

# Macrolactonization Driven by Supramolecular Interactions

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Macrolactones constitute a privileged class of natural and synthetic products with a broad range of applications in the fine chemicals and pharmaceutical industry. Despite all the progresses made towards their synthesis, notably from seco-acids, a macrolactonization promoter system that is effective, selective, flexible, readily available, and, insofar as possible, compatible with manifold functional groups is still lacking. Herein, we describe an alternative strategy relying on a speculated supramolecular template to enable a convenient access to macrolactones, macrodiolides and esters with a versatility that had not been reached with classic methods.

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# Macrolactonization Driven by Supramolecular Interactions.

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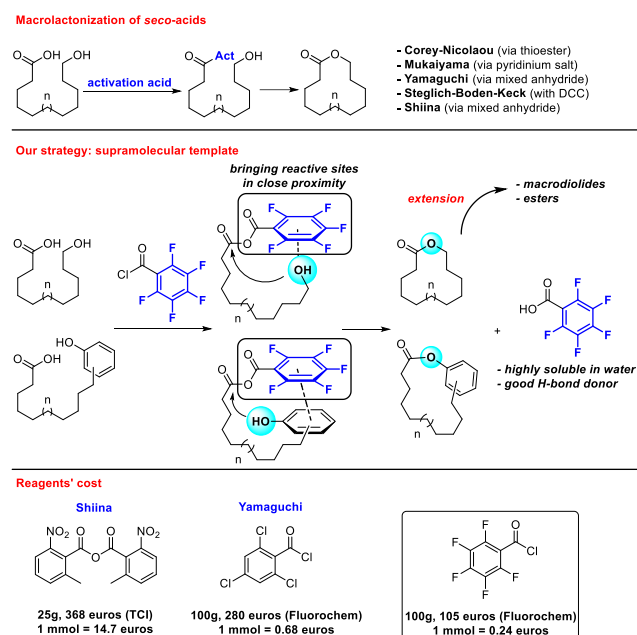
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Supporting Information Placeholder

**ABSTRACT:** Macrolactones constitute a privileged class of natural and synthetic products with a broad range of applications in the fine chemicals and pharmaceutical industry. Despite all the progresses made towards their synthesis, notably from *seco*-acids, a macrolactonization promoter system that is effective, selective, flexible, readily available, and, insofar as possible, compatible with manifold functional groups is still lacking. Herein, we describe an alternative strategy relying on a speculated supramolecular template to enable a convenient access to macrolactones, macrodiolides and esters with a versatility that had not been reached with classic methods.

Macrolactones are encountered in a broad range of natural products, notably marine macrolides, pharmaceuticals, cosmetics and agrochemicals.<sup>1</sup> They are one of the foremost pillars of the flavor and fragrance industry with compounds such as Exaltolide® (Firmenich) and Musc T® (Takasago) that are prevalent in our everyday lives.<sup>1c</sup> In light of their industrial relevance and the challenges associated with their synthesis, the design of efficient and inventive strategies to access macrolactones has sparked relentless efforts in the synthetic community and the interest in this field is not likely to wane.<sup>2</sup> Though the methods devised for macrolactonizations are numerous, they remain substrate-dependent and the quest for a user-friendly system applicable to a vast array of substrates is as compelling as ever. One of the most common approaches involves the macrocyclization of *seco*-acids (Scheme 1). In the seventies, a groundbreaking discovery by Yamaguchi revealed that the stoichiometric activation of the carboxylic acid, via the formation of a mixed anhydride, could be used as a driving force to promote macrocyclizations.<sup>3</sup> This approach was further improved by Shiina with the development of the 2-methyl-6-nitrobenzoic anhydride (MNBA) reagent and related compounds.<sup>4</sup> Other classic examples based on the same concept include Corey-Nicolaou,<sup>5</sup> Steglich-Keck-Boden<sup>6</sup> and Mukaiyama macrolactonizations.<sup>7</sup> However, most of these methods are fraught with distinctive drawbacks that can limit their appeal. To cite but a few examples, they can require highly diluted reactions and a sophisticated slow addition procedure to prevent oligomerizations. Moreover, their use is often accompanied by the formation of several side-products, which can make the purification of the targeted product cumbersome and are potentially toxic, without forgetting to mention their cost-effectiveness as they must be used in stoichiometric amounts. Those issues might become even more critical given

**Scheme 1.** Approaches towards the Macrolactonization of *Seco*-acids.



that macrolactonizations usually take place in the last steps of a total synthesis, where they are performed on a small scale and with unpredictable outcomes. To answer these various challenges, synthetic chemists have mainly focused on two alternative strategies, namely the development of catalytic systems featuring transition metals, Brønsted and Lewis acids in order to limit the formation of side products,<sup>2h,8</sup> and the use of pre-organized substrates relying in general on non-covalent interactions to facilitate and control the macrocyclization process.<sup>2g</sup> However, these variants have their own limitations, such as a narrow substrate scope or the requirement for additional synthetic steps to introduce the reactive functional groups. In this context, we wished to combine the best aspects of the various approaches to achieve a general method for macrolactonizations. Based on their respective efficacy, we reasoned that using a supramolecular template combined with the formation of a mixed anhydride featuring pentafluorobenzoyl chloride as an activating agent might allow a convenient and optimal access to macrolactones. This type of electron-poor receptor can be suitable for numerous non-covalent interactions such as  $\pi$ - $\pi$  interactions via a charge-transfer complex and overlooked  $\pi$ -anion and  $\pi$ -lone pair (lp)

interactions.<sup>9</sup> The latter was particularly of interest as we hypothesized that such interaction could bring both reactive sites in close proximity, removing the need for slow reagent addition.<sup>10–12</sup> Surprisingly, such interactions have hardly been used in synthesis, which might be explained by the lack of understanding regarding their true nature and the controversy related to their directionality.<sup>13</sup> To the best of our knowledge, the only major application of those interactions was reported by Collins' group to aid the pre-organization in ring-closing metathesis.<sup>14,15</sup> Another major advantage of this approach would be the potential extension to less reactive and underexplored phenol derivatives via  $\pi$ - $\pi$  interactions. Pentafluorobenzoyl chloride is also much less expensive than Yamaguchi's and Shiina's reagents, and the highly water-soluble byproduct (pentafluorobenzoic acid) can be easily removed by aqueous treatment, counterbalancing the fact that a stoichiometric amount of pentafluorobenzoyl chloride had to be used. With respect to our strategy, one might argue that, if the lone pair of the alcohol is involved in such non-covalent interactions, its nucleophilicity might be reduced, but this problem could be remedied by the excellent H-bond donating ability of pentafluorobenzoic acid that could activate the mixed anhydride<sup>16</sup> and favor the nucleophilic addition. Herein, we describe the development of a simple and efficient protocol to access not only macrolactones but also macrodiolides and esters from aliphatic alcohols and phenols with excellent functional group tolerance.

In our initial studies, we investigated the reactivity of **1a** to provide access to Exaltolide® (**2a**) by screening a large variety of benzoyl chlorides and benzoic anhydrides in toluene (Table 1). For practical reasons, we set the reaction time at 24 h to facilitate the comparison between the various sources of activating agent. To test our initial assumption, we employed pentafluorobenzoyl chloride as an activating agent and triethylamine as a base, which gratifyingly delivered the targeted product in an excellent yield of 88% along with a high selectivity with respect to the macrodiolide **3a** (ratio 16:1). To our delight, NMR spectra of the crude product did not show any traces of the pentafluorobenzoic acid (see the Supporting Information for details). As anticipated, reducing the number of fluorine atoms on the benzoyl chloride reagent, which should in theory weaken the interaction between the alcohol and the arene, led to a corresponding decrease in selectivity. Interestingly, 3,5-bis(trifluoromethyl)benzoyl chloride gave a selectivity similar to pentafluorobenzoyl chloride with a slightly lower yield (83%). However, the resulting benzoic acid byproduct proved not to be soluble in water, which led us to discard this option. On the other hand, in the presence of electron-withdrawing groups other than fluorine, notably with Yamaguchi's reagent, little or no product was observed, emphasizing the critical role of fluorine for smooth reactivity. Additionally, the reaction was conducted in the presence of Shiina's reagent, which showed a poor outcome. Pentafluorobenzoic anhydride gave identical results as pentafluorobenzoyl chloride. A careful monitoring of the reaction allowed us to determine that the reaction was reaching its full conversion within 2 h. Moreover, the transformation could be achieved at room temperature (48 h), but at the expense of the selectivity. Of note, the macrolactonization did not require the use of a distilled solvent as neither the selectivity nor the yield were affected in these conditions. Unfortunately, we did not circumvent the high dilution, which is required to avoid a significant drop in yield because of the formation of oligomers. We also performed a large survey of bases and solvents, without success in terms of

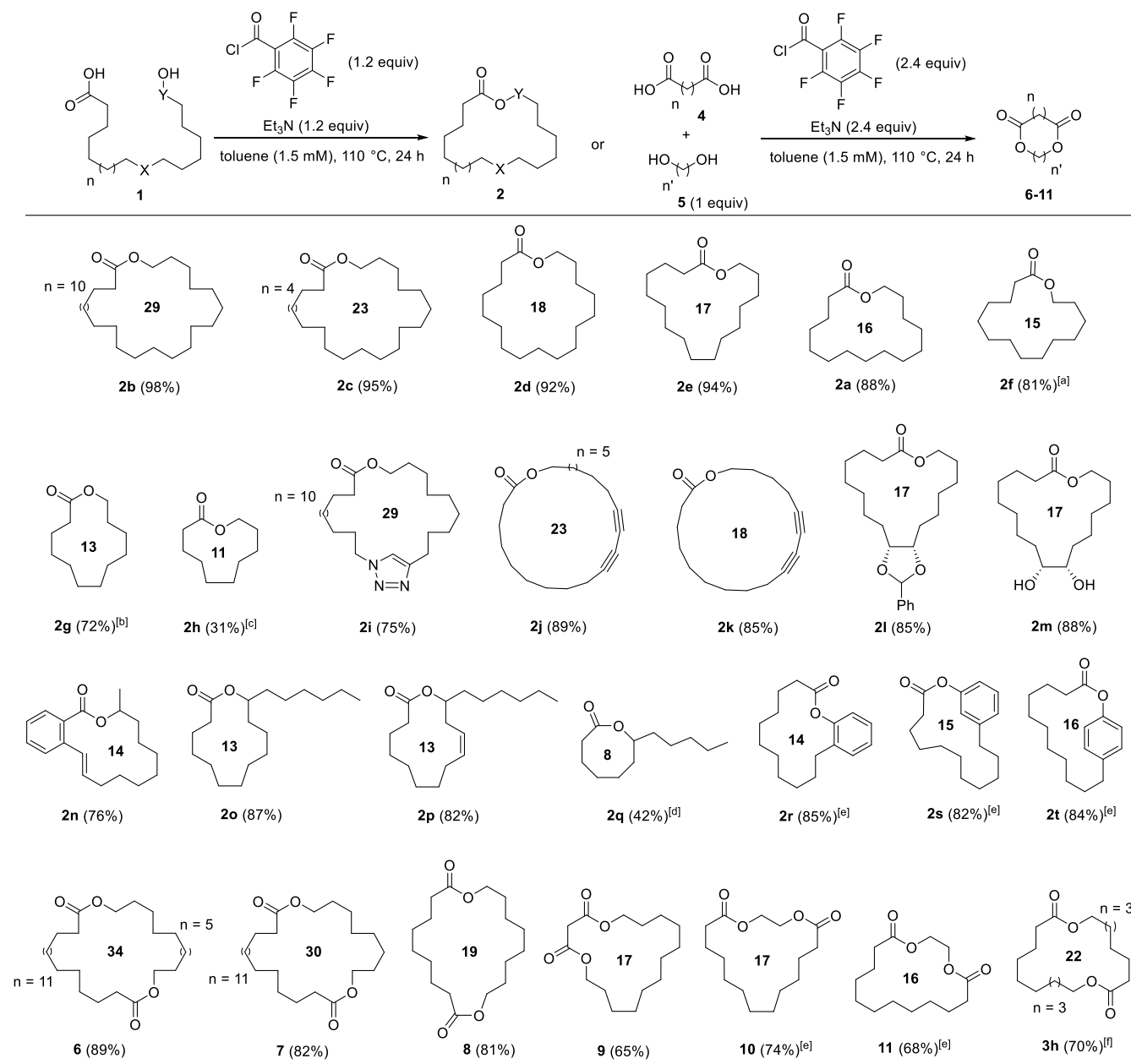
**Table 1.** Optimization of the Macrolactonization of **1a**.<sup>[a]</sup>

 <b>1a</b>	 <b>2a</b>	 <b>3a</b>	$n = 10$
 88% (16:1) 86% (17:1) <sup>[b]</sup> 83% (11.8:1) <sup>[c]</sup>	 86% (14.5:1)	 82% (11:1)	 81% (9:1)
 73% (6.1:1)	 44% (4.4:1)	 83% (16:1)	 75% (12.5:1)
 20% (ND)	 - (ND)	 - (ND)	 13% (ND) 69% (4.6:1) <sup>[d]</sup>
 27% (ND) 74% (5.7:1) <sup>[d]</sup>	 87% (16:1)		

[a] The yields given are the isolated yields for **2a**. The ratios were determined by <sup>1</sup>H NMR using *para*-anisaldehyde as an external standard. [b] Reaction conducted with toluene not distilled. [c] Reaction conducted at room temperature for 48 h. [d] Reaction performed in the presence of pentafluorobenzoic acid (1 equiv).

efficiency and selectivity (see the Supporting Information for details). Predictably, the utilization of coordinating solvents (THF and MeCN), which might compete with the alcohol for the electron-poor host receptor, tends to diminish the selectivity (10.4:1 and 11.7:1, respectively). Regarding our hypothesis that pentafluorobenzoic acid could activate the mixed anhydride, we evaluated the reactivity of Yamaguchi's and Shiina's reagents in the presence of pentafluorobenzoic acid and, while the selectivity was moderate, the conversion of the substrate to the products was no longer an issue. With these optimized conditions in hand, we began to explore the scope of the reaction using simple all-carbon linkers (**2a–2h**, Scheme 2). The macrolactonization was particularly effective for large ring sizes (from 17- to 29-membered rings **2b–2e**, yields up to 98%), without observing the formation of the corresponding macrodiolides. On the other hand, the proportion of macrodiolide increased with smaller ring sizes (**2f–2h**). While the yields remained good for 13- and 15-membered rings (72% and 81%, respectively), the ratio between macrolactone and macrodiolide attained 1 to 1 with 10-hydroxydecanoic acid **1h**, providing **2h** in a low yield of 31%. Then, we evaluated the reactivity of *seco*-acids incorporating various functional groups. In summary, the reaction proved to be compatible with triazole, strained 1,3-butadiyne, alkene and diol (protected or not) moieties to afford the targeted macrolactones in yields ranging from 65% to 89%. Using this method allowed us to access notably the framework of resorcylic lactones (**2n**) in 76% yield.<sup>17</sup> In addition, the reaction could be applied to secondary alcohols and even challenging 8-membered rings

**Scheme 2.** Reaction Scope for the Formation of Macrolactones and Macrodiolides.



[a] Ratio macrolactone/macrodiolide 8:1 (separable by flash column chromatography). [b] Ratio macrolactone/macrodiolide 8:1 (separable by flash column chromatography). Ratio macrolactone/macrodiolide 1:1 (separable by flash column chromatography). [d] Reaction conducted at 50 °C. [e] Reaction conducted for 48 h. [f] Reaction conditions: *seco*-acid **1h** (1 equiv), pentafluorobenzoyl chloride (1.2 equiv) and triethylamine (2.4 equiv) in toluene (2 mM).

such as **2q** could be obtained in a moderate yield (42%) by employing this method.<sup>18</sup> Satisfactorily, the transformation was not limited to aliphatic alcohols, but could also be extended to phenols,<sup>19</sup> delivering the desired products, notably *meta*- and *para*-cyclophanes in good yields (82 to 85%), creating a new avenue for the synthesis of these compounds that have many applications in materials science and supramolecular chemistry.<sup>20</sup> Nevertheless, the reaction with phenols proved to be slower had to be carried for 48h to reach full conversion. Finally, we turned our attention to the preparation of macrodiolides, which are widespread scaffolds in medicinal chemistry.<sup>21</sup> Their synthesis is obviously not as trivial as the precedent case since two chemical events (esterification then macrolactonization) are involved when starting from *seco*-acids or diacids.<sup>22</sup> While Yamaguchi's approach is known to be incompatible with the formation of these types of

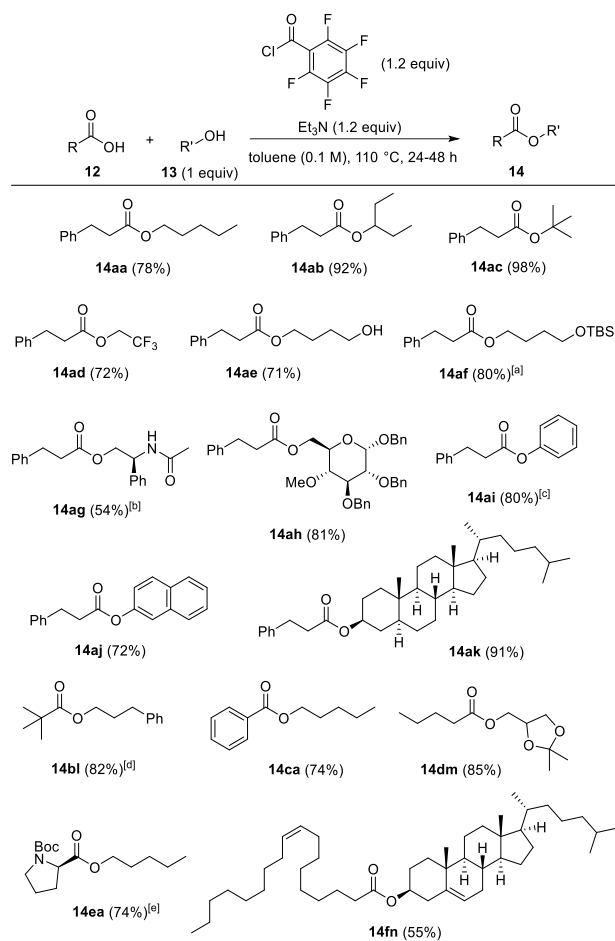
compounds,<sup>22b</sup> we were pleased to find that 16- to 34-membered macrodiolides could be rapidly afforded in good to excellent yields (up to 89%). Besides, two compounds with major industrial applications, Musc T<sup>®</sup> and Zenolide<sup>®</sup> (**10** and **11**), could be generated in a single step within 48 h in 74% and 68% yields. Head-to-tail dimerizations are also achievable, as exemplified by **3h** (70%), provided that the concentration is slightly increased.

To further determine the potential of our method, we investigated intermolecular esterifications (Scheme 3). Once more, this procedure showcased a striking functional group tolerance. The reaction proved to be compatible with primary as well as secondary and tertiary alcohols (up to 98%). In a similar manner, primary, secondary and tertiary carboxylic acids exhibited the same efficiency. Moreover, we succeeded to



accomplish the mono-acetylation of 1,4-butanediol (**14ae**) in a good yield (71%). Even a poorly nucleophilic alcohol, trifluoroethanol, could be employed to deliver the corresponding ester **14ad** in 72% yield. Less reactive aryl alcohols such as phenol and naphthol could also be subjected to the reaction conditions to provide the desired products in 80% and 72%, respectively, in 48 h. Of note, substrates bearing acid-sensitive functional groups (TBS, Boc and acetal) were well-tolerated. Finally, compounds of interest such as amino alcohols (**14ag**), amino acids (**14ba**), carbohydrates (**14ah**), steroids (**14ak**) and fatty acids (**14em**) underwent smooth esterifications with yields ranging from 54% to 91%.

**Scheme 3.** Reaction Scope for Intermolecular Esterifications.



[a] The yield was determined by  $^1\text{H}$  NMR using *para*-anisaldehyde as an external standard as the silyl group was cleaved on silica gel to give **14ae**. [b] Reaction conducted at 80 °C. [c] Phenol (2 equiv). [d] Alcohol **13l** (0.8 equiv). [e] Alcohol **13a** (1.5 equiv).

In summary, we have discovered an efficient and user-friendly protocol to achieve macrolactonizations of interest to a variety of applications in our society. This transformation, which featured the formation of a mixed anhydride based on the utilization of an inexpensive activating agent (pentafluorobenzoyl chloride), displayed a remarkable efficacy and functional group versatility, while overcoming most of the common limitations associated with such processes. For instance, this unique method could be equally applied to intramolecular macrolactonizations of *seco*-acids or to the intermolecular formation of macrodiolides and even esters. Mechanistic investigations to shed light on its function are ongoing and will be reported in due course.

## ASSOCIATED CONTENT

### Supporting Information

Experimental procedures, characterization data and NMR spectra of all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org/>

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### Notes

The authors declare no competing financial interests.

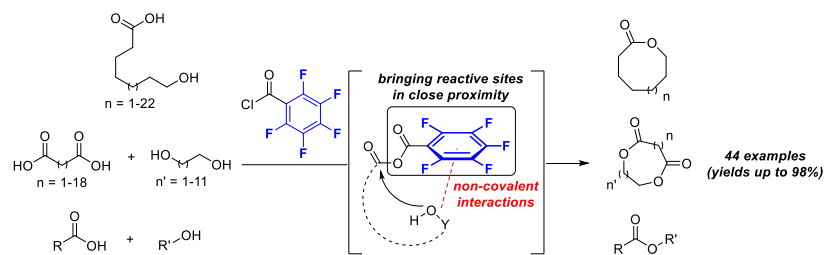
## ACKNOWLEDGMENT

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## SUPPORTING INFORMATION

### Macrolactonization Driven by Supramolecular Interactions

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#### General Information

Unless otherwise stated, reactions were carried out in oven-dried flasks. Analytical thin layer chromatography was carried out using TLC-aluminum sheets with 0.2 mm of silica gel (Merck GF234) using UV light as the visualizing agent and a solution of phosphomolybdic acid in ethanol as the developing agent. Chromatography purifications were carried out using flash grade silica gel (SDS Chromatogel 60 ACC, 40-60 mm). Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator. NMR spectra were recorded at 298 K on AM250, AV300 or AV360 MHz Bruker spectrometer and are reported in ppm. Mass spectra were recorded on MicrOTOFq Bruker spectrometer by electrospray ionization. Melting points were determined using a Reichert melting point apparatus. Infrared spectra were recorded on a FTIR spectrometer (Perkin-Elmer spectrum one, NaCl pellets or Bruker Vertex 70 ATR Pike Germanium) and are reported in cm<sup>-1</sup>.

Compounds **1a**, **1d**, **1e**, **1f**, **1g**, **1h**, **1m**, **1o** and **1p** are commercially available.

Compounds **1l**,<sup>1</sup> **1n**<sup>2</sup> and **1q**<sup>3</sup> were prepared according to known protocols.

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<sup>1</sup> I. Shiina, M. Kubota, H. Oshiumi, M. Hashizume, *J. Org. Chem.* **2004**, 69, 1822.

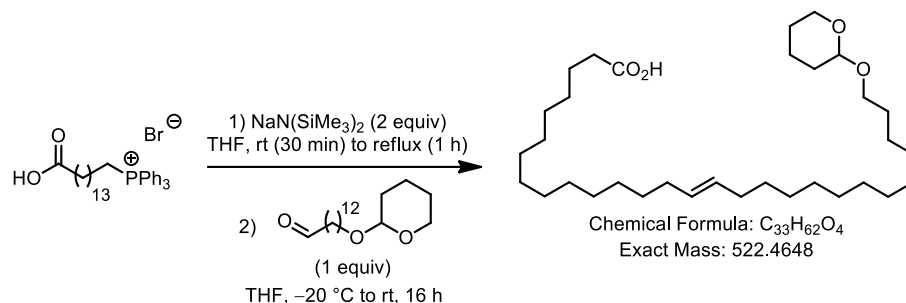
<sup>2</sup> G. W. Heberlig, M. Wirz, M. Wang, C. N. Boddy, *Org. Lett.* **2014**, 16, 5858.

<sup>3</sup> M. H. Kaspersen, L. Jenkins, J. Dunlop, G. Milligan, T. Ulven, *Med. Chem. Commun.* **2017**, 8, 1360.

## Experimental Procedures

### Synthesis of precursors

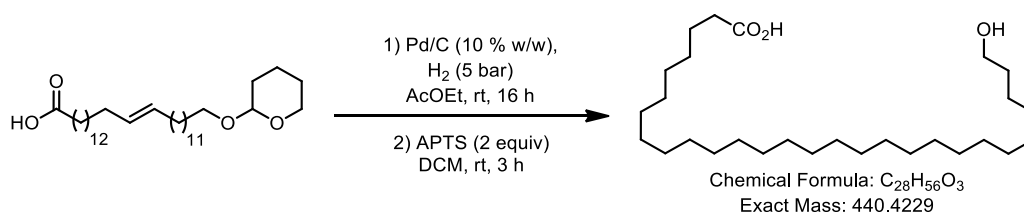
#### 28-((tetrahydro-2H-pyran-2-yl)oxy)octacos-15-enoic acid (**S1b**)



To a solution of sodium bis(trimethylsilyl)amide (2.84 mL, 2.84 mmol, 2 equiv, 1M in THF) in freshly distilled THF (8 mL) was added portionwise (14-carboxytetradecyl)triphenylphosphonium bromide (826 mg, 1.42 mmol, 1 equiv) at room temperature under argon. After 30 minutes, the mixture was heated at reflux for 1 h. Then, it was cooled down to  $-20^\circ\text{C}$  and a solution of 13-((tetrahydro-2H-pyran-2-yl)oxy)tridecanal<sup>4</sup> (423 mg, 1.42 mmol, 1 equiv) in THF (2 mL) was added. The reaction mixture was slowly warmed up to room temperature and stirred for 15 h. It was then quenched with saturated  $\text{NH}_4\text{Cl}$  aqueous solution (2 mL) before being acidified with concentrated  $\text{HCl}$  (1 mL) and extracted with diethyl ether (3 x 5 mL). The combined organic layers were washed with water (3 mL), dried over anhydrous  $\text{MgSO}_4$  and filtered. The solvent was removed by rotary evaporation. The crude product was purified by flash column chromatography using PE/EtOAc as eluent (8:2 to 1:1) to give **S1b** as a yellow oil (180 mg, 24%).

**$^1\text{H}$  NMR** (360 MHz,  $\text{CDCl}_3$ )  $\delta$  = 5.37–5.29 (m, 2H), 4.62–4.53 (m, 1H), 3.87 (ddd,  $J$  = 11.2, 7.5, 3.4 Hz, 1H), 3.72 (dt,  $J$  = 9.6, 6.9 Hz, 1H), 3.54–3.45 (m, 1H), 3.37 (dt,  $J$  = 9.6, 6.7 Hz, 1H), 2.33 (t,  $J$  = 7.5 Hz, 2H), 2.07–1.95 (m, 4H), 1.89–1.68 (m, 2H), 1.66–1.48 (m, 10H), 1.41–1.14 (m, 36H),  $\text{CO}_2\text{H}$  unobserved.  **$^{13}\text{C}$  NMR** (91 MHz,  $\text{CDCl}_3$ )  $\delta$  = 179.6, 130.0, 98.9, 67.8, 62.4, 34.2, 30.9, 29.9 (2C), 29.8, 29.7 (2C), 29.6, 29.5, 29.4 (2C), 29.2, 27.3, 26.4, 25.6, 24.8, 19.8, 11 carbons hidden. **IR** (film,  $\text{cm}^{-1}$ ):  $\nu_{\text{max}}$  = 3448, 2947, 2862, 1749, 1630, 1338, 1217, 1010, 967. **HRMS** ( $\text{ESI}^+$ ):  $m/z$  calcd for  $\text{C}_{33}\text{H}_{62}\text{NaO}_4$   $[\text{M}+\text{Na}]^+$ : 545.4546, found: 545.4513.

#### 28-hydroxyoctacosanoic acid (**1b**)



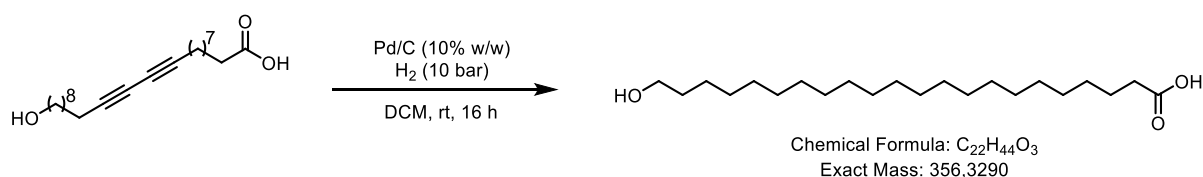
<sup>4</sup> K. Ando, K. Narumiya, H. Takada, T. Teruya, *Org. Lett.* **2010**, 12, 1460.

In a vial were placed **S1b** (100 mg, 0.191 mmol, 1 equiv), Pd/C (10 mg, 10% w/w) and ethyl acetate (3 mL). In an autoclave, the reaction mixture was purged three times with H<sub>2</sub> (5 bar) and stirred at room temperature for 16 h under H<sub>2</sub> (5 bar). Then, the mixture was passed through a short pad of Celite and rinsed with ethyl acetate. The solvent was removed by rotary evaporation and the crude product was engaged in the next step without further purification.

To a solution of the crude product in dichloromethane (4 mL) was added APTS (66 mg, 0.382 mmol, 2 equiv). The reaction mixture was stirred at room temperature for 3 h. Then, it was then quenched with saturated NaHCO<sub>3</sub> aqueous solution (3 mL) and extracted with chloroform (3 x 5 mL). The combined organic layers were washed with brine, dried over anhydrous MgSO<sub>4</sub> and filtered. The solvent was removed by rotary evaporation to give **1b** as a white solid without requiring any further purification (60 mg, 71% over two steps).

**Mp** = 95-97 °C. **<sup>1</sup>H NMR** (360 MHz, CDCl<sub>3</sub>)  $\delta$  = 3.65 (t, *J* = 6.5 Hz, 2H), 2.35 (t, *J* = 7.5 Hz, 2H), 1.68–1.51 (m, 4H), 1.42–1.15 (m, 46H), CO<sub>2</sub>H and OH unobserved. **<sup>13</sup>C NMR** (91 MHz, DMSO)  $\delta$  = 174.4, 60.7, 33.6, 32.5, 29.1, 29.0 (2C), 28.9, 28.7, 28.5, 25.5, 24.5, 16 carbons hidden. **IR** (film, cm<sup>-1</sup>):  $\nu_{\max}$  = 3298, 2915, 2849, 1651, 1469, 1453, 1234, 1098, 725. **HRMS** (ESI<sup>+</sup>): *m/z* calcd for C<sub>28</sub>H<sub>56</sub>NaO<sub>3</sub> [M+Na]<sup>+</sup>: 463.4127, found: 463.4136.

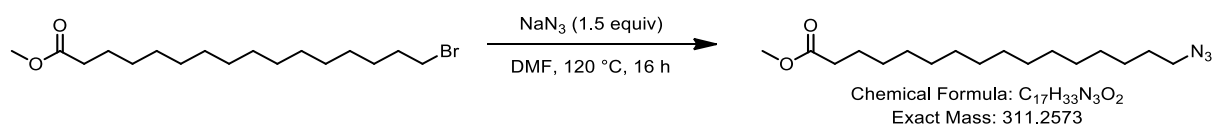
### 22-hydroxydocosanoic acid (**1c**)



In a vial were placed methyl 22-hydroxydocosa-10,12-dienoic acid **1j** (100 mg, 0.287 mmol, 1 equiv.), Pd/C (10 mg, 10% w/w) and DCM (8 mL). In an autoclave, the reaction mixture was purged three times with H<sub>2</sub> (10 bar) and stirred at room temperature for 16 h under H<sub>2</sub> (10 bar). Then the solution was passed through a short pad of Celite and rinsed with ethyl acetate. The solvent was removed by rotary evaporation to give **1c** as a white solid without requiring any further purification (100 mg, 98%).

**Mp** = 90-92 °C. **<sup>1</sup>H NMR** (360 MHz, DMSO)  $\delta$  = 11.95 (brs, 1H), 4.30 (brs, 1H), 3.36 (t, *J* = 6.5 Hz, 2H), 2.17 (t, *J* = 7.3 Hz, 2H), 1.56–1.46 (m, 2H), 1.41–1.37 (m, 2H), 1.23–1.13 (m, 34H). **<sup>13</sup>C NMR** (91 MHz, DMSO)  $\delta$  = 174.4, 60.7, 33.6, 32.5, 29.1, 29.0 (2C), 28.9, 28.7, 28.5, 25.5, 24.5, 10 carbons hidden. **IR** (film, cm<sup>-1</sup>):  $\nu_{\max}$  = 3298, 2915, 2849, 1651, 1469, 1453, 1234, 1098, 725. **HRMS** (ESI<sup>-</sup>): *m/z* calcd for C<sub>22</sub>H<sub>43</sub>O<sub>3</sub> [M-H]<sup>-</sup>: 355.3218, found: 355.3214.

### Methyl 16-azidohexadecanoate (**S1i**)

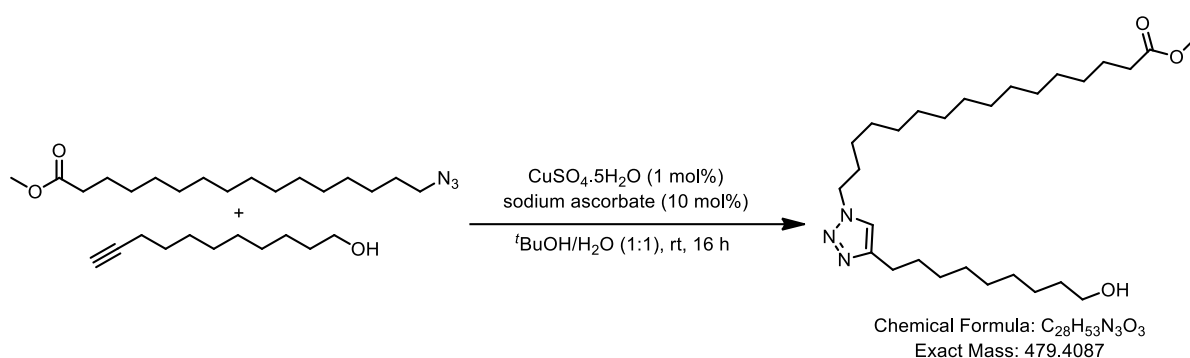


To a solution of methyl 16-bromohexadecanoate (500 mg, 1.43 mmol, 1 equiv) in DMF (10 mL) was added sodium azide (140 mg, 2.15 mmol, 1.5 equiv). The reaction mixture was stirred at 120 °C for 16

h. A part of the solvent was removed by rotary evaporation. Water was then added and the crude mixture was extracted with ethyl acetate (3 x 5 mL). The combined organic layers were washed with water (5 x 10 mL), dried over anhydrous  $\text{MgSO}_4$  and filtered. The solvent was removed by rotary evaporation to give **S1i** as a yellow oil without requiring any further purification (440 mg, 99%).

**$^1\text{H}$  NMR** (360 MHz,  $\text{CDCl}_3$ )  $\delta$  = 3.60 (s, 3H), 3.19 (t,  $J$  = 6.9 Hz, 2H), 2.24 (t,  $J$  = 7.5 Hz, 2H), 1.59–1.47 (m, 4H), 1.36–1.11 (m, 22H).  **$^{13}\text{C}$  NMR** (91 MHz,  $\text{CDCl}_3$ )  $\delta$  = 174.2, 51.4, 51.3, 34.0, 29.6 (2C), 29.5 (2C), 29.4, 29.2, 29.1, 28.8, 26.7, 24.9, 3 carbons hidden. **IR** (film,  $\text{cm}^{-1}$ ):  $\nu_{\text{max}}$  = 2925, 2849, 1718, 1652, 1385, 1011, 980. **HRMS** (ESI<sup>+</sup>):  $m/z$  calcd for  $\text{C}_{17}\text{H}_{33}\text{NaN}_3\text{O}_2$   $[\text{M}+\text{Na}]^+$ : 334.2470, found: 334.2482.

#### Methyl 16-(4-(9-hydroxynonyl)-1*H*-1,2,3-triazol-1-yl)hexadecanoate (**S1i'**)

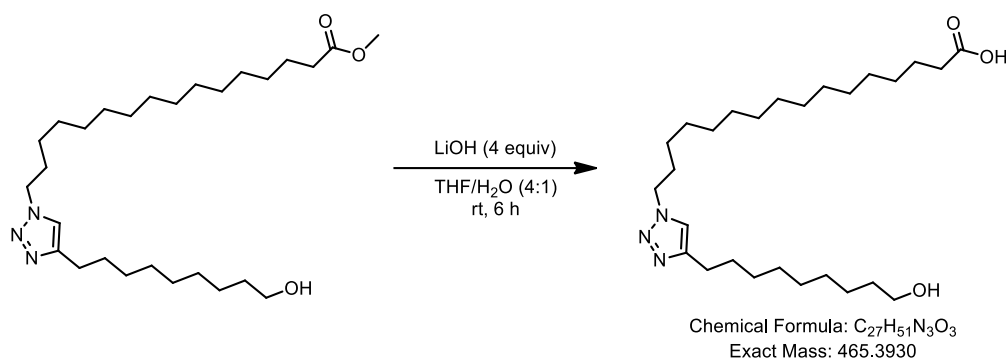


In a round bottom flask were placed **S1i** (252 mg, 0.809 mmol, 1 equiv) and undec-10-yn-1-ol (136 mg, 0.809 mmol, 1 equiv) in a solution  $t\text{BuOH}/\text{H}_2\text{O}$  (12 mL, 1:1). To this mixture were added a solution of copper sulfate pentahydrate in water (3 mg in 150  $\mu\text{L}$ , 0.0809 mmol, 1 mol%) and a solution of sodium ascorbate in water (4 mg in 300  $\mu\text{L}$ , 0.809 mmol, 10 mol%). The reaction mixture was stirred vigorously for 16 h and water (50 mL) was then added. After having cooled down it to 0 °C, it was filtered to obtain the product **S1i'** as a white solid without requiring any further purification (300 mg, 76%).

**Mp** = 73–75 °C.  **$^1\text{H}$  NMR** (360 MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.23 (s, 1H), 4.28 (t,  $J$  = 7.2 Hz, 2H), 3.65 (s, 3H), 3.70–3.59 (m, 2H), 2.68 (t,  $J$  = 7.7 Hz, 2H), 2.28 (t,  $J$  = 7.5 Hz, 2H), 1.98–1.77 (m, 2H), 1.66–1.43 (m, 8H), 1.43–1.22 (m, 30H), OH unobserved.  **$^{13}\text{C}$  NMR** (91 MHz,  $\text{CDCl}_3$ )  $\delta$  = 174.5, 148.5, 120.5, 63.1, 51.6, 50.3, 34.2, 32.9, 30.5, 29.7, 29.6, 29.5, 29.4, 29.3, 29.2, 29.1, 26.6, 25.8 (2C), 25.0, 8 carbons hidden. **IR** (film,  $\text{cm}^{-1}$ ):  $\nu_{\text{max}}$  = 3362, 2917, 2847, 1730, 1653, 1466, 1435, 1210, 1197, 1061, 1029, 1011, 978, 856, 721. **HRMS** (ESI):  $m/z$  calcd for  $\text{C}_{28}\text{H}_{54}\text{N}_3\text{O}_3$   $[\text{M}+\text{H}]^+$ : 480.4160, found: 480.4144.

#### 16-(4-(9-hydroxynonyl)-1*H*-1,2,3-triazol-1-yl)hexadecanoic acid (**1i**)

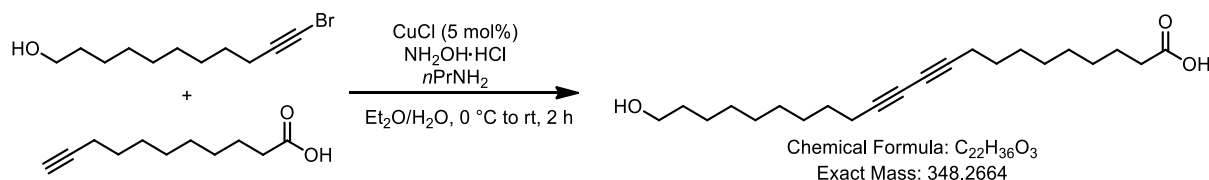




To a solution of **S1i'** (70 mg, 0.146 mmol, 1 equiv) in THF (6 mL) was added LiOH (14 mg, 0.58 mmol, 4 equiv) and water (1.5 mL). The reaction mixture was stirred at room temperature for 6 h. Then, the reaction mixture was cooled down to room temperature and HCl (1M) was added until it was neutralized (pH = 7). After extraction with ethyl acetate (3 x 5 mL), the combined organic layers were washed with brine, dried over anhydrous MgSO<sub>4</sub> and filtered. The solvent was removed by rotary evaporation to give **1i** as a white solid without requiring any further purification (33 mg, 48%).

**Mp** = 98–100 °C. <sup>1</sup>H NMR (360 MHz, MeOD)  $\delta$  = 7.72 (s, 1H), 4.35 (t,  $J$  = 7.0 Hz, 2H), 3.53 (t,  $J$  = 6.6 Hz, 2H), 2.68 (t,  $J$  = 7.6 Hz, 2H), 2.27 (t,  $J$  = 6.9 Hz, 2H), 1.92–1.86 (m, 2H), 1.68–1.50 (m, 6H), 1.40–1.23 (m, 32H), OH and CO<sub>2</sub>H unobserved. <sup>13</sup>C NMR (91 MHz, DMSO)  $\delta$  = 174.5, 146.8, 121.6, 60.7, 49.1, 33.7, 32.6, 29.7, 29.1, 29.0 (2C), 28.9 (2C), 28.8, 28.7, 28.5, 28.3, 25.8, 25.5, 25.0, 24.5, 6 carbons hidden. **IR** (film, cm<sup>-1</sup>):  $\nu_{\text{max}}$  = 3368, 2934, 2854, 1736, 1698, 1523, 1504, 1461, 1435, 1218, 1197, 995, 800. **HRMS** (ESI):  $m/z$  calcd for C<sub>27</sub>H<sub>52</sub>N<sub>3</sub>O<sub>3</sub> [M+H]<sup>+</sup>: 466.4003, found: 466.3982.

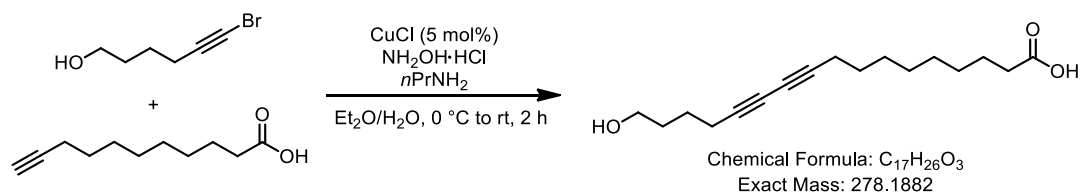
## 22-hydroxydocosa-10,12-diynoic acid (**1j**)



Copper(I) chloride (6.2 mg, 0.063 mmol, 5 mol%) was added to a 30% *n*-propylamine aqueous solution (7 mL) at room temperature, which resulted in the formation of a blue solution. A few crystals of hydroxylamine hydrochloride were added to discharge the blue color. A solution of 11-bromoundec-10-yn-1-ol (310 mg, 1.25 mmol, 1 equiv) in diethyl ether (2 mL) was added to the mixture. After having cooled down it to 0 °C with an ice-water bath, a solution of undec-10-ynoic acid (208 mg, 1.13 mmol, 0.9 equiv) in diethyl ether (2 mL) was added dropwise. The reaction mixture was stirred at room temperature for 2 h. Occasionally, adding a small amount of hydroxylamine hydrochloride was necessary to keep the color of the reaction light brown. The reaction was quenched with HCl (2M) until pH = 2. After extraction with ethyl acetate (3 x 10 mL), the combined organic layers were washed with water, brine, dried over anhydrous MgSO<sub>4</sub> and filtered. The solvent was removed by rotary evaporation. The crude product was purified by flash column chromatography using PE/EtOAc (1:1) as eluent to give **1j** as a white solid (260 mg, 66%).

**Mp** = 59-61 °C. **<sup>1</sup>H NMR** (360 MHz, CDCl<sub>3</sub>)  $\delta$  = 6.00 (brs, 1H), 3.63 (t,  $J$  = 6.7 Hz, 2H), 2.32 (t,  $J$  = 7.5 Hz, 2H), 2.23 (t,  $J$  = 6.9 Hz, 4H), 1.69–1.46 (m, 8H), 1.40–1.23 (m, 18H), one H unobserved. **<sup>13</sup>C NMR** (91 MHz, CDCl<sub>3</sub>)  $\delta$  = 179.4, 77.6 (2C), 65.4 (2C), 63.1, 34.1, 32.7, 29.5, 29.4, 29.2, 29.1 (2C), 29.0, 28.9, 28.8, 28.4 (2C), 25.8, 24.8, 19.3, one carbon hidden. **IR** (film, cm<sup>-1</sup>):  $\nu_{\text{max}}$  = 3380, 2916, 2850, 2158, 1702, 1470, 1056, 717. **HRMS** (ESI<sup>+</sup>):  $m/z$  calcd for C<sub>22</sub>H<sub>36</sub>NaO<sub>3</sub> [M+Na]<sup>+</sup>: 371.2557, found: 301.2538.

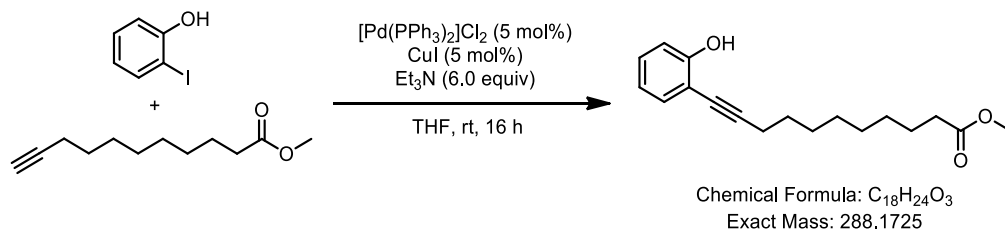
### 17-hydroxyheptadeca-10,12-diyonic acid (**1k**)



Copper(I) chloride (12.5 mg, 0.127 mmol, 5 mol%) was added to a 30% *n*-propylamine aqueous solution (15 mL) at room temperature, which resulted in the formation of a blue solution. A few crystals of hydroxylamine hydrochloride were added to discharge the blue color. A solution of 6-bromohex-5-yn-1-ol (450 mg, 2.54 mmol, 1 equiv) in diethyl ether (4 mL) was added to the mixture. After having cooled down it to 0 °C with an ice-water bath, a solution of undec-10-ynoic acid (417 mg, 2.29 mmol, 0.9 equiv) in diethyl ether (4 mL) was added dropwise. The reaction mixture was stirred at room temperature for 2 h. Occasionally, adding a small amount of hydroxylamine hydrochloride was necessary to keep the color of the reaction light brown. The reaction was quenched with HCl (2M) until pH = 2. After extraction with ethyl acetate (3 x 10 mL), the combined organic layers were washed with water, brine, dried over anhydrous MgSO<sub>4</sub> and filtered. The solvent was removed by rotary evaporation. The crude product was purified by flash column chromatography using PE/EtOAc (1:1) as eluent to give **1k** as a white solid (549 mg, 78%).

**Mp** = 54-56 °C. **<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>)  $\delta$  = 5.94 (brs, 1H), 3.67 (t,  $J$  = 6.2 Hz, 2H), 2.39–2.18 (m, 6H), 1.74–1.57 (m, 6H), 1.55–1.46 (m, 2H), 1.42–1.24 (m, 8H), CO<sub>2</sub>H unobserved. **<sup>13</sup>C NMR** (63 MHz, CDCl<sub>3</sub>)  $\delta$  = 179.3, 77.8, 77.0, 65.8, 65.3, 62.3, 34.1, 31.6, 29.1, 29.0, 28.9, 28.8, 28.3, 24.7 (2C), 19.2, 19.1. **IR** (film, cm<sup>-1</sup>):  $\nu_{\text{max}}$  = 3378, 2923, 2849, 2190, 1698, 1465, 1360, 1219, 1053, 987, 929, 725. **HRMS** (ESI<sup>+</sup>):  $m/z$  calcd for C<sub>17</sub>H<sub>26</sub>NaO<sub>3</sub> [M+Na]<sup>+</sup>: 301.1774, found: 301.1758.

### Methyl 11-(2-hydroxyphenyl)undec-10-ynoate (**S1r**)

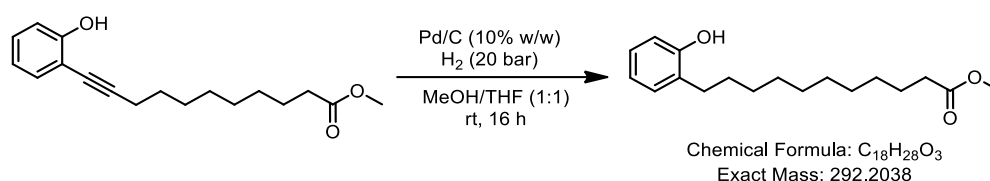


To a solution of 2-iodophenol (820 mg, 3.72 mmol, 1 equiv) in THF (25 mL) were added [Pd(PPh<sub>3</sub>)<sub>2</sub>]Cl<sub>2</sub> (130 mg, 0.186 mmol, 5 mol%) and CuI (35 mg, 0.186 mmol, 5 mol%) under argon. Triethylamine (3.1 mL, 22.32 mmol, 6 equiv.) and methyl undec-10-ynoate (804 mg, 4.10 mmol, 1.1 equiv) were then added and the reaction mixture was stirred at room temperature for 16 h. Then, it was quenched with

water (20 mL) and extracted with ethyl acetate (3 x 7 mL). The combined organic layers were washed with brine, dried over anhydrous  $\text{MgSO}_4$  and filtered. The solvent was removed by rotary evaporation. The crude product was purified by flash column chromatography using PE/EtOAc (8:2) as eluent to give **S1r** as a yellow oil (898 mg, 84%).

**$^1\text{H}$  NMR** (360 MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.28 (dd,  $J$  = 7.7, 1.5 Hz, 1H), 7.21–7.15 (m, 1H), 6.92 (dd,  $J$  = 8.2, 0.7 Hz, 1H), 6.83 (td,  $J$  = 7.5, 1.0 Hz, 1H), 5.96 (brs, 1H), 3.66 (s, 3H), 2.46 (t,  $J$  = 7.1 Hz, 2H), 2.30 (t,  $J$  = 7.5 Hz, 2H), 1.70–1.54 (m, 4H), 1.51–1.40 (m, 2H), 1.36–1.25 (m, 6H).  **$^{13}\text{C}$  NMR** (91 MHz,  $\text{CDCl}_3$ )  $\delta$  = 174.5, 156.6, 131.6, 129.6, 120.2, 114.4, 110.3, 97.9, 74.7, 51.6, 34.1, 29.2, 29.1, 29.0, 28.9, 28.7, 25.0, 19.6. **IR** (film,  $\text{cm}^{-1}$ ):  $\nu_{\text{max}}$  = 3445, 2930, 2856, 1738, 1602, 1455, 1354, 1252, 1170, 750. **HRMS** ( $\text{ESI}^+$ ):  $m/z$  calcd for  $\text{C}_{18}\text{H}_{24}\text{NaO}_3$   $[\text{M}+\text{Na}]^+$ : 311.1618, found: 311.1604.

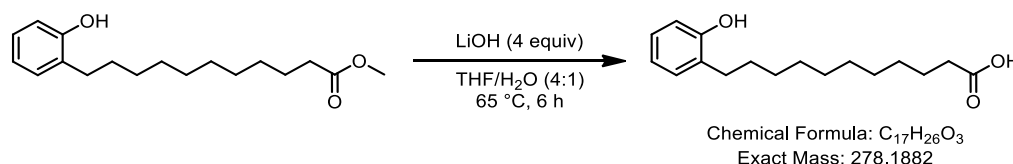
### Methyl 11-(2-hydroxyphenyl)undecanoate (**S1r'**)



In a vial were placed **S1r** (386 mg, 1.34 mmol, 1 equiv), Pd/C (38.6 mg, 10% w/w), methanol (4 mL) and THF (4 mL). In an autoclave, the reaction mixture was purged three times with  $\text{H}_2$  (10 bar) and stirred at room temperature for 16 h under  $\text{H}_2$  (20 bar). Then, the mixture was passed through a short pad of Celite and rinsed with ethyl acetate. The solvent was removed by rotary evaporation. The crude product was purified by flash column chromatography using PE/EtOAc (7:3) as eluent to give **S1r'** as a white solid (305 mg, 78%).

**Mp** = 37–39 °C.  **$^1\text{H}$  NMR** (300 MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.09 (d,  $J$  = 7.3 Hz, 1H), 7.03 (t,  $J$  = 7.3 Hz, 1H), 6.84 (d,  $J$  = 7.3 Hz, 1H), 6.78 (t,  $J$  = 7.3 Hz, 1H), 6.15 (s, 1H), 3.67 (s, 3H), 2.60 (t,  $J$  = 7.6 Hz, 2H), 2.31 (t,  $J$  = 7.3 Hz, 2H), 1.70–1.55 (m, 4H), 1.42–1.23 (m, 12H).  **$^{13}\text{C}$  NMR** (75 MHz,  $\text{CDCl}_3$ )  $\delta$  = 175.2, 153.9, 130.1, 129.0, 126.8, 120.3, 115.2, 51.7, 34.2, 30.0, 29.8, 29.6, 29.5, 29.4, 29.2, 29.1, 24.9, one carbon hidden. **IR** (film,  $\text{cm}^{-1}$ ):  $\nu_{\text{max}}$  = 3391, 2918, 2848, 1700, 1606, 1594, 1505, 1456, 1351, 1268, 1190, 1111, 750. **HRMS** ( $\text{ESI}^+$ ):  $m/z$  calcd for  $\text{C}_{18}\text{H}_{28}\text{NaO}_3$   $[\text{M}+\text{Na}]^+$ : 315.1931, found: 315.1913.

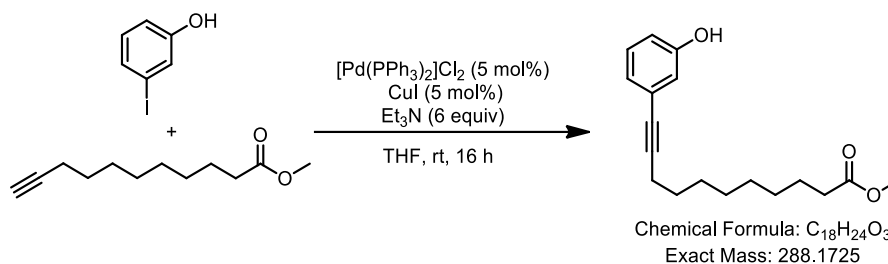
### 11-(2-hydroxyphenyl)undecanoic acid (**1r**)



To a solution of **S1s'** (190 mg, 0.650 mmol, 1 equiv) in THF (4 mL) was added LiOH (63 mg, 2.60 mmol, 4 equiv) and water (1 mL). The reaction mixture was stirred at 65 °C for 6 h. Then, the reaction mixture was cooled down to room temperature and HCl (1M) was added until it was neutralized (pH = 7). After extraction with ethyl acetate (3 x 5 mL), the combined organic layers were washed with brine, dried over anhydrous  $\text{MgSO}_4$  and filtered. The solvent was removed by rotary evaporation to give **1r** as a white solid without requiring any further purification (134 mg, 74%).

**Mp** = 62–64 °C. **<sup>1</sup>H NMR** (360 MHz, CDCl<sub>3</sub>)  $\delta$  = 7.96 (brs, 1H), 7.12 (d,  $J$  = 7.3 Hz, 1H), 7.07 (t,  $J$  = 7.7 Hz, 1H), 6.86 (t,  $J$  = 7.3 Hz, 1H), 6.76 (d,  $J$  = 7.7 Hz, 1H), 2.60 (t,  $J$  = 7.6 Hz, 2H), 2.39–2.29 (m, 2H), 1.71–1.55 (m, 4H), 1.40–1.20 (m, 12H), CO<sub>2</sub>H unobserved. **<sup>13</sup>C NMR** (91 MHz, CDCl<sub>3</sub>)  $\delta$  = 180.2, 153.6, 130.2, 128.9, 127.0, 120.7, 115.3, 34.6, 30.1, 29.9, 29.6, 29.5 (2C), 29.3, 29.2, 24.9, one carbon hidden. **IR** (film, cm<sup>-1</sup>):  $\nu_{\text{max}}$  = 3445, 2917, 2850, 1683, 1460, 1411, 1337, 1204, 1098, 952, 750. **HRMS** (ESI<sup>-</sup>):  $m/z$  calcd for C<sub>17</sub>H<sub>25</sub>O<sub>3</sub> [M-H]<sup>-</sup>: 277.1809, found: 277.1823.

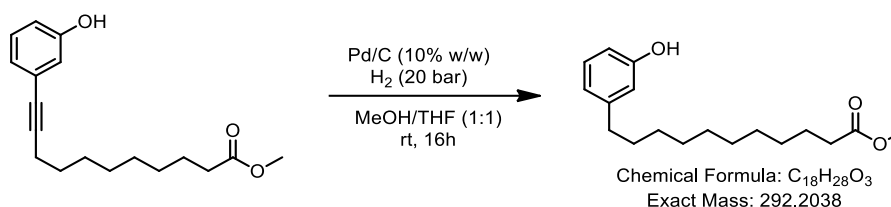
### Methyl 11-(3-hydroxyphenyl)undec-10-ynoate (**S1s**)



To a solution of 3-iodophenol (820 mg, 3.72 mmol, 1 equiv) in THF (25 mL) were added [Pd(PPh<sub>3</sub>)<sub>2</sub>]Cl<sub>2</sub> (130 mg, 0.186 mmol, 5 mol%) and CuI (35 mg, 0.186 mmol, 5 mol%) under argon. Triethylamine (3.1 mL, 22.32 mmol, 6 equiv.) and methyl undec-10-ynoate (804 mg, 4.10 mmol, 1.1 equiv) were then added and the reaction mixture was stirred at room temperature for 16 h. Then, it was quenched with water (20 mL) and extracted with ethyl acetate (3 x 7 mL). The combined organic layers were washed with brine, dried over anhydrous MgSO<sub>4</sub> and filtered. The solvent was removed by rotary evaporation. The crude product was purified by flash column chromatography using PE/EtOAc (8:2) as eluent to give **S1s** as a yellow solid (405 mg, 38%).

**Mp** = 48–50 °C. **<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>)  $\delta$  = 7.11 (t,  $J$  = 7.9 Hz, 1H), 6.96 (s, 1H), 6.92–6.90 (m, 1H), 6.78 (ddd,  $J$  = 8.2, 2.6, 0.9 Hz, 1H), 3.68 (s, 3H), 2.37 (t,  $J$  = 6.9 Hz, 2H), 2.33 (t,  $J$  = 7.5 Hz, 2H), 1.71–1.51 (m, 4H), 1.49–1.39 (m, 2H), 1.37–1.25 (m, 6H), OH unobserved. **<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>)  $\delta$  = 175.5, 155.8, 129.4, 125.1, 123.7, 118.3, 115.1, 90.3, 80.6, 51.9, 34.2, 29.1, 29.00, 28.8, 28.7, 28.5, 24.9, 19.3. **IR** (film, cm<sup>-1</sup>):  $\nu_{\text{max}}$  = 3333, 2928, 2850, 1708, 1572, 1467, 1317, 1247, 1212, 1178, 784, 501. **HRMS** (ESI<sup>+</sup>):  $m/z$  calcd for C<sub>18</sub>H<sub>24</sub>NaO<sub>3</sub> [M+Na]<sup>+</sup>: 311.1618, found: 311.1606.

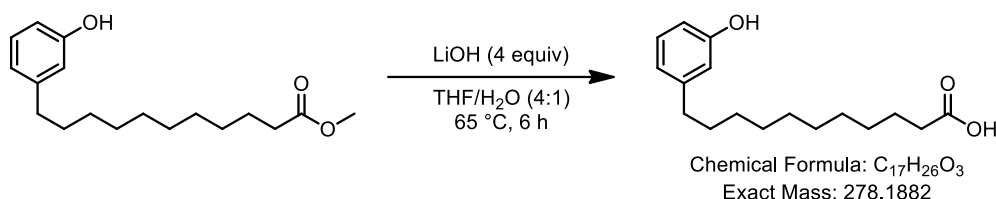
### Methyl 11-(3-hydroxyphenyl)undecanoate (**S1s'**)



In a vial were placed **S1s** (335 mg, 1.16 mmol, 1 equiv), Pd/C (33.5 mg, 10% w/w), methanol (4 mL) and THF (4 mL). In an autoclave, the reaction mixture was purged three times with H<sub>2</sub> (10 bar) and stirred at room temperature for 16 h under H<sub>2</sub> (20 bar). Then, the mixture was passed through a short pad of Celite and rinsed with ethyl acetate. The solvent was removed by rotary evaporation to give **S1t'** as a white solid without requiring any further purification (310 mg, 93%).

**Mp** = 50-52 °C. **<sup>1</sup>H NMR** (360 MHz, CDCl<sub>3</sub>)  $\delta$  = 7.12 (t,  $J$  = 7.7 Hz, 1H), 6.79–6.67 (m, 3H), 6.45 (brs, 1H), 3.69 (s, 3H), 2.54 (t,  $J$  = 7.2 Hz, 2H), 2.33 (t,  $J$  = 7.5 Hz, 2H), 1.72–1.55 (m, 4H), 1.41–1.27 (m, 12H). **<sup>13</sup>C NMR** (91 MHz, CDCl<sub>3</sub>)  $\delta$  = 175.2, 156.0, 144.8, 129.3, 120.6, 115.5, 112.6, 51.8, 35.9, 34.2, 31.3, 29.5, 29.4, 29.3, 29.2, 29.1, 25.0, one carbon hidden. **IR** (film, cm<sup>-1</sup>):  $\nu_{\text{max}}$  = 3369, 2920, 2849, 1712, 1618, 1588, 1469, 1316, 1224, 1179, 951, 689, 495. **HRMS** (ESI<sup>+</sup>):  $m/z$  calcd for C<sub>18</sub>H<sub>28</sub>NaO<sub>3</sub> [M+Na]<sup>+</sup>: 315.1931, found: 315.1916.

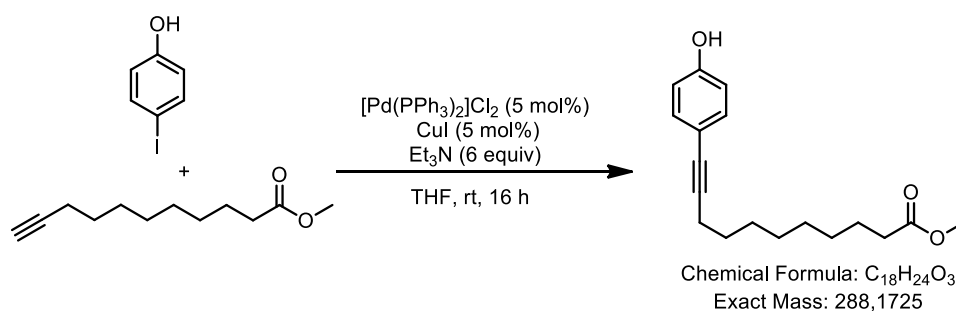
### 11-(3-hydroxyphenyl)undecanoic acid (**1s**)



To a solution of **S1s**' (300 mg, 1.03 mmol, 1 equiv) in THF (4 mL) was added LiOH (98 mg, 4.1 mmol, 4 equiv) and water (1 mL). The reaction mixture was stirred at 65 °C for 6 h. Then, the reaction mixture was cooled down to room temperature and HCl (1M) was added until it was neutralized (pH = 7). After extraction with ethyl acetate (3 x 5 mL), the combined organic layers were washed with brine, dried over anhydrous MgSO<sub>4</sub> and filtered. The solvent was removed by rotary evaporation to give **1s** as a white solid without requiring any further purification (210 mg, 73%).

**Mp** = 65-67 °C. **<sup>1</sup>H NMR** (360 MHz, MeOD)  $\delta$  = 7.04 (t,  $J$  = 7.8 Hz, 1H), 6.66–6.54 (m, 3H), 2.51 (t,  $J$  = 7.6 Hz, 2H), 2.26 (t,  $J$  = 7.3 Hz, 2H), 1.70–1.57 (m, 4H), 1.46–1.15 (m, 12H), CO<sub>2</sub>H and OH unobserved. **<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>)  $\delta$  = 178.5, 158.2, 145.5, 130.1, 120.7, 116.2, 113.5, 36.9, 32.5, 30.6, 30.5, 30.4, 30.3, 26.3, 3 carbons hidden. **IR** (film, cm<sup>-1</sup>):  $\nu_{\text{max}}$  = 3436, 2925, 2851, 1687, 1412, 1378, 1204, 1098, 941, 725. **HRMS** (ESI<sup>+</sup>):  $m/z$  calcd for C<sub>17</sub>H<sub>26</sub>NaO<sub>3</sub> [M+Na]<sup>+</sup>: 301.1774, found: 301.1761.

### Methyl 11-(4-hydroxyphenyl)undec-10-ynoate (**S1t**)

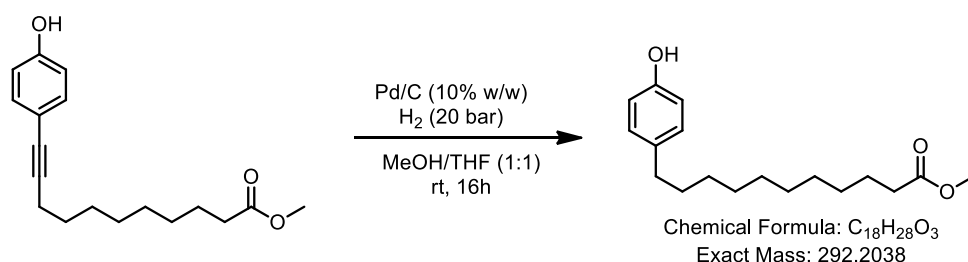


To a solution of 4-iodophenol (644 mg, 2.93 mmol, 1 equiv) in THF (25 mL) were added [Pd(PPh<sub>3</sub>)<sub>2</sub>]Cl<sub>2</sub> (102 mg, 0.146 mmol, 5 mol%) and CuI (28 mg, 0.146 mmol, 5 mol%) under argon. Triethylamine (2.4 mL, 17.60 mmol, 6 equiv.) and methyl undec-10-ynoate (632 mg, 3.22 mmol, 1.1 equiv) were then added and the reaction mixture was stirred at room temperature for 16 h. Then, it was quenched with water (20 mL) and extracted with ethyl acetate (3 x 7 mL). The combined organic layers were washed

with brine, dried over anhydrous  $\text{MgSO}_4$  and filtered. The solvent was removed by rotary evaporation. The crude product was purified by flash column chromatography using PE/EtOAc (8:2) as eluent to give **S1t** as a brown solid (370 mg, 44%).

**Mp** = 56–58 °C.  $^1\text{H}$  NMR (360 MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.25 (d,  $J$  = 8.7 Hz, 2H), 6.75 (d,  $J$  = 8.7 Hz, 2H), 6.60 (brs, 1H), 3.67 (s, 3H), 2.40–2.26 (m, 4H), 1.69–1.52 (m, 4H), 1.46–1.39 (m, 2H), 1.29–1.23 (m, 6H).  $^{13}\text{C}$  NMR (91 MHz,  $\text{CDCl}_3$ )  $\delta$  = 175.3, 155.6, 133.1, 116.0, 115.5, 115.4, 88.6, 80.4, 51.8, 34.2, 29.2, 29.1, 29.0, 28.9, 25.0, 19.4. **IR** (film,  $\text{cm}^{-1}$ ):  $\nu_{\text{max}}$  = 3325, 2930, 2853, 1710, 1697, 1509, 1467, 1268, 1247, 1097, 801. **HRMS** ( $\text{ESI}^+$ ):  $m/z$  calcd for  $\text{C}_{18}\text{H}_{24}\text{NaO}_3$  [ $\text{M}+\text{Na}$ ] $^+$ : 311.1618, found: 311.1606.

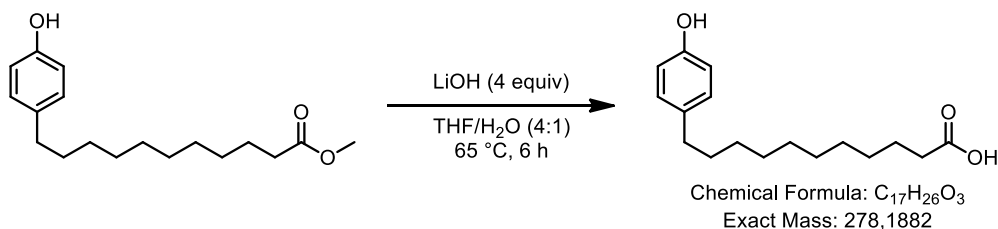
#### Methyl 11-(4-hydroxyphenyl)undecanoate (**S1t'**)



In a vial were placed **S1t** (350 mg, 1.21 mmol, 1 equiv), Pd/C (35 mg, 10% w/w), methanol (4 mL) and THF (4 mL). In an autoclave, the reaction mixture was purged three times with  $\text{H}_2$  (10 bar) and stirred at room temperature for 16 h under  $\text{H}_2$  (20 bar). Then, the mixture was passed through a short pad of Celite and rinsed with ethyl acetate. The solvent was removed by rotary evaporation to give **S1t'** as a brown solid without requiring any further purification (323 mg, 91%).

**Mp** = 61–63 °C.  $^1\text{H}$  NMR (360 MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.03 (d,  $J$  = 8.4 Hz, 2H), 6.78 (d,  $J$  = 8.4 Hz, 2H), 6.06 (s, 1H), 3.69 (s,  $J$  = 3.9 Hz, 3H), 2.53 (t,  $J$  = 7.7 Hz, 2H), 2.32 (t,  $J$  = 7.6 Hz, 2H), 1.69–1.52 (m, 4H), 1.42–1.15 (m, 12H).  $^{13}\text{C}$  NMR (91 MHz,  $\text{CDCl}_3$ )  $\delta$  = 175.1, 153.9, 134.8, 129.4, 115.2, 51.7, 35.1, 34.3, 31.8, 29.6, 29.5, 29.4, 29.3, 29.2 (2C), 25.0. **IR** (film,  $\text{cm}^{-1}$ ):  $\nu_{\text{max}}$  = 3427, 2921, 2851, 1716, 1615, 1518, 1437, 1353, 1236, 1171, 1030, 897. **HRMS** ( $\text{ESI}^+$ ):  $m/z$  calcd for  $\text{C}_{18}\text{H}_{28}\text{NaO}_3$  [ $\text{M}+\text{Na}$ ] $^+$ : 315.1931, found: 315.1922.

#### 11-(4-hydroxyphenyl)undecanoic acid (**1t**)



To a solution of **S1t'** (323 mg, 1.11 mmol, 1 equiv) in THF (4 mL) was added LiOH (106 mg, 4.44 mmol, 4 equiv) and water (1 mL). The reaction mixture was stirred at 65 °C for 6 h. Then, the reaction mixture was cooled down to room temperature and HCl (1M) was added until it was neutralized (pH = 7). After extraction with ethyl acetate (3 x 5 mL), the combined organic layers were washed with brine,

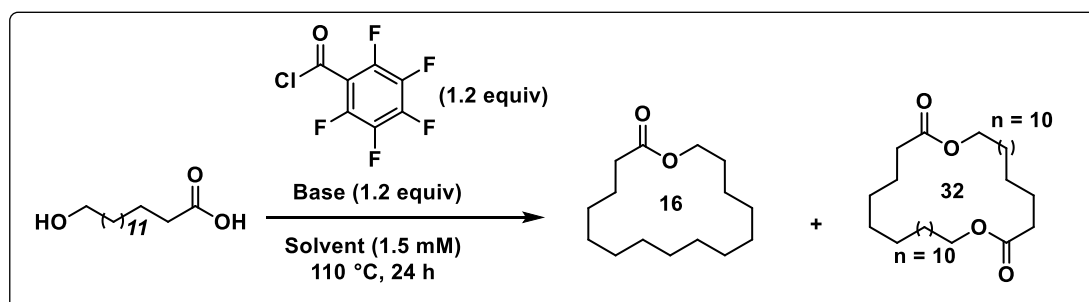
dried over anhydrous  $\text{MgSO}_4$  and filtered. The solvent was removed by rotary evaporation to give **1t** as a white off solid without requiring any further purification (275 mg, 89%).

**Mp** = 90–92 °C.  **$^1\text{H}$  NMR** (360 MHz, MeOD)  $\delta$  = 6.96 (d,  $J$  = 8.4 Hz, 2H), 6.68 (d,  $J$  = 8.4 Hz, 2H), 2.49 (t,  $J$  = 7.7 Hz, 2H), 2.27 (t,  $J$  = 7.4 Hz, 2H), 1.65–1.48 (m, 4H), 1.40–1.21 (m, 12H),  $\text{CO}_2\text{H}$  and OH unobserved.  **$^{13}\text{C}$  NMR** (91 MHz, MeOD)  $\delta$  = 177.7, 156.2, 134.8, 130.2, 116.0, 36.0, 35.0, 33.0, 30.6, 30.5, 30.4, 30.2, 26.1, 2 carbons hidden. **IR** (film,  $\text{cm}^{-1}$ ):  $\nu_{\text{max}}$  = 3429, 2931, 2850, 1715, 1687, 1507, 1412, 1380, 1098, 1110, 941. **HRMS** (ESI<sup>+</sup>):  $m/z$  calcd for  $\text{C}_{17}\text{H}_{26}\text{NaO}_3$   $[\text{M}+\text{Na}]^+$ : 301.1774, found: 301.1770.

## General procedure for Macrolactonizations and Esterifications

Pentafluorobenzoyl chloride (1.2 equiv) and triethylamine (1.2 equiv) were added to a solution of **(i)** hydroxyacid derivative (1.0 equiv)/ **(ii)** diacid (0.5 equiv.) and diol (0.5 equiv)/ **(iii)** acid (1 equiv) and alcohol (1.0 equiv.) in dry toluene (0.015 M for macrolactonization and 0.1 M for esterification). The reaction mixture was stirred at 110 °C for the indicated time. Then, the solvent was removed by rotary evaporation. The crude product was re-dissolved in ethyl acetate (20 mL) and washed with saturated solution of  $\text{NaHCO}_3$ , brine, dried over anhydrous  $\text{MgSO}_4$  and filtered. The solvent was removed by rotary evaporation and the crude product was purified by flash column chromatography using gradients of various eluents.

## Optimizations



Base	macrolactone	macrodiolide	ratio
DIPEA	86%	7%	12.3:1
$\text{K}_2\text{CO}_3$	71%	14%	4.9:1
DMAP	24%	8%	3:1
$\text{Et}_3\text{N}$	88%	5.5%	16:1
DABCO	65%	10%	6.5:1
NaH	44%	14%	3.1:1

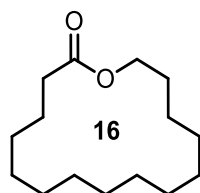
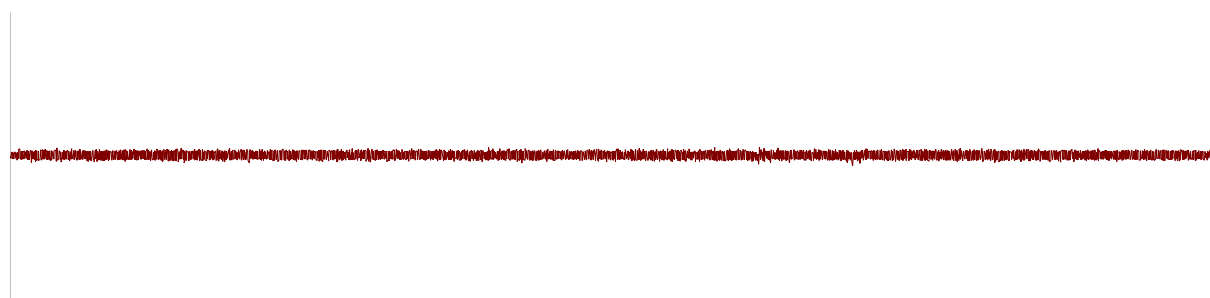
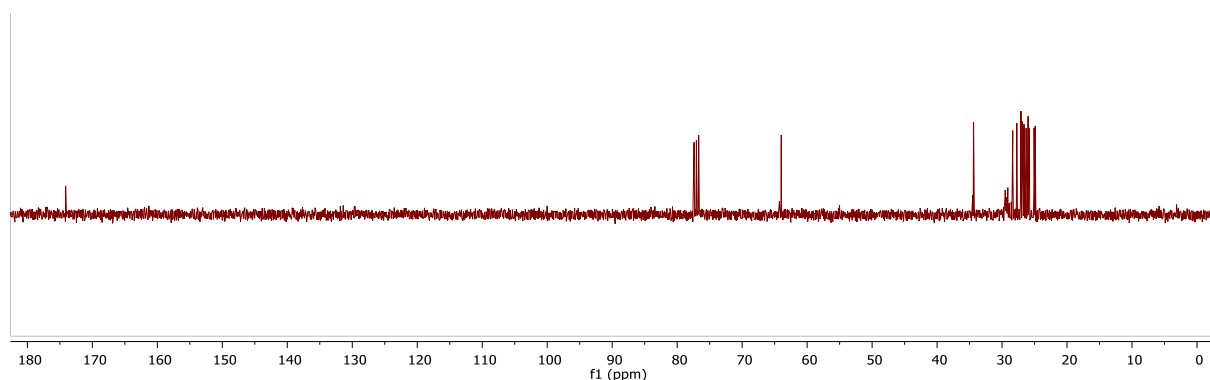
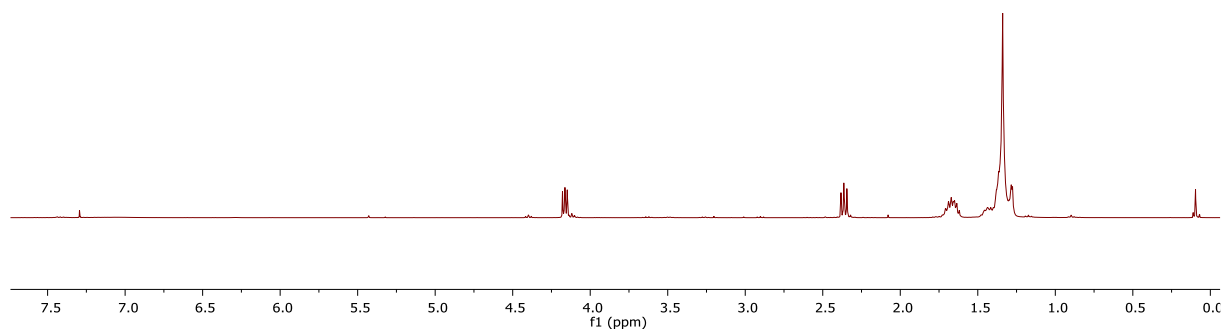
  

Solvent	macrolactone	macrodiolide	ratio
Dry Toluene	88%	5.5%	16:1
Toluene	86%	5%	17:1
Toluene (rt)	83%	7%	11.8:1
THF	83%	8%	10.4:1
$\text{CH}_3\text{CN}$	82%	7%	11.7:1
1,2-DCE	54%	7%	7.7:1

## Oxacyclohexadecan-2-one (2a) and 1,17-dioxacyclodotriacontane-2,18-dione (3a)

Following the general procedure, starting from 15-hydroxypentadecanoic acid **1a** (50 mg, 0.193 mmol, 1 equiv), pentafluorobenzoyl chloride (33  $\mu$ L, 0.231 mmol, 1.2 equiv), triethylamine (32  $\mu$ L, 0.231 mmol, 1.2 equiv) and toluene (128 ml) for 24 h. The crude product was purified by flash column chromatography (100 to 96/4 PE/EtOAc) to afford **2a** as a white solid (40 mg, 88%) and **3a** as a white solid (5 mg, 5.5%).

#### NMR of crude product (proton, carbon and fluorine)

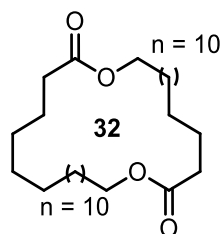


Chemical Formula:  $C_{15}H_{28}O_2$   
Molecular Weight: 240,3816



**<sup>1</sup>H NMR** (360 MHz, CDCl<sub>3</sub>)  $\delta$  = 4.12 (t,  $J$  = 6.1 Hz, 2H), 2.32 (t,  $J$  = 7.2 Hz, 2H), 1.69–1.57 (m, 4H), 1.44–1.24 (m, 20H). **<sup>13</sup>C NMR** (63 MHz, CDCl<sub>3</sub>)  $\delta$  = 174.2, 64.1, 34.6, 28.5, 27.9, 27.2, 27.0, 26.8, 26.4, 26.1, 26.0, 25.9, 25.2, 25.1, one carbon hidden. **HRMS** (ESI<sup>+</sup>):  $m/z$  calcd for C<sub>15</sub>H<sub>28</sub>NaO<sub>2</sub> [M+Na]<sup>+</sup>: 263.1982, found: 263.1972.

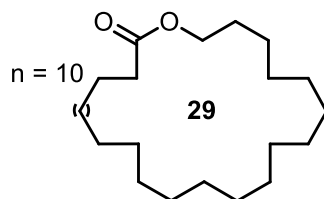
Data are in agreement with: M. De Léséleuc, S. K. Collins, *ACS Catal.* **2015**, 5, 1462.



Chemical Formula: C<sub>30</sub>H<sub>56</sub>O<sub>4</sub>  
Molecular Weight: 480,7632

**Mp** = 95–97 °C. **<sup>1</sup>H NMR** (360 MHz, CDCl<sub>3</sub>)  $\delta$  = 4.09 (t,  $J$  = 6.1 Hz, 4H), 2.30 (t,  $J$  = 7.2 Hz, 4H), 1.65–1.58 (m, 8H), 1.40–1.21 (m, 40H). **<sup>13</sup>C NMR** (91 MHz, CDCl<sub>3</sub>)  $\delta$  = 174.2, 64.4, 34.7, 29.7 (2C), 29.6 (2C), 29.5, 29.3, 29.1, 28.8, 26.2, 25.3, 2 carbons hidden. **IR** (film, cm<sup>-1</sup>):  $\nu_{\max}$  = 2913, 2849, 1731, 1457, 1277, 1110, 920, 734. **HRMS** (ESI<sup>+</sup>):  $m/z$  calcd for C<sub>30</sub>H<sub>56</sub>NaO<sub>4</sub> [M+Na]<sup>+</sup>: 503.4070, found: 503.4056.

#### Oxacyclononacosan-2-one (2b)

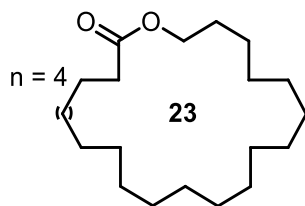


Chemical Formula: C<sub>28</sub>H<sub>54</sub>O<sub>2</sub>  
Molecular Weight: 422,4124

Following the general procedure, starting from 28-hydroxypentadecanoic acid **1b** (36 mg, 0.071 mmol, 1 equiv), pentafluorobenzoyl chloride (14  $\mu$ L, 0.096 mmol, 1.2 equiv), triethylamine (14  $\mu$ L, 0.096 mmol, 1.2 equiv) and toluene (54 ml) for 24 h. The crude product was purified by flash column chromatography (100 to 95/5 PE/EtOAc) to afford **2b** as a colorless oil (33 mg, 95%).

**<sup>1</sup>H NMR** (360 MHz, CDCl<sub>3</sub>)  $\delta$  = 4.08 (t,  $J$  = 6.3 Hz, 1H), 2.30 (t,  $J$  = 7.3 Hz, 1H), 1.70–1.60 (m, 4H), 1.32–1.22 (m, 46H). **<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>)  $\delta$  = 174.2, 64.5, 34.7, 29.8, 29.4, 29.1, 28.9, 26.2, 25.2, 19 carbons hidden. **IR** (film, cm<sup>-1</sup>):  $\nu_{\max}$  = 2945, 2852, 1738, 1500, 1468, 1298, 1249, 1097, 1001, 968. **HRMS** (ESI<sup>+</sup>):  $m/z$  calcd for C<sub>28</sub>H<sub>54</sub>NaO<sub>2</sub> [M+Na]<sup>+</sup>: 445.4016, found: 445.3996.

#### Oxacyclotricosan-2-one (2c)

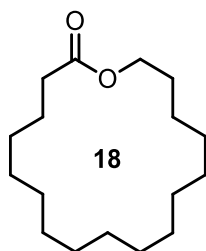


Chemical Formula:  $C_{22}H_{42}O_2$   
Molecular Weight: 338,5677

Following the general procedure, starting from 22-hydroxypentadecanoic acid **1c** (30 mg, 0.084 mmol, 1 equiv), pentafluorobenzoyl chloride (15  $\mu$ L, 0.102 mmol, 1.2 equiv), triethylamine (15  $\mu$ L, 0.102 mmol, 1.2 equiv) and toluene (57 ml) for 24 h. The crude product was purified by flash column chromatography (100 to 95/5 PE/EtOAc) to afford **2c** as a white solid (27 mg, 95%).

**Mp** = 89–91 °C.  **$^1H$  NMR** (360 MHz,  $CDCl_3$ )  $\delta$  = 4.09 (t,  $J$  = 6.1 Hz, 2H), 2.31 (t,  $J$  = 7.1 Hz, 2H), 1.70–1.58 (m, 4H), 1.38–1.23 (m, 34H).  **$^{13}C$  NMR** (91 MHz,  $CDCl_3$ )  $\delta$  = 174.2, 64.5, 34.8, 29.8, 29.2, 29.1 (2C), 29.0 (2C), 28.9, 28.8, 28.7, 28.4, 28.3, 28.2, 28.1, 27.8, 26.2, 25.2, 3 carbons hidden. **IR** (film,  $cm^{-1}$ ):  $\nu_{max}$  = 2933, 2858, 1741, 1502, 1461, 1328, 1237, 1097, 998, 725. **MS** (IE):  $m/z$  (%): 338.2 (13) [M], 320.2 (10) [M–H<sub>2</sub>O].

#### Oxacyclooctadecan-2-one (2d)



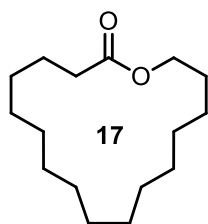
Chemical Formula:  $C_{17}H_{32}O_2$   
Molecular Weight: 268,4348

Following the general procedure, starting from 17-hydroxypentadecanoic acid **1d** (30 mg, 0.105 mmol, 1 equiv), pentafluorobenzoyl chloride (18  $\mu$ L, 0.126 mmol, 1.2 equiv), triethylamine (17  $\mu$ L, 0.126 mmol, 1.2 equiv) and toluene (70 ml) for 24 h. The crude product was purified by flash column chromatography (100 to 95/5 PE/EtOAc) to afford **2d** as a white solid (26 mg, 92%).

**$^1H$  NMR** (360 MHz,  $CDCl_3$ )  $\delta$  = 4.10 (t,  $J$  = 6.2 Hz, 2H), 2.31 (t,  $J$  = 7.1 Hz, 2H), 1.77–1.58 (m, 4H), 1.40–1.25 (m, 24H).  **$^{13}C$  NMR** (91 MHz,  $CDCl_3$ )  $\delta$  = 174.1, 64.3, 35.0, 28.7, 28.4 (2C), 28.3, 27.9, 27.4 (2C), 27.3, 27.1, 26.8, 26.3, 25.5, 25.2, one carbon hidden. **MS** (IE):  $m/z$  (%): 268.2 (8) [M], 250.2 (10) [M–H<sub>2</sub>O].

Data are in agreement with: K. Nishikawa, Y. Yoshimi, K. Maeda, T. Morita, I. Takahashi, T. Itou, S. Inagaki, M. Hatanaka, *J. Org. Chem.* **2013**, 78, 582.

#### Oxacycloheptadecan-2-one (2e)



Chemical Formula: C<sub>16</sub>H<sub>30</sub>O<sub>2</sub>  
Molecular Weight: 254,4082

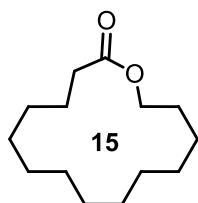
Following the general procedure, starting from 16-hydroxypentadecanoic acid **1e** (50 mg, 0.184 mmol, 1 equiv), pentafluorobenzoyl chloride (32  $\mu$ L, 0.221 mmol, 1.2 equiv), triethylamine (30  $\mu$ L, 0.221 mmol, 1.2 equiv) and toluene (122 ml) for 24 h. The crude product was purified by flash column chromatography (100 to 95/5 PE/EtOAc) to afford **2e** as a white solid (44 mg, 94%).

**<sup>1</sup>H NMR** (360 MHz, CDCl<sub>3</sub>)  $\delta$  = 4.12 (t,  $J$  = 6.2 Hz, 2H), 2.32 (t,  $J$  = 7.2 Hz, 2H), 1.69–1.59 (m, 4H), 1.41–1.25 (m, 22H). **<sup>13</sup>C NMR** (63 MHz, CDCl<sub>3</sub>)  $\delta$  = 174.2, 64.5, 34.9, 28.9, 28.4, 28.1, 28.0, 27.9, 27.8, 27.2, 27.1 (2C), 27.0, 25.8, 25.2, one carbon hidden. **HRMS** (ESI<sup>+</sup>):  $m/z$  calcd for C<sub>16</sub>H<sub>30</sub>NaO<sub>2</sub> [M+Na]<sup>+</sup>: 277.2138, found: 277.2129.

Data are in agreement with: M. De Léséleuc, S. K. Collins, *ACS Catal.* **2015**, 5, 1462.

#### Oxacyclopentadecan-2-one (**2f**) and 1,16-dioxacyclotriacontane-2,17-dione (**3f**)

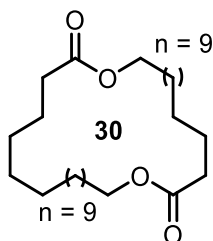
Following the general procedure, starting from 14-hydroxydecanoic acid **1f** (75 mg, 0.307 mmol, 1 equiv), pentafluorobenzoyl chloride (53  $\mu$ L, 0.368 mmol, 1.2 equiv), triethylamine (51  $\mu$ L, 0.368 mmol, 1.2 equiv) and toluene (204 ml) for 24 h. The crude product was purified by flash column chromatography (100 to 95/5 PE/EtOAc) to afford **2f** as a white solid (56 mg, 81%) and **3f** as a white solid (6.5 mg, 9%).



Chemical Formula: C<sub>14</sub>H<sub>26</sub>O<sub>2</sub>  
Molecular Weight: 226,3550

**<sup>1</sup>H NMR** (360 MHz, CDCl<sub>3</sub>)  $\delta$  = 4.12 (t,  $J$  = 6.0 Hz, 2H), 2.34 (t,  $J$  = 7.2 Hz, 2H), 1.74–1.56 (m, 4H), 1.42–1.17 (m, 18H). **<sup>13</sup>C NMR** (91 MHz, CDCl<sub>3</sub>)  $\delta$  = 174.4, 64.1, 34.2, 28.4, 27.9, 26.9, 26.7, 26.6, 26.5, 26.2, 25.3, 25.0, 24.9, one carbon hidden. **HRMS** (ESI<sup>+</sup>):  $m/z$  calcd for C<sub>14</sub>H<sub>26</sub>NaO<sub>2</sub> [M+Na]<sup>+</sup>: 249.1825, found: 249.1816.

Data are in agreement with: M. De Léséleuc, S. K. Collins, *ACS Catal.* **2015**, 5, 1462.



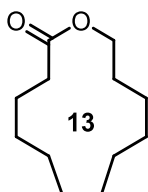
Chemical Formula:  $C_{28}H_{52}O_4$

Molecular Weight: 452,7101

**Mp** = 94–96 °C.  **$^1H$  NMR** (360 MHz,  $CDCl_3$ )  $\delta$  = 4.09 (t,  $J$  = 6.1 Hz, 4H), 2.30 (t,  $J$  = 7.2 Hz, 4H), 1.67–1.55 (m, 8H), 1.38–1.18 (m, 36H).  **$^{13}C$  NMR** (91 MHz,  $CDCl_3$ )  $\delta$  = 174.2, 64.4, 34.8, 29.7, 29.6 (2C), 29.5, 29.3, 29.1, 28.8, 26.2, 25.4, 2 carbons hidden. **IR** (film,  $cm^{-1}$ ):  $\nu_{max}$  = 2920, 2850, 1736, 1460, 1268, 1110, 907, 736. **HRMS** (ESI<sup>+</sup>):  $m/z$  calcd for  $C_{28}H_{53}O_4$  [M+H]<sup>+</sup>: 453.3938, found: 453.3918.

### Oxacyclotridecan-2-one (2g) and 1,14-dioxacyclohexacosane-2,15-dione (3g)

Following the general procedure, starting from 12-hydroxydecanoic acid **1g** (100 mg, 0.462 mmol, 1 equiv), pentafluorobenzoyl chloride (80  $\mu$ L, 0.555 mmol, 1.2 equiv), triethylamine (77  $\mu$ L, 0.555 mmol, 1.2 equiv) and toluene (308 ml) for 24 h. The crude product was purified by flash column chromatography (100 to 95/5 PE/EtOAc) to afford **2g** as a white solid (66 mg, 72%) and **3g** as a white solid (19 mg, 12%).

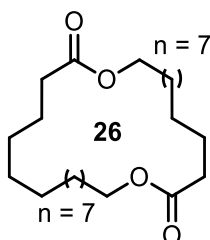


Chemical Formula:  $C_{12}H_{22}O_2$

Molecular Weight: 198,3019

**$^1H$  NMR** (360 MHz,  $CDCl_3$ )  $\delta$  = 4.15 (t,  $J$  = 5.9 Hz, 2H), 2.35 (t,  $J$  = 7.2 Hz, 2H), 1.68 – 1.62 (m, 4H), 1.43 – 1.23 (m, 14H).  **$^{13}C$  NMR** (91 MHz,  $CDCl_3$ )  $\delta$  = 174.3, 64.7, 34.8, 27.5, 26.7, 26.5, 25.54, 25.5, 25.1, 24.6, 24.3 (one carbon hidden). **HRMS** (ESI<sup>+</sup>):  $m/z$  calcd for  $C_{12}H_{22}NaO_2$  [M+Na]<sup>+</sup>: 221.1512, found: 221.1502.

Data are in agreement with: M. De Léséleuc, S. K. Collins, *ACS Catal.* **2015**, 5, 1462.



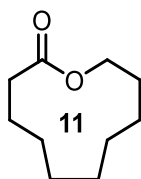
Chemical Formula:  $C_{24}H_{44}O_4$

Molecular Weight: 396,6038

**Mp** = 89-91 °C. **<sup>1</sup>H NMR** (360 MHz, CDCl<sub>3</sub>)  $\delta$  = 4.10 (t,  $J$  = 5.8 Hz, 4H), 2.35 (t,  $J$  = 7 Hz, 4H), 1.65–1.57 (m, 8H), 1.36–1.21 (m, 28H). **<sup>13</sup>C NMR** (91 MHz, CDCl<sub>3</sub>)  $\delta$  = 174.1, 64.3, 34.9, 29.7, 29.6, 29.5, 29.3, 29.1, 28.8, 26.2, 25.4, one carbon hidden. **IR** (film, cm<sup>-1</sup>):  $\nu_{\text{max}}$  = 2916, 2850, 1733, 1452, 1262, 1105, 910, 735. **HRMS** (ESI<sup>+</sup>):  $m/z$  calcd for C<sub>24</sub>H<sub>44</sub>NaO<sub>4</sub> [M+Na]<sup>+</sup>: 419.3132, found: 419.3112.

### Oxacycloundecan-2-one (2h) and 1,12-dioxacyclodocosane-2,13-dione (3h)

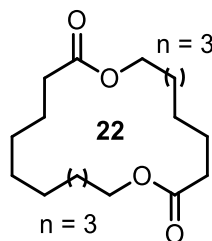
Following the general procedure, starting from 10-hydroxydecanoic acid **1h** (47 mg, 0.250 mmol, 1 equiv), pentafluorobenzoyl chloride (47  $\mu$ L, 0.300 mmol, 1.2 equiv), triethylamine (43  $\mu$ L, 0.300 mmol, 1.2 equiv) and toluene (125 ml) for 24 h. The crude product was purified by flash column chromatography (100 to 95/05 Petroleum ether/EtOAc) to afford **2h** as a white solid (13 mg, 31%) and **3h** as a white solid (13.2 mg, 32%).



Chemical Formula: C<sub>10</sub>H<sub>18</sub>O<sub>2</sub>  
Molecular Weight: 170,2487

**<sup>1</sup>H NMR** (360 MHz, CDCl<sub>3</sub>)  $\delta$  = 4.18 (t,  $J$  = 6.2 Hz, 2H), 2.36–2.31 (m, 2H), 1.79–1.67 (m, 4H), 1.55–1.28 (m, 10H). **<sup>13</sup>C NMR** (91 MHz, CDCl<sub>3</sub>)  $\delta$  = 174.4, 64.9, 35.4, 26.4, 25.5, 25.4, 24.9, 24.2, 22.5, 21.4. **HRMS** (ESI<sup>+</sup>):  $m/z$  calcd for C<sub>10</sub>H<sub>18</sub>NaO<sub>2</sub> [M+Na]<sup>+</sup>: 170.1307, found: 170.1315.

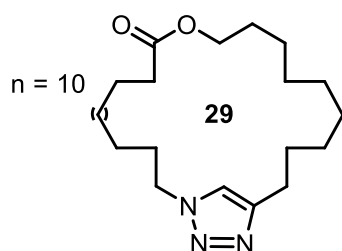
Data are in agreement with: M. De Léséleuc, S. K. Collins, *ACS Catal.* **2015**, 5, 1462.



Chemical Formula: C<sub>20</sub>H<sub>36</sub>O<sub>4</sub>  
Molecular Weight: 340,4974

**Mp** = 83-85 °C. **<sup>1</sup>H NMR** (360 MHz, CDCl<sub>3</sub>)  $\delta$  = 4.10 (t,  $J$  = 6.1 Hz, 4H), 2.31 (t,  $J$  = 7 Hz, 4H), 1.65–1.56 (m, 8H), 1.35–1.23 (m, 20H). **<sup>13</sup>C NMR** (91 MHz, CDCl<sub>3</sub>)  $\delta$  = 174.0, 64.1, 35.0, 29.5, 29.22, 29.17, 29.1, 28.8, 26.2, 25.5. **IR** (film, cm<sup>-1</sup>):  $\nu_{\text{max}}$  = 2924, 2850, 1732, 1460, 1271, 1105, 907, 734, 726. **HRMS** (ESI<sup>+</sup>):  $m/z$  calcd for C<sub>20</sub>H<sub>37</sub>O<sub>4</sub> [M+H]<sup>+</sup>: 341.2687, found: 341.2666.

### 18-oxa-1,29,30-triazabicyclo[26.2.1]hentriaconta-28(31),29-dien-17-one (2i)



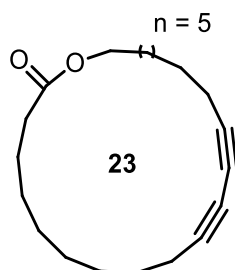
Chemical Formula:  $C_{27}H_{49}N_3O_2$

Molecular Weight: 447,3825

Following the general procedure, starting from **1i** (32 mg, 0.069 mmol, 1 equiv), pentafluorobenzoyl chloride (12  $\mu$ L, 0.083 mmol, 1.2 equiv), triethylamine (12  $\mu$ L, 0.083 mmol, 1.2 equiv) and toluene (46 ml) for 24 h. The crude product was purified by flash column chromatography (100 to 1/1 Hexane/EtOAc) to afford **2i** as a white solid (23 mg, 75%).

**Mp** = 38–40 °C. **<sup>1</sup>H NMR** (360 MHz,  $CDCl_3$ )  $\delta$  = 7.25 (s, 1H), 4.32 (t,  $J$  = 6.8 Hz, 2H), 4.07 (t,  $J$  = 6.1 Hz, 2H), 2.72 (t,  $J$  = 7.4 Hz, 2H), 2.29 (t,  $J$  = 7.3 Hz, 2H), 1.93–1.81 (m, 2H), 1.74–1.54 (m, 8H), 1.34–1.23 (m, 30H). **<sup>13</sup>C NMR** (91 MHz,  $CDCl_3$ )  $\delta$  = 174.2, 148.4, 120.7, 64.5, 50.3, 34.6, 30.1, 29.4, 29.3, 29.2 (2C), 29.1, 29.0, 28.9 (2C), 28.8 (2C), 28.7, 26.2 (2C), 25.7, 25.1, 5 carbons hidden. **IR** (film,  $cm^{-1}$ ):  $\nu_{max}$  = 2926, 2854, 1734, 1702, 1521, 1502, 1461, 1217, 1100, 993, 898, 799. **HRMS** (ESI<sup>+</sup>):  $m/z$  calcd for  $C_{27}H_{50}N_3O_2$  [M+H]<sup>+</sup>: 448.3897, found: 448.3874.

#### Oxacyclodocosa-11,13-diyn-2-one (2j)



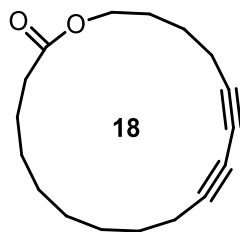
Chemical Formula:  $C_{22}H_{34}O_2$

Molecular Weight: 330,5042

Following the general procedure, starting from **1j** (30 mg, 0.086 mmol, 1 equiv), pentafluorobenzoyl chloride (16  $\mu$ L, 0.103 mmol, 1.2 equiv), triethylamine (14  $\mu$ L, 0.103 mmol, 1.2 equiv) and toluene (58 ml) for 24 h. The crude product was purified by flash column chromatography (9/1 PE/EtOAc) to afford **2j** as a yellow oil (24 mg, 89%).

**<sup>1</sup>H NMR** (360 MHz,  $CDCl_3$ )  $\delta$  = 4.08 (t,  $J$  = 6.5 Hz, 2H), 2.36–2.22 (m, 6H), 1.68–1.59 (m, 4H), 1.53–1.44 (m, 6H), 1.40–1.25 (16H). **<sup>13</sup>C NMR** (91 MHz,  $CDCl_3$ )  $\delta$  = 174.1, 77.7, 77.6, 66.0, 65.8, 64.4, 34.4, 29.0, 28.8, 28.5, 28.4 (2C), 28.3, 28.2, 28.0, 27.7, 25.9, 25.1, 19.2, 19.1, 2 carbons hidden. **IR** (film,  $cm^{-1}$ ):  $\nu_{max}$  = 2932, 2858, 2231, 1732, 1501, 1462, 1237, 1180, 1097, 800, 725. **HRMS** (ESI<sup>+</sup>):  $m/z$  calcd for  $C_{22}H_{34}NaO_2$  [M+Na]<sup>+</sup>: 353.2451, found: 353.2430.

#### Oxacyclooctadeca-11,13-diyn-2-one (2k)



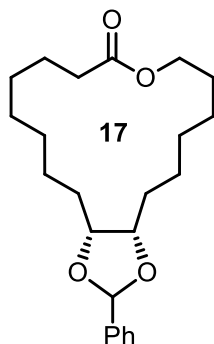
Chemical Formula:  $C_{17}H_{24}O_2$   
Molecular Weight: 260,3713

Following the general procedure, starting from **1k** (69 mg, 0.250 mmol, 1 equiv), pentafluorobenzoyl chloride (43  $\mu$ L, 0.300 mmol, 1.2 equiv), triethylamine (41  $\mu$ L, 0.300 mmol, 1.2 equiv) and toluene (167 ml) for 24 h. The crude product was purified by flash column chromatography (9/1 PE/EtOAc) to afford **2k** as an orange oil (56 mg, 85%).

**$^1H$  NMR** (300 MHz,  $CDCl_3$ )  $\delta$  = 4.16 (t,  $J$  = 6.3 Hz, 2H), 2.36–2.24 (m, 6H), 1.87–1.77 (m, 2H), 1.68–1.58 (m, 4H), 1.55–1.30 (m, 10H).  **$^{13}C$  NMR** (101 MHz,  $CDCl_3$ )  $\delta$  = 173.9, 78.2, 77.9, 66.8, 66.4, 63.7, 34.9, 28.9, 28.2, 28.0, 27.7, 27.2, 26.9, 25.2, 24.8, 19.0, 18.9. **HRMS** (ESI<sup>+</sup>):  $m/z$  calcd for  $C_{17}H_{24}NaO_2$  [M+Na]<sup>+</sup>: 283.1669, found: 283.1659.

Data are in agreement with: A.-C. Bédart, S. K. Collins, *J. Am. Chem. Soc.* **2011**, *133*, 19976.

#### 2-phenyltetradecahydro-[1,3]dioxolo[4,5-*h*][1]oxacycloheptadecin-11(3*aH*)-one (**2l**)



Chemical Formula:  $C_{23}H_{34}O_4$   
Molecular Weight: 374,5137

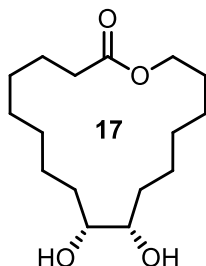
Following the general procedure, starting from 8-(5-(6-hydroxyhexyl)-2-phenyl-1,3-dioxolan-4-yl)octanoic acid **1l** (75 mg, 0.246 mmol, 1 equiv), pentafluorobenzoyl chloride (47  $\mu$ L, 0.300 mmol, 1.2 equiv), triethylamine (43  $\mu$ L, 0.300 mmol, 1.2 equiv) and toluene (166 ml) for 24 h. The crude product was purified by flash column chromatography (9/1 PE/EtOAc) to afford **2l** as a white solid (80 mg, 85%).

**$^1H$  NMR** (360 MHz,  $CDCl_3$ )  $\delta$  = 7.49–7.45 (m, 2H), 7.40–7.32 (m, 3H), 5.86–5.84 (m, 1H), 4.15 (t,  $J$  = 5.6 Hz, 2H), 3.88–3.80 (m, 2H), 2.34 (td,  $J$  = 5.9, 2.4 Hz, 2H), 1.90–1.61 (m, 8H), 1.56–1.25 (m, 14H).  **$^{13}C$  NMR** (91 MHz,  $CDCl_3$ )  $\delta$  = 174.1, 138.3, 138.2, 129.3, 128.5, 126.8, 102.6, 102.5, 82.3, 82.2, 80.9, 80.7, 64.4, 64.3, 34.7, 33.0, 32.9, 32.2, 32.1, 28.9, 28.7, 28.6, 28.5, 28.3, 27.8, 25.8 (2C), 25.4, 25.0,

24.8 (2C), 24.2, two diastereoisomers. **HRMS** (ESI<sup>+</sup>):  $m/z$  calcd for C<sub>23</sub>H<sub>34</sub>NaO<sub>4</sub> [M+Na]<sup>+</sup>: 397.2349, found: 397.2330.

Data are in agreement with: I. Shiina, M. Kubota, H. Oshiumi, M. Hashizume, *J. Org. Chem.* **2004**, 69, 1822.

#### 10,11-dihydroxyoxacycloheptadecan-2-one (2m)



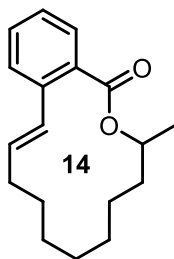
Chemical Formula: C<sub>16</sub>H<sub>30</sub>O<sub>4</sub>  
Molecular Weight: 286,4070

Following the general procedure, starting from aleuritic acid **1m** (75 mg, 0.246 mmol, 1 equiv), pentafluorobenzoyl chloride (42  $\mu$ L, 0.296 mmol, 1.2 equiv), triethylamine (40  $\mu$ L, 0.296 mmol, 1.2 equiv) and toluene (164 ml) for 24 h. The crude product was purified by flash column chromatography (6/4 PE/EtOAc) to afford **2m** as a white solid (66 mg, 88%).

**<sup>1</sup>H NMR** (360 MHz, CDCl<sub>3</sub>)  $\delta$  = 4.15–4.08 (m, 2H), 3.48–3.41 (m, 2H), 2.50 (brs, 2H), 2.31 (t,  $J$  = 7.4 Hz, 2H), 1.63–1.51 (m, 6H), 1.49–1.23 (m, 16 H). **<sup>13</sup>C NMR** (91 MHz, CDCl<sub>3</sub>)  $\delta$  = 174.2, 74.3, 73.5, 64.3, 34.7, 32.6, 31.6, 28.8, 28.3 (2C), 27.9, 27.8, 25.6, 25.2, 24.0, 23.3. **HRMS** (ESI<sup>+</sup>):  $m/z$  calcd for C<sub>16</sub>H<sub>30</sub>NaO<sub>4</sub> [M+Na]<sup>+</sup>: 309.2036, found: 309.2030.

Data are in agreement with: I. Shiina, M. Hashizume, *Tetrahedron* **2006**, 62, 7934.

#### (E)-3-methyl-3,4,5,6,7,8,9,10-octahydro-1H-benzo[c][l]oxacyclotetradecin-1-one (2n)



Chemical Formula: C<sub>18</sub>H<sub>24</sub>O<sub>2</sub>  
Molecular Weight: 272,1776

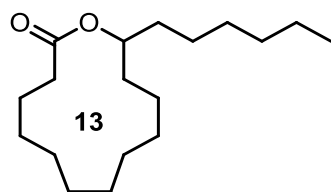
Following the general procedure, starting from **1n** (32 mg, 0.110 mmol, 1 equiv), pentafluorobenzoyl chloride (19  $\mu$ L, 0.132 mmol, 1.2 equiv), triethylamine (18  $\mu$ L, 0.132 mmol, 1.2 equiv) and toluene (73 ml) for 24 h. The crude product was purified by flash column chromatography (9/1 PE/EtOAc) to afford **2n** as a white solid (23 mg, 76%).



**<sup>1</sup>H NMR** (360 MHz, CDCl<sub>3</sub>)  $\delta$  = 7.81 (dd,  $J$  = 7.8, 1.3 Hz, 1H), 7.49 (d,  $J$  = 7.2 Hz, 1H), 7.41 (td,  $J$  = 7.7, 1.3 Hz, 1H), 7.27 (td,  $J$  = 7.6, 1.2 Hz, 1H), 7.01 (d,  $J$  = 15.7 Hz, 1H), 5.91 (dt,  $J$  = 15.5, 7.2 Hz, 1H), 5.23 (dq,  $J$  = 12.5, 6.2 Hz, 1H), 2.30 (td,  $J$  = 7.0, 1.2 Hz, 2H), 1.72–1.63 (m, 2H), 1.58–1.26 (m, 13H). **<sup>13</sup>C NMR** (91 MHz, CDCl<sub>3</sub>)  $\delta$  = 168.9, 138.3, 133.8, 131.5, 130.3, 130.2, 127.4, 126.7, 72.5, 34.7, 30.8, 27.0, 26.6, 24.0, 23.9, 21.8, 20.2, one carbon hidden. **HRMS** (ESI<sup>+</sup>):  $m/z$  calcd for C<sub>18</sub>H<sub>25</sub>O<sub>2</sub> [M+H]<sup>+</sup>: 273.1849, found: 273.1844.

Data are in agreement with: G. W. Heberlig, M. Wirz, M. Wang, C. N. Boddy, *Org. Lett.* **2014**, *16*, 5858.

### 13-hexyloxacyclotridecan-2-one (2o)



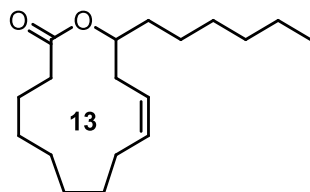
Chemical Formula: C<sub>18</sub>H<sub>34</sub>O<sub>2</sub>  
Molecular Weight: 282,4614

Following the general procedure, starting from 12-hydroxyoctadecanoic acid **1o** (75 mg, 0.250 mmol, 1 equiv), pentafluorobenzoyl chloride (47  $\mu$ L, 0.300 mmol, 1.2 equiv), triethylamine (43  $\mu$ L, 0.300 mmol, 1.2 equiv) and toluene (167 ml) for 24 h. The crude product was purified by flash column chromatography (9/1 Hexane/EtOAc) to afford **2o** as a white solid (61 mg, 87%).

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>)  $\delta$  = 4.98–4.87 (m, 1H), 2.43 (ddd,  $J$  = 13.8, 8.2, 3.3 Hz, 1H), 2.25 (ddd,  $J$  = 13.8, 7.6, 3.3 Hz, 1H), 1.77–1.25 (m, 28H), 0.87 (t,  $J$  = 6.5 Hz, 3H). **<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>)  $\delta$  = 174.0, 74.6, 35.2, 35.0, 33.5, 31.9, 29.8, 29.4, 26.9, 26.5, 26.1, 25.6, 25.1, 24.9, 24.7, 24.6, 22.7, 14.2. **HRMS** (ESI<sup>+</sup>):  $m/z$  calcd for C<sub>18</sub>H<sub>34</sub>NaO<sub>2</sub> [M+Na]<sup>+</sup>: 305.2451, found: 305.2441.

Data are in agreement with: Y. Nishio, A. Kawazu, H. Matsubara. *Tetrahedron* **2016**, *72*, 720.

### (Z)-13-hexyloxacyclotridec-10-en-2-one (2p)



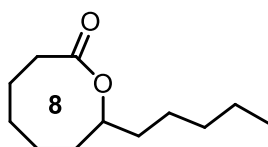
Chemical Formula: C<sub>18</sub>H<sub>32</sub>O<sub>2</sub>  
Molecular Weight: 280,4455

Following the general procedure, starting from ricinoleic acid **1p** (75 mg, 0.251 mmol, 1 equiv), pentafluorobenzoyl chloride (43  $\mu$ L, 0.302 mmol, 1.2 equiv), triethylamine (41  $\mu$ L, 0.302 mmol, 1.2

equiv) and toluene (167 ml) for 24 h. The crude product was purified by flash column chromatography (9/1 PE/EtOAc) to afford **2p** as a colorless oil (57 mg, 82%).

**<sup>1</sup>H NMR** (360 MHz, CDCl<sub>3</sub>)  $\delta$  = 5.55–5.42 (m, 1H), 5.39–5.30 (m, 1H), 4.99–4.89 (m, 1H), 2.41–2.24 (m, 4H), 2.12–1.94 (m, 2H), 1.71–1.52 (m, 4H), 1.43–1.20 (m, 16H), 0.91 (t,  $J$  = 6.7 Hz, 3H). **<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>)  $\delta$  = 174.5, 132.6, 125.0, 74.0, 35.3, 34.0, 32.0, 31.9, 29.6, 29.2, 27.5, 26.3, 25.9, 24.7, 23.6, 22.7, 14.2, one carbon hidden. **IR** (film, cm<sup>-1</sup>):  $\nu_{\text{max}}$  = 3009, 2925, 2856, 1731, 1652, 1524, 1501, 1455, 1328, 1229, 1184, 1099, 1012, 954, 837, 692. **HRMS** (ESI<sup>+</sup>):  $m/z$  calcd for C<sub>18</sub>H<sub>32</sub>NaO<sub>2</sub> [M+Na]<sup>+</sup>: 303.2294, found: 303.2285.

### 8-pentylloxocan-2-one (2q)

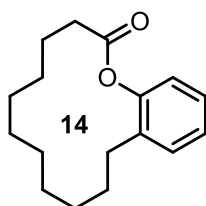


Chemical Formula: C<sub>12</sub>H<sub>22</sub>O<sub>2</sub>  
Molecular Weight: 198,1620

Following the general procedure, starting from 7-hydroxydodecanoic acid **1q** (60 mg, 0.278 mmol, 1 equiv), pentafluorobenzoyl chloride (48  $\mu$ L, 0.333 mmol, 1.2 equiv), triethylamine (46  $\mu$ L, 0.333 mmol, 1.2 equiv) and toluene (185 ml) for 24 h. The crude product was purified by flash column chromatography (100 to 95/5 PE/EtOAc) to afford **2q** as a colorless oil (24 mg, 42%).

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>)  $\delta$  = 4.59–4.46 (m, 1H), 2.60–2.40 (m, 2H), 2.00–1.38 (m, 12H), 1.35–1.20 (m, 4H), 0.88 (t,  $J$  = 6.8 Hz, 3H). **<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>)  $\delta$  = 177.2, 79.0, 37.4, 35.7, 32.5, 31.7, 29.0, 26.5, 25.6, 24.0, 22.7, 14.2. **IR** (film, cm<sup>-1</sup>):  $\nu_{\text{max}}$  = 2935, 2849, 1733, 1518, 1436, 1277, 1110, 1001, 923. **HRMS** (ESI<sup>+</sup>):  $m/z$  calcd for C<sub>12</sub>H<sub>22</sub>NaO<sub>2</sub> [M+Na]<sup>+</sup>: 221.1512, found: 221.1506.

### 3,4,5,6,7,8,9,10,11,12-decahydro-2H-benzo[*b*][1]oxacyclotetradecin-2-one (2r)

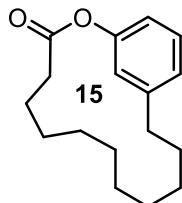


Chemical Formula: C<sub>17</sub>H<sub>24</sub>O<sub>2</sub>  
Molecular Weight: 260,3713

Following the general procedure, starting from **1r** (53 mg, 0.190 mmol, 1 equiv), pentafluorobenzoyl chloride (33  $\mu$ L, 0.228 mmol, 1.2 equiv), triethylamine (31  $\mu$ L, 0.228 mmol, 1.2 equiv) and toluene (127 ml) for 48 h. The crude product was purified by flash column chromatography (9/1 PE/EtOAc) to afford **2r** as a white solid (42 mg, 85%).

**Mp** = 38-40 °C. **<sup>1</sup>H NMR** (360 MHz, CDCl<sub>3</sub>)  $\delta$  = 7.26 (dd,  $J$  = 7.1, 2.1 Hz, 1H), 7.22–7.12 (m, 2H), 7.02 (dd,  $J$  = 7.7, 1.6 Hz, 1H), 2.70–2.62 (m, 2H), 2.57–2.48 (m, 2H), 1.85–1.74 (m, 2H), 1.58–1.32 (m, 14H). **<sup>13</sup>C NMR** (91 MHz, CDCl<sub>3</sub>)  $\delta$  = 172.6, 148.7, 134.8, 130.8, 126.9, 126.1, 122.6, 34.0, 29.4, 29.2, 27.6, 26.0, 25.7, 25.6, 25.0, 24.4, 24.0. **IR** (film, cm<sup>-1</sup>):  $\nu_{\text{max}}$  = 2932, 2858, 1758, 1487, 1460, 1352, 1213, 1129, 1097, 750. **HRMS** (ESI<sup>+</sup>):  $m/z$  calcd for C<sub>17</sub>H<sub>25</sub>O<sub>2</sub> [M+H]<sup>+</sup>: 261.1849, found: 261.1844.

#### 2-oxa-1(1,3)-benzenacyclotetradecaphan-3-one (2s)

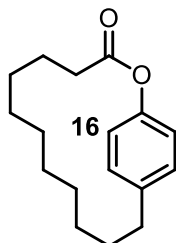


Chemical Formula: C<sub>17</sub>H<sub>24</sub>O<sub>2</sub>  
Molecular Weight: 260,3713

Following the general procedure, starting from **1s** (53 mg, 0.190 mmol, 1 equiv), pentafluorobenzoyl chloride (33  $\mu$ L, 0.228 mmol, 1.2 equiv), triethylamine (31  $\mu$ L, 0.228 mmol, 1.2 equiv) and toluene (127 ml) for 48 h. The crude product was purified by flash column chromatography (9/1 PE/EtOAc) to afford **2s** as a white solid (41 mg, 82%).

**Mp** = 40-42 °C. **<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>)  $\delta$  = 7.38 – 7.30 (m, 1H), 7.12 (d,  $J$  = 7.7 Hz, 1H), 7.09 – 7.01 (m, 2H), 2.64 (t,  $J$  = 7.5 Hz, 2H), 2.34 (t,  $J$  = 7.5 Hz, 2H), 1.67 – 1.57 (m, 2H), 1.40 – 1.20 (m, 14H). **<sup>13</sup>C NMR** (63 MHz, CDCl<sub>3</sub>)  $\delta$  = 179.5, 150.1, 145.3, 129.5, 127.0, 121.2, 118.5, 35.9, 34.1, 31.3, 29.6, 29.5, 29.4, 29.2, 24.8, 2 carbons hidden. **IR** (film, cm<sup>-1</sup>):  $\nu_{\text{max}}$  = 2931, 2856, 1748, 1633, 1502, 1328, 1211, 1003, 946, 721. **HRMS** (ESI<sup>+</sup>):  $m/z$  calcd for C<sub>17</sub>H<sub>24</sub>NaO<sub>2</sub> [M+Na]<sup>+</sup>: 283.1669, found: 283.1663.

#### 2-oxa-1(1,4)-benzenacyclotridecaphan-3-one (2t)

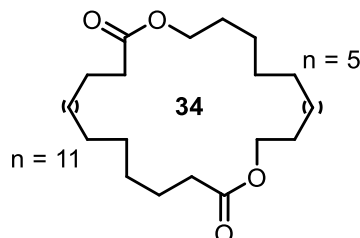


Chemical Formula: C<sub>17</sub>H<sub>24</sub>O<sub>2</sub>  
Molecular Weight: 260,3713

Following the general procedure, starting from **1t** (50 mg, 0.180 mmol, 1 equiv), pentafluorobenzoyl chloride (31  $\mu$ L, 0.216 mmol, 1.2 equiv), triethylamine (30  $\mu$ L, 0.216 mmol, 1.2 equiv) and toluene (119 ml) for 48 h. The crude product was purified by flash column chromatography (9/1 PE/EtOAc) to afford **2t** as a yellow solid (39 mg, 84%).

**Mp** = 78-80 °C. **<sup>1</sup>H NMR** (360 MHz, CDCl<sub>3</sub>)  $\delta$  = 7.24 (d, *J* = 8.6 Hz, 2H), 7.14 (d, *J* = 8.6 Hz, 2H), 2.62 (t, *J* = 7.7 Hz, 2H), 2.35 (t, *J* = 7.5 Hz, 2H), 1.69–1.54 (m, 4H), 1.39–1.21 (m, 12H). **<sup>13</sup>C NMR** (91 MHz, CDCl<sub>3</sub>)  $\delta$  = 180.2, 148.1, 141.7, 129.7, 121.0, 35.5, 34.2, 31.6, 29.6 (2C), 29.5, 29.3, 29.2, 24.8, 1 carbon hidden. **IR** (film, cm<sup>-1</sup>):  $\nu_{\text{max}}$  = 2942, 2849, 1719, 1633, 1478, 1254, 1211, 1010, 987. **HRMS** (ESI<sup>+</sup>): *m/z* calcd for C<sub>17</sub>H<sub>24</sub>NaO<sub>2</sub> [M+Na]<sup>+</sup>: 283.1669, found: 283.1661.

#### 1,14-dioxacyclotetratetriacontane-15,34-dione (6)

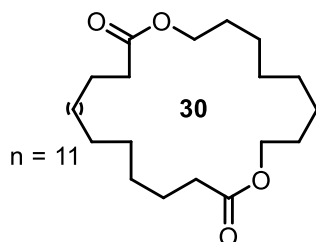


Chemical Formula: C<sub>32</sub>H<sub>60</sub>O<sub>4</sub>  
Molecular Weight: 508,4492

Following the general procedure, starting from icosanedioic acid (103 mg, 0.300 mmol, 1 equiv), 1,12-dodecanediol (61 mg, 0.300 mmol, 1 equiv), pentafluorobenzoyl chloride (103  $\mu$ L, 0.720 mmol, 2.4 equiv), triethylamine (100  $\mu$ L, 0.720 mmol, 2.4 equiv) and toluene (200 ml) for 24 h. The crude product was purified by flash column chromatography (100 to 95/5 PE/EtOAc) to afford **6** as a white solid (136 mg, 89%).

**Mp** = 60-62 °C. **<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>)  $\delta$  = 4.07 (t, *J* = 6.4 Hz, 4H), 2.29 (t, *J* = 7.1 Hz, 4H), 1.70–1.57 (m, 8H), 1.36–1.17 (m, 44H). **<sup>13</sup>C NMR** (91 MHz, CDCl<sub>3</sub>)  $\delta$  = 174.2, 64.4, 34.6, 29.6, 29.5 (2C), 29.4, 29.3, 29.0, 28.9, 28.8, 26.2, 25.2, 3 carbons hidden. **Mp** = 60-62 °C. **IR** (film, cm<sup>-1</sup>):  $\nu_{\text{max}}$  = 2935, 2854, 1738, 1728, 1695, 1505, 1455, 1329, 1155, 1108, 997. **HRMS** (ESI<sup>+</sup>): *m/z* calcd for C<sub>32</sub>H<sub>61</sub>O<sub>4</sub> [M+H]<sup>+</sup>: 509.4564, found: 509.4541.

#### 1,10-dioxacyclotetriacontane-11,30-dione (7)

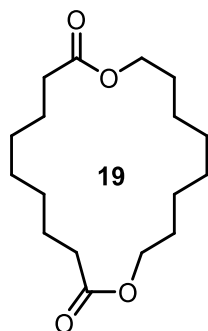


Chemical Formula: C<sub>28</sub>H<sub>52</sub>O<sub>4</sub>  
Molecular Weight: 452,3866

Following the general procedure, starting from icosanedioic acid (89 mg, 0.260 mmol, 1 equiv), 1,8-octanediol (38 mg, 0.260 mmol, 1 equiv), pentafluorobenzoyl chloride (90  $\mu$ L, 0.624 mmol, 2.4 equiv), triethylamine (87  $\mu$ L, 0.624 mmol, 2.4 equiv) and toluene (173 ml) for 24 h. The crude product was purified by flash column chromatography (100 to 95/5 PE/EtOAc) to afford **7** as a colorless oil (94 mg, 82%).

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>)  $\delta$  = 4.07 (t,  $J$  = 6.5 Hz, 4H), 2.30 (t,  $J$  = 7.3 Hz, 4H), 1.70–1.54 (m, 8H), 1.42–1.21 (m, 36H). **<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>)  $\delta$  = 174.2, 64.4, 34.6, 29.3, 29.2 (2C), 29.1, 28.9, 28.8, 26.1, 25.1, 3 carbons hidden. **IR** (film, cm<sup>-1</sup>):  $\nu_{\text{max}}$  = 2936, 2856, 1740, 1510, 1461, 1323, 1098, 997. **HRMS** (ESI<sup>+</sup>):  $m/z$  calcd for C<sub>28</sub>H<sub>53</sub>O<sub>4</sub> [M+H]<sup>+</sup>: 453.3938, found: 453.3950.

### 1,10-dioxacyclononadecane-11,19-dione (8)



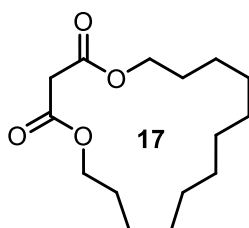
Chemical Formula: C<sub>17</sub>H<sub>30</sub>O<sub>4</sub>  
Molecular Weight: 298,4177

Following the general procedure, starting from azelaic acid (50 mg, 0.266 mmol, 1 equiv), 1,8-octanediol (38.9 mg, 0.266 mmol, 1 equiv), pentafluorobenzoyl chloride (92  $\mu$ L, 0.638 mmol, 2.4 equiv), triethylamine (89  $\mu$ L, 0.638 mmol, 2.4 equiv) and toluene (177 ml) for 24 h. The crude product was purified by flash column chromatography (100 to 95/5 PE/EtOAc) to afford **8** as a white solid (63 mg, 81%).

**<sup>1</sup>H NMR** (360 MHz, CDCl<sub>3</sub>)  $\delta$  = 4.09 (t,  $J$  = 5.7 Hz, 4H), 2.30 (t,  $J$  = 6.7 Hz, 4 H), 1.71–1.53 (m, 8H), 1.41–1.24 (m, 14H). **<sup>13</sup>C NMR** (91 MHz, CDCl<sub>3</sub>)  $\delta$  = 174.1, 64.4, 34.9, 29.4, 29.3, 29.0, 28.8, 26.2, 25.4. **HRMS** (ESI<sup>+</sup>):  $m/z$  calcd for C<sub>17</sub>H<sub>31</sub>O<sub>4</sub> [M+H]<sup>+</sup>: 299.2217, found: 299.2207.

Data are in agreement with: M. De Léséleuc, S. K. Collins, *Chem. Commun.* **2015**, 51, 10471.

### 1,5-dioxacycloheptadecane-2,4-dione (9)

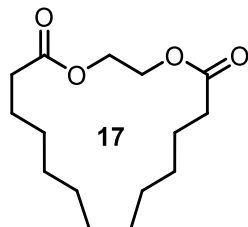


Chemical Formula: C<sub>15</sub>H<sub>26</sub>O<sub>4</sub>  
Molecular Weight: 270,1831

Following the general procedure, starting from malonic acid (21 mg, 0.200 mmol, 1 equiv), 1,12-dodecanediol (40 mg, 0.200 mmol, 1 equiv), pentafluorobenzoyl chloride (69  $\mu$ L, 0.480 mmol, 2.4 equiv), triethylamine (67  $\mu$ L, 0.480 mmol, 2.4 equiv) and toluene (133 ml) for 24 h. The crude product was purified by flash column chromatography (100 to 95/5 PE/EtOAc) to afford **9** as a colorless oil (35 mg, 65%).

**<sup>1</sup>H NMR** (360 MHz, CDCl<sub>3</sub>)  $\delta$  = 4.17 (t,  $J$  = 7.6 Hz, 4H), 3.37 (s,  $J$  = 3.9 Hz, 2H), 1.68–1.59 (m, 4H), 1.41–1.24 (m, 16H). **<sup>13</sup>C NMR** (91 MHz, CDCl<sub>3</sub>)  $\delta$  = 166.8, 65.6, 42.2, 28.4, 27.4, 27.1, 26.5, 25.0. **IR** (film, cm<sup>-1</sup>):  $\nu_{\text{max}}$  = 2934, 2854, 1760, 1729, 1506, 1463, 1412, 1386, 1138, 1029, 997. **HRMS** (ESI<sup>+</sup>):  $m/z$  calcd for C<sub>15</sub>H<sub>27</sub>O<sub>4</sub> [M+H]<sup>+</sup>: 271.1904, found: 271.1896.

**1,4-dioxacycloheptadecane-5,17-dione (10)**



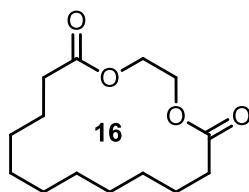
Chemical Formula: C<sub>15</sub>H<sub>26</sub>O<sub>4</sub>  
Molecular Weight: 270,1831

Following the general procedure, starting from undecanedioic acid (75 mg, 0.307 mmol, 1 equiv), ethylene glycol (17  $\mu$ L, 0.307 mmol, 1 equiv), pentafluorobenzoyl chloride (115  $\mu$ L, 0.798 mmol, 2.4 equiv), triethylamine (111  $\mu$ L, 0.798 mmol, 2.4 equiv) and toluene (204 ml) for 48 h. The crude product was purified by flash column chromatography (100 to 95/5 PE/EtOAc) to afford **10** as a white solid (62 mg, 74%).

**<sup>1</sup>H NMR** (360 MHz, CDCl<sub>3</sub>)  $\delta$  = 4.27 (s, 4H), 2.31 (t,  $J$  = 6.9 Hz, 4 H), 1.71–1.58 (m, 4H), 1.40–1.29 (m, 14H). **<sup>13</sup>C NMR** (91 MHz, CDCl<sub>3</sub>)  $\delta$  = 173.7, 62.3, 34.0, 27.6, 26.9, 26.8, 26.6, 24.5. **HRMS** (ESI<sup>+</sup>):  $m/z$  calcd for C<sub>15</sub>H<sub>27</sub>O<sub>4</sub> [M+H]<sup>+</sup>: 271.1904, found: 271.1896.

Data are in agreement with: Y. Luchi, Y. Obora, Y. Ishii, *J. Am. Chem. Soc.* **2010**, *132*, 8, 2536.

**1,4-dioxacyclohexadecane-5,16-dione (11)**

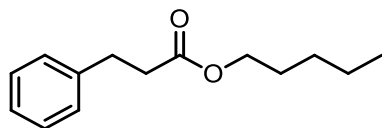


Chemical Formula: C<sub>14</sub>H<sub>24</sub>O<sub>4</sub>  
Exact Mass: 256,1675

Following the general procedure, starting from dodecanedioic acid (70 mg, 0.307 mmol, 1 equiv), ethylene glycol (17  $\mu$ L, 0.307 mmol, 1 equiv), pentafluorobenzoyl chloride (115  $\mu$ L, 0.798 mmol, 2.4 equiv), triethylamine (111  $\mu$ L, 0.798 mmol, 2.4 equiv) and toluene (204 ml) for 48 h. The crude product was purified by flash column chromatography (100 to 95/5 PE/EtOAc) to afford **11** as a colorless oil (53 mg, 68%).

**<sup>1</sup>H NMR** (360 MHz, CDCl<sub>3</sub>)  $\delta$  = 4.30 (s, 4H), 2.35 (t,  $J$  = 7.0 Hz, 4 H), 1.71–1.60 (m, 4H), 1.36–1.25 (m, 12H). **<sup>13</sup>C NMR** (91 MHz, CDCl<sub>3</sub>)  $\delta$  = 173.9, 62.4, 34.0, 27.2, 26.4, 26.3, 24.6. **IR** (film, cm<sup>-1</sup>):  $\nu_{\text{max}}$  = 2938, 2852, 1729, 1680, 1528, 1444, 1297, 1138, 1030, 998. **HRMS** (ESI<sup>+</sup>):  $m/z$  calcd for C<sub>14</sub>H<sub>25</sub>O<sub>4</sub> [M+H]<sup>+</sup>: 257.1747, found: 257.1737.

#### Pentyl 3-phenylpropanoate (14aa)



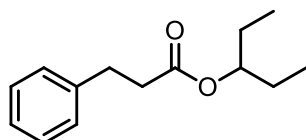
Chemical Formula: C<sub>14</sub>H<sub>20</sub>O<sub>2</sub>  
Molecular Weight: 220.3074

Following the general procedure, starting from 3-phenylpropionic (150 mg, 1 mmol, 1 equiv), pentanol (108  $\mu$ L, 1 mmol, 1 equiv), pentafluorobenzoyl chloride (172  $\mu$ L, 1.2 mmol, 1.2 equiv), triethylamine (557  $\mu$ L, 4 mmol, 4 equiv) and toluene (10 ml) for 48 h. The crude product was purified by flash column chromatography (9/1 PE/EtOAc) to afford **14aa** as a colorless oil (172 mg, 78%).

**<sup>1</sup>H NMR** (360 MHz, CDCl<sub>3</sub>)  $\delta$  = 7.34–7.26 (m, 2H), 7.26–7.18 (m, 3H), 4.08 (t,  $J$  = 6.7 Hz, 2H), 2.97 (t,  $J$  = 7.8 Hz, 2H), 2.64 (t,  $J$  = 7.8 Hz, 2H), 1.68–1.54 (m, 2H), 1.43–1.23 (m, 4H), 0.92 (t,  $J$  = 6.9 Hz, 3H). **<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>)  $\delta$  = 172.9, 140.6, 128.5, 128.3, 126.2, 64.6, 35.9, 31.0, 28.4, 28.1, 22.3, 14.0. **HRMS** (ESI<sup>+</sup>):  $m/z$  calcd for C<sub>14</sub>H<sub>20</sub>NaO<sub>2</sub> [M+Na]<sup>+</sup>: 243.1355, found: 243.1348.

Data are in agreement with: J. Liu, C. Shao, Y. Zhang, G. Shi, S. Pan, *Org. Biomol. Chem.* **2014**, 12, 2637.

#### Pentan-3-yl 3-phenylpropanoate (14ab)

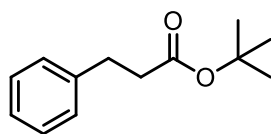


Chemical Formula: C<sub>14</sub>H<sub>20</sub>O<sub>2</sub>  
Molecular Weight: 220.1463

Following the general procedure, starting from 3-phenylpropionic (150 mg, 1 mmol, 1 equiv), pentan-3-ol (108  $\mu$ L, 1 mmol, 1 equiv), pentafluorobenzoyl chloride (172  $\mu$ L, 1.2 mmol, 1.2 equiv), triethylamine (167  $\mu$ L, 1.2 mmol, 1.2 equiv) and toluene (10 ml) for 36 h. The crude product was purified by flash column chromatography (95/5 PE/EtOAc) to afford **14ab** as a colorless oil (202 mg, 92%).

**<sup>1</sup>H NMR** (360 MHz, CDCl<sub>3</sub>)  $\delta$  = 7.31–7.25 (m, 2H), 7.21–7.16 (m, 3H), 4.80–4.70 (m, 1H), 2.95 (t,  $J$  = 7.8 Hz, 2H), 2.63 (t,  $J$  = 7.8 Hz, 2H), 1.59–1.46 (m, 4H), 0.82 (t,  $J$  = 7.5 Hz, 6H). **<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>)  $\delta$  = 172.3, 140.8, 128.6, 128.4, 126.3, 76.8, 36.3, 31.3, 26.6, 9.7. **IR** (film, cm<sup>-1</sup>):  $\nu_{\text{max}}$  = 2970, 2936, 2880, 17231, 1645, 1521, 1375, 1174, 997. **HRMS** (ESI<sup>+</sup>):  $m/z$  calcd for C<sub>14</sub>H<sub>20</sub>NaO<sub>2</sub> [M+Na]<sup>+</sup>: 243.1355, found: 243.1347.

### ***Tert*-butyl 3-phenylpropanoate (14ac)**



Chemical Formula: C<sub>13</sub>H<sub>18</sub>O<sub>2</sub>

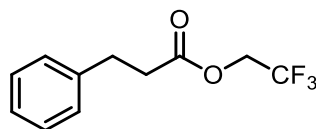
Molecular Weight: 206,2808

Following the general procedure, starting from 3-phenylpropionic (150 mg, 1 mmol, 1 equiv), *tert*-butanol (286  $\mu$ L, 3 mmol, 3 equiv), pentafluorobenzoyl chloride (172  $\mu$ L, 1.2 mmol, 1.2 equiv), triethylamine (557  $\mu$ L, 4 mmol, 4 equiv) and toluene (10 ml) for 36 h. The crude product was purified by flash column chromatography (95/5 PE/EtOAc) to afford **14ac** as a colorless oil (203 mg, 98%).

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  = 7.31–7.26 (m, 2H), 7.22–7.17 (m, 3H), 2.92 (t, *J* = 7.8 Hz, 2H), 2.55 (t, *J* = 7.8 Hz, 2H), 1.43 (s, 9H). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$  = 172.3, 140.8, 128.4, 128.3, 126.2, 80.3, 37.1, 31.2, 28.1. HRMS (ESI<sup>+</sup>): *m/z* calcd for C<sub>13</sub>H<sub>18</sub>NaO<sub>2</sub> [M+Na]<sup>+</sup>: 229.1199, found: 229.1210.

Data are in agreement with: M. T. La, H. -K. Kim. *Tetrahedron* **2018**, 74, 3748.

### **2,2,2-trifluoroethyl 3-phenylpropanoate (14ad)**



Chemical Formula: C<sub>11</sub>H<sub>11</sub>F<sub>3</sub>O<sub>2</sub>

Molecular Weight: 232,0711

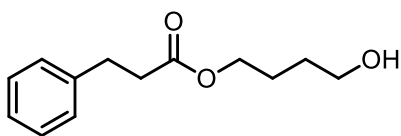
Following the general procedure, starting from 3-phenylpropionic (150 mg, 1 mmol, 1 equiv), 2,2,2-trifluoroethanol (73  $\mu$ L, 1 mmol, 1 equiv), pentafluorobenzoyl chloride (172  $\mu$ L, 1.2 mmol, 1.2 equiv), triethylamine (167  $\mu$ L, 1.2 mmol, 1.2 equiv) and toluene (10 ml) for 24 h. The crude product was purified by flash column chromatography (9/1 PE/EtOAc) to afford **14ad** as a colorless oil (167 mg, 72%).

<sup>1</sup>H NMR (360 MHz, CDCl<sub>3</sub>)  $\delta$  = 7.37–7.28 (m, 2H), 7.28–7.18 (m, 3H), 4.47 (q, *J* = 8.4 Hz, 2H), 3.01 (t, *J* = 7.7 Hz, 2H), 2.77 (t, *J* = 7.7 Hz, 2H). <sup>13</sup>C NMR (91 MHz, CDCl<sub>3</sub>)  $\delta$  = 171.4, 139.9, 128.7, 128.4, 126.6, 123.1 (q, *J* = 277.2 Hz), 60.4 (q, *J* = 36.5 Hz), 35.3, 30.7. <sup>19</sup>F NMR (235 MHz, CDCl<sub>3</sub>)  $\delta$  = -73.80 (t, *J* = 8.4 Hz).

Data are in agreement with: B. A. Tschaen, J. R. Schmink, G. A. Molander, *Org. Lett.* **2013**, 15, 500.

### **4-hydroxybutyl 3-phenylpropanoate (14ae)**



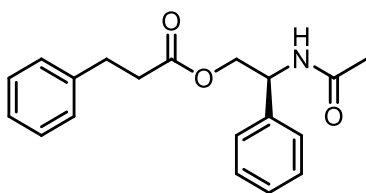


Chemical Formula: C<sub>13</sub>H<sub>18</sub>O<sub>3</sub>  
Molecular Weight: 222,1256

Following the general procedure, starting from 3-phenylpropionic (150 mg, 1 mmol, 1 equiv), 1,4-butanediol (132  $\mu$ L, 1.5 mmol, 1.5 equiv), pentafluorobenzoyl chloride (172  $\mu$ L, 1.2 mmol, 1.2 equiv), triethylamine (170  $\mu$ L, 1.2 mmol, 1.2 equiv) and toluene (10 ml) for 24 h. The crude product was purified by flash column chromatography (9/1 PE/EtOAc) to afford **14ae** as a colorless oil (159 mg, 71%).

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>)  $\delta$  = 7.34–7.27 (m, 2H), 7.24–7.15 (m, 3H), 4.40 (t,  $J$  = 5.9 Hz, 2H), 4.14 (t,  $J$  = 5.9 Hz, 2H), 2.98 (t,  $J$  = 7.7 Hz, 2H), 2.66 (t,  $J$  = 7.8 Hz, 2H), 1.85–1.69 (m, 4H), OH unobserved. **<sup>13</sup>C NMR** (91 MHz, CDCl<sub>3</sub>)  $\delta$  = 173.0, 140.6, 128.6, 128.4, 126.4, 66.4, 63.8, 36.0, 31.1, 25.3 (2C). **IR** (film, cm<sup>-1</sup>):  $\nu_{\text{max}}$  = 2942, 2853, 1718, 1660, 1470, 1289, 1170, 980. **HRMS** (ESI<sup>+</sup>):  $m/z$  calcd for C<sub>13</sub>H<sub>18</sub>NaO<sub>3</sub> [M+Na]<sup>+</sup>: 245.1148, found: 245.1142.

**(S)-2-acetamido-2-phenylethyl 3-phenylpropanoate (14ag)**

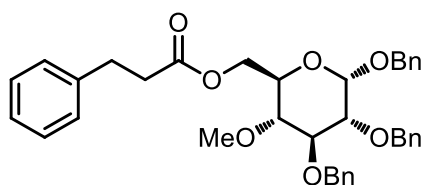


Chemical Formula: C<sub>19</sub>H<sub>21</sub>NO<sub>3</sub>  
Molecular Weight: 311,3749

Following the general procedure, starting from 3-phenylpropionic (17 mg, 0.112 mmol, 1 equiv), (*S*)-*N*-(2-hydroxy-1-phenylethyl)acetamide (20 mg, 0.112 mmol, 1 equiv), pentafluorobenzoyl chloride (19  $\mu$ L, 0.134 mmol, 1.2 equiv), triethylamine (18  $\mu$ L, 0.134 mmol, 1.2 equiv) and toluene (2.8 ml) for 24 h at 80 °C. The crude product was purified by flash column chromatography (8/2 PE/EtOAc) to afford **14ag** as a white solid (19 mg, 54%).

**Mp** = 116–118 °C. **<sup>1</sup>H NMR** (360 MHz, CDCl<sub>3</sub>)  $\delta$  = 7.37–7.11 (m, 10H), 6.05 (d,  $J$  = 7.9 Hz, 1H), 5.31–5.22 (m, 1H), 4.40 (dd,  $J$  = 11.5, 7.0 Hz, 1H), 4.26 (dd,  $J$  = 11.5, 4.7 Hz, 1H), 2.91 (t,  $J$  = 7.6 Hz, 2H), 2.64 (t,  $J$  = 7.6 Hz, 2H), 1.95 (s,  $J$  = 3.9 Hz, 3H). **<sup>13</sup>C NMR** (91 MHz, CDCl<sub>3</sub>)  $\delta$  = 173.2, 169.7, 140.3, 138.4, 128.9, 128.7, 128.3, 128.1, 126.8, 126.5, 66.2, 52.6, 35.7, 30.8, 23.4. **IR** (film, cm<sup>-1</sup>):  $\nu_{\text{max}}$  = 2930, 2857, 1729, 1645, 1543, 1454, 1373, 1289, 1170, 997, 847, 752, 699. **HRMS** (ESI<sup>+</sup>):  $m/z$  calcd for C<sub>19</sub>H<sub>22</sub>NO<sub>3</sub> [M+H]<sup>+</sup>: 312.1594, found: 312.1585.

**((2*R*,3*R*,4*S*,5*R*,6*S*)-(4,5,6-tris(benzyloxy)-3-methoxytetrahydro-2*H*-pyran-2-yl)methyl 3-phenylpropanoate (14ah)**

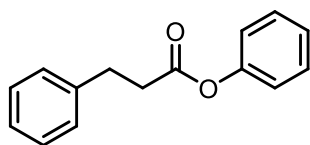


Chemical Formula: C<sub>37</sub>H<sub>40</sub>O<sub>7</sub>  
Molecular Weight: 596,2774

Following the general procedure, starting from 3-phenylpropionic (20 mg, 0.133 mmol, 1 equiv), (4,5,6-tris(benzyloxy)-3-methoxytetrahydro-2H-pyran-2-yl)methanol (60 mg, 0.133 mmol, 1 equiv), pentafluorobenzoyl chloride (24  $\mu$ L, 0.159 mmol, 1.2 equiv), triethylamine (22  $\mu$ L, 0.159 mmol, 1.2 equiv) and toluene (2 ml) for 48 h. The crude product was purified by flash column chromatography (8/2 PE/EtOAc) to afford **14ah** as a colorless oil (62 mg, 81%).

**<sup>1</sup>H NMR** (360 MHz, CDCl<sub>3</sub>)  $\delta$  = 7.40–7.11 (m, 20H), 4.99 (d,  $J$  = 10.8 Hz, 1H), 4.83–4.78 (m, 3H), 4.66 (d,  $J$  = 12.1 Hz, 1H), 4.57 (d,  $J$  = 3.5 Hz, 1H), 4.45 (d,  $J$  = 10.8 Hz, 1H), 4.31–4.23 (m, 2H), 3.99 (t,  $J$  = 9.2 Hz, 1H), 3.79 (dt,  $J$  = 10.0, 3.3 Hz, 1H), 3.51 (dd,  $J$  = 9.6, 3.5 Hz, 1H), 3.45–3.38 (m, 1H), 3.34 (s, 3H), 2.92 (t,  $J$  = 7.7 Hz, 2H), 2.70–2.54 (m, 2H). **<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>)  $\delta$  = 172.7, 140.4, 138.7, 138.2, 137.9, 128.64, 128.58, 128.5, 128.4, 128.3, 128.2, 128.1, 128.0, 127.8, 126.4, 98.1, 82.1, 79.9, 76.0, 75.2, 73.5, 68.7, 63.1, 55.3, 35.7, 30.9, 3 carbons hidden. **IR** (film, cm<sup>-1</sup>):  $\nu_{\text{max}}$  = 3063, 3030, 2924, 1738, 1604, 1496, 1454, 1360, 1161, 1073, 1028, 914, 740, 698. **HRMS** (ESI<sup>+</sup>):  $m/z$  calcd for C<sub>37</sub>H<sub>40</sub>NaO<sub>7</sub> [M+Na]<sup>+</sup>: 619.2666, found: 619.2632.

#### Phenyl 3-phenylpropanoate (**14ai**)



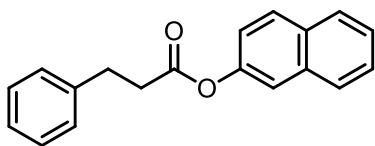
Chemical Formula: C<sub>15</sub>H<sub>14</sub>O<sub>2</sub>  
Molecular Weight: 226,2705

Following the general procedure, starting from 3-phenylpropionic (150 mg, 1 mmol, 1 equiv), phenol (189 mg, 2 mmol, 2 equiv), pentafluorobenzoyl chloride (172  $\mu$ L, 1.2 mmol, 1.2 equiv), triethylamine (557  $\mu$ L, 4 mmol, 4 equiv) and toluene (10 ml) for 48 h. The crude product was purified by flash column chromatography (95/5 PE/EtOAc) to afford **14ai** as a colorless oil (181 mg, 80%).

**<sup>1</sup>H NMR** (360 MHz, CDCl<sub>3</sub>)  $\delta$  = 7.40–7.20 (m, 8H), 7.06–7.01 (m, 2H), 3.13 (t,  $J$  = 7.6 Hz, 1H), 2.94 (t,  $J$  = 7.6 Hz, 1H). **<sup>13</sup>C NMR** (91 MHz, CDCl<sub>3</sub>)  $\delta$  = 171.5, 150.8, 140.2, 129.5, 128.7, 128.5, 126.6, 125.9, 121.7, 36.1, 31.1. **HRMS** (ESI<sup>+</sup>):  $m/z$  calcd for C<sub>15</sub>H<sub>14</sub>NaO<sub>2</sub> [M+Na]<sup>+</sup>: 249.0886, found: 249.0886.

Data are in agreement with: T. Miyazaki, S. Kasai, Y. Ogiwara, N. Sakai, *Eur. J. Org. Chem.* **2016**, 1043.

#### Naphthalen-2-yl 3-phenylpropanoate (**14aj**)



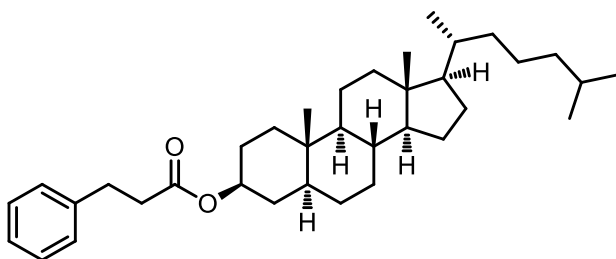
Chemical Formula: C<sub>19</sub>H<sub>16</sub>O<sub>2</sub>  
Molecular Weight: 276,1150

Following the general procedure, starting from 3-phenylpropionic (150 mg, 1 mmol, 1 equiv), naphth-2-ol (144 mg, 1 mmol, 1 equiv), pentafluorobenzoyl chloride (172  $\mu$ L, 1.2 mmol, 1.2 equiv), triethylamine (557  $\mu$ L, 4 mmol, 4 equiv) and toluene (10 ml) for 24 h. The crude product was purified by flash column chromatography (95/5 PE/EtOAc) to afford **14aj** as a white solid (209 mg, 72%).

**<sup>1</sup>H NMR** (360 MHz, CDCl<sub>3</sub>)  $\delta$  = 7.86 (d,  $J$  = 8.9 Hz, 2H), 7.82 (d,  $J$  = 9.1 Hz, 1H), 7.56–7.46 (m, 3H), 7.40–7.27 (m, 5H), 7.19 (dd,  $J$  = 8.9, 2.3 Hz, 1H), 3.16 (t,  $J$  = 7.7 Hz, 2H), 2.98 (t,  $J$  = 7.5 Hz, 2H). **<sup>13</sup>C NMR** (91 MHz, CDCl<sub>3</sub>)  $\delta$  = 171.7, 148.4, 140.2, 133.8, 131.5, 129.5, 128.7, 128.6, 127.9, 127.7, 126.7, 126.6, 125.8, 121.2, 118.6, 36.2, 31.1. **HRMS** (ESI<sup>+</sup>):  $m/z$  calcd for C<sub>19</sub>H<sub>17</sub>O<sub>2</sub> [M+H]<sup>+</sup>: 277.1223, found: 277.1213.

Data are in agreement with: E. Alden-Danforth, M. T. Scerba, T. Lectka, *Org. Lett.* **2008**, *10*, 21, 4951.

**(3*S*,5*S*,8*R*,9*S*,10*S*,13*R*,14*S*,17*R*)-10,13-dimethyl-17-((*R*)-6-methylheptan-2-yl)hexadecahydro-1*H*-cyclopenta[*a*]phenanthren-3-yl 3-phenylpropanoate, (+)-5 $\alpha$ -Cholestan-3 $\beta$ -yl-3-phenylpropanoate (**14ak**)**



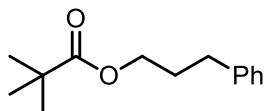
Chemical Formula: C<sub>36</sub>H<sub>56</sub>O<sub>2</sub>  
Molecular Weight: 520,4280

Following the general procedure, starting from 3-phenylpropionic (150 mg, 1 mmol, 1 equiv), 5 $\alpha$ -cholestan-3 $\beta$ -ol (388 mg, 1 mmol, 1 equiv), pentafluorobenzoyl chloride (172  $\mu$ L, 1.2 mmol, 1.2 equiv), triethylamine (167  $\mu$ L, 1.2 mmol, 1.2 equiv) and toluene (10 ml) for 24 h. The crude product was purified by flash column chromatography (98/2 PE/EtOAc) to afford **14ak** as a white solid (472 mg, 91%).

**<sup>1</sup>H NMR** (360 MHz, CDCl<sub>3</sub>)  $\delta$  = 7.28 (t,  $J$  = 7.6 Hz, 2H), 7.20 (d,  $J$  = 7.2 Hz, 3H), 4.75–4.66 (m, 1H), 2.94 (t,  $J$  = 7.8 Hz, 2H), 2.59 (t,  $J$  = 7.8 Hz, 2H), 2.04–1.85 (m, 3H), 1.75–1.46 (m, 8H), 1.38–1.22 (m, 10H), 1.18–1.07 (m, 7H), 1.04–0.96 (m, 3H), 0.91 (d,  $J$  = 6.3 Hz, 3H), 0.88 (d,  $J$  = 6.6 Hz, 6H), 0.82 (s, 3H), 0.66 (s, 3H). **<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>)  $\delta$  = 172.5, 140.7, 128.5, 128.4, 126.3, 73.8, 56.5, 56.4, 54.3, 44.7, 42.7, 40.1, 39.6, 36.8, 36.4, 36.3, 35.9, 35.5, 34.1, 32.1, 31.2, 28.7, 28.4, 28.1, 27.5, 24.3, 24.0, 22.9, 22.7, 21.3, 18.8, 12.3, 12.2, one carbon hidden. **HRMS** (ESI<sup>+</sup>):  $m/z$  calcd for C<sub>36</sub>H<sub>57</sub>O<sub>2</sub> [M+H]<sup>+</sup>: 521.4353, found: 521.4331.

Data are in agreement with: I. Shiina, M. Kubota, H. Oshiumi, M. Hashizume, *J. Org. Chem.* **2004**, *69*, 1822.

### 3-phenylpropyl pivalate (**14bl**)



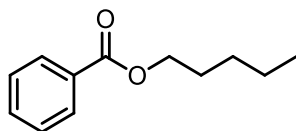
Chemical Formula: C<sub>14</sub>H<sub>20</sub>O<sub>2</sub>  
Exact Mass: 220,1463

Following the general procedure, starting from pivalic acid (102 mg, 1 mmol, 1 equiv), 3-phenylpropan-1-ol (109  $\mu$ L, 0.8 mmol, 0.8 equiv), pentafluorobenzoyl chloride (172  $\mu$ L, 1.2 mmol, 1.2 equiv), triethylamine (167  $\mu$ L, 1.2 mmol, 1.2 equiv) and toluene (10 ml) for 48 h. The crude product was purified by flash column chromatography (95/5 PE/EtOAc) to afford **14bl** as a colorless oil (144 mg, 82%).

**<sup>1</sup>H NMR** (360 MHz, CDCl<sub>3</sub>)  $\delta$  = 7.35–7.26 (m, 2H), 7.22–7.15 (m, 3H), 4.09 (t,  $J$  = 6.4 Hz, 2H), 2.70 (t,  $J$  = 6.6 Hz, 2H), 2.01–1.93 (m, 2H), 1.22 (s, 9H). **<sup>13</sup>C NMR** (91 MHz, CDCl<sub>3</sub>)  $\delta$  = 178.7, 141.4, 128.6, 128.5, 126.1, 63.7, 38.9, 32.3, 30.4, 27.4. **HRMS** (ESI<sup>+</sup>):  $m/z$  calcd for C<sub>14</sub>H<sub>21</sub>O<sub>2</sub> [M+H]<sup>+</sup>: 221.1536, found: 221.1526.

Data are in agreement with: A. Sakakura, K. Kawajiri, T. Ohkubo, Y. Kosugi, K. Ishihara, *J. Am. Chem. Soc.* **2007**, *129*, 47, 14775.

### Pentyl benzoate (**14ca**)



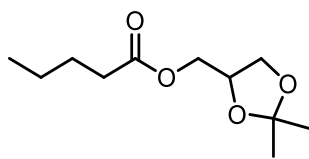
Chemical Formula: C<sub>12</sub>H<sub>16</sub>O<sub>2</sub>  
Molecular Weight: 192,1150

Following the general procedure, starting from benzoic acid (122 mg, 1 mmol, 1 equiv), pentanol (216  $\mu$ L, 2 mmol, 2 equiv), pentafluorobenzoyl chloride (172  $\mu$ L, 1.2 mmol, 1.2 equiv), triethylamine (167  $\mu$ L, 1.2 mmol, 1.2 equiv) and toluene (10 ml) for 48 h. The crude product was purified by flash column chromatography (95/5 PE/EtOAc) to afford **14ca** as a colorless oil (143 mg, 74%).

**<sup>1</sup>H NMR** (360 MHz, CDCl<sub>3</sub>)  $\delta$  = 8.05 (d,  $J$  = 7.4 Hz, 2H), 7.55 (t,  $J$  = 7.4 Hz, 1H), 7.44 (t,  $J$  = 7.6 Hz, 2H), 4.32 (t,  $J$  = 6.7 Hz, 2H), 1.83–1.71 (m, 2H), 1.33–1.50 (m, 4H), 0.93 (t,  $J$  = 6.9 Hz, 3H). **<sup>13</sup>C NMR** (91 MHz, CDCl<sub>3</sub>)  $\delta$  = 166.8, 132.9, 130.7, 129.7, 128.5, 65.3, 28.6, 28.3, 22.5, 14.1. **HRMS** (ESI<sup>+</sup>):  $m/z$  calcd for C<sub>12</sub>H<sub>16</sub>NaO<sub>2</sub> [M+Na]<sup>+</sup>: 215.1042, found: 215.1033.

Data are in agreement with: J. B. C. Mack, J. D. Gipson, J. Du Bois, M. S. Sigman *J. Am. Chem. Soc.* **2017**, *139*, 28, 9503.

**(2,2-dimethyl-1,3-dioxolan-4-yl)methyl pentanoate (14dm)**



Chemical Formula: C<sub>11</sub>H<sub>20</sub>O<sub>4</sub>

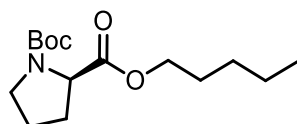
Molecular Weight: 216,2741

Following the general procedure, starting from valeric acid (108  $\mu$ L, 1 mmol, 1 equiv), solketal (124  $\mu$ L, 1 mmol, 1 equiv), pentafluorobenzoyl chloride (172  $\mu$ L, 1.2 mmol, 1.2 equiv), triethylamine (167  $\mu$ L, 1.2 mmol, 1.2 equiv) and toluene (10 ml) for 24 h. The crude product was purified by flash column chromatography (95/5 PE/EtOAc) to afford **14dm** as a colorless oil (184 mg, 85%).

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>)  $\delta$  = 4.29–4.17 (m, 1H), 4.12–3.94 (m, 3H), 3.65 (dd,  $J$  = 8.4, 6.0 Hz, 1H), 2.26 (t,  $J$  = 7.5 Hz, 2H), 1.59–1.46 (m, 2H), 1.34 (s, 3H), 1.31–1.20 (m, 2H), 1.27 (s, 3H), 0.82 (t,  $J$  = 7.3 Hz, 3H). **<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>)  $\delta$  = 173.5, 109.7, 73.6, 66.3, 64.4, 33.7, 26.9, 26.6, 25.3, 22.2, 13.6. **HRMS** (ESI<sup>+</sup>):  $m/z$  calcd for C<sub>11</sub>H<sub>20</sub>NaO<sub>4</sub> [M+Na]<sup>+</sup>: 239.1254, found: 239.1240.

Data are in agreement with: M. De Léséleuc, S. K. Collins, *ACS Catal.* **2015**, 5, 1462.

**(R)-1-tert-butyl 2-pentyl pyrrolidine-1,2-dicarboxylate (14ea)**



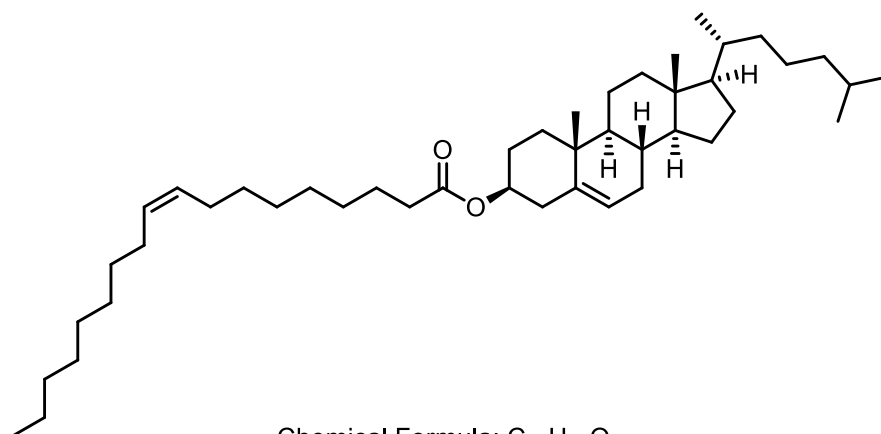
Chemical Formula: C<sub>15</sub>H<sub>27</sub>NO<sub>4</sub>

Molecular Weight: 285,1940

Following the general procedure, starting from *N*-(tert-butoxycarbonyl)-proline (215 mg, 1 mmol, 1 equiv), pentanol (162  $\mu$ L, 1.5 mmol, 1.5 equiv), pentafluorobenzoyl chloride (258  $\mu$ L, 1.5 mmol, 1.5 equiv), triethylamine (250  $\mu$ L, 1.5 mmol, 1.5 equiv) and toluene (10 ml) for 24 h. The crude product was purified by flash column chromatography (8/2 PE/EtOAc) to afford **14ea** as a colorless oil (209 mg, 74%).

**<sup>1</sup>H NMR** (360 MHz, CDCl<sub>3</sub>)  $\delta$  = 4.32–3.95 (m, 3H), 3.59–3.29 (m, 2H), 2.37–2.13 (m, 1H), 2.8–1.78 (m, 3H), 1.68–1.55 (m, 2H), 1.46–1.16 (m, 13H), 0.91–0.81 (m, 3H). **<sup>13</sup>C NMR** (91 MHz, CDCl<sub>3</sub>)  $\delta$  = 173.3, 173.0, 154.3, 153.8, 79.7, 79.6, 65.6, 65.0, 59.2, 58.9, 46.5, 46.3, 30.9, 29.9, 29.5, 28.4, 28.3, 28.1, 28.0, 24.3, 24.2, 23.6, 22.2, 13.9, 13.8, one carbon hidden. **IR** (film, cm<sup>-1</sup>):  $\nu_{\max}$  = 2936, 2832, 1726, 1604, 1479, 1073, 1010, 987. **HRMS** (ESI<sup>+</sup>):  $m/z$  calcd for C<sub>15</sub>H<sub>28</sub>NO<sub>4</sub> [M+H]<sup>+</sup>: 286.2013, found: 286.2006.

**(3S,8S,9S,10R,13R,14S,17R)-10,13-dimethyl-17-((R)-6-methylheptan-2-yl)-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[*a*]phenanthren-3-yl Cholesteryl oleate (14fn)**

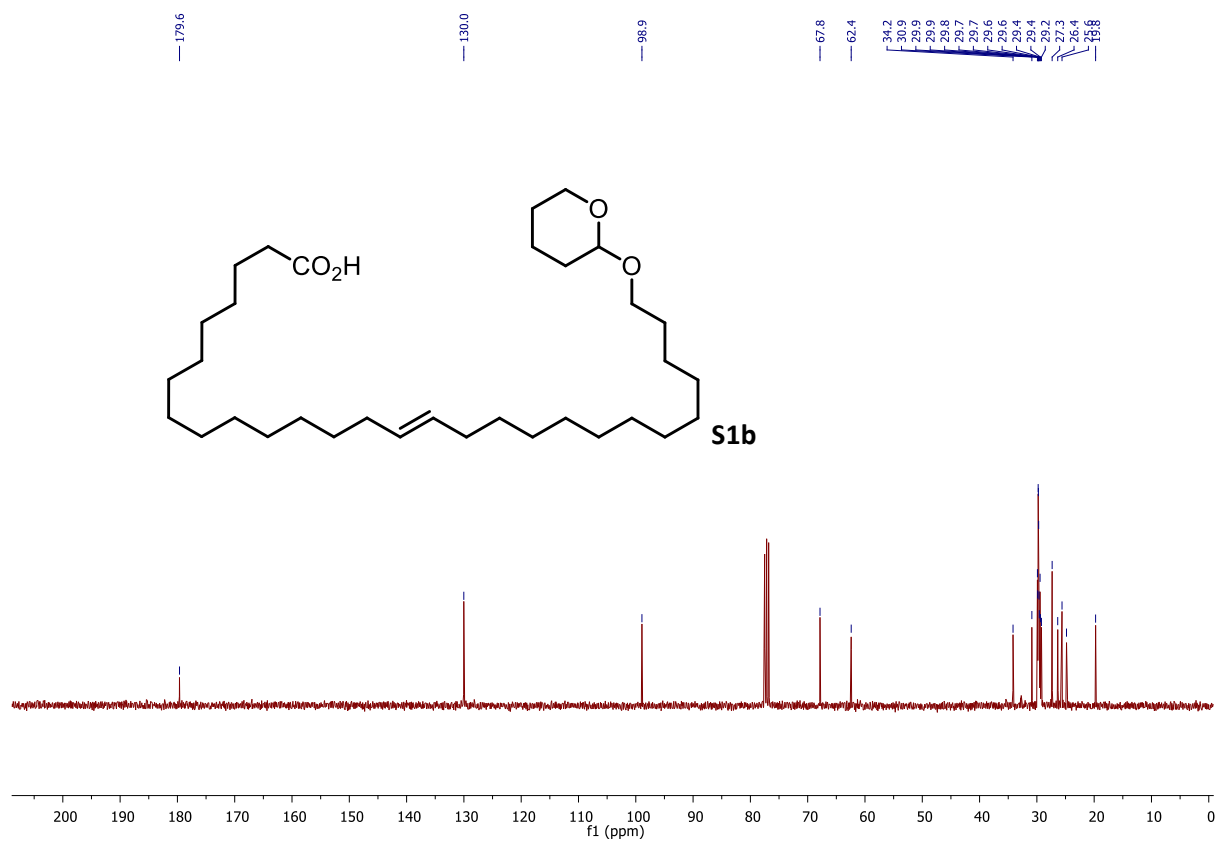
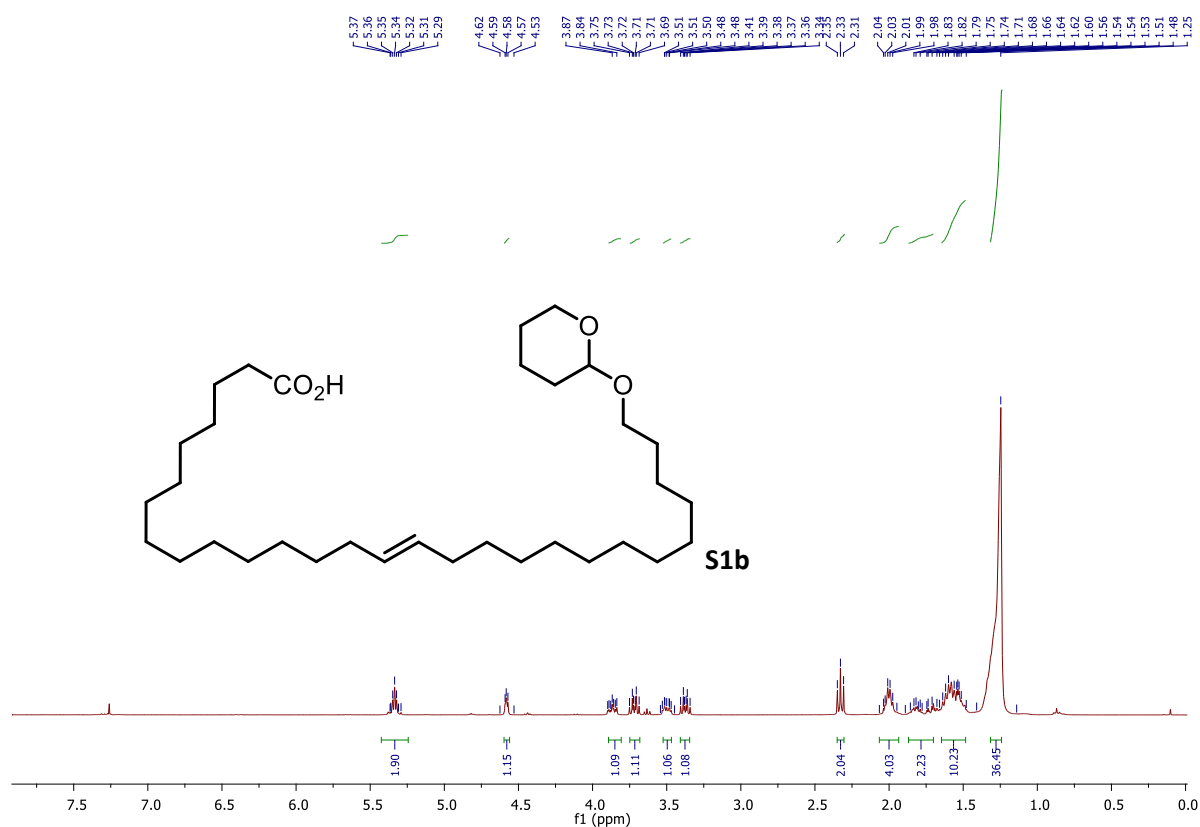


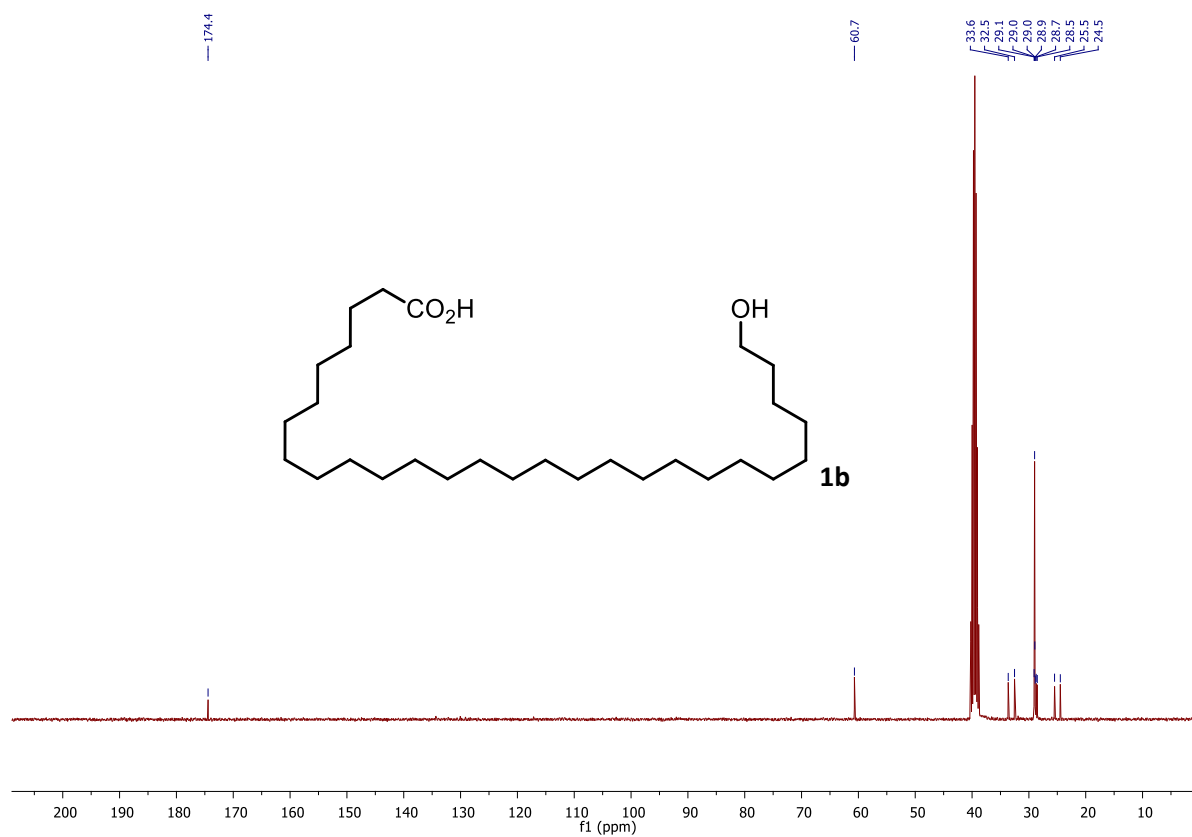
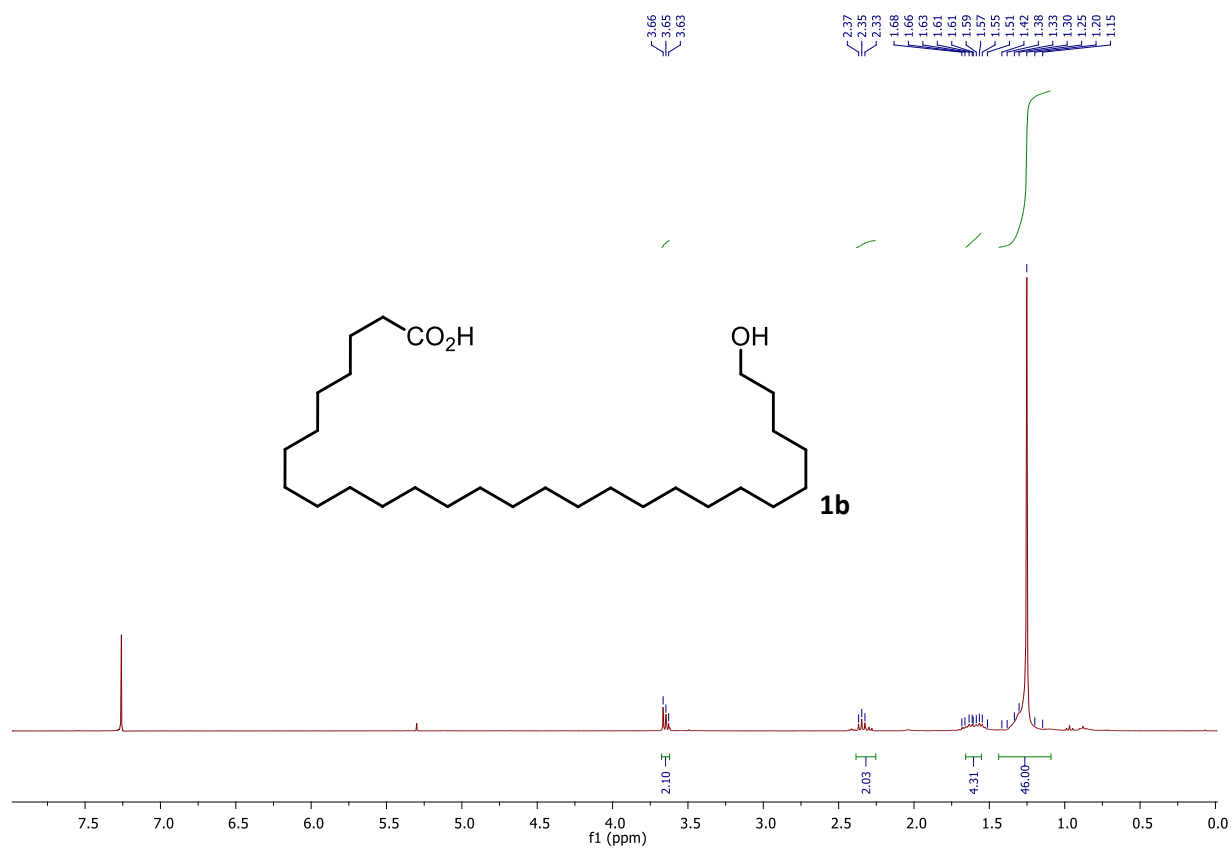
Chemical Formula:  $C_{45}H_{78}O_2$   
Molecular Weight: 650.6002

Following the general procedure, starting from oleic acid (282 mg, 1 mmol, 1 equiv), cholesterol (386 mg, 1 mmol, 1 equiv), pentafluorobenzoyl chloride (172  $\mu$ L, 1.2 mmol, 1.2 equiv), triethylamine (167  $\mu$ L, 1.2 mmol, 1.2 equiv) and toluene (10 ml) for 48 h. The crude product was purified by flash column chromatography (95/5 PE/EtOAc) to afford **14fn** as a white solid (357 mg, 55%).

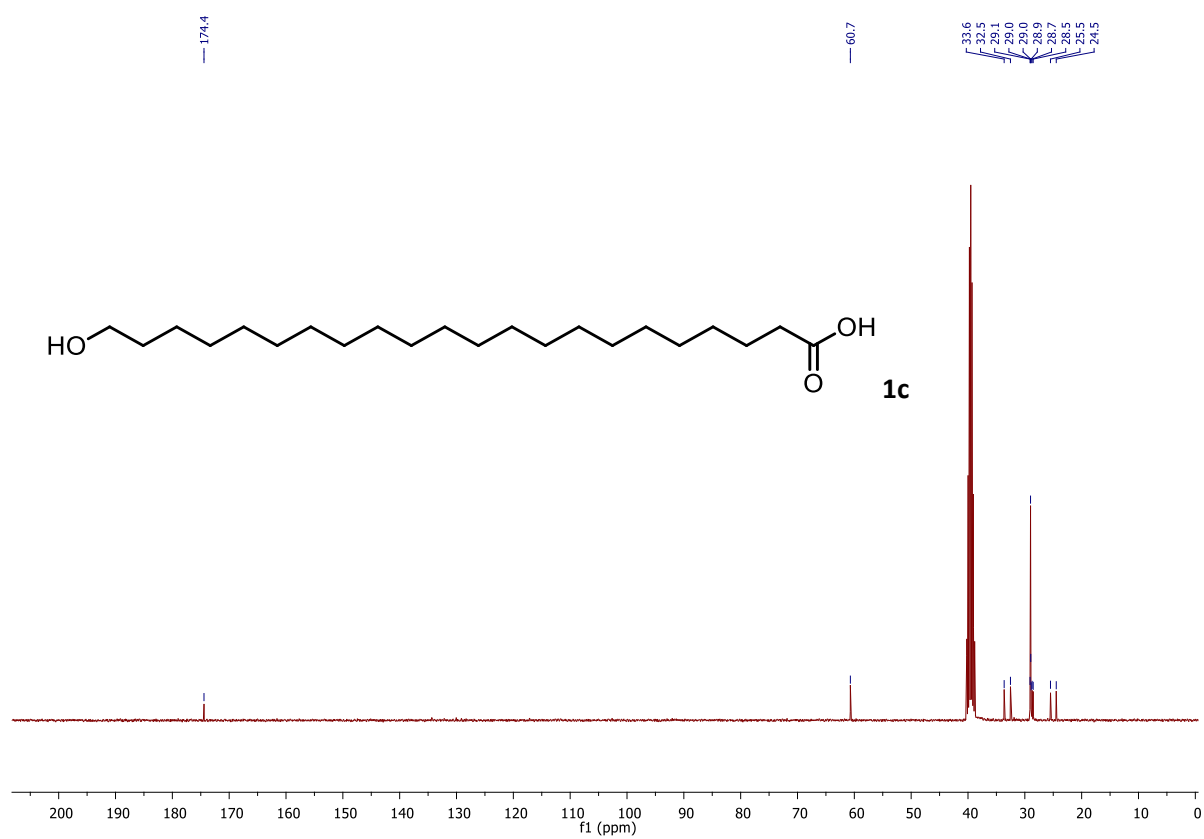
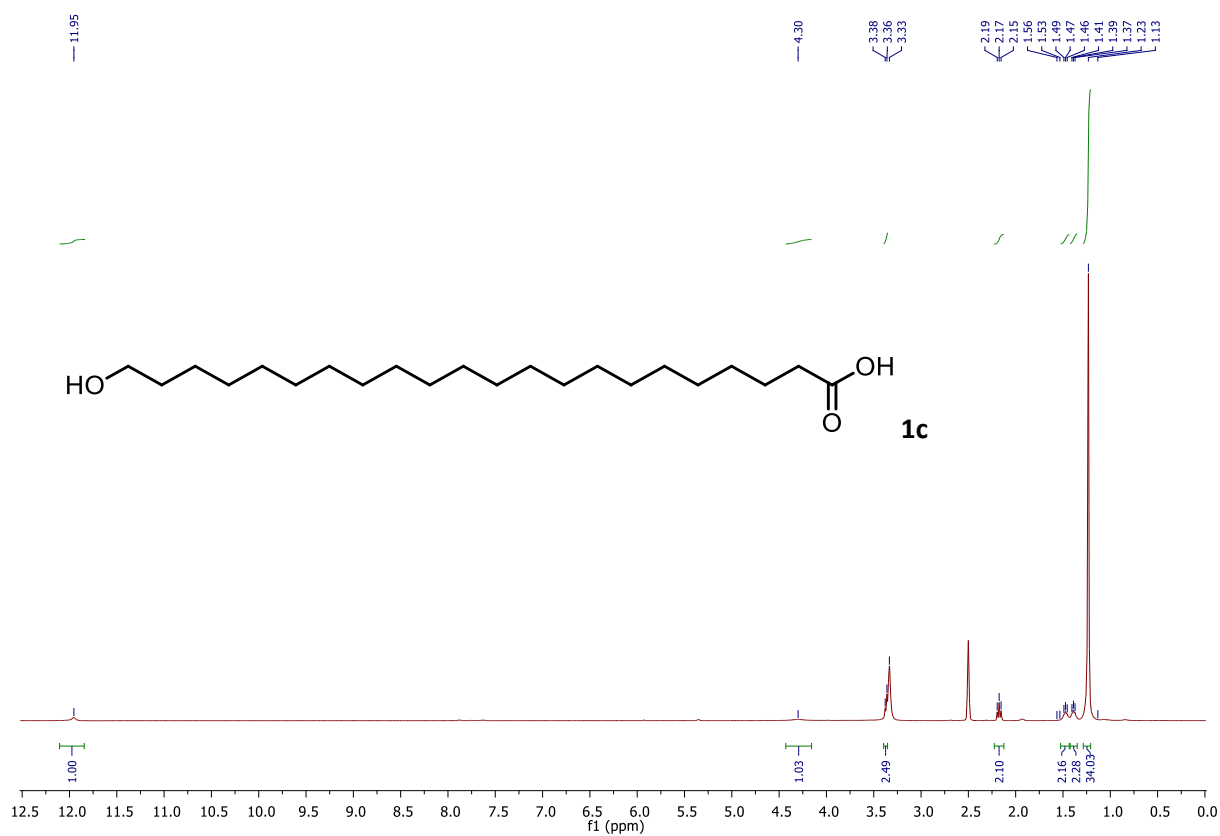
**$^1H$  NMR** (360 MHz,  $CDCl_3$ )  $\delta$  = 5.45–5.29 (m, 3H), 4.69–4.52 (m, 1H), 2.37–2.18 (m, 4H), 2.10–1.94 (m, 6H), 1.86–1.78 (m, 3H), 1.68–1.42 (m, 10H), 1.40–1.20 (m, 25H), 1.19–1.05 (m, 8H), 1.01 (s, 3H), 0.98–0.92 (m, 3H), 0.91 (d,  $J$  = 6.5 Hz, 3H), 0.86 (dd,  $J$  = 6.6, 1.3 Hz, 6H), 0.67 (s, 3H).  **$^{13}C$  NMR** (91 MHz,  $CDCl_3$ )  $\delta$  = 173.4, 139.8, 130.1, 129.9, 122.7, 73.8, 56.8, 56.3, 50.1, 42.4, 39.9, 39.6, 38.3, 37.1, 36.7, 36.3, 35.9, 34.8, 32.0, 32.0, 29.9, 29.8, 29.7, 29.5, 29.4, 29.3, 29.2, 28.4, 28.1, 27.9, 27.3, 27.3, 25.2, 24.4, 24.0, 23.0, 22.8, 22.7, 21.2, 19.4, 18.8, 14.3, 12.0, 2 carbons hidden. **IR** (film,  $cm^{-1}$ ):  $\nu_{max}$  = 2940, 2836, 1729, 1616, 1604, 1578, 1479, 1426, 1258, 1116, 1073, 1012, 987.

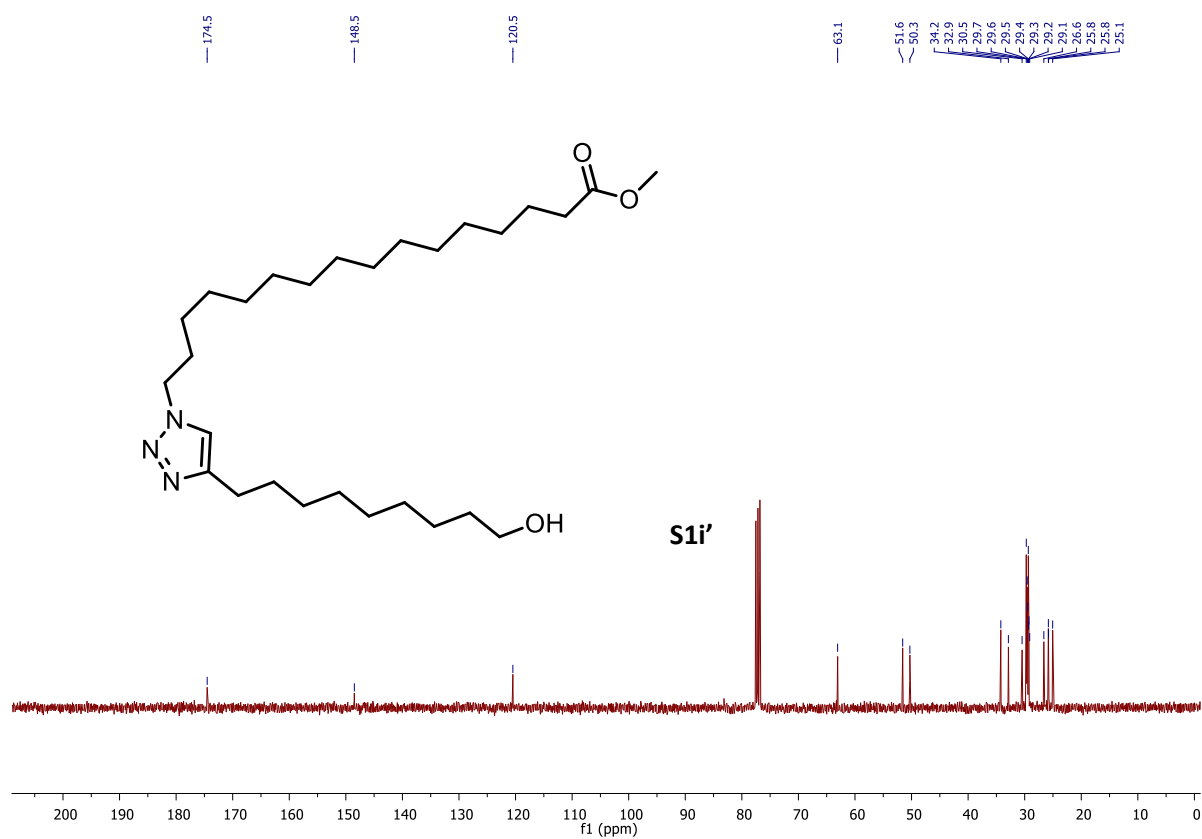
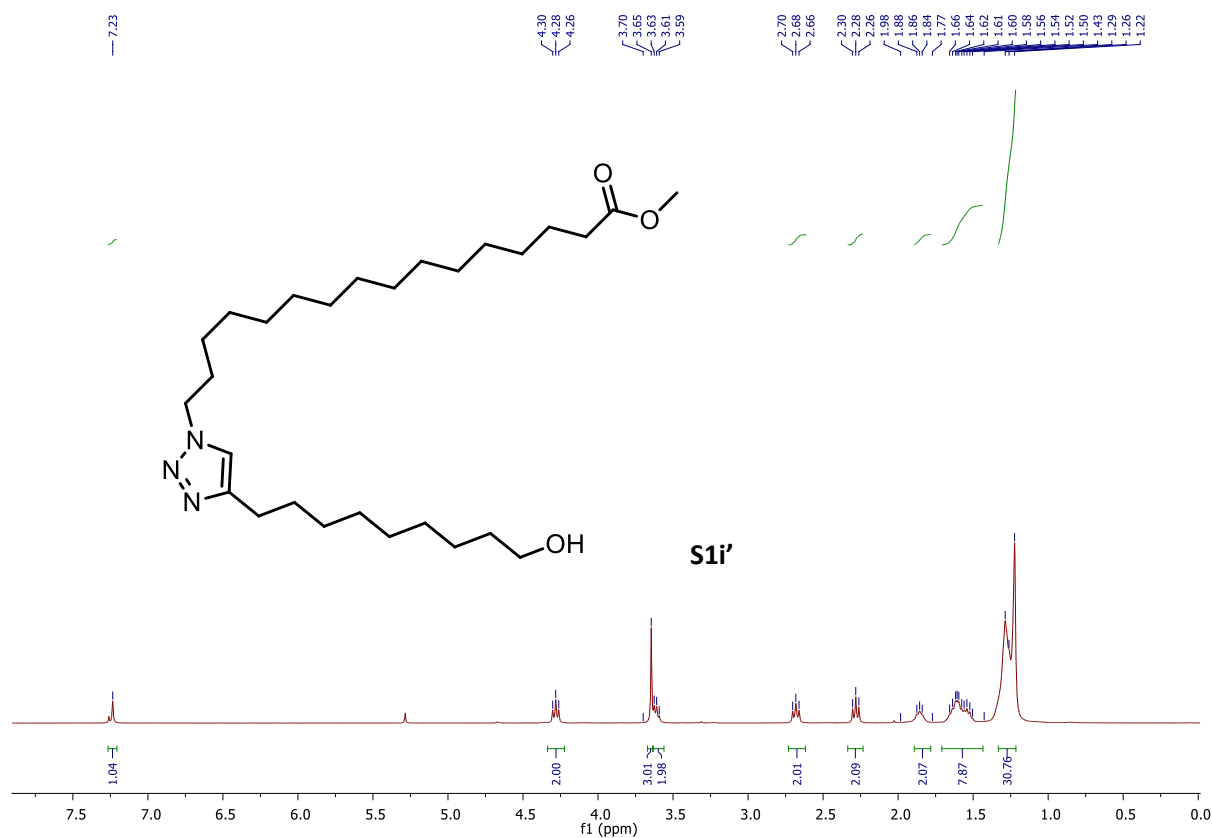
# NMR SPECTRA



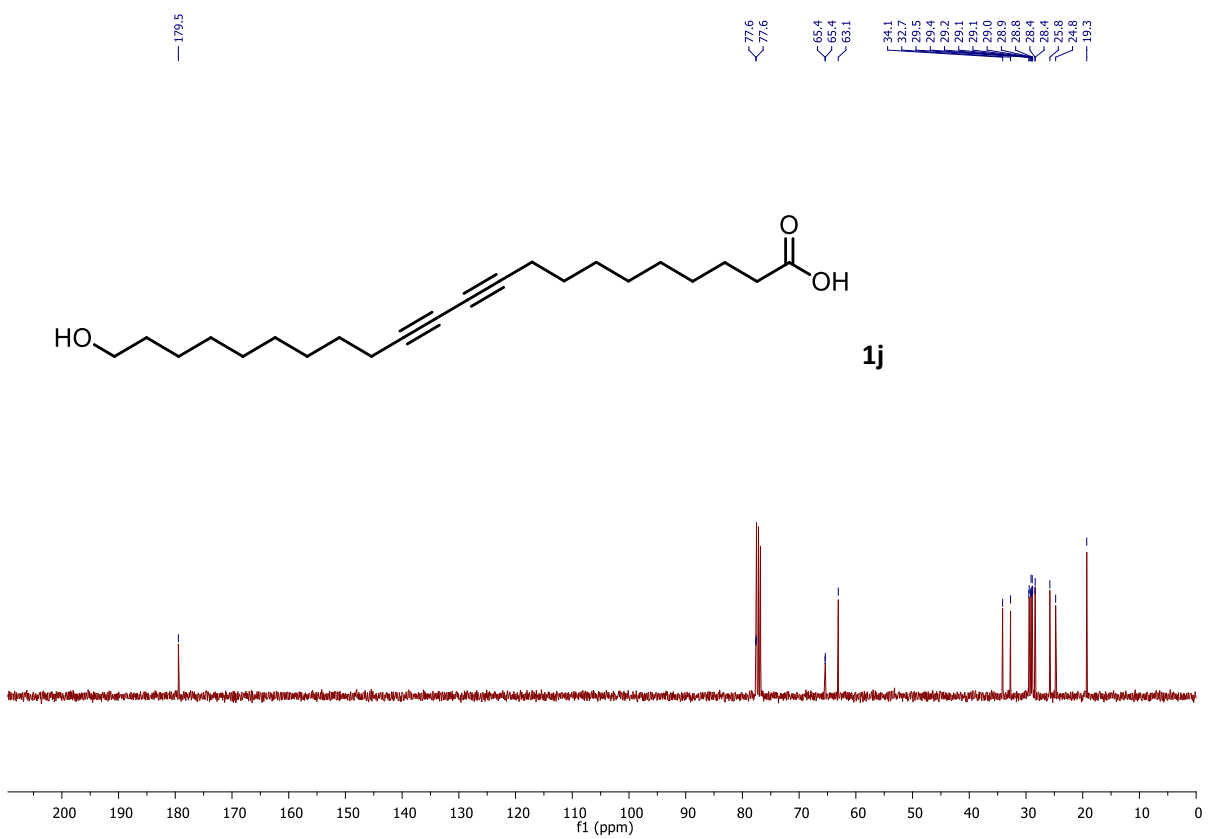
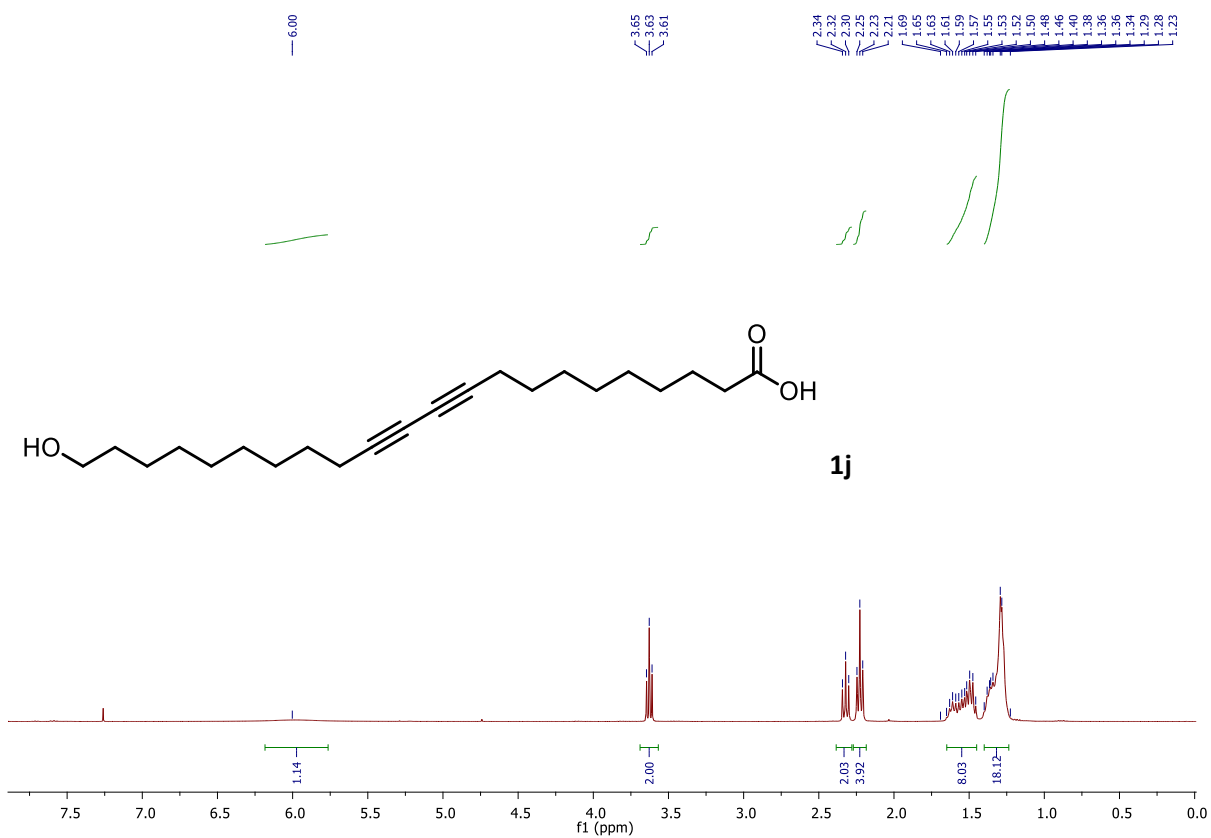


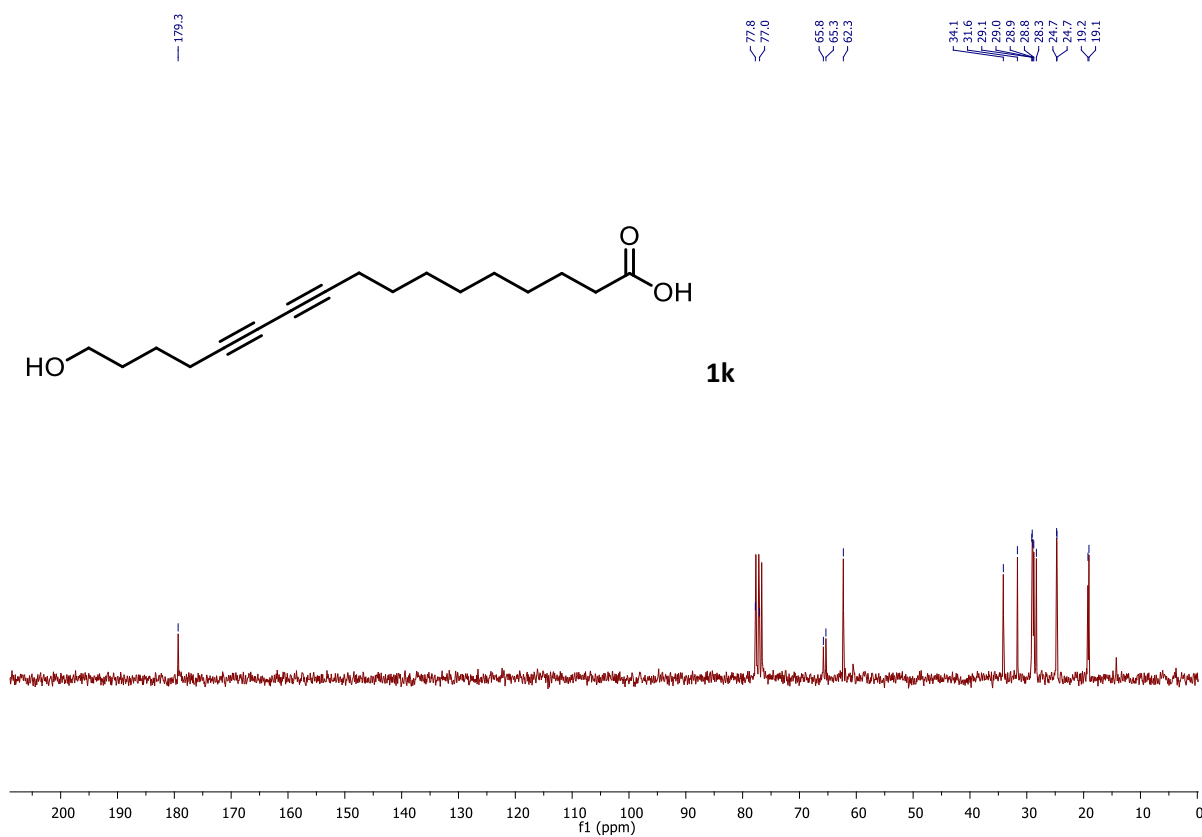
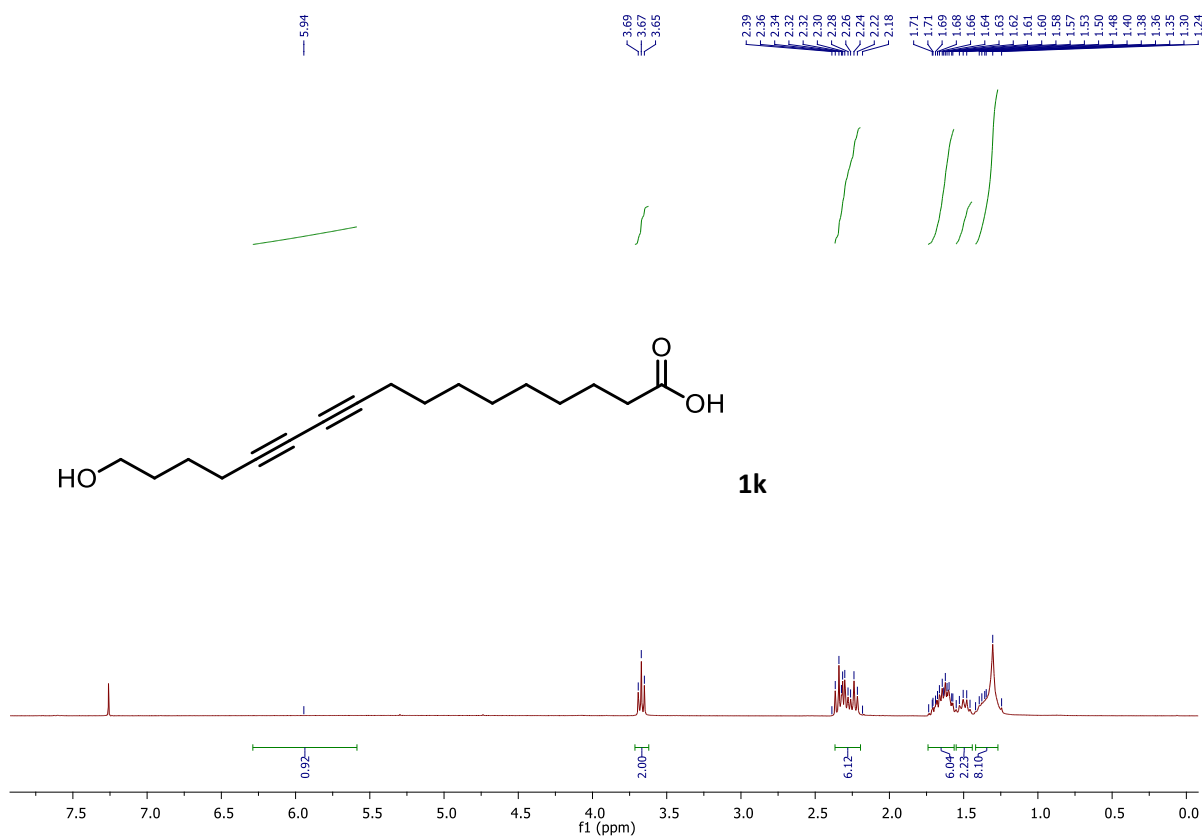


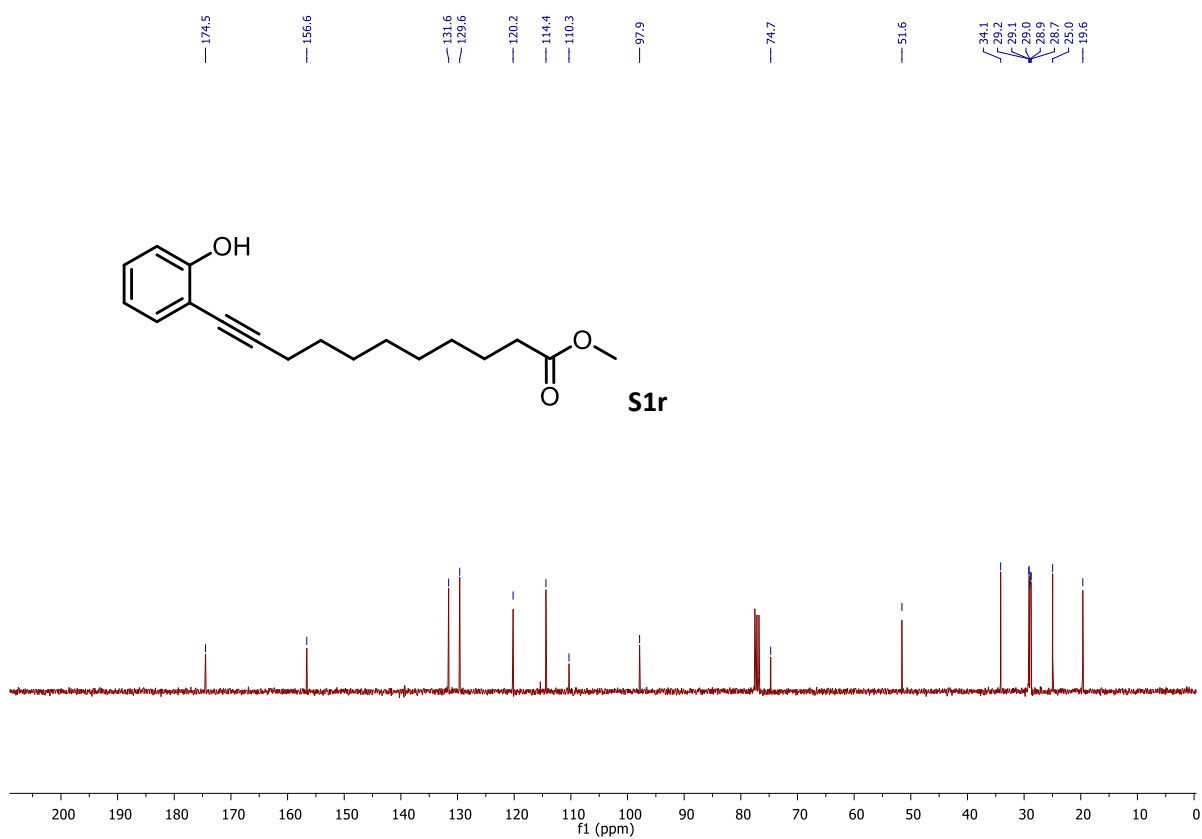
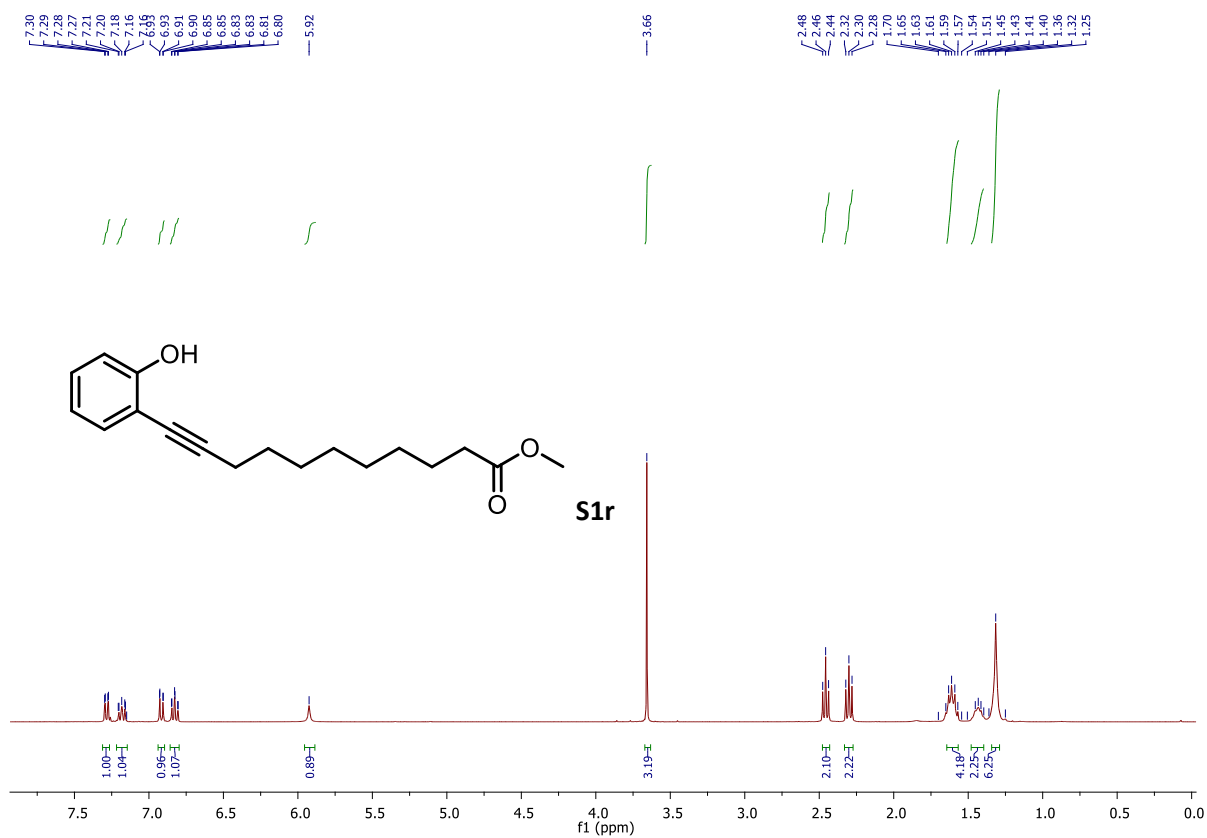


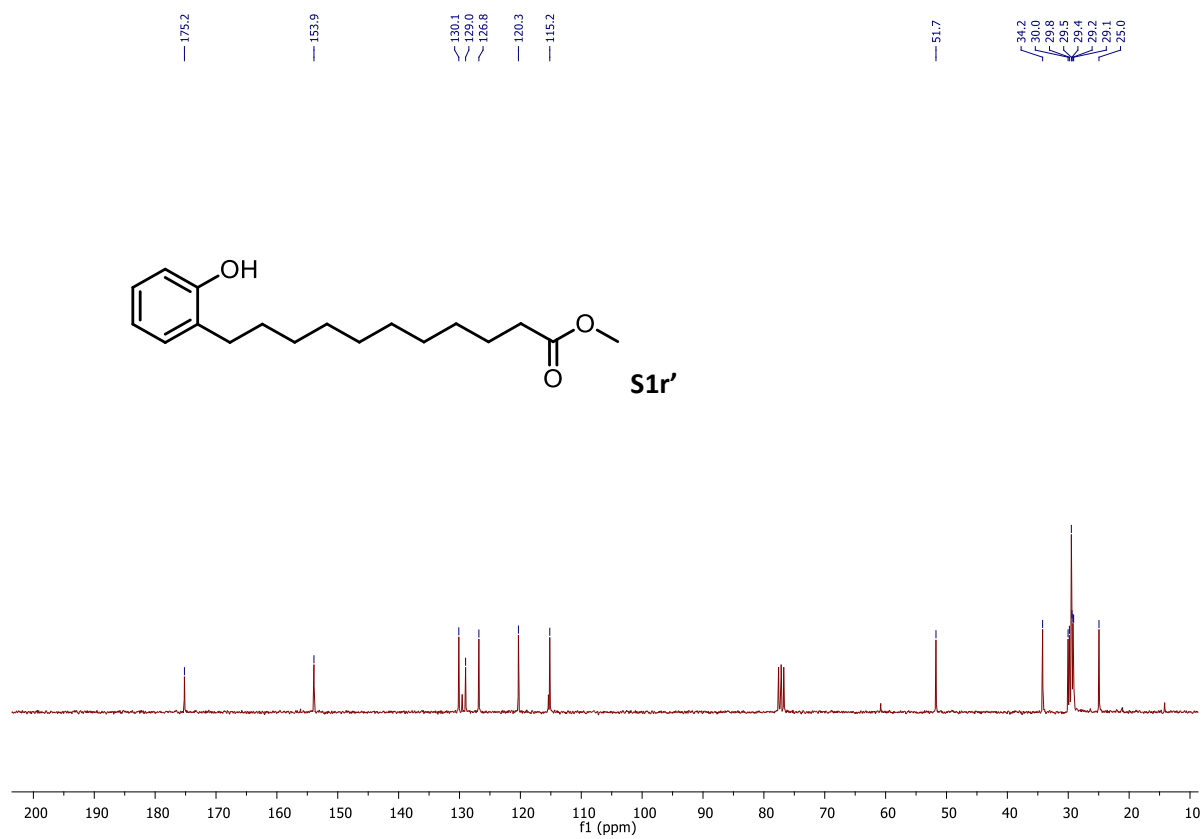
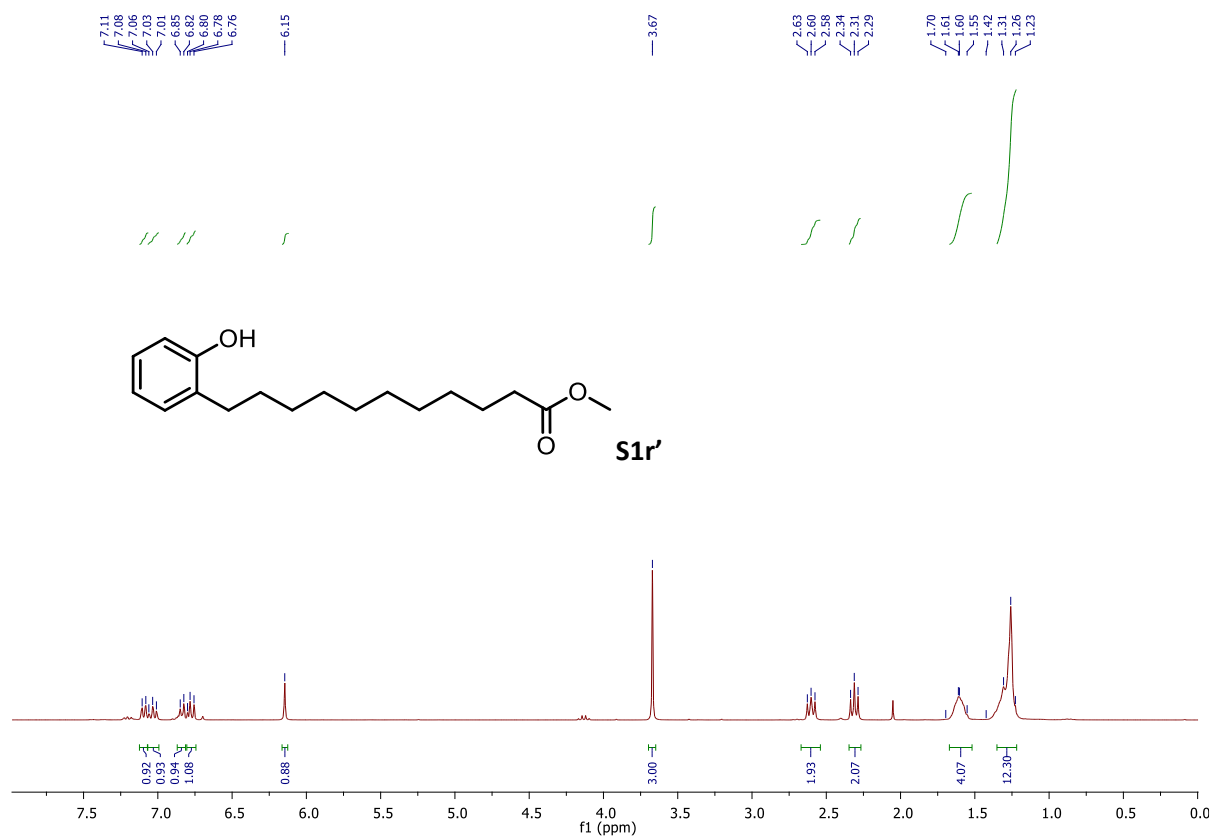


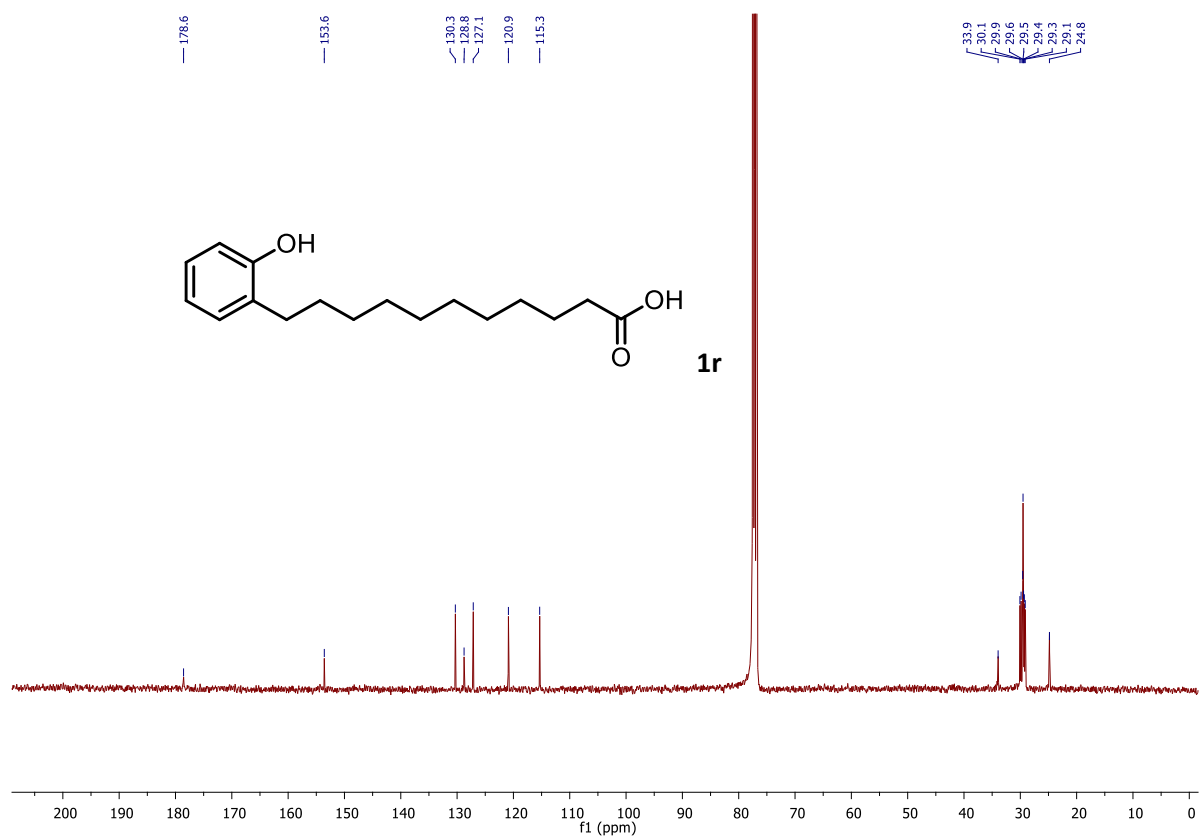
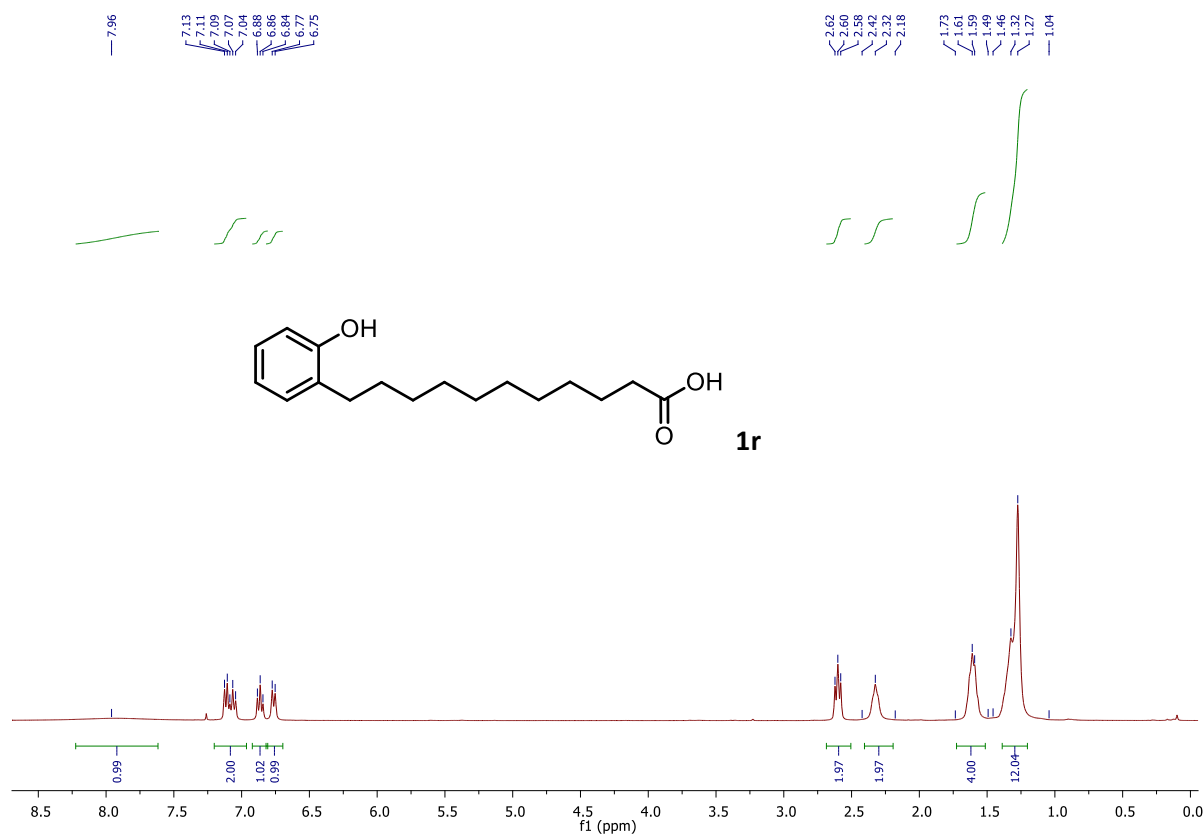




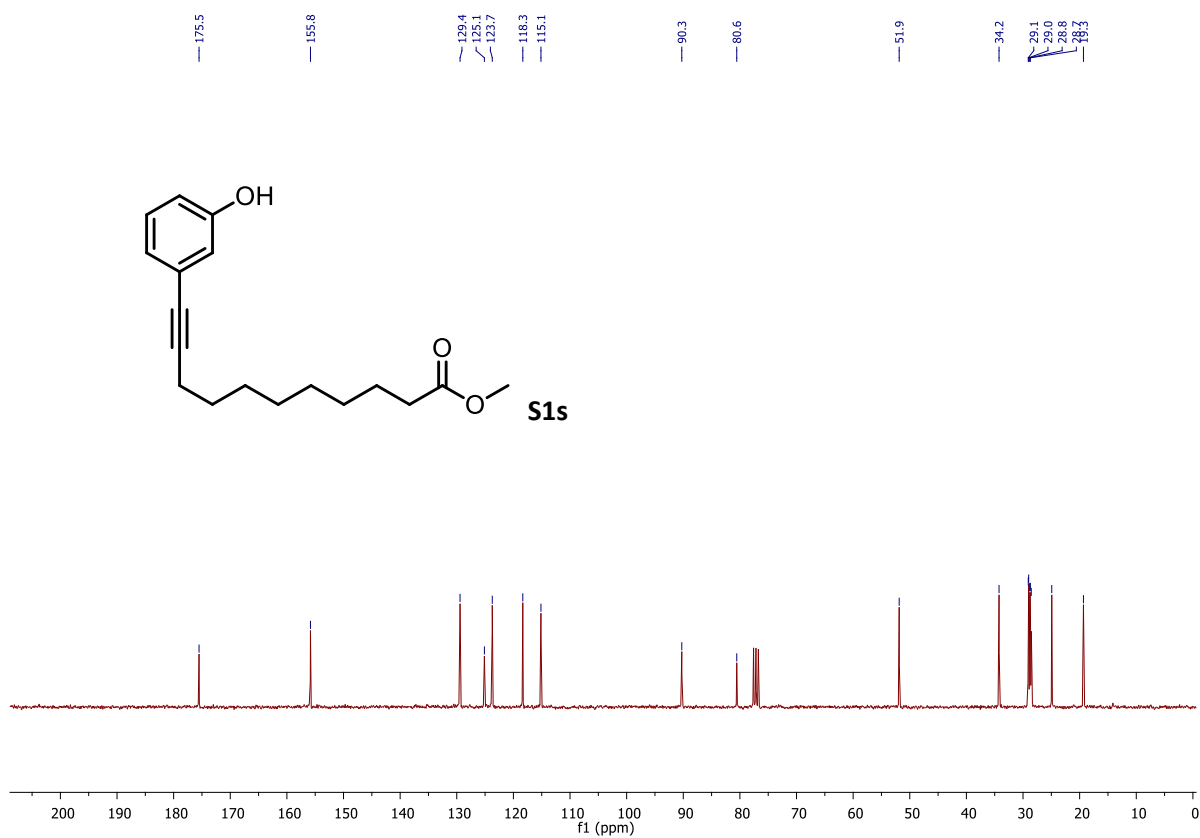
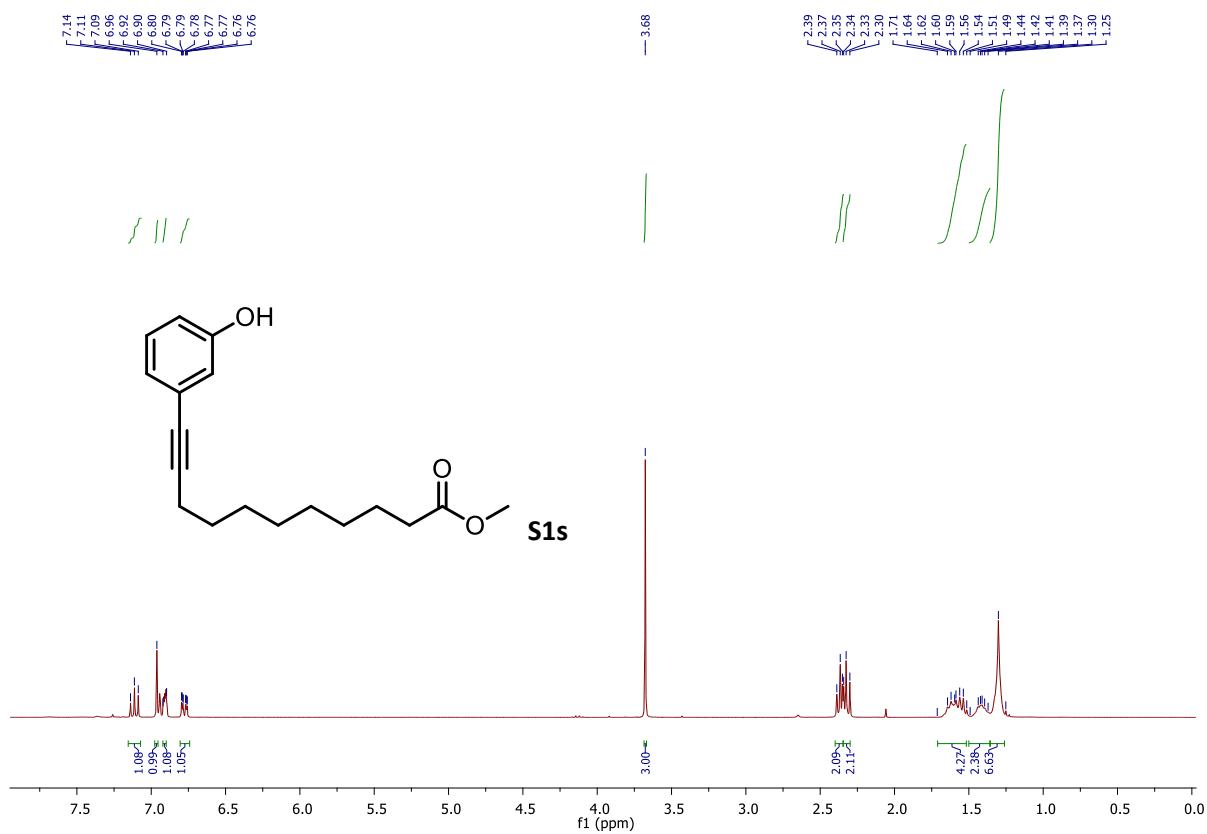


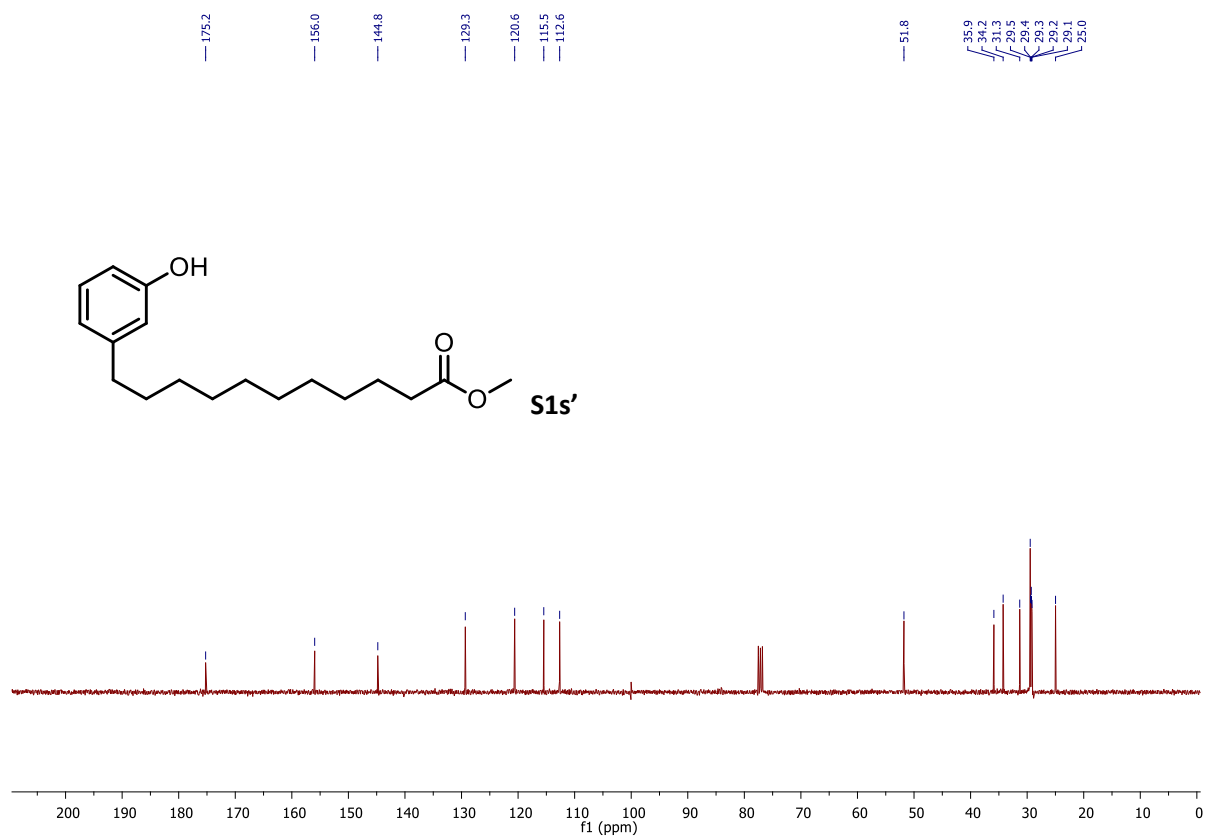
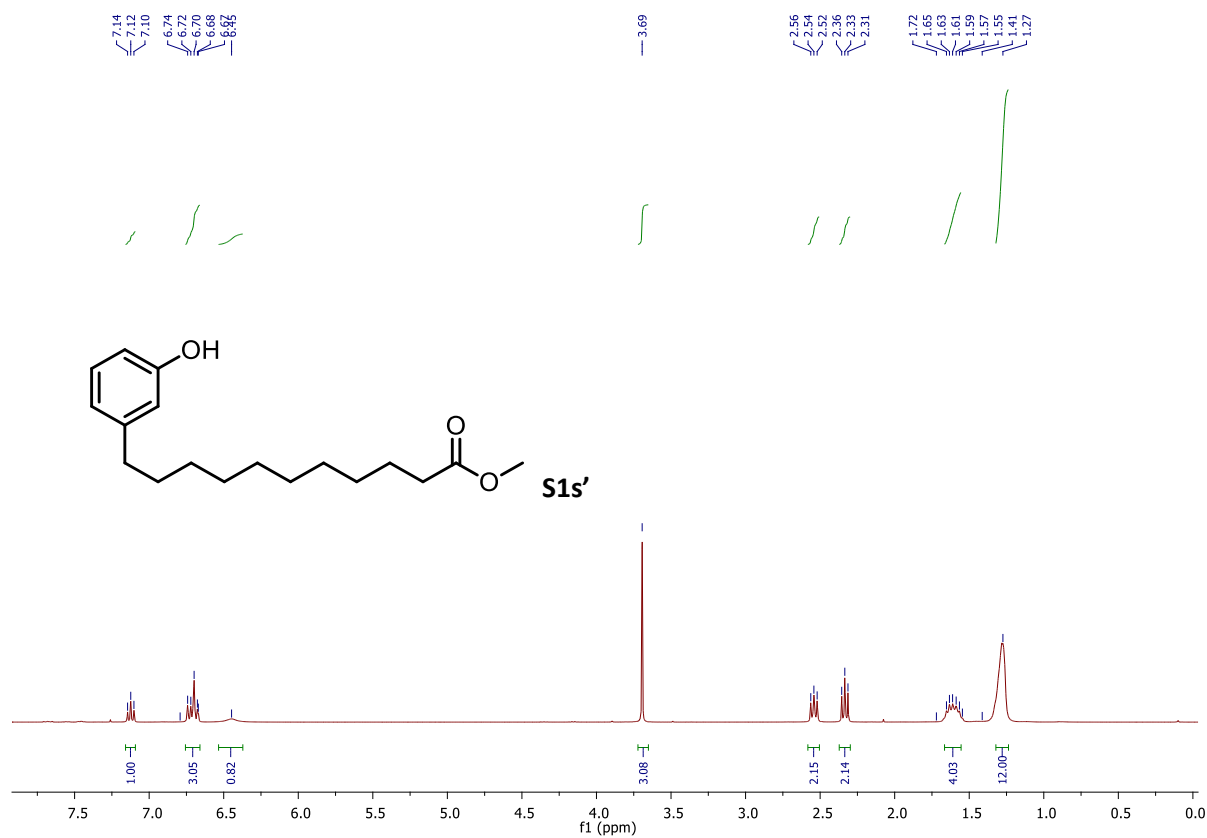


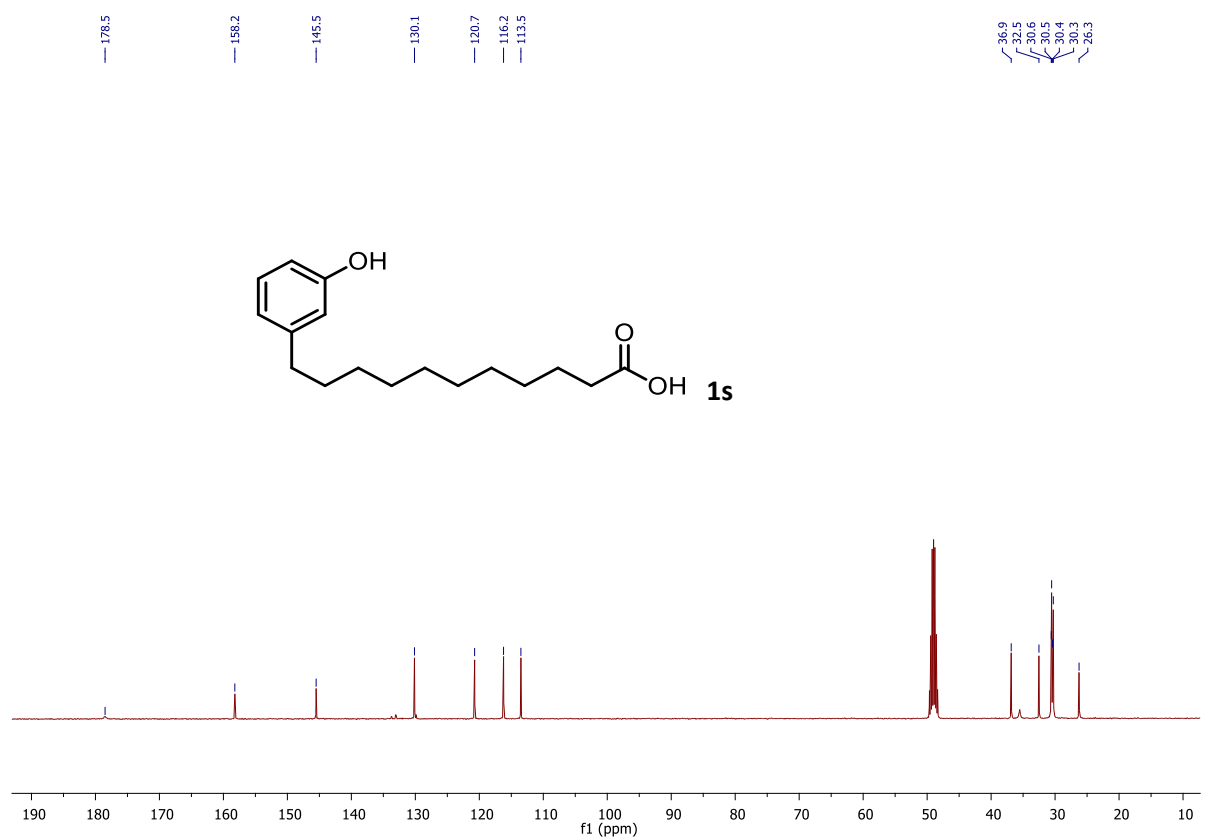
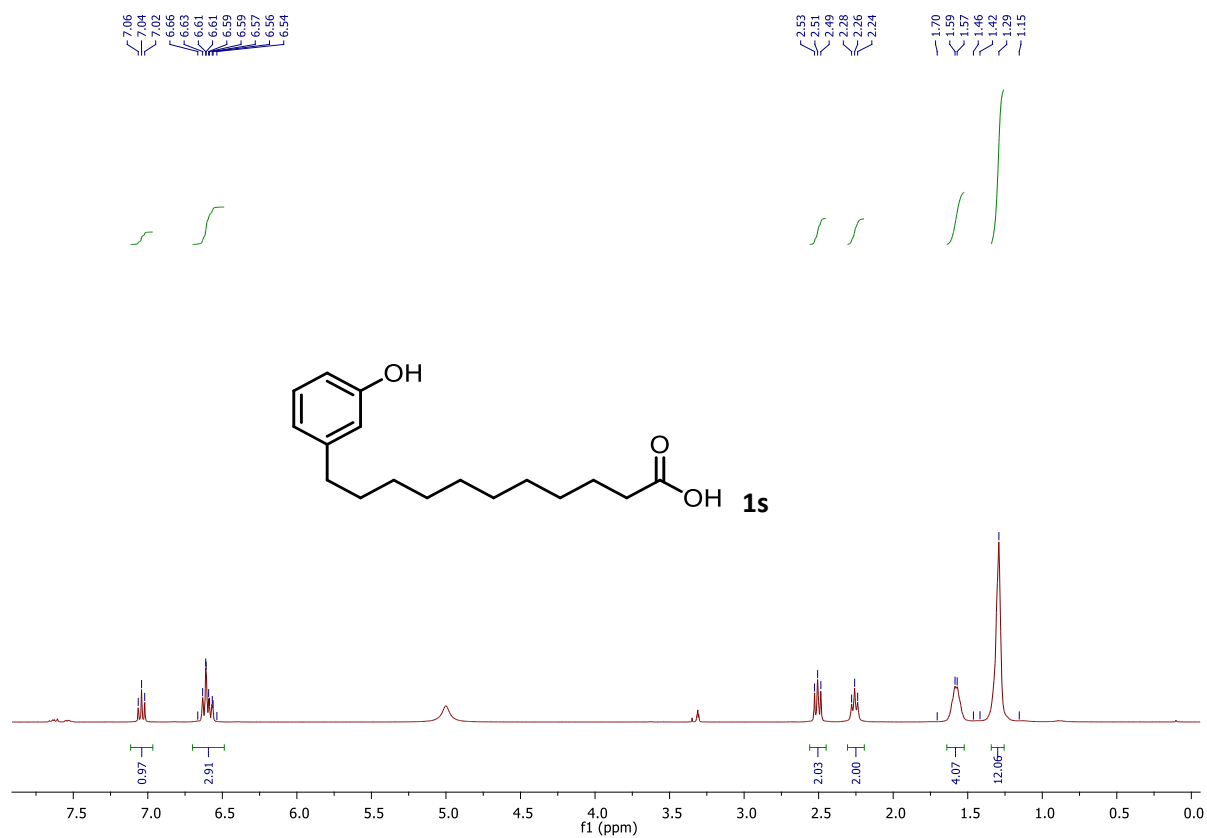


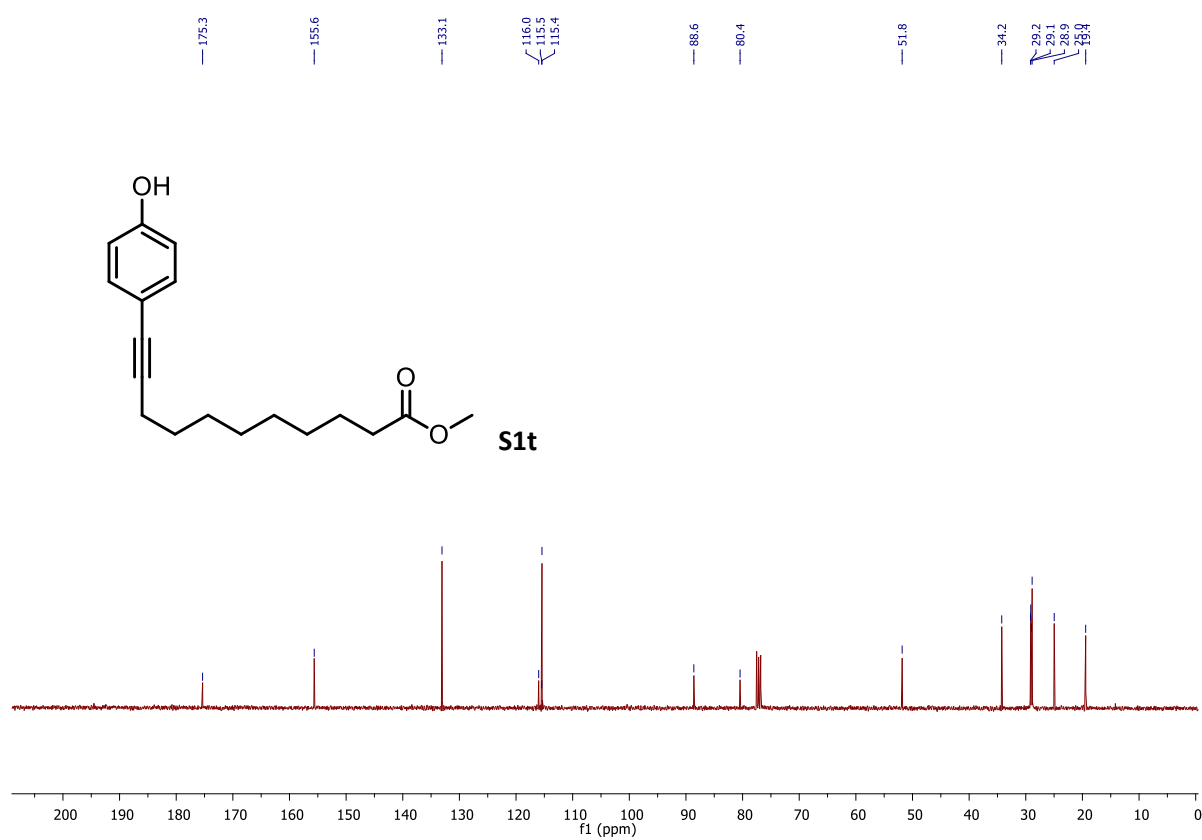
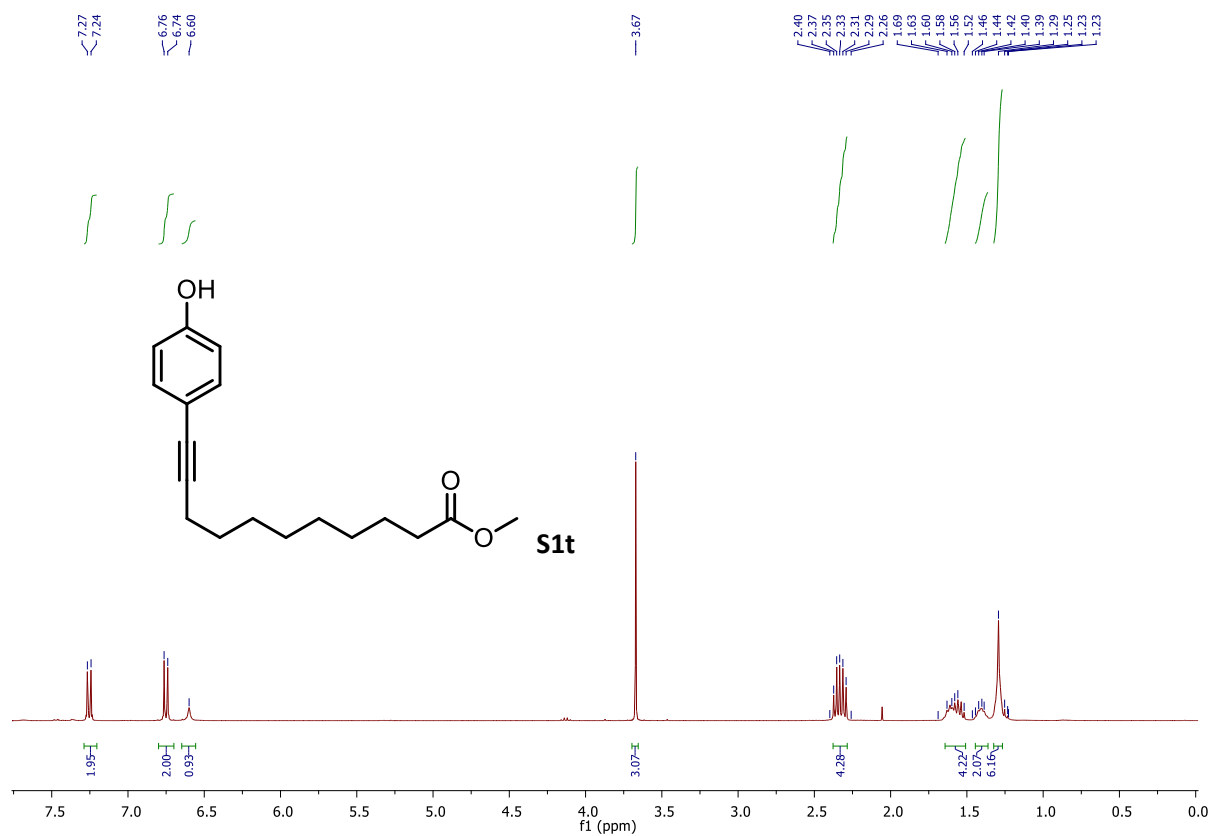


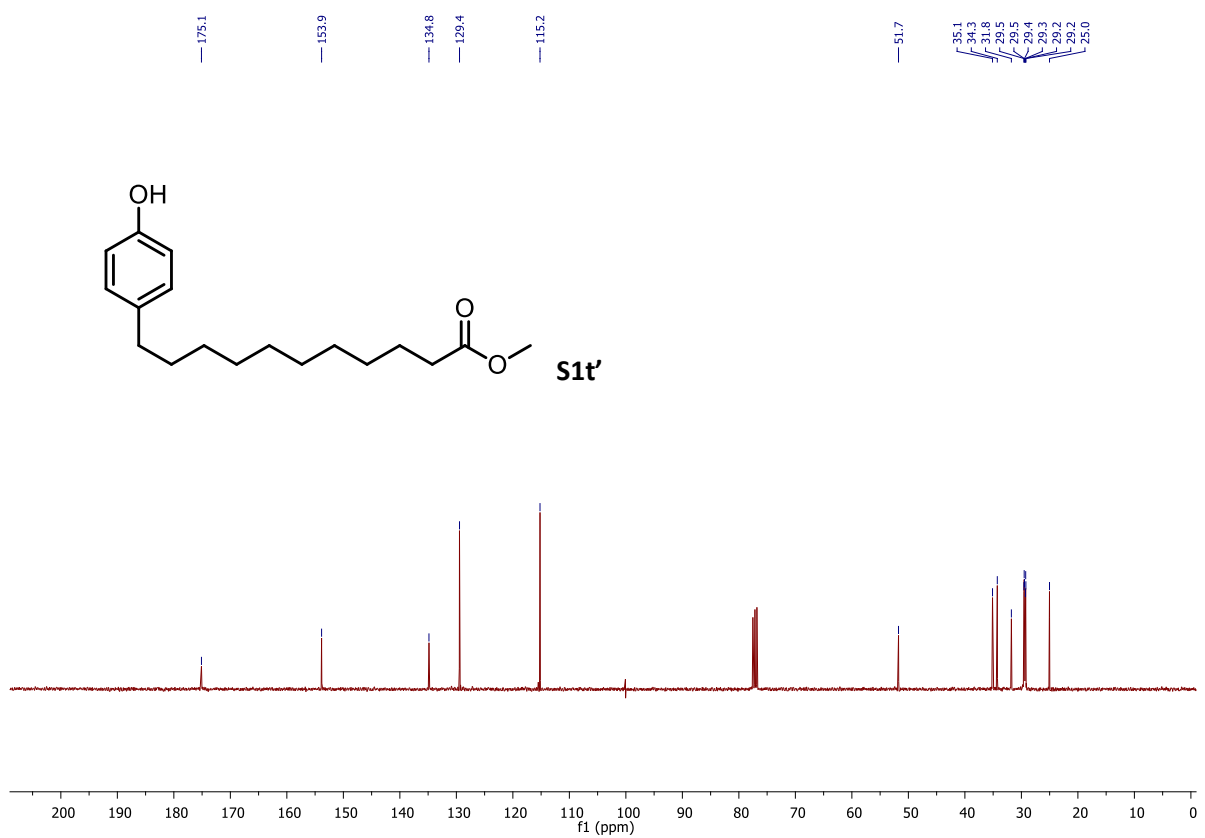
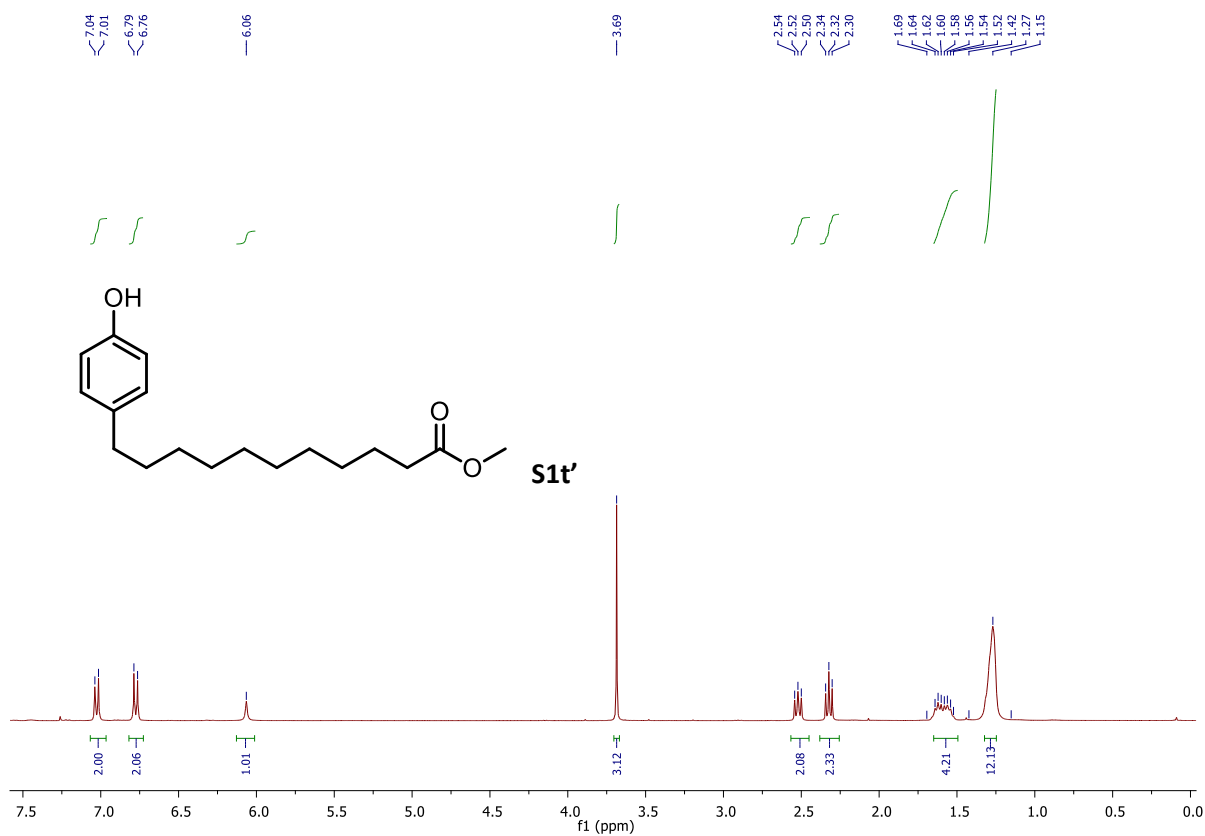


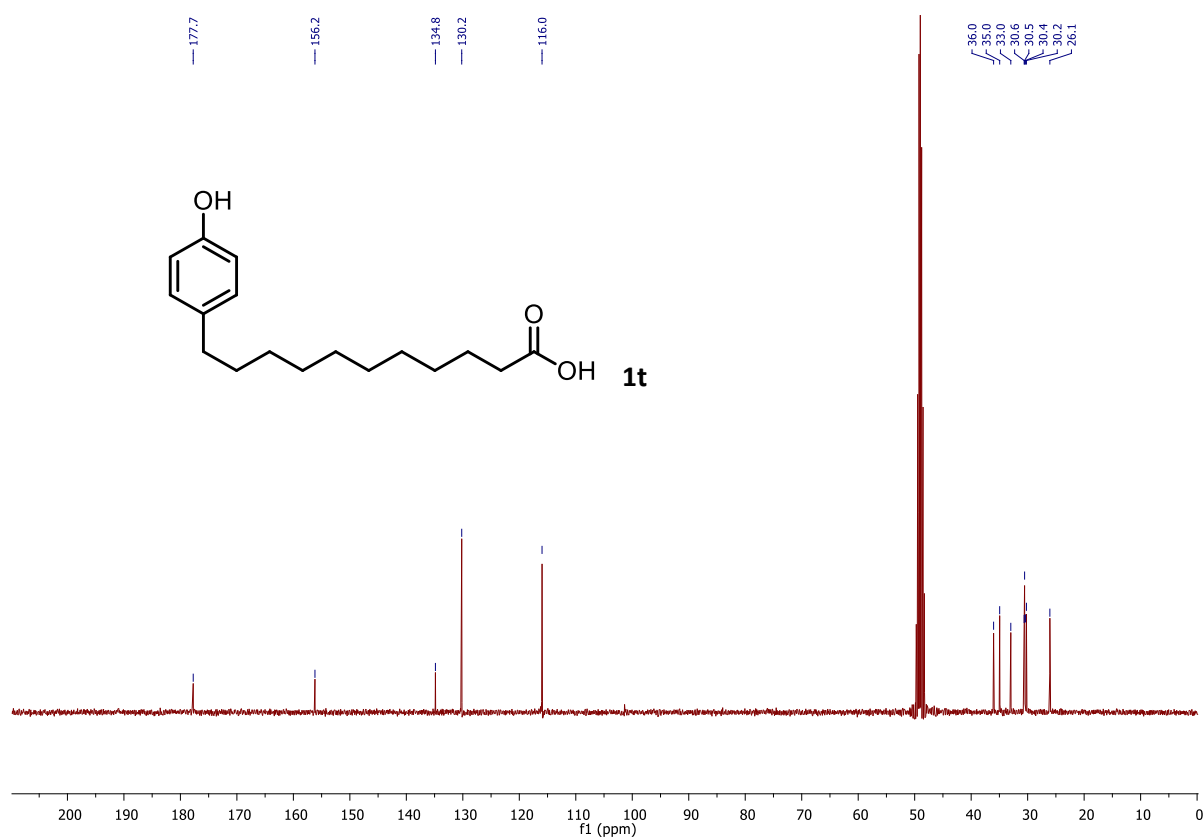
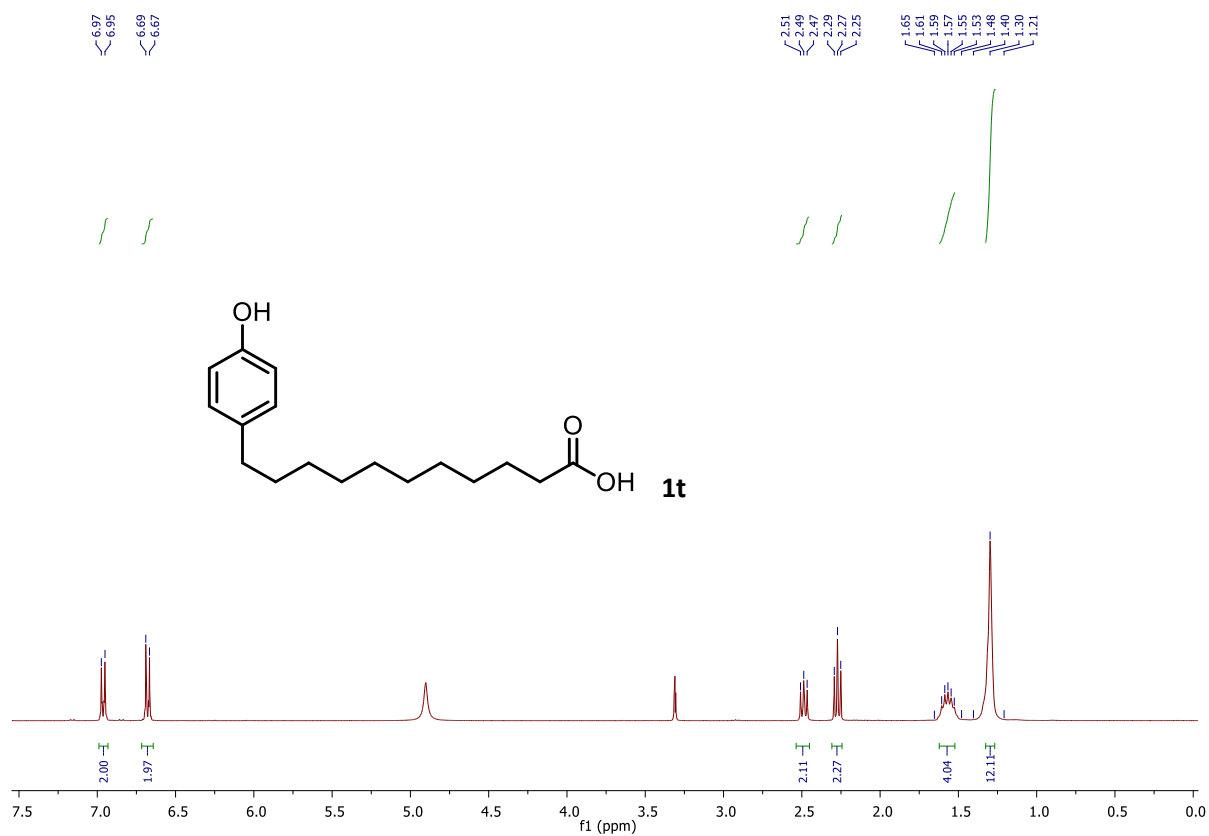


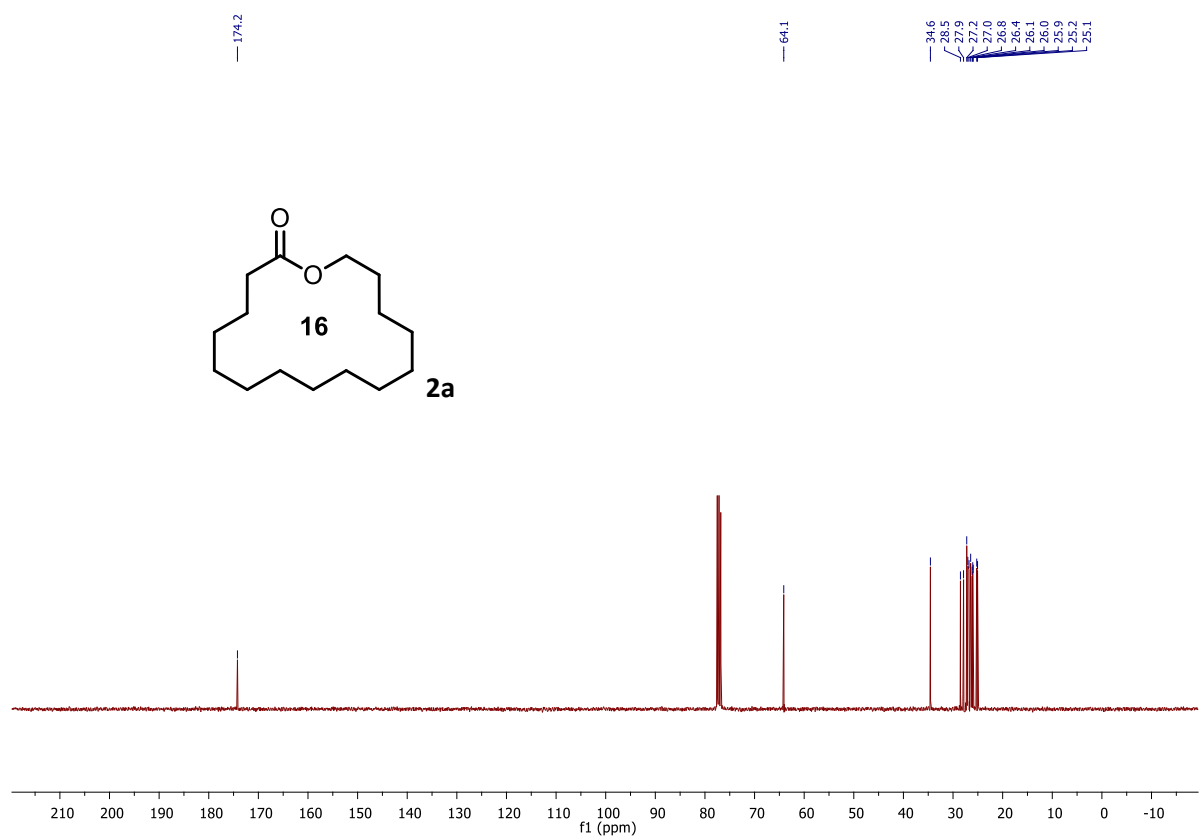
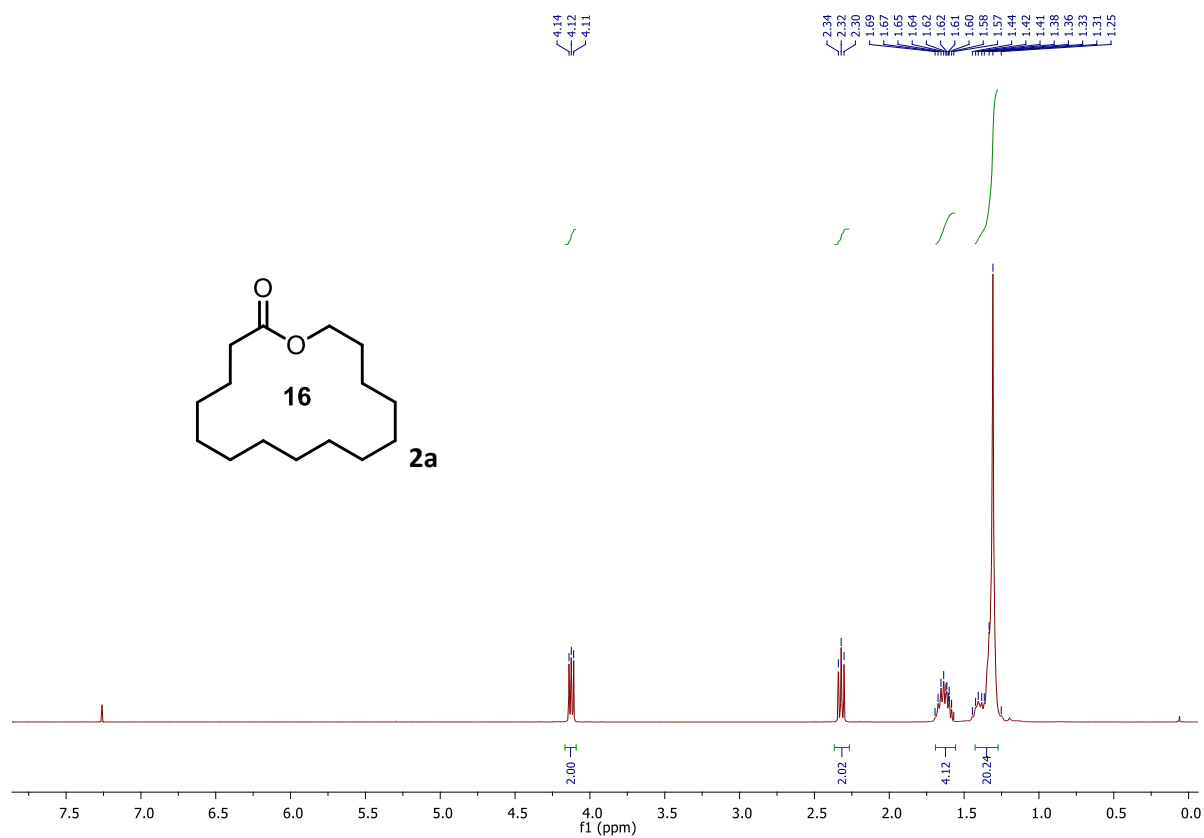


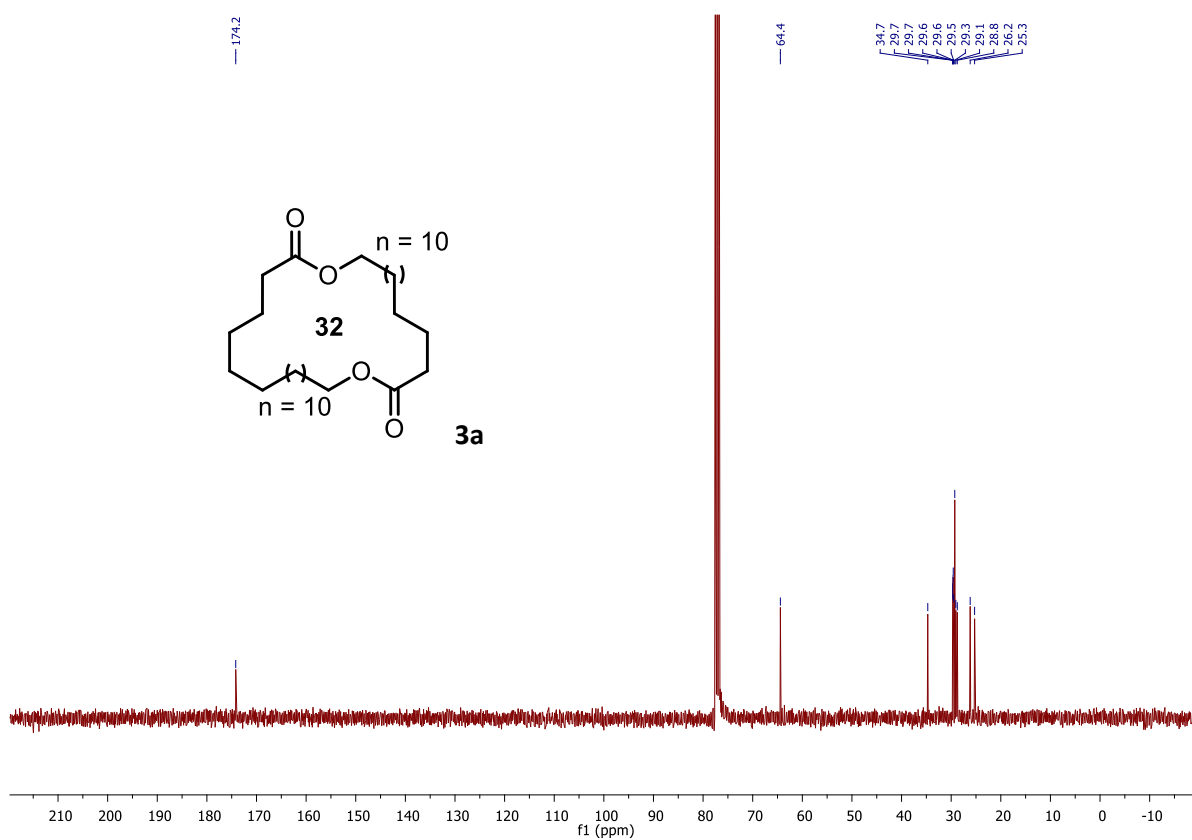
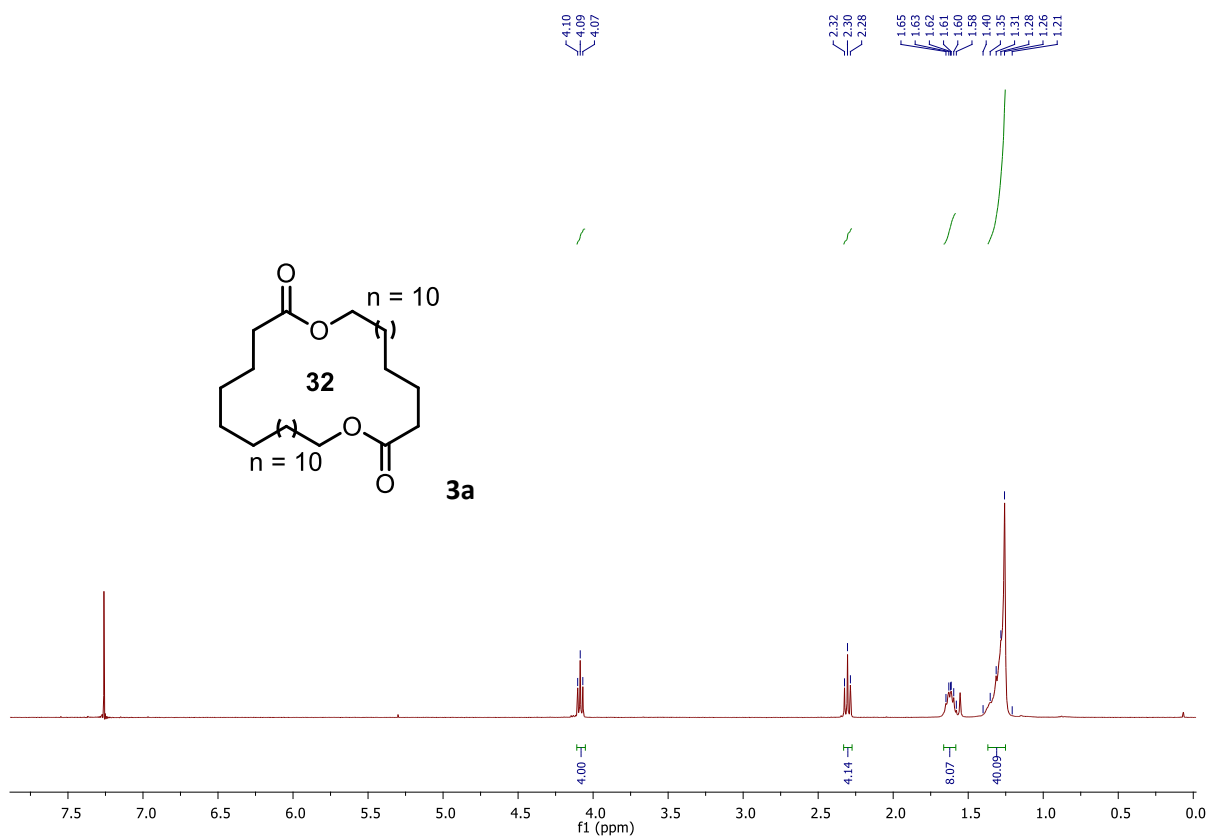




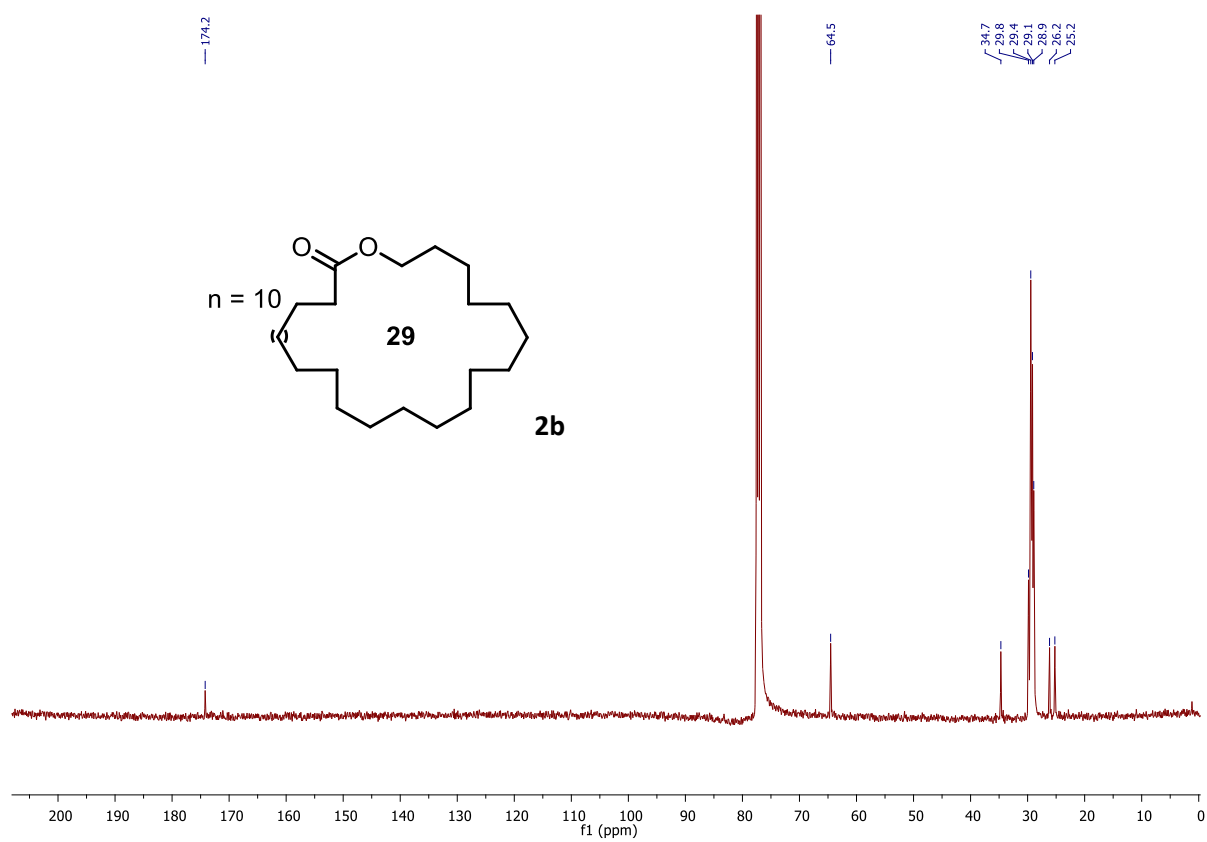
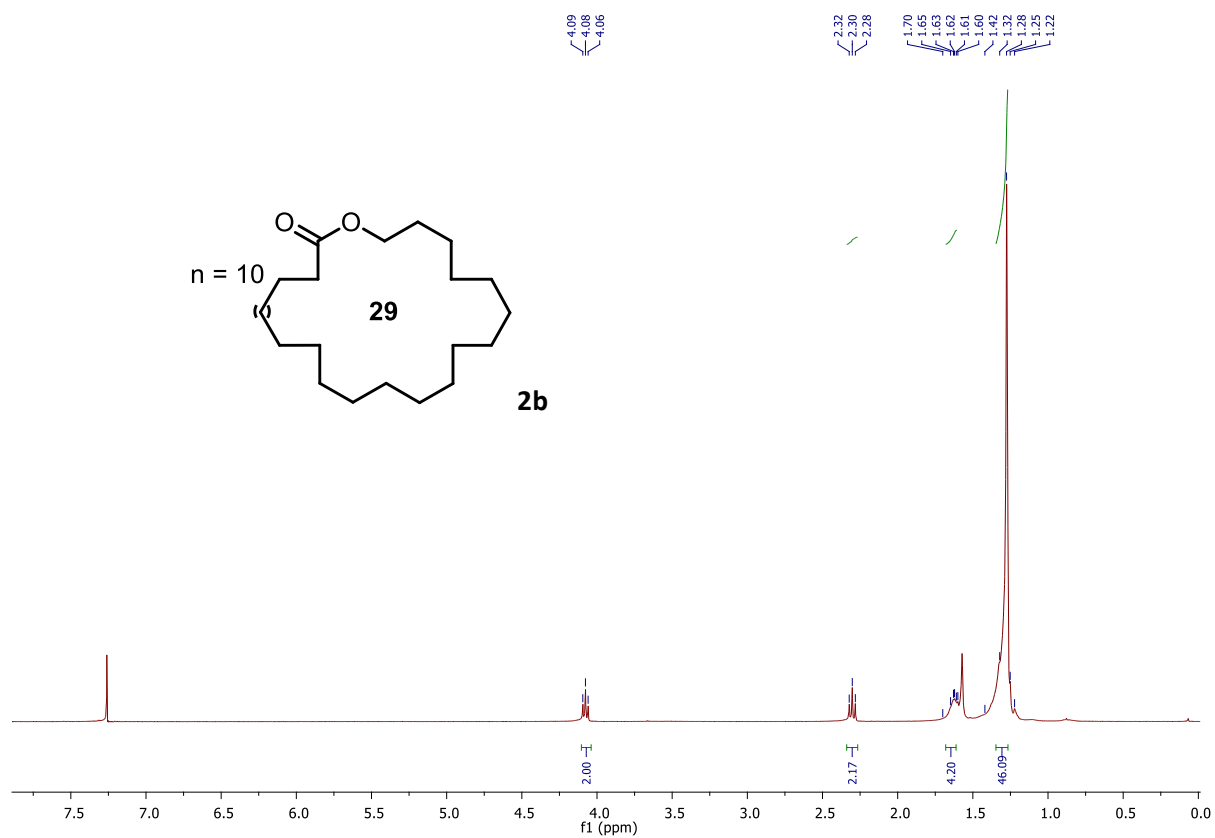


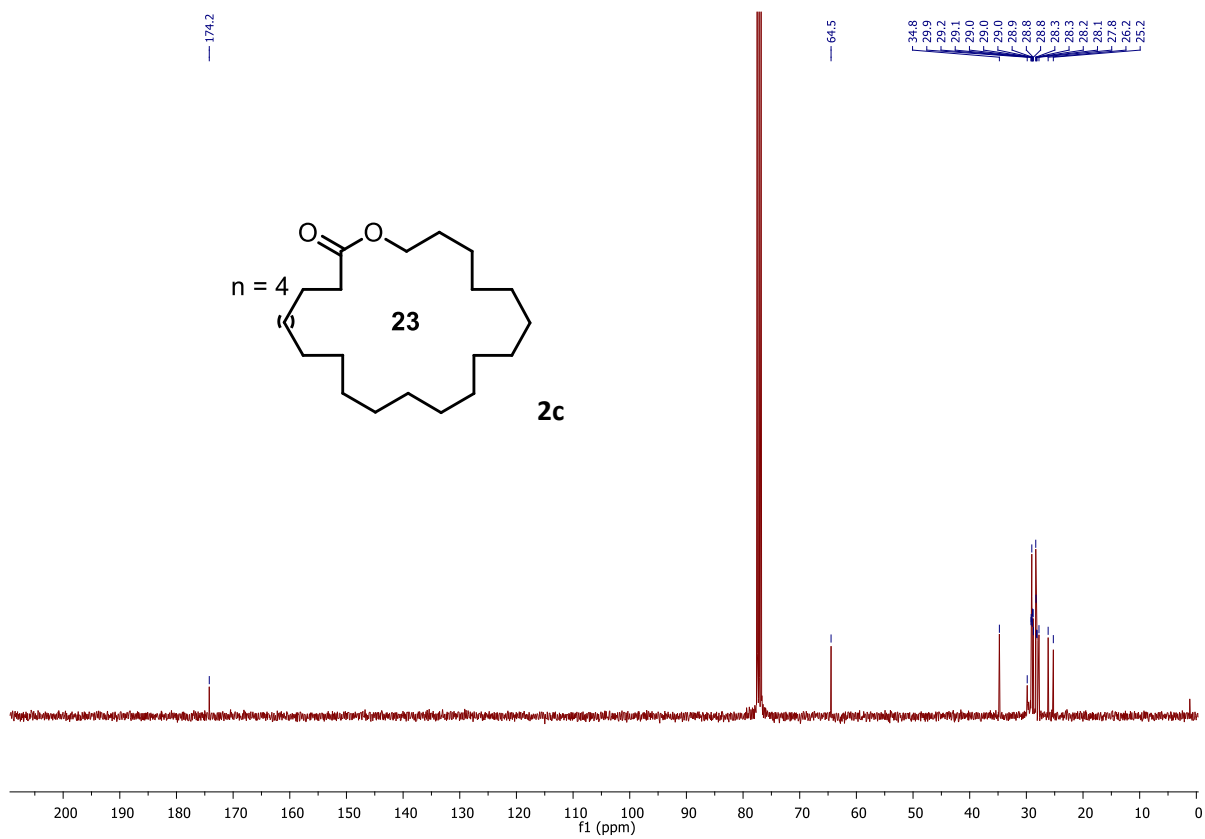
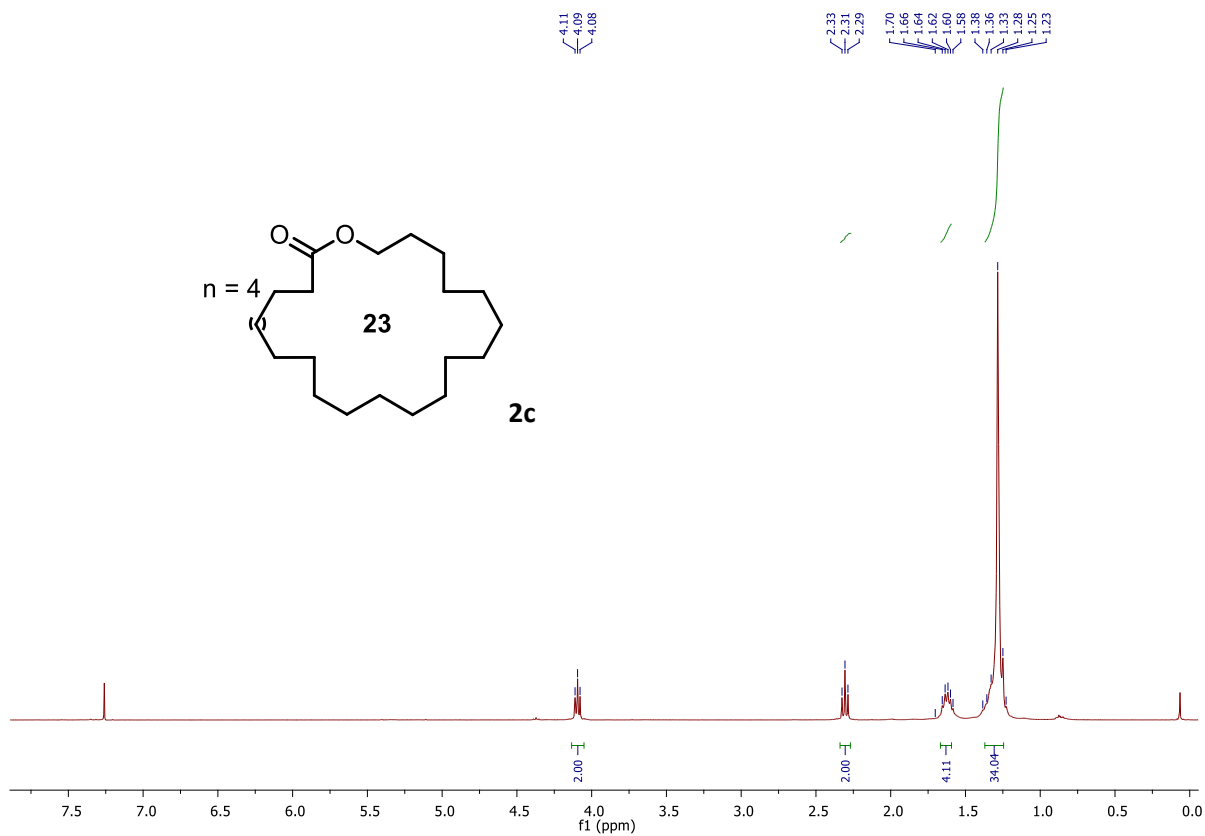


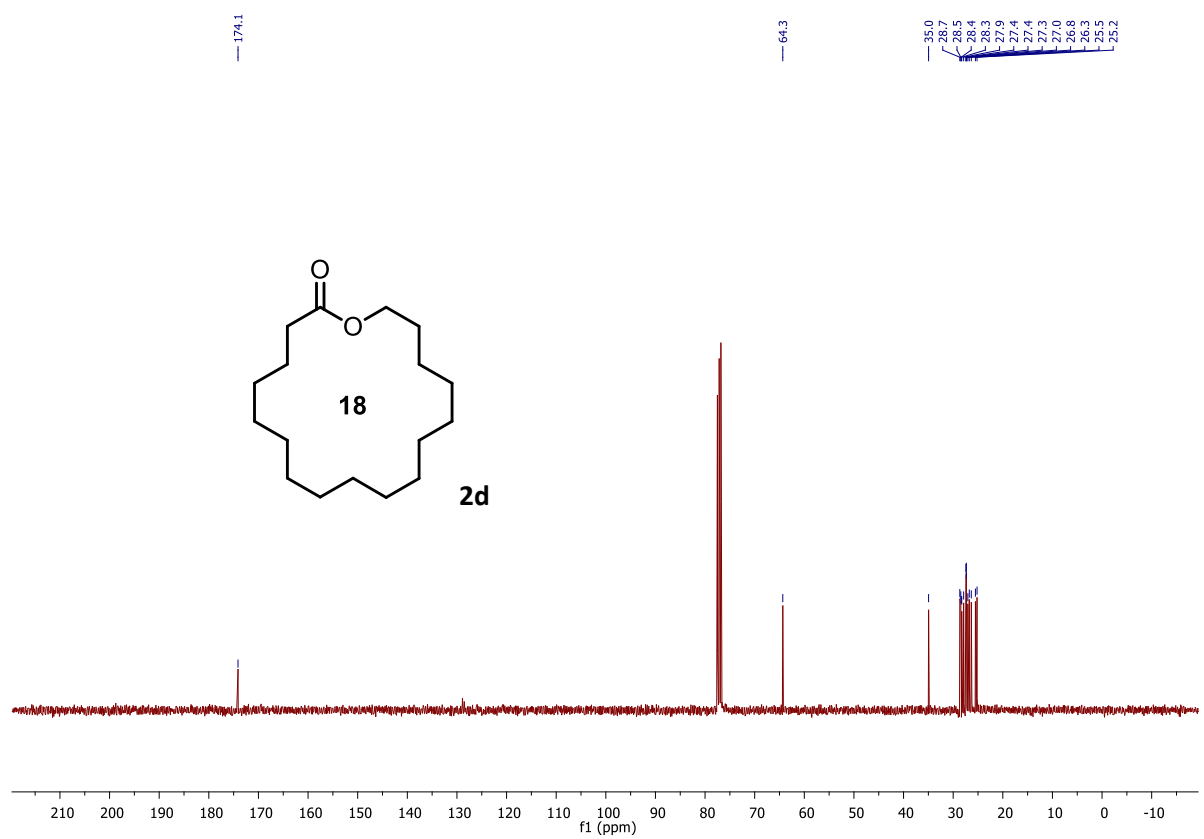
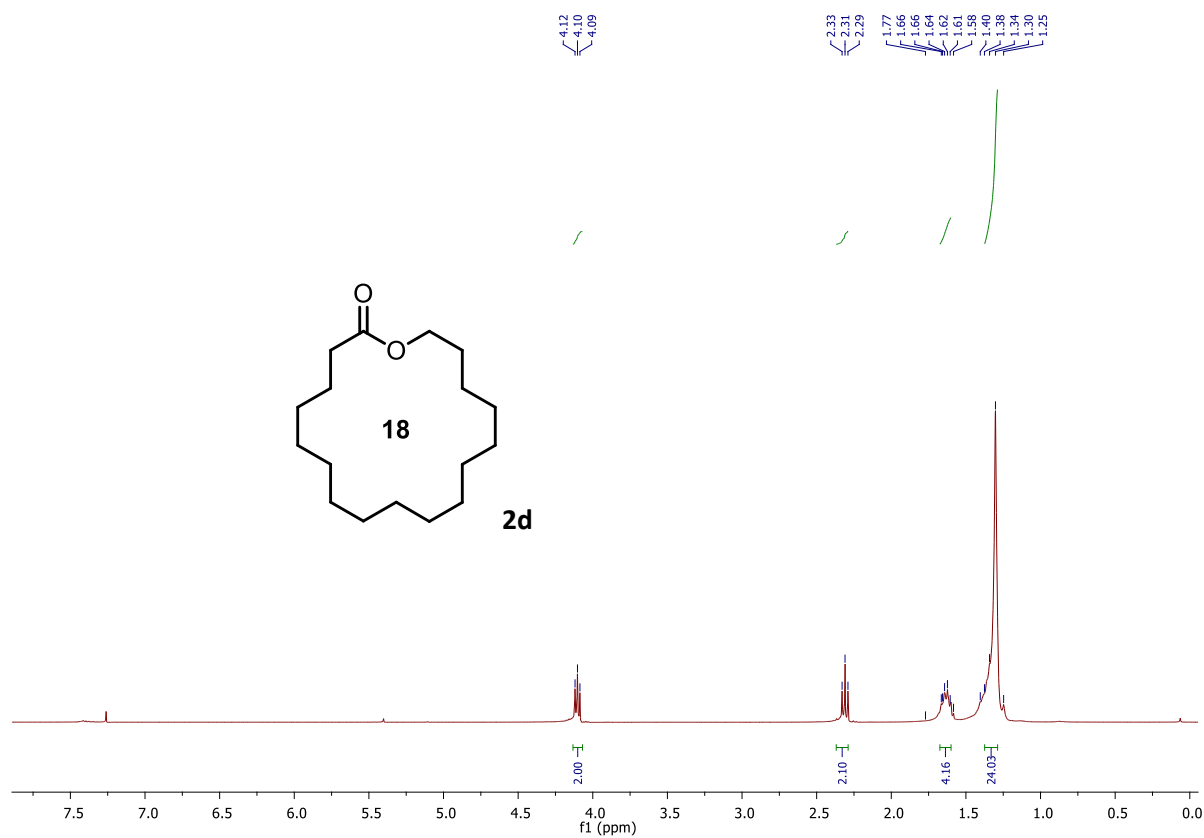


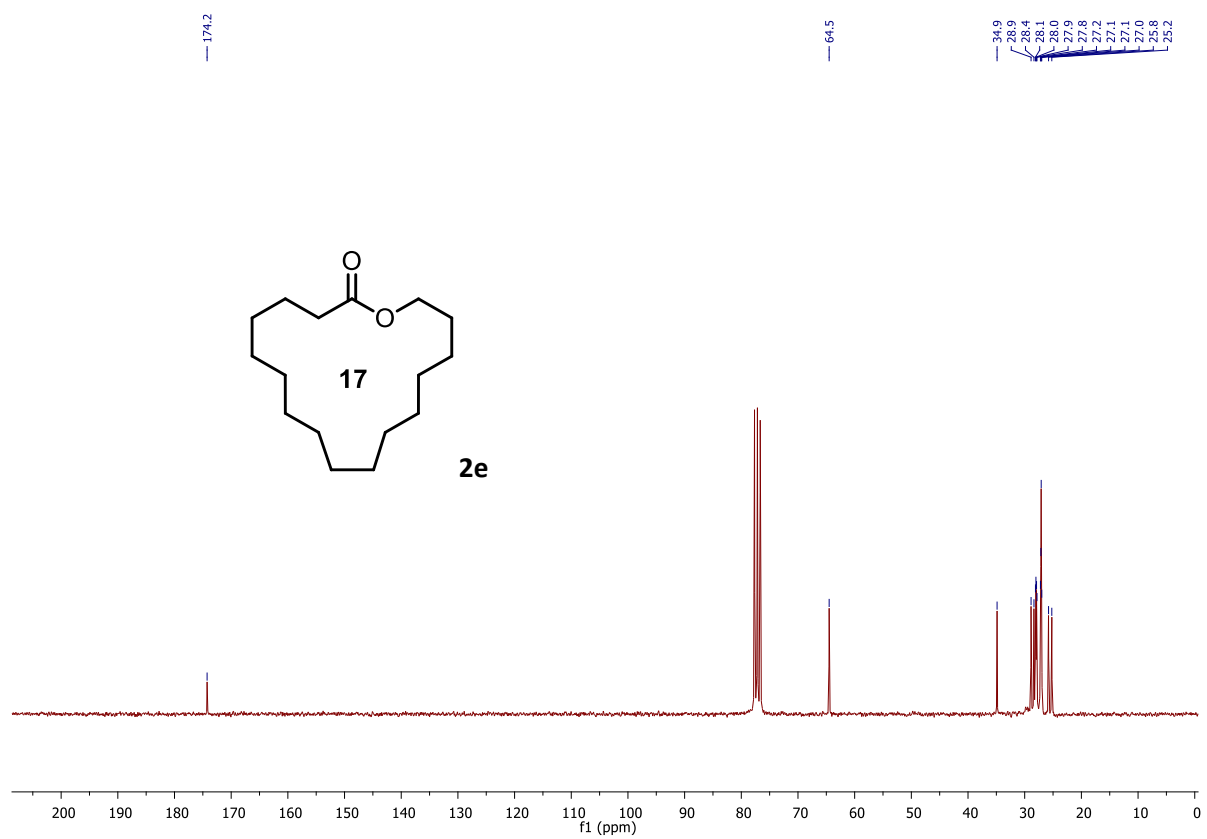
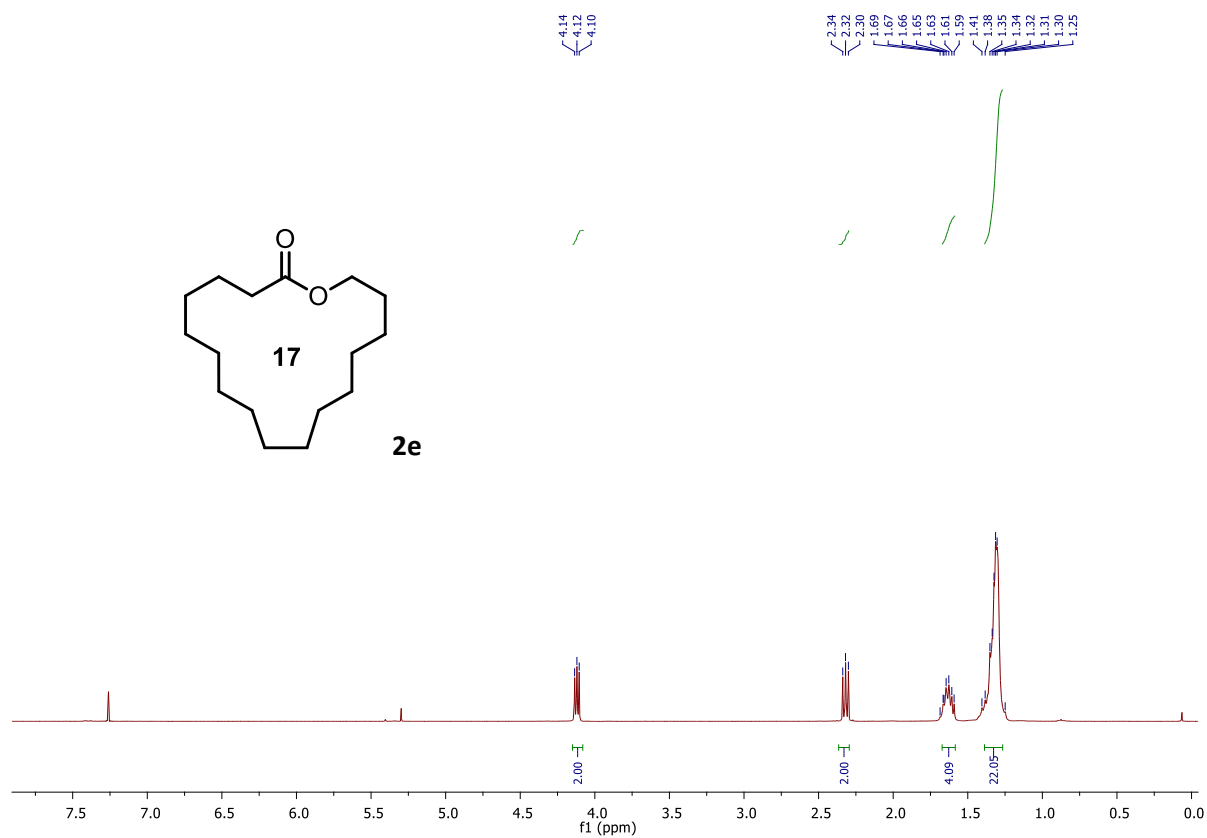


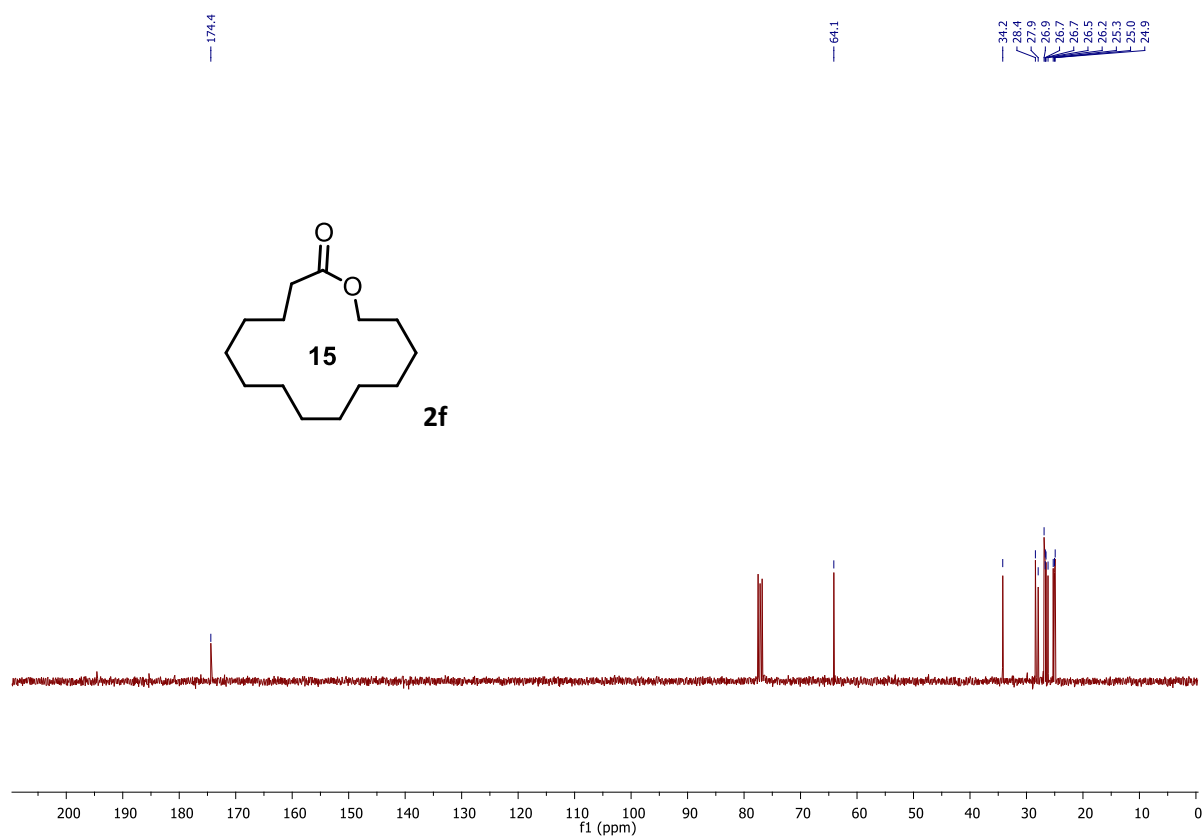
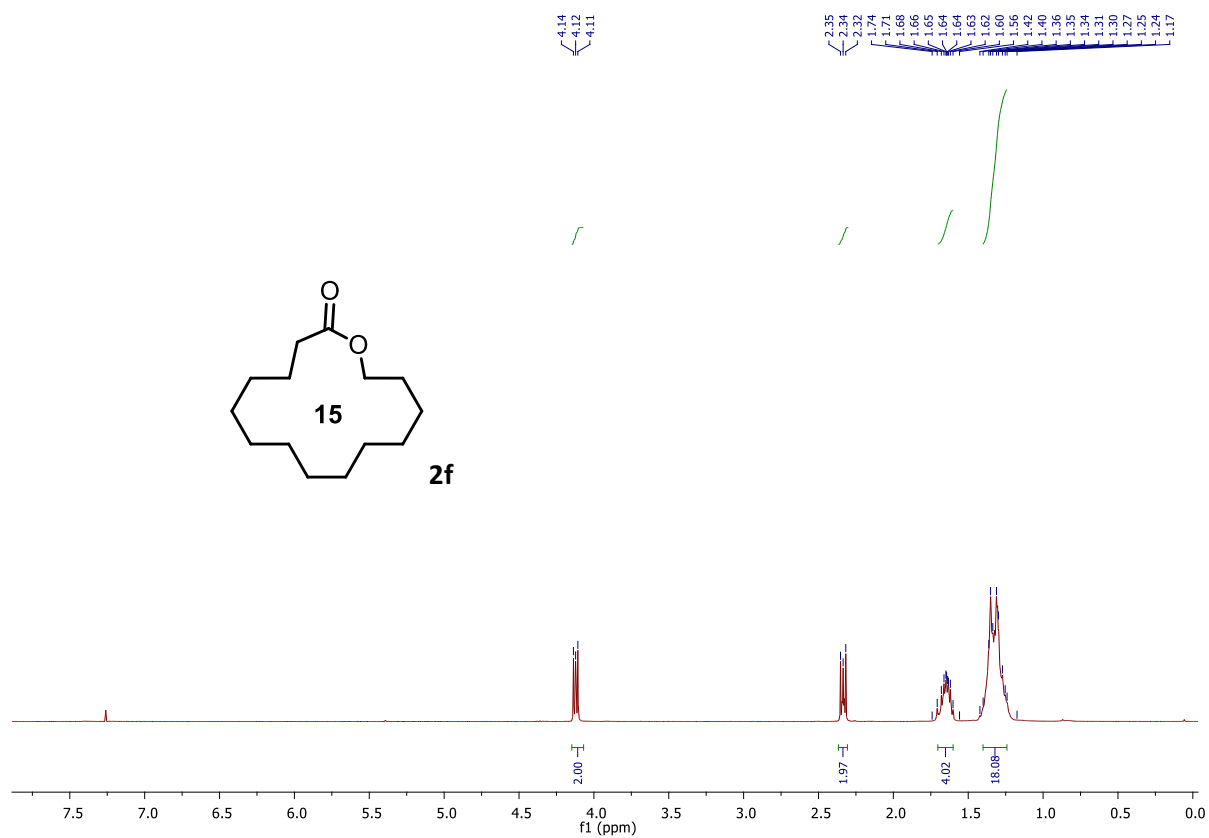


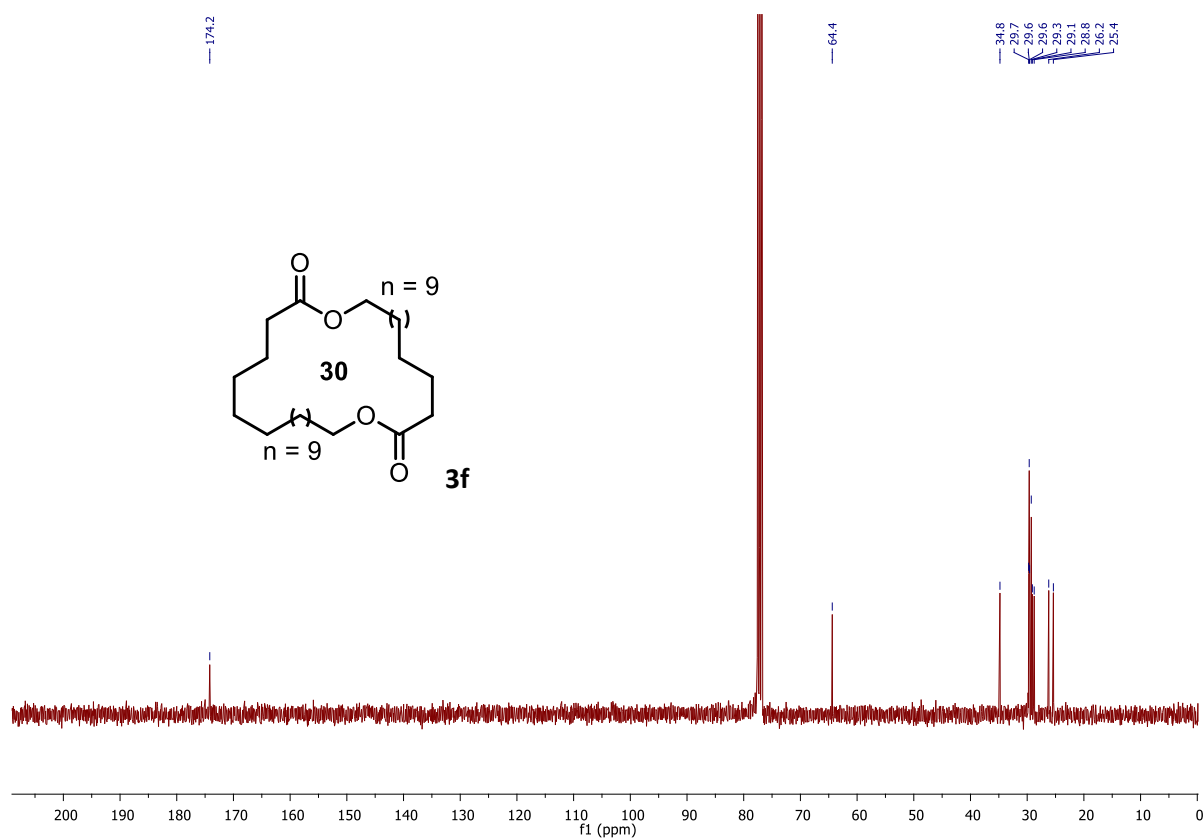
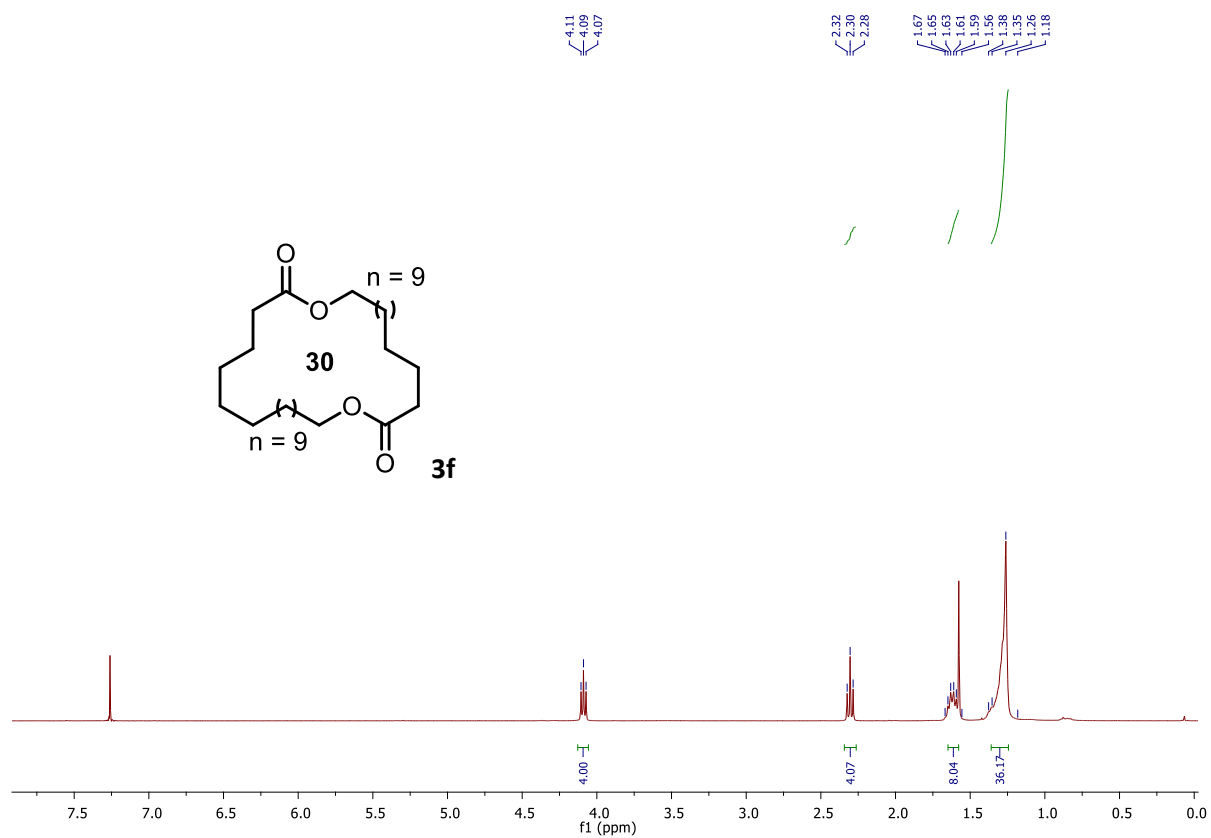


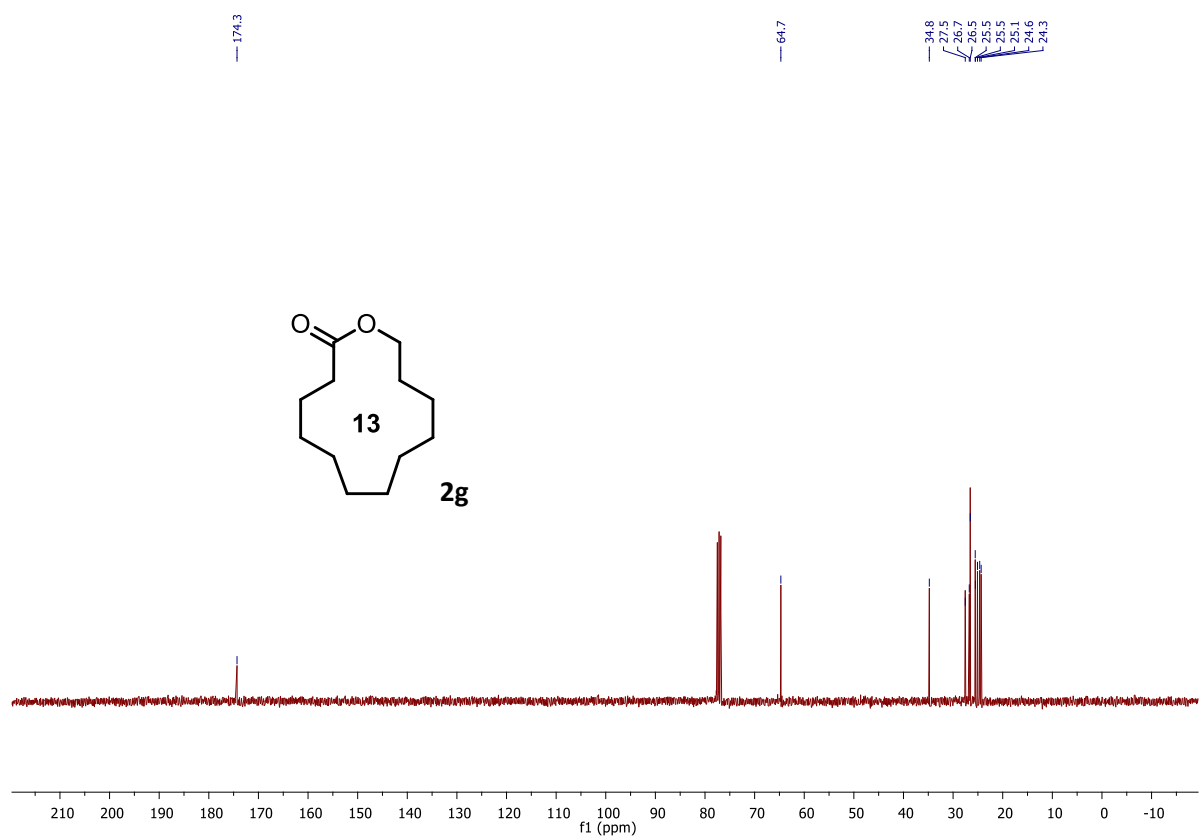
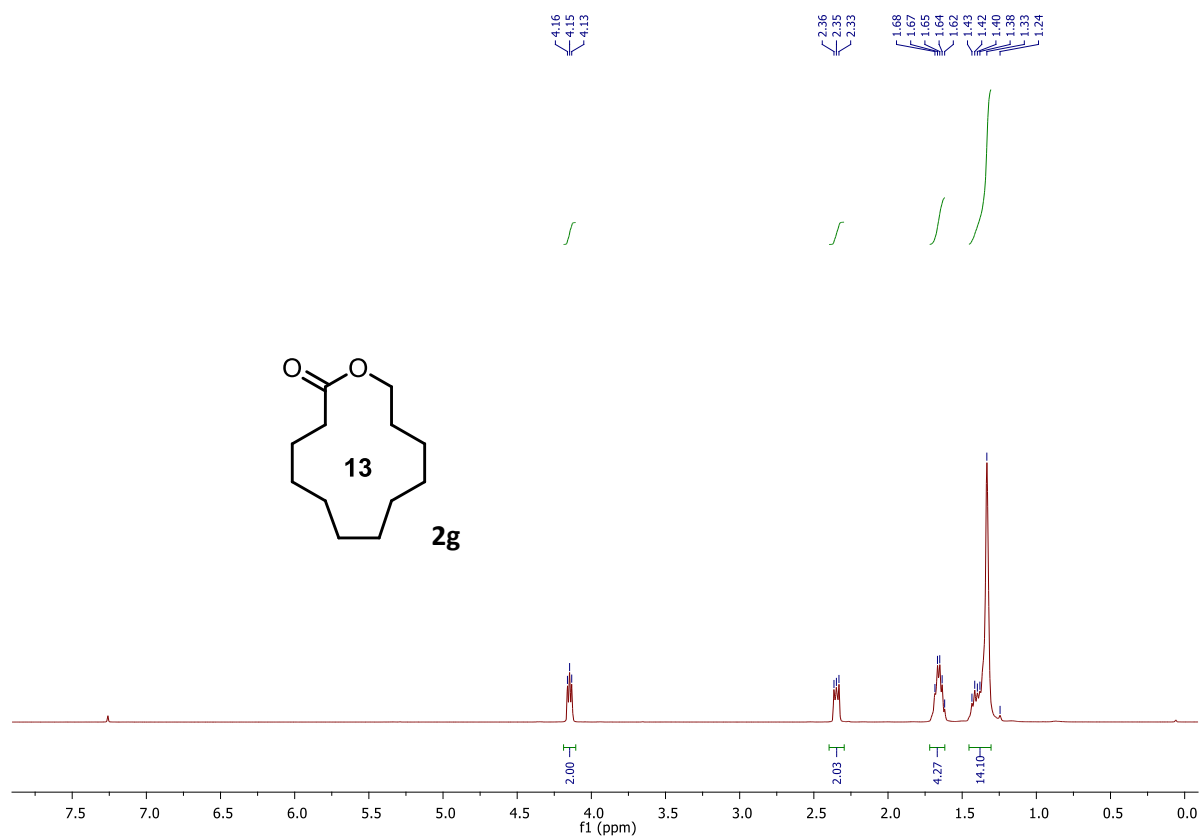


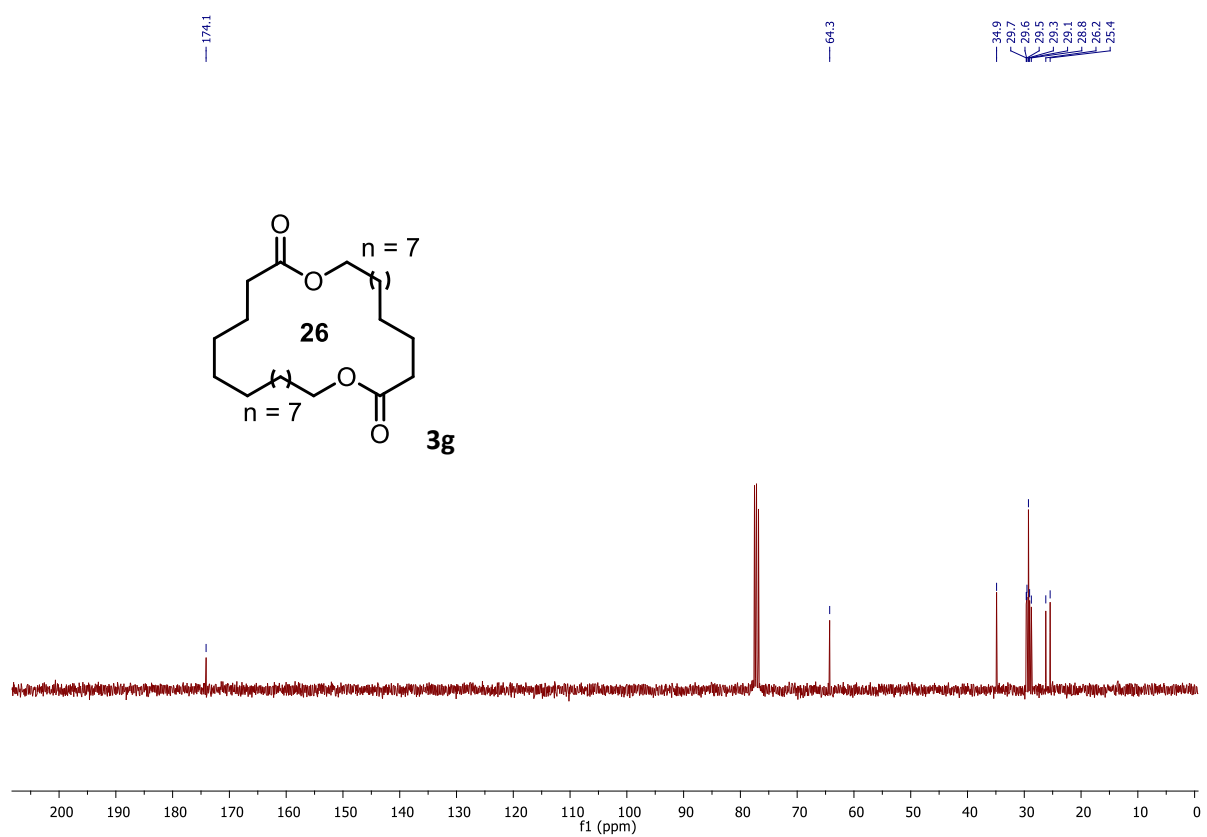
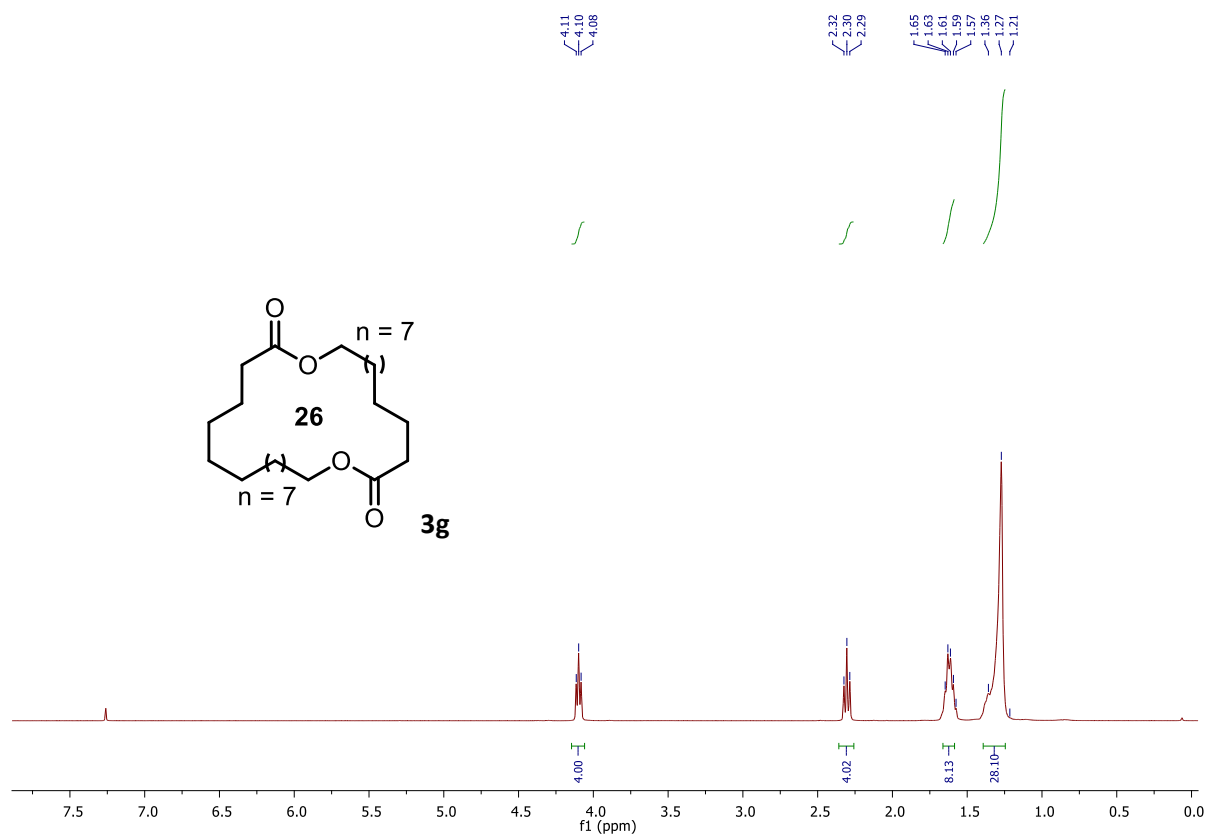




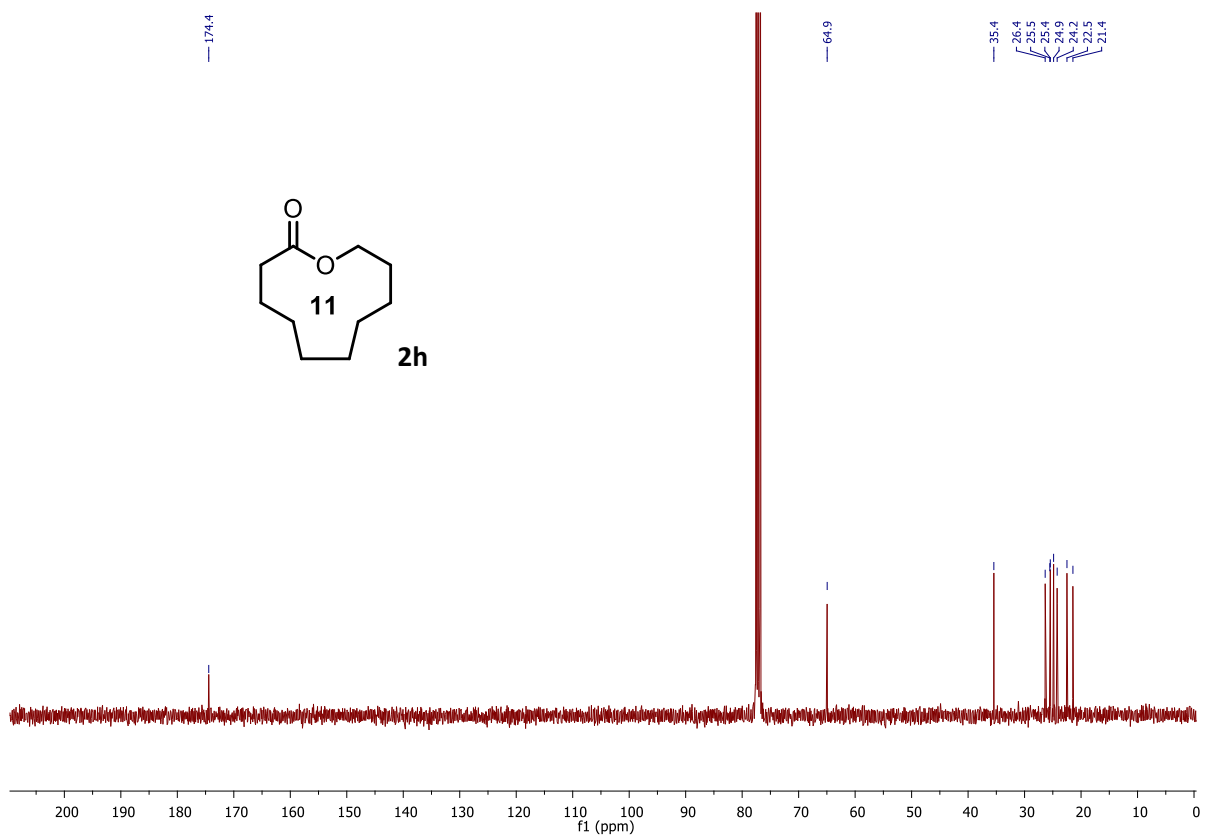
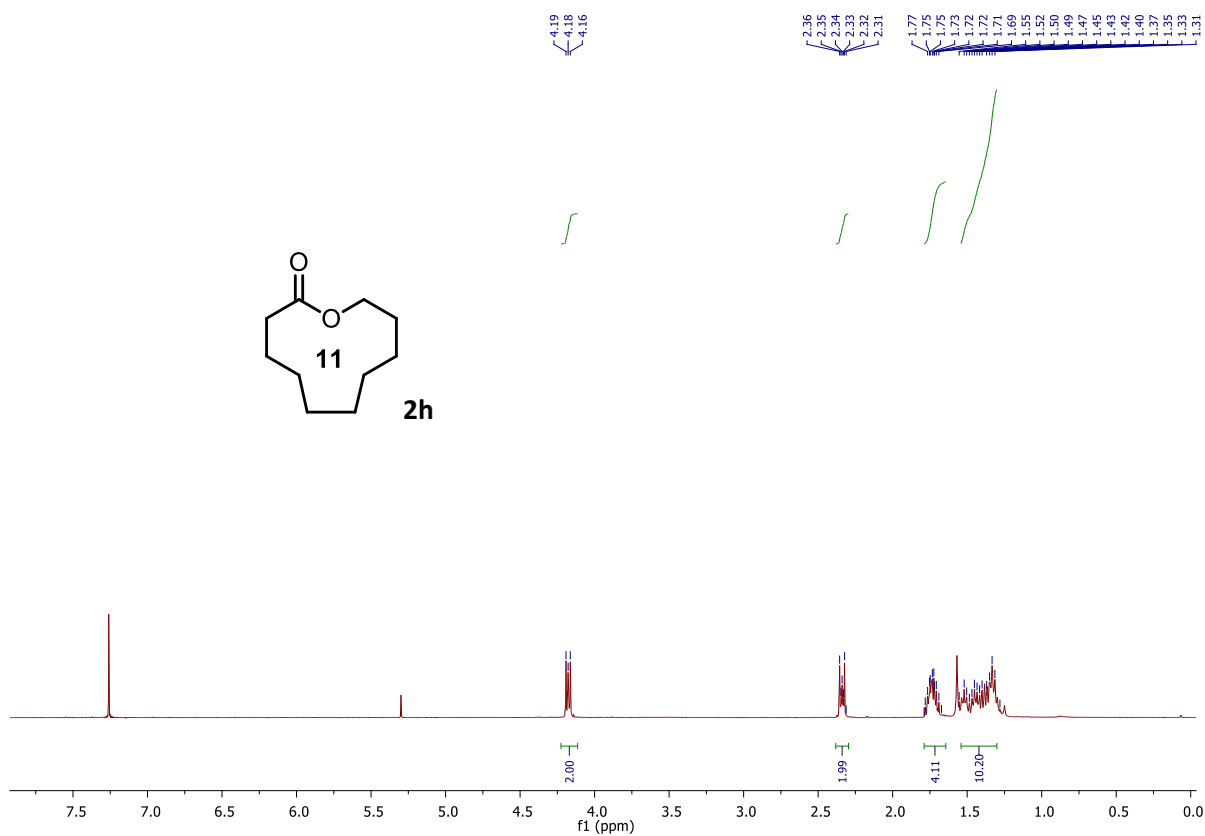


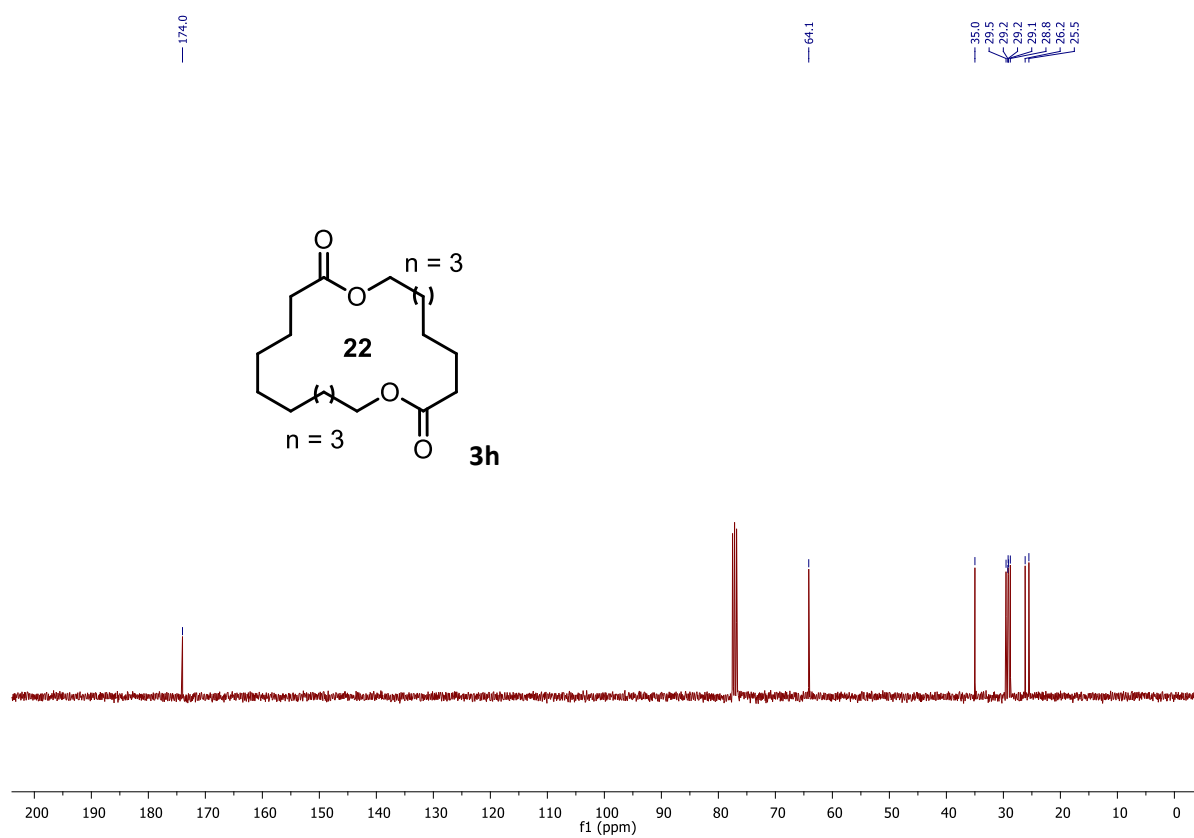
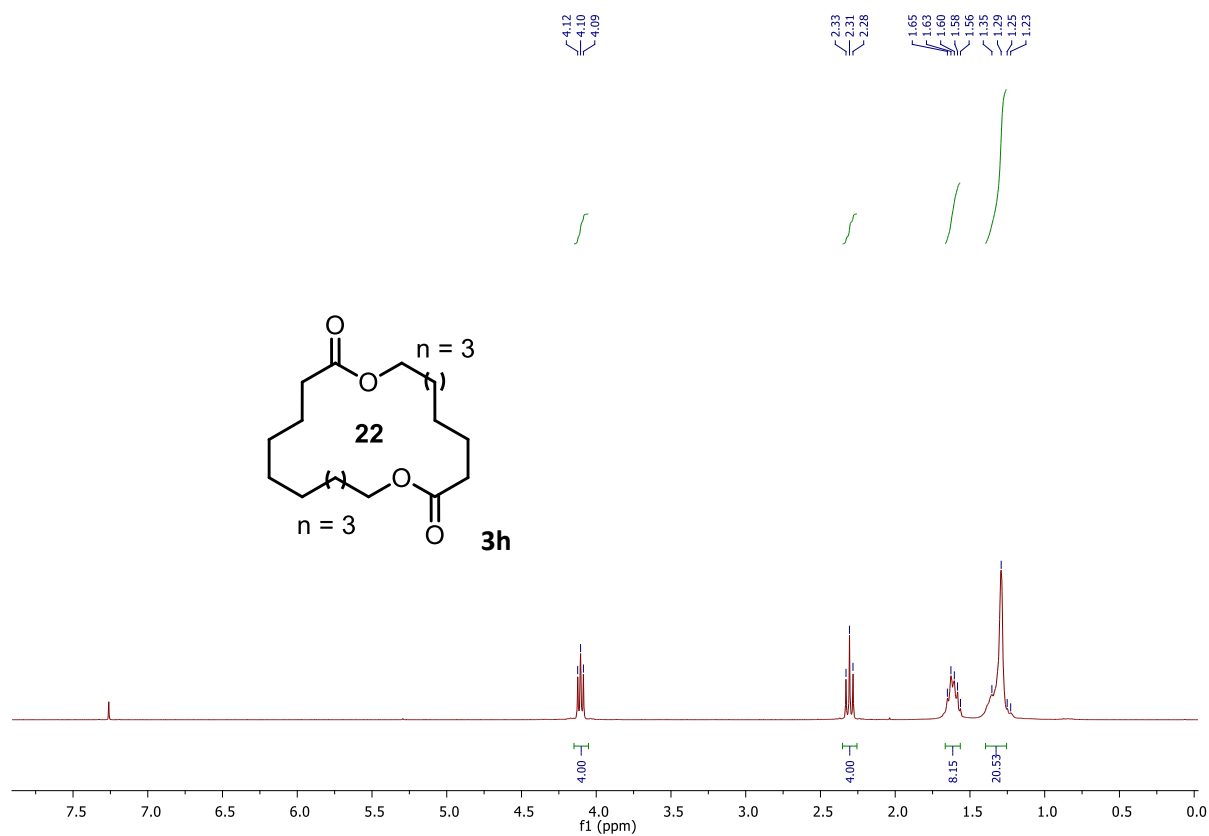


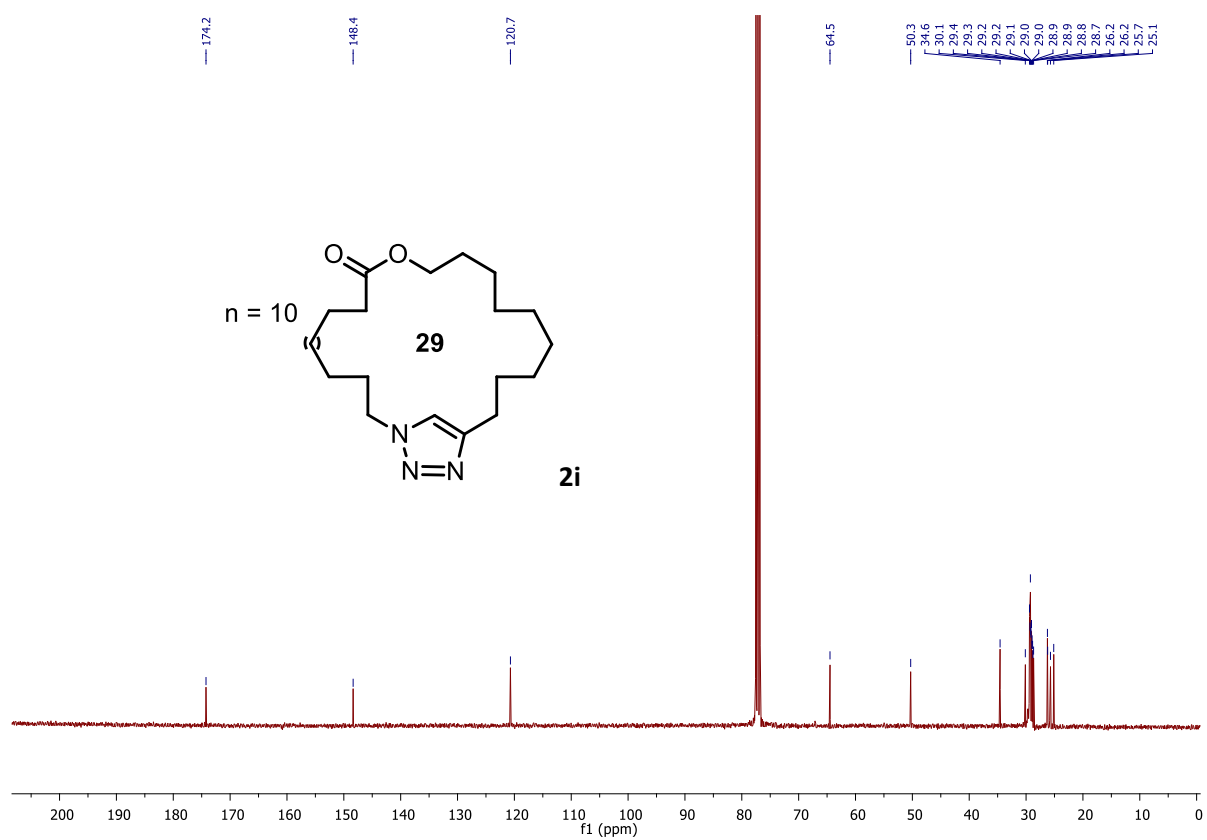
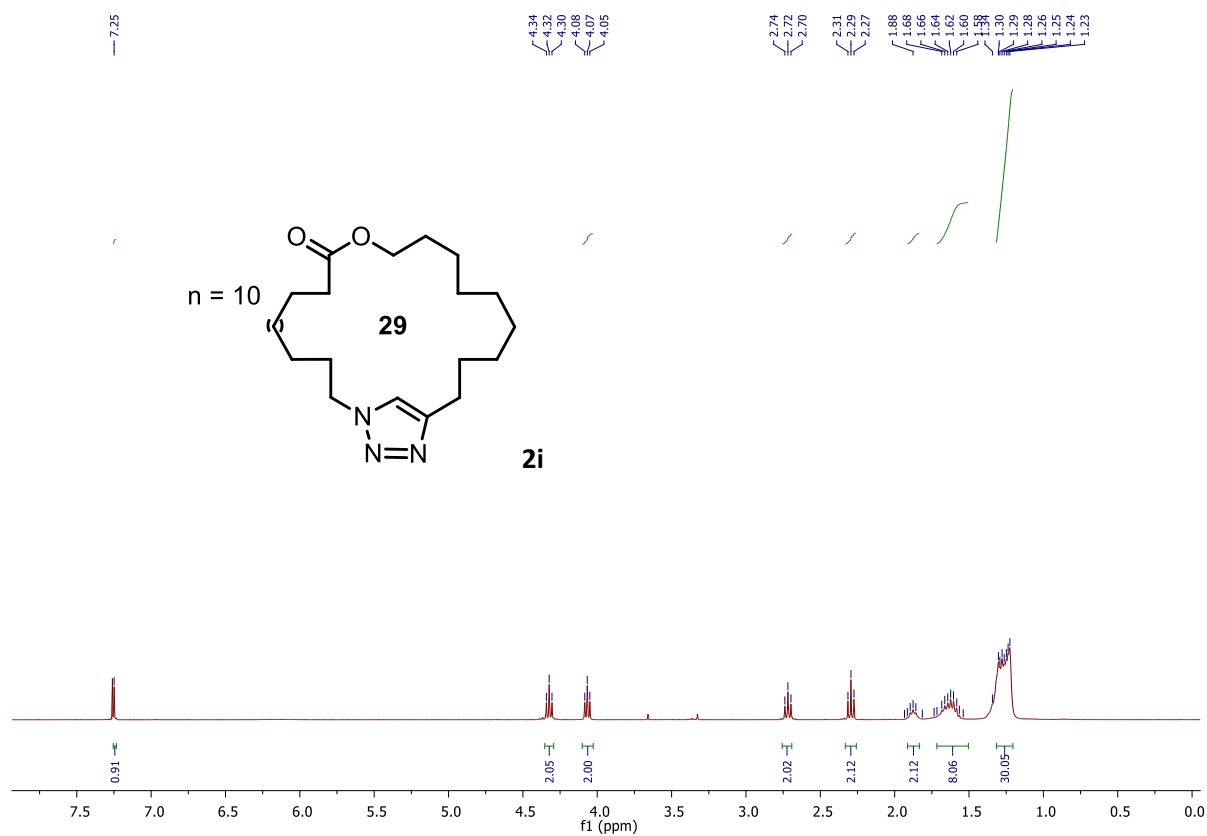


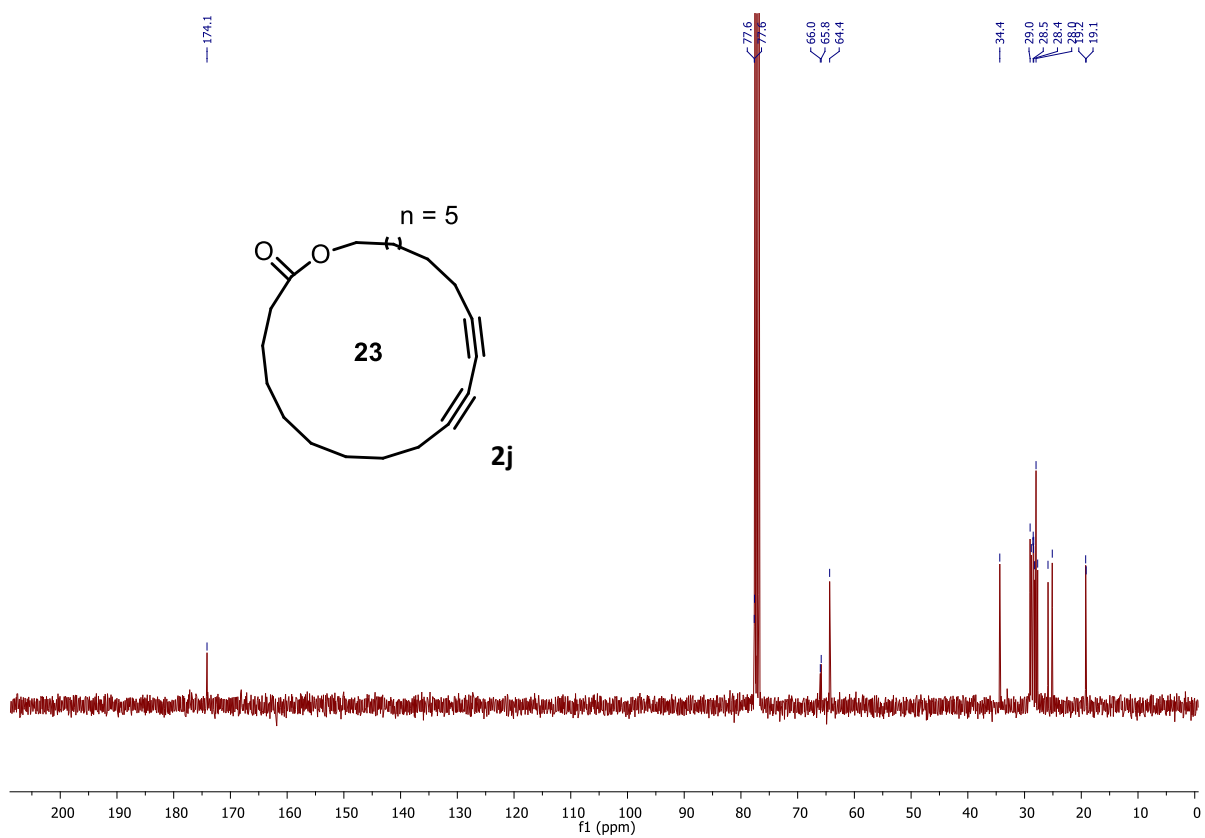
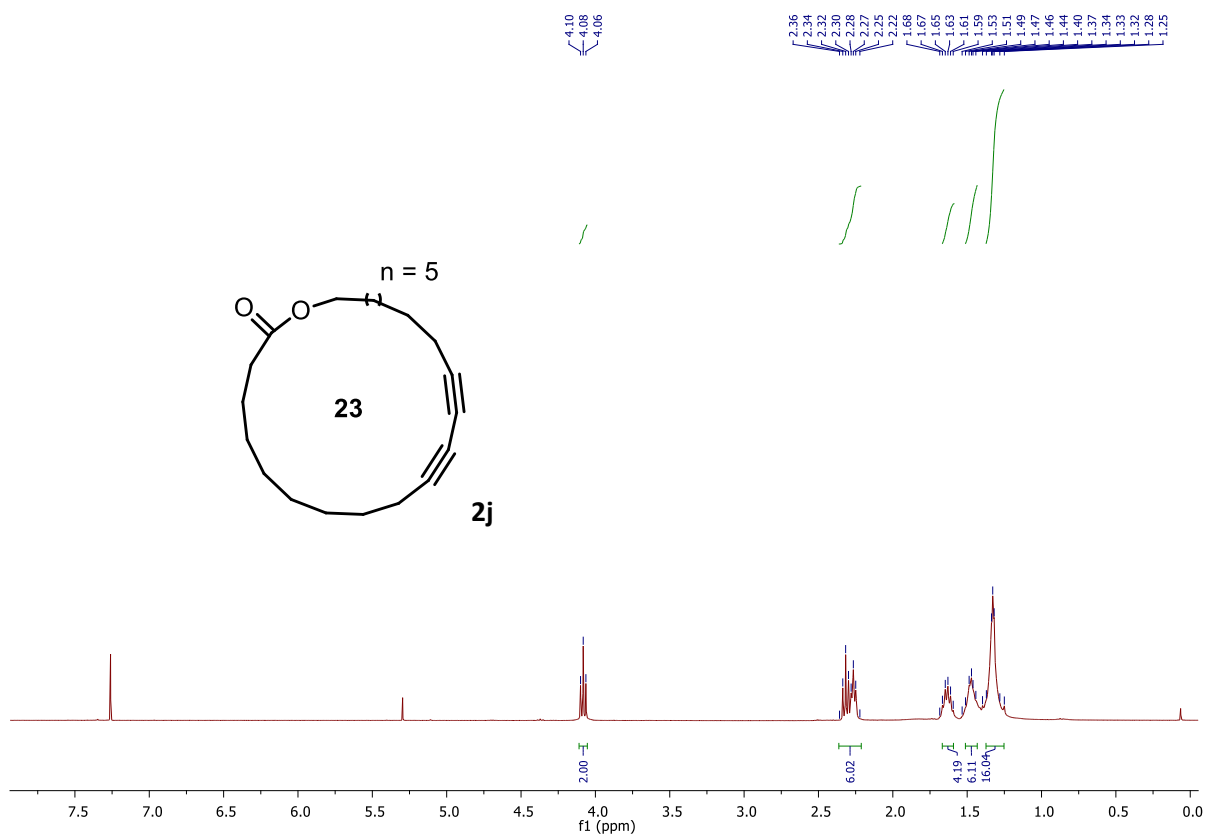


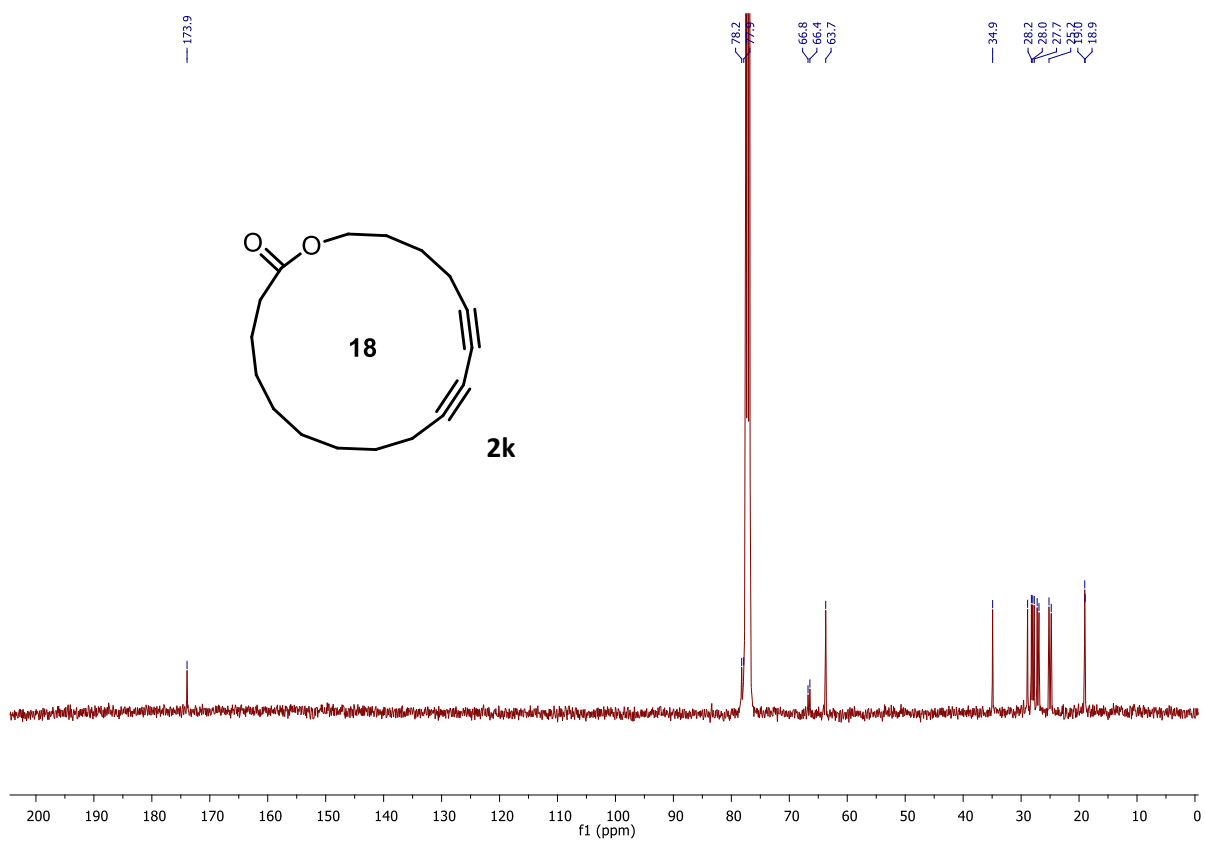
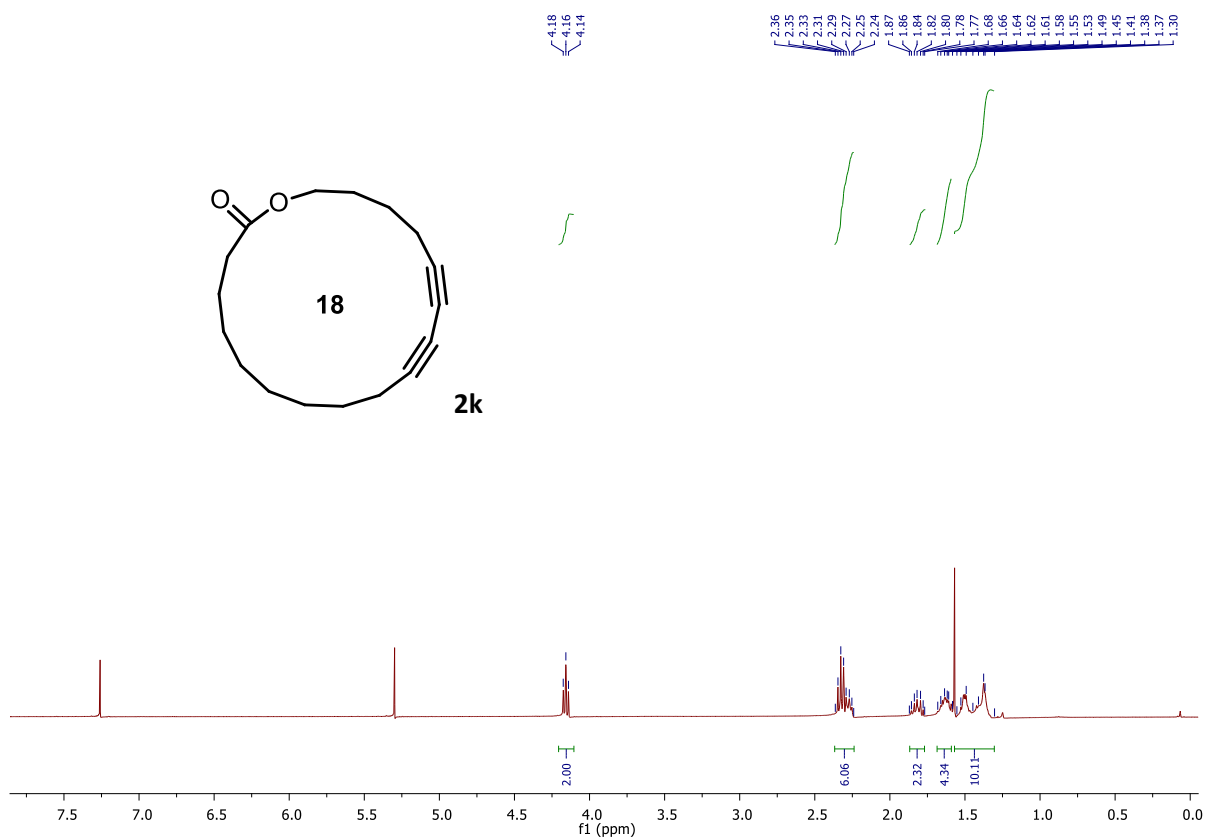


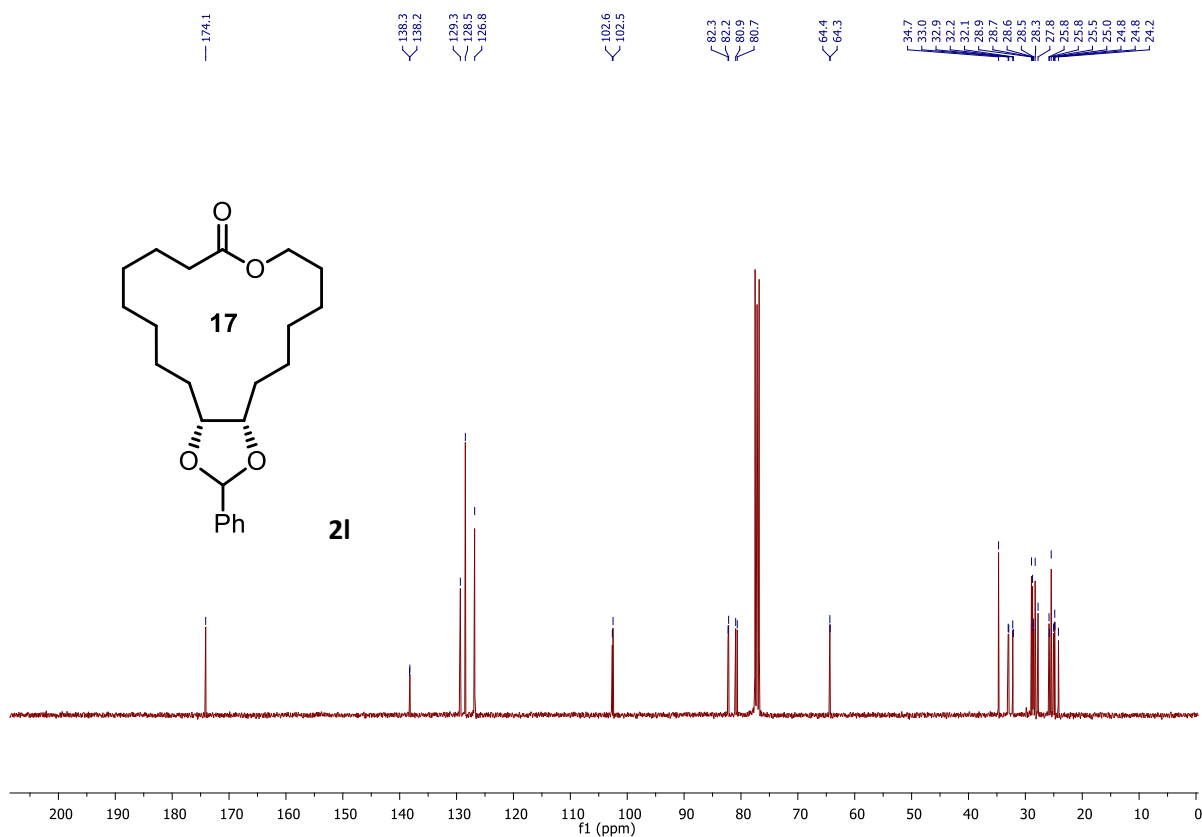
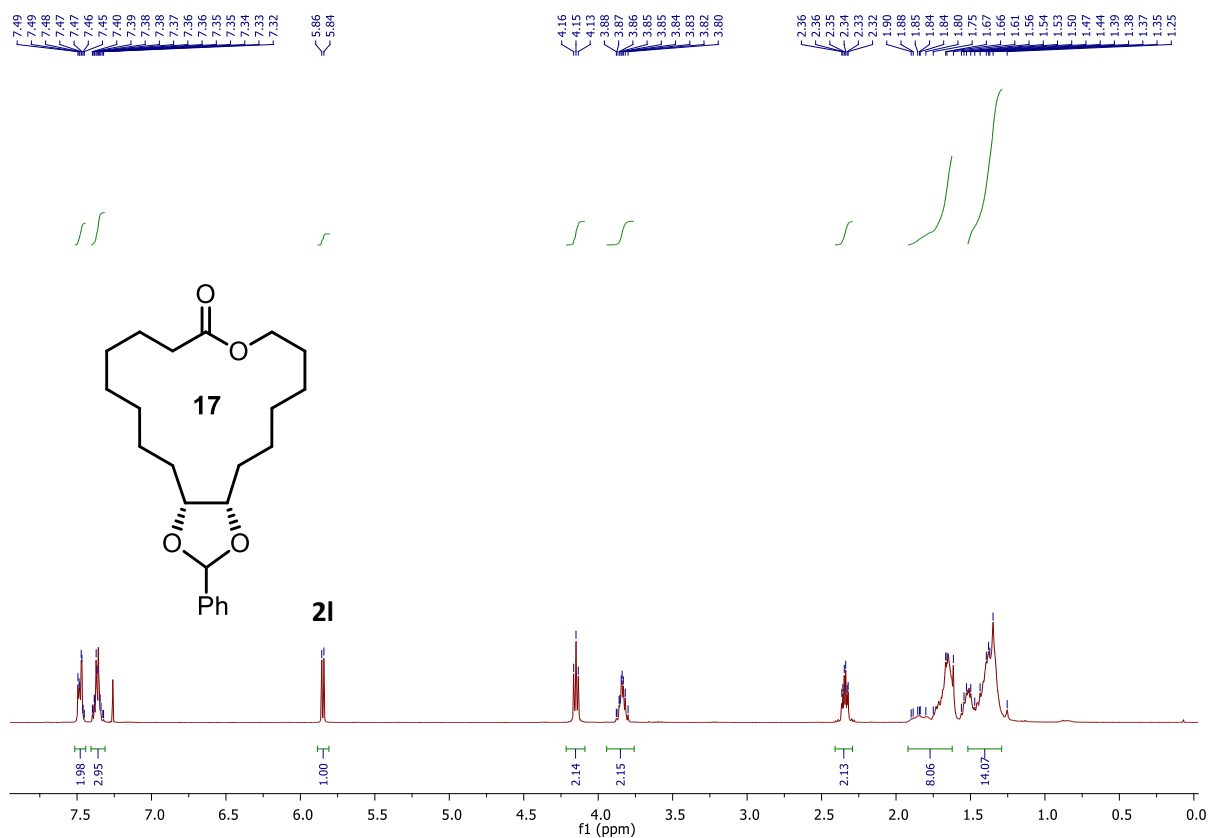


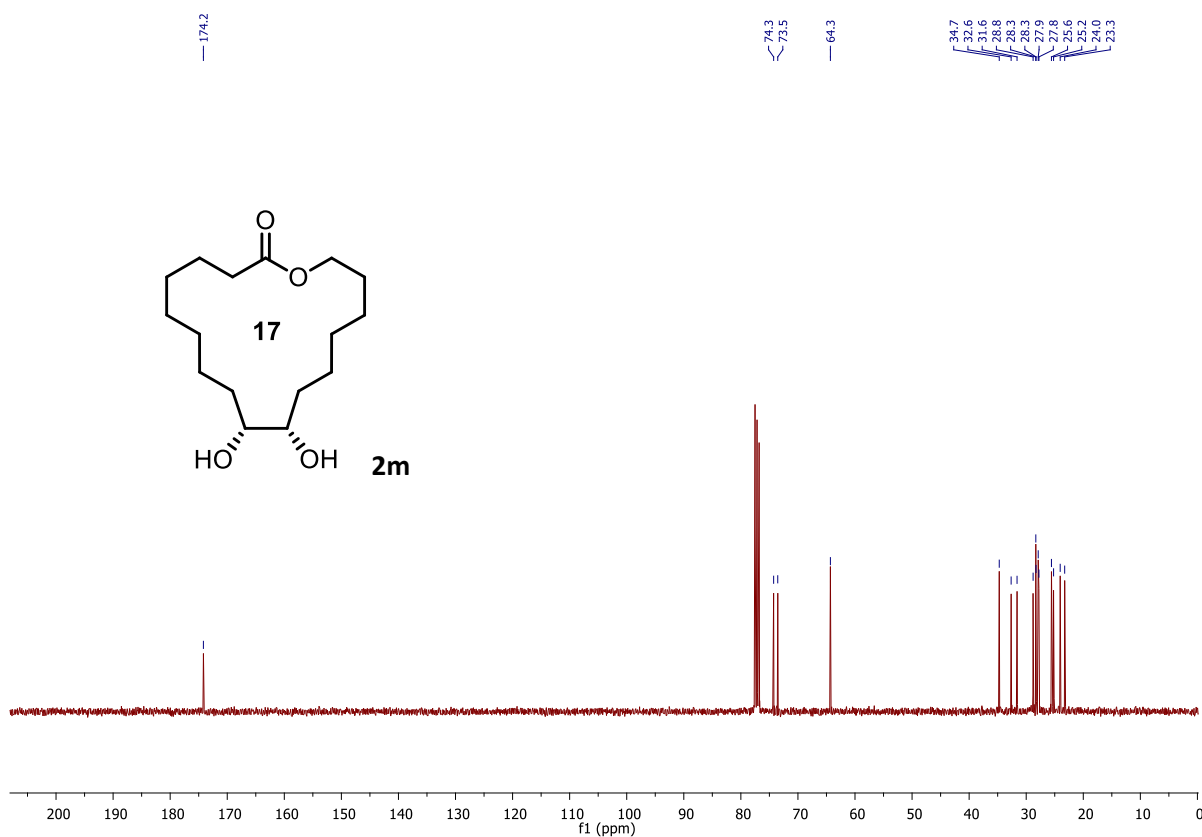
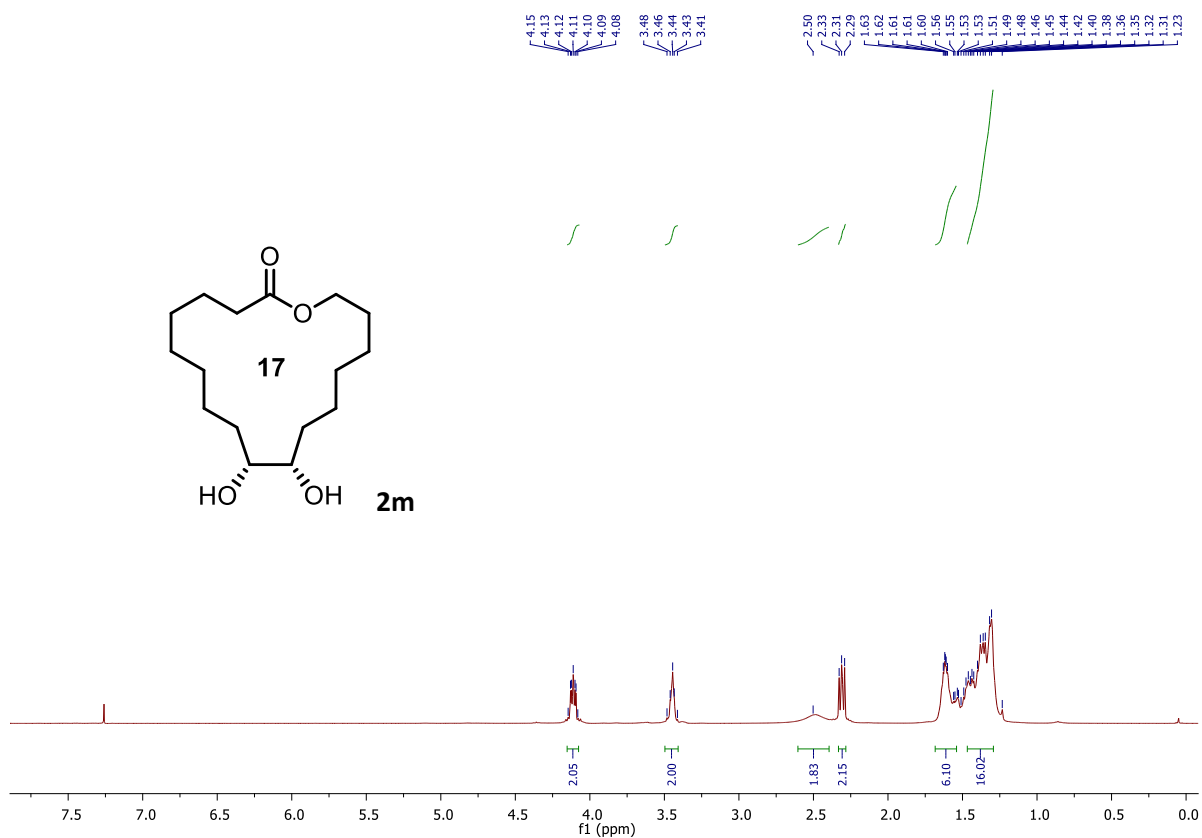


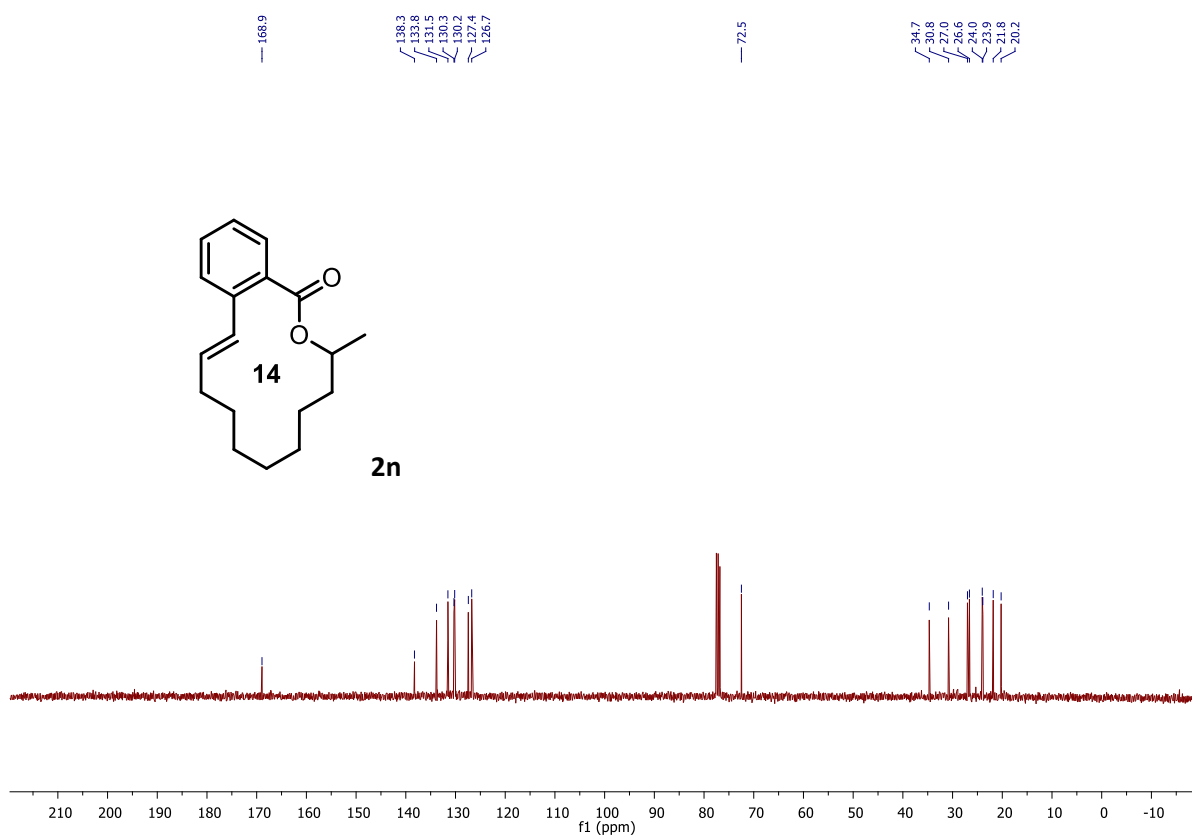
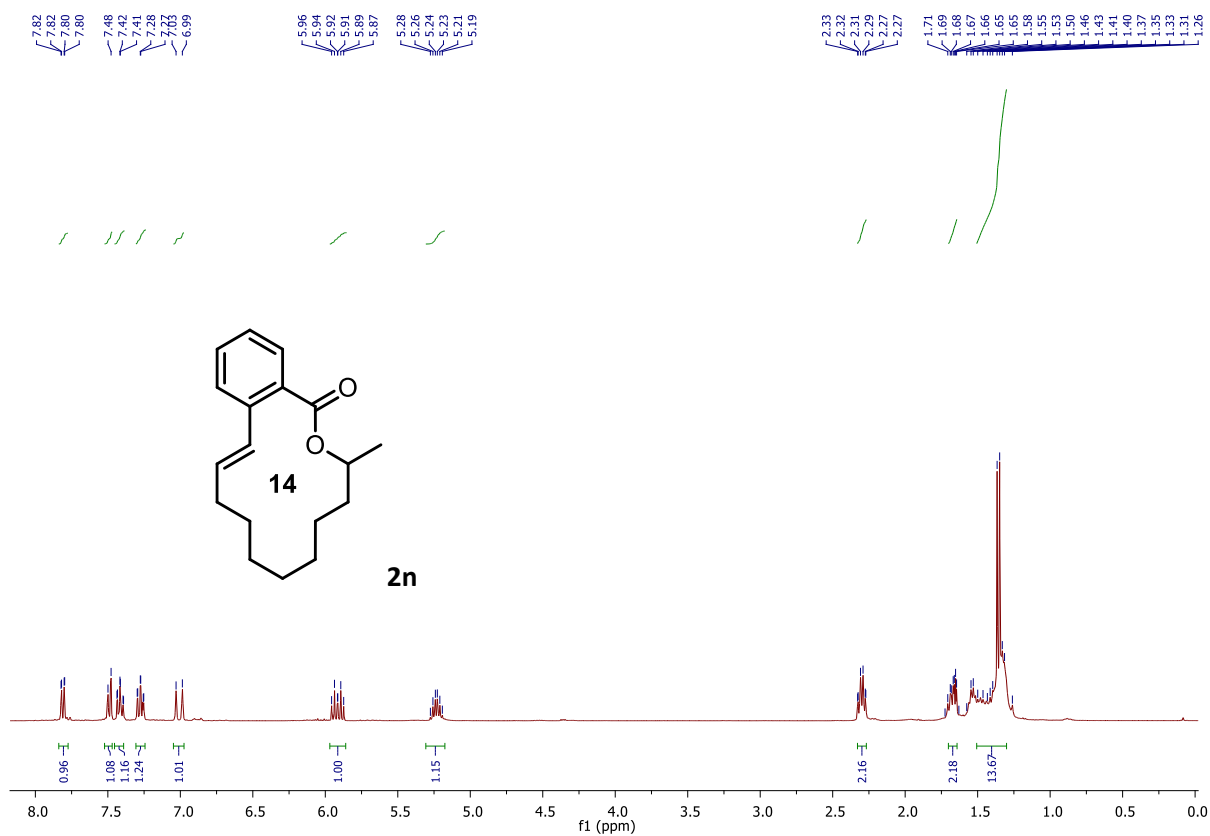




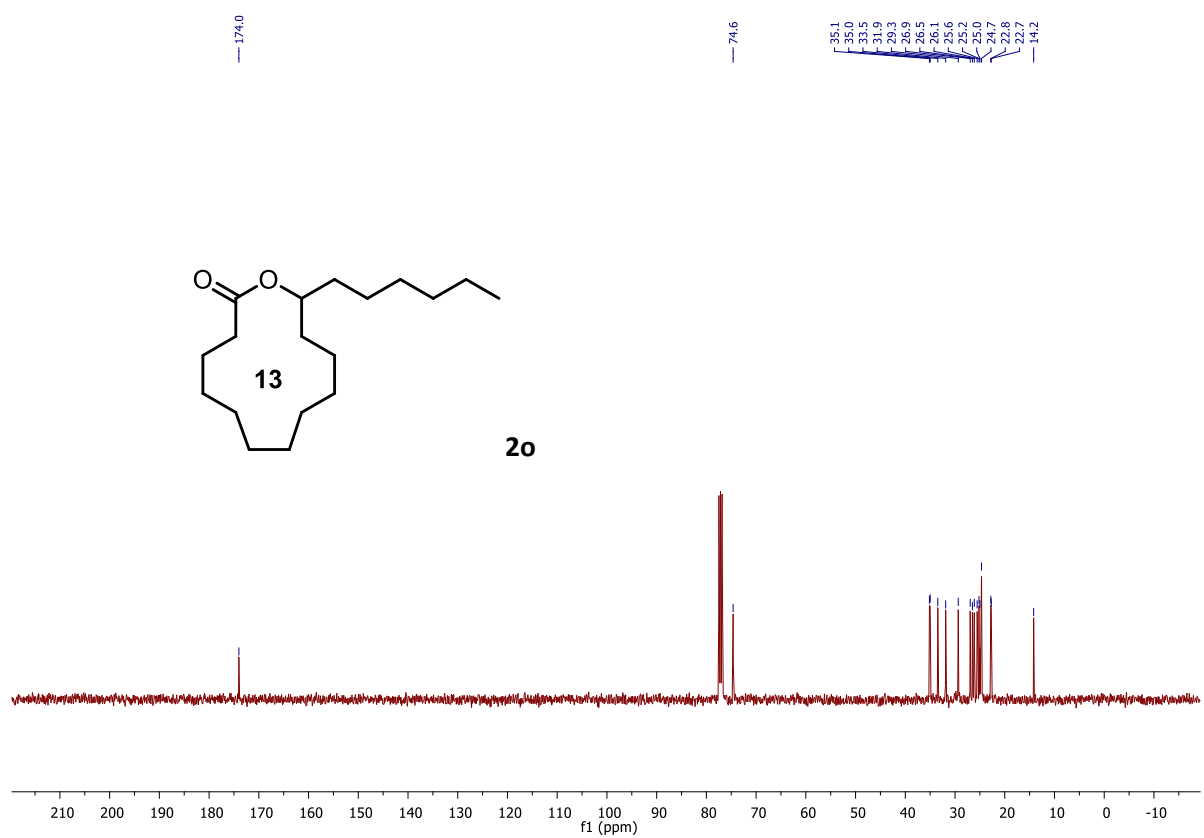
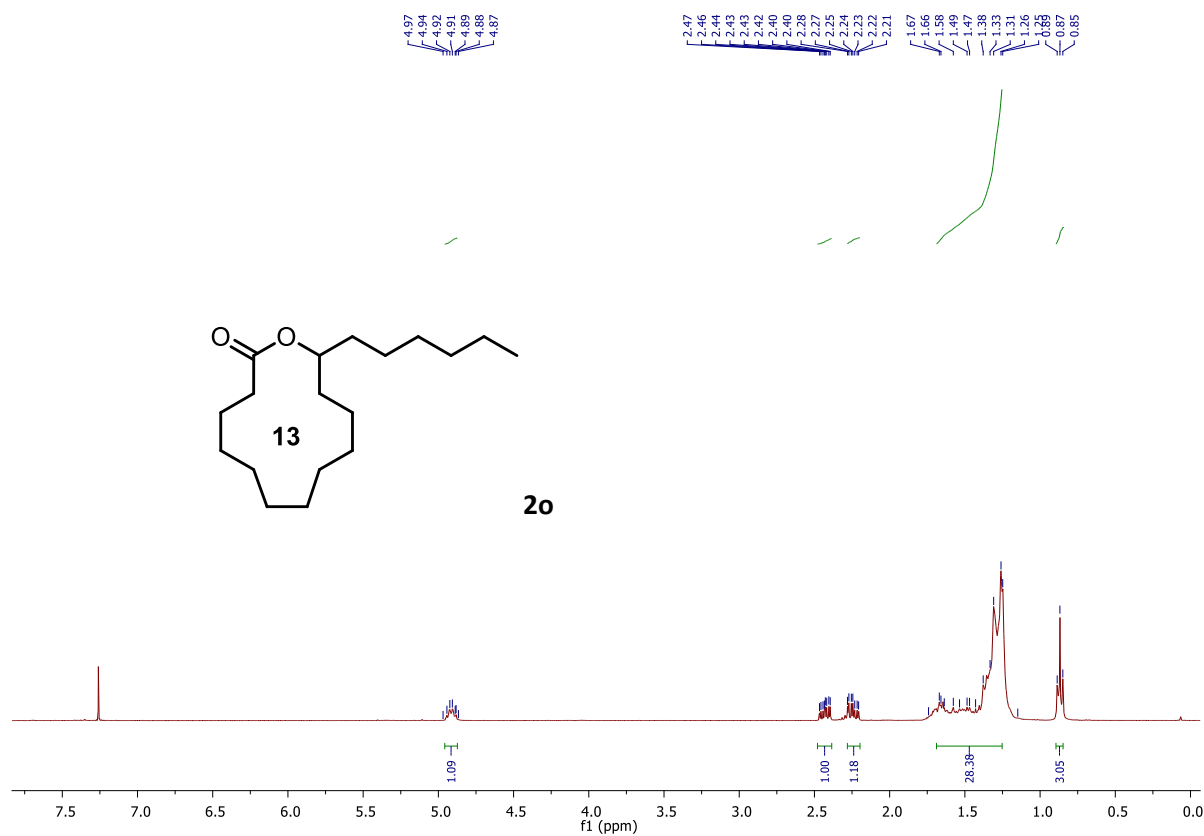


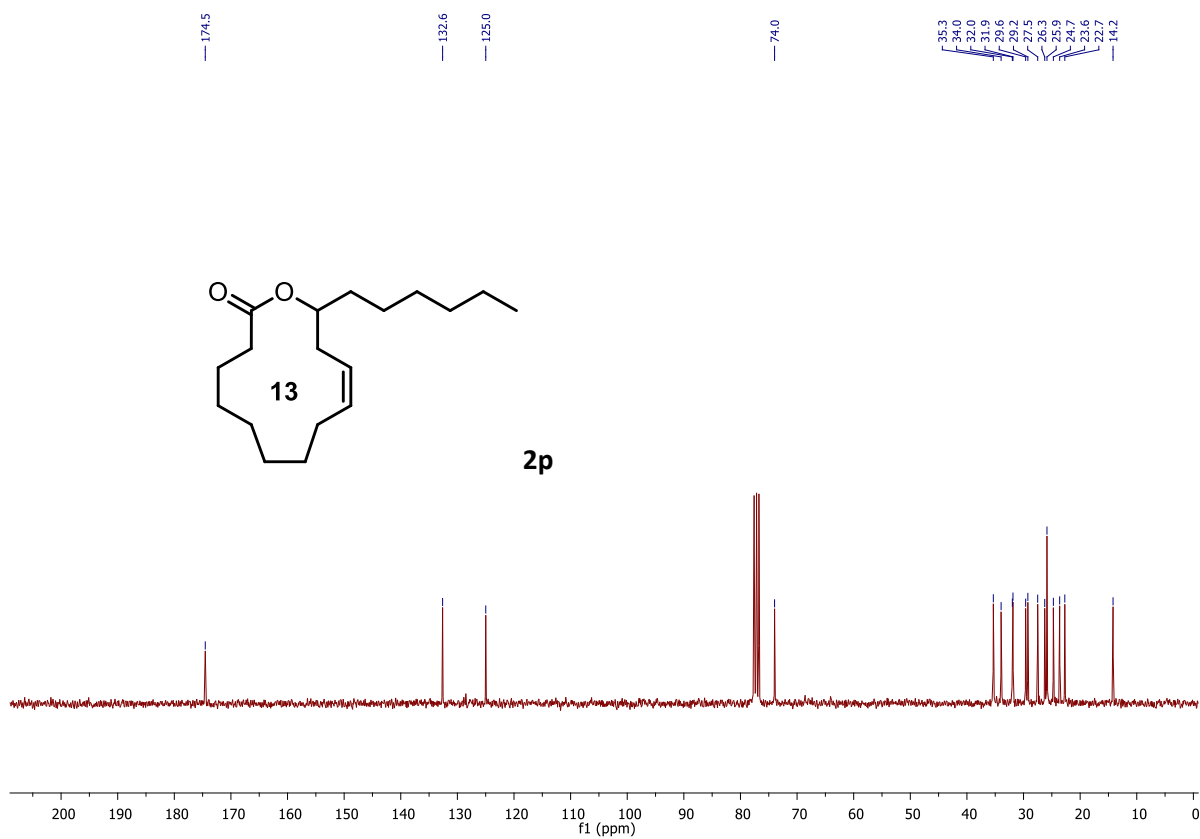
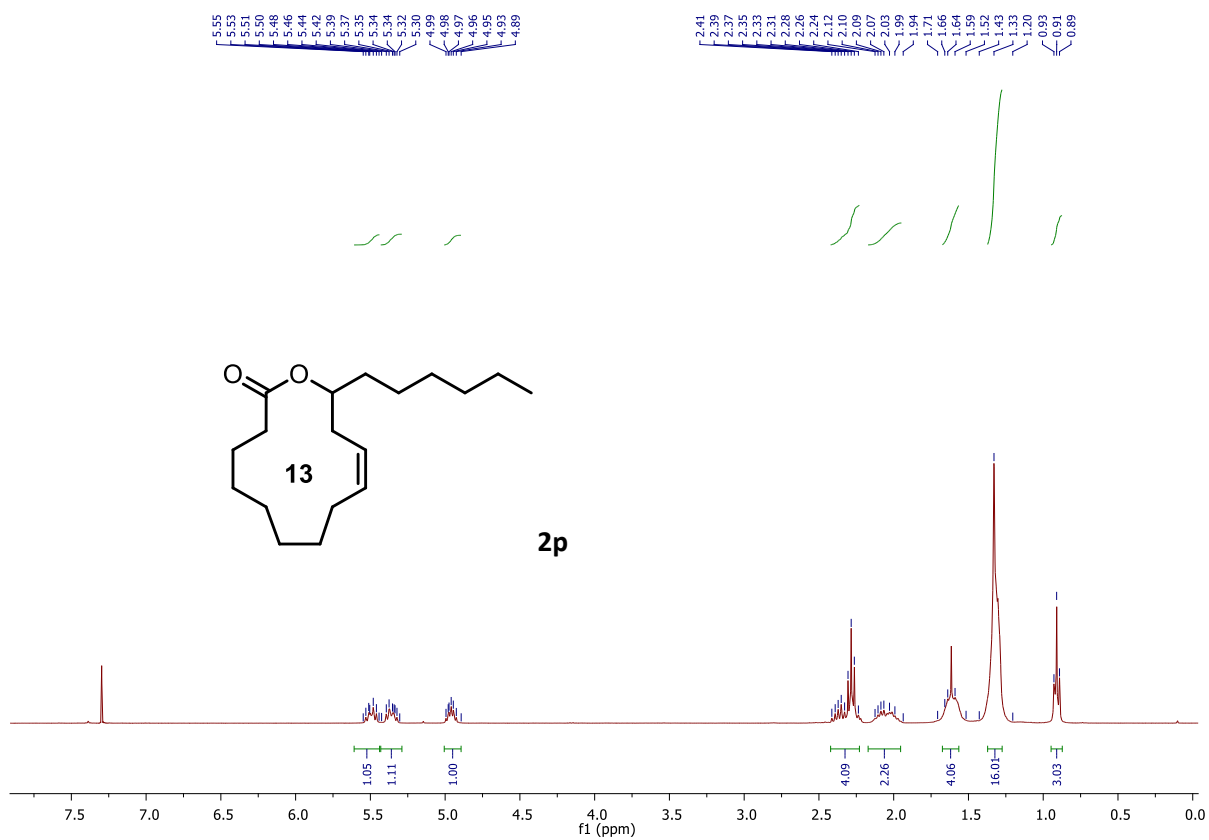


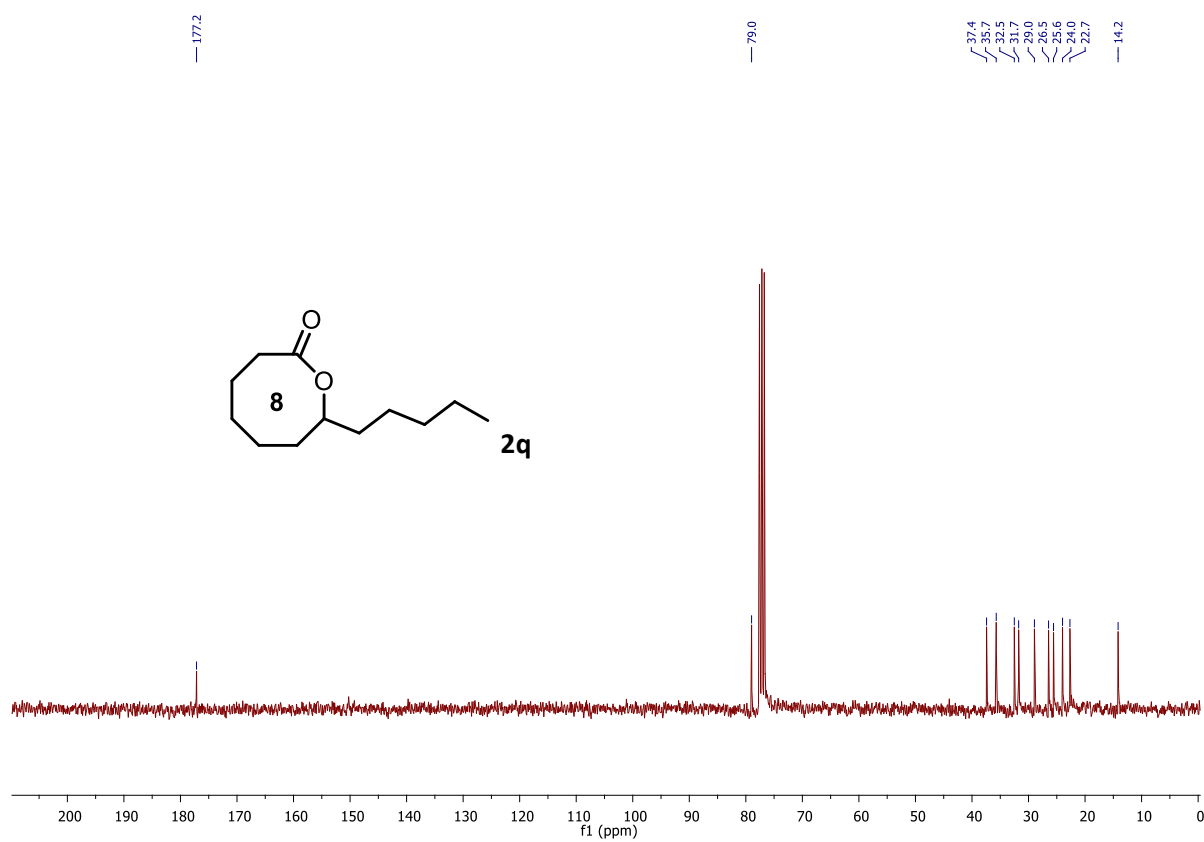
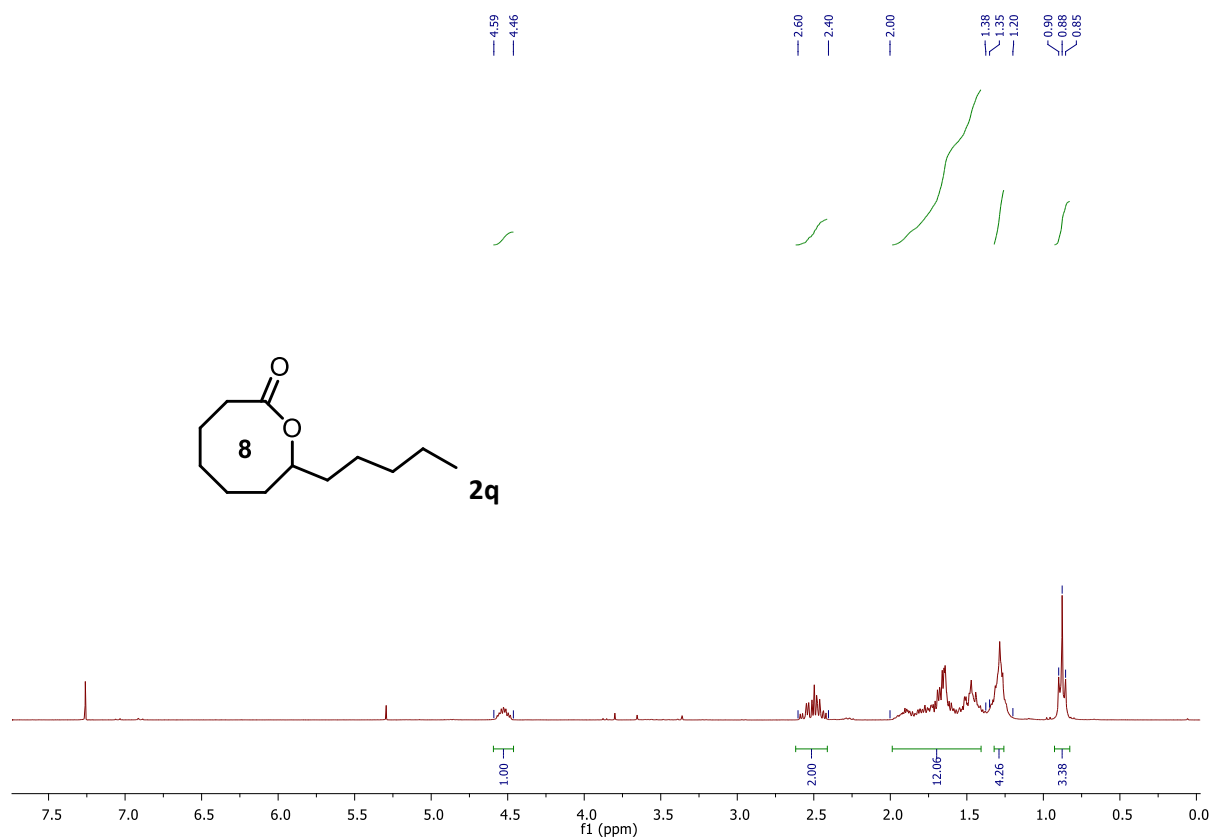


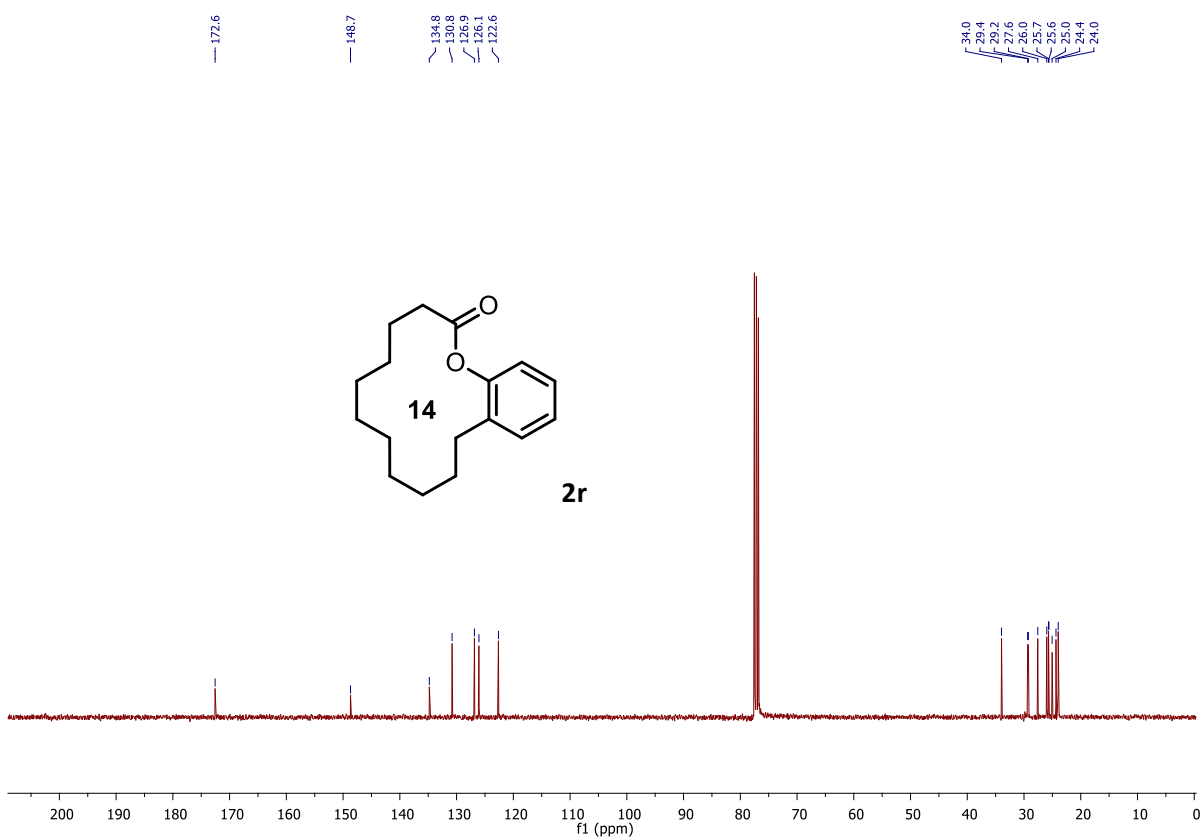
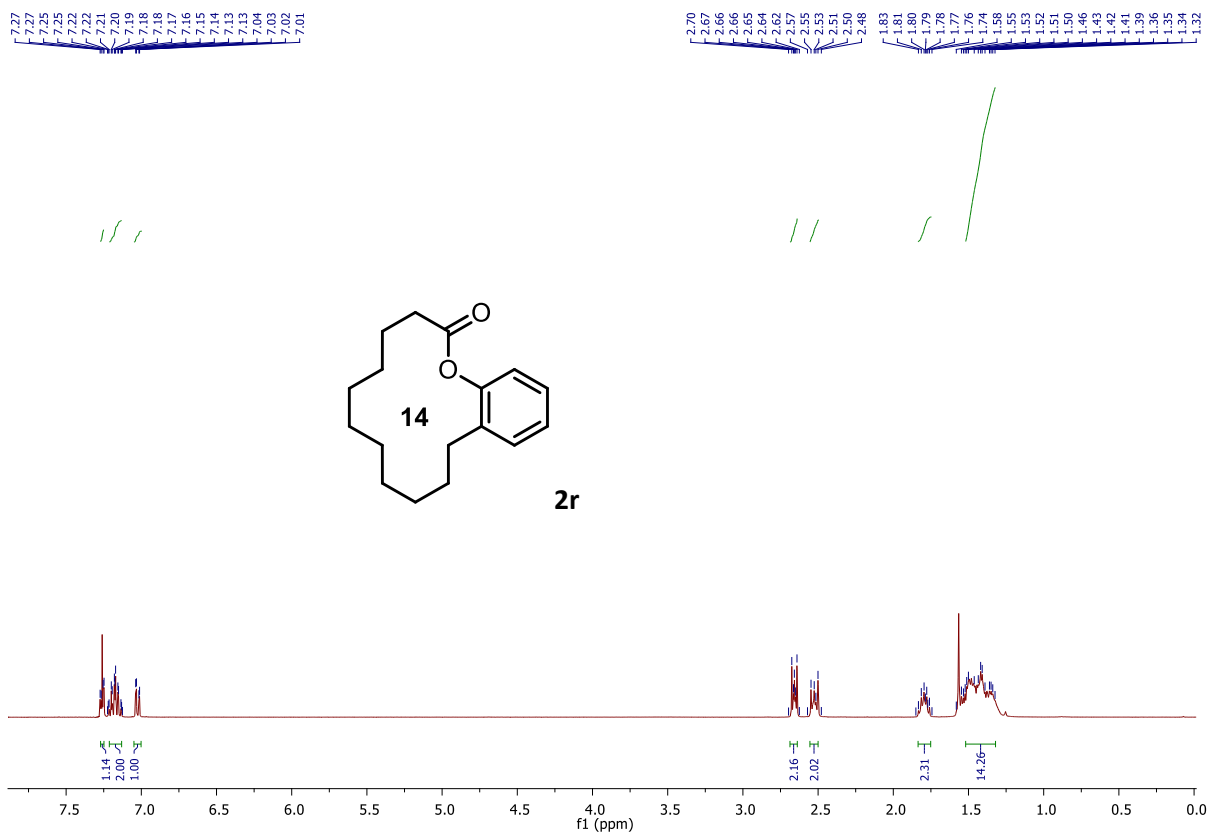


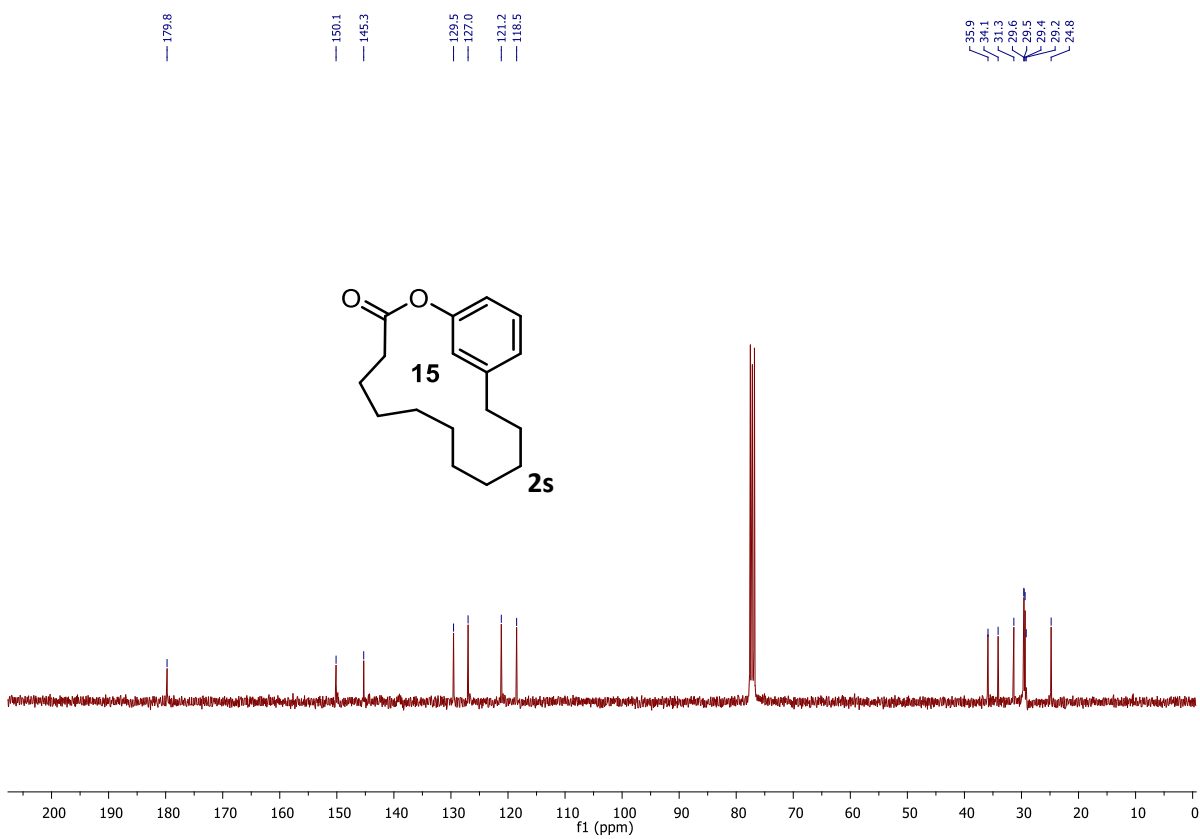
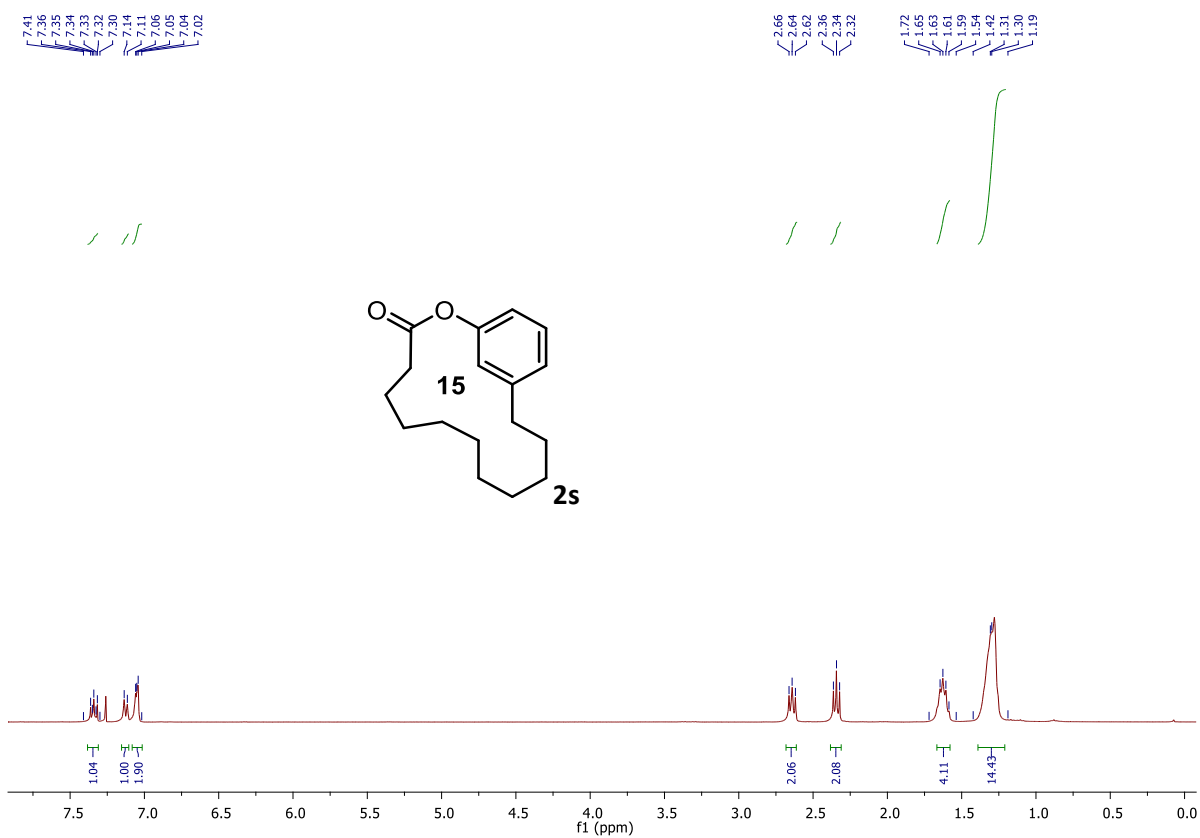


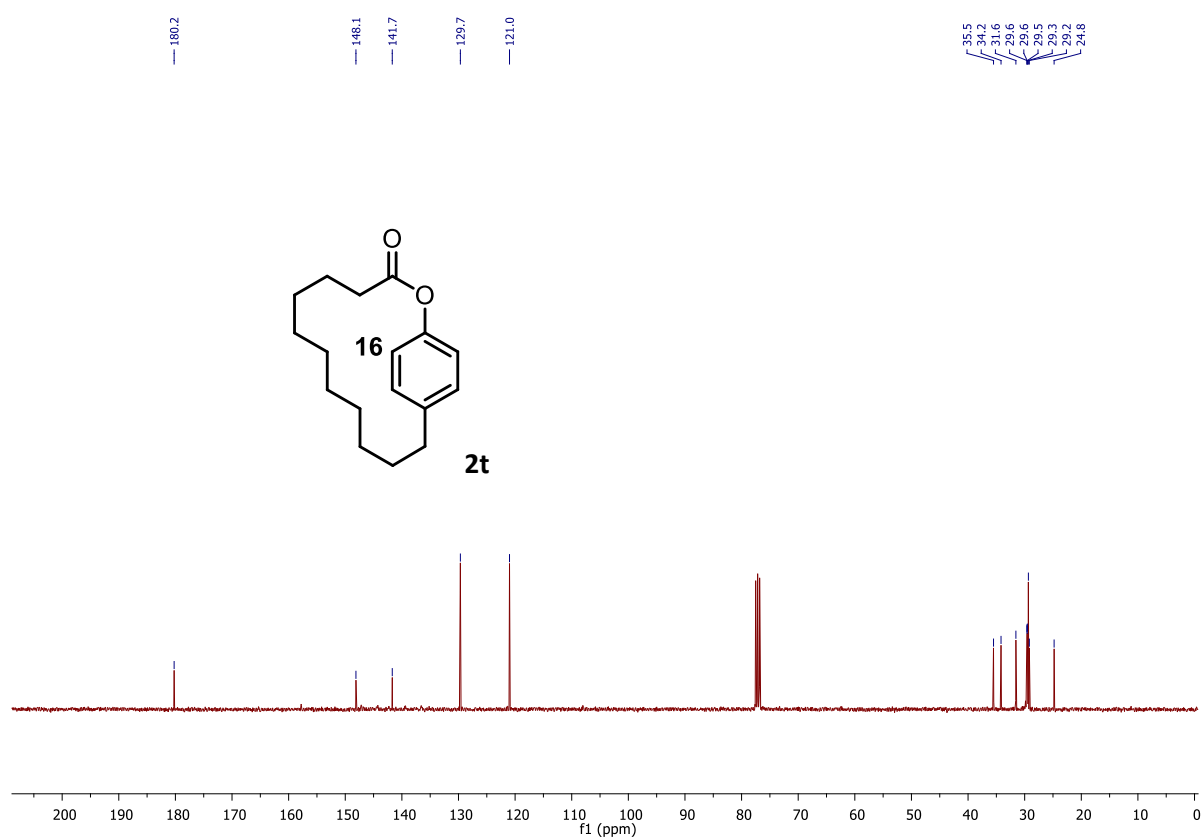
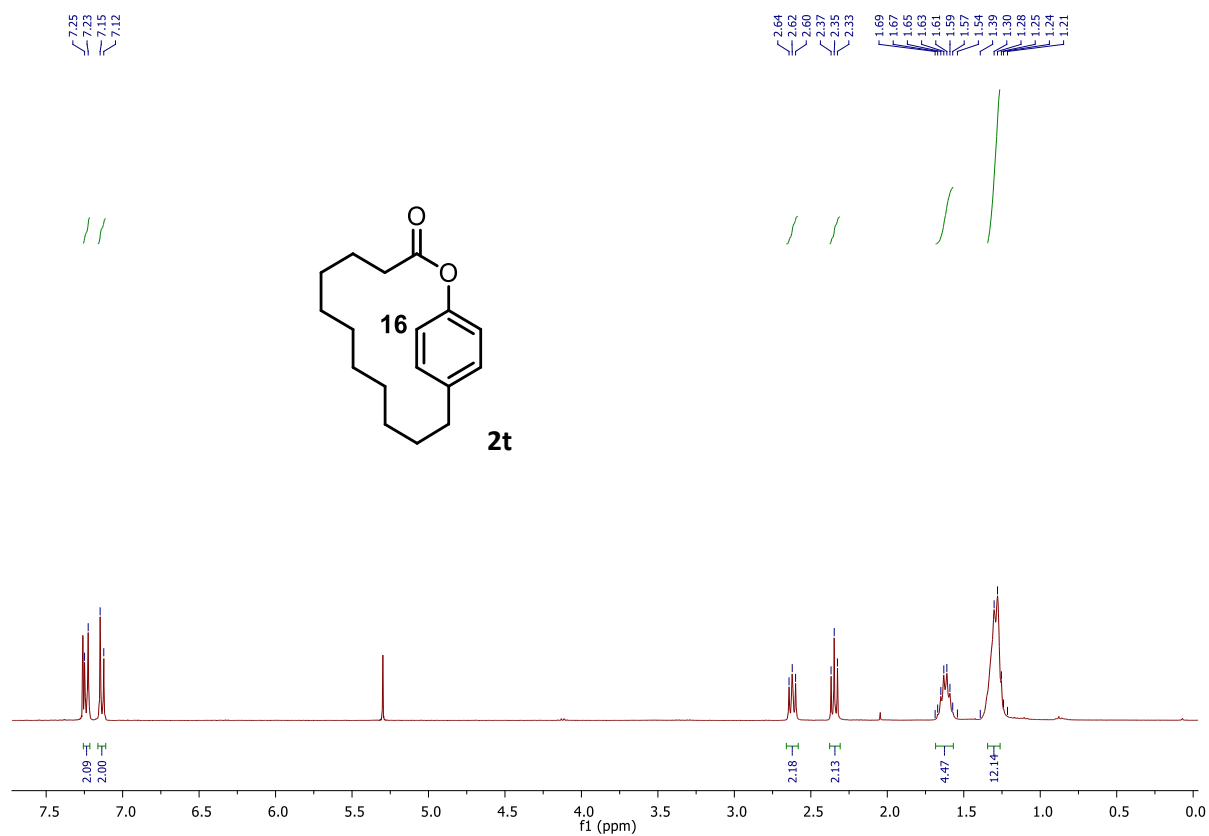


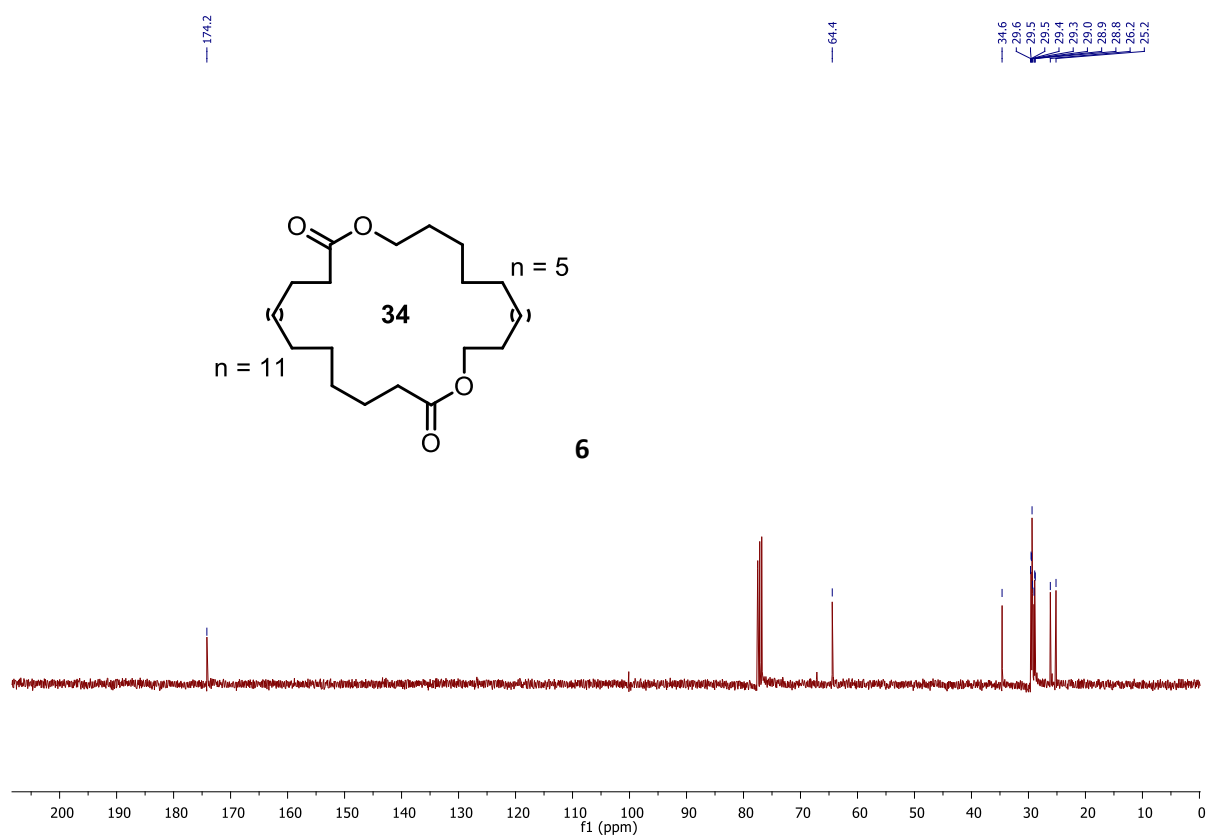
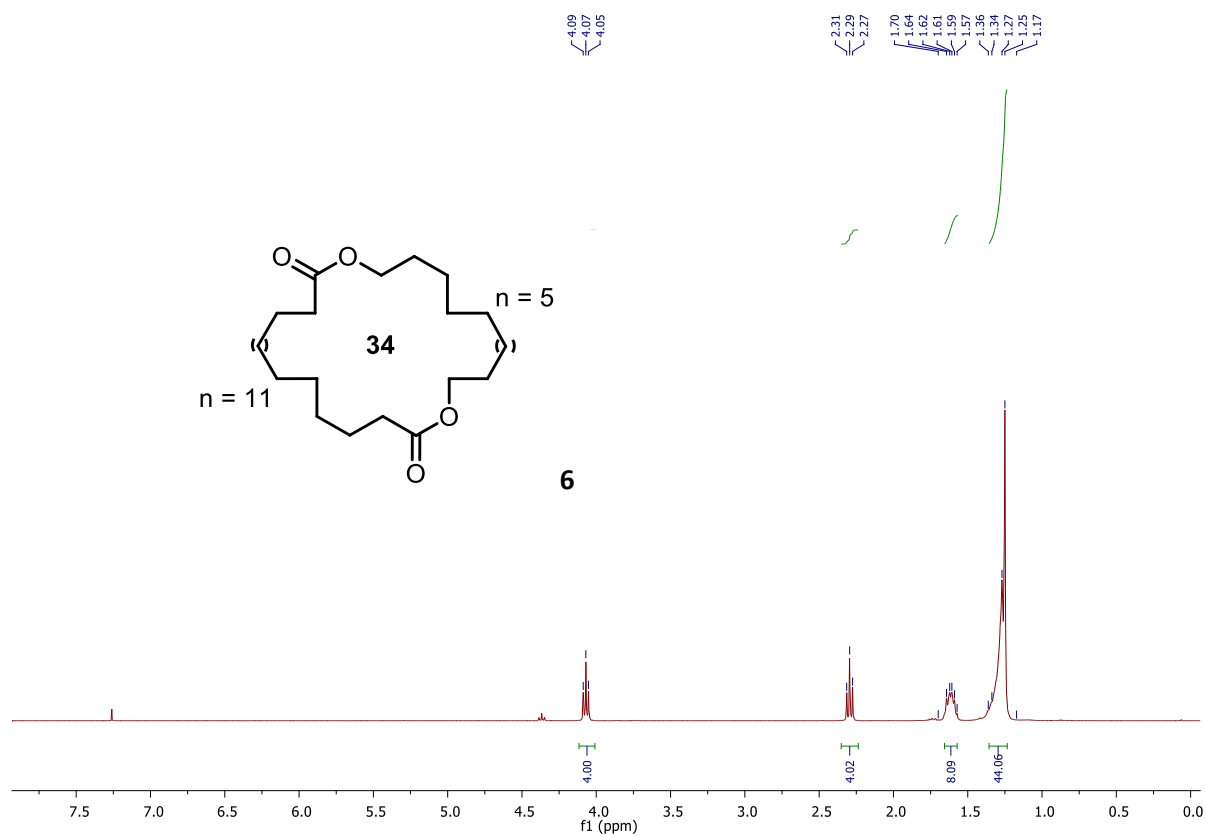


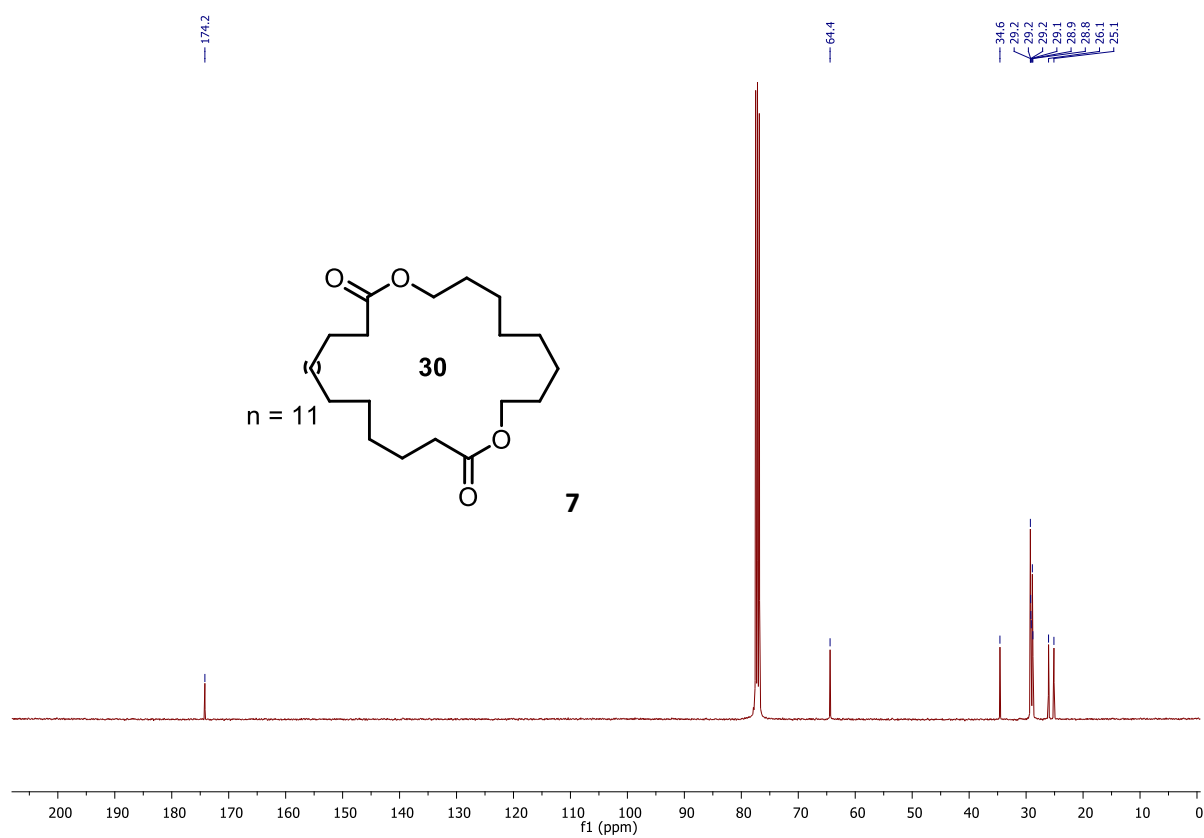
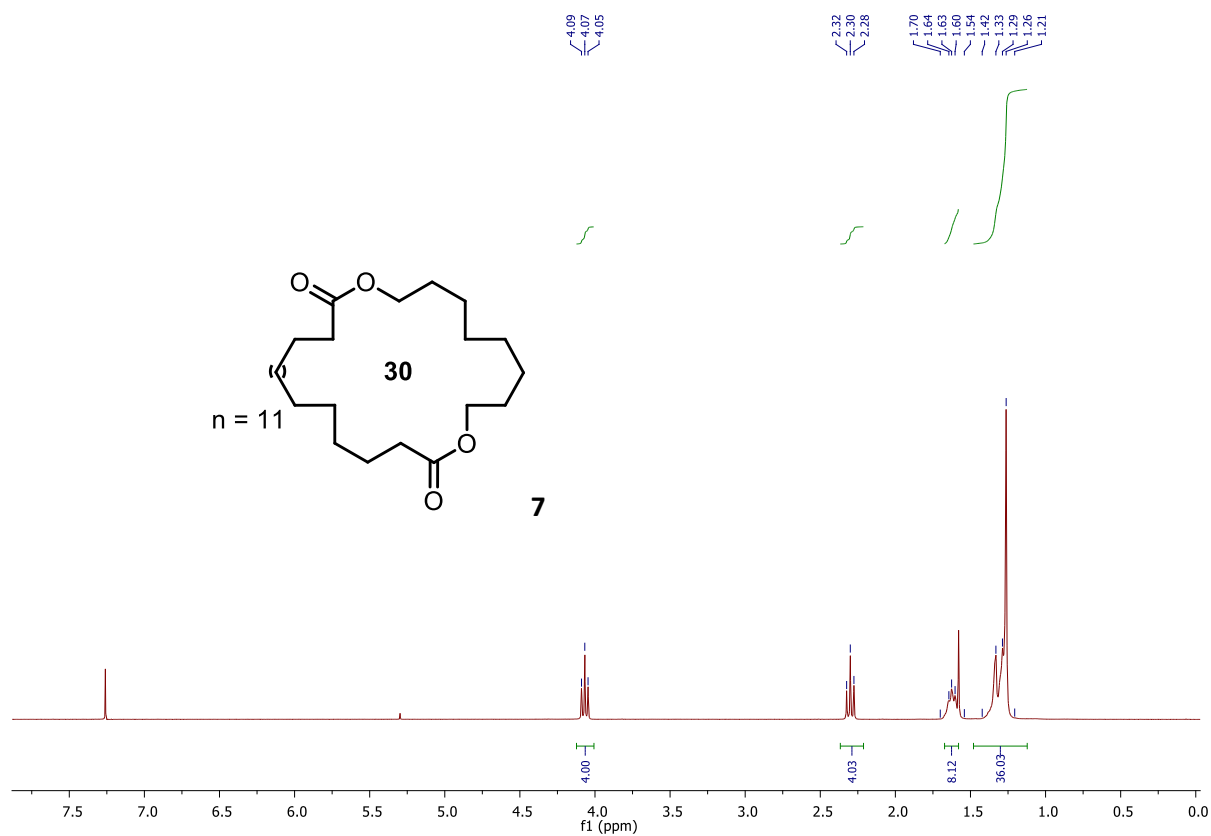




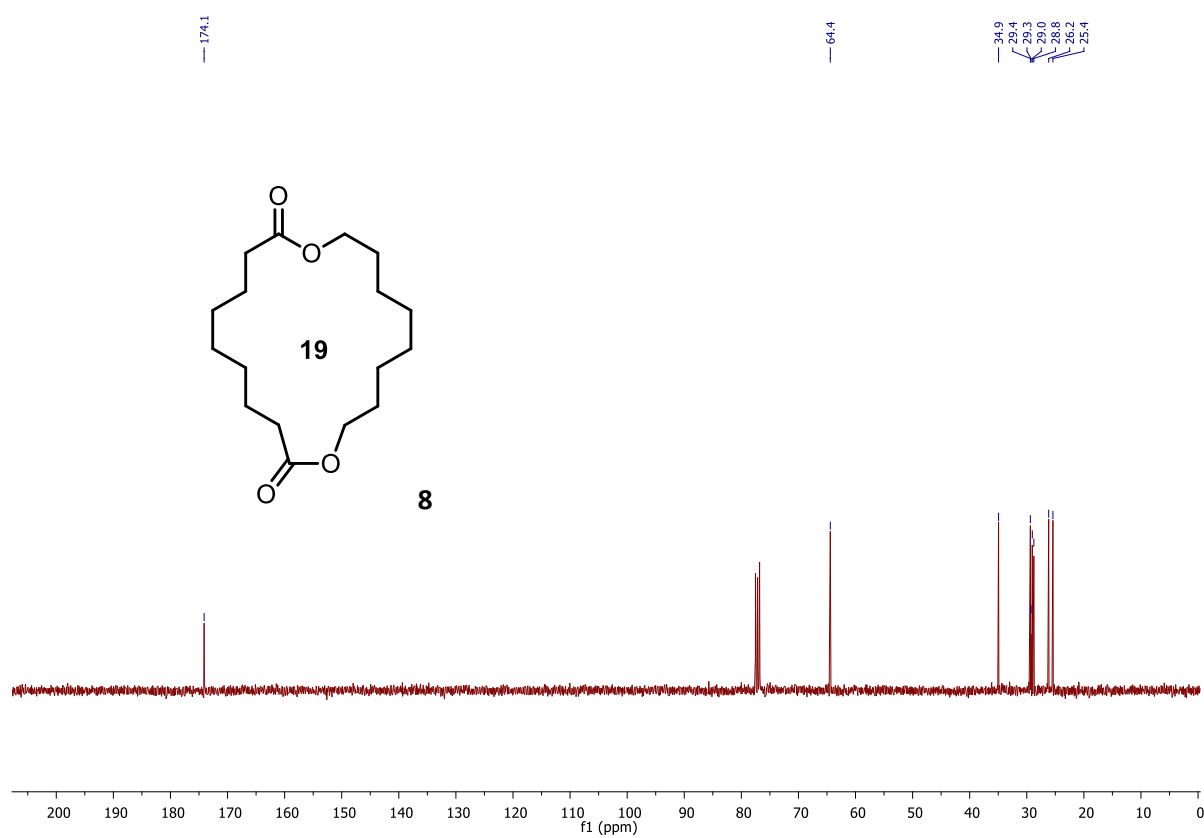
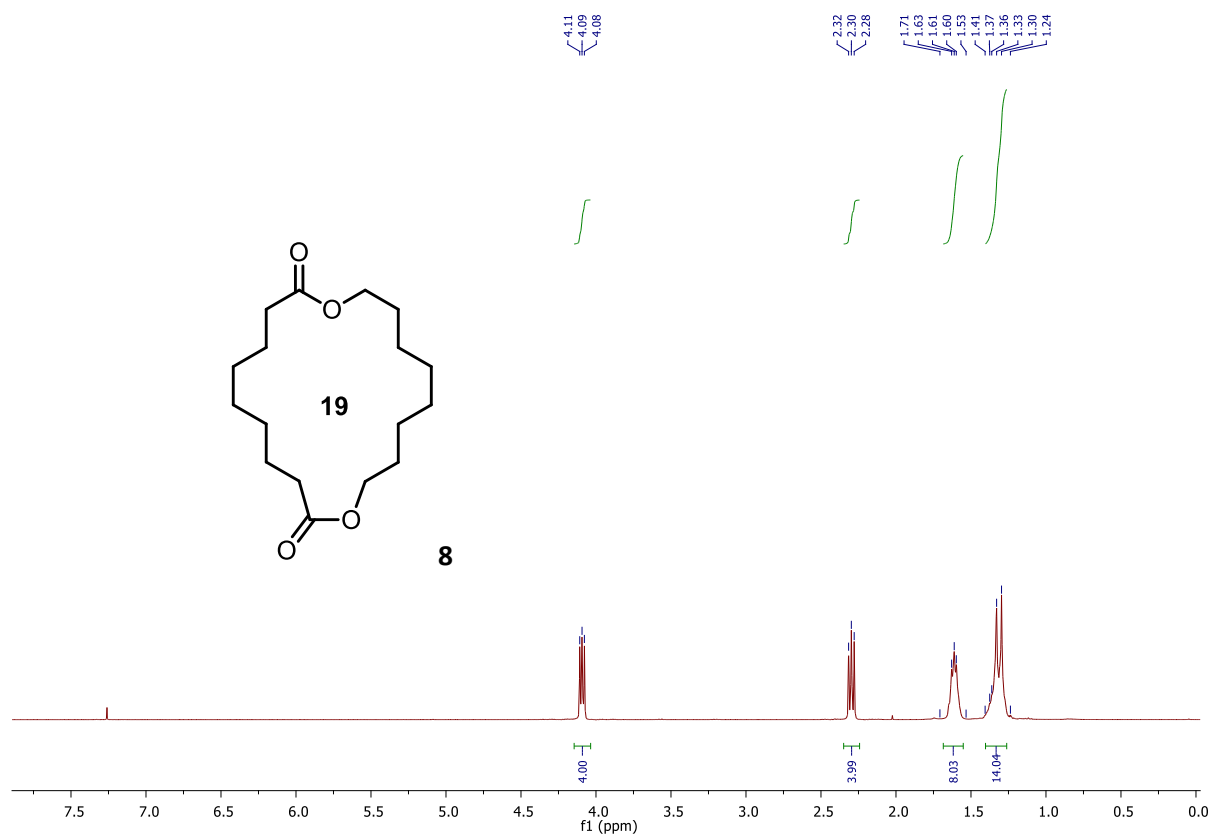


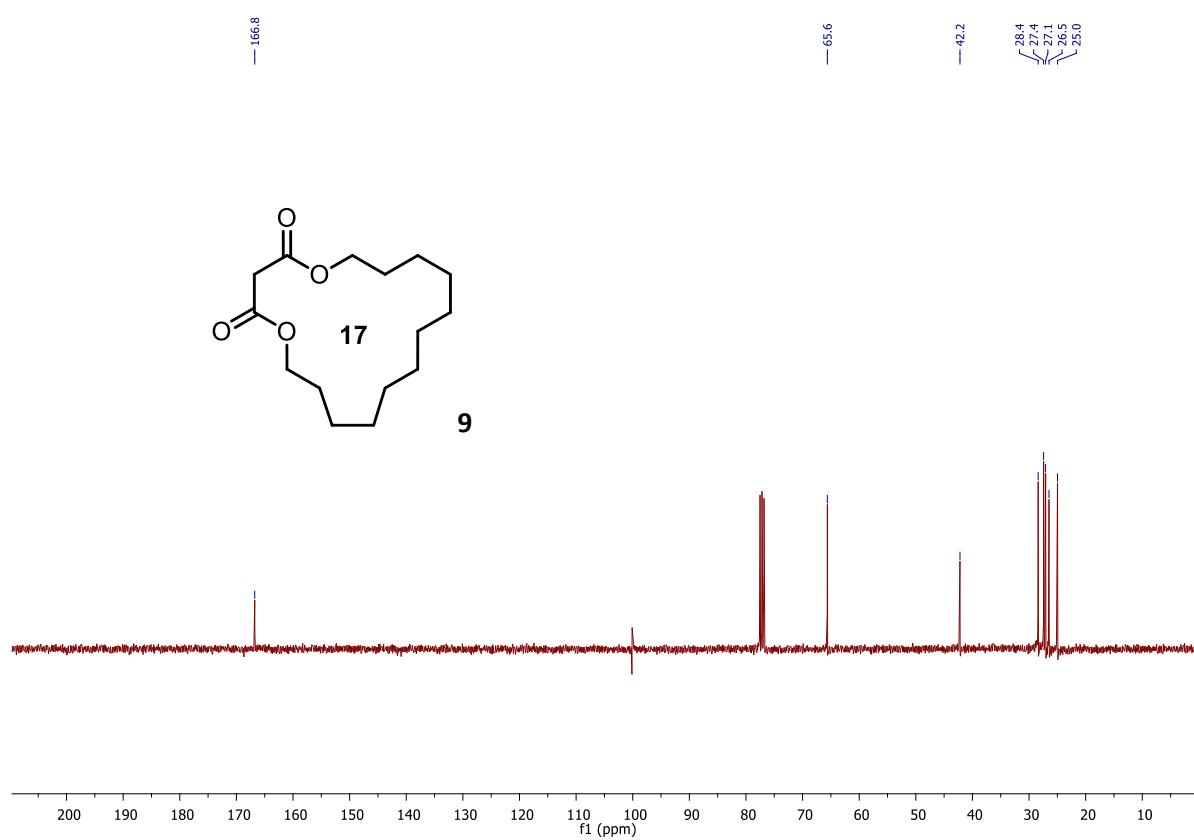
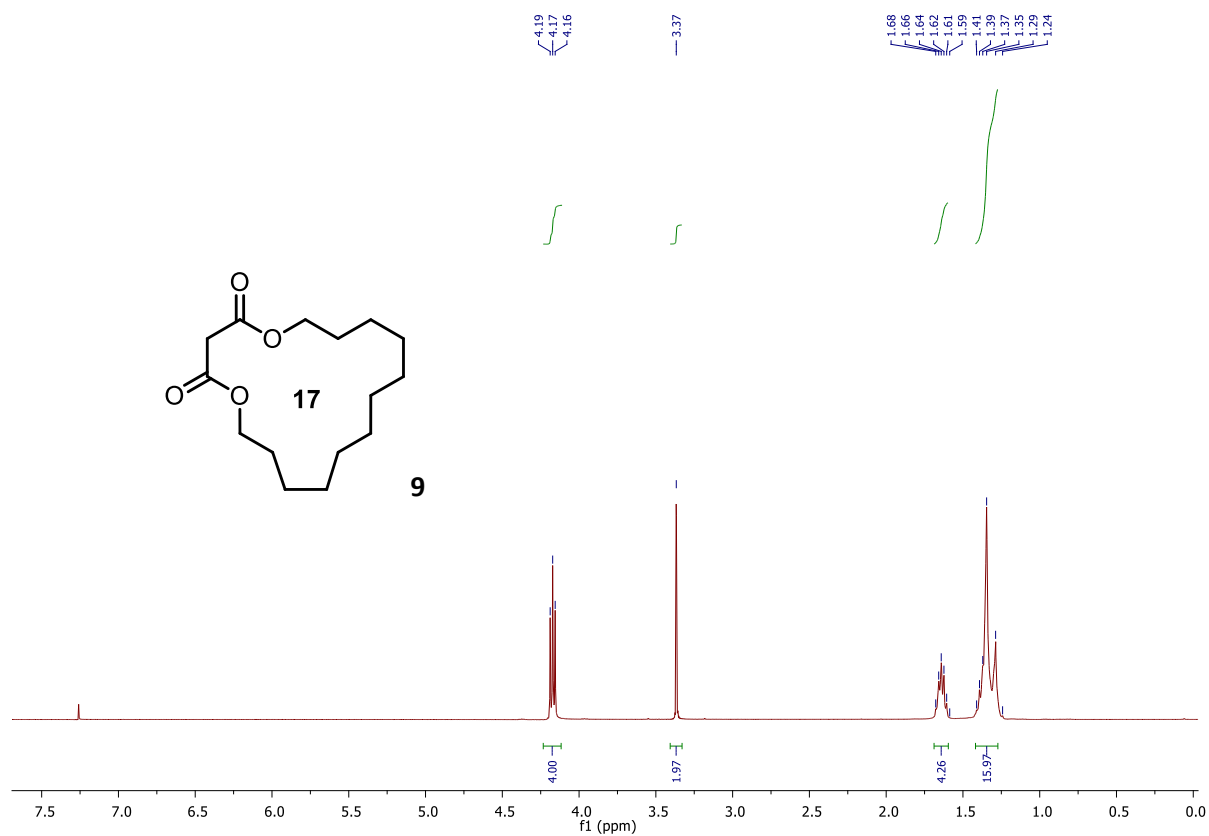


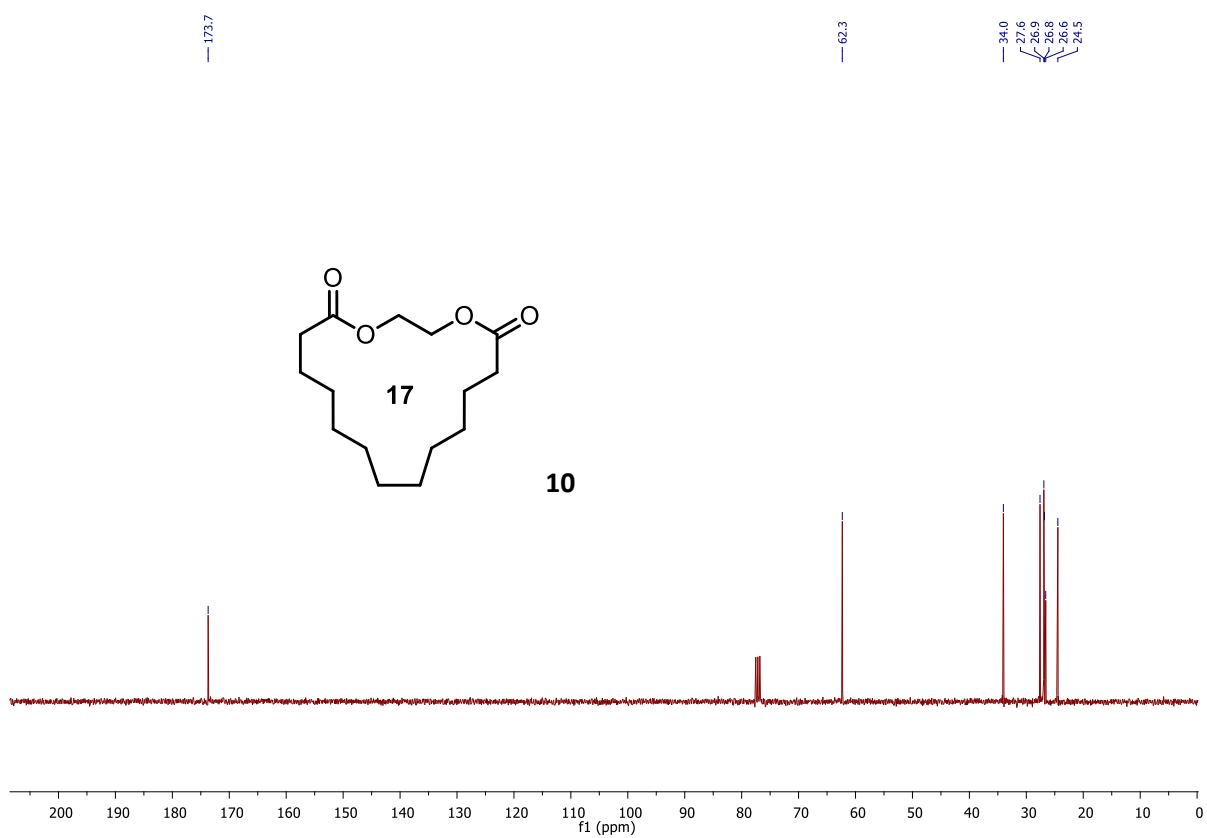
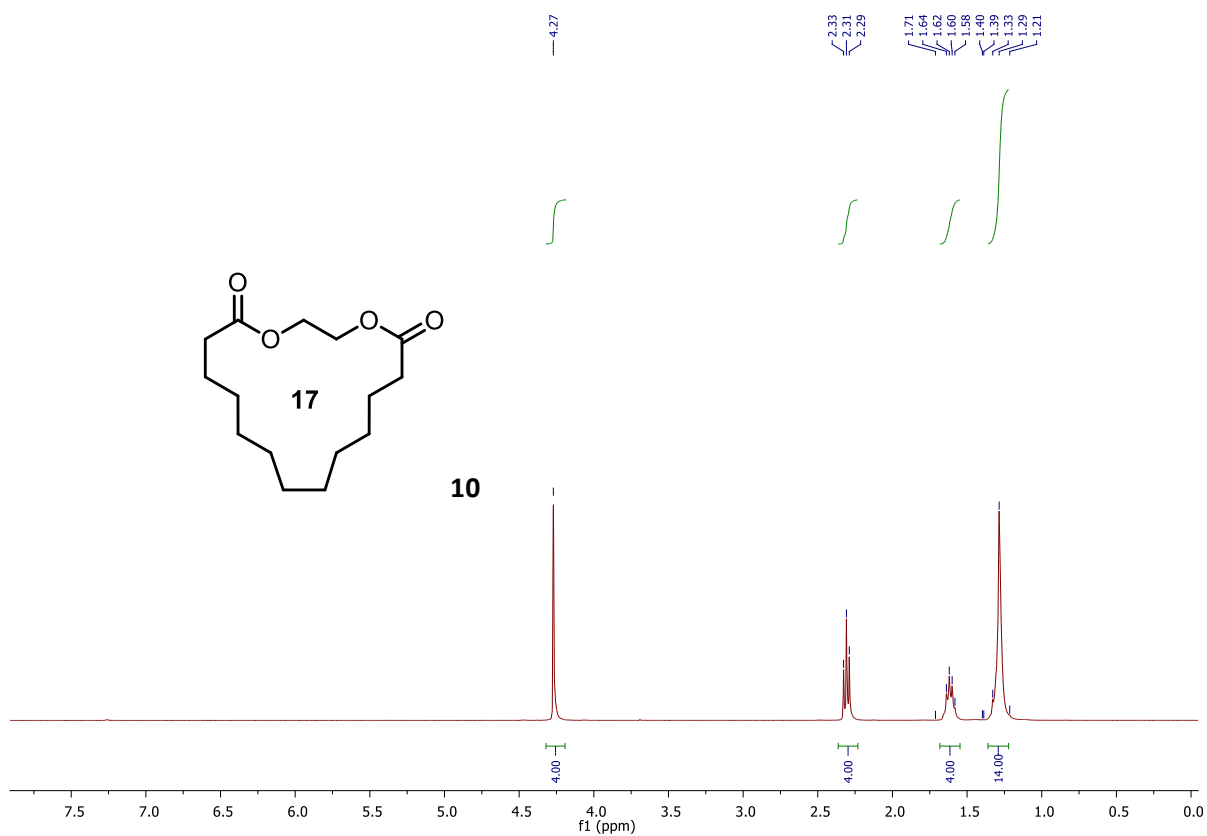


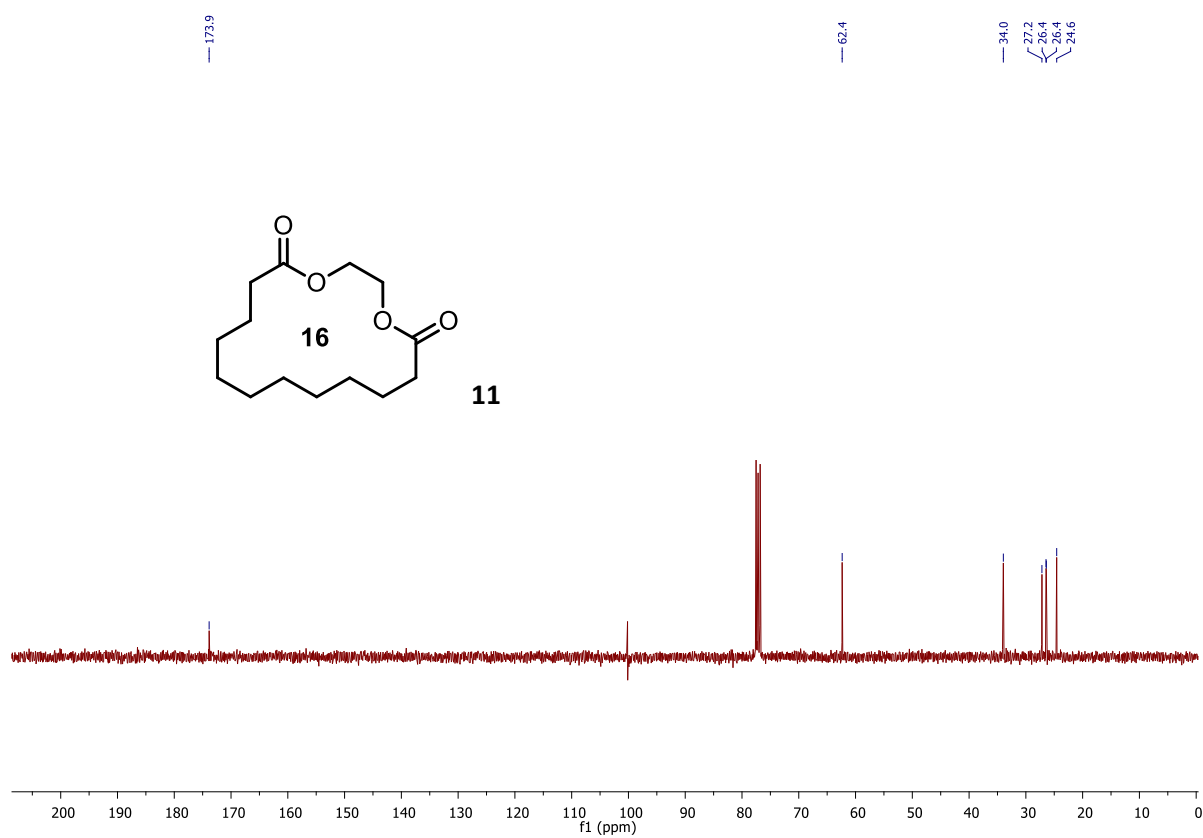
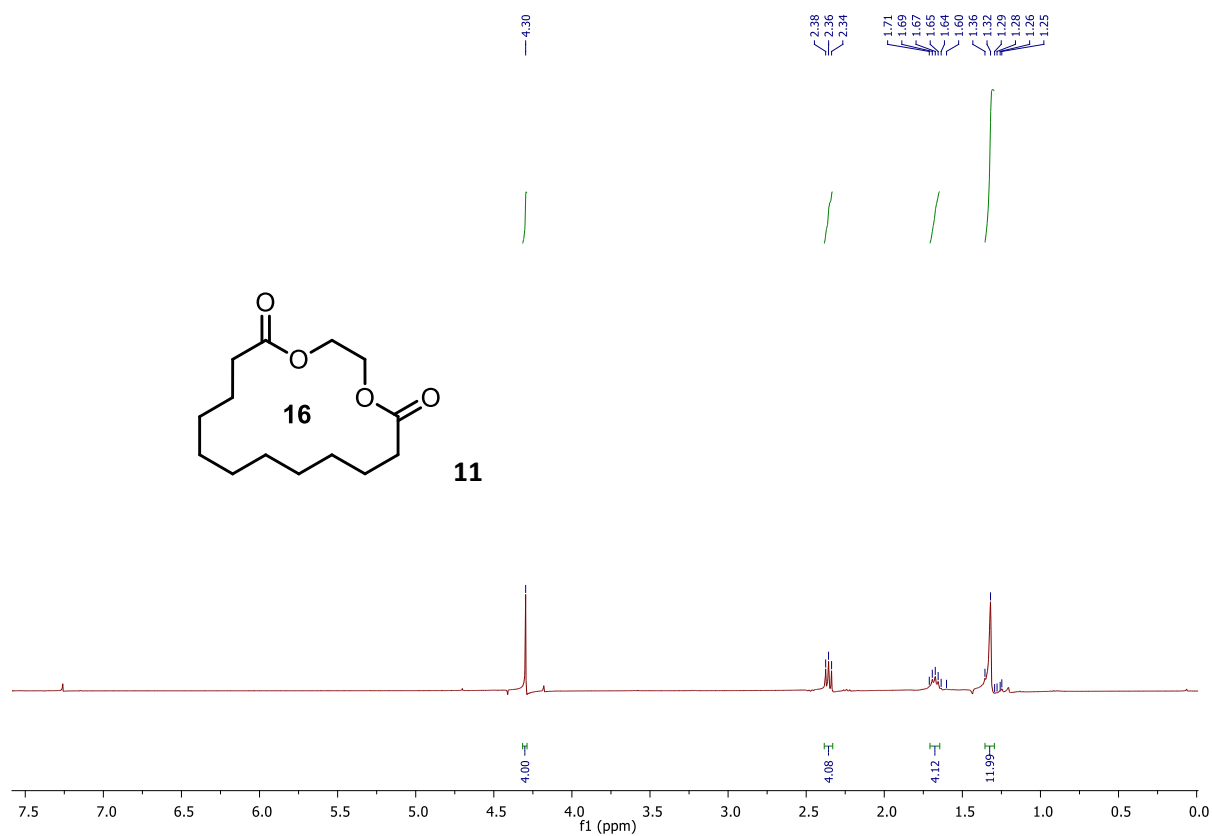


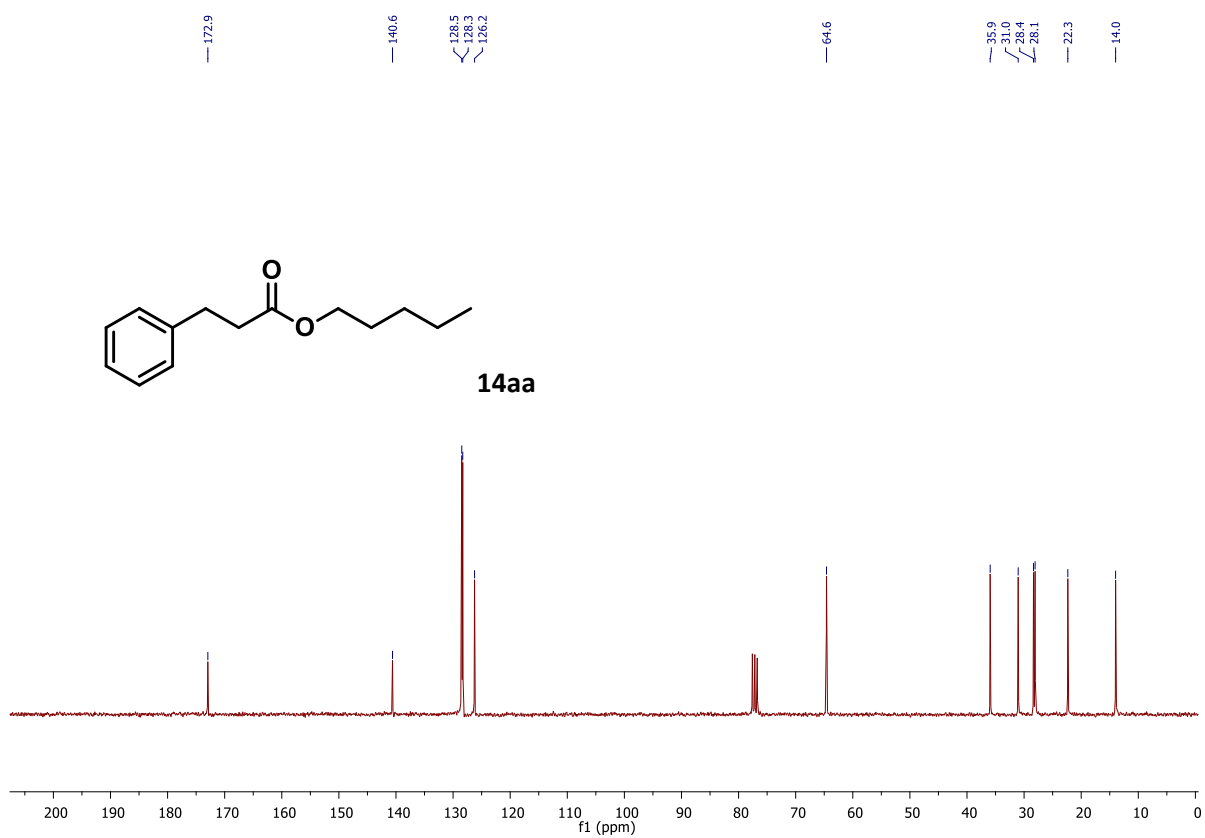
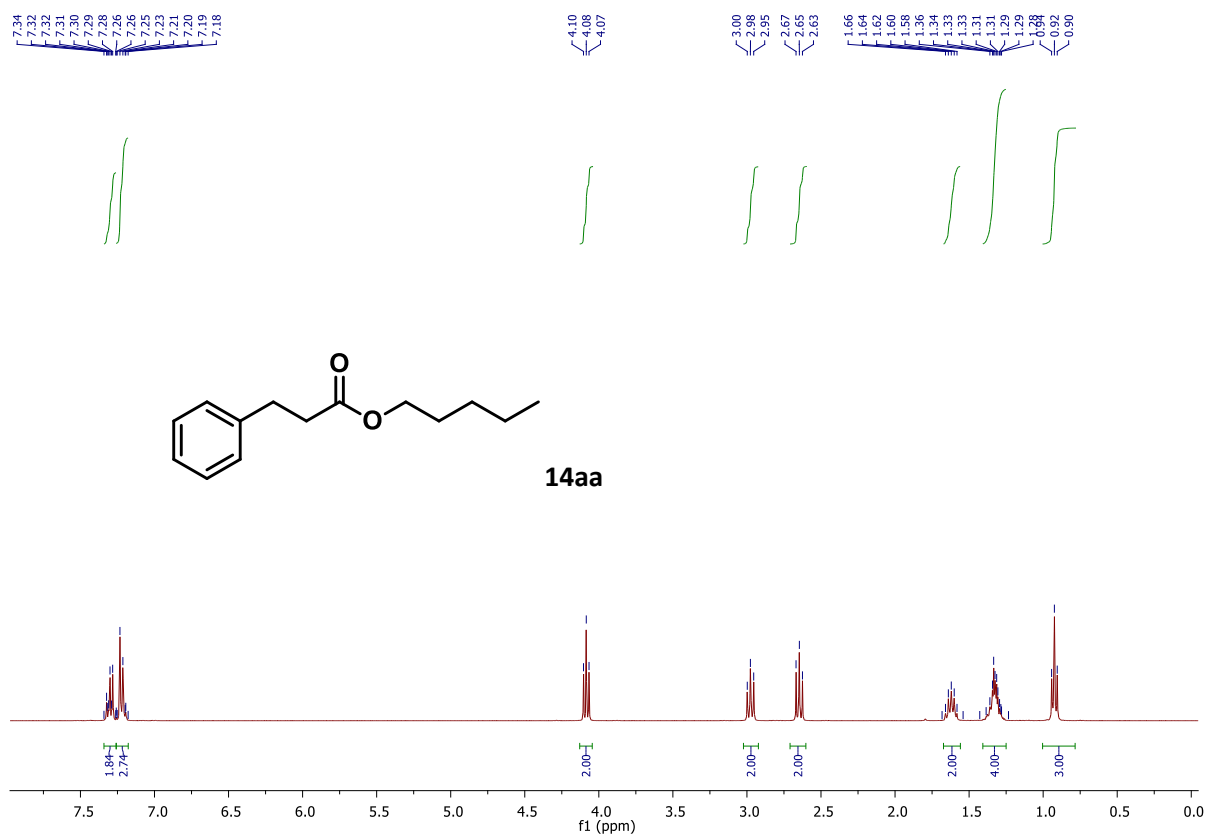


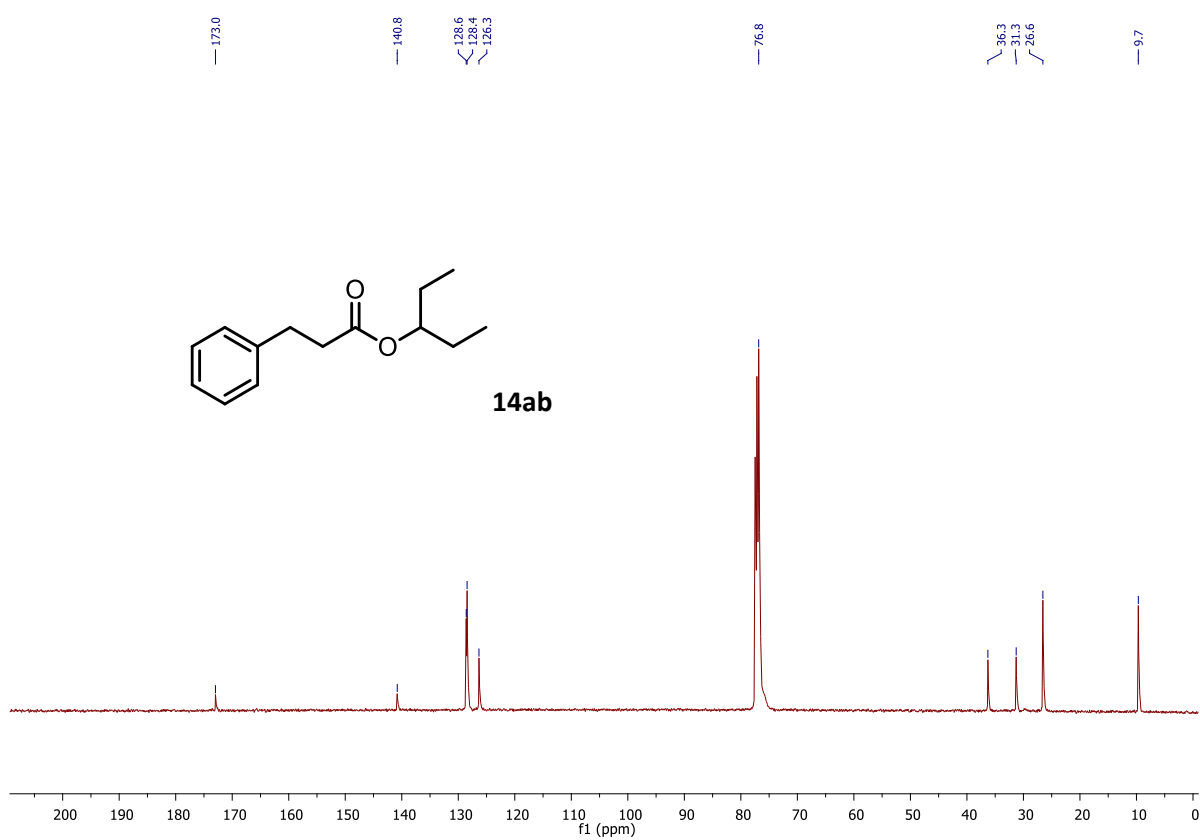
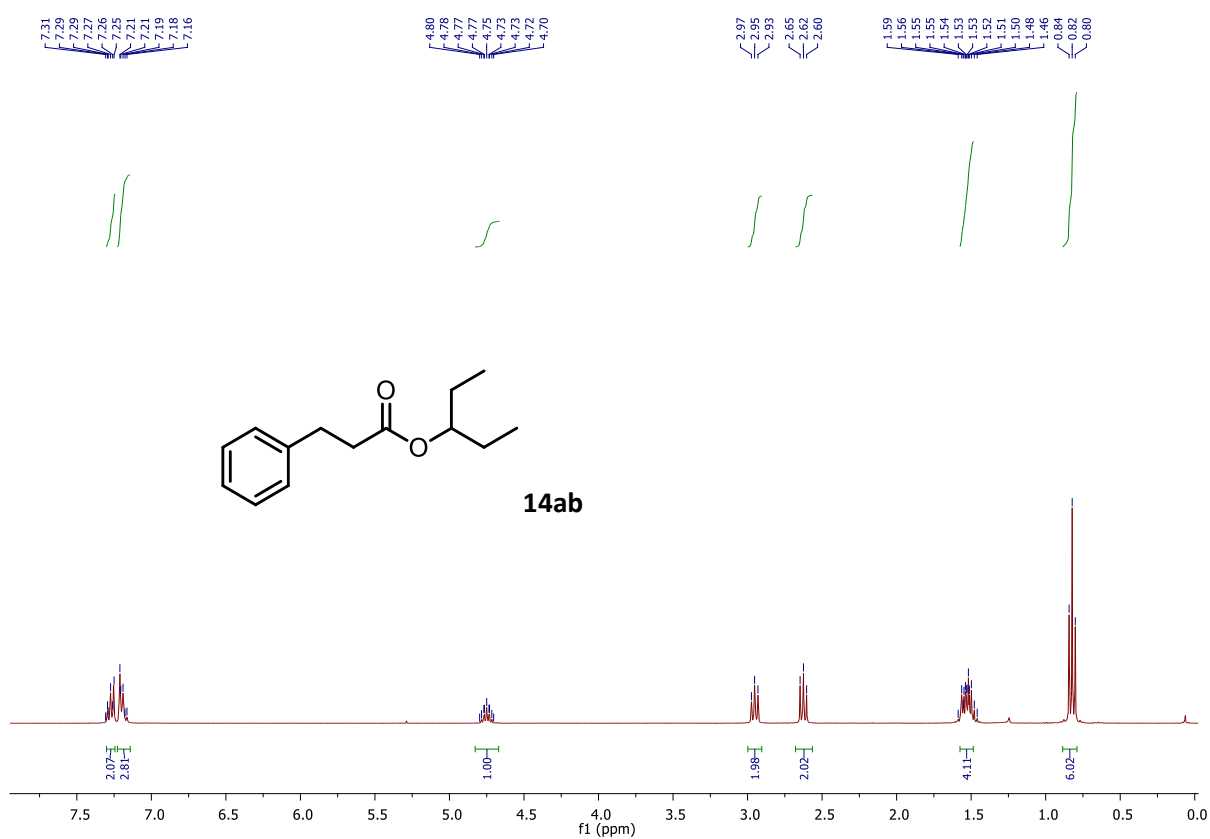


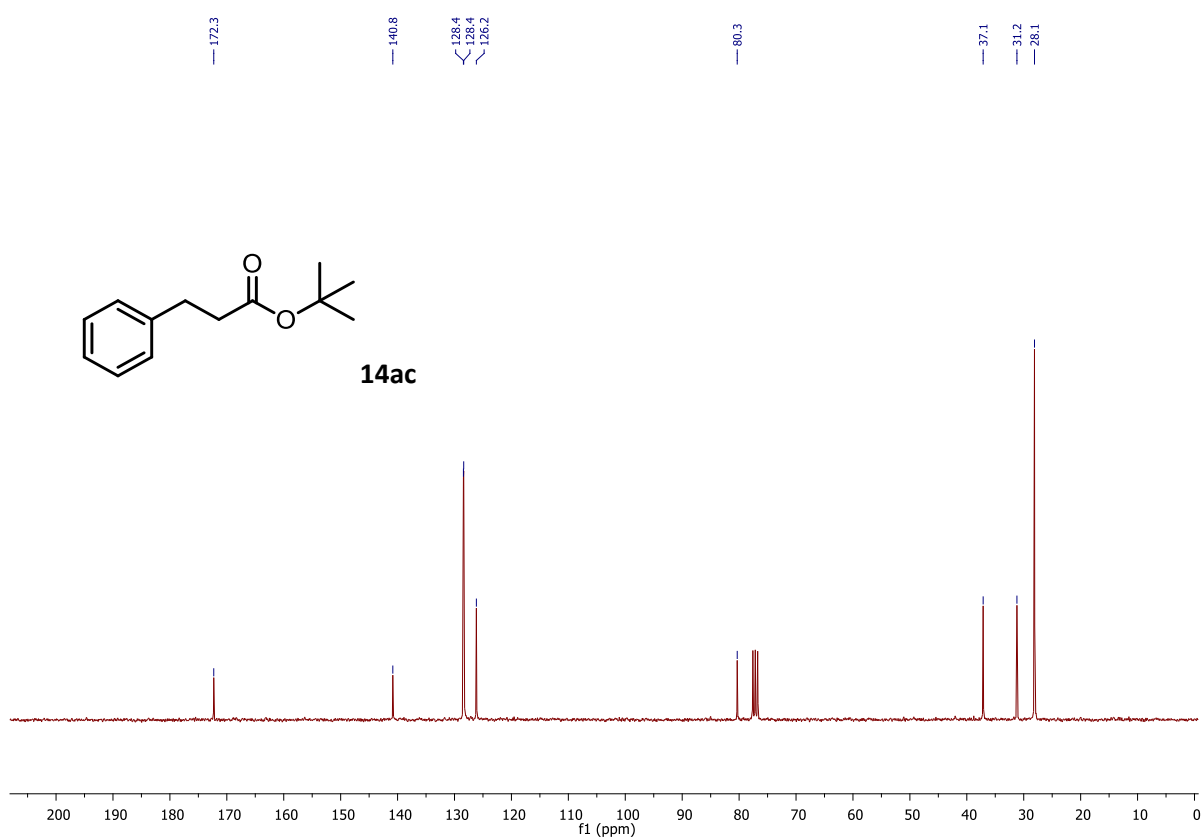
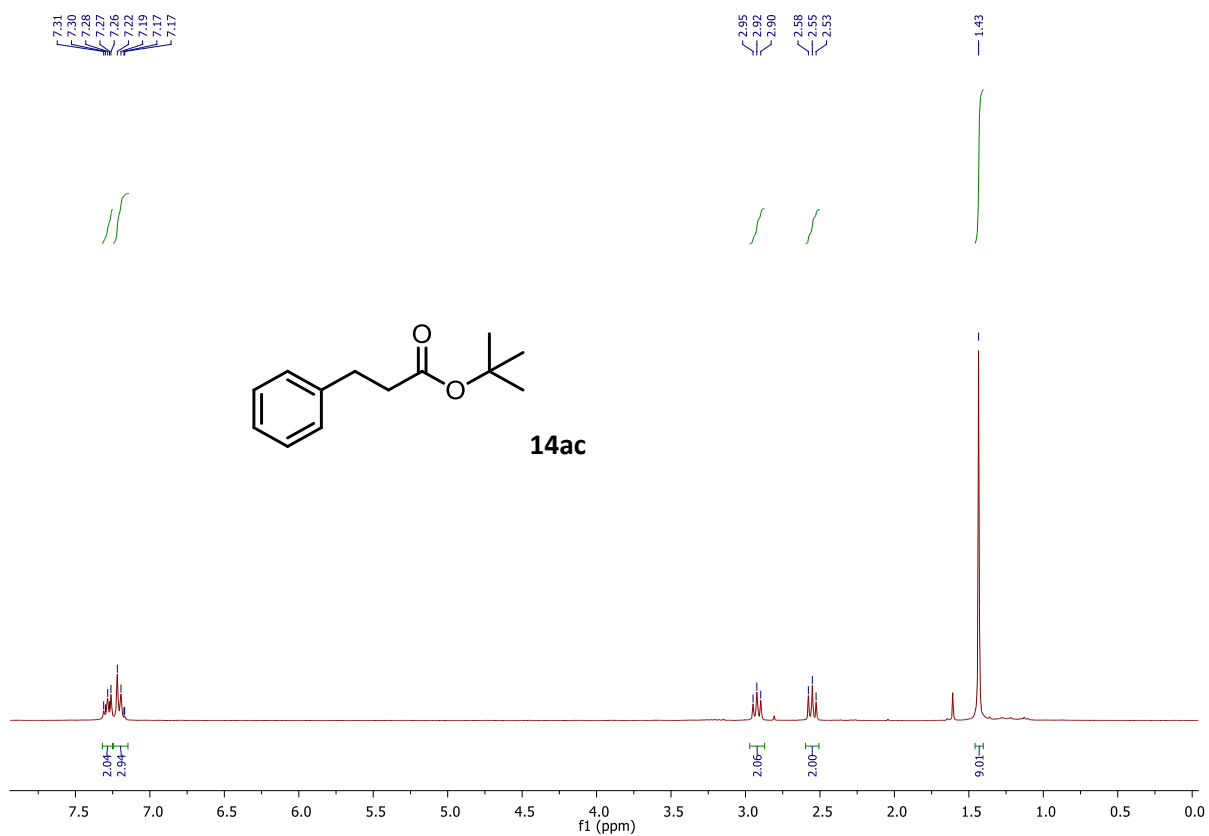


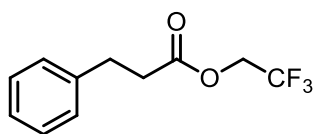
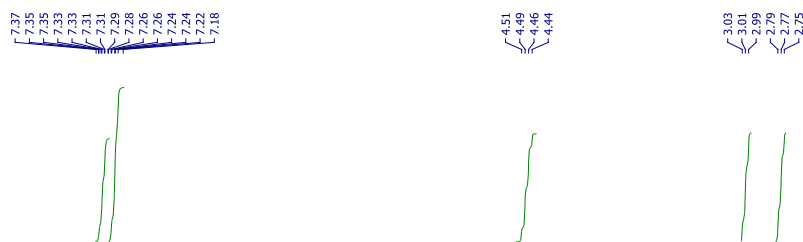




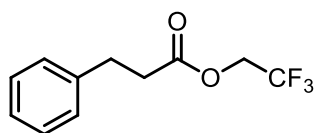
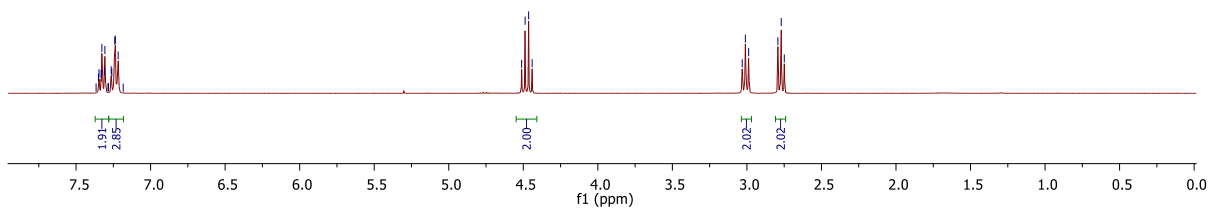




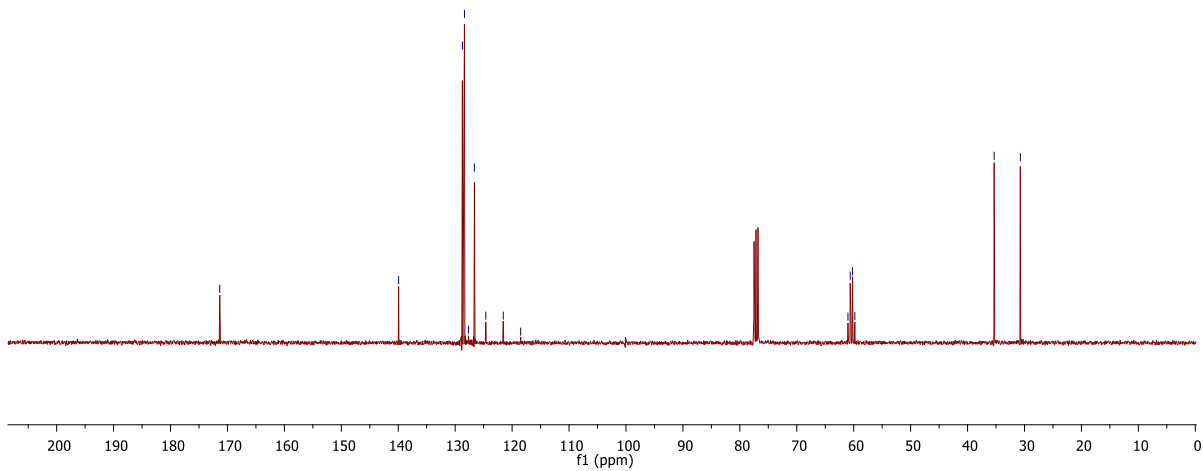




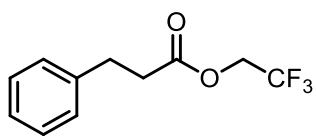
**14ad**



**14ad**

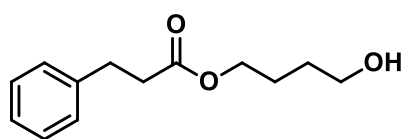
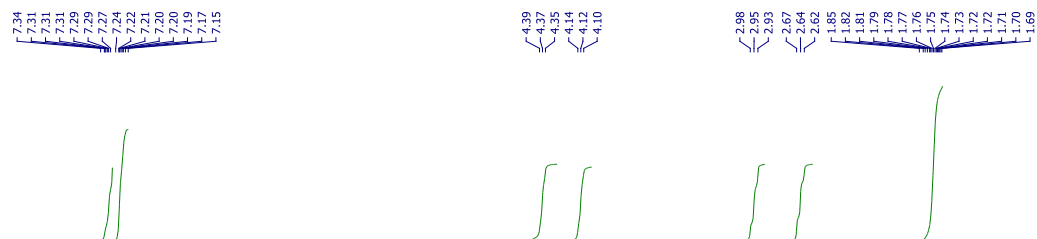
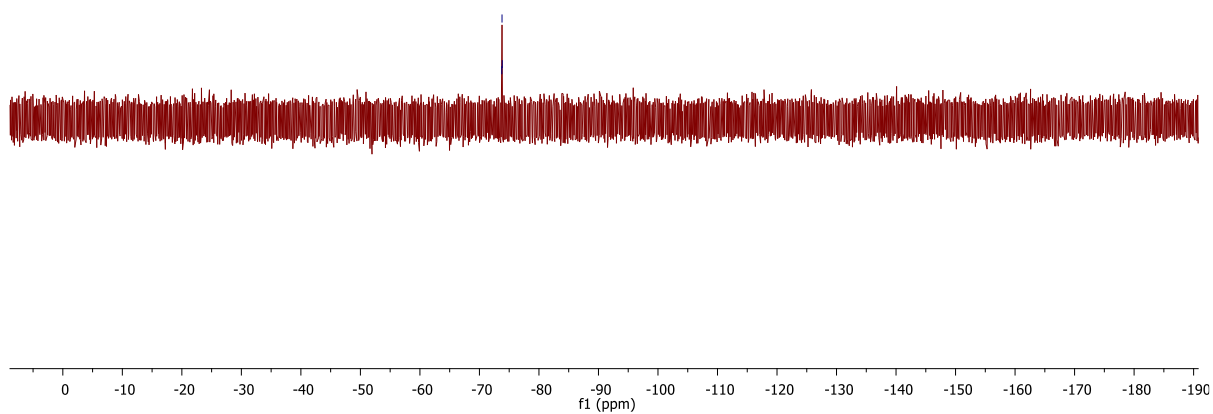




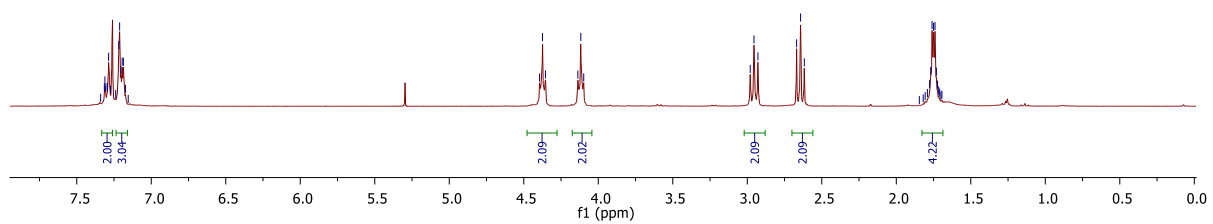


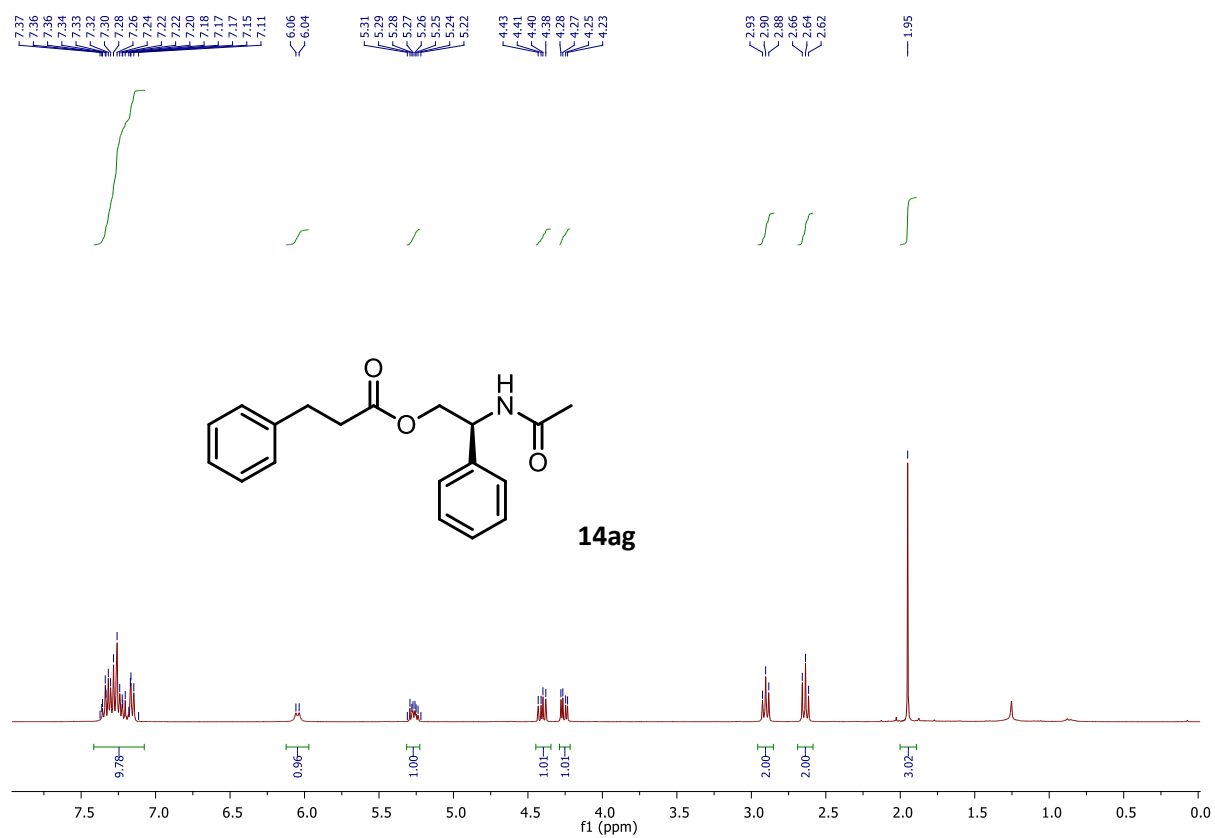
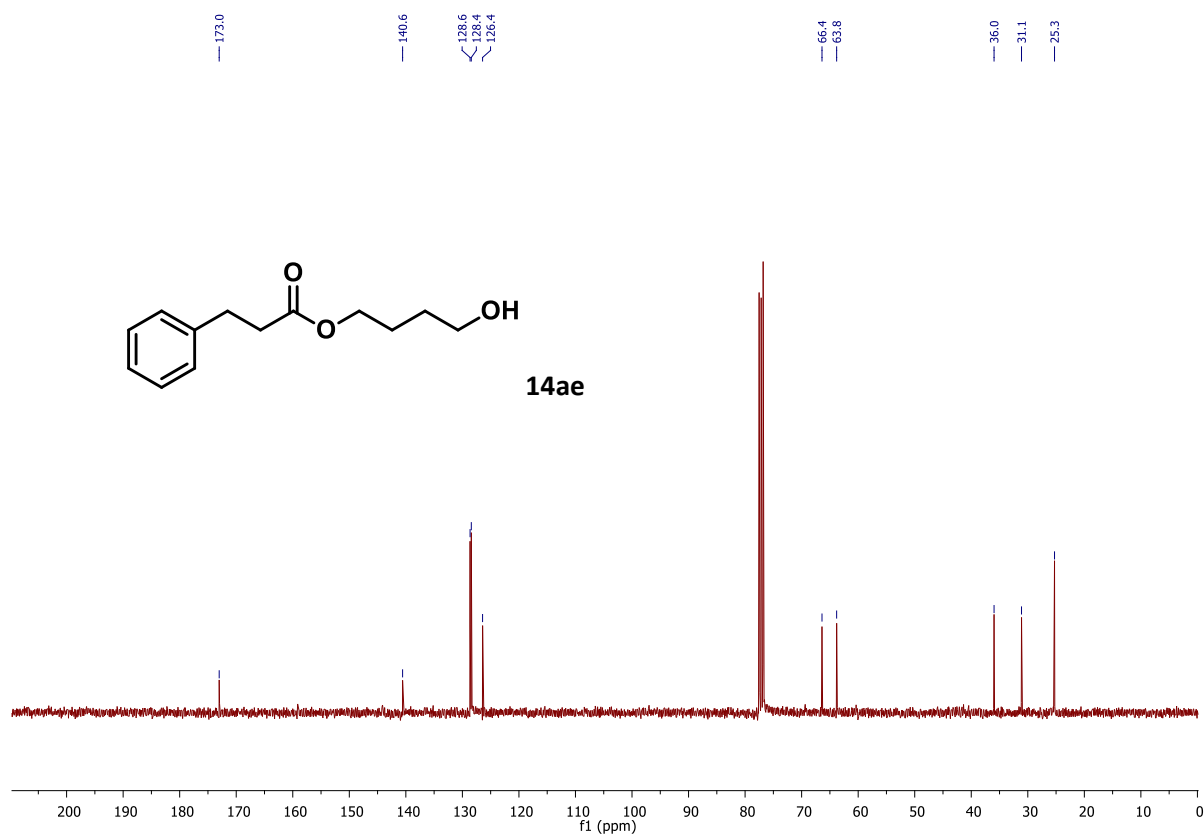
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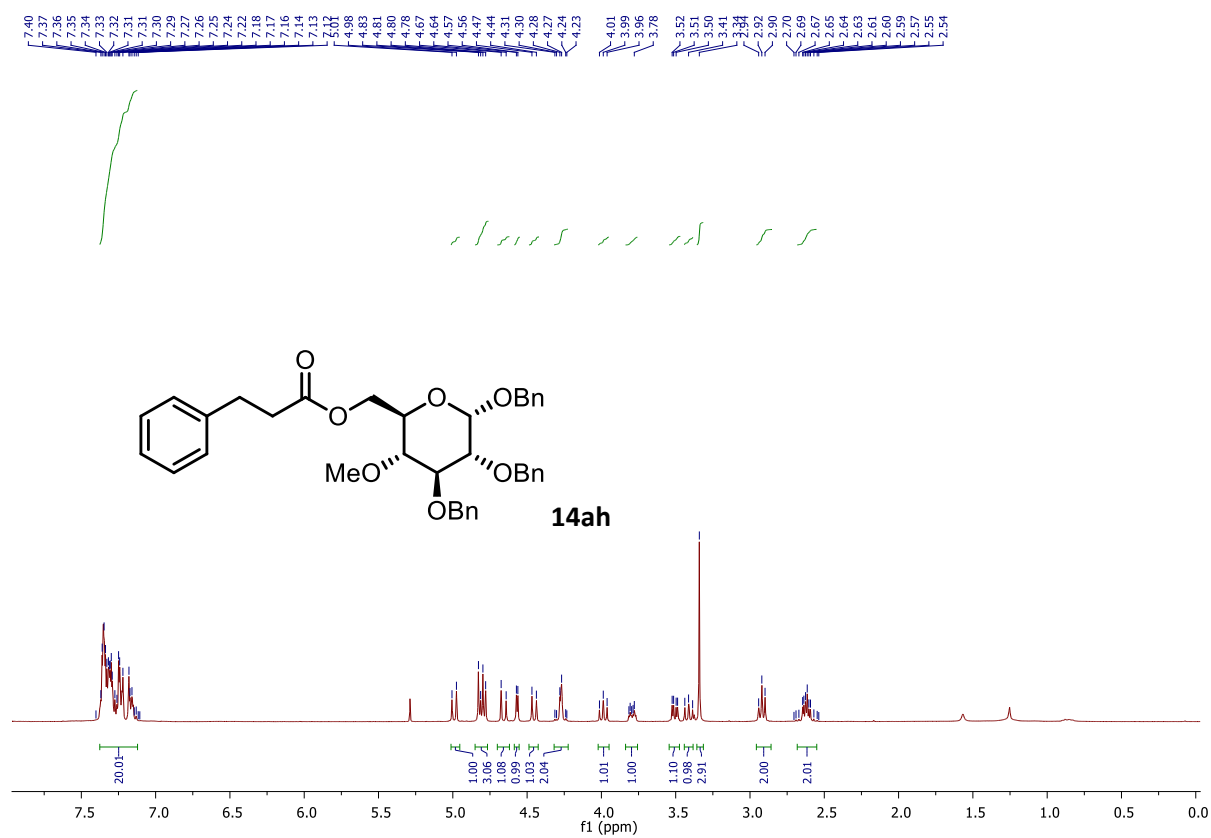
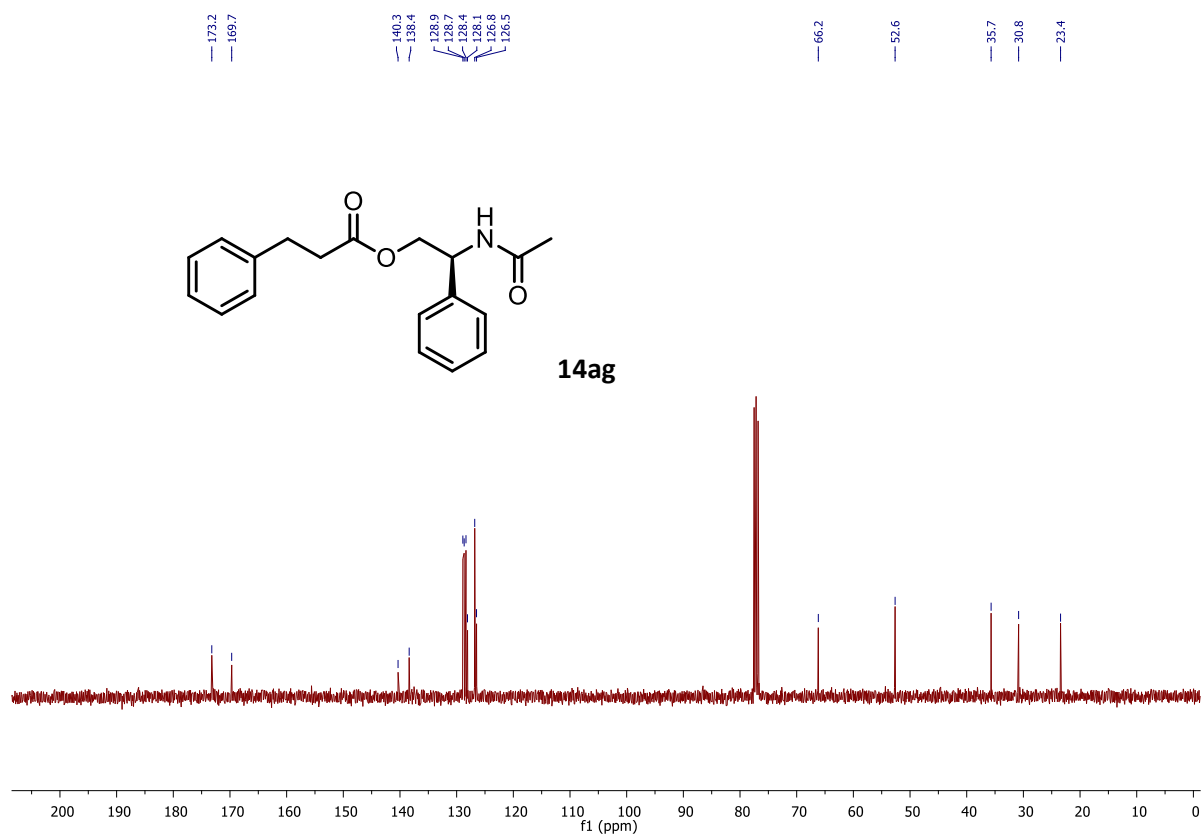
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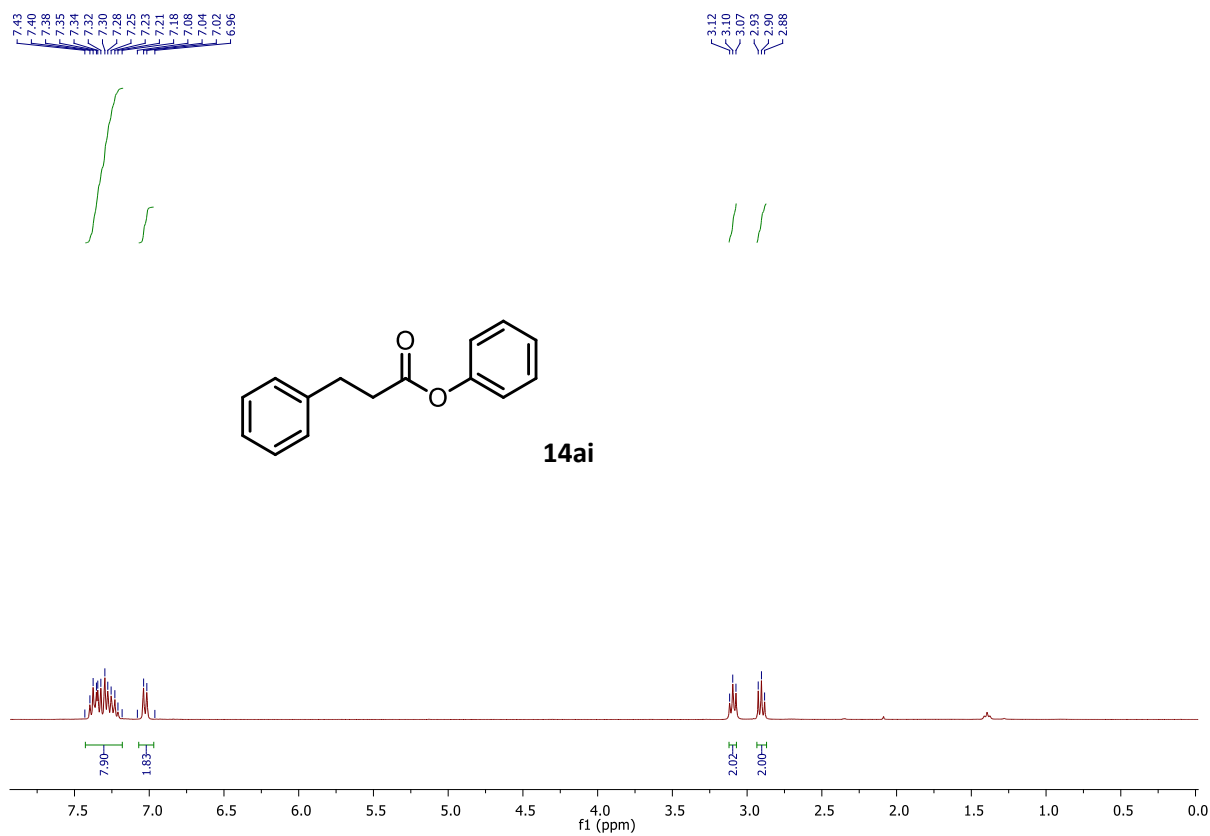
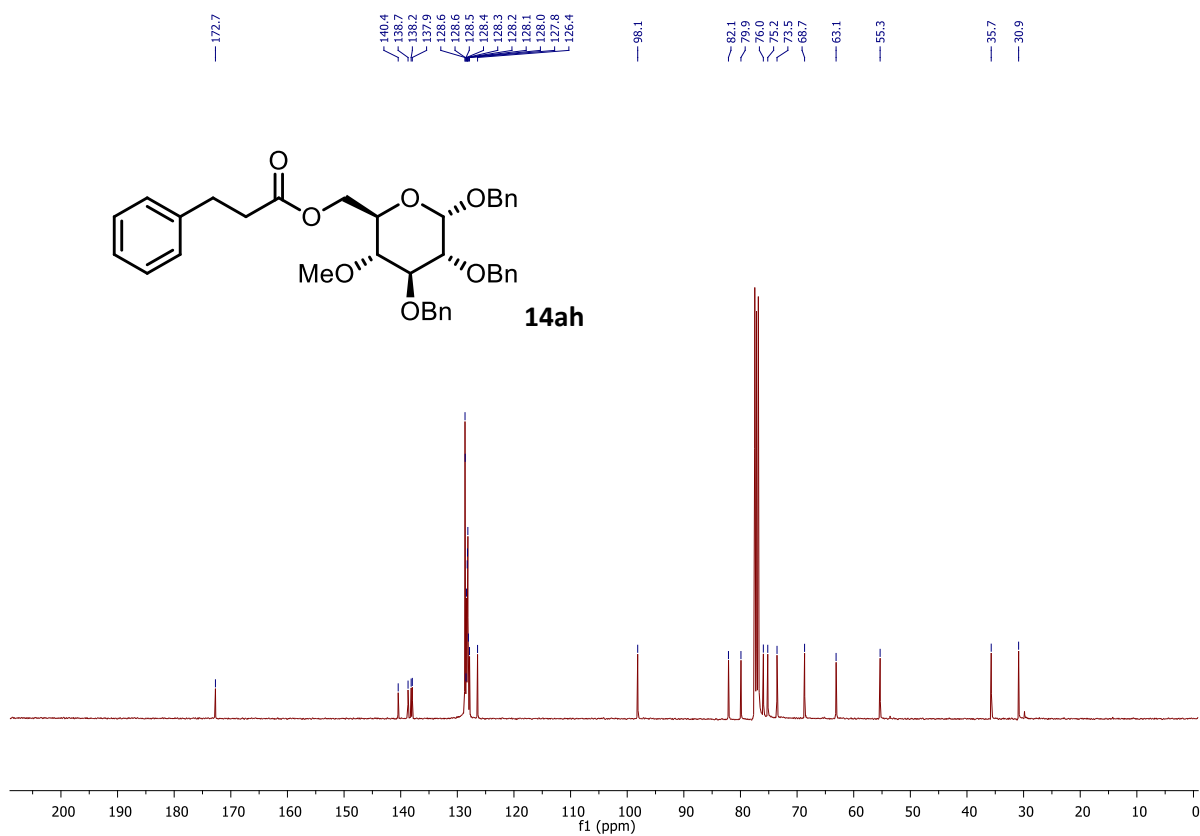


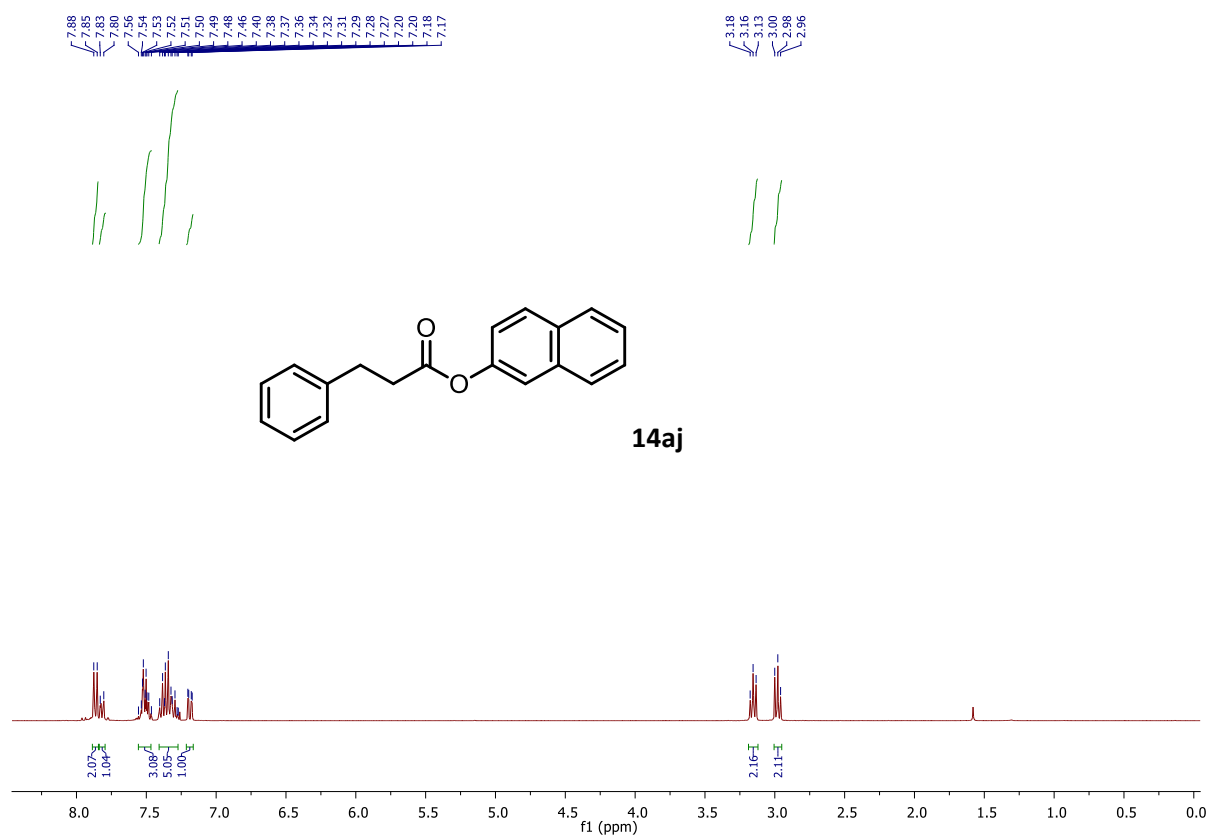
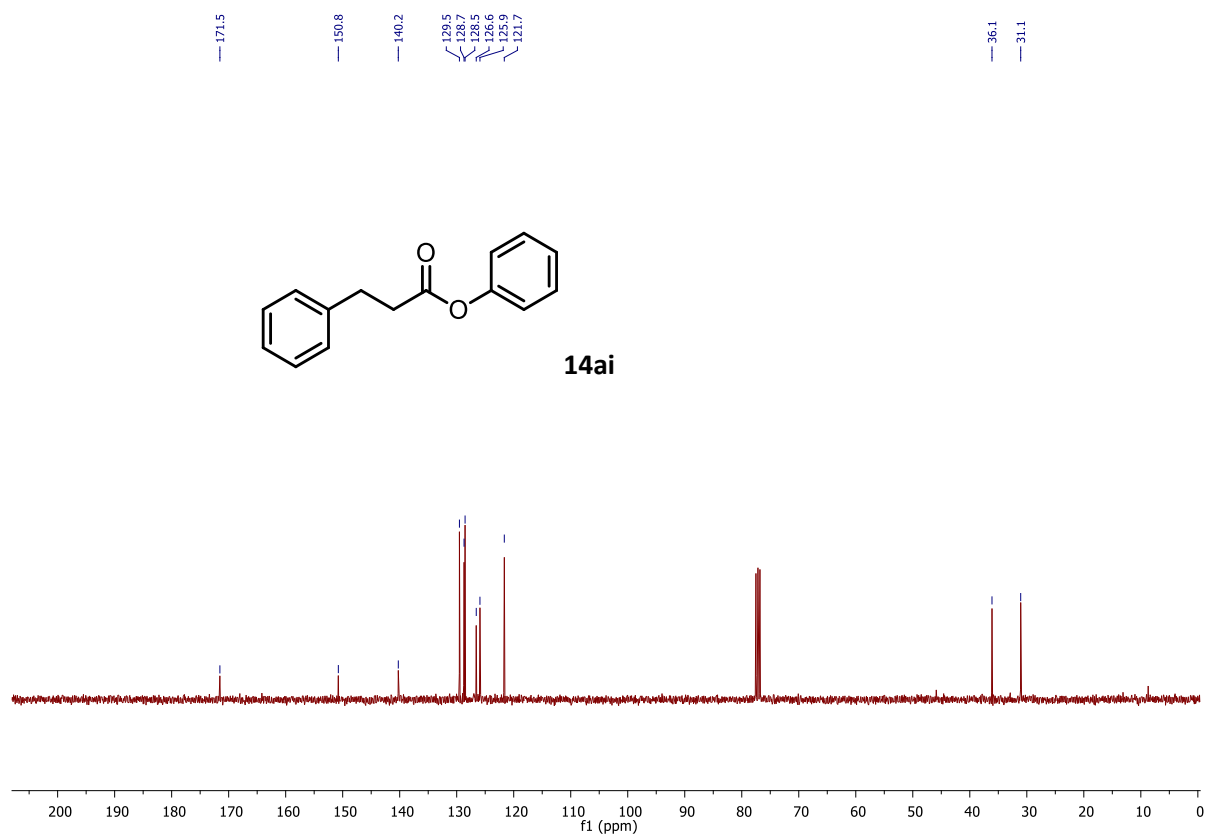
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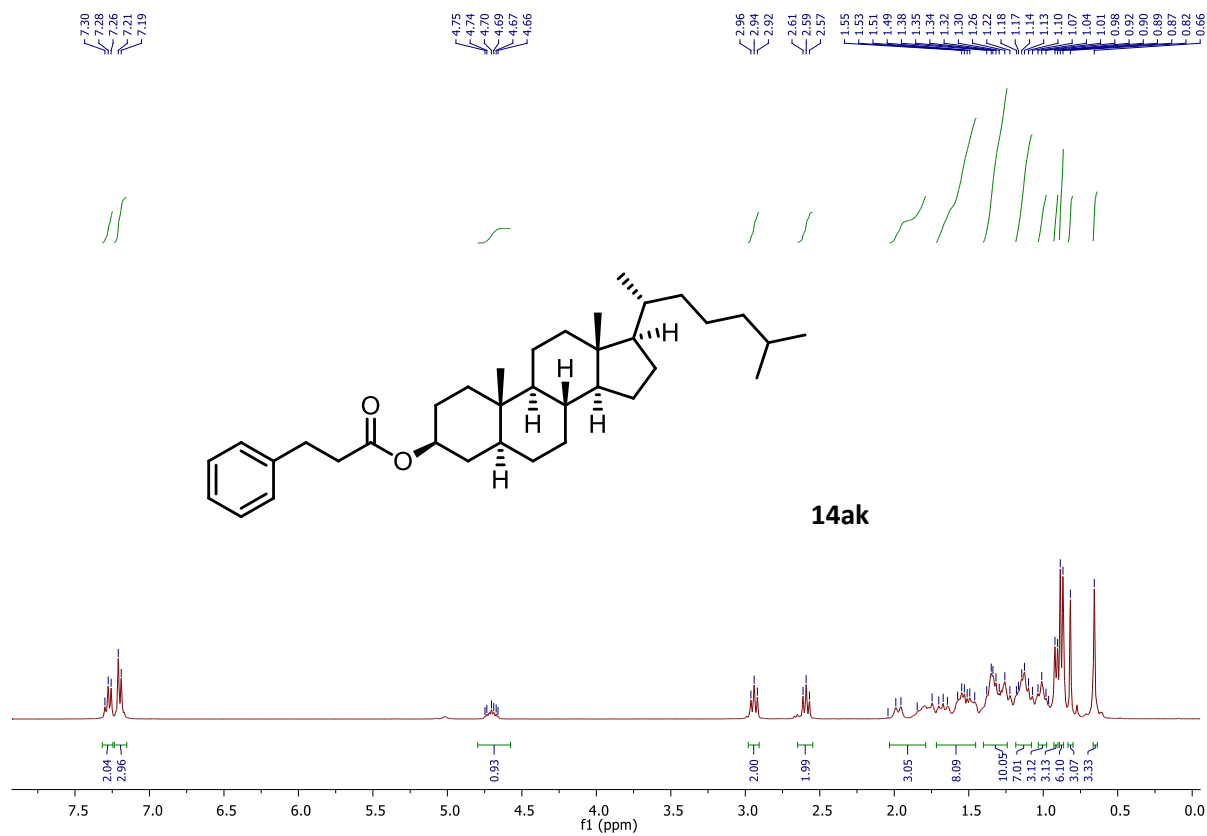
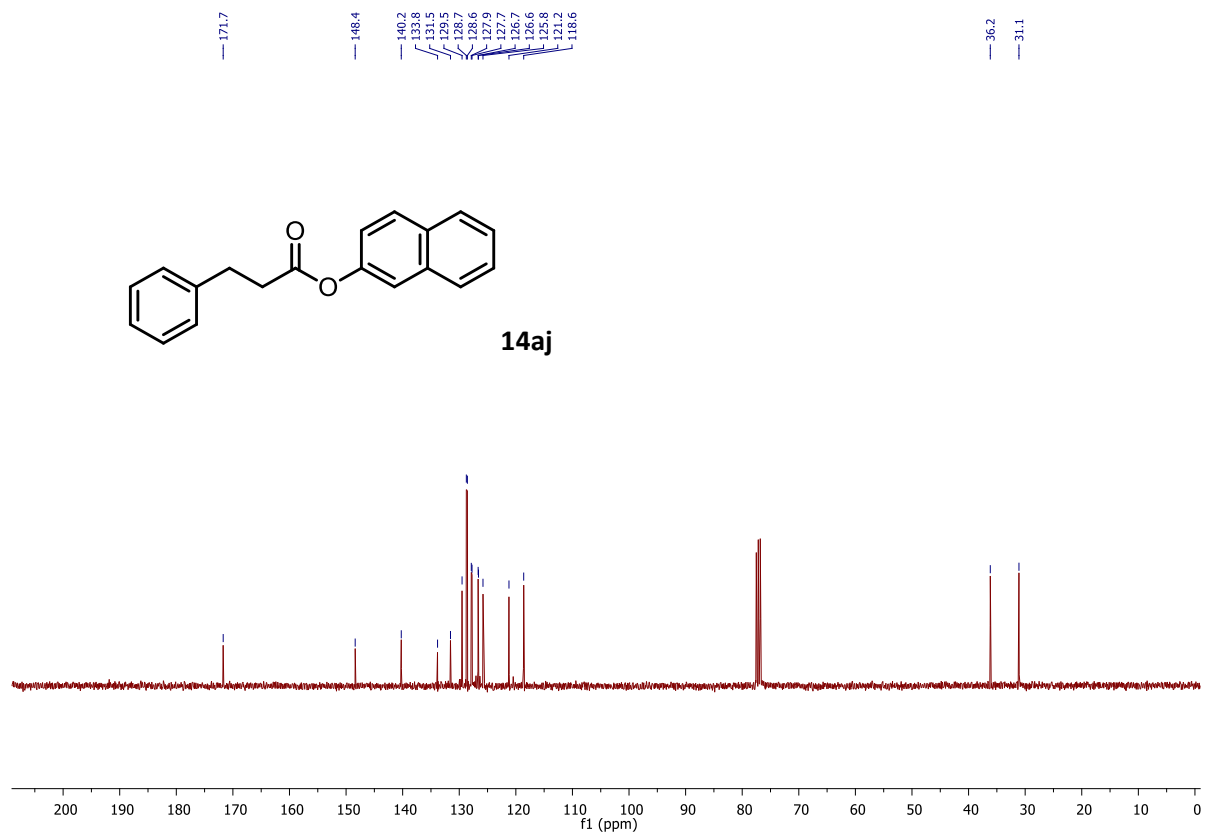


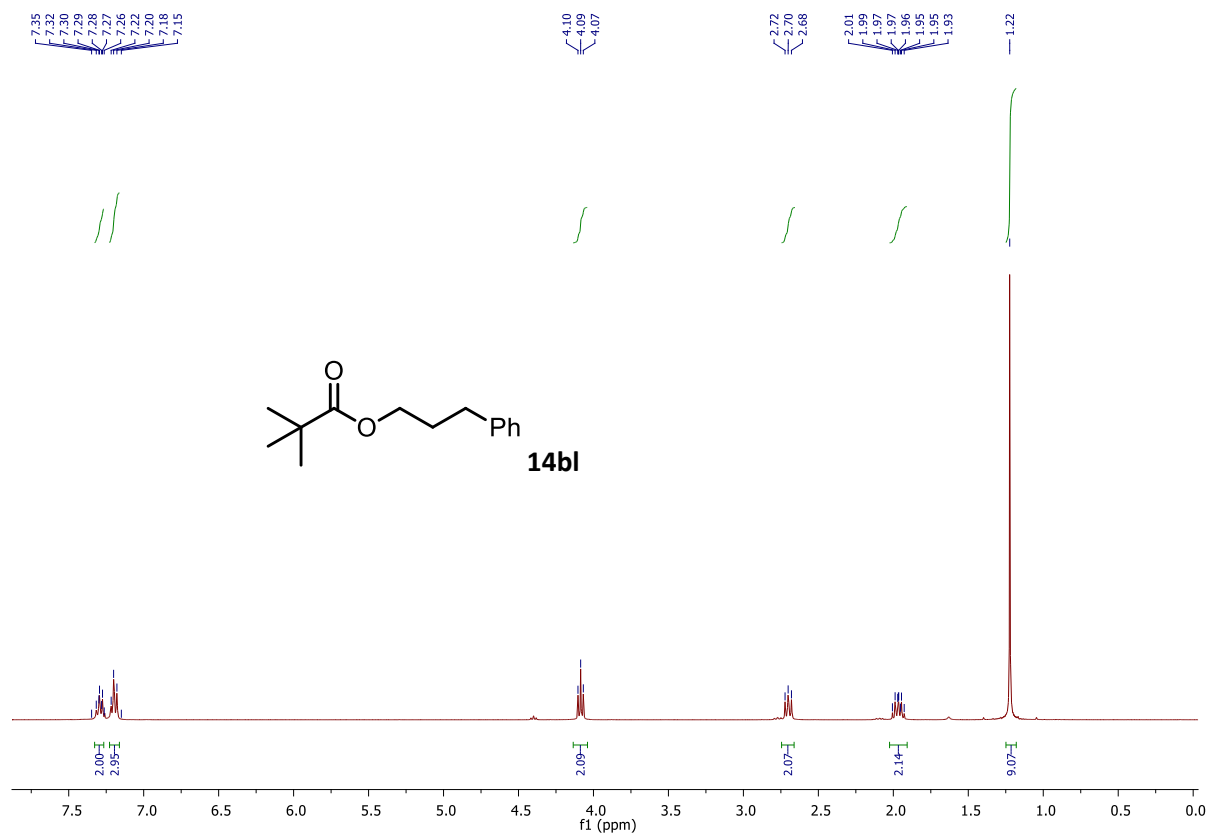
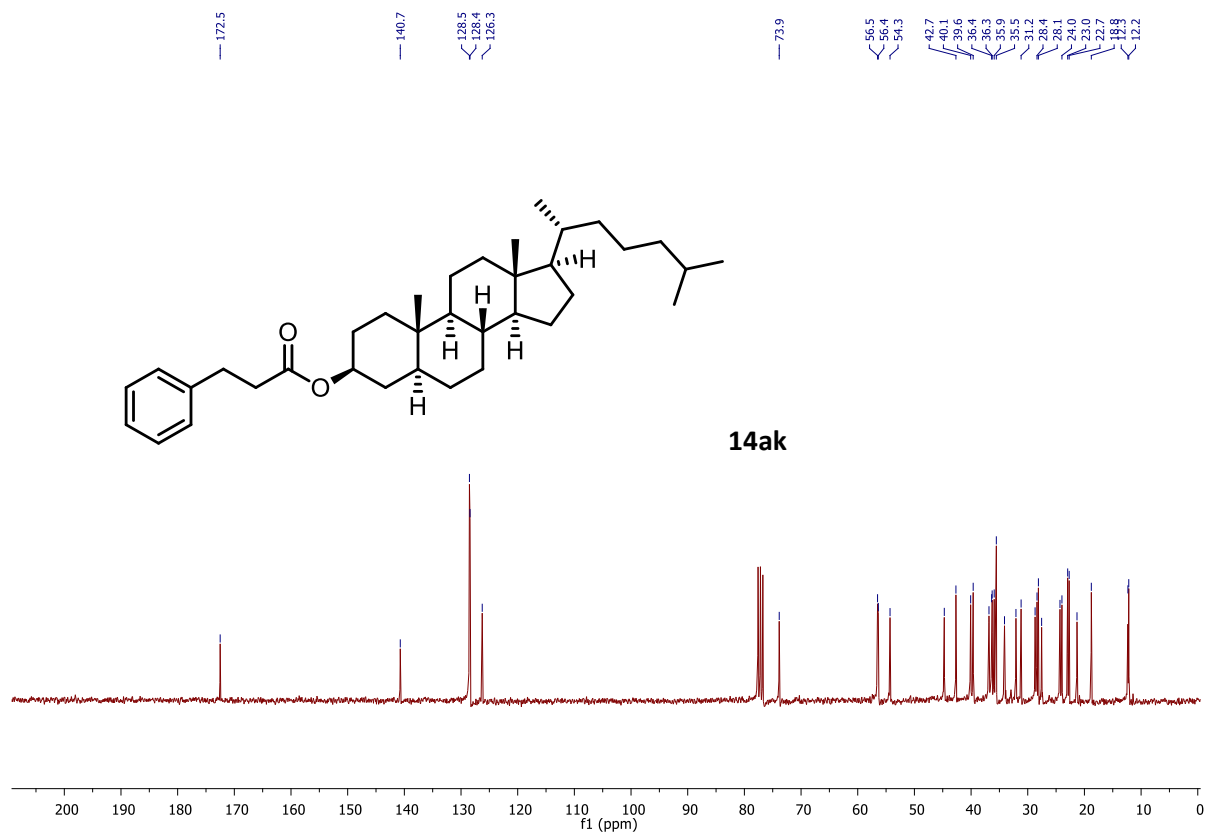


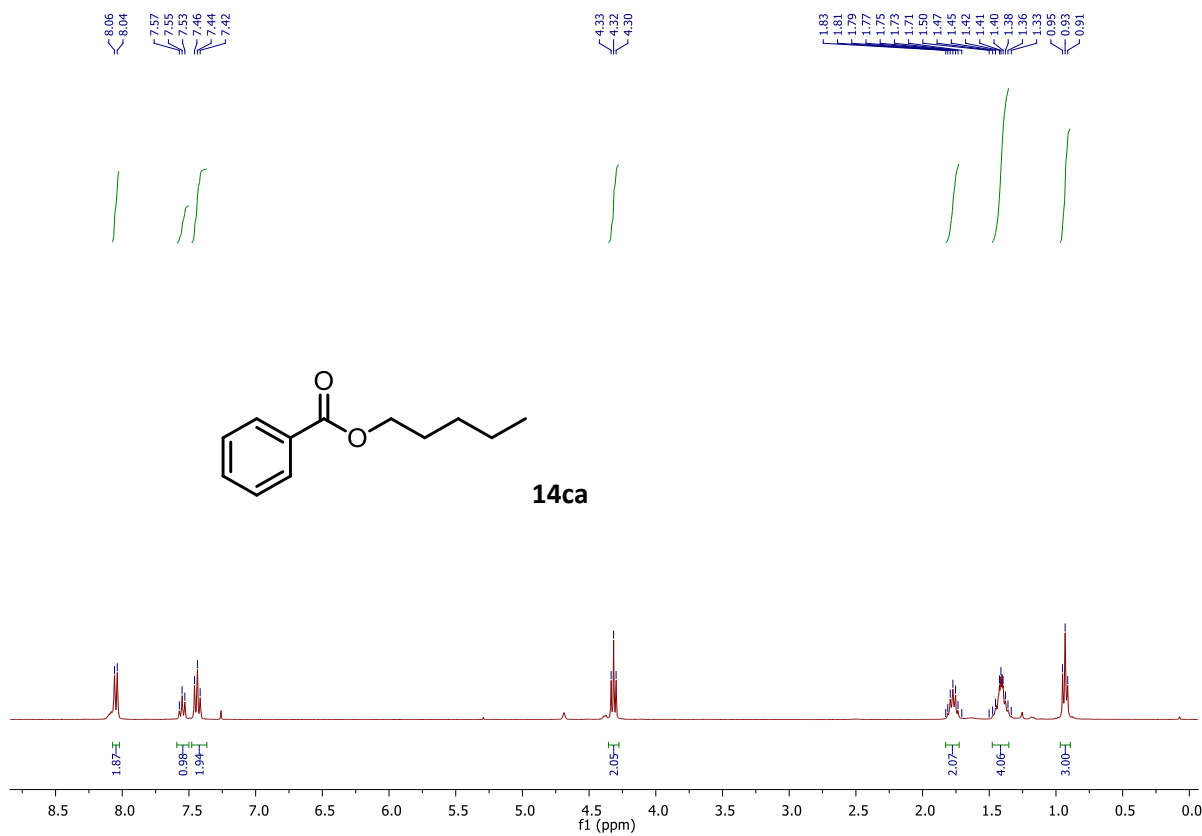
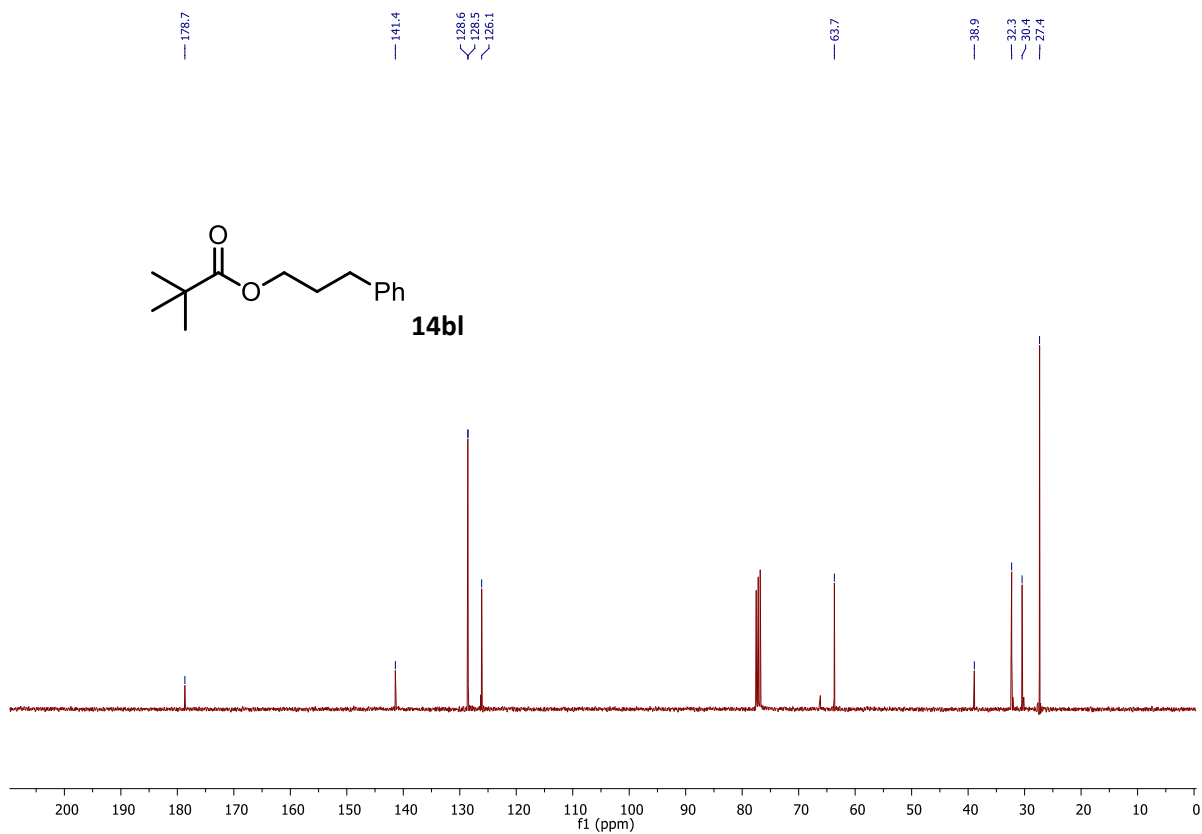




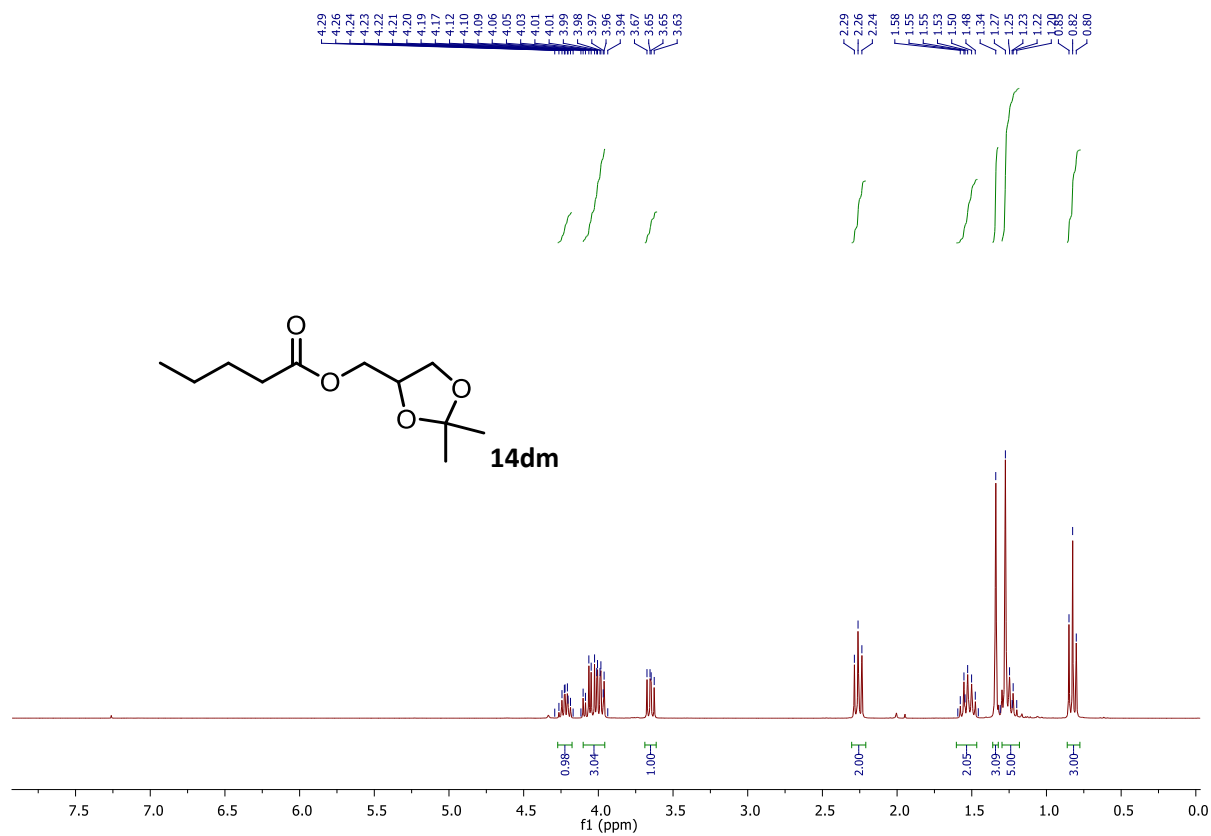
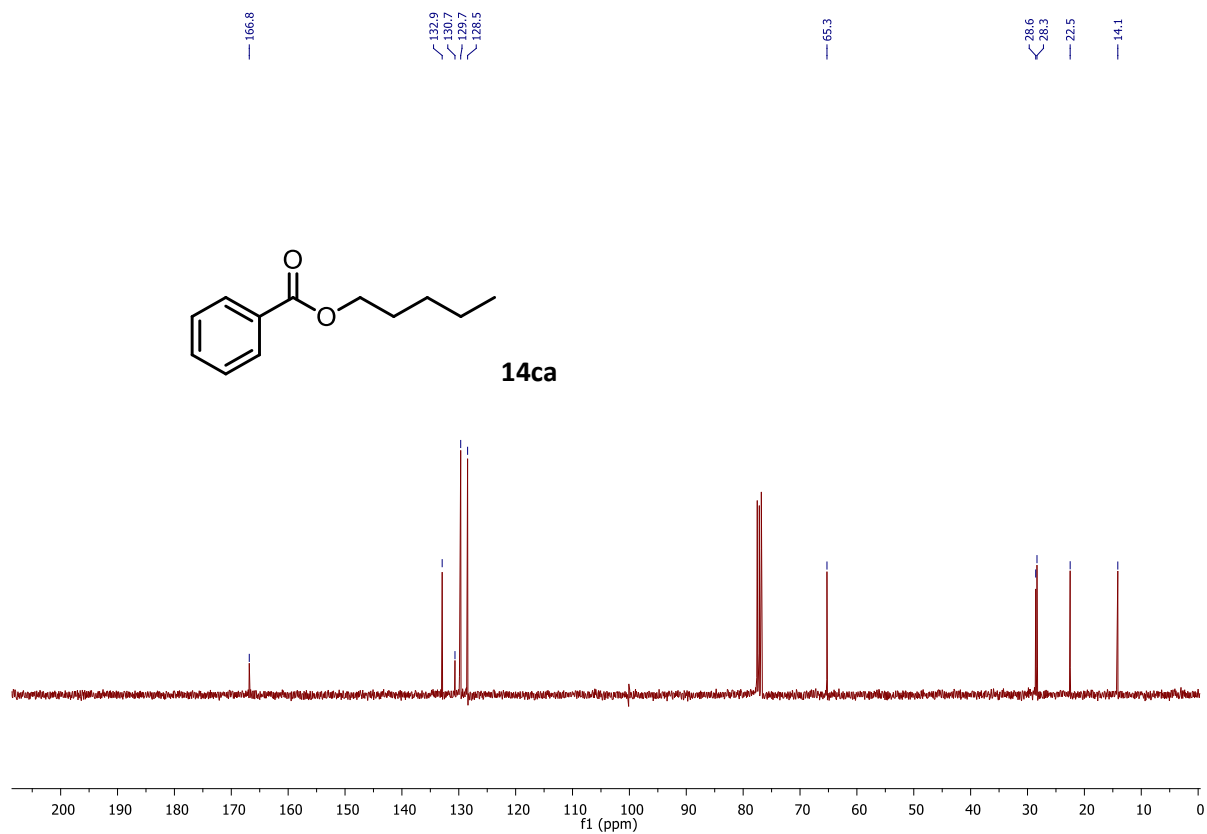


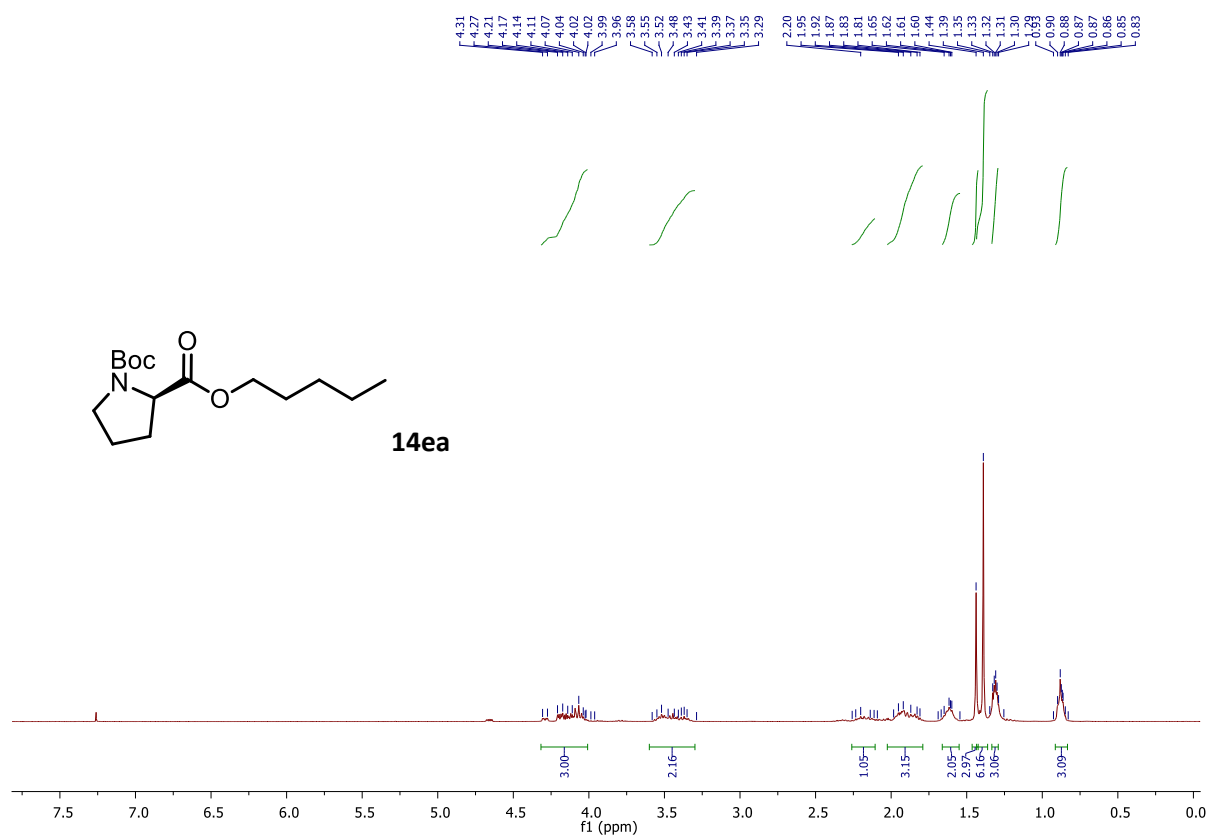
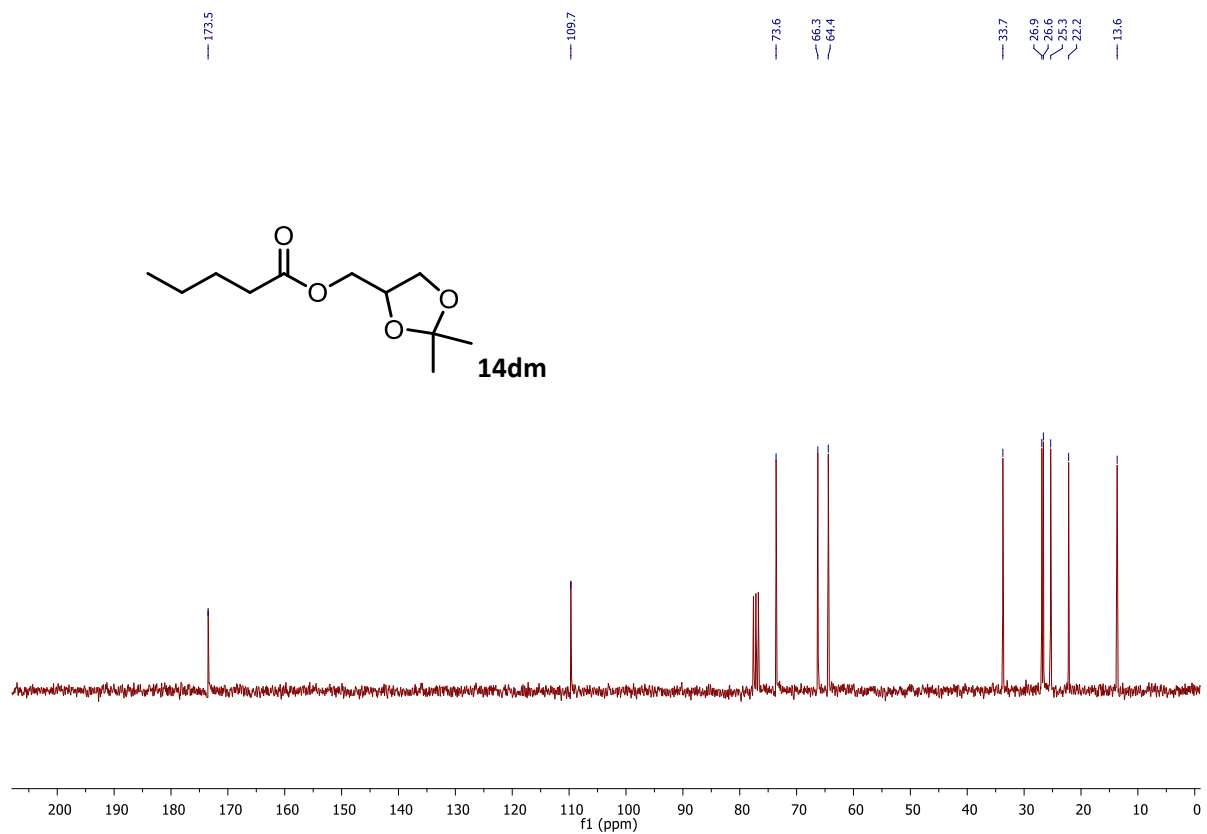


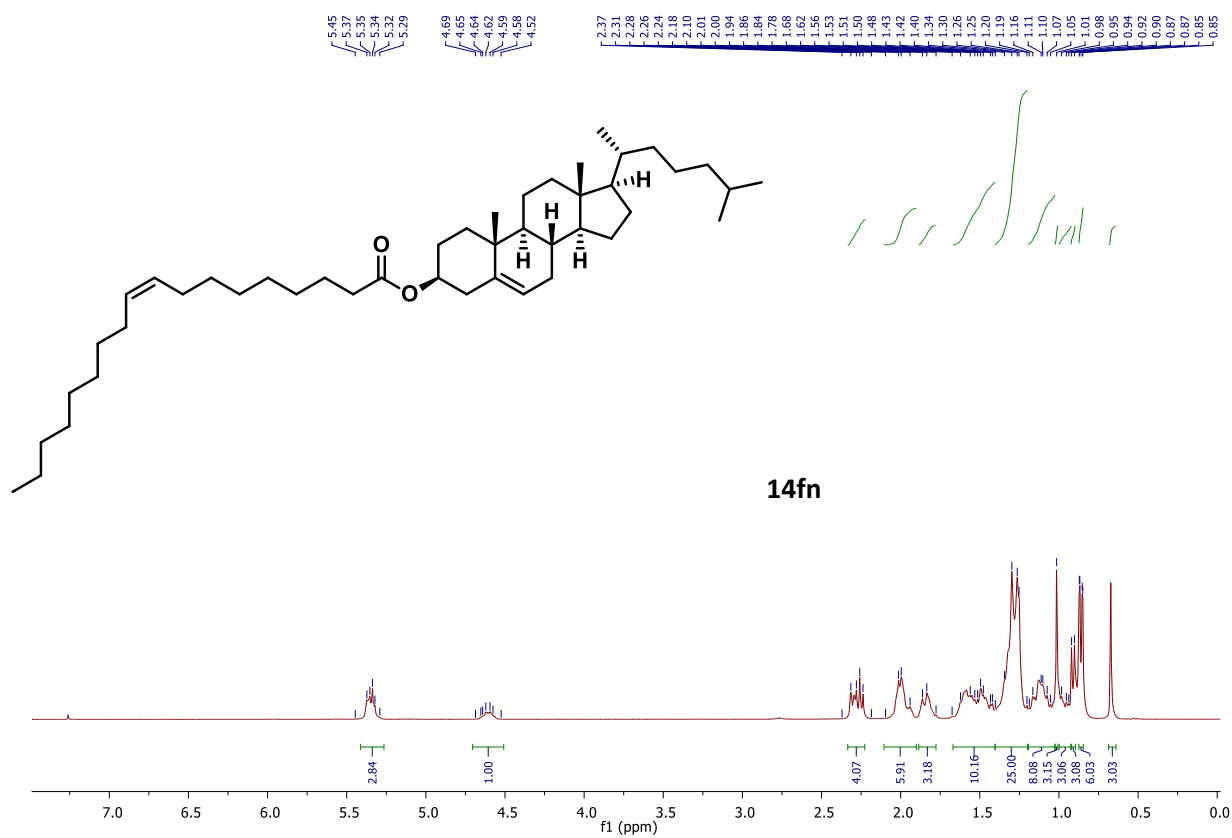
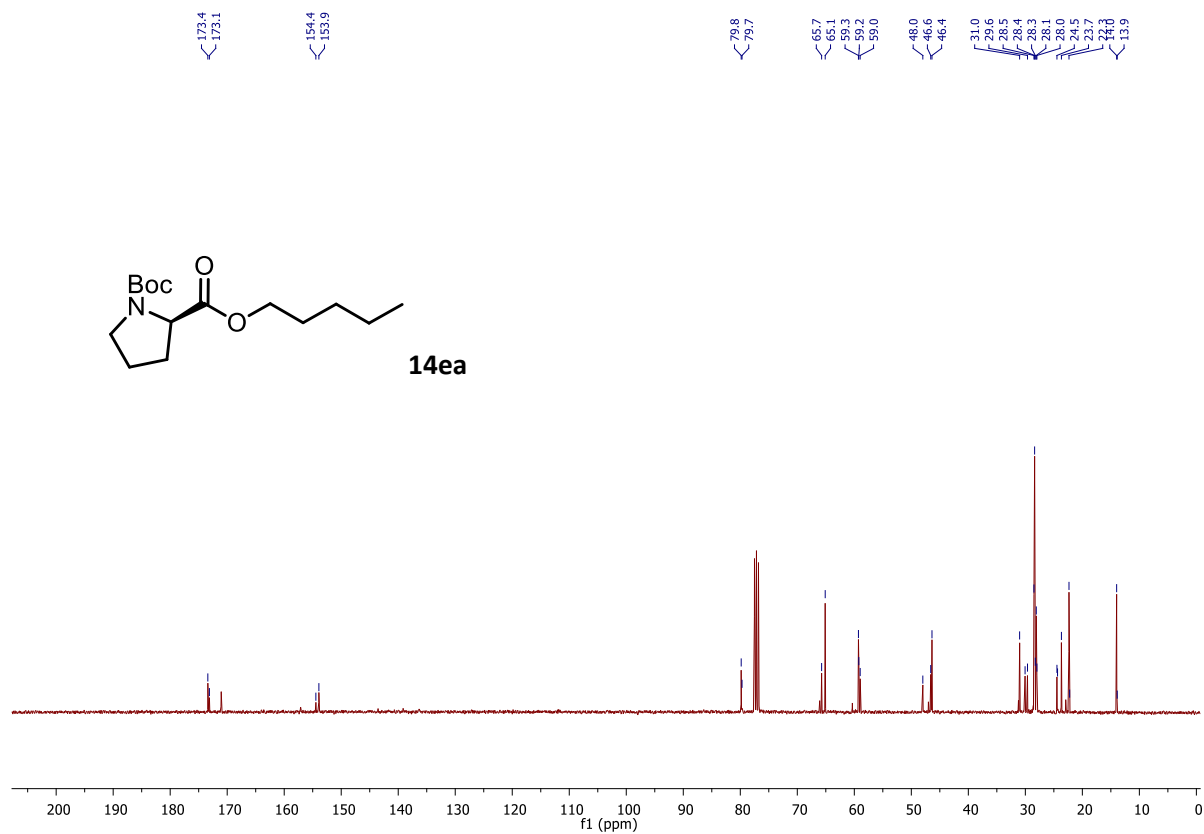


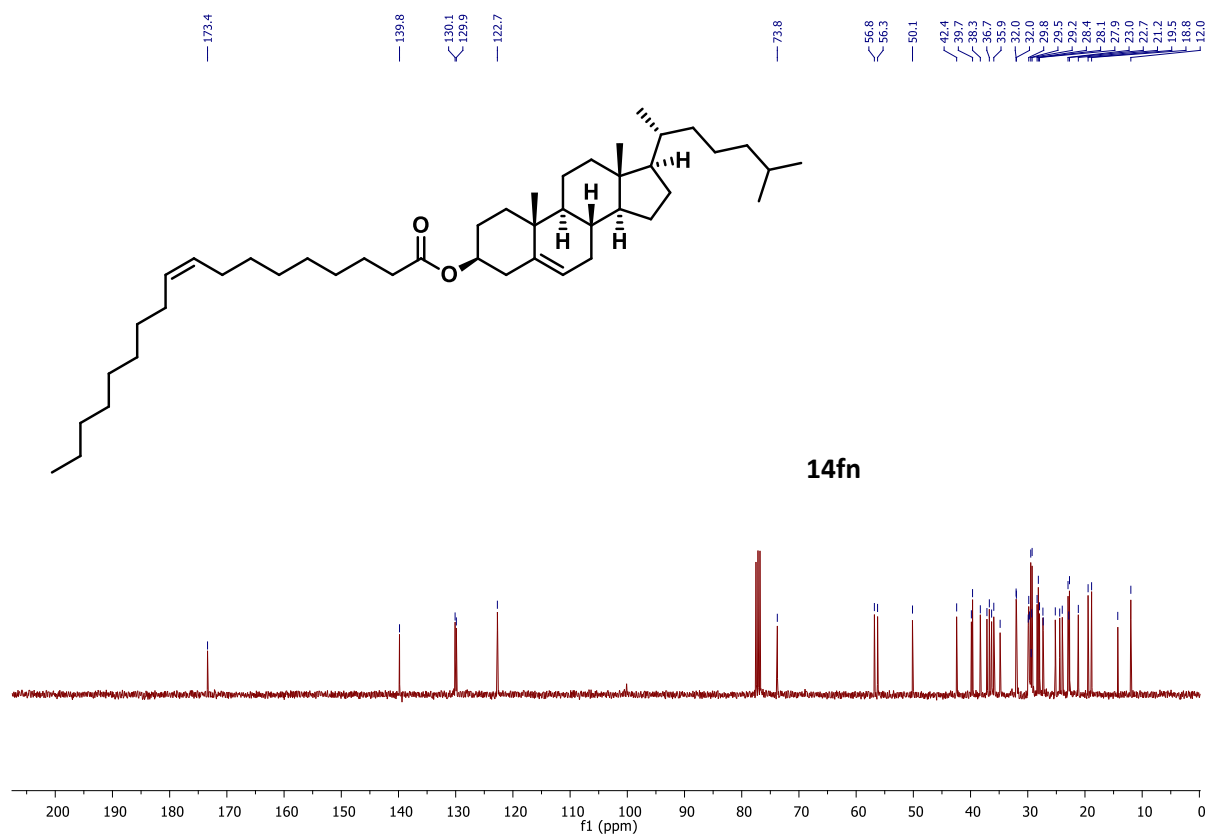












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