Université de Montréal

Direct Catalytic Macrolactonization and Application of the Phase Separation Strategy in Complex Molecule Synthesis

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Résumé

Les macrolactones sont des squelettes structuraux importants dans de nombreuses sphères de l'industrie chimique, en particulier dans les marchés pharmaceutiques et cosmétiques. Toutefois, la stratégie traditionnelle pour la préparation de macrolactones demeure incommode en requérant notamment l'ajout (super)stœchiométrique d'agents activateurs. Conséquemment, des quantités stœchiométriques de sous-produits sont générées; ils sont souvent toxiques, dommageables pour l'environnement et nécessitent des méthodes de purification fastidieuses afin de les éliminer.

La présente thèse décrit le développement d'une macrolactonisation efficace catalysée au hafnium directement à partir de précurseurs portant un acide carboxylique et un alcool primaire, ne générant que de l'eau comme sous-produit et ne nécessitant pas de techniques d'addition lente et/ou azéotropique. Le protocole a également été adapté à la synthèse directe de macrodiolides à partir de mélanges équimolaires de diols et de diacides carboxyliques et à la synthèse de dimères tête-à-queue de seco acides. Des muscs macrocycliques ainsi que des macrolactones pertinentes à la chimie médicinale ont pu être synthétisés avec l'approche développée. Un protocole pour l'estérification directe catalysée au hafnium entre des acides carboxyliques et des alcools primaires a aussi été développé. Différentes méthodes pour la macrolactonisation catalytique directe entre des alcools secondaires et des acides carboxyliques ont été étudiées.

En outre, la stratégie de séparation de phase en macrocyclisation en débit continu a été appliquée lors de la synthèse totale formelle de la macrolactone ivorenolide A. Les étapes-clés

de la synthèse incluent une macrocyclisation par le couplage d'alcynes de Glaser-Hay et une réaction de métathèse d'alcènes *Z*-sélective.

Mots-clés : Macrolactonisation, macrolactones, macrodiolides, esters, catalyse, hafnium, synthèse totale formelle, ivorenolide A, macrocyclisation, séparation de phase, débit continu

Abstract

Macrolactones are important structural motifs in numerous chemical industries particularly in the pharmaceutical and cosmetic markets. However, the traditional strategy for the preparation of macrolactones remains cumbersome, often requiring stoichiometric or excess amounts of activating reagents. Consequently, stoichiometric quantities of by-products are generated. They are often toxic, environmentally damaging, and/or require tedious purification methods to remove them.

The following thesis describes the development of an efficient hafnium-catalyzed direct macrolactonization between carboxylic acid and primary alcohol functionalities, generating only water as a by-product and without the need for slow addition or azeotropic techniques. The protocol was also adapted for the direct synthesis of macrodiolides from equimolar mixtures of diols and dicarboxylic acids and for the selective head-to-tail dimerization of seco-acids. Macrocyclic musks and macrolactones relevant to medicinal chemistry were synthesized using the developed approach. A hafnium-catalyzed esterification protocol between carboxylic acids and primary alcohols was also developed. Different methods for the direct catalytic macrolactonization from secondary alcohols and carboxylic acids were studied.

Furthermore, the phase separation strategy for macrocyclization in continuous flow was applied in the formal total synthesis of the macrolactone ivorenolide A. The key steps of the synthesis include the Glaser-Hay alkyne coupling macrocyclization and a *Z*-selective olefin metathesis reaction.

Keywords: Macrolactonization, macrolactones, macrodiolides, esters, catalysis, hafnium, formal total synthesis, ivorenolide A, macrocyclization, phase separation, continuous flow

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List of Schemes

List of Abbreviations

α	Alpha
β	Beta
Δ	Heat
δ	Chemical shift
ω	Omega
Å	Angström
Ac	Acetyl
atm	Atmosphere (pressure)
bipy	2,2'-Bipyridine
Bn	Benzyl
Boc	*tert*-Butoxycarbonyl
br	Broad
brsm	based on recovered starting materials
Bu	Butyl
C	Celsius
CALB	*Candida antarctica* Lipase B
CBz	Carboxybenzyl
COD	Cycloctadiene
Cp	Cyclopentadienyl
Cy	Cyclohexyl
d	Day
DCC	*N*,*N*'-Dicyclohexylcarbodiimide

DCM	Dichloromethane
DEAD	Diethyl azodicarboxylate
DIAD	Diisopropyl azodicarboxylate
DIPA	*N*, *N* -Diisopropylamine
DIPEA	*N*, *N* –Diisopropylethylamine
DIPP	2,6-Diisopropylphenyl
DMAP	4-Dimethylaminopyridine
DMF	*N*, *N* -Dimethylformamide
DMSO	Dimethylsulfoxide
DPEPhos	(Oxydi-2,1-phenylene)bis(diphenylphosphine)
E	Entgegen (opposite)
EDC	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide
Et	Ethyl
Equiv.	Equivalents
ESI	Electrospray ionization mass spectrometry
g	Gram
h	Hours
HCV	Hepatitis C virus
HOBt	Hydroxybenzotriazole
HPLC	High pressure liquid chromatography
HR-ESIMS	High resolution electrospray ionization mass spectrometry
HRMS	High resolution mass spectrometry
i-Pr	Isopropyl
IUPAC	International Union of Pure and Applied Chemistry

k	Rate
kcal	Kilocalorie
kg	Kilogram
L	Liter
m/z	Mass on charge
m	*meta*
Me	Methyl
Mes	2,4,6-Trimethylphenyl
mg	Milligram
MHz	Megahertz
min	Minutes
mL	Milliter
mM	Millimolar
mmol	Millimole
M_n	Average molecular weight
MNBA	2-Methyl-6-nitrobenzoic anhydride
mol	Mole
MOM	Methoxymethyl
MS	Mass spectrometry
Ms	Methanesulfonyl
MW	Microwave (irradiation)
NMR	Nuclear magnetic resonance
o	*ortho*
OTf	Trifluoromethylsulfonate

OPiv	Pivaloate
p	*para*
PCC	Pyridinium chlorochromate
Ph	Phenyl
Phe	Phenylalanine
phen	1,10-Phenanthroline
PhMe	Toluene
pK_a	Acid dissociation constant at logarithm scale
ppm	Parts per million
*p*TsOH	*para*-Toluenesulfonic acid
rac	Racemic
rt	Room temperature
R&D	Research & Development
s	Second
SAR	Structure activity relationship
TBAF	Tetrabutylammonium fluoride
TBS	*tert*-Butyldimethylsilyl
*t*Bu	*tert*-Butyl
TCDI	1,1'-Thiocarbodiimidazole
TFA	Trifluroacetic acid
THF	Tetrahydrofuran
TIPS	Triisopropylsilyl
TMEDA	Tetramethylethylenediamine
TMS	Trimethylsilyl

Ts	Toluenesulfonyl
Z	Zusammen (together)
°	Degree
%	Percent

Acknowledgments

I would first like to start by thanking my supervisor Shawn. Labmates come and go during Ph. D. studies, but Shawn, you were the steady and safe lighthouse in the rough sea of graduate studies. “Never talk yourself out of an experiment” and “don’t trust anyone or anything other than your TLC and your NMR spectrum” are phrases which are now engraved in my mind as an organic synthetic chemist. I thank you for having kept your youthful heart, making the days in the lab a little easier. Your passion for chemistry is contagious and your mentoring skills are off the roof!

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1. Introduction

A macrocycle is defined by the IUPAC as being a cyclic molecule containing twelve or more atoms in its ring skeleton,[1] although it is common in the literature that cycles containing a ring of eight or more members are considered macrocycles. Generally, it is thought that macrocycles have floppy conformations, easily interchangeable at low temperatures. However, in practice, only a few conformations are stable enough to have an appreciable population at ambient temperature.[2] As an example, only two conformers of cyclohexadecane, the simplest sixteen-membered ring cycloalkane, contribute to more than a quarter of all populations at room temperature (Figure 1.1). In comparison, all other possible conformers have an individual contribution lower than 4 %.[3]

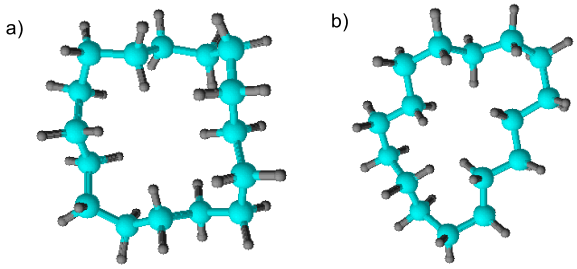


Figure 1.1. The two most populated conformers of cyclohexadecane calculated by molecular dynamic studies: a) conformer (4,4,4,4) and b) conformer (3,4,4,5).

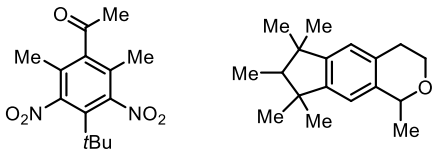
The following sections (1.1 and 1.2) will provide a brief background into two of the most common applications of macrocycles in aroma chemistry and medicinal chemistry.

1.1. Macrocycles in Aroma Chemistry

Aroma chemistry is defined by the synthesis and the application of aroma compounds in various fields of the industry. Aroma compounds are chemicals which possess an odor, pleasant

or unpleasant, and are also known as fragrances or flavors, the latter also affecting the sense of taste.[4] Aroma chemicals are by definition volatile and therefore usually have a relatively low molecular weight. They can be found in Nature and have an enjoyable presence in food and spices. Macrocyclic musks are an important class of molecules comprised within the category of aroma compounds.

Musks are a type of aroma chemical which are divided into three categories based on their structure: nitro-musks, polycyclic musks and macrocyclic musks. Musks have a sweet and fruity smell and have been synthesized for over a hundred years for their olfactory properties. However, nitro-musks, such as musk ketone **1.1**, were found to be explosive and carcinogenic (Figure 1.2).[5] Some countries, like Japan, have banned their usage, while others have restricted it. For example, since 1979, the USA does not allow the use of nitro-musks in cosmetics that may potentially be ingested and, since 1993, Germany has removed them from all detergents.[6] Polycyclic musks, such as Galaxolide (**1.2)**, were synthesized as an alternative to nitro-musks, but have weaker olfactory properties and there have been concerns about their bioaccumulation.[7] Despite other concerns regarding their toxicity and biodegradability, polycyclic musks are still widely used in the aroma chemical industry.[7]



1.1 **1.2**

Figure 1.2. Musk ketone **1.1**, a member of the nitro-musks and Galaxolide (**1.2)**, a member of the polycyclic musks.

Macrocyclic musks are naturally occurring compounds, but they were not commercially produced before the late 1990's due to challenges associated with their synthesis.[8] They can be divided into two categories: macrocyclic ketones, naturally found in animals, and macrocyclic

lactones, naturally found in plants. As examples, Muscone (**1.3**) is isolated from the testicular glands of the musk deer and Exaltolide® (**1.4**) is found in blackberries (Figure 1.3).[5] Macrocyclic musks have not shown any appreciable bioaccumulation or toxicity and are biodegradable, all while maintaining olfactory properties that are more powerful than those of nitro- or polycyclic musks.[8]

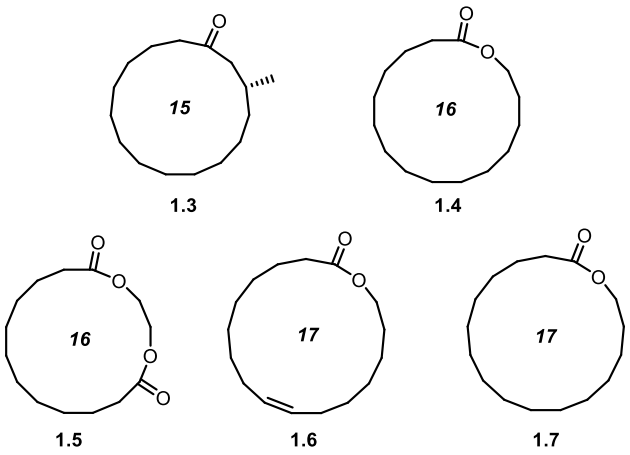


Figure 1.3. Commercial macrocyclic musks: Muscone (**1.3**), Exaltolide® (**1.4**), Zenolide (**1.5**), isoambrettolide (**1.6**) and dihydroambrettolide (**1.7**).

Today macrocyclic musks are commonly found in many perfumes, detergents, shampoos, shower gels and soaps.[9] Their worldwide production is considerable; in 2008, Exaltolide **1.4** was produced at an annual amount of up to 1000 metric tons and the same quantity was applicable to Zenolide (**1.5**). Other notable manufactured macrocyclic musks are isoambrettolide (**1.6**) and dihydroambrettolide (**1.7**), each being produced at an annual amount of up to 100 metric tons (Figure 1.3).[10]

1.2. Macrocycles in Medicinal Chemistry

In medicinal chemistry, most orally active drug-candidates are designed to obey Lipinski's rules:[11] compounds should have 1) no more than 5 hydrogen-bond donors; 2) no more than 10

hydrogen-bond acceptors; 3) a molecular mass inferior to 500 Daltons and 4) a partition coefficient[12] comprised between -0.4 and +5.6. In contrast, biologically active macrocycles often possess large molecular weights and can be disregarded as promising drug candidates for failing Lipinski's rules. Although other guidelines[13] for producing drug candidate compounds suggest that molecules having ten or less rotatable bonds and a polar surface area equal or less to 140 Å would better predict the oral activity of a drug candidate. Even though macrocycles would fulfill the latter criteria, they are still scarcely explored in drug design.

Macrocyclic structures can often have a rigid conformation that would facilitate binding onto the target and would satisfy the "ten or less rotatable bonds" requirement. As such, macrocycles can be considered to have an advantage over most linear molecules in medicinal chemistry. However, the synthetic challenges associated with macrocyclization often make linear compounds the most preferred option when designing a compound with biological properties. Notably, two of the most well-known antibiotics in the world, Erythromycin **1.8** and Vancomycin **1.9** (Figure 1.4), are macrocycles which rely on a bacterial synthesis for production as a chemical synthesis is considered too costly.[14,15]

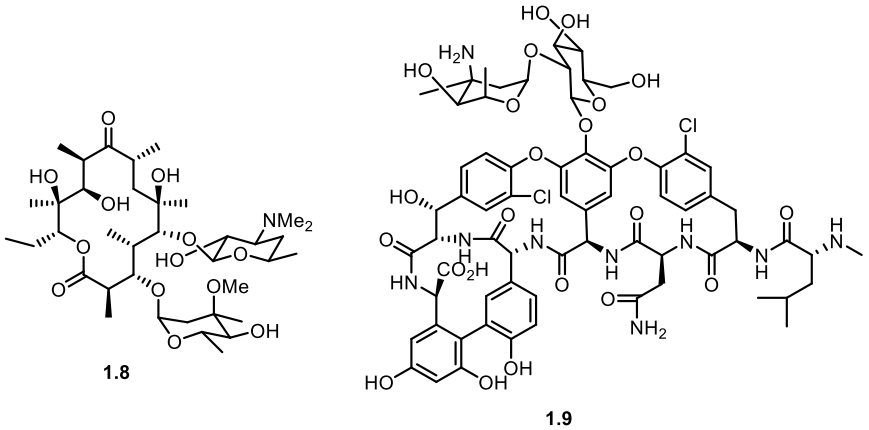


Figure 1.4. Examples of macrocyclic antibiotics: Erythromycin **1.8** and Vancomycin **1.9**.

The isolation and total syntheses of a variety of biologically potent macrocycles are reported by academic research groups in the literature.[16] The syntheses of these macrocycles most often possess a common feature: a challenging macrocyclization step that would make their synthesis unfeasible on an industrial scale. In the early stages of drug design, medicinal chemists are also reluctant in using a macrocyclization step when building libraries or when studying SAR (structure activity relationship).[16] Nonetheless, some R&D groups have built synthetic macrocycles, such as BILN-2061[17] **1.10** and SB-T-2054[18] **1.11**, which possess promising potency (Figure 1.5). BILN-2061 **1.10** is a NS3-protease inhibitor which has shown anti-viral effects in humans and SB-T-2054 **1.11** was found to be as active in terms of cytotoxicity as the commercial anti-cancer drug Taxol (paclitaxel).

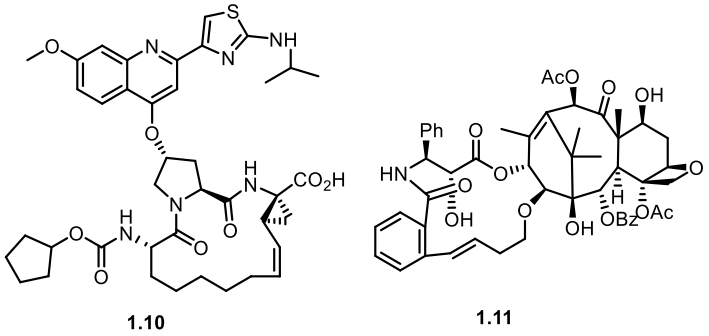


Figure 1.5. Potent synthetic macrocycles: BILN-2061 **1.10** and SB-T-2054 **1.11**.

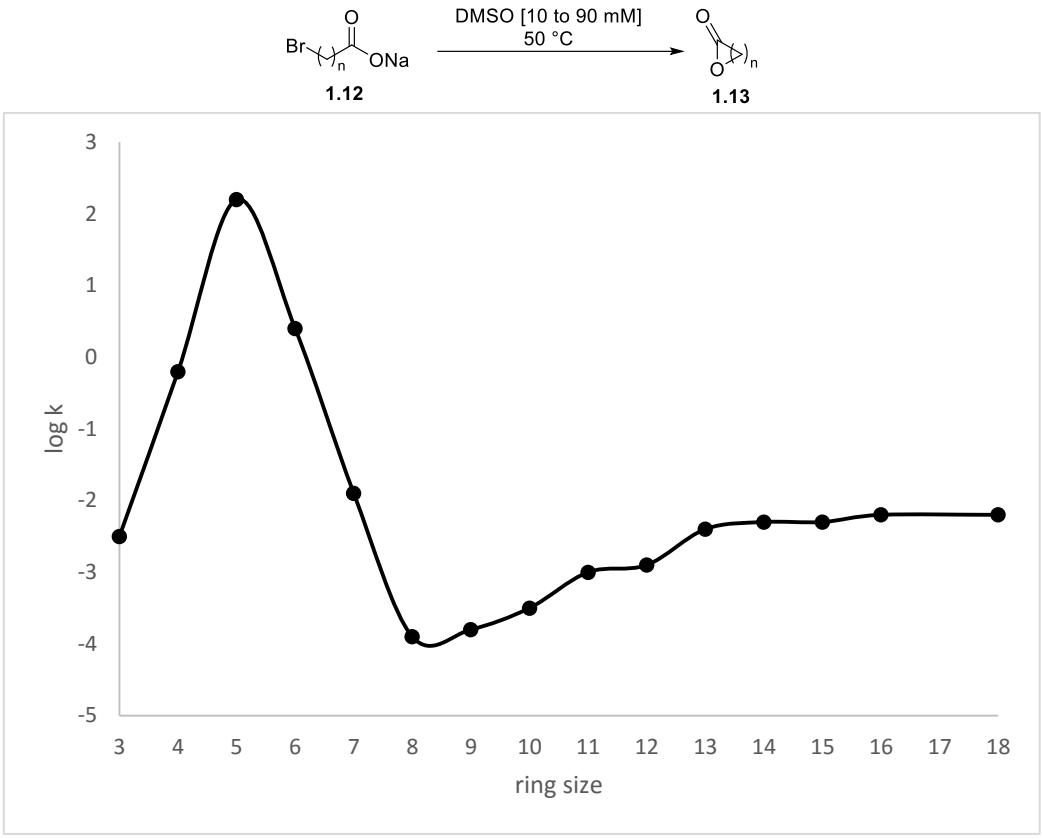
1.3. Synthetic Challenges in Macrocyclization Reactions

Although macrocycles have numerous applications in the chemical industry, challenges associated with their synthesis remain a preoccupation for organic chemists. It is important to understand that direct transposition of catalytic methods for intermolecular reactions, and for intramolecular ring closing of small cycles, to the synthesis of macrocycles is not often possible due to inherent thermodynamic constraints of macrocyclic precursors which will be be discussed

hereafter. Therefore, the development of synthetic strategies aimed specifically toward the synthesis of macrocycles is needed.

Macrocyclization reactions present challenges due to issues regarding both entropy and enthalpy. Thermodynamic laws associated with entropy state that a system always tends to disorder; however, a macrocyclic system is more ordered than its acyclic counterpart, often having a conformational population that is nearly homogeneous.[2] Thermodynamic laws associated with enthalpy point to three types of strain that can influence the formation of a macrocycle:[19] 1) Pitzer strain, also known as torsional strain, is described as the result of forcing bonds to be in an eclipsed conformation to allow for alignment of reactive orbitals; 2) Baeyer strain arises from the deformation of bond angles to allow for the appropriate alignment for cyclization, and 3) Prelog strain, or transannular strain, reflects repulsive interactions of atoms across the ring. Moreover, it has been described that the probability of an encounter between two reactive functionalities decreases as the number of atoms between them increases.[20] As a result of the above thermodynamic factors, macrocyclization reactions often require long reaction times and high reaction temperatures, the latter of which can promote decomposition of one or more of the reactants, reagents or catalysts.

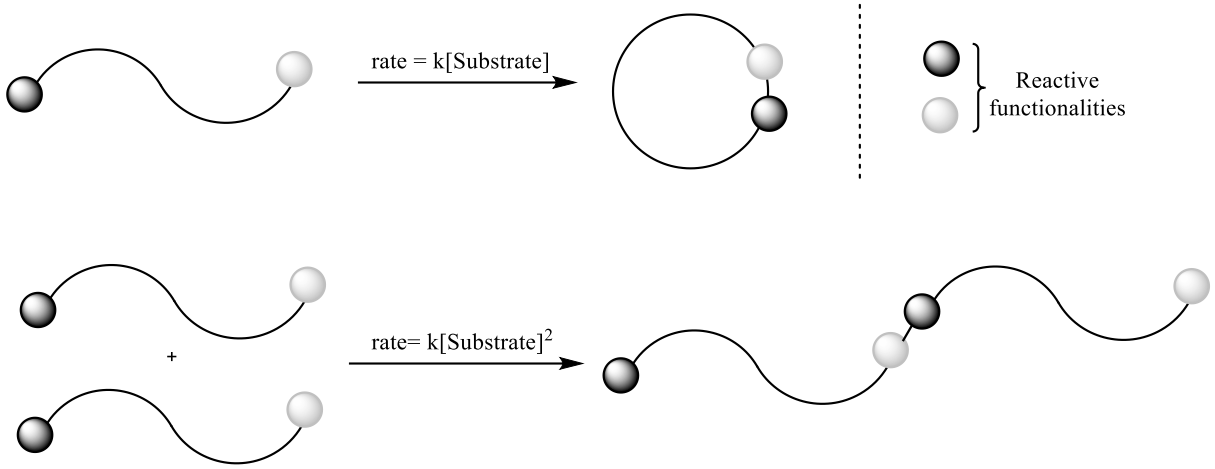
Pioneering work by Illuminati and Mandolini has been utilized to graphically represent the challenges associated with the formation of large rings.[21] When the formation of different ring-sized lactones was explored, 4- to 6-membered ring lactones were found to be the fastest produced under the conditions reported in Scheme 1.1. The slowest ring-closing reactions are those that form 8- to 12-membered ring lactones. The rates of cyclization reach a plateau at 13-membered rings which are similar to the ring-closing of α-lactone **1.13** (n = 1).



Scheme 1.1. Rate of formation of different ring-sized lactones by cyclization of bromocarboxylates.

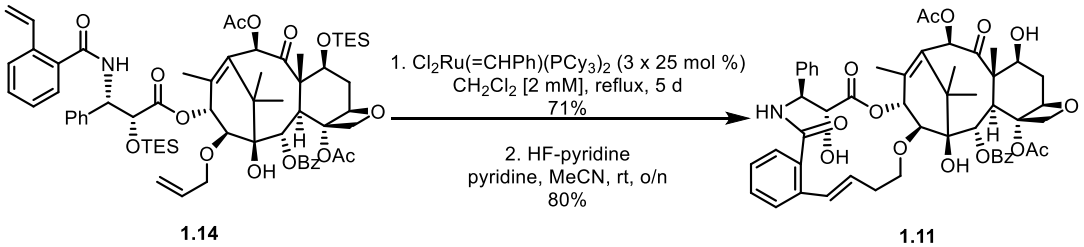
1.4. Traditional Synthetic Strategies in Macrocyclization

As a result of the inherent unfavorable thermodynamic properties of macrocyclization, several synthetic strategies have been developed by chemists. As early as 1933,[22] it was demonstrated that macrocyclization in a highly diluted medium would favor intramolecular reactions over intermolecular processes. As the undesired oligomerization is a second order reaction, decreasing the concentration of the reactants affects the rate of the reaction exponentially (Scheme 1.2).



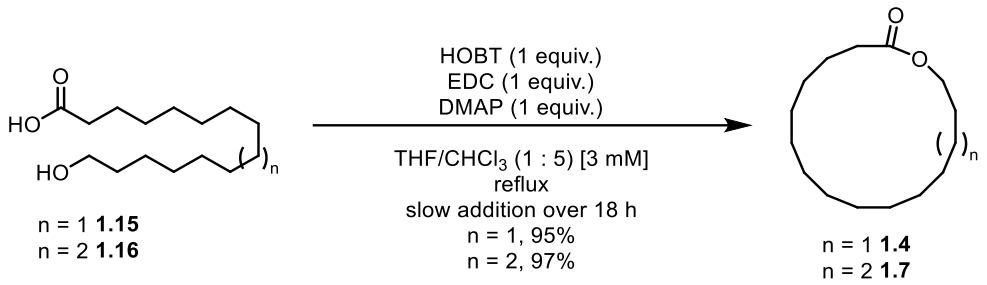
Scheme 1.2. Reaction rates of both macrocyclization and oligomerization reactions.

The high dilution strategy for the synthesis of macrocycles has evolved to the point where the typical concentration for macrocyclization tends to be in the low mM range. During the synthesis of the previously mentioned SB-T-2054 **1.11**,[18] the ring-closing step was achieved by a Ru-promoted reaction at a concentration of 2 mM in dichloromethane (Scheme 1.3). To put it in perspective, if one gram of the precursor **1.14** (1163 g/mol) were to be cyclized at a 2 mM concentration, 430 mL of solvent would be required. Further extrapolation to the kilogram scale would suggest 430 L of required solvent. Not only are the solvent requirements not environmentally friendly, but they are costly and not easily applicable to industrial production scales. In addition, a total of 75 mol % of Ru complex (added in three portions) was needed to achieve complete conversion after five days, pointing to the need for improved reactivity for macrocyclization.



Scheme 1.3. Ru-promoted macrocyclization for the synthesis of SB-T-2054.

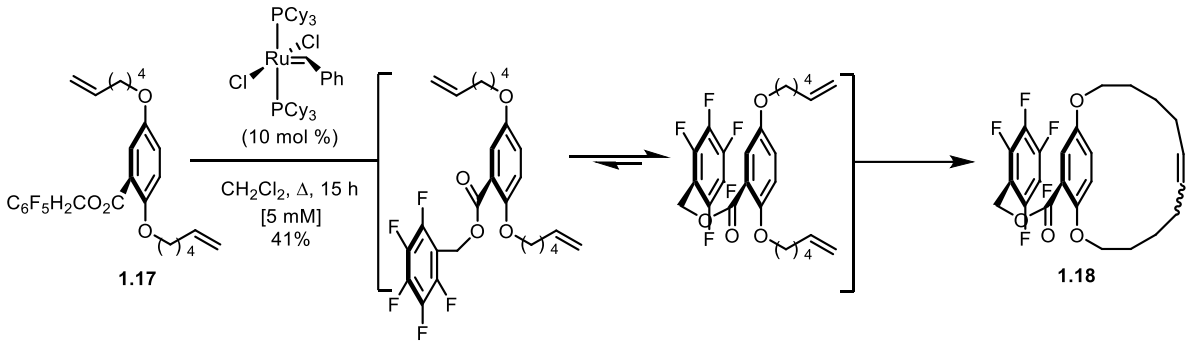
Alternatively, a way to achieve high dilution using less solvent is to employ slow addition techniques. A syringe pump is used to slowly add the linear precursor (at times, a reagent or a catalyst can also be added simultaneously) to the reaction flask, so that at any given moment, there is only a small amount of the reactive species in solution. Although slow addition techniques can be viewed as a greener alternative to standard high dilution, at industrial scales, the concentrations are often still too low and the slow addition infrastructure is tedious and cumbersome. Despite these drawbacks, the process can result in high yields of desired product. For example slow addition was used in combination with high dilution to obtain macrocyclic musks Exaltolide® **1.4** and dihydroambrettolide **1.7** from the corresponding seco acids, **1.15** and **1.16** respectively, in almost quantitative yields (Scheme 1.4).[23]



Scheme 1.4. Macrolactonization employing both high dilution and slow addition for the synthesis of macrocyclic musks.

An alternative strategy to improve the efficiency of macrocyclization reactions is conformational control, whereby structural modification of the macrocyclic precursor favors a conformation that brings the two reactive functionalities closer in space. The main disadvantages of the strategy are: 1) the addition of synthetic steps, specifically the installation and cleavage of groups added to enforce conformations and, 2) the limitation in the choice of substrates, which must have the necessary functionality for the structural modifications. An example of conformational control in the synthesis of macrocycles is the use of auxiliaries that

enforce conformation via π-stacking. A perfluorophenyl ring-containing auxiliary can be covalently attached to the diene **1.17** to help favor cyclization through non-covalent interaction with the core of the precursor promoted by π-stacking of rings with complementary electroninc properties (Scheme 1.5).[24]



Scheme 1.5. Conformation control of a macrocyclization by attachment of an auxiliary.

Other methods of conformational control that do not require covalent attachment of an auxiliary include chelation of the functionality within the acyclic compound with metal ions[25] or through systematically planned intramolecular H-bonding.[26] In the latter aforementioned strategies for conformational control, the addition of synthetic steps is mostly avoided, but the substrate scope remains limited.

1.5. Conclusions

Synthetic macrocycles are omnipresent in many fields of the chemical industries, including aroma chemistry and medicinal chemistry. Nevertheless, the synthesis of macrocycles remains problematic because of unfavorable thermodynamics. The most common approaches to overcome the challenges of macrocyclization are costly and not environmentally friendly.

The present thesis will focus on the development of strategies in macrocyclization for the formation of relevant molecules in aroma chemistry and medicinal chemistry. The strategies are designed to exploit catalysis and limit the production of by-products,[27] as the industries are ever

more aware and concerned about sustainability.[28] The thesis will first discuss the development of a direct catalytic macrolactonization reaction (Chapters 2 to 5), and will then present the application of a phase separation strategy in complex molecule synthesis (Chapters 6 and 7).

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2. Macrolactonization via Formation of the Ester Functional Group

Macrolactones, a category of macrocycles that incorporate an ester moiety, are present in numerous fields of the chemical industry, notably as perfumes, as insecticides and as pharmaceuticals. As representative examples, Exaltolide® **2.1**[1] is a macrocyclic musk widely used in detergents, soaps and perfumes, Spinosyn A **2.2**[2] is found in the commercial biopesticide Spinosad, and Erythromycin **2.3**[3] and Epothilone B **2.4**[4] are a common antibiotic and a cytotoxic drug candidate, respectively. Given the popularity of macrolactones, a number of macrocyclization reactions have been developed for their synthesis. Some of the more common routes to macrolactones involve formation of carbon-carbon (C-C) bonds. Intramolecular Wittig reactions remain a staple of macrocyclization strategy, but alternatives that rely upon catalysis such as ring-closing olefin metathesis (RCM) and intramolecular Pd-catalyzed cross-coupling, have become the widely used methods. Despite the emergence of an increasingly varied toolbox for the synthesis of macrolactones, the most common method remains the macrolactonization from a corresponding seco acid.[5] The following chapter describes a brief overview of the stoichiometric and catalytic methods for macrolactonization that result in the formation of an ester linkage (R^2-O-C(O)-R^1).

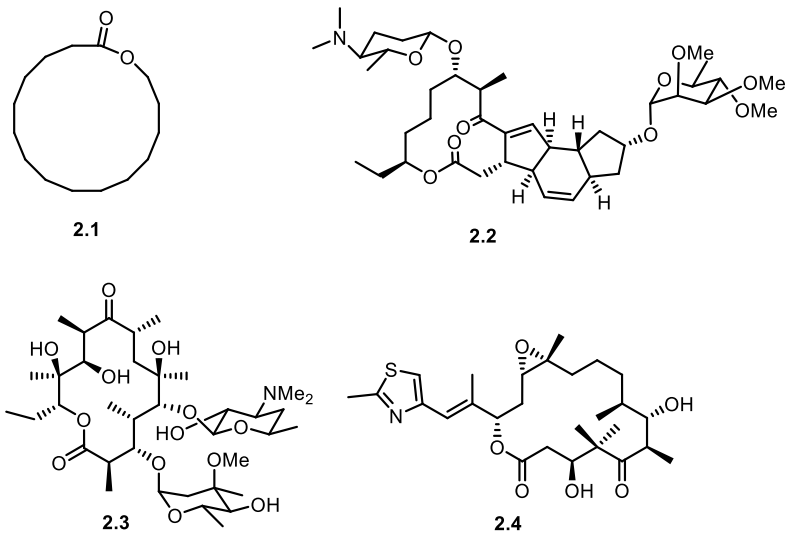
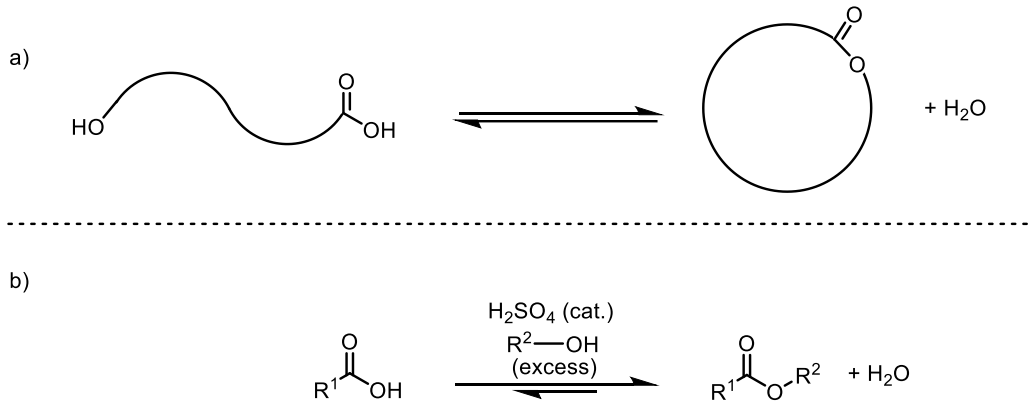


Figure 2.1. Macrolactones as perfumes, insecticides and as pharmaceuticals.

2.1. Challenges Associated with Macrolactonization from a Seco Acid

Macrocyclization is a challenging transformation that generally suffers from slow rates of ring closure and allows for competing intermolecular oligomerization or substrate decomposition to plague the desired cyclization. In addition to the typical difficulties of macrocyclization, macrolactonization from seco acids has inherent challenges of its own. The condensation between an alcohol functionality and a carboxylic acid functionality is a reversible process, in which the water produced as a by-product can participate in a ring-opening hydrolysis. In an analogous intermolecular esterification reaction, the problematic equilibrium is controlled via LeChatelier's principle,[6] whereby adding an excess of one of the two reagents pushes a reaction towards the desired ester product. In many esterification processes, the alcohol is often a cheap and abundant reagent and can be used as the solvent for the reaction. In addition, the equilibrium can be influenced by the removal of water from the reaction mixture through the addition of molecular sieves or the installation of a Dean-Stark apparatus.[7] Esterification

often requires activation of one or both of either the carboxylic acid or hydroxyl functionalities. The Fischer esterification is a prime example that exploits a strong acid, such as sulfuric acid, to catalyze the addition of the alcohol to the carbonyl group of a carboxylic acid.[8] When comparing the intermolecular esterification and intramolecular macrolactonization, it is clear that Fischer-type esterification protocols cannot help promote the latter, where the reactive functionalities are intrinsically equimolar. As such a number of methods have been developed to effect macrolactonization without invoking problematic equilibria.

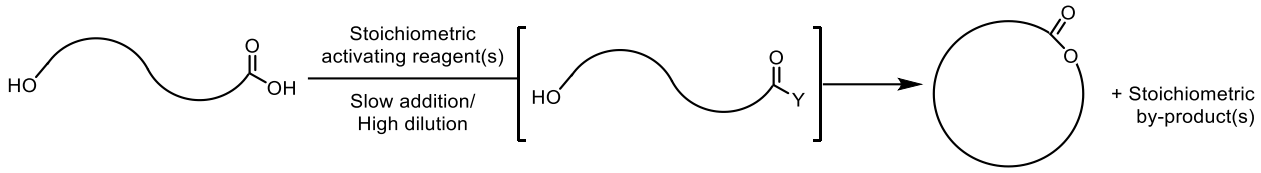


Scheme 2.1. Condensation reactions between alcohol and carboxylic acid functionalities: a) Equilibrium-controlled lactonization. b) Fischer esterification following LeChatelier's principle.

2.2. Stoichiometric Methods for the Synthesis of Macrolactones

In general, chemists perform the direct macrolactonization of seco acids using not more than a handful of different general protocols. Unfortunately, they all share a major drawback in stoichiometric activation of the carboxylic acid moiety or, in some cases, activation of the alcohol moiety, which produces a stoichiometric waste by-product that is often toxic or difficult to remove during purification of the desired product. As it is generally the case in

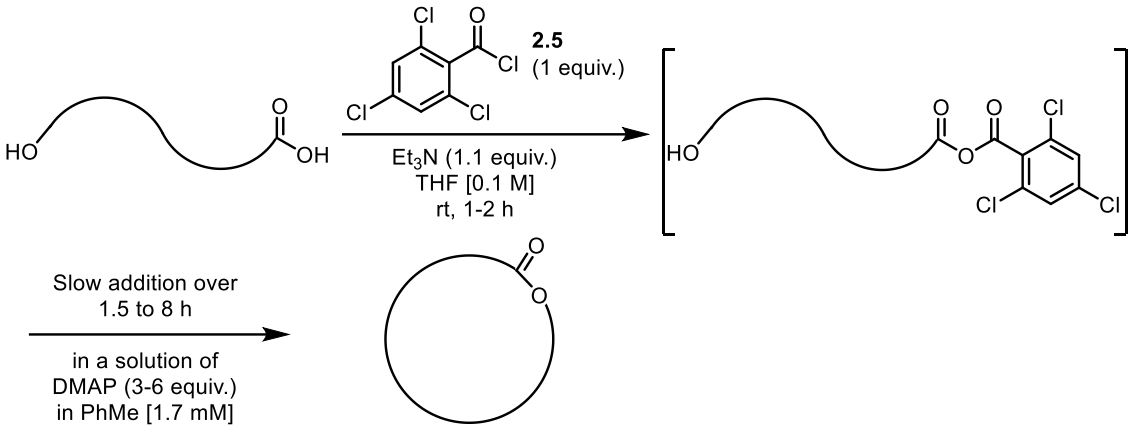
macrocyclization reactions, high dilution and slow addition techniques are also trademarks in macrolactonization.



Scheme 2.2. Stoichiometric-activated macrolactonization.

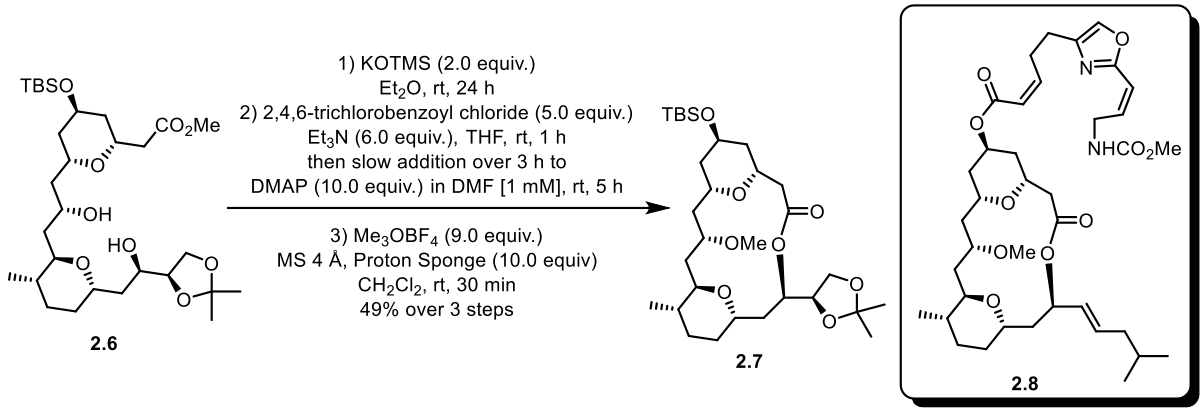
2.2.1. The Yamaguchi Macrolactonization

The Yamaguchi reaction, first reported in 1979,[9] involves formation of a mixed anhydride from 2,4,6-trichlorobenzoyl chloride **2.5** and a carboxylic acid and subsequent esterification to synthesize macrolactones. The seminal report stipulates the necessity of slow addition and high dilution reaction conditions; the mixed anhydride is slowly added to a refluxing solution of DMAP in toluene, where conversion of the anhydride to a DMAP-adduct takes place prior to cyclization (Scheme 2.3). The Yamaguchi macrolactonization is arguably the most employed methodology in macrolactonization, with over 340 publications having reported using the protocol,[5] most often in the context of total synthesis of natural products. Its popularity is most probably linked to its reliability to promote macrocyclization over oligomerization due to the high reactivity of the slowly added intermediate in the DMAP solution. In other words, the cyclization is the dominant pathway because the concentration of the reactive precursor remains low all along the slow addition step.



Scheme 2.3. Macrolactonization via the formation of a mixed anhydride: the Yamaguchi protocol.

As the Yamaguchi cyclization is often a late-stage step in the synthesis of complex macrocycles, some modifications to the general protocol are often used and are typically substrate specific. For instance, in Carreira's synthesis of leucascandrolide A **2.8** (Scheme 2.4),[10] oligomerization was observed during macrocyclization and was presumed to be due to intramolecular hydrogen bonds which enforce a conformation that is not conducive to ring closure. Using a highly polar solvent such as DMF to compete for hydrogen-bonding sites allowed the formation of the desired 14-membered macrocycle **2.7** in 49% yield. Several other modifications have been reported to the original protocol, notably by Yonemitsu.[11] In addition, different reagents have been developed to aid in the formation of the initial mixed anhydride: 2,6-dichlorobenzyl chloride **2.9**,[12] *m*-nitrobenzoic anhydride (MNBA) **2.10**[13] and pivaloyl chloride **2.11**[14] are among published alternative activating reagents (Figure 2.2).



Scheme 2.4. Macrolactonization via a modified Yamaguchi protocol for the synthesis of leucascandrolide A **2.8**.

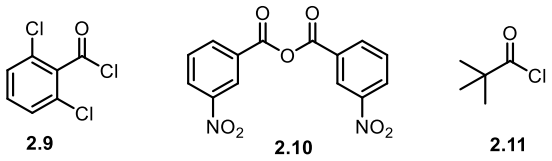
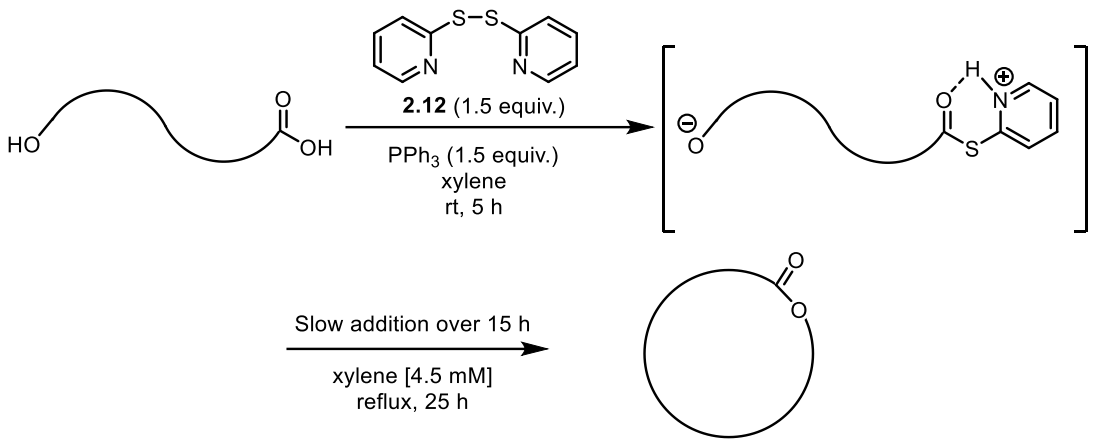


Figure 2.2. Other common reagents for the formation of a mixed anhydride.

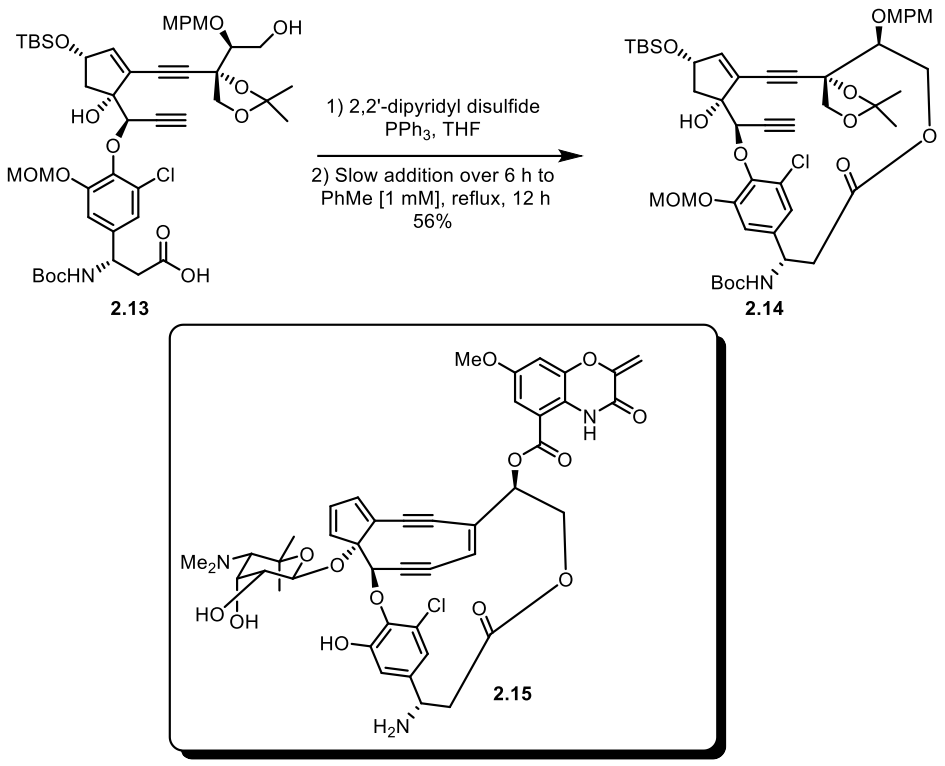
2.2.2. The Corey-Nicolaou Macrolactonization

Another popular method for macrolactonization of seco acids is through the formation of a thioester, a method inspired by the biosynthesis of macrolactones.[15] The most common procedure was reported by Corey and Nicolaou in 1974.[16] The method relies on the activation of both the carboxylic acid and the alcohol functionalities (Scheme 2.5). The 2-pyridine thioester intermediate can be formed after the addition of 2,2'-dipyridyl disulfide **2.12** and triphenylphosphine (PPh_3) to a solution of the seco acid in xylene. The reaction mixture containing the thioester is then slowly added to refluxing xylene to promote cyclization in a highly dilute medium. An internal proton transfer, facilitated at a high temperature, forms a zwitterionic species which undergoes an electrostatically driven cyclization.



Scheme 2.5. Macrolactonization via the formation of a thioester: the Corey-Nicolaou protocol.

The Corey-Nicolaou approach has been used in the synthesis of many complex macrocycles,[5] notably for intermediates in the preparation of the antibiotic C-1027 chromophore **2.15** where other traditional methods, such as the Yamaguchi macrolactonization, were proven unsuccessful.[17] Though no specific equivalents were reported for the activating reagents, slow addition over six hours, and a total reaction time of twelve hours at a 1 mM concentration were needed to obtain macrocycle **2.14** in a 56% yield (Scheme 2.6).



Scheme 2.6. Macrolactonization via Corey-Nicolaou protocol toward the synthesis of C-1027 chromophore **2.15**.

In the procedure, two by-products are generated in stoichiometric amounts. It has been reported that elimination of the by-products can be problematic.[18] Indeed, a difficult chromatographic separation is necessary to isolate the desired macrolactone from triphenylphosphine oxide and thiopyridone, but also from residual triphenylphosphine and 2,2'-dipyridyl disulfide. The difficulty has prompted chemists to propose alternative reagents to the reaction (Figure 2.3). Thionylchloroformate **2.16** can be synthesized, isolated and be used to promote the lactonization reaction, making the use of triphenylphosphine unnecessary and, thus, limiting the amount of generated by-products.[15] Disulfide **2.17** requires milder conditions and its steric hindrance prevents side reactions.[19] Disulfides **2.18** and **2.19** were also found to be more reactive than the seminal disulfide **2.12**.[20]

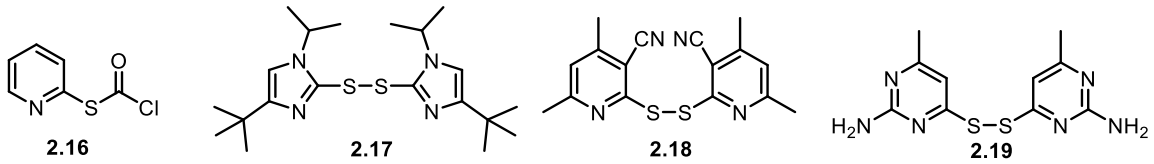
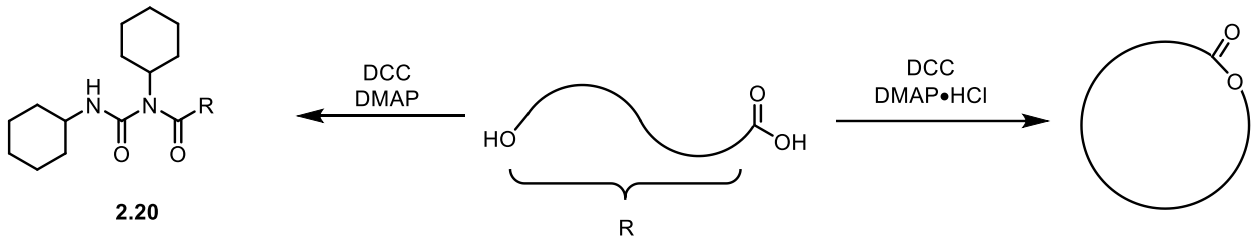


Figure 2.3. Alternative reagents to the Corey-Nicolaou protocol.

2.2.3. The Boden-Keck Macrolactonization

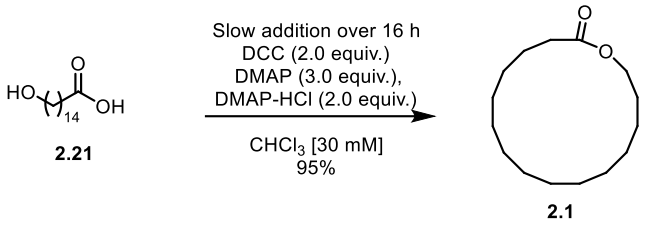
The use of carbodiimide reagents in combination with DMAP is well established in the synthesis of esters and amides and is known as the Steglich reaction.[21] Boden and Keck have published a modification allowing the transposition of the protocol to macrolactonization. Indeed, the standard Steglich reaction conditions were found to produce fair amounts of the side-product **2.20** when applied to the macrolactonization of seco acids (Scheme 2.7).[22] As the cyclization reaction is slow, the *N*-acyl urea **2.20** is formed preferentially and is unreactive to cyclization. However, adding the hydrochloride salt of the amine base (DMAP-HCl) can effectively promote cyclization by accelerating the proton transfer steps.



Scheme 2.7. The ineffective traditional Steglich reaction and the Boden-Keck-modified reaction conditions applied to macrolactonization.

Macrocyclic musks were synthesized using the Boden-Keck approach in excellent yields.[22] For example Exaltolide® **2.1** was formed in 95% yield by the slow addition of seco-acid **2.21** to superstoichiometric amounts of the activating reagents (Scheme 2.8). The Boden-Keck procedure has been utilized in many total syntheses,[23] but a major drawback associated with the method is the stoichiometric production of the *N*,*N'*-dicyclohexylurea. Due to

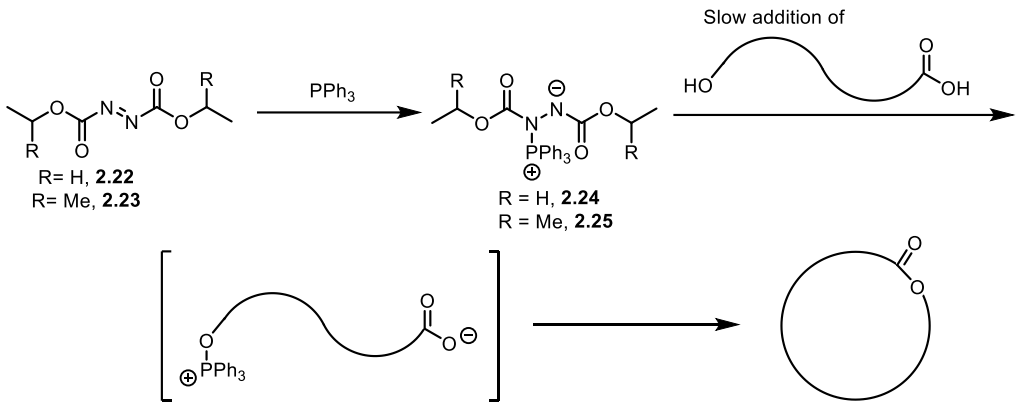
complications arising from the toxicity and purification of the urea,[24] several modifications have been published which include the use of supported DCC,[25] or the use of EDC-HCl,[26] to help with the purification of the desired macrolactones.



Scheme 2.8. The Boden-Keck procedure for the synthesis of Exaltolide® (**2.1**).

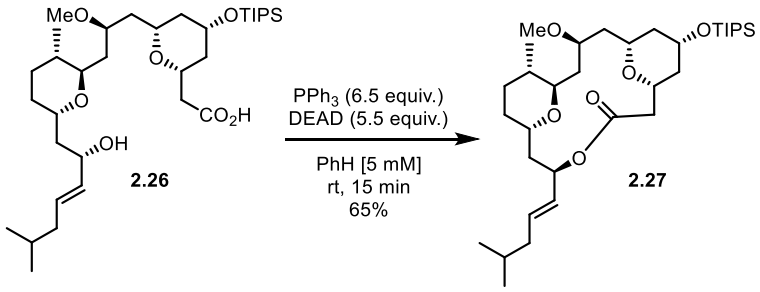
2.2.4. The Mitsunobu Macrolactonization

Direct macrolactonization from seco acids can also occur via activation of the alcohol functionality, such as in the Mitsunobu reaction. In the Mitsunobu procedure (Scheme 2.9), an azodicarboxylate reagent, often DEAD **2.22** or DIAD **2.23**, is reacted with triphenylphosphine and the macrocyclic precursor. An alkoxyphosphonium intermediate is produced and an intramolecular cyclization can occur via an attack of the carboxylate moiety. Slow addition of the seco acid to the *in situ* formed intermediate **2.24** or **2.25** is necessary to selectively produce the macrolactone. Indeed, when slow addition is not used, the major product obtained from the reaction conditions is often the head-to-tail cyclic dimer.[5] The stoichiometric by-products formed include a hydrazide and triphenylphosphine oxide. Roush and co-workers have described the challenges associated with purification from the by-products,[27] and it should be noted that supported reagents have been used to facilitate the purification step.[28]



Scheme 2.9. General procedure for the synthesis of macrolactone via the Mitsunobu reaction.

The Mitsunobu macrolactonization approach has been exploited in many total syntheses of natural products, notably for the synthesis of previously mentioned leucascandrolide A **2.8**.[29] The reaction time for the cyclization of precursor **2.26** (15 min) is quite impressive, but excess PPh_3 and DEAD were necessary to produce macrocycle **2.27** in 65% yield with a clean inversion of configuration (Scheme 2.10).

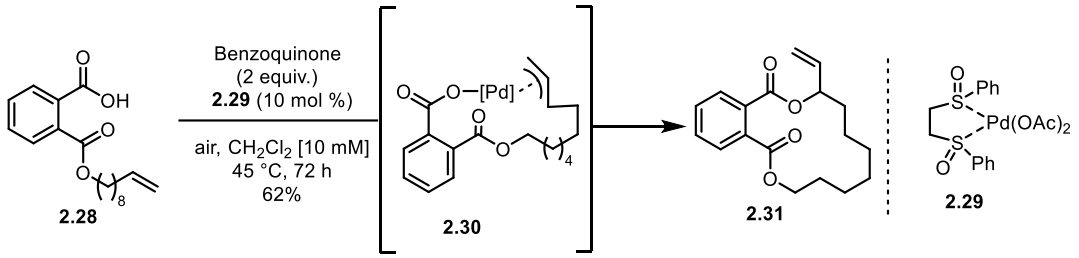


Scheme 2.10. Macrolactonization via the Mitsunobu protocol for the synthesis of leucascandrolide A.

2.3. Catalysis in the Synthesis of Macrolactones

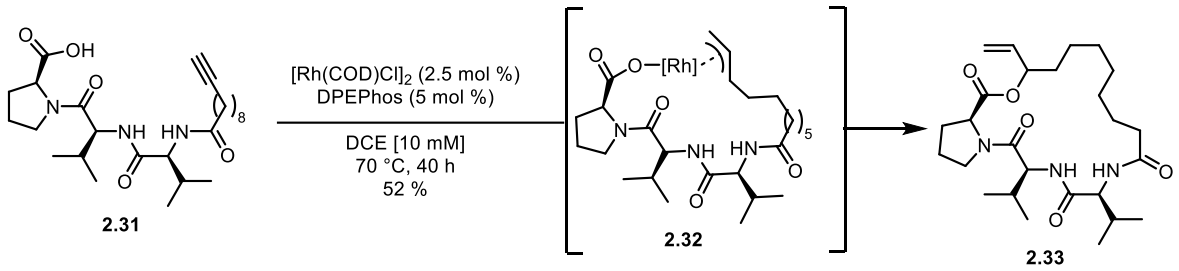
In recent years, organic synthetic chemists have developed catalytic alternatives to the stoichiometric macrolactonization reactions that form the ester moiety of macrolactones. In 2006, White and co-workers reported a first macrolactonization protocol via an allylic C-H oxidation from ω-alkenoic acids.[30] The reaction proceeds via a Pd(II)-catalyzed C-H bond

cleavage, and an oxidative C-O bond-forming event is subsequently promoted by benzoquinone. Slow addition and high dilution are not necessary, hypothetically because the catalyst activates both reactive moieties simultaneously as in the intermediate **2.30** depicted in Scheme 2.11. The study of the scope of the reaction pertained to 14- to 17-membered macrolactones with yields varying between 52 and 63%. Some limitations include long reaction times and the need for the precursors to possess a terminal olefin.



Scheme 2.11. Macrolactonization via Pd-catalyzed allylic C-H oxidation.

More recently and similarly to White's method, Breit and co-workers have developed a Rh-catalyzed propargylic C-H oxidation to produce macrolactones bearing an exocyclic olefin at the ω-position.[31] Once again, the bis-activation of the reactive functional groups permits reaction conditions which are moderately diluted without the need for slow addition. Furthermore, no stoichiometric oxidant is necessary in the procedure, therefore there is no stoichiometric by-product formed, and relatively low catalyst/ligand loadings are required. However, the reaction is air-sensitive and must be performed under an inert atmosphere. The scope of macrocycles that could be formed included 12- to 23-membered ring macrolactones and included polypeptides such as **2.33** as shown in Scheme 2.12.



Scheme 2.12. Macrolactonization via Rh-catalyzed propargylic C-H oxidation.

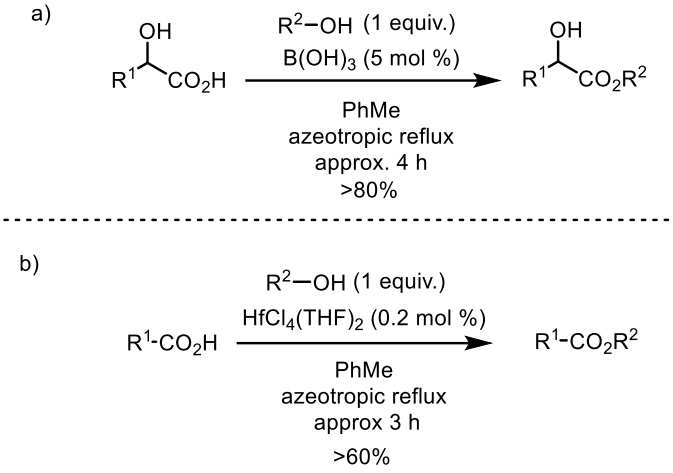
2.4. Summary

Macrolactonizations of seco acids typically rely on stoichiometric activation of the carboxylic acid and/or the alcohol moiety. The stoichiometric by-products formed can be toxic and can render purification steps laborious. In addition, much like macrocyclization reactions in general, slow addition and high dilution are required to avoid oligomerization. Some catalytic methods have been developed for the synthesis of macrolactones that by-pass the reactivity problems of the condensation of alcohols onto carboxylic acids, but also suffer from long reaction times and limitations in the choice of substrates.

2.5. Inspiration and Research Goals for Improving Macrolactonization

The intermolecular synthesis of esters has recently moved away from methods such as the Fischer esterification or stoichiometric activation methods, towards catalytic dehydrative condensations.[32] Indeed, catalysis-based esterification methodologies have been developed to promote esterification between equimolar amounts of alcohols and carboxylic acids. As examples, Blanchfield and co-workers have shown that boric acid can effectively catalyze the selective esterification under azeotropic reflux in toluene but the method was limited to α-

hydroxyacids (Scheme 2.13a). A more general methodology has been published by Yamamoto and co-workers in which $HfCl_4(THF)_2$ catalyzes the esterification of various carboxylic acids with alcohols, also under azeotropic reflux in toluene (Scheme 2.13b). However, these methods have not found common applications for the intermolecular synthesis of esters by synthetic organic chemists, perhaps due to the fact that they do not tolerate the presence of water and require azeotropic reflux conditions. Curiously, these methods have not been applied to the synthesis of macrolactones.



Scheme 2.13. Catalytic dehydrative condensations: a) boric acid-catalyzed esterification of α-hydroxyacids and b) Hf-catalyzed esterification of carboxylic acids.

A direct catalytic macrolactonization procedure from seco acids would be a much needed alternative to the stoichiometric methods used for the synthesis of macrolactones. Thus, the next three chapters will be dedicated to the development of catalyzed direct macrolactonization protocols for the formation of macrolactones and macrodiolides that are relevant in aroma and medicinal chemistry-type industries. The research goals would place an emphasis on catalysis, preferably using commercially available compounds as catalysts. In addition, the protocols for macrolactonization will aim for simplicity: catalysts must be "water-tolerant" (no azeotropic conditions necessary) and no tedious slow addition techniques should be necessary. Preferably,

the method developed for macrolactone synthesis would be applicable to the synthesis of compounds relevant to aroma chemistry and medicinal chemistry.

2.6. Bibliography

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3. Direct Macrolactonization of Seco Acids via Hafnium (IV) Catalysis

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Contributions :

- Mylène de Léséleuc participated in the design of the experiments, did all the experimental work and contributed to the writing of the manuscript.
- Shawn K. Collins participated in the design of the experiments and writing of the manuscript.

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3.1. Abstract

Efficient direct macrolactonization of seco acids can be catalyzed by $Hf(OTf)_4$ in high yields, forming water as the sole byproduct. The $Hf(OTf)_4$ catalyst possesses unique reactivity characteristics relative to other Lewis acids, as it promotes macrolactonization over hydrolysis even in the presence of excess water. In addition to forming a variety of macrolactones and benzolactones (55−90%), intermolecular direct esterifications of carboxylic acids and alcohols were also possible and demonstrated compatibility with common carbamate, silyl ether, alkoxymethyl ether, and acetal protecting groups. All of the macrolactonization and esterification processes developed are operationally simple, "one-pot" reactions that exploit a commercially available catalyst without the need for slow addition or azeotropic techniques.

3.2. Introduction

Macrolactones are one of the most common cyclic motifs found in Nature. In addition to their application in pharmaceuticals,[1] macrolactones have had a tremendous impact on the cosmetic industry.[2-4] Macrocyclic musks have attracted increased attention from the perfume industry as they do not exhibit the toxicity or bioaccumulation properties associated with traditional nitro-aromatic and polycyclic musks.[5] In 2011, it was estimated that the market for flavors and fragrances was worth over 21 billion dollars.[6] The production of macrocyclic musk is of considerable industrial impact; for example in 2008 the production of the 16-membered Exaltolide® (**2**)[7] was on the order of ~1000 metric tons.[8] Consequently, synthetic chemists in both academia and industry have continued to develop new strategies to prepare macrolactones, where Exaltolide® and its derivatives have often served as targets for new methodologies. Olefin metathesis,[9] most recently employing Z-selective catalysts,[10] as well C-H

functionalization have recently been explored for the synthesis of macrocyclic musk-like structures.[11] Surprisingly, catalysis has rarely been examined for macrocyclization from the commonly occurring seco acids.[12,13] Macrolactones formed via condensation of the corresponding seco acid are equilibrium-controlled processes where the reverse hydrolysis reaction can be problematic. While in an analogous intermolecular esterification the alcohol can be added in large excess (often as the solvent) in order to push unfavorable equilibria towards the formation of the desired ester,[14] the stoichiometry of the alcohol and acid functionalities in macrolactonization remains fixed in a 1:1 ratio. In 1936,[13a] Carothers reported a Lewis acid catalyzed transesterification process for the formation of macrolactone **2**. Following thermal polymerization of the seco acid **1**, $MgCl_2$ was used to promote "back-biting" of the oligomer to afford macrolactone **2**, which was concurrently distilled away from the reaction mixture as it formed, thus controlling any unfavorable equilibria.

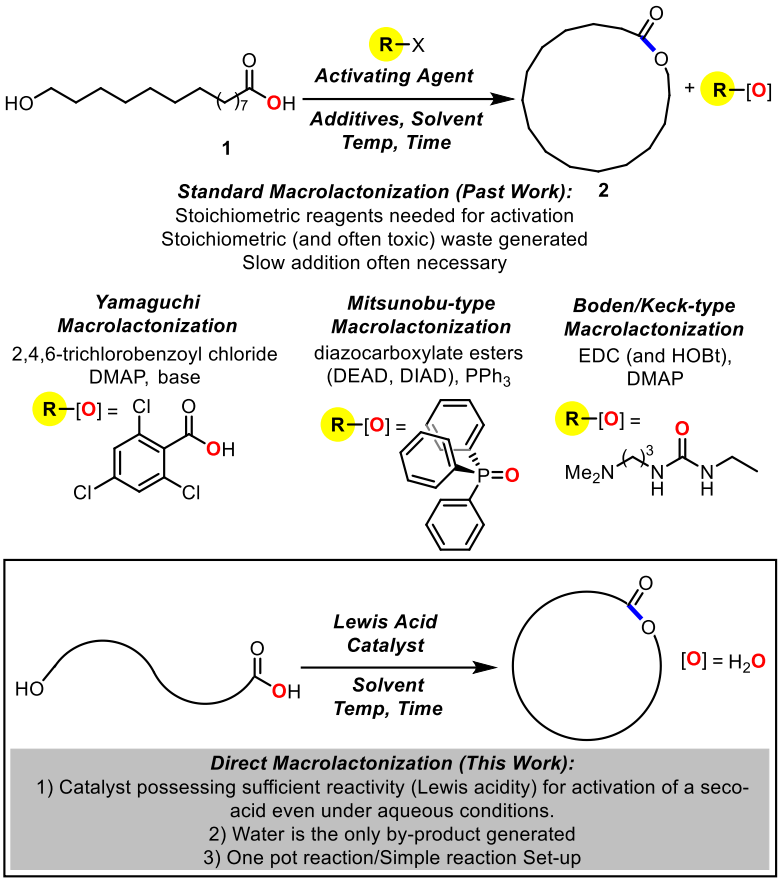


Figure 3.1. Traditional macrolactonization strategies.

Current strategies to promote macrolactonization from seco acids involve stoichiometric activation of the carboxylic acid,[15] which is eventually eliminated as a thermodynamically favorable leaving group. (Figure 1). Some of the more popular strategies employing this concept for macrolactone synthesis include the Corey–Nicolaou,[16] Boden/Keck,[17] Mitsunobu[18] and Yamaguchi lactonizations.[19] In each of the above examples, reactions are normally all conducted under high dilution conditions and the stoichiometric by-products can be toxic and difficult to remove even via chromatographic separation. The Yamaguchi macrolactonization has been particularly favored amongst synthetic chemists since its inception in 1979, as almost 200 examples of the macrolactonization protocol have been reported.[20] Recently, modified anhydride reagents inspired by the Yamaguchi method have attracted increased attention for the

synthesis of naturally occurring macrolactones.[21] Surprisingly, efficient catalytic direct macrolactonization of seco acids is rare and underdeveloped.[8] Herein, we report on a hafnium-catalyzed macrolactonization protocol for the formation of macrolactones that produces water as the only by-product.

3.3. Discovery of Hf(IV)-Catalyzed Macrolactonization

In developing an ideal direct macrolactonization of seco acids, several goals were identified. First, an operationally simple, "one pot" process was desired which avoided the use of azeotropic techniques (drying tubes, Dean-Stark traps) and slow addition/high dilution apparatus (syringe pumps). Second, the direct macrolactonization would produce water as the only by-product. These goals present significant challenges for catalysis, as a suitable Lewis acid must not only possess sufficient acidity to activate the macrocyclization, but must retain that reactivity even as the reaction media becomes increasingly "contaminated" by water. An additional requirement is that the Lewis acid must also refrain from catalyzing hydrolysis of the desired macrolactone. Although a thorough investigation surveying a wide variety of Lewis acids from across the periodic table was envisioned, particular focus in the present study was placed on lanthanide-based Lewis acids, including Lewis acids based on elements of groups III and IV that have demonstrated the ability to promote Lewis acid catalysis in aqueous media.[22] The macrolactonization of seco acid **1** to provide Exaltolide® **2** was selected as a model substrate for cyclization (Figure 3.2).[23] The investigations began with various oxophilic Lewis acid catalysts. Although these Lewis acids are known to react readily with water, no precautions to exclude water (such as adding drying tubes or molecular sieves) were taken and no slow addition techniques were exploited (Figure 2). As expected, titanium, iron, magnesium, boron and aluminum catalysts in general did not afford any of the desired macrolactone **2** (entries 1→10),

and either quantitative recovery of the starting material **1** was observed, or the highly acidic conditions caused decomposition of **1**. Some productive macrocyclization was observed when using copper-based catalysts. While $CuCl_2$ and $CuBr_2$ did not promote any macrolactonization, both $Cu(OAc)_2$ and $Cu(OTf)_2$ resulted in unsatisfactory yields of macrocycle **2** (25 and 54% yield respectively). While AgOTf and $ZrCl_4(THF)_2$ did provide low yields of the macrolactone **2** (22 and 13% respectively), other transition metal-based Lewis acids displayed little reactivity even with other electrophilic complexes of Zr, Zn, Pd, Ni and Co.

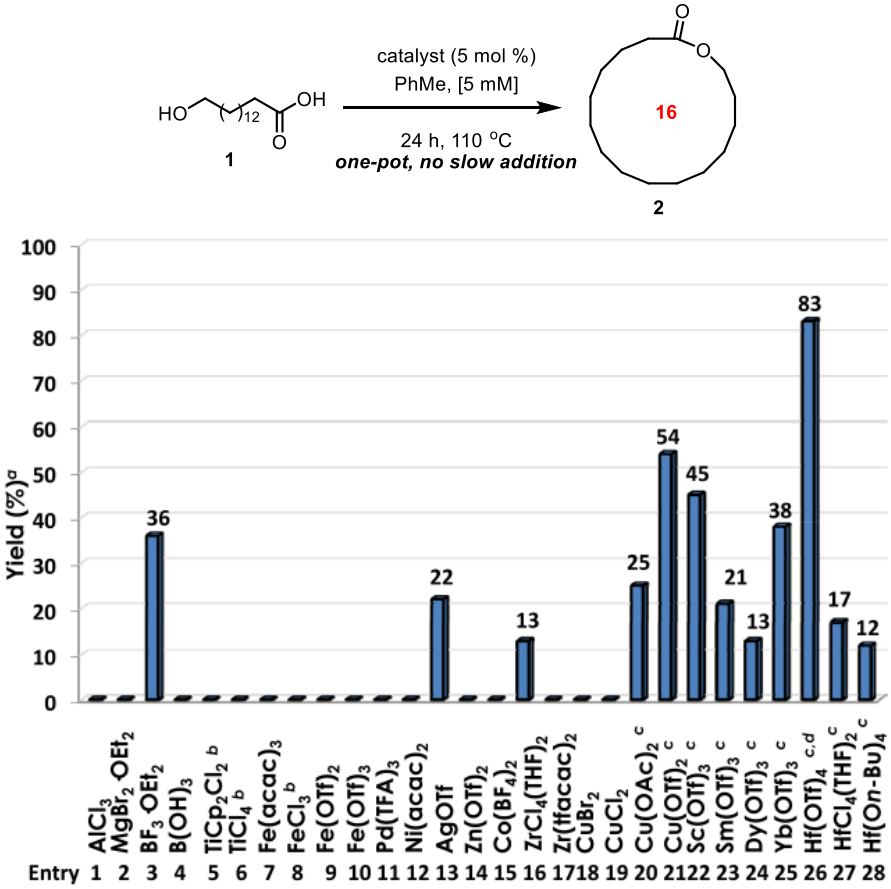


Figure 3.2. Optimization of a Lewis acid catalyzed macrolactonization process.

[a] Isolated yields following silica gel chromatography. Remaining mass balance is unreacted 1 unless otherwise noted. [b] No trace of 1 was isolated. [c] Polymerization of 1 is observed. [d] Lower catalyst loadings provided lower yields. When 2.5 mol % $Hf(OTf)_4$ was used 72% of 2 and 27% re-isolated 1 were obtained. At a concentration of 10mM, 32% of 2 was obtained along with a complex mixture of cyclic and acyclic dimers. Lowering the temperature resulted in low conversions, even when the catalyst loading was increased.

Next, Lewis acids from groups III and IV, including lanthanide-based Lewis acids were investigated. Given the success of electrophilic triflate catalysts for macrocyclization of **1**, $Sc(OTf)_3$ (45%), $Sm(OTf)_3$ (21%) $Dy(OTf)_3$ (13%) and $Yb(OTf)_3$ (38%) were evaluated and showed encouraging but low yields (entries 22→25). Interestingly, when $Hf(OTf)_4$ was used an 83% yield of the macrolactone **2** was isolated.[24] Yamamoto and co-workers reported that efficient direct intermolecular esterifications using low loadings of $HfCl_4(THF)_2$ were possible, albeit under azeotropic reflux.[25,26] Disappointingly, when the hafnium-based catalysts $HfCl_4(THF)_2$ and $Hf(O\textit{n}\text{-}Bu)_4$ were investigated in the protocol without the use of azeotropic techniques, only low yields were obtained (entries 26 and 27). Given the success of the $Hf(OTf)_4$ complex, the possibility of catalysis via *in-situ* formed HOTf was investigated. In a control reaction, it was found that HOTf did catalyze the macrolactonization (**1**→**2**), albeit in much lower yield (39% vs. 83% with $Hf(OTf)_4$). Consequently, macrolactonization using $Hf(OTf)_4$ with added $(\textit{i}\text{-}Pr)_2NEt$ (50 mol % or 10 equiv of base with respect to $Hf(OTf)_4$) to quench traces of protic acids was performed. In the macrolactonization with added base, the desired macrolactone **2** was isolated in 79% yield.[27] The almost identical yields obtained in either the presence or absence of added base suggests that successful macrolactonization is due to catalysis via the Hf-based Lewis acid.

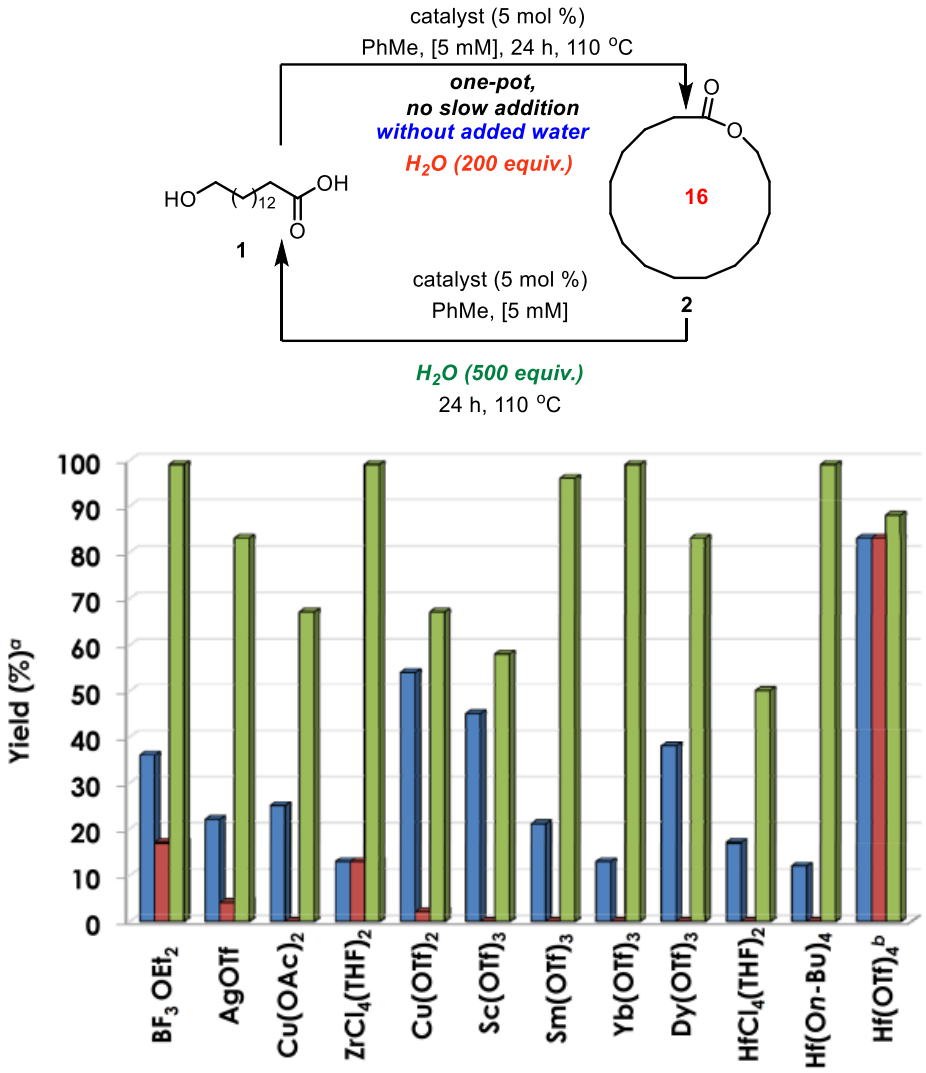


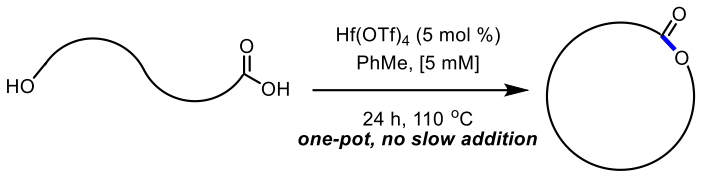
Figure 3.3. Evaluation of various Lewis acids for a catalytic macrolactonization strategy.

The most efficient complex is judged to have yields of macrocyclization under the optimized conditions (blue), under the optimized reactions conditions in the presence of excess water (red) and provide high recovered yields of macrolactone **2** under hydrolysis conditions (green). [a] All entries represent isolated yields following silica gel chromatography. [b] The re-isolated yield of **2** remained high (>80%) even when using 1000 equiv. of added H_2O.

As stated previously, no precautions were taken to exclude or remove water from the reaction media during the macrolactonization reactions. Hence, efficient Lewis acid catalysis must not only be able to promote macrolactonization in high yields, but must be able to do so in the presence of water without catalyzing the reverse hydrolysis reaction. Consequently, all Lewis acid catalysts that displayed some activity for macrocyclization were re-evaluated in two

additional control reactions. First, the macrolactonization was performed under the identical reaction conditions utilized in the catalyst survey, but the reaction solvent (PhMe) was pre-treated with an excess of water (200 equiv). Under these conditions, the majority of the complexes which demonstrated some measure of activity for direct macrolactonization were now significantly inhibited (isolated yields in **2** shown in red, Figure 3). Gratifyingly, the $Hf(OTf)_4$ catalyst maintained the same level of reactivity (83% yield of macrolactone **2**). Second, all active Lewis acid catalysts were evaluated for their ability to catalyze the hydrolysis of macrolactone **2**. Exaltolide **2** was resubmitted to the macrocyclization conditions with added excess water (500 equiv.) for 24 h and then the remaining macrolactone was isolated (isolated yields of recovered **2** in green, Figure 3.3). In general, most catalysts promoted some degree of hydrolysis of the macrolactone **2**. Once again, the Hf-based Lewis acids demonstrated ideal reactivity patterns for direct macrolactonization, as they were poor hydrolysis catalysts and greater than 80% of **2** could be re-isolated, even when 1000 equiv. of excess water was added.

Table 3.1. Substrate Scope of the $Hf(OTf)_4$-Catalyzed Macrolactonization.



	Macrocycle	Yield (%)[a]		Macrocycle	Yield (%)[a]
1	**3** n = 1	<5	10	**11**	73
2	**4** n = 3	55			
3	**2** n = 6	83			
4	**5** n = 7	87			
5	**6** n = 1	90	11	**12**	86
6	**7** n = 3	84			
7	**8** n = 1	56	12	**13**	74
8	**9** n = 11	72			
9	**10**	72	13	**14**	57

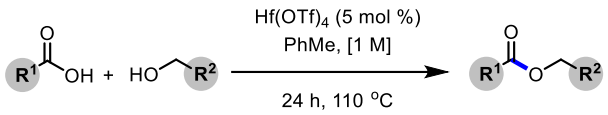
[a] Isolated yields following flash chromatography.

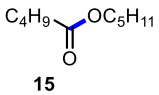
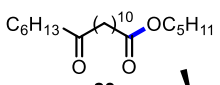
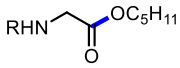
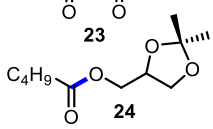
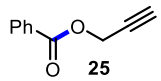
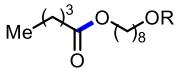
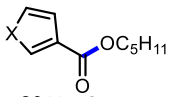
Given the unique ability of $Hf(OTf)_4$ to catalyze the macrolactonization reaction, the synthesis of various macrolactones was investigated under the optimized conditions (Table 3.1). The medium 13-membered macrolactones **4** was prepared in 55% yield[28] (the smaller 11-membered macrocycle **3** could not be formed under the optimized conditions). Larger rings such as the 16- and 17-membered macrolactones **2** and **5** were isolated in higher yields (83%[29] and

87% respectively). The yields of the macrolactones obtained via Hf catalysis are either comparable or higher than those obtained using stoichiometric methods. Cardenas and co-workers prepared the 13-, 16- and 17-membered macrolactones using a Boden/Keck-type method in 69-78% yield, but stoichiometric amounts of EDC, HOBt and DMAP and high dilution/slow addition techniques were required.[30] Recently, Zhang and co-workers reported a hypervalent iodine(III) reagent for the preparation of macrolactones **2**, **3** and **5** in 56-94% yields.[31] Although the iodine-based reagent was recyclable, the procedure still required stoichiometric DMAP and PPh_3 as co-reagents and subsequent purification/separation of the associated by-products (PPh_3O) was necessary. Given the abundance and biological activity of benzolactone natural products,[32] the synthesis of four different macrocycles with benzoic acid cores was investigated. The 14- and 16-membered macrolactones **6** and **7** were each isolated in good yields (90% and 84% respectively). The presence of an alkyne spacer in an analogous macrolactone **8** was well tolerated, albeit the product was isolated in a lower yield (56%). When the ring size was increased, the 26-membered ring **9** was isolated in 72% yield. The synthesis of other 17-membered macrolactones related to the isoambrettolide[33] family of musks was also investigated (entries 9 and 10). Macrolactonization afforded (9*Z*)-isoambrettolide **10** in good yield (72%) without any isomerization of the *cis*-olefin. Protection of the diol moiety of *erythro*-aleuritic acid as its bis-pivaloate ester and subsequent macrocyclization afforded the macrolactone **11** in 73% yield. Finally, macrolactonization of more strained rings, such as the 1,3-diyne containing 21-membered macrolactone **12** also proceeded in high yield (86%). The $Hf(OTf)_4$-catalyzed protocol also evaluated in the cyclization of structures has enolizable stereocenters and steric bulk adjacent to the reacting carboxylic acid. The 19-membered macrolactone **13** derived from iso-leucine was cyclised in 74% yield. Similarly, the 22-

membered dipeptide macrocycle **14** was formed in 57% yield. Both macrocycles **13** and **14** were obtained without any observed epimerization.

Table 3.2. Evaluation of Functional and Protecting Group Compatibility in the $Hf(OTf)_4$-Catalyzed Esterifications.



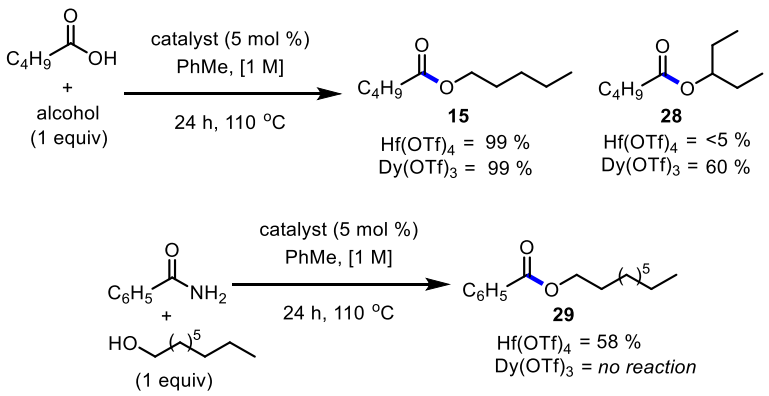
	Ester	Yield (%)[a]		Ester	Yield (%)[a]
1	 **15**	99	9	 **23**	92
			10	 **24**	60[b]
2	**16** R = Boc	72			
3	**17** R = Ts	75			
4	**18** R = Cbz	79	11	 **25**	78
					
5	**19** R = TBS	66[b]			
6	**20** R = TIPS	62[b]			
7	**21** R = MOM	77[b]	12	 **26** X = O	75
8	**22** R = Ac	89[b]	13	**27** X = S	89

[a] Yields following flash chromatography. [b] With added Hünig's base (50 mol %).

To further probe the functional group tolerance of the $Hf(OTf)_4$-catalyzed macrolactonization, several intermolecular esterifications were performed (Table 3.2). The esterification of a simple aliphatic acid and alcohol to provide the ester **15** occurred in quantitative yield (99%, entry 1). Esterification provided Boc-, tosyl-, and Cbz-protected glycine derivatives in good yields (72%). Both TBS and TIPS-protecting silyl ethers were utilized in the esterification to afford the corresponding esters **19** and **20** in 66 and 62% yield respectively (entries 5 and 6). The addition of Hünig's base (50 mol %) was necessary to avoid cleavage of the TBS and TIPS groups. Similarly, MOM and acetate protected alcohols were

also tolerated and esterification afforded the corresponding esters **21** and **22** in 77 and 89% yields respectively. Both acetonide-protected diols and ketone groups were tolerated and the esters **24** and **23** were obtained in 77 and 92% yields respectively. A propargyl ester **25** was compatible with the esterification protocol and was isolated in 78% yield.[34] Additionally, carboxylic acids bearing furan and thiophene heterocycles were easily esterified and the n-pentyl esters **26** and **27** were isolated in 75 and 89% yields respectively (entries 10 and 11). The esterification protocol also demonstrated selectivity for condensation with primary alcohols over secondary or tertiary alcohols or primary amines to provide the ester **15**.[35]

In an effort to understand the reactivity of the $Hf(OTf)_4$ complex in direct macrolactonization, several control experiments were performed (Scheme 1). The intermolecular esterification of 1-pentanoic acid with 1-pentanol was performed with both $Hf(OTf)_4$ and $Dy(OTf)_3$. The stability and catalytic activity of $Dy(OTf)_3$ in water is largely attributed to the cation's large ionic radii and favorable hydrolysis constants.[22c] Although Hf-derived Lewis acids do not possess the same hydrolytic stability as the lanthanide triflates, both $Hf(OTf)_4$ and $Dy(OTf)_3$ provided identical yields of the ester **15** (~99%). Interestingly, when the esterification of benzamide with 1-nonanol was examined under identical reaction conditions, only $Hf(OTf)_4$ promoted the formation of the ester **29** (58% yield).[36] The useful Lewis acidity of Hf-based complexes for a variety of transformations is well documented.[37] Finally, esterification of 1-pentanoic acid was carried out with a secondary alcohol (3-pentanol). While $Hf(OTf)_4$ did afford any of the desired product, $Dy(OTf)_3$ provided a 60% of ester **28**. As a whole, these preliminary studies suggest that the direct esterification/macrolactonization is influenced by the Lewis acidity, hydrolytic stability and steric bulk of the catalyst.



Scheme 3.1. Investigations into the mechanism of the Hf(IV)-catalyzed esterification.

3.4. Conclusions

A protocol for an efficient direct Hf(IV)-catalyzed macrolactonization of seco acids has been described. Following a survey of > 25 various Lewis acids, $Hf(OTf)_4$ was identified as the most efficient catalyst, promoting macrolactonization in high yields at relatively high concentrations (5 mM). Further investigations into the activity of the $Hf(OTf)_4$ complex demonstrated that: 1) $Hf(OTf)_4$ is significantly more efficient relative to other Lewis acids in catalyzing direct macrolactonization even in the presence of excess water and 2) $Hf(OTf)_4$ is a poor catalyst for hydrolysis of macrolactones. A variety of macrolactone and benzolactone skeletons could be prepared, including important macrocycles for the perfume industry. Intermolecular direct esterifications of carboxylic acids and alcohols were also possible and demonstrated compatibility with common carbamate, silyl ether, alkoxymethyl ether, and acetal protecting groups. All of the macrolactonization processes developed are operationally simple, using commercially available catalysts, "one-pot" reactions without the need for slow addition or azeotropic techniques. Importantly, the catalytic process forms environmentally benign water as the only by-product. Preliminary investigations demonstrate that the Lewis acidity, hydrolytic stability and steric bulk of the catalyst play important roles in the macrolactonization.

The effectiveness of the Hf(IV)-catalyzed macrolactonization should be highly useful, given the prevalence of macrolactone structures in pharmaceutically and biologically active products and current interest in sustainability in reagent selection for industrially relevant processes.

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Associated content. Experimental procedures and spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(23) All data is presented in tabular form in the Supporting Information.

(24) Alternative solvents such as dioxane, TFE, DME and THF did not afford macrolactone **2** and quantitative recovery of **1** was obtained. PhCl as solvent afforded a slightly better yield of **2** (88 %), but for convenience, PhMe was selected as the solvent.

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(27) Proton Sponge® could also be used (10 mol %, 63 % yield of **2**).

(28) Conducting the macrocyclization at [10 mM] produced the head-to-tail 26-membered dimer in 60 % yield.

(29) Macrolactonization on a 1 gram scale afforded 67 % of **2**.

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(34) Curiously, an esterification with allyl alcohol was not productive and afforded a black reaction mixture with numerous products.

(35) See Supporting Information for additional experiments involving secondary alcohols.

(36) The activation of primary amides to form esters may suggest that the macrolactonizations proceed via carboxylic acid activation. For more information on the mechanistic aspects of macrolactonization, see reference 12.

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4. Direct Synthesis of Macrodiolides via Hafnium(IV) Catalysis

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Contributions:

- Mylène de Léséleuc participated in the design of the experiments, did all the experimental work and contributed to the writing of the manuscript.
- Shawn K. Collins participated in the design of the experiments and writing of the manuscript.

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4.1. Abstract

Efficient direct synthesis of macrodiolides via catalysis using $Hf(OTf)_4$ is possible in high yields, forming water as the sole by-product. The first protocol for the direct synthesis of macrodiolides from equimolar mixtures of diols and dicarboxylic acids was developed (58-96 %). In addition, modification of the reaction concentration allows for the synthesis of head-to-tail macrodiolides from the corresponding seco acids. The catalytic preparation of the macrodiolides using a commercially available catalyst without the need for slow addition or azeotropic conditions provide an operationally simple alternative to protocols which employ toxic tin catalysts or stoichiometric activation strategies.

4.2. Introduction

Macrodiolides make up an important class of macrocyclic natural products. The macrocyclic dilactones are structurally diverse[1] as they can be found as both hetero- or homodimers, in a wide array of rings sizes, and decorated with various functionality. Not surprisingly, the macrocycles have been shown to exhibit a wide range of biological activities including antibiotic, antifungal, and antileukemic activities.[2] Macrodiolides have also had a striking impact in the cosmetic industry,[3-5] as the yearly worldwide production of macrocycle diolide musks such as Astratone® and Zenolide® is estimated at ~1000 metric tons. In general, the synthesis of macrodiolides involves a macrolactonization event and is consequently prone to competing oligomerization and high dilution reaction conditions.[6,7] Template-directed cyclodimerizations have also been employed to improve macrodiolide synthesis.[8] Macrodiolides formed via the corresponding seco acids typically involve stoichiometric activation of the carboxylic acid employing a Yamaguchi,[9] Corey–Nicolaou,[10] Boden/Keck,[11]

or Mitsunobu lactonization (Figure 4.1).[12] In each of the above examples, the stoichiometric by-products can be toxic and difficult to remove even via chromatographic separation. A catalytic alternative employing the closely related seco-esters involves the use of distannoxane catalysis,[13] which can effectively promote the synthesis of head-to-tail homodimers in good yields.[14] Perhaps due to the difficulties in preparing macrodiolides from the corresponding seco acids, the development of catalytic C-H functionalization[15] and olefin metathesis strategies[16] for the synthesis of macrodiolides has also been recently reported.

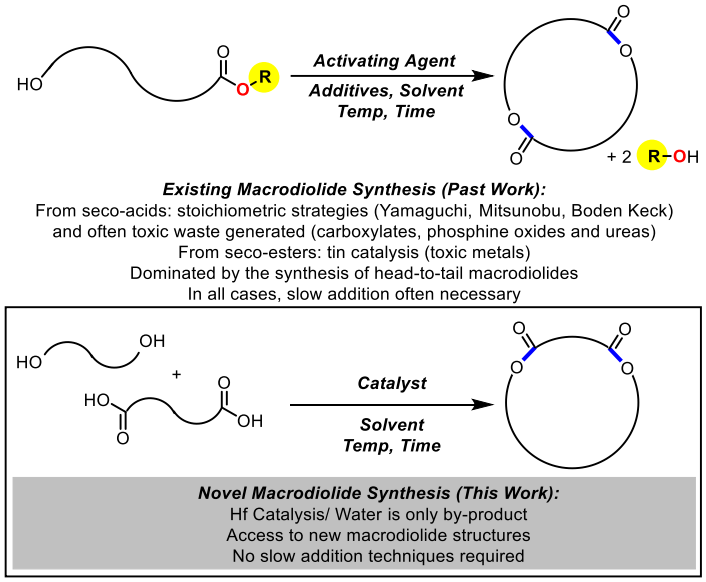


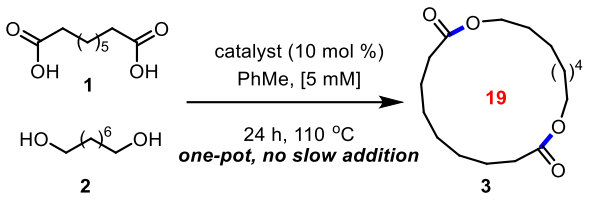
Figure 4.1. Syntheses of macrodiolides.

Recently, our group has reported that Hf(IV)-catalysis can be employed to promote direct macrolactonization of seco acids, generating only water as the stoichiometric by-product.[17] Given the interest in macrodiolide frameworks, the lack of catalytic methods for their synthesis is surprising. Herein, we report the development of a Lewis acid-catalyzed synthesis of macrodiolides, including the first efficient diolide synthesis from diols and diacids in a one-step process.

4.3. Results and Discussion

An ideal direct synthesis of macrodiolides from a diacid and diol would involve a "one pot" process which would avoid the use of azeotropic techniques (drying tubes, Dean-Stark traps), slow addition/high dilution apparatus (syringe pumps) and allow for all starting materials to be added simultaneously. Previous work identified lanthanide triflate Lewis acids as capable of promoting macrolactonization even in the presence of aqueous media[18] without catalyzing the hydrolysis of the desired macrodiolide. Consequently, a survey of the ability of various transition metal triflates to catalyze the formation of the 16-membered macrodiolide **3** from diacid **1** and diol **2** was investigated (Table 4.1).

Table 4.1. Optimization of a Lewis acid catalyzed macrodiolide synthesis.



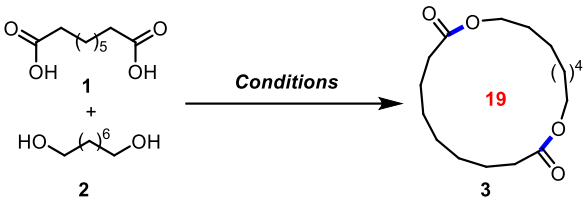
Entry	Catalyst	Yield **3** (%)[a]
1	$Zn(OTf)_2$	<5
2	$Cu(OTf)_2$	50
3	$Sc(OTf)_3$	34
4	$Dy(OTf)_3$	18
5	$Sm(OTf)_3$	0
6	$La(OTf)_3$	29
7	$Yb(OTf)_3$	17
8	$Hf(OTf)_4$	67[b]
9	$Hf(OTf)_4$	55
10	$Hf(OTf)_4$	92[c]
11	$Hf(OTf)_4$	84[d]
12	$Hf(OTf)_4$	90[e]

[a] Yields following chromatography. [b] With 5 mol % $Hf(OTf)_4$. [c] 48 h. [d] With 200 equiv of water added. [e] Macrodiolide **3** was resubmitted to the reaction conditions with 500 equiv. of added water. The yield reported represents the yield of recovered **3**.

The evaluation of Lewis acid catalysts began with $Zn(OTf)_2$, which afforded only trace amounts of the desired macrodiolide **3** (Table 4.1, entry 1). Low yields of **3** were also observed

with other catalysts such as $Sc(OTf)_3$ (34 %), $Sm(OTf)_3$ (0 %) and $Yb(OTf)_3$ (17 %), $Dy(OTf)_3$ (18 %) and $La(OTf)_3$ (29 %). Higher yields of macrodiolide **3** were observed with $Cu(OTf)_2$ (50 %) and $Hf(OTf)_4$ (55 %). Finally, extending the reaction time to 48 h provided a slight increase in the yield of **3** to 92 %. When the catalyst loading of $Hf(OTf)_4$ was decreased to 5 mol %, a drop in the yield to 67 % of macrodiolide **3** was observed. It was found that $Hf(OTf)_4$ was remarkably tolerant to aqueous reactions: 1) when 200 equiv. of water was added to the reaction mixture, $Hf(OTf)_4$ remained highly active forming the desired macrodiolide in 84 % yield and 2) $Hf(OTf)_4$ did not catalyze ring opening of the macrodiolide product, as submitting **3** to the optimized reaction conditions resulted in almost quantitative recovery of the macrocycle **3** (90 %).[19] The exact mechanism by which the $Hf(OTf)_4$ complex functions is still under study. It is known that similar reactivity exhibited by lanthanide triflates is attributed to the cation's large ionic radii and favorable hydrolysis constants.[20] The Lewis acidity of the $Hf(OTf)_4$ complex[21] is well documented and both $Hf(OTf)_4$ as well as other hafnium complexes[22] have been demonstrated to promote direct amidation, suggesting a mechanism proceeding by activation of the carboxylic acid. Some zirconium complexes have also demonstrated activity in amidations.[23] To evaluate the efficiency of the newly developed method, the synthesis of macrodiolide **3** from diacid **1** and diol **2** was examined using common stoichiometric activation strategies (Scheme 1). When a Mitsunobu-type macrocyclization was pursued, the desired macrodiolide was obtained in only 23 % yield, while requiring stoichiometric DIAD/PPh_3 and slow addition of the diol **2**. Using DCC as a coupling agent (Steglich-type esterification) for the synthesis of macrocycle **3** did not result in any formation of the desired product, even when employing slow addition of the diol **2**. A Yamaguchi-type macrolactonization did not afford any of the desired macrolide, however a Corey/Nicolaou approach afforded a 35 % yield of the

macrocycle **3**. It should be noted that the 35 % yield is based on ^{1}H NMR data, as Ph_3PO contaminated the final product and was difficult to remove completely from the product.



"Mitsunobu": DIAD (1.5 equiv.), (slow addition over 5 minutes), PPh_3 (1.5 equiv.), PhMe (4.0 mM), 21 °C, 48 h, **23 %**

"Steglich": DCC (2.0 equiv.), DMAP (2.0 equiv.), $CHCl_3$ (2.8 mM), reflux, 48 h, slow addition over 16 h, **0 %**

"Yamaguchi": 1. 2,4,6-trichlorobenzoyl chloride (2.6 equiv.), Et_3N (4.0 equiv.), THF, 0 °C, 1 h, then 2. Slow addition over 1 h to a solution of 1,8-octanediol (1.0 equiv.), DMAP (5.0 equiv.), PhMe [2.65 mM], 75 °C, 18 h, **0 %**

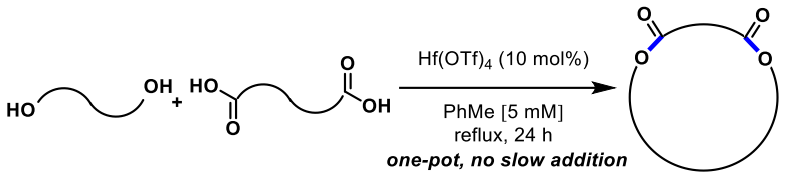
"Corey/Nicolaou": 1. PPh_3 (3.0 equiv.), 2,2'-dipyridyl disulfide (3.0 equiv.), PhMe, 21 °C, 5 h 2. Diluted with PhMe Slow addition over 15 h to a solution of 1,8-octanediol (1.0 equiv.) PhMe [4.25 mM], 75 °C, 18 h, **35 %**

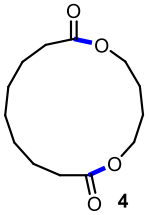
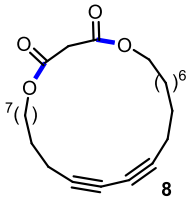
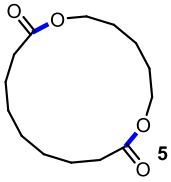
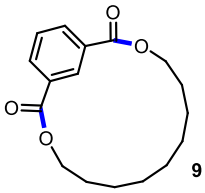
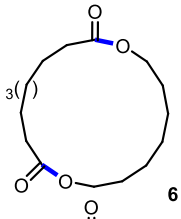
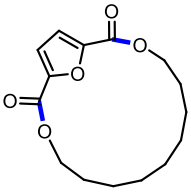
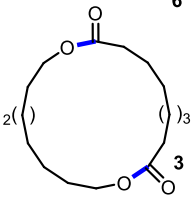
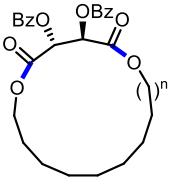
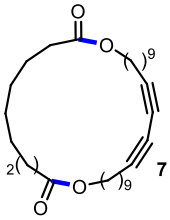
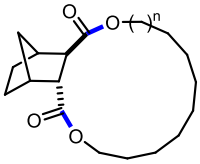
Scheme 4.1. Alternative syntheses of macrodiolides using stoichiometric activation methods.

With optimized conditions in hand, the synthesis of a variety of macrodiolides from their corresponding diacids and diols was investigated (Table 4.2). Treating 1,4-butanediol or 1,5-pentanediol with a dicarboxylic acid afforded the 15- and 16-membered diolides **4** and **5** in 58 and 60 % isolated yields. The synthesis of larger ring sizes was found to require longer reaction times, but still afforded the diolide products in excellent yields. Upon extension of the reaction time to 48 h, the 18- and 19-membered diolides **6** and **3** were isolated in 96 and 92 % yield respectively. The $Hf(OTf)_4$-catalyzed macrolactonization could be used to prepare very large macrocycles: the 33-membered diyne-containing macrodiolide **7** was isolated in 62 % yield and the 27-membered macrodiolide **8** was isolated in a similar 64 % yield. A 16-membered cyclophane derived diolide **9** was prepared in 79 %. Similarly, the incorporation of heterocycles into diolide structures was well tolerated and the 16-membered furan-containing macrocycle **10** was obtained in 79 % yield. To demonstrate the efficiency of the protocol on more complex substrates, the synthesis of macrocycles containing stereogenic centers or chiral bicycles was

performed. Macrodiolides **11** and **12**, derived from enantiopure tartrate derivatives, were isolated in good yields (58 and 65 % for the 15- and 18-membered macrocycles respectively) after 48 h. Similarly, two macrodiolides **13** and **14** were prepared based upon a norbornanedicarboxylic acid structure. The 15- and 18-membered macrodiolides **13** and **14** were both isolated in 68 % yields after 48 h.

Table 4.2. Substrate Scope of the $Hf(OTf)_4$-Catalyzed Macrodiolide Synthesis.[a]



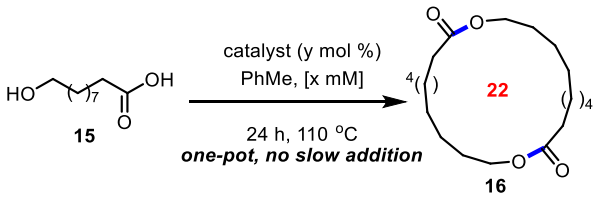
entry	product	yield (%)[a]	entry	product	yield (%)[a]
1	 **4**	58	6	 **8**	64[b]
2	 **5**	60	7	 **9**	79[b]
3	 **6**	96[b]	8	 **10**	79[b]
4	 **3**	92[b]	9	 **11** n = 1 **12** n = 4	58[b] 65[b]
5	 **7**	62[b]	10	 **13** n = 1 **14** n = 4	68[b] 68[b]

[a] Isolated yields following flash chromatography. [b] Macrocyclizations were run over 48 h.

In an effort to expand the substrate scope of the methodology, the optimization of the method towards the synthesis of head-to-tail type macrodiolides was pursued (Table 4.3). The

seco acid **15** was initially treated with $Hf(OTf)_4$ at 10 mol % at a higher concentration (10 mM) to try and force dimerization.[24] The desired 22-membered macrodiolide **16** was obtained following purification in 54 % yield. None of the corresponding 11-membered macrolactone was isolated. Performing the macrocyclization under more dilute conditions (5 mM) surprisingly afforded a lower yield of 31 % of the desired macrodiolide **16**, however dropping the catalyst loading again to 5 mol % re-increased the yield to 51 % (entry 3). When the catalyst loading was further decreased to 2.5 mol %, at 5 mM a 37 % yield was obtained, but by simply extending the reaction time to 48 h, a yield of 74 % of the desired head-to-tail dimer **16** could be obtained.[25] Furthermore, a smaller 18-membered macrodiolide **17** could be formed under the optimized conditions in 77 % yield (Table 4.4). In addition, macrodiolides based upon both meta- and paracyclophanes could be prepared (macrocycles **18** and **19** in 72 % and 74 % yield respectively).

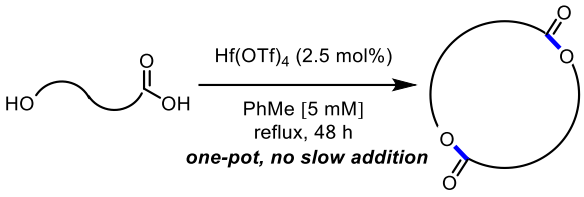
Table 4.3. Optimization of a catalytic synthesis of head-to-tail macrodiolides from the corresponding seco acids

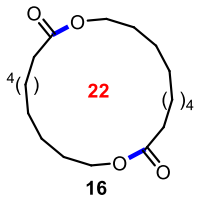
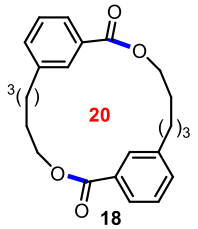
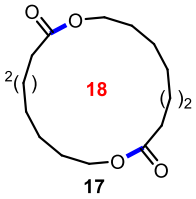
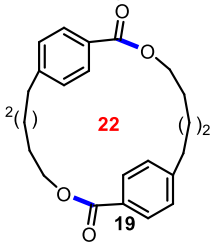


Entry	Catalyst Loading (mol %)	Concentration ([mM])	Yield **16** (%)[a]
1	10	10	54
2	10	5	31
3	5	5	51
4	2.5	5	37
5	2.5	5	74[b]

[a] Yields following chromatography. [b] 48 h reaction time.

Table 4.4. Substrate Scope of the $Hf(OTf)_4$-Catalyzed Head-to-Tail Macrodiolide Synthesis.



entry	product	yield (%)[a]	entry	product	yield (%)[a]
1		74	3		72
2		77	4		74

[a] Isolated yields following flash chromatography.

4.4. Conclusions

A protocol for an efficient catalytic synthesis of macrodiolides has been developed. The Lewis acid, $Hf(OTf)_4$, was identified as the most efficient catalyst and its utility was demonstrated in a rare example of the synthesis of macrodiolides derived from equimolar mixtures of diacids and diols. In addition, through optimization of the catalyst loading and reaction concentration, optimization of a protocol for the synthesis of a head-to-tail macrodiolide was demonstrated from the corresponding seco acid. The macrocyclization processes developed herein are catalytic, producing water as the sole by-product. In addition, the reaction conditions exploit a commercially available catalyst and are "one-pot" reactions

without the need for slow addition or azeotropic techniques. Given the prevalence of macrodiolides in biologically active natural products, in macrocyclic musks, their utility for macrocyclic library generation, and the absence of toxic stoichiometric by-products, the Hf(IV)-catalyzed macro-cyclizations should be highly useful.

Acknowlegements: The authors acknowledge the Natural Sciences and Engineering Research Council of Canada (NSERC), Université de Montreal and the Centre for Green Chemistry and Catalysis for generous funding.

4.5. Bibliography

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(19) The possibility of catalysis via in-situ formed HOTf in hafnium catalyzed direct esterifications has previously been shown to be negligible. See ref 17. In addition, macrocyclizations (1+2→3) performed with added K_2CO_3 afforded the desired product in 70 % yield.

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(24) At high concentration, linear dimers can be observed by analysis of crude 1H NMR and mass spectrometric analyses.

(25) The reaction was scalable, on a 1 mmol scale = 65 % of **14**

5. Direct Catalytic Macrolactonization from Secondary Alcohols and Carboxylic Acids

5.1. Introduction

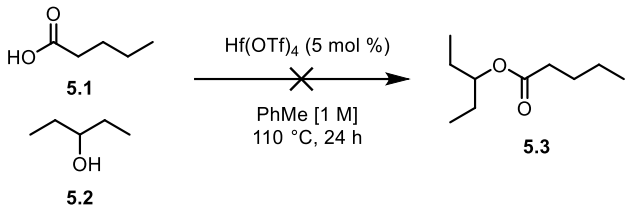
Many macrolactones found in Nature possess substitution in the ω-position.[1] In the corresponding linear precursors, the substitution, normally in the form of a secondary alcohol, augments the complexity of the macrolactonization reaction. The secondary alcohol functionality of the precursors for macrolactonization possesses increased steric hindrance, defined stereochemistry as well as modified electronics. As discussed previously, macrolactonization of seco acids having secondary alcohols typically occurs through stoichiometric activation of either the alcohol or the carboxylic acid. The mode of activation is often determined through cyclization of an enantioenriched macrocyclic precursor: 1) retention of configuration implies attack of the hydroxyl group onto the carbonyl, while 2) inversion of configuration or racemization implies attack of the carboxylic acid onto an activated hydroxyl group. It should be noted that isotopic labelling of oxygen can also be used to reinforce mechanistic proposals.

It was envisioned that employing the previously developed catalytic method of cyclization using $Hf(OTf)_4$ as a Lewis acid would represent an improvement over established methods for macrolactonization involving secondary alcohols. The absence of an activating group on either the carboxylic acid or the alcohol would help to diminish the steric effects during the cyclization process, and would produce only water as the by-product. An added benefit of investigating the cyclization of secondary alcohols would be to help elucidate mechanistic details of the Hf-catalyzed esterification. As discussed in the preceding chapters, an ideal

catalytic system for macrolactonization would have to tolerate the presence of water in the reaction medium. Consequently, an effort was made to develop new reaction conditions that would not require azeotropic heating or the addition of drying agents, such as molecular sieves. In addition, for practicality, slow addition was avoided. In the following chapter, a variety of catalyst systems were evaluated to develop the first direct catalytic macrolactonization from carboxylic acids and secondary alcohols.

5.2. Preliminary Results with $Hf(OTf)_4$ as Catalyst

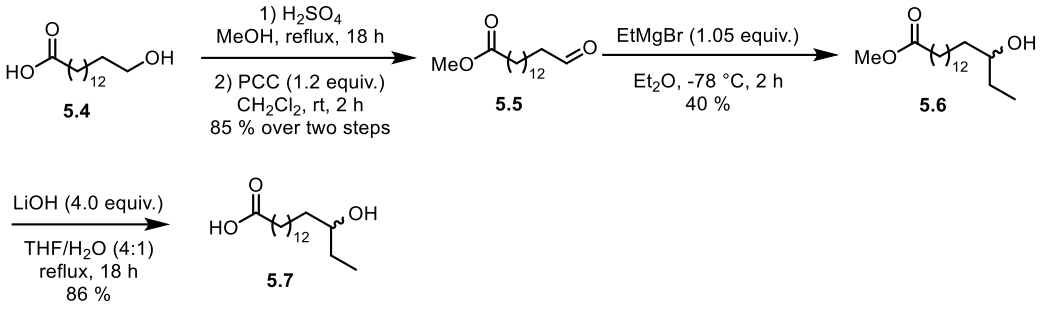
Preliminary studies on the possibility of performing macrolactonization using seco acids containing secondary alcohols began with both inter- and intramolecular studies (Scheme 5.1 and 5.3). First the $Hf(OTf)_4$-catalyzed method developed in Chapters 3 and 4 was applied to the esterification of valeric acid **5.1** and 3-pentanol **5.2**. Unfortunately, no desired ester **5.3** was produced. Instead, **5.1** was recovered in quantitative amount as opposed to **5.2**, which was not recovered, but converted to non-isolable side-products.



Scheme 5.1. Attempted catalytic esterification of secondary alcohols in an intermolecular process.

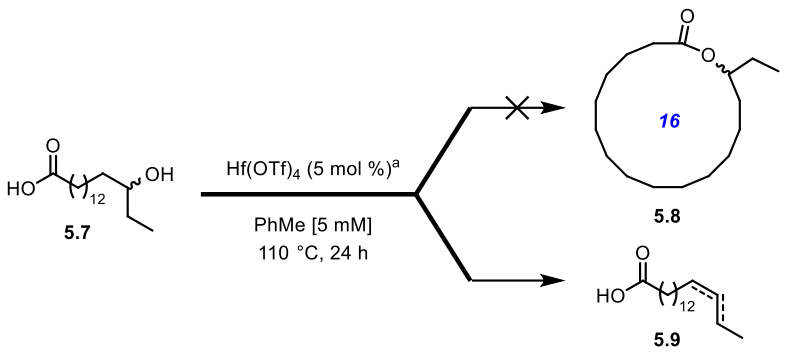
In parallel, an intramolecular macrocyclic precursor was synthesized in four steps from the commercially available 15-hydroxypentadecanoic acid **5.4** (Scheme 5.2). The seco acid **5.4** was first esterified using methanol and the alcohol functionality was oxidized to the corresponding aldehyde **5.5** using PCC in a combined yield of 85 %. Addition of

ethylmagnesium bromide afforded the secondary alcohol **5.6** in 40 % yield. The reaction was closely monitored by TLC to avoid competitive addition on the ester moiety and the starting material **5.5** could often be isolated (≈10-30 %) and resubmitted to the reaction conditions. Finally, saponification of **5.6** produced the desired macrocyclic precursor **5.7** in 86 % yield.



Scheme 5.2. Synthesis of seco acid **5.7**, possessing a secondary alcohol.

When seco acid **5.7** was treated to the $Hf(OTf)_4$-catalyzed macrolactonization conditions, only undesired elimination products **5.9** were observed (the internal alkenes were identified by ^1H NMR analysis (Scheme 5.3)). When the cyclization of seco acid **5.7** was repeated with the addition of Proton Sponge® to quench traces of HOTf, elimination was again observed. It is not clear if the formation of elimination products suggests the ability of $Hf(OTf)_4$ to activate the alcohol group during macrolactonization, or whether alcohol activation became the dominant pathway due to slow macrocyclization. As a result, a broader survey of possible catalysts for macrolactonization of seco acids containing secondary alcohols was undertaken.



Scheme 5.3. Attempted catalytic macrolactonization of a secondary alcohol seco acid.

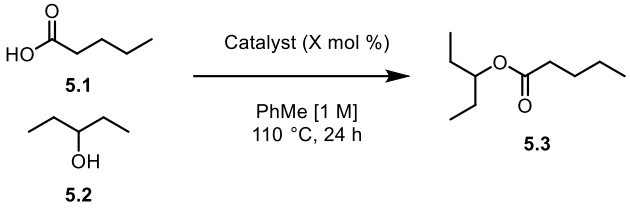
[a] Same results were obtained with the addition of Proton Sponge® (50 mol %).

5.3. Evaluation of Different Catalyst Systems for Macrolactonization of Seco Acids Possessing Secondary Alcohols

The evaluation of a catalytic activation system for macrolactonization of seco acids bearing secondary alcohols began with a survey of different transition metal-based and lanthanide-based Lewis acids that exhibited activity in macrocyclization of precursors bearing primary alcohols. Using a selection of catalysts surveyed in previous studies, esterifications were first examined on an intermolecular model (**5.1**+**5.2**→**5.3**, Table 5.1). First, another hafnium-based catalyst, $HfCl_4(THF)_2$, a complex known to promote esterification under strictly anhydrous and azeotropic conditions,[2] produced 24 % of the desired ester **5.3** when a catalyst loading of 5 mol % was used without any precaution taken to remove water from the reaction medium (entry 1). Increasing the catalyst loading to 20 mol % produced only a modest improvement in yield (40 % of **5.3**, entry 2). Another Hf-based Lewis acid showed no conversion toward esterification (entry 3). While $Sc(OTf)_3$ (entry 5) did not provide appreciable yields of ester product, the lanthanide-based catalyst $Dy(OTf)_3$ (entry 4) afforded a 60 % yield

of the desired ester **5.3**. Softer Lewis acid $Cu(OTf)_2$ also promoted esterification to afford **5.3** in 55 % yield (entry 6), but disappointingly, boosting the catalyst loading did not further improve the yield (entry 7). As $Cu(OTf)_2$ is known to produce HOTf in the reaction medium,[3] the addition of either Hünig's base or Proton Sponge® was investigated but did not improve the yield. The use of $Cu(OAc)_2$, in which the ligand has a weaker conjugate acid, did not produce any esterification product (entry 8).

Table 5.1. Brief catalyst survey for the intermolecular esterification.



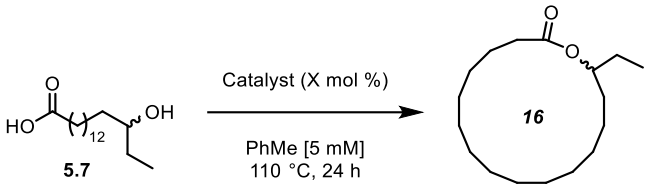
Entry	Catalyst	Catalyst Loading (mol %)	Yield (%)
1	$HfCl_4(THF)_2$	5	24
2	$HfCl_4(THF)_2$	20	40
3	$Hf(O\textit{n}Bu)_4$	5	< 5
4	$Dy(OTf)_3$	5	60
5	$Sc(OTf)_3$	5	0
6	$Cu(OTf)_2$	5	55
7	$Cu(OTf)_2$[a]	10	32
8	$Cu(OAc)_2$	5	< 5

[a] Addition of Hünig's base (50 mol %) or Proton Sponge® (50 mol %) did not affect the yield.

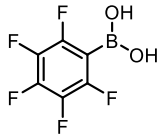
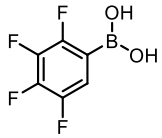
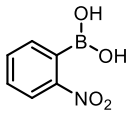
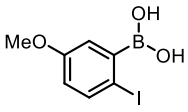
In addition, the cyclization of the macrocyclic precursor **5.7** was also surveyed with various transition metal-based and lanthanide-based Lewis acids (Table 5.2). The investigations began with $Cu(OTf)_2$, which was identified during the studies of the intermolecular version of the reaction. Once again, $Cu(OTf)_2$ was able to promote the reaction, albeit in lower yield than

what was observed in the intermolecular case (34 % of macrocycle **5.8**, entry 1). To discern if water was having an effect on the catalysis, the reaction was repeated with the addition of 200 equivalents of water (entry 2). Unfortunately, the addition of water significantly altered the reaction profile, as no macrolactonization product was observed and elimination products were isolated. Increasing the catalyst loading had a detrimental effect, as no desired macrocycle could be isolated when 10 mol % of $Cu(OTf)_2$ was added (entry 3). As the lanthanide catalyst $Dy(OTf)_3$ was found to be a promising candidate from the intermolecular studies, it was evaluated next (entry 4). In contrast to the intermolecular esterifications, $Dy(OTf)_3$ did not promote any macrocyclization. In addition, none of the other lanthanide-based or transition metal-based Lewis acids tested afforded significant yields of the desired macrolactone **5.8** (entry 5 to 12).

Table 5.2. Catalyst survey for the intramolecular esterification.

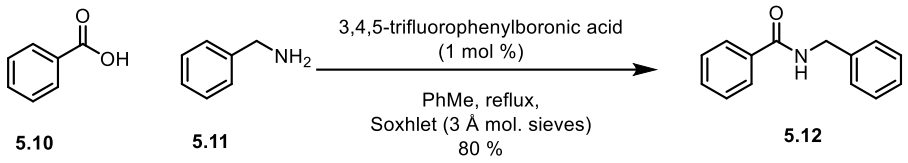


5.7 5.8

Entry	Catalyst	Catalyst Loading (mol %)	Yield (%)
1	$Cu(OTf)_2$	5	34[a]
2	$Cu(OTf)_2$[b]	5	< 5[a]
3	$Cu(OTf)_2$	10	< 5[a]
4	$Dy(OTf)_3$	10	< 5[a]
5	$Sm(OTf)_3$	5	15[a]
6	$Sm(OTf)_3$	10	< 5[a]
7	$La(OTf)_3$	5	< 5[a]
8	$Yb(OTf)_3$	5	< 5[a]
9	$Sc(OTf)_3$	5	< 5
10	$HfCl_4(THF)_2$	5	< 5
11	$ZrCl_4(THF)_2$	5	< 5
12	AgOTf	5	< 5
13		5	< 5
14		5	< 5
15		5	< 5
16		5	< 5

[a] A mixture of elimination products was observed. [b] 200 equiv. of H_2O were added.

Following the disappointing results with metal-based Lewis acids, an alternative option was envisaged using boronic acids. Boronic acid catalysis (BAC) has been recently developed to promote activation of alcohols and carboxylic acids in a covalent fashion.[4] Numerous reactions[5] can be promoted by BAC, and often in a milder environment than other previously established methods.[5p,5q] As an example, 3,4,5-trifluorophenylboronic acid (1 mol %) can promote the condensation between benzoic acid and benzylamine in 80 % yield in 22 hours (Scheme 5.4).[6]

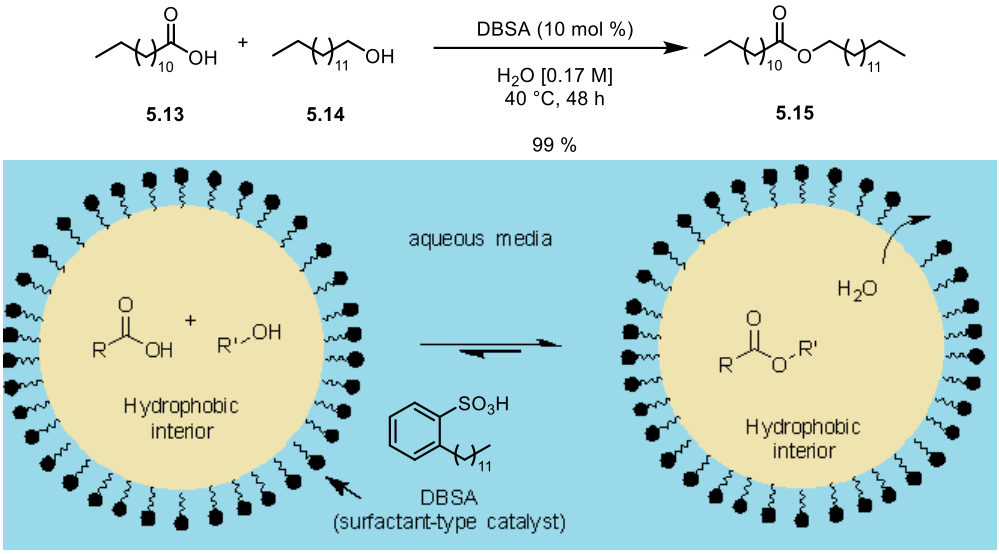


Scheme 5.4. BAC direct amidation of benzoic acid.

It then seemed reasonable to think that BAC could efficiently produce macrolactones directly from carboxylic acids and secondary alcohols. Four catalysts were then tested (entries 13 to 16, Figure 5.1) in the cyclization of the intramolecular macrocyclic precursor **5.7**. However, the precursor was recovered in quantitative yield in all cases, and the BAC method was not pursued any further.

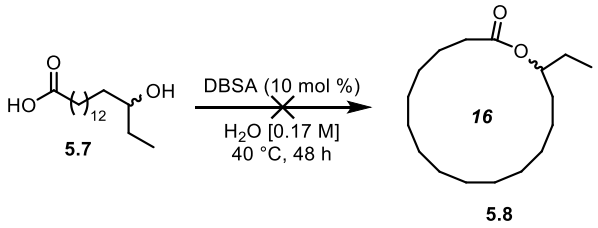
Brønsted acid catalysis is also a possible alternative in the synthesis of esters from secondary alcohols. Dodecylbenzenesulfonic acid (DBSA) can play a dual role of catalyst and surfactant (Scheme 5.5) to catalyze esterification between fatty acids and fatty alcohols in water.[7] The fatty substrates are solubilized in the hydrophobic interior of the DBSA droplets, and Brønsted-acid activation, by the sulfonic acid moiety of DBSA, promotes the dehydrative esterification. The water formed during condensation is preferentially ejected out of the hydrophobic droplet, preventing reversible hydrolysis. As such, the micellar catalysis controls

the equilibrium, favoring the formation of the ester even when an equimolar amount of alcohol is used.



Scheme 5.5. Direct esterification of fatty acid using a surfactant-type catalyst.[7]

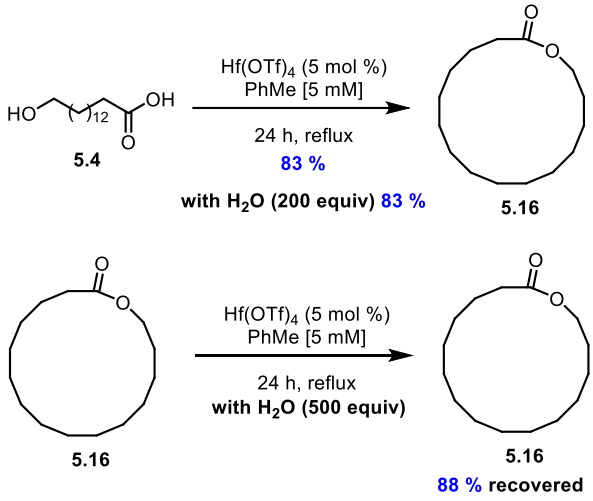
Given the potential to develop a macrolactonization using water as solvent, often a key goal among the principles of green chemistry,[8] the macrocyclic precursor **5.7** was submitted to the reported reaction conditions used for intermolecular coupling. Disappointingly, DBSA did not demonstrate any reactivity and the seco acid **5.7** was recovered in quantitative yield (scheme 5.6).



Scheme 5.6. Attempted DBSA-catalyzed macrolactonization of seco acid **5.7**.

5.4. Mechanistic Discussion of the Hf-Catalyzed Macrolactonization

The direct catalytic macrolactonization using $Hf(OTf)_4$ from primary seco acids has been demonstrated to afford good yields of macrocycles, producing only water as the sole by-product. In addition, preliminary explorations demonstrated that the $Hf(OTf)_4$ catalyst was one of the few Lewis acids surveyed which retained its activity to promote macrolactonization when water was directly added to the reaction mixture. In addition, when the product macrolactone was resubmitted to the reaction conditions with an excess of added water, very little ring-opening was observed (Scheme 5.7). However, the methodology developed was not effective for the macrocyclization of secondary seco acids. The following section presents several mechanistic scenarios although no definitive mechanism has to date been elucidated.



Scheme 5.7. Macrolactonization via $Hf(OTf)_4$ catalysis.

Considering that $Hf(OTf)_4$ has been synthesized for the first time only in 1995,[9] there is still little information available about its properties as a Lewis acid catalyst. We know that it is

a rather large molecule with the four OTf groups, but with a strong acidity due to the additive electron withdrawing effect of the four groups. It is interesting to note that titanium can accommodate up to only three OTf groups, as opposed to Zr(IV) and Hf(IV) which can accommodate the four groups, both having a similar atomic radius (between 0.72 and 0.75 Å).[10] It would have been useful to compare the reactivity of $Hf(OTf)_4$ with $Zr(OTf)_4$, but the latter was not commercially available and there was no information regarding its stability to air. On the other hand, $Hf(OTf)_4$ is known to be air stable and also stable at 300 °C[10] and would not degrade during the course of the macrolactonization reaction, in refluxing toluene.

5.4.1. Thermodynamic Parameters in Macrolactonization

The most common mechanistic possibility would involve an addition/elimination type mechanism similar to what is accepted for typical Brønsted acid-catalyzed (Fischer) esterification. Such esterifications are known to be reversible processes with similar activation energies between key intermediates (Figure 5.1).[11] The activation energy necessary to reach **TS-1** from the protonated intermediate **Int-1** is very similar to the activation energy required to form **TS-2** from **Int-3**, leading to the formation of a thermodynamic equilibrium as the principle of microscopic reversibility states that for an equilibrium reaction, each mechanistic step must be at equilibrium, meaning that the catalyst promotes both the esterification and the hydrolysis through the same mechanistic pathway. In Fischer-type esterification processes, the forward reaction can be driven by either using an excess of one of the reactants or by removing the by-product (water) from the reaction mixture according to the equilibrium constant equations.

$$(1)\ K_{eq} = \frac{[ester][water]}{[alcohol][acid]}$$

$$(2)\ \Delta G° = \Delta H° - T\Delta S°$$

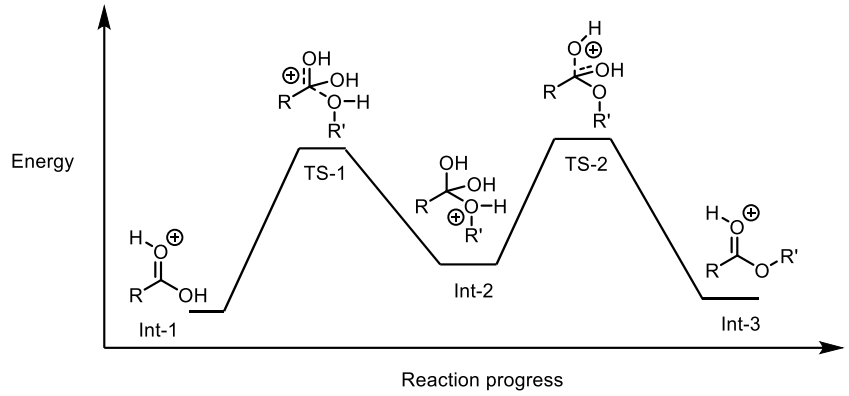


Figure 5.1. Energy diagram and thermodynamic equations related to a Brønsted-acid catalyzed esterification reaction

When considering the thermodynamic parameters of a general macrolactonization, one is to expect a similar equilibrium. In considering the entropic parameter (ΔS), there are two factors to take into account, one which favors the cyclization and the other favoring the hydrolysis. The macrolactonization of seco acids is a unimolecular process, activated by a catalyst, which produces two molecules: a macrolactone and water. The increased disorder brought by the generation of two molecules in the system is thus favorable to cyclization. However, the macrolactone formed is often more rigid than the seco-acid and would thus favor the hydrolysis process.[12] The enthalpic parameter (ΔH) would also be similar to the esterification reaction; the same types of bonds are cleaved and formed in the reactant and in the products and the most stable conformer of **5.16** could have a similar energy than the one of **5.4**. Indeed, in large non-substituted macrocycle, the ester moiety is capable of adopting the more stable *Z*-geometry (as opposed to, for example, the ester moiety in tetrahydro-2*H*-pyran-2-one which is forced to adopt an *E*-geometry). As such, the thermodynamic factors lead to an equilibrium constant which would not favor either the formation of the macrocycle or the hydrolysis.

5.4.2. Kinetic Parameters in Macrolactonization

We also have to consider the kinetic factors to understand why the reaction proceeds in such good yield. As the reaction is conducted in a highly diluted medium, bimolecular reactions, such as both oligomerization and hydrolysis, are slowed down as the concentration of the reactants are directly affects the rate of the reaction (Scheme 5.8). Although both the hydrolysis and the macrocyclization undergo via reverse mechanisms (microreversibility), they have different molecularity and order of reaction. It is then possible that the reaction is kinetically controlled rather than thermodynamically controlled. A simple control reaction to verify the hypothesis would be to run the reaction for a longer time to reach thermodynamic control and to compare the conversion and the yields. However, good yields were also obtained in intermolecular esterifications, in which the rate of both the forward and reverse reaction are similarly affected by the concentration (Scheme 5.8, (3) and (4)). Kinetic control then seems to not be a plausible explanation.

$$(1)\ r = k[\text{seco acid}]$$

$$(2)\ r = k[\text{seco acid}][\text{seco acid}]$$

$$(3)\ r = k[macrolactone][water]$$

$$(4)\ r = k[acid][alcohol]$$

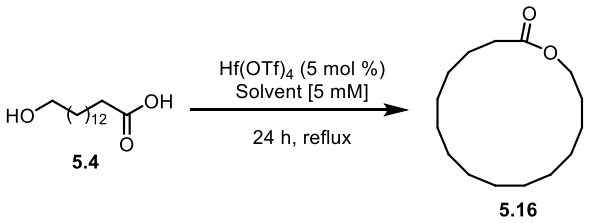
$$(5)\ r = k[ester][water]$$

Scheme 5.8. Rate equations of macrolactonization (1), dimerization (2), macrolactone hydrolysis (3), esterification (4) and ester hydrolysis (5) reactions.

Moreover, the equilibrium constant and the rate of the hydrolysis reaction can be influenced through removal of water from the reaction mixture, thereby driving the $Hf(OTf)_4$ macrolactonization reaction to completion. Although no precaution was taken to remove water from the reaction mixture of the $Hf(OTf)_4$-catalyzed macrolactonization of seco acids, one cannot be certain how much water remains in the mixture during the course of the reaction. As the reaction is conducted in toluene (which forms a heterogeneous pressure maximum azeotrope with water)[13] using a water condenser, one can assume that just enough water produced during the course of the reaction is being collected in the head-space of the round-bottom flask or glass joints, to allow the reaction to proceed in good yield. It should be noted that control reactions were performed in which excess water was added and the reaction still proceeded in good yields. Some control experiments were performed to assess the importance of water removal and solvent effects in the macrolactonization (Table 5.3). When more polar ethereal solvents such as 1,4-dioxane (b.p. 101 °C, entry 2) or 1,2-dimethoxyethane (DME, b.p. 85 °C, entry 3) were used, only the starting seco acid **5.4** was recovered after 24 hours. However, when chlorobenzene was used (b.p. 132 °C, entry 4), 88 % yield of **5.16** was isolated. It is intriguing to see that only both arene-containing solvents provided reactivity. It is a possibility that PhMe and PhCl destabilize the macrocyclic precursor by interactions with the carboxylic acid or the alcohol. They could also force it to adopt a conformation that is prone to cyclization. Such destabilization of the precursor changes the thermodynamic properties of the reaction and could thus favor the formation of the macrolactone. As the solvent scan is relatively limited, it is difficult to make any firm conclusions. The inability of DME or 1,4-dioxane to promote reactivity could be due to competitive coordination of the solvent for available Lewis acidic sites on the hafnium catalyst. Another possible conclusion would be that DME and 1,4-dioxane

retain water to a greater degree than PhMe or PhCl. An additional control experiment was performed where the water condenser was exchanged for a sealed tube vessel. The sealed tube was placed in an oil bath so that only the reaction mixture was submerged and the head-space remained above the oil bath. While $Hf(OTf)_4$ was still able to promote a good yield of the desired macrolactone **5.16**, the yield dropped from 88 % to 69 % (entry 5). Although the water formed would still be able to be separated from the reaction mixture and therefore from the equilibrium, the increased internal pressure of the sealed tube[14] could partly force the molecules of water to condense back into the mixture which could explain the slight drop in yield. Such results could support that the removal of water from the reaction mixture is important to obtain a good yield.

Table 5.3. The $Hf(OTf)_4$-catalyzed macrolactonization in different solvents



Entry	Solvent	Setup	Yield (%)
1	Toluene (PhMe)	Round-bottom flask with water condenser	83
2	1,4-dioxane	Round-bottom flask with water condenser	0
3	1,2-dimethoxyethane (DME)	Round-bottom flask with water condenser	0
4	Chlorobenzene (PhCl)	Round-bottom flask with water condenser	88
5	Toluene (PhMe)	Sealed tube vessel	69

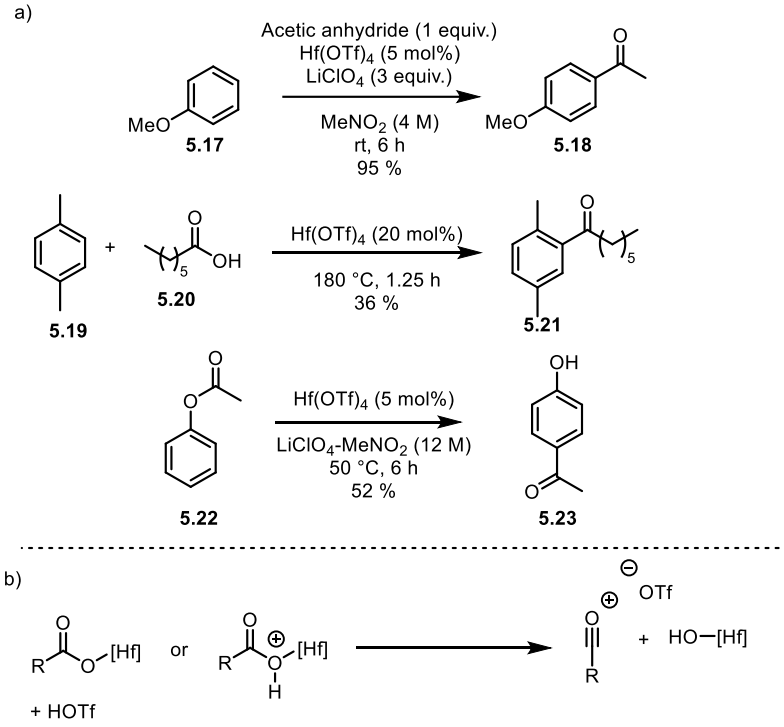
It is also possible, that as water is mostly insoluble in toluene, a vigorous stirring is necessary to equally distribute water in the reaction mixture. If the stirring was not sufficient, it could also explain why the hydrolysis reaction was not observed. Further experiments with an

improved mixing, with other solvents and vessel types would be necessary to draw more concrete conclusions.

5.4.3. Alternative Mechanistic Scenarios

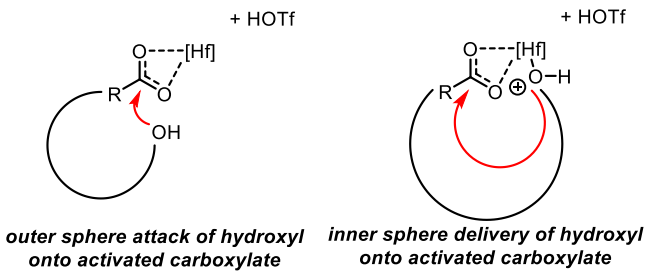
It should be noted that other mechanistic scenarios are possible for the formation of the macrolactones as $Hf(OTf)_4$ is capable of activating different functionalities.[10] The selectivity of primary versus secondary alcohols could be explained by the different possible scenarios.

One of the possibilities is Lewis acid activation of the C-O unit of the carboxylic acid (Scheme 5.9). It is important to consider that $Hf(OTf)_4$ has been used to promote Friedel-Crafts acylation reactions[15] and to promote Fries rearrangement reactions of acylated phenols and naphthols,[16] where acylium ions have been proposed as intermediates (note that there has been no direct observation of discrete acylium ion intermediates in the published examples). Such a change in the mechanistic pathway would modify the transition state of the rate-determining step and therefore would also modify the rate of both the forward and the reverse reactions, although could not explain the selectivity of primary seco acids over secondary seco acids. Furthermore, for the acylation reaction between **5.19** and **5.20**, $Hf(OTf)_4$ was not the optimal catalyst found. Indeed, $Er(NTf_2)_3$ was found to be the more productive catalyst[15b] and it would be informative to test $Er(NTf_2)_3$ for the macrolactonization reaction or other $Ln(NTf_2)_3$. To the best of our knowledge, $Hf(NTf_2)_4$ has not been synthesized yet, but testing other strong electron-withdrawing ligands could also prove to be enlightening.



Scheme 5.9. a) Acylation reactions promoted by $Hf(OTf)_4$. b) Possible formation of an acylium ion by a hafnium catalyst.

Another plausible mode of activation could involve bidentate coordination of the hafnium to both the carbonyl oxygen and carboxylate oxygen (Scheme 5.10). It has been reported that hafnium is able to coordinate up to 8 ligands within its coordination ion spheres.[17] In discussing the coordination sphere of hafnium, it is worth noting that in all of the mechanistic scenarios presented, the hydroxyl group does not necessarily need to attack the carbonyl group via an outer sphere mechanism, as it could rather come from an inner sphere delivery (Scheme 5.10, *right*).



Scheme 5.10. Possible bidentate modes of activation on the carboxylic acid by the hafnium catalyst.

At first glance, the steric bulk of the nucleophile could be invoked as a reason for lack of macrocyclization with secondary alcohols. The influence of steric hindrance would be even more considerable if one were to consider an inner sphere delivery of the nucleophile. However, it should be noted that increased steric hindrance in the α-position of the carboxylic acid was not observed to be deleterious to the macrocyclization, as macrocycles **5.24** and **5.25** were synthesized in similar yields to less sterically encumbered macrocycles (Figure 5.2).

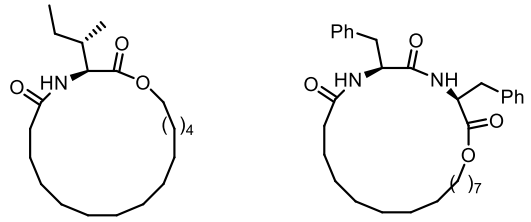
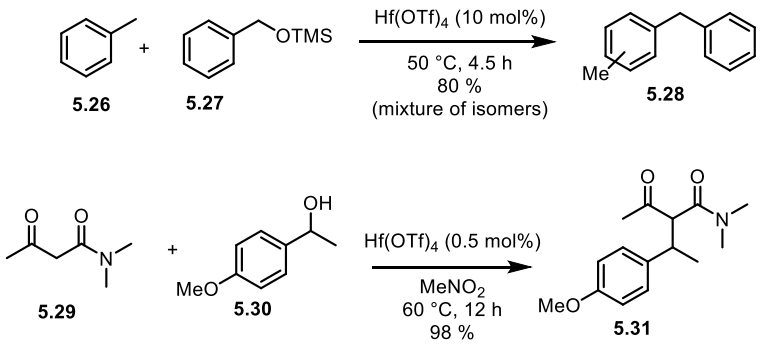


Figure 5.2. Macrolactones synthesized via $Hf(OTf)_4$ catalysis in which α-substituents are present.

In considering whether the hydroxyl group of the seco acid could bind to the hafnium catalyst, we can also imagine an alternative mechanistic scenario: substitution reaction via hydroxyl group activation[18] (Scheme 5.11) rather than carbonyl or carboxyl activation.



Scheme 5.11. Examples of $Hf(OTf)_4$-catalyzed substitution reaction.

When the macrocyclization of seco acids having a secondary alcohol was investigated, the formation of alkenyl side-products was observed. Elimination processes (E1 and E2) are known to become competitive reactive pathways when leaving groups are bonded to secondary carbons. The elimination processes are much slower on primary carbons and therefore S_N2 reactions become favored mechanistic pathways.[19] The observation of alkene by-products in some macrocyclization attempts with a secondary alcohol-bearing substrate could support a mechanism which invokes alcohol activation. To further explore the alcohol-activation hypothesis, typically esterifications are performed on chiral secondary alcohol substrates and the products are examined to determine whether the chiral center underwent retention or inversion of configuration. Given the absence of productive reactivity in the Hf-catalyzed system with secondary alcohols, an alternative would be to conduct the reaction with a chiral deuterated primary alcohol[20] as a substrate or to do oxygen-labeling studies in the future. It should also be noted that the formation of elimination products may just be due to a background reaction becoming competitive when macrocyclization is slow. Other future work could also include pK_a relationship studies to see the effect on both the alcohol and the carboxylic acid functionalities.

5.5. Summary

In summary, several mechanistic pathways are available for the $Hf(OTf)_4$-catalyzed macrolactonization. While the available data does not point with 100 % certainty to one mechanism, it may in fact be that several mechanistic pathways are available and the mechanism could change based on the nature of the substrate. Further studies would be necessary to draw conclusions as to why the hydrolysis reaction is not observed and to why secondary alcohols do not undergo cyclization.

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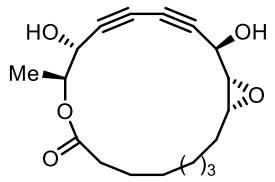
6. Alternative Strategies for the Synthesis of Macrolactones: Application of the Phase Separation Strategy for the Synthesis of Ivorenolide A

The preceeding chapters of the present thesis outlined new catalytic methods for the synthesis of macrolactones via its defining ester functionality. However, analysis of the given structure of a macrolactone does not always point to cyclization via its corresponding seco acid as the most efficient retrosynthetic disconnection. Indeed, carbon-carbon bond formation, particularly via catalysis, can often present new avenues for preparing desired macrocycles. Even when catalysis allows for new synthetic routes, both prefunctionalization of substrates as well as the ultimate macrocyclization event each present their own challenges, the latter of which often limits practicality of eventual large-scale synthesis. As a solution to the challenges, our group has developed a phase separation strategy for improving macrocyclization reactions that exploits catalysis and unique solvent effects which allow cyclization to be conducted at relatively high concentrations. As a demonstration of the applicability of the phase separation strategy toward the synthesis of complex macrolactones, the formal total synthesis of ivorenolide A (Figure 6.1) was pursued.



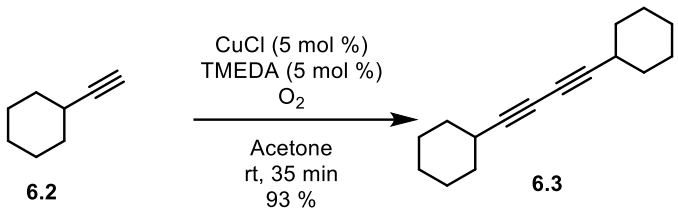
Ivorenolide A
6.1

Figure 6.1. The macrolactone ivorenolide A.

Consequently, the present chapter first provides a brief background on our group's previous work involving the phase separation strategy for macrocyclization using the Glaser-Hay reaction, a catalytic, oxidative coupling of terminal alkynes. Subsequently, background into the ivorenolides and previous syntheses will be presented. The following chapter (Chapter 7) will describe our results into the formal total synthesis of ivorenolide A via the phase separation strategy.

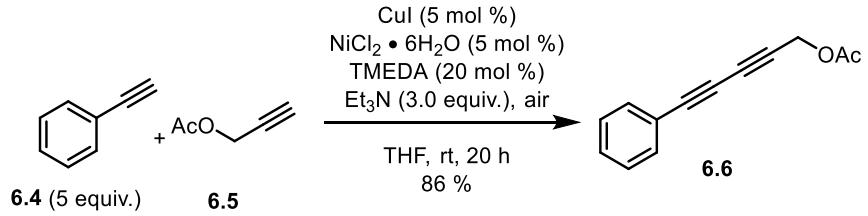
6.1. The Glaser-Hay Coupling Reaction

The Glaser-Hay reaction was first introduced in 1962 when Hay discovered that TMEDA could serve as a ligand for Cu(I) salts to form soluble, catalytically active species for the dimerization of terminal alkynes (Scheme 6.1).[1] Since then, the reaction has been widely utilized to form symmetrical 1,3-diynes.[2] However, heterocoupling is challenging under the standard reactions conditions due to differences in the relative rates of coupling for different alkynes (aryl alkynes are much more reactive than alkyl alkynes) and because of unfavorable statistical probabilities.[1b] Nonetheless, it is possible to use the standard reaction conditions to form unsymmetrical diynes if one of the partners is immobilized onto a solid support.[3] However, the formation of unsymmetrical 1,3-diynes is most commonly achieved under Cadiot-Chodkiewicz reaction conditions which require pre-functionalization (halogenation) of one of the reaction partners. Other types of catalysis have also been developed for heterocoupling where one of the partners is prefunctionalized.[4]



Scheme 6.1. The first Glaser-Hay reaction reported in 1962.

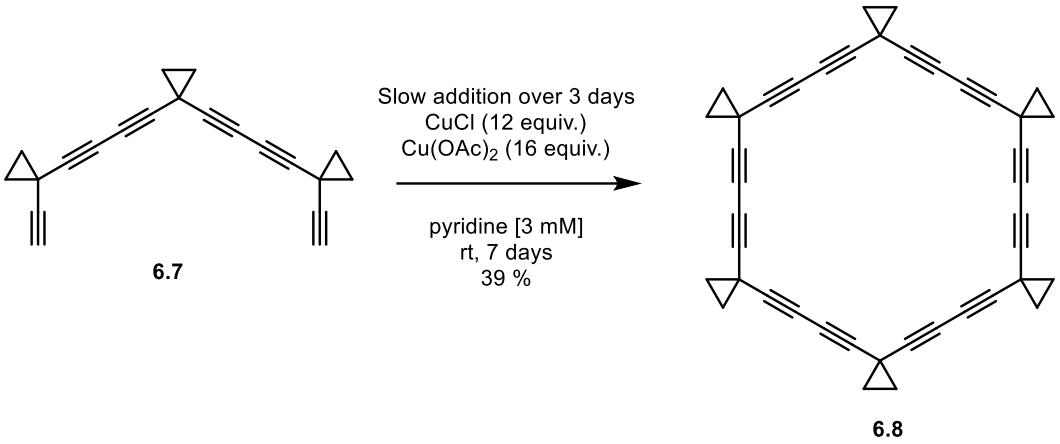
In 2009, Lei and co-workers developed a co-catalyzed terminal alkyne heterocoupling reaction.[5] They found that $NiCl_2 \cdot 6H_2O$ and CuI, under an aerobic atmosphere, could efficiently catalyze the formation of unsymmetrical 1,3-diynes when using TMEDA as a ligand and Et_3N as a base. Although five equivalents of the more reactive aryl alkyne were necessary to compete with the unwanted homocoupling reactions, good yields were obtained after 20 hours at room temperature. The mechanism still remains under investigation to fully understand the co-catalysis.[5]



Scheme 6.2. Lei's synthesis of unsymmetrical diynes.

The Glaser-Hay reaction is somewhat underutilized in the synthesis of conjugated diyne-containing small molecules as organic chemists have privileged the Cadiot-Chodkiewicz approach, especially for heterocoupling. The main contribution of the Glaser-Hay reaction has been found in the synthesis of molecules in materials and supramolecular chemistry. Macrocyclic polyynes for instance, such as the cyclic hexamer **6.8,** have been synthesized by oxidative coupling of terminal alkynes.[6] Typical macrocyclic reaction conditions were used; superstoichiometric quantities of two Cu salts, slow addition, high dilution and long reaction

times provided macrocycle **6.8** in 39 % yield. Such reaction conditions have certainly been a drawback for chemists and both more efficient and user-friendly protocols are still needed.

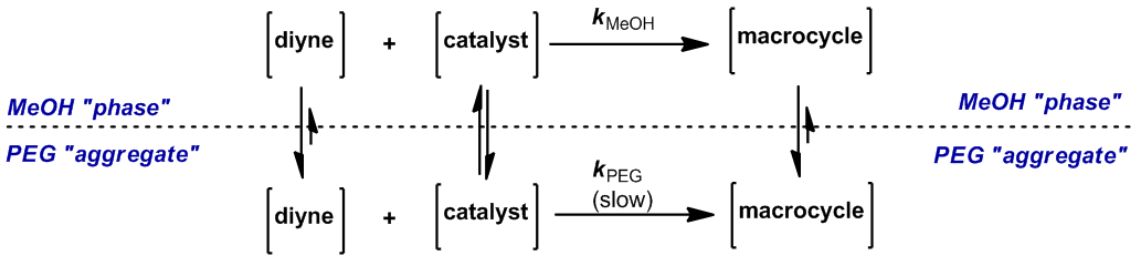


Scheme 6.3. Synthesis of a macrocyclic polyyne under Glaser-Hay conditions.

6.2. The Phase Separation Strategy for Macrocyclization employing the Glaser-Hay Coupling Reaction

In 2011, our group reported a phase separation strategy that allows for macrocyclic Glaser-Hay reactions to be performed at relatively high concentrations.[7] The principles behind the strategy involve the use of poly(ethylene) glycol (PEG) as a co-solvent and its aggregation properties, substrate solubility preferences therein and ability for catalyst inhibition. When macrocyclizations of diynes are performed in solvent mixtures of PEG and a hydrophilic solvent like MeOH, surface tension measurements show that PEG has a tendency to form aggregates.[8] A survey of solvent effects in the phase separation strategy found that the chain length, end groups and branching characteristics of the PEG co-solvent all influenced the aggregation properties.[9] Furthermore, UV-vis spectroscopy points to PEG preferentially solubilizing lipophilic organic compounds, like the diyne precursors for macrocyclization via a Glaser-Hay coupling, in preference to the hydrophilic solvent MeOH.[10] If a catalytic system is introduced

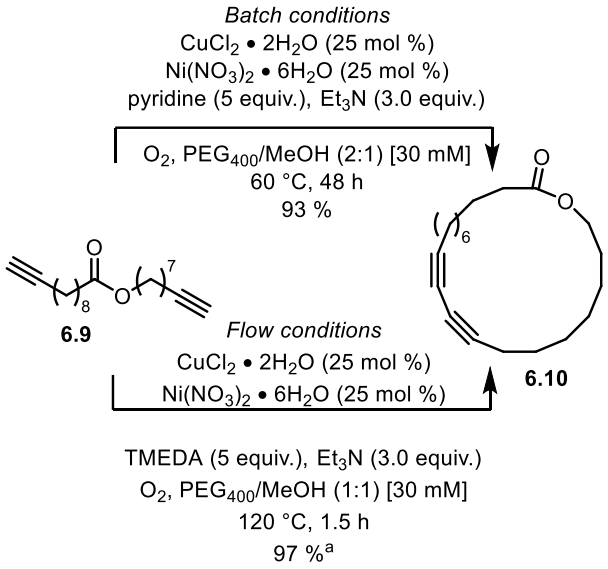
and is exhibiting higher reactivity in the MeOH phase than the PEG phase, then the cyclization theoretically occurs preferentially in MeOH, where the catalytic system is active but the diyne substrate is only present in a low concentration (Scheme 6.4). In other words, the phase separation strategy mimics high dilution conditions without the need for large quantities of solvents.



Scheme 6.4. Representation of the phase separation reaction conditions.

As proof-of-principle for the phase separation strategy, the Glaser-Hay coupling of diyne **6.9** could be promoted by a Cu/Ni co-catalyst system in a 2:1 mixture of PEG_{400}/MeOH.[10] The macrocyclization was performed at a concentration of 30 mM, affording the desired 21-membered macrocycle **6.10** without producing significant amounts of oligomers (Scheme 6.5 *top*). Macrocycle **6.10** could be attained in 93 % yield at concentrations 150 to 500 times the concentrations normally reported in the literature (yield of **6.10** was 13 % at 0.2 mM), and some betterment in the reaction time could be found when using microwave heating.[11] To further ameliorate the reaction, the phase separation strategy was transposed for macrocyclization in a continuous flow setup.[12] As the macrocyclization reaction times under phase separation were long under batch conditions (48 h), the improved mixing and heat transfer associated with continuous flow could help reduced reaction time.[13] Continuous flow is also regarded as an industrially viable method to scale up reactions in a safe fashion.[14] Impressively, the transposition of the batch reaction conditions to continuous flow conditions for the cyclization

of **6.9** allowed **6.10** to be formed in 97 % yield while drastically diminishing the reaction time (48 h vs. 1.5 h) (Scheme 6.5 *bottom*). When the reaction (**6.9→6.10**) was carried on a 1 mmol scale, the excellent yield was maintained (93 %). Importantly, the PEG_{400}/MeOH ratio was slightly lowered (1:1) due to the viscosity of the PEG in the flow reactor; however, similar yields could be achieved, often with reduced catalyst loadings while using an alternative polymeric co-solvent derived from poly(propylene) glycol (PPG_{425}), which also had a reduced viscosity.[12]



Scheme 6.5. Phase separation strategy for macrocyclic Glaser-Hay coupling. *Top*: Batch conditions. *Bottom:* Continuous flow conditions. [a] 93 % yield was obtained on a 1 mmol scale.

While our research group has begun to explore the utility of the phase separation strategy in other catalytic transformations such as copper-catalyzed azide-alkyne cycloadditions[15] and ring-closing olefin metathesis,[16] several important avenues remain to be explored within the Glaser-Hay variant. The substrate scope that was explored was limited, and did not address the influence of racemizable chiral centers, steric hindrance about the alkyne reaction centers or tolerance to common protecting groups. In addition, although macrocyclization could be adapted for continuous flow applications, no investigation of the feasibility of scale-up of

complex macrocycles at the gram scale had been demonstrated. To respond to these questions, the formal total synthesis of ivorenolide A **6.1**, a rare macrolide bearing a 1,3-diyne unit embedded within its macrocyclic framework, was targeted.

6.3. The Ivorenolide Macrolactones

Many natural macrolactones possess interesting biological activities such as antibiotic, cytotoxic and antiangiogenesis properties, and have an important range of structural diversity.[17] Ivorenolides A **6.1** and B **6.11** are natural macrocycles that have been recently isolated from the stem bark of *K. ivorensis*[18] and have shown impressive immunosuppressive properties (Figure 6.2).[19] Ivorenolides A and B possess a conjugated 1,3-diyne moiety, rarely seen in macrocyclic natural products, embedded in an 18- and a 17-membered ring macrolactone, respectively. Motivated by the need for long-term tolerated immunosuppressive agents with less side effects,[19] total syntheses of ivorenolides soon followed their reported isolation.

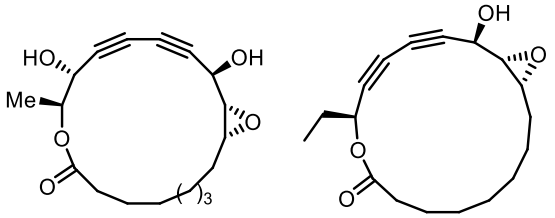
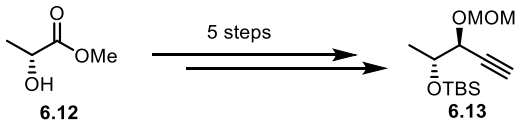


Figure 6.2. Naturally occurring members of the ivorenolide family.

6.3.1. Total Synthesis of the Unnatural Enantiomer of Ivorenolide A

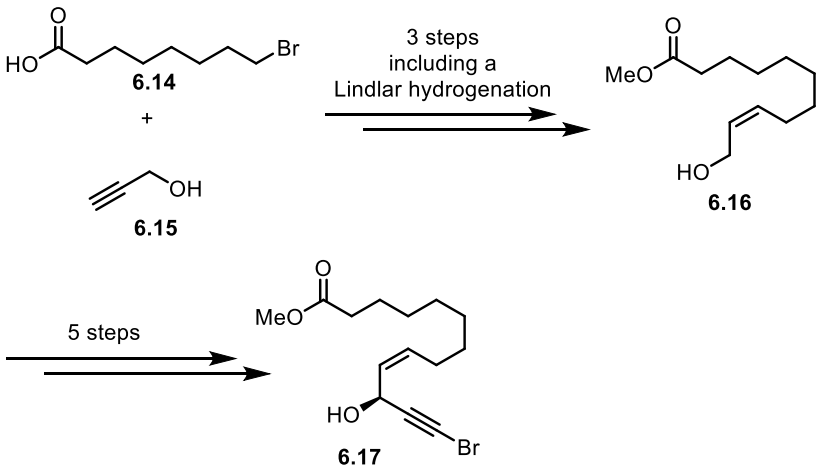
The first total synthesis of a member of the ivorenolide family was reported in 2012 by Yue and co-workers.[18a] The key steps of the synthesis of ***ent*-6.1** are an intermolecular Cadiot-Chodkiewicz reaction to form the conjugated diyne moiety and a Yamaguchi macrolactonization reaction as the ring-closing step. The synthesis commenced with the

derivatization of (*R*)-methyl lactate **6.12** into bis-protected diol **6.13** which would serve as one of the two Cadiot-Chodkiewicz reaction partners in five steps (Scheme 6.6).



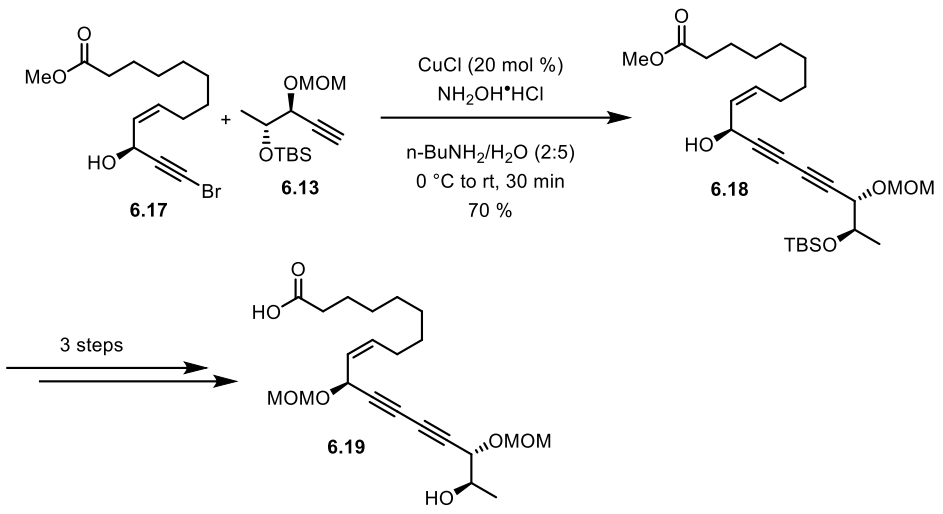
Scheme 6.6. Synthesis of the first Cadiot-Chodkiewicz coupling reaction partner.

In parallel, the second Cadiot-Chodkiewicz reaction partner **6.17** was synthesized from 8-bromooctanoic acid (**6.14**) and propargyl alcohol (**6.15**) in eight discrete steps in which the *Z*-alkene **6.16** was selectively obtained by a Lindlar hydrogenation of the corresponding alkyne (Scheme 6.7). Furthermore, differentiation of the two alkynes by bromination of one of the cross-coupling partner is necessary in the Cadiot-Chodkiewicz reaction and the required halogen was then installed on the long-chained coupling partner **6.17**.



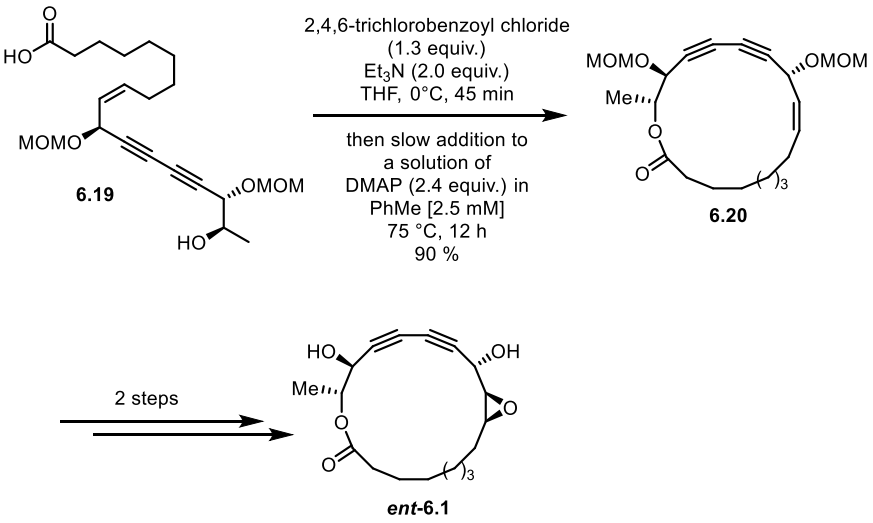
Scheme 6.7. Synthesis of the second Cadiot-Chodkiewicz coupling reaction partner.

Under the Cadiot-Chodkiewicz reaction conditions, diyne **6.18** was prepared from alkyne **6.13** and bromoalkyne **6.17** in 70 % yield (Scheme 6.8). Hydroxylamine hydrochloride was added in an unspecified amount to maintain the oxidation state of the copper (I) catalyst.[20] A protection and deprotection sequence followed to achieve macrocyclic precursor **6.19**.



Scheme 6.8. Synthesis of the macrocyclic precursor **6.19**.

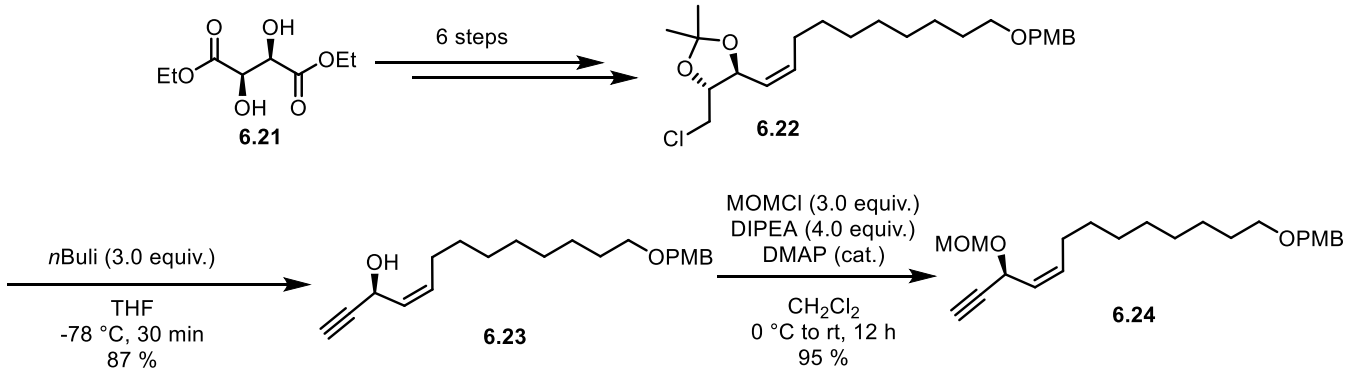
The macrocyclization reaction proceeded under the traditional Yamaguchi protocol in which slow addition of the *in situ* formed mixed anhydride is slowly added to a highly diluted solution of DMAP in toluene (Scheme 6.9). Although the yield of **6.20** is excellent, the protocol was only performed on a very small scale (20 mg, 0.050 mmol of substrate). The total synthesis was achieved with two subsequent steps; a double MOM-deprotection allowed the subsequent directed epoxidation of the *Z*-alkene.



Scheme 6.9. Completion of the total synthesis of the unnatural enantiomer of ivorenolide A.

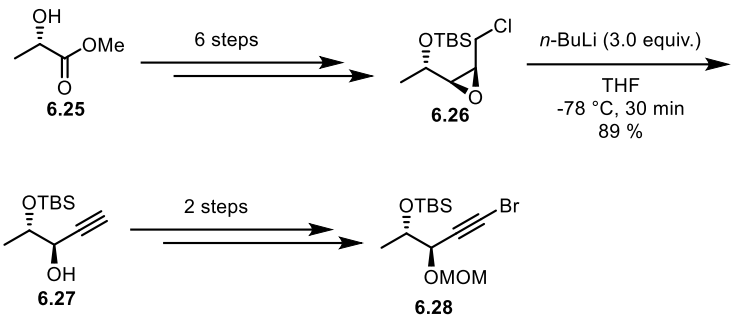
6.3.2. Total Synthesis of Ivorenolide A

In 2015, Yadav and co-workers provided the first total synthesis of the natural enantiomer of ivorenolide A **6.1**.[3] Their synthetic route involved a base-induced elimination reaction for the synthesis of two terminal alkynes, a Sonogashira-type cross-coupling of the two alkynes and a MNBA-promoted macrolactonization as key steps. (+)-Diethyl tartrate **6.21** was derivatized to the alkyl chloride **6.22** in six steps and the alkyne **6.23** was obtained under strong basic elimination conditions in 87 % yield. The completion of the synthesis of the first alkynyl reaction partner **6.24** was obtained after a MOM-protection of the secondary alcohol.



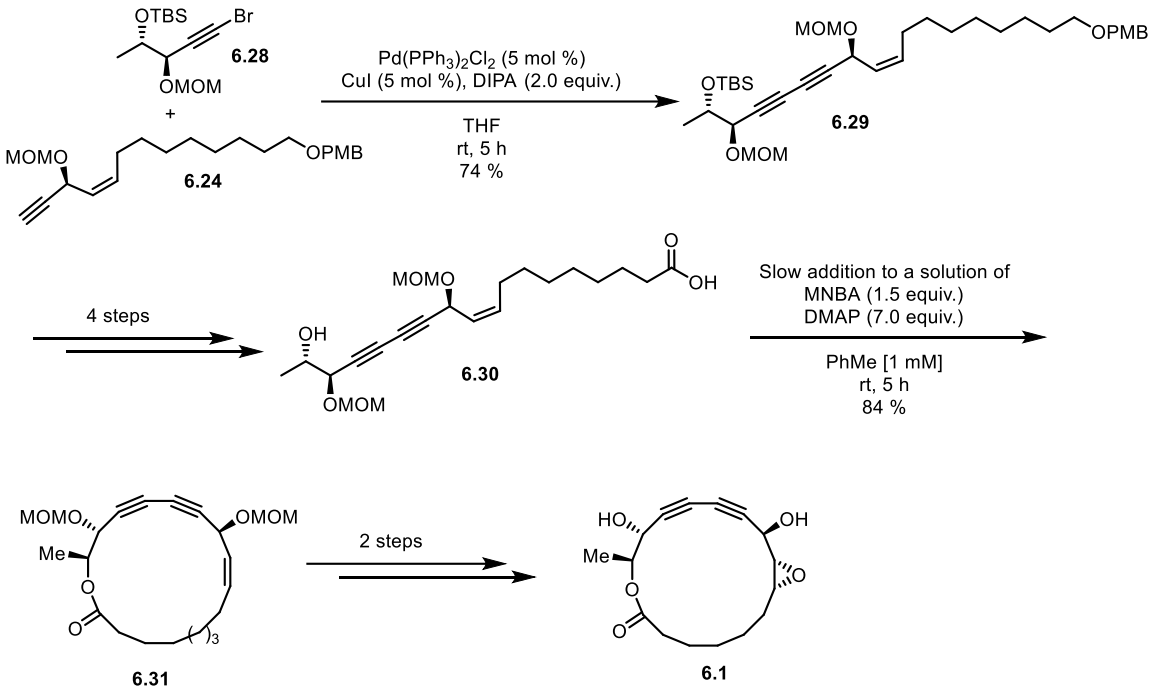
Scheme 6.10. Synthesis of the alkynyl reaction partner **6.15**.

The second bromoalkyne fragment was obtained from (*S*)-methyl lactate **6.25** in nine steps, once again by going through the base-induced elimination reaction to form the alkyne moiety on **6.27** (Scheme 6.11). Subsequent bromination of the latter formed the coupling reaction partner **6.28**.



Scheme 6.11. Synthesis of the second Sonogashira-type reaction partner.

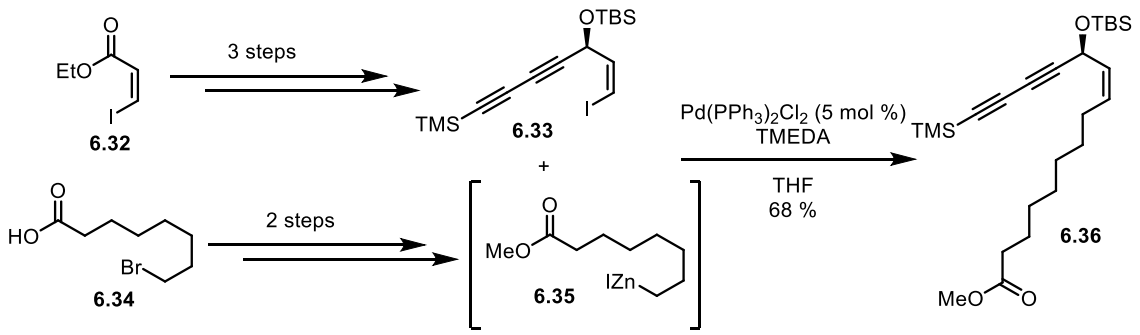
A Sonogashira-type coupling between alkyne **6.24** and bromoalkyne **6.28** provided the conjugated diyne **6.29** in 74 % yield (Scheme 6.12). Deprotection and oxidation steps followed to achieve macrocyclic precursor **6.30**. The macrocyclization reaction was effected through the formation of a mixed anhydride with MNBA. Slow addition of the substrate in a highly dilute medium was necessary and similarly to the previously discussed synthetic route to the ivorenolides, the macrocyclization was performed on small scale (15 mg, 0.030 mmol of substrate) to form **6.31** in 84 % yield. The completion of the total synthesis of **6.1** was achieved after MOM-deprotection and epoxidation reactions.



Scheme 6.12. Completion of the total synthesis of ivorenolide A.

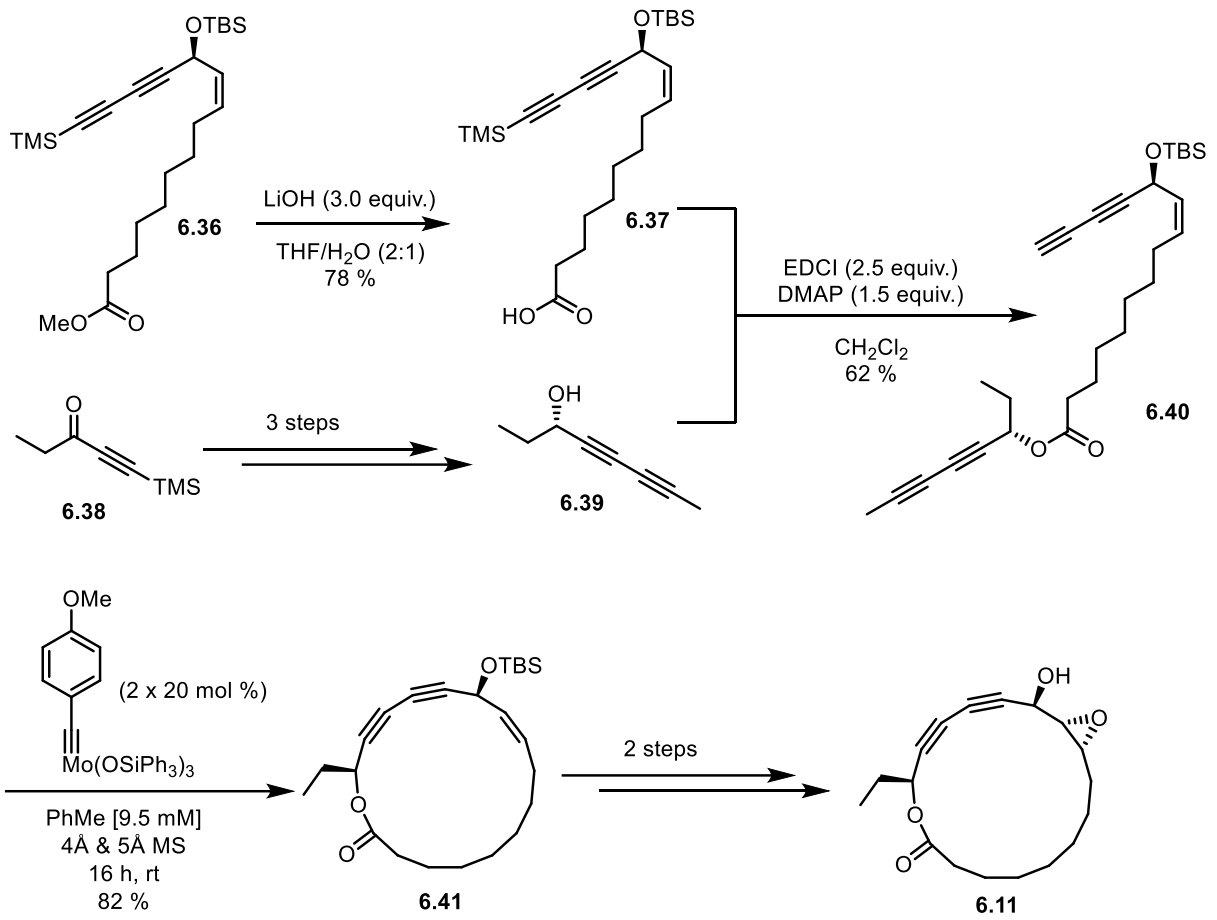
6.3.3. Total Synthesis of Ivorenolide B

During the course of our own work in 2015, Fürstner published the first total synthesis of ivorenolide B **6.2**,[21] only a year after its isolation and characterization. Contrary to the syntheses of the other members of the family, Fürstner proposed a macrocyclization step using catalysis via an alkyne metathesis reaction, thus taking advantage of the presence of the conjugated 1,3-diyne moiety. The synthesis began with the construction of diyne **6.36**. Starting from ethyl (*Z*)-iodoacrylate **6.32**, silylated diyne **6.33** was formed in three steps (Scheme 6.13). In parallel, 8-bromooctanoic acid **6.34** was converted to the organozinc intermediate **6.35,** which could be subsequently subjected to a Pd-catalyzed coupling to afford **6.36** in 68 % yield. The authors commented that the moderate yield was in part due to side-reactions between the propargyl/allylic position and the palladium catalyst and to the isomerization of the *Z*-alkene.



Scheme 6.13. Construction of the first bis-alkyne unit fragment.

The synthesis of the second diyne unit **6.39** was accomplished in three steps from ketone **6.38**, and the product was coupled promptly after the saponification of ester **6.36**, as the corresponding carboxylic acid **6.37** was highly unstable (Scheme 6.14). The macrocyclization to form the core of ivorenolide B was performed using a ring-closing alkyne metathesis reaction. As is common in macrocyclic ring-closing metathesis, the ring closure required high catalyst loading of the catalyst (2 portions of 20 mol % each of the Mo-based catalyst were added). Key to the successful ring-closing alkyne metathesis was the use of one terminal diyne partner and one internal diyne partner. At the current time, it is not known why the particular structural requirements are necessary for successful alkyne metathesis of diynes. In addition, the macrocyclization required an inert atmosphere and molecular sieves, but the desired macrocycle **6.41** was isolated in 82 % yield. Ivorenolide B (**6.11**) was formed after subsequent epoxidation of the *Z*-alkene and TBS-deprotection of the secondary alcohol functionality.



Scheme 6.14. Completion of the total synthesis of ivorenolide B.

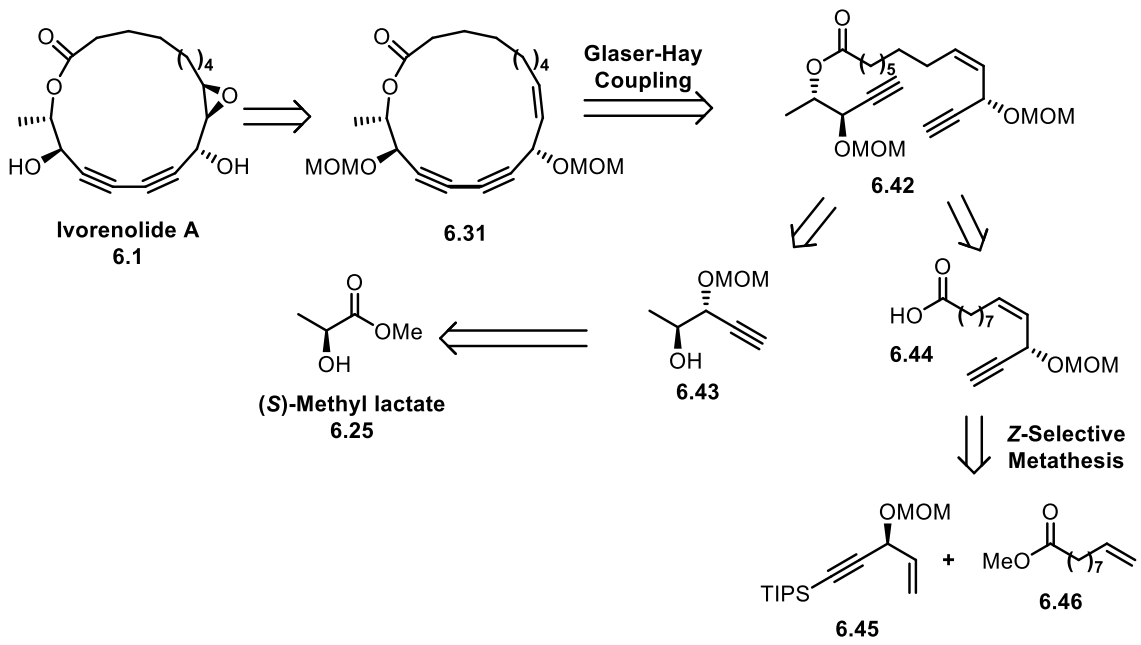
Although Fürstner and co-workers developed a catalytic process for the macrocyclic ring-closing step of ivorenolide B, the installation of the two 1,3-diyne units on the macrocyclic precursor required a number of additional synthetic steps. However, taking advantage of the conjugated 1,3-diyne moiety found in ivorenolides for the ring-closing step is an alternative strategy to synthesize the macrocycles of the family compared to the traditional macrolactonization reactions used by Yue and Yadav.

Our group would propose a macrocyclic Glaser-Hay reaction in combination with a phase separation strategy in continuous flow for the synthesis of ivorenolide A. Advantages of such a route include catalysis via a direct oxidative coupling of terminal alkynes, using a

relatively high concentration and possible ease of scale-up exploiting continuous flow conditions.

6.4. Application of the Phase Separation Strategy for the Synthesis of Ivorenolide A: Retrosynthetic Analysis & Conclusion

The goal of the project was to further explore the Glaser-Hay/phase separation strategy for the synthesis of complex macrolactones through a formal synthesis of ivorenolide A via the cyclization of diyne **6.42** (Scheme 6.15) to give the known macrocyclic intermediate **6.31**. As such, the study would demonstrate tolerance to racemizable stereogenic centers, steric hindrance about the alkyne reaction centers and common protecting groups. In addition, macrocyclization under continuous flow would be investigated at the gram scale. Retrosynthetic analysis of the diyne precursor **6.42** suggested that the synthesis be carried out by a coupling secondary alcohol **6.43** with carboxylic acid **6.44.** Fragment **6.43** would result from the derivatization of cheap and commercially available (*S*)-methyl lactate **6.25**. Fragment **6.44**, on the other hand, could arise from a *Z*-selective cross olefin metathesis of alkenes **6.45** and **6.46**. The retrosynthetic analysis using a Glaser-Hay coupling allows for a macrocyclization based on catalysis where prefunctionalization of the alkynes is not required. The phase separation strategy would help promote macrocyclization at high concentrations in a manner which would be easily scaled. In addition, the synthesis of key intermediates would be simplified via a *Z*-selective cross olefin metathesis reaction.



Scheme 6.15. Retrosynthetic analysis of ivorenolide A via a macrocyclic Glaser-Hay coupling.

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7. Catalytic Macrocyclization Strategies Using Continuous Flow: Formal Total Synthesis of Ivorenolide A

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Contributions:

- Mylène de Léséleuc and Eric Godin participated in the design of the experiments, did experimental work and contributed to the writing of the manuscript.
- Shawn Parisien-Collette contributed to the large scale synthesis of building block **3**.
- Alexandre Lévesque contributed to the large scale synthesis of building block **8** and to preliminary continuous flow experiments.
- Shawn K. Collins participated in the design of the experiments and writing of the manuscript.

7.1. Abstract

A formal total synthesis of ivorenolide A has been accomplished employing a *Z*-selective olefin cross metathesis and a macrocyclic Glaser-Hay coupling as key steps. The macrocyclization protocol employed a phase separation/continuous flow manifold whose advantages include catalysis, fast reaction times, high concentrations, and facile scale-up.

7.2. Introduction

Macrolides are a family of macrocyclic natural products having a wide array of biological activities.[1] From a synthetic perspective, several methods have evolved as the most popular candidates for macrocyclization. Macrolactonization[2] via stoichiometric activation of seco-acids, such as the Yamaguchi protocol,[3] is without a doubt the most popular method for constructing the ester motif of macrolides. Another common synthetic route to form macrocycles involves carbon-carbon bond formation involves transition metal catalysis, usually via olefin metathesis or cross-coupling strategies.[4] Despite the utility displayed by the above-mentioned transformations, the macrocyclizations are usually performed at low concentration, and rely upon slow addition techniques. Consequently, scale-up of the target macrocycles becomes problematic,[5] which is disappointing when promising biological activity is observed. The ivorenolides A[6] and B[7] are a unique class of macrolides which possess 1,3-diyne motifs isolated from the stem bark of *K. ivorensis* (Figure 7.1). Their immunosuppressive activities make them attractive targets for medicinal chemistry investigations given the need for new immunosuppressants with improved therapeutic profiles. Total syntheses of both the natural and unnatural enantiomers of ivorenolide A have appeared in the literature, each exploiting a macrolactonization employing stoichiometric activation strategies and high dilution and/or slow

addition as the key macrocyclization step (Figure 7.1).[6,8] As such, the development of alternative methods for macrocyclization that would employ catalysis and high concentrations and facilitate scale-up would be highly desirable.[9] Our group has put forth an alternative strategy for the synthesis of macrocycles via Glaser-Hay coupling using a "phase separation" strategy.[10] The protocol was shown to exploit aggregation effects caused by mixtures of poly(ethylene) glycol (PEG) cosolvents.[11] During the development of the "phase separation" technology, it was apparent that the substrate scope explored to date was limited, and did not address the influence of stereogenic centers, steric hindrance about the alkyne reaction centers, or tolerance to common protecting groups. In addition, no investigation of the feasibility of scale-up of complex macrocycles at the gram scale had been demonstrated. To respond to the aforementioned questions, the formal total synthesis of ivorenolide A by application of the "phase separation" strategy under continuous flow techniques is described herein (Figure 7.1).

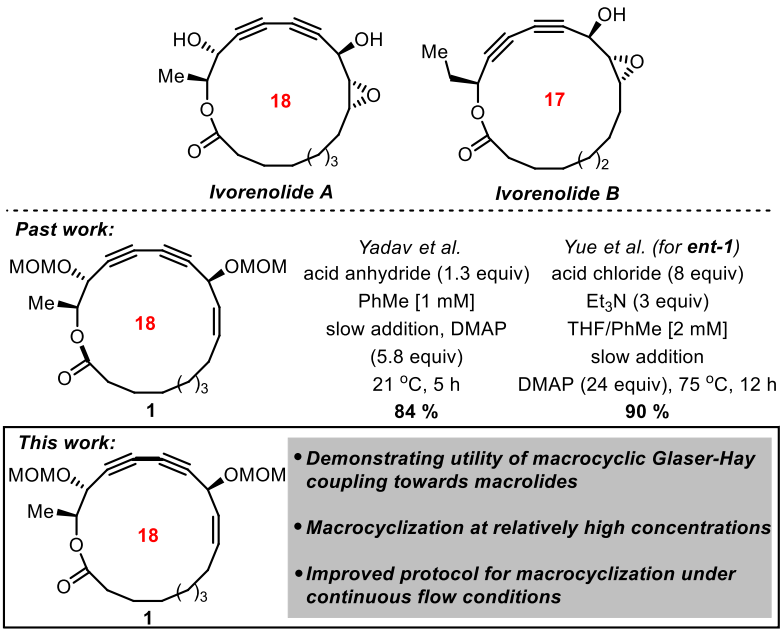


Figure 7.1. Macrocyclization strategies via continuous flow toward ivorenolide A. Ring sizes are in red.

Results and Discussion

The retrosynthetic analysis for the development of a phase separation/continuous flow macrocyclization toward the synthesis of ivorenolide A aimed to prepare the 18-membered macrolactone **1** intermediate, which was previously prepared by Yadav[12] and Yue[6] as well as a simplified model **1a** (Figure 7.2). By envisioning the macrocyclization event arising from Glaser-Hay coupling of two terminal alkynes, the linear precursor **2** was selected as a target for the formation of macrocycle **1**, while the macrocyclization of the model 18-membered macrolactone **1a** was also imagined arising from Glaser-Hay coupling of linear precursor **2a**. Each ester (**2** and **2a**) could be prepared from esterification of the alcohol **3** with a corresponding carboxylic acid derivative.

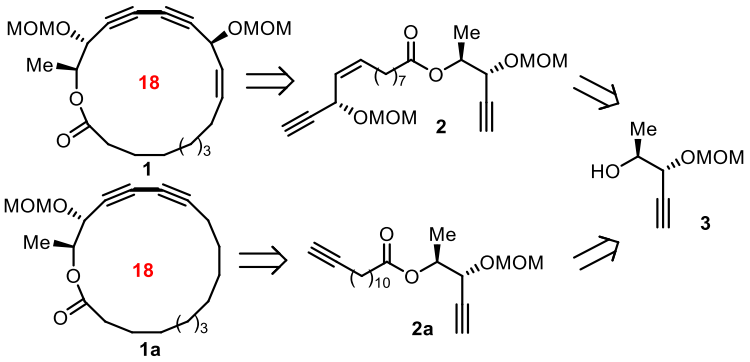
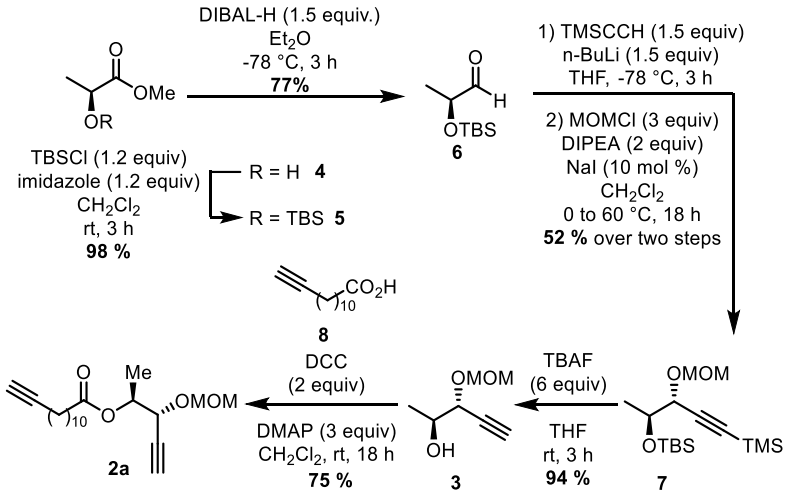


Figure 7.2. Retrosynthetic analysis toward the macrocyclic core of ivorenolide A (**2**→**1**) and a simplified model (**2a**→**1a**).

Ring sizes are indicated in red.

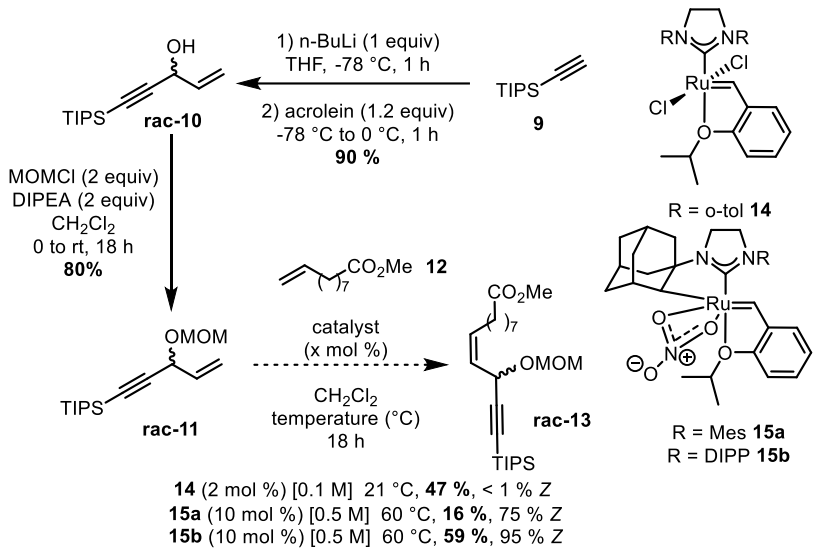
The synthesis of alkynyl alcohol **3** from (*L*)-methyl lactate began with protection of the hydroxyl group as its *t*-butyldimethylsilyl (TBS) ether in nearly quantitative yield (Scheme 7.1). Reduction of the ester **5** to the corresponding aldehyde **6** using DIBAL-H was achieved in 77 % on gram scales. Addition of the organolithium reagent derived from trimethylsilylacetylene afforded solely the desired diastereomer. Subsequent protection of the hydroxyl group as its

MOM ether afforded the fully protected alkyne **7** in 52 % yield over two steps. Removal of both silyl protecting groups using an excess of TBAF at room temperature unmasked the terminal alkyne and secondary alcohol functionality, providing **3** in 94 % yield. Esterification of alcohol **3** using DCC/DMAP conditions with known carboxylic acid **8** provided the macrocyclization precursor **2a** in 75 % yield.



Scheme 7.1. Synthesis of Alcohol **3** and Diyne **2a** Analysis Toward the Macrocyclic Core of Ivorenolide A (**2** → **1**) and a Simplified Model (**2a** → **1a**)

The carboxylic alkynyl synthon **1a** required for the synthesis of macrocycle **1** was then prepared. The *cis*-olefin was envisioned arising from a *Z*-selective cross metathesis process.[13] To test the synthetic route, several cross metathesis reactions were evaluated on the racemic, MOM-protected secondary alcohol **rac-11** (Scheme 7.2).

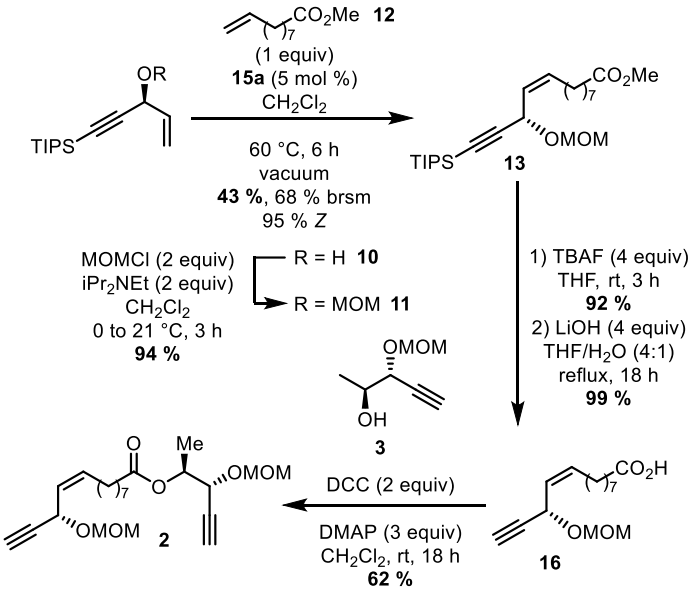


Scheme 7.2. Optimization of a Z-Selective Cross Metathesis to Prepare Racemic **13**.

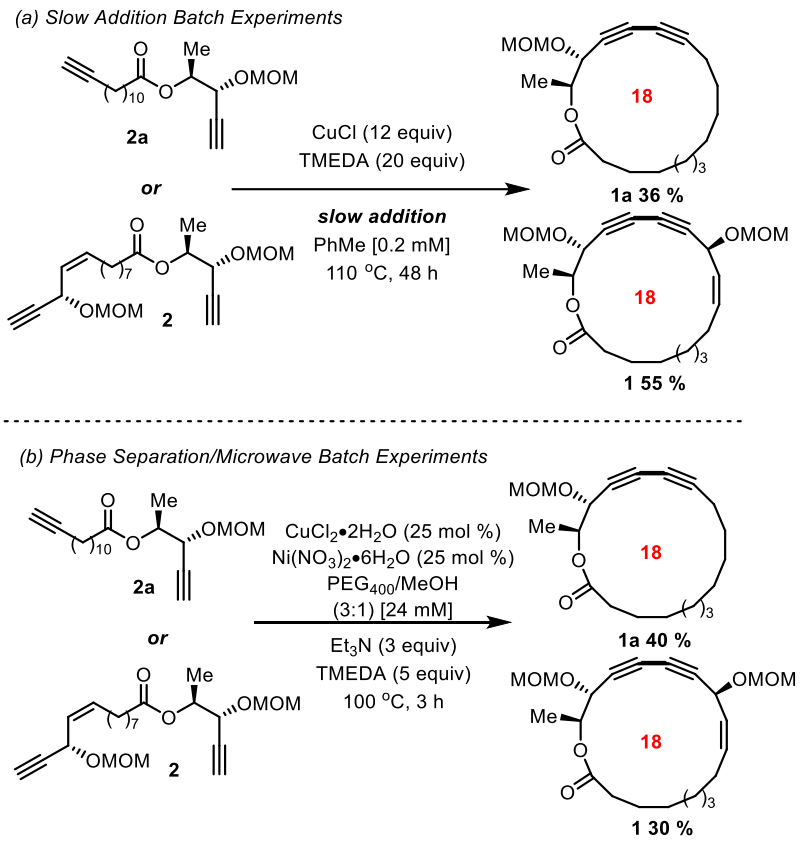
Cross metathesis was first evaluated with 1.0 equiv of methyl ester **12** at room temperature using the Stewart−Grubbs catalyst **14**.[14] The desired product rac-**13** was obtained in 47% yield and isolated as the pure *E*-isomer. Next, two Ru-based Zselective catalysts were evaluated, each having a different NHC in which the N-aryl substituent differed.[15] After a brief survey of reaction conditions,[16] it was found that the DIPP-bearing catalyst **15b** at 10 mol %, 60 °C, and [0.5 M] afforded a 59% yield of the desired olefin rac-**13**, in excellent *Z*-selectivity (95% Z). Cross metathesis using the mesityl catalyst **15a**[17] was not as selective (75% Z). With optimized conditions for the cross metathesis procedure in hand, the synthesis of the enantioenriched carboxylic acid **16** was undertaken (Scheme 7.3). First the enantiomerically pure alcohol **10** could be obtained via a previously reported CBS reduction, or via diastereomeric

resolution.[18] The alcohol 10 was protected as its MOM ether **11** in 94% yield and subsequently subjected to Z-selective cross metathesis. To improve reproducibility at larger scales, an applied vacuum was used for removing ethylene.[19] Consequently, the yield and selectivity of

the reaction remained reproducible at 43% (68% based on recovered starting material) and >95% Z with a shorter reaction time (6 h vs 18 h). With enantiopure olefin **13** in hand, desilylation was performed using TBAF to provide the corresponding terminal alkyne in 92% yield (Scheme 7.3). Saponification of the ester afforded the carboxylic acid **16** in 99% yield. Esterification of acid **16** with secondary alcohol **3** was promoted by reaction with DCC and DMAP to provide the desired compound **2** in 62% yield.



Scheme 7.3. Synthesis of linear precursor **1a** for macrocyclization to form the macrocyclic core of ivorenolide A.

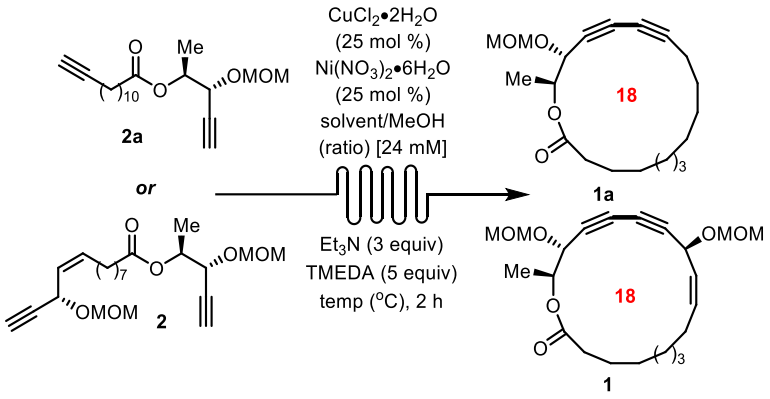


Scheme 7.4. Traditional macrocyclizations under slow addition conditions (a) and macrocyclizations under phase separation/microwave heating (b) to form macrocycles **1** and **1a**. Ring sizes are in red.

With both key linear precursors in hand, macrocyclization was first performed using the simplified model **2a** (Scheme 7.4). As such, the bis-alkyne **2a** was cyclized under slow addition conditions, using superstoichiometric amounts of CuCl (12 equiv) and ligand (TMEDA, 20 equiv) in refluxing toluene. Slow addition was performed over 36 h, and the refluxing reaction mixture (final concentration 0.2 mM) was stirred for another 12 h to promote conversion of all the starting material **2a**. Macrocycle 1a was isolated following silica gel chromatography in 36% yield. When identical reaction conditions were used to cyclize the more complex macrocyclization precursor **2**, the yield of the desired macrocycle **1** was higher at 55%. Next, the macrocyclization precursors were subjected to phase separation conditions at ~120 times

the concentration employing reaction conditions previously developed for cyclization under microwave heating.[20] For the cyclization of **2a**, a 40 % yield of macrocycle **1a** was isolated. Similar yields (30 %) were also observed using the linear precursor **1**. Each bis-alkyne was observed to be sensitive to the basic conditions of the phase separation/microwave protocol for macrocyclization and it was hoped that the precise control over temperature and reaction time using continuous flow would be advantageous.[21]

Table 7.1. Macrocyclization Using the Phase Seperation Strategy in Continuous Flow



	PEG solvent	Ratio (PEG:MeOH)	Temp. (°C)	Yield (%)[a]
		macrocyclization **2a→1a**		
1	PEG_{400}	1:1	120	49 (17)
2	PEG_{400}	2:1	120	26 (<5)
3	PEG_{400}	4:1	120	19 (24)
4	PEG_{400}	8:1	120	14 (18)[b]
5	PPG_{425}	2:1	120	38-40[c]
		macrocyclization **2→1**		
6	PEG_{400}	1:1	120	52 (0)
7	PEG_{400}	2:1	120	37 (<5)
8	PEG_{400}	4:1	100	27 (30)

[a] Yields following chromatography. Recovered starting material in parentheses. [b] 4 h reaction time. [c] Reactions performed at 80 or 100 °C afforded similar yields with small amounts of unreacted **2a**. For ease of purification, the reaction was kept at 120 °C. Ring sizes in red.

For the model precursor **2a**, macrocyclizations under continuous flow conditions[22] were evaluated with different ratios of PEG solvent to MeOH (Table 7.1). Based upon previous work,[23] residence times of 1−2 h were selected for study. Consequently, a low flow rate (0.167 mL/min) combined with a 20 mL reactor volume was necessary (two 10 mL reactor coils were connected in series). In addition, since higher ratios of PEG_{400}/MeOH typically provide higher selectivity for macrocyclization versus oligomerization, albeit with longer reaction times, the optimization of the macrocyclization was conducted with a 2 h residence time. When precursor **2a** was cyclized at 120 °C, with a residence time of 2 h in PEG_{400}/MeOH (1:1), a 30% yield of macrocycle 1a was isolated. Efforts to boost yields through increasing the ratio of PEG400/MeOH to 4:1 resulted in lower yields, and a ratio of PEG400/MeOH (8:1) required longer reaction times (4 h). By switching the solvent from PEG_{400} to PPG_{425}, a poly(propylene)glycol solvent, previously demonstrated to be efficient in "phase separation"-type macrocyclizations, provided the best yield of macrocycle **1a** (38−40% yield). To demonstrate the feasibility of using the "phase separation" strategy alongside continuous flow for large scale preparation of macrolide type macrocycles, the macrocyclization (**2a** → **1a**) was repeated at gram scale and provided identical yields to what was observed at smaller scales (50−150 mg). Gram scale cyclization of diyne 2a required 120 mL of the PPG_{425}/MeOH (2:1) solvent mixture, while the equivalent slow addition experiment would have required >14 L of PhMe. When a similar set of conditions were used for the macrocyclization of precursor **2** possessing the additional *Z*-olefin and propargylic stereocenter, the best conditions surveyed utilized 120 °C, with a residence time of 2 h in PEG_{400}/MeOH (1:1) for a 52% yield of macrocycle **1**. The higher yield of macrocycle 1 (52%) versus the model macrocycle **1a** under similar reaction conditions could be explained by the effects of the additional *cis*-olefin and

stereocenter in the respective precursor **2** versus **2a**. The addition of the olefin and hydroxyl motifs could promote a conformational bias to help bring the alkyne functionalities closer to one another.[24] Consequently, the use of the phase separation/continuous flow conditions for the preparation of the ivorenolide macrocycle **1** provided several advantages to using a traditional slow addition type strategy. In addition to providing a similar yield (55 vs 52% of **1**), reaction under the phase separation/continuous flow manifold was catalytic as opposed to using superstoichiometric quantities of ligand and a metal source, the reaction time was significantly shortened (48 vs 2 h), and the concentration was greater by more than 2 orders of magnitude (0.2 vs 24 mM).

7.4. Conclusions

In summary, a formal total synthesis of ivorenolide A has been accomplished using a macrocyclic catalytic oxidative coupling of terminal alkynes and a Z-selective cross metathesis as key steps. Macrocyclization has been demonstrated employing a phase separation/continuous flow method that is applicable to complex macrolides bearing stereogenic centers, steric hindrance about the alkynes, and common protecting groups. The macrocyclization also described for the first time that continuous flow protocols allow for much more facile scaleup which would be highly problematic using high dilution strategies or microwave heating. The phase separation strategy produced good yields of the desired macrocycles employing catalysis in place of stoichiometric reagents, faster reaction times than the corresponding batch reactions, and concentrations ~120× greater than those used in the stoichiometric slow addition strategy. Given the rarity of macrocyclizations performed under continuous flow, and the importance of macrocycles in both

natural product synthesis and medicinal chemistry, the use of the phase separation/continuous flow method would be expected to have significant impact.

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8. Conclusions and Perspectives

The present thesis has described efforts to improve the synthesis of macrolactones through catalysis. The research projects that have been undertaken aimed to provide alternative strategies that could replace the cumbersome slow addition and stoichiometric activating reagents that currently dominate the synthetic landscape of macrocylization methods. Below are specific conclusions for each of the two major subsections of the thesis, and each summary also comments on possible perspectives for future work.

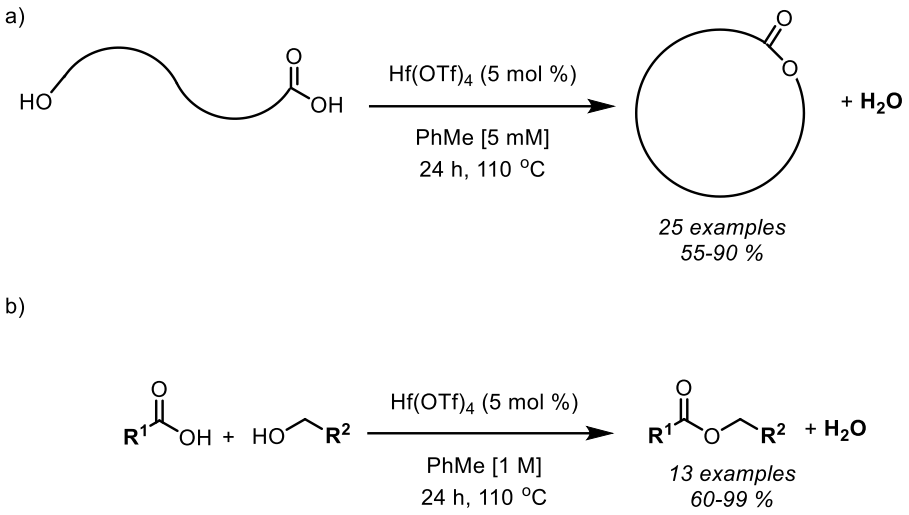
8.1. Direct Synthesis of Macrolactones and Macrodiolides via Hafnium (IV) Catalysis

8.1.1. Summary of the Results Obtained on the Direct Synthesis of Macrolactones and Macrodiolides

We have developed an efficient hafnium-catalyzed direct macrolactonization between carboxylic acid and alcohol functionalities, generating only water as a by-product. In addition to forming a variety of macrolactones and benzolactones (25 examples) in moderate to excellent yield (55-90 %), intermolecular direct esterifications of carboxylic acids and alcohols were also possible and demonstrated compatibility with common carbamate, silyl ether, alkoxymethyl ether, and acetal protecting groups.[1]

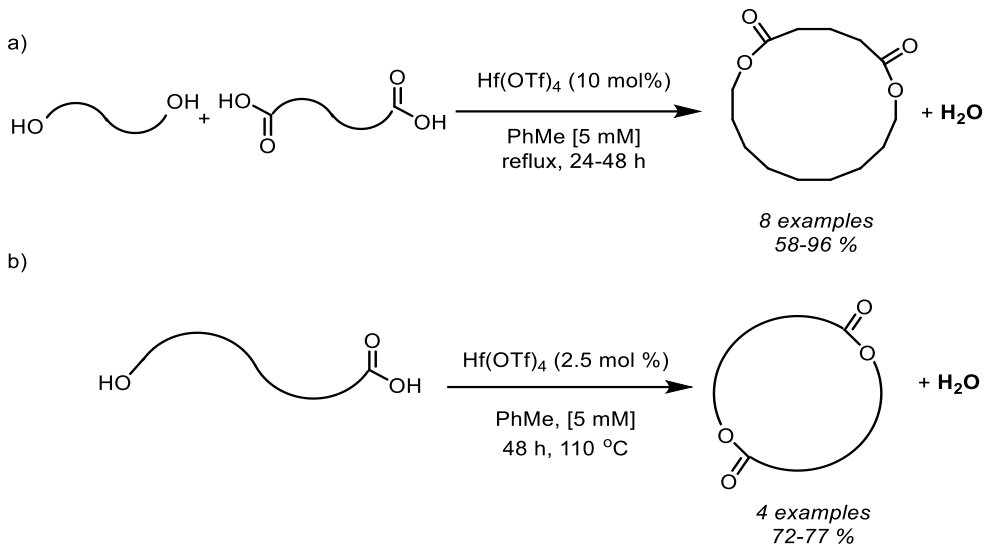
Among these examples include several macrolactones relevant to the perfume industry, such as Exaltolide®, isoambrettolide and dihydroambrettolide, as well macrolactones that could interest the pharmaceutical industry, such as complex peptide-containing macrocycles. All of the macrolactonization and esterification processes developed are operationally simple, “one-

pot" reactions that exploit a commercially available catalyst without the need for slow addition or azeotropic techniques.



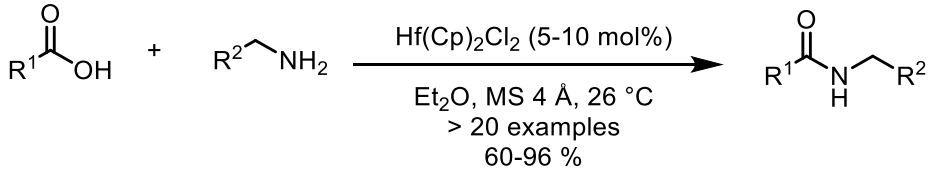
Scheme 8.1.Direct synthesis of macrolactones (a) and esters (b) via Hf(IV)-catalysis.

The protocol was further adapted to the direct synthesis of macrodiolides from equimolar mixtures of diols and dicarboxylic acids (8 examples, 58-96 %) by increasing the catalyst loading to 10 mol %. To the best of our knowledge, the hafnium-catalyzed method is the first catalytic method for forming the head-head-to-tail-tail macrodiolides. By decreasing the catalyst loading to 2.5 mol %, selective formation of head-to-tail macrodiolides from 8- to 10-carbon long seco acids was demonstrated (4 examples, 72-77 %).[2]



Scheme 8.2. Direct synthesis of macrodiolides via Hf(IV)-catalysis from (a) diol and dicarboxylic acids and from (b) selected seco acids.

An interesting aspect left to be studied in the methodology is its application to other important chemical transformations. Due to its excellent tolerance of functional and protecting groups, hafnium-based Lewis acids could potentially catalyze other condensation reactions in macrocyclization, such as macrolactamization. Other potential esterifications to study could include the formation of boronic esters or phosphonate esters. Interestingly, following our intial report on macrolactonization reactions with $Hf(OTf)_4$, Lundberg and Adolfsson[3] published a $Hf(Cp)_2Cl_2$-catalyzed direct amidation of carboxylic acids with primary amines (Scheme 8.3). The adaptation of the protocol to macrocyclization is something worth investigating as the lactam moiety is a common feature in biologically active natural and unnatural macrocycles.[4]

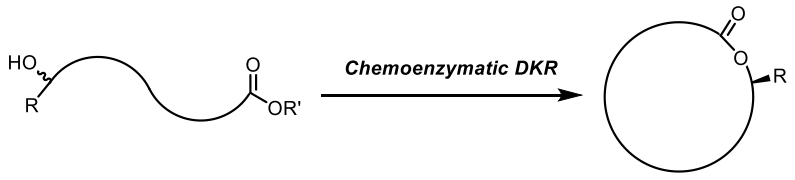


Scheme 8.3. Hf-catalyzed direct amidation.

8.1.2. Future work on the Direct Synthesis of Macrolactones and Macrodiolides

One of the limitations described in the thesis is the inability to synthesize macrolactones bearing functionalities at the ω-position (i.e. secondary alcohols) via $Hf(OTf)_4$ catalysis. As the $Hf(OTf)_4$-catalyzed macrolactonization mechanism is still unknown, mechanistic studies would be helpful to understand the selectivity observed between primary and secondary alcohols. Such investigations should be conducted in the near future in our research group.

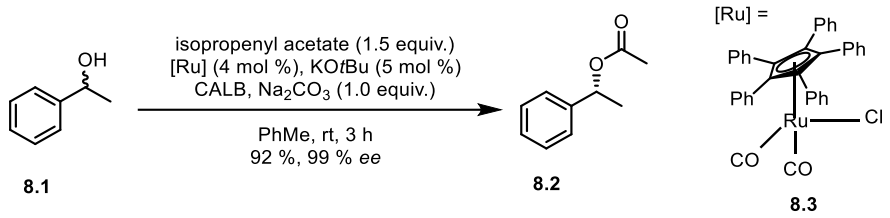
In the meantime, alternative catalyst systems, including metal-based Lewis acids, boronic acids and a Brønsted acid, were evaluated but did not afford the desired reactivity. During the aforementioned investigations, another strategy was envisioned which would not only promote catalytic macrolactonization of substrates bearing secondary alcohols, but would also result in enantioenriched products from racemic starting materials (Scheme 8.4). Chemoenzymatic dynamic kinetic resolution (DKR) is a method used for the conversion of mixtures of racemic secondary alcohols and amines into enantiopure esters and amides respectively.[5]



Scheme 8.4. Synthesis of ω-substituted macrolactones via a chemoenzymatic DKR

The concept relies on a dual catalyst system: a racemization catalyst and an enantiospecific enzyme-based transesterification catalyst. For example, (±)-1-phenylethanol can be treated with the enzyme CALB, which selectively transfers acetate on one enantiomer of the alcohol to form (*R*)-1-phenylethyl acetate. In parallel, the Ru-catalyst **8.3** racemizes the

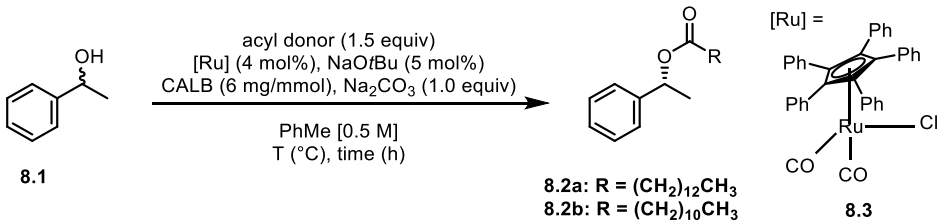
remaining alcohol (*S*)-**8.1**. The concerted action of the two catalysts results in the transformation of the racemic alcohol **8.1** into is (*R*)-acetate derivative **8.2** in 92 % yield and 99 % *ee* (Scheme 8.5).[6]



Scheme 8.5. DKR of 1-phenylethanol using a dual catalyst system of an enzyme and transition metal catalyst.

DKR processes are normally used to synthesize small chiral building blocks, and the acyl groups that become appended to the final products are often removed following the resolution process. To the best of our knowledge, analogous DKR processes have not been developed where the acyl donor is a part of the desired product. In addition, no intramolecular version of the DKR of secondary alcohols has been reported. To develop a DKR macrolactonization process as exemplified in Scheme 8.4, a model intermolecular reaction would be investigated where the acyl donors would be adorned with long aliphatic chains to resemble intramolecular substrates. In addition, the DKR process requires the installation of a leaving group on the carboxylic acid,[7] ideally recyclable and non-toxic, but most importantly not interfering in the purification process of the desired macrolactone. A wide variety of racemization catalysts are commercially available,[8] but for preliminary results, Ru-catalyst **8.3**[6] was chosen due to its wide use in analogous DKR reactions. Enzyme CALB[6] was selected as the enantiospecific transesterification catalyst and 1-phenylethanol (**8.1**) was chosen as the racemic secondary alcohol.

Table 8.1. DKR of 1-phenylethanol with long-chain aliphatic acyl donors.



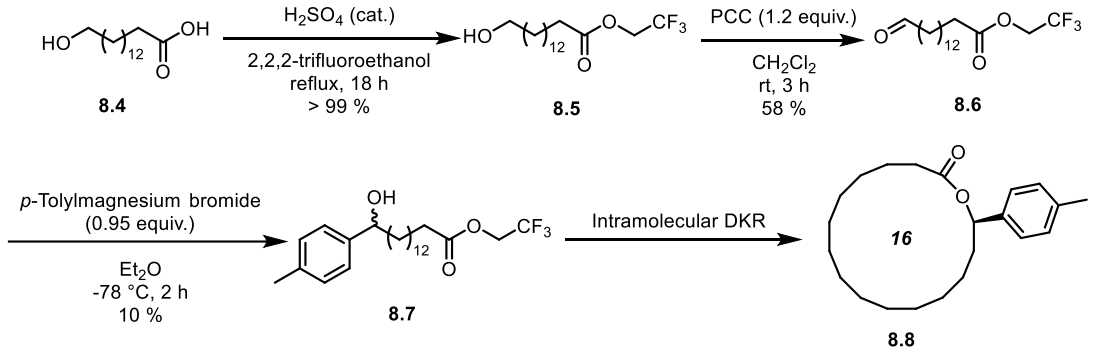
Entry	Acyl donor	Temperature (°C)	Time (h)	Yield (%)
1	4-chlorophenyl myristate	22	18	0[a]
2	2,2,2-trifluoroethyl myristate	60	18	44
3	2,2,2-trifluoroethyl myristate	60	48	64
4	2,2,2-trifluoroethyl myristate	90	18	70
5	vinyl laurate	22	18	54
6	vinyl laurate	60	18	76

[a] The acyl donor was hydrolyzed under the reaction conditions.

The DKR of 1-phenylethanol with 4-chlorophenyl myristate as the acyl donor did not promote acylation at room temperature (Table 8.1, entry 1); instead 4-chlorophenol and myristic acid were isolated after the reaction. However, both 2,2,2-trifluoroethyl myristate (entries 2 to 4) and vinyl laurate (entries 5 to 6) were found to be compatible acyl donors, although heating or long reaction times are necessary to achieve good conversion for the acylation of **8.1**. Both leaving groups are volatile and simplify the purification of the desired product. A slight preference was made for the 2,2,2-trifluoroethyl[8] derivative as it is an easier group to install on a carboxylic acid than a vinyl group.[9] Enantiomeric excess were not calculated on these

preliminary results due to time constraints, but a control reaction showed that CALB does not catalyze acylation of (*S*)-1-phenylethanol (*(S)*-**8.1**)with vinyl acetate.

In parallel, a macrocyclic intramolecular model substrate bearing a racemic secondary alcohol such as **8.7** was synthesized. Seco acid **8.4** was esterified with 2,2,2-trifluoroethanol to form **8.5** in quantitative yield and the alcohol moiety was oxidized with PCC to form aldehyde **8.6** in 58 % yield. *p*-Tolylmagnesium bromide was added at -78 °C to produce the racemic secondary alcohol precursor **8.7** in a low 10 % yield. Side-products are formed in the reaction and the conditions will be optimized. Intramolecular DKR to form **8.9** will also be investigated by a colleague who undertook the project. Full characterization of intermediates **8.5** to **8.7** is also in progress.[10]



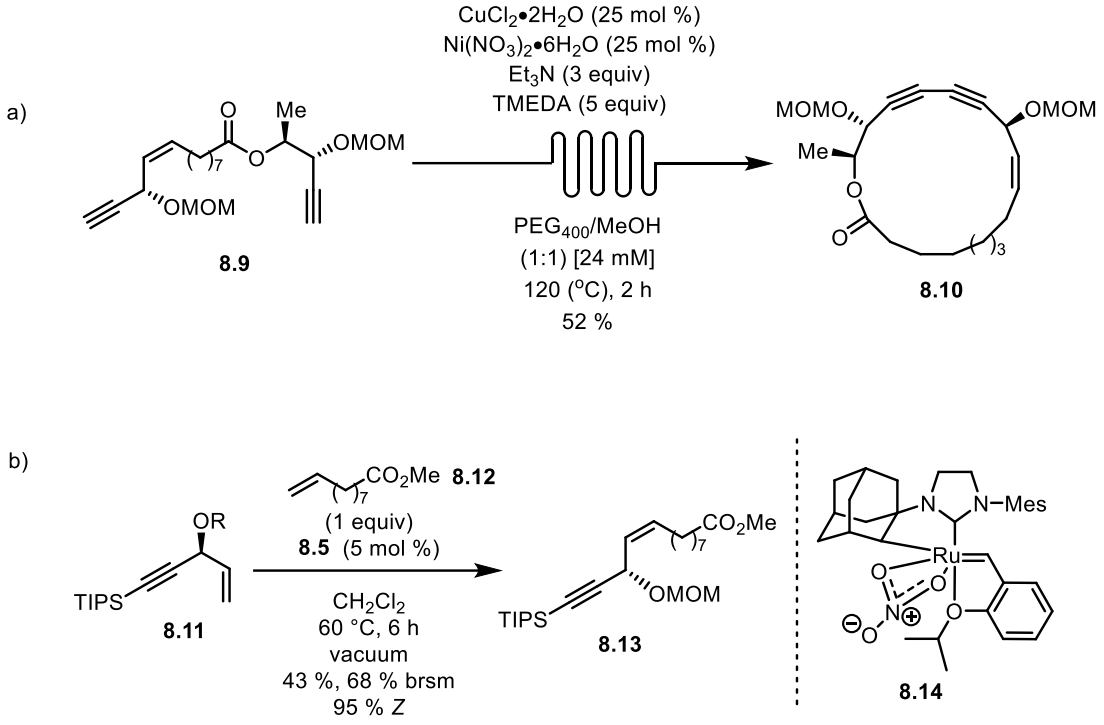
Scheme 8.6. Synthesis of a racemic seco acid containing a secondary alcohol for evaluation in intramolecular DKR.

8.2. Application of the Phase Separation Strategy in Complex Molecule Synthesis

8.2.1. Formal Synthesis of Ivorenolide A

The second subsection of the thesis reported the successful application of the macrocyclic Glaser-Hay coupling of terminal alkynes using a phase separation strategy for the

synthesis of a complex natural product. The strategy allows for macrocyclizations at high concentrations without the need for slow addition[5] and was adapted from the protocol developed under continuous flow conditions.[11] A formal total synthesis of ivorenolide A, an 18-membered ring macrolactone, that possesses a conjugated diyne moiety, was accomplished.[12] The key macrocyclic Glaser-Hay coupling reaction was conducted in continuous flow, employing a mixture of 1:1 PEG_{400} and MeOH at a concentration of 24 mM and afforded the desired macrocycle **8.10** in 52 % yield in only two hours (Scheme 8.7a). The key steps also included a *Z*-selective olefin metathesis, a technique that remains underutilized in the total synthesis of natural products. Ruthenium complex **8.14** efficiently catalyzed the cross-coupling between **8.11** and **8.12** to yield **8.13** (68 % brsm, > 95 % *Z*) with an excellent selectivity on the alkene geometry (Scheme 8.7b). The Glaser-Hay reaction permits direct cross-coupling without differentiation of the partners and, consequently, our synthesis of ivorenolide A is the shortest achieved so far. The key macrocyclization step could also efficiently be scaled up to gram quantities due to the facile adaptation of continuous flow setups.

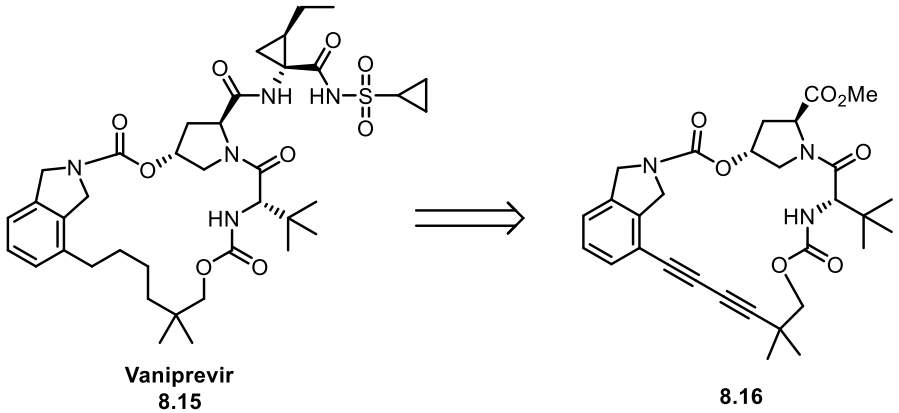


Scheme 8.7. Key steps of the formal total synthesis of ivorenolide A: a) Macrocyclic Glaser-Hay coupling under continuous flow and b) *Z*-selective olefin metathesis.

8.2.2. Future Work in Complex Molecule Synthesis via the Phase Separation Strategy

Despite the successful synthesis of ivorenolide A via the phase separation strategy in continuous flow, several challenges remain to be investigated for the Glaser-Hay methodology. The synthesis of macrocycles having basic nitrogen-containing heterocycles is a common challenge in drug discovery efforts. Peptide-containing macrocycles often have amides which enforce specific conformations upon macrocyclic precursors and therefore do not always allow for facile ring closure. In addition, the synthesis of peptide macrocycles in industry often targets concentrations of approximately 120-200 mM which are not always feasible using the current phase separation strategy.[13] Consequently, our group is currently investigating the synthesis of the macrocyclic core of Vaniprevir **8.15** (Scheme 8.6). The key cyclization would occur to form

intermediate **8.16** which contains several different heterocycles, sterically different amides and a slightly strained 1,3-diyne unit. Subsequent hydrogenation of macrocycle **8.16** would afford the Vaniprevir macrocyclic core. In addition, our group is investigating the use of dendritic PEGs as new co-solvents, which typically have enhanced aggregation in hydrophilic media compared to analogous linear polymeric PEGs, which could help to promote macrocyclization at even higher concentrations.



Scheme 8.8. Retrosynthesis of Vaniprevir.

8.3. Bibliography

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(9) Although characterization is not available, procedures are reported in the supporting information.

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Annexe 1. Supporting Information of Chapter 3

General:

All reactions that were carried out under anhydrous conditions were performed under an inert argon or nitrogen atmosphere in glassware that had previously been dried overnight at 120 ºC or had been flame dried and cooled under a stream of argon or nitrogen.[1] All commercial reagents were obtained from Sigma-Aldrich Chemical Company or Strem Chemicals and were reagent quality. Technical solvents were obtained from VWR International Co. Methyl 3-iodobenzoate[2], 9-(*tert*-butyldimethylsilyloxy)non-1-yne[3], 11-(*tert*-butyldimethylsilyloxy)undec-1-yne[4], 20-heneicosan-1-ol[5], 8-(triisopropylsilyloxy)octanol[6], 8-(*tert*-butyldimethylsilyloxy)octanol[7], (2,2-dimethyl-1,3-dioxolan-4-yl) methanol[8], 15-(*tert*-butyldimethylsilyloxy)pentadecanoic acid[9], methyl (15-hydroxypentadecyl)-*L*-phenylalanyl-*L*-phenylalaninium trifluoroacetate[10], 8-hydroxyoctan-1-ol acetate[11] and 12-oxooctadecanoic acid[12] were prepared according to literature procedure. Anhydrous solvents (CH_2Cl_2, Et_2O, THF, DMF, toluene, and *n*-hexane) were dried and deoxygenated using a GlassContour system

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(Irvine, CA). Isolated yields reflect the mass obtained following flash column silica gel chromatography. Organic compounds were purified using the method reported by Still[13] and using silica gel obtained from Silicycle Chemical division (40-63 nm; 230-240 mesh). Analytical thin-layer chromatography (TLC) was performed on glass-backed silica gel 60 coated with a fluorescent indicator (Silicycle Chemical division, 0.25 mm, F_{254}.). Visualization of TLC plates was performed by UV (254 nm), $KMnO_4$ or *p*-anisaldehyde stains. All mixed solvent eluents are reported as v/v solutions. Concentration refers to removal of volatiles at low pressure on a rotary evaporator. All reported compounds were homogeneous by thin layer chromatography (TLC) and by ^1H NMR. NMR spectra were taken in deuterated $CDCl_3$ using Bruker AV-300 and AV-400 instruments unless otherwise noted. Signals due to the solvent served as the internal standard ($CHCl_3$: δ 7.27 for ^1H, δ 77.0 for ^{13}C). The acquisition parameters are shown on all spectra. The ^1H NMR chemical shifts and coupling constants were determined assuming first-order behavior. Multiplicity is indicated by one or more of the following: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad); the list of coupling constants (*J*) corresponds to the order of the multiplicity assignment. High resolution mass spectroscopy (HRMS) was done by the Centre régional de spectrométrie de masse at the Département de Chimie, Université de Montréal from an Agilent LC-MSD TOF system using ESI mode of ionization unless otherwise noted.

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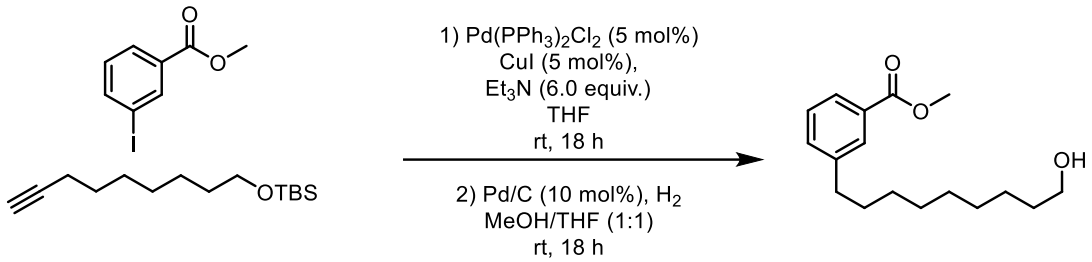
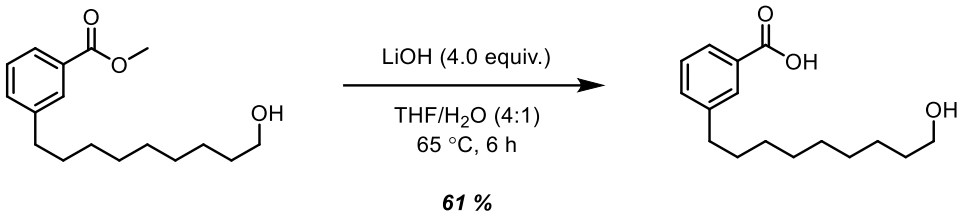
SYNTHESIS OF MACROCYCLE PRECURSORS



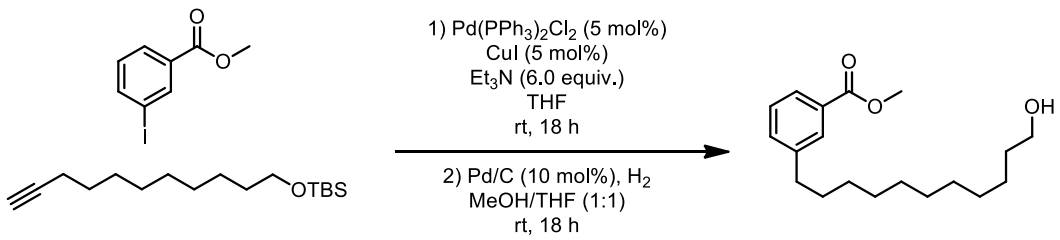
54 %

Methyl 3-(9-hydroxynon-1-yl)benzoate (S1) Methyl 3-iodobenzoate (500 mg, 1.91 mmol, 1.0 equiv.) was dissolved in tetrahydrofuran (10 mL, 0.2 M). $Pd(PPh_3)_2Cl_2$ (67 mg, 0.096 mmol, 0.05 equiv.) and CuI (18.3 mg, 0.096 mmol, 0.05 equiv.) were added to the solution and the reaction mixture was purged with N_2 for 5 min. Triethylamine (1.59 mL, 11.5 mmol, 6.0 equiv.) and the alkyne (592 mg, 2.10 mmol, 1.1 equiv.) were added and the reaction mixture was stirred at room temperature for 18 h. Silica (~ 10 mL) was added and the slurry was concentrated under reduced pressure and passed through a short pad of silica (20 % EtOAc in hexanes). The crude product was dissolved in a mixture of methanol (5 mL) and tetrahydrofuran (5 mL). Pd/C (405 mg, 5% w/w, 0.191 mmol, 0.100 equiv.) was added and the reaction mixture was purged with H_2 for 10 min. A balloon filled with H_2 equipped with a syringe was put on the septum and the reaction mixture was stirred at room temperature for 18 h. The reaction mixture was passed through a short pad of Celite® and concentrated under reduced pressure. Purification by flash chromatography (10% to 30% EtOAc in hexanes) was performed to afford the desired product as a colorless oil (253 mg, 54 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (m, 2H), 7.36 (m, 2H), 3.92 (s, 3H), 3.64 (t, J = 6.8 Hz), 2.65 (t, J = 8.0 Hz) 1.65-1.55 (m, 4H), 1.38-1.31 (m, 10H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.3, 143.2, 133.1, 130.0, 129.5, h128.2, 126.9, 63.0,

52.0, 35.7, 32.7, 31.3, 29.4, 29.3, 29.3, 29.1, 25.7 ppm; HRMS (ESI+) for $C_{17}H_{27}O_3$ $[M + H]^+$ calculated: 278.1882 found: 278.1893.

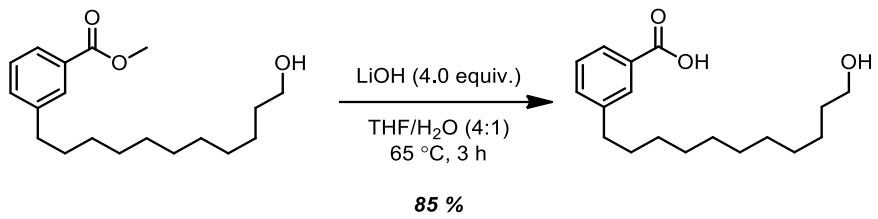


3-(9-Hydroxynon-1-yl)benzoic acid (S2) Methyl 3-(9-hydroxynon-1-yl)benzoate (253 mg, 0.910 mmol, 1.00 equiv.) was dissolved in tetrahydrofuran (4.8 mL). LiOH (87.0 mg, 3.64 mmol, 4.00 equiv.) was added as an aqueous solution (1.2 mL). The reaction mixture was stirred at 65 ºC for 6 h. The reaction mixture was cooled to room temperature and HCl 1M was added until the mixture was neutralized (pH = 7). Extraction with EtOAc (3 X 5 mL) was performed and the combined organic phases were washed with brine (15 mL). The organic phase was dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford the desired product as a white solid (145 mg, 61 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (m, 2H), 7.43-7.36 (m, 2H), 6.78 (br s, 1H (OH)), 3.66 (t, *J* = 6.4 Hz, 2H), 2.67 (t, *J* = 7.6 Hz, 2H), 1.66-1.55 (m, 4H), 1.31 (m, 10H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.8, 143.3, 133.8, 130.0, 129.4, 128.4, 127.5, 63.0, 35.6, 32.6, 31.2, 29.4, 29.32, 29.29, 29.1, 25.7 ppm; HRMS (ESI+) for $C_{16}H_{25}O_3$ $[M + H]^+$ calculated: 264.1725 found: 264.1738.



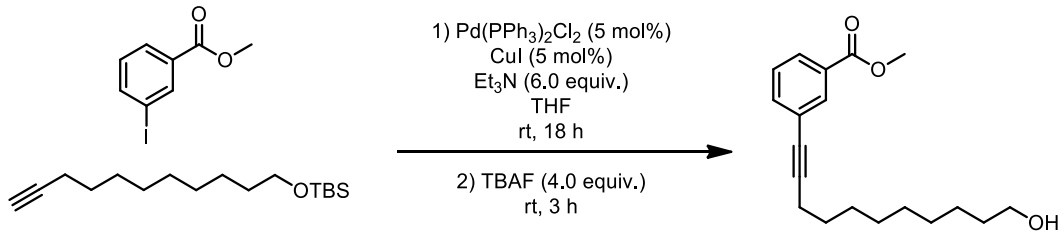
44 %

Methyl 3-(11-hydroxyundec-1-yl)benzoate (S3) Methyl 3-iodobenzoate (300 mg, 1.15 mmol, 1.0 equiv.) was dissolved in tetrahydrofuran (6 mL, 0.2 M). $Pd(PPh_3)_2Cl_2$ (40 mg, 0.057 mmol, 0.050 equiv.) and CuI (11 mg, 0.057 mmol, 0.050 equiv.) were added to the solution and the reaction mixture was purged under N_2 for 5 min. Triethylamine (0.95 mL, 6.9 mmol, 6.0 equiv.) and the alkyne (355 mg, 1.26 mmol, 1.10 equiv.) were added and the reaction mixture was stirred at room temperature for 18 h. Silica (~ 10 mL) was added and the slurry was concentrated under reduce pressure and passed through a short padof silica (20 % EtOAc in hexanes). The crude was dissolved in a mixture of methanol (5 mL) and tetrahydrofuran (5 mL). Pd/C (244 mg, 5% w/w, 1.15 mmol, 0.1 equiv.) was added and the reaction mixture was purged with H_2 for 10 min. A balloon filled with H_2 equipped with a syringe was put on the septum and the reaction mixture was stirred at room temperature for 18 h. The reaction mixture was passed through a short pad of Celite® and concentrated under reduced pressure. Purification by flash chromatography (10 % to 30 % EtOAc in hexanes) was performed to the desired product as a colorless oil (154 mg, 44 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (m, 2H), 7.36 (m, 2H), 3.92 (s. 3H), 3.64 (t, J = 6.8 Hz, 2H), 2.65 (t, J = 7.2 Hz), 1.65-1.55 (m, 4H), 1.31-1.27 (m, 14H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.3, 143.2, 133.1, 130.0, 129.5, 128.2, 126.9, 63.1, 52.0, 35.7, 32.8, 31.3, 29.55, 29.51, 29.48, 29.42, 29.38, 29.2, 25.7 ppm; HRMS (ESI+) for $C_{19}H_{31}O_3$ $[M + H]^+$ calculated: 306.2195 found: 306.2207.



85 %

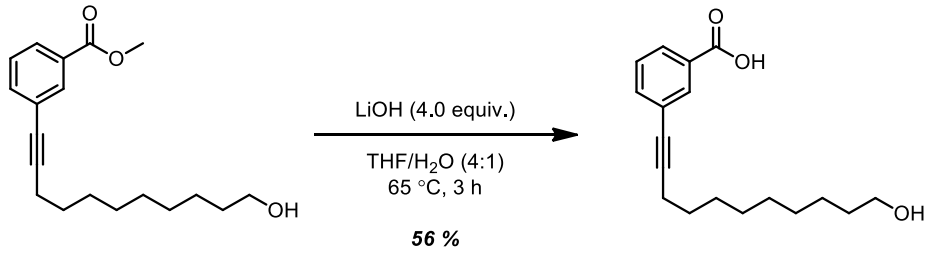
3-(11-Hydroxyundec-1-yl)benzoic acid (S4) Methyl 3-(11-hydroxyundec-1-yl)benzoate (154 mg, 0.500 mmol, 1.00 equiv.) was dissolved in tetrahydrofuran (4 mL). LiOH (48 mg, 2.01 mmol, 4.0 equiv.) was added as an aqueous solution (1 mL). The reaction mixture was stirred at 65 ºC for 3h. The reaction mixture was cooled down to room temperature and HCl 1M was added until the mixture was neutralized (pH = 7). Extraction with EtOAc (3X 5 mL) was performed and the combined organic phases were washed with brine (15 mL). The organic phase was dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford the desired product acid as a white solid (125 mg, 85 %).^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (m, 2H), 7.44-7.37 (m, 2H), 3.67 (t, *J* = 6.6 Hz, 2H), 2.68 (t, *J* = 7.4 Hz, 2H), 1.67-1.55 (m, 4H), 1.33-1.28 (m, 14H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.9, 143.3, 133.9, 130.1, 129.1, 128.4, 127.5, 63.1, 35.6, 32.7, 31.2, 29.5, 29.44, 29.42, 29.38, 29.3, 29.0, 25.7 ppm; HRMS (ESI+) for $C_{18}H_{29}O_3$ $[M + H]^+$ calculated: 293.2111 found: 293.2110.



39 %

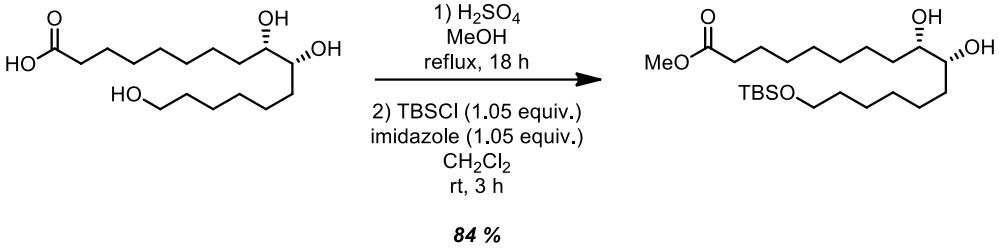
Methyl 3-(11-hydroxyundec-1-yn-1-yl)benzoate (S5) Methyl 3-iodobenzoate (165 mg, 0.629 mmol, 1.00 equiv.) was dissolved in tetrahydrofuran (3 mL, 0.2 M). $Pd(PPh_3)Cl_2$ (22 mg, 0.032 mmol, 0.050 equiv.) and CuI (6.1 mg, 0.032 mmol, 0.050 equiv.) were added to the solution and the reaction mixture was purged under N_2 for 5 min. Triethylamine (0.53 mL, 3.8 mmol, 6.0

equiv.) and the alkyne (195 mg, 0.691 mmol, 1.10 equiv.) were added and the reaction mixture was stirred at room temperature for 18 h. Silica (~ 10 mL) was added and the slurry was concentrated under reduced pressure and passed through a short pad of silica (20 % EtOAc in hexanes). The crude was dissolved in THF (12 mL) and TBAF (2.43 mL as 1M solution in THF, 2.43 mmol, 4.00 equiv.) was added to the solution. The reaction mixture was stirred at room temperature for 3 h and was then quenched by adding NH_4Cl saturated solution (10 mL). Extraction with EtOAc was performed (2 x 10 mL) and the organic phase was washed with water (20 mL) and brine (20 mL). The organic phase was then dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude was purified by flash chromatography (20% EtOAc in hexanes) to afford the desired product as a colorless oil (74 mg, 39 % over two steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (s, 1H), 7.93 (d, *J* = 7.7 Hz, 1H), 7.56 (d, *J* = 7.4 Hz, 1H), 7.36 (dd, *J* = 7.6 Hz, 7.6 Hz, 1H), 3.92 (s, 3H), 3.65 (t, *J* = 6.6Hz, 2H), 2.42 (t, *J* = 7.0Hz, 2H), 1.65-1.55 (m, 4H), 1.50-1.42 (m, 2H), 1.34 (m, 8H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.6, 135.7, 132.7, 130.2 128.4, 128.3, 124.5, 91.5, 79.6, 63.0, 52.2, 32.8, 29.4, 29.3, 29.0, 28.8, 28.6, 25.7, 19.3 ppm; HRMS (ESI+) for $C_{19}H_{27}O_3$ $[M + H]^+$ calculated: 303.1955, found: 303.1965.



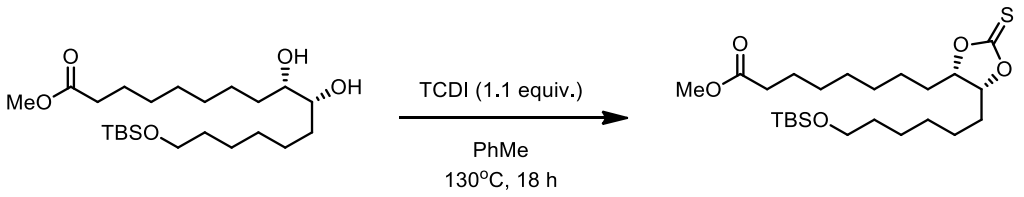
3-(11-Hydroxyundec-1-yn-1-yl)benzoic acid (S6) Methyl 3-(11-hydroxyundec-1-yn-1-yl)benzoate (74 mg, 0.24 mmol, 1.0 eq) was dissolved in tetrahydrofuran (3.2 mL). LiOH (23 mg, 0.97 mmol, 4.00 eq) was added as an aqueous solution (0.8 mL). The reaction mixture was stirred at 65 °C for 3 h. The reaction mixture was cooled down to room temperature and HCl

1M was added until the mixture was neutralized (pH = 7). Extraction with EtOAc (3X 5 mL) was performed and the combined organic phases were washed with brine (15 mL). The organic phase was dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford the desired product as a white solid (39 mg, 56 %) (Note: Seco acid **S6** is highly insoluble in $CDCl_3$ which made it difficult to obtain quality ^1H and ^{13}C spectra). ^1H NMR (400 MHz, $CDCl_3$) δ 8.14 (s, 1H), 7.99 (d, *J* = 7.6 Hz, 1H), 7.61 (d, *J* = 8.0 Hz, 1H), 7.40 (dd, *J* = 8.0 Hz, 8.0 Hz, 1H), 7.49 (br s, 1H (OH)), 3.67 (t, *J* = 6.4Hz, 2H), 2.42 (t, *J* = 6.8 Hz, 2H), 1.64-1.58 (4H), 1.50-1.47 (m, 2H), 1.35 (m, 10H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.8, 136.4, 133.3, 129.0, 128.4, 124.7, 91.8, 79.6, 63.0, 32.6, 29.4, 29.3, 29.0, 28.8, 28.5, 25.7, 19.3 ppm; HRMS (ESI+) for $C_{18}H_{25}O_3$ $[M + H]^+$ calculated: 289.1798, found: 289.1800.



***(±)-erythro*-Methyl 16-*tert*-butyldimethylsilyloxy-9,10-dihydroxyhexadecanoate (S7)** (±)-*erythro*-aleuritic acid (500 mg, 1.64 mmol, 1.00 equiv.) was dissolved in MeOH (40 mL). Concentrated H_2SO_4 (5-10 drops) was added to the solution. The reaction mixture was heated to reflux for 18 h and then brought back to room temperature and quenched by the addition of a K_2CO_3 saturated solution (until pH = 7). Extraction was performed by the addition of EtOAc (100 mL) and water (50 mL). The aqueous phase was extracted with EtOAc (2 x 50 mL). The combined organic phases were washed with H_2O (100 mL) and brine (75 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was the dissolved in CH_2Cl_2 (15 mL). TBSCl (260 mg, 1.72 mmol, 1.05 equiv.) and imidazole (117 mg, 1.72

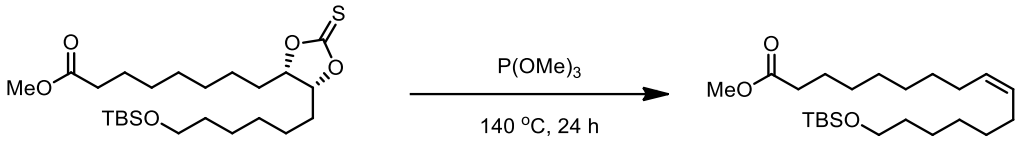
mmol, 1.05 equiv.) were added to the solution. The reaction mixture was stirred at room temperature for 3 h and was quenched by the addition of water (10 mL). Extraction was performed with EtOAc (2 x 25 mL) and the combined organic phases were washed with water (20 mL) and brine (20 mL). Silica gel was added (10 mL) and the slurry was concentrated under reduced pressure. Flash chromatography was performed (25 % EtOAc in hexanes) to afford the desired product as a white solid (534 mg, 84 % over two steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.68 (s, 3H), 3.62 (t, J = 6.8Hz, 2H), 3.42-3.40 (m, 2H), 2.32 (t, *J* = 7.2Hz, 2H), 2.08-2.04 (br s, 2H (OH)), 1.65-1.62 (m, 2H), 1.53-1.34 (m, 20H), 0.92 (s, 9H), 0.06 (s, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.3, 74.5, 74.4, 63.2, 51.4, 34.0, 33.6 (2C), 32.8, 29.5, 29.4, 29.1, 29.0, 26.0, 25.8, 25.6, 25.5, 24.9, 18.4, -5.3 ppm; HRMS (ESI+) for $C_{23}H_{49}O_5Si$ $[M + H]^+$ calculated : 433.3344 found: 433.3364.



98 %

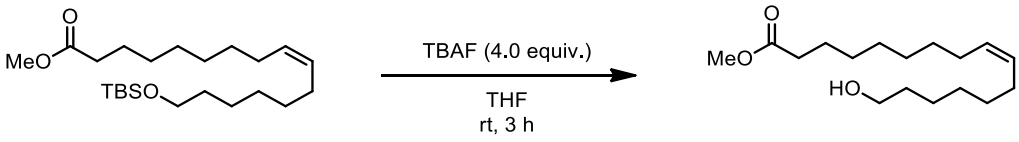
(±)-*erythro*-Methyl 8-((6-*tert*-butyldimethylsilyloxy)hexyl-2-thioxo-1,3-dioxolan-4-yl)octanoate (S8) The diol **S7** (200 mg, 0.462 mmol, 1.00 equiv.) was dissolved in PhMe (3.0 mL) in a sealed tube. TCDI (90.4 mg, 0.508 mmol, 1.10 equiv.) was added and the reaction vial was sealed and the mixture was stirred at 130°C for 18 h. The solution was cooled down to room temperature and silica gel (10 mL) was added and the slurry was concentrated under reduced pressure. Flash chromatography was performed (5-10 % EtOAc in hexanes) to afford the desired product (215 mg, 98 %) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.46-4.44 (m, 2H), 3.68 (s, 3H), 3.61 (t, *J* = 6.4Hz, 2H), 2.32 (t, *J* =7.2 Hz, 2H), 1.80-1.60 (m, 6H), 1.53-1.50 (m,

4H), 1.40-1.30 (m, 12H), 0.90 (s, 9H), 0.05 (s, 6H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 191,7, 174.2, 86.8 (2C), 63.0, 51.5, 34.0, 33.25, 33.21, 32.6, 29.0, 28.92 (2C), 28.90, 25.9, 25.6, 24.8, 24.64, 24.59, 18.4, -5.3 ppm; HRMS (ESI+) for $C_{24}H_{47}O_5SSi$ $[M + H]^+$ calculated: 475.2908 found: 475.2927.



62 %

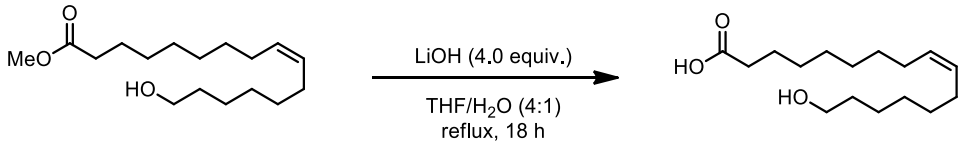
Methyl (*Z*)-16-(*tert*-butyldimethylsilyloxy)hexadec-9-enoate (S9) The thiocarbonate **S8** (200 mg, 0.423 mmol, 1.00 equiv.) was dissolved in trimethylphosphite (10 mL) in a sealed tube. The reaction mixture was stirred at 140 °C for 24 h. The solution was cooled to room temperature and concentrated under reduced pressure. Flash chromatrography (3 % EtOAc in hexanes) was performed to afford the desired product as a colorless oil (101 mg, 62 %) ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.39-5.38 (m, 2H), 3.67 (s, 3H), 3.60 (t, *J* = 6.4Hz, 2H), 2.31 (t, *J* = 6.8Hz, 2H), 1.94 (m, 4H), 1.35-1.30 (m, 4H), 1,30 (m, 14H), 0.90 (s, 9H), 0.05 (s, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.3, 130.3 (2C), 63.3, 51.4, 34.1, 32.8, 32.54, 32.52, 29.6, 29.5, 29.1 (2C), 28.9(2C), 26.0, 25.6, 24.9, 18.4, -5.3 ppm; HRMS (ESI+) for $C_{23}H_{47}O_3Si$ $[M + H]^+$ calculated: 399.3289 found: 399.3301.



58 %

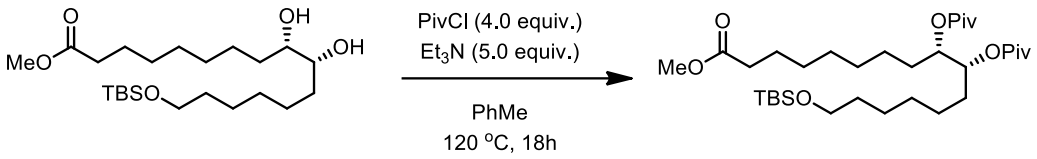
Methyl (*Z*)-16-hydroxyhexadec-9-enoate (S10) Compound **S9** (100 mg, 0.263 mmol, 1.00 equiv.) was dissolved in THF (4 mL). A solution of TBAF (1M in THF) (1.05 mL, 4.00 equiv.) was added and the mixture was stirred at room temperature for 3 h. The reaction was quenched

by the addition of water (5 mL). Extraction with EtOAc (2 x 10 mL) was performed and the combined organic layers were washed with water (20 mL) and brine (20 mL). The organic phase was then dried under Na_2SO_4, filtered and concentrated under reduced pressure. Flash chromatography (40 % EtOAc in hexanes) was performed to afford the desired product as a colorless oil (41 mg, 58 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.38-5.36 (m, 2H), 3.66 (s, 3H), 3.63 (t, *J* = 6.8Hz, 2H), 2.30 (t, *J* =7.2Hz, 2H), 1.96, (m, 4H), 1.62-1.54 (m, 4H), 1.35-1.28 (m, 14H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.3, 130.3, 130.2, 63.0, 51.4, 34.1, 32.7, 32.5, 32.4, 29.50, 29.48, 29.1 (2C), 28.9, 28.8, 25.6, 24.9 ppm; HRMS (ESI+) for $C_{17}H_{33}O_3$ $[M + H]^+$ calculated: 285.2424 found: 285.2436.



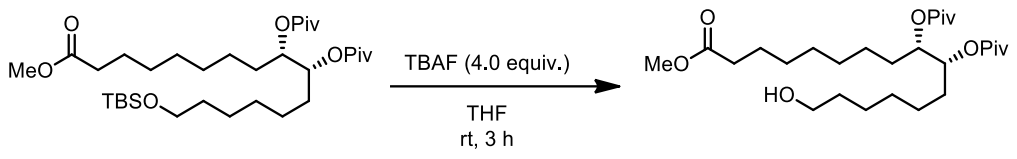
(*Z*)-16-Hydroxyhexadec-9-enoic acid (S11) The methyl ester **S10** (41 mg, 0.15 mmol, 1.0 equiv.) was dissolved in THF (1.6 mL). LiOH (15 mg, 0.61 mmol, 4.0 equiv.) was dissolved in water (0.4 mL) and added to the previous mixture. The solution was stirred at reflux for 18 h. The reaction mixture was cooled down to room temperature and HCl 1M was added until the mixture was neutralized (pH = 7). Extraction with EtOAc (3 X 5 mL) was performed and the combined organic phases were washed with brine (15 mL). The organic phase was dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford the product as a white solid (39 mg, 96 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.38-5.37 (m, 2H), 3.65 (t, *J* = 6.7 Hz, 2H), 2.34 (t, *J* = 7.4 Hz, 2H), 1.99-1.96 (m, 4H), 1.63-1.57 (m, 4H), 1.40-1.25 (m, 14H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.9, 130.4, 130.3, 63.0, 34.0, 32.6, 32.45, 32.43, 29.5, 29.03, 29.00, 28.8,

28.7, 25.6, 24.7 ppm; HRMS (ESI+) for $C_{16}H_{31}O_3$ [M + H]$^+$ calculated 271.2268 found: 271.2273.



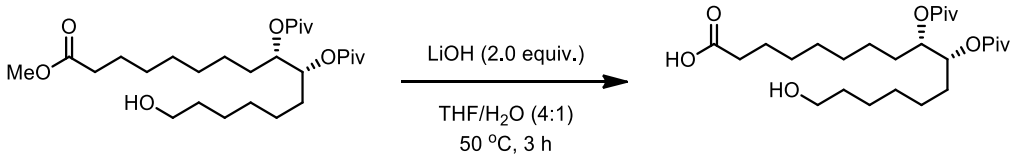
88 %

(±)-*erythro*-Methyl 16-(*tert*-butyldimethylsilyloxy)heptadecane-8,9-diyl[bis(2,2-dimethylpropanoate)]oate (S12) The diol **S7** (206 mg, 0.476 mmol, 1.00 equiv.) was dissolved in PhMe (5 mL) in a sealed tube. Et_3N (0.33 mL, 2.30 mmol, 5.00 equiv.) was added followed by PivCl (0.23 mL, 1.9 mmol, 4.0 equiv.). The reaction mixture was stirred at 120 °C for 18 h. The reaction was quenched by addition of water (5 mL). Extraction with EtOAc was performed (2 x 5 mL) and the combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. Flash chromatography (10 % EtOAc in hexanes) was performed to afford the desired product (252 mg, 88 %) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.98 (m, 2H), 3.67 (s, 3H), 3.59 (t, *J* = 6.8Hz, 2H), 2.30 (t, *J* = 7.6Hz, 2H), 1.63-1.48 (m, 8H), 1.30-1.23 (m, 12H), 1.22 (s, 18H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.8 (2C), 174.2, 73.3 (2C), 63.1, 51.4, 38.9 (2C), 34.1, 32.7, 30.8, 29.23, 29.20, 29.02, 29.00, 27.2 (2 x **C**(**C**H_3)$_3$), 26.0, 25.6, 25.0, 24.9, 18.4, -5.3ppm; HRMS (ESI+) for $C_{33}H_{64}O_7SiNa$ [M + Na]$^+$ calculated 623.4314 found: 623.4310.



70 %

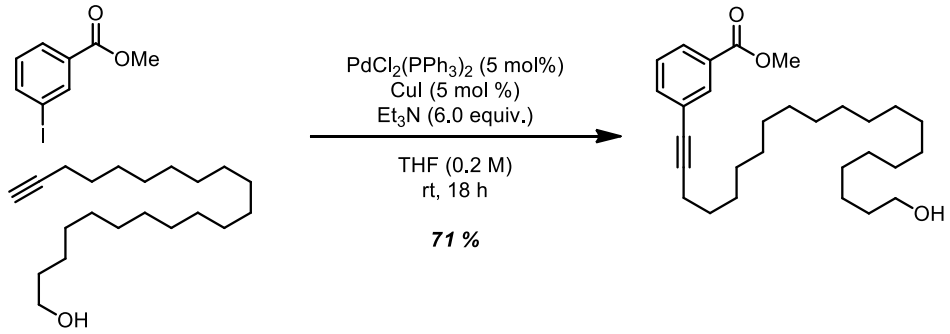
(±)-*erythro*-Methyl 16-hydroxyheptadecane-9,10-diyl[bis(2,2-dimethylpropanoate)] oate (S13) Compound **S12** (163 mg, 0.272 mmol, 1.00 equiv.) was dissolved in THF (1.5 mL). A solution of TBAF (1M in THF) (1.09 mL, 4.00 equiv.) was added and the mixture was stirred at room temperature for 3 h. The reaction was quenched by the addition of water (5 mL). Extraction with EtOAc (2 x 10 mL) was performed and the combined organic layers were washed with water (20 mL) and brine (20 mL). The organic phase was then dried under Na_2SO_4, filtered and concentrated under reduced pressure. Flash chromatography (40 % EtOAc in hexanes) was performed to afford the desired product as a colorless oil (93 mg, 70 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.98 (m, 2H), 3.67 (s, 3H), 3.63 (t, J = 6.6Hz, 2H), 2.29 (t, J = 7.8Hz, 2H), 1.65-1.50 (m, 8H), 1.45-1.30 (m, 16H), 1.22 (s, 18H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.8 (2C), 174.3, 73.2 (2C), 62.9, 51.4, 38.9 (2C), 34.0, 32.6, 30.8, 30.7, 29.2, 29.1, 29.01, 29.00, 27.2 (2 x **C**($\underline{\mathbf{C}}$H$_3$)$_3$), 25.5, 25.0, 24.9 ppm; HRMS (ESI+) for $C_{27}H_{51}O_7$ $[M + H]^+$ calculated 487.3629 found: 487.3652.



58 %

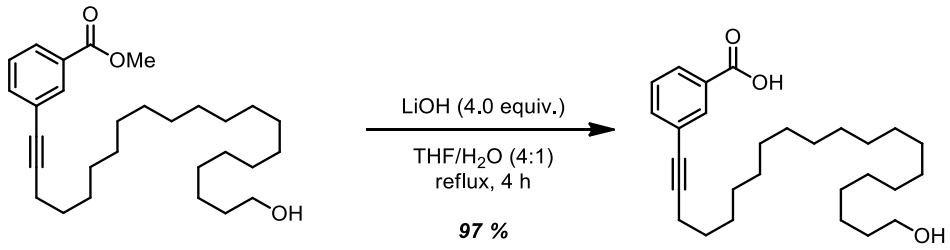
(±)-*erythro*-16-Hydroxyheptadecane-9,10-diyl[bis(2,2-dimethylpropanoate)]oic acid (S14) Compound **S13** (93 mg, 0.191 mmol, 1.00 equiv.) was dissolved in THF (2.0 mL). LiOH (16 mg, 0.38 mmol, 2.0 equiv.) was dissolved in water (0.5 mL) and added to the THF solution of

S13. The solution was stirred at 50 °C for 3 h. The reaction mixture was cooled down to room temperature and HCl 1M was added until the mixture was neutralized (pH = 7). Extraction with EtOAc (3 X 5 mL) was performed and the combined organic phases were washed with brine (15 mL). The organic phase was dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford the desired product as a colorless oil (52 mg, 58 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.99-4.96 (m, 2H), 3.63 (t, *J* = 6.5 Hz, 2H), 2.33 (t, *J* = 7.2 Hz, 2H), 1.64-1.23 (m, 24H), 1.21 (s, 18H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.9, 177.9 (2C), 73.2 (2C), 62.8, 38.9 (2C), 33.9, 32.4, 30.7, 30.6, 29.0 (2C), 28.9, 28.8, 27.2 (2 x C(**C**H_3)$_3$), 25.4, 24.9, 24.6 ppm; HRMS (ESI+) for $C_{26}H_{48}O_7Na$ $[M + Na]^+$ calculated 495.3292 found: 495.3306.



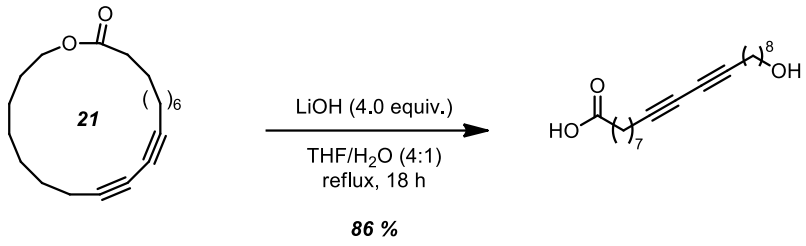
Methyl 3-(21-hydroxyheneicosan-1-yn-1-yl)benzoate (S15) Methyl 3-iodobenzoate (218 mg, 0.832 mmol, 1.00 equiv.) was dissolved in tetrahydrofuran (5 mL, 0.2 M). $Pd(PPh_3)_2Cl_2$ (29 mg, 0.042 mmol, 0.050 equiv.) and CuI (8.0 mg, 0.042 mmol, 0.050 equiv.) were added to the solution and the reaction mixture was purged under N_2 for 5 min. Triethylamine (0.69 mL, 4.99 mmol, 6.00 equiv.) and the alkyne (256 mg, 0.832 mmol, 1.00 eq) were added and the reaction mixture was stirred at room temperature for 18 h. Silica (~ 5 mL) was added and the slurry was concentrated under reduced pressure. Flash chromatography (5 to 20 % EtOAc in hexanes) was performed to afford the desired product (261 mg, 71 %) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (dd, *J* = 1.6 Hz, 1.6 Hz, 1H), 7.93 (dd, *J* = 7.6 Hz, 7.6Hz, 1.6 Hz, 1H), 7.56 (ddd,

J = 7.6 Hz, 7.6 Hz, 1.6 Hz, 1H), 7.36 (dd, *J* = 7.6 Hz, 7.6 Hz, 1H), 3.92 (s, 3H), 3.64 (t, *J* = 6.4 Hz, 2H), 2.41 (t, *J* = 6.8 Hz, 2H), 1.65-1.52 (m, 4H), 1.48-1.35 (m, 2H), 1.26 (m, 28H) ppm ; ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.6, 135.7, 132.7, 130.2, 128.4, 128.3, 124.5, 91.6, 79.6, 63.1, 52.2, 32.8, 29.7 (4C), 29.62, 29.59, 29.58, 29.5, 29.4, 29.1, 28.9, 28.6, 25.7, 19.4 ppm; HRMS (ESI+) for $C_{29}H_{47}O_3$ $[M + H]^+$ calculated: 443.3520 found: 443.3520.



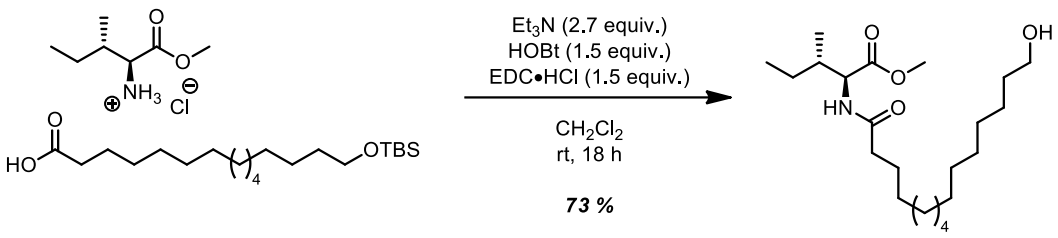
3-(21-Hydroxyheneicosan-1-yn-1-yl)benzoic acid (S16) The methyl ester **S15** (100 mg, 0.226 mmol, 1.00 equiv.) was dissolved in THF (4.0 mL). LiOH (38 mg, 0.90 mmol, 4.0 equiv.) was dissolved in water (1.0 mL) and added to the previous mixture. The solution was stirred at reflux for 4 h. The reaction mixture was cooled down to room temperature and HCl 1M was added until the mixture was neutralized (pH = 7). Extraction with EtOAc (3 X 5 mL) was performed and the combined organic phases were washed with brine (15 mL). The organic phase was dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford the desired product as white solid (94 mg, 97 %).(Note: Seco acid **S16** is highly insoluble in $CDCl_3$ which made it difficult to obtain quality ^{1}H and ^{13}C spectra). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (s, 1H), 7.98 (d, *J* = 7.7 Hz, 1H), 7.61 (d, *J* = 7.7 Hz, 1H), 7.39 (dd, *J* = 7.7 Hz, 7.7 Hz, 1H), 3.67 (t, *J* = 6.3 Hz, 2H), 2.42 (t, *J* = 7.0 Hz, 2H), 1.64-1.58 (m, 4H), 1.52-1.42 (m, 2H), 1.40-1.22 (m, 26H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 168.4, 136.3, 133.2, 129.2, 129.0, 128.4, 124.7, 91.8, 79.5, 63.2, 32.7, 29.64, 29.63, 29.62, 29.61, 29.60 (2C), 29.58 (2C) 29.6, 29.55, 29.47, 29.4, 29.1, 28.9,

28.6, 25.7, 19.4 ppm; HRMS (ESI+) for $C_{28}H_{44}O_3Na$ $[M + Na]^+$ calculated: 451.3191 found: 451.3183.

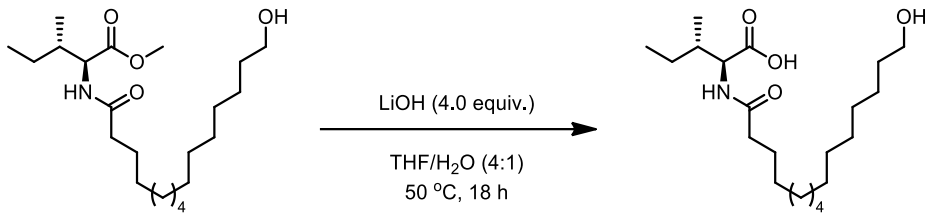


20-Hydroxyicosa-10,12-diynoic acid (S17) The macrolactone[14] (150 mg, 0.47 mmol, 1.00 equiv) was dissolved in tetrahydrofuran (8.0 mL). LiOH (79 mg, 1.88 mmol, 4.00 equiv.) was added as dissolved in water (2.0 mL) and added to the previous mixture. The solution was stirred at reflux for 18 h. The reaction mixture was cooled down to room temperature and HCl 1M was added until the mixture was neutralized (pH = 7). Extraction with EtOAc (3 x 10 mL) was performed and the combined organic phases were washed with brine (25 mL). The organic phase was dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford the desired product as a white solid (130 mg, 86 %). (Note: Seco acid **S17** is highly insoluble in $CDCl_3$ which made it difficult to obtain quality ^1H and ^{13}C spectra). ^1H NMR (400 MHz, $CDCl_3$) δ 6.46 (bs, OH), 3.66 (t, *J* = 5.0 Hz, 2H), 2.45-2.32 (m, 2H), 2.25 (t, *J* = 5.6 Hz, 4H), 1.72-1.46 (m, 6H), 1.43-1.22 (m, 16H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.6, 77.42 (2C), 65.3 (2C), 63.0, 33.9, 32.6, 29.7, 29.0 (2C), 28.9, 28.8, 28.7, 28.2 (2C), 25.5, 24.6, 24.5, 19.2 ppm; HRMS (ESI+) for $C_{20}H_{33}O_3$ $[M + H]^+$ calculated: 321.2426 found: 321.2424.

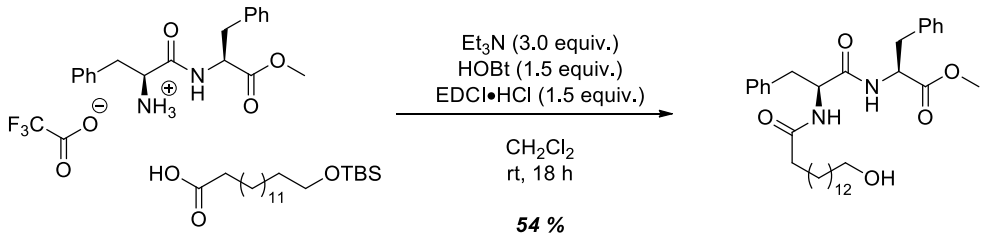
[14] Bédard, A.-C.; Collins, S. K. *J. Am. Chem. Soc* **2011**, *133*, 19976-19981.



Methyl (15-hydroxypentadecanoyl)-*L*-isoleucinate (S18) The isoleucine salt (500 mg, 2.75 mmol, 1.20 equiv.) and Et_3N (0.86 mL, 6.18 mmol, 2.70 equiv.) were added in CH_2Cl_2 (10 mL) and the mixture was stirred at room temperature upon complete dissolution. 15-(tert-butyldimethylsilyloxy)pentadecanoic acid was added (854 mg, 2.29 mmol, 1.00 equiv.) to the solution followed by HOBt (464 mg, 3.44 mmol, 1.5 equiv.) and EDC●HCl (660 mg, 3.44 mmol, 1.5 equiv.) and the mixture was stirred at room temperature for 18 h. The mixture was diluted with CH_2Cl_2 (5 mL) and washed with a 5 % w/w citric acid aqueous solution (10 mL) and a $NaHCO_3$ saturated aqueous solution (10 mL). The organic phase was dried over Na_2SO_4, filtered and concentrated under reduced pressure. Flash chromatography (10 to 40 % EtOAc in hexanes) was performed to afford the *in-situ* TBS-deprotected product (640 mg, 73 %) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.08 (d, J = 8.4 Hz, 1H (NH)), 4.59 (dd, J = 8.7 Hz, 5.0 Hz, 1H), 3.70 (s, 3H), 3.60 (t, J = 6.6 Hz, 2H), 2.20 (t, J = 7.3 Hz, 2H), 1.90 (br, s, 1H (OH)), 1.89-1.80 (m, 1H), 1.65-1.50 (m, 4H), 1.48-1.35 (m, 1H), 1.34-1.20 (m, 20H), 1.19-1.05 (m, 1H), 0.92-0.86 (m, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.9, 172.7, 62.8, 56.1, 51.9, 37.9, 36.6, 32.7, 29.5 (2C), 29.4 (3C), 29.35, 29.33, 29.2, 29.1, 25.7, 25.6, 25.1., 15.3, 11.4 ppm; HRMS (ESI+) for $C_{22}H_{44}NO_4$ $[M + H]^+$ calculated 386.3265 found: 386.3282.

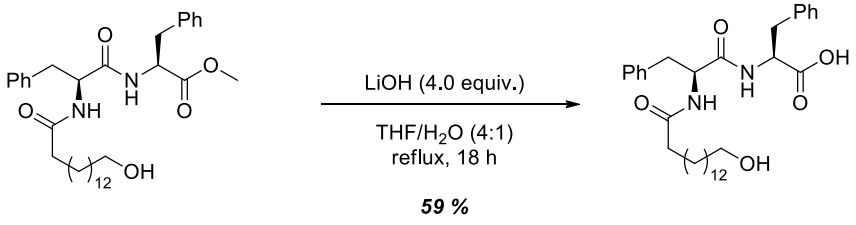


(15-Hydroxypentadecanoyl)-*L*-isoleucine (S19) The methyl ester **S18** (527 mg, 1.37 mmol, 1.00 equiv.) was dissolved in THF (20 mL). LiOH (230 mg, 548 mmol, 4.00 equiv.) was dissolved in H_2O (5 mL) and was added to the previous solution. The reaction mixture was stirred at 50 °C for 18 h and was then cooled down to room temperature. HCl 1M was added until the mixture was neutralized (pH = 7). Extraction with EtOAc (3 x 25 mL) was performed and the combined organic phases were washed with brine (100 mL). The organic phase was dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford the desired product as a white solid (421 mg, 83 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.17 (d, J = 8.5 Hz, 1H (NH)), 5.64 (br s, 1H (OH), 4.61 (dd, J = 8.5 Hz, 4.8 Hz, 1H), 3.66 (t, J = 6.7 Hz, 2H), 2.25 (t, J = 7.4 Hz, 2H), 1.97-1.87 (m, 1H), 1.68-1.45 (m, 5H), 1.40-1.12 (m, 21H), 0.95-0.92 (m, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.8, 173.8, 63.0, 56.4, 37.6, 36.6, 32.6, 29.5, 29.43 (2C), 29.41 (2C), 29.32, 29.30, 29.1, 29.1, 25.6 (2C), 25.1, 15.4, 11.6 ppm; HRMS (ESI+) for $C_{21}H_{40}NO_4$ $[M + H]^+$ calculated 370.2963 found: 370.2962.



Methyl (15-hydroxypendecyl)-*L*-phenylalanyl-*L*-phenylalaninate (S20) Phe-Phe methyl ester TFA salt (343 mg, 0.780 mmol, 1.00 equiv.) was dissolved in CH_2Cl_2 (8 mL). 15-(tert-

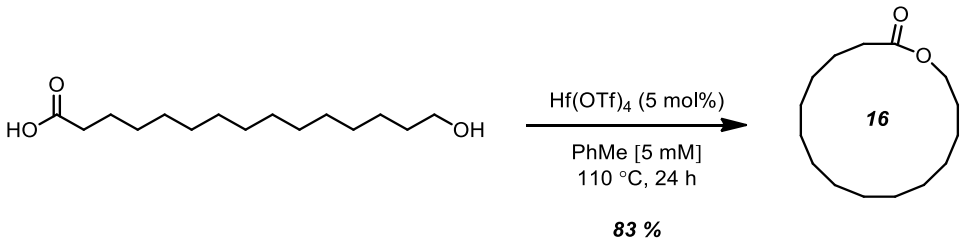
butyldimethylsilyloxy)pentadecanoic acid was added (290 mg, 0.780 mmol, 1.0 equiv.) to the solution followed by HOBt (158 mg, 1.17 mmol, 1.5 equiv.), EDC●HCl (225 mg, 1.17 mmol, 1.5 equiv.) and Et_3N (0.33 mL, 2.3 mmol, 3.0 equiv.) and the mixture was stirred at room temperature for 18 h. The mixture was diluted with CH_2Cl_2 (5 mL) and washed with a 5 % w/w citric acid aqueous solution (10 mL) and a $NaHCO_3$ saturated aqueous solution (10 mL). The organic phase was dried over Na_2SO_4, filtered and concentrated under reduced pressure. Flash chromatography (30 % to 100 % EtOAc in hexanes) was performed to afford the desired product (237 mg, 54 %) as a white solid. ^1H NMR ($CDCl_3$, 400 MHz) δ 7.29-7.18 (m, 8H), 7.02-7.00 (m, 2H), 6.39 (d, J = 7.4 Hz, 1H), 6.11 (d, J = 7.6 Hz, 1H), 4.74 (ddd, J = 7.4 Hz, 7.4 Hz, 6.3 Hz, 1H), 4.66 (ddd, J = 7.6 Hz, 7.6Hz, 7.1 Hz, 1H), 3.68 (s, 3H), 3.63 (t, J = 6.6 Hz, 2H), 3.10-2.94 (m, 4H), 2.11 (t, J = 7.0 Hz, 2H), 1.60-1.48 (m, 4H), 1.37-1.20 (m, 20H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 173.0, 171.2, 170.6, 136.4, 135.6, 129.3, 129.1, 128.54, 128.50, 127.1, 126.9, 63.0, 54.0, 53.4, 52.2, 38.0, 37.8, 36.5, 32.8, 29.51 (2C), 29.49 (2C), 29.37, 29.35, 29.2, 29.1, 25.7, 25.5 ppm; HRMS (ESI +) for $C_{34}H_{51}N_2O_5$ ($M + H^+$) calculated mass : 567.3793, found 567.3805.



(15-Hydroxypentadecyl)-*L*-phenylalanyl-*L*-phenylalanine (S21) The methyl ester **S20** (210 mg, 0.371 mmol, 1.0 equiv.) was dissolved in THF (6 mL). LiOH (62 mg, 1.5 mmol, 4.0 equiv.) was dissolved in H_2O (1.5 mL) and was added to the previous solution. The reaction mixture was stirred at 50 °C for 18 h and was then cooled down to room temperature. HCl 1M was added

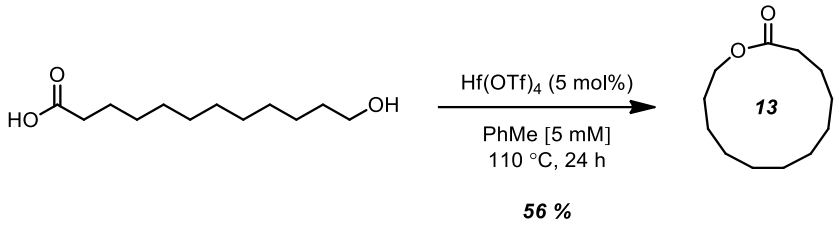
until the mixture was neutralized (pH = 7). Extraction with EtOAc (3 x 10 mL) was performed and the combined organic phases were washed with brine (20 mL). The organic phase was dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford the desired product as a white solid (120 mg, 59 %). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 12.71 (br s, 1H), 8.19 (d, J =7.8 Hz, 1H), 7.92 (d, J = 8.7 Hz, 1H), 7.27-7.15 (m, 10H), 4.55 (ddd, J = 7.8 Hz, 5.2 Hz, 4.0 Hz, 1H), 4.44 (ddd, J = 10.4 Hz, 8.7 Hz, 8.4 Hz, 1H), 4.33 (br s, 1H), 3.37 (t, J = 6.6 Hz, 2H), 3.08 (dd, J = 13.9 Hz, 5.2 Hz, 1H), 2.98 (dd, J = 14.0 Hz, 4.0 Hz, 1H), 2.93 (dd, J = 13.6 Hz, 8.4 Hz, 1H), 2.68 (dd, J = 13.9 Hz, 10.4 Hz, 1H), 1.96 (t, J = 6.8 Hz, 2H), 1.41-1.02 (m, 24 H) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz) δ 172.7, 171.9, 171.5, 138.0, 137.4, 129.1 (2C), 128.1, 127.8, 126.4, 126.1, 60.7, 53.4, 37.4, 36.6, 35.2, 32.5, 29.11, 29.06 (2C), 29.04 (3C), 28.97, 28.89, 28.8, 28.4, 25.5, 25.2 ppm; HRMS (ESI +) for $C_{33}H_{48}N_2O_5Na$ (M + Na^+) calculated mass : 575.3455, found 575.3460.

SYNTHESIS OF MACROLACTONES

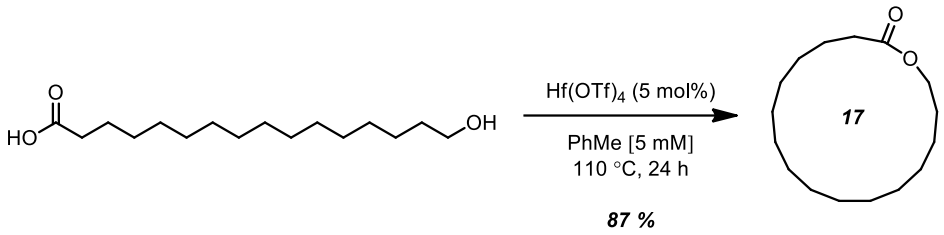


1-Oxacyclohexadecan-2-one (2) 15-Hydroxypentadecanoic acid (26 mg, 0.10 mmol, 1.0 equiv.) was dissolved in toluene (20 mL, 5 mM). $Hf(OTf)_4$ (3.9 mg, 0.0050 mmol, 0.05 equiv.) was added to the solution and the reaction mixture heated to 110 ºC. The reaction mixture was stirred at this temperature for 24 h. After cooling down to room temperature, silica gel (~ 1 mL) was added and the slurry was concentrated under reduced pressure and purified by flash

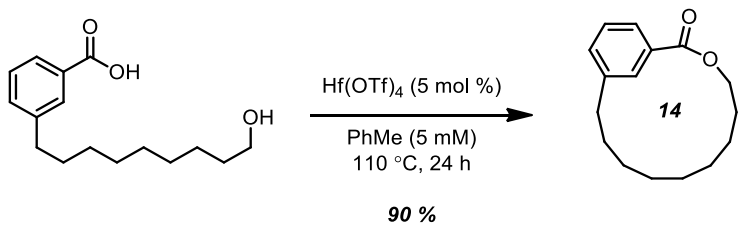
chromatography (3 % Et_2O in hexanes) to the desired product as a white solid (20 mg, 83 %). Spectral data were in accordance with those previously reported in the literature.[9]



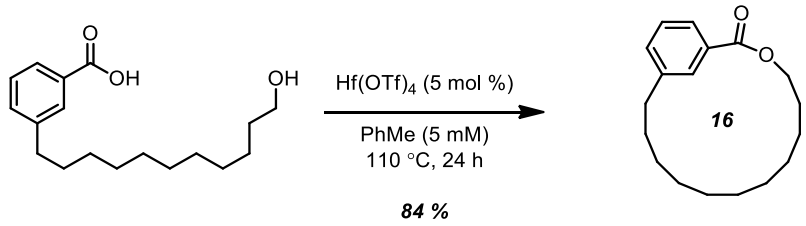
1-Oxacyclotridecan-2-one (4) 12-Hydroxypentadecanoic acid (22 mg, 0.10 mmol, 1.0 equiv.) was dissolved in toluene (20 mL, 5 mM). $Hf(OTf)_4$ (3.9 mg, 0.0050 mmol, 0.05equiv.) was added to the solution and the reaction mixture heated to 110 ºC. The reaction mixture was stirred at this temperature for 24 h. After cooling down to room temperature, silica gel (~ 1 mL) was added and the slurry was concentrated under reduced pressure and purified by flash chromatography (3 % Et_2O in hexanes) to afford the desired product as a colorless oil (11 mg, 56 %). Spectral data were in accordance with those previously reported in the literature.[9]



1-Oxacycloheptadecan-2-one (5): 16-Hydroxypentadecanoic acid (27 mg, 0.10 mmol, 1.0 equiv.) was dissolved in toluene (20 mL, 5 mM). $Hf(OTf)_4$ (3.9 mg, 0.0050 mmol, 0.05equiv.) was added to the solution and the reaction mixture heated to 110 ºC. The reaction mixture was stirred at this temperature for 24 h. After cooling down to room temperature, silica gel (~ 1 mL) was added and the slurry was concentrated under reduced pressure and purified by flash chromatography (3 % Et_2O in hexanes) to afford the desired product as a white solid (22 mg, 87 %). Spectral data were in accordance with those previously reported in the literature.[9]

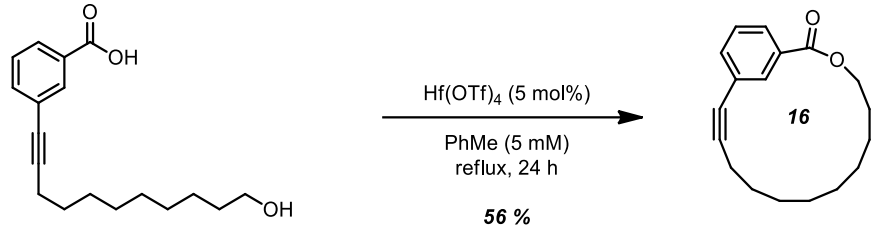


3-Oxabiclyclo[11.3.1]heptadeca-1(17),13,15-trien-2-one (6): 3-(9-Hydroxynon-1-yl)benzoic acid (26 mg, 0.10 mmol, 1.0 equiv.) was dissolved in toluene (20 mL, 5 mM). $Hf(OTf)_4$ (3.9 mg, 0.0050 mmol, 0.05 equiv.) was added to the solution and the reaction mixture heated to 110 °C. The reaction mixture was stirred at this temperature for 24 h. After cooling down to room temperature, silica gel (~ 1 mL) was added and the slurry was concentrated under reduced pressure and purified by flash chromatography (3 % EtOAc in hexanes) to the desired product as a white solid (22 mg, 90 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (s, 1H), 7.85 (d, *J* =6.7 Hz, 1H), 7.39-7.35 (m, 2H), 4.38 (t, *J* = 5.0 Hz, 2H), 2.81(t, *J* = 5.5 Hz, 2H), 1.82-1.78 (m, 4H), 1.66-1.62 (m, 2H), 1.52 (m, 6H), 1.38-1.36 (m, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.7, 141.2, 133.8, 130.4, 128.6, 128.4, 126.5, 66.3, 31.8, 28.5, 27.9, 27.5, 26.7, 26.6, 25.1, 24.3 ppm; HRMS (ESI+) for $C_{16}H_{23}O_2$ $[M + H]^+$ calculated: 247.1693 found: 247.1693.

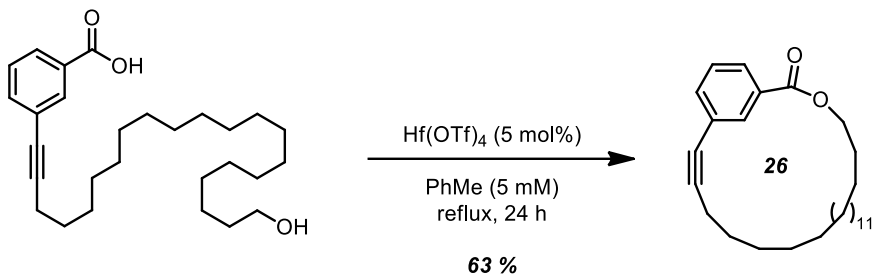


3-Oxabicyclo[13.3.1]nonadeca-1(19),15,17-trien-2-one (7) : 3-(11-Hydroxyundec-1-yl)benzoic acid (29 mg, 0.10 mmol, 1.0 equiv.) was dissolved in toluene (20 mL, 5 mM). $Hf(OTf)_4$ (3.9 mg, 0.0050 mmol, 0.05equiv.) was added to the solution and the reaction mixture heated to 110 °C. The reaction mixture was stirred at this temperature for 24 h. After cooling down to room temperature, silica gel (~ 1 mL) was added and the slurry was concentrated under

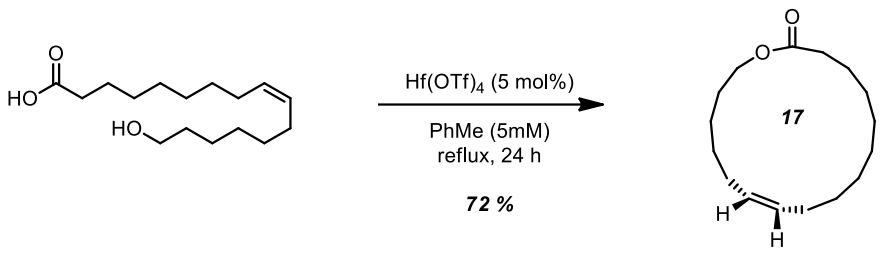
reduced pressure and purified by flash chromatography (3 % EtOAc in hexanes) to afford the desired product (23 mg, 84 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92-7.90 (m, 2H), 7.39-7.35 (m, 2H), 4.38 (t, *J* = 5.4 Hz, 2H), 2.75 (t, *J* = 6.2Hz, 2H), 1.80-1.68 (m, 4H), 1.58-1.52 (m, 2H), 1.31-1.24 (m, 12H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.8, 142.1, 133.6, 130.3, 129.1, 128.5, 127.2, 65.0, 33.4, 28.5, 27.51, 27.48, 27.45, 27.37, 27.3, 26.9, 25.6, 25.4 ppm; HRMS (ESI+) for $C_{18}H_{27}O_2$ $[M + H]^+$ calculated: 275.2006 found: 275.2005.



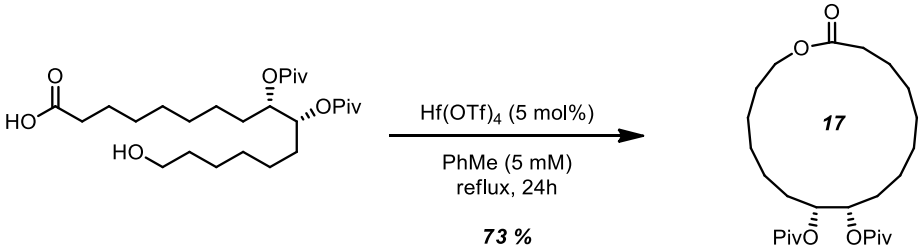
3-Oxobicyclo[13.3.1]nonadeca-1(19)-15,17-trien-13-yn-2-one (8) The hydroxyacid **S6** (29 mg, 0.10 mmol, 1.0 equiv.) was dissolved in toluene (20 mL, 5 mM). $Hf(OTf)_4$ (3.9 mg, 0.0050 mmol, 0.05 equiv.) was added to the solution and the reaction mixture heated to 110 ºC. The reaction mixture was stirred at this temperature for 24 h. After cooling down to room temperature, silica gel (~ 1 mL) was added and the slurry was concentrated under reduced pressure and purified by flash chromatography (3 % EtOAc in hexanes) to afford the desired product (15 mg, 56 %) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.30 (dd, *J* = 1.5 Hz, 1.5 Hz 1H), 7.92 (dd, *J* = 7.7 Hz, 7.7 Hz, 1.5 Hz, 1H), 7.42 - 7.49 (m, 1H), 7.34-7.42 (m, 1H), 4.34 - 4.41 (m, 2H), 2.41 - 2.48 (m, 2H), 1.82-1.80 (m, 2H), 1.77 -1.65 (m, 8H), 1.57-1.41 (m, 4H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 165.8, 136.2, 132.5, 130.6, 128.6, 128.1, 124.5, 93.6, 82.1, 66.4, 30.6, 30.1, 29.9, 28.8, 28.4, 28.2, 27.7, 19.2 ppm; HRMS (ESI) m/z calculated for $C_{18}H_{23}O_2$ $[M+H]^+$ 271.1693; found 271.1693.



3-Oxobicyclo[23.3.1]nonacosa-1(29)-25,27-trien-23-yn-2-one (9) The hydroxyacid **S16** (43 mg, 0.10 mmol, 1.0 equiv.) was dissolved in toluene (20 mL, 5 mM). $Hf(OTf)_4$ (3.9 mg, 0.0050 mmol, 0.05 equiv.) was added to the solution and the reaction mixture heated to 110 °C. The reaction mixture was stirred at this temperature for 24 h. After cooling down to room temperature, silica gel (~ 1 mL) was added and the slurry was concentrated under reduced pressure and purified by flash chromatography (3 % EtOAc in hexanes) to afford the desired product as a white solid (26 mg, 63 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (dd, *J* = 1.6 Hz, 1.6 Hz, 1H), 7.96 (ddd, *J* = 8.0 Hz, 8.0 Hz, 1.6 Hz, 1H), 7.57 (ddd, *J* = 8.4 Hz, 8.4 Hz, 1.6 Hz, 1H), 7.37 (dd, *J* = 8.0 Hz, 8.0 Hz, 1H), 4.34 (t, *J* = 6.4 Hz, 2H), 2.44 (t, *J* = 7.2 Hz, 2H), 1.82-1.62 (m, 2 H), 1.66-1.60 (m, 2H), 1.51-1.35 (m, 4H), 1.27 (m, 26H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.2, 135.5, 132.5, 130.7, 128.7, 128.3, 124.4, 91.5, 79.9, 65.3, 29.6, 28.96, 28.91, 28.84, 28.82, 28.80, 28.79, 28.77, 28.74, 28.72 (2C), 28.70, 28.65, 28.60, 28.4, 28.3, 26.0, 19.3 ppm; HRMS (ESI+) for $C_{28}H_{42}O_2$ $[M+H]^+$ calculated: 411.3258 found: 411.3249.



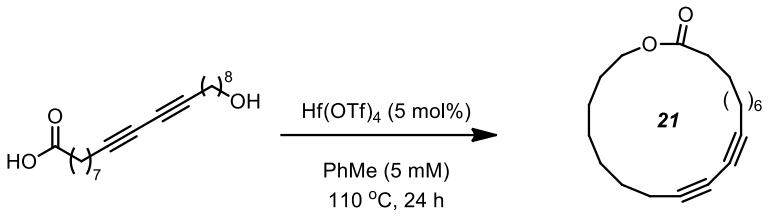
(9*Z*)-Isoambrettolide (10) (*Z*)-16-Hydroxyhexadec-9-enoic acid (27 mg, 0.10 mmol, 1.0 equiv.) was dissolved in toluene (20 mL, 5 mM). $Hf(OTf)_4$ (3.9 mg, 0.0050 mmol, 0.05 equiv.) was added to the solution and the reaction mixture heated to 110 °C. The reaction mixture was stirred at this temperature for 24 h. After cooling down to room temperature, silica gel (~ 1 mL) was added and the slurry was concentrated under reduced pressure and purified by flash chromatography (3 % Et_2O in hexanes) to afford the desired product as a white solid (18 mg, 72 %). Spectral data were in accordance with those previously reported in the literature[15].



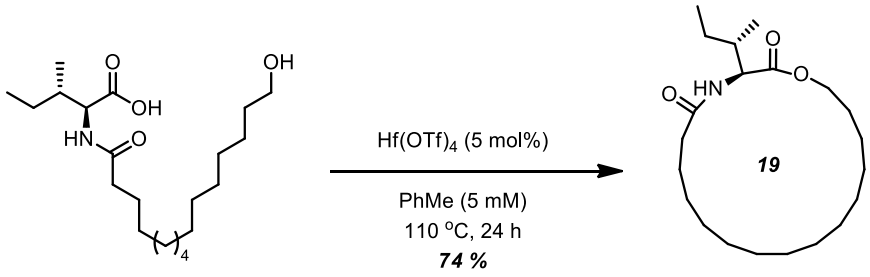
(±)-*erythro*-10,11-Bis[2,2-(dimethyl)propanoate]oxaheptadecan-2-one (11) The hydroxyacid **S14** (47 mg, 0.10 mmol, 1.0 equiv.) was dissolved in toluene (20 mL, 5 mM). $Hf(OTf)_4$ (3.9 mg, 0.0050 mmol, 0.05 equiv.) was added to the solution and the reaction mixture heated to 110 °C. The reaction mixture was stirred at this temperature for 24 h. After cooling down to room temperature, silica gel (~ 1 mL) was added and the slurry was concentrated under reduced pressure and purified by flash chromatography (10 % Et_2O in hexanes) to afford the

[15] Delphis, C. *Cis-isoambrettolide of High Degree of Isomer Purity and Use Thereof* **2001,** Patent No.: US 6,284,900 B1.

desired product as a colorless oil (33 mg, 73 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.10-5.05 (m, 1H), 5.03-4.98 (m, 1H), 4.18-4.10 (m, 2H), 2.34 (t, *J* = 6.4 Hz, 2H), 1.75-1.25 (m, 22H), 1.19 (s, 9H), 1.18 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.8, 177.7, 174.0, 73.2, 72.3, 64.1, 38.8, 34.6, 30.0, 29.2, 28.6, 28.1, 28.0, 27.7, 27.5, 27.22, 27.20, 25.6, 25.0, 23.7, 22.7 ppm; HRMS (ESI+) for $C_{26}H_{46}O_6Na$ $[M+Na]^+$ calculated: 477.3187 found: 477.3166.

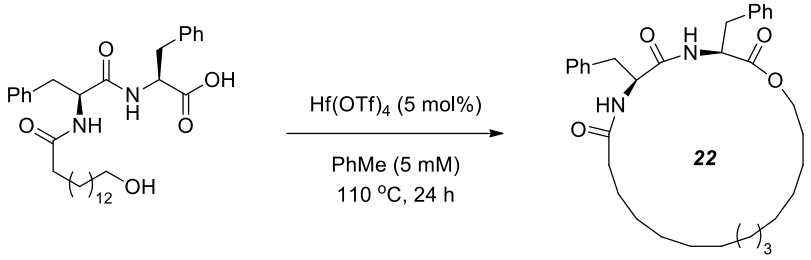


Oxacycloicosa-10,12-diyne-2-one (12) The hydroxyacid **S17** (32 mg, 0.10 mmol, 1.0 equiv.) was dissolved in toluene (20 mL, 5 mM). $Hf(OTf)_4$ (3.9 mg, 0.0050 mmol, 0.05 equiv.) was added to the solution and the reaction mixture heated to 110 °C. The reaction mixture was stirred at this temperature for 24 h. After cooling down to room temperature, silica gel (~ 1 mL) was added and the slurry was concentrated under reduced pressure and purified by flash chromatography (10 % EtOAc in hexanes) to afford the macrocycle as a white solid (26 mg, 86 %). Spectral data were in accordance with those previously reported in the literature[14].



(*S*)-3-((*S*)-*sec*-Butyl)-1-oxa-4-azacyclononadecane-2,5-dione (13)The hydroxyacid **S19** (64 mg, 0.17 mmol, 1.0 equiv.) was dissolved in toluene (35 mL, 5 mM). $Hf(OTf)_4$ (6.7 mg, 0.0087 mmol, 0.05 equiv.) was added to the solution and the reaction mixture heated to 110 °C. The

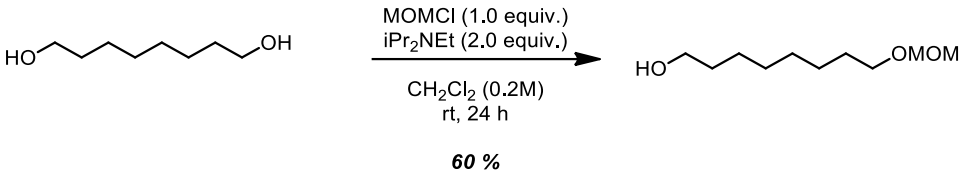
reaction mixture was stirred at this temperature for 24 h. After cooling down to room temperature, silica gel (~ 2 mL) was added and the slurry was concentrated under reduced pressure and purified by flash chromatography (10 to 50 % EtOAc in hexanes) to afford the macrocycle as a white solid (45 mg, 74 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.90 (d, J = 8.5 Hz, 1H (NH)), 4.61 (dd, J = 8.7 Hz, 5.2 Hz, 1H), 4.40-4.34 (m, 1H), 3.99 (dt, J = 10.7 Hz, 5.7 Hz, 1H), 2.33 (dt, J = 14.6 Hz, 6.4 Hz, 1H), 2.19-2.12 (m, 1H), 1.92-1.86 (m, 1H), 1.80-1.50 (m, 4H), 1.49-1.38 (m, 1H), 1.37-1.20 (m, 20H), 1.20-1.10 (m, 1H), 0.95-0.91 (m, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.7, 171.8, 64.9, 56.6, 38.0, 36.5, 28.5, 28.09, 28.07, 28.04, 28.01, 27.9, 27.5, 27.1, 27.0, 25.20, 25.19, 25.0, 15.4, 11.5 ppm; HRMS (ESI+) for $C_{21}H_{40}NO_3$ [M + H]$^+$ calculated: 354.3003 found: 354.3008.



(3*S*, 6*S*)-3,6-Dibenzyl-1-oxa-4,7-diazacyclodocosane-2,5-dione (14) The hydroxyacid (**S21)** (65 mg, 0.11 mmol, 1.0 equiv.) was dissolved in toluene (24 mL, 5 mM). $Hf(OTf)_4$ (4.6 mg, 0.0056 mmol, 0.05 equiv.) was added to the solution and the reaction mixture heated to 110 °C. The reaction mixture was stirred at this temperature for 24 h. After cooling down to room temperature, silica gel (~ 2 mL) was added and the slurry was concentrated under reduced pressure and purified by flash chromatography (10 to 60 % EtOAc in hexanes) to afford the macrocycle as a white solid (37 mg, 57 %). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.37-7.19 (m, 8H), 6.92-6.89 (m, 2H), 6.26 (d, J = 6.8 Hz, 1H), 5.83 (d, J = 7.1 Hz, 1H), 4.67-4.58 (m, 2H), 4.23-4.15 (m, 1H), 4.12-4.05 (m, 1H), 3.22-2.90 (m, 4H), 2.20-2.05 (m, 6H), 1.63-1.54 (m, 8 H),

1.28-1.25 (m, 16 H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 173.3, 170.8, 170.2, 136.8, 135.8, 129.5, 129.2, 128.8, 128.4, 127.2, 127.1, 65.4, 54.1, 53.9, 37.6, 37.4, 36.3, 28.09 (3C), 28.05 (2C), 28.01 (3C), 27.96, 27.91, 25.1 (2C) ppm; ; HRMS (ESI +) for $C_{33}H_{47}N_2O_4$ ($M + H^+$) calculated mass : 535.3530, found 535.3529.

SYNTHESIS OF ESTERIFICATION PRECURSORS

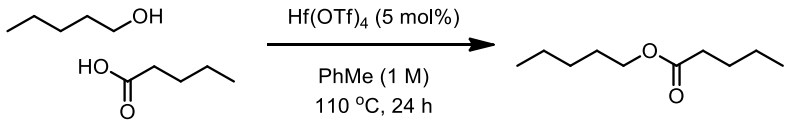


8-(Methoxymethoxy)octanol (S22) 1,8-octanediol (1.00 g, 6.84 mmol, 1.00 equiv.) was dissolved in CH_2Cl_2 (34 mL). iPr_2NEt (2.38 mL, 13.7 mmol, 2.00 equiv.) was added followed by MOMCl (0.52 mL, 6.8 mmol, 1.0 equiv.). The reaction mixture was stirred at room temperature for 24 h and was subsequently quenched by the addition of a saturated solution of NH_4Cl (25 mL). Extraction with CH_2Cl_2 (2 x 30 mL) was performed and the combined organic layers were washed with water (30 mL) and brine (30 mL) and dried over Na_2SO_4, filtered and concentrated under reduced pressure. Flash chromatography (20 % EtOAc in hexanes) was performed to afford the product as a colorless oil (775 mg, 60 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.61 (s, 2H), 3.62 (t, J = 6.6 Hz, 2H), 3.51 (t, J = 6.6 Hz, 2H), 3.35 (s, 3H), 1.75 (br s, 1H (OH)), 1.70-1.50 (m, 4H), 1.35-1.25 (m, 8H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 96.3, 67.8, 62.9, 55.0, 32.7, 29.6, 29.32, 29.30, 26.1, 25.6 ppm; HRMS (ESI+) for $C_{10}H_{22}O_3Na$ $[M + Na]^+$ calculated 213.1461 found: 213.1469.

SYNTHESIS OF ESTERS

General procedure A: An open oven-dried sealable tube was charged with the carboxylic acid (1.00 mmol, 1.00 equiv.) and dissolved in toluene (1 mL, 1M). $Hf(OTf)_4$ (38 mg, 0.050 mmol, 0.050 equiv.) and the alcohol (1.0 mmol, 1.0 equiv.) were then added to the mixture and the tube was sealed. The reaction mixture was stirred at 110 ºC for 24 h and then cooled down to room temperature. The tube was opened and silica gel (~ 5 mL) was added. The slurry was concentrated under reduced pressure and purified by flash chromatography.

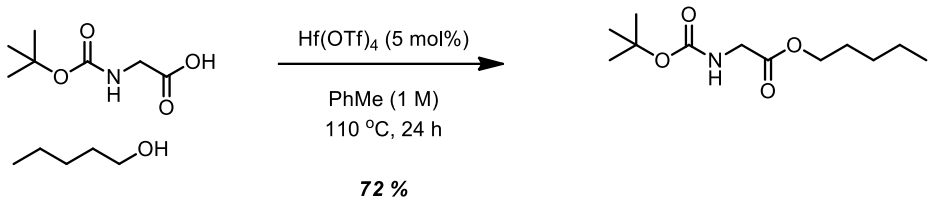
General procedure B: An open oven-dried sealable tube was charged with the carboxylic acid (1.00 mmol, 1.00 equiv.), *i*Pr_2NEt (0.087 mL, 0.50 mmol, 0.5 equiv.) and dissolved toluene (1 mL, 1M). $Hf(OTf)_4$ (38 mg, 0.050 mmol, 0.050 equiv.) and the alcohol (1.0 mmol, 1.0 equiv.) were then added to the mixture and the tube was sealed. The reaction mixture was stirred at 110 ºC for 24 h and then cooled down to room temperature. The tube was opened and silica gel (~ 5 mL) was added. The slurry was concentrated under reduced pressure and purified by flash chromatography.



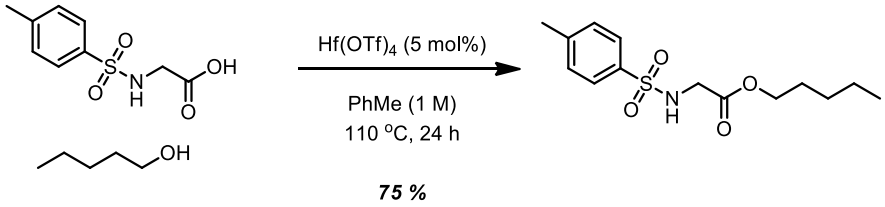
>99 %

Pentyl pentanoate (15) Following general procedure A, flash chromatography (5 % EtOAc in hexanes) afforded the product as a colorless oil (171 mg, >99 %). Spectral data were in accordance with those previously reported in the literature.[16]

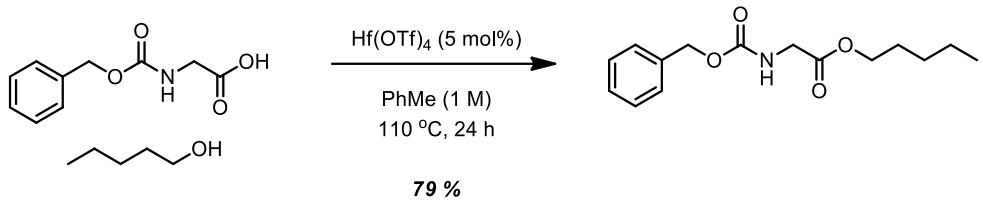
[16] Solvhoj, A; Madsen, R. *Organometallics* **2011**, *30*, 6044-6048.



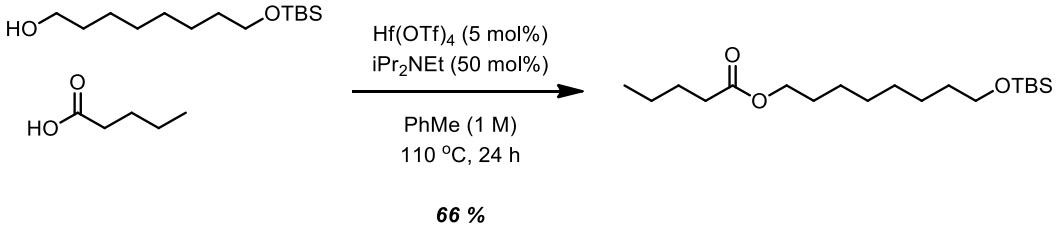
Pentyl ((*tert*-butyloxy)carbonyl)glycinate (16) Following general procedure A, flash chromatography (15 % EtOAc in hexanes) was performed to afford the product as a colorless oil (176 mg, 72 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.09 (br s, 1H (NH)), 4.11 (t, *J* = 6.7 Hz, 2H), 3.87 (d, *J* = 5.4 Hz, 2H), 1.65-1.57 (m, 2H), 1.44-1.40 (m, 11H), 1.35-1.28 (m, 4H), 0.88 (t, *J* = 6.4 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 155.7, 79.8, 65.4, 42.3, 28.2, 28.1, 27.8, 22.2, 13.8 ppm; HRMS (ESI+) for $C_{12}H_{23}NO_4Na$ $[M + Na]^+$ calculated 268.1519 found: 268.1525.



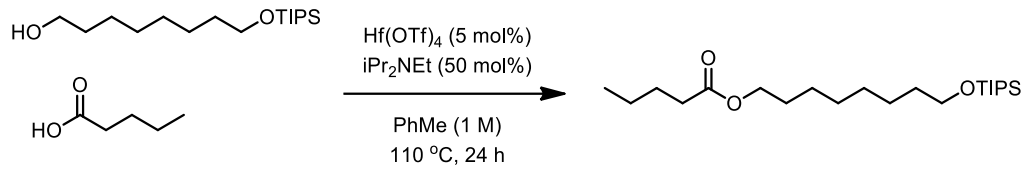
Pentyl *N*-(*p*-tosyl)glycinate (17) Following general procedure A, flash chromatography (10 % EtOAc in hexanes) was performed to afford the product as a white solid (224 mg, 75 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.1 Hz, 2H), 7.30 (d, *J* = 8.1 Hz, 2H), 5.23 (br s, 1H (NH)), 4.01 (t, *J* = 6.9 Hz, 2H), 3.77 (d, *J* = 5.5 Hz, 2H), 2.42 (s, 3H), 1.55-1.50 (m, 2H), 1.30-1.22 (m, 4H), 0.88 (t, *J* = 6.8 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.8, 143.7, 136.2, 129.7, 127.2, 65.9, 44.1, 28.0, 27.7, 22.1, 21.4, 13.8 ppm; HRMS (ESI+) for $C_{14}H_{22}NO_4S$ $[M + H]^+$ calculated 300.1264 found: 300.1278.



Pentyl ((benzyloxy)carbonyl)glycinate (18) Following general procedure A, flash chromatography (10 % EtOAc in hexanes) was performed to afford the product as a colorless oil (220 mg, 79 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33-7.28 (m, 5H), 5.64 (br s, 1H (NH)), 5.10 (s, 2H), 4.11 (t, *J* = 6.8 Hz), 3.92 (d, *J* = 7.0 Hz, 2H), 1.65-1.55 (m, 2H), 1.35-1.25 (m, 4H), 0.90 (t, *J* = 6.9 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.0, 156.2, 136.1, 128.2, 127.85, 127.79, 66.7, 65.3, 42.5, 27.9, 27.7, 22.0, 13.7 ppm; $C_{15}H_{22}NO_4$ $[M + H]^+$ calculated 280.1543 found: 280.1551.

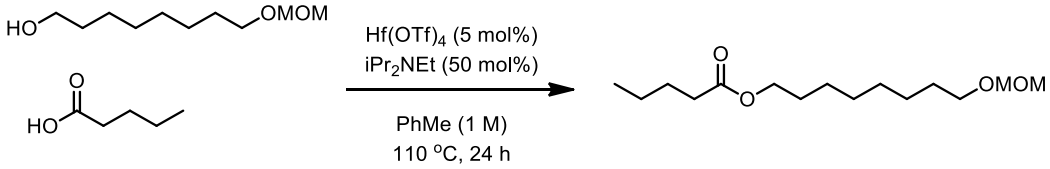


8-(*tert*-Butyldimethylsilyloxy)octyl pentanoate (19) Following general procedure B, flash chromatography (5 % EtOAc in hexanes) afforded the product as a colorless oil (178 mg, 66 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.,06 (t, *J* = 6.7Hz, 2H), 3.61 (t, *J* = 6.5Hz, 2H), 2.31 (t, *J* = 7.3 Hz, 2H), 1.64-1.60 (m, 2H), 1.55-1.48 (m, 2H), 1.40-1.30 (m, 8H), 0.94-0.90 (m, 12H), 0.05 (s, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.9, 64.3, 63.2, 34.1, 32.8, 29.3, 29.2, 28.6, 27.1, 26.0, 25.9, 25.7, 22.2, 18.3, 13.7, -5.3 ppm; HRMS (ESI+) for $C_{19}H_{41}O_3Si$ $[M + H]^+$ calculated 345.2820 found: 345.2831.



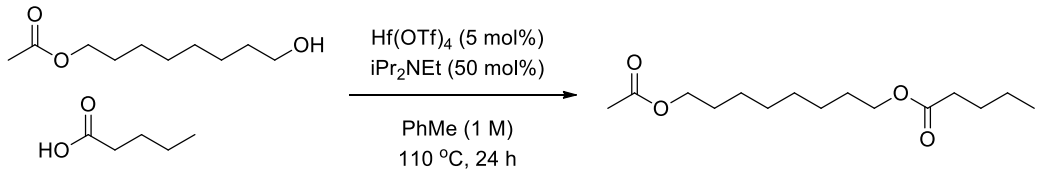
62 %

8-(Triisopropylsilyloxy)octyl pentanoate (20) Following general procedure B, flash chromatography (5 % EtOAc in hexanes) afforded the product as a colorless oil (217 mg, 62 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.06 (t, *J* = 6.8 Hz, 2H), 3.68 (t, *J* = 6.7 Hz, 2H), 2.30 (t, *J* = 7.4 Hz, 2H), 1.65-1.50 (m, 6H), 1.35-1.25 (m, 10H), 1.09-1.06 (m, 21 H), 0.92 (t, *J* = 7.3 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.9, 64.3, 63.4, 34.1, 33.0, 29.3, 29.2, 28.6, 27.1, 25.9, 25.7, 22.2, 17.9, 13.6, 12.0 ppm; HRMS (ESI+) for $C_{22}H_{46}O_3SiNa$ $[M + Na]^+$ calculated 409.3108 found: 409.3128.



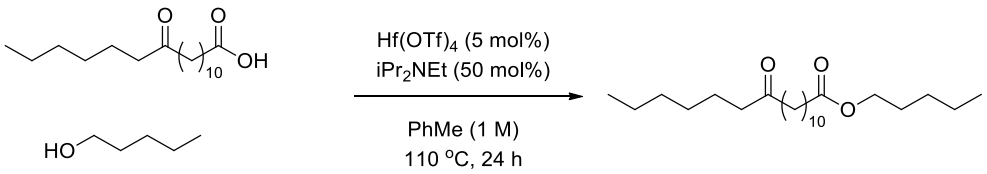
77 %

8-(Methoxymethoxy)octyl pentanoate (21) Following general procedure B, flash chromatography (10 % EtOAc in hexanes) afforded the product as a colorless oil (210 mg, 77 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.58 (s, 2H), 4.02 (t, *J* = 6.8Hz, 2H), 3.48 (t, *J* = 6.6Hz, 2H), 3.32 (s, 3H), 2.26 (t, *J* = 7.5 Hz, 2H), 1.60-1.50 (m, 6H), 1.35-1.25 (m, 10H), 0.88 (t, *J* = 7.3 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.8, 96.3, 67.7, 64.2, 54.9, 34.0, 29.6, 29.2, 29.1, 28.5, 27.0, 26.0, 25.8, 22.2, 13.6 ppm; HRMS (ESI+) for $C_{15}H_{30}O_4Na$ $[M + Na]^+$ calculated 297.2036 found: 297.2047.



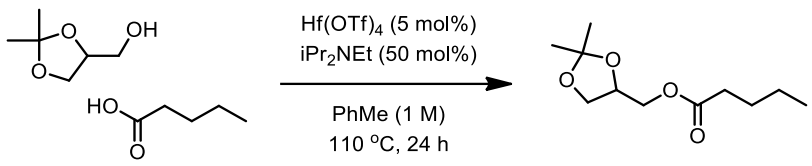
89 %

8-acetoxyoctyl pentanoate (22) Following general procedure B, flash chromatography (5 % EtOAc in hexanes) afforded the product as a colorless oil (129 mg, 89 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.035 (t, J = 6.7 Hz, 2H), 4.030 (t, J = 6.8 Hz, 2H), 2.28 (t, J = 7.4 Hz, 2H), 2.02 (s, 3H), 1.63-1.55 (m, 6H), 1.35-1.25 (m, 10H), 0.89 (t, J = 7.3 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.9, 171.1, 64.5, 64.2, 34.0, 29.03, 29.02, 28.53, 28,49, 27.0, 25.8, 25.7, 22.2, 20.9, 13.6 ppm; HRMS (ESI+) for $C_{15}H_{29}O_4$ ($M + H^+$) calculated mass: 273.2060, found 273.2059.

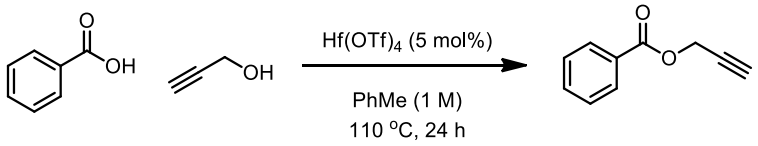


92 %

Pentyl 12-oxooctadecanoate (23) Following general procedure A, flash chromatography (5 % EtOAc in hexanes) afforded the product as a colorless solid (170 mg, 89 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.04 (t, J = 6.6 Hz, 2H), 2.38-2.34 (m, 4H), 2.27 (t, J = 7.3 Hz, 2H), 1.70-1.50 (m, 8 H), 1.45-1.20 (m, 22H), 0.90-0.84 (m, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.6, 173.9, 64.3, 42.7, 34.3, 31.6, 29.3 (4C), 29.2 (2C), 29.1, 28.9, 28.3, 28.0, 24.9, 23.81, 28.78, 22.4, 22.3, 13.95, 13.89 ppm; HRMS (ESI+) for $C_{23}H_{45}O_3$ ($M + H^+$) calculated mass: 369.3363, found 369.3369.

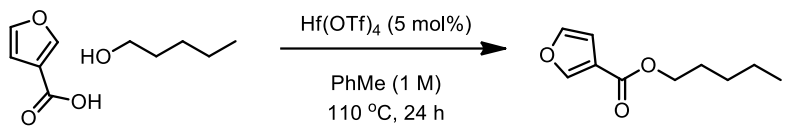


(2,2-Dimethyl-1,3-dioxolan-4-yl)methyl pentanoate (24) Following general procedure B, flash chromatography (15 % EtOAc in hexanes) afforded the product as a colorless oil (130 mg, 61 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.35-4.27 (m, 1H), 4.19-4.05 (m, 3H), 3.74 (dd, *J* = 8.4 Hz, 6.2 Hz, 1H), 2.35 (t, *J* = 7.4 Hz, 2H), 1.66-1.58 (m, 2H), 1.43 (s, 3H), 1.40-1.30 (m, 5H), 0.91 (t, *J* = 7.3 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.6, 109.8, 73.6, 66.3, 64.5, 33.8, 26.9, 29.6, 25.4, 22.2, 13.6 ppm; HRMS (ESI+) for $C_{11}H_{20}O_4Na$ $[M + Na]^+$ calculated 239.1254 found: 239.1255.



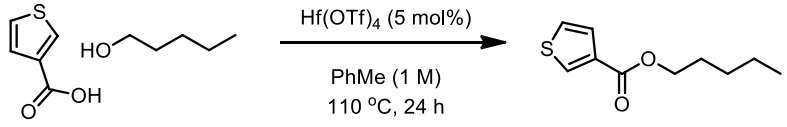
2-propargyl benzoate (25) Following general procedure A, flash chromatography (10 % EtOAc in hexanes) afforded the product as a colorless oil (124 mg, 78 %). Spectral data were in accordance with those previously reported in the literature.[17]

[17] Pereira, G. R.; Brandao, G. C.; Arantes, L. M.; de Oliveira Jr., H. A.; de Paula, R. C.; do Nascimento, M. F. A.; dos Santos, F. M.; da Rocha, R. K.; Lopez, J. C. D.; de Oliveira, A. B. *Eur. J. Med. Chem.* **2014**, *73*, 295-309.



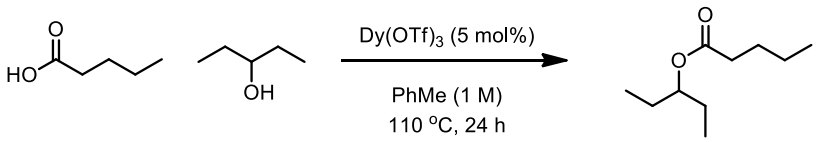
75 %

Pentyl furan-3-carboxylate (26) Following general procedure A, flash chromatography (10 % EtOAc in hexanes) afforded the product as a colorless oil (144 mg, 75 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (s, 1H), 7.40 (d, *J* = 1.2 Hz, 1H), 6.73 (d, *J* = 1.2 Hz, 1H), 4.23 (t, *J* = 6.8 Hz, 2H), 1.70-1.65 (m, 2H), 1.40-1.30 (m, 4H), 0.90 (t, *J* = 7.0 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.1, 147.5, 143.6, 119.6, 109.8, 64.5, 28.3, 28.1, 22.3, 13.9 ppm; HRMS (ESI+) for $C_{10}H_{15}O_3[M + H]^+$ calculated 183.1016 found: 183.1015.



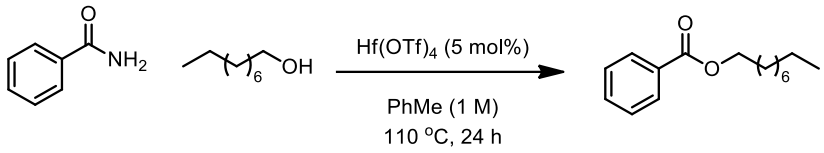
89 %

Pentyl thiophen-3-carboxylate (27) Following general procedure A, flash chromatography (10 % EtOAc in hexanes) afforded the product as a colorless oil (177 mg, 89 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (dd, *J* = 3.1, 1.2 Hz, 1H), 7.53 (dd, *J* = 5.0, 1.2 Hz, 1H), 7.29 (dd, *J* = 5.0, 3.1 Hz, 1H), 4.27 (t, *J* = 6.7 Hz, 2H), 1.77-1.73 (m, 2H), 1.45-1.30 (m, 4H), 0.93 (t, *J* = 7.0 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.8, 134.0, 132.4, 127.9, 125.8, 64.8, 28.4, 28.1, 22.3, 13.9 ppm; HRMS (ESI+) for $C_{10}H_{15}O_2S$ $[M + H]^+$ calculated 199.0787 found: 199.0790.



89 %

Pentan-3-yl pentanoate (36) Following general procedure A using $Dy(OTf)_3$ (30.5 mg, 0.050 mmol, 0.05 equiv.), flash chromatography (5 % EtOAc in hexanes) afforded the product as a colorless oil (103 mg, 60 %). Spectral data were in accordance with those previously reported in the literature.[18]



58 %

Nonyl benzoate (37) An open oven-dried sealable tube was charged with the benzamide acid (121 mg mL, 1.00 mmol, 1.00 equiv.) and dissolved in toluene (1 mL, 1M). $Hf(OTf)_4$ (38 mg, 0.050 mmol, 0.050 equiv.) and nonanol (0.174 mL, 1.0 mmol, 1.0 equiv.) were then added to the mixture and the tube was sealed. The reaction mixture was stirred at 110 °C for 24 h and then cooled down to room temperature. The tube was opened and silica gel (~ 5 mL) was added. The slurry was concentrated under reduced pressure and purified by flash chromatography (5% EtOAc in hexanes) to afford the product as a colorless oil (145 mg, 58 %). Spectral data were in accordance with those previously reported in the literature.[19]

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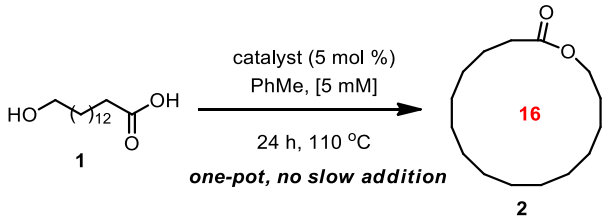
[18] Srimani, D.; Balarama, E.; Gnanaprakasam, B.; Ben-David, Y.; Milstein, D. *Adv. Synth. Cat.* **2012**, *354* (13), 2403-2406.

[19] Ahmad, I.; Malik, A.; Afza, N.; Anis, I.; Fatima, I.; Nawaz, S. A.; Tareen, R. B.; Iqbal, C. *ZNB* **2005**, *60*, 2403-2406.

TABULAR DATA

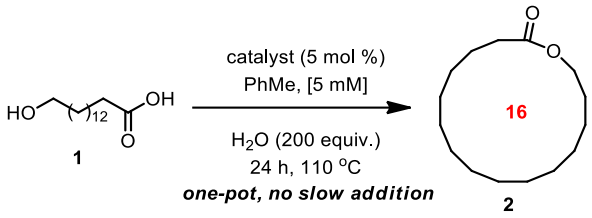
Table S1: Optimization of a Lewis acid catalyzed macrolactonization process.



	Catalyst	Yield 2 (%)		Catalyst	Yield 2 (%)
1	$AlCl_3$	0	16	$ZrCl_4(THF)_2$	13
2	$MgBr_2 \cdot OEt_2$	0	17	$Zr(tfacac)_3$	0
3	$BF_3 \cdot OEt_2$	36	18	$CuBr_2$	0
4	$B(OH)_3$	0	19	$CuCl_2$	0
5	$TiCp_2Cl_2$	0	20	$Cu(OAc)_2$	25
6	$TiCl_4$	0	21	$Cu(OTf)_2$	54
7	$Fe(acac)_3$	0	22	$Sc(OTf)_3$	45
8	$FeCl_3$	0	23	$Sm(OTf)_3$	21
9	$Fe(OTf)_2$	0	24	$Dy(OTf)_3$	13
10	$Fe(OTf)_3$	0	25	$Yb(OTf)_3$	38
11	$Pd(TFA)_3$	0	26	$Hf(OTf)_4$	83
12	$Ni(acac)_2$	0	26	$HfCl_4(THF)_2$	17
13	AgOTf	22	27	$Hf(On\text{-}Bu)_4$	12
14	$Zn(OTf)_2$	0			
15	$Co(OAc)_2$	0			

[a] Isolated yields following silica gel chromatography. Remaining mass balance is unreacted **1** unless otherwise noted. [b] No trace of **1** was isolated. [c] Polymerization of **1** is observed. [d] Lower catalyst loadings provided lower yields. When 2.5 mol % $Hf(OTf)_4$ was used 72 % of **2** and 27 % re-isolated **1** were obtained.

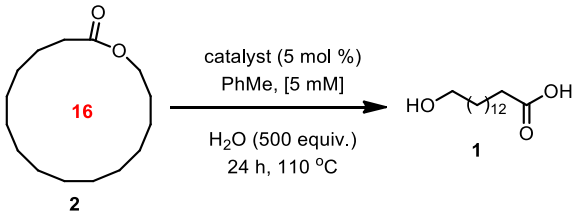
Table S2: Macrolactonization in the presence of excess water.



	Catalyst	Yield 2 (%)[a]		Catalyst	Yield 2 (%)[a]
1	$BF_3{\cdot}OEt_2$	17	7	$Sm(OTf)_3$	0
2	AgOTf	4	8	$Yb(OTf)_3$	0
3	$Cu(OAc)_2$	0	9	$HfCl_4(THF)_2$	0
4	$ZrCl_4(THF)_2$	13	10	$Hf(On\text{-}Bu)_4$	0
5	$Cu(OTf)_2$	<5	11	$Hf(OTf)_4$	83[b]
6	$Sc(OTf)_3$	0	12	$Dy(OTf)_3$	0

[a] Isolated yields following silica gel chromatography. [b] Increasing the water content to 400 equiv. resulted in a decrease in yield to 23 % of **2**.

Table S3: Ring-opening (hydrolysis) of macrolactone **2** under Lewis acid conditions.

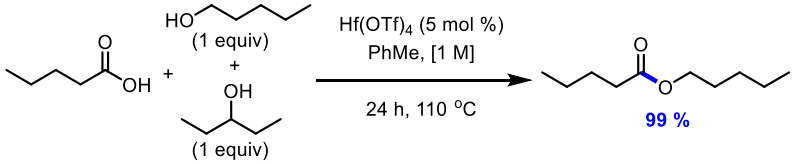


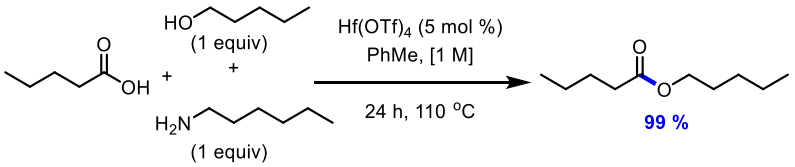
	Catalyst	2 (%)[a]		Catalyst	2 (%)[a]
1	$BF_3{\cdot}OEt_2$	99	7	$Sm(OTf)_3$	96
2	AgOTf	83	8	$Yb(OTf)_3$	83
3	$Cu(OAc)_2$	67	9	$HfCl_4(THF)_2$	50
4	$ZrCl_4(THF)_2$	99	10	$Hf(On\text{-}Bu)_4$	99
5	$Cu(OTf)_2$	67	11	$Hf(OTf)_4$	88[b]
6	$Sc(OTf)_3$	58	12	$Dy(OTf)_3$	99

[a] Yields of recovered **2** following silica gel chromatography. [b] The re-isolated yield of **2** remained high (>80 %) even when using 1000 equiv. of added H_2O.

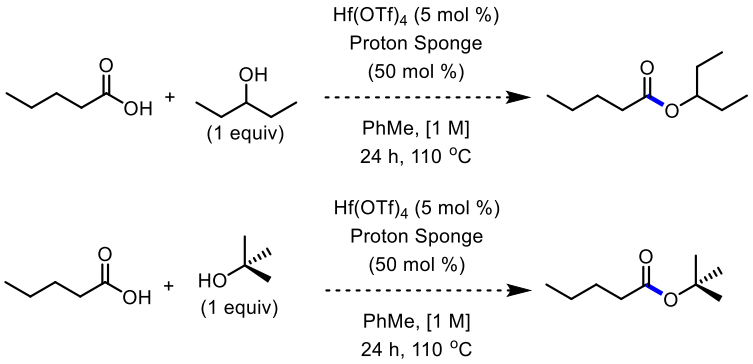
COMPETITION EXPERIMENTS

Competition experiments confirmed selectivity for primary alcohols over secondary alcohols and amines.



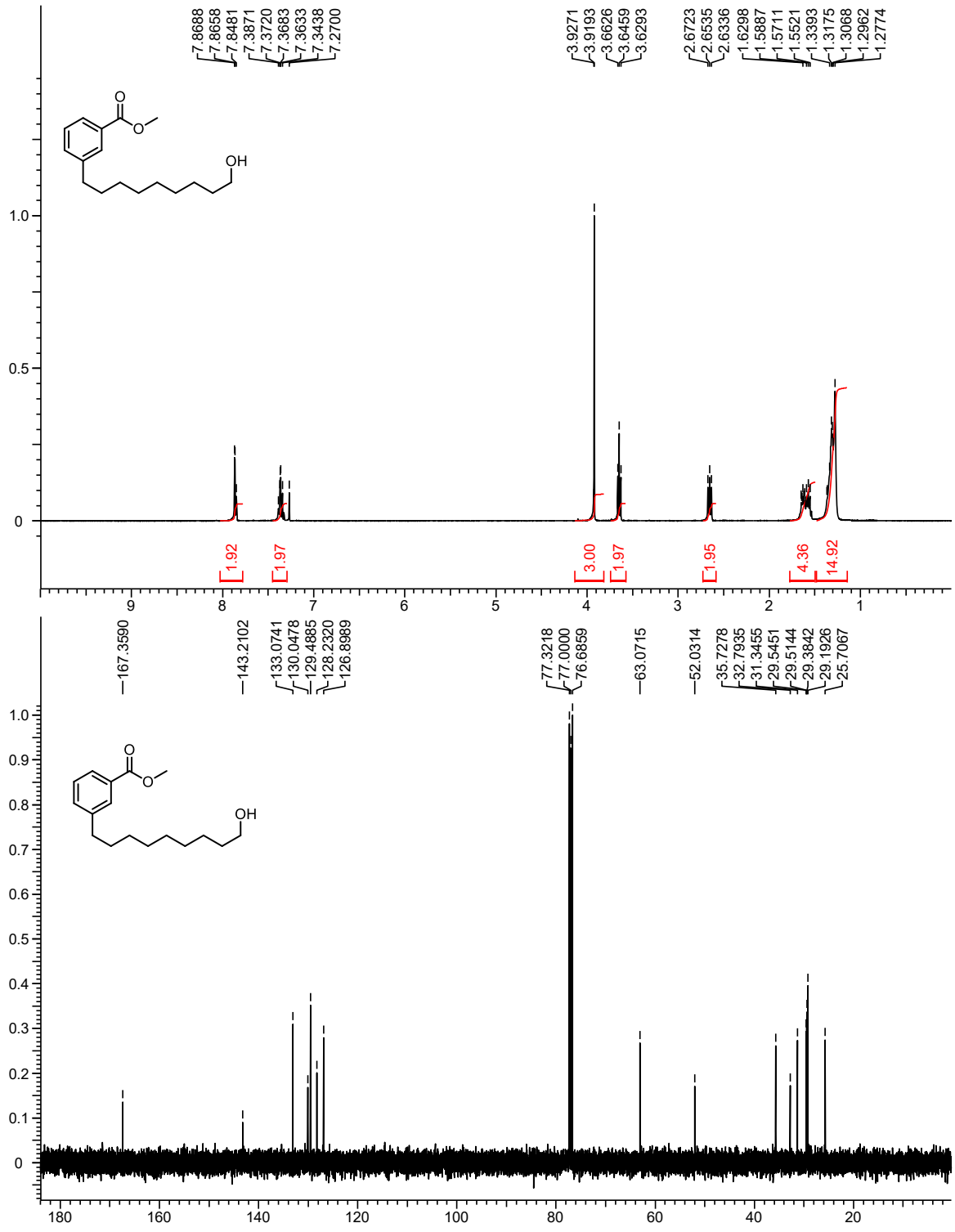


Forcing conditions with secondary or tertiary alcohols did not afford the desired esters.

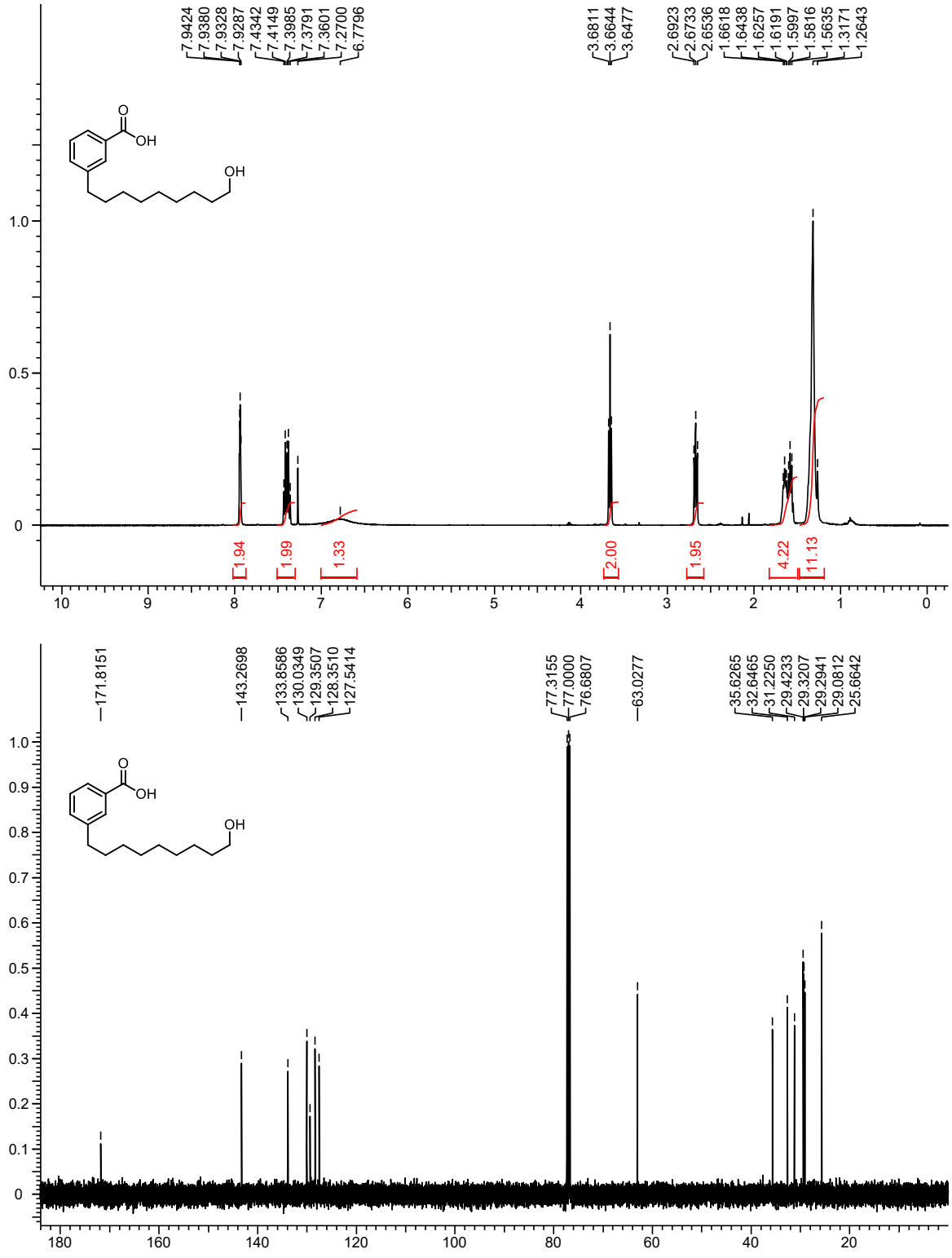


SPECTRAL DATA

Compound S1



Compound S2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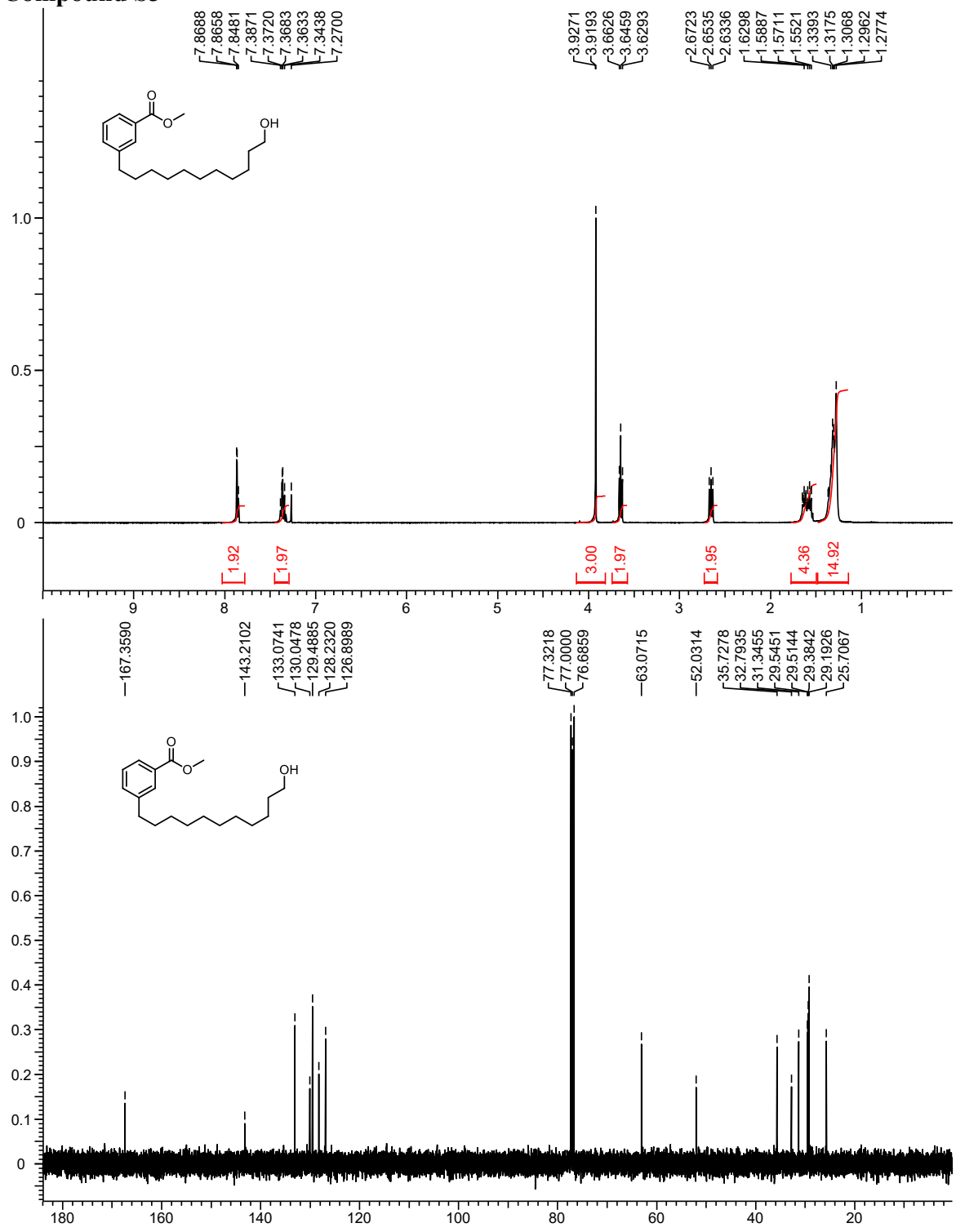
Compound S3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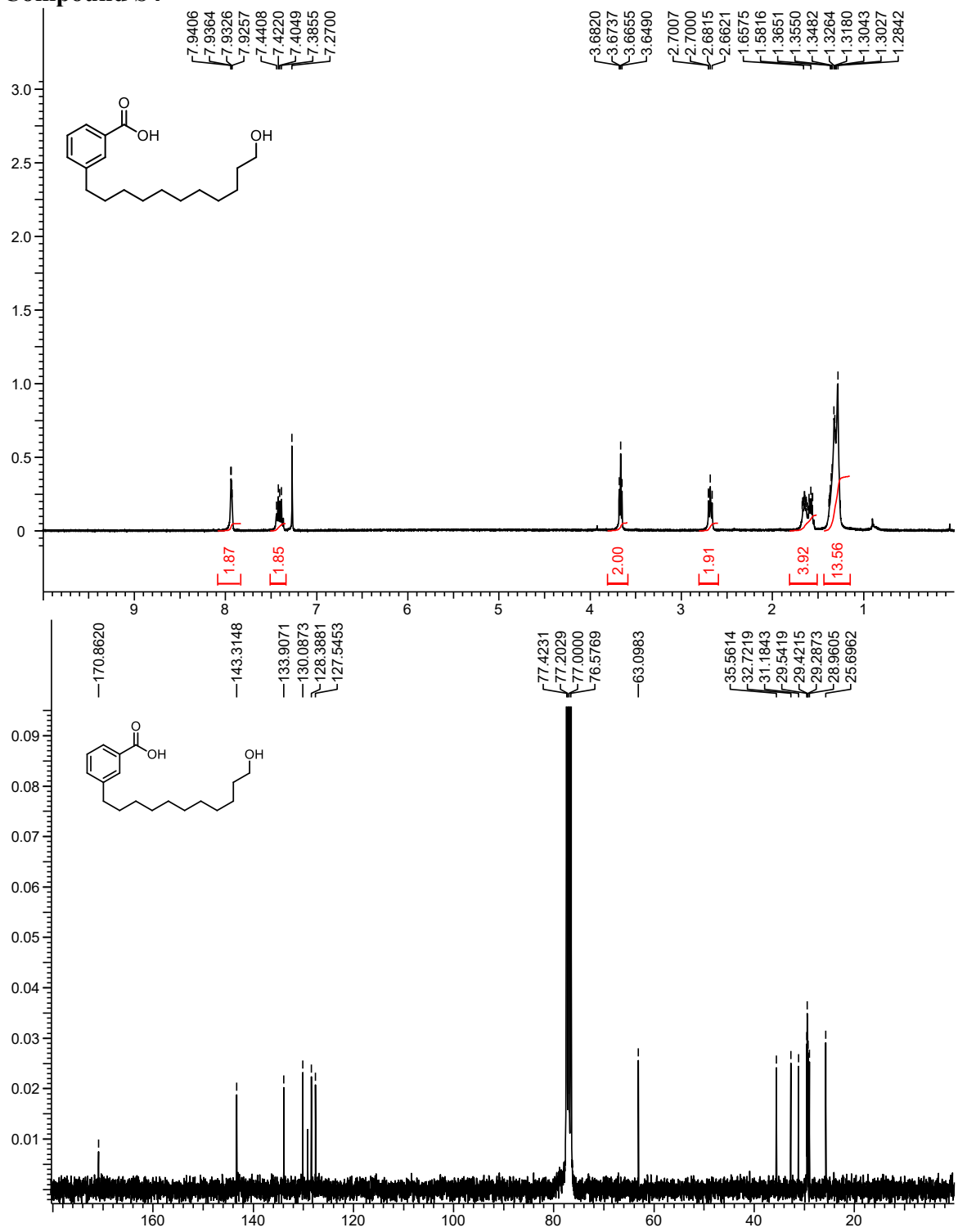
Compound S4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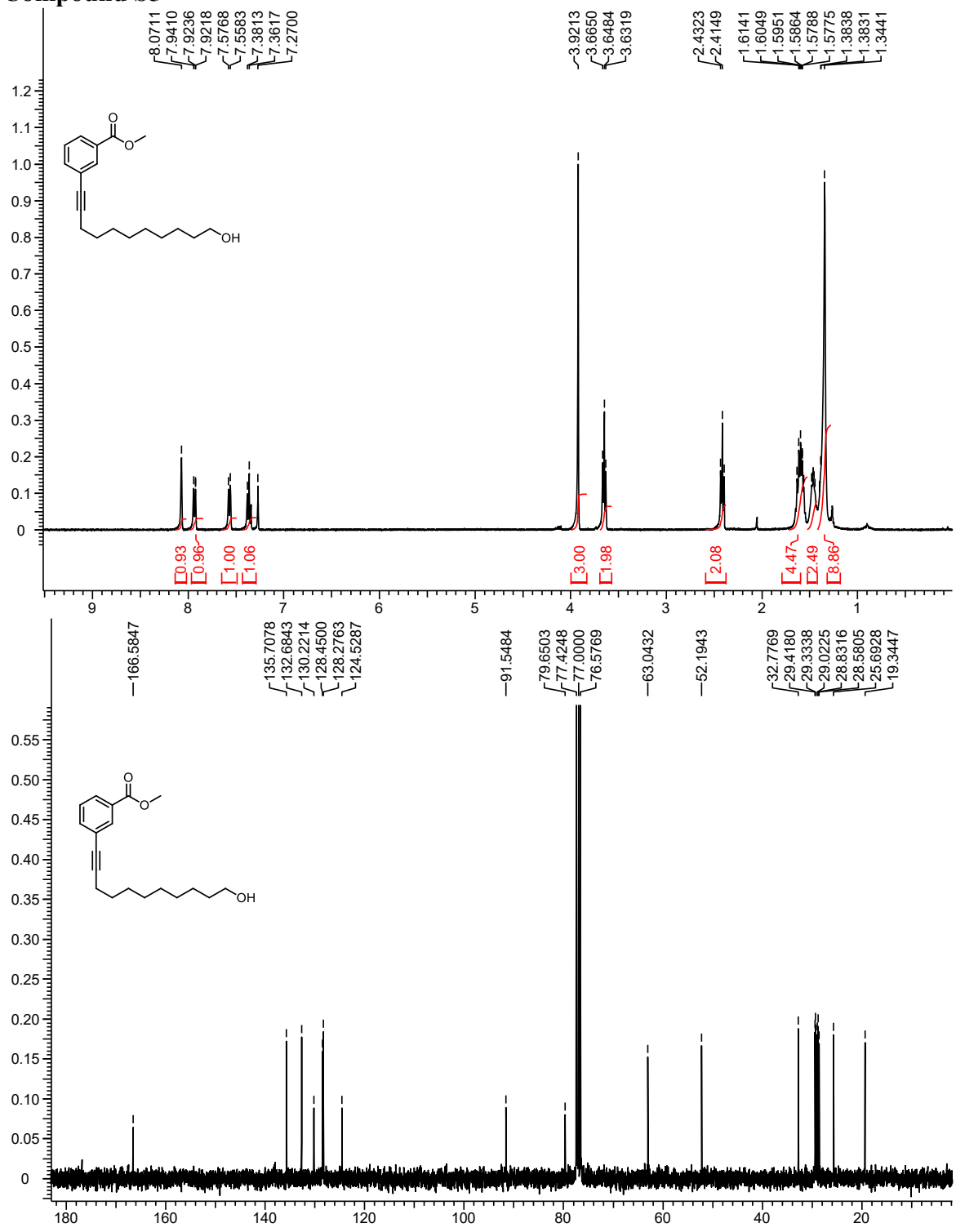
Compound S5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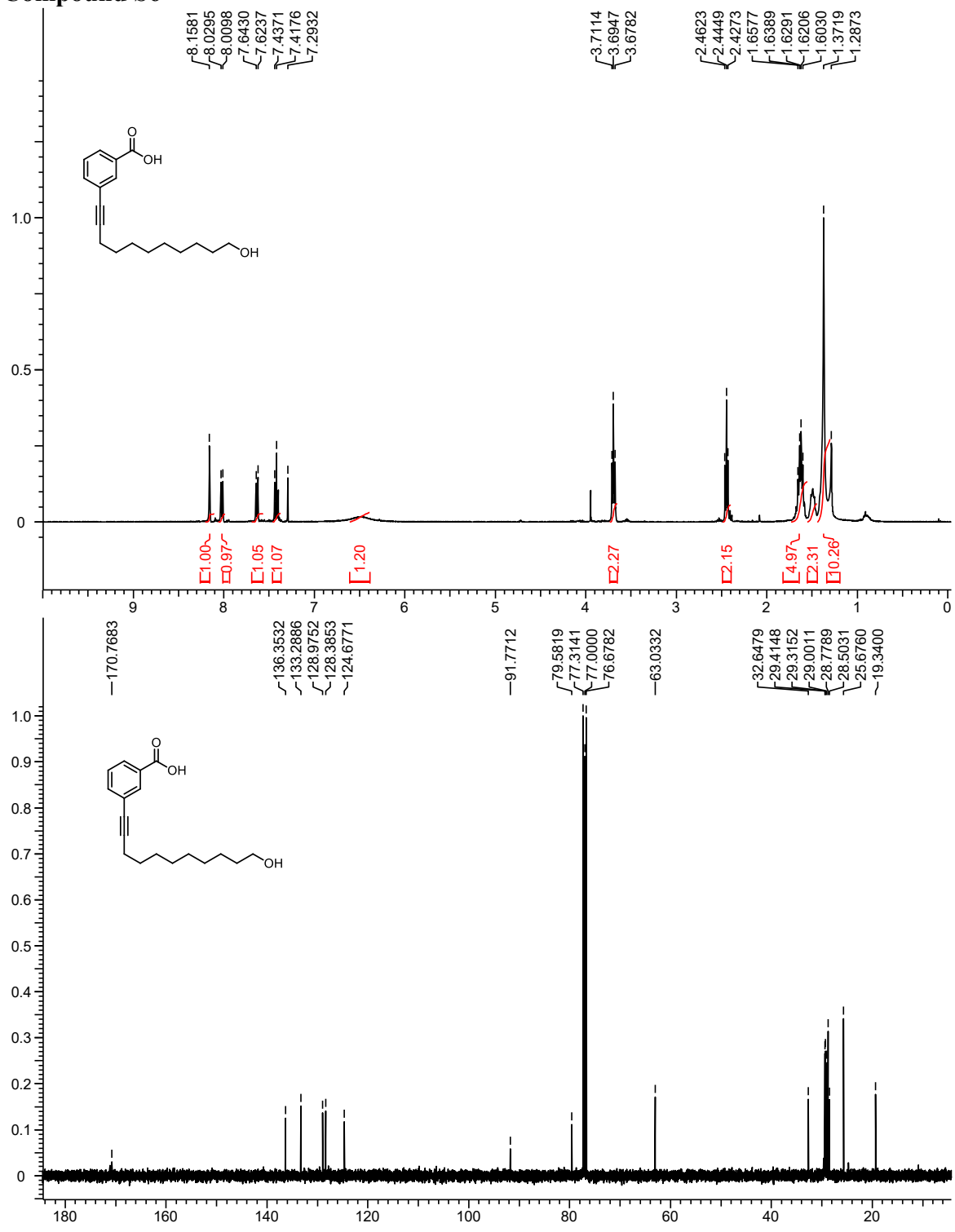
Compound S6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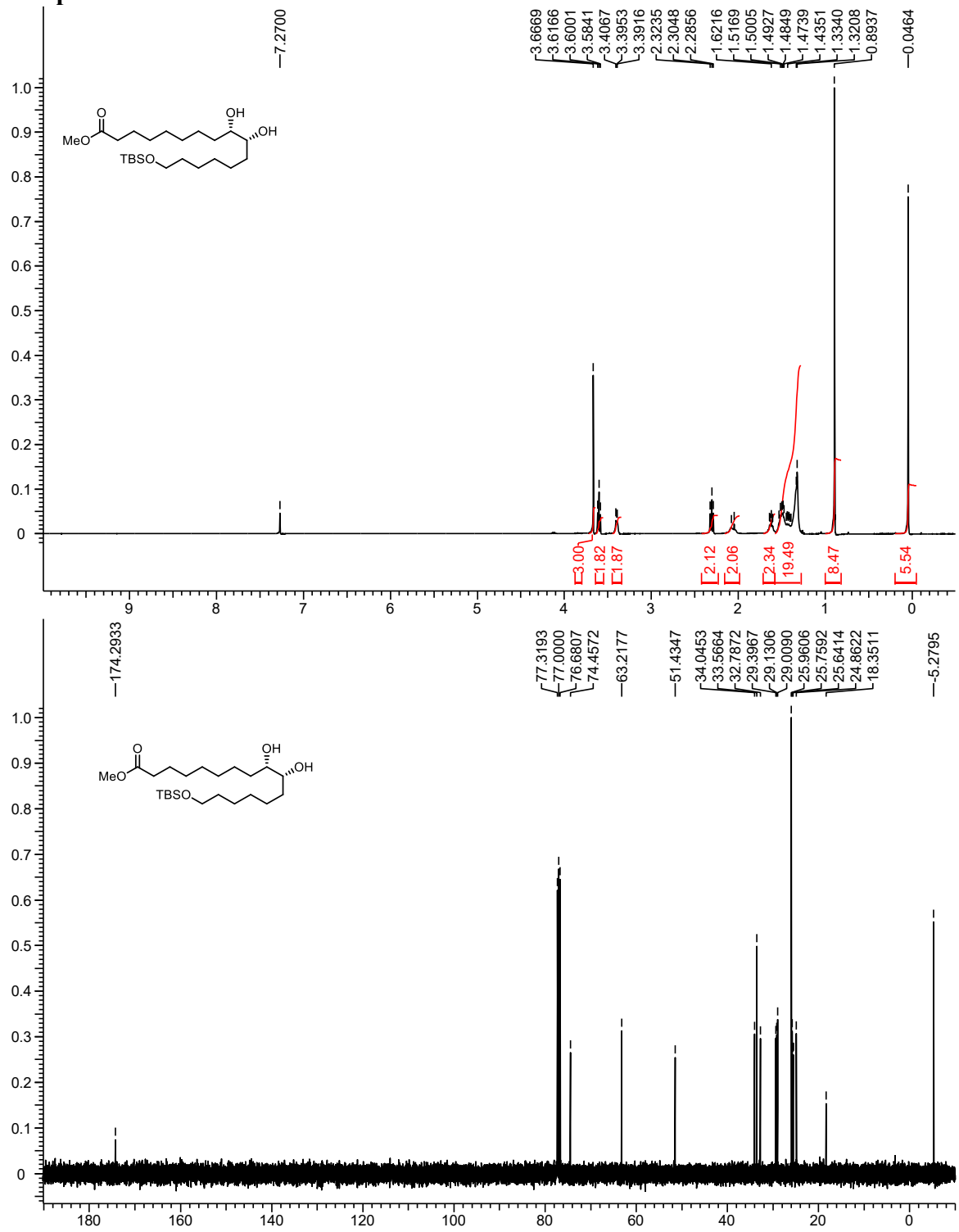
Compound S7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OH
TBSO
3.00
1.82
1.87
2.12
2.06
2.34
19.49
8.47
5.54
174.2933
77.3193
77.0000
76.6807
74.4572
63.2177
51.4347
34.0453
33.5664
32.7872
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25.7592
25.6414
24.8622
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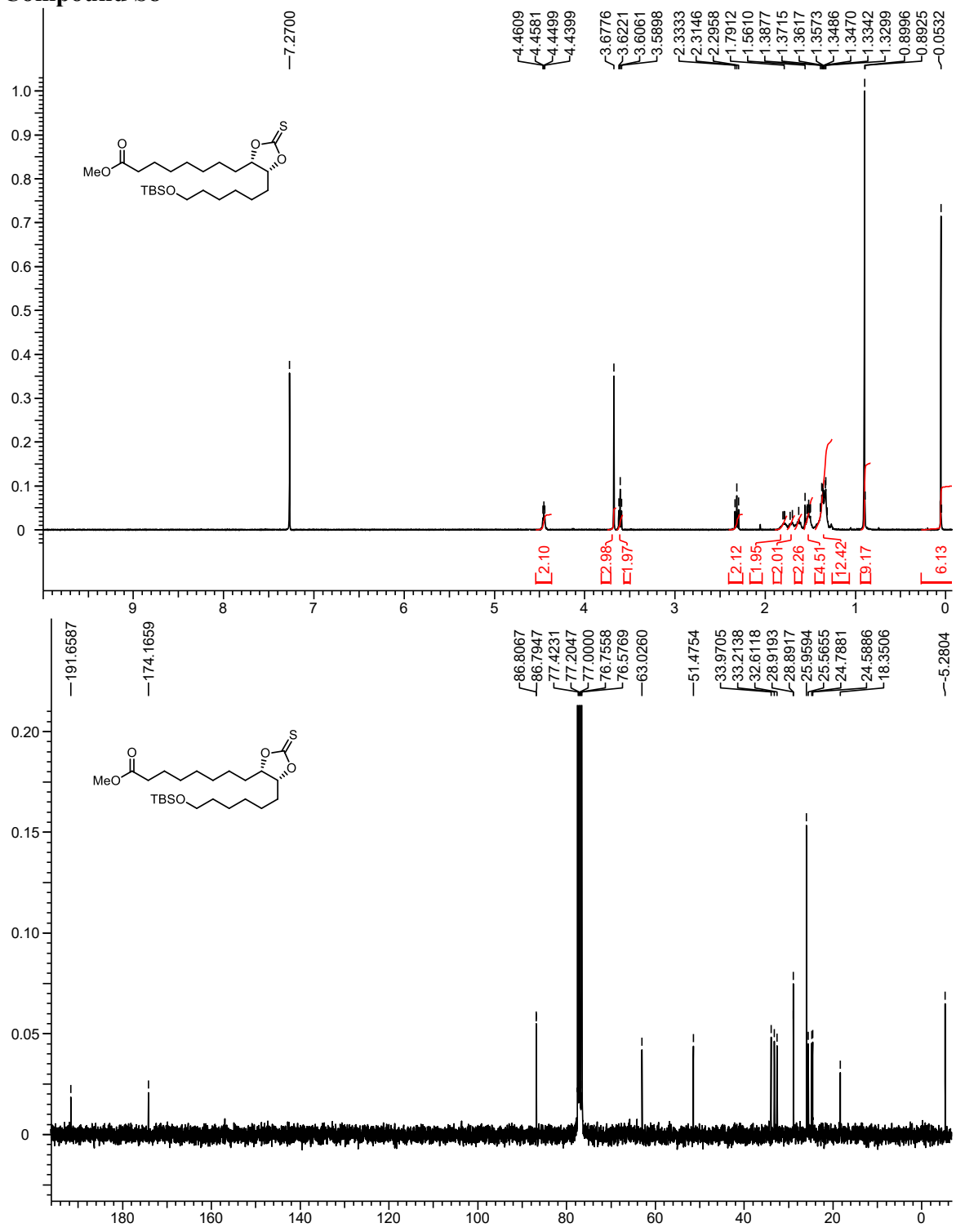
-5.2795

Compound S8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3.6221
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3.5898
2.3333
2.3146
2.2958
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1.5610
1.3877
1.3715
1.3617
1.3573
1.3486
1.3470
1.3342
1.3299
0.8996
0.8925
0.0532
2.10
2.98
1.97
2.12
1.95
2.01
2.26
4.51
12.42
9.17
6.13
MeO
TBSO
191.6587
174.1659
86.8067
86.7947
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77.2047
77.0000
76.7558
76.5769
63.0260
51.4754
33.9705
33.2138
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28.8917
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25.5655
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24.5886
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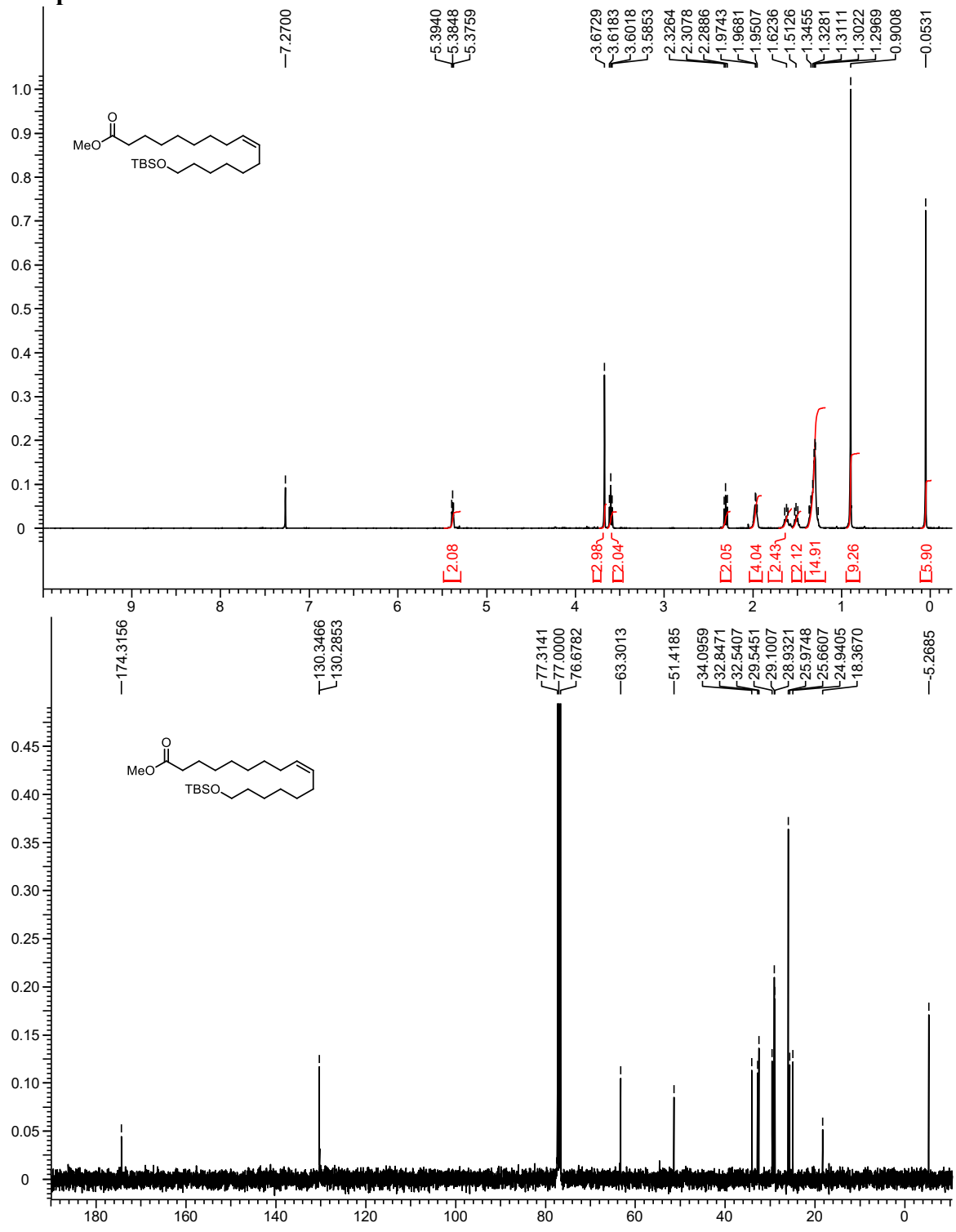
-5.2804

Compound S9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3.6729
3.6183
3.6018
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2.3264
2.3078
2.2886
1.9743
1.9681
1.9507
1.6236
1.5126
1.3455
1.3281
1.3111
1.3022
1.2969
0.9008
0.0531
MeO
TBSO
2.08
2.98
2.04
2.05
4.04
2.43
2.12
14.91
9.26
5.90
174.3156
130.3466
130.2853
77.3141
77.0000
76.6782
63.3013
51.4185
34.0959
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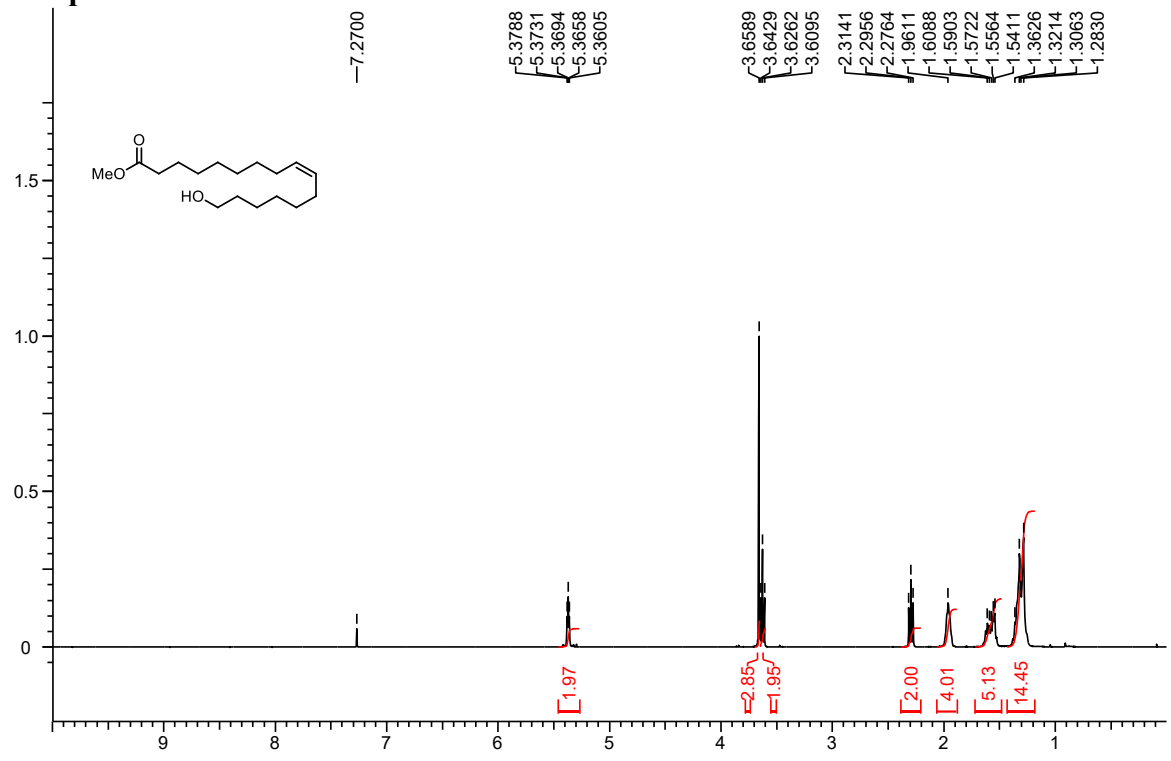
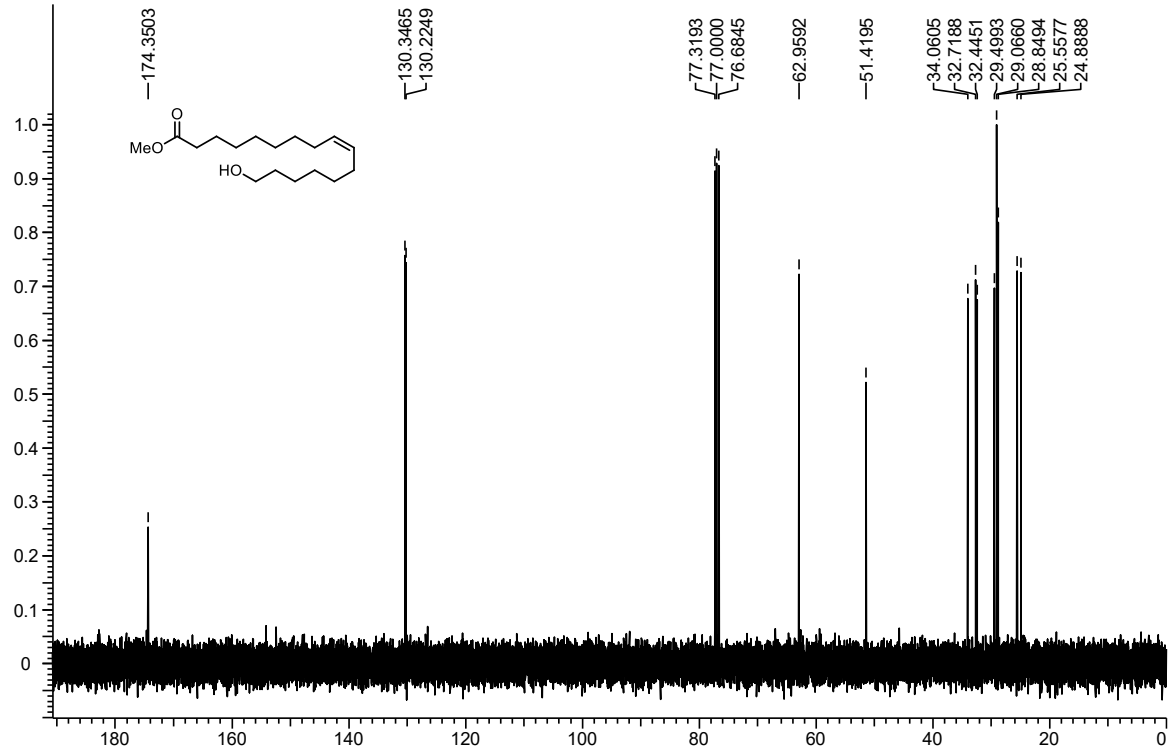
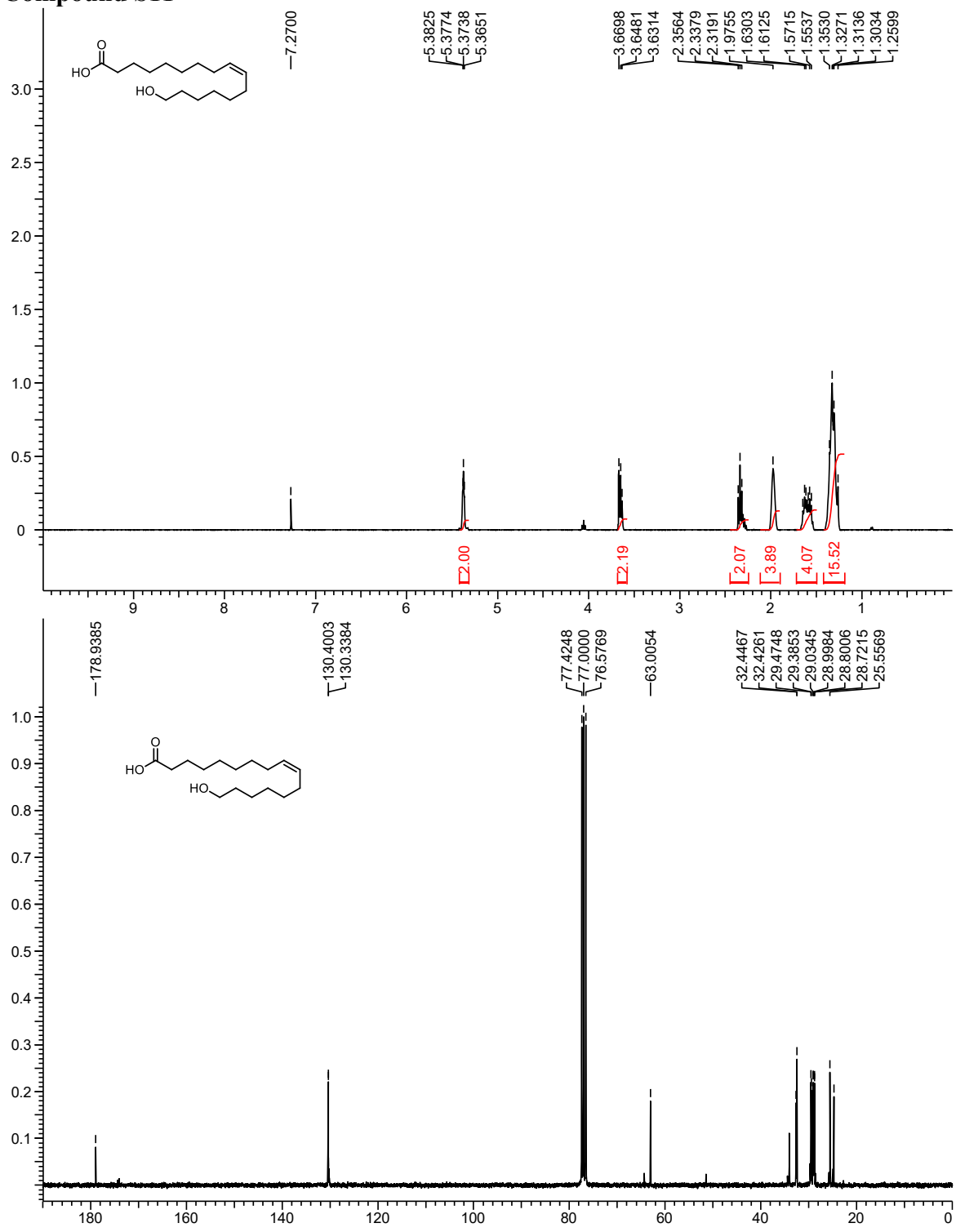
Compound S10

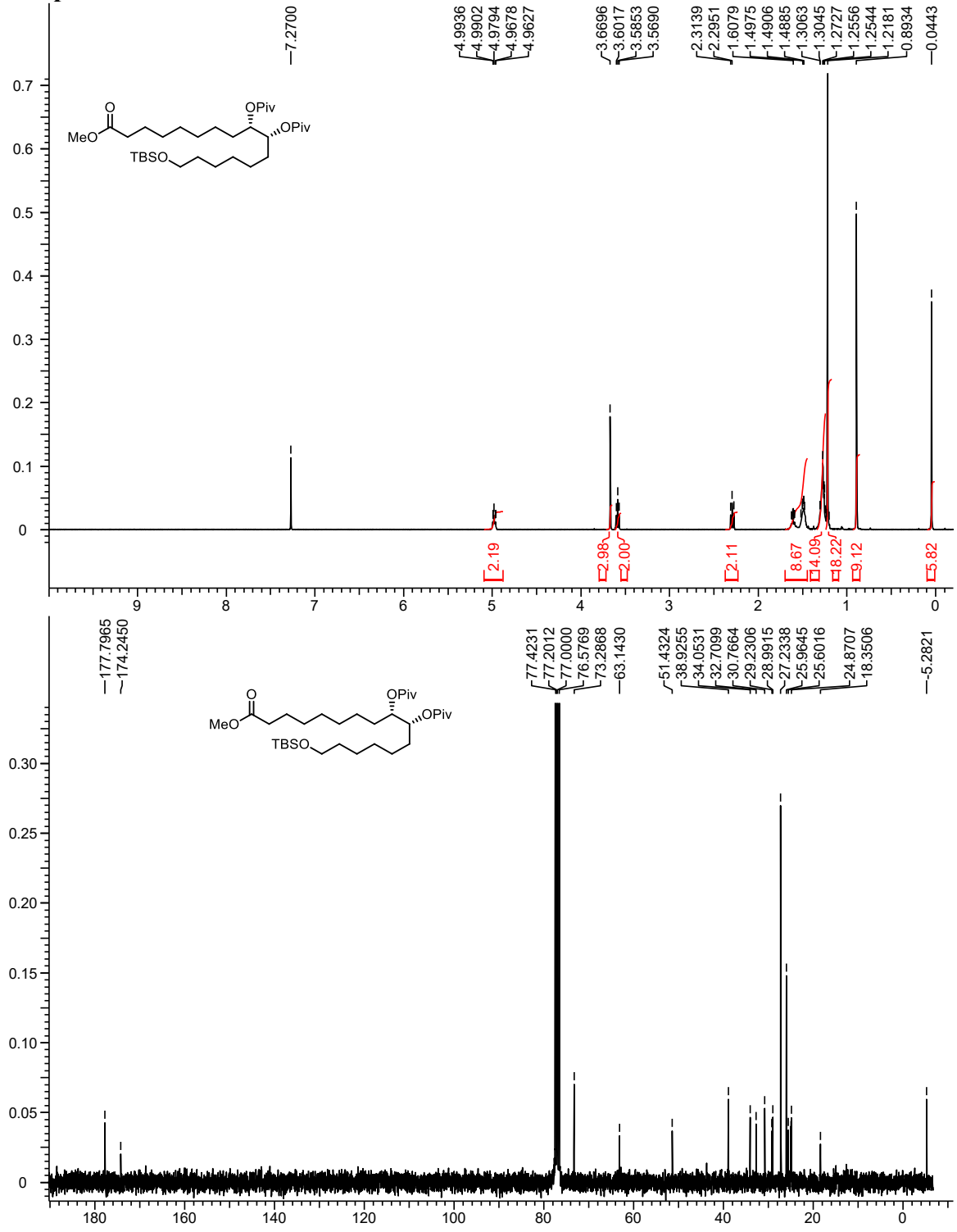




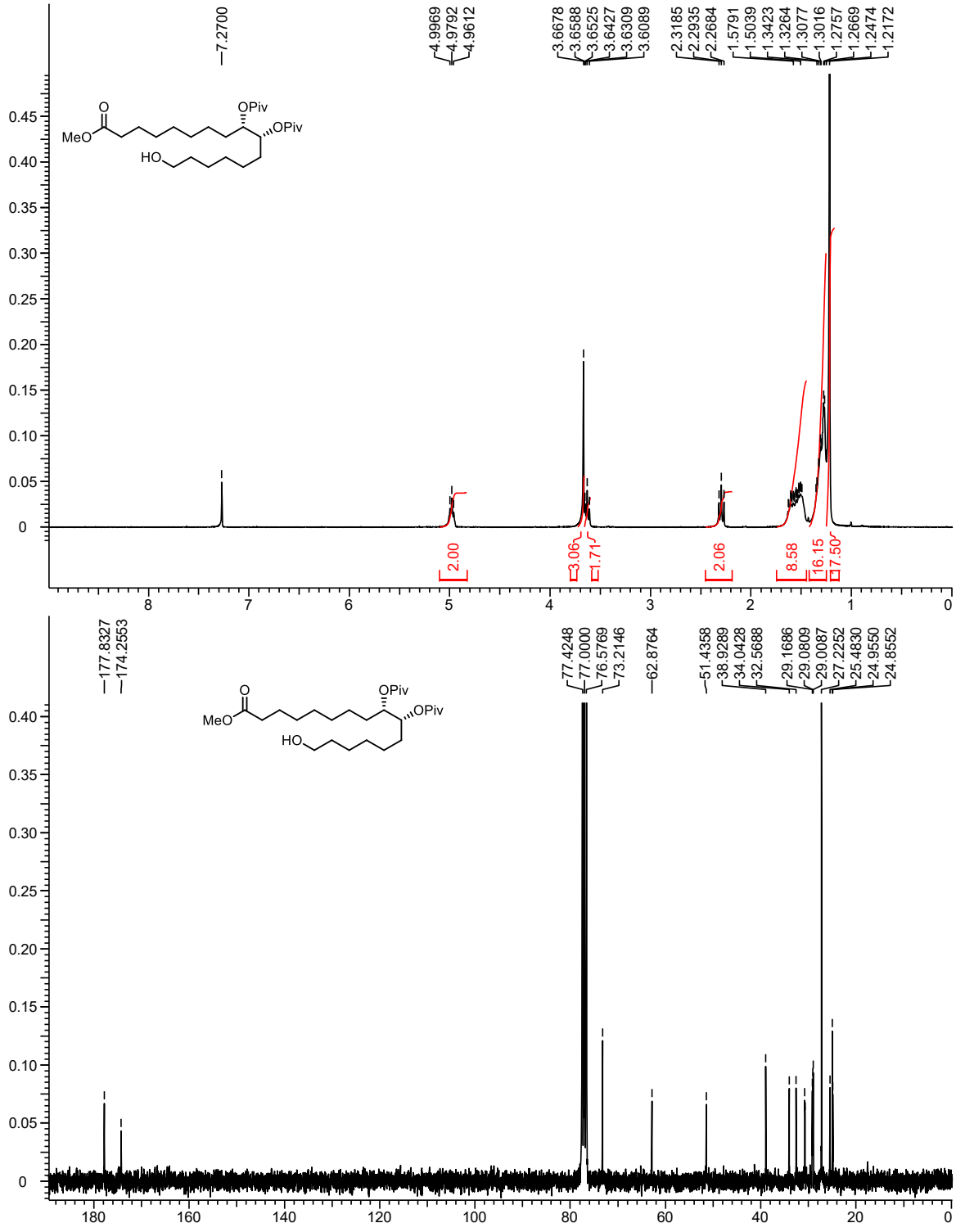
Compound S11



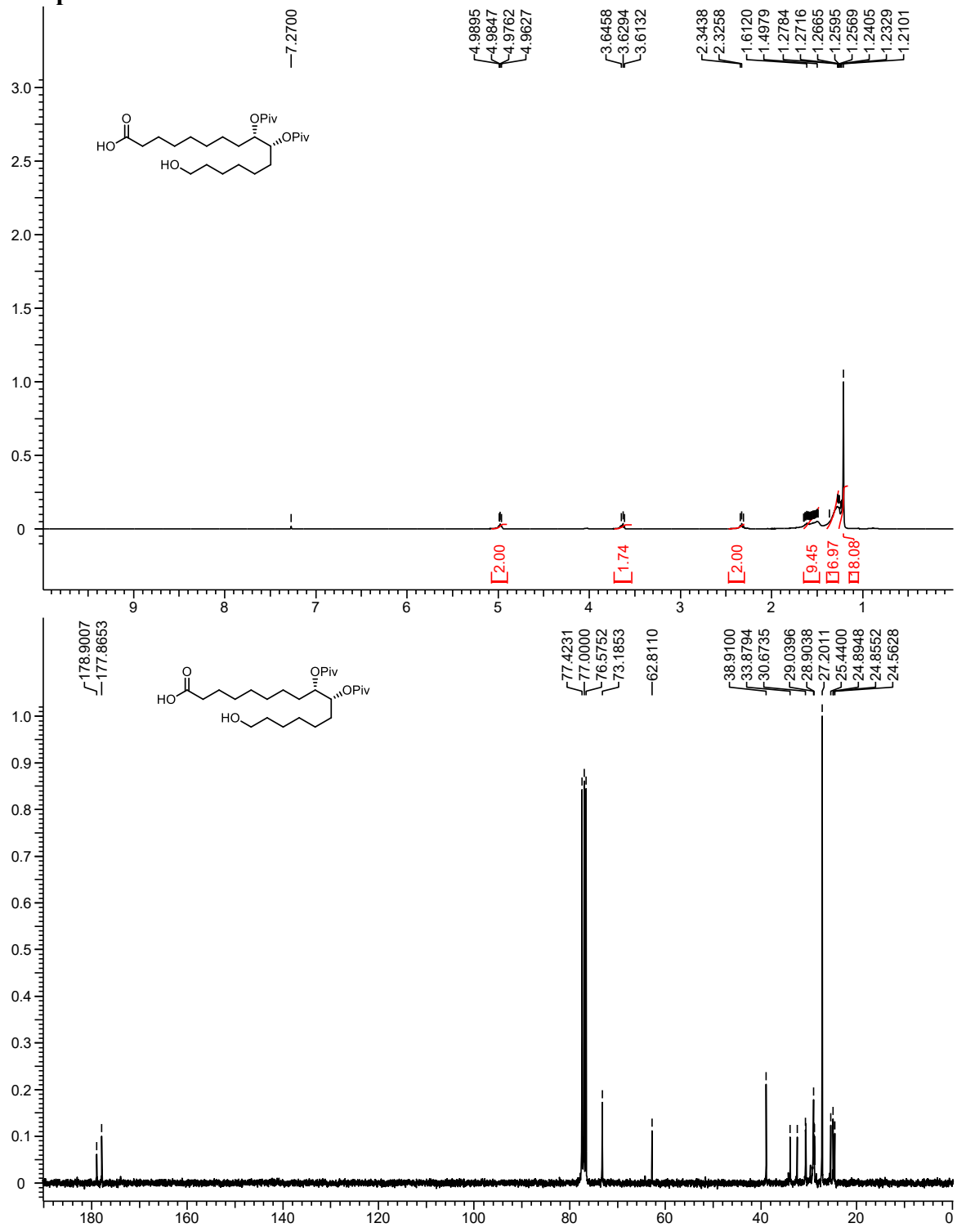
Compound S12



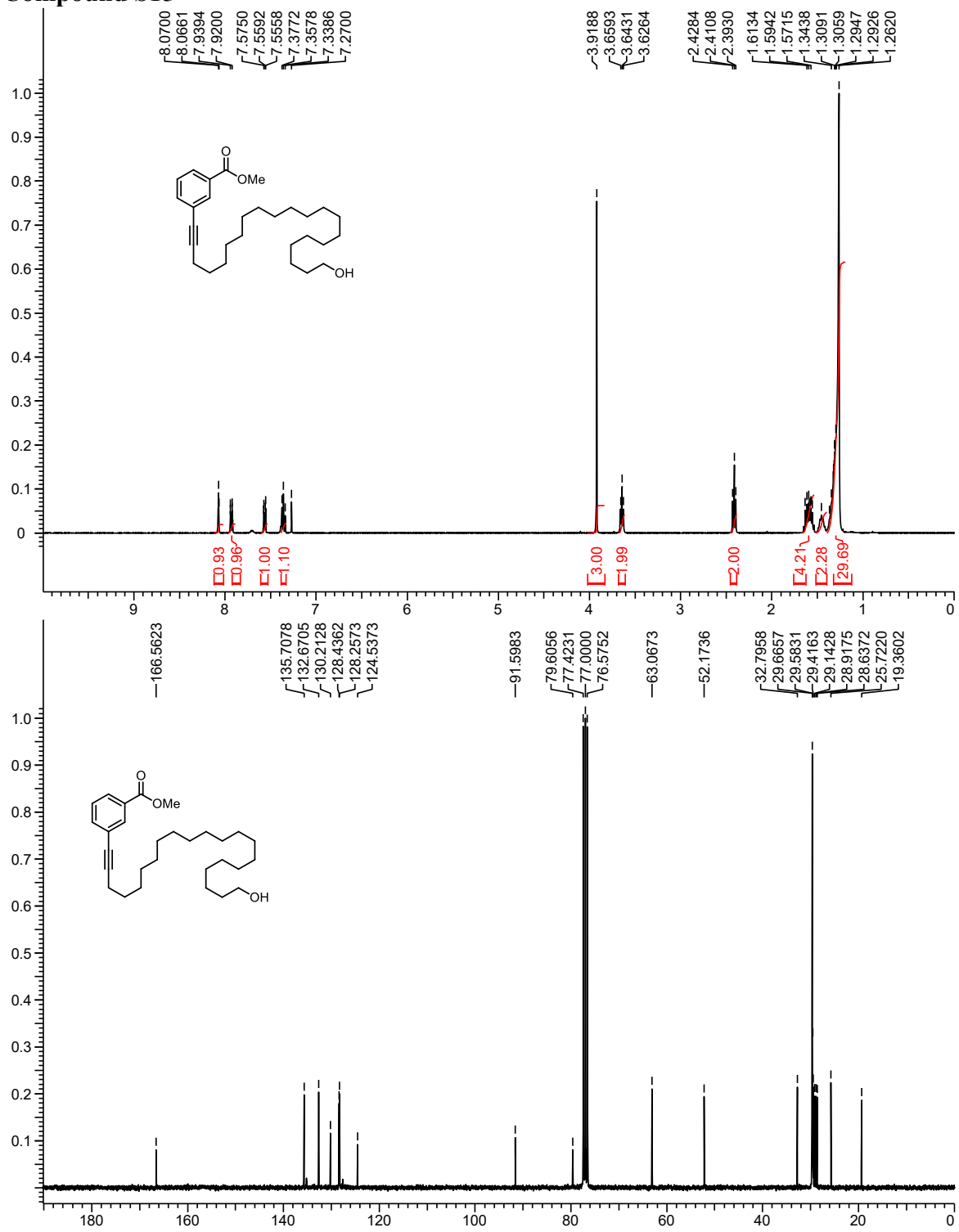
Compound S13



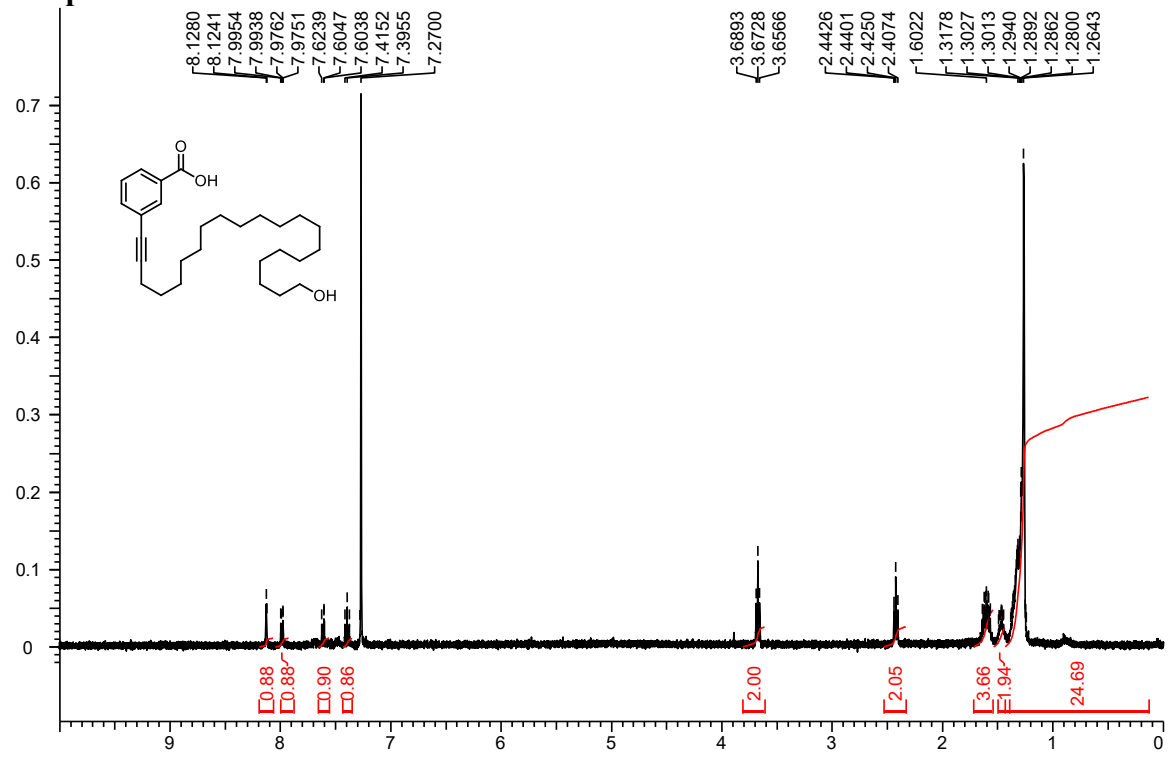
Compound S14

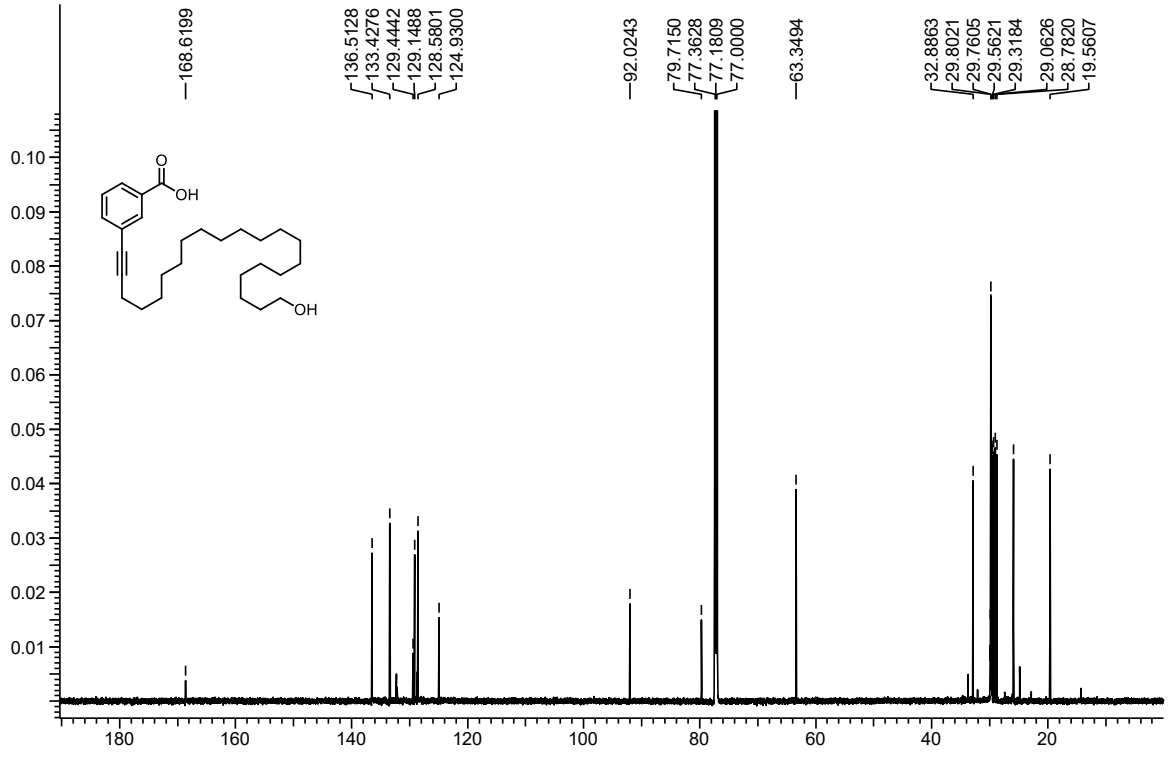


Compound S15

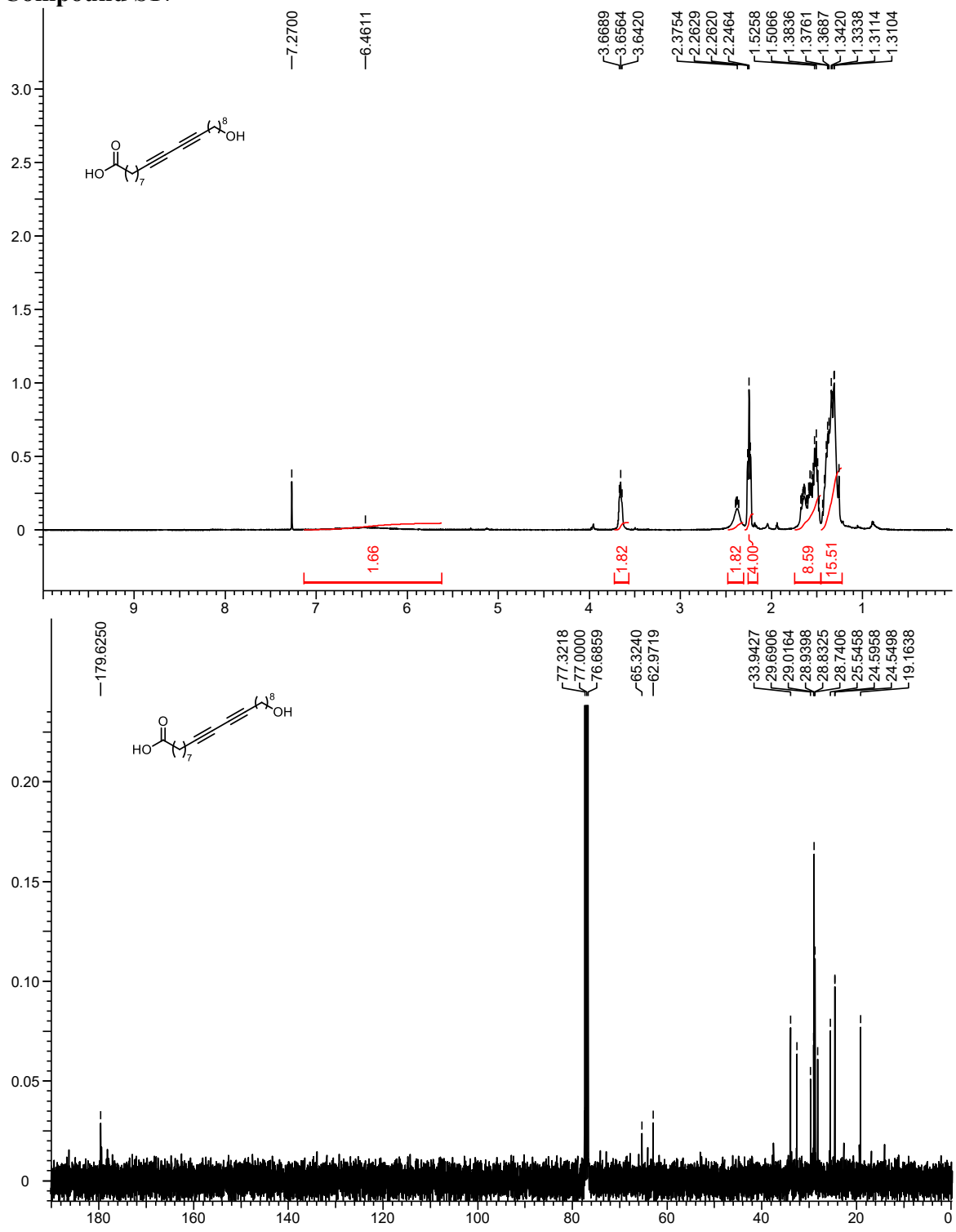


Compound S16

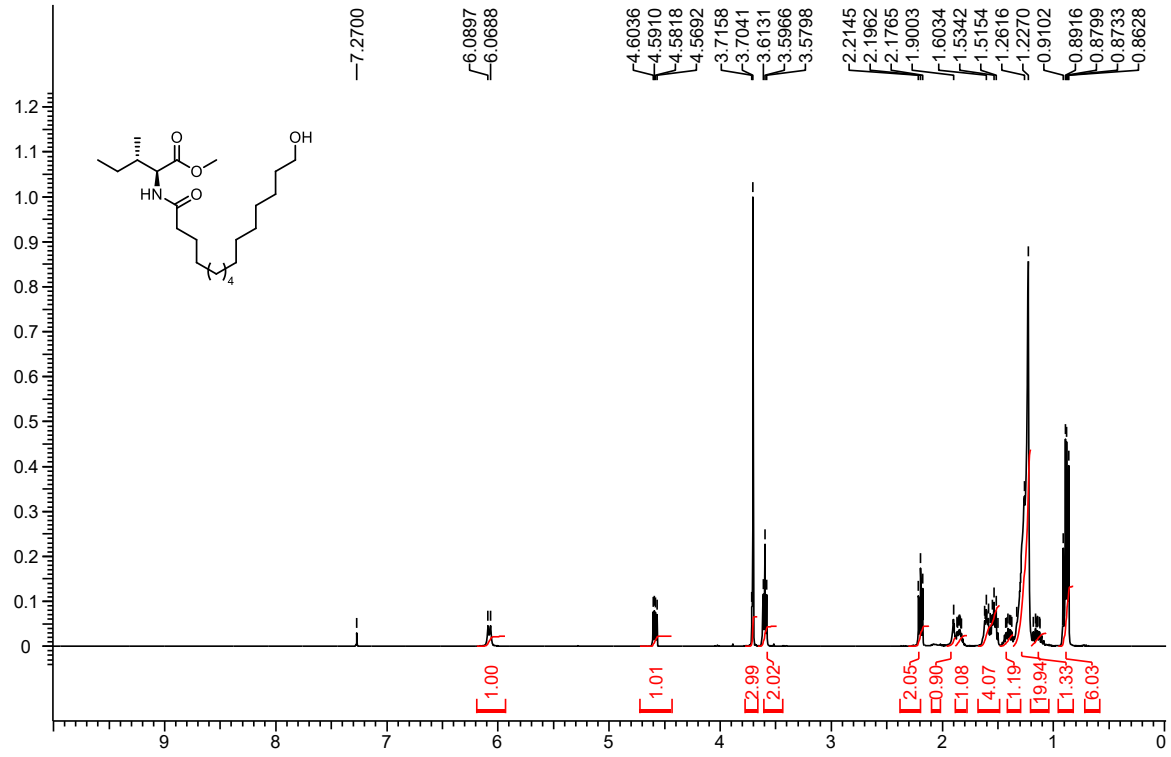


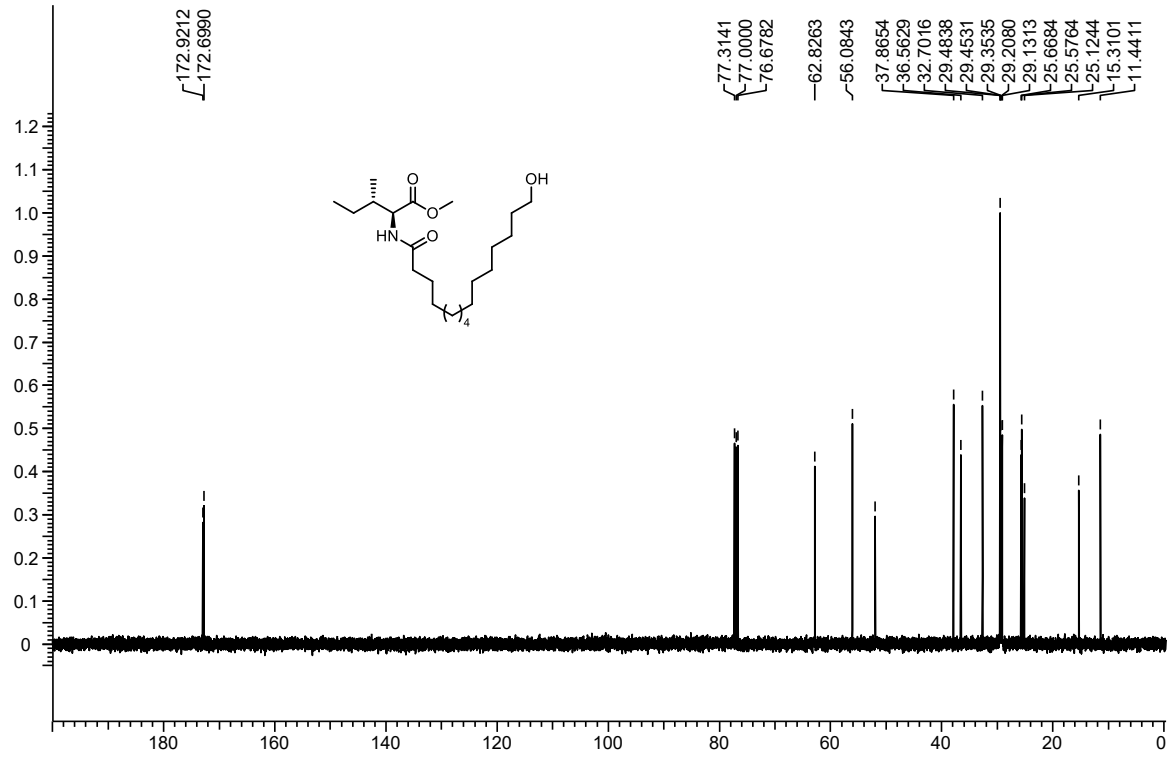


Compound S17

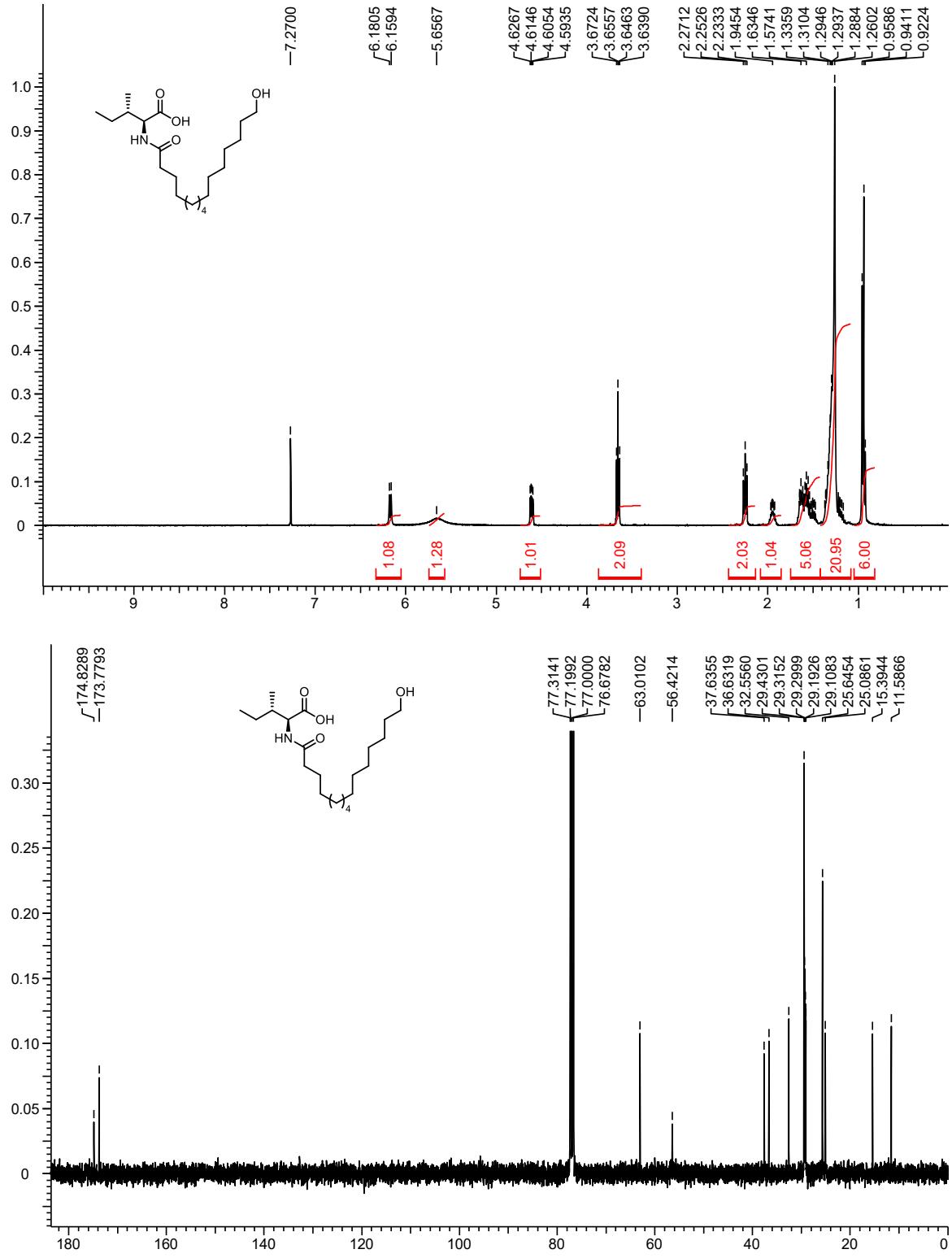


Compound S18

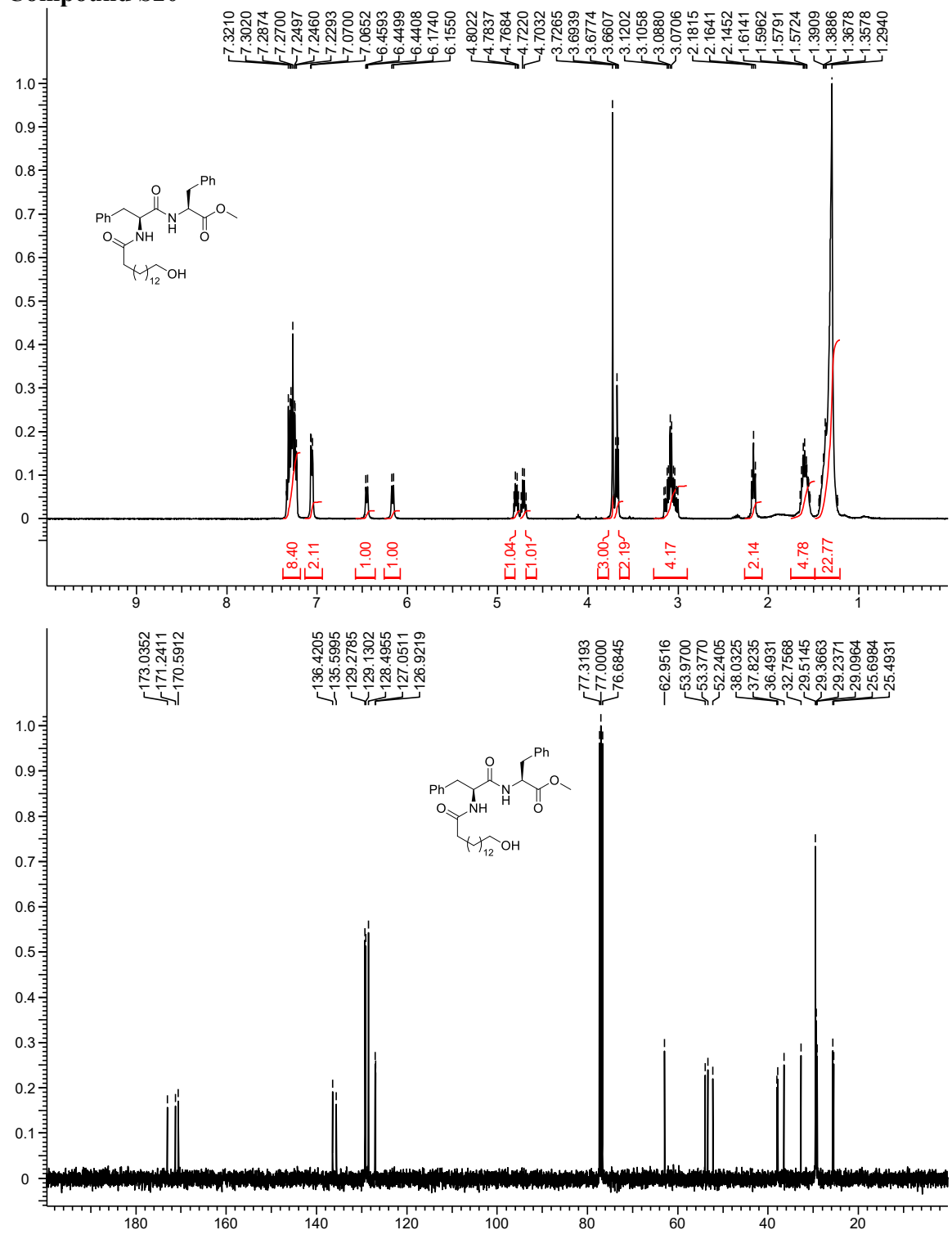




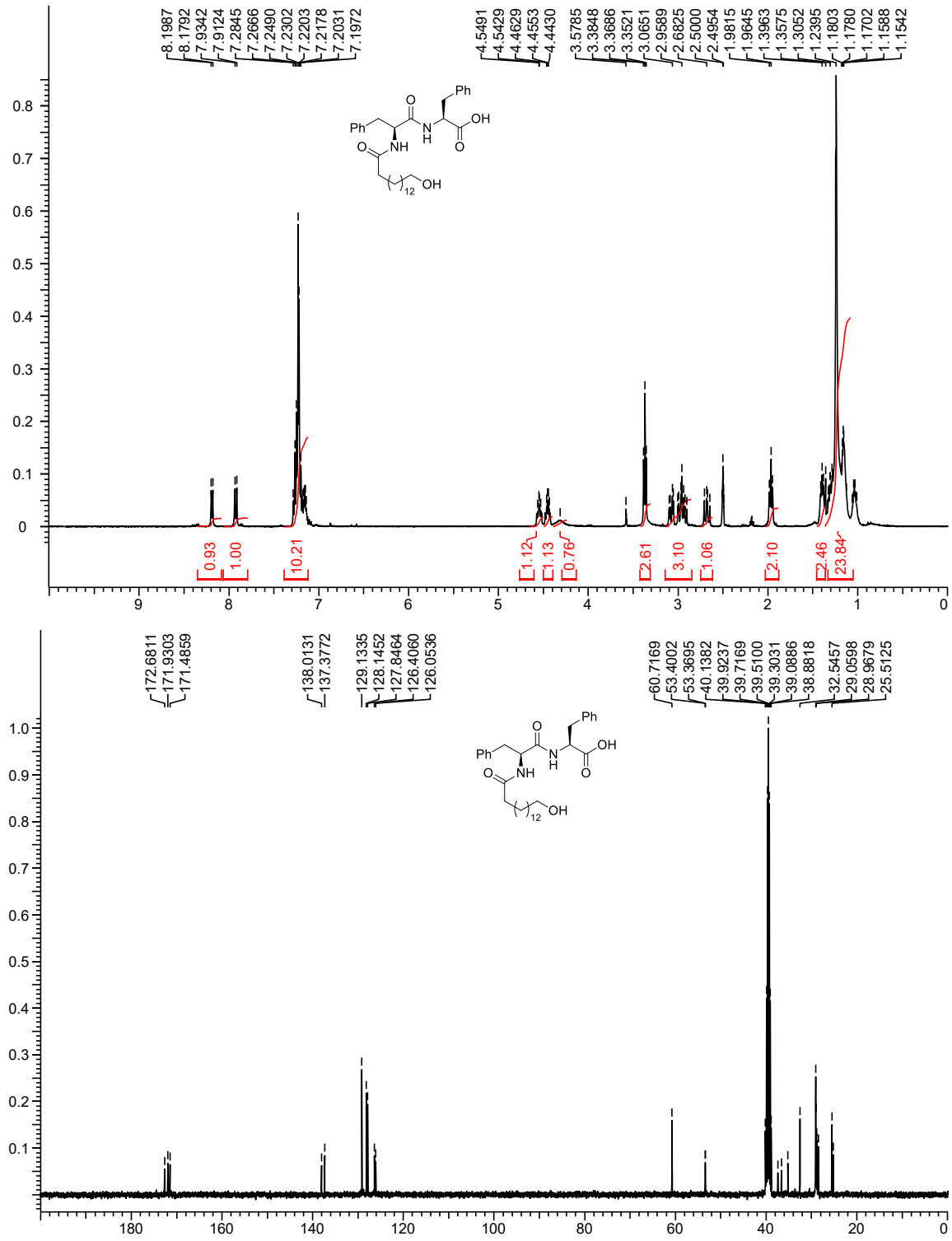
Compound S19



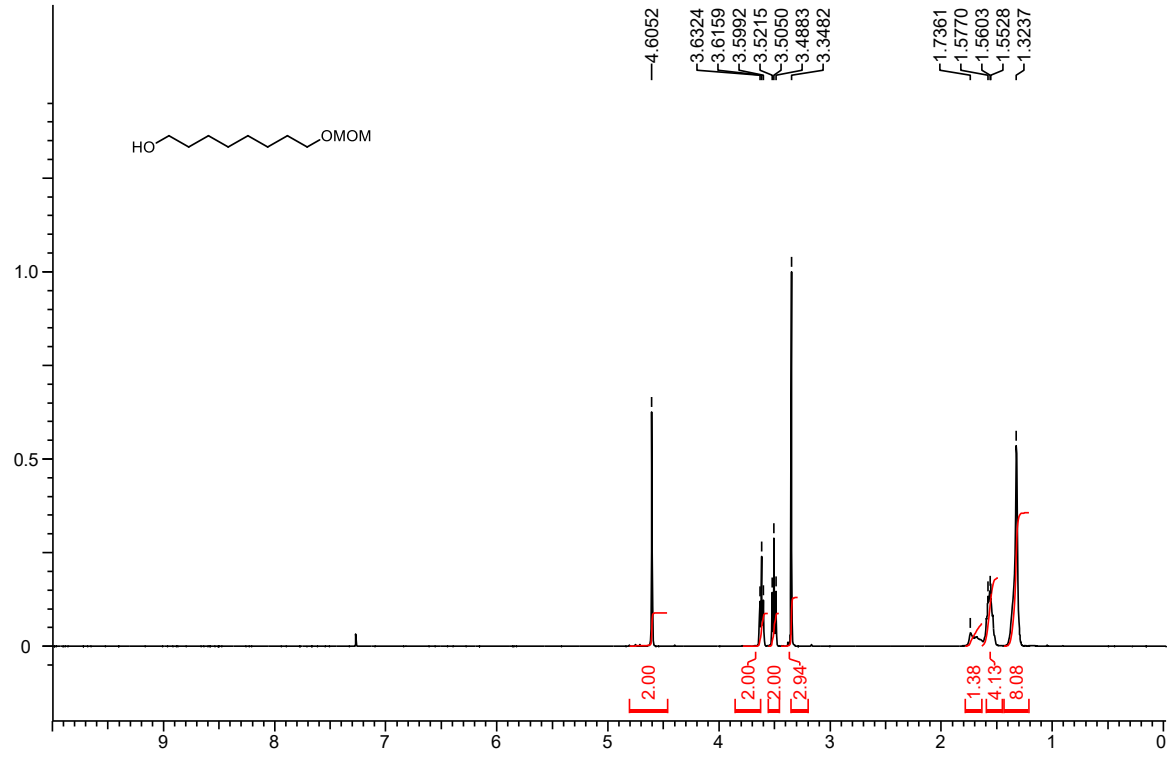
Compound S20

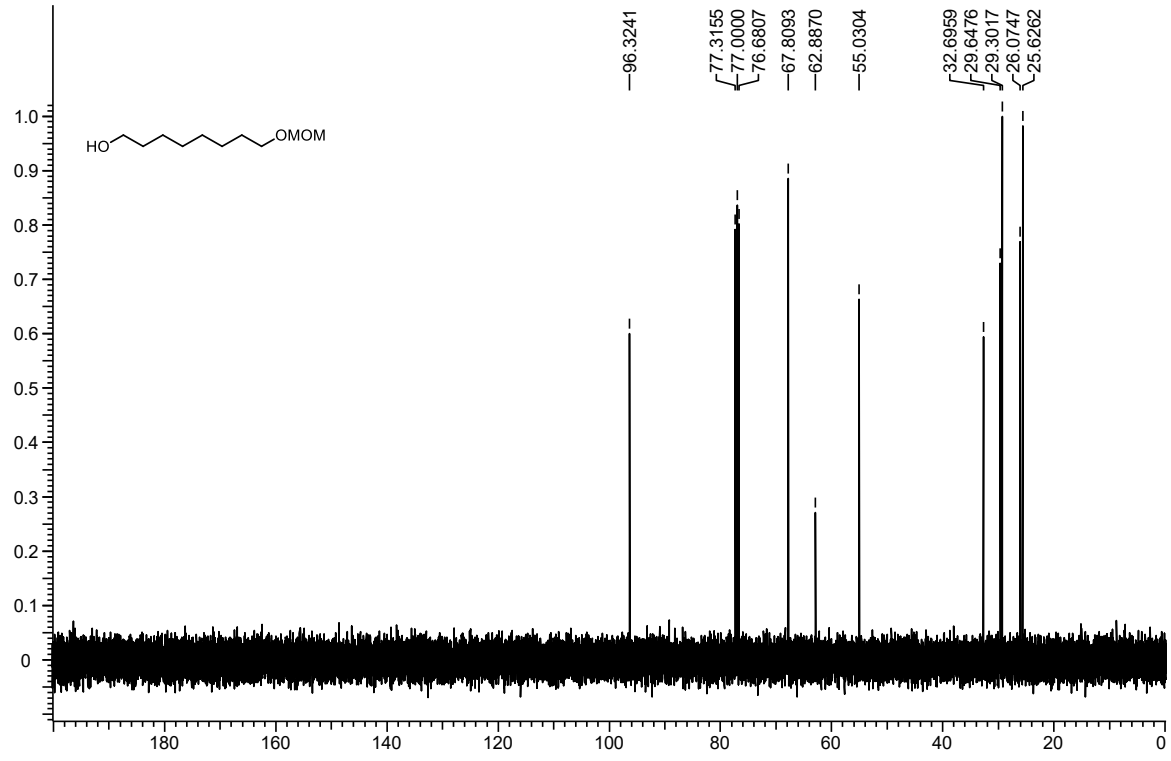


Compound S21

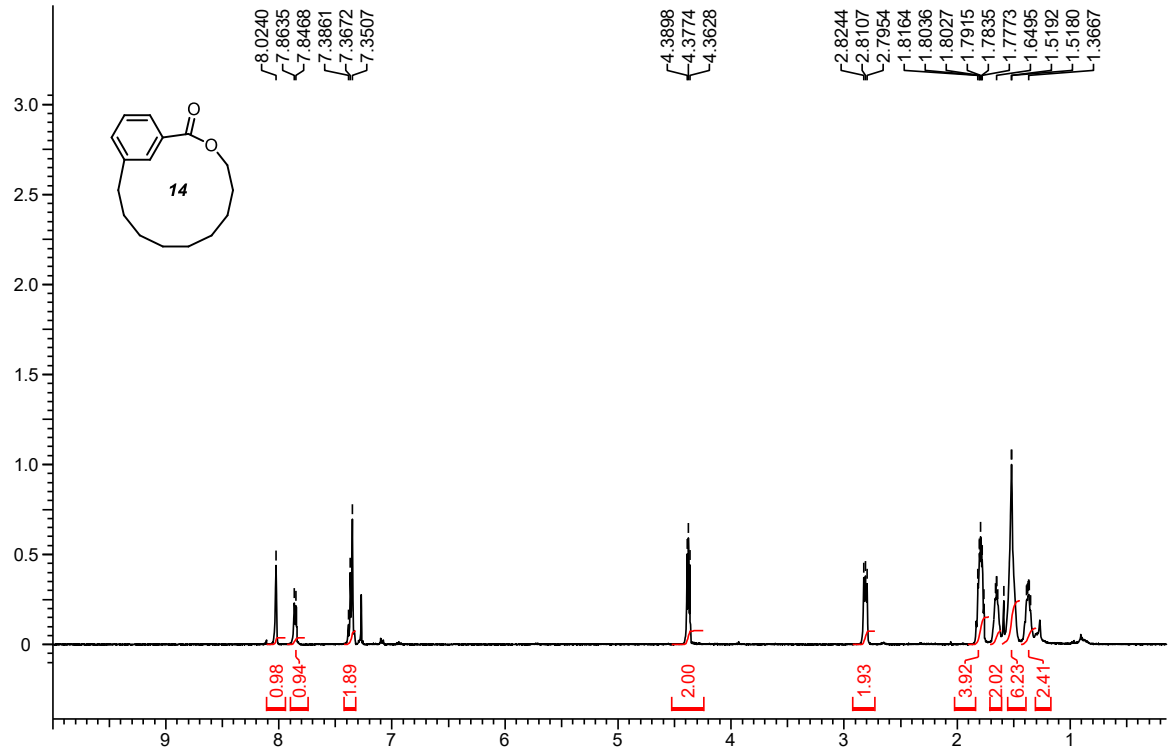


Compound S22





Compound 6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7.8468
7.3861
7.3672
7.3507
4.3898
4.3774
4.3628
2.8244
2.8107
2.7954
1.8164
1.8036
1.8027
1.7915
1.7835
1.7773
1.6495
1.5192
1.5180
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14
0.98
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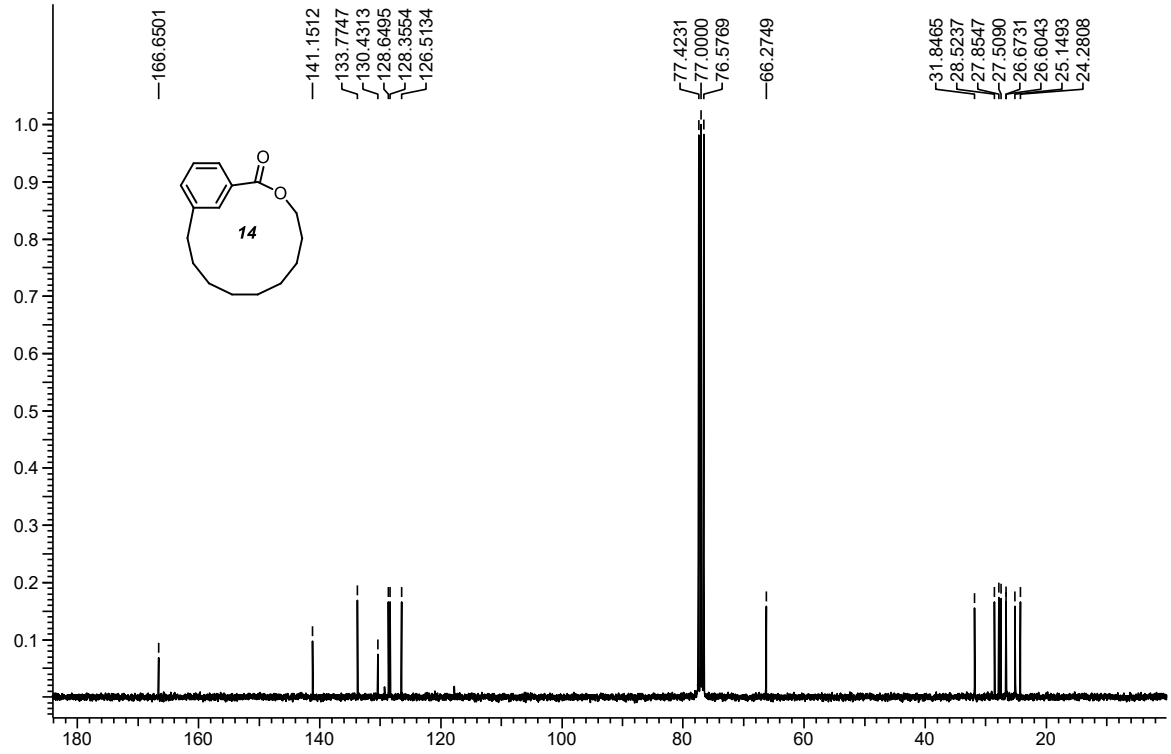
1.89
2.00
1.93
3.92
2.02
6.23
2.41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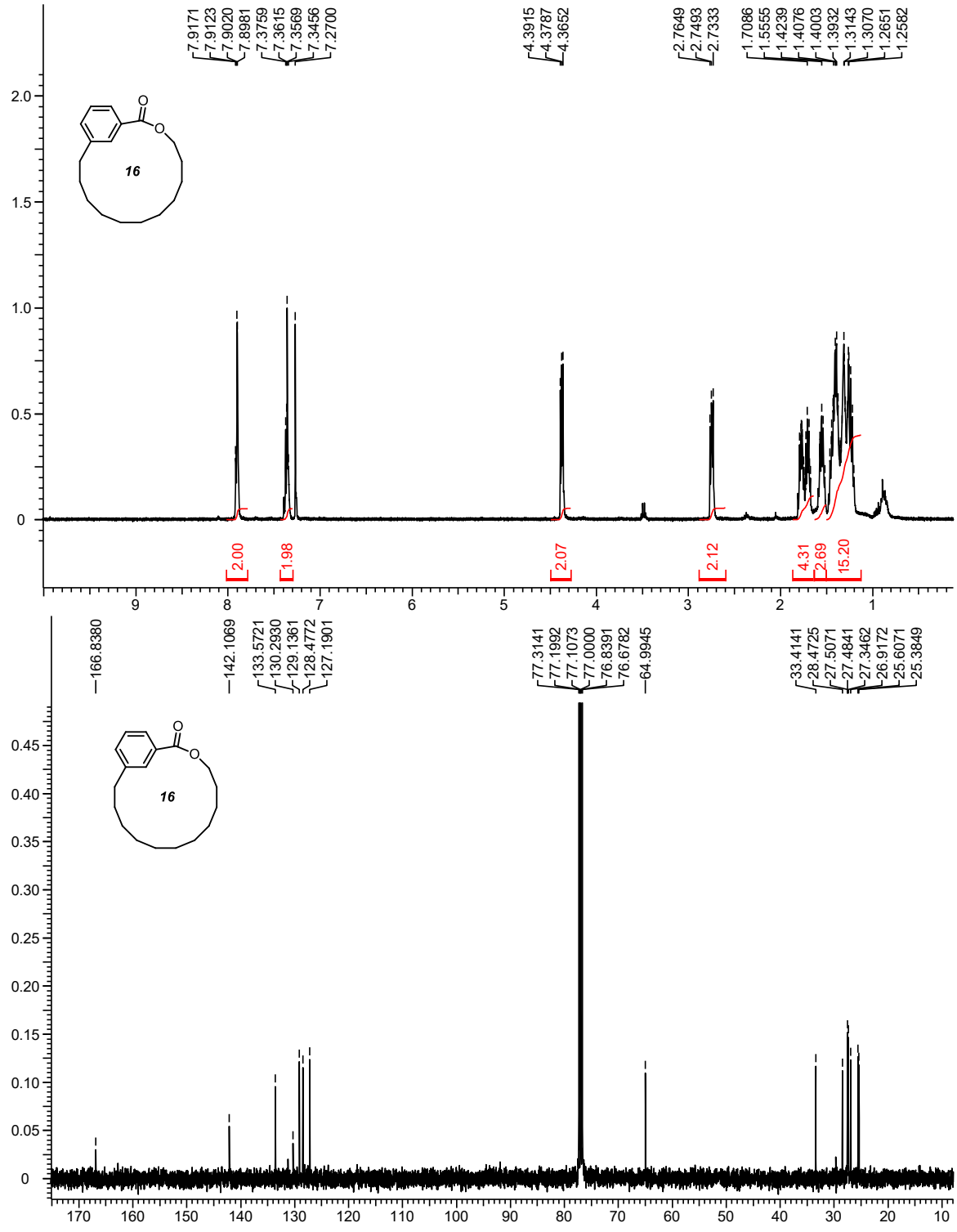
130.4313
128.6495
128.3554
126.5134
77.4231
77.0000
76.5769
66.2749
31.8465
28.5237
27.8547
27.5090
26.6731
26.6043
25.1493
24.2808
14

Compound 7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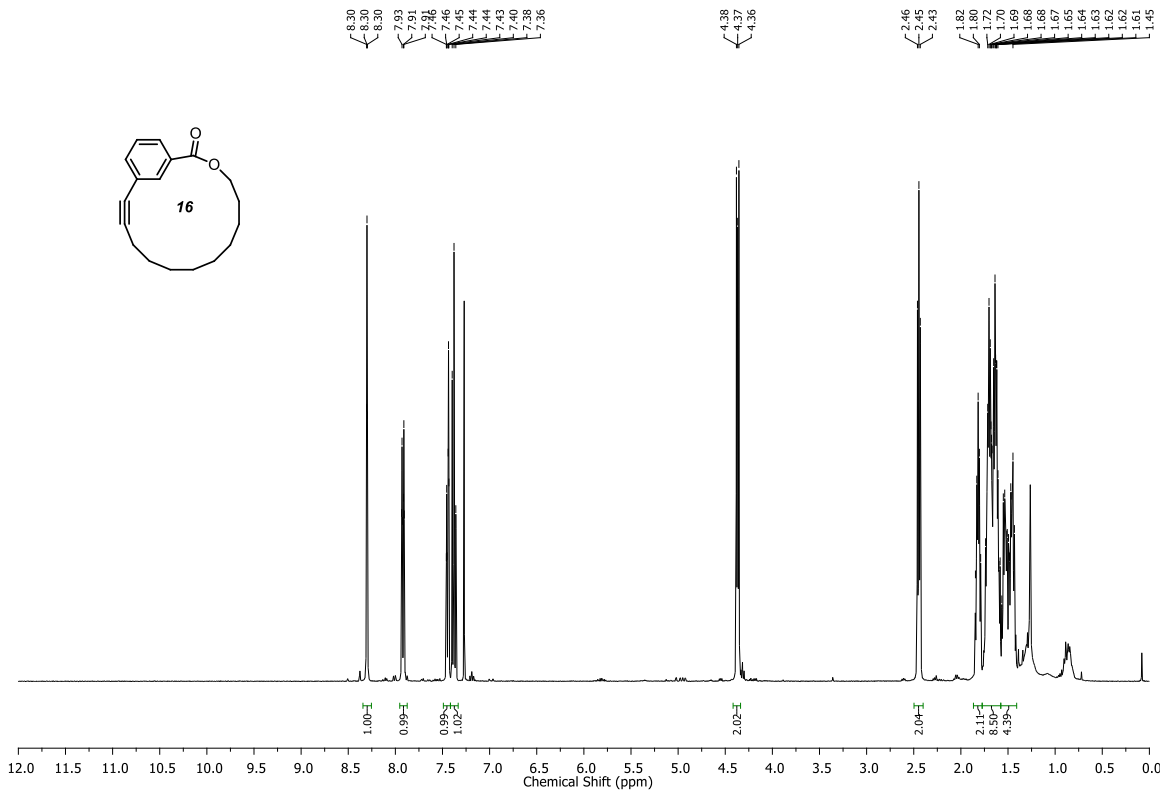
7.9123
7.9020
7.8981
7.3759
7.3615
7.3569
7.3456
7.2700
4.3915
4.3787
4.3652
2.7649
2.7493
2.7333
1.7086
1.5555
1.4239
1.4076
1.4003
1.3932
1.3143
1.3070
1.2651
1.2582
16
2.00
1.98
2.07
2.12
4.31
2.69
15.20
166.8380
142.1069
133.5721
130.2930
129.1361
128.4772
127.1901
77.3141
77.1992
77.1073
77.0000
76.8391
76.6782
64.9945
33.4141
28.4725
27.5071
27.4841
27.3462
26.9172
25.6071
25.3849
16

Compound 8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8.30
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7.91
7.91
7.46
7.46
7.45
7.44
7.44
7.43
7.40
7.38
7.36
4.38
4.37
4.36
2.46
2.45
2.43
1.82
1.80
1.72
1.70
1.69
1.68
1.68
1.67
1.65
1.64
1.63
1.62
1.62
1.61
1.45
16
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0.99
0.99
1.02
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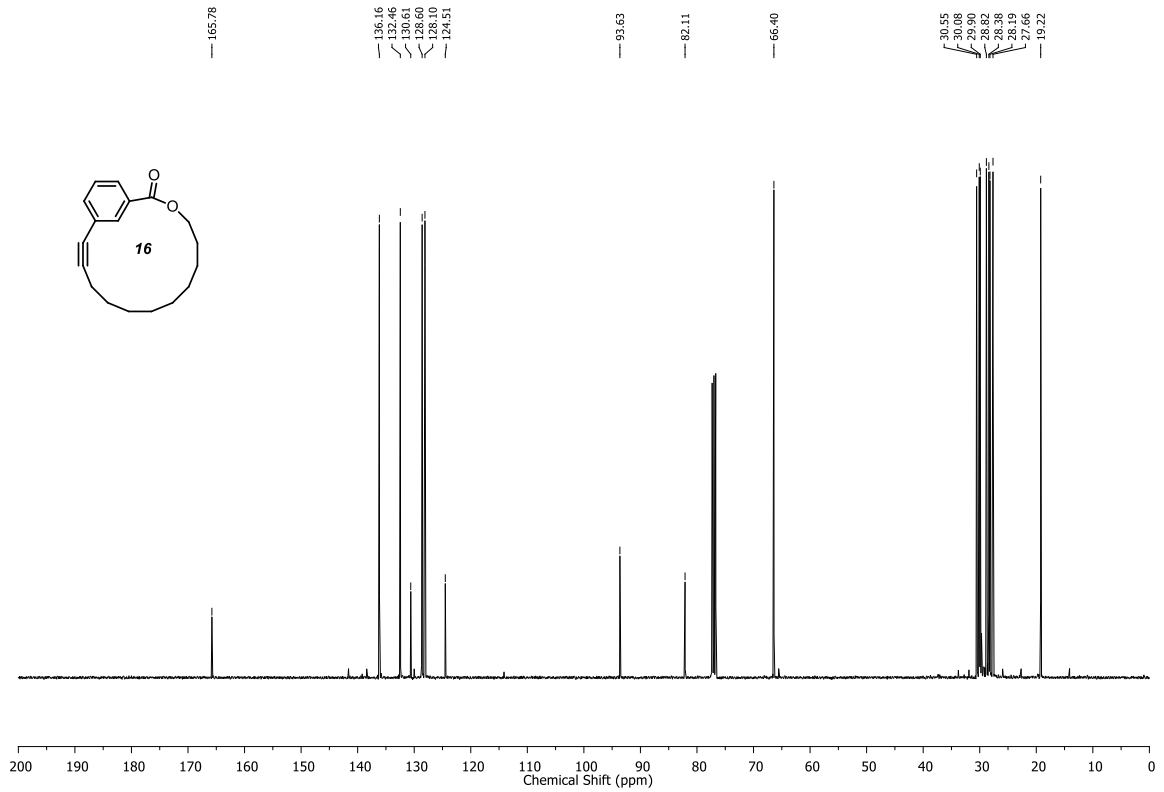
2.04
2.11
8.50
4.39
Chemical Shift (ppm)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136.16
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130.61
128.60
128.10
124.51
93.63
82.11
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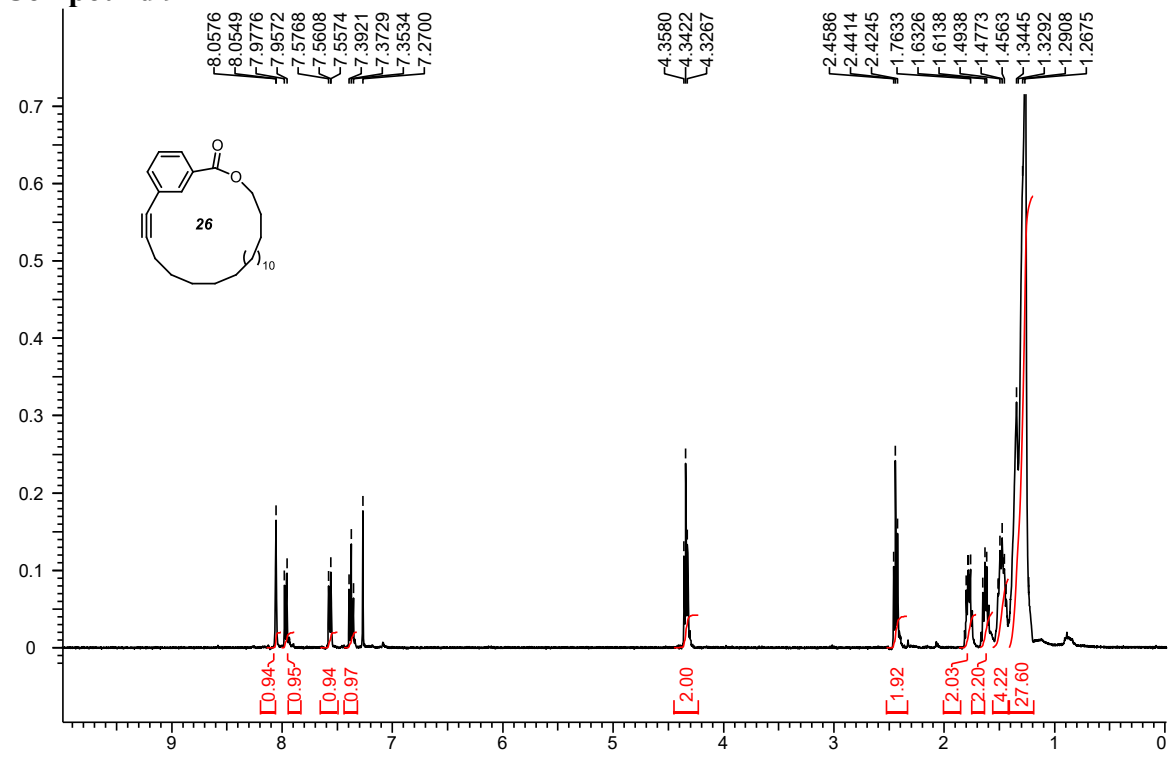
30.55
30.08
29.90
28.82
28.38
28.19
27.66
19.22
16
Chemical Shift (ppm)

Compound 9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7.9776
7.9572
7.5768
7.5608
7.5574
7.3921
7.3729
7.3534
7.2700
4.3580
4.3422
4.3267
2.4586
2.4414
2.4245
1.7633
1.6326
1.6138
1.4938
1.4773
1.4563
1.3445
1.3292
1.2908
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0.95
0.94
0.97
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2.03
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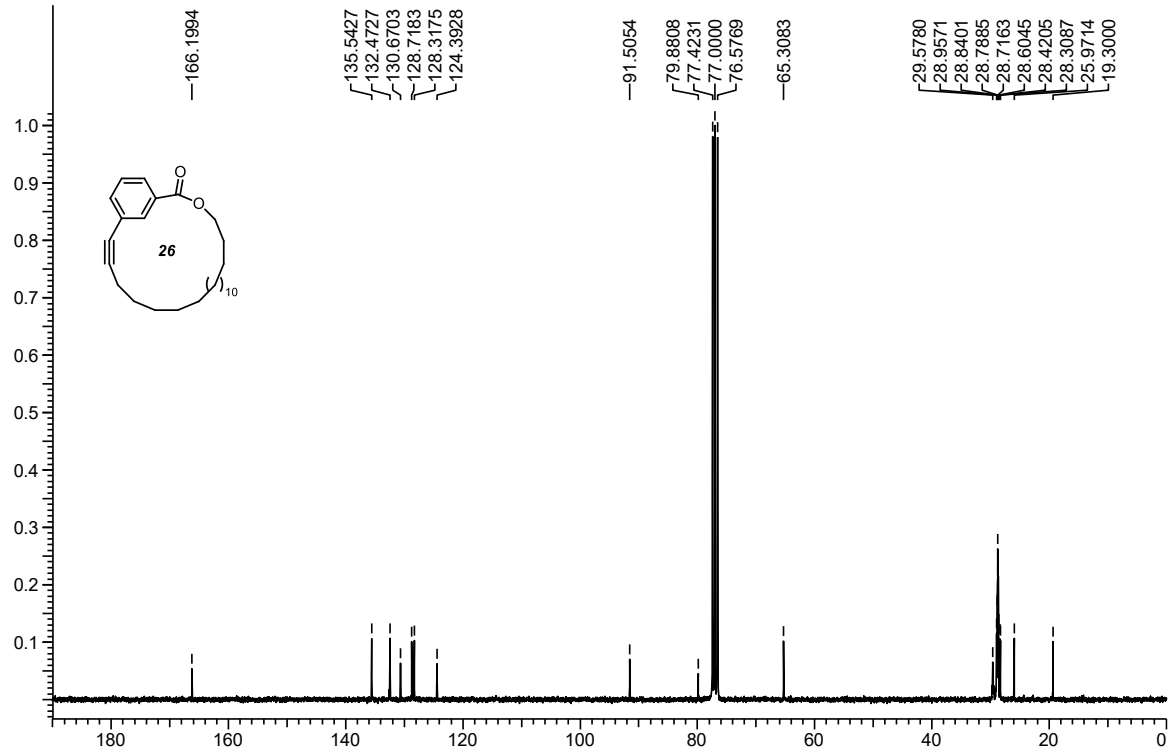
4.22
27.60
26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79.8808
77.4231
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65.3083
29.5780
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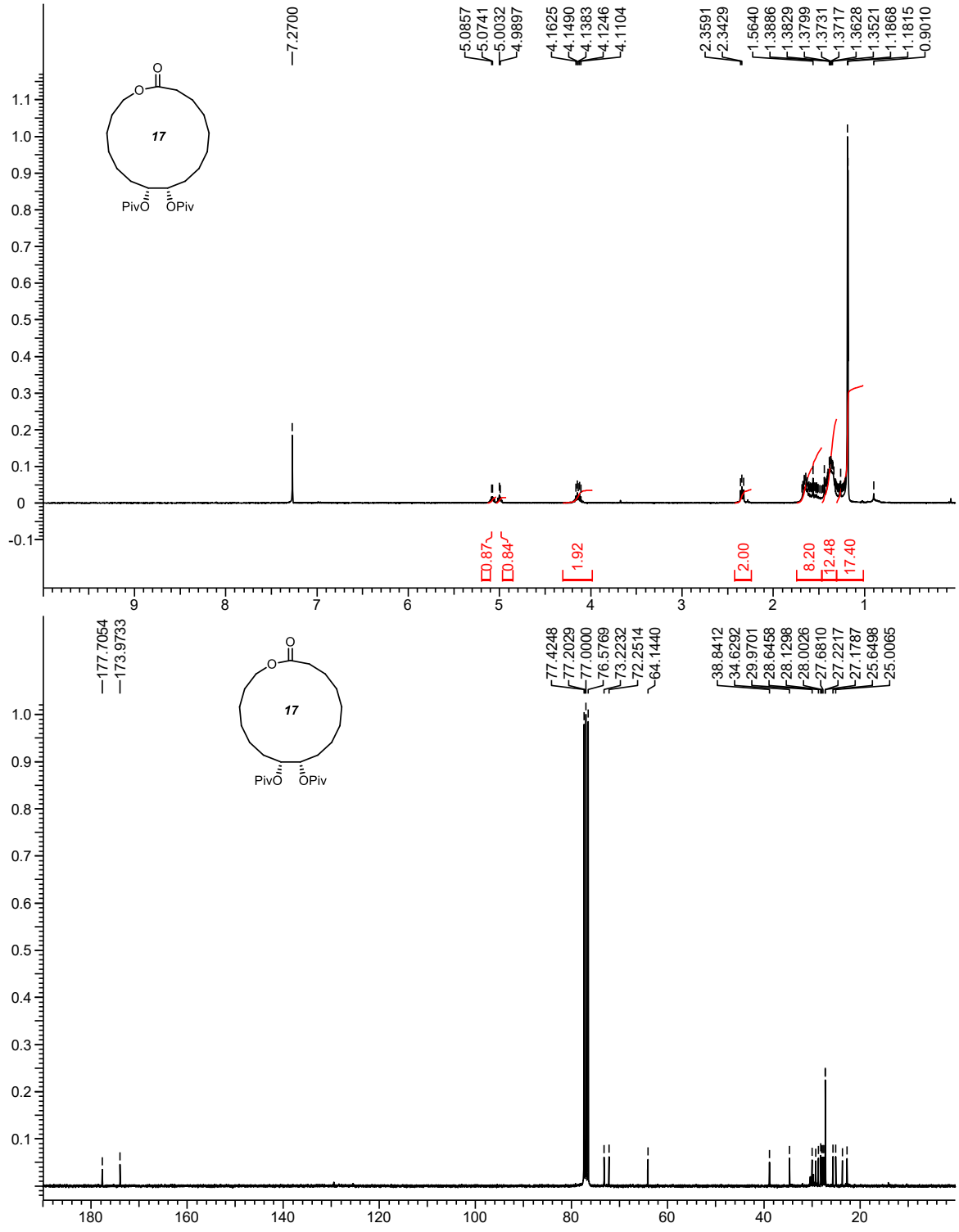
28.7885
28.7163
28.6045
28.4205
28.3087
25.9714
19.3000
26

Compound 11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5.0032
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4.1490
4.1383
4.1246
4.1104
2.3591
2.3429
1.5640
1.3886
1.3829
1.3799
1.3731
1.3717
1.3628
1.3521
1.1868
1.1815
0.9010
17
PivO
OPiv
0.87
0.84
1.92
2.00
8.20
2.48
17.40
177.7054
173.9733
77.4248
77.2029
77.0000
76.5769
73.2232
72.2514
64.1440
38.8412
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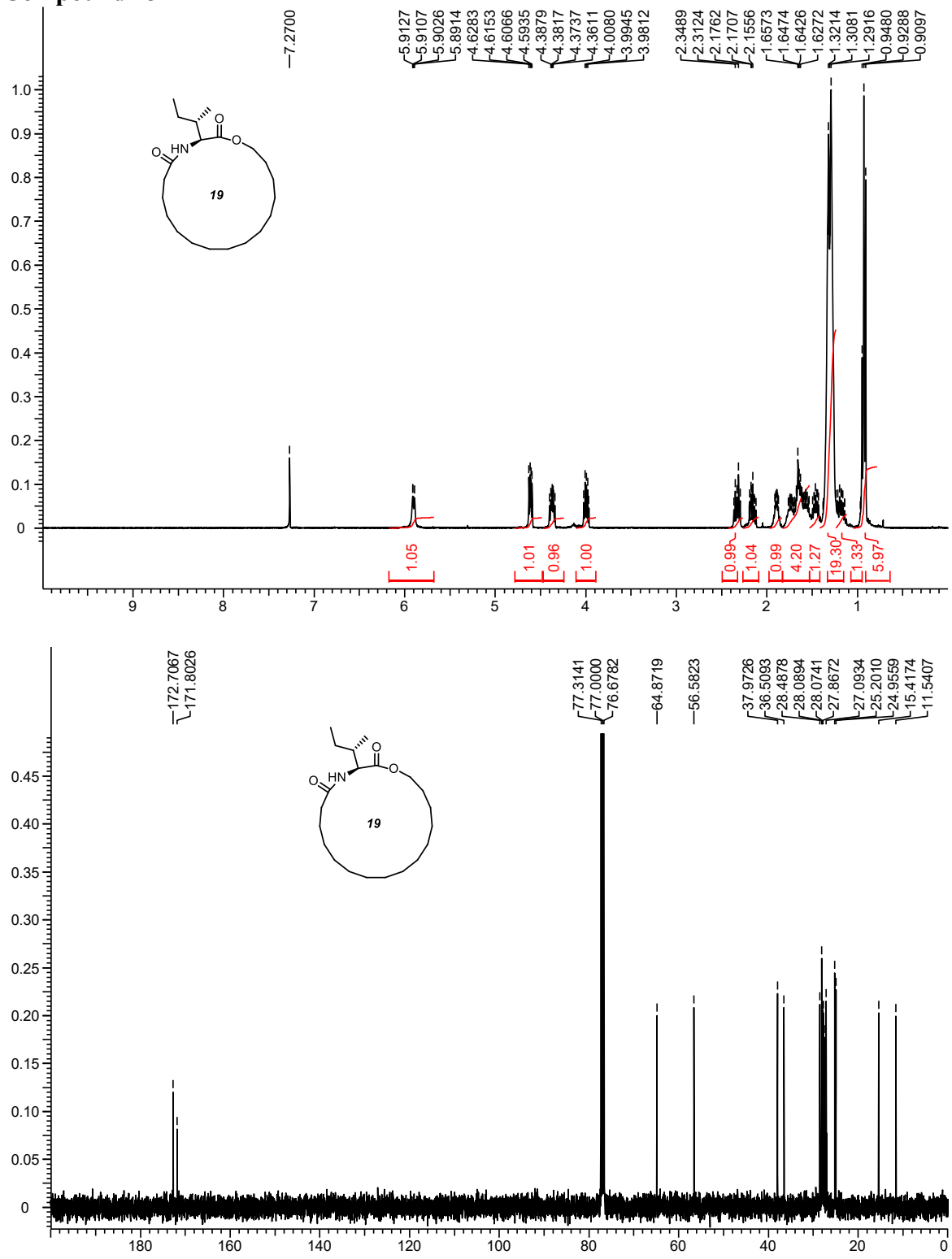
28.1298
28.0026
27.6810
27.2217
27.1787
25.6498
25.0065

Compound 13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4.6153
4.6066
4.5935
4.3879
4.3817
4.3737
4.3611
4.0080
3.9945
3.9812
2.3489
2.3124
2.1762
2.1707
2.1556
1.6573
1.6474
1.6426
1.6272
1.3214
1.3081
1.2916
0.9480
0.9288
0.9097
1.05
1.01
0.96
1.00
0.99
1.04
0.99
4.20
1.27
19.30
1.33
5.97
19
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171.8026
77.3141
77.0000
76.6782
64.8719
56.5823
37.9726
36.5093
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27.0934
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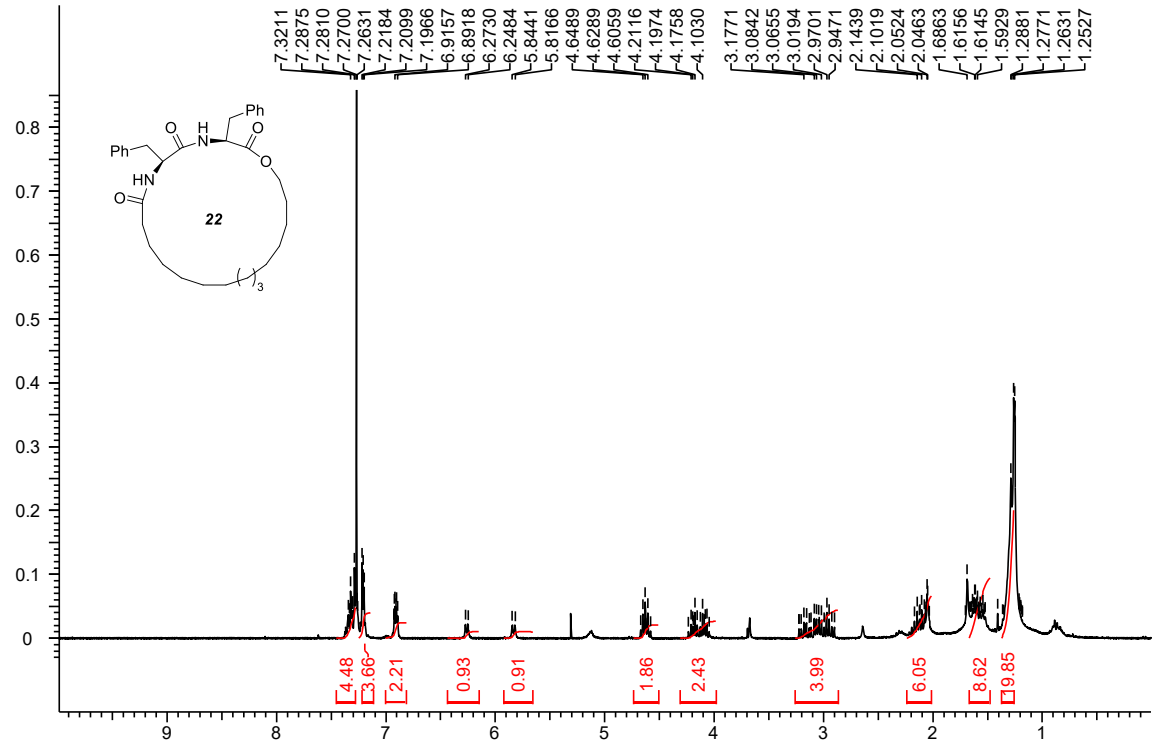
11.5407
19

Compound 14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7.2700
7.2631
7.2184
7.2099
7.1966
6.9157
6.8918
6.2730
6.2484
5.8441
5.8166
4.6489
4.6289
4.6059
4.2116
4.1974
4.1758
4.1030
3.1771
3.0842
3.0655
3.0194
2.9701
2.9471
2.1439
2.1019
2.0524
2.0463
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1.6156
1.6145
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1.2881
1.2771
1.2631
1.2527
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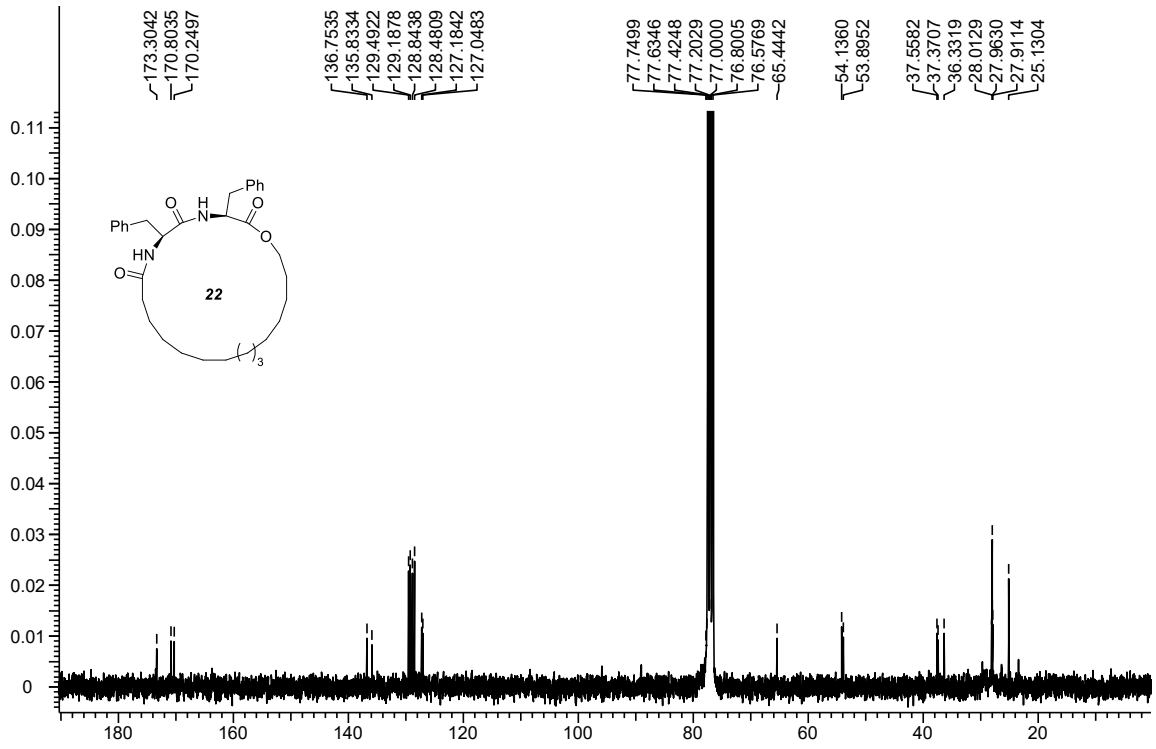
3.99
6.05
8.62
9.85
22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127.0483
77.7499
77.6346
77.4248
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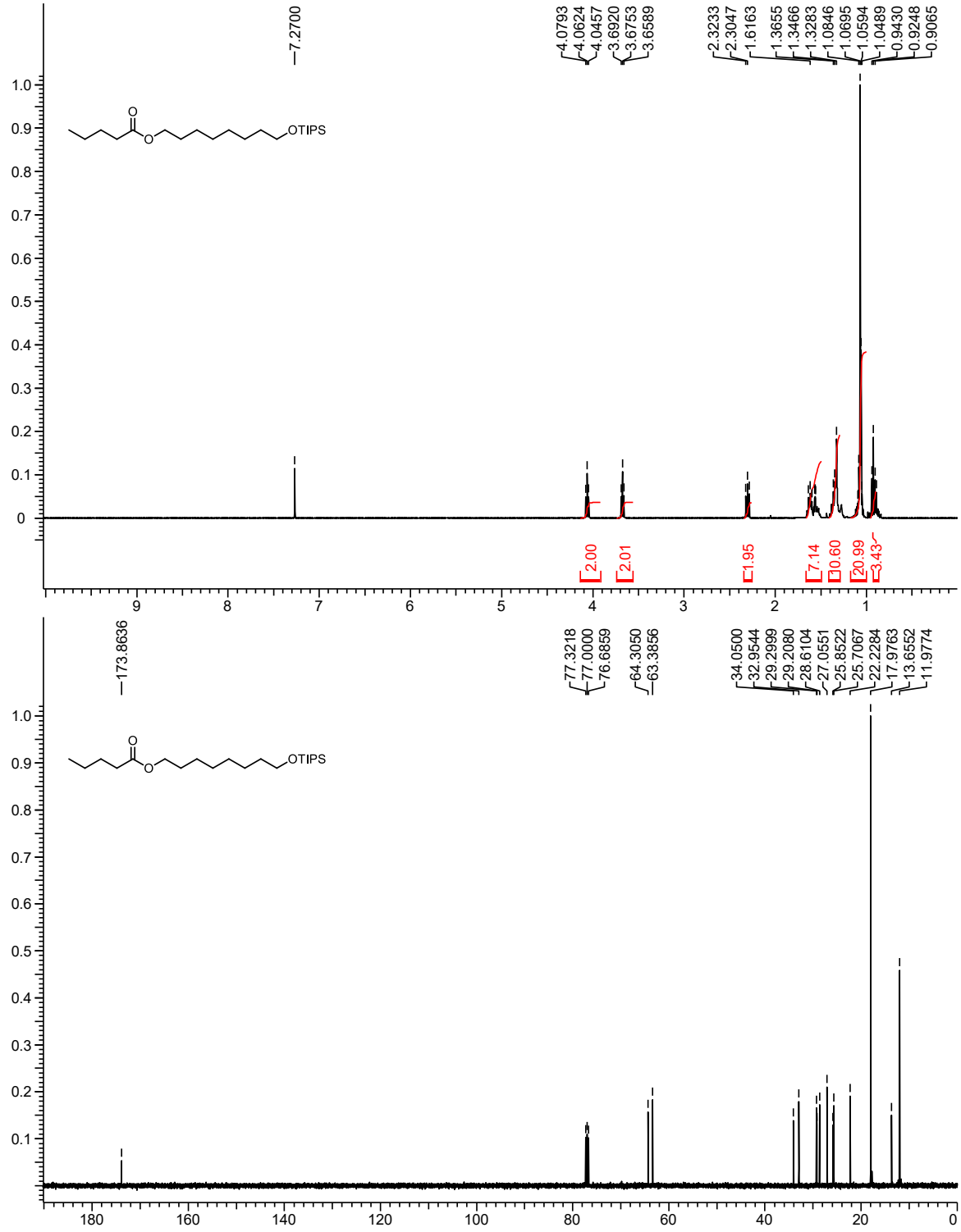
77.0000
76.8005
76.5769
65.4442
54.1360
53.8952
37.5582
37.3707
36.3319
28.0129
27.9630
27.9114
25.1304
22

Compound 20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1.3466
1.3283
1.0846
1.0695
1.0594
1.0489
0.9430
0.9248
0.9065
OTIPS
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2.01
1.95
7.14
10.60
20.99
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77.0000
76.6859
64.3050
63.3856
34.0500
32.9544
29.2999
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25.7067
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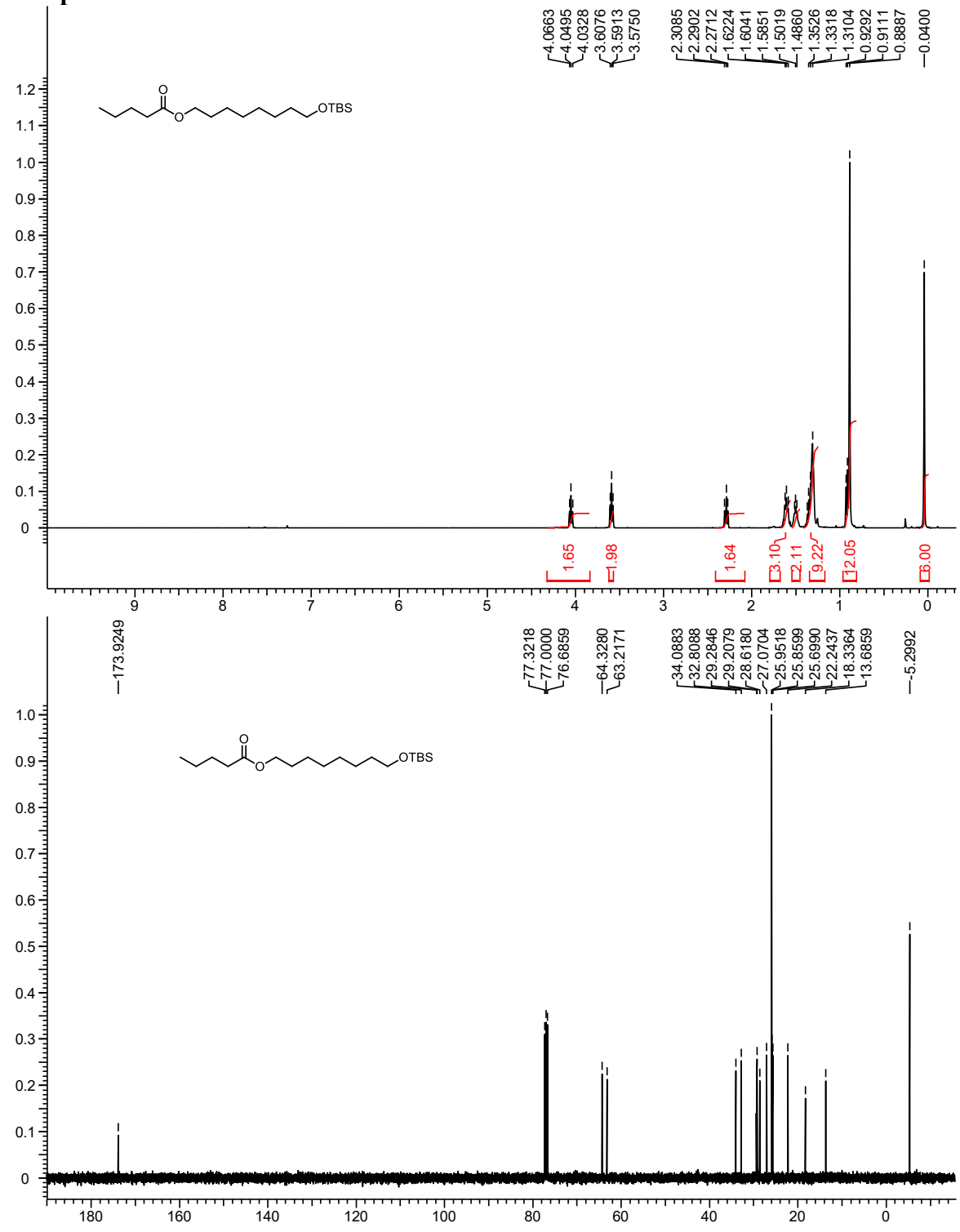
Compound 19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1.6041
1.5851
1.5019
1.4860
1.3526
1.3318
1.3104
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0.9111
0.8887
0.0400
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1.98
1.64
3.10
2.11
9.22
2.05
6.00
173.9249
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63.2171
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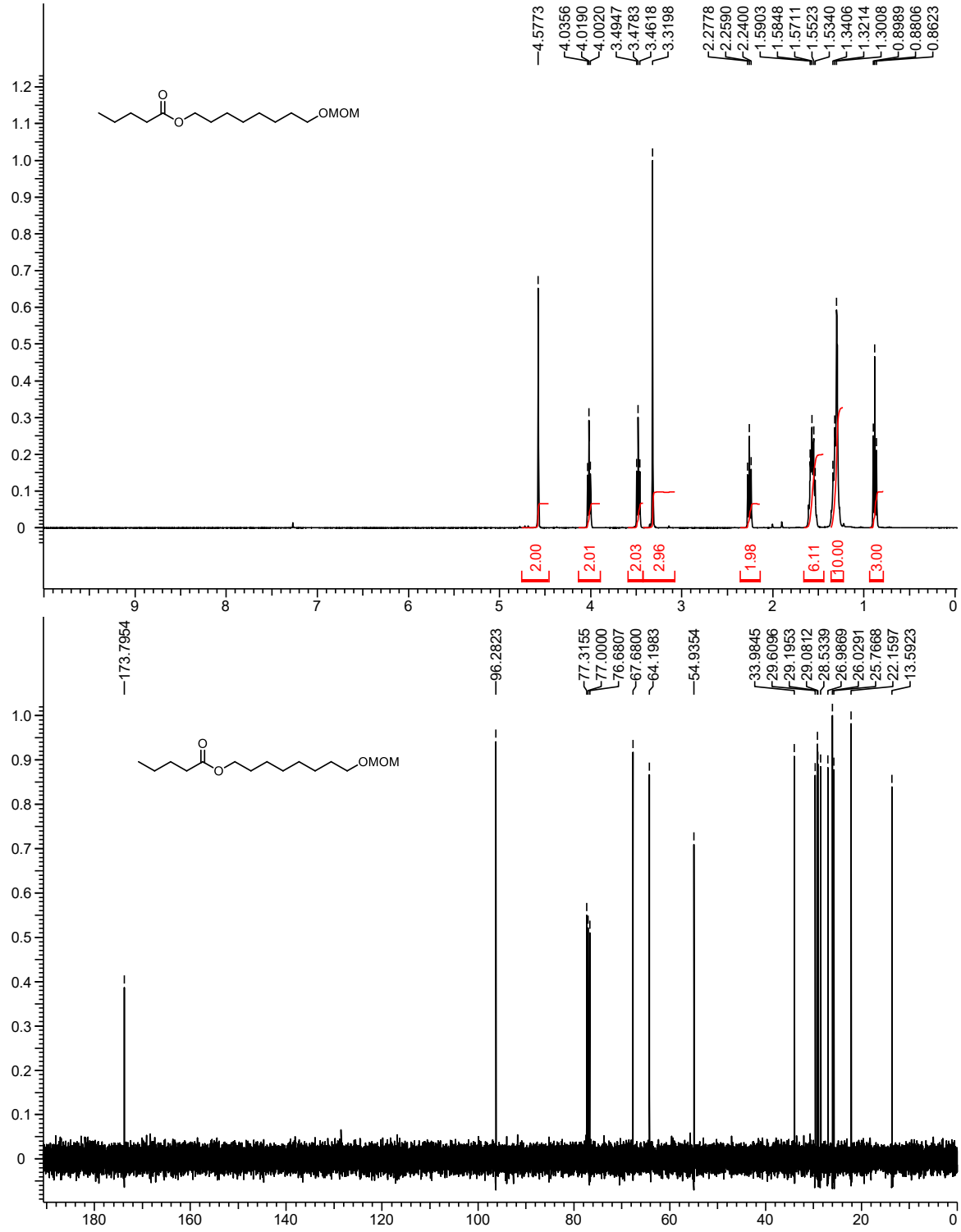
Compound 21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2.2400
1.5903
1.5848
1.5711
1.5523
1.5340
1.3406
1.3214
1.3008
0.8989
0.8806
0.8623
OMOM
2.00
2.01
2.03
2.96
1.98
6.11
10.00
3.00
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96.2823
77.3155
77.0000
76.6807
67.6800
64.1983
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33.9845
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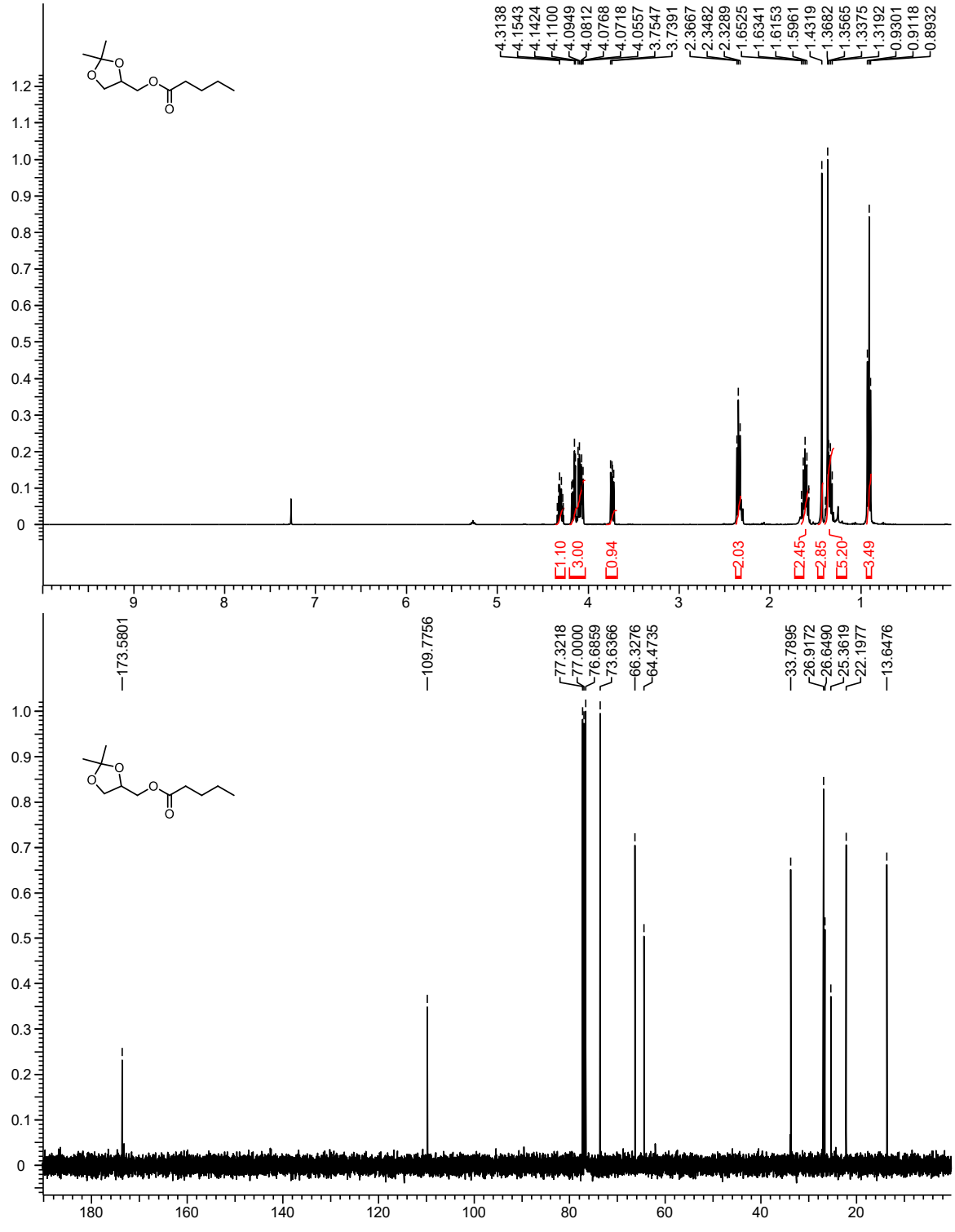
Compound 24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2.3667
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2.3289
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1.6341
1.6153
1.5961
1.4319
1.3682
1.3565
1.3375
1.3192
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0.9118
0.8932
1.10
3.00
0.94
2.03
2.45
2.85
5.20
3.49
173.5801
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77.3218
77.0000
76.6859
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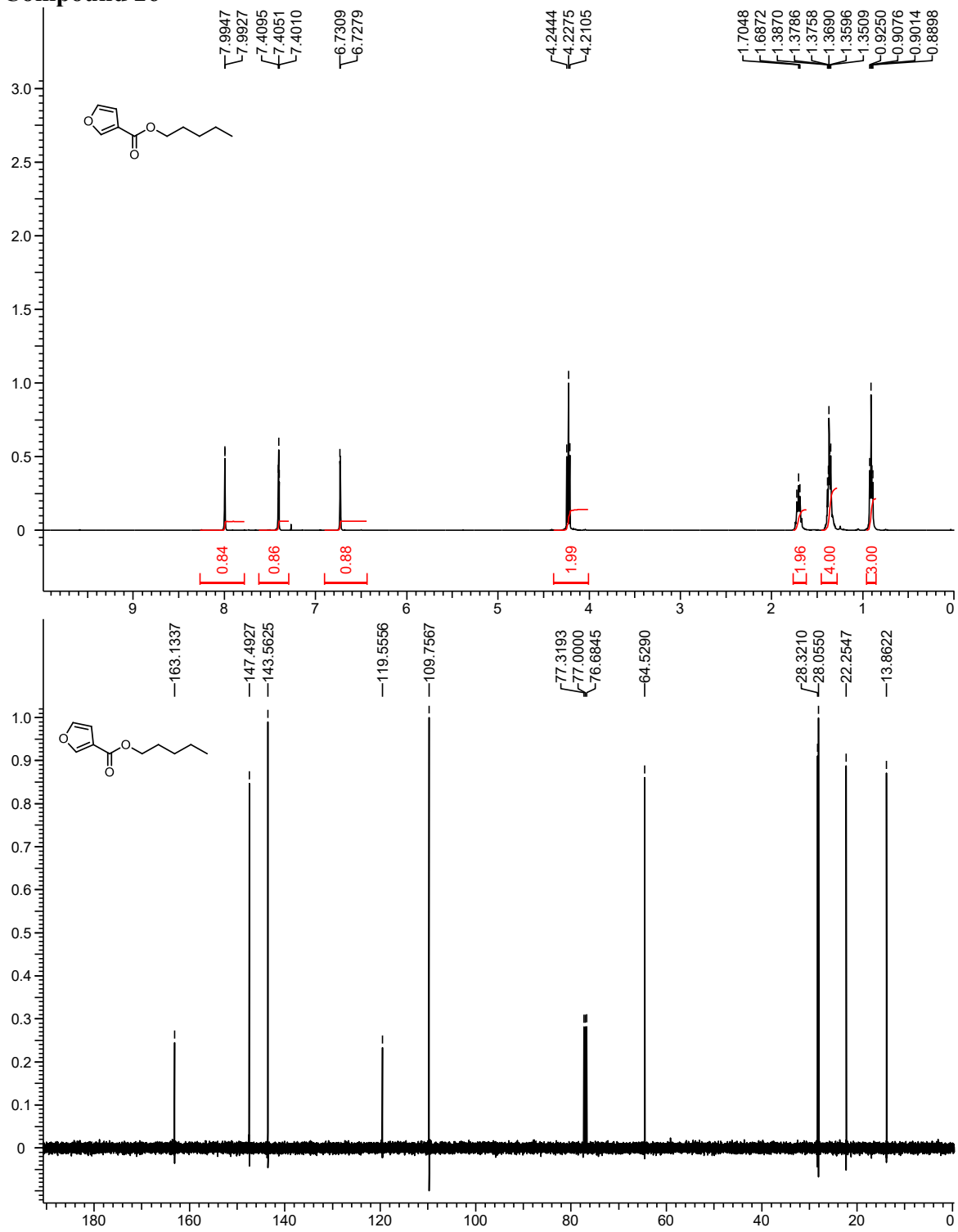
Compound 26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1.3758
1.3690
1.3596
1.3509
0.9250
0.9076
0.9014
0.8898
0.84
0.86
0.88
1.99
1.96
4.00
3.00
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147.4927
143.5625
119.5556
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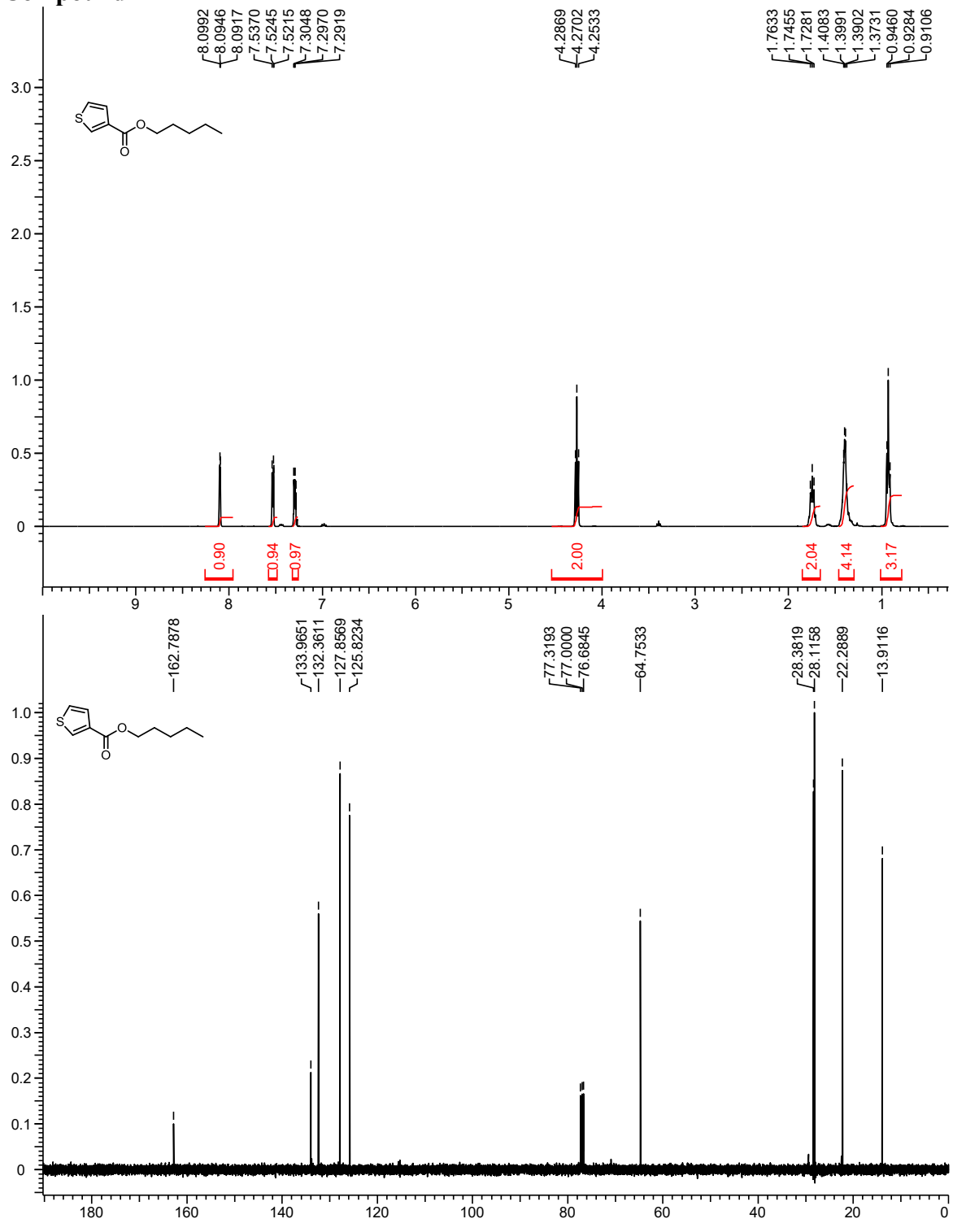
13.8622

Compound 27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1.3902
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0.9106
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0.94
0.97
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2.04
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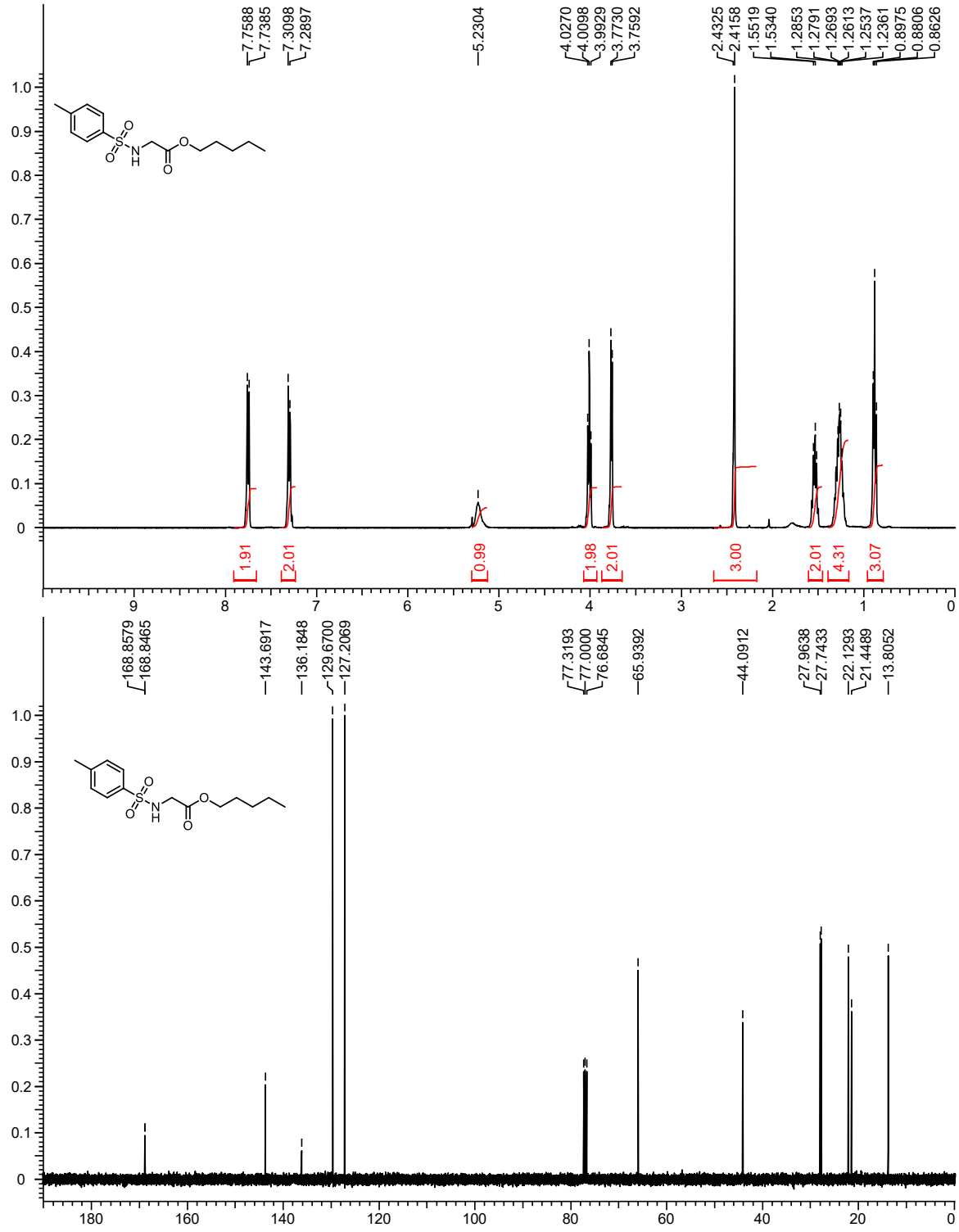
Compound 17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1.2791
1.2693
1.2613
1.2537
1.2361
0.8975
0.8806
0.8626
1.91
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2.01
3.00
2.01
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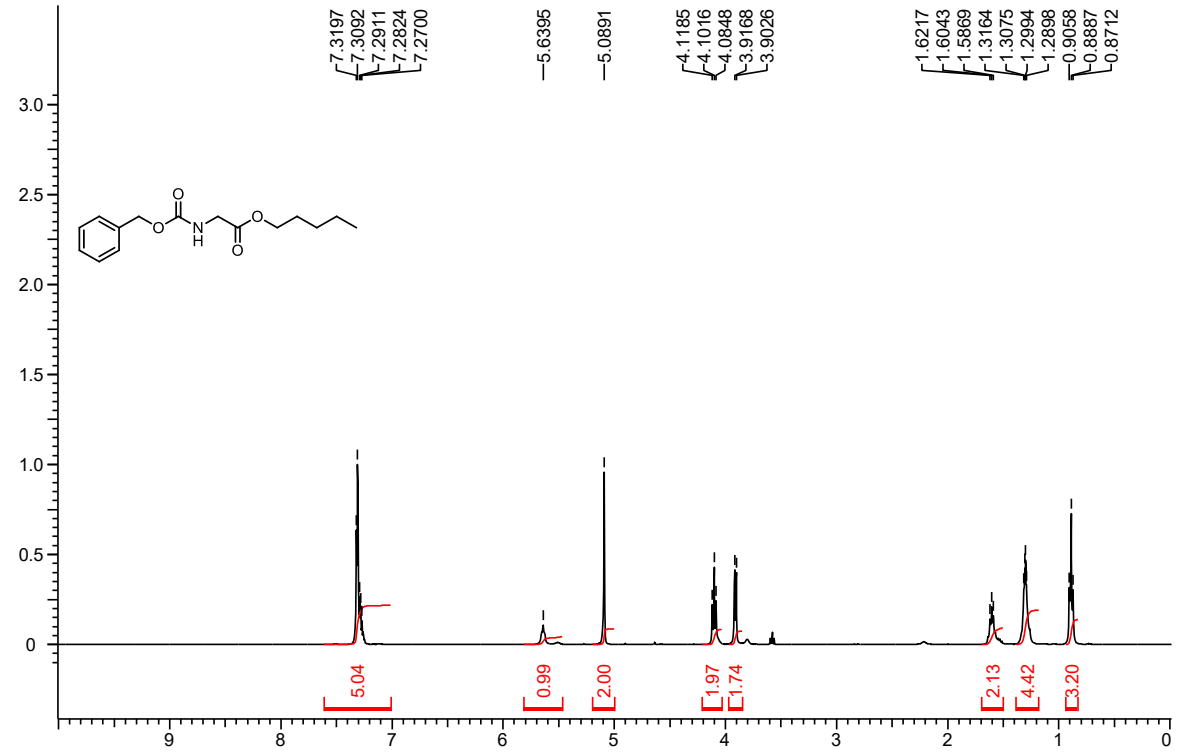
Compound 18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1.6043
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1.3164
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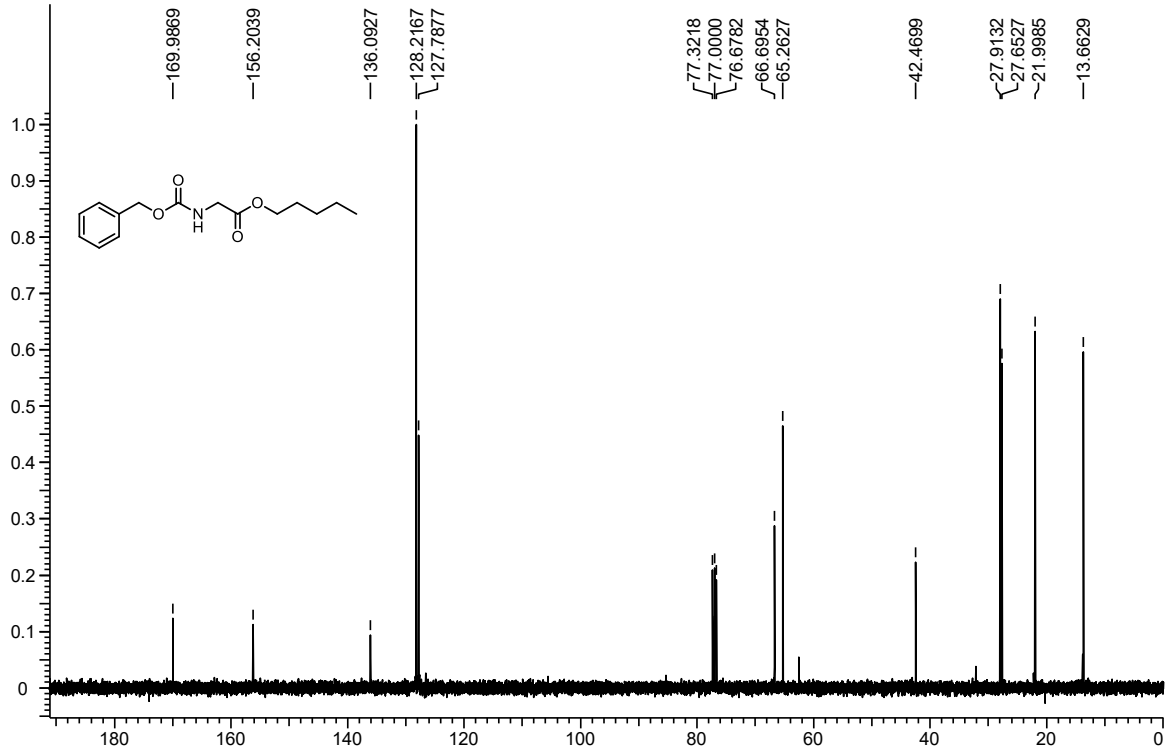
3.20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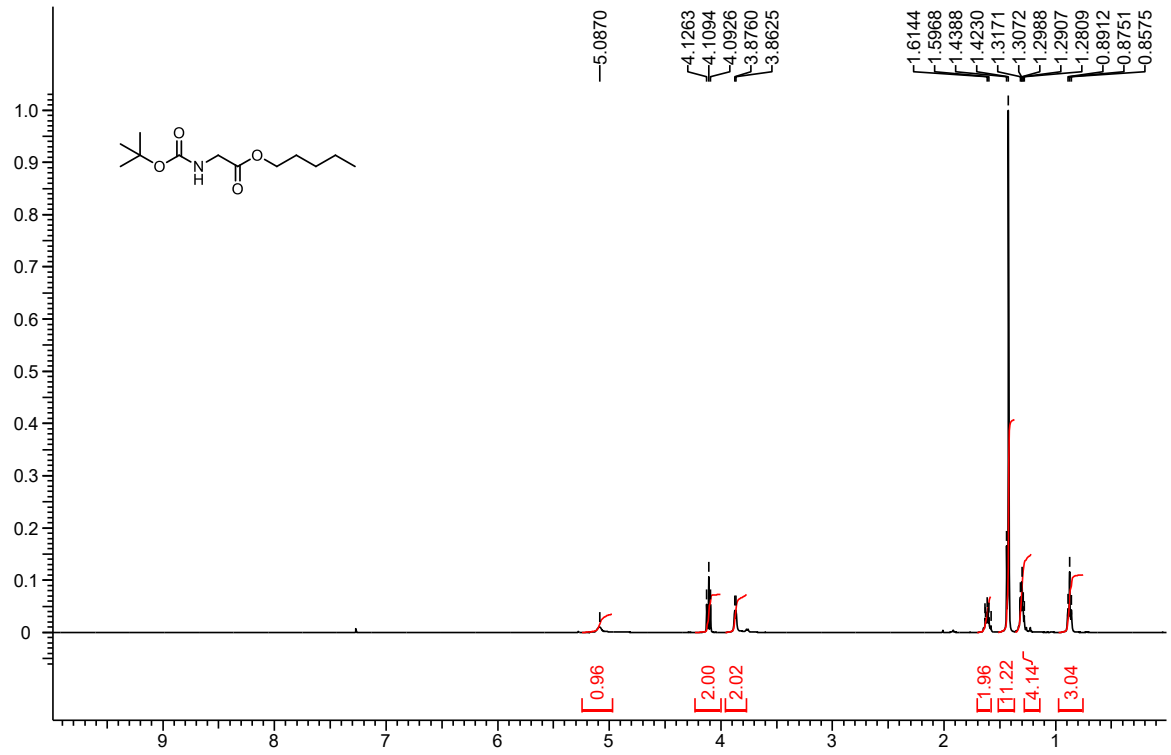
Compound 16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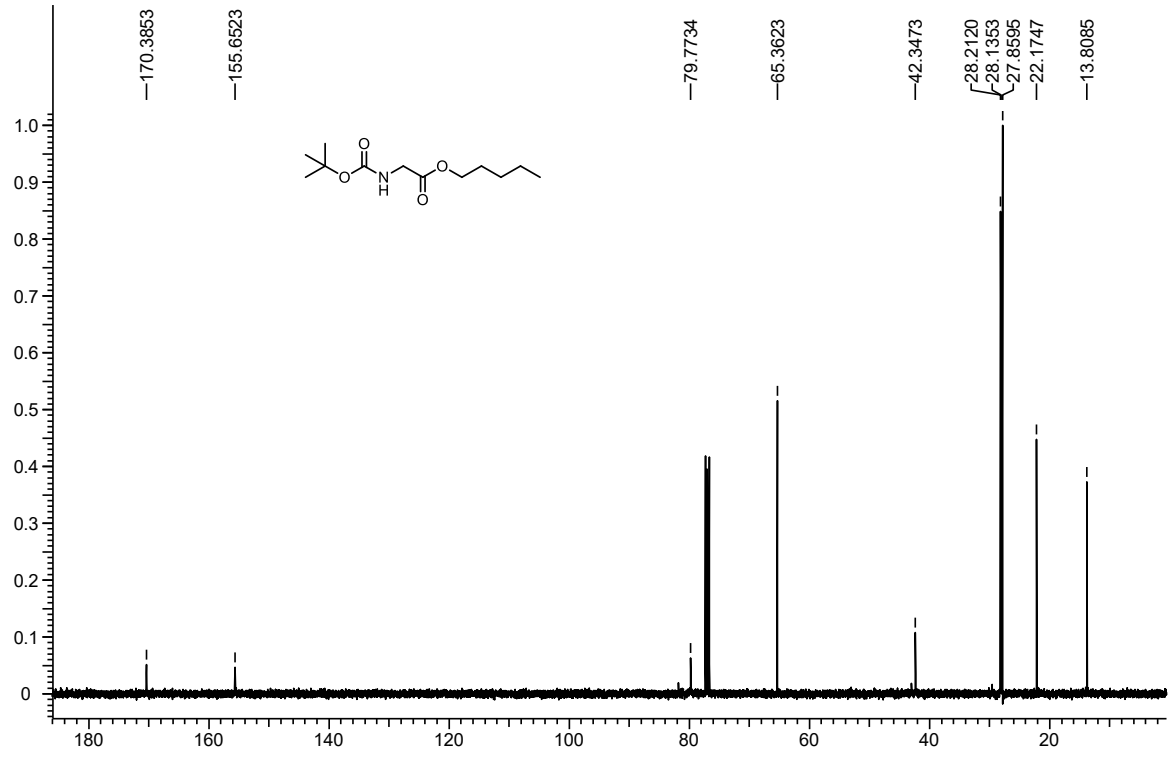
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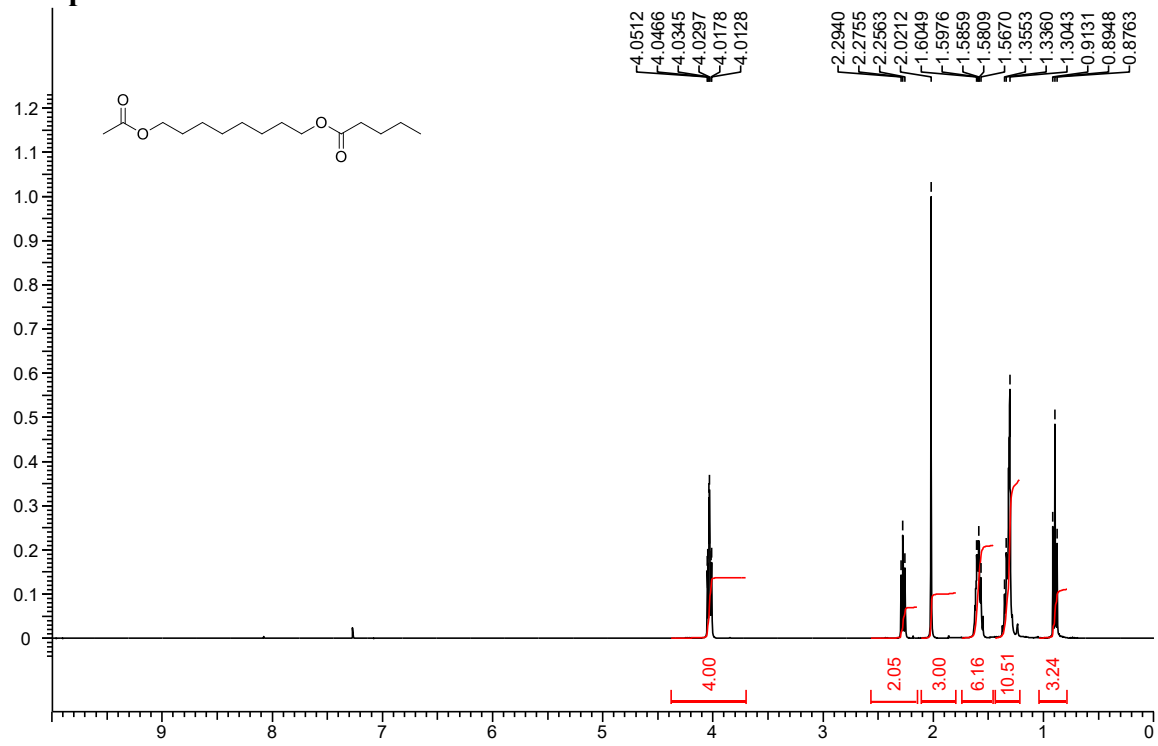
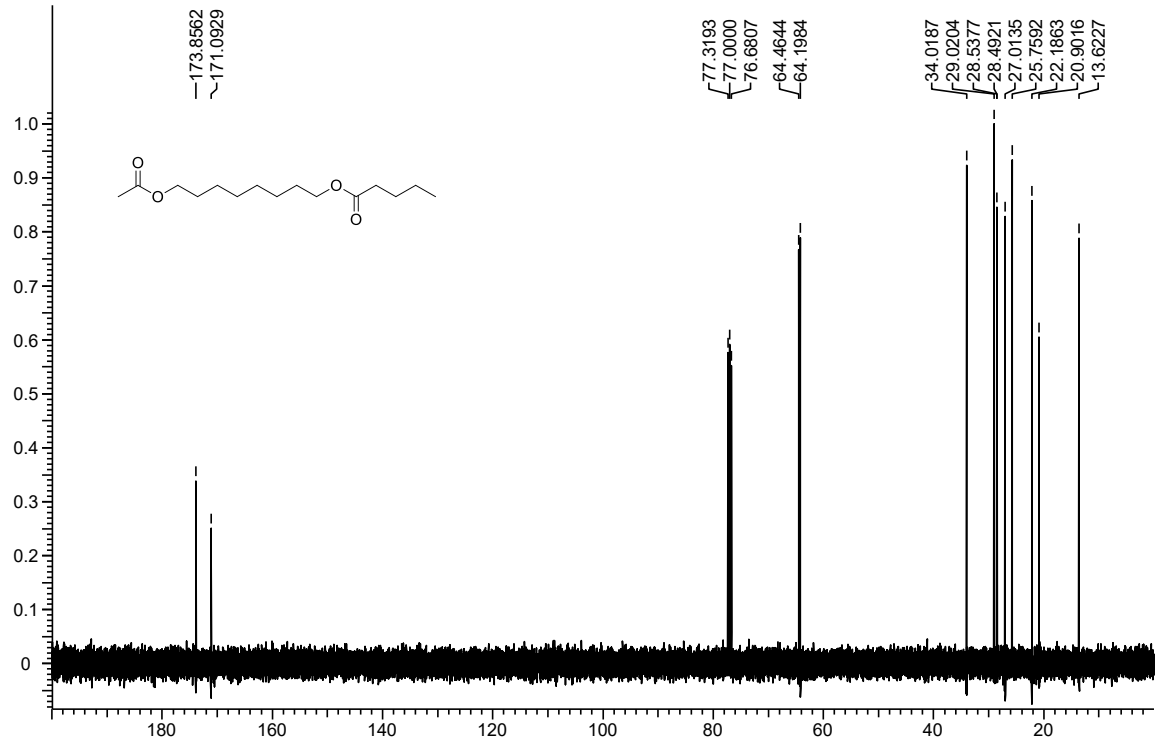
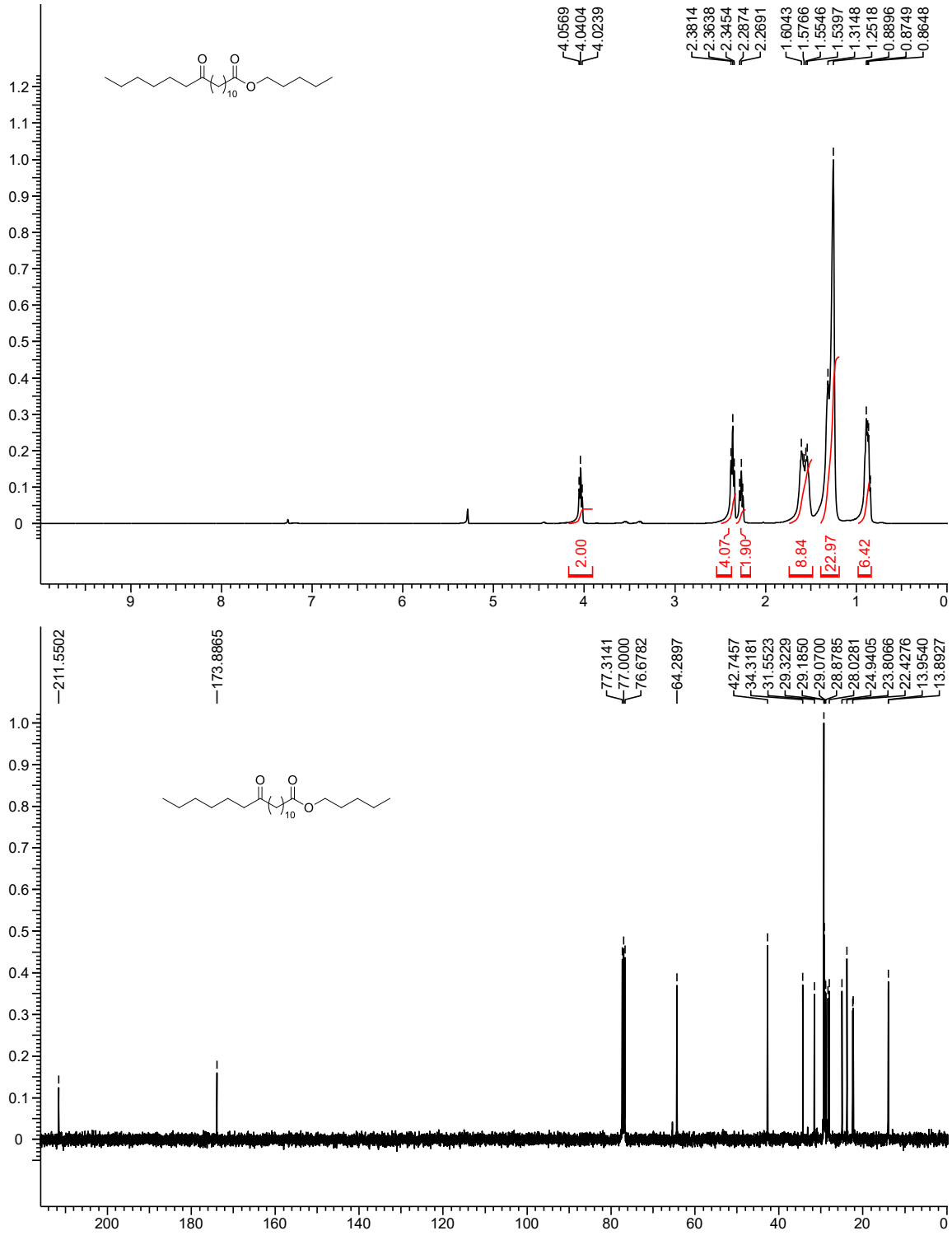
Compound 22





Compound 23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23.8066
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13.9540
13.8927

Annexe 2. Supporting Information of Chapter 4

General:

All reactions that were carried out under anhydrous conditions were performed under an inert argon or nitrogen atmosphere in glassware that had previously been dried overnight at 120 ^{o}C or had been flame dried and cooled under a stream of argon or nitrogen.[1] All commercial reagents were obtained from Sigma-Aldrich Chemical Company or Strem Chemicals and were reagent quality. Technical solvents were obtained from VWR International Co. Methyl 3-iodobenzoate[2] and methyl 4-iodobenzoate[2] were prepared according to literature procedures. Anhydrous solvents (CH_2Cl_2, Et_2O, THF, DMF, toluene, and *n*-hexane) were dried and deoxygenated using a GlassContour system (Irvine, CA). Isolated yields reflect the mass obtained following flash column silica gel chromatography. Organic compounds were purified using the method reported by Still[3] and using silica gel obtained from Silicycle Chemical division (40-63 nm; 230-240 mesh). Analytical thin-layer chromatography (TLC) was performed on glass-backed silica gel 60 coated with a fluorescent indicator (Silicycle Chemical division, 0.25 mm, F_{254}.). Visualization of TLC plates was performed by UV (254 nm), $KMnO_4$ or *p*-anisaldehyde stains. All mixed solvent eluents are reported as v/v solutions. Concentration refers to removal of volatiles at low pressure on a rotary evaporator. All reported compounds were homogeneous by thin layer chromatography (TLC) and by ^{1}H NMR. NMR spectra were taken in deuterated $CDCl_3$ using Bruker AV-300 and AV-400 instruments unless otherwise

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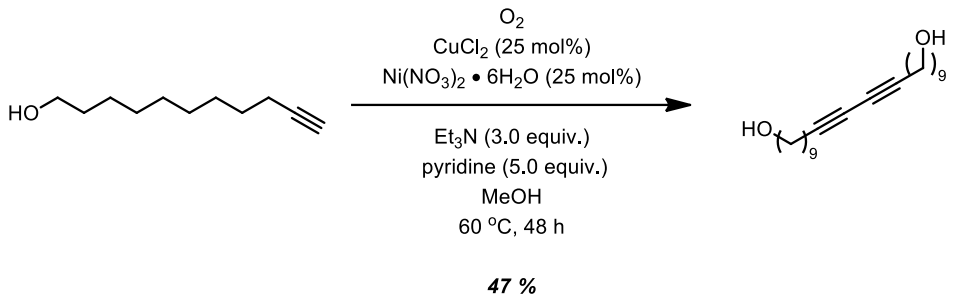
[1] Shriver, D. F.; Drezdon, M. A. in *The Manipulation of Air-Sensitive Compounds*; Wiley-VCH: New York, 1986.

[2] Leatherbarrow, R. J.; Mo, B.; Offermann, D. A.; Sejberg, J. J. P.; Spivey, A. C.; McKendrick, J. E.; Beavil, A. J.; Holdom, M. D.; Sutton, B. J.; Helm, B. A. *J. Org. Chem.* **2012** , *77*, 3197-3214

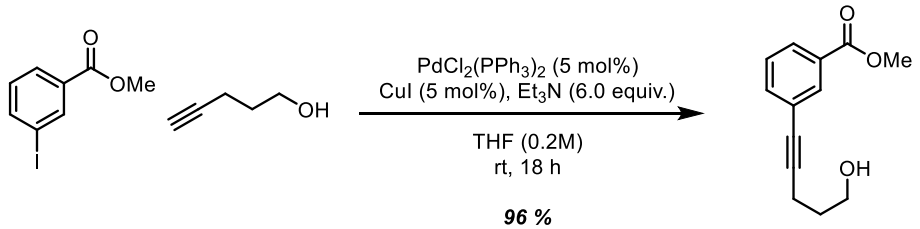
[3] Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem*. **1978**, *43*, 2923-2925.

noted. Signals due to the solvent served as the internal standard ($CHCl_3$: δ 7.27 for ^1H, δ 77.0 for ^{13}C). The acquisition parameters are shown on all spectra. The ^1H NMR chemical shifts and coupling constants were determined assuming first-order behavior. Multiplicity is indicated by one or more of the following: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad); the list of couplings constants (*J*) corresponds to the order of the multiplicity assignment. High resolution mass spectroscopy (HRMS) was done by the Centre régional de spectrométrie de masse at the Département de Chimie, Université de Montréal using an Agilent LC-MSD TOF system with the ESI mode of ionization unless otherwise noted.

SYNTHESIS OF MACROCYCLE PRECURSORS

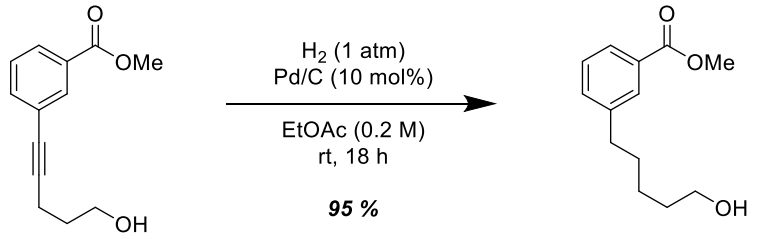


Docosa-10,12-diyne-1,22-diol (S1) $CuCl_2$ (55 mg, 0.41 mmol, 0.25 equiv.) and $Ni(NO_3)_2 \cdot 6H_2O$ (120 mg, 0.413 mmol, 0.25 equiv.) were dissolved in MeOH (15 mL). Then Et_3N (0.69 mL, 5.0 mmol, 3.0 equiv.) and pyridine (0.67 mL, 8.3 mmol, 5.0 equiv.) were added to the solution followed by 9-undecyn-1-ol (277 mg, 1.65 mmol, 1.0 equiv.). The reaction mixture was purged with O_2 and was stirred at 60 °C for 48 h (The reaction mixture was purged O_2 every 12 h). The mixture was then cooled down to room temperature and silica gel was added. The slurry was concentrated under reduced pressure and flash chromatography (30 % EtOAc in hexanes) was performed to afford the desired product (130 mg, 47 %) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.65 (t, *J* = 6.8 Hz, 4H), 2.25 (t, *J* = 6.8 Hz, 4H), 1.60-1.50 (m, 8H), 1.45-1.26 (m, 22H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 77.2, 65.3, 63.1, 32.8, 29.4, 29.0, 28.8, 28.3, 25.73, 25.70, 19.2 ppm; HRMS (ESI+) for $C_{22}H_{39}O_2$ $[M + H]^+$ calculated 335.2945 found: 335.2945.



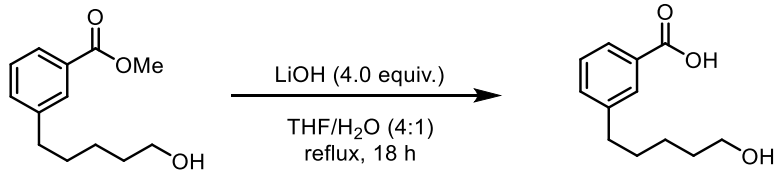
Methyl 3-(5-hydroxypent-1-yn-1-yl)benzoate (S2) Methyl 3-iodobenzoate (1.00 g, 3.82 mmol, 1.0 equiv.) was dissolved in tetrahydrofuran (20 mL, 0.2 M). Then $Pd(PPh_3)_2Cl_2$ (134 mg, 0.191 mmol, 0.05 equiv.) and CuI (36 mg, 0.19 mmol, 0.05 equiv.) were added to the

solution and the reaction mixture was purged under N_2 for 5 min. Triethylamine (3.19 mL, 22.9 mmol, 6.0 equiv.) and the alkyne (0.35 mL, 3.8 mmol, 1.0 equiv.) were added and the reaction mixture was stirred at room temperature for 18 h. Silica gel (~ 5 mL) was added and the slurry was concentrated under reduced pressure and flash chromatography (20-40 % EtOAc in hexanes) was performed to afford the desired product as a colorless oil (796 mg, 96 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (s, 1H), 7.94 (d, *J* = 7.9 Hz, 1H), 7.56 (d, *J* = 7.7 Hz, 1H), 7.36 (dd, *J* = 7.8, 7.7 Hz, 1H), 3.92 (s, 3H), 3.83 (t, *J* = 6.2 Hz, 2H), 2.56 (t, *J* = 7.0 Hz, 2H), 1.91-1.84 (m, 2H), 1.59 (br s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.5, 135.7, 132.7, 130.3, 128.6, 128.3, 124.2, 90.4, 80.1, 61.7, 52.2, 31.3, 15.9 ppm; HRMS (ESI+) for $C_{13}H_{15}O_3$ $[M + H]^+$ calculated: 219.1016 found: 219.1018.



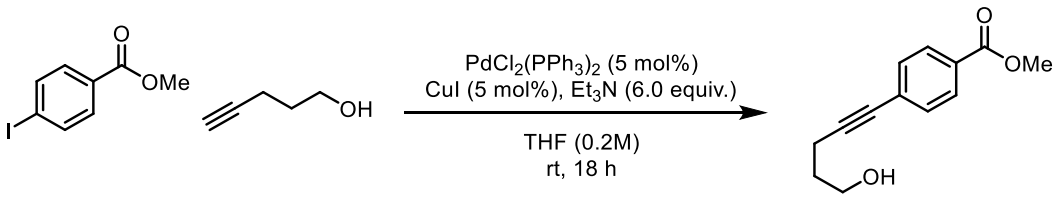
Methyl 3-(5-hydroxypent-1-yl)benzoate (S3) The alkyne (218 mg, 1.00 mmol) was dissolved in ethyl acetate (5 mL) under N_2. Then Pd/C (212 mg, 5% w/w, 0.100 mmol, 0.1 equiv.) was added and the reaction mixture was purged with H_2 for 10 min. A balloon, filled with H_2 and equipped with a syringe, was pierced into the septum and the reaction mixture was stirred at room temperature for 18 h. The reaction mixture was passed through a short pad of Celite® after being purged by bubbling with N_2 for 10 min and concentrated under reduced pressure. Purification by flash chromatography (30% EtOAc in hexanes) was performed to afford the desired product as a colorless oil (212 mg, 95 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89-7.88 (m, 2H), 7.39-7.37 (m, 2H), 3.94 (s, 3H), 3.67 (t, *J* = 6.5 Hz, 2H), 2.70 (t, *J* = 8.6 Hz, 2H), 1.74-1.60 (m, 4H), 1.46-1.41 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.3, 142.8, 133.0, 130.1,

129.5, 128.3, 127.0, 62.8, 52.0, 35.6, 32.6, 31.1, 25.3 ppm; HRMS (ESI+) for $C_{13}H_{18}O_3Na$ [M + Na]$^+$ calculated: 245.1148 found: 245.1146.



99 %

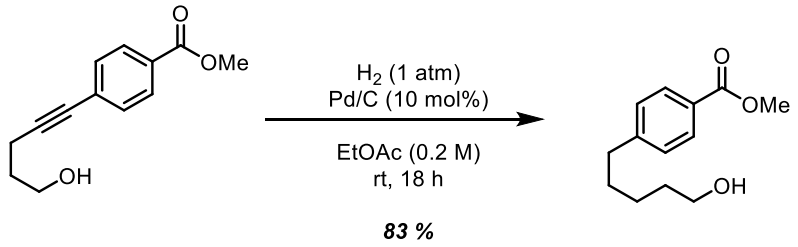
3-(5-Hydroxypent-1-yl)benzoic acid (S4) Methyl 3-(5-hydroxypent-1-yl)benzoate (200 mg, 0.901 mmol, 1.0 equiv.) was dissolved in tetrahydrofuran (8 mL). Then LiOH (87 mg, 3.6 mmol, 4.0 equiv.) was added as an aqueous solution (2 mL). The reaction mixture was stirred at 65 ºC for 18 h. The reaction mixture was cooled to room temperature and HCl (1 M) was added until the pH was neutralized (pH = 7). Extraction with EtOAc (3 X 5 mL) was performed and the combined organic phases were washed with brine (15 mL). The organic phase was dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford the desired product as a white solid (187 mg, 99 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95-7.94 (m, 2H), 7.44-7.36 (m, 2H), 3.67 (t, *J* = 6.6 Hz, 2H), 2.71 (t, *J* = 7.5 Hz, 2 H), 1.73-1.59 (m, 4H), 1.46-1.38 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.5, 142.9, 133.7, 129.9, 129.5, 128.4, 127.6, 62.7, 35.6, 32.3, 31.0, 25.3 ppm; HRMS (ESI+) for $C_{12}H_{16}O_3Na$ [M + Na]$^+$ calculated: 231.0992 found: 231.0986.



68 %

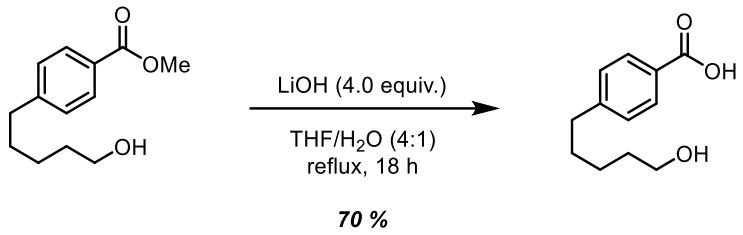
Methyl 4-(5-hydroxypent-1-yn-1-yl)benzoate (S5) Methyl 3-iodobenzoate (1.00 g, 3.82 mmol, 1.0 equiv.) was dissolved in tetrahydrofuran (20 mL, 0.2 M). Then $Pd(PPh_3)_2Cl_2$ (134

mg, 0.191 mmol, 0.05 equiv.) and CuI (36 mg, 0.19 mmol, 0.05 equiv.) were added to the solution and the reaction mixture was purged under N_2 for 5 min. Triethylamine (3.19 mL, 22.9 mmol, 6.0 equiv.) and the alkyne (0.35 mL, 3.8 mmol, 1.0 equiv.) were added and the reaction mixture was stirred at room temperature for 18 h. Silica gel (~ 5 mL) was added and the slurry was concentrated under reduced pressure and flash chromatography (20-40 % EtOAc in hexanes) was performed to afford the desired product as a white solid (563 mg, 68 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, *J* = 8.6 Hz, 2H), 7.45 (d, *J* = 8.4 Hz, 2H), 3.92 (s, 3H), 3.84 (m, 2H), 2.58 (t, *J* = 7.0 Hz, 2H), 1.91-1.87 (m, 2H), 1.50 (br s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.6, 131.5, 129.4, 129.0, 128.6, 92.8, 80.6, 61.7, 52.2, 31.2, 16.1 ppm; HRMS (ESI+) for $C_{13}H_{15}O_3$ $[M + H]^+$ calculated: 219.1016 found: 219.1018.



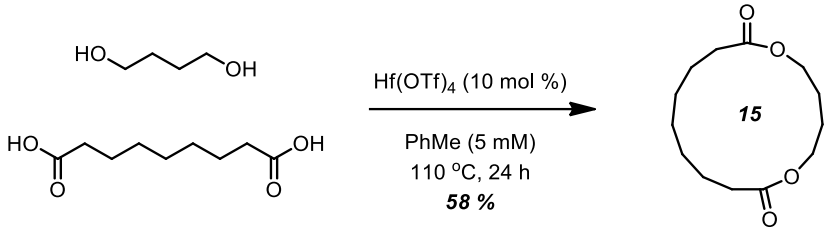
Methyl 4-(5-hydroxypent-1-yl)benzoate (S6) The alkyne (250 mg, 1.15 mmol, 1.00 equiv.) was dissolved in ethyl acetate (6 mL) under N_2. Then Pd/C (243 mg, 5% w/w, 0.115 mmol, 0.1 equiv.) was added and the reaction mixture was purged with H_2 for 10 min. A balloon filled with H_2 and equipped with a syringe and a needle and the needle was pierced into the septum and the reaction mixture was stirred at room temperature for 18 h. The reaction mixture was passed through a short pad of Celite® after being purged by bubbling with N_2 for 10 min and concentrated under reduced pressure. Purification by flash chromatography (30% EtOAc in hexanes) was performed to afford the desired product as a white solid (212 mg, 95 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, *J* = 8.2 Hz, 2H), 7.24 (d, *J* = 8.0 Hz, 2H), 3.90 (s, 3H), 3.64 (t, *J*

= 6.6 Hz, 2H), 2.68 (t, *J* = 7.7 Hz, 2H), 1.72-1.57 (m, 4H), 1.45-1.37 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.2, 148.1, 129.6, 128.4, 127.7, 62.8, 51.9, 35.9, 32.5, 30.9, 25.4 ppm; HRMS (ESI+) for $C_{13}H_{19}O_3$ $[M + H]^+$ calculated: 223.1329 found: 223.1321.

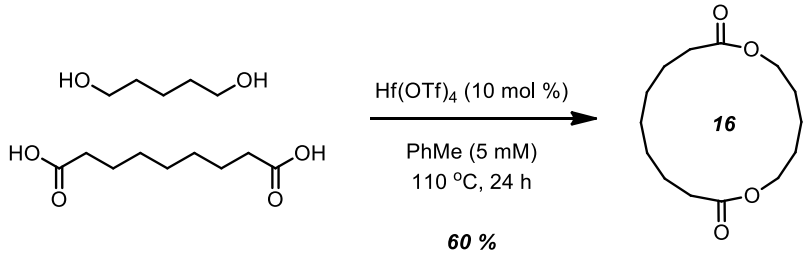


4-(5-Hydroxypent-1-yl)benzoic acid (S7) Methyl 4-(5-hydroxypent-1-yl)benzoate (200 mg, 0.900 mmol, 1.0 equiv.) was dissolved in tetrahydrofuran (7.2 mL). Then LiOH (86 mg, 3.6 mmol, 4.0 equiv.) was added as an aqueous solution (1.8 mL). The reaction mixture was stirred at 65 ºC for 18 h. The reaction mixture was cooled to room temperature and HCl (1 M) was added until the pH of the mixture was neutralized (pH = 7). Extraction with EtOAc (3 X 5 mL) was performed and the combined organic phases were washed with brine (15 mL). The organic phase was dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford the desired product as a white solid (130 mg, 70 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, *J* = 8.1 Hz, 2H), 7.29 (d, *J* = 8.2 Hz, 2H), 3.67 (t, *J* = 6.6 Hz, 2H), 2.71 (t, *J* = 7.5 Hz, 2H), 1.72-1.60 (m, 4H), 1.47-1.40 (m, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.2, 149.1, 130.3, 128.6, 126.8, 62.8, 36.0, 32.5, 30.9, 25.4 ppm; HRMS (ESI+) for $C_{12}H_{16}O_3Na$ $[M + Na]^+$ calculated: 231.0992 found: 231.0988.

SYNTHESIS OF MACROCYCLES

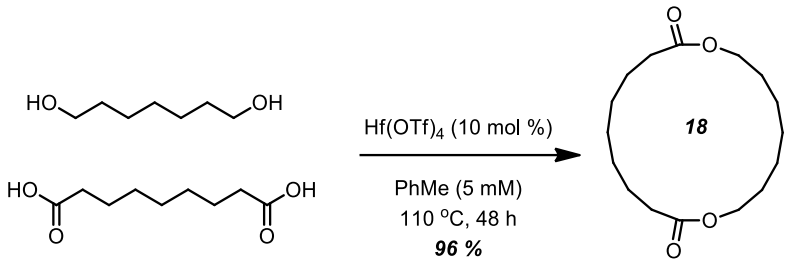


1,6-Dioxapentadecane-7,15-dione (4): 1,4-Butanediol (0.017 mL, 0.20 mmol, 1.0 equiv.) and 1,9-nonanedioic acid (38 mg, 0.20 mmol, 1.0 equiv.) were dissolved in toluene (40 mL, 5 mM). Then $Hf(OTf)_4$ (15.5 mg, 0.0200 mmol, 0.1equiv.) was added to the solution and the reaction mixture heated to 110 °C. The reaction mixture was stirred at this temperature for 48 h. After cooling to room temperature, silica gel (~ 1 mL) was added and the slurry was concentrated under reduced pressure and purified by flash chromatography (5 % EtOAc in hexanes) to afford the desired product as a white solid (28 mg, 58 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.21 (m, 4H), 2.34 (m, 4H), 1.77 (m, 4H), 1.64 (m, 4H), 1.37-1.34 (m 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.7, 63.6, 34.6, 27.8, 27.5, 26.5, 24.6 ppm; HRMS (ESI+) for $C_{13}H_{23}O_4$ $[M + H]^+$ calculated: 243.1591 found: 243.1599.

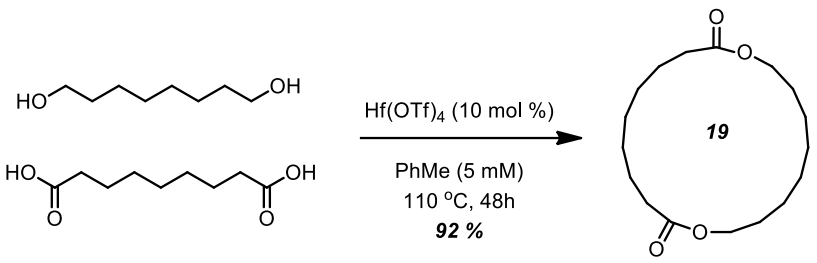


1,7-Dioxahexadecane-8,16-dione (5): 1,4-Pentanediol (0.021 mL, 0.20 mmol, 1.0 equiv.) and 1,9-nonanedioic acid (38 mg, 0.20 mmol, 1.0 equiv.) were dissolved in toluene (40 mL, 5 mM). Then $Hf(OTf)_4$ (15.5 mg, 0.0200 mmol, 0.1equiv.) was added to the solution and the reaction mixture heated to 110 °C. The reaction mixture was stirred at this temperature for 48 h. After cooling to room temperature, silica gel (~ 1 mL) was added and the slurry was concentrated

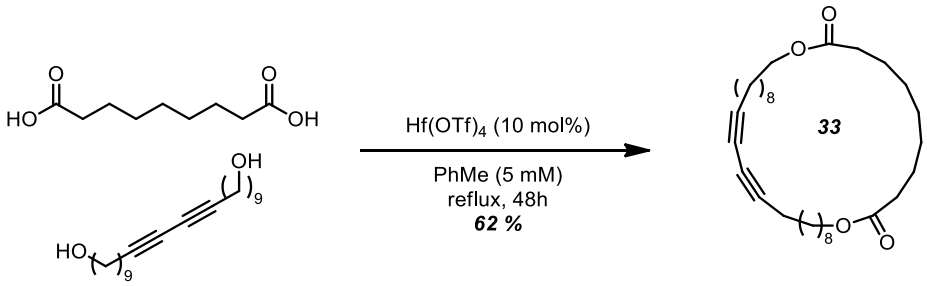
under reduced pressure and purified by flash chromatography (5 % EtOAc in hexanes) to afford the desired product as a white solid (30 mg, 60 %). ^{1}H NMR (400MHz, $CDCl_3$) δ 4.14 (t, *J* = 5.4 Hz, 4H), 2.36 (t, *J* = 6.5 Hz, 4H), 1.71-1.62 (m, 8H), 1.57-1.48 (m, 2H), 1.37-1.30 (m, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.8, 64.1, 34.3, 28.7, 28.3, 27.7, 24.9, 23.9 ppm; HRMS (ESI+) for $C_{14}H_{25}O_4$ $[M + H]^+$ calculated: 257.1756 found: 257.1747.



1,9-Dioxaoctadecane-10,18-dione (6): 1,7-Heptanediol (0.030 mL, 0.20 mmol, 1.0 equiv.) and 1,9-nonanedioic acid (38 mg, 0.20 mmol, 1.0 equiv.) were dissolved in toluene (40 mL, 5 mM). Then $Hf(OTf)_4$ (15.5 mg, 0.0200 mmol, 0.1 equiv.) was added to the solution and the reaction mixture heated to 110 ºC. The reaction mixture was stirred at this temperature for 48 h. After cooling to room temperature, silica gel (~ 1 mL) was added and the slurry was concentrated under reduced pressure and purified by flash chromatography (5 % EtOAc in hexanes) to afford the desired product as a white solid (55 mg, 96 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.13 (t, *J* = 5.6 Hz, 4H), 2.32 (t, *J* = 6.4 Hz, 4H), 1.65-1.59 (m, 8H), 1.41-1.30 (m, 12H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.8, 63.7, 34.9, 29.2, 28.8, 28.4, 28.0, 25.6, 25.5 ppm; HRMS (ESI+) for $C_{16}H_{29}O_4$ $[M + H]^+$ calculated: 285.2060 found: 285.2051.

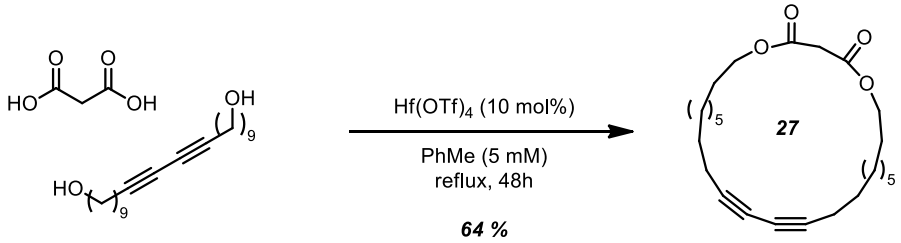


1,10-Dioxanonadecane-11,19-dione (3): 1,8-Octanediol (29, 0.20 mmol, 1.0 equiv.) and 1,9-nonanedioic acid (38 mg, 0.20 mmol 1.0 equiv.) were dissolved in toluene (40 mL, 5 mM). Then $Hf(OTf)_4$ (7.8 mg, 0.010 mmol, 0.1 equiv.) was added to the solution and the reaction mixture heated to 110 °C. The reaction mixture was stirred at this temperature for 48 h. After cooling to room temperature, silica gel (~ 1 mL) was added and the slurry was concentrated under reduced pressure and purified by flash chromatography (5 % EtOAc in hexanes) to the desired product as a white solid (55 mg, 92 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.12 (t, J = 6.0 Hz, 4H), 2.32 (t, J = 6.8 Hz, 4H), 1.65-1.60 (m, 8H), 1.40-1.30 (m, 14H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.0, 64.3, 34.8, 29.3, 29.1, 28.9, 28.7, 26., 25.3 ppm; HRMS (ESI+) for $C_{17}H_{31}O_4$ $[M + H]^+$ calculated: 299.2217 found: 299.2226.

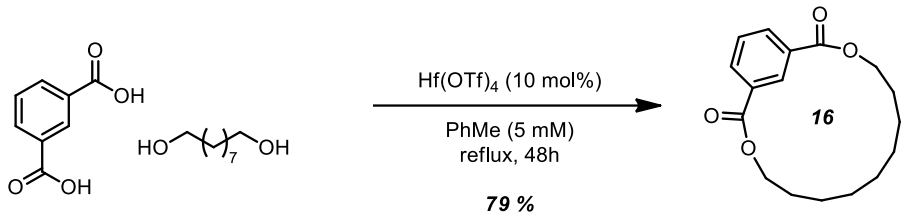


1,11-Dioxacyclotritriaconta-21,23-diyne-2,10-dione (7) The diol **S1** (33 mg, 0.10 mmol, 1.0 eq) and the diacid (19 mg, 0.10 mmol 1.0 eq) were dissolved in toluene (20 mL, 5 mM). Then $Hf(OTf)_4$ (7.8 mg, 0.010 mmol, 0.1 equiv.) was added to the solution and the reaction mixture heated to 110 °C. The reaction mixture was stirred at this temperature for 48 h. After cooling to room temperature, silica gel (~ 2 mL) was added and the slurry was concentrated under reduced

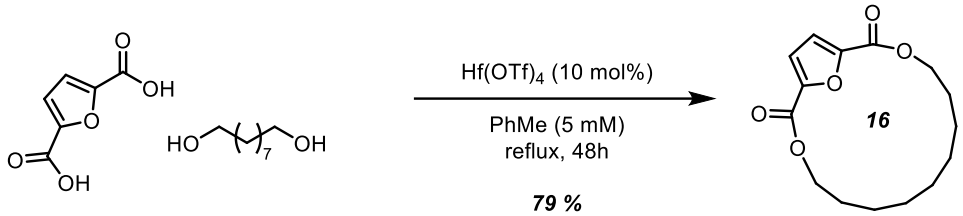
pressure and purified by flash chromatography (5 % EtOAc in hexanes) to afford the desired product as a yellow solid (30 mg, 62 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.08 (t, *J* = 6.0 Hz, 4H), 2.30 (t, *J* =7.4 Hz, 4H), 2.26 (t, *J* =6.5 Hz, 4H), 1.65-1.60 (m, 8H), 1.55-1.48 (m, 4H), 1.40-1.30 (m, 26H) ppm ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.9, 77.4, 65.4, 64.3, 34.4, 29.1, 29.0, 28.9, 28.7, 28.6, 28.5, 28.0, 25.9, 24.9, 19.1 ppm; HRMS (ESI+) for $C_{31}H_{50}O_4Na$ $[M + Na]^+$ calculated 509.3601 found: 509.3596.



1,5-Dioxacycloheptacosa-15,17-diyne-2,4-dione (8) The diol **S1** (33 mg, 0.10 mmol, 1.0 equiv.) and the diacid (11 mg, 0.10 mmol 1.0 equiv.) were dissolved in toluene (20 mL, 5 mM). Then $Hf(OTf)_4$ (7.8 mg, 0.010 mmol, 0.1 equiv.) was added to the solution and the reaction mixture heated to 110 ºC. The reaction mixture was stirred at this temperature for 48 h. After cooling to room temperature, silica gel (~ 2 mL) was added and the slurry was concentrated under reduced pressure and purified by flash chromatography (5 % EtOAc in hexanes) to afford the desired product as a white solid (26 mg, 64 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.15 (t, *J* = 6.8 Hz, 4H), 3.38 (s, 2H), 2.28 (t, *J* =6.0 Hz, 4H), 2.26 (t, *J* =6.5 Hz, 4H), 1.70-1.60 (m, 4H), 1.53-1.30 (m, 24H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.6, 77.4, 65.6, 41.8, 29.2, 28.8, 28.7, 27.8, 25.8, 19.1 ppm; HRMS (ESI+) for $C_{25}H_{38}O_4Na$ $[M + Na]^+$ calculated 425.2662 found: 425.2672.

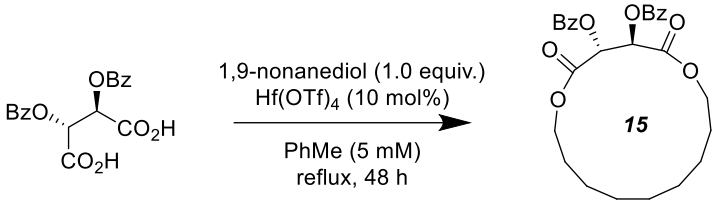


3,13-Dioxa-1(1,13)-benzenacyclotetradecaphane-2,14-dione (9) 1,9-Nonanediol (16 mg, 0.1 mmol, 1.0 equiv.) and isophthalic acid (17 mg, 0.1 mmol 1.0 equiv.) were dissolved in toluene (20 mL, 5 mM). Then $Hf(OTf)_4$ (7.8 mg, 0.01 mmol, 0.1 equiv.) was added to the solution and the reaction mixture heated to 110 ºC. The reaction mixture was stirred at this temperature for 48 h. After cooling to room temperature, silica gel (~ 2 mL) was added and the slurry was concentrated under reduced pressure and purified by flash chromatography (10 % EtOAc in hexanes) to afford the desired product as a white solid (23 mg, 79 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.76 (s, 1H), 8.26-8.23 (m, 2H), 7.57 (t, J = 7.8 Hz, 1H), 4.39 (t, J = 5.2 Hz, 4H), 1.82-1.20 (m, 14H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.5, 133.7, 130.91, 130.89, 128.8, 65.3, 28.9, 28.4, 28.1, 26.2 ppm; HRMS (ESI+) for $C_{17}H_{23}O_4$ $[M + H]^+$ calculated 291.1591 found: 291.1592.

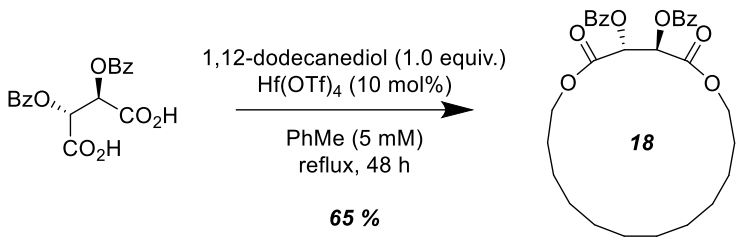


3,13-Dioxa-1(2,5)-furanacyclotetradecaphane-2,14-dione (10) 1,9-Nonanediol (16 mg, 0.1 mmol, 1.0 equiv.) and 2,5-furandicarboxylic acid (15 mg, 0.10 mmol 1.0 equiv.) were dissolved in toluene (20 mL, 5 mM). Then $Hf(OTf)_4$ (7.8 mg, 0.010 mmol, 0.1 equiv.) was added to the solution and the reaction mixture heated to 110 ºC. The reaction mixture was stirred at this temperature for 48 h. After cooling to room temperature, silica gel (~ 2 mL) was added and the slurry was concentrated under reduced pressure and purified by flash chromatography (10 %

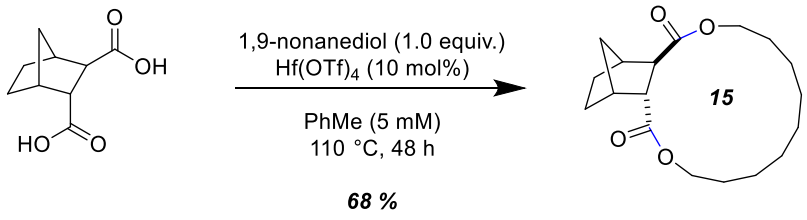
EtOAc in hexanes) to afford the desired product as a white solid (22 mg, 79 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (s, 2H), 4.37 (t, *J* = 5.5 Hz, 4H), 1.80-1.75 (m, 4H), 1.63-1.35 (m, 10H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.1, 146.5, 118.0, 65.8, 29.1, 28.4, 27.7, 26.2 ppm; HRMS (ESI+) for $C_{15}H_{20}O_5Na$ $[M + Na]^+$ calculated 303.1203 found: 303.1205.



(3R, 4R)-2,5-Dioxo-1,6-dioxacyclopentadecane-3,4-diyl dibenzoate (11) 1,9-Nonanediol (32 mg, 0.20 mmol, 1.0 equiv.) and dibenzoyl-L-tartaric acid (71 mg, 0.20 mmol 1.0 equiv.) were dissolved in toluene (40 mL, 5 mM). Then $Hf(OTf)_4$ (15.5 mg, 0.020 mmol, 0.1 equiv.) was added to the solution and the reaction mixture heated to 110 ºC. The reaction mixture was stirred at this temperature for 48 h. After cooling to room temperature, silica gel (~ 2 mL) was added and the slurry was concentrated under reduced pressure and purified by flash chromatography (10-20 % EtOAc in hexanes) to afford the desired product as a colorless oil (56 mg, 58 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, *J* = 7.9 Hz, 4H), 7.57 (t, *J* = 7.2 Hz, 2H), 7.43 (t, *J* = 7.6 Hz, 4H), 5.88 (s, 2H), 4.36-4.32 (m, 4H), 1.75-1.65 (m, 4H), 1.43-1.38 (m, 10H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.6, 165.1, 133.7, 130.1, 128.6, 128.5, 70.6, 65.6, 27.8, 26.4, 25.6, 23.5 ppm; HRMS (ESI+) for $C_{30}H_{36}O_8Na$ $[M + Na]^+$ calculated 547.2302 found: 547.2322.

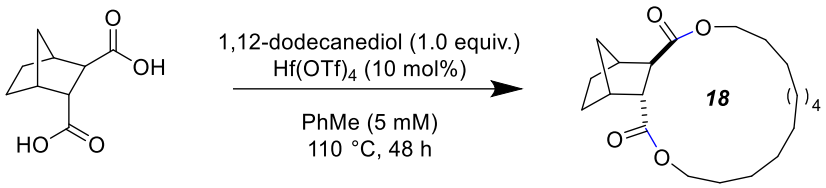


(3R, 4R)-2,5-Dioxo-1,6-dioxacyclooctadecane-3,4-diyl dibenzoate (12) 1,12-Dodecanediol (40 mg, 0.2 mmol, 1.0 equiv.) and dibenzoyl-L-tartaric acid (71 mg, 0.20 mmol 1.0 equiv.) were dissolved in toluene (40 mL, 5 mM). Then $Hf(OTf)_4$ (15.5 mg, 0.020 mmol, 0.1 equiv.) was added to the solution and the reaction mixture heated to 110 ºC. The reaction mixture was stirred at this temperature for 48 h. After cooling to room temperature, silica gel (~ 2 mL) was added and the slurry was concentrated under reduced pressure and purified by flash chromatography (10-20 % EtOAc in hexanes) to afford the desired product as a colorless oil (68 mg, 65 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (d, J = 7.8 Hz, 4H), 7.62 (t, J = 7.4 Hz, 2H), 7.49 (t, J = 7.7 Hz, 4H), 5.95 (s, 2H), 4.40-4.35 (m, 2H), 4.16-4.10 (m, 4H), 1.73-1.64 (m, 2H), 1.52-1.43 (m, 8H), 1.43-1.38 (m, 10H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.5, 165.3, 133.7, 130.2, 128.7, 128.5, 71.4, 66.9, 28.5, 27.9, 27.8, 27.4, 25.9 ppm; HRMS (ESI+) for $C_{27}H_{30}O_8Na$ $[M + Na]^+$ calculated 505.1833 found: 3505.1848.

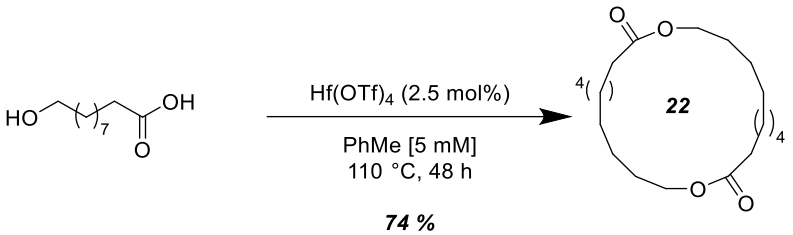


Nonane-1,9-diyl norbornene-2-*endo*,3-*exo*-dicarboxylate (13) 1,9-Nonanediol (32 mg, 0.20 mmol, 1.0 equiv.) and norbornane-2-*endo*,3-*exo*-dicarboxylic acid (37 mg, 0.20 mmol 1.0 equiv.) were dissolved in toluene (40 mL, 5 mM). Then $Hf(OTf)_4$ (15.5 mg, 0.0200 mmol, 0.1 equiv.) was added to the solution and the reaction mixture heated to 110 ºC. The reaction mixture

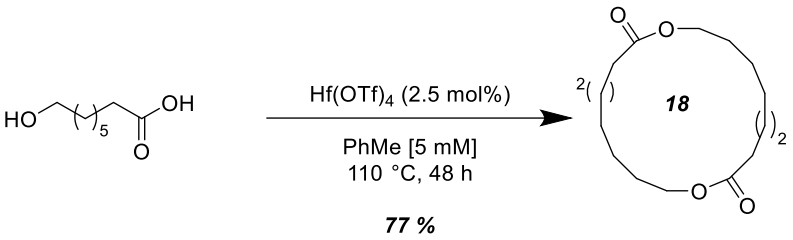
was stirred at this temperature for 48 h. After cooling to room temperature, silica gel (~ 2 mL) was added and the slurry was concentrated under reduced pressure and purified by flash chromatography (5% Et_2O in hexanes) to afford the desired product as a colorless oil (42 mg, 68 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.42 (ddd, *J* = 12, 9.1, 3.0 Hz, 1H), 4.33 (ddd, *J* = 12, 8.4, 3.0 Hz, 1H), 3.98-3.89 (m, 2H), 3.05-3.01 (m, 1H), 2.75 (dd, *J* = 6.1, 1.4 Hz, 1H), 2.63-2.60 (m, 2H), 1.78-1.52 (m, 6H), 1.50-1.28 (m, 14H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.7, 173.2, 63.8, 63.7, 51.1, 49.2, 40.5, 39.8, 38.7, 29.0, 28.0, 27.8, 26.7, 25.9, 25.6, 23.9, 23.7, 23.6 ppm; HRMS (ESI+) for $C_{18}H_{29}O_4$ $[M + H]^+$ calculated 309.2060 found: 309.2064.



Dodecane-1,12-diyl norbornene-2-*endo*,3-*exo*-dicarboxylate (14) 1,12-Dodecanediol (40 mg, 0.20 mmol, 1.0 equiv.) and norbornane-2-*endo*,3-*exo*-dicarboxylic acid (37 mg, 0.20 mmol 1.0 equiv.) were dissolved in toluene (40 mL, 5 mM). Then $Hf(OTf)_4$ (15.5 mg, 0.0200 mmol, 0.1 equiv.) was added to the solution and the reaction mixture heated to 110 ºC. The reaction mixture was stirred at this temperature for 48 h. After cooling down to room temperature, silica gel (~ 2 mL) was added and the slurry was concentrated under reduced pressure and purified by flash chromatography (5% Et_2O in hexanes) to afford the desired product as a colorless oil (42 mg, 68 %).^{1}H NMR (400 MHz, $CDCl_3$) δ 4.35 (ddd, *J* = 18, 8.2, 4.2 Hz, 1H), 4.27 (ddd, *J* = 18, 8.2, 4.2 Hz, 1H), 3.98-3.93 (m, 2H), 3.15-3.12 (m, 1H), 2.83 (d, *J* = 5.3 Hz, 1H), 2.64-2.60 (m, 2H), 1.70-1.57 (m, 6H), 1.48-1.27 (m, 20H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.7, 173.4, 64.7, 64.5, 50.1, 48.9, 41.4, 40.4, 38.3, 28.7, 28.5, 28.4, 28.1, 27.9, 27.6, 27.2, 27.0, 26.9, 25.5, 25.3, 24.2 ppm; HRMS (ESI+) for $C_{21}H_{34}O_4Na$ $[M + Na]^+$ calculated 373.2349 found: 373.2353.

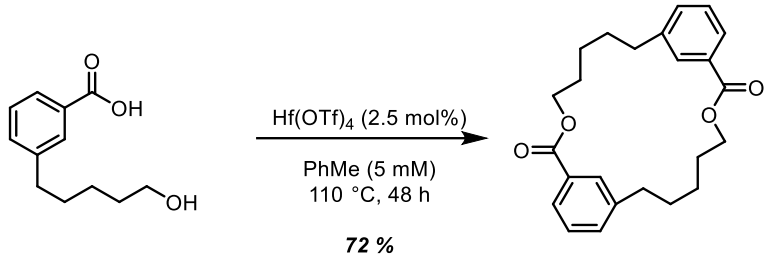


1,12-Dioxacyclodocosane-2,13-dione (16) 10-Hydroxydecanoic acid (38.8 mg, 0.200 mmol 1.0 equiv.) was dissolved in toluene (40 mL, 5 mM). Then $Hf(OTf)_4$ (3.9 mg, 0.0050 mmol, 0.025 equiv.) was added to the solution and the reaction mixture heated to 110 ºC. The reaction mixture was stirred at this temperature for 48 h. After cooling to room temperature, silica gel (~ 2 mL) was added and the slurry was concentrated under reduced pressure and purified by flash chromatography (10 % EtOAc in hexanes) to afford the desired product as a white solid (26 mg, 74 %).^{1}H NMR (400 MHz, $CDCl_3$) δ 4.12 (t, *J* = 5.9 Hz, 4H), 2.32 (t, *J* = 7.0 Hz, 4H), 1.65-1.60 (m, 4H), 1.40-1.28 (m, 20H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.9, 64.0, 34.8, 29.4, 29.1, 29.0, 28.9, 28.6, 26.0, 25.4 ppm; HRMS (ESI+) for$C_{20}H_{37}O_4$ $[M + H]^+$ calculated: 341.2686 found: 341.2700.

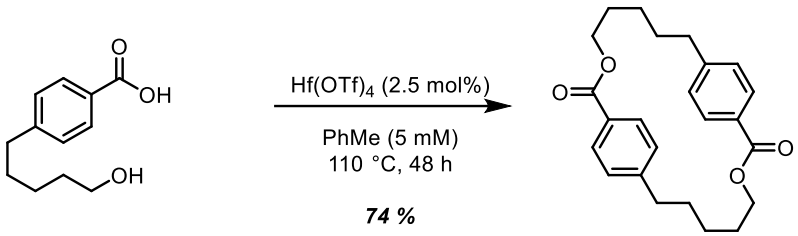


1,10-Dioxacyclooctadecane-2,11-dione (17) 8-Hydroxydecanoic acid (32.0 mg, 0.200 mmol 1.0 equiv.) was dissolved in toluene (40 mL, 5 mM). Then $Hf(OTf)_4$ (3.9 mg, 0.0050 mmol, 0.025 equiv.) was added to the solution and the reaction mixture heated to 110 ºC. The reaction mixture was stirred at this temperature for 48 h. After cooling to room temperature, silica gel (~ 2 mL) was added and the slurry was concentrated under reduced pressure and purified by flash chromatography (10 % EtOAc in hexanes) to afford the desired product as a white solid (22 mg,

77 %).[1]H NMR (400 MHz, $CDCl_3$) δ 4.12 (t, J = 5.9 Hz, 4H), 2.32 (t, J = 6.9 Hz, 4H), 1.67-1.57 (m, 8 H), 1.45-1.30 (m, 12 H) ppm; [13]C NMR (100 MHz, $CDCl_3$) δ 173.7, 63.8, 34.9, 28.7, 28.60, 28.56, 25.7, 25.2 ppm; HRMS (ESI+) for $C_{16}H_{29}O_4$ $[M + H]^+$ calculated: 285.2060 found: 285.2069.



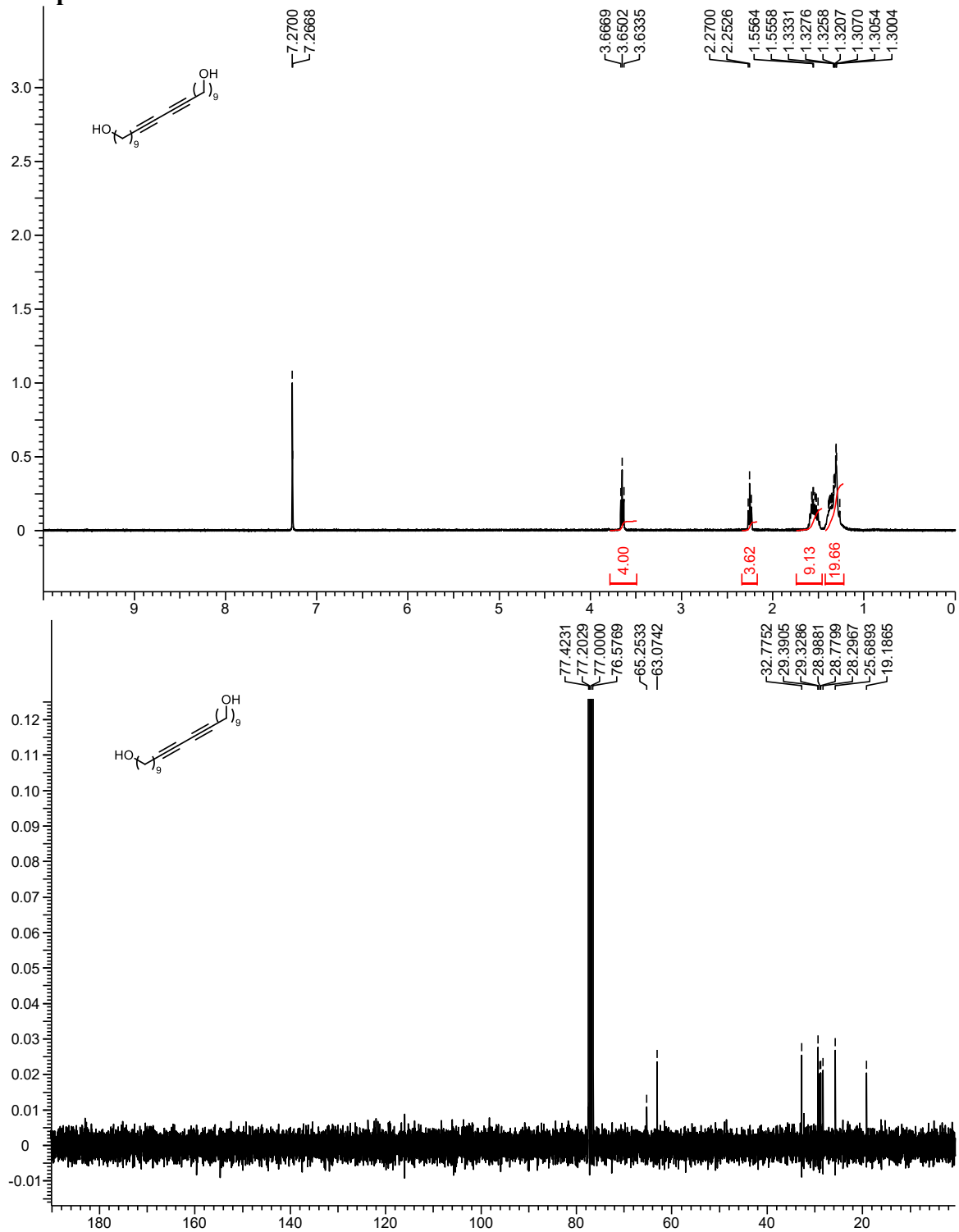
3,11-Dioxa-1,9(1,3)-dibenzenacyclohexadecaphane-2,10-dione (18) The hydroxyacid (67 mg, 0.32 mmol 1.0 equiv.) was dissolved in toluene (60 mL, 5 mM). Then $Hf(OTf)_4$ (6.2 mg, 0.0080 mmol, 0.025 equiv.) was added to the solution and the reaction mixture heated to 110 ºC. The reaction mixture was stirred at this temperature for 48 h. After cooling to room temperature, silica gel (~ 2 mL) was added and the slurry was concentrated under reduced pressure and purified by flash chromatography (10 % EtOAc in hexanes) to afford the desired product as a white solid (44 mg, 72 %).[1]H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, *J* = 7.0 Hz, 2H), 7.70 (s, 2 H), 7.35-7.30 (m, 4H), 4.32 (t, *J* = 5.3 Hz, 4H), 2.69 (t, *J* = 6.7 Hz, 4H), 1.77-1.68 (m, 8H), 1.43-1.40 (m, 4H) ppm; [13]C NMR (100 MHz, $CDCl_3$) δ 166.7, 142.3, 133.1, 130.2, 129.4, 128.3, 127.2, 64.7, 35.8, 30.4, 28.4, 25.5 ppm; HRMS (ESI+) for $C_{24}H_{28}O_4$ $[M + H]^+$ calculated: 381.2060 found: 381.2049.



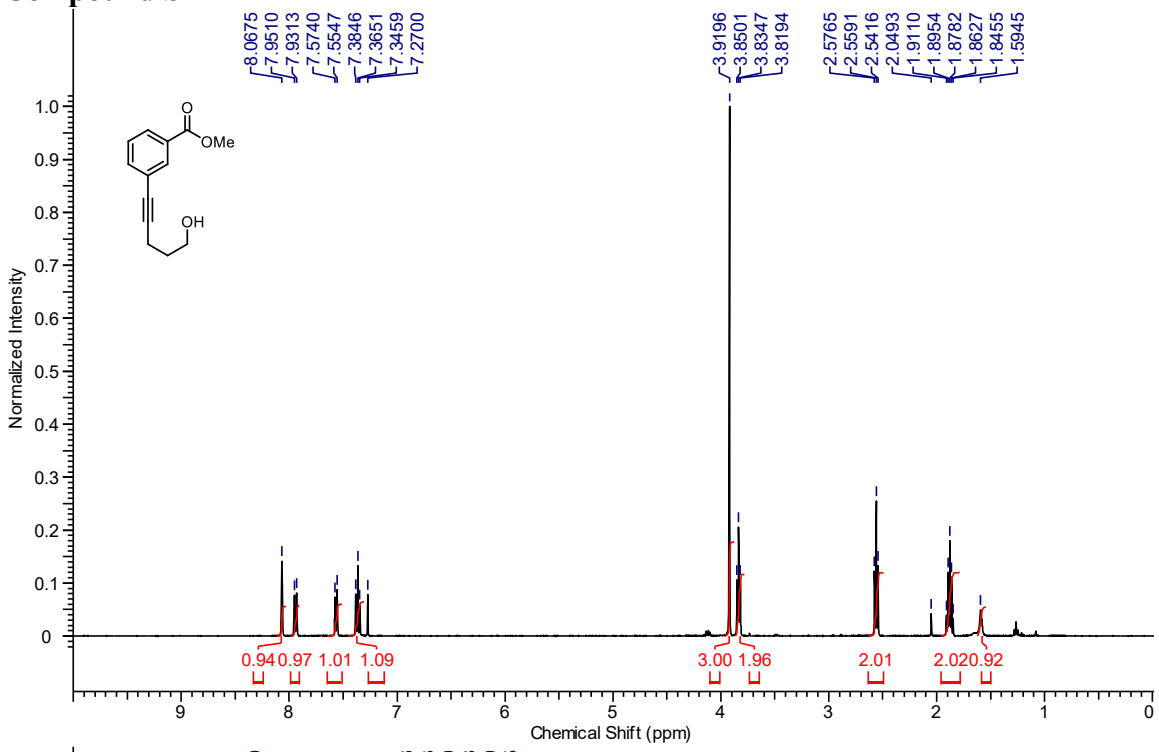
3,11-Dioxa-1,9(1,4)-dibenzenacyclohexadecaphane-2,10-dione (19) The hydroxyacid (42 mg, 0.20 mmol 1.0 equiv.) was dissolved in toluene (40 mL, 5 mM). Then $Hf(OTf)_4$ (3.9 mg, 0.0050mmol, 0.025 equiv.) was added to the solution and the reaction mixture heated to 110 ºC. The reaction mixture was stirred at this temperature for 48 h. After cooling to room temperature, silica gel (~ 2 mL) was added and the slurry was concentrated under reduced pressure and purified by flash chromatography (10 % EtOAc in hexanes) to afford the desired product as a white solid (28 mg, 74 %).^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8.3 Hz, 4H), 7.15 (d, *J* = 8.2 Hz, 4H), 4.35 (t, *J* = 5.3 Hz, 4H), 2.74 (t, *J* = 6.0 Hz, 4H), 1.80-1.70 (m, 8 H), 1.37-1.32 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.5, 147.0, 129.4, 128.7, 127.8, 63.5, 34.1, 28.4, 27.7, 22.9 ppm; HRMS (ESI+) for $C_{24}H_{28}O_4$ $[M + H]^+$ calculated: 381.2060 found: 381.2061.

SPECTRAL DATA

Compound S1



Compound S2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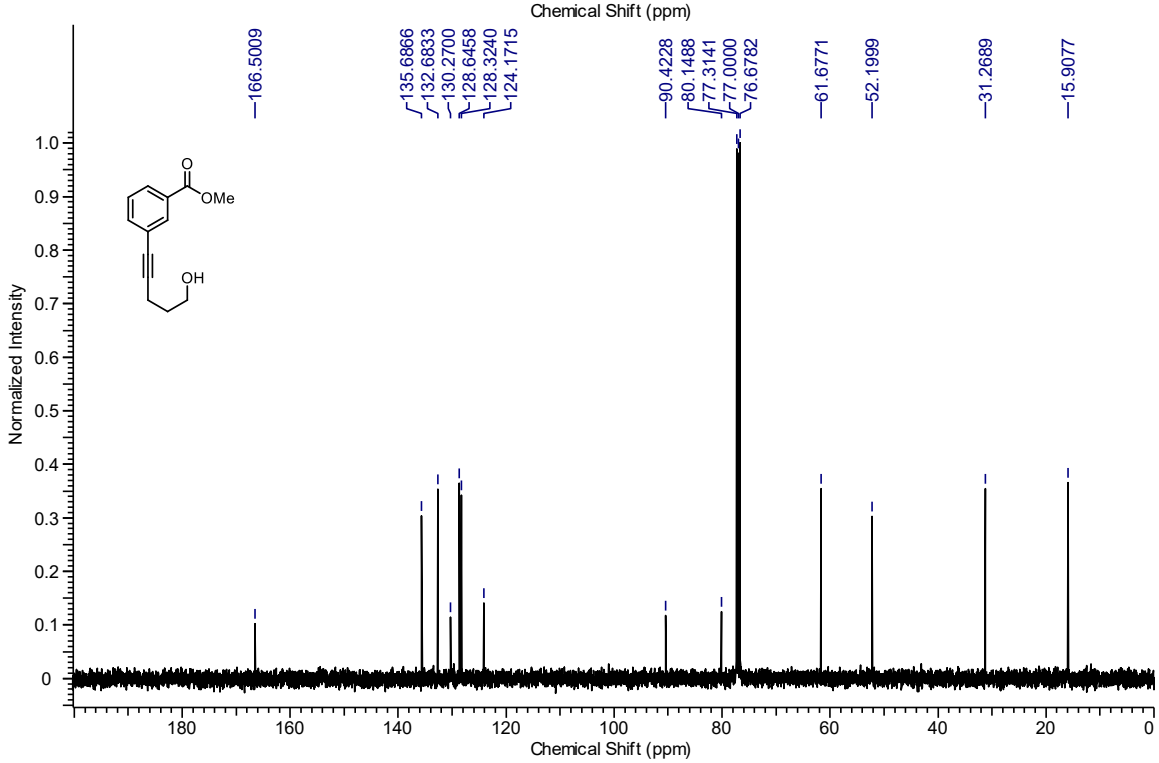
3.8347
3.8194
2.5765
2.5591
2.5416
2.0493
1.9110
1.8954
1.8782
1.8627
1.8455
1.5945
O
OMe
OH
0.94 0.97 1.01 1.09
3.00 1.96
2.01
2.02 0.92
Normalized Intensity
Chemical Shift (ppm)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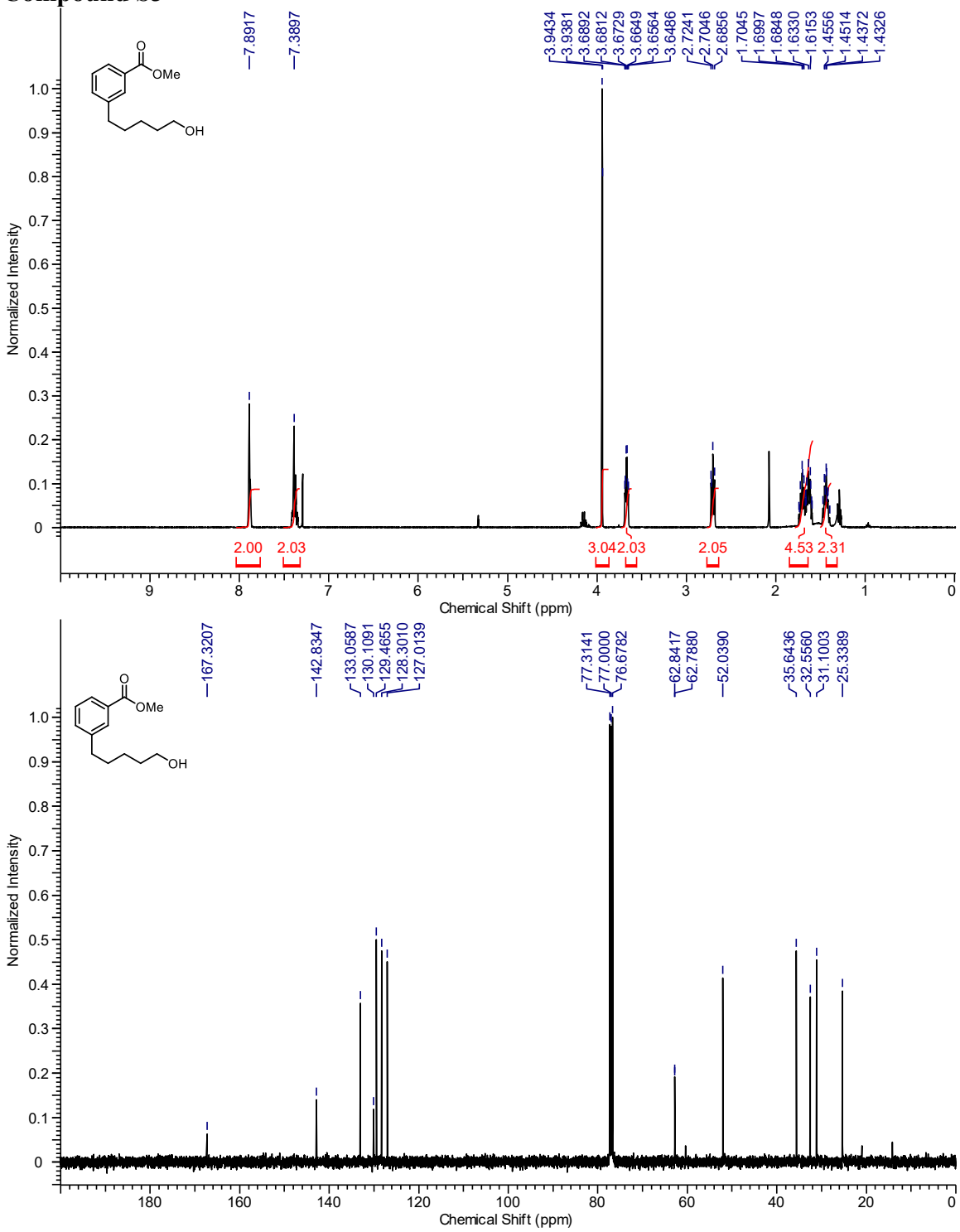
128.6458
128.3240
124.1715
90.4228
80.1488
77.3141
77.0000
76.6782
61.6771
52.1999
31.2689
15.9077
O
OMe
OH
Normalized Intensity
Chemical Shift (ppm)

Compound S3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3.9434
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3.6729
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3.6564
3.6486
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2.7046
2.6856
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1.6997
1.6848
1.6330
1.6153
1.4556
1.4514
1.4372
1.4326
OMe
OH
2.00
2.03
3.04
2.03
2.05
4.53
2.31
Normalized Intensity
Chemical Shift (ppm)
167.3207
142.8347
133.0587
130.1091
129.4655
128.3010
127.0139
77.3141
77.0000
76.6782
62.8417
62.7880
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32.5560
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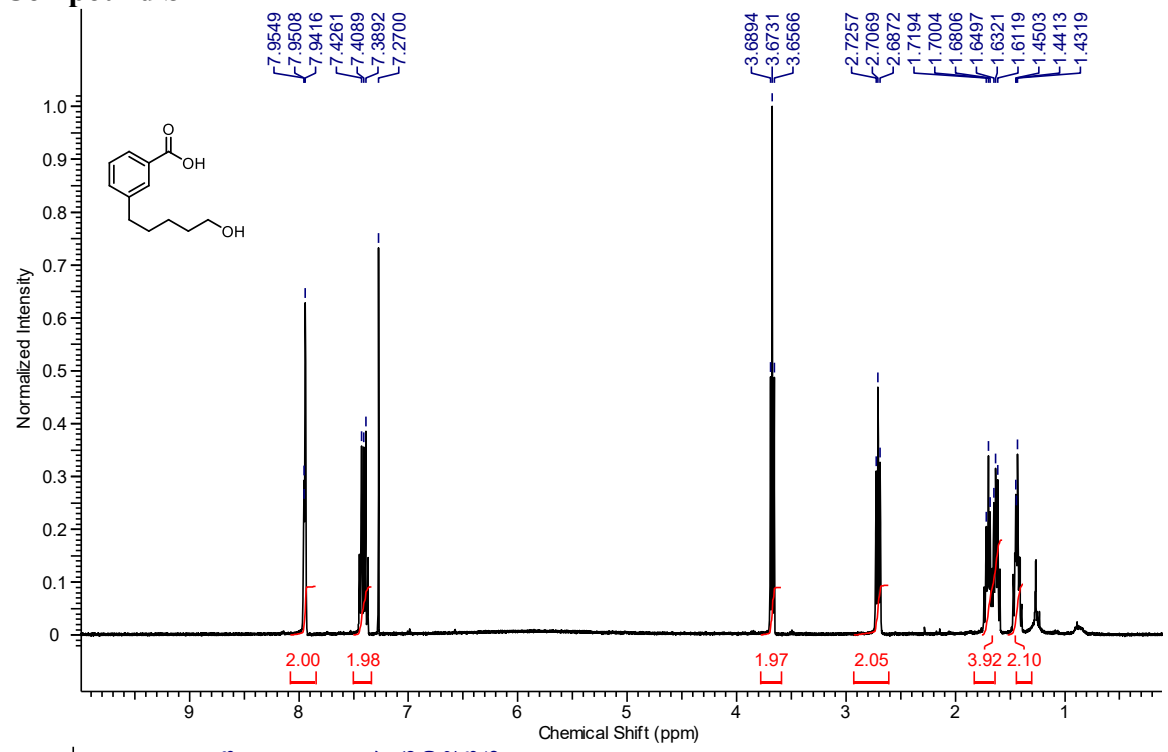
OMe
OH
Normalized Intensity
Chemical Shift (ppm)

Compound S4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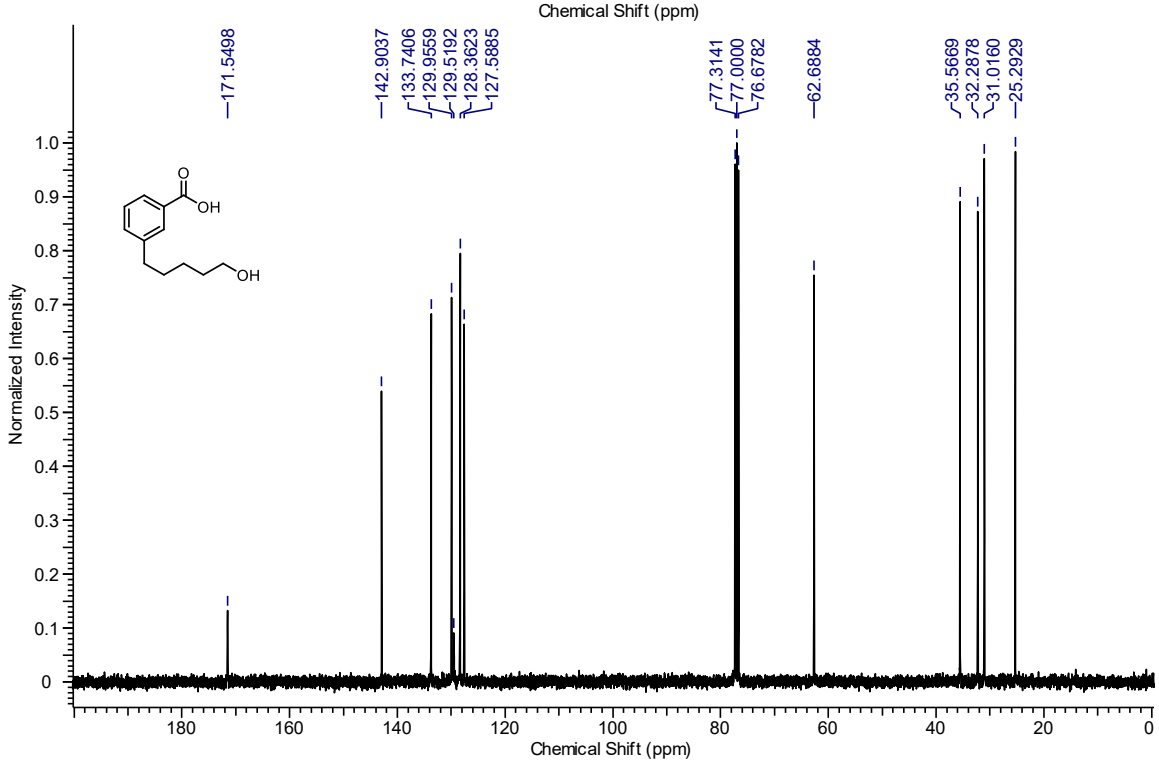
3.6566
2.7257
2.7069
2.6872
1.7194
1.7004
1.6806
1.6497
1.6321
1.6119
1.4503
1.4413
1.4319
2.00
1.98
1.97
2.05
3.92
2.10
Normalized Intensity
Chemical Shift (ppm)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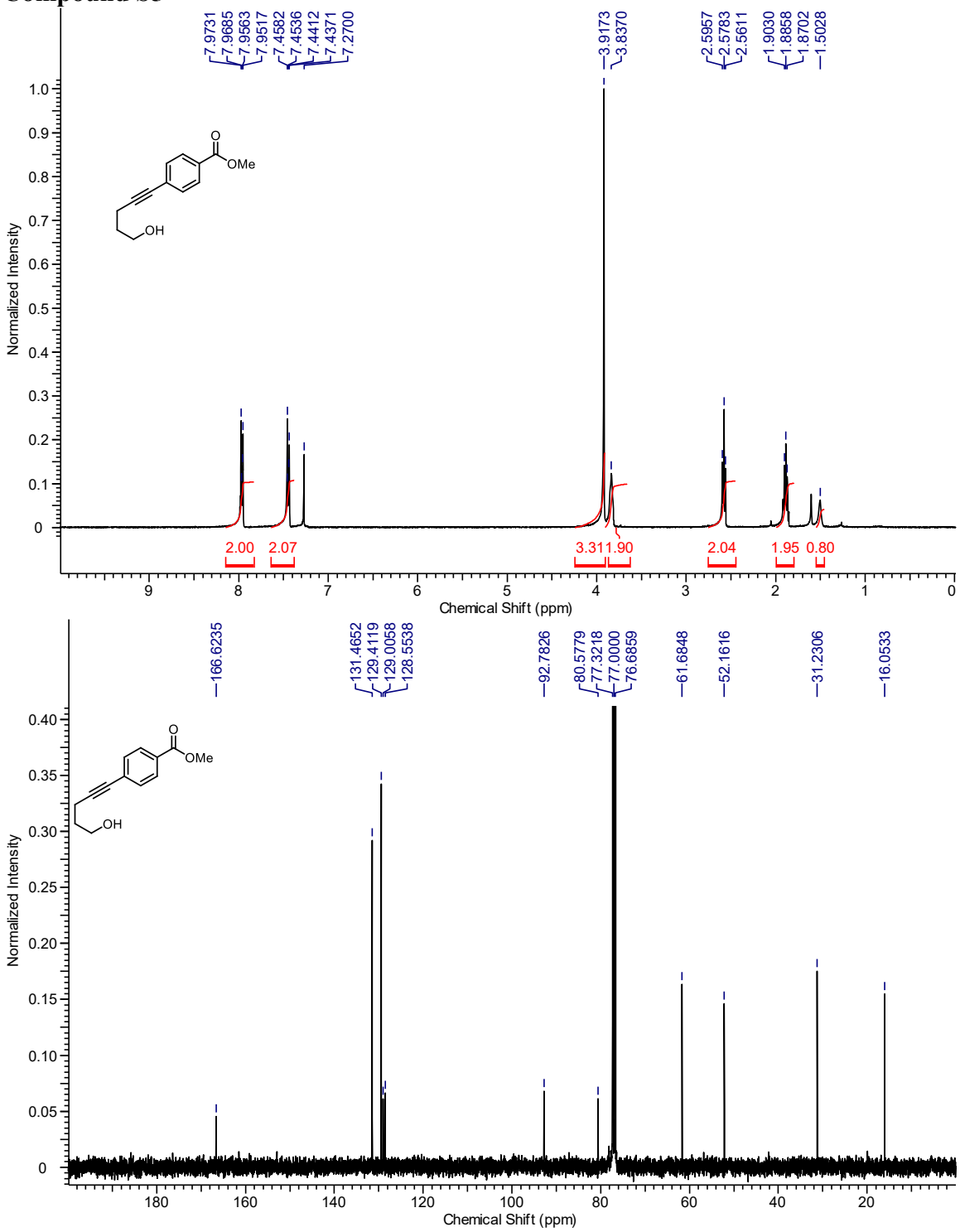
62.6884
35.5669
32.2878
31.0160
25.2929
Normalized Intensity
Chemical Shift (ppm)

Compound S5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7.9563
7.9517
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7.4412
7.4371
7.2700
3.9173
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2.5611
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1.8858
1.8702
1.5028
O
OMe
OH
Normalized Intensity
2.00
2.07
3.31
1.90
2.04
1.95
0.80
Chemical Shift (ppm)
166.6235
131.4652
129.4119
129.0058
128.5538
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80.5779
77.3218
77.0000
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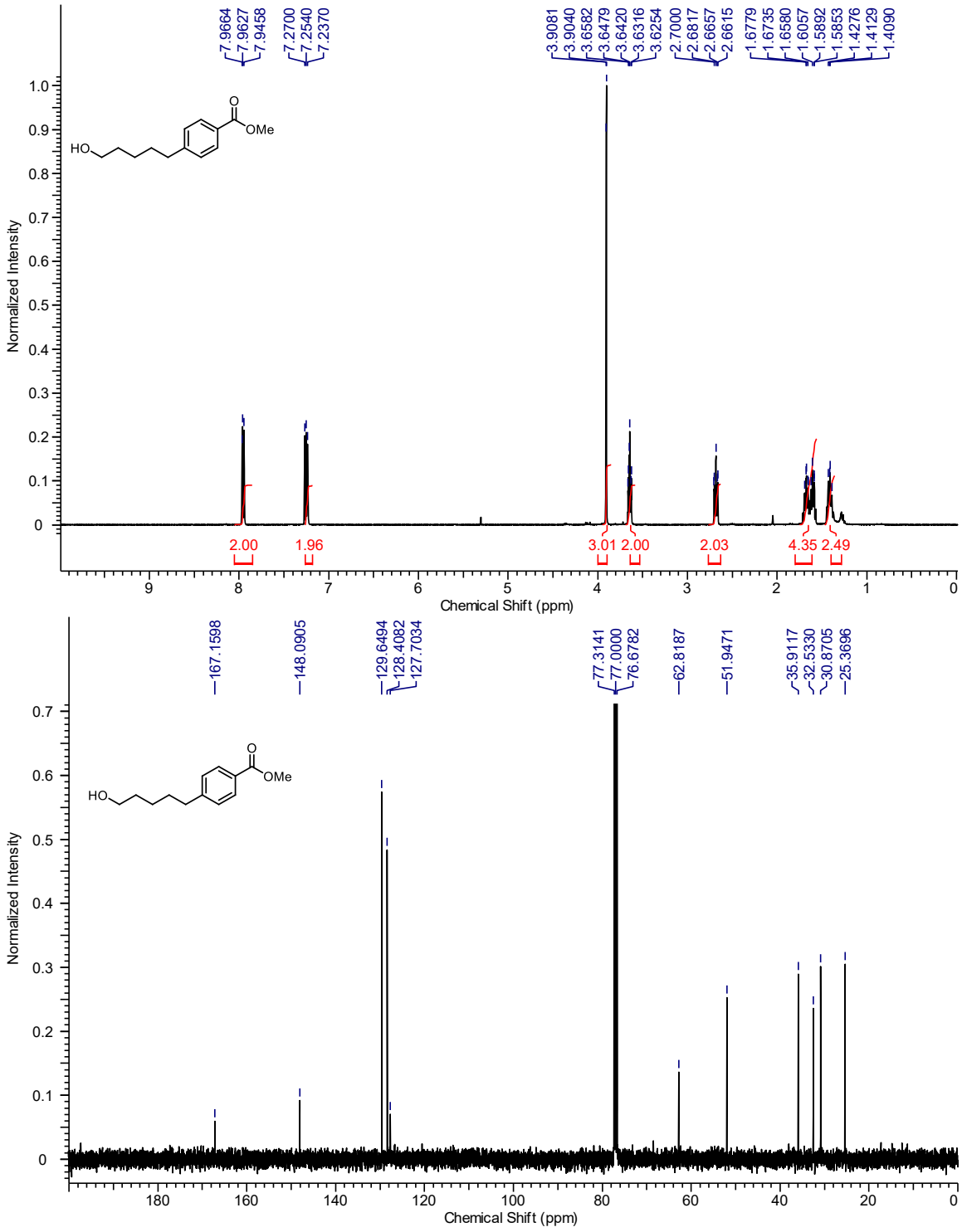
16.0533
O
OMe
OH
Normalized Intensity
Chemical Shift (ppm)

Compound S6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3.6420
3.6316
3.6254
2.7000
2.6817
2.6657
2.6615
1.6779
1.6735
1.6580
1.6057
1.5892
1.5853
1.4276
1.4129
1.4090
HO
O
OMe
Normalized Intensity
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1.96
3.01
2.00
2.03
4.35
2.49
Chemical Shift (ppm)
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129.6494
128.4082
127.7034
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77.0000
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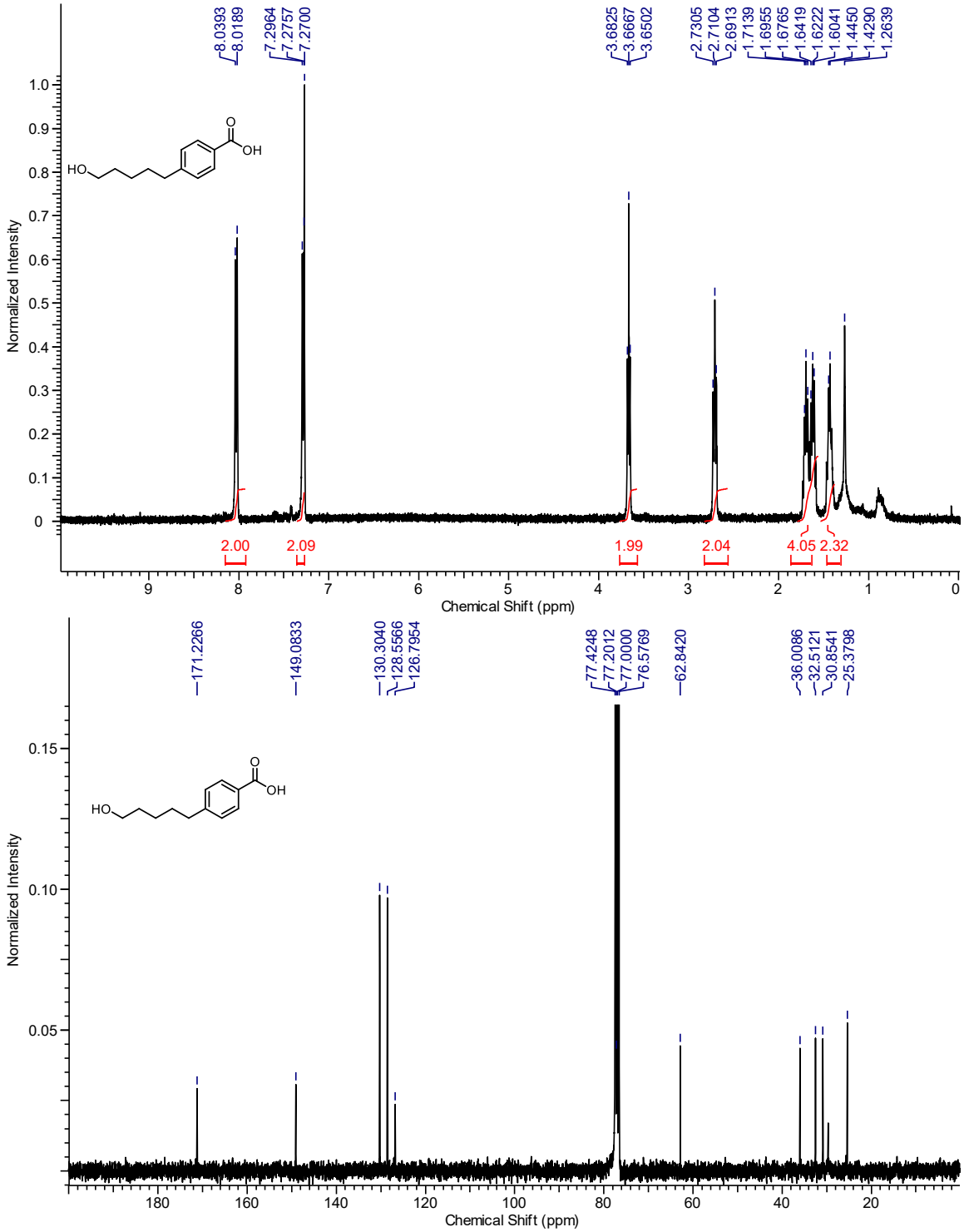
O
OMe
Normalized Intensity
Chemical Shift (ppm)

Compound S7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2.7104
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1.7139
1.6955
1.6765
1.6419
1.6222
1.6041
1.4450
1.4290
1.2639
HO
OH
Normalized Intensity
2.00
2.09
1.99
2.04
4.05
2.32
Chemical Shift (ppm)
171.2266
149.0833
130.3040
128.5566
126.7954
77.4248
77.2012
77.0000
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36.0086
32.5121
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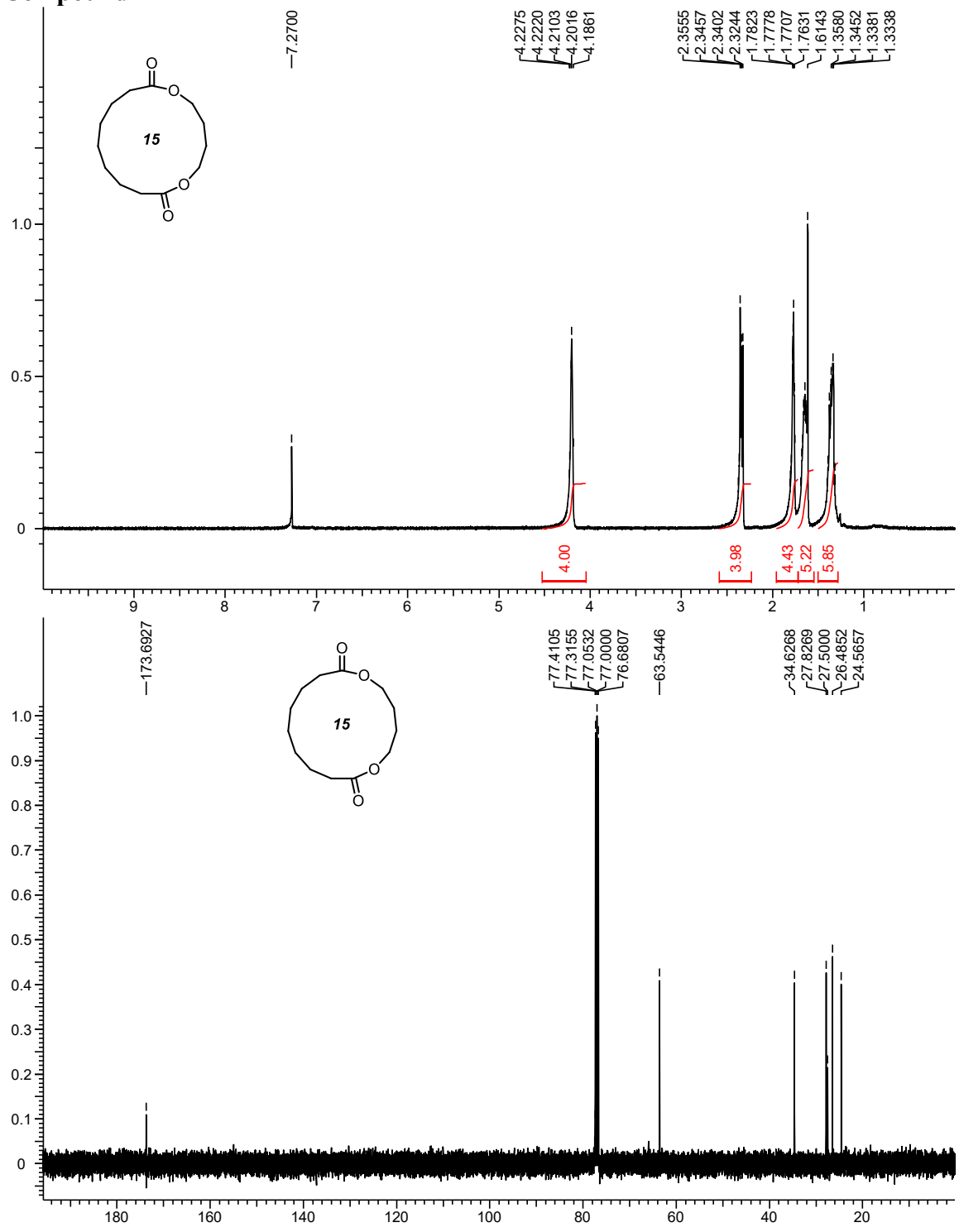
HO
OH
Normalized Intensity
Chemical Shift (ppm)

Compound 4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4.2016
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1.7707
1.7631
1.6143
1.3580
1.3452
1.3381
1.3338
15
4.00
3.98
4.43
5.22
5.85
173.6927
77.4105
77.3155
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76.6807
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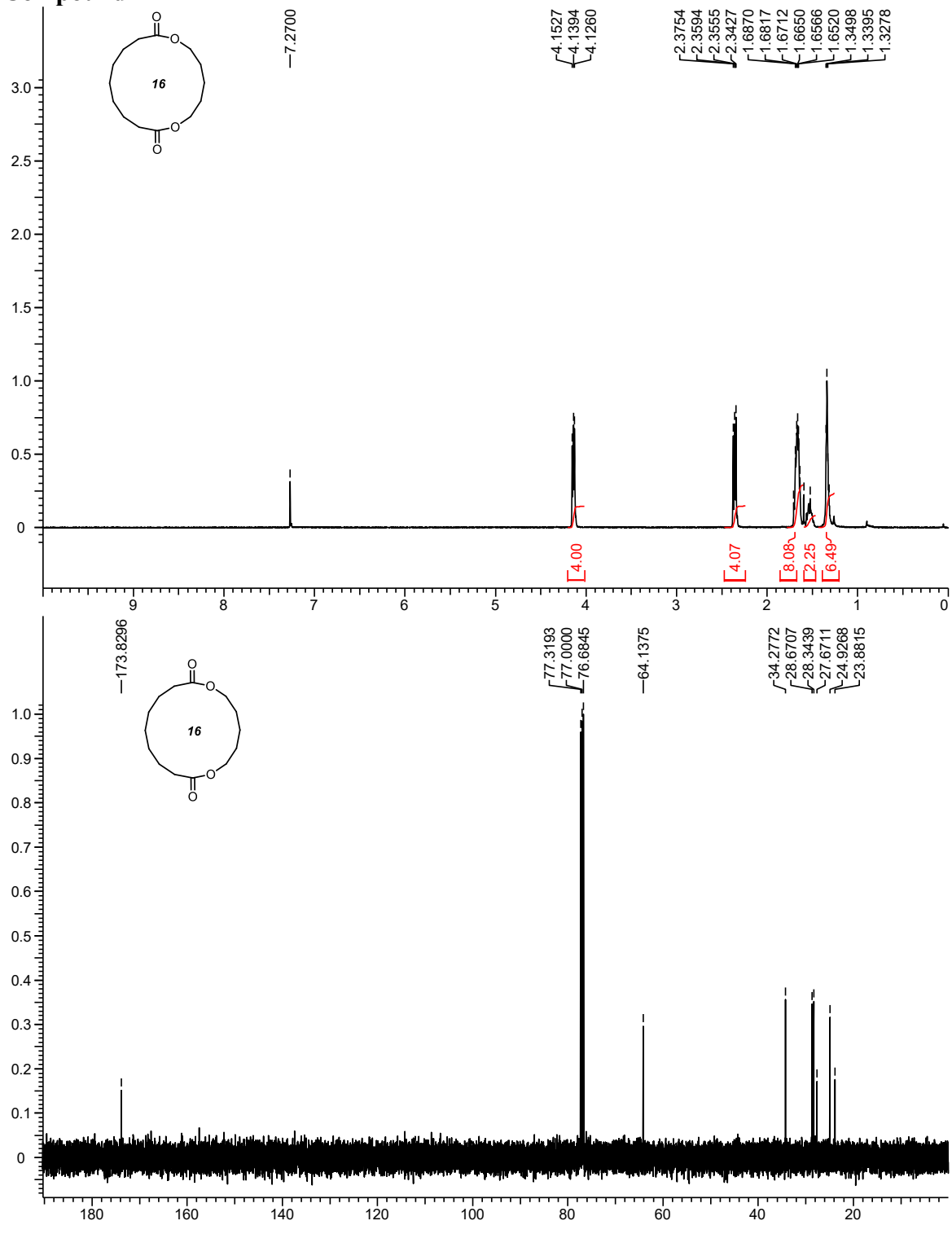
24.5657

Compound **5**


16
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2.3427
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1.6712
1.6650
1.6566
1.6520
1.3498
1.3395
1.3278
4.00
4.07
8.08
2.25
6.49
173.8296
77.3193
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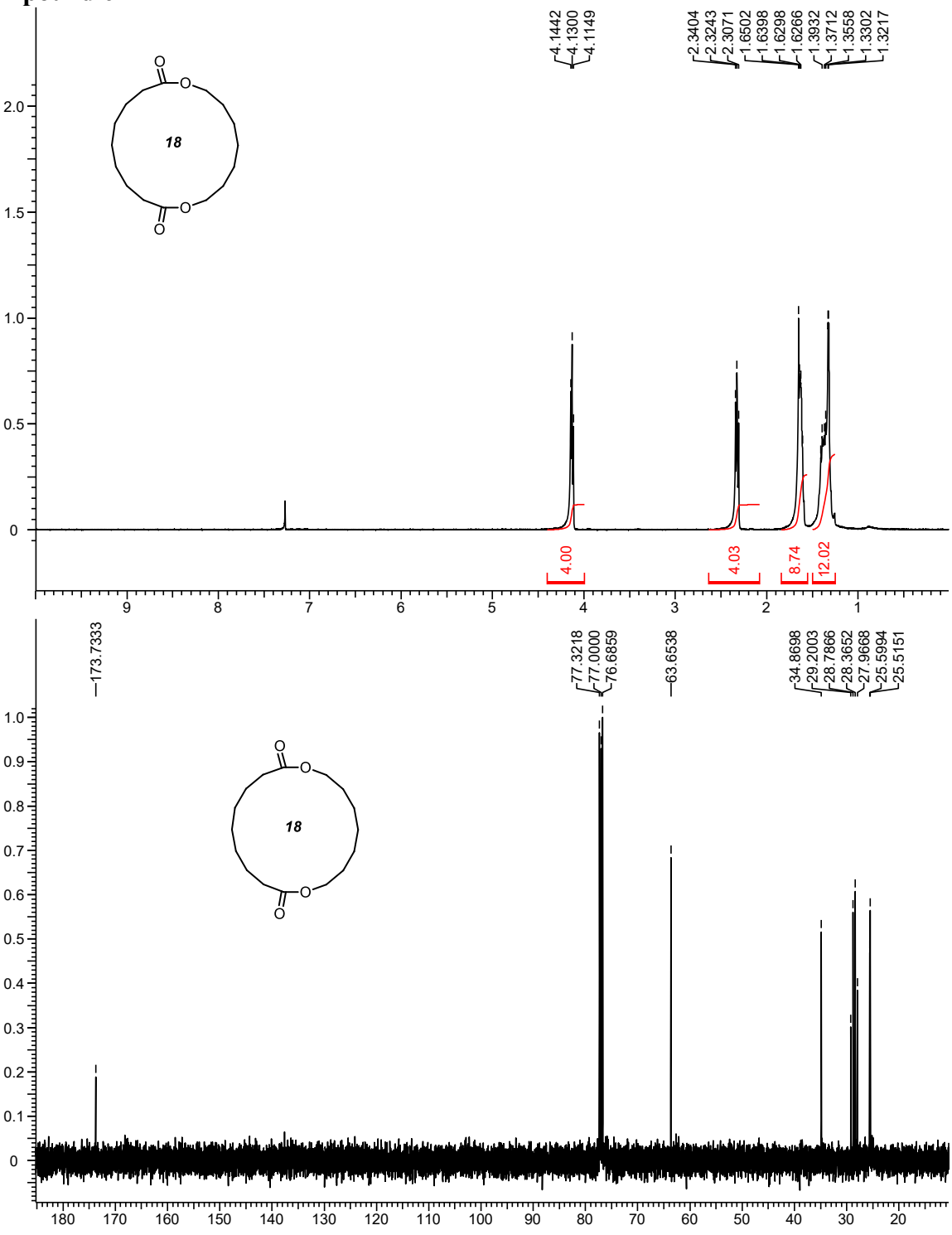
Compound 6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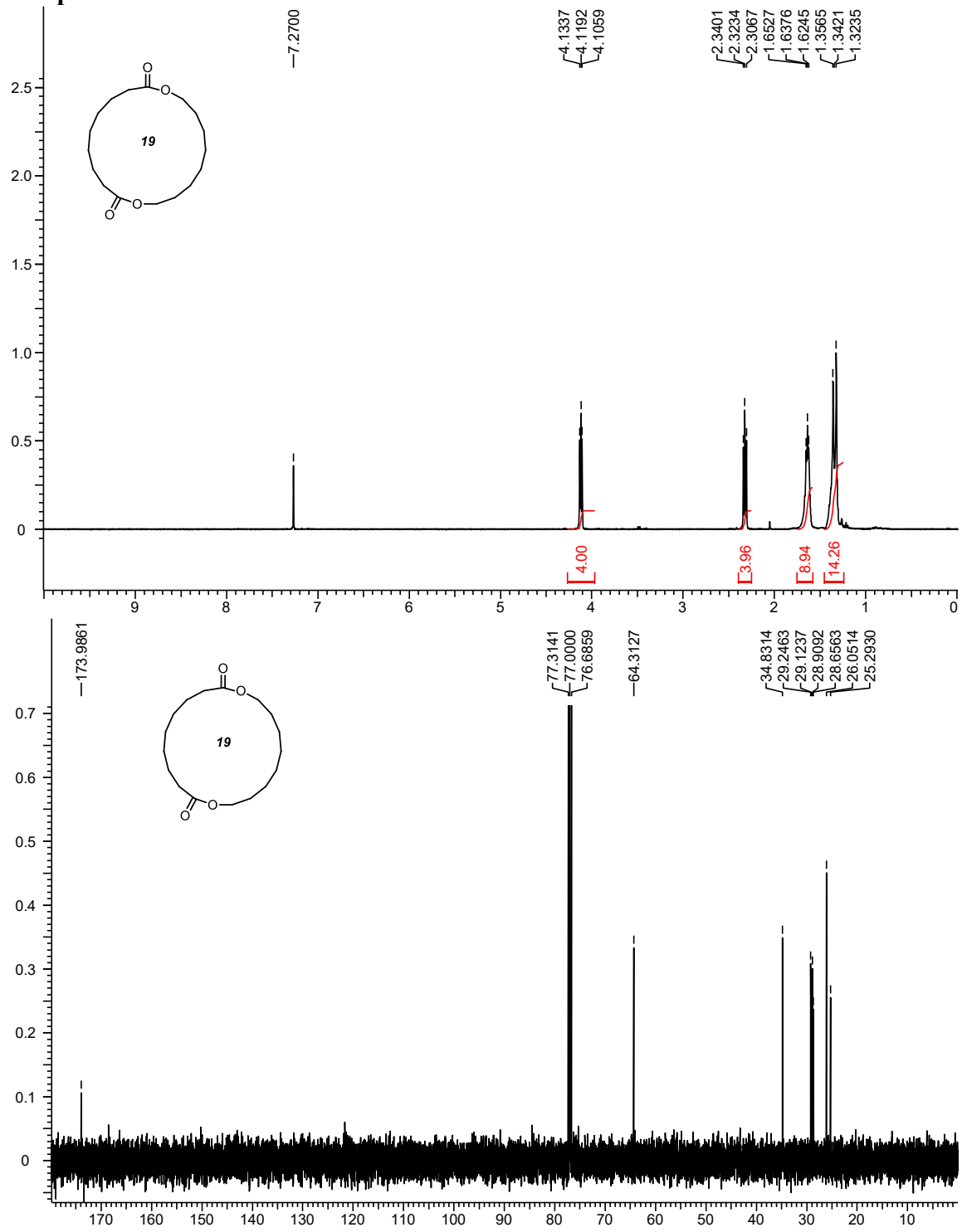
18

Compound 3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1.6376
1.6245
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1.3421
1.3235
4.00
3.96
8.94
14.26
19
173.9861
77.3141
77.0000
76.6859
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34.8314
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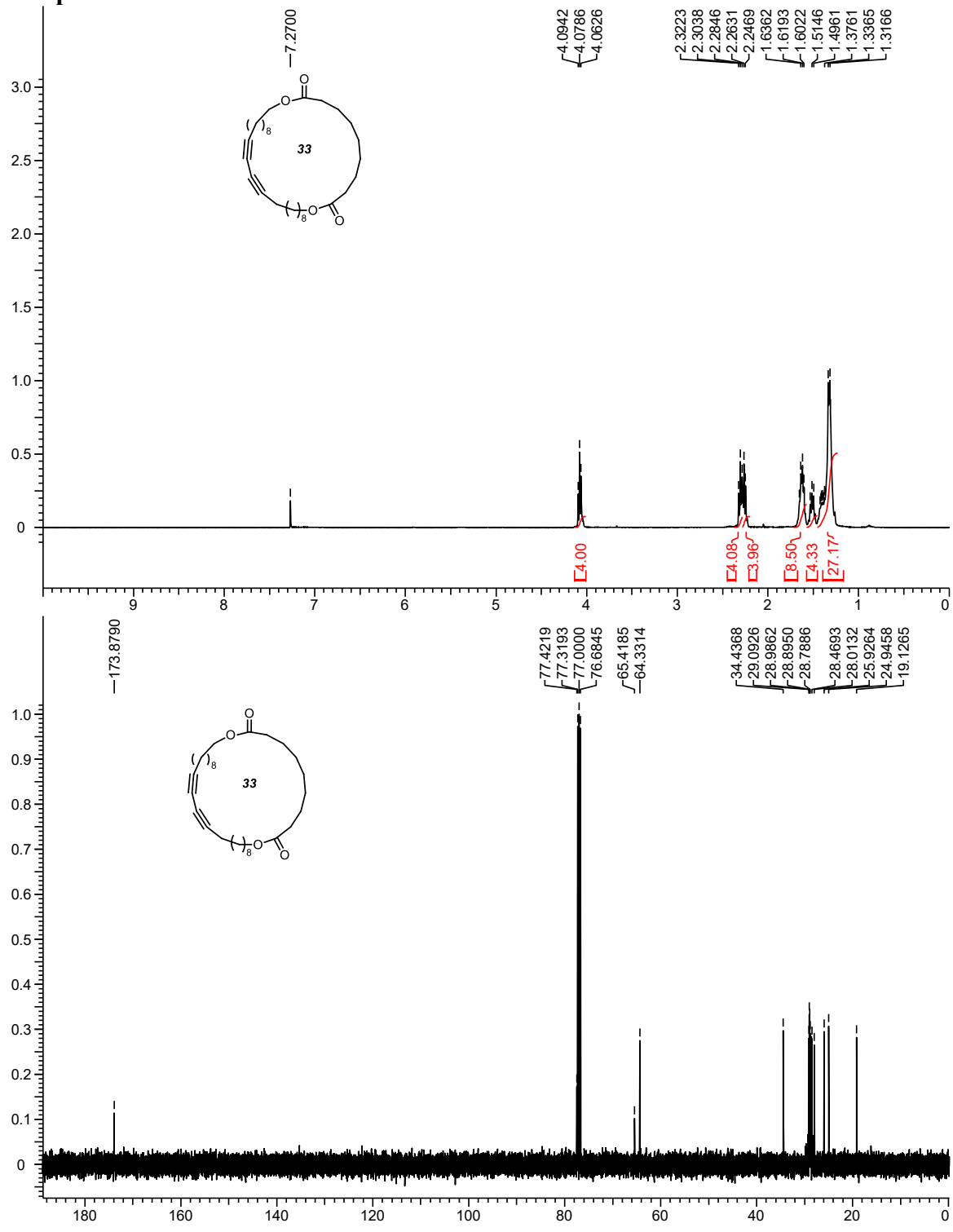
28.6563
26.0514
25.2930

Compound 7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8.50
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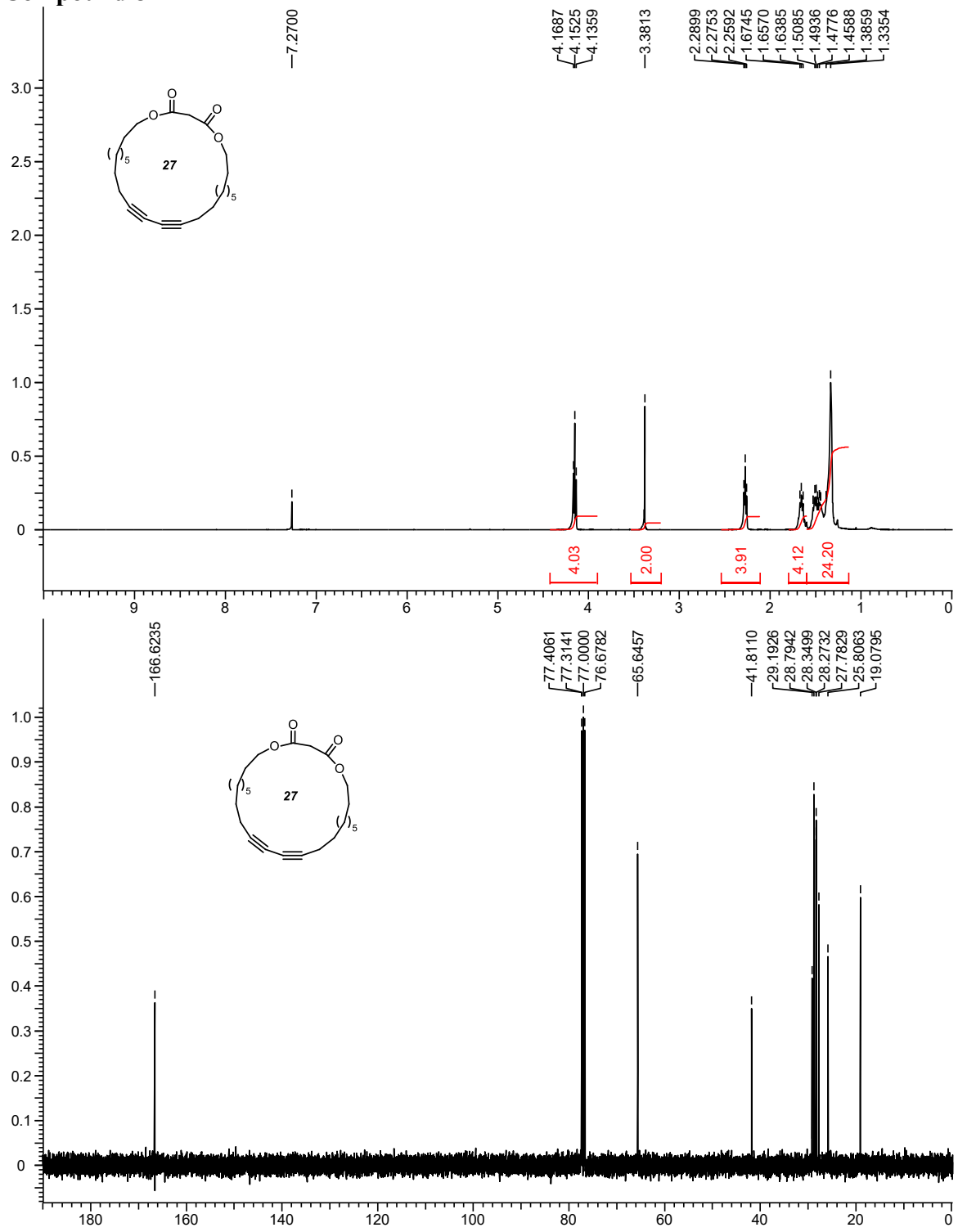
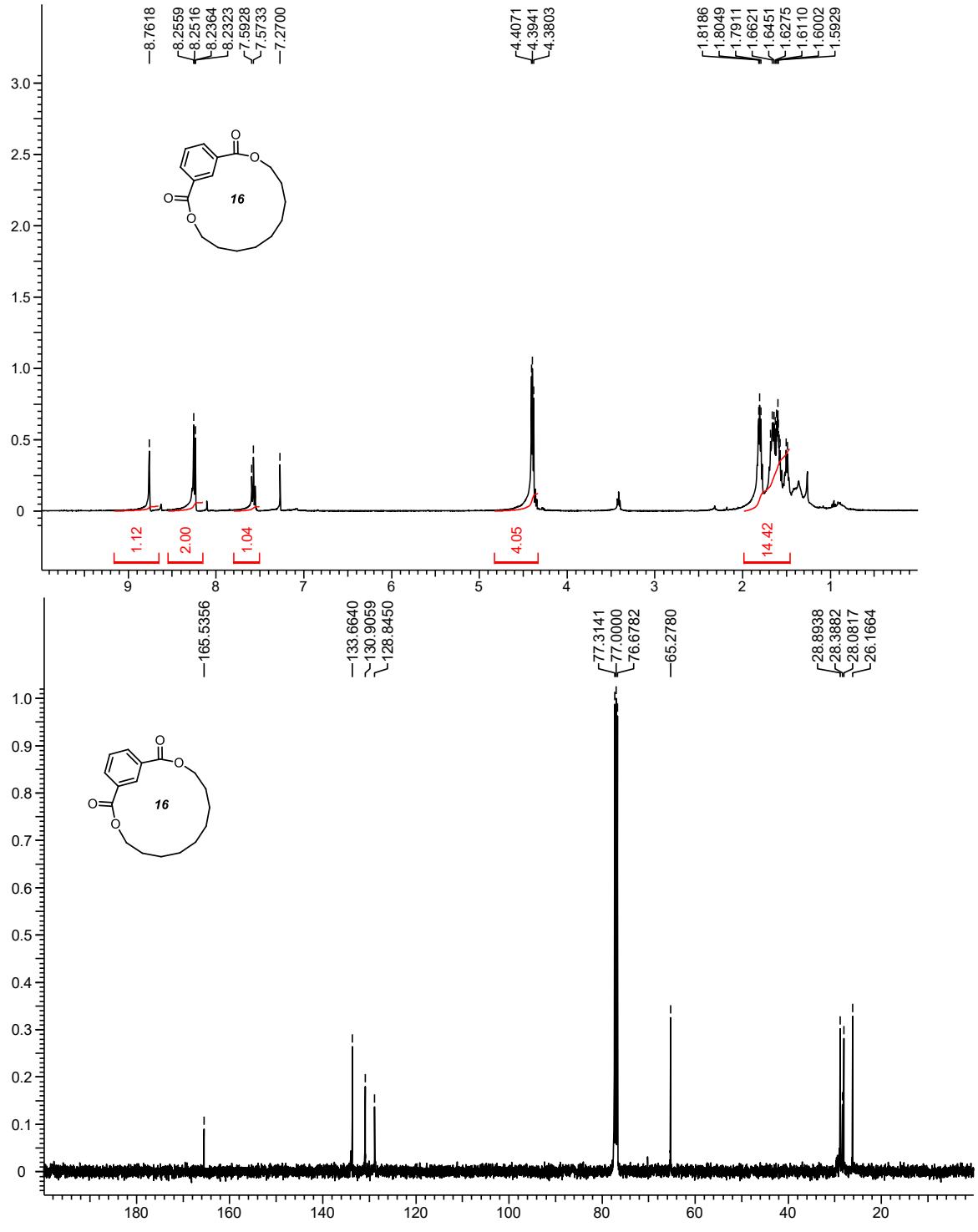
64.3314
34.4368
29.0926
28.9862
28.8950
28.7886
28.4693
28.0132
25.9264
24.9458
19.1265
33

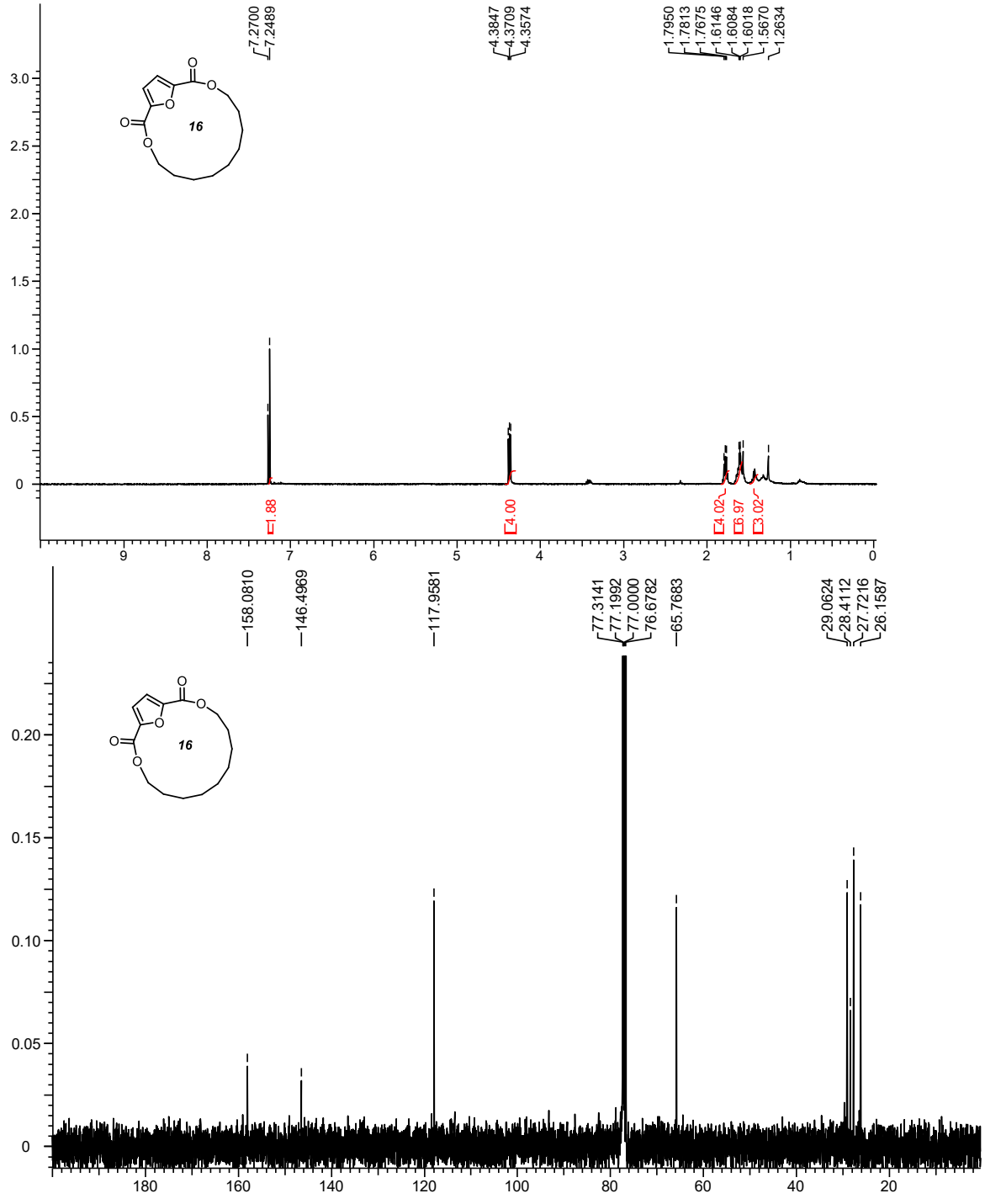
Compound 8


7.2700
4.1687
4.1525
4.1359
3.3813
2.2899
2.2753
2.2592
1.6745
1.6570
1.6385
1.5085
1.4936
1.4776
1.4588
1.3859
1.3354
4.03
2.00
3.91
4.12
24.20
166.6235
77.4061
77.3141
77.0000
76.6782
65.6457
41.8110
29.1926
28.7942
28.3499
28.2732
27.7829
25.8063
19.0795
27

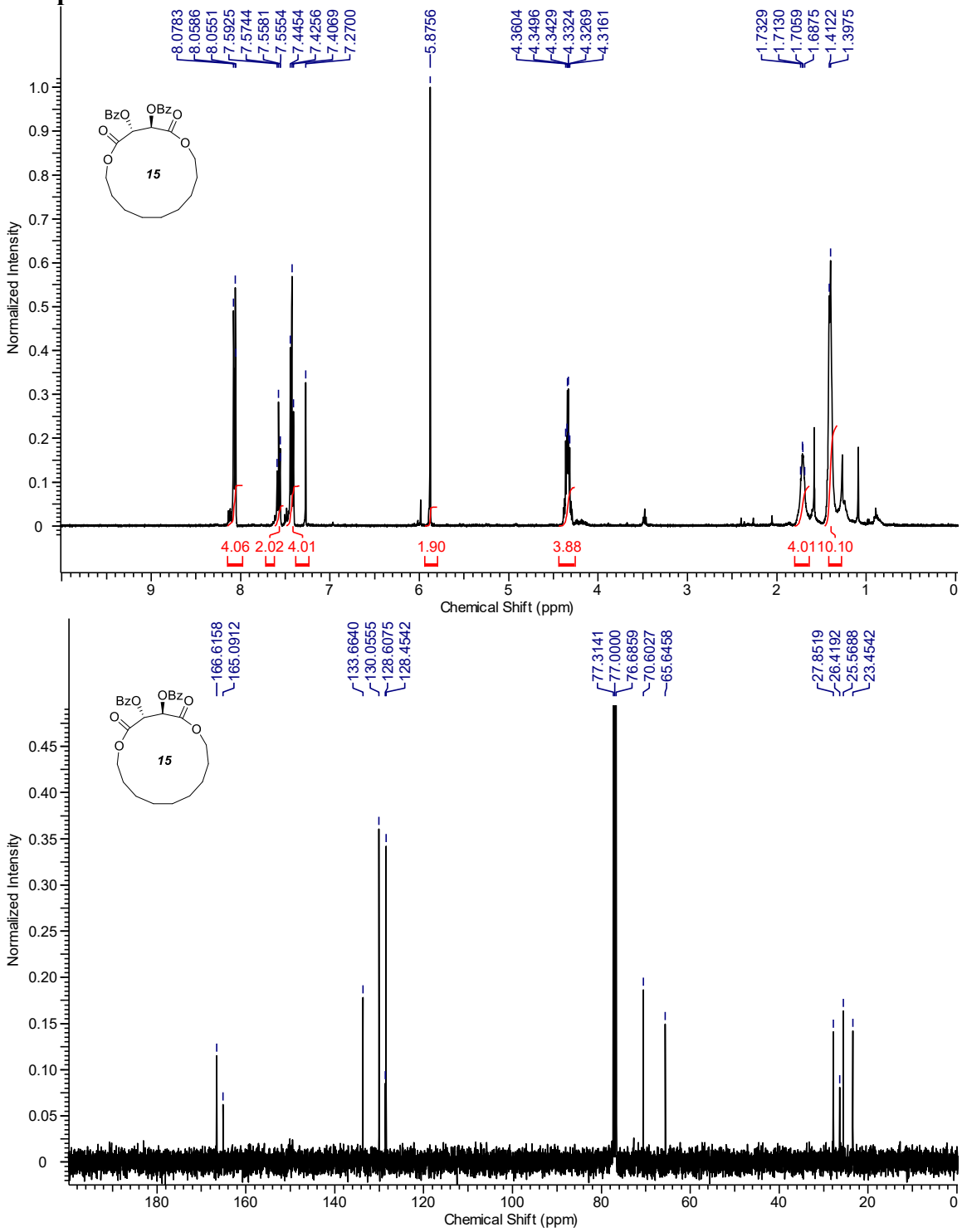
Compound 9


8.7618
8.2559
8.2516
8.2364
8.2323
7.5928
7.5733
7.2700
4.4071
4.3941
4.3803
1.8186
1.8049
1.7911
1.6621
1.6451
1.6275
1.6110
1.6002
1.5929
16
1.12
2.00
1.04
4.05
14.42
165.5356
133.6640
130.9059
128.8450
77.3141
77.0000
76.6782
65.2780
28.8938
28.3882
28.0817
26.1664
16

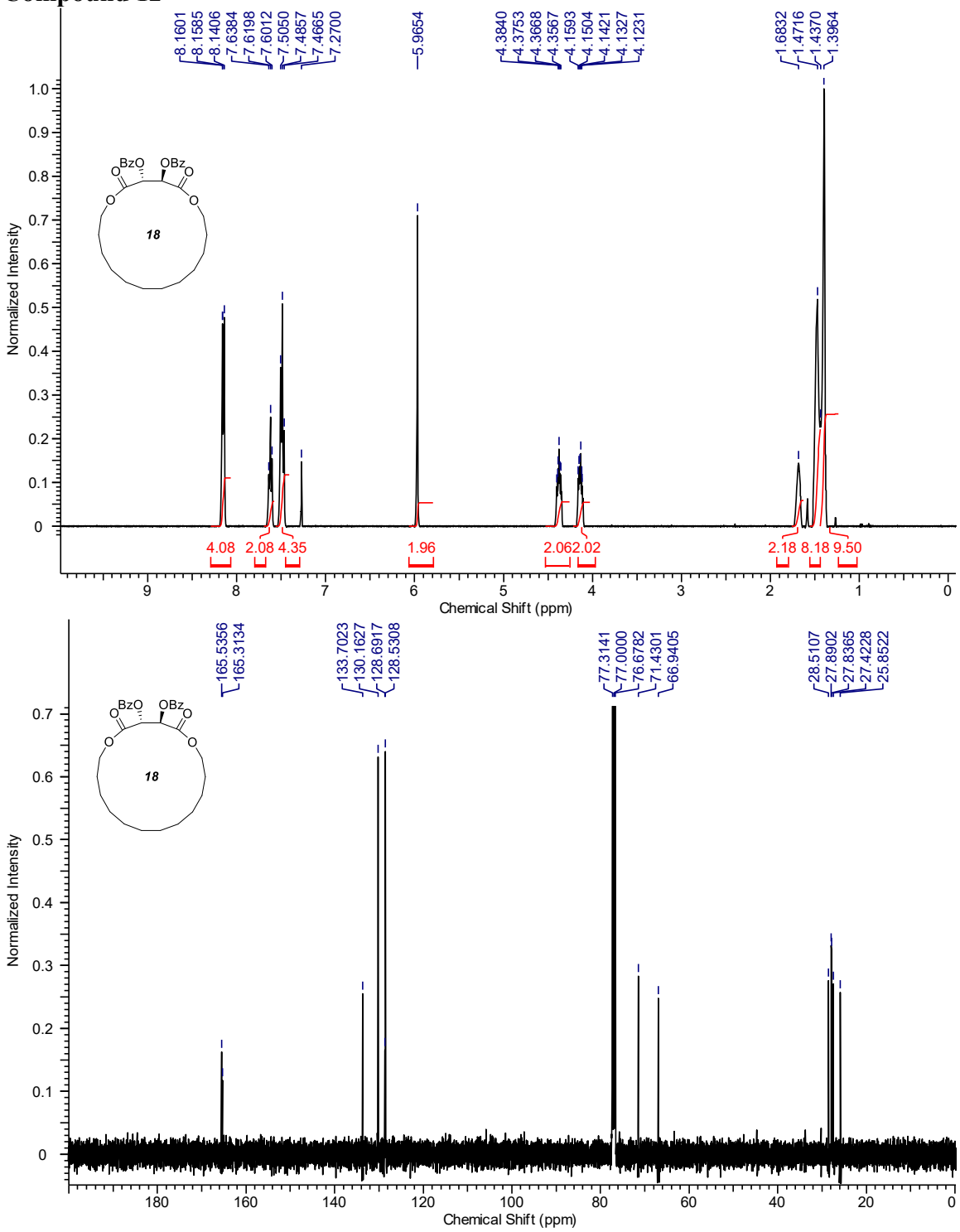
Compound 10


7.2700
7.2489
4.3847
4.3709
4.3574
1.7950
1.7813
1.7675
1.6146
1.6084
1.6018
1.5670
1.2634
16
1.88
4.00
4.02
6.97
3.02
158.0810
146.4969
117.9581
77.3141
77.1992
77.0000
76.6782
65.7683
29.0624
28.4112
27.7216
26.1587
16

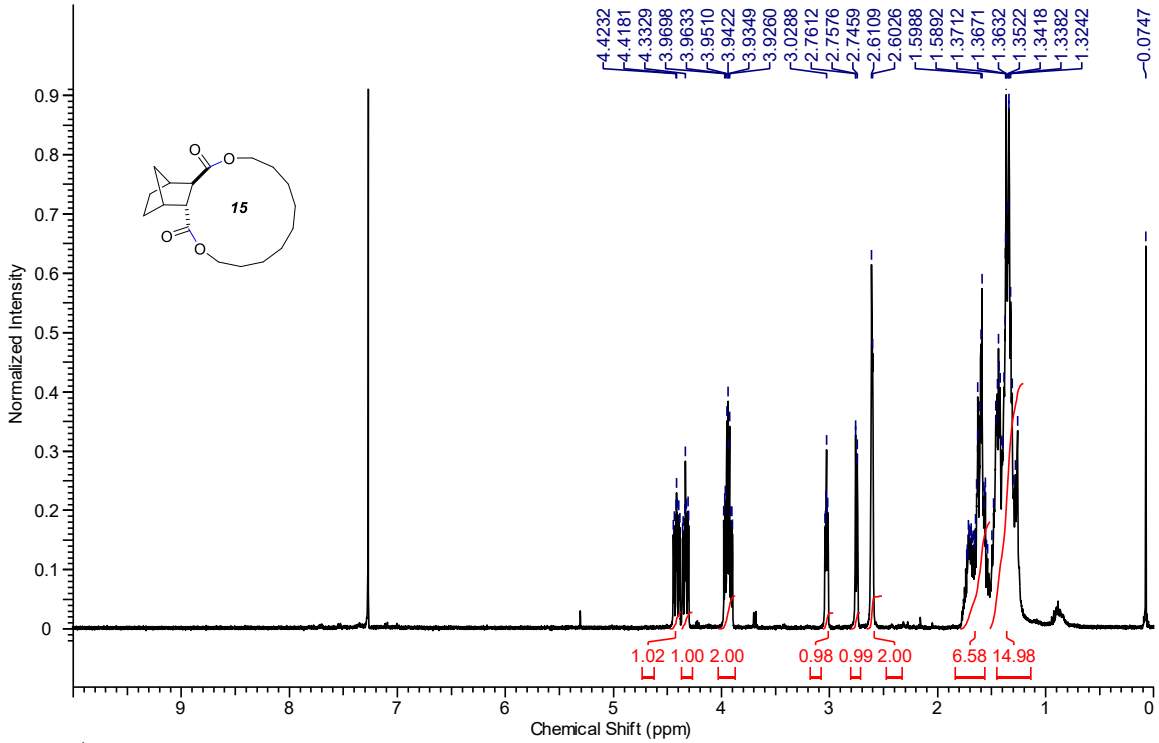
Compound 11

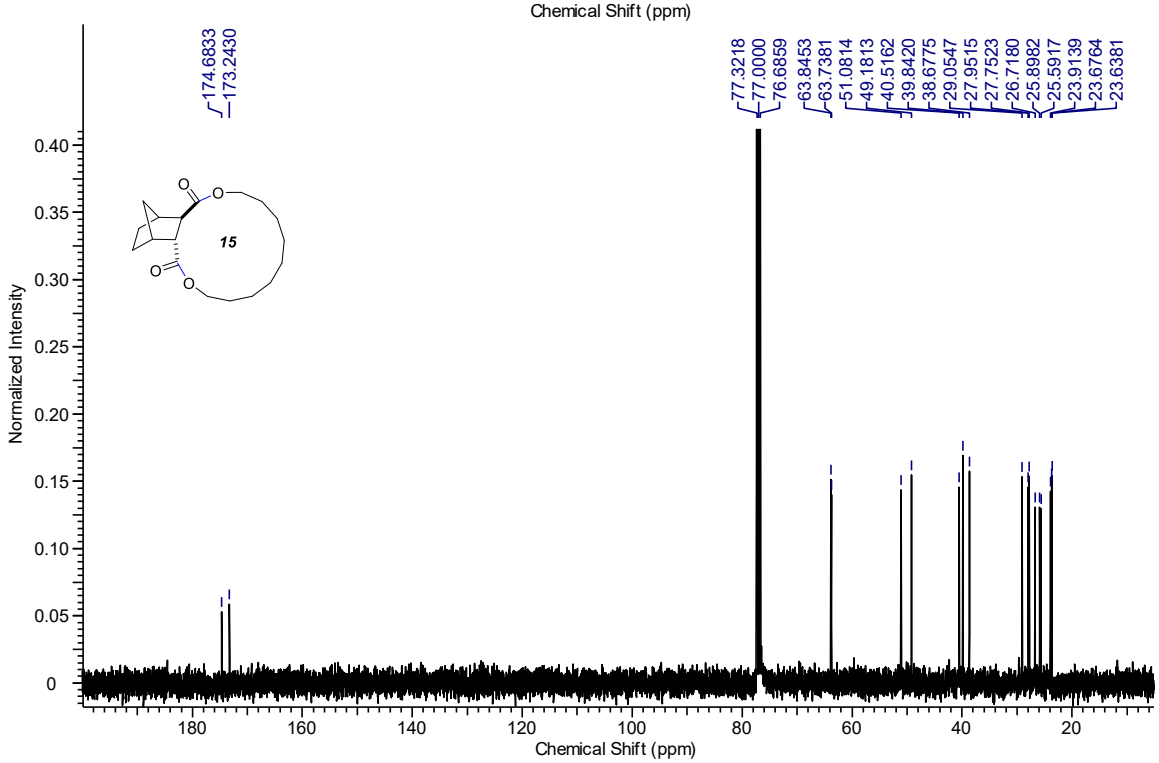

8.0783
8.0586
8.0551
7.5925
7.5744
7.5581
7.5554
7.4454
7.4256
7.4069
7.2700
5.8756
4.3604
4.3496
4.3429
4.3324
4.3269
4.3161
1.7329
1.7130
1.7059
1.6875
1.4122
1.3975
BzO
OBz
O
15
Normalized Intensity
4.06 2.02 4.01
1.90
3.88
4.01 10.10
Chemical Shift (ppm)
166.6158
165.0912
133.6640
130.0555
128.6075
128.4542
77.3141
77.0000
76.6859
70.6027
65.6458
27.8519
26.4192
25.5688
23.4542
Normalized Intensity
Chemical Shift (ppm)

Compound 12

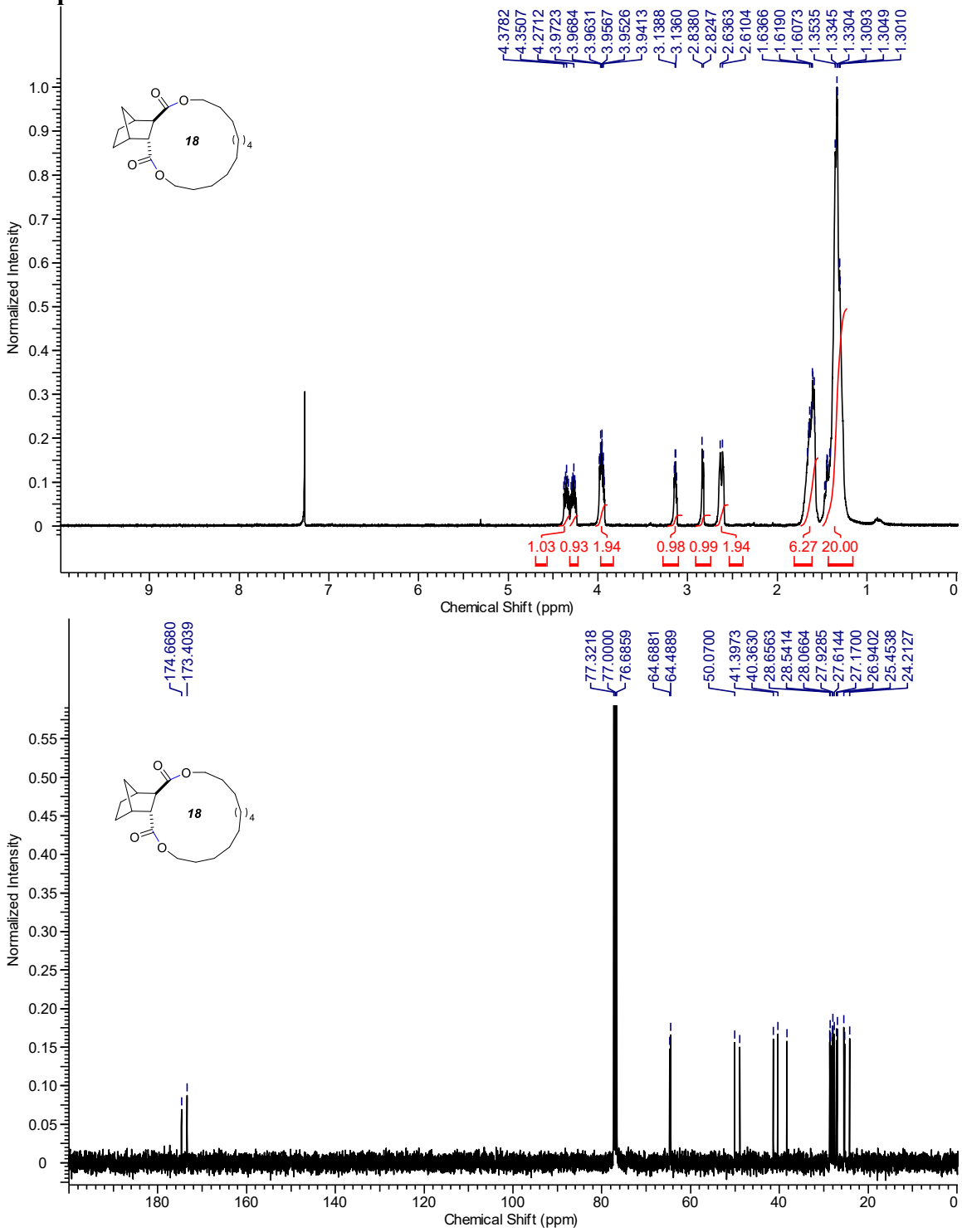

8.1601
8.1585
8.1406
7.6384
7.6198
7.6012
7.5050
7.4857
7.4665
7.2700
5.9654
4.3840
4.3753
4.3668
4.3567
4.1593
4.1504
4.1421
4.1327
4.1231
1.6832
1.4716
1.4370
1.3964
BzO
OBz
18
Normalized Intensity
4.08
2.08
4.35
1.96
2.06
2.02
2.18
8.18
9.50
Chemical Shift (ppm)
165.5356
165.3134
133.7023
130.1627
128.6917
128.5308
77.3141
77.0000
76.6782
71.4301
66.9405
28.5107
27.8902
27.8365
27.4228
25.8522
BzO
OBz
18
Normalized Intensity
Chemical Shift (ppm)

Compound 13

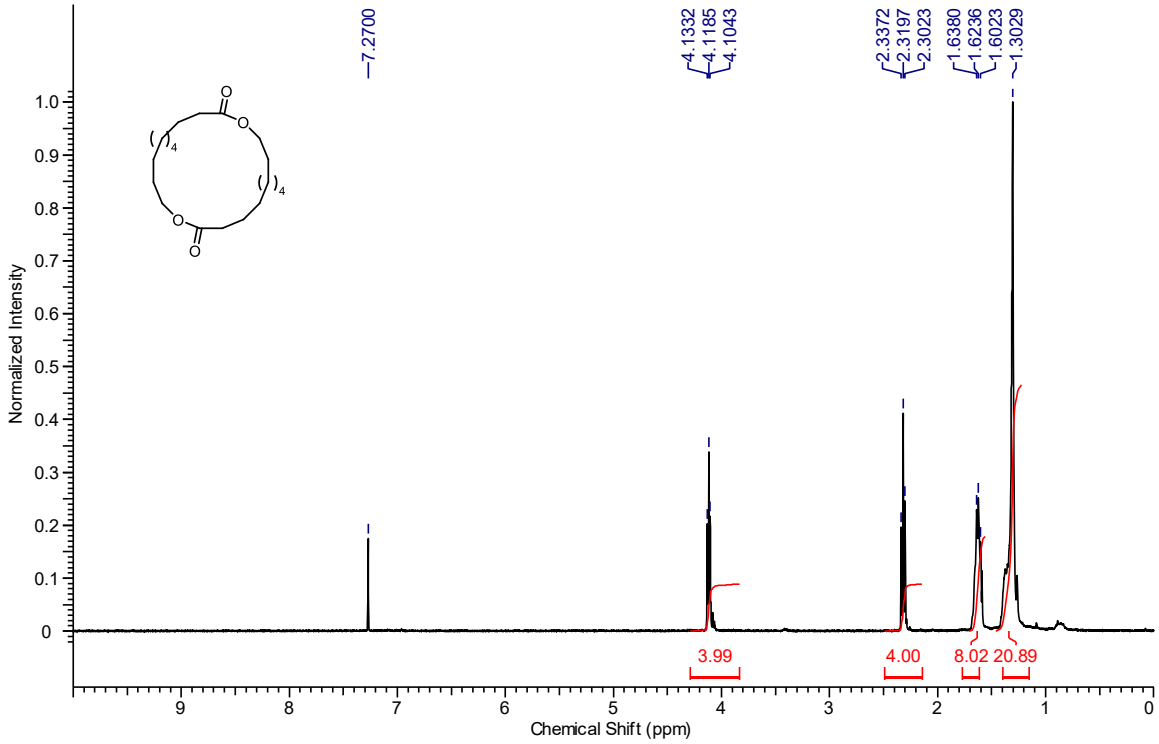

4.4232
4.4181
4.3329
3.9698
3.9633
3.9510
3.9422
3.9349
3.9260
3.0288
2.7612
2.7576
2.7459
2.6109
2.6026
1.5988
1.5892
1.3712
1.3671
1.3632
1.3522
1.3418
1.3382
1.3242
0.0747
15
Normalized Intensity
Chemical Shift (ppm)
1.02 1.00 2.00
0.98 0.99 2.00
6.58 14.98

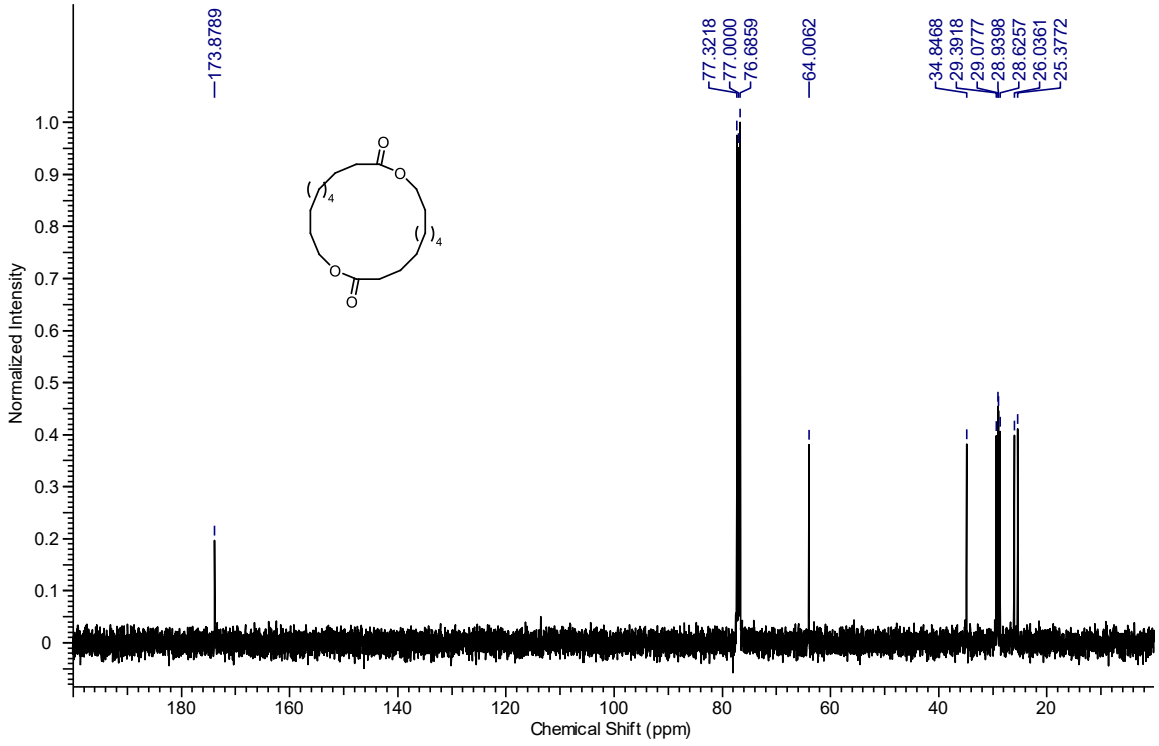

174.6833
173.2430
77.3218
77.0000
76.6859
63.8453
63.7381
51.0814
49.1813
40.5162
39.8420
38.6775
29.0547
27.9515
27.7523
26.7180
25.8982
25.5917
23.9139
23.6764
23.6381
15
Normalized Intensity
Chemical Shift (ppm)

Compound 14

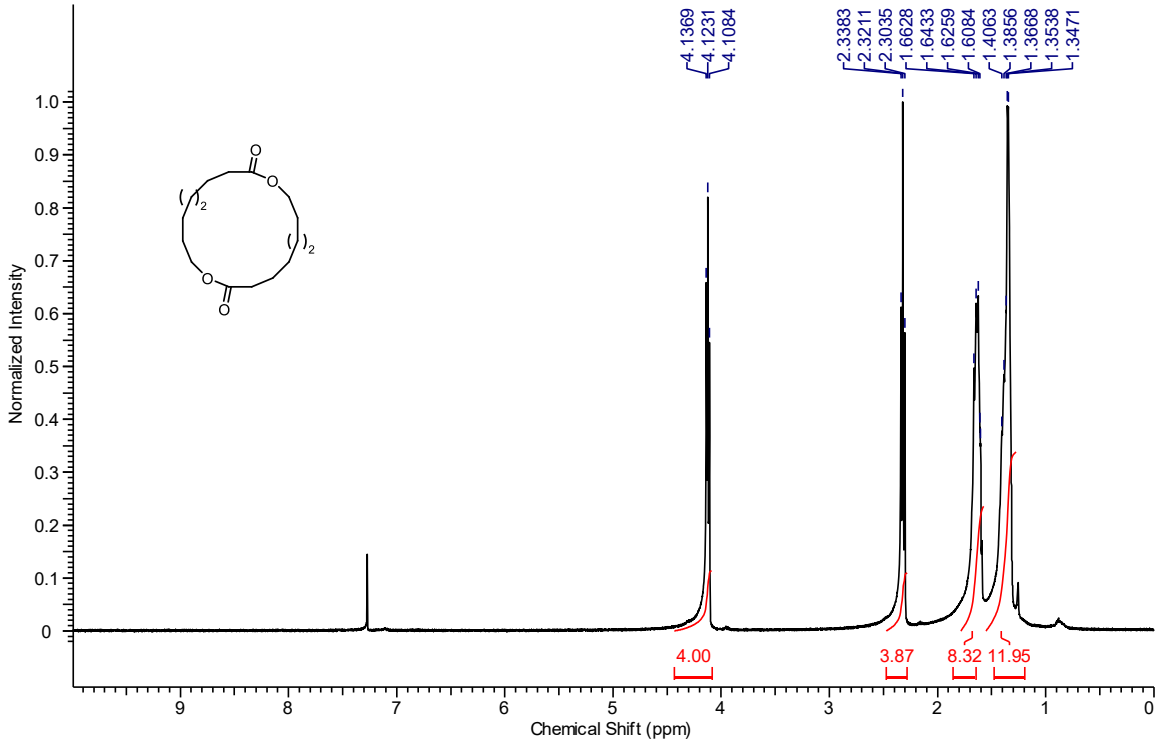

4.3782
4.3507
4.2712
3.9723
3.9684
3.9631
3.9567
3.9526
3.9413
3.1388
3.1360
2.8380
2.8247
2.6363
2.6104
1.6366
1.6190
1.6073
1.3535
1.3345
1.3304
1.3093
1.3049
1.3010
1.03 0.93 1.94
0.98 0.99 1.94
6.27 20.00
Normalized Intensity
Chemical Shift (ppm)
174.6680
173.4039
77.3218
77.0000
76.6859
64.6881
64.4889
50.0700
41.3973
40.3630
28.6563
28.5414
28.0664
27.9285
27.6144
27.1700
26.9402
25.4538
24.2127
Normalized Intensity
Chemical Shift (ppm)

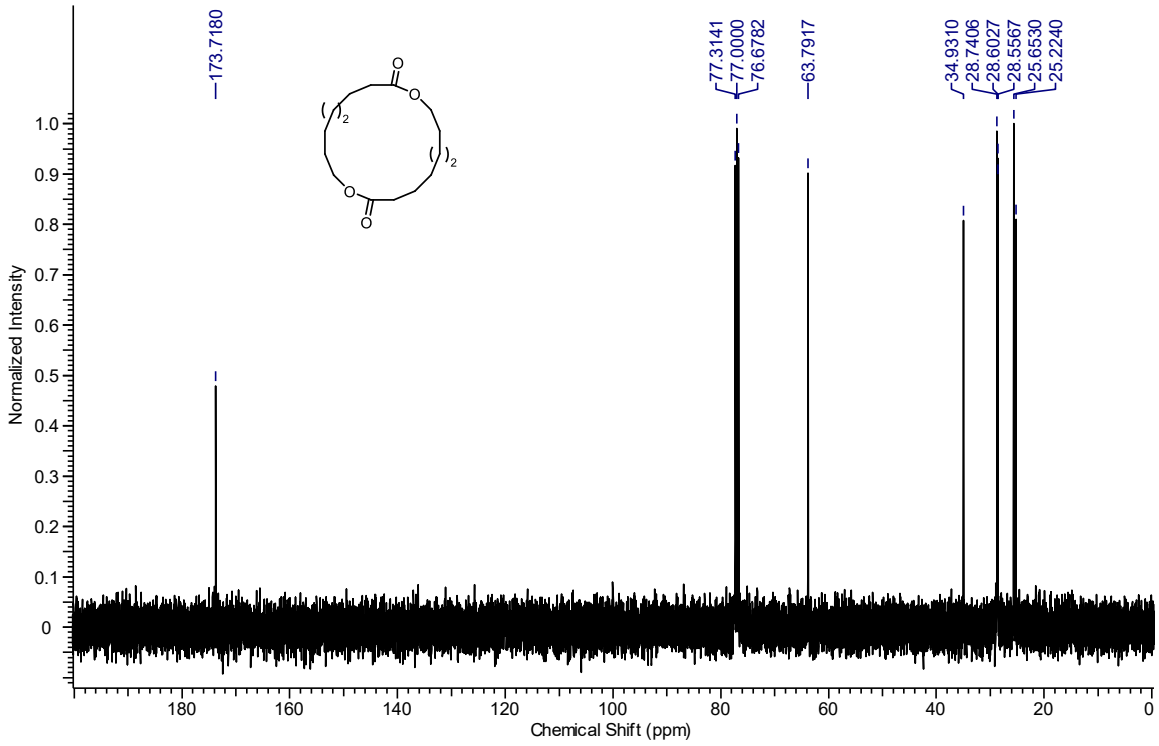
Compound 16


7.2700
4.1332
4.1185
4.1043
2.3372
2.3197
2.3023
1.6380
1.6236
1.6023
1.3029
3.99
4.00
8.02
20.89
Normalized Intensity
Chemical Shift (ppm)

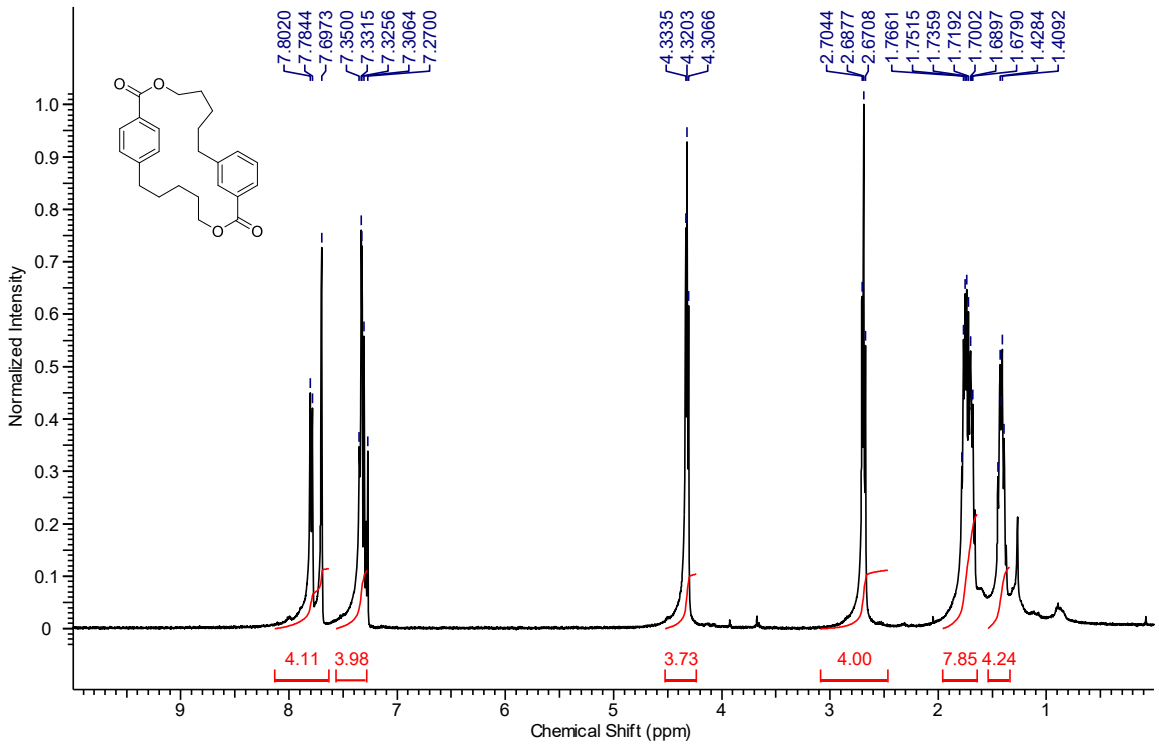

173.8789
77.3218
77.0000
76.6859
64.0062
34.8468
29.3918
29.0777
28.9398
28.6257
26.0361
25.3772
Normalized Intensity
Chemical Shift (ppm)

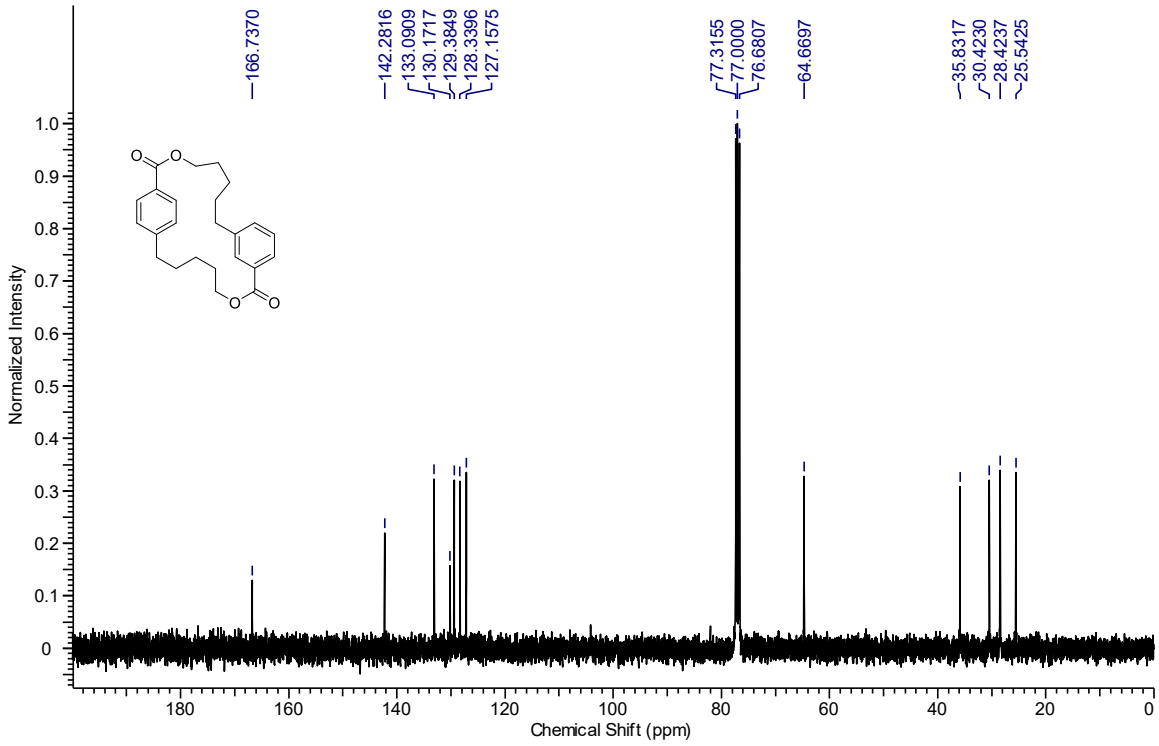
Compound 17


4.1369
4.1231
4.1084
2.3383
2.3211
2.3035
1.6628
1.6433
1.6259
1.6084
1.4063
1.3856
1.3668
1.3538
1.3471
4.00
3.87
8.32
11.95
Normalized Intensity
Chemical Shift (ppm)

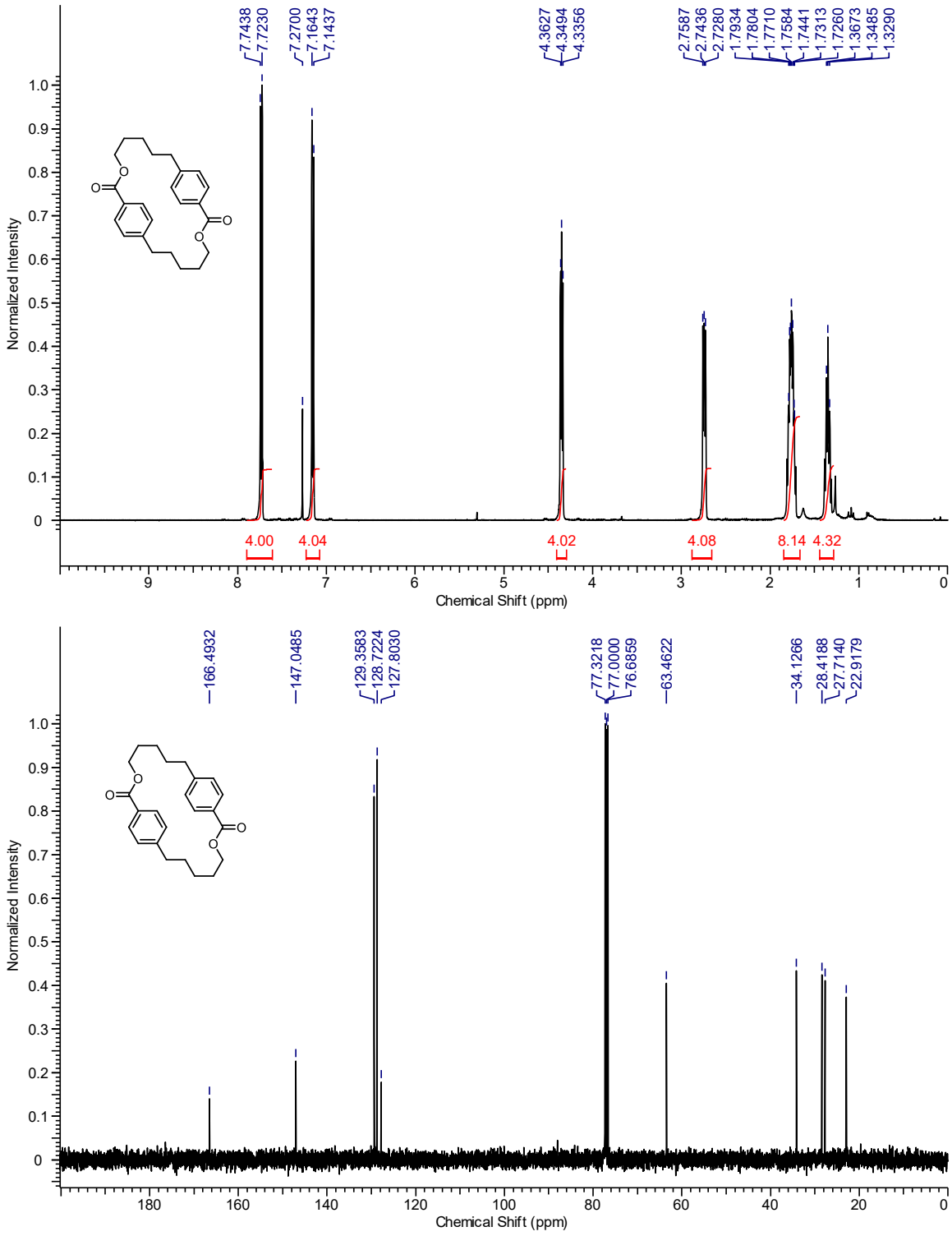

173.7180
77.3141
77.0000
76.6782
63.7917
34.9310
28.7406
28.6027
28.5567
25.6530
25.2240
Normalized Intensity
Chemical Shift (ppm)

Compound 18


7.8020
7.7844
7.6973
7.3500
7.3315
7.3256
7.3064
7.2700
4.3335
4.3203
4.3066
2.7044
2.6877
2.6708
1.7661
1.7515
1.7359
1.7192
1.7002
1.6897
1.6790
1.4284
1.4092
4.11
3.98
3.73
4.00
7.85
4.24
Normalized Intensity
Chemical Shift (ppm)


166.7370
142.2816
133.0909
130.1717
129.3849
128.3396
127.1575
77.3155
77.0000
76.6807
64.6697
35.8317
30.4230
28.4237
25.5425
Normalized Intensity
Chemical Shift (ppm)

Compound 19


7.7438
7.7230
7.2700
7.1643
7.1437
4.3627
4.3494
4.3356
2.7587
2.7436
2.7280
1.7934
1.7804
1.7710
1.7584
1.7441
1.7313
1.7260
1.3673
1.3485
1.3290
4.00
4.04
4.02
4.08
8.14
4.32
Normalized Intensity
Chemical Shift (ppm)
166.4932
147.0485
129.3583
128.7224
127.8030
77.3218
77.0000
76.6859
63.4622
34.1266
28.4188
27.7140
22.9179
Normalized Intensity
Chemical Shift (ppm)

Annexe 3. Supporting Information of Chapter 5

GENERAL

All reactions that were carried out under anhydrous conditions were performed under an inert argon or nitrogen atmosphere in glassware that had previously been dried overnight at 120 °C or had been flame dried and cooled under a stream of argon or nitrogen.[1] All commercial reagents were obtained from Sigma-Aldrich Chemical Company or Strem Chemicals and were reagent quality. Technical solvents were obtained from VWR International Co. Methyl 15-hydroxypentadecanoate[2] and methyl 15-oxopentadecanoate[3] were prepared according to literature procedure. Anhydrous solvents (CH_2Cl_2, Et_2O, THF, DMF, toluene, and *n*-hexane) were dried and deoxygenated using a GlassContour system (Irvine, CA). Isolated yields reflect the mass obtained following flash column silica gel chromatography. Organic compounds were purified using the method reported by Still[4] and using silica gel obtained from Silicycle Chemical division (40-63 nm; 230-240 mesh). Analytical thin-layer chromatography (TLC) was performed on glass-backed silica gel 60 coated with a fluorescent indicator (Silicycle Chemical division, 0.25 mm, F_{254}.). Visualization of TLC plates was performed by UV (254 nm), $KMnO_4$ or *p*-anisaldehyde stains. All mixed solvent eluents are reported as v/v solutions. Concentration refers to removal of volatiles at low pressure on a rotary evaporator. All reported compounds were homogeneous by thin layer chromatography (TLC) and by ^{1}H NMR. NMR spectra were

[1] Shriver, D. F.; Drezdon, M. A. in *The Manipulation of Air-Sensitive Compounds*; Wiley-VCH: New York, 1986.

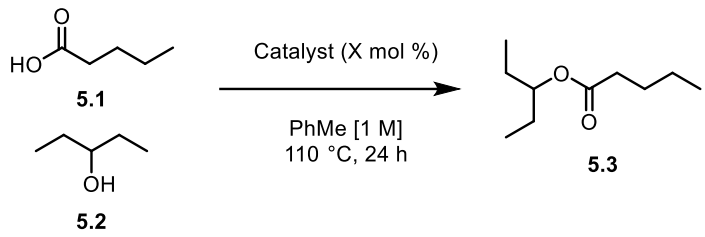
[2] Yamashita, Y.; Mutoh, Y.; Yamasaki, R.; Kasama, T.; Saito, S. *Chem. Eur. J.* **2015**, *21*, 2139-2145.

[3] Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem*. **1978**, *43*, 2923-2925.

taken in deuterated $CDCl_3$ using Bruker AV-300 and AV-400 instruments unless otherwise noted. Signals due to the solvent served as the internal standard ($CHCl_3$: δ 7.27 for ^1H, δ 77.0 for ^{13}C). The ^1H NMR chemical shifts and coupling constants were determined assuming first-order behavior. Multiplicity is indicated by one or more of the following: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad); the list of couplings constants (*J*) corresponds to the order of the multiplicity assignment. High resolution mass spectroscopy (HRMS) was done by the Centre régional de spectrométrie de masse at the Département de Chimie, Université de Montréal using an Agilent LC-MSD TOF system with the ESI mode of ionization unless otherwise noted.

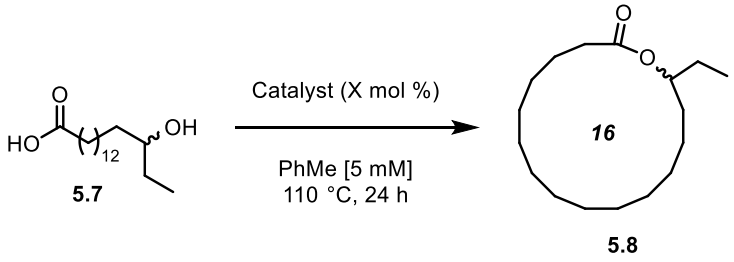
GENERAL PROCEDURES

A. General Procedure for the Synthesis of 5.3 via Lewis Acid Activation



Pentan-3-yl pentanoate (5.3) 3-Pentanol (0.11 mL, 1.0 mmol, 1.0 equiv.) and valeric acid (0.11 mL, 1.0 mmol 1.0 equiv.) were dissolved in toluene (1.0 mL, 1.0 M). The Lewis acid catalyst (see Table 5.1) was added to the solution and the reaction mixture was stirred at 110 ºC for 24 h. After cooling down to room temperature, silica gel (~ 5 mL) was added and the slurry was concentrated under reduced pressure and purified by flash chromatography (10 to 40 % EtOAc in hexanes) to afford the desired product as a colorless oil. Spectral data were in accordance with those previously reported in the literature.[5]

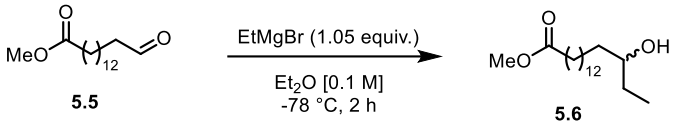
B. General Procedure for the Synthesis of 5.5 via Lewis Acid Activation



[5] Srimani, D.; Balaraman, E.; Gnanaprakasam, B.; Ben-David, Y.; Milstein, D. *Adv.. Syn. Cat.* **2012**, *354* (13), 2403-2406.

15-Heptadecanolide (5.5) 15-Hydroxyheptadecanoic acid (28 mg, 0.1 mmol, 1.0 equiv.) was dissolved in toluene (20.0 mL, 5.0 mM). The Lewis acid catalyst (see Table 5.2) was added to the solution and the reaction mixture heated to 110 ºC. The reaction mixture was stirred at this temperature for 24 h. After cooling down to room temperature, silica gel (~ 2 mL) was added and the slurry was concentrated under reduced pressure and purified by flash chromatography (5 to 40 % EtOAc in hexanes) to afford the desired product as a white solid. Spectral data were in accordance with those previously reported in the literature.[6]

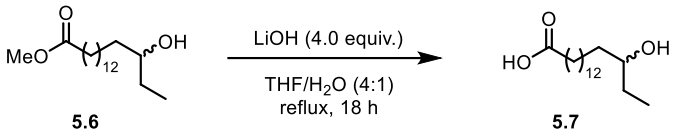
PROCEDURES FOR THE MACROCYCLIC PRECURSOR 5.7



Methyl 15-hydroxyheptadecanoate 5.6 Et_2O (16 mL, 0.1 M) was added to a round-bottom flask under N_2. Methyl 15-oxopentadecanoate (437 mg, 1.60 mmol, 1.00 equiv.) was added and the mixture was allowed to cool down to -78 °C. A solution of ethylmagnesium bromide in THF (1.12 mL, 1.68 mmol, 1.5 M) was added dropwise and the reaction mixture was stirred at -78 °C for 2 h. The reaction was quenched by the addition of a saturated solution of NH_4Cl (5 mL) and extracted with EtOAc (10 mL). The organic phase was washed with water (20 mL) and brine (20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. Flash chromatography (10 % EtOAc in hexanes) was performed to afford **5.6** as a white solid (193 mg, 40%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.67 (s, 3H), 3.55-3.50 (m, 1H), 2.30 (t, J = 7.6 Hz, 2H), 1.65-1.60 (m, 2H), 1.55-1.35 (m, 6H), 1.30-1.25 (m, 18H), 0.94 (t, J = 7.4 Hz, 3H) ppm;

[6] Bollbuck, B.; Tochtermann, W. *Tetrahedron* **1999**, *55* (23), 7209-7220.

^{13}C NMR (75 MHz, $CDCl_3$) δ 174.4, 73.3, 36.9, 34.1, 30.1, 29.7, 29.6 (4C), 29.5, 29.4, 29.2, 29.1, 25.6, 24.9, 9.9 ppm; HRMS (ESI+) for $C_{18}H_{37}O_3$ $[M + H]^+$ calculated: 301.2698 found: 301.2711.

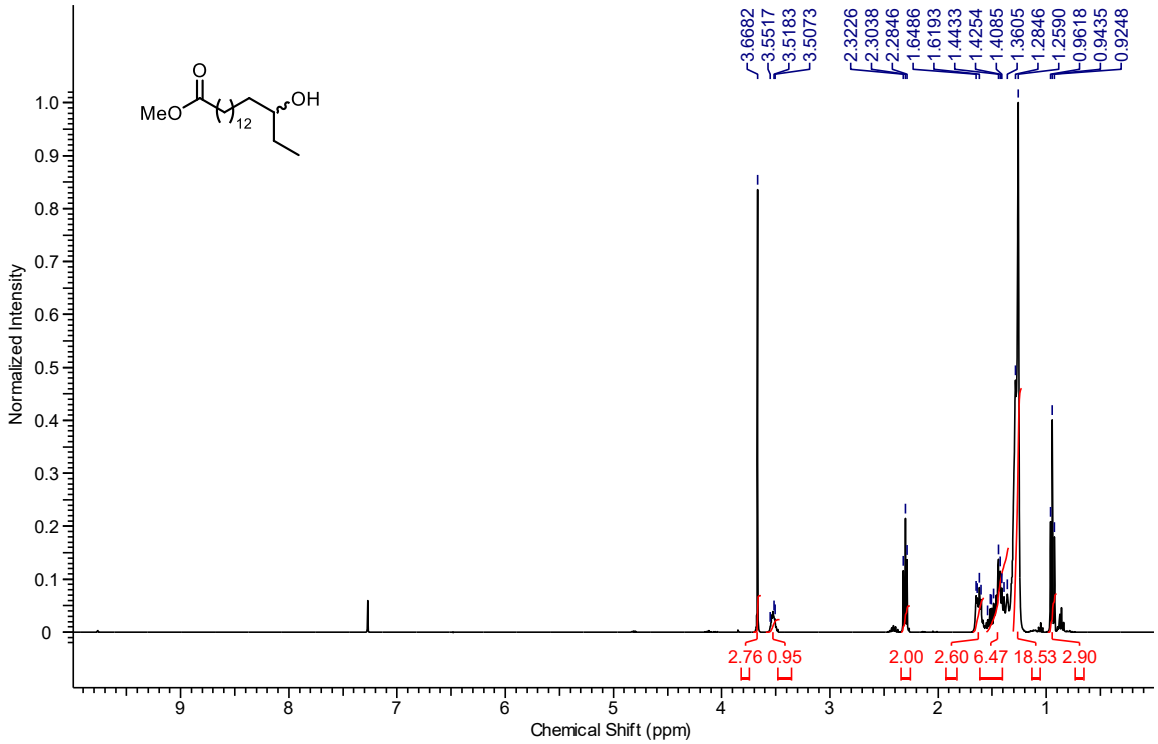


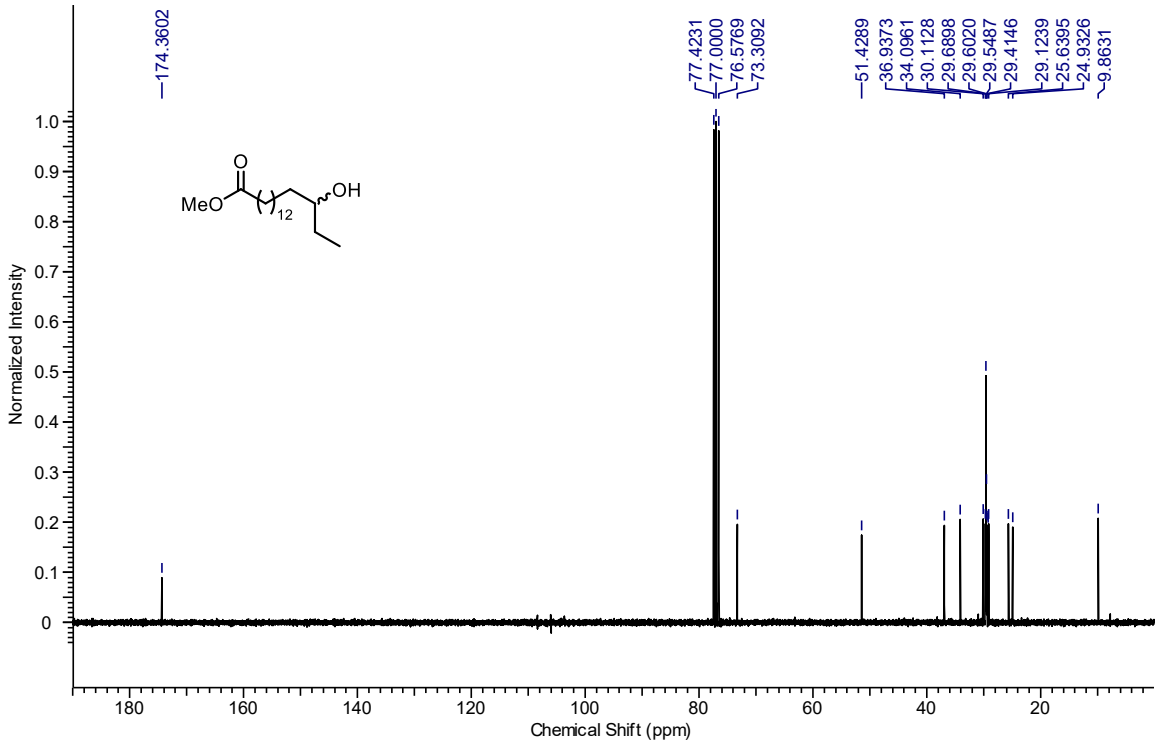
5.6 **5.7**

15-hydroxyheptadecanoic acid 5.7 Methyl 15-hydroxyheptadecanoate (403 mg, 1.34 mmol, 1.00 equiv.) was dissolved in THF (11 mL). LiOH (225 mg, 5.36 mmol, 4.00 equiv.) was added as a solution in water (3 mL). The reaction mixture was stirred at reflux for 18 h. The mixture was cooled down to room temperature and HCl 1M was added until the mixture was neutralized (pH = 7). Extraction with EtOAc (3 X 15 mL) was performed and the combined organic phases were washed with brine (45 mL). The organic phase was dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford **5.7** as a white solid (326 mg, 86 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.60-3.52 (m, 1H), 2.34 (t, *J* = 7.5 Hz, 2H), 1.68-1.60 (m, 2H), 1.54-1.40 (m, 6H), 1.35-1.23 (m, 18H), 0.94 (t, *J* = 7.4 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.2, 73.4, 36.9, 34.0, 30.0, 29.7, 29.6 (2C), 29.5 (2C), 29.4, 29.3, 29.2, 29.0 25.6, 24.7, 9.8 ppm; HRMS (ESI+) for $C_{17}H_{35}O_3$ $[M + H]^+$ calculated: 287.2541 found: 287.2573.

Spectral Data

Compound 5.6

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77.0000
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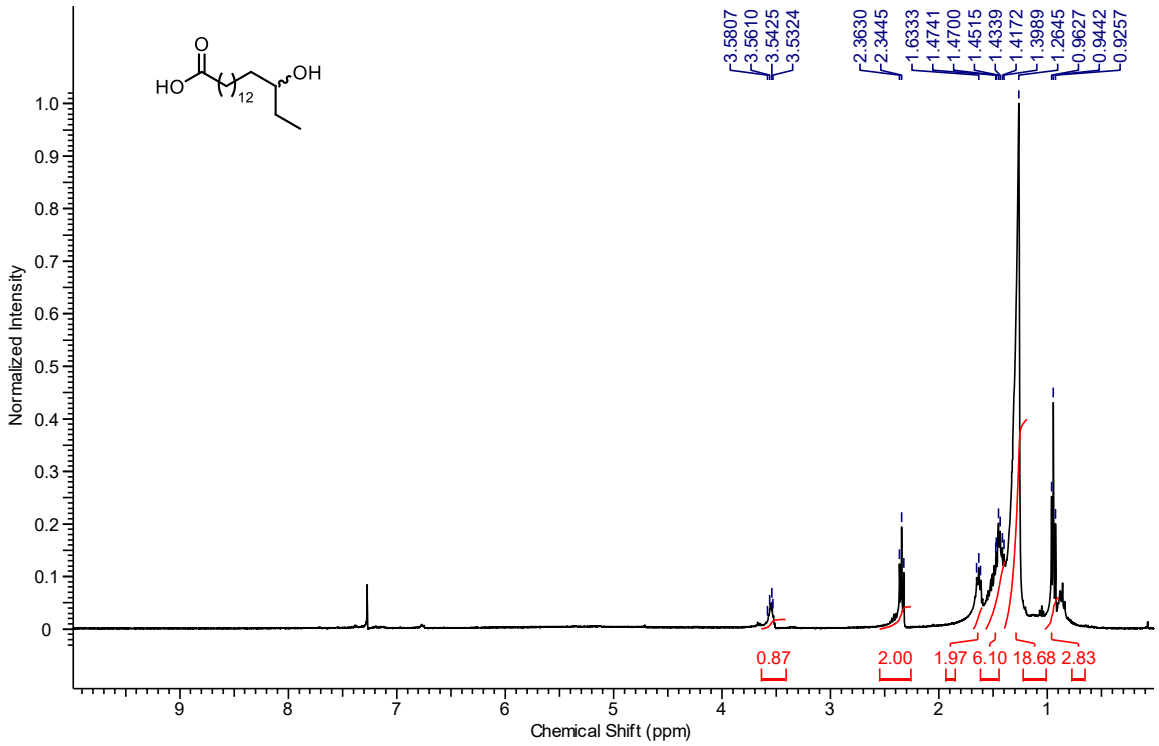
29.6898
29.6020
29.5487
29.4146
29.1239
25.6395
24.9326
9.8631
MeO
12
OH
Normalized Intensity
Chemical Shift (ppm)

Compound 5.7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1.4172
1.3989
1.2645
0.9627
0.9442
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OH
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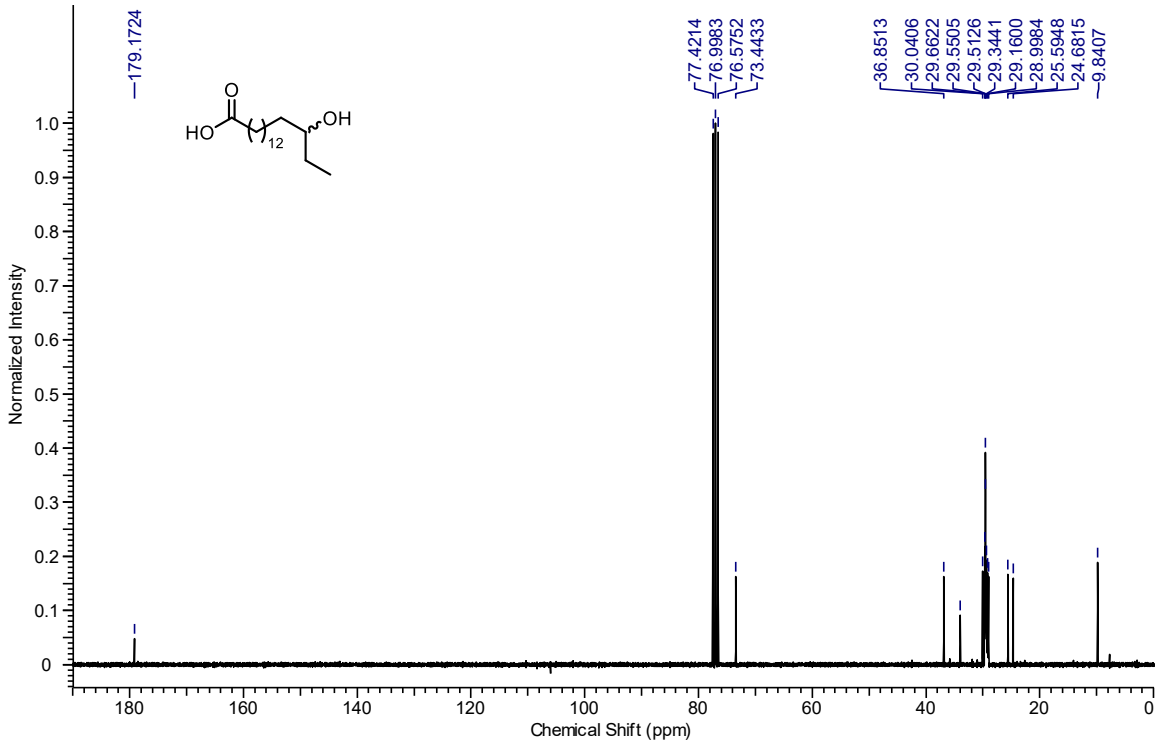
1.97
6.10
18.68
2.83
Normalized Intensity
Chemical Shift (ppm)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29.3441
29.1600
28.9984
25.5948
24.6815
9.8407
HO
O
OH
12
Normalized Intensity
Chemical Shift (ppm)

Annexe 4. Supporting Information of Chapter 7

GENERAL:

All reactions that were carried out under anhydrous conditions were performed under an inert argon or nitrogen atmosphere in glassware that had previously been dried overnight at 120 °C or had been flame dried and cooled under a stream of argon or nitrogen.[1] All chemical products were obtained from Sigma-Aldrich Chemical Company or Strem Chemicals and were reagent quality. Technical solvents were obtained from VWR International Co. Tridec-12-ynoic acid[2], (±)-3-hydroxy-5-(triisopropylsilyl)pent-1-en-4-yne,[3] (3*S*)-3-hydroxy-5-(triisopropylsilyl)pent-1-en-4-yne[3] and methyl dec-9-enoate[4] were prepared according to literature procedure. Anhydrous solvents (CH_2Cl_2, Et_2O, THF, DMF, toluene, and *n*-hexane) were dried and deoxygenated using a GlassContour system (Irvine, CA). Isolated yields reflect the mass obtained following flash column silica gel chromatography. Organic compounds were purified using the method reported by W. C. Still[5] and using silica gel obtained from Silicycle Chemical division (40-63 nm; 230-240 mesh). Analytical thin-layer chromatography (TLC) was performed on glass-backed silica gel 60 coated with a fluorescence indicator (Silicycle Chemical division, 0.25 mm, F_{254}.). Visualization of TLC plate was performed by UV (254 nm), $KMnO_4$ or *p*-anisaldehyde stains. All mixed solvent eluents are reported as v/v solutions. Concentration refers to removal of volatiles at low pressure on a rotary evaporator. All reported

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[1] Shriver, D. F.; Drezdon, M. A. in *The Manipulation of Air-Sensitive Compounds*; Wiley-VCH: New York, 1986.

[2] Lumbroso, A.; Abermil, N.; Breit, B. *Chem. Sci.*, **2012**, *3*, 789.

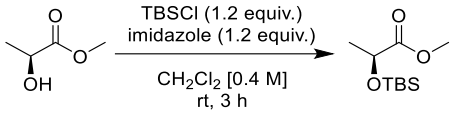
[3] Mann, T. J.; Speed, Alexander W. H.; Schrock, R. R.; Hoveyda, A. H. *Angew. Chem., Int.Ed*. **2013** , *52*, 8395. An alternative synthesis, via diastereomeric resolution, can be used. See page S6.

[4] Ranganathan, D.; Ranganathan, S.; Mehrotra, M. M. *Tetrahedron* **1980**, *36*, 1869.

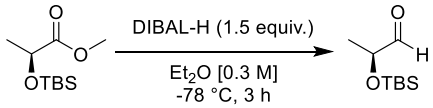
[5] Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem*. **1978**, *43*, 2923-2925.

compounds were homogeneous by thin layer chromatography (TLC) and by ^{1}H NMR. NMR spectra were taken in deuterated $CDCl_3$ using Bruker AV-300 and AV-400 instruments unless otherwise noted. Signals due to the solvent served as the internal standard ($CHCl_3$: δ 7.27 for ^{1}H, δ 77.0 for ^{13}C). The acquisition parameters are shown on all spectra. The ^{1}H NMR chemical shifts and coupling constants were determined assuming first-order behavior. Multiplicity is indicated by one or more of the following: s (singlet), d (doublet), t (triplet), q (quartet), appquin (apparent quintet), m (multiplet), br (broad); the list of couplings constants (*J*) corresponds to the order of the multiplicity assignment. High resolution mass spectroscopy (HRMS) was done by the Centre régional de spectrométrie de masse at the Département de Chimie, Université de Montréal from an Agilent LC-MSD TOF system using ESI mode of ionization unless otherwise noted. The microwave used is a Biotage Initiator Sixty®.

SYNTHESIS OF MACROCYCLE PRECURSORS



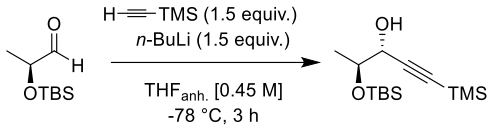
Methyl (*S*)-2-((*tert*-butyldimethylsilyl)oxy)propanoate (5) TBSCl (8.68 g, 57.6 mmol, 1.2 equiv.) and imidazole (3.92 g, 57.6 mmol, 1.2 equiv.) were added to a solution of Methyl (*S*)-2-hydroxypropanoate **(4)** (4.6 mL, 48.0 mmol, 1.0 equiv.) in CH_2Cl_2 (120 mL) at 0 °C. The solution was stirred for 3 h at room temperature. Brine was then added and the organic and aqueous layers were separated. The aqueous phase was extracted with CH_2Cl_2 (3X) and the combined organic phases were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Flash chromatography (6% EtOAc in hexanes) was performed to afford the product as a colorless oil (10.27 g, 98 %). Spectral data were in accordance with those previously reported in the literature.[6]



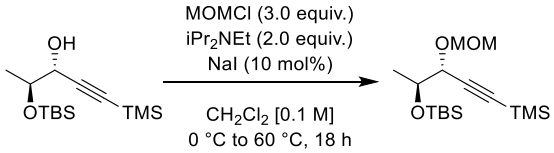
(*S*)-2-((*tert*-butyldimethylsilyl)oxy)propanal (6) DIBAL-H 1 M in hexanes (20.0 mL, 20.0 mmol, 1.5 equiv.) was added dropwise to a solution of methyl (*S*)-2-((*tert*-butyldimethylsilyl)oxy)propanoate **(5)** (2.92 g, 13.35 mmol, 1.0 equiv.) in anhydrous Et_2O (45 mL) at -78 °C and stirred for 3 h. The solution was then quenched with a solution of sodium and potassium tartrate and the organic and aqueous layers were separated. The aqueous layer was extracted with Et_2O (3X). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Flash chromatography

[6] Massad, S. K.; Hawkins, L. D.; Baker, D. C. *J. Org. Chem.,* **1983**, *48*, 5180.

(10% Et_2O in hexanes) was performed to afford the product as a colorless oil (1.92 g, 77 %). Spectral data were in accordance with those previously reported in the literature.[6]



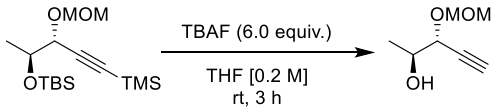
(*3R,4S*)-4-((*tert*-butyldimethylsilyl)oxy)-1-(trimethylsilyl)pent-1-yn-3-ol (S1) *n*-BuLi 1.35 M in THF (11.5 mL, 15.6 mmol, 1.5 equiv.) was added dropwise to a solution of ethynyltrimethylsilane (2.2 mL, 15.6 mmol, 1.5 equiv.) in anhydrous THF (23 mL) at -78 °C. The solution was stirred for 2 h at 0 °C. (*S*)-2-((*tert*-butyldimethylsilyl)oxy)propanal **(6)** (1.96 g, 10.4 mmol, 1.0 equiv.) was added to the solution at -78 °C and stirred for an additional hour. The solution was then quenched with a solution of sodium and potassium tartrate. The resulting mixture was vigorously stirred for 2 h before Et_2O (30 mL) was added to the mixture. The organic and aqueous layers were separated. The aqueous layer was extracted with Et_2O (3X). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Flash chromatography (100 % Hexanes to 4 % EtOAc in hexanes) was performed to afford exclusively the desired diastereoisomer as a white solid (1.55 g, 52 %). Spectral data were in accordance with those previously reported in the literature.[7]



(*5R,6S*)-6,8,8,9,9-pentamethyl-5-((trimethylsilyl)ethynyl)-2,4,7-trioxa-8-siladecane (7) In a sealable tube, NaI (135 mg, 0,89 mmol, 10 mol%) was added to a solution of (*3R,4S*)-4-((*tert*-butyldimethylsilyl)oxy)-1-(trimethylsilyl)pent-1-yn-3-ol **(S1)** (2.58 g, 8.9 mmol, 1.0 equiv.) in

[7] Marshall, J. A.; Bourbeau, M. P. *Org. Lett.*, **2003**, *5*, 3197.

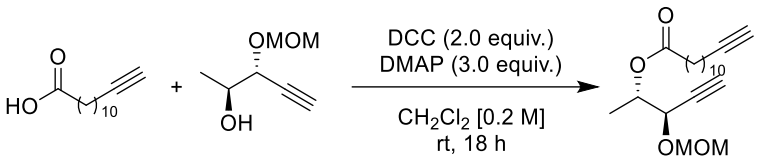
CH_2Cl_2 (90 mL). The solution was cooled to 0 °C and *i*Pr_2NEt (3.13 mL, 17.9 mmol, 2.0 equiv.) and MOMCl (2.05 mL, 26.9 mmol, 3.0 equiv.) were added. The mixture was stirred for 18 h at 60 °C then quenched with water and the organic and aqueous layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3X). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Flash chromatography (100 % Hexanes to 5 % EtOAc in hexanes) was performed to afford the product as a yellow oil (2.97 g, 99 %). Spectral data were in accordance with those previously reported in the literature.[8]



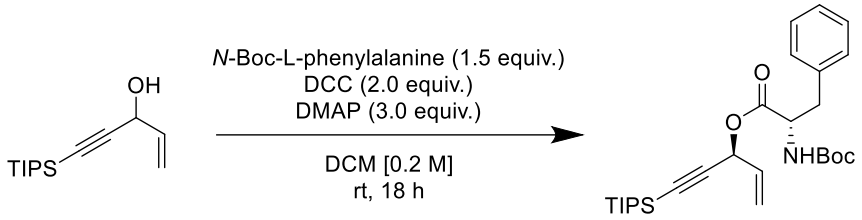
(*2S,3R*)-3-(methoxymethoxy)pent-4-yn-2-ol (3) TBAF (1 M in THF) (53.9 mL, 53.9 mmol, 6 equiv.) was added to a solution of (*5R,6S*)-6,8,8,9,9-pentamethyl-5-((trimethylsilyl)ethynyl)-2,4,7-trioxa-8-siladecane **(7)** (2.97 g, 9.0 mmol, 1.0 equiv.) in anhydrous THF (45 mL) and stirred for 3 h at room temperature. The solution was then quenched with water and the organic and aqueous layers were separated. The aqueous layer was extracted with EtOAc (3X). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Flash chromatography (30 % EtOAc in hexanes) was performed to afford the product as a yellow oil (1.22 g, 94 %). **^{1}H NMR** (400 MHz, CDCl3) δ 4.96 (d, *J* = 8 Hz, 1H), 4.70 (d, *J* = 8 Hz, 1H), 4.31-4.29 (m, 1H), 3.98-3.95 (m, 1H), 3.42 (s, 3H), 2.50 (d, *J* = 2 Hz, 1H), 2.38 (bs, 1H) 1.31 (d, *J* = 4 Hz, 3H) ppm. **^{13}C NMR** (75 MHz,

[8] Zhang, B.; Wang, Y.; Yang, S. P.; Zhou, Y.; Wu, W. B.; Tang, W.; Zuo, J. P.; Li, Y.; Yue, J. M. *J. Am. Chem. Soc.,* **2012**, *134*, 20605.

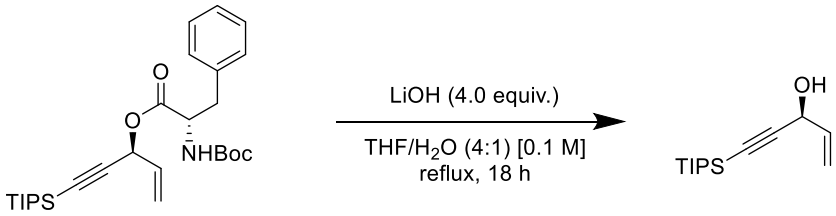
$CDCl_3$) δ 94.4, 79.0, 75.8, 70.8, 69.1, 55.9, 18.1 ppm. **HRMS** (ESI^+) m/z calculated for $C_7H_{12}NaO_3$ $[M+Na]^+$: 167.0679; found: 167.0675.



(*2S,3R*)-3-(methoxymethoxy)pent-4-yn-2-yl tridec-12-ynoate (2a) DCC (946 mg, 4.6 mmol, 2 equiv.), DMAP (840 mg, 6.9 mmol, 3 equiv.) and (*2S,3R*)-3-(methoxymethoxy)pent-4-yn-2-ol **(3)** (331 mg, 2.3 mmol, 1 equiv.) were added to a solution of tridec-12-ynoic acid **(8)** (723 mg, 3.4 mmol, 1.5 equiv.) in CH_2Cl_2 (10 mL) and stirred for 18 h at room temperature. The solution was then placed in the freezer for 12 h and the precipitated urea was filtered. Silica gel was added to the filtrate and the slurry was concentrated under reduced pressure. Flash chromatography (100 % hexanes to 10 % EtOAc in hexanes) was performed to afford the product as a colorless oil (579 mg, 75 %). **^{1}H NMR** (400 MHz, CDCl3) δ 5.1-5.10 (m, 1H), 4.92 (d, *J* = 6.8 Hz, 1H), 4.64 (d, *J* = 6.9 Hz, 1H), 4.42 (dd, *J* = 4 Hz, *J* = 2.1 Hz, 1H), 3.40 (s, 3H), 2.45 (d, *J* = 2.2 Hz, 1H), 2.33 (t, *J* = 7.5 Hz, 2H), 2.19 (td, *J* = 7.1 Hz, *J* = 2.7 Hz, 2H), 1.95 (t, *J* = 2.7 Hz, 1H), 1.65-1.61 (m, 2H), 1.56-1.49 (m, 2H), 1.40-1.28 (m, 15H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 173.1, 94.2, 84.8, 79.1, 75.0, 70.8, 68.0, 67.4, 55.7, 34.4, 29.40, 29.36, 29.2, 29.0 (2C), 28.7, 28.5, 24.9, 18.4, 15.1 ppm. **HRMS** (ESI^+) m/z calculated for $C_{20}H_{36}NO_4$ $[M+NH_4]^+$: 354.2639; found: 354.2648.

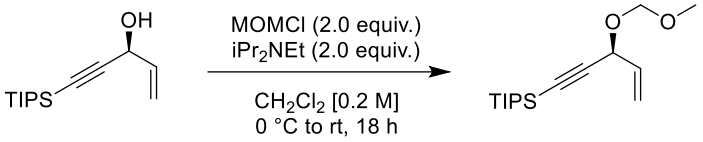


(3S)-3-(*N*-Boc-L-phenylalanine)-5-(triisopropylsilyl)pent-1-en-4-yne (S2) DCC (2.74 g, 13.3 mmol, 2 equiv.), DMAP (2.43 g, 19.9 mmol, 3 equiv.) and (±)-3-hydroxy-5-(triisopropylsilyl)pent-1-en-4-yne **(rac-10)** (1.58 g, 6.64 mmol, 1 equiv.) were added to a solution of *N*-Boc-L-phenylalanine (2.64 g, 9.96 mmol, 1.5 equiv.) in CH_2Cl_2 (10 mL) and stirred for 18 h at room temperature. The solution was then placed in the freezer for 12 h and the precipitated urea was filtered. Silica gel was added to the filtrate and the slurry was concentrated under reduced pressure. Flash chromatography (100 % hexanes to 7 % Et_2O in hexanes) was performed to separate the diastereomers and isolate **S2** as a colorless oil (923 mg, 29 %). **^{1}H NMR** (400 MHz, CDCl3) δ 7.29-7.15 (m, 5H), 5.92 (d, *J* = 4.4Hz, 1H), 5.98-5.81 (m, 1H), 5.61 (d, *J* = 13.7 Hz, 1H), 5.34 (d, *J* = 9.8Hz, 1H), 4.96 (d, *J* = 6.8 Hz, 1H), 4.63 (d, *J* = 5.8 Hz, 1H), 3.13-3.06 (m, 2H), 1.42 (s, 9H), 1.10-1.09 (m, 21 H) ppm. **^{13}C NMR** (100 MHz, $CDCl_3$) δ 170.5, 155.0, 135.8, 132.5, 129.5, 129.4, 128.5, 127.0, 119.6, 119.4, 101.4, 89.7, 79.9, 65.6, 54.2, 37.9, 54.2, 37.9, 28.3, 18.5, 11.1 ppm. **HRMS** (ESI^+) m/z calculated for $C_{28}H_{43}NO_4SiNa$ $[M+Na]^+$: 508.2854; found: 508.2865.



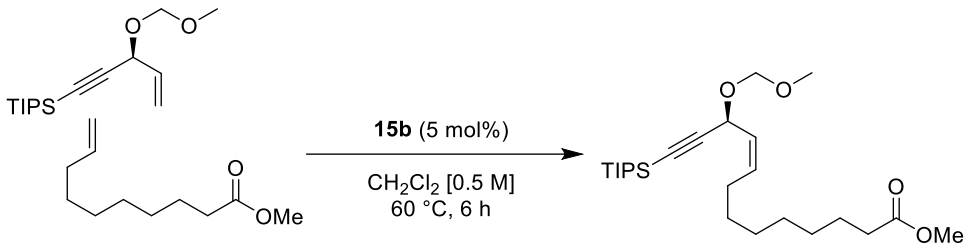
(±)-3-hydroxy-5-(triisopropylsilyl)pent-1-en-4-yne (10) The amino acid adduct **(S3)** (960 mg, 1.98 mmol, 1.0 equiv.) was dissolved in tetrahydrofuran (16 mL). Then LiOH (190 mg, 7.92 mmol, 4.0 equiv.) was added as an aqueous solution (4 mL). The reaction mixture was stirred

at 65 ºC for 18 h. The reaction was then cooled to room temperature and HCl (1 M) was added until the mixture was neutralized (pH = 7). Extraction with EtOAc (3 X 5 mL) was performed and the combined organic phases were washed with brine (15 mL). The organic phase was dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford the desired product as a white solid (421 mg, 89 %). Spectral data were in accordance with those previously reported in the literature.[3]



(3S)-3-(methoxymethoxy)-5-(triisopropylsilyl)pent-1-en-4-yne (11) The alcohol **(10)** (1.50 g, 6.30 mmol, 1.00 equiv.) was dissolved in CH_2Cl_2 (31 mL). iPr_2NEt (2.19 mL, 12.6 mmol, 2.00 equiv.) was added to the solution. MOMCl (0.96 mL, 12.6 mmol, 2.00 equiv.) was carefully added at 0 °C and the reaction mixture was stirred at room temperature for 18 h. The reaction was quenched by addition of water (20 mL) and extracted with CH_2Cl_2 (2 x 15 mL). The combined organic phases were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Flash chromatography (5 % Et_2O in hexanes) was performed to obtain the product as a colorless oil (1.42 g, 80 %). **^{1}H NMR** ($CDCl_3$, 400 MHz) δ = 5.94 (ddd, *J* = 17.0 Hz, 10.2 Hz, 5.5 Hz, 1H), 5.56 (dt, *J* = 17.0 Hz, 1.2 Hz, 1H), 5.28 (dt, *J* = 10.2 Hz, 1.2 Hz, 1H), 4.98 (d, *J* = 6.7 Hz, 1H), 4.90 (dt, *J* = 5.5 Hz, 1.2 Hz, 1H), 4.68 (d, *J* = 6.7 Hz, 1H), 3.41 (s, 3H), 1.10-1.03 (m, 21H) ppm; **^{13}C NMR** ($CDCl_3$, 75 MHz) δ = 134.9, 117.7, 103.6, 93.7,

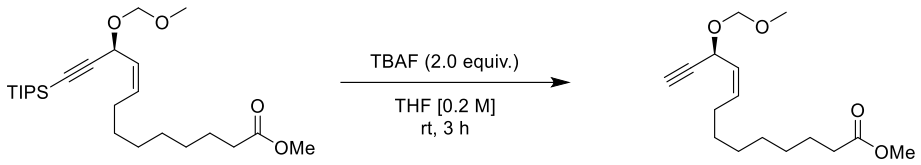
88.4, 66.7, 5.7, 18.6, 11.1 ppm; **HRMS** (ESI$^+$) calculated for $C_{16}H_{30}O_2SiNa$ $[M + Na]^+$ 305.1907, found 305.1907.[9]



Methyl (11S, 9Z)-11-(methoxymethoxy)-13-(triisopropylsilyl)tridec-9-en-12-ynoate (13) A flame-dried sealable tube was charged with CH_2Cl_2 (2.75 mL), Methyl dec-9-enoate (254 mg, 1.38 mmol, 1.00 equiv.) and ther ester (**12**) (390 mg, 1.38 mmol, 1.00 equiv.). The catalyst **(15b)** (47 mg, 0.069 mmol, 0.05 equiv.) was added and the tube was sealed. The reaction mixture was allowed to stir for 3 h at 60 °C. A second equivalent of Methyl dec-9-enoate **(12)** (254 mg, 1.38 mmol, 1.00 equiv.) was added and the reaction mixture was allowed to stir for an additional 3 h. During the reaction time, the mixture was put under vacuum for 5 seconds every hour to eliminate the ethylene formed. After being cooled down to room temperature, silica was added and the slurry was concentrated under reduced pressure. Flash chromatography (5 to 10 % Et_2O in hexanes) was performed to afford the product as a colorless oil (258 mg, 43 % (68 % BRSM), >95:5 Z : E). **^{1}H NMR** ($CDCl_3$, 400 MHz) δ = 5.64-5.52 (m, 2H), 5.14 (d, *J* = 8.2 Hz, 1H), 4.95 (d, *J* = 6.8 Hz, 1H), 4.63 (d, *J* = 6.8 Hz, 1H), 3.67 (s, 3H), 3.40 (s, 3H), 2.30 (t, *J* = 7.5 Hz, 2H), 2.17-2.11 (m, 2H), 1.66-1.60 (m, 2H), 1.42-1.29 (m, 8 H), 1.11-1.05 (m, 21 H) ppm; **^{13}C NMR** ($CDCl_3$, 100 MHz) δ = 174.2, 133.9, 127.1, 105.2, 93.3, 86.6 61.5, 55.6, 51.4, 34.1, 29.3,

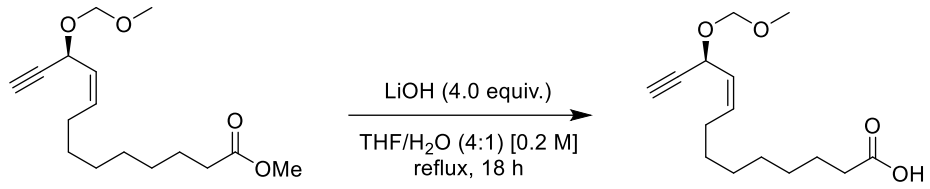
[9] The same procedure was used for the synthesis of **(±)-3-(methoxymethoxy)-5-(triisopropylsilyl)pent-1-en-4-yne (rac-11).** The product was obtained as a colorless oil (1.70 g, 80 %).

29.11, 29.05, 29.03, 27.7, 24.9, 18.6. 11.1 ppm; **HRMS** (ESI^+) calculated for $C_{25}H_{46}O_4SiNa$ [M + Na]$^+$ 461.3058, found 461.3063.[10]

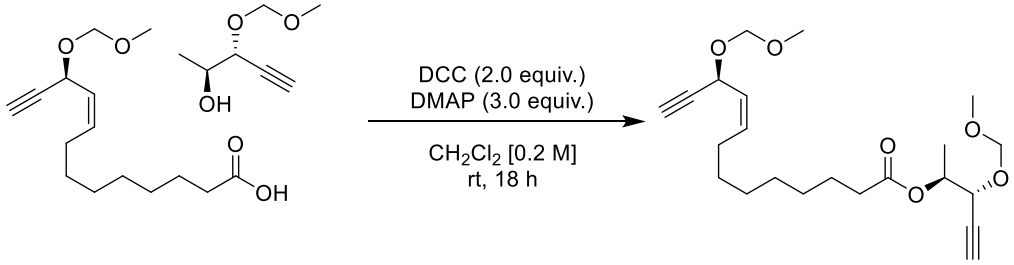


Methyl (11S, 9Z)-11-(methoxymethoxy)tridec-9-en-12-ynoate (S3) The protected alkyne **(13)** (390 mg, 0.890 mmol, 1.00 equiv.) and THF (2.67 mL) was added to a flame-dried round-bottom flask under N_2. TBAF (1 M in THF, 1.78 mL, 1.78 mmol, 2.0 equiv.) was slowly added and the reaction mixture was stirred at room temperature for 3 h. The reaction was quenched by addition of H_2O (2 mL) and extracted with Et_2O (2 x 5 mL). The combined organic phases were washed with H_2O (10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. Flash chromatography (5 % to 10 % EtOAc in hexanes) was performed to afford the product as a colorless oil (230 mg, 92 %). **^{1}H NMR** ($CDCl_3$, 400 MHz) δ = 5.69-5.62 (m, 1H), 5.54-5.48 (m, 1H), 5.13 (ddd, *J* = 8.8 Hz, 2.1 Hz, 0.9 Hz, 1H), 4.85 (d, *J* = 6.9 Hz, 1H), 4.63 (d, *J* = 6.9 Hz, 1H), 3.67 (s, 3H), 3.40 (s, 3H), 2.48 (d, *J* = 2.1 Hz, 1H), 2.30 (t, *J* = 7.5 Hz, 2H), 2.16-2.10 (m, 2H), 1.66-1.58 (m, 2H), 1.43-1.29 (m, 8H) ppm; **^{13}C NMR** ($CDCl_3$, 100 MHz) δ = 174.2, 134.7, 126.4, 93.2, 81.8, 73.5, 60.5, 55.6, 51.4, 34.1, 29.2, 29.0 (2C), 28.9, 27.5, 24.9 ppm; **HRMS** (ESI^+) calculated for $C_{16}H_{26}O_4Na$ [M + Na]$^+$ 305.1723, found 302.1715.

[10] A similar procedure was used for the synthesis of **Methyl (±, 9Z)-11-(methoxymethoxy)-13-(triisopropylsilyl)tridec-9-en-12-ynoate (rac-13)**. The modifications were: the reaction was run for 18 h, there was no second equivalent of ester added, no vacuum was performed and 10 mol% catalyst was used. The product was obtained as a colorless oil (250 mg, 59 %).



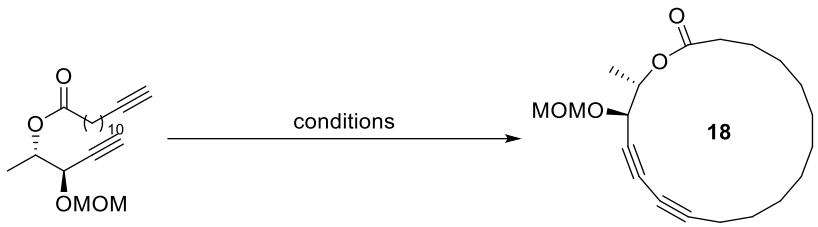
(9Z, 11S)-11-(methoxymethoxy)tridec-9-en-12-ynoic acid (16) Methyl ester **(S3)** (251 mg, 0.890 mmol, 1.0 equiv.) was dissolved in tetrahydrofuran (4 mL). Then LiOH (85 mg, 3.56 mmol, 4.0 equiv.) was added as an aqueous solution (1 mL). The reaction mixture was stirred at 65 ºC for 18 h. The reaction was then cooled to room temperature and HCl (1 M) was added until the mixture was neutralized (pH = 7). Extraction with EtOAc (3 X 5 mL) was performed and the combined organic phases were washed with brine (15 mL). The organic phase was dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford the desired product as a white solid (238 mg, 99 %). **^{1}H NMR** ($CDCl_3$, 400 MHz) δ = 5.66 (dt, *J* = 10.6, 7.5 Hz, 1H), 5.52 (m, 1H), 5.13 (dd, *J* = 8.8, 2.2 Hz, 1H), 4.86 (d, *J* = 6.9 Hz, 1H), 4.64 (d, *J* = 6.9 Hz, 1H), 3.41 (s, 3H), 2.48 (d, *J* = 2.2 Hz, 1H), 2.36 (t, *J* = 7.5 Hz, 2H), 2.16-2.11 (m, 2H), 1.64-1.62 (m, 2H), 1.42-1.33 (m, 8H) ppm; **^{13}C NMR** ($CDCl_3$, 100 MHz) δ = 179.8, 134.6, 126.3, 93.1, 81.6, 73.5, 60.5, 55.5, 33.9, 29.1, 28.9, 28.8 (2C), 27.4, 24.5 ppm; **HRMS** (ESI^+) calculated for $C_{15}H_{23}O_4$ $[M+H]^+$: 267.1602, found 267.1609.



(2S, 3R)-3-(methoxymethoxy)pent-4-yn-2-yl (S, Z)-11-(methoxymethoxy)tridec-12-ynoate (2) DCC (472 mg, 2.29 mmol, 2 equiv.), DMAP (419 mg, 3.44 mmol, 3 equiv.) and (*2S,3R*)-3-(methoxymethoxy)pent-4-yn-2-ol **(3)** (165 mg, 1.15 mmol, 1 equiv.) were added to a solution

of (9Z, 11S)-11-(methoxymethoxy)tridec-9-en-12-ynoic acid (307 mg, 1.15mmol, 1 equiv.) in CH_2Cl_2 (4 mL) and stirred for 18 h at room temperature. The solution was then placed in the freezer for 12 h and the precipitated urea was filtered. Silica gel was added to the filtrate and the slurry was concentrated under reduced pressure. Flash chromatography (100 % hexanes to 20 % EtOAc in hexanes) was performed to afford the product as a colorless oil (282 mg, 62 %).**^{1}H NMR** ($CDCl_3$, 400 MHz) δ = 5.65 (dt, *J* = 11 Hz, 7.3 Hz, 1H), 5.51 (t, *J* = 8.9 Hz, 1H), 5.14-5.09 (m, 2H), 4.92 (d, *J* = 6.9 Hz, 1H), 4.85 (d, *J* = 6.9 Hz, 1H), 4.63 (d, *J* = 6.9 Hz, 2H), 4.42 (dd, *J* = 3.8 Hz, 2.1 Hz, 1H), 3.40 (s, 3H), 3.39 (s, 3H), 2.47 (dd, *J* = 9.9 Hz, 2.1 Hz, 2H), 2.33 (t, *J* = 7.5 Hz, 2H), 2.17-2.10 (m, 2H), 1.66-1.60 (m, 2H), 1.39-1.29 (m, 11H) ppm; **^{13}C NMR** ($CDCl_3$, 100 MHz) δ = 173.0, 134.7, 126.4, 94.2, 93.3, 81.8, 79.1, 75.0, 73.5, 70.8, 67.4, 55.6, 34.4, 29.2, 29.1, 29.0, 27.5, 24.9, 15.1 ppm; **HRMS** (ESI^+) m/z calculated for $C_{22}H_{34}NaO_6$ $[M+Na]^+$: 417.2248; found: 417.2260.

SYNTHESIS OF MACROCYCLES



(*17R,18S*)-17-(methoxymethoxy)-18-methyloxacyclooctadeca-13,15-diyn-2-one (1a)

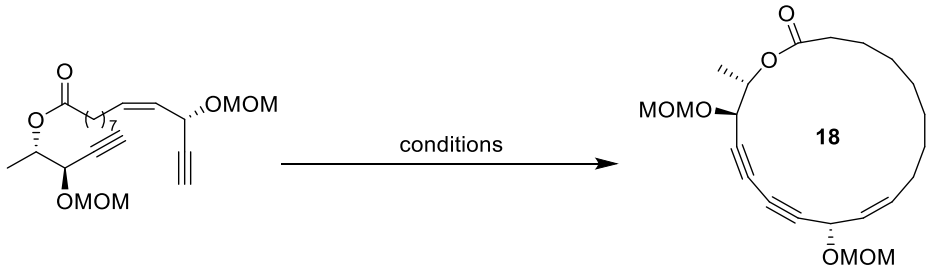
Slow Addition Procedure: To a triple-neck round-bottom flask equipped with a stirring bar and a condenser, CuCl (154 mg, 1.56 mmol, 12 equiv.) and TMEDA (0.4 mL, 2.6 mmol, 20 equiv.) was added to PhMe (550 mL). The mixture was stirred and warmed at 110 °C. To the mixture, a solution of **2a** (44 mg, 0.13 mmol, 1 equiv.) in PhMe (50 mL) was slowly added over 36 h (0.023 mL/min) with a syringe pump. The mixture was stirred and heated for an additional 12 h. The reaction was then cooled down to room temperature and concentrated under reduced

pressure. Flash chromatography was performed (5 % to 20 % EtOAc in hexanes) to afford the desire product as a colorless oil (15.6 mg, 36 %). $[\alpha]_D^{25} = -0.221$ (c = 0.0044, MeOH); **^{1}H NMR** (300 MHz, CDCl3) δ 5.04 (appquint, *J* = 6 Hz, 1H), 4.93 (d, *J* = 9 Hz, 1H), 4.61 (d, *J* = 6 Hz, 1H), 4.30 (d, *J* = 6 Hz, 1H), 3.38 (s, 3H), 2.36-2.31 (m, 4H), 1.74-1.67 (m, 4H), 1.37-1.26 (m, 15H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 172.8, 94.2, 81.0, 71.4, 71.0, 70.7, 69.0, 65.1, 55.9, 35.3, 29.7, 29.2, 28.4, 27.5, 26.8, 26.3, 25.7, 24.9, 18.8, 17.4 ppm. **HRMS** (ESI^+) m/z calculated for $C_{20}H_{30}NaO_4$ $[M+Na]^+$: 357.2036; found: 357.2029.

Microwave Procedure: To a microwave vial equipped with a stirring bar was dissolved the diyne (41 mg, 0.12 mmol, 1 equiv.) in MeOH. To the mixture was added polyethylene glycol 400 (3.75 mL), $CuCl_2 \cdot 2H_2O$ (5 mg, 0.03 mmol, 25 mol %) and $Ni(NO_3)_2 \cdot 6H_2O$ (8.7 mg, 0.03 mmol, 25 mol %) and the mixture was stirred at room temperature for 30 seconds or until the metals were solubilized. Oxygen was bubbled in the solution for 5 min then TMEDA (0.09 mL, 0.6 mmol, 5 equiv.) and Et_3N (0.05 mL, 0.36 mmol, 3 equiv.) were added and the mixture was stirred at room temperature for an additional 30 seconds. The vial was then sealed with a microwave cap. The reaction was warmed to 100 °C for 3 h. The crude mixture was loaded directly onto silica gel for purification by chromatography (10 % to 20 % EtOAc in hexanes) to afford the desire product as a colorless oil (16 mg, 40 %).

Continuous Flow Procedure: To a 200 mL pear-shaped flask equipped with a stirring bar, $CuCl_2 \cdot 2H_2O$ (118 mg, 0.70 mmol, 25 mol%), $Ni(NO_3)_2 \cdot 6H_2O$ (204 mg, 0.70 mmol, 25 mol%), TMEDA (2.07 mL, 13.9 mmol, 5 equiv.) and Et_3N (1.16 mL, 8.34 mmol, 3 equiv.) was dissolved in MeOH (20 mL) and the mixture was stirred at room temperature for 30 seconds or until the metals were solubilized. Poly(propylene glycol) 425 (77.2 mL) was added and the mixture was stirred at room temperature for an additional 30 seconds. **2a** (935 mg, 2.78 mmol, 1 equiv.) was

dissolved in 18.6 mL of MeOH then added to the solution. The reaction mixture was pumped into the flow reactor for a reaction time of 120 min (2 x 10 mL Stainless Steel reactors) at a flow rate of 0.167 mL/min at 120 °C. The flow reaction was conducted in a VapourTec R4 reactor and a R2+ pumping module. The continuous flow setup is ended with two in-line back pressures regulators (VapourTec 8 bar + IDEX 17 bar). Upon completion, the mixture was extracted with EtOAc, washed with water and the combined organic phases were washed with brine. The organic phase was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude mixture was purified by chromatography (5 to 10 % EtOAc in hexanes) to afford the desire product as a yellowish oil (353 mg, 38 %).



(10Z,12S,17R,18S)-12,17-di(methoxymethoxy)-18-methyloxacyclooctadec-10-ene-13,15-diyn-2-one (1)

Slow Addition Procedure: To a triple-neck round-bottom flask equipped with a stirring bar and a condenser, CuCl (119 mg, 1.2 mmol, 12 equiv.) and TMEDA (0.3 mL, 2.0 mmol, 20 equiv.) was added to PhMe (405 mL). The mixture was stirred and warmed at 110 °C. To the mixture, a solution of **2** (40 mg, 0.10 mmol, 1 equiv.) in PhMe (50 mL) was slowly added over 24 h (0.035 mL/min) with a syringe pump. The mixture was stirred and heated for an additional 24 h. The reaction was then cooled down to room temperature and concentrated under reduced pressure. Flash chromatography was performed (5 % to 20 % EtOAc in hexanes) to afford the desire product as a colorless oil (21.4 mg, 55 %). $[\alpha]_D^{25} = -62.1$(c = 0.00145, MeOH); **^{1}H NMR**

(400 MHz, $CDCl_3$) δ 5.63−5.56 (td, J = 10.8, 5.5 Hz, 1H), 5.49 (app t, J = 10.9 Hz, 1H), 5.20 (d, J = 8 Hz, 1H) 5.06−5.01 (m, 1H), 4.91 (d, J = 6.9 Hz, 1H), 4.81 (d, J = 6.7 Hz, 1H), 4.61 (t, J = 5.5 Hz, 1H), 4.28 (d, J = 7.7 Hz, 1H), 3.38 (s, 3H), 3.38 (s, 3H), 2.38−2.29 (m, 2H), 2.20−2.06 (m, 2H), 1.73−1.57 (m, 4H), 1.39−1.29 (m, 9H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 172.8, 134.3, 126.5, 94.4, 93.6, 75.7, 70.6, 70.5, 69.5, 68.9, 61.5, 56.0, 55.7, 35.2, 29.7, 29.5, 29.4, 28.6, 28.5, 27.7, 25.4, 17.6 ppm

Microwave Procedure: To a microwave vial equipped with a stirring bar was dissolved **2** (38 mg, 0.10 mmol, 1 equiv.) in MeOH (1.05 mL). To the mixture was added polyethylene glycol 400 (3.15 mL), $CuCl_2 \cdot 2H_2O$ (4.2 mg, 0.025 mmol, 25 mol %) and $Ni(NO_3)_2 \cdot 6H_2O$ (7 mg, 0.025 mmol, 25 mol %) and the mixture was stirred at room temperature for 30 seconds or until the metals were solubilized. Oxygen was bubbled in the solution for 5 min then TMEDA (0.07 mL, 0.5 mmol, 5 equiv.) and Et_3N (0.04 mL, 0.3 mmol, 3 equiv.) were added and the mixture was stirred at room temperature for an additional 30 seconds. The vial was then sealed with a microwave cap. The reaction was warmed to 100 °C for 3 h. The crude mixture was loaded directly onto silica gel for purification by chromatography (10 % EtOAc in hexanes) to afford the desire product as a colorless oil (11.5 mg, 30 %).

Continuous Flow Procedure: To a 20mL-reaction vial equipped with a stirring bar, $CuCl_2 \cdot 2H_2O$ (3 mg, 0.018 mmol) and $Ni(NO_3)_2 \cdot 6H_2O$ (5.2 mg, 0.018 mmol) was dissolved in MeOH (1.5 mL) and the mixture was stirred at room temperature for 30 seconds or until the metals were solubilized. Polyethylene glycol 400 (1.5 mL), TMEDA (0.05 mL, 0.33 mmol) and Et_3N (0.03 mL, 0.22 mmol) were added and the mixture was stirred at room temperature for an additional 30 seconds. **2** (19.9 mg, 0.051 mmol, 1 equiv.) was mixed 2 mL of the previous solution. The mixture was stirred at room temperature until everything was soluble then taken

into a syringe. The reaction mixture was injected using a 2 mL injection loop into the flow reactor for a reaction time of 120 min (2 x 10 mL Stainless Steel reactors) at a flow rate of 0.167 mL/min at 120 °C. The flow reaction was conducted in a VapourTec R4 reactor and a R2+ pumping module. The continuous flow setup is ended with two in-line back pressures regulators (VapourTec 8 bar + IDEX 17 bar). Upon completion, silica gel was added to the collection flask and the volatiles were removed under vacuum. The crude mixture was purified by chromatography (20 % EtOAc in hexanes) to afford the desire product as a colorless oil (10.2 mg, 52 %).

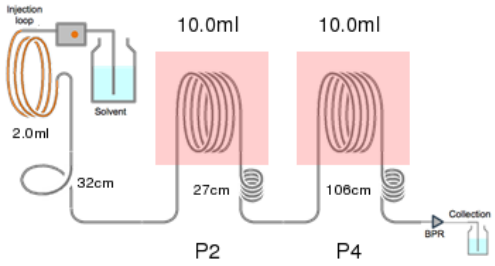
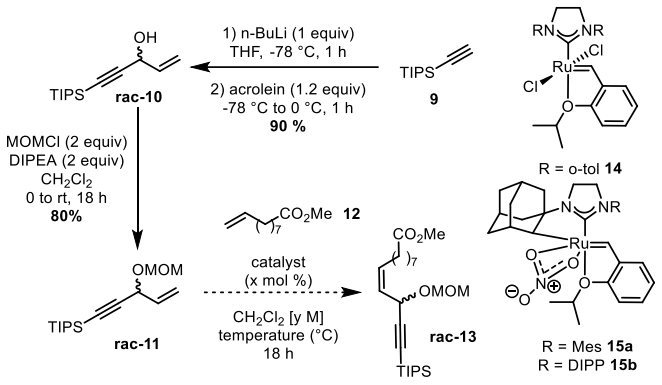


Figure 1. Continuous flow setup.

OPTIMIZATION OF A Z-SELECTIVE CROSS METATHESIS

Table S1 Optimization of a Z-selective cross metathesis to prepare racemic 13.

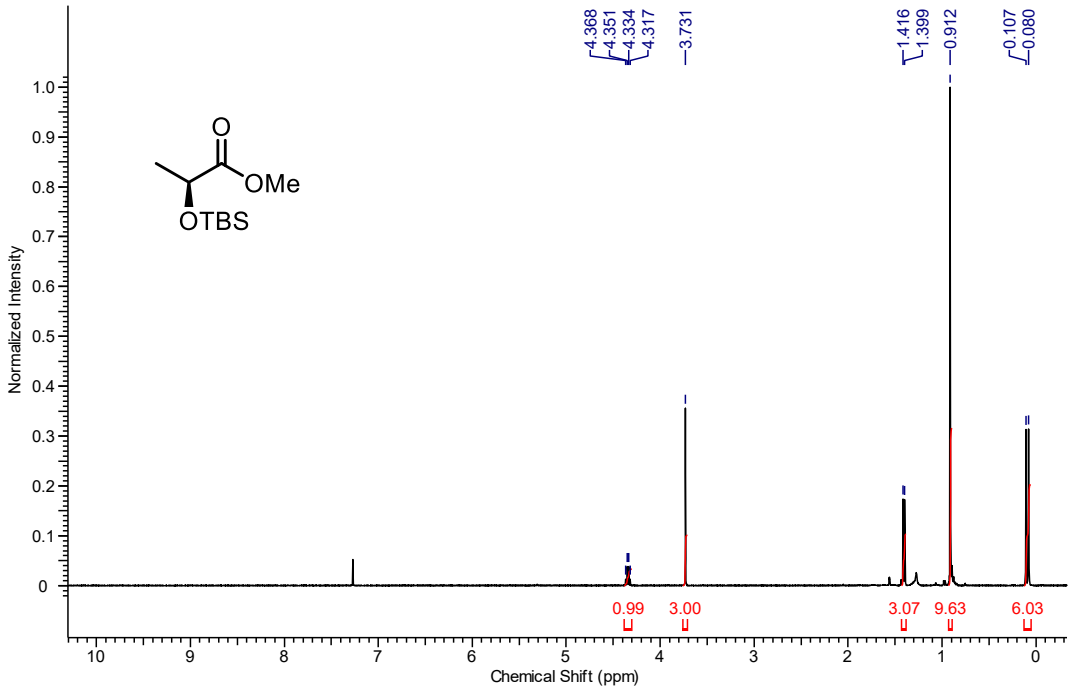


	Catalyst (mol %)	[M]	Temp. (°C)	Yield (%)[a]	% Z[b]
1	**14** (2)	0.1	21	47	< 1
2	**14** (2)	0.1	40	40	< 1
3	**15b** (2)	0.1	21	0	-
4	**15b** (5)	0.5	60	40	~98
5	**15b** (10)	0.5	60	59	95
6	**15a** (10)	0.5	60	16	75

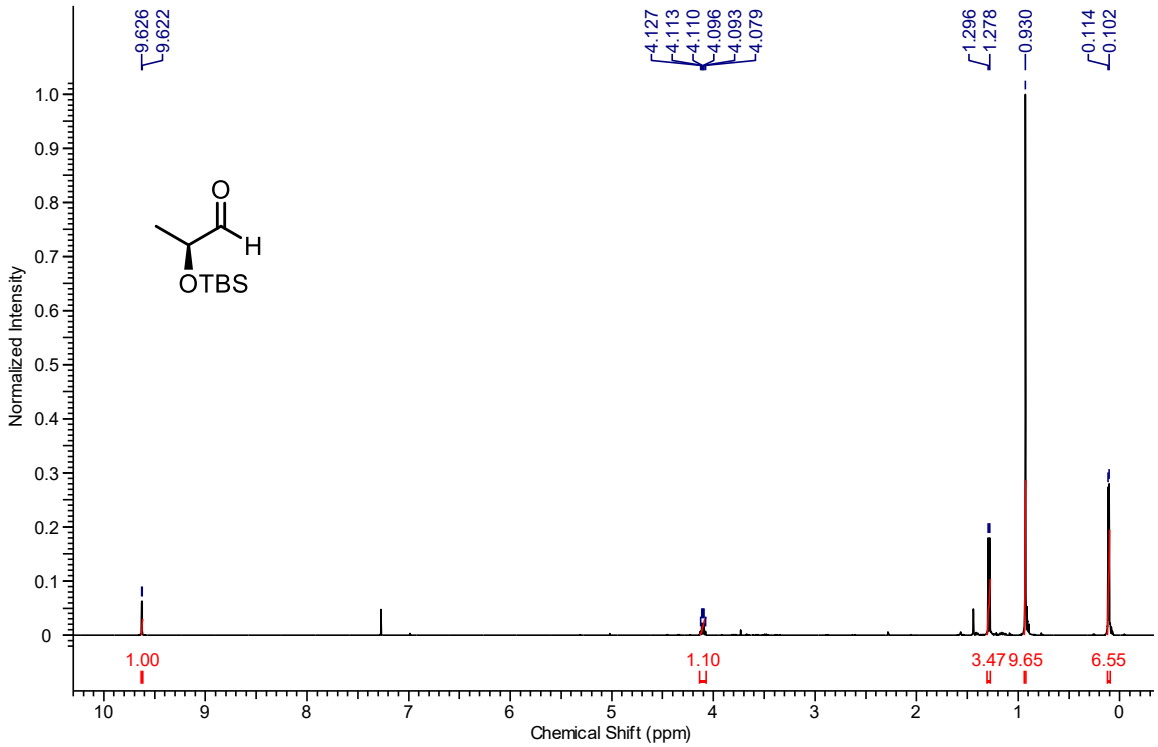
[a] Yields following chromatography. [b] Determined by ^{1}H NMR Mes = 2,4,6-trimethylphenyl, DIPP = 2,6-di-*iso*-propylphenyl.

SPECTRAL DATA FOR KNOWN COMPOUNDS

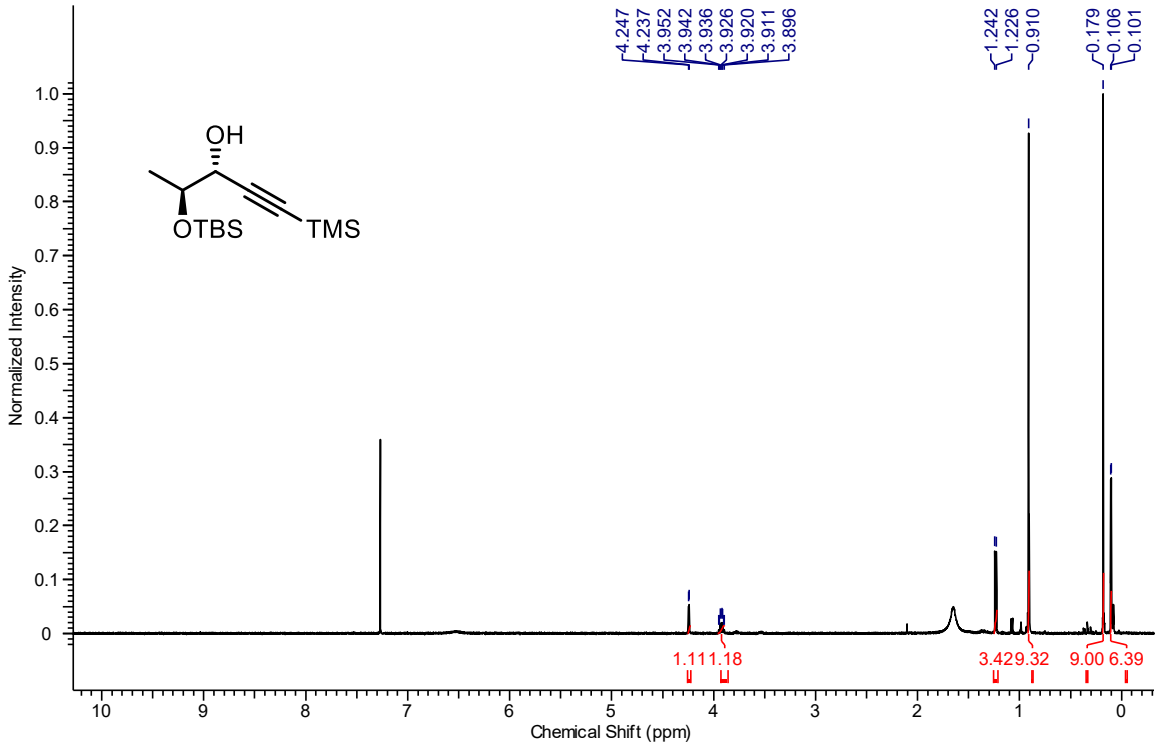
Compound 5



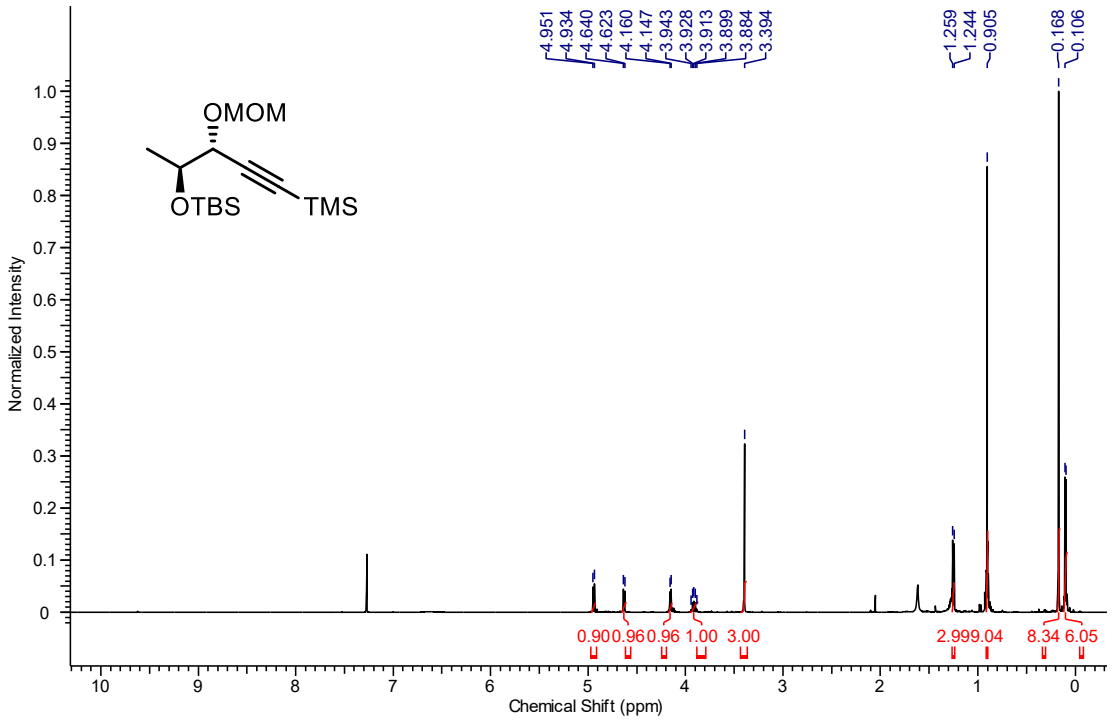
Compound 6



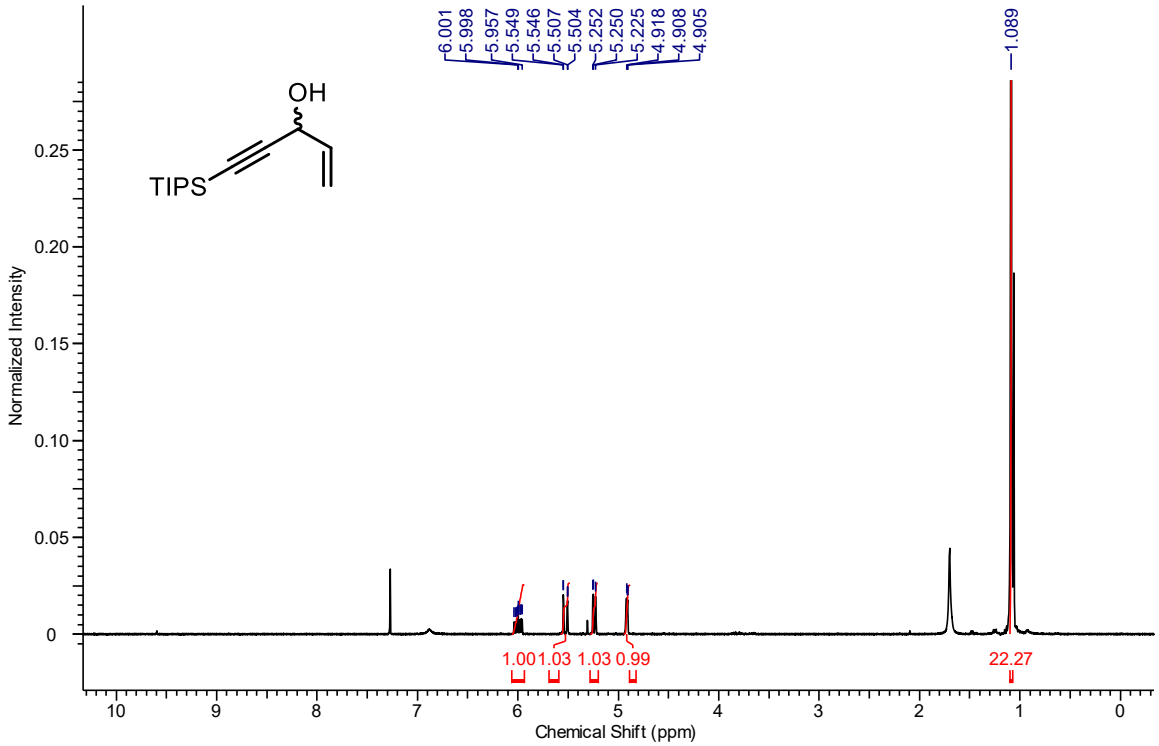
Compound S1



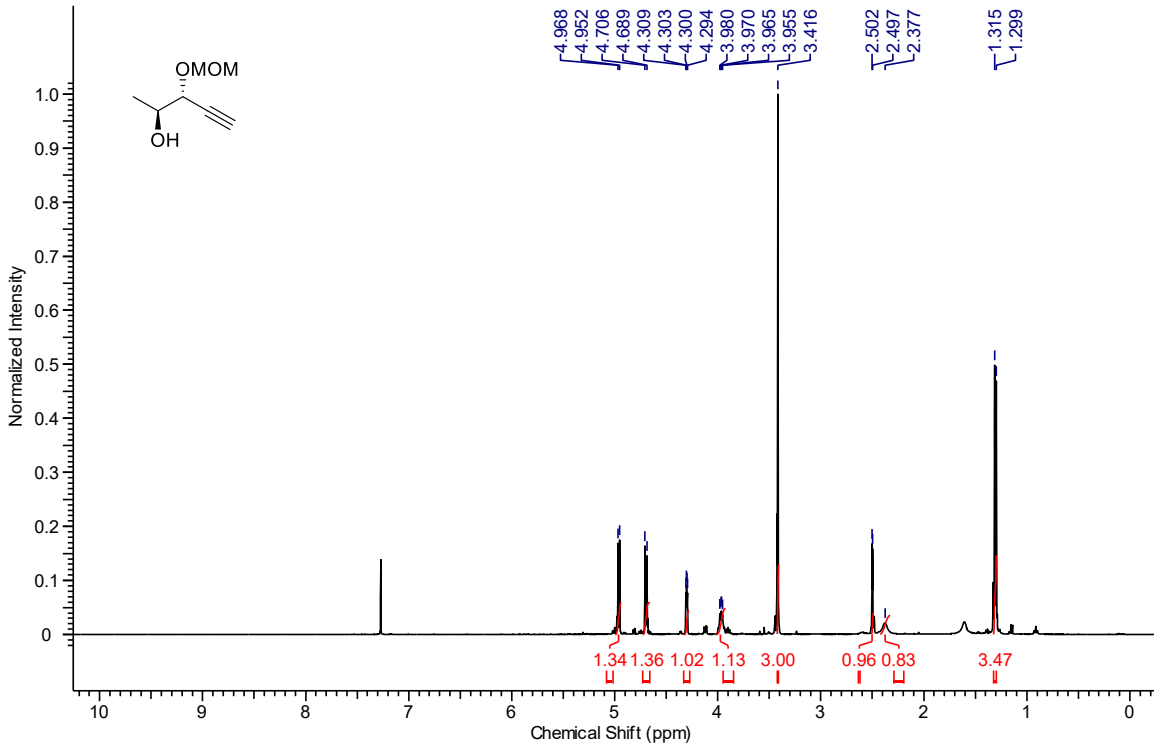
Compound 7



Compound 10


6.001
5.998
5.957
5.549
5.546
5.507
5.504
5.252
5.250
5.225
4.918
4.908
4.905
1.089
OH
TIPS
Normalized Intensity
0.25
0.20
0.15
0.10
0.05
0
1.00 1.03 1.03 0.99
22.27
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

Compound 3


OMOM
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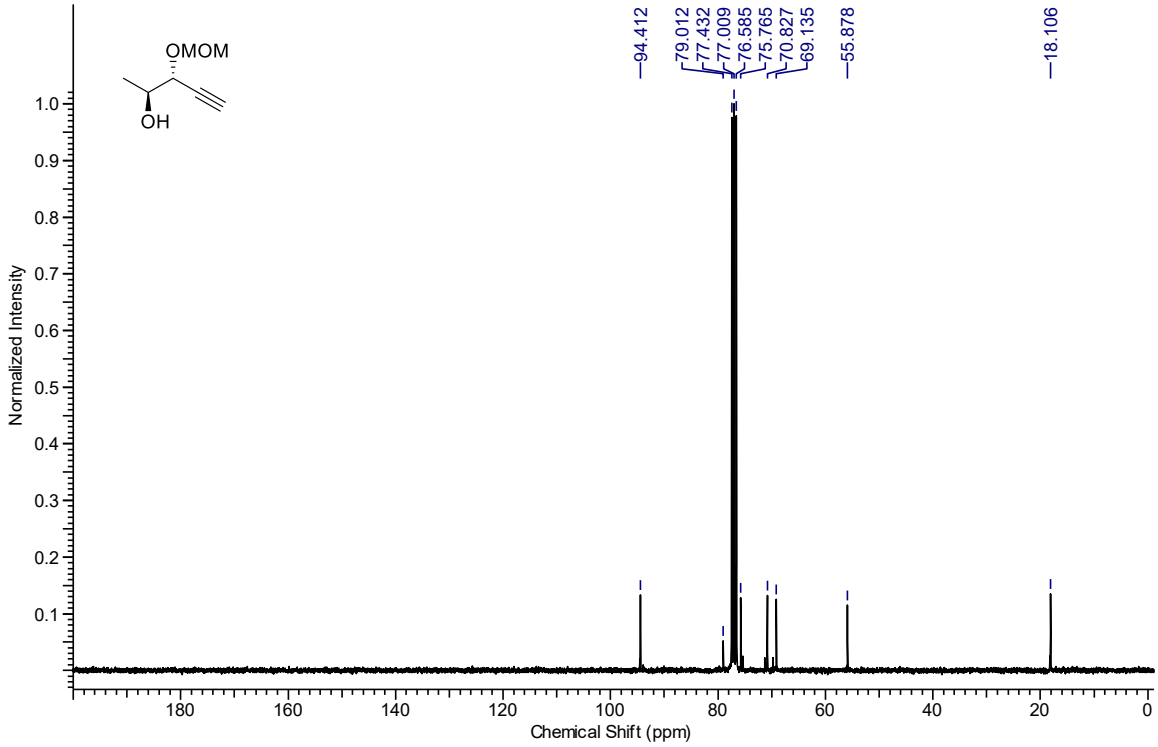
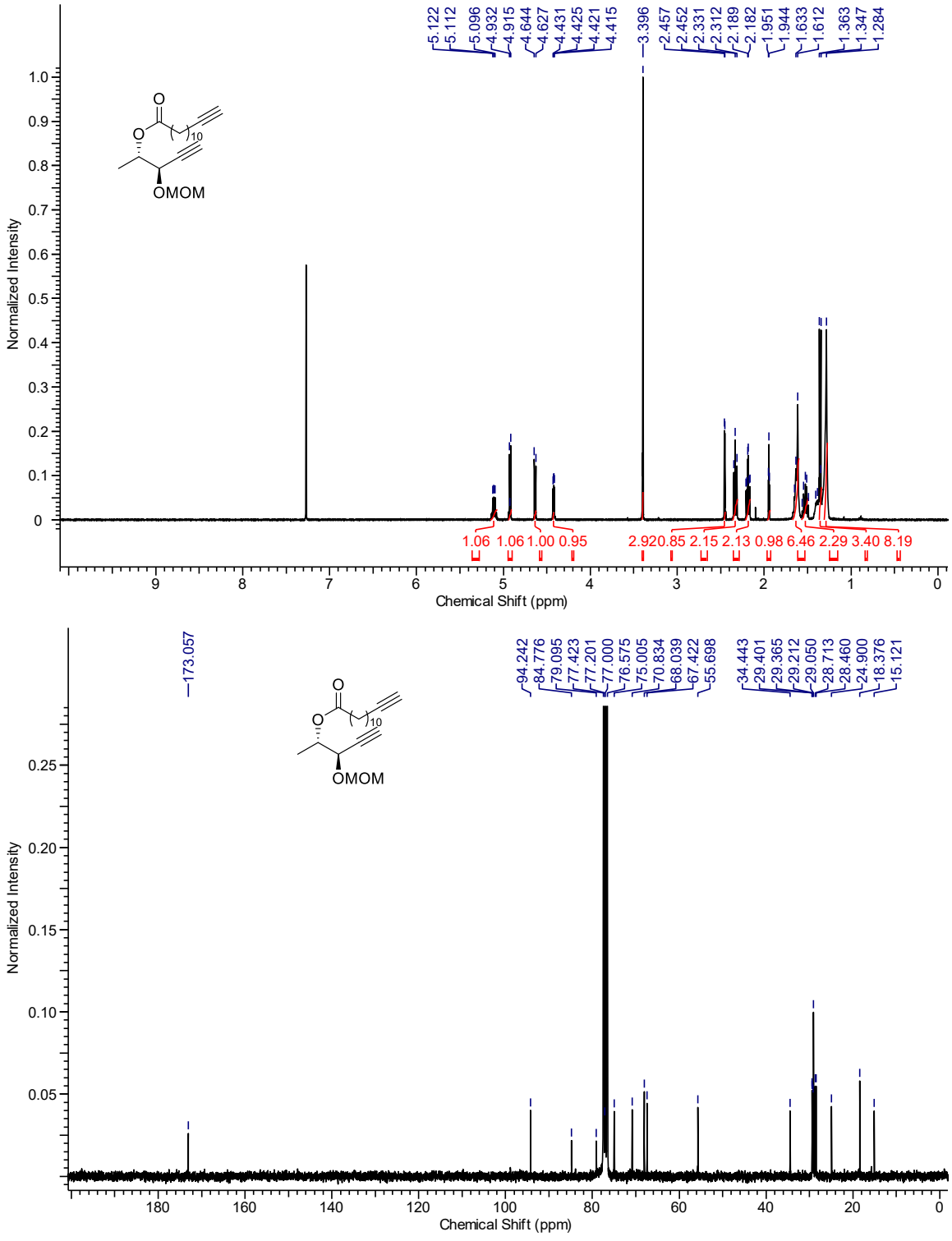
4.706
4.689
4.309
4.303
4.300
4.294
3.980
3.970
3.965
3.955
3.416
2.502
2.497
2.377
1.315
1.299
1.34
1.36
1.02
1.13
3.00
0.96
0.83
3.47
Normalized Intensity
Chemical Shift (ppm)


OMOM
OH
94.412
79.012
77.432
77.009
76.585
75.765
70.827
69.135
55.878
18.106
Normalized Intensity
Chemical Shift (ppm)

Compound 2a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5.112
5.096
4.932
4.915
4.644
4.627
4.431
4.425
4.421
4.415
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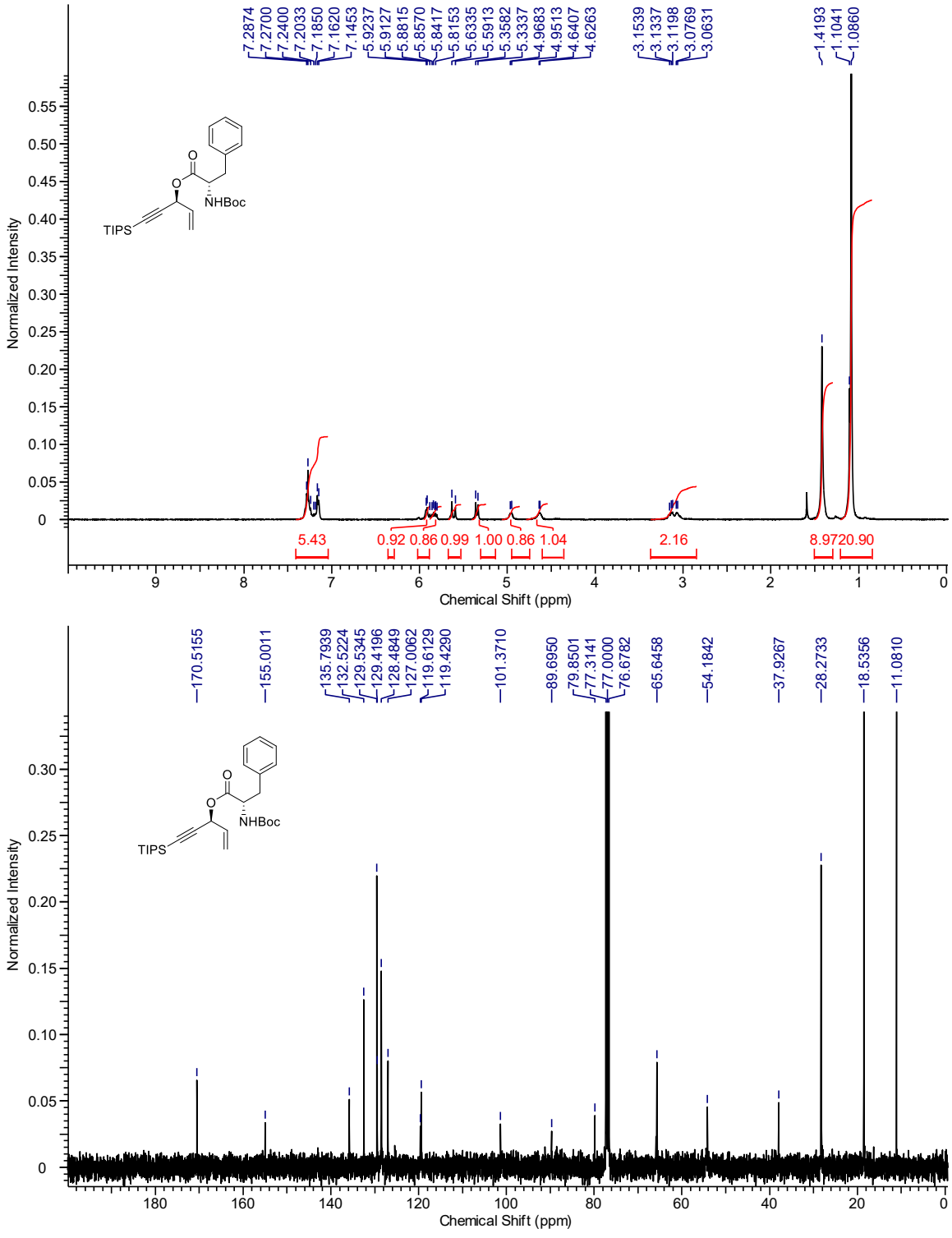
2.452
2.331
2.312
2.189
2.182
1.951
1.944
1.633
1.612
1.363
1.347
1.284
OMOM
Normalized Intensity
Chemical Shift (ppm)
1.06 1.06 1.00 0.95
2.92 0.85 2.15 2.13 0.98 6.46 2.29 3.40 8.19
173.057
94.242
84.776
79.095
77.423
77.201
77.000
76.575
75.005
70.834
68.039
67.422
55.698
34.443
29.401
29.365
29.212
29.050
28.713
28.460
24.900
18.376
15.121
OMOM
Normalized Intensity
Chemical Shift (ppm)

Compound S2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7.2400
7.2033
7.1850
7.1620
7.1453
5.9237
5.9127
5.8815
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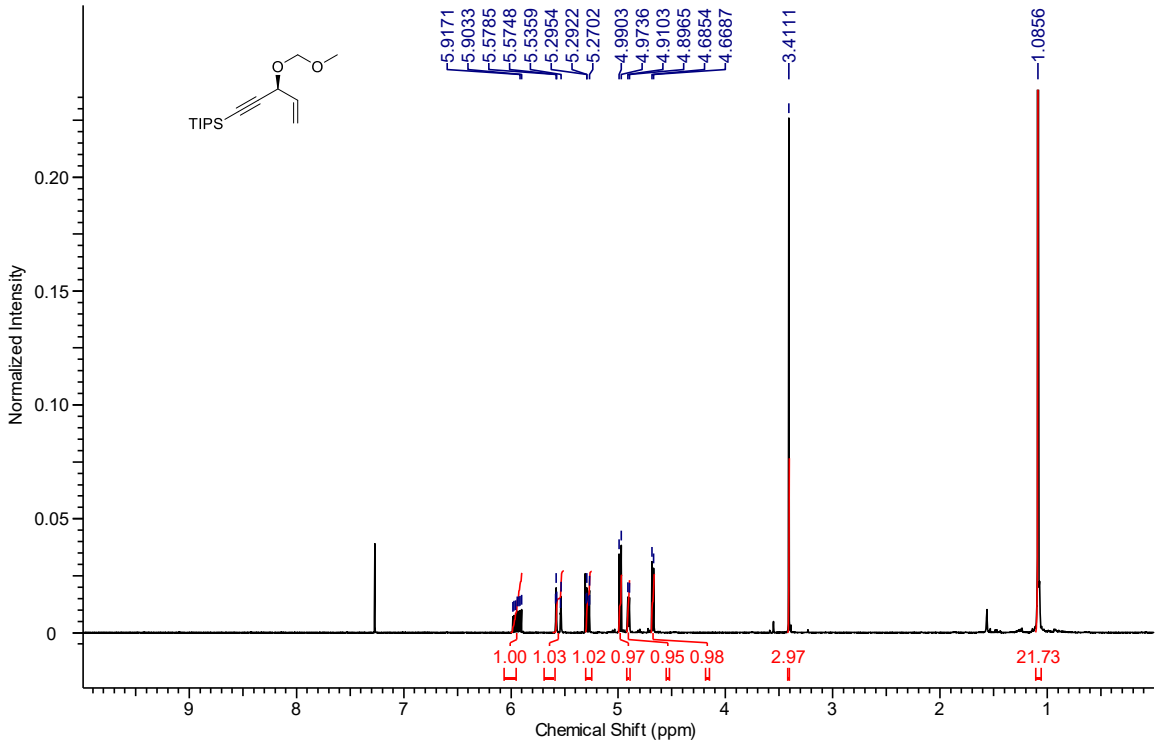
5.8417
5.8153
5.6335
5.5913
5.3582
5.3337
4.9683
4.9513
4.6407
4.6263
3.1539
3.1337
3.1198
3.0769
3.0631
1.4193
1.1041
1.0860
NHBoc
TIPS
Normalized Intensity
5.43
0.92
0.86
0.99
1.00
0.86
1.04
2.16
8.97
20.90
Chemical Shift (ppm)
170.5155
155.0011
135.7939
132.5224
129.5345
129.4196
128.4849
127.0062
119.6129
119.4290
101.3710
89.6950
79.8501
77.3141
77.0000
76.6782
65.6458
54.1842
37.9267
28.2733
18.5356
11.0810
NHBoc
TIPS
Normalized Intensity
Chemical Shift (ppm)

Compound 11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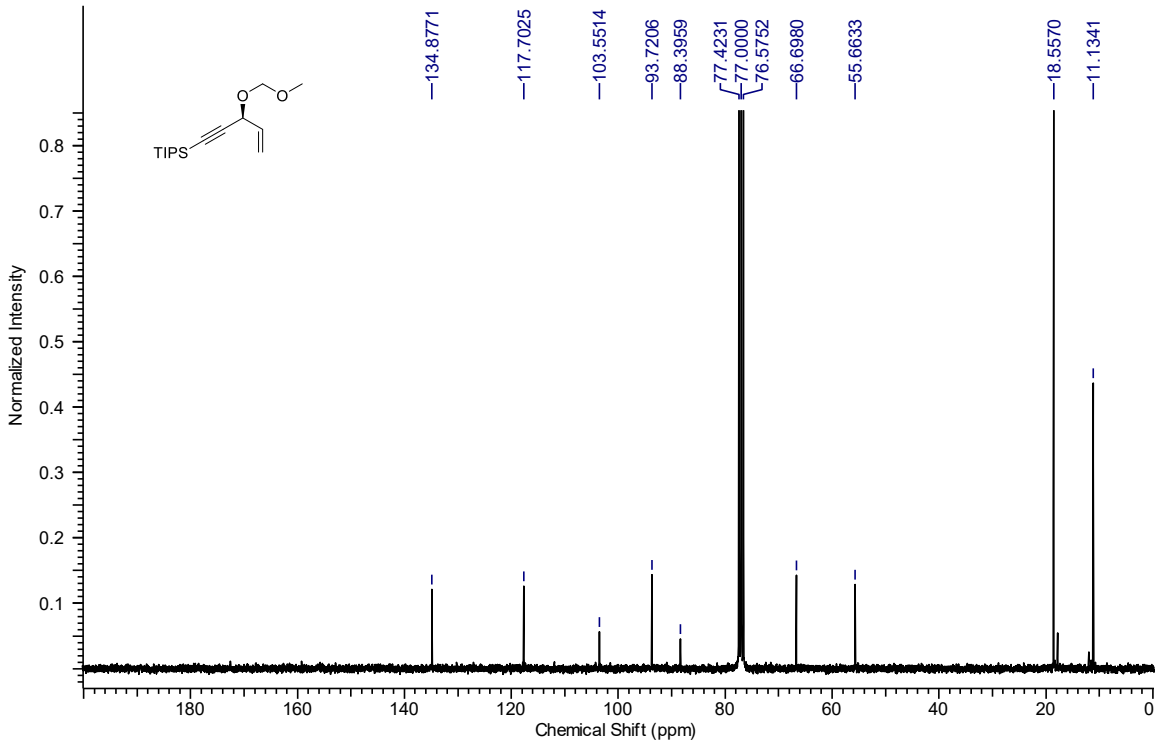
5.9033
5.5785
5.5748
5.5359
5.2954
5.2922
5.2702
4.9903
4.9736
4.9103
4.8965
4.6854
4.6687
3.4111
1.0856
TIPS
Normalized Intensity
0.20
0.15
0.10
0.05
0
1.00 1.03 1.02 0.97 0.95 0.98
2.97
21.73
9
8
7
6
5
4
3
2
1
Chemical Shift (ppm)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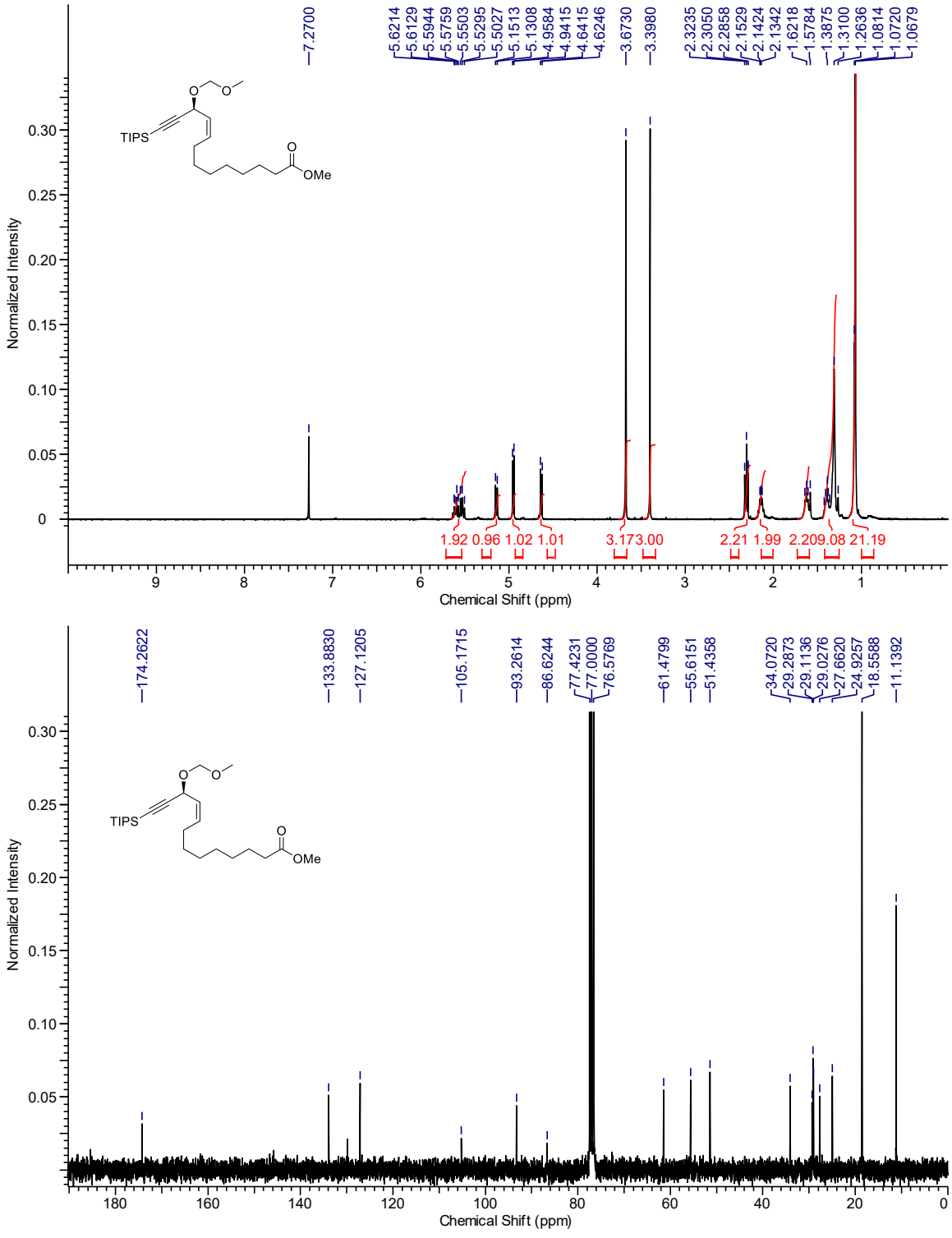
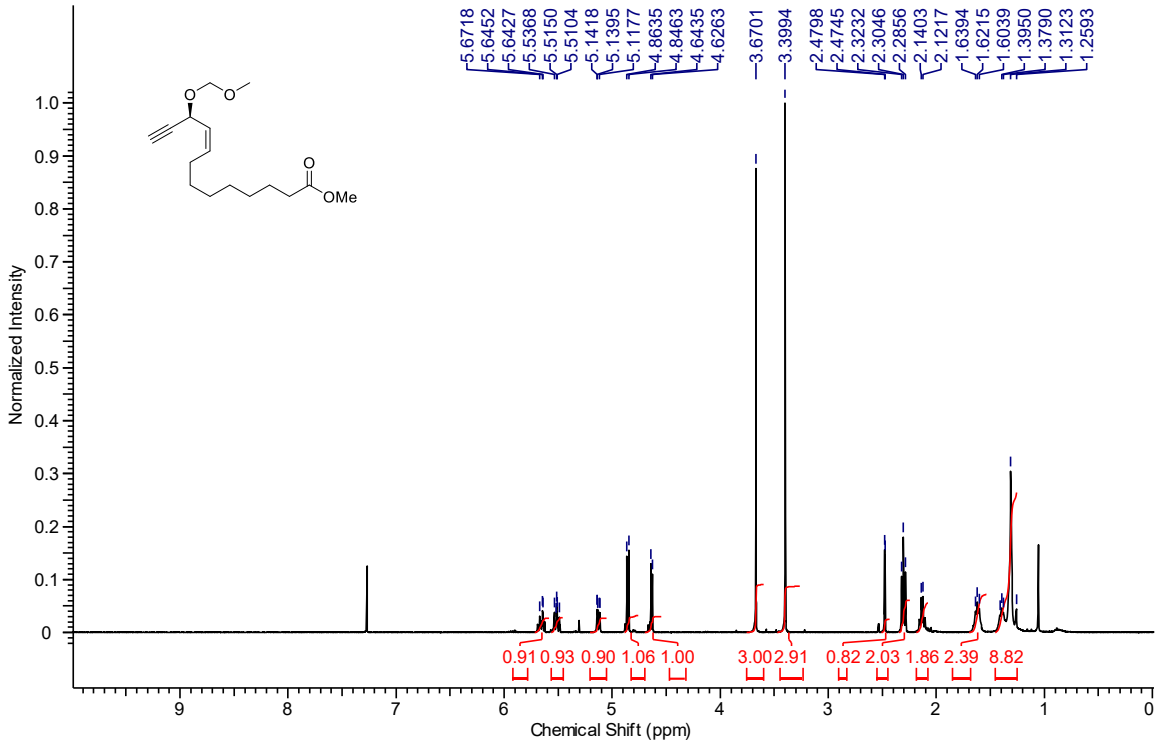
117.7025
103.5514
93.7206
88.3959
77.4231
77.0000
76.5752
66.6980
55.6633
18.5570
11.1341
TIPS
Normalized Intensity
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)

Compound 13


7.2700
5.6214
5.6129
5.5944
5.5759
5.5503
5.5295
5.5027
5.1513
5.1308
4.9584
4.9415
4.6415
4.6246
3.6730
3.3980
2.3235
2.3050
2.2858
2.1529
2.1424
2.1342
1.6218
1.5784
1.3875
1.3100
1.2636
1.0814
1.0720
1.0679
TIPS
OMe
Normalized Intensity
Chemical Shift (ppm)
1.92 0.96 1.02 1.01 3.17 3.00 2.21 1.99 2.20 9.08 21.19
174.2622
133.8830
127.1205
105.1715
93.2614
86.6244
77.4231
77.0000
76.5769
61.4799
55.6151
51.4358
34.0720
29.2873
29.1136
29.0276
27.6620
24.9257
18.5588
11.1392

Compound S3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5.6452
5.6427
5.5368
5.5150
5.5104
5.1418
5.1395
5.1177
4.8635
4.8463
4.6435
4.6263
3.6701
3.3994
2.4798
2.4745
2.3232
2.3046
2.2856
2.1403
2.1217
1.6394
1.6215
1.6039
1.3950
1.3790
1.3123
1.2593
OMe
Normalized Intensity
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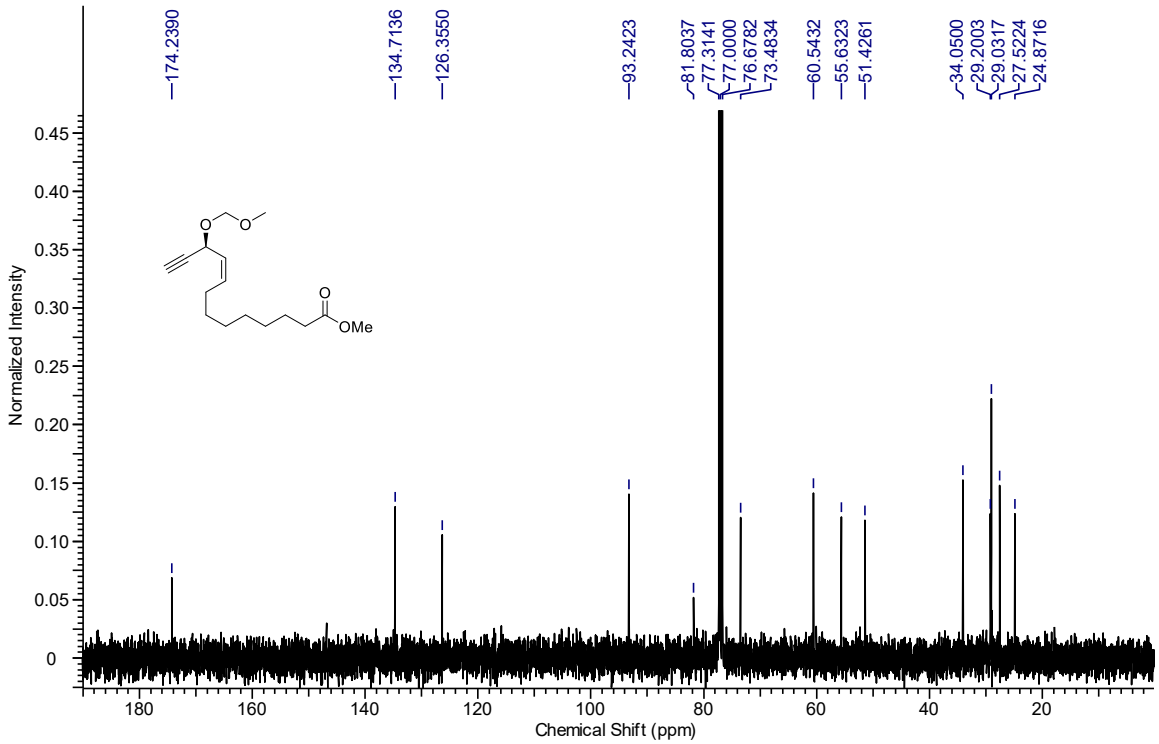
3.00 2.91
0.82 2.03 1.86 2.39 8.82
Chemical Shift (ppm)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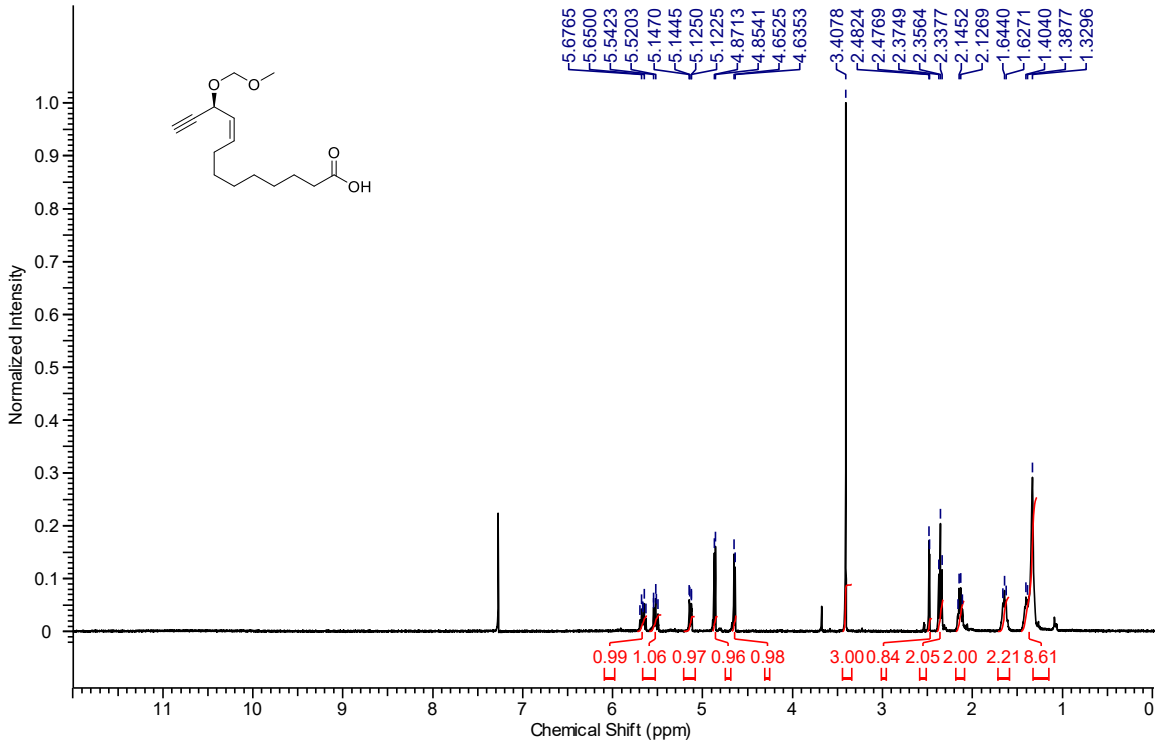
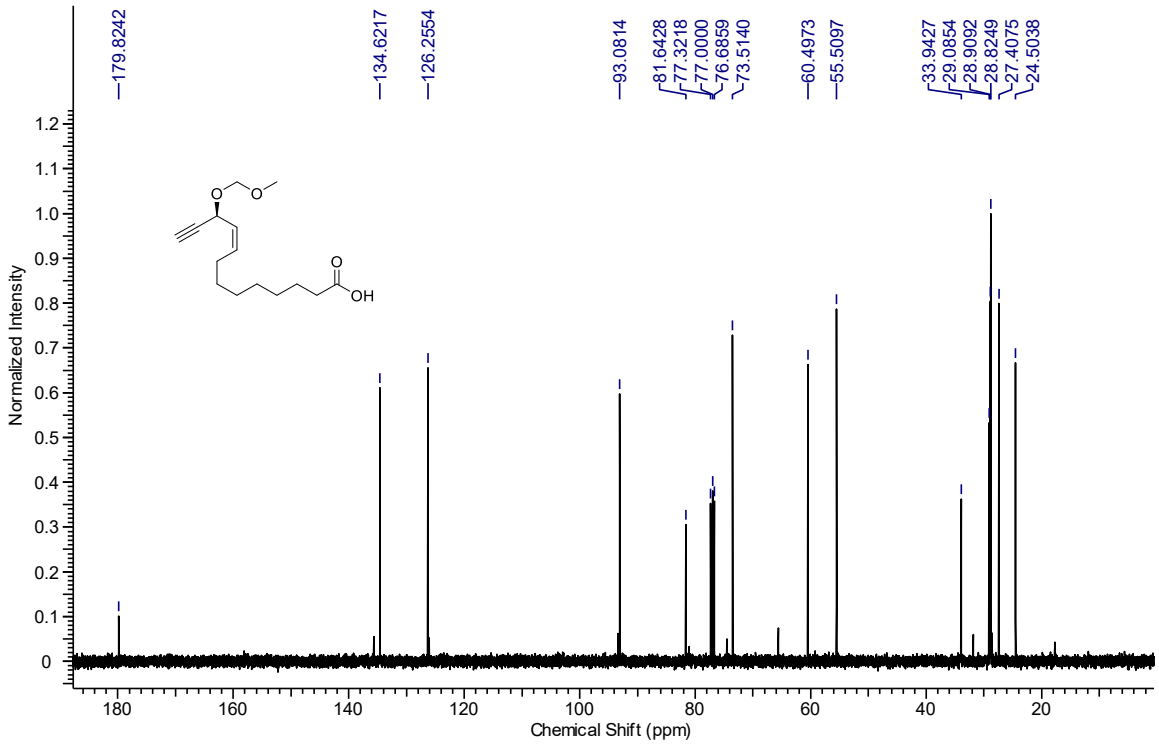
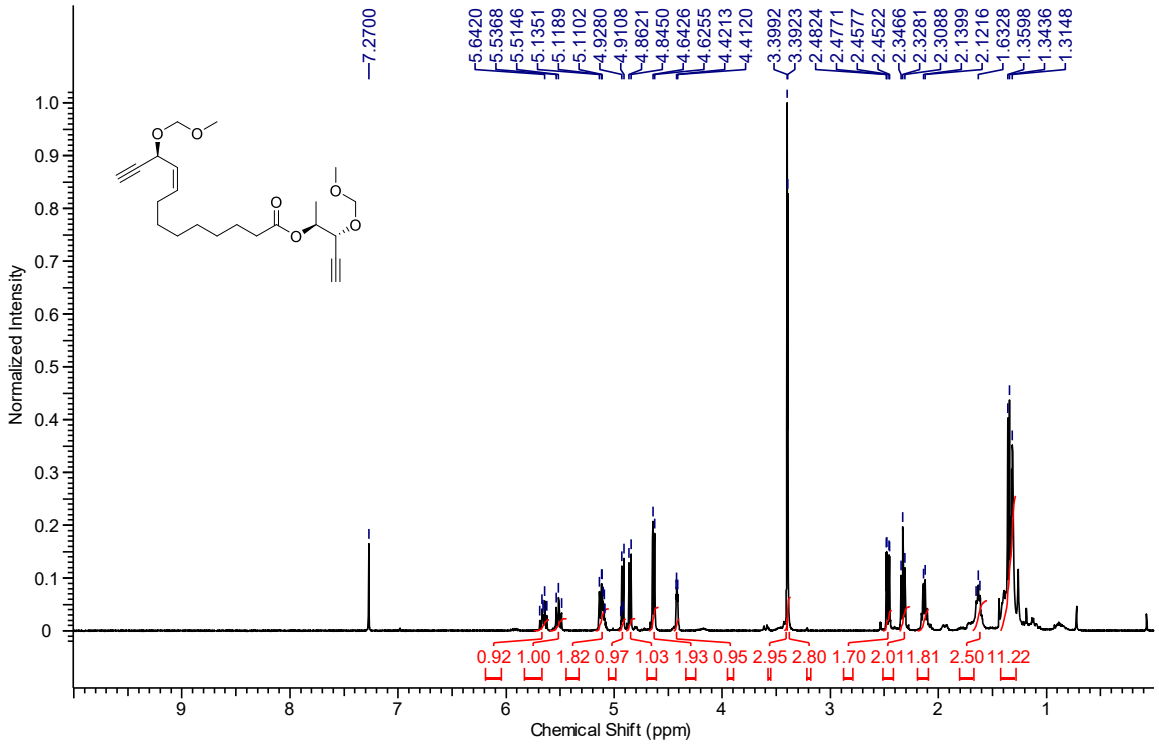
126.3550
93.2423
81.8037
77.3141
77.0000
76.6782
73.4834
60.5432
55.6323
51.4261
34.0500
29.2003
29.0317
27.5224
24.8716
OMe
Normalized Intensity
Chemical Shift (ppm)

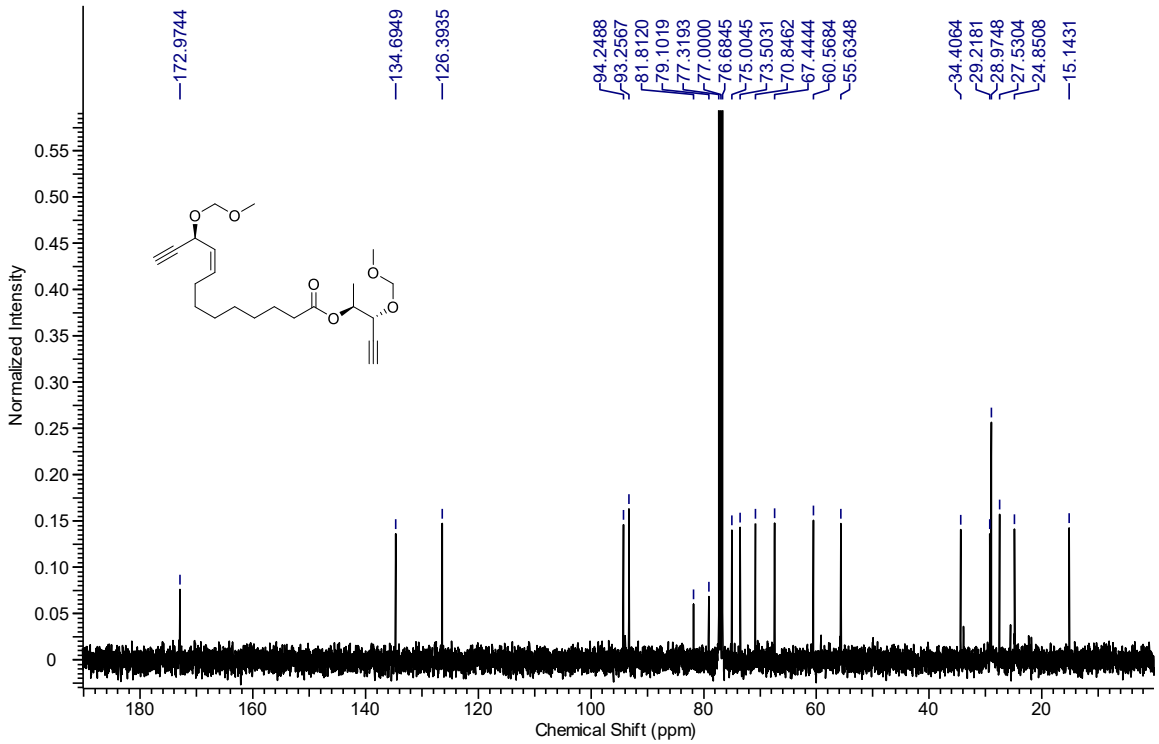
Compound 16


5.6765
5.6500
5.5423
5.5203
5.1470
5.1445
5.1250
5.1225
4.8713
4.8541
4.6525
4.6353
3.4078
2.4824
2.4769
2.3749
2.3564
2.3377
2.1452
2.1269
1.6440
1.6271
1.4040
1.3877
1.3296
0.99 1.06 0.97 0.96 0.98
3.00 0.84 2.05 2.00 2.21 8.61
Normalized Intensity
Chemical Shift (ppm)

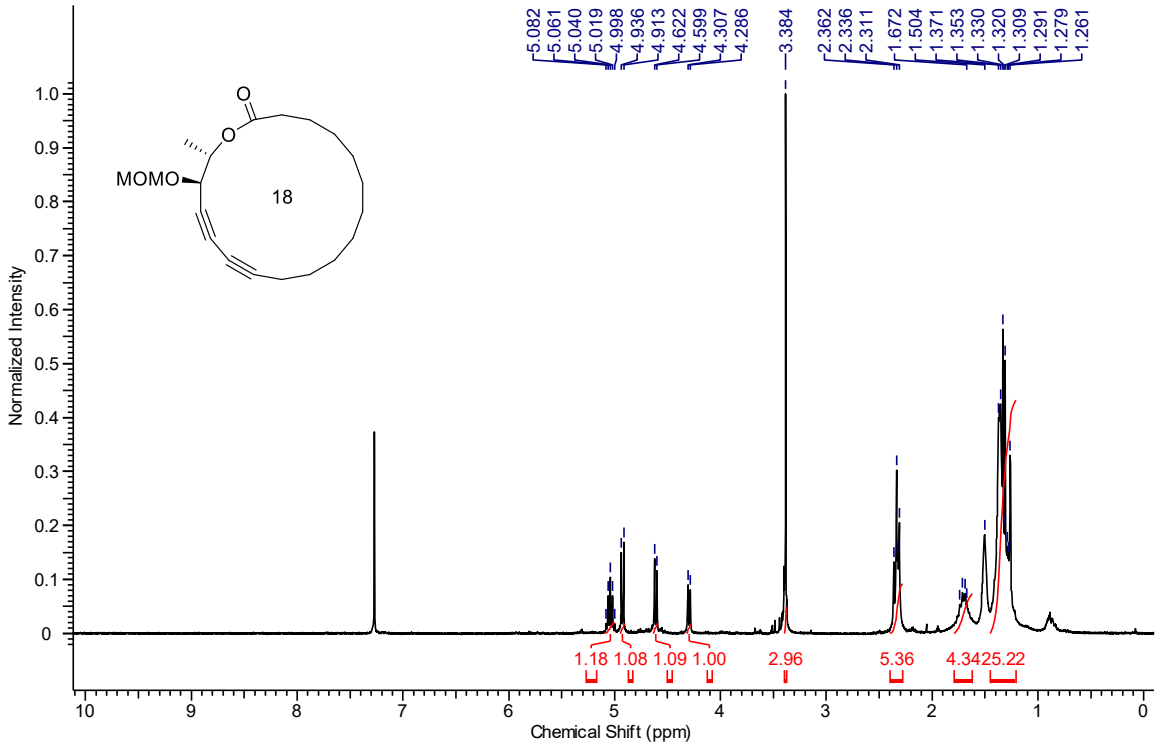

179.8242
134.6217
126.2554
93.0814
81.6428
77.3218
77.0000
76.6859
73.5140
60.4973
55.5097
33.9427
29.0854
28.9092
28.8249
27.4075
24.5038
Normalized Intensity
Chemical Shift (ppm)

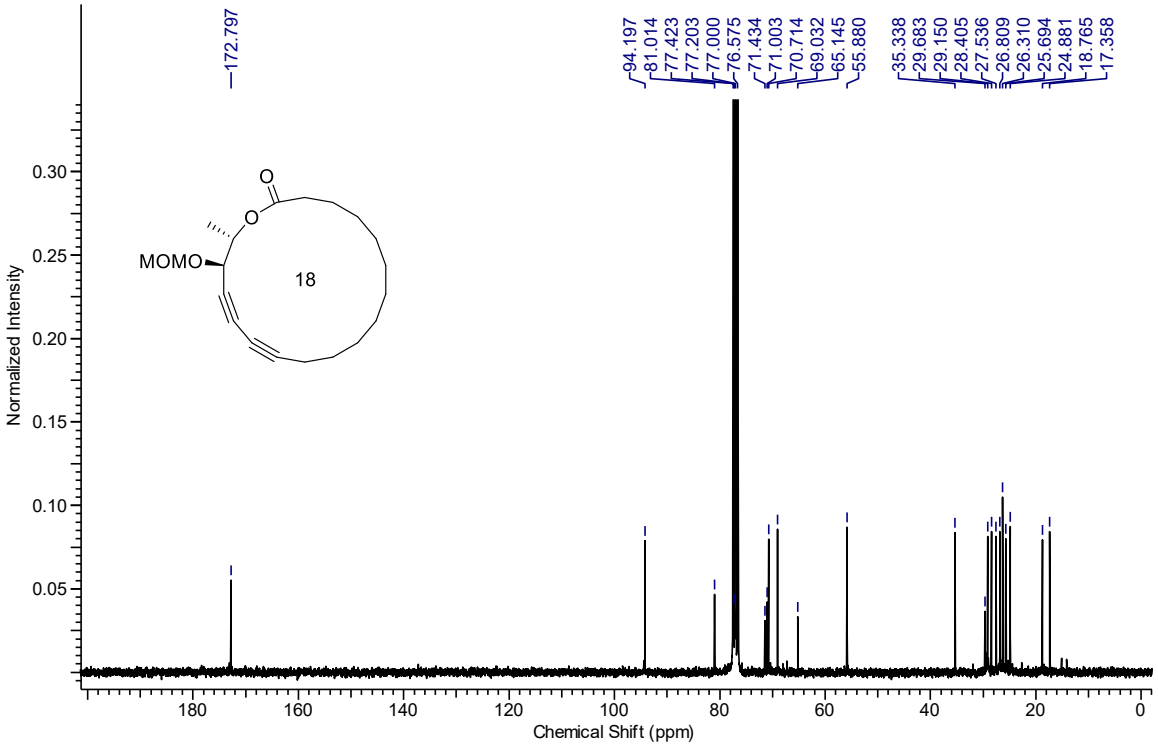
Compound 2


7.2700
5.6420
5.5368
5.5146
5.1351
5.1189
5.1102
4.9280
4.9108
4.8621
4.8450
4.6426
4.6255
4.4213
4.4120
3.3992
3.3923
2.4824
2.4771
2.4577
2.4522
2.3466
2.3281
2.3088
2.1399
2.1216
1.6328
1.3598
1.3436
1.3148
0.92 1.00 1.82 0.97 1.03 1.93 0.95 2.95 2.80 1.70 2.01 1.81 2.50 11.22
Normalized Intensity
Chemical Shift (ppm)

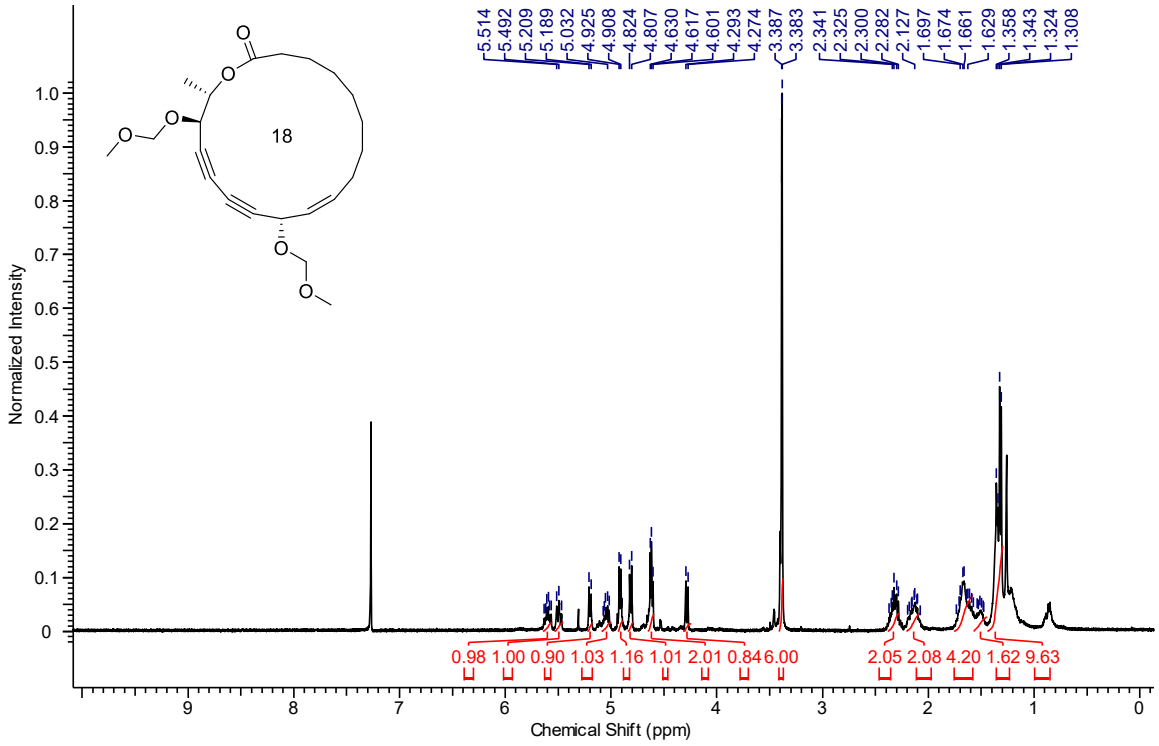

172.9744
134.6949
126.3935
94.2488
93.2567
81.8120
79.1019
77.3193
77.0000
76.6845
75.0045
73.5031
70.8462
67.4444
60.5684
55.6348
34.4064
29.2181
28.9748
27.5304
24.8508
15.1431
Normalized Intensity
Chemical Shift (ppm)

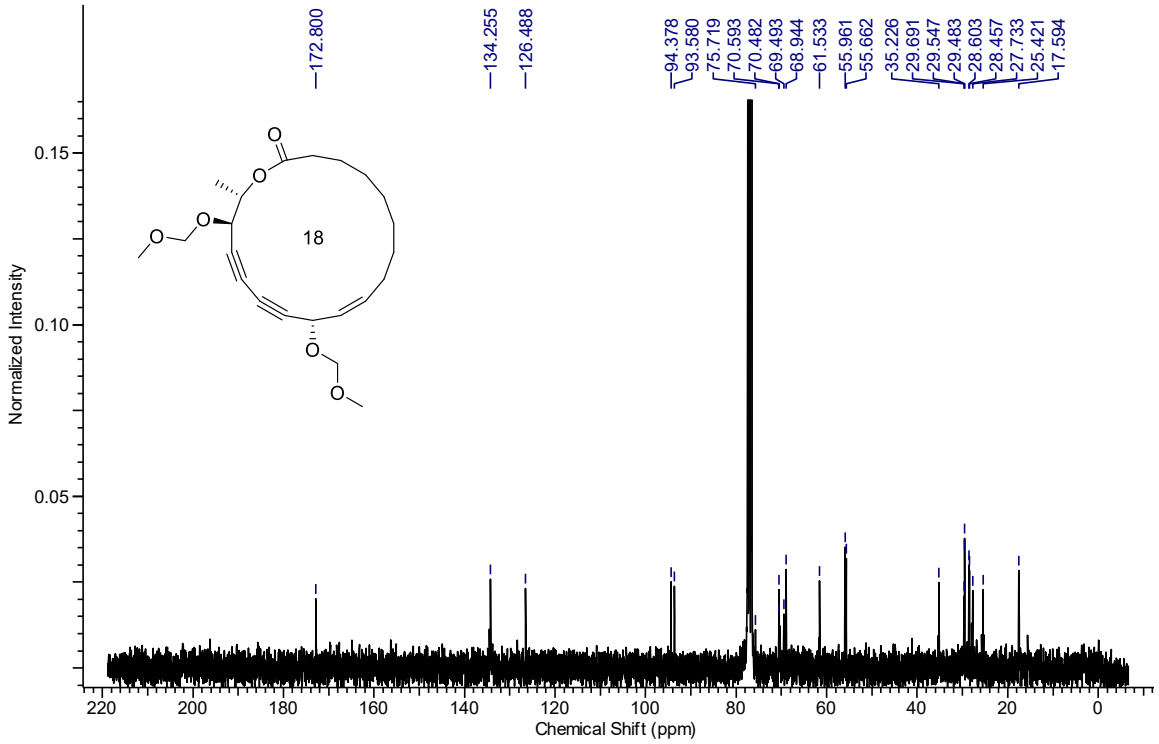
Compound 1a





Compound 1


5.514
5.492
5.209
5.189
5.032
4.925
4.908
4.824
4.807
4.630
4.617
4.601
4.293
4.274
3.387
3.383
2.341
2.325
2.300
2.282
2.127
1.697
1.674
1.661
1.629
1.358
1.343
1.324
1.308
18
Normalized Intensity
0.98 1.00 0.90 1.03 1.16 1.01 2.01 0.84 6.00
2.05 2.08 4.20 1.62 9.63
Chemical Shift (ppm)


172.800
134.255
126.488
94.378
93.580
75.719
70.593
70.482
69.493
68.944
61.533
55.961
55.662
35.226
29.691
29.547
29.483
28.603
28.457
27.733
25.421
17.594
18
Normalized Intensity
Chemical Shift (ppm)

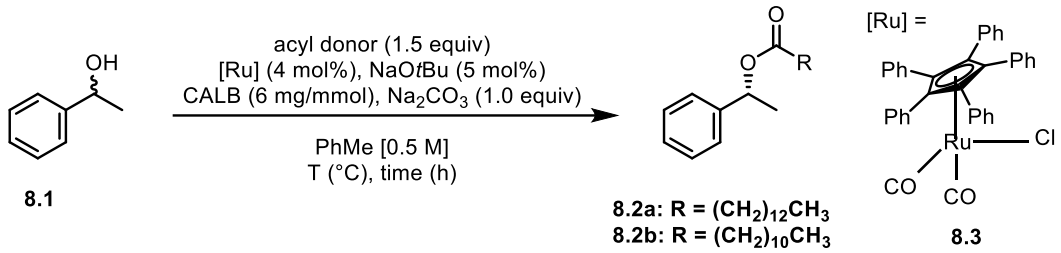
Annexe 5. Supporting Information of Chapter 8

General:

All reactions that were carried out under anhydrous conditions were performed under an inert argon or nitrogen atmosphere in glassware that had previously been dried overnight at 120 ^{o}C or had been flame dried and cooled under a stream of argon or nitrogen.[1] All commercial reagents were obtained from Sigma-Aldrich Chemical Company or Strem Chemicals and were reagent quality. Technical solvents were obtained from VWR International Co. Anhydrous solvents were dried and deoxygenated using a GlassContour system (Irvine, CA). Isolated yields reflect the mass obtained following flash column silica gel chromatography. Organic compounds were purified using the method reported by Still[2] and using silica gel obtained from Silicycle Chemical division (40-63 nm; 230-240 mesh). Analytical thin-layer chromatography (TLC) was performed on glass-backed silica gel 60 coated with a fluorescent indicator (Silicycle Chemical division, 0.25 mm, F_{254}.). Visualization of TLC plates was performed by UV (254 nm), $KMnO_4$ or *p*-anisaldehyde stains. All mixed solvent eluents are reported as v/v solutions. Concentration refers to removal of volatiles at low pressure on a rotary evaporator. All reported compounds were homogeneous by thin layer chromatography (TLC) and by ^{1}H NMR.

[1] Shriver, D. F.; Drezdon, M. A. in *The Manipulation of Air-Sensitive Compounds*; Wiley-VCH: New York, 1986.
[2] Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem*. **1978**, *43*, 2923-2925.

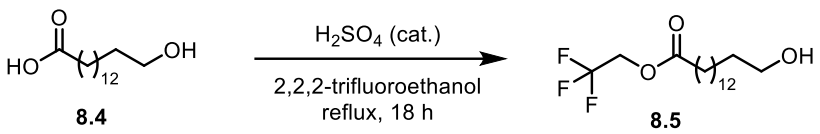
General Procedure for the DKR of 1-phenylethanol



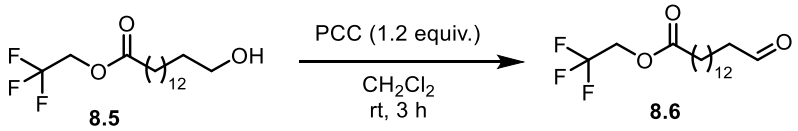
(R)-1-phenylethyl myristate 8.2a and (R)-1-phenylethyl laurate 8.2b In a glove-box, **8.3** (25 mg, 0.040 mmol, 4.0 mol %) and NaO*t*Bu (4.8 mg, 0.050 mmol, 5 mol %) were added to a round-bottom flask. The flask was removed from the glove-box and kept under an N_2 atmosphere. CALB[3] (6 mg), Na_2CO_3 (106 mg, 1.00 mmol, 1.0 equiv.) were quickly added and the mixture was dissolved with PhMe (2 mL, 0.5 M) and stirred for 5 min. **8.1** (0.12 mL, 1.00 mmol, 1.00 equiv.) was added and the reaction mixture was stirred for another 5 min. The acyl donor (See Table 5.3, 1.50 mmol, 1.50 equiv.) was added and the reaction mixture was stirred at the temperature and for the time specified in Table 5.3. The reaction mixture was then filtered and concentrated under reduced pressure. Purification by flash chromatography (5 to 10 % EtOAc in hexanes) afforded the desired esters **8.2a** or **8.2b**. Spectral data were in accordance with those previously reported in the literature.[4]

[3] Immobilized and commercially available as Novozyme-435.

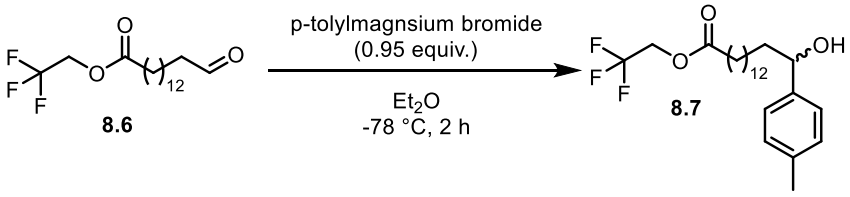
[4] Monteiro, C. M.; Lourenco, N. M. T.; Afonso, C. A. M. *Tet. Asymmetry* **2010**, *21*, 952-956.



2,2,2-trifluoroethyl 15-hydroxypentadecanoate 8.4 15-hydroxypentadecanoic acid (5.00 g, 19.4 mmol) was dissolved in 2,2,2-trifluoroethanol (70 mL). Drops (15-20) of concentrated H_2SO_4 were added and the mixture was stirred at reflux. After 18 h, the mixture was cooled down and neutralized (pH = 7) with a saturated solution of K_2CO_3. The mixture was extracted with EtOAc (3 x 50 mL). The combined organic phases were washed with water (2 x 100 mL) and brine (1 x 100 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford **5.20** as a white solid (6.00 g, 99 %) which was used without any further purification.



2,2,2-trifluoroethyl 15-oxopentadecanoate 8.6 Compound **8.5** (943 mg, 2.91 mmol) was dissolved in CH_2Cl_2 (15 mL) and PCC (754 mg, 3.49 mmol) was added. The reaction mixture was stirred for 3 h at room temperature. Silica gel was added and the slurry was concentrated under reduced pressure and flash chromatography (5 to 10 % EtOAc in hexanes) was performed to afford **5.21** as a colorless oil (545 mg, 58 %).



2,2,2-trifluoroethyl 15-hydroxy-15-(4-methylphenyl)pentadecanoate 8.7 Compound **8.6** (200 mg, 0.621 mmol) was dissolved in Et_2O (7 mL) and the mixture was cooled down to -78 °C. *p*-Tolylmagnesium bromide (0.93 mL, 0.466 mmol, 0.5 M in Et_2O) was added dropwise and

the mixture was stirred at -78 °C for 2 h upon which a saturated solution of NH_4Cl (10 mL) was added to quench the reaction and the biphasic mixture was stirred and allowed to warm up to room temperature. The mixture was extracted with Et_2O (2 x 10 mL). The combined organic layers were washed with water (10 mL) and brine (10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash chromatography (0 to 20 % EtOAc in hexanes) afforded **8.7** as a colorless oil (22 mg, 10 %).