:

Both iron(II) and iron(III) fluorides, chlorides, and bromides, iron(II) iodide and iron(III) acetylacetonate were tested in the reaction and surprisingly both iron(II) and iron(III) chlorides, bromides, and $Fe(acac)_3$ gave a similar yields (see Table S2, entries 3-6, 8) which were indicating the no influence of the iron counterion and the plausible formation of a common intermediate responsible of the cross-coupling reaction. Iron(II) and iron(III) fluorides and iron(II) iodide (see Table S2, entries 1-2, 7) possess some handling difficulties with regard to solubility and hygroscopy respectively which could explain the different behavior of those with respect to the aforementioned.

Table S2. Iron source investigations of the alkyl-alkyl cross-coupling reaction.



Entry[a]	Fe (mol%)	Ligand (mol%)	Yield[b]
1	FeF_2 (5)	IMes·HCl (12)	30%
2	FeF_3 (5)	IMes·HCl (12)	46%

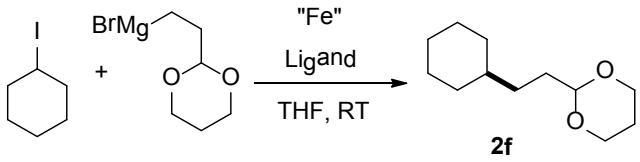
3	$FeCl_2$ (5)	IMes·HCl (12)	70%
4	$FeCl_3$ (5)	IMes·HCl (12)	73%
5	$FeBr_2$ (5)	IMes·HCl (12)	72%
6	$FeBr_3$ (5)	IMes·HCl (12)	69%
7	FeI_2 (5)	IMes·HCl (12)	32%
8	$Fe(acac)_3$ (5)	IMes·HCl (12)	70%

[a] Reaction was carried out following the general procedure. [b] Yield of isolated product.

Flow Rate:

A study on the flow addition rate was carried out using iodocyclohexane as starting material. As we and other authors noted, the presence of a large excess of Grignard reagent in the reaction media provoked a reducing or even the inhibition of the cross-coupling. That means a control on the flow rate is required for the success of the reaction. As we can see in the Table S4, lower yields were obtained when faster additions rates were used.

Table S3. Flow rates investigations of the alkyl-alkyl cross-coupling reaction.



2f

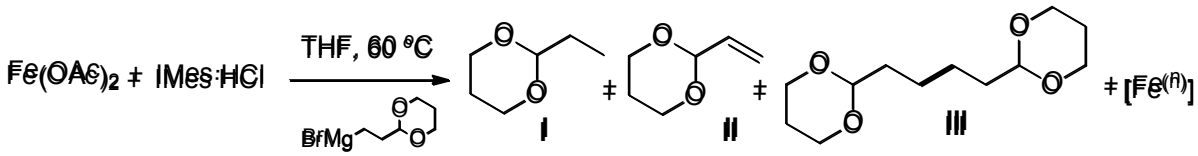
Entry[a]	Ligand (mol%)	Flow rate	Yield[b]
1	IMes·HCl (12)	0.16 mL/h	88%
2	IMes·HCl (12)	0.32 mL/h	53%
3	IMes·HCl (12)	60 mL/h	22%

[a] Reaction was carried out following the general procedure. [b] Yield of isolated product.

3. Determination of Iron Oxidation State by GC Monitoring

Compounds 2-ethyl-1,3-dioxane **I**,[13] 2-vinyl-1,3-dioxane **II**,[14] and 1,4-di(1,3-dioxanyl)butane **III** were prepared according to the modified procedures described in the literature. These compounds were synthesized in order to obtain the calibration curves in which dodecane was used as internal standard. The acquired data were collected from the experiment described as follows: Iron(II) acetate (17.4 mg, 0.1 mmol) and 1,3-dimesityl-1H-imidazol-3-ium chloride (82 mg, 0.24 mmol) were placed in Schlenk flask and dried under vacuum. Then, dry THF (20 mL) was added and the mixture was heated at 50-60 ºC under Ar. A 0.5 M solution of alkylmagnesium bromide (in THF) was added and reactions were stirred for 20 min. Internal standard (dodecane) was added and reactions were hydrolyzed by passing the mixtures through a short pad of silica-gel. Data were collected for the addition of 0.1, 0.2, 0.3, 0.4, 0.6, 0.8, 1.0, 1.2, 1.4, and 1.6 mmol of Grignard reagent (Table S4). 2-Vinyl-1,3-dioxane **II** was not detected in any experiment and 2-ethyl-1,3-dioxane **I** showed as a highly volatile compound and values of its concentration did not correspond with those used in the iron activation reaction. Line of purple points represents the uncorrected data collected directly from the experiment. However in order to obtain a reliable value of the homocoupling **III**, the amount of this homocoupling product **III** already present in the Grignard reagent must be subtracted from the original line giving the line of blue points (Figure S1). A more representative graphic could be obtained by representation of the electrons that are intervening in the reaction per mmol of iron and the equivalent of Grignard reagent (Figure S2).

Table S4. Collected data recorded from GC monitoring in order to determine the iron oxidation state.



Grignard reagent (equiv.)	internal standard (area)	homocoupled (area)	homocoupled (mmol)	homocoupled (corrected mmol)	e^- / Fe
1	723028	5538	0,006	0,0034	0,07
2	689675	7917	0,008	0,0040	0,08
3	715996	9959	0,010	0,0035	0,07
4	697583	19883	0,021	0,0120	0,24
6	661095	40442	0,045	0,0314	0,63
8	641311	47069	0,053	0,0359	0,72
10	83633	7320	0,064	0,0418	0,84
12	565112	49397	0,064	0,0373	0,75
14	515489	46597	0,066	0,0351	0,70
16	456949	46401	0,074	0,0388	0,78

Figure S1. Formation of Grignard homocoupled product **III** (mmol) with respect to the added equivalent of Grignard reagent.

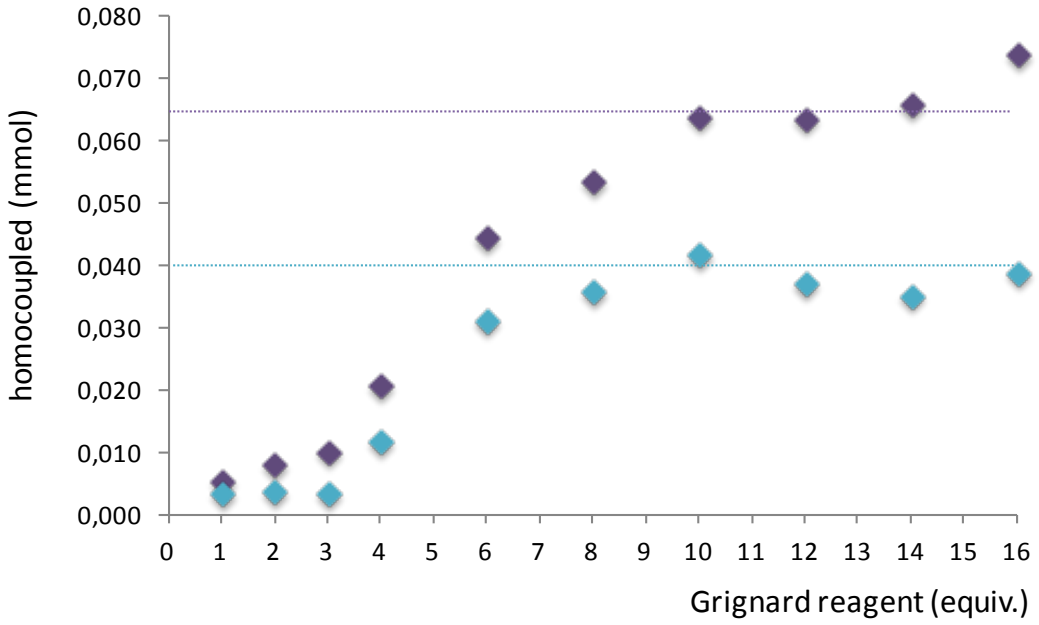
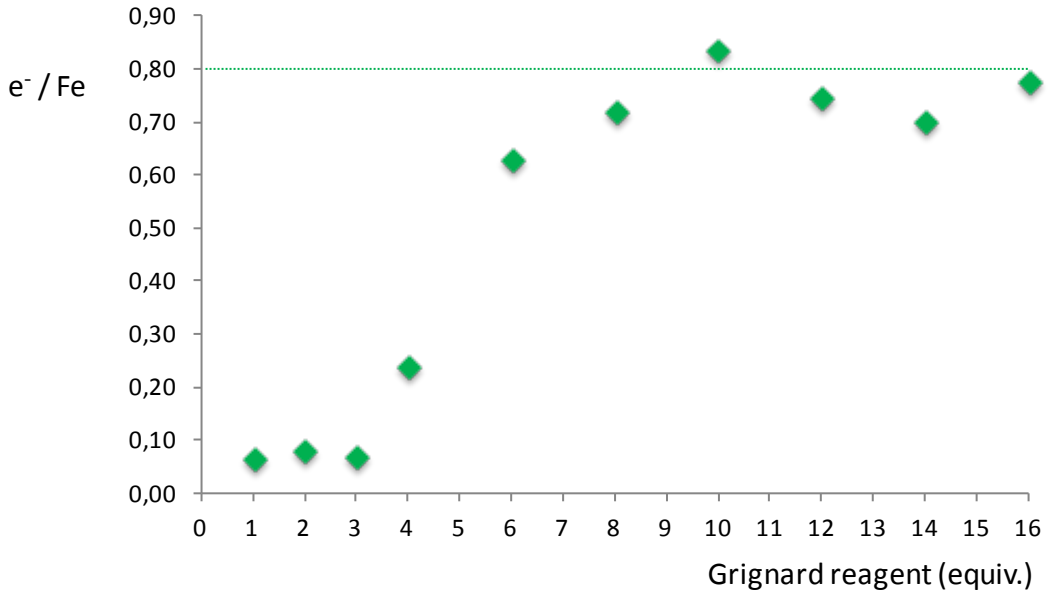
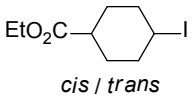


Figure S2. Electrons that are intervening in the reaction per mmol of iron and the equivalent of Grignard reagent



4. Compound Characterization

***trans*- and *cis*-Ethyl 4-iodocyclohexanecarboxylate:** Products were synthesized following the described procedure in the literature[5] however spectroscopy data did not match with those reported in the *reference 5*. 1H-imidazole (1.0 g, 14.91 mmol), triphenylphosphine (3.91 g, 14.91 mmol), and ethyl 4-hydroxycyclohexanecarboxylate (2.0 ml, 12.43 mmol) were combined in THF (10 ml) and cooled in an ice bath to 2-3 °C under argon. A freshly prepared solution of I_2 (3.78 g, 14.91 mmol) in THF (10 ml) was added dropwise maintaining the internal temperature below 10 °C. After the addition was complete, the reaction was allowed to warm to RT and stirred overnight. Then, 10 wt % aqueous solution of $NaHSO_3$ (5 mL) was added in one portion and Et_2O (5 mL) was added. The aqueous layer was extracted with Et_2O (3 × 5 mL) and the combined organic layer were washed with water and dried over $MgSO_4$. Solvent was evaporated under vacuum and products were purified by column chromatography in hexane/Et_2O 97:3 affording a 72:28 mixture of *trans*/*cis* isomers with a 50% combined yield and as colorless oil. The spectroscopy data for the ***trans*-isomer** were obtained from a pure sample: ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 4.63 (bs, 1H), 4.13 (q, *J* = 7.1 Hz, 2H), 2.45-2.32 (m, 1H), 2.18-1.88 (m, 4H), 1.84-1.64 (m, 4H), 1.24 (q, *J* = 7.1 Hz, 3H) ppm; ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 174.8 (C), 60.4 (CH_2), 41.6 (CH), 36.0 (2 × CH_2), 32.7 (CH), 26.3 (2 × CH_2), 14.3 (CH_3) ppm; MS (CI) *m/z* 283 (M+H), 155, 41. The spectroscopy data for the ***cis*-isomer** were extracted from a 34:66 mixture of the *cis*/*trans*-isomers. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 4.63 (bs, 1H), 4.06 (q, *J* = 7.1 Hz, 2H), 2.45-2.32 (m, 1H), 2.18-1.63 (m, 7H), 1.60-1.41 (m, 1H), 1.17 (q, *J* = 7.1 Hz, 3H) ppm; ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 175.3 (C), 60.4 (CH_2), 41.6 (CH), 39.0 (2 × CH_2), 30.8 (2 × CH_2), 28.4 (CH), 14.2 (CH_3) ppm; MS (EI) *m/z* 283 (M+H), 155, 41.



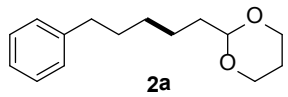
cis / *trans*

General procedure for the sp^3-sp^3 cross coupling reaction catalyzed by Iron:

Iron(II) acetate (2.5 mol%) and 1,3-dimesityl-1H-imidazol-3-ium chloride (6 mol%) were placed in Schlenk flask and dried under vacuum. Then dry THF (2 mL) was added and the mixture was heated at 50-60 ºC under Ar. A 0.5 M solution of alkylmagnesium bromide (30 mol%) was slowly added and the reaction mixture was stirred at 50-60 ºC for 20 min. After cooling at RT, alkyl iodide (0.407 mmol) was added followed by the slow addition of 0.5 M solution of alkylmagnesium bromide (1.5 mmol) with syringe pump (flow rate = 0.16 mL/h). After the addition of the Grignard reagent, the reaction was stirred for 8 h and then, hydrolyzed with saturated aqueous NH4Cl solution (5 mL). The aqueous phase was extracted with DCM (3 × 5 mL) and the combined organic

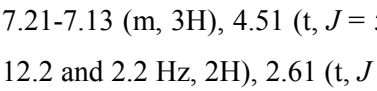
phases were dried over MgSO4. The solvent was evaporated under vacuum and the product was purified by column chromatography in silica-gel.

2-(5-Phenylpentyl)-1,3-dioxane (2a): Product was obtained following the general procedure and using (3-iodopropyl)benzene as starting iodide. The compound **2a** was purified by column chromatography (hexane/EtOAc 95:5) as colorless oil with a 70% yield. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.32-7.24 (m, 2H), 7.21-7.13 (m, 3H), 4.51 (t, *J* = 5.1 Hz, 1H), 4.10 (ddd, *J* = 10.7, 5.0 and 1.1 Hz, 2H), 3.76 (dt, *J* = 12.2 and 2.2 Hz, 2H), 2.61 (t, *J* = 7.3 Hz, 2H), 2.18-1.98 (m, 1H), 1.71-1.54 (m, 4H), 1.49-1.25 (m, 5H) ppm; ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 142.9 (C), 128.5 (2 × CH), 128.3 (2 × CH), 125.7 (CH), 102.5 (CH), 67.0 (2 × CH_2), 35.9 (CH_2), 35.3 (CH_2), 31.5 (CH_2), 29.2 (CH_2), 26.0 (CH_2), 23.9 (CH_2) ppm; HRMS (EI) calcd. for $C_{15}H_{21}O_2$ [M-H]: 233.1542; Found: 233.1545; Anal. calcd. for $C_{15}H_{21}O_2$: C, 76.88; H, 9.46; Found: C, 76.79; H, 9.39.



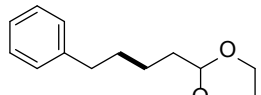
2a

2-[5-(4-Methoxyphenyl)pentyl]-1,3-dioxane (2b): Product was obtained following the general procedure and using 1-(3-iodopropyl)-4-methoxybenzene as starting iodide. The compound was purified by column chromatography in silica-gel (hexane/EtOAc 90:10) as colorless oil with 67% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.08 (d, *J* = 8.7 Hz, 2H), 6.82 (d, *J* = 8.7 Hz, 2H), 4.50 (t, *J* = 5.1 Hz, 1H), 4.09 (dd, *J* = 10.7 and 4.7 Hz, 2H), 3.78 (s, 3H), 3.75 (td, *J* = 12.3 and 2.5 Hz, 2H), 2.54 (t, *J* = 7.5 Hz, 2H), 2.16-1.97 (m, 1H), 1.65-1.51 (m, 4H), 1.45-1.25 (m, 5H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.8 (C), 135.0 (C), 129.4 (2 × CH), 113.8 (2 × CH), 102.5 (CH), 67.1 (2 × CH_2), 55.4 (CH_3), 35.3 (CH_2), 35.0 (CH_2), 31.7 (CH_2), 29.2 (CH_2), 26.0 (CH_2), 23.9 (CH_2) ppm; HRMS (EI) calcd. for $C_{16}H_{24}O_3$: 264.1725; Found: 264.1726; Anal. calcd. for $C_{16}H_{24}O_3$: C, 72.69; H, 9.15; Found C, 72.70; H, 9.01.



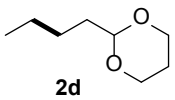
2b

2-(4-Phenylbuty)-1,3-dioxane (2c): Product was obtained following the general procedure and using (2-iodoethyl)benzene as starting iodide. The compound **2c** was purified by column chromatography (hexane/EtOAc 95:5) as colorless oil with a 66% yield. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.32-7.24 (m, 2H), 7.21-7.14 (m, 3H), 4.52 (t, *J* = 5.1 Hz, 1H), 4.10 (ddd, *J* = 12.0, 5.0 and 1.1 Hz, 2H), 3.75 (dt, *J* = 12.0 and 2.5 Hz, 2H), 2.62 (t, *J* = 7.6 Hz, 2H), 2.19-1.98 (m, 1H), 1.70-1.58 (m, 4H), 1.52-1.39 (m, 2H), 1.38-1.26 (m, 1H) ppm; ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 142.7 (C), 128.5 (2 × CH), 128.4 (2 × CH), 125.7 (CH), 102.5 (CH), 67.0 (2 × CH_2), 36.0 (CH_2), 35.2 (CH_2), 31.5 (CH_2), 26.0 (CH_2), 23.9 (CH_2) ppm; HRMS (EI) calcd. for $C_{14}H_{19}O_2$ [M-H]: 219.1385; Found: 219.1386; Anal. calcd. for $C_{14}H_{20}O_2$: C, 76.33; H, 9.15; Found: C, 76.12; H, 9.13.



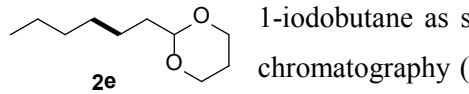
2c

2-Butyl-1,3-dioxane (2d): Product was obtained following the general procedure and using 1-iodoethane as starting iodide. The compound **2d** was purified by column chromatography (pentane/Et_2O 95:5) as volatile colorless oil with a 59% yield. ^{1}H-NMR (300 MHz, CD_2Cl_2) δ: 4.47 (t, *J* = 5.6 Hz, 1H), 4.04 (ddd, *J* = 11.8, 4.9 and 1.3 Hz, 2H), 3.72 (dt, *J* = 12.3 and 2.4 Hz, 2H), 2.08-1.90 (m, 1H), 1.59-1.47 (m, 2H), 1.39-1.22 (m, 5H), 0.89 (t, *J* = 6.8 Hz, 3H) ppm; ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 103.0 (CH), 67.4 (2 × CH_2), 35.5 (CH_2), 26.8 (CH_2), 26.6 (CH_2), 23.2 (CH_2), 14.3 (CH_3) ppm; HRMS (EI) calcd. for $C_8H_{15}O_2$ [M-H]: 143.1072; Found: 143.1071.



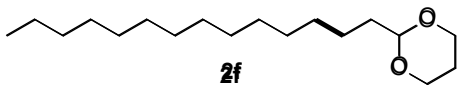
2d

2-Hexyl-1,3-dioxane (2e): Product was obtained following the general procedure and using 1-iodobutane as starting iodide. The compound **2e** was purified by column chromatography (hexane/EtOAc 95:5) as colorless oil with a 60% yield. ^{1}H-NMR (300 MHz, CD_2Cl_2) δ: 4.50 (t, *J* = 5.3 Hz, 1H), 4.09 (ddd, *J* = 11.9, 4.7 and 1.1 Hz, 2H), 3.75 (dt, *J* = 12.4 and 2.6 Hz, 2H), 2.16-1.97 (m, 1H), 1.64-1.52 (m, 2H), 1.43-1.19 (m, 9H), 0.87 (t, *J* = 7.1 Hz, 3H) ppm; ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 102.6 (CH), 67.0 (2 × CH_2), 35.4 (CH_2), 31.9 (CH_2), 29.3 (CH_2), 26.0 (CH_2), 24.1 (CH_2), 22.7 (CH_2), 14.2 (CH_3) ppm; HRMS (EI) calcd. for $C_{10}H_{19}O_2$ [M-H]: 172.1385; Found: 172.1392; Anal. calcd. for $C_{10}H_{20}O_2$: C, 69.72; H, 11.70; Found: C, 69.61; H, 11.34.



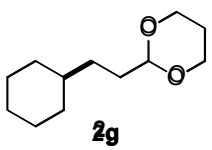
2e

2-Tetradecyl-1,3-dioxane (2f): Product was obtained following the general procedure and using 1-iodododecane as starting iodide. The compound was purified by column chromatography in silica-gel (hexane/EtOAc 97:3) as pale yellow oil (solid below 25 ºC) with 60% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.50 (t, *J* = 5.1 Hz, 1H), 4.09 (dd, *J* = 11.3 and 4.8 Hz, 2H), 3.75 (td, *J* = 12.3 and 2.5 Hz, 2H), 2.17-1.97 (m, 1H), 1.63-1.53 (m, 2H), 1.42-1.17 (m, 25H), 0.88 (t, *J* = 6.7 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 102.7 (CH), 67.1 (2 × CH_2), 35.4 (CH_2), 32.1 (CH_2), 29.8 (5 × CH_2), 29.7 (3 × CH_2), 29.5 (CH_2), 26.0 (CH_2), 24.1 (CH_2), 22.8 (CH_2), 14.3 (CH_3) ppm; HRMS (EI) calcd. for $C_{18}H_{36}O_2$: 284.2715; Found: 284.2710; Anal. calcd. for $C_{18}H_{36}O_2$: C, 76.00; H, 12.76; Found C, 76.36; H, 12.26.



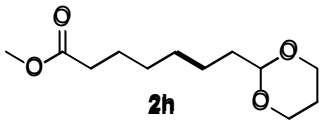
2f

2-(2-Cyclohexylethyl)-1,3-dioxane (2g): Although this compound was previously described in the literature,[16] some controversial spectroscopy data were found. Product was obtained following the general procedure using iodocyclohexane as starting iodide. The compound was purified by column chromatography in silica-gel (hexane/EtOAc 95:5) as colorless oil with 88% yield. ^{1}H NMR (300 MHz,

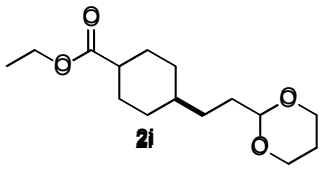


2g

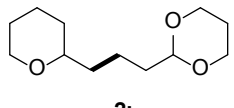
$CDCl_3$) δ 4.48 (t, *J* = 5.2 Hz, 1H), 4.09 (dd, *J* = 11.8 and 5.0 Hz, 2H), 3.75 (td, *J* = 12.3 and 2.3 Hz, 2H), 2.16-1.98 (m, 1H), 1.76-1.52 (m, 7H), 1.38-1.07 (m, 7H), 0.95-0.77 (m, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 103.0 (CH), 67.1 (2 × CH_2), 37.7 (CH), 33.4 (2 × CH_2), 32.8 (CH_2), 31.6 (CH_2), 26.8 (CH_2), 26.5 (2 × CH_2), 26.0 (CH_2) ppm; HRMS (EI) calcd. for $C_{12}H_{22}O_2$: 198.1620; Found: 198.1579; Anal. calcd. for $C_{12}H_{22}O_2$: C, 72.68; H, 11.18; Found C, 72.63; H, 11.22.

Methyl 7-(1,3-dioxan-2-yl)heptanoate (2h): Product was obtained following the general procedure and using methyl 5-iodovalerate as starting iodide. The compound was purified by column chromatography in silica-gel (hexane/EtOAc 90:10) as colorless oil with 57% yield. 
2h

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.49 (t, *J* = 5.1 Hz, 1H), 4.09 (dd, *J* = 10.7 and 5.0 Hz, 2H), 3.75 (td, *J* = 12.4 and 2.4 Hz, 2H), 3.65 (s, 3H), 2.29 (t, *J* = 7.5 Hz, 2H), 2.14-1.98 (m, 1H), 1.70-1.50 (m, 4H), 1.45-1.23 (m, 7H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.4 (C), 102.5 (CH), 67.0 (2 × CH_2), 51.6 (CH_3), 35.3 (CH_2), 34.2 (CH_2), 29.2 (CH_2), 29.2 (CH_2), 26.0 (CH_2), 25.0 (CH_2), 23.9 (CH_2) ppm; HRMS (EI) calcd. for $C_{12}H_{22}O_4$: 230.1518; Found: 230.1506; Anal. calcd. for $C_{12}H_{22}O_4$: C, 62.58; H, 9.63; Found C, 62.99; H, 6.56.

***cis*- and *trans*-Ethyl 4-[2-(1,3-dioxan-2-yl)ethyl]cyclohexanecarboxylate 2i:** Products were obtained following the general procedure and using a 34:66 mixture of both isomers of ethyl 4-iodocyclohexanecarboxylate as starting iodides. Compounds were purified by column chromatography in silica-gel (hexane/EtOAc 90:10) as colorless oil with 65% combined yield (22:78 mixture of both isomers). 
2i

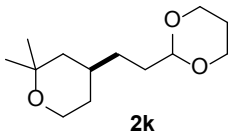
^{1}H NMR (300 MHz, $CDCl_3$, signals of major isomer) δ: 4.46 (t, *J* = 5.1 Hz, 1H), 4.14-4.03 (m, 4H), 3.73 (td, *J* = 12.4 and 1.8 Hz, 2H), 2.25-1.87 (m, 4H), 1.86-1.73 (m, 2H), 1.66-1.14 (m, 11H), 1.00-0.80 (m, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$, signals of major isomer) δ: 176.4 (C), 102.7 (CH), 67.1 (2 × CH_2), 60.2 (CH_2), 43.7 (CH_2), 36.9 (CH_2), 32.8 (CH_2), 32.3 (2 × CH_2), 31.3 (CH_2), 29.1 (2 × CH_2), 26.0 (CH_2), 14.4 (CH_3) ppm; HRMS (EI) calcd. for $C_{15}H_{25}O_4$ [M-H]: 269.1753; Found: 269.1744.

2-[3-(Tetrahydro-2H-pyran-2-yl)propyl]-1,3-dioxane (2j): Product was obtained following the general procedure and using 2-(iodomethyl)tetrahydro-2H-pyran as starting iodide. The compound was purified by column chromatography (hexane/EtOAc 80:20) as colorless oil with a 63% yield. 
2j

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 4.49 (t, *J* = 5.0 Hz, 1H), 4.07 (ddd, *J* = 11.8, 5.0 and 1.2 Hz, 2H), 3.97-3.88 (m, 1H), 3.73 (dt, *J* = 12.5 and 2.6 Hz, 2H), 3.37 (dt, *J* = 11.3 and 2.6 Hz, 1H), 3.25-3.12 (m, 1H), 2.14-1.95 (m, 1H), 1.82-1.73 (m, 1H), 1.62-1.13 (m, 12H) ppm; ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 102.5 (CH),

77.8 (CH), 68.6 (CH_2), 67.0 (2 × CH_2), 36.5 (CH_2), 35.3 (CH_2), 32.0 (CH_2), 26.3 (CH_2), 26.0 (CH_2), 23.7 (CH_2), 20.2 (CH_2) ppm; HRMS (EI) calcd. for $C_{12}H_{21}O_3$ [M-H]: 213.1491; Found: 213.1484; Anal. Calcd. for $C_{13}H_{24}O_3$: C, 68.38; H, 10.59; Found: C, 68.25; H, 10.45.

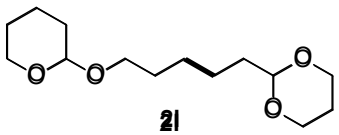
2-[2-(2,2-Dimethyltetrahydro-2H-pyran-4-yl)ethyl]-1,3-dioxane (2k): Product was obtained following the general procedure and using 4-iodo-2,2-dimethyltetrahydro-2H-pyran as starting iodide. The compound was purified by column chromatography (hexane/EtOAc 80:20) as colorless oil with an 83% yield.



2k

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 4.49 (t, *J* = 5.0 Hz, 1H), 4.10 (dd, *J* = 11.4 and 5.0 Hz, 2H), 3.82-3.56 (m, 4H), 2.18-1.97 (m, 1H), 1.69-1.47 (m, 5H), 1.39-1.23 (m, 3H), 1.92-0.97 (m, 2H), 1.19 (s, 3H), 1.18 (s, 3H) ppm; ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 102.5 (CH), 71.7 (CH), 67.0 (2 × CH_2), 61.7 (CH_2), 43.7 (CH_2), 32.8 (CH_2), 32.3 (CH), 31.8 (CH_2), 31.4 (CH_3), 31.1 (CH_2), 25.9 (CH_2), 22.0 (CH_2) ppm; HRMS (EI) calcd. for $C_{13}H_{23}O_3$ [M-H]: 227.1647; Found: 227.1657; Anal. calcd. for $C_{12}H_{22}O_3$: C, 67.26; H, 10.35; Found: C, 67.16; H, 10.01.

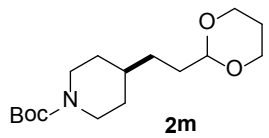
2-[5-(Tetrahydro-2H-pyran-2-yloxy)pentyl]-1,3-dioxane (2l): Product was obtained following the general procedure and using 2-(3-iodopropoxy)tetrahydro-2H-pyran as starting iodide. The compound was purified by column chromatography in silica-gel (hexane/EtOAc 80:20) as colorless oil with 54% yield.



2l

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.56 (t, *J* = 3.5 Hz, 1H), 4.51 (t, *J* = 5.1 Hz, 1H), 4.09 (dd, *J* = 11.0 and 4.9 Hz, 2H), 3.91-3.81 (m, 1H), 3.80-3.67 (m, 3H), 3.54-3.44 (m, 1H), 3.38 (dt, *J* = 9.6 and 6.6 Hz, 1H), 2.15-1.99 (m, 1H), 1.86-1.30 (m, 15H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 102.5 (CH), 99.0 (CH), 67.7 (CH_2), 67.0 (2 × CH_2), 62.5 (CH_2), 35.3 (CH_2), 30.9 (CH_2), 29.8 (CH_2), 26.3 (CH_2), 26.0 (CH_2), 25.7 (CH_2), 24.0 (CH_2), 19.8 (CH_2) ppm; HRMS (EI) calcd. for $C_{14}H_{25}O_4$ [M-H]: 257.1753; Found: 257.1743; Anal. calcd. for $C_{14}H_{26}O_4$: C, 65.09; H, 10.14; Found C, 64.73; H, 9.88.

***tert*-Butyl 4-[2-(1,3-dioxan-2-yl)ethyl]piperidine-1-carboxylate (2m)**: Product was obtained following the general procedure and using *tert*-butyl 4-iodopiperidine-1-carboxylate as starting iodide. The compound was purified by column chromatography (hexane/EtOAc 80:20) as colorless oil with a 67% yield.

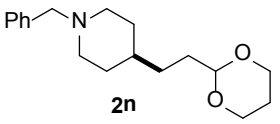


2m

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 4.49 (t, *J* = 5.0 Hz, 1H), 4.15-3.95 (m, 4H), 3.75 (dt, *J* = 12.3 and 2.3 Hz, 2H), 2.65 (t, *J* = 12.3 Hz, 2H), 2.19-1.97 (m, 1H), 1.71-1.52 (m, 5H), 1.51-1.23 (m, 3H), 1.44 (s, 9H), 1.16-0.97 (m, 2H) ppm; ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 154.9 (C), 102.5 (CH), 79.2

(C), 67.0 (2 × CH_2), 44.1 (2 × CH_2), 36.0 (CH), 32.5 (CH_2), 32.1 (CH_2), 30.6 (CH_2), 28.5 (2 × CH_3), 25.9 (CH_2) ppm; HRMS (EI) calcd. for $C_{11}H_{20}NO_2$ [M-CO_2tBu]: 198.1494; Found: 198.1497; Anal. calcd. for $C_{16}H_{29}NO_4$: C, 64.18; H, 9.76; N, 4.68; Found: C, 64.09; H, 9.51; N, 4.33.

4-[2-(1,3-Dioxan-2-yl)ethyl]-1-benzylpiperidine (2n): Product was obtained following the general procedure and using 1-benzyl-4-iodopiperidine as starting iodide. The compound was purified by column chromatography (hexane/EtOAc/Et_3N 80:20:1) as colorless oil with a 78% yield. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.34-7.17 (m, 5H), 4.48 (t, *J* = 5.0 Hz, 1H), 4.09 (dd, *J* = 11.2 and 4.7 Hz, 2H), 3.74 (dt, *J* = 12.1 and 2.1 Hz, 2H), 3.47 (s, 2H), 2.85 (d, *J* = 11.2 Hz, 2H), 2.16-1.97 (m, 1H), 1.91 (t, *J* = 10.6 Hz, 2H), 1.72-1.50 (m, 4H), 1.40-1.12 (m, 6H) ppm; ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 138.7 (C), 129.3 (2 × CH), 128.2 (2 × CH), 126.9 (CH), 102.7 (CH), 67.0 (2 × CH_2), 63.6 (CH_2), 54.0 (2 × CH_2), 35.8 (CH), 32.8 (CH_2), 32.4 (2 × CH_2), 30.8 (CH_2), 25.9 (CH_2) ppm; HRMS (EI) calcd. for $C_{18}H_{26}NO_2$ [M-H]: 288.1964; Found: 288.1963.

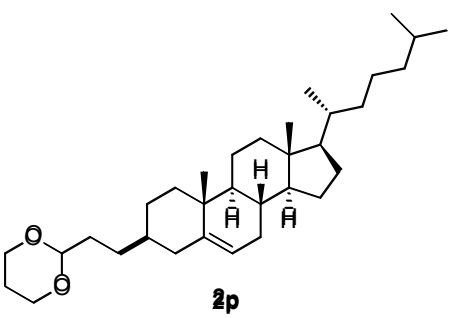


2n

2-[4-(1,3-Dioxan-2-yl)butyl]-1-tosyl-1H-indole (2o): Product was obtained following the general procedure and using 2-(2-iodoethyl)-1-tosyl-1H-indole as starting iodide. The compound was purified by column chromatography (hexane/Acetone 90:10) as pale yellow oil with a 36% yield. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.16 (d, *J* = 8.3 Hz, 1H), 7.60 (d, *J* = 8.3 Hz, 2H), 7.40 (d, *J* = 8.3 Hz, 1H), 7.28-7.13 (m, 4H), 6.38 (s, 1H), 4.54 (t, *J* = 5.2 Hz, 1H), 4.11 (dd, *J* = 11.4 and 5.2 Hz, 2H), 3.76 (dt, *J* = 12.1 and 1.7 Hz, 2H), 2.98 (t, *J* = 7.6 Hz 2H), 2.33 (s, 3H), 2.12-1.99 (m, 1H), 1.84-1.44 (m, 6H), 1.39-1.23 (m, 1H) ppm; ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 144.7 (C), 142.4 (C), 137.4 (C), 136.4 (C), 130.0 (C), 129.9 (2 × CH), 126.4 (2 × CH), 123.9 (CH), 123.6 (CH), 120.2 (CH), 115.0 (CH), 108.8 (CH), 102.3 (CH), 67.0 (2 × CH_2), 35.1 (CH_2), 29.1 (CH_2), 28.9 (CH_2), 26.0 (CH_2), 23.9 (CH_2), 21.7 (CH_3) ppm; HRMS (EI) calcd. for $C_{23}H_{27}NO_4S$ [M]: 413.1661; Found: 413.1677.

2o

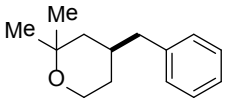
2-(2-Cholesterylethyl)-1,3-dioxane (2p): Product was obtained following the general procedure and using cholesteryl iodide as starting iodide. The compound was purified by column chromatography in silica-gel (hexane/EtOAc 97:3) as white solid with 75% yield. Mp: 114-116 °C (acetone); $[\alpha]_D^{22}$ = -19 (*c* 0.66, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCL_3$) δ 5.30-5.23 (m, 1H), 4.49 (t, *J* = 5.2 Hz, 1H), 4.10 (dd, *J* = 10.7 and 5.0 Hz,



2p

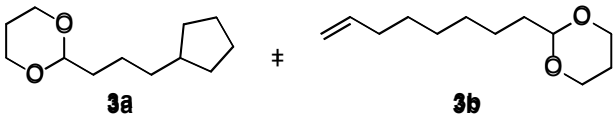
2H), 3.75 (td, *J* = 12.4 and 2.5 Hz, 2H), 2.17-0.82 (m, 45H), 0.67 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.5 (C), 119.4 (CH), 102.8 (CH), 67.1 (2 × CH_2), 57.0 (CH), 56.3 (CH), 50.7 (CH), 42.5 (C), 40.0 (CH_2), 39.7 (CH_2), 39.7 (2 × CH_2), 39.4 (CH), 37.4 (C), 36.4 (CH_2), 36.0 (CH), 32.8 (CH_2), 32.1 (CH and CH_2), 31.4 (CH_2), 29.2 (CH_2), 28.4 (CH_2), 28.2 (CH), 26.0 (CH_2), 24.4 (CH_2), 24.0 (CH_2), 23.0 (CH_3), 22.7 (CH_3), 21.1 (CH_2), 19.6 (CH_3), 18.9 (CH_3), 12.0 (CH_3) ppm; HRMS (EI) calcd. for $C_{33}H_{56}O_2$: 484.4280; Found: 484.4267; Anal. calcd. for $C_{33}H_{56}O_2$: C, 81.76; H, 11.64; Found C, 82.18; H, 11.21.

4-Benzyl-2,2-dimethyltetrahydro-2H-pyran (2q): Product was obtained following the general procedure and using 4-iodo-2,2-dimethyltetrahydro-2H-pyran as starting iodide and benzylmagnesium chloride (0.5 M in THF) as Grignard reagent. The compound was purified by column chromatography in silica-gel (hexane/EtOAc 97:3) as colorless oil with 52% yield. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.33-7.25 (m, 2H), 7.24-7.11 (m, 3H), 3.72 (ddd, *J* = 11.9, 5.3 and 1.6 Hz, 1H), 3.60 (dt, *J* = 11.9 and 1.9 Hz, 1H), 2.49 (d, *J* = 7.4 Hz, 2H), 2.01-1.83 (m, 1H), 1.63-1.45 (m, 2H), 1.29-1.06 (m, 2H), 1.20 (s, 3H), 1.16 (s, 3H) ppm; ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 140.3, 129.2, 128.3, 126.0, 71.8, 61.7, 44.0, 43.6, 33.4, 32.7, 31.9, 22.0 ppm; HRMS (EI) calcd. for $C_{14}H_{20}O$ [M]: 204.1514; Found: 204.1518.



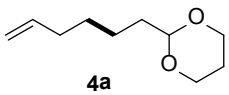
2q

2-(3-Cyclopentylpropyl)-1,3-dioxane (3a) and 2-(oct-7-enyl)-1,3-dioxane (3b): Products were obtained following the general procedure as a 1:1.4 mixture of **3a** and **3b** using 6-iodohex-1-ene as starting iodide. The compounds were purified by column chromatography in silica-gel (hexane/EtOAc 95:5) as colorless oil with 36% combined yield. ^{1}H NMR (300 MHz, $CDCl_3$, **3a** + **3b**) δ 5.80 (ddt, *J* = 16.9, 10.2 and 6.7 Hz, 1H), 4.95 (m, 2H), 4.50 (t, *J* = 5.1 Hz, 2H), 4.10 (dd, *J* = 11.0 and 4.9 Hz, 4H), 3.75 (td, *J* = 12.3 and 2.1 Hz, 4H), 2.19-0.98 (m, 31H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$, **3a** + **3b**) δ 139.2 (CH), 114.1 (CH_2), 102.5 (CH), 102.5 (CH), 66.9 (4 × CH_2), 40.1(CH), 36.1 (CH_2), 35.5 (CH_2), 35.2 (CH_2), 33.7 (CH_2), 32.7 (2 × CH_2), 29.3(CH_2), 29.0 (CH_2), 28.8 (CH_2), 25.9 (2 × CH_2), 25.2 (2 × CH_2), 23.9 (CH_2), 23.2(CH_2) ppm; HRMS (EI) calcd. for $C_{12}H_{22}O_2$ (**3a**): 198,1620; Found: 198.1560 HRMS (EI) calcd. for $C_{12}H_{22}O_2$ (**3b**): 198.1620; Found: 198.1610.



3a **3b**

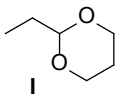
2-(Hex-5-en-1-yl)-1,3-dioxane 4a: Product was obtained following the general procedure and using (iodomethyl)cyclopropane as starting iodide. The compound was purified by column chromatography (pentane/Et_2O 95:5) as volatile colorless



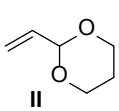
4a

oil with a 63% yield. ^{1}H-NMR (300 MHz, acetone-d_6) δ: 5.94-5.74 (m, 1H), 5.03 (dd, J = 17.2 and 1.8 Hz, 1H), 4.95 (dd, J = 10.2 and 1.0 Hz, 1H), 4.57-4.50 (m, 1H), 4.04 (ddd, J = 11.4, 4.8 and 1.0 Hz, 2H), 3.76 (dt, J = 12.0 and 1.9 Hz, 2H), 2.14-1.86 (m, 1H), 1.62-1.28 (m, 7H) ppm; ^{13}C-NMR (75 MHz, acetone-d_6) δ: 139.7 (CH), 114.8 (CH_2), 102.8 (CH), 67.2 (2 × CH_2), 35.9 (CH_2), 34.4 (CH_2), 29.6 (CH_2), 26.7 (CH_2), 24.2 (CH_2) ppm; HRMS (EI) calcd. for $C_{10}H_{17}O_2$ [M-H]: 169.1229; Found: 169.1226.

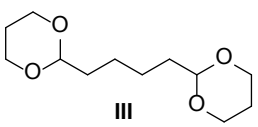
2-Ethyl-1,3-dioxane[12] I: $MgSO_4$ (2 g) and 4-methylbenzenesulfonic acid monohydrate (26 mg, 0.13 mmol) were added to a solution of acetaldehyde (0.8 g, 13.77 mmol) and 1,3-propanediol (1.05 g, 13.77 mmol) in CH_2Cl_2 (10 mL). Reaction was stirred for 48 h at RT and filtered through a short pad of Celite. The filtrate was carefully evaporated and product was purified by column chromatography (pentane/Et_2O 95:5) affording the product as highly volatile colorless oil with a 50% yield. ^{1}H-NMR (300 MHz, acetone-d_6) δ: 4.44 (t, J = 4.8 Hz, 1H), 4.02 (ddd, J = 11.9, 5.0 and 1.3 Hz, 2H), 3.73 (dt, J = 11.9 and 2.1 Hz, 2H), 2.03-1.84 (m, 1H), 1.52 (dq, J = 7.8 and 5.2 Hz, 2H), 0.88 (t, J = 7.8 Hz, 3H) ppm; ^{13}C-NMR (75 MHz, acetone-d_6) δ: 103.9 (CH), 67.5 (2 × CH_2), 29.3 (CH_2), 27.0 (CH_2), 8.8 (CH_3) ppm; MS (EI) *m/z* 115 (M-H), 87 (100%).


I

2-Vinyl-1,3-dioxane[13] II: $MgSO_4$ (4 g) and 4-methylbenzenesulfonic acid monohydrate (71 mg, 0.37 mmol) were added to a solution of acryaldehyde (2.1 g, 37.5 mmol) and 1,3-propanediol (2.85 g, 37.5 mmol) in CH_2Cl_2 (20 mL). Reaction was stirred for 48 h at RT and filtered through a short pad of Celite. The filtrate was carefully evaporated and product was purified by column chromatography (pentane/Et_2O 95:5) affording the product as highly volatile colorless oil with a 32% yield. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 5.92-5.77 (m, 1H), 5.46 (d, J = 17.2 Hz, 1H), 5.29 (d, J = 10.7 Hz, 1H), 4.96 (d, J = 4.3 Hz, 1H), 4.16 (dd, J = 11.7 and 4.3 Hz, 2H), 3.84 (t, J = 12.0 Hz, 2H), 2.23-2.03 (m, 1H), 1.42-1.32 (m, 1H) ppm; ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 135.1 (CH), 118.5 (CH_2), 100.8 (CH), 67.1 (2 × CH_2), 25.9 (CH_2) ppm; MS (EI) *m/z* 113 (M-H), 87 (100%).


II

1,4-Di(1,3-dioxanyl)butane III: According to the procedure reported in literature,[15] compound **III** was synthesized as follows: A round bottom flask containing silver triflate (4.2 mg, 0.015 mmol) was purged three times with an argon/vacuum cycle. Dry THF (2 mL) was added to the flask followed by the addition of 1,2-dibromoethane (338 mg, 1.8 mmol). Reaction was stirred at RT under argon and then (1,3-dioxan-2-ylethyl)magnesium bromide (3 mL. 1.5 mmol) was slowly added (about 1 h). After stirring for 30 min, the reaction was hydrolyzed with a saturated solution of NH_4Cl (2 mL). Phases were


III

separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic phases were drier over $MgSO_4$ and solvent was evaporated under vacuum. The residue was purified by column chromatography (hexane/EtOAc 70:30) affording the product as colorless oil with a 38% yield. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 4.50 (t, J = 4.7 Hz, 2H), 4.09 (dd, J = 10.9 and 5.2 Hz, 4H), 3.74 (dt, J = 12. and 2.1 Hz, 4H), 2.16-1.95 (m, 2H), 1.65-1.51 (m, 4H), 1.44-1.25 (m, 6H) ppm; ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 102.2 (2 × CH), 66.8 (4 × CH_2), 35.1 (2 × CH_2), 25.8 (2 × CH_2), 23.9 (2 × CH_2) ppm; MS (EI) *m/z* 229 (M-H), 171, 127, 87 (100%).

5. References

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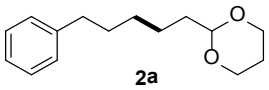
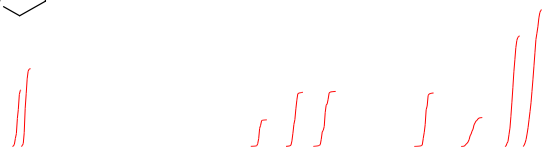
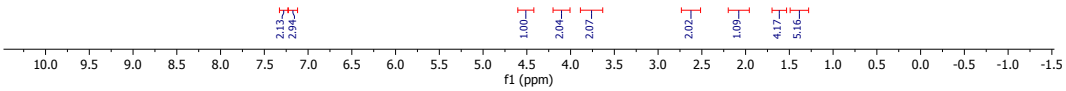
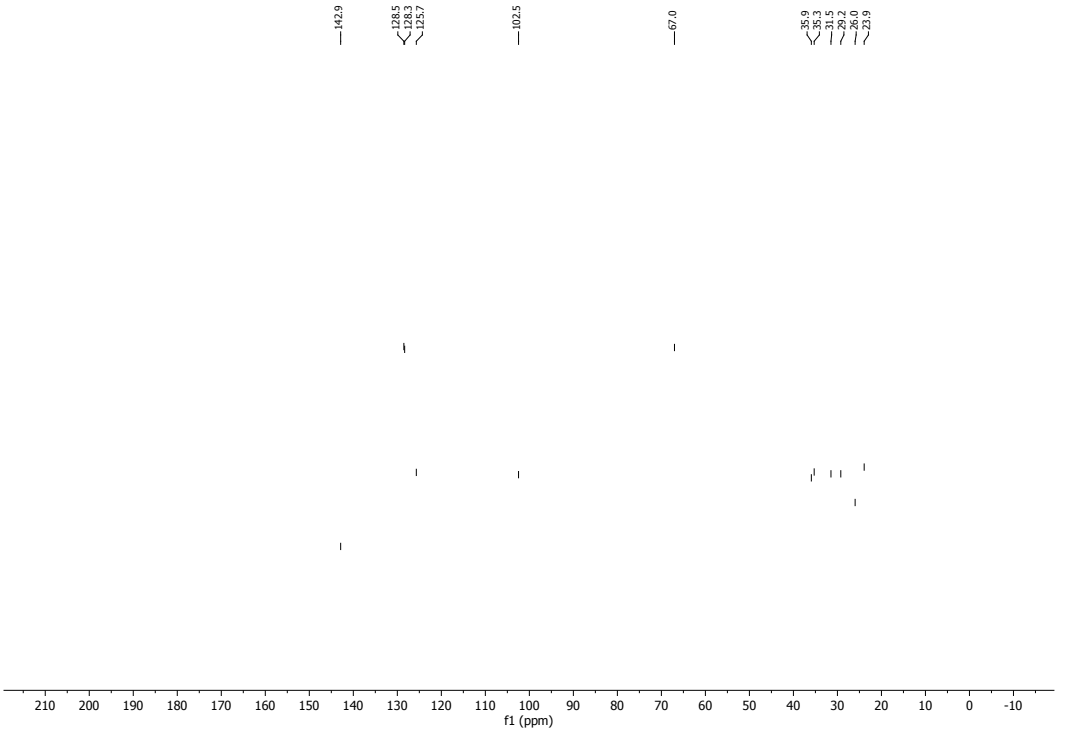
6. Copy of ^{1}H RMN and ^{13}C NMR.

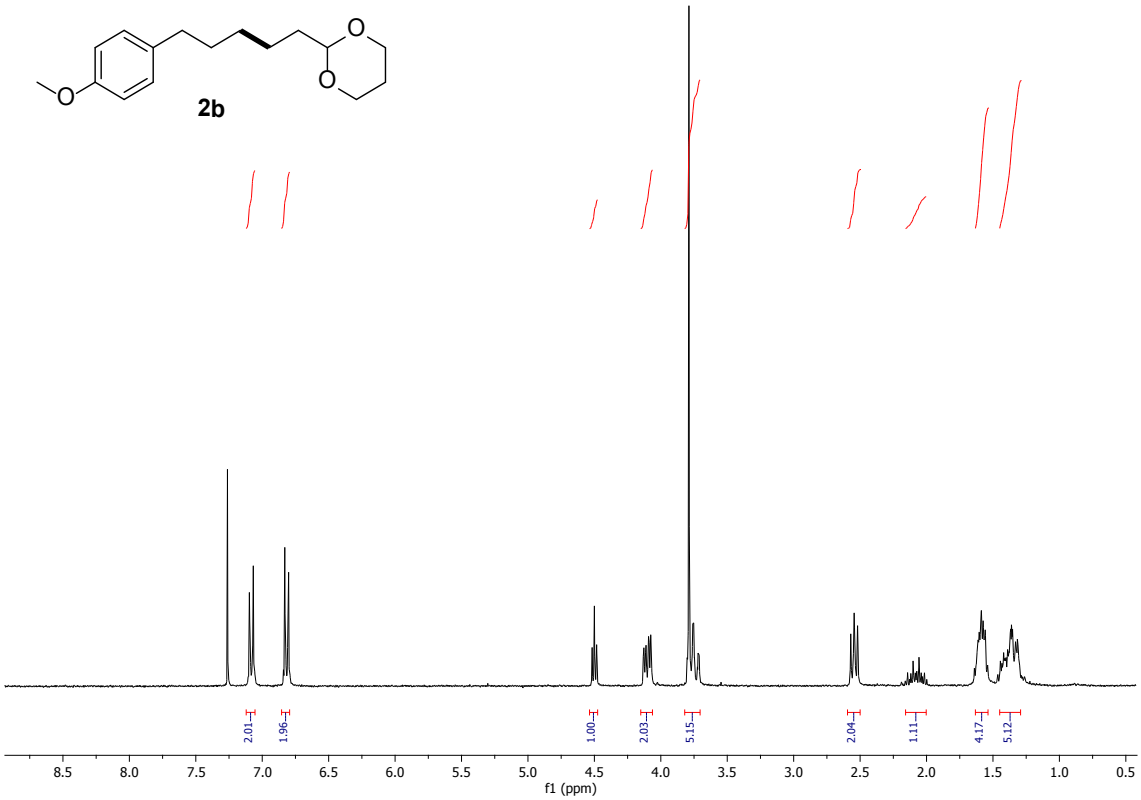


2a





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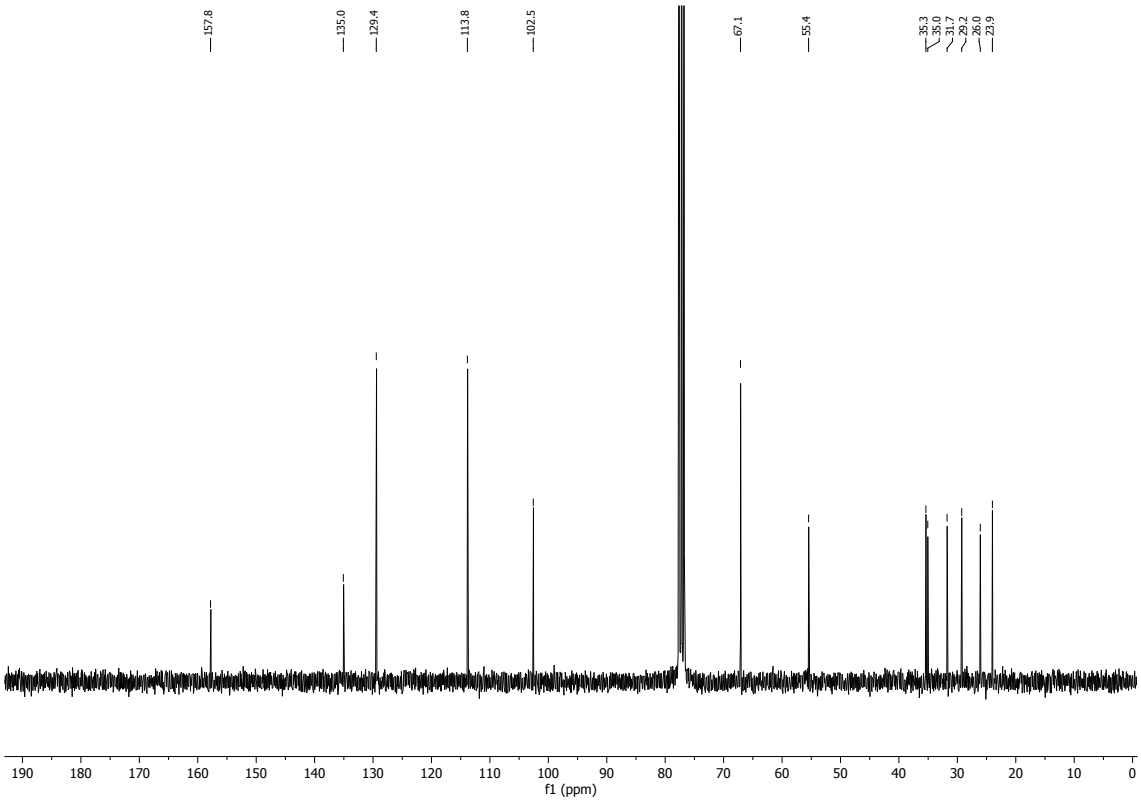
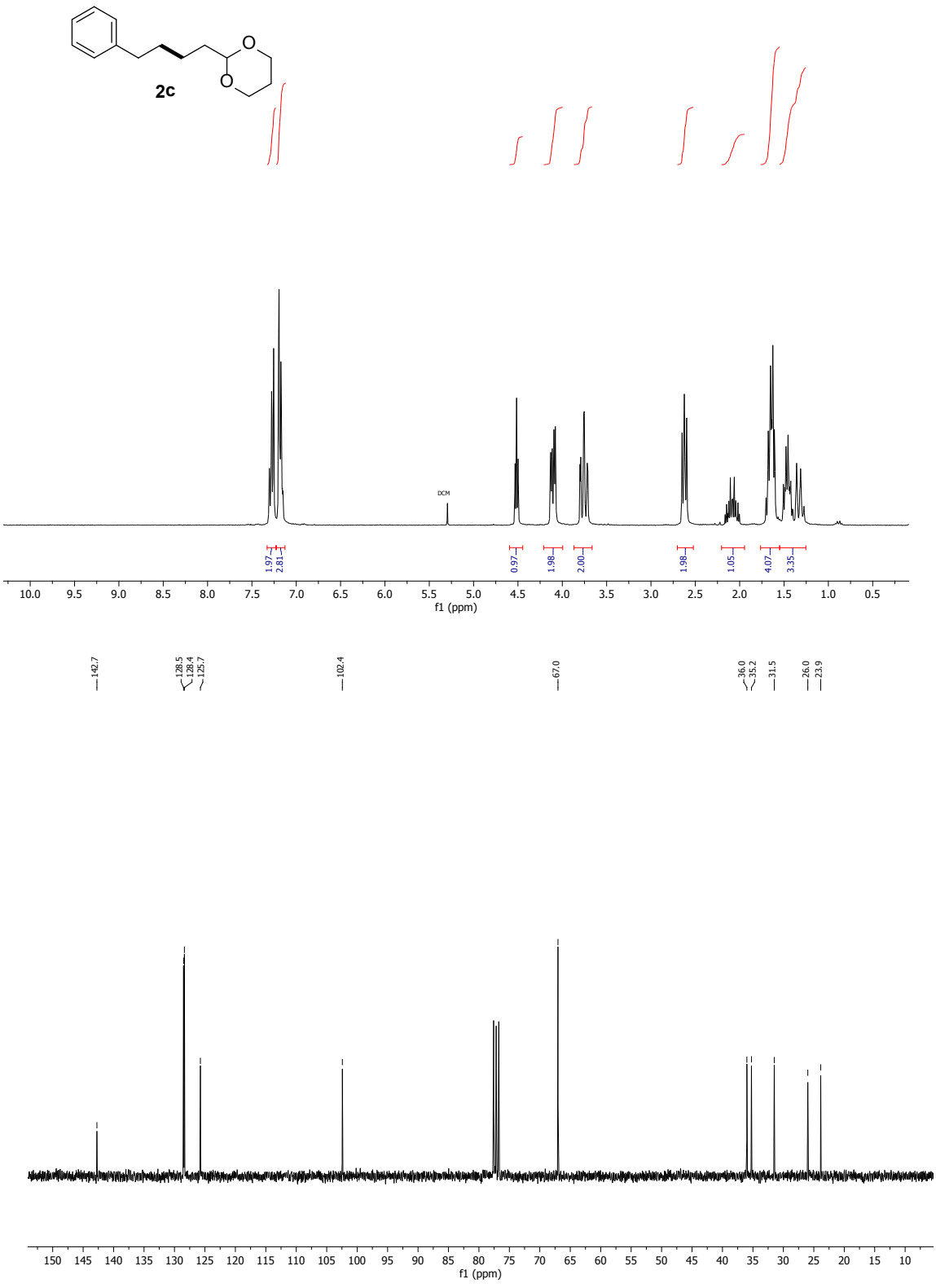
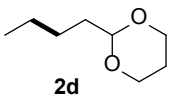
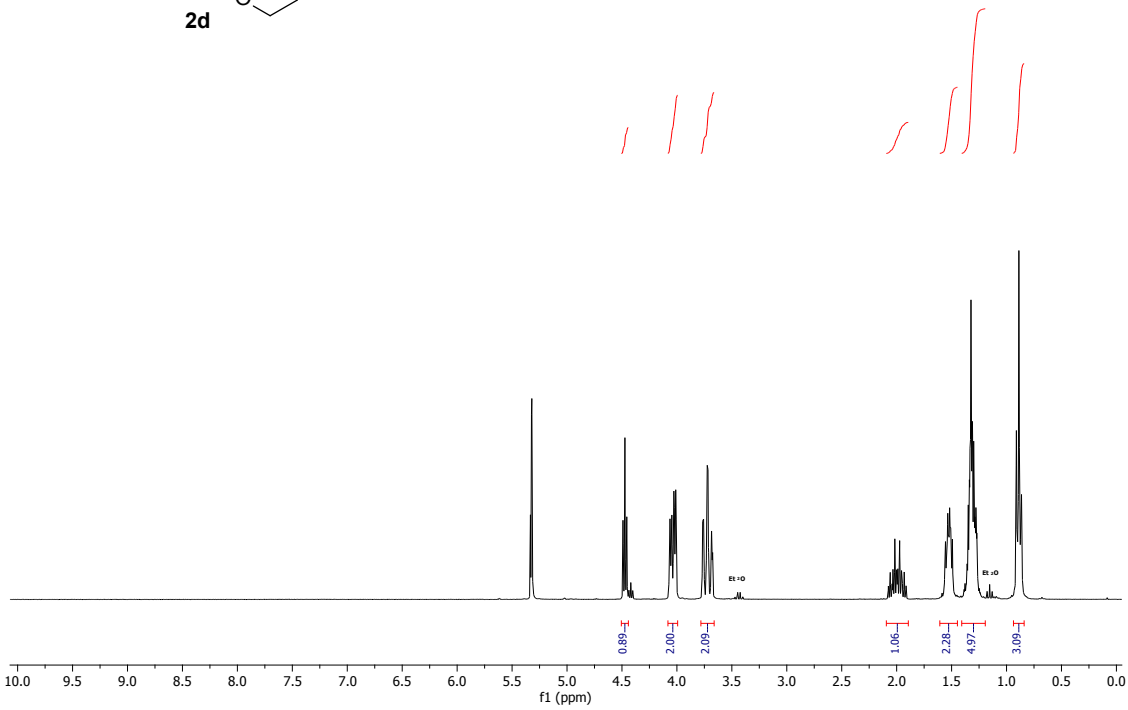
2.01
1.96
1.00
2.03
5.15
2.04
1.11
4.17
5.12
f1 (ppm)


157.8
135.0
129.4
113.8
102.5
67.1
55.4
35.3
35.0
31.7
29.2
26.0
23.9
f1 (ppm)


2c
O
O
DCM
1.97
2.81
0.97
1.98
2.00
1.98
1.05
4.07
3.35
f1 (ppm)
142.7
128.5
128.4
125.7
102.4
67.0
36.0
35.2
31.5
26.0
23.9
f1 (ppm)



2d


Et ₂O
Et ₂O
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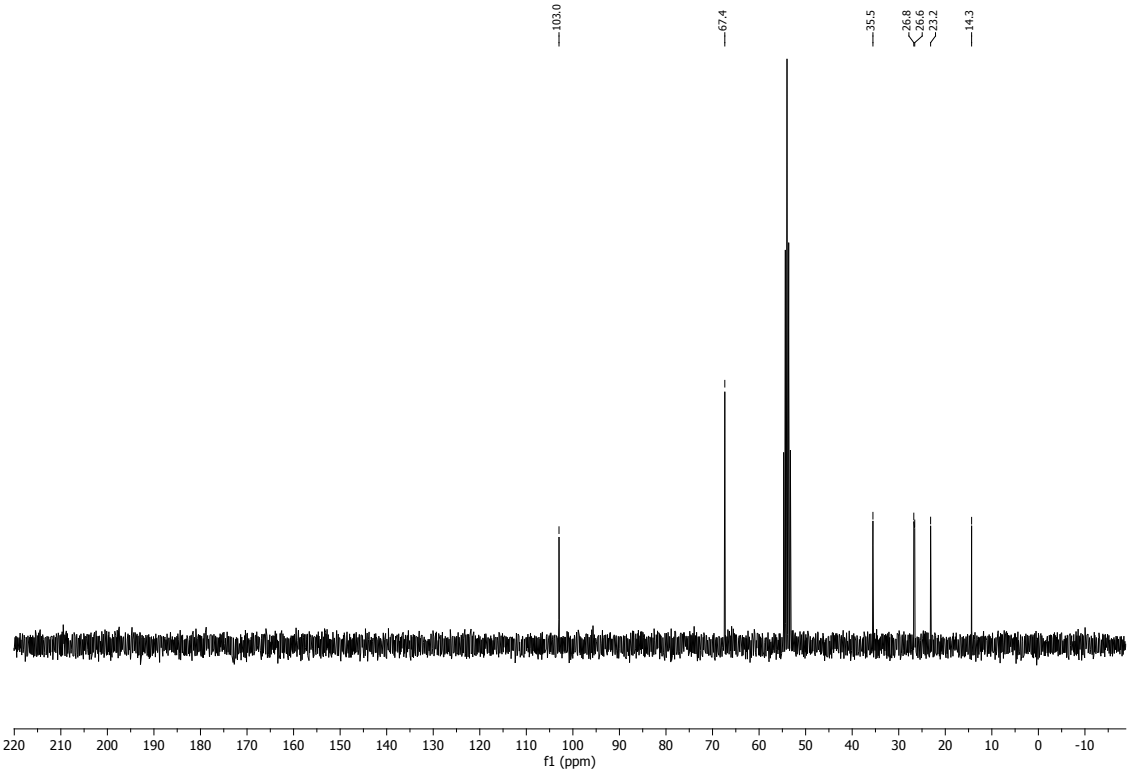
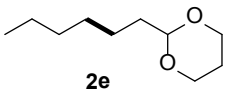
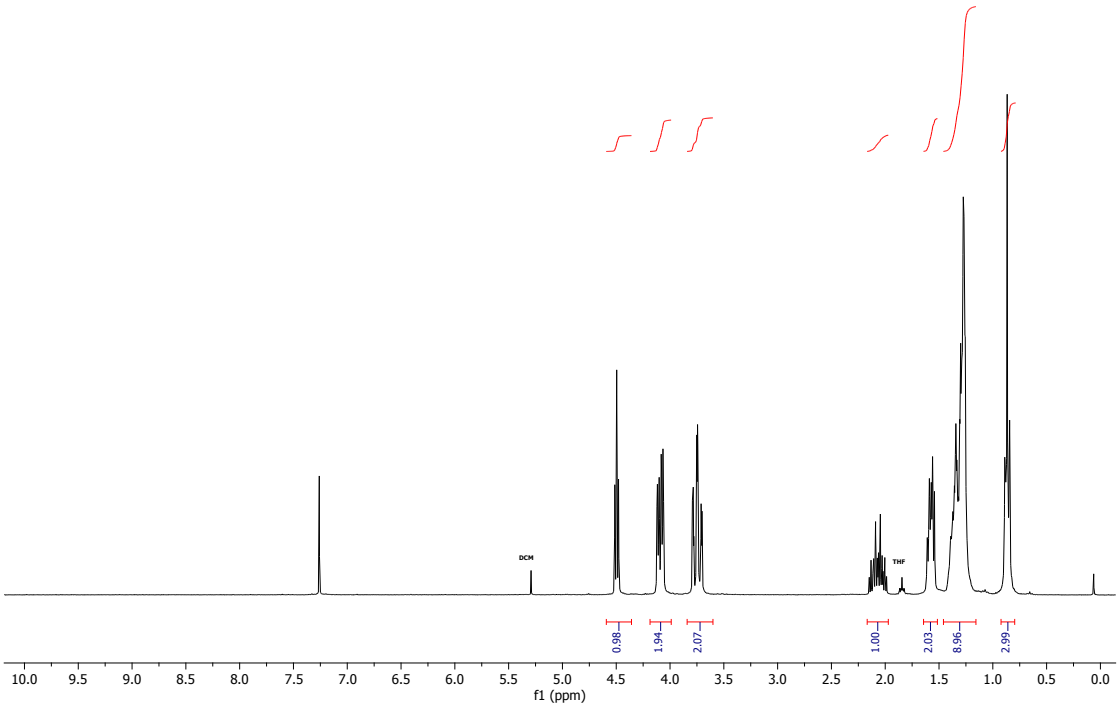
2.00
2.09
1.06
2.28
4.97
3.09
f1 (ppm)


103.0
67.4
35.5
26.8
26.6
23.2
14.3
f1 (ppm)



2e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THF
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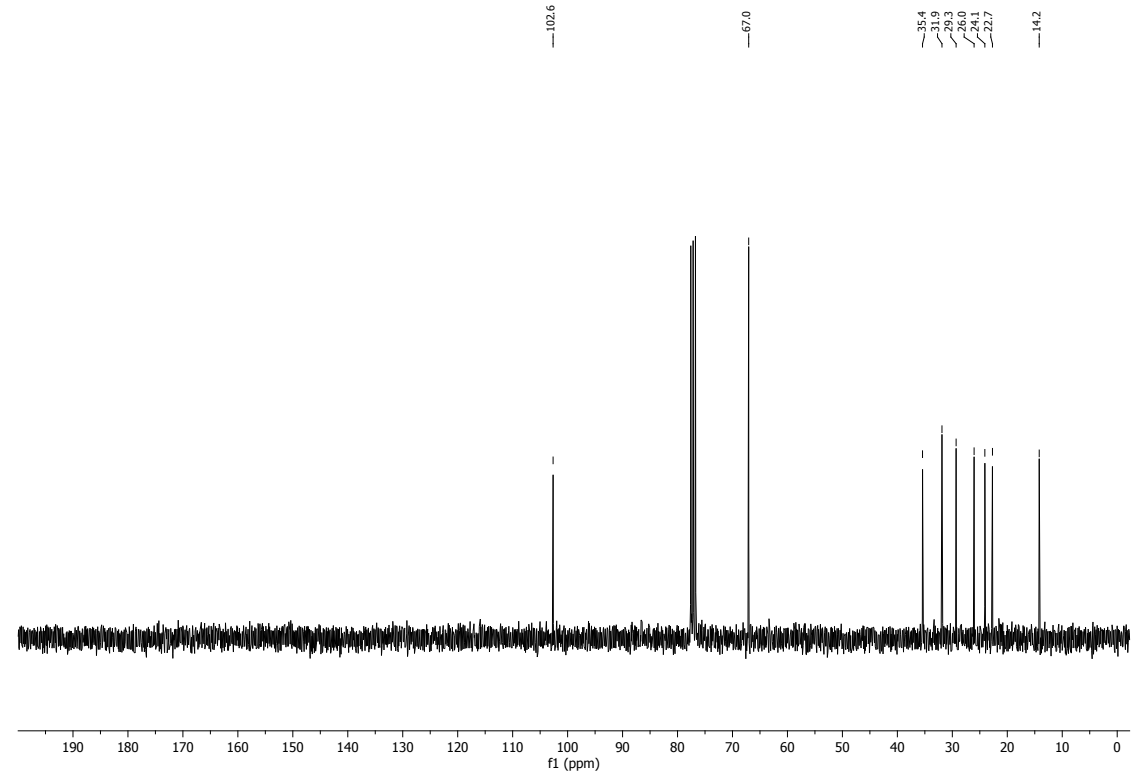
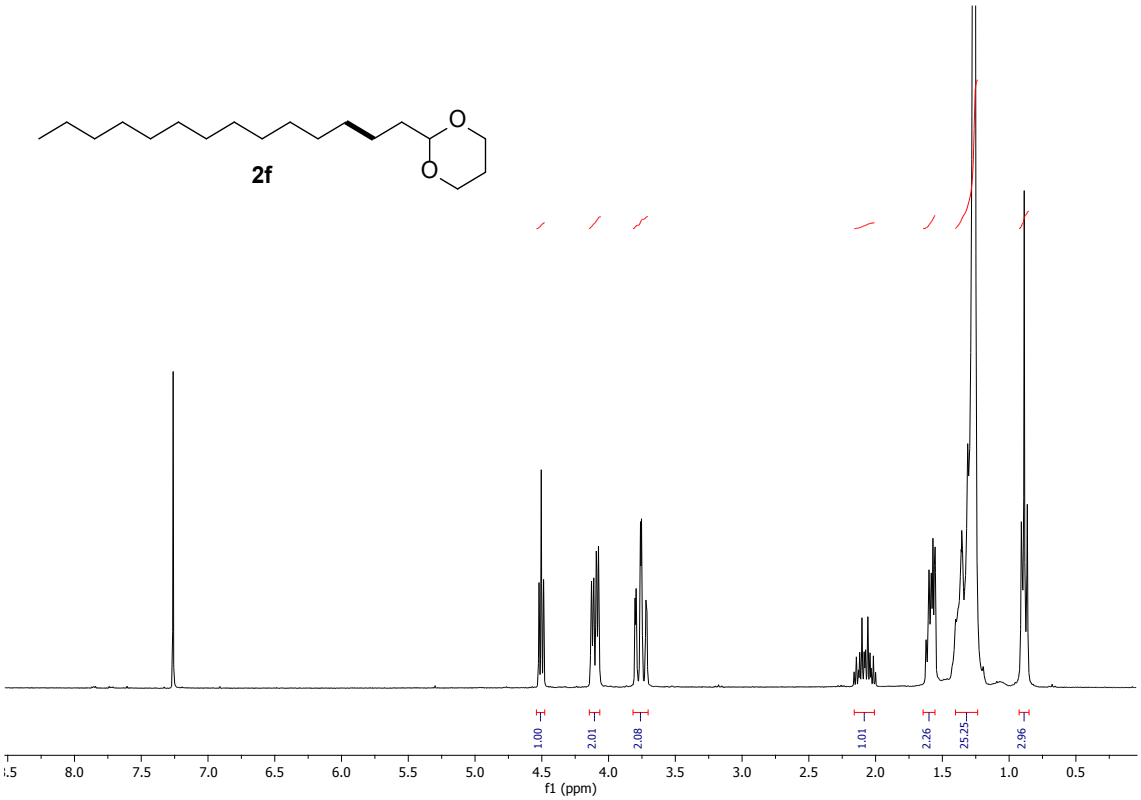
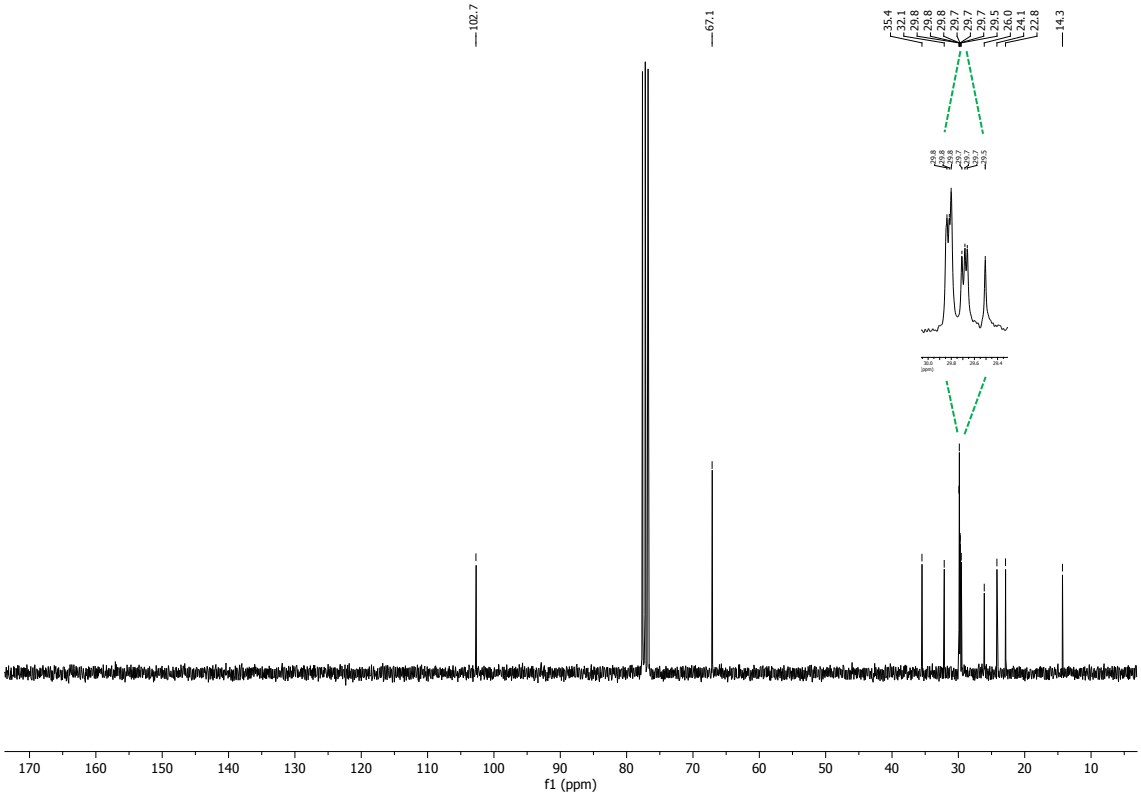
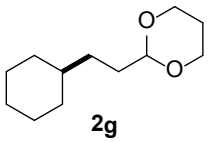
1.00
2.03
8.96
2.99
f1 (ppm)

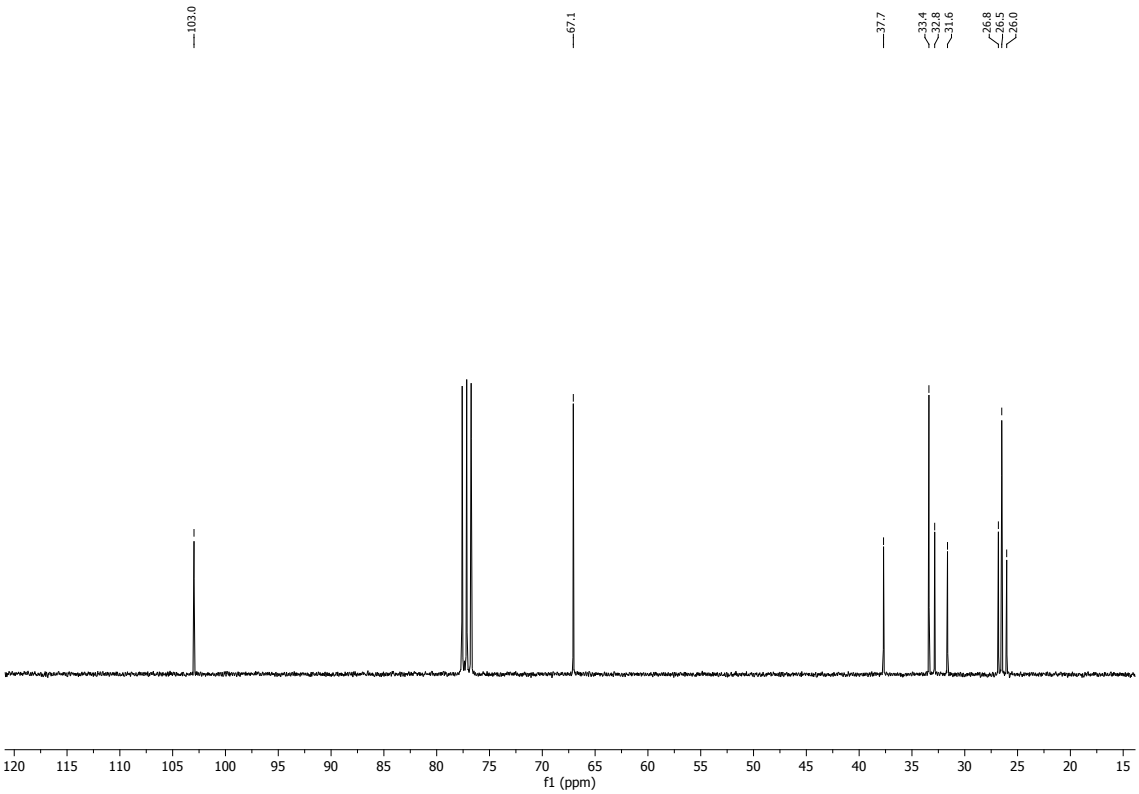

102.6
67.0
35.4
31.9
29.3
26.0
24.1
22.7
14.2
f1 (ppm)

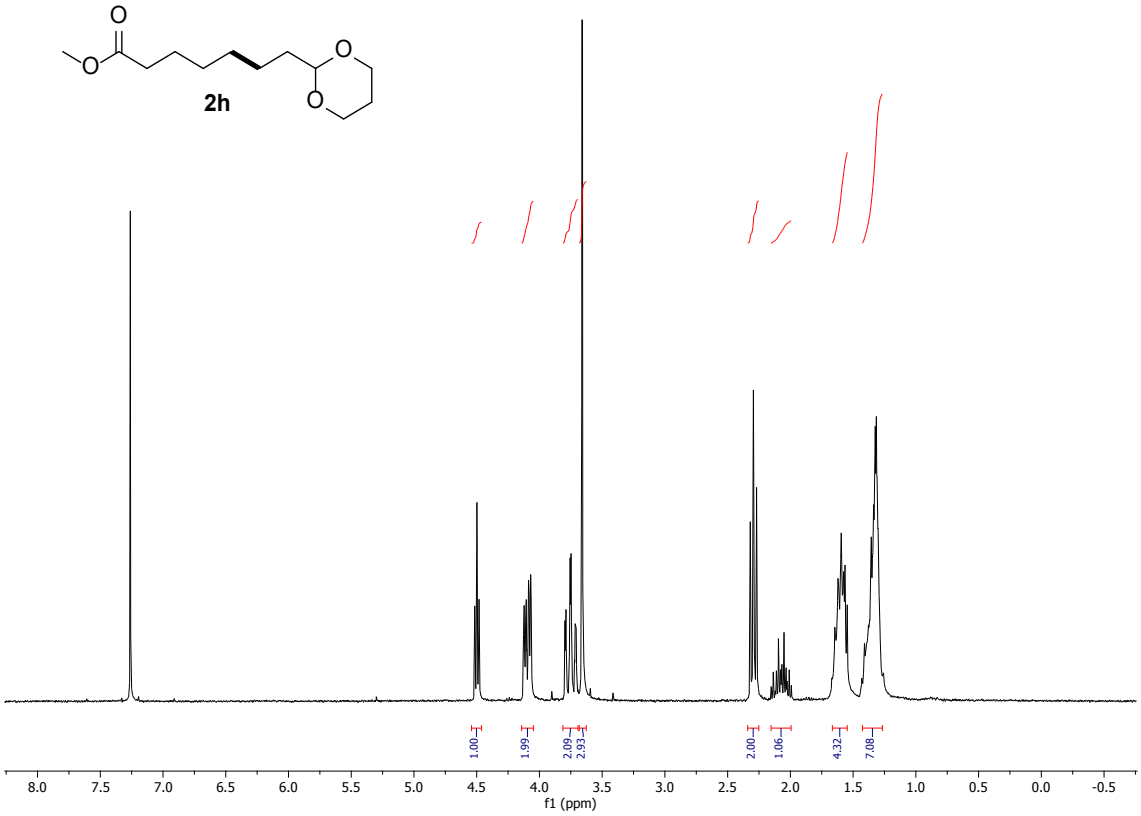


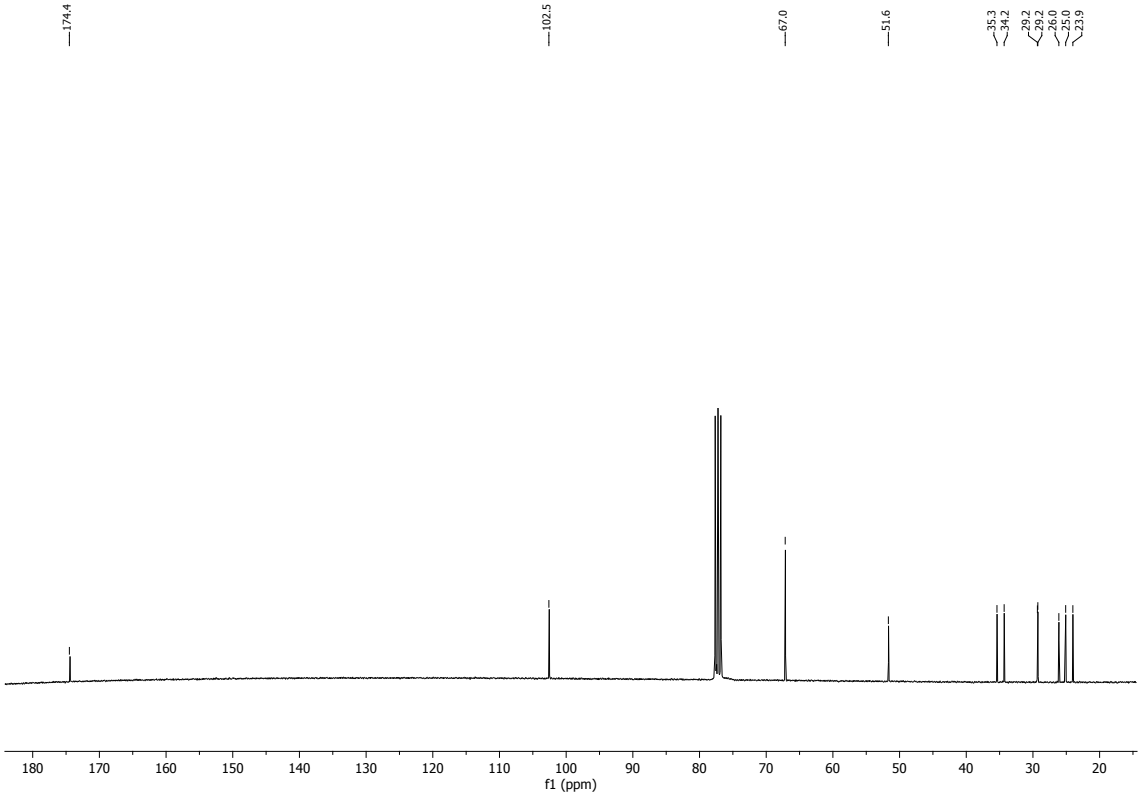


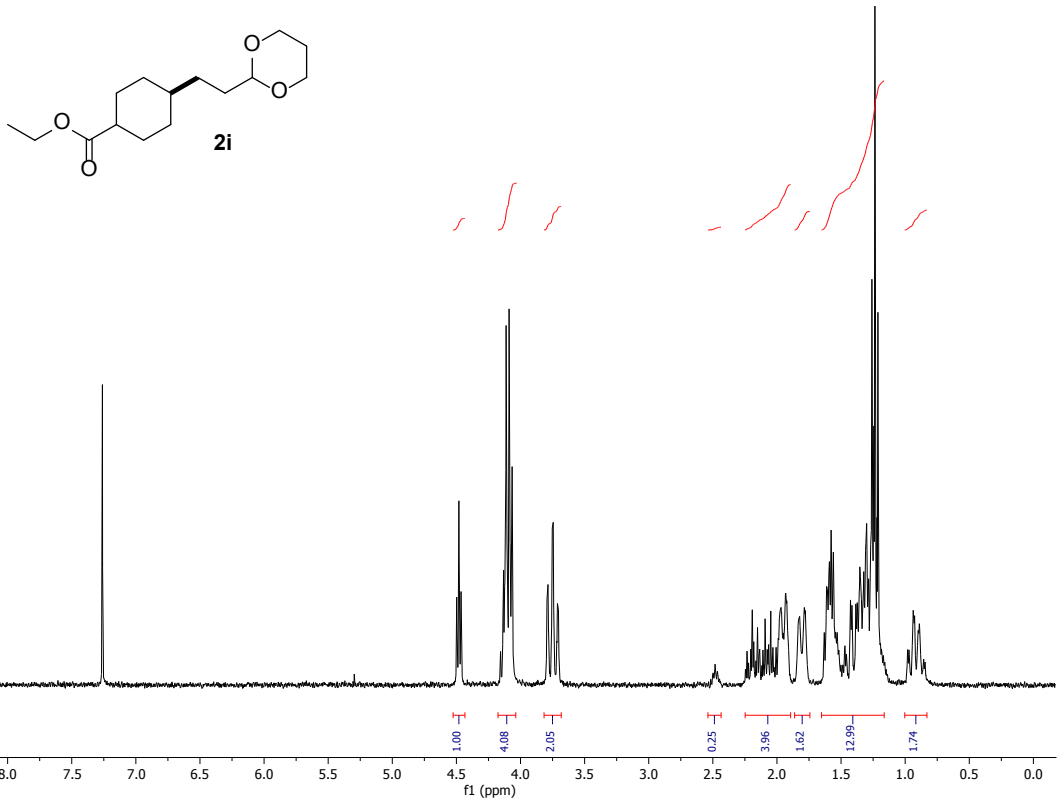


2g





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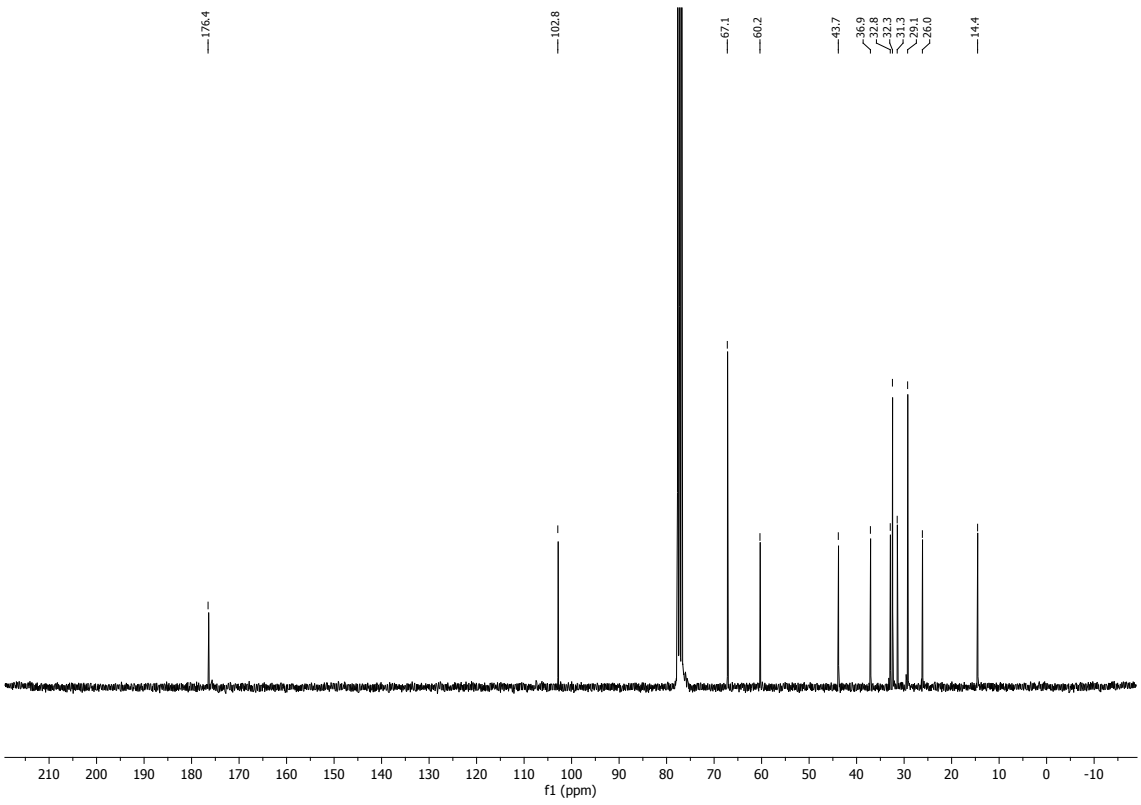
4.08
2.05
0.25
3.96
1.62
12.99
1.74
f1 (ppm)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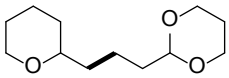
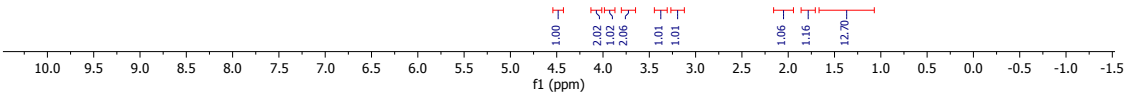
67.1
60.2
43.7
36.9
32.8
32.3
31.3
29.1
26.0
14.4
f1 (ppm)



2j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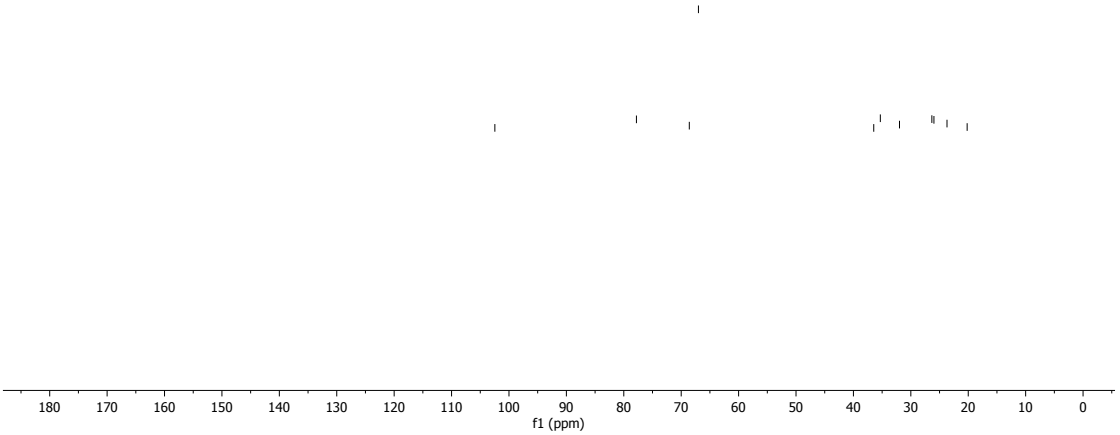
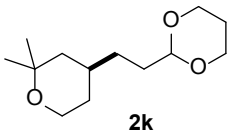
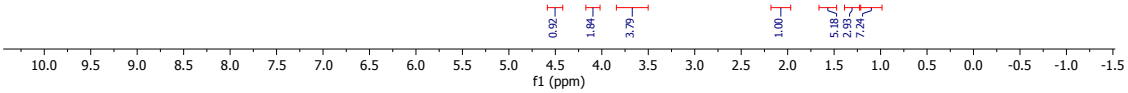
2.02
1.02
2.06
1.01
1.01
1.06
1.16
12.70
f1 (ppm)

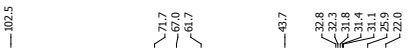

102.5
77.8
68.6
67.0
36.5
35.3
32.0
26.3
26.0
23.7
20.2


f1 (ppm)



2k


0.92
1.84
3.79
1.00
5.18
2.93
7.24
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0 -1.5
f1 (ppm)


102.5
71.7
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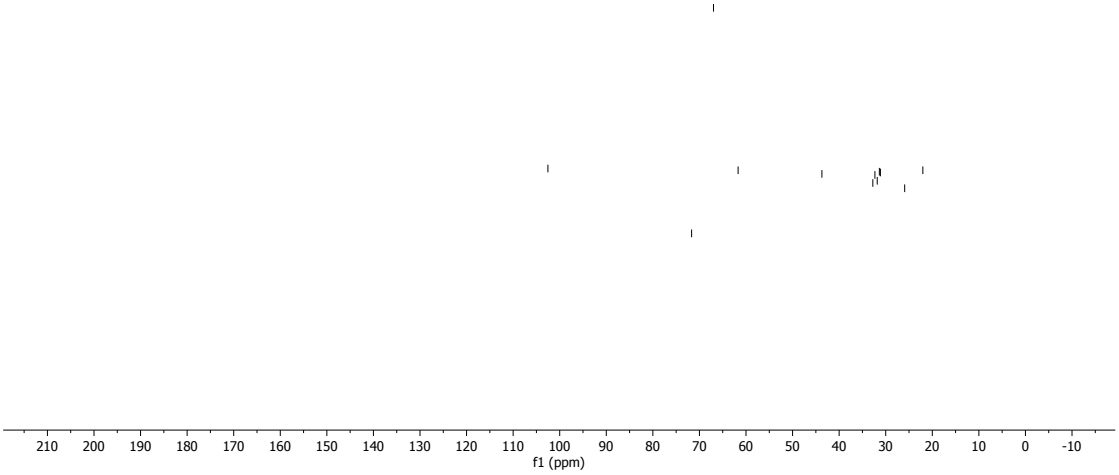
61.7
43.7
33.8
32.3
31.8
31.4
31.1
25.9
22.0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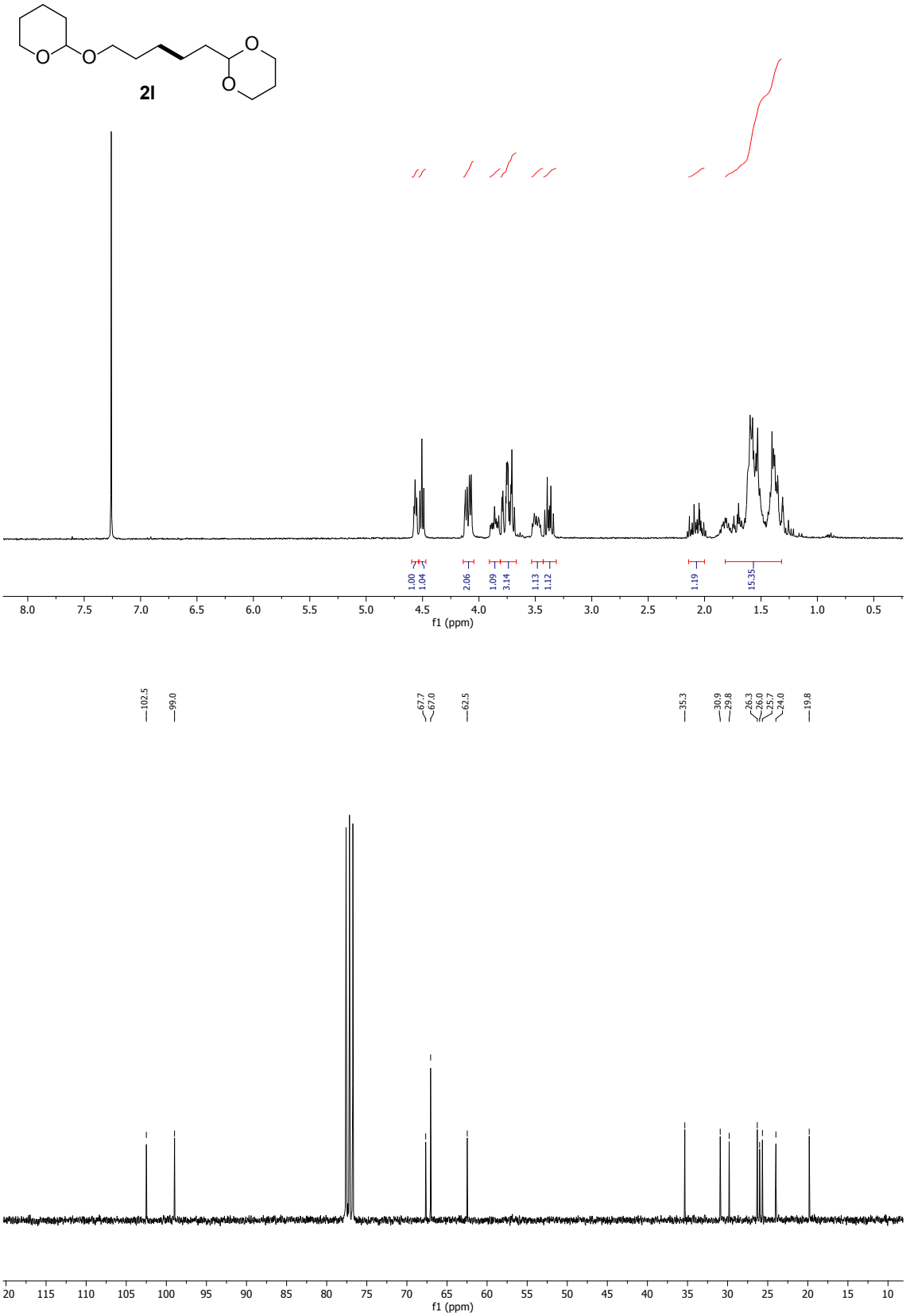
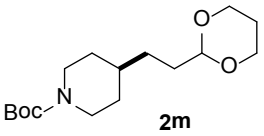
f1 (ppm)





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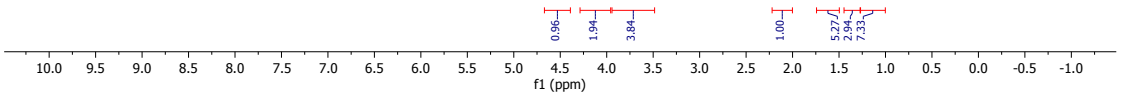

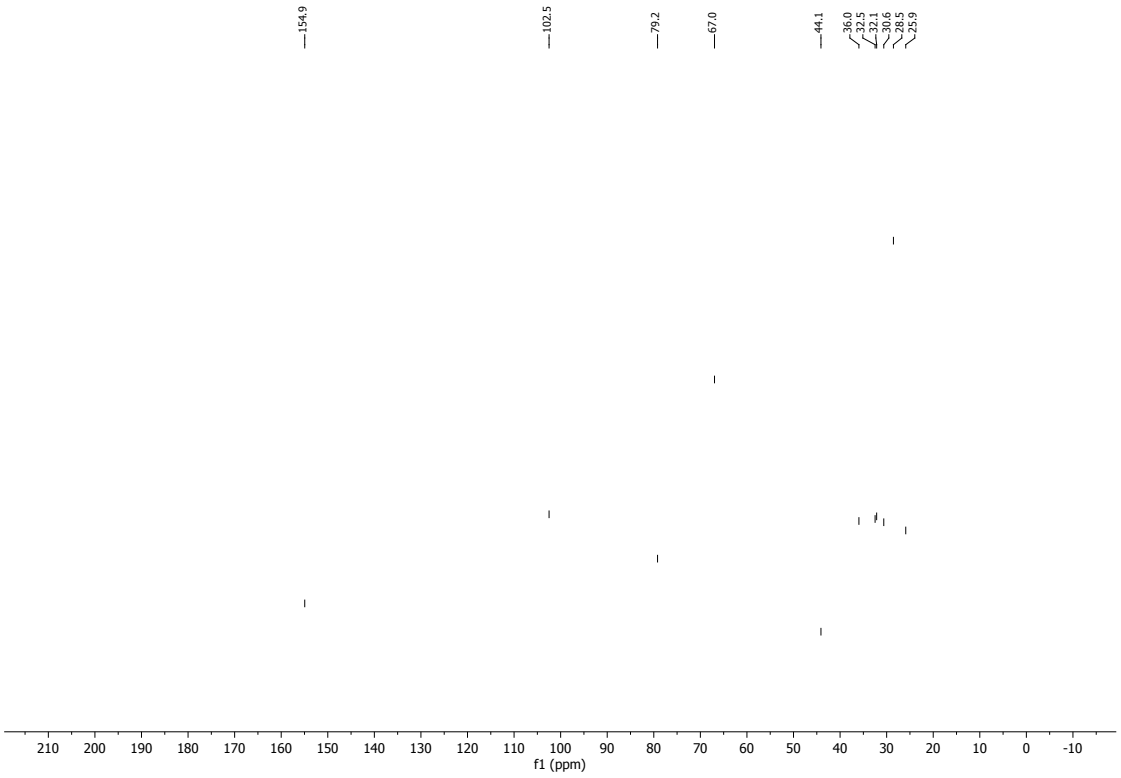

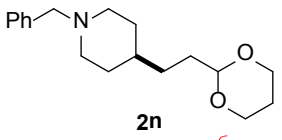

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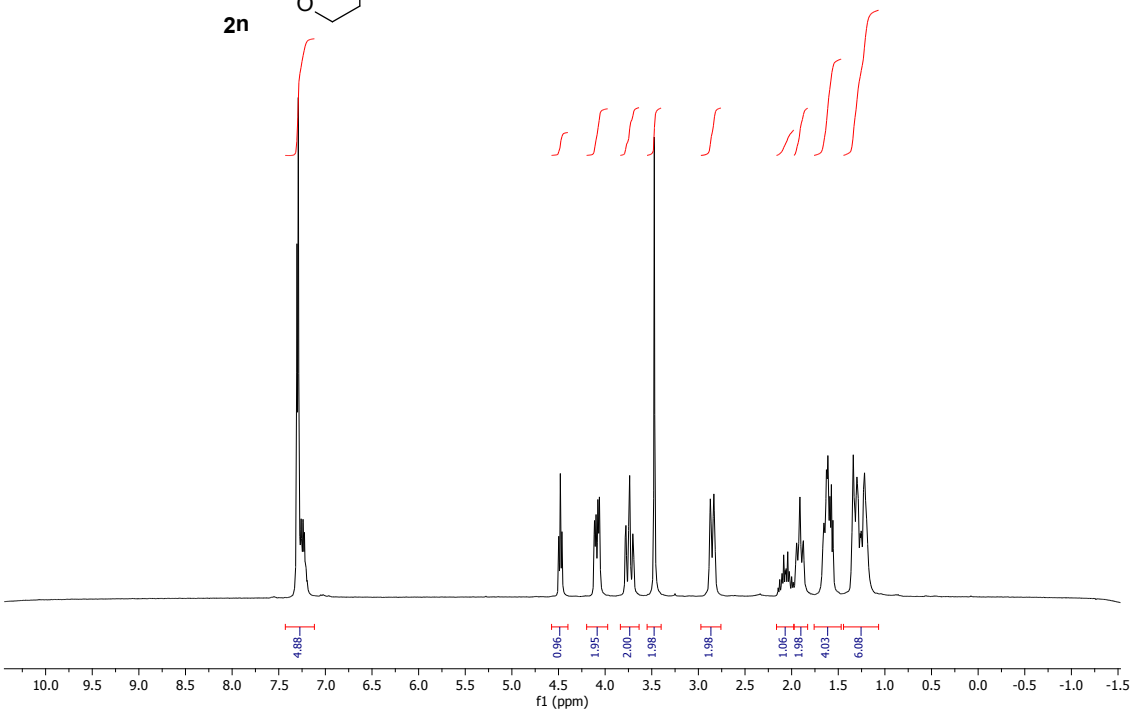
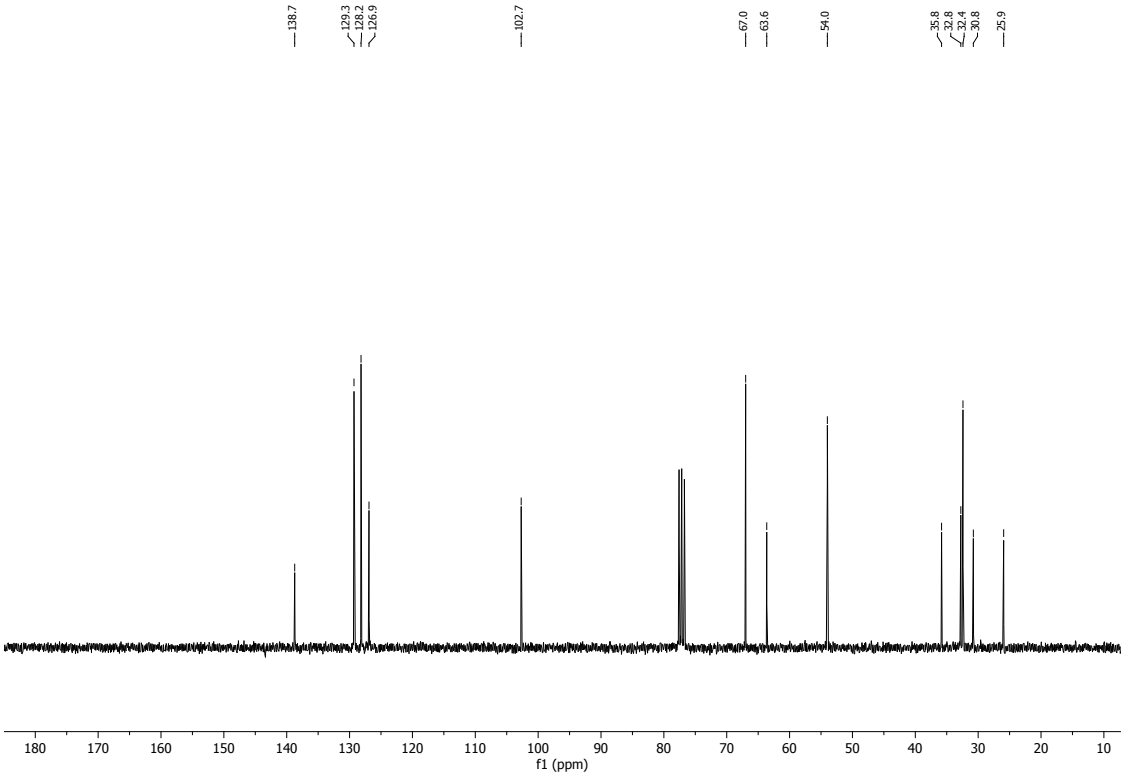
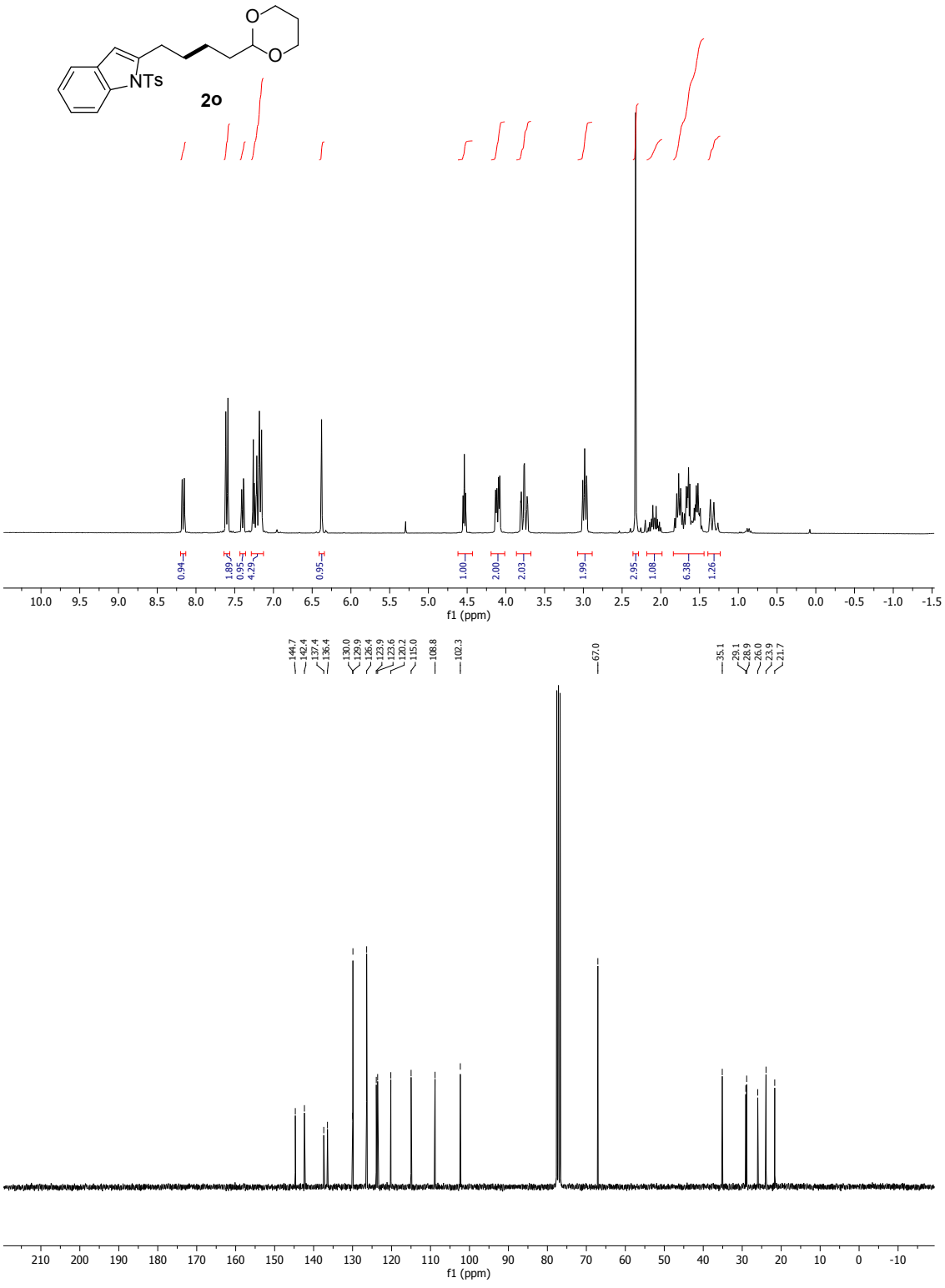
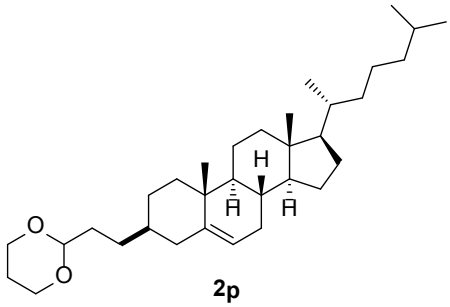
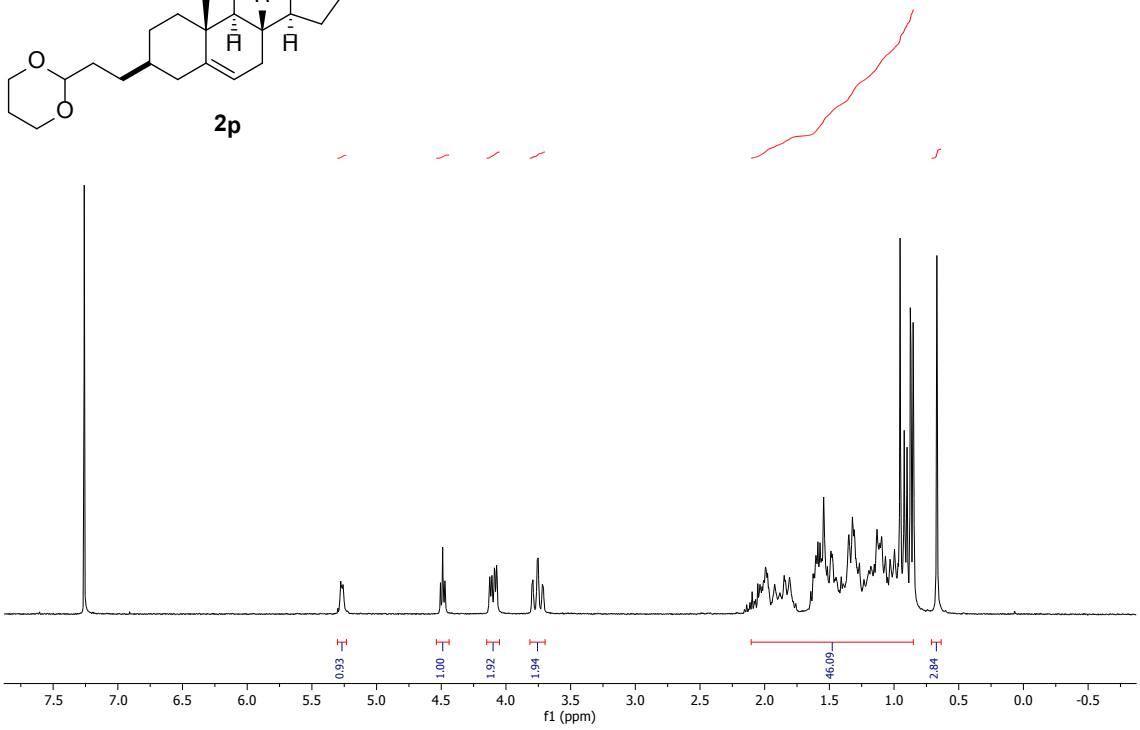


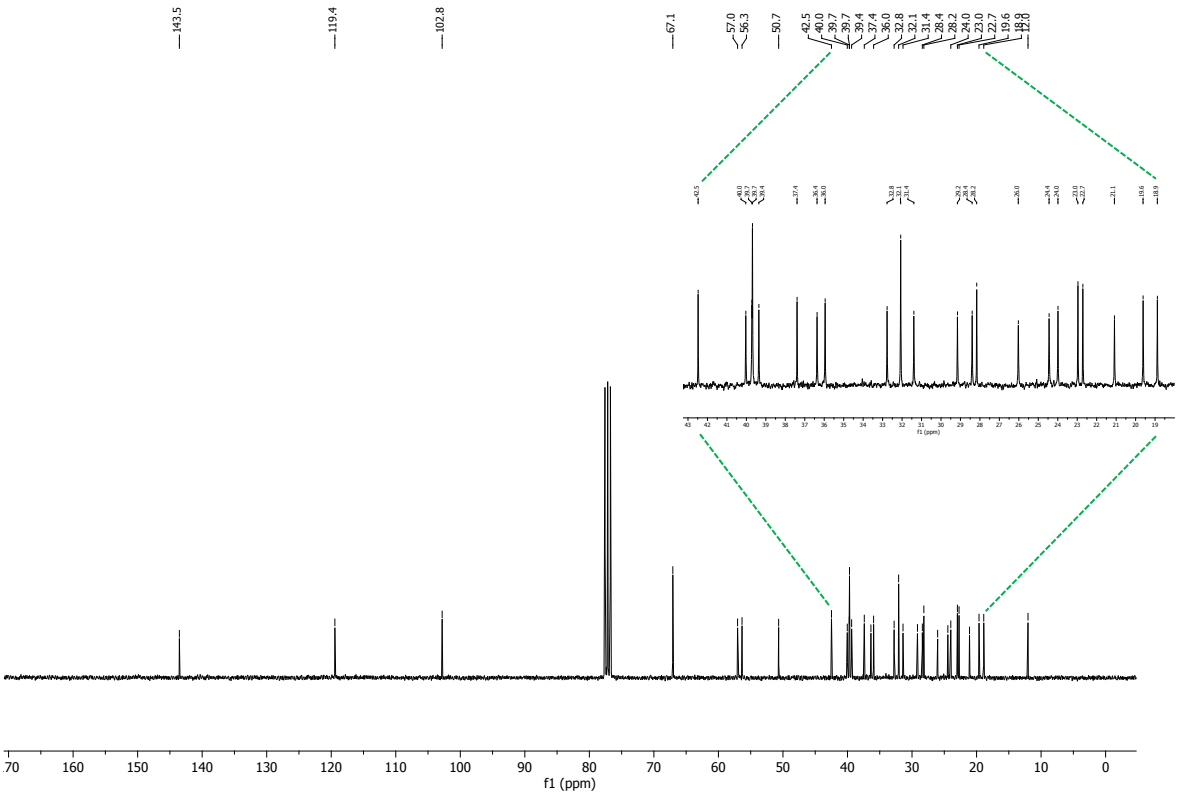


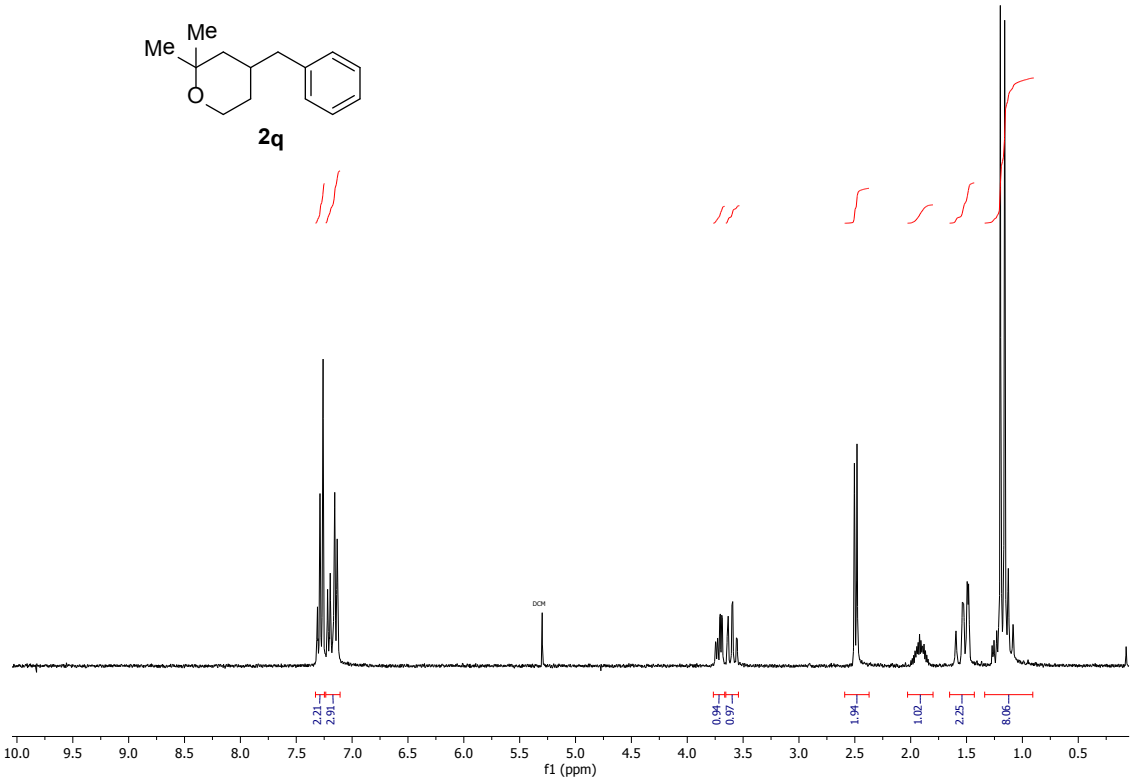



O
O
H
H
H

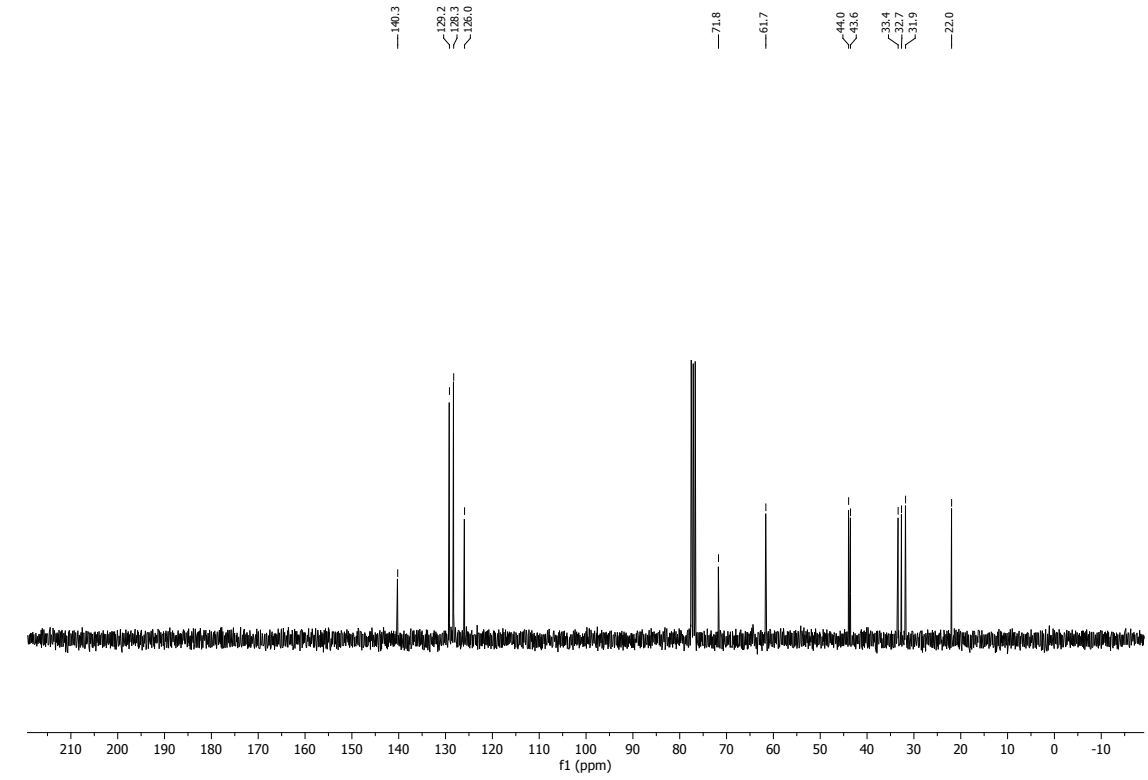
2p

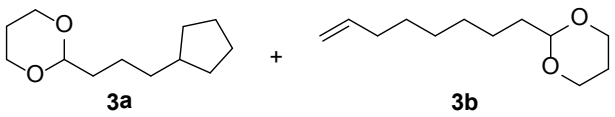

0.93
1.00
1.92
1.94
46.09
2.84
f1 (ppm)

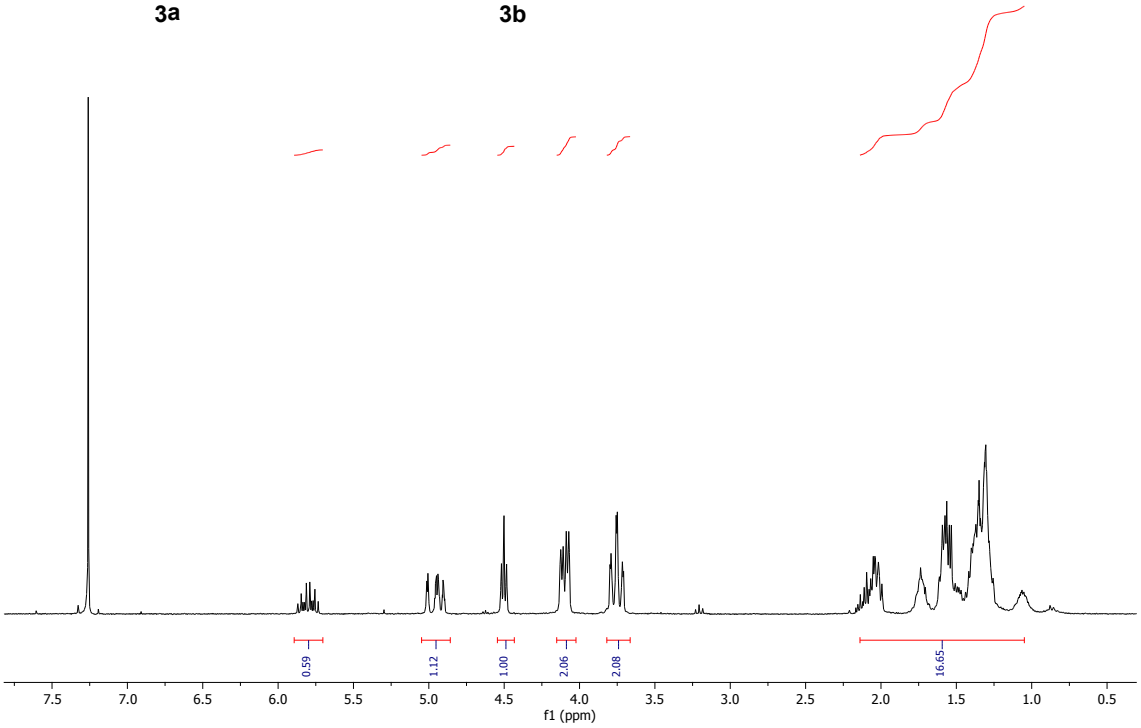

143.5
119.4
102.8
67.1
57.0
56.3
50.7
42.5
40.0
39.7
39.7
39.4
37.4
36.0
32.8
32.1
31.4
28.4
28.2
24.0
23.0
22.7
19.6
18.8
18.6
f1 (ppm)

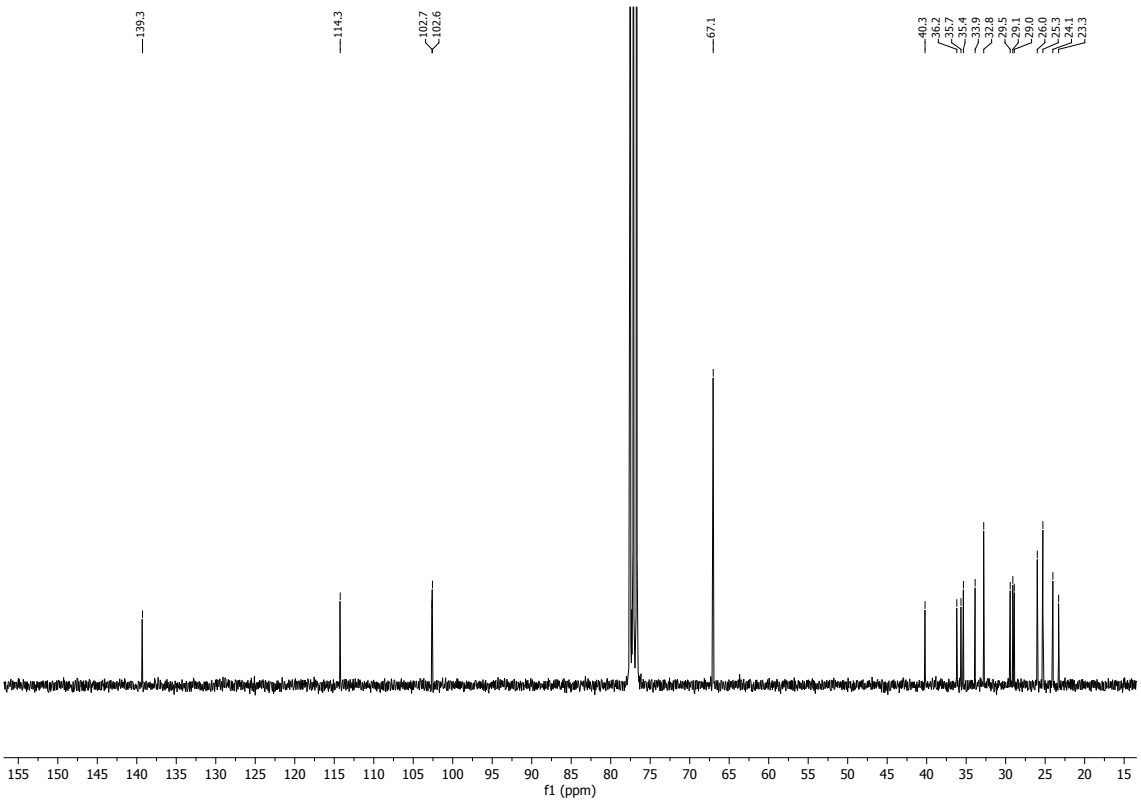


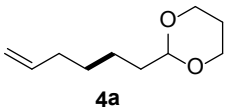
2q




3a
+
3b


0.59
1.12
1.00
2.06
2.08
16.65
f1 (ppm)


139.3
114.3
102.7
102.6
67.1
40.3
36.2
35.7
35.4
33.9
32.8
30.5
29.1
29.0
26.0
25.3
24.1
23.3
f1 (ppm)



4a