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New Reactions of Ring Strained Allyl Silanes

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New Reactions of Ring Strained Allyl Silanes

By

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Accepted in Partial Completion
of the Requirements for the Degree
Master of Science

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Master's Thesis

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Elizabeth Jane Cummins

August 6, 2018

New Reactions of Ring Strained Allyl Silanes

A Thesis
Presented to
The Faculty of
Western Washington University

In Partial Fulfillment
Of the Requirements for the Degree
Master of Science

by
Elizabeth Jane Cummins
August 2018

Abstract

Herein, we report new allylation reactions using ring-strained allylalkoxysiletanes. These reactions can achieve high yield and have high chemoselectivity, as evidenced by carefully designed substrates. Based on previous evidence, we propose that the reaction proceeds through an exchange mechanism, where first the alkoxy group of the siletane exchanges with the hydroxyl group of the substrate, followed by coordination of the substrate carbonyl to the siletane, and then intramolecular allylation of the carbonyl.

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And to my mom and grandparents, who have supported me tirelessly over the years, and encouraged me to pursue my dreams in chemistry. I would not be the person I am today without their love and support.

Table of Contents

List of Abbreviations

R	Generic carbon chain
Mg	Magnesium
X	Generic halide
Li	Lithium
OH	Hydroxide
C	Carbon
H_2O	Water
MgBr	Magnesium bromide
$TiCl_4$	Titanium tetrachloride
β	Beta
σ	Sigma
π	Pi
Si	Silicon
α	Alpha
LAH / $LiAlH_4$	Lithium aluminum hydride
Al	Aluminum
$NaBH_4$	Sodium borohydride
H_2	Hydrogen gas
TBAF	Tetra-*n*-butylammonium fluoride
Ph_2SiHCl	Diphenylchlorosilane
ImH.	Imidazole
Et_3N	Triethylamine
DCM	Dichloromethane
DMAP	4-Dimethylaminopyridine
NMI	1-Methylimidazole
HCl	Hydrochloric acid
MO(s)	Molecular orbital(s)
Me	Methyl
DMF	N,N-Dimethylformamide
n-Bu	n-Butyl
HOCy	Cyclohexanol
I_2	Iodine
SI	Silicon intermediate
NMR	Nuclear magnetic resonance
THF	Tetrahydrofuran
DMSO	Dimethyl sulfoxide
NaH	Sodium hydride
MeOH	Methyl alcohol
HMPA	Hexamethylphosphoramide
MeCN	Acetonitrile
CH_3I	Methyl iodide / iodomethane
NaOH	Sodium hydroxide
KOH	Potassium hydroxide

Eq.	Equivalent(s)
$CDCl_3$	Chloroform-*d*
*i*Pr	Isopropyl
H_3O^+	Hydronium ion
N_2	Nitrogen gas
TLC	Thin layer chromatography
Et_2O	Diethyl ether
HO*i*Pr	Isopropyl alcohol
$MgSO_4$	Magnesium sulfate
NH_4Cl	Ammonium chloride
Hex	Hexanes
EtOAc	Ethyl acetate
MTBE	Methyl *tert*-butyl ether
pTSA	*p*-Toluenesulfonic acid
$NaHCO_3$	Sodium Bicarbonate
TBDPS	*Tert*-butyldiphenylsilyl
$TMSCHN_2$	(Trimethylsilyl)diazomethane
AcOH	Acetic acid

List of Figures

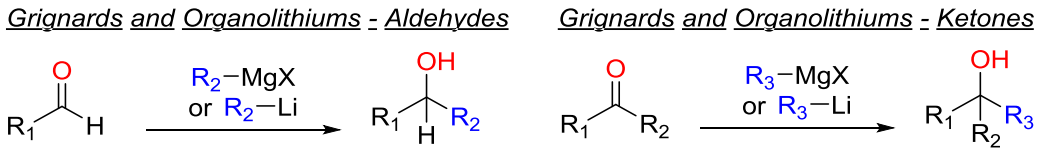
List of Tables

List of Schemes

Chapter 1: Introduction

1.1 Carbon-Carbon Bond Formation of Carbonyl Additions

With over 100 different named reactions, carbon-carbon bond formation is easily one of the most studied types of reactions in synthetic organic chemistry. The enterprise of organic synthesis, that is using simple building blocks to construct more complex structures, requires making new carbon-carbon bonds. An important subset of these reactions focuses on carbonyl addition – the formation of a new carbon-carbon bond between the carbon of a carbonyl and an incoming nucleophile. These reactions most commonly use Grignard or organolithium reagents to alkylate aldehydes or ketones, forming secondary and tertiary alcohols, respectively (Scheme 1-1).[1]



Scheme 1-1. Formation of secondary and tertiary alcohols using Grignard or organolithium reagents.

When considering these reactions, the reactivity of carbonyl compounds is worth mentioning (Figure 1-1). The reactivity of carbonyl compounds toward Grignard reagents is determined by the stability of each carbonyl relative to its transition state during the addition – where stabilized transition states promote greater reactivity.[2] In the case of aldehydes and ketones in regards to Grignard-type reactions, aldehydes react more readily, due to hydrogen being less sterically bulky than any carbon chain.

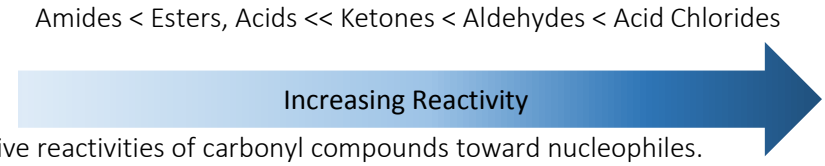
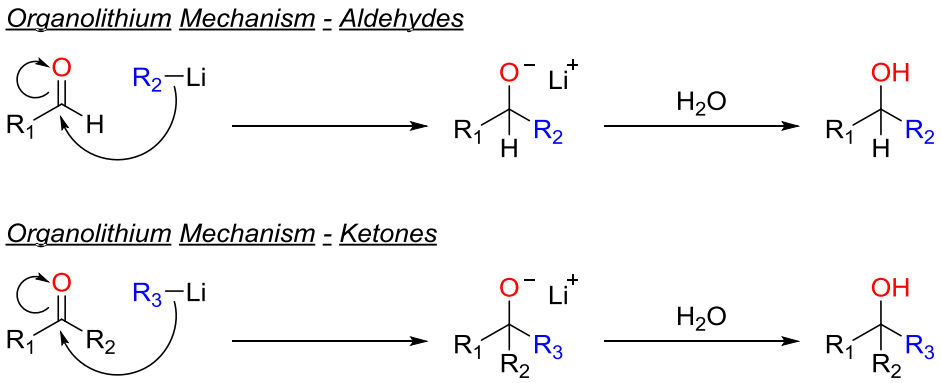


Figure 1-1. Relative reactivities of carbonyl compounds toward nucleophiles.

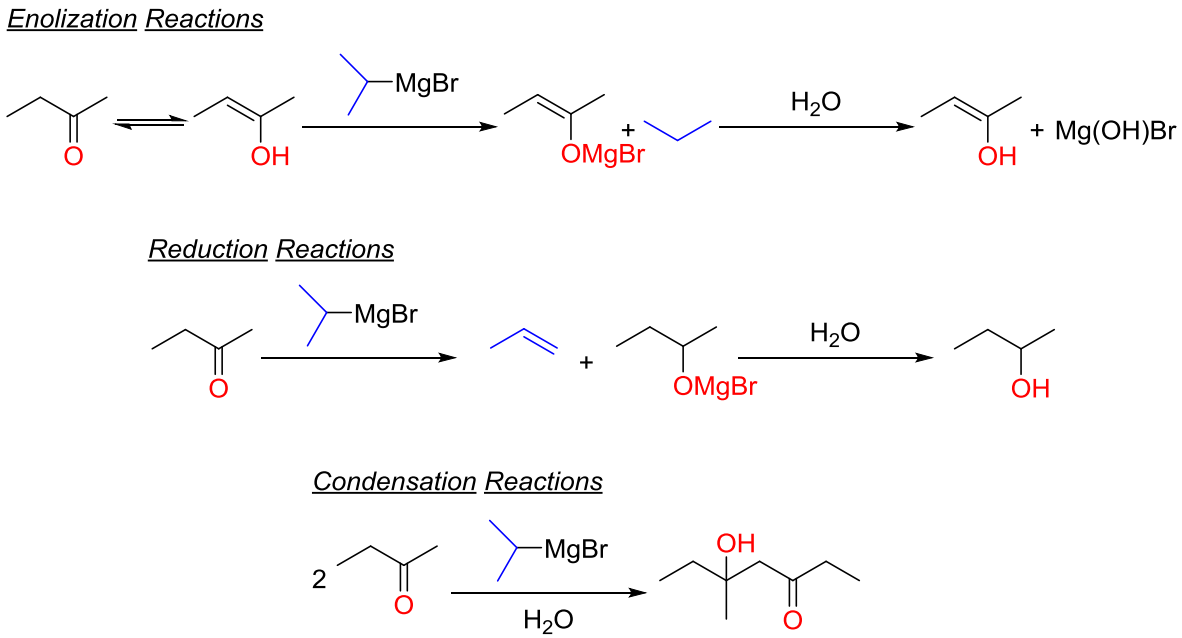
While the exact mechanism of Grignard reagent addition is debated, the mechanism of organolithium addition is well known.[3] These reagents are hard nucleophiles that take advantage of the strong, polar nature of C-Li bonds in order to generate highly basic species. The acidity of aliphatic

hydrocarbons decreases with the degree of substitution, making *tert*-butyl lithium the most basic, and therefore most aggressive alkyllithium reagent.[4] However, alkyllithium reagents can be slow to react, even as thermodynamically strong bases, and as a result, optimization of reaction conditions is required.[5] Once conditions are established, the mechanism is straightforward. The nucleophilic R-Li bond attacks the carbonyl carbon, resulting in a new carbon-carbon bond and an alkoxide. The positively charged lithium coordinates to the negatively charged oxygen, and during an aqueous work-up, the oxygen is protonated, producing the alcohol (Scheme 1-2).[2]



Scheme 1-2. Mechanism of organolithium reagents with aldehydes and ketones.

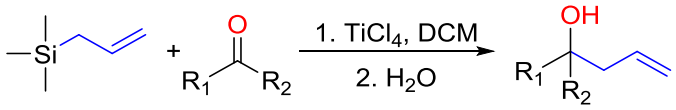
As fundamental and versatile as Grignard and organolithium reagents are, there are also drawbacks to utilizing them in synthesis. Grignards, for example, have the potential to cause enolization, reduction, or condensation reactions (Scheme 1-3).[1,6,7] Meanwhile, organolithiums are pyrophoric, and as a result will react violently with air or water. Additionally, they may generate volatile compounds which may ignite due to the high temperatures of decomposition.[4]



Scheme 1-3. Side reactions of Grignard reagents.

In contrast to Grignards and organolithiums, organosilanes are useful in carbonyl alkylations while being relatively non-toxic, with low molecular weights, and simple to handle.[8] Most notable is the work of Hosomi and Sakurai, who discovered that allylations of carbonyls (ketones or aldehydes) occur with allyltrimethylsilane in the presence of a Lewis acid such as $TiCl_4$ (Scheme 1-4).[9] The reaction mechanism proceeds through a cyclic transition state which involves a nucleophilic attack of the allylsilane to the carbonyl carbon, which has been polarized by the added Lewis acid. This was an improvement on the previously reported methods of carbonyl allylation due to the variety of carbonyl compounds that could be reacted (aliphatic, alicyclic, aromatic), and the reaction was regiospecific.[9] The reaction between electrophiles and allylsilanes has been explained by the β-silyl carbocation effect, where the β-silyl carbocation has stabilization caused by the σ-π conjugation between the σ Si-C orbital and the empty p_π orbital.[10] The majority of the following thesis focuses on allylsilylations of a specific subset of carbonyl compounds – α-oxocarboxylic acids, which contain a keto-acid moiety, as well as a variety of other

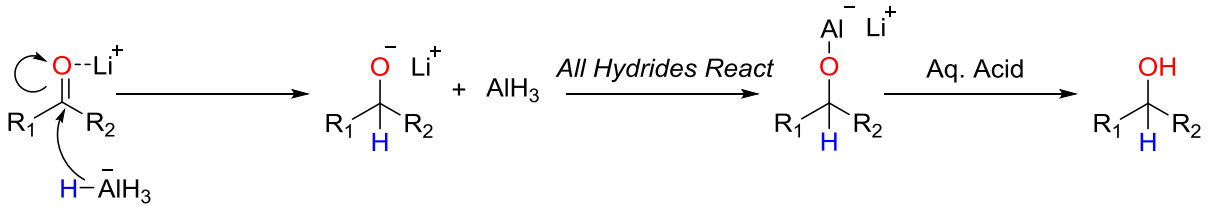
functional groups. Benefits of these new methods compared to the approaches previously reported include: chemoselectivity, air and moisture stability, and mild reaction conditions.



Scheme 1-4. Sakurai allylations.

1.2 Hydrosilylations and Carbosilylations

Traditional methods to reduce ketones or aldehydes to hydroxyl groups include metal hydrides, such as LAH ($LiAlH_4$), or $NaBH_4$. Because of the electronegativity difference between aluminum and hydrogen, the hydrogen atoms of LAH carry a great amount of negative charge. As a result, LAH serves as a source of hydride ions. Generally, the reaction involves the nucleophilic attack of the hydride ion to the carbonyl carbon, while the lithium ion provides Lewis acidity to the reaction by coordinating to the carbonyl oxygen, thereby making the carbon more electrophilic, and susceptible to nucleophilic attack. After the addition, the resulting alkoxide salt further reacts with remaining AlH_3, forming an aluminum alkoxide compound, which is further converted to the resulting alcohol in a protonation step with aqueous acid (Scheme 1-5). An advantage of using LAH in reduction reactions arises from the fact that all four hydrogen atoms can participate in reductions, therefore the reaction occurs in sub-stoichiometric amounts.[2]

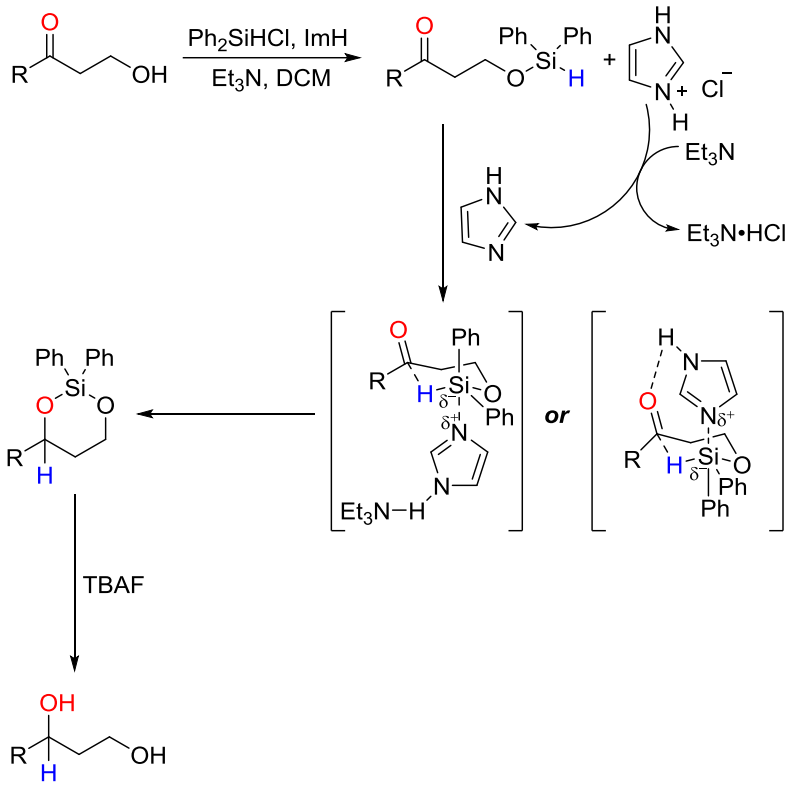


Scheme 1-5. Mechanism of LAH reductions.

Sodium borohydride ($NaBH_4$) works much the same way as LAH, with the main difference being that sodium is not as acidic as lithium, and therefore does not activate the carbonyl oxygen to the same

extent. Additionally, the B-H bond is not as polarized as Al-H, giving the hydrogen less hydride character than LAH. Because of this, reactions with $NaBH_4$ are often carried out in protic solvents such as alcohols that coordinate to the carbonyl oxygen via hydrogen bonding, thus activating the carbonyl.[2] Similarly to LAH, $NaBH_4$ can be used in sub-stoichiometric quantities. However, protonation of the alcohol occurs via deprotonation of the solvent, instead of during a separate step. A significant benefit of using $NaBH_4$ over LAH is its functional group tolerance. LAH possesses such basic hydrides that it reacts with alkyl halides, esters, alkyl tosylates, and nitro groups. Although $NaBH_4$ is a slower reaction, in the presence of these functional groups it is a better choice to reduce aldehydes and ketones.[2]

Much like Grignard and organolithium reagents, LAH and $NaBH_4$ suffer from similar problems that make their use potentially hazardous (e.g. reactions with moisture to generate H_2). In contrast to these standard methods, carbonyl hydrosilylations have uses as a mild, selective alternative in carbonyl reductions.[11] There are examples of Lewis acid- and Lewis base-mediated hydrosilylations of ketones and aldehydes, as well as a variety of transition metal catalyzed reactions.[12-14] In general, organosilicon hydrides undergo spontaneous reactions with organic compounds only if the organic reactant is a strong electrophile or the silane has been first activated by a nucleophilic species at the silicon center.[15] Often, this involves activation of the silicon species by fluoride, or the production of an extremely basic hydride species in the case of many of the transition metal catalyzed hydrosilylations.[12-14] Previous work by the O'Neil group showed an alternative mechanism for activating silanes toward hydrosilylation. They demonstrated that β-hydroxyketones can be intramolecularly reduced, forming cyclic disiloxanes when treated with diphenylchlorosilane, imidazole (ImH) and an amine base such as triethylamine (Et_3N). Due to product instability, the resulting cyclic disiloxanes were typically treated with tetra-*n*-butylammonium fluoride (TBAF) to afford the diol (Scheme 1-6).[15]

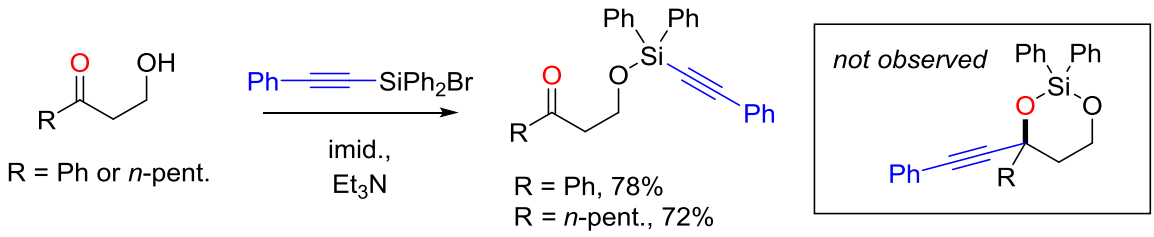


Scheme 1-6. Cooperative-base mediated hydrosilylation.

The proposed mechanism as illustrated in Scheme 1-6 is based on key elements of this process that were identified. For instance, imidazole is necessary for the reaction to occur. In cases where the reaction was performed in the presence of Et_3N, but not imidazole, no hydrosilylation occurred, and only the non-cyclized β-hydridosilyloxyketone product was present.[15] Also of note, a large excess of imidazole did not increase the amount of hydrosilylated product. Replacing imidazole with other bases, such as DMAP or NMI failed to produce hydrosilylated product.[15] Additionally, the β-hydroxy functionality is required for hydrosilylation to occur under these conditions. The O'Neil group reacted propiophenone according to their standard procedure (Ph_2SiHCl, imidazole, Et_3N), and recovered exclusively starting material, even after prolonged reaction times.[15] Based on these observations, a nucleophilic activation mechanism was proposed.

The reactivity of silicon in these reactions is predicted to arise from a valence-expanded, pentacoordinate hydrosilanide species that has stronger reducing power than the tetravalent precursor.[16] The specificity of the reaction for diphenylchlorosilane (as opposed to di-*tert*-butyl and diisopropyl derivatives) can be explained by stabilization of developing negative charge on silicon during the reaction by the phenyl substituents of Ph_2SiHCl.[15] Additionally, the amine base is thought to promote hydrosilanide formation by abstracting the proton from imidazole when bound to silicon (Scheme 1-6).

It was proposed that by using a carbon nucleophile, that an intramolecular *carbo*silylation reaction under similar conditions could be developed. The original model used by the O'Neil group involved diphenylbromosilane with phenylacetylene replacing the previous hydrogen. The idea was very similar to the hydrosilylation experiments. The halogen leaving group would exchange with the incoming alcohol, and carbosilylation followed by cyclization would afford the desired product (Scheme 1-7). However, under the same conditions for hydrosilylation, the product recovered was the silyl ether where no carbosilylation or cyclization had occurred. In thinking about how to potentially affect the carbosilylation, a few key points were made clear. The leaving group needed to be present in order for the incoming alcohol to attach to the silicon center, the substituents on silicon needed to be *more activating* than phenyl, and the nucleophile used had to be more nucleophilic than phenylacetylene.

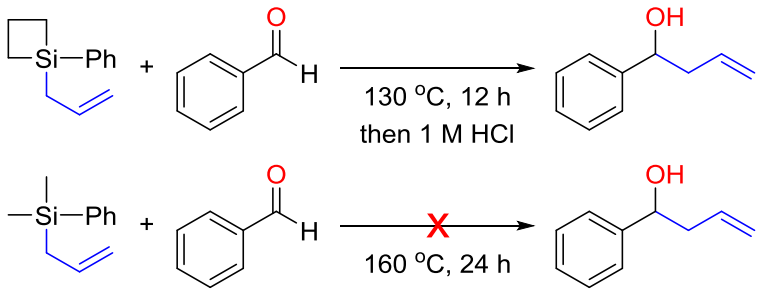


Scheme 1-7. Attempted carbosilylations by the O'Neil group.

Chapter 2: Silacyclobutanes (Siletanes)

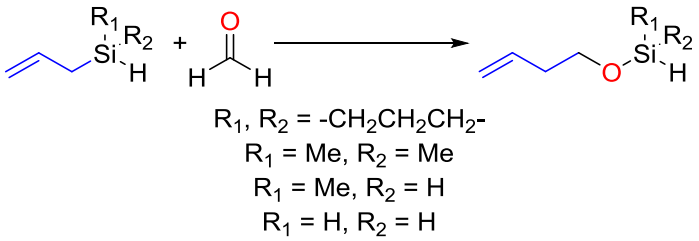
2.1 Reactivity of Siletanes and Carbonyls

Matsumoto and coworkers observed that silacyclobutanes (siletanes) are easily activated by the attack of a nucleophile to give a pentacoordinate silicate.[17,18] This is thought to arise from relief of ring strain upon rehybridization for the 5-coordinate siletane (*vide infra*). Matsumoto's group then hypothesized that allylsiletanes could add to carbonyl compounds without the addition of a catalyst.[17] Indeed, when 1-allyl-1-phenylsilacyclobutane was reacted with benzaldehyde at 130 °C, the result was 1-phenyl-3-buten-1-ol in 85% yield (scheme 2-1). The same reaction performed with allyldimethylphenylsilane only afforded starting material, even after increased temperature and prolonged reaction times (Scheme 2-1).[17] Thus, it was confirmed that the increased Lewis acidity of the siletane is critical for the allylation of aldehydes.



Scheme 2-1. Matsumoto's allylation of benzaldehyde using 1-allyl-1-phenylsilacyclobutane.

In order to investigate whether a pentacoordinate species is a transition state, Fujimoto and coworkers studied computational molecular orbitals (MOs) on simplified model systems.[19] To do this, they tested four models which consisted of allylsilanes and formaldehyde (Scheme 2-2).



Scheme 2-2. Fujimoto's models to study the reactivity of allylsilanes.

While studying the siletane system, it was noted that a six-membered cyclic transition state was formed, which involved the silicon center, the allyl substituent, and the carbonyl of formaldehyde; the silicon center was seen to be pentacoordinate, where the carbonyl oxygen and C^3 of the siletane occupied the apical positions.[19] In the tetravalent species, silicon is sp^3 hybridized, with preferred bond angles of 109.5°. In the activated, pentavalent species, silicon becomes sp^3d hybridized, with preferred bond angles of 90°and 120° (Figure 2-1). Indeed, it was observed that the angle between the apical and equatorial positions was smaller than the angle between the bonds in the tetravalent species, and they proposed this to be a reason why the C^1-Si-C^3 angle of the siletane ring is slightly reduced in the transition state. It was also observed that the bond length between Si and C^3 of the siletane is actually elongated in the transition state, causing ring strain to be partially released.[19] In comparing the data from all of the systems, it was found that the siletane not only had the lowest activation barrier, but it was observed that in the transition state, the C-Si-C bond angle of the siletane ring was 75.7°, whereas in the dimethyl system the Me-Si-Me bond angle was 100.8°.[19] Computations were carried out to test the effect of the C-Si-C bond angle on reactivity, and it was discovered that the activation barrier is reduced as the C-Si-C bond angle is made smaller; therefore the reactivity of allylsilanes is closely related to the local arrangement of bonds at the silicon center.[19]

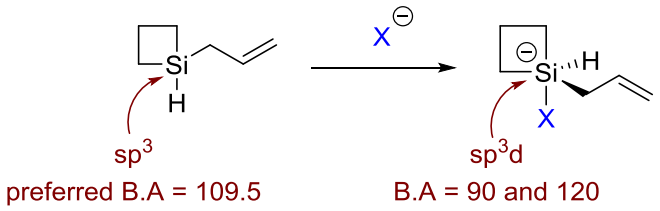
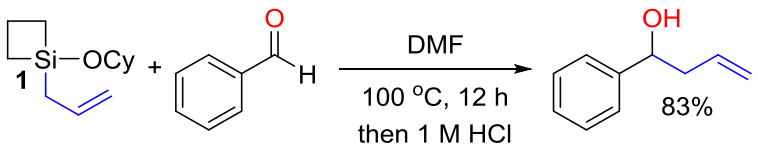


Figure 2-1. Preferred bond angles for tetracoordinate and pentacoordinate silicon species.

Studies to investigate the Lewis acidity of siletanes were also performed by Fujimoto. A molecular orbital of silicon must extend in the direction from which the carbonyl attacks, which is generated from the 3s, 3p, and 3d atomic orbitals of the silicon atom. As Fujimoto states in his work, "if the orbital consists mainly of low-lying unoccupied MOs of an allylsilane molecule, the silicon center will be a strong electron acceptor…if the orbital is found for the most part in the occupied MOs or in the high-lying unoccupied MOs of an allylsilane molecule, the silicon center will be a poor electron acceptor."[19] Based on the results from their previous studies, and the work by Matsumoto, it was predicted that the silicon of a siletane would be a strong electron acceptor. Indeed, the siletane model showed a low-lying unoccupied orbital relative to allyldimethylsilane, confirming that the siletane should be a stronger electron acceptor, and therefore more reactive than silanes that do not contain the siletane moiety.[19]

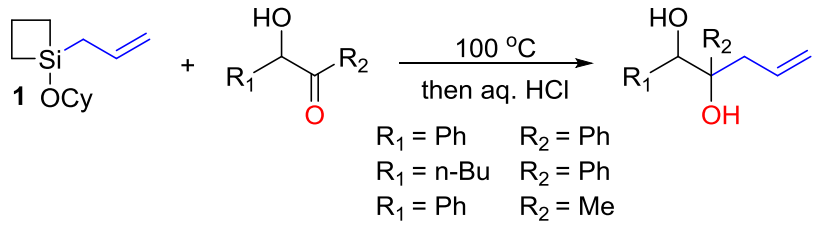
2.2 Reactions of Allylalkoxysilacyclobutanes

Matsumoto and coworkers then tuned the Lewis acidity of allylphenylsilacyclobutane by exchanging the phenyl for an alkoxy group. The reaction between 1-allyl-1-(cyclohexyloxy)silacyclobutane (**1**) with a variety of aldehydes proceeded at a lower temperature than the phenyl precursor due to the increased Lewis acidity associated with having an electronegative atom bound to silicon.[17] For example, the reaction of benzaldehyde and 1-allyl-1-(cyclohexyloxy)silacyclobutane proceeded at 100 °C in N,N-dimethylformamide (DMF), as opposed to 130 °C for allylphenylsilacyclobutane (Scheme 2-3).



Scheme 2-3. Matsumoto's reaction of 1-allyl-1-(cyclohexyloxy)silacyclobutane and benzaldehyde.

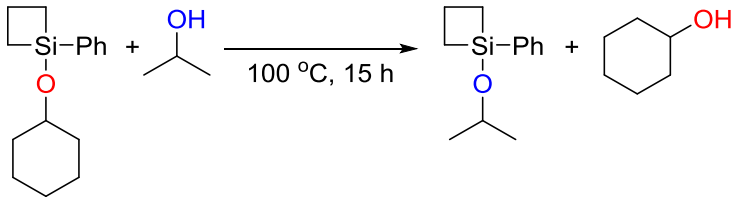
Acetophenone was also subjected to the same conditions, and only starting material was recovered.[17] This result is rationalized by the general reactivity of carbonyls. As previously mentioned, aldehydes react more readily than ketones (Figure 1-1). In the context of carbonyl additions, aldehydes are more reactive due to not only sterics, but electronics. The carbonyl carbon of ketones is less reactive due to the weak electron-donating nature of the alkyl groups on either side of the carbonyl. This makes the carbonyl carbon less electrophilic, and it is therefore less likely to react with an incoming nucleophile. On the other hand, aldehydes only have one alkyl group attached to the carbonyl carbon that can donate electrons, so the carbon is less negatively (more positively) charged compared to a ketone, making it more willing to react with an incoming nucleophile.



Scheme 2-4. Reaction of **1** with various α-hydroxy ketones.

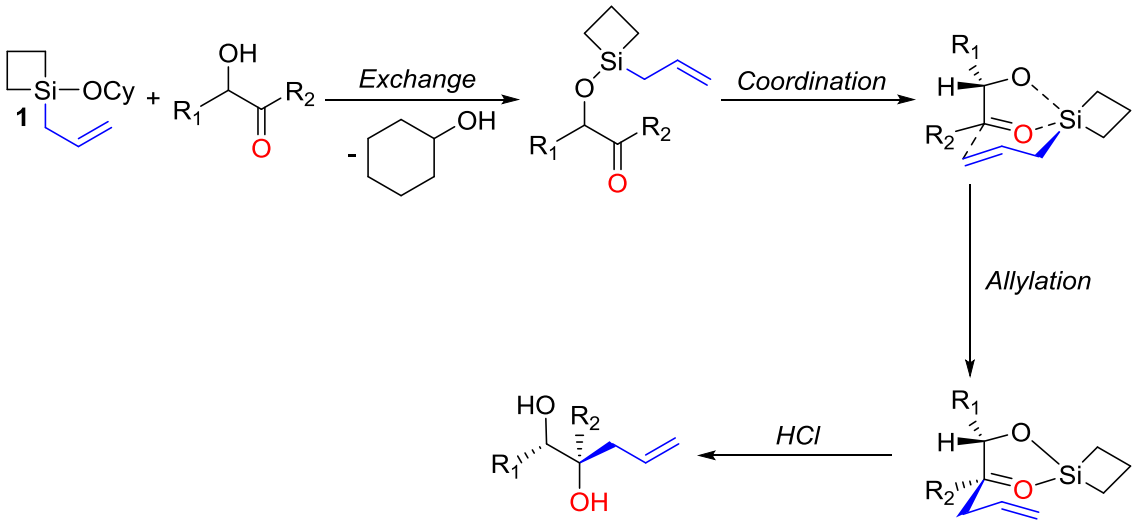
Based on **1** showing reactivity with benzaldehyde and benzoin, Matsumoto's group examined the reactivity of **1** with α-hydroxy ketones (Scheme 2-4). Because free cyclohexanol was observed in the products of these reactions, *and* mindful of the fact that acetophenone showed no reaction, it was predicted that the mechanism first involves exchange of the alkoxy group on silicon. To test this, 1-(cyclohexyloxy)-1-phenylsilacyclobutane was treated with isopropyl alcohol at 100 °C, which yielded 1-

isopropyl-1-phenylsilacyclobutane and free cyclohexanol (HOCy), leaving behind only a trace of the original alkoxy silane (Scheme 2-5). This exchange reaction even occurred at room temperature, and a mixture of silanes and free alcohols were observed in a 1:1:1:1 ratio.[17] Further proving the unique reactivity of siletanes, the same exchange reaction was attempted using dimethylphenyl(cyclohexyloxy)silane and isopropyl alcohol. Under the same reaction conditions, only starting material was obtained.[17]



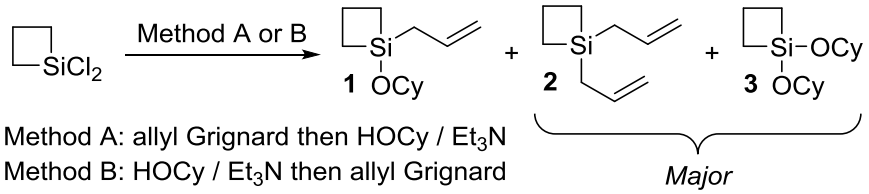
Scheme 2-5. Matsumoto's alkoxy exchange.

Having evidence for alkoxy exchange, Matsumoto suggested a non-catalyzed allylation mechanism that involves an intramolecularly activated pentacoordinate silicon species. It is proposed that first the alkoxy exchange occurs, followed by the coordination of the nucleophilic carbonyl oxygen to silicon, yielding the activated pentacoordinate silicon species in a five-membered chelate, and finally stereoselective intramolecular addition of the allyl group from the silicon to the carbonyl (Scheme 2-6).[17]



Scheme 2-6. Matsumoto's proposed reaction mechanism.

The O'Neil group became interested in compound **1** for the purposes of our carbosilylation experiments. Compound **1**, however, first needed to be synthesized as it is not commercially available. In their original report, Matsumoto reported a 29% yield of **1** when 1,1-dichlorosilacyclobutane was reacted with allyl Grignard (1 eq.) followed by etherification with HOCy in the presence of Et_3N (Method A, Scheme 2-7).[17] However, when attempting this chemistry, very low yields (~10%) of **1** were consistently obtained. Reversing the order of addition (i.e. HOCy/Et_3N followed by allyl Grignard) gave similar results (Method B, Scheme 2-7, Figure 2-2).



Scheme 2-7. First attempts to synthesize **1.**

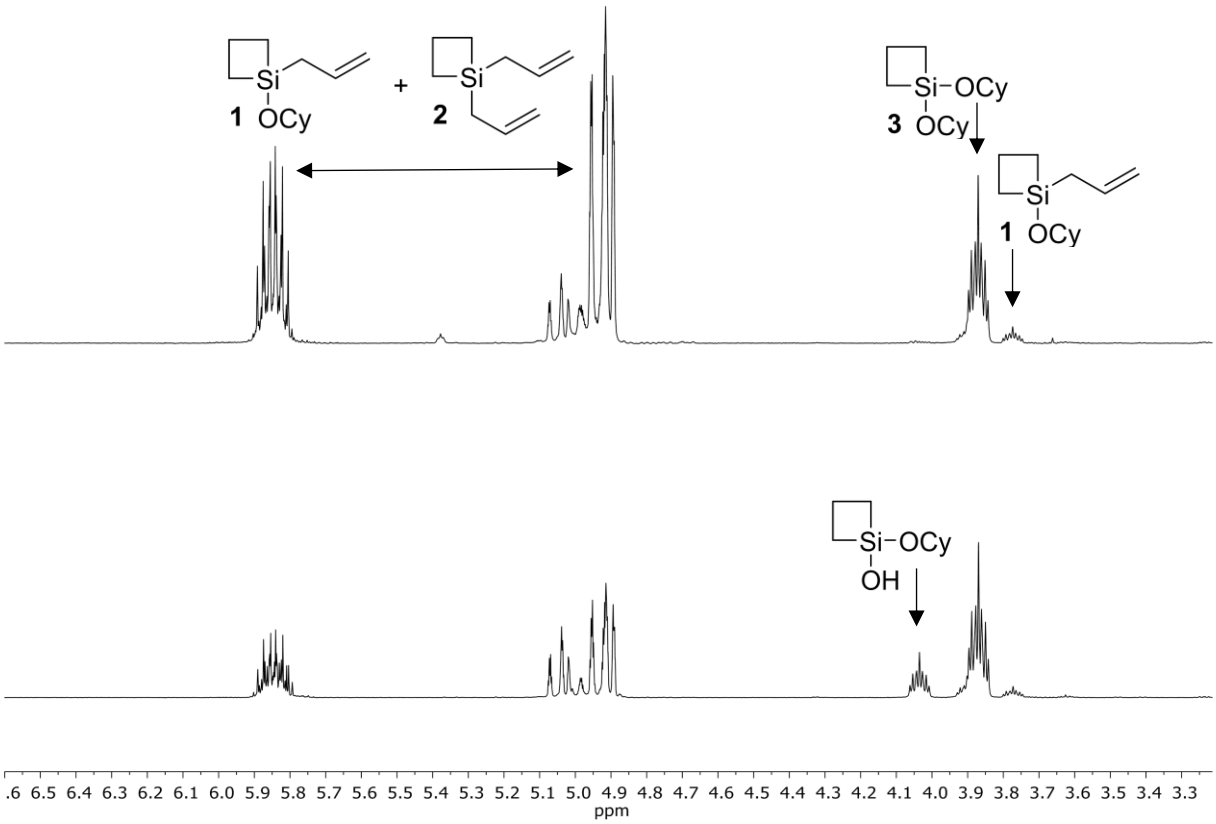
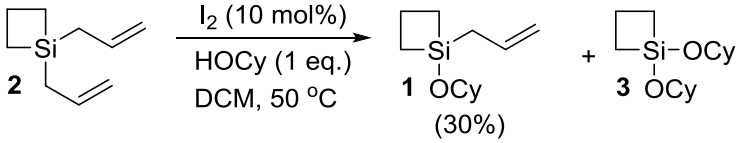


Figure 2-2. ^1H NMR – Products from Methods A and B.

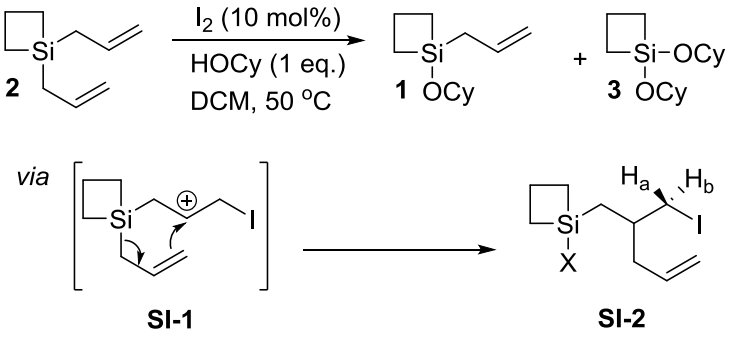
With significant amounts of diallylsilacyclobutane (**2**) obtained from those reactions, we then turned to Hosomi and Sakurai's method of iodine-promoted silyl etherification of alcohols in an attempt to convert **2** into the desired mono-silylether **1**.[20] Treating **2** with catalytic iodine (10 mol%) and HOCy (1 eq.) at 50 °C gave a mixture of **1**, **2**, and diether **3** in a statistical mixture. From this process, **1** could be consistently isolated in ~ 30% yield (Scheme 2-8).



Scheme 2-8. Iodine-promoted silyl etherification of cyclohexanol.

2.3 Iodine Mediated Rearrangement of Diallylsiletane

The crude ^{1}H NMR of the previous reaction showed small peaks that were characteristic of a diastereotopic methylene group (Figure 2-3). It was thought that products of type **SI-2** could result from the initial cation intermediate **SI-1**, based on previous reports of electrophile-promoted rearrangements of diallylsilanes (Scheme 2-9).[21,22] Inspired by the potential synthetic utility of **SI-2**, we continued to explore this possible iodine-mediated rearrangement.



Scheme 2-9. Iodine-promoted rearrangement of diallylsiletane.

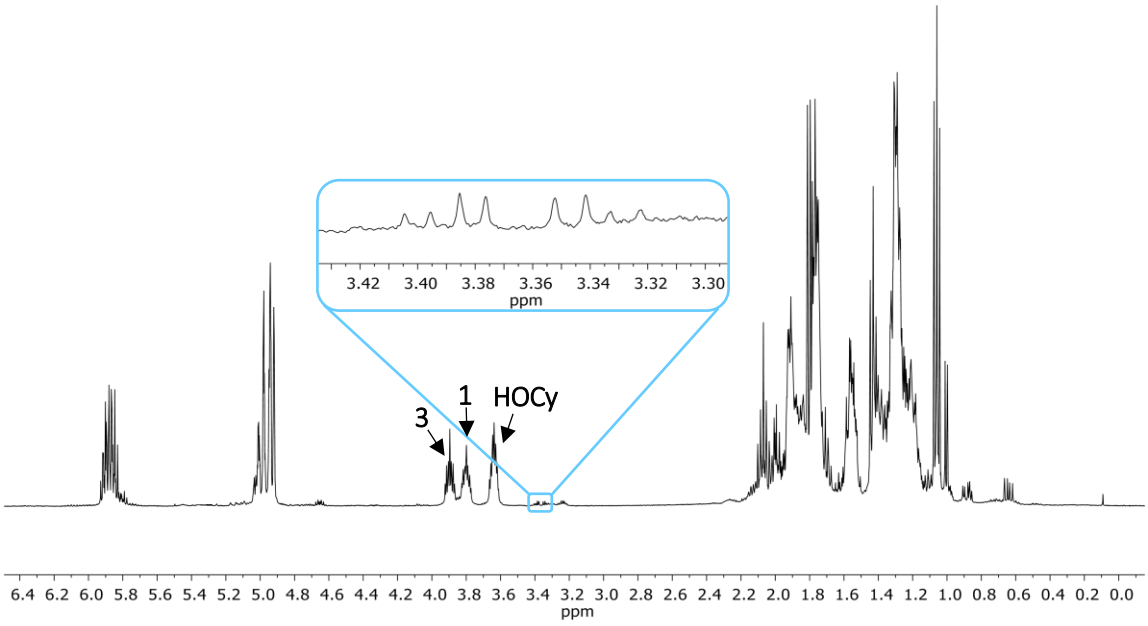
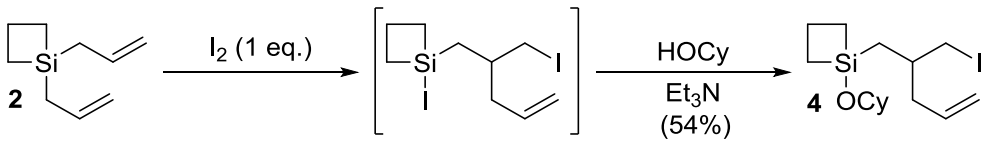


Figure 2-3. ^{1}H NMR – Iodine promoted silyl etherification of cyclohexanol.

It was hypothesized that increasing the amount of iodine should also increase the amount of rearranged product, and indeed, silyl ether **4** was isolated in 54% yield when **2** was treated with 1.0 equivalent of I_2 followed by HOCy/Et_3N (Scheme 2-10).



Scheme 2-10. Synthesis of compound **4**.

It has been noted that the substituents on silicon can have a significant effect on reaction outcomes.[15,23,24] Therefore, the reaction was also performed with diallyldimethyl, diallyldiisopropyl, and diallyldiphenyl silanes. The reactions were monitored by NMR and ratios of rearranged product to non-rearranged product were determined by the presence of allyl iodide (as an indicator of non-

rearrangement). As shown in Figure 2-3, diallyldiphenylsilane gave the highest ratio of rearranged product (7.86:1), and diallyldimethylsilane yielded the lowest degree of rearrangement (1.48:1), potentially indicating some steric effects. Comparing results for diallyldiphenyl- and diallyldiisopropyl- silanes (7.86:1 and 6.63:1, respectively), suggests there is also an electronic factor to the selectivity for these silanes to rearrange (Figure 2-4). This may arise from the ability of nearby Si-C bonds to stabilize the cation intermediate, **SI-1**, through hyperconjugation.[25]

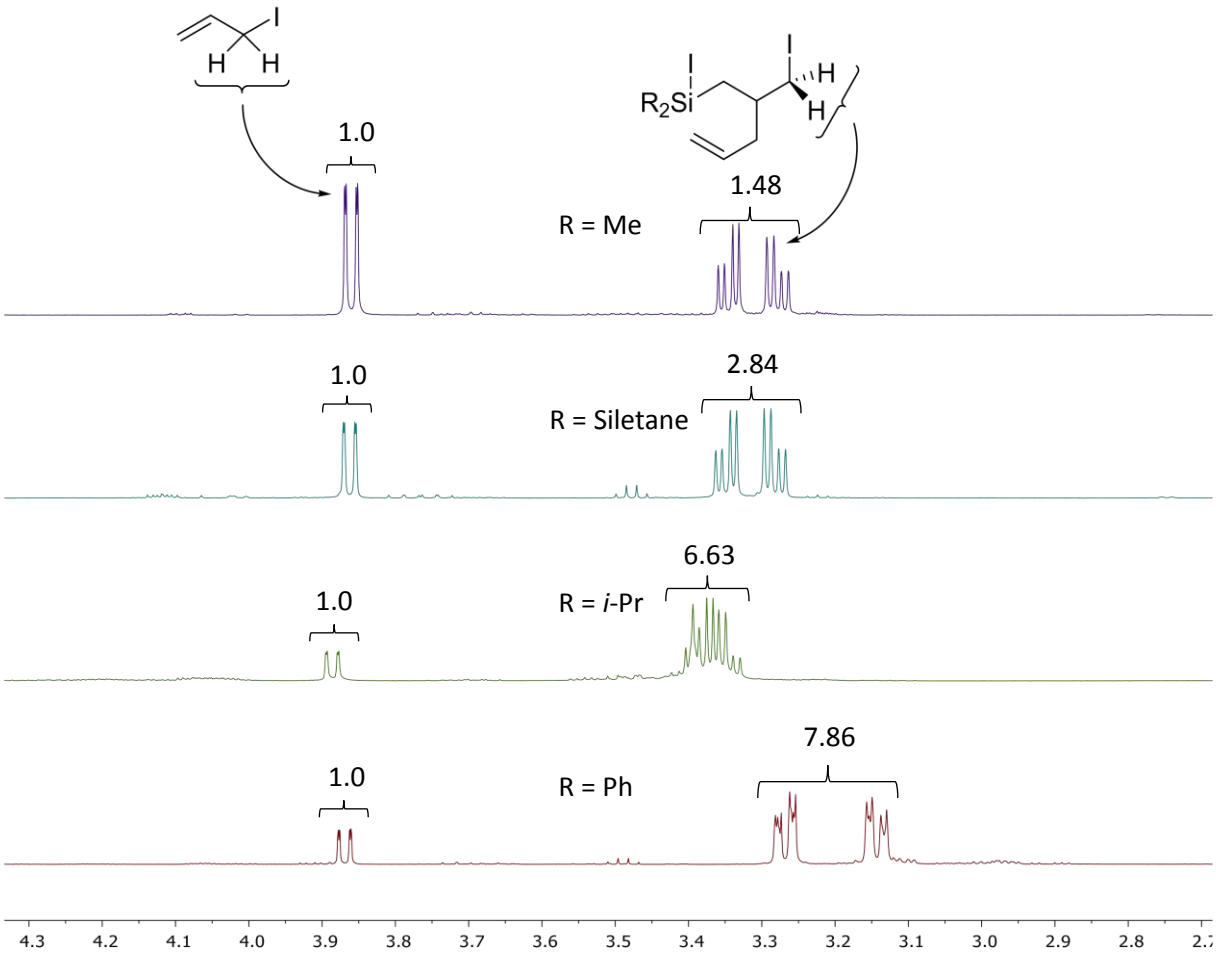
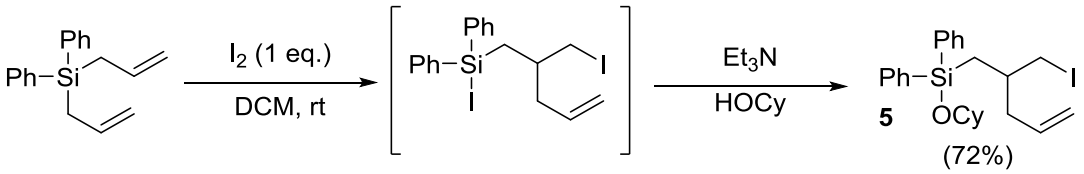


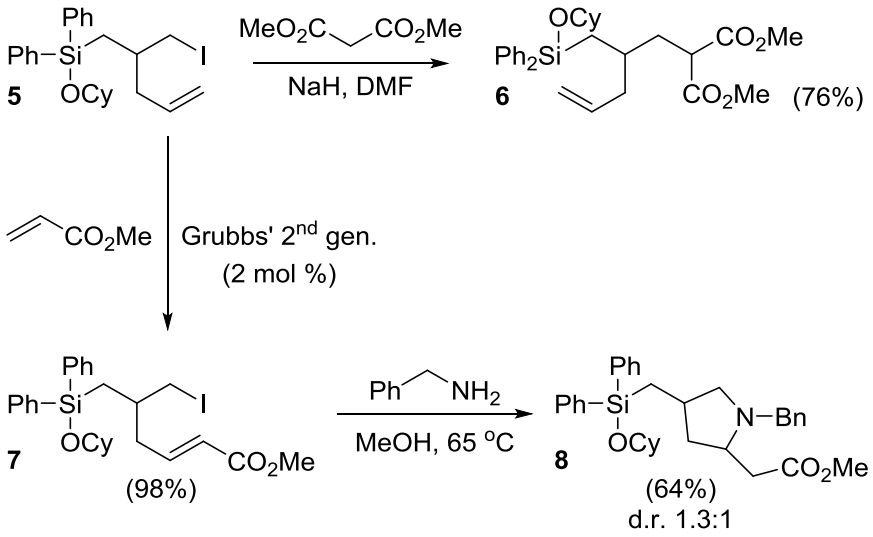
Figure 2-4. ^{1}H NMR – Comparison of different substituted diallylsilanes subjected to rearrangement conditions.

The reactions performed at 50 °C and room temperature gave the same ratios of rearranged to non-rearranged product. However, cooling the reaction to 0 °C displayed a destruction of selectivity for the rearranged product. Chloroform or dichloromethane (DCM) were favorable solvents for rearrangement to occur, while toluene, tetrahydrofuran (THF), DMF, and dimethyl sulfoxide (DMSO) all yielded trace amounts, at best, of rearranged product. Using the optimal conditions, compound **5** was isolated in 72% yield (Scheme 2-11).



Scheme 2-11. Synthesis of compound **5**.

The rearranged products have proven to be quite versatile synthetic intermediates. For instance, compound **5** could be alkylated with dimethylmalonate, producing silyl diester **6** in 76% yield (Scheme 2-12). Additionally, cross-metathesis between **5** and methyl acrylate generated **7** in 98% yield, which was then treated with benzylamine to give the silylmethyl-functionalized pyrrolidine **8** (Scheme 2-12).



Scheme 2-12. Synthetic utility of compound **5**.

Chapter 3: Carbosilylations Using 1-Allyl-1-Cyclohexyloxysiletane

3.1 α-Oxocarboxylic Acids

Tertiary α-hydroxy carboxylic acids are common functional units in many natural products, such as integerrimine, and monocrotaline (Figure 3-1).[27-29] Because of this, several synthetic methods have emerged for the formation of the α-hydroxy carboxylic acid moiety, including dihydroxylation of α,β-unsaturated ketones and enolate addition of α-keto esters.[30,31] However, there are not many reports of creating α-hydroxy carboxylic acids directly from α-keto acid starting materials.

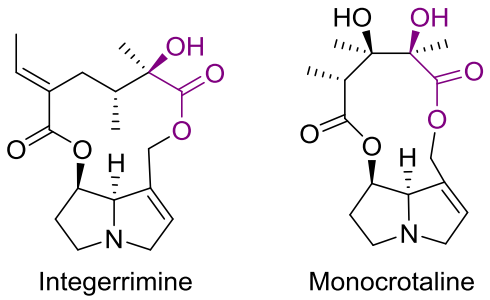
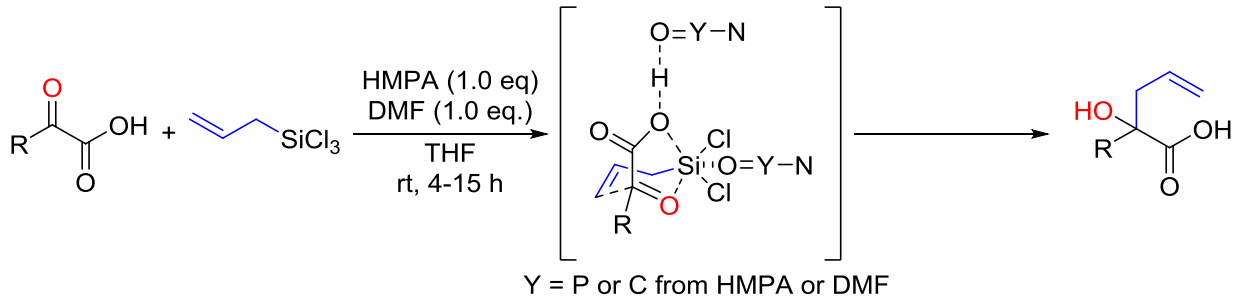


Figure 3-1. Two natural products, integerrimine and monocrotaline, containing the α-hydroxy carboxylic acid functionality.

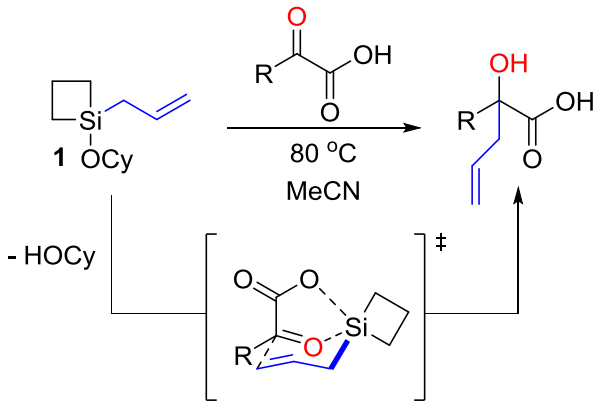
One example from Wang et al., describes the reaction of α-oxocarboxylic acids with allyltrichlorosilane.[27] While many allylsilations of aldehydes have been reported, addition of allyltrihalosilanes to ketones are limited. Initially using methods put forth by Sakurai (allyltrihalosilane in the presence of Et_3N), Wang and coworkers found that the reaction afforded very low yields of the desired product.[27,32] Their focus then turned to the work of Kobayashi and Denmark, who found that DMF or HMPA coordinates to silicon, forming a hypervalent silicate, which is then more nucleophilic.[33,34] Using DMF and/or HMPA in their own studies, Wang discovered that either additive successfully catalyzed the reaction. However, after optimization, it was found that using 1.0 equivalent of *both* DMF and HMPA was necessary for complete conversion (Scheme 3-1).[27] The reaction of α-oxocarboxylic acids under optimized conditions

occurred relatively quickly, with the shortest reaction times being about 3-4 hours. Notably, it was found that α-oxocarboxylic esters or ketones under the same conditions reacted very slowly (> 60 hours), if at all.[27] It was determined that the α-carboxylic group not only activates its ketone neighbor, but also plays a key role in the allylation step, by complexing with the silicon atom, which in turn complexes with the keto group, as also seen in Matsumoto's work (Scheme 3-1).[27,17]



Scheme 3-1. Allylation of α-oxocarboxylic acids using allyltrichlorosilane, HMPA, and DMF.

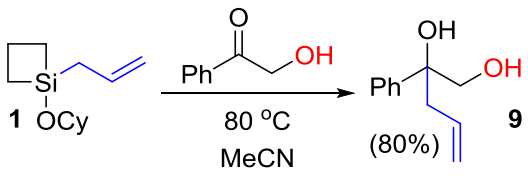
With allyltrichlorosilane being highly unstable to air and moisture (and HMPA being toxic), it was our goal to investigate the reaction of **1** as an alternative for allyl additions to ketones of α-oxocarboxylic acids. Combining the work of Wang, Matsumoto, and Sakurai, the hypothesis was that a chemoselective, non-catalyzed, intramolecular allylation would occur between **1** and α-oxocarboxylic acids with no use of additives (due to the enhanced Lewis acidity of the siletane), through a similar mechanism proposed by both Matsumoto and Wang, i.e. first alkoxy exchange, followed by the intramolecular allylsilylation of the ketone that has been activated by the Lewis acidic siletane ring (Scheme 3-2).



Scheme 3-2. Allylation of α-oxocarboxylic acids using **1**.

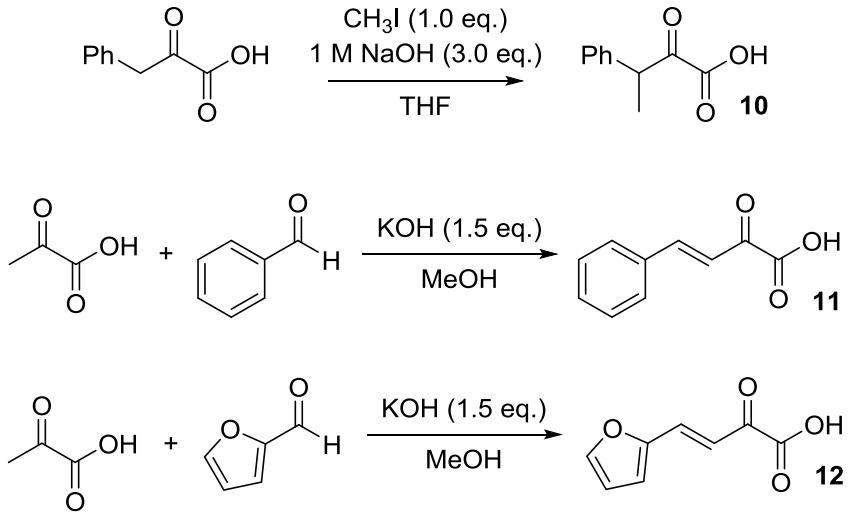
These studies began with an initial investigation of the work reported by Matsumoto on reactions of **1** with α-hydroxycarboxylic acids.[17] The reaction of **1** and 2-hydroxyacetophenone was performed under the same reaction conditions (i.e. using DMF as solvent, and heating the mixture to 100 °C). While analyzing the products of this reaction, it was noticed that the residual DMF was extremely difficult to remove during an aqueous workup procedure. Additionally, from the work by Kobayashi and Denmark, it was also thought that DMF could be activating the silicon.[33,34] We considered switching to acetonitrile (MeCN), another polar, aprotic solvent, but were concerned that DMF might be needed due to its aforementioned activating ability. Moreover, with the lower boiling point of MeCN, the reaction temperature necessarily would also decrease (80 °C as opposed to 100 °C).

To our delight, the use of MeCN had no negative effect on the efficiency of the reaction, and **9** was isolated in 80% yield (Scheme 3-3).



Scheme 3-3. Allylation of 2-hydroxyacetophenone.

We then set out to investigate the allylation of α-oxocarboxylic acids under these same reaction conditions. It was first found that commercially available phenylglyoxylic acid could be successfully allylated with **1** in MeCN at 80 °C. Having proof of principle, a library of α-oxocarboxylic acids were either purchased or synthesized as outlined in Scheme 3-4. The objective was to allylate an assortment of compounds with various characteristics including alkyl, alkenyl, aryl, and heteroaryl functional groups in order to understand the scope and potential limitations of the reaction.



Scheme 3-4. Synthesis of compounds **10-12.**

As can be seen in Figure 3-2, all of the α-oxocarboxylic acid allylation products could be obtained in good yield (51-88%) after a simple basic extraction purification. To demonstrate that exchangeable groups are required on both the silane and carbonyl substrate, two control experiments were performed (Scheme 3-5). First, diallylsiletane and 2-hydroxyacetophenone were subjected to the reaction conditions. In this case, the silane does not contain an alkoxy group with which the substrate can exchange, and the reaction did not proceed. Next, identical conditions were applied to acetophenone and **1**. Similarly, acetophenone does not have a hydroxyl group with which the cyclohexyloxy can exchange, and therefore no reaction occurred. Combined, these experiments add additional support to the proposed mechanism shown in Scheme 3-2.

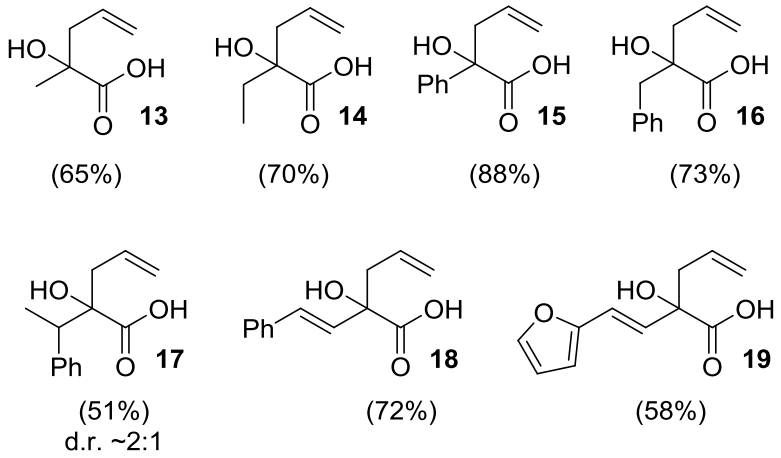
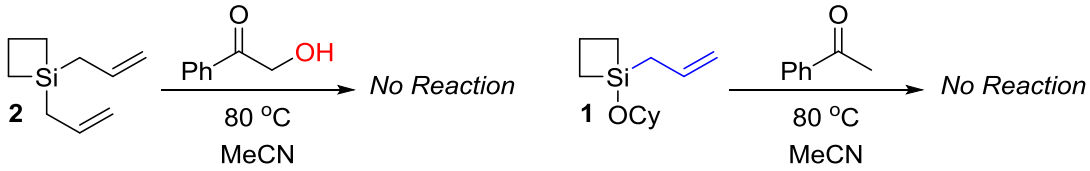


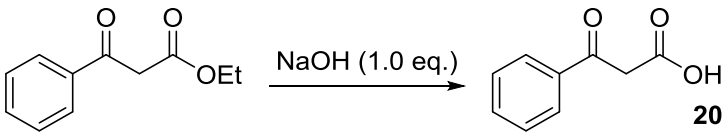
Figure 3-2. Allylation products of various α-oxocarboxylic acids.



Scheme 3-5. Control experiments proving exchangeable groups are required for allylation.

3.2 β-Oxocarboxylic Acid

To determine whether allylation occurs with both α- and β-carboxylic acids, substrate **20** was prepared (Scheme 3-6). It is worth noting that in the ^{1}H NMR spectrum, the peak observed at 5.72 ppm arises from the enolization of **20**, while the peak seen at 4.09 ppm comes from the β-oxocarboxylic acid. Interestingly, when subjected to the reaction conditions, only silane byproducts and acetophenone, formed from decarboxylation of **20**, were recovered (Figure 3-3). A series of experiments were then performed to investigate the effects of solvent on the rate of decarboxylation.



Scheme 3-6. Synthesis of β-oxocarboxylic acid **20**.

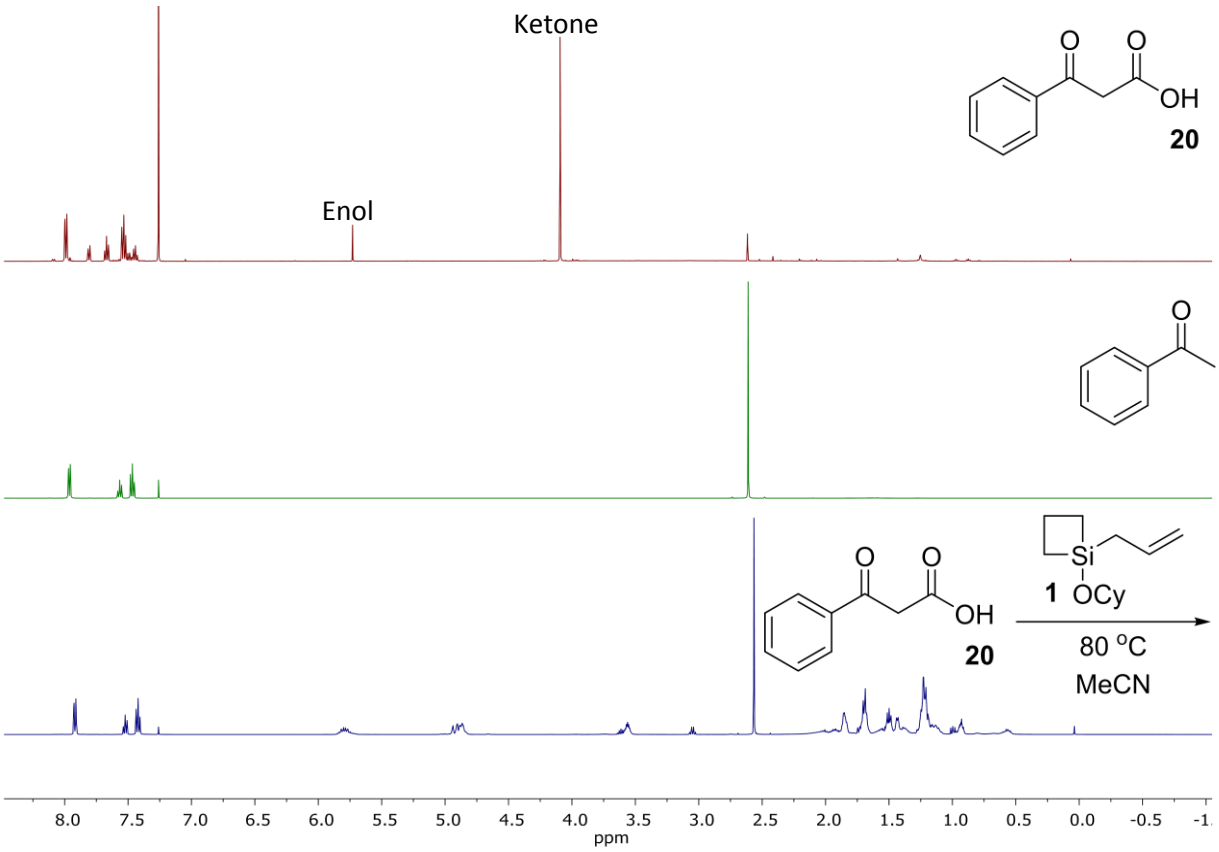
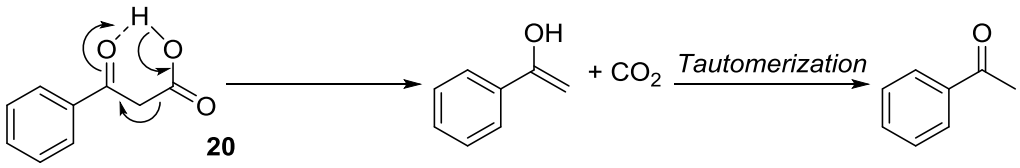


Figure 3-3. ^{1}H NMR – Comparison of starting material, acetophenone, and reaction mixture for the attempted allylation of **20**.

To begin, **20** was heated (80 °C) in MeCN without the addition of **1**, and it was noticed that decarboxylation still occurred. The proposed mechanism of this decomposition is shown in Scheme 3-7. Next, solvent studies were performed using $CDCl_3$, benzene (d-6), and DMSO (d-6). The mixtures were left at room temperature, and decarboxylation was tracked by NMR over the course of 3 hours. The solubility of **20** in each solvent is worth noting – while slightly soluble in $CDCl_3$, and fully soluble in DMSO, the starting material was almost completely insoluble in benzene. Table 3-1 shows the ratios of starting material (enol + ketone form) to decarboxylation product (acetophenone) over the duration of 3 hours for each solvent. The apparent reappearance of starting material at 1 hr in $CDCl_3$ is thought to arise from a solubility effect, while the observed enhanced rate of decarboxylation in DMSO was likely due to the fact that both **20** and

acetophenone were completely soluble in the solvent. However, even with solubility playing a role, as can be seen in the table, a steady increase of decarboxylation product was observed in all solvents with the greatest amount of decarboxylation occurring in DMSO. Even after just 15 minutes, some amount of acetophenone was visible by NMR (Table 3-1).



Scheme 3-7. Decomposition of 20 to acetophenone.

Table 3-1. Ratios of starting material (20) to decarboxylation product (acetophenone) in various solvents.

S.M. : Acetophenone	15 Min.	1 h	2 h	3 h
$CDCl_3$	12 : 1	18 : 1	11 : 1	7.8 : 1
Benzene (d-6)	12 : 1	11 : 1	8.4 : 1	7.2 : 1
DMSO (d-6)	7.1 : 1	2.0 : 1	1 : 1.2	1 : 1.9

A second experiment was performed to investigate whether or not the addition of a silane had any effect on the rate of decarboxylation. Dialkoxysilanes (i.e. silanes with two exchangeable sites) were introduced to the reaction mixture and the rate of decarboxylation was again monitored over the course of 3 hours. Due to the ability of DMSO to be a nucleophilic activator of silanes, the experiments all used $CDCl_3$ as the solvent.[33-35] Figure 3-4 shows the ^1H NMR of each of these experiments after 3 hours; Table 3-2 shows the ratios of starting material to acetophenone with the addition of each silane. As can be seen from both the figure and the table, the rate of decarboxylation was 4.5 times faster with the addition of dicyclohexyloxysiletane (3) while the addition of diphenyldicyclohexyloxysilane had no effect (Figure 3-4, Table 3-2).

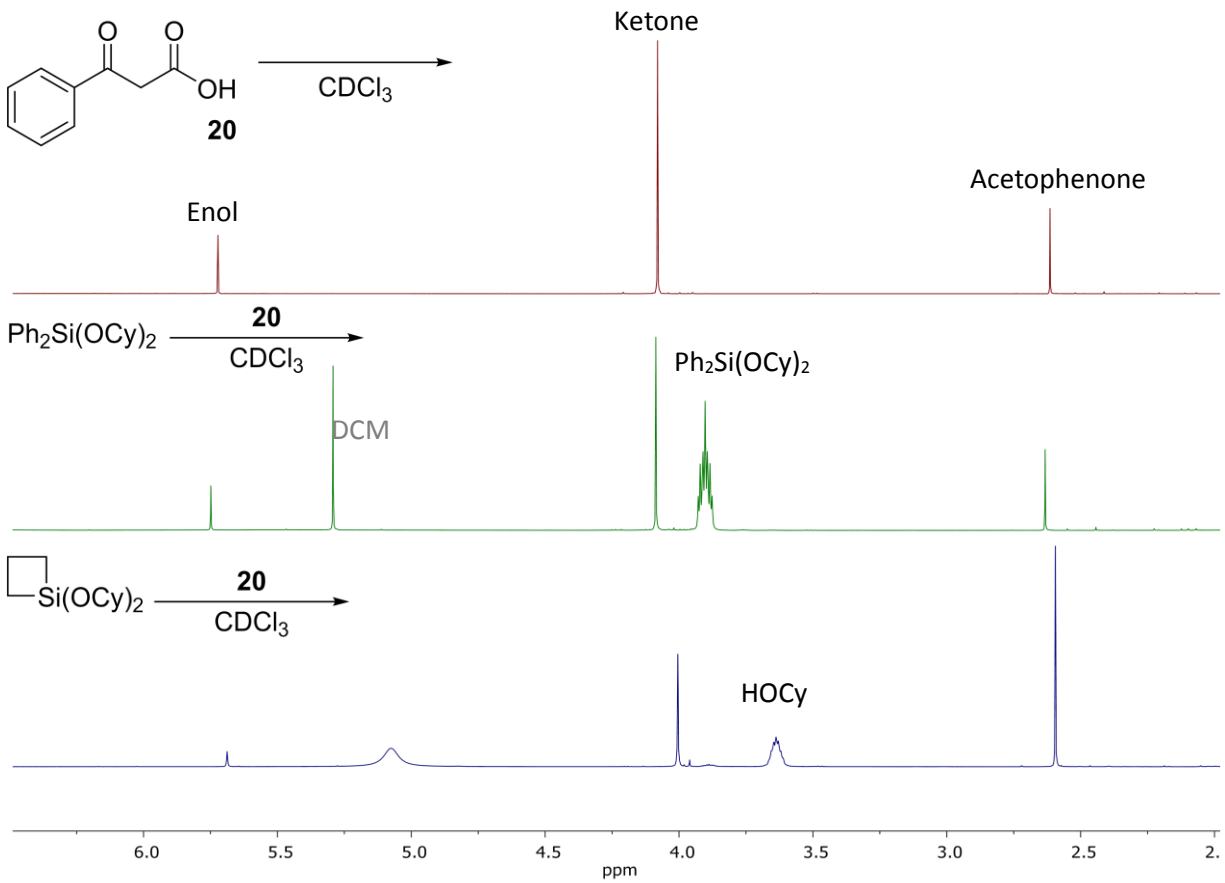


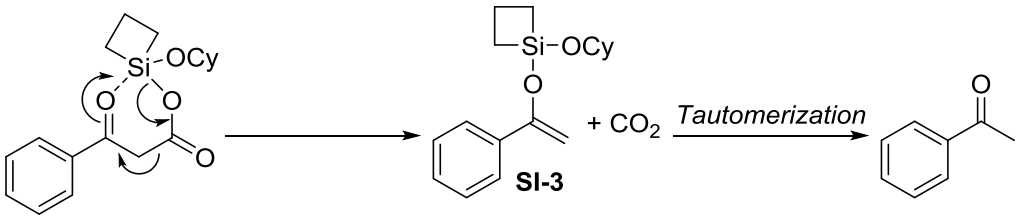
Figure 3-4. ^{1}H NMR – Comparison of decomposition reactions involving diphenyldicyclohexyloxysilane and dicyclohexyloxysiletane.

Table 3-2. Comparison of decomposition experiments with **20** and two dialkoxy silanes.

S.M. : Acetophenone	15 Min.	1 H	2 H	3 H
No Silane Additive	12 : 1	18 : 1	11 : 1	7.8 : 1
Diphenyldicyclohexyloxysilane	21 : 1	14 : 1	9.5 : 1	7.2 : 1
Dicyclohexyloxysiletane	19 : 1	3.5 : 1	2.3 : 1	1.6 : 1

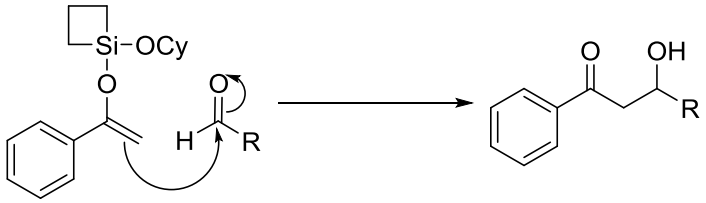
As the NMR shows, when dicyclohexyloxysiletane (**3**) was used, the release of free cyclohexanol was rapidly observed and no starting silane was present after 3 hours, indicating that exchange occurred between **20** and cyclohexanol. It is proposed that after exchange with cyclohexanol, the mechanism of decomposition is similar to the mechanism shown in 3-7, with silicon replacing hydrogen (Scheme 3-8). It

is also worth noting that no exchange occurred at all between **20** and diphenyldicyclohexyloxysilane, as indicated by the absence of free cyclohexanol in the ^{1}H NMR.



Scheme 3-8. Proposed decomposition mechanism of **20** to acetophenone in the presence of dicyclohexyloxysiletane.

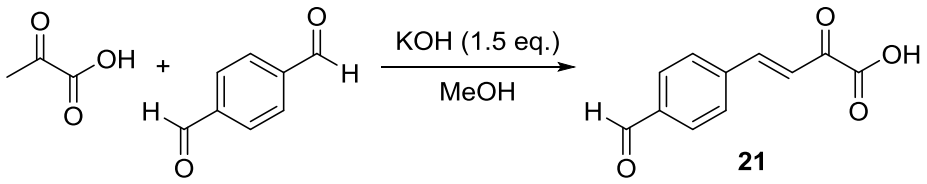
Future investigations into the utility of these types of reactions may involve trapping silylenolethers of type **SI-3** with electrophiles such as aldehydes (Scheme 3-9).[36-38] This would yield yet another novel way to form carbon-carbon bonds without the addition of a catalyst.



Scheme 3-9. Future work involving trapping silylenolethers with electrophiles.

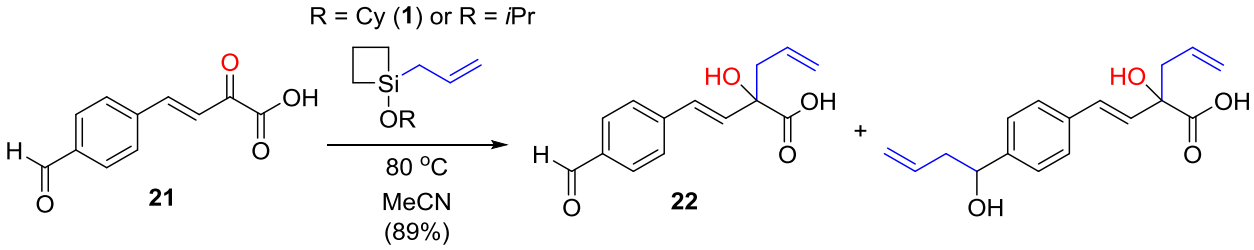
3.3 Allylation of Aldehyde Containing α-Oxocarboxylic Acids

As previously mentioned, nucleophilic additions can occur preferentially to aldehydes in the presence of other carbonyl groups (e.g. ketones) due to their increased reactivity. However, if the mechanism of allylations using compound **1** occurs as proposed in Scheme 3-2, we hypothesized that certain α-oxocarboxylic acid substrates might react differently than normal electrophilicity trends would predict. For instance, compound **21** was prepared to test if the ketone might be selectively allylated in the presence of an aldehyde (Scheme 3-10).

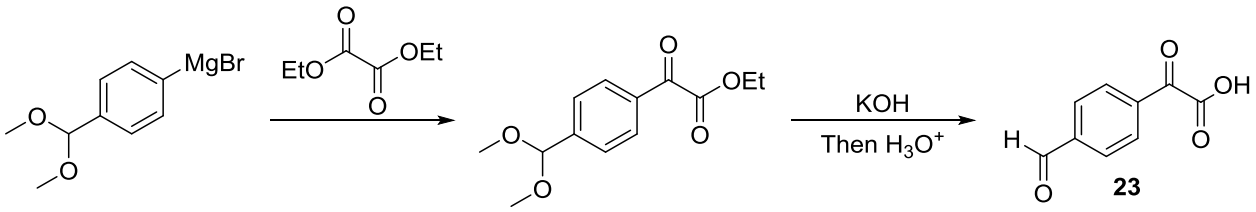


Scheme 3-10. Synthesis of compound **21**.

When treated with **1** in MeCN at 80 °C, chemoselective addition of the allyl group to the ketone occurred giving a 5.7:1 mixture in favor of the monoallylated compound **22** along with smaller amounts of the diallylated product in 89% yield (Scheme 3-11). This result is quite impressive, as **21** has five *different* electrophilic sites – 3 carbonyls, including one α,β-unsaturated carbonyl that can participate in Michael addition, and an acidic proton. Furthermore, this is one of only a few examples of the addition of a carbon electrophile to a ketone in the presence of an aldehyde, *and* those examples generally involve protection and deprotection of the aldehyde *in situ*.[39-41] In addition, many of these other examples still involve the use of organolithium reagents, Grignard reagents, or transition metal additions such as trimethylaluminum.[39-42] The same result could also be obtained using an isopropoxy (instead of cyclohexyloxy) siletane (**1-*i*Pr**). The switch did not have an effect on yield, and aided in the purification process, as isopropanol can be evaporated, whereas cyclohexanol must be removed via column chromatography.

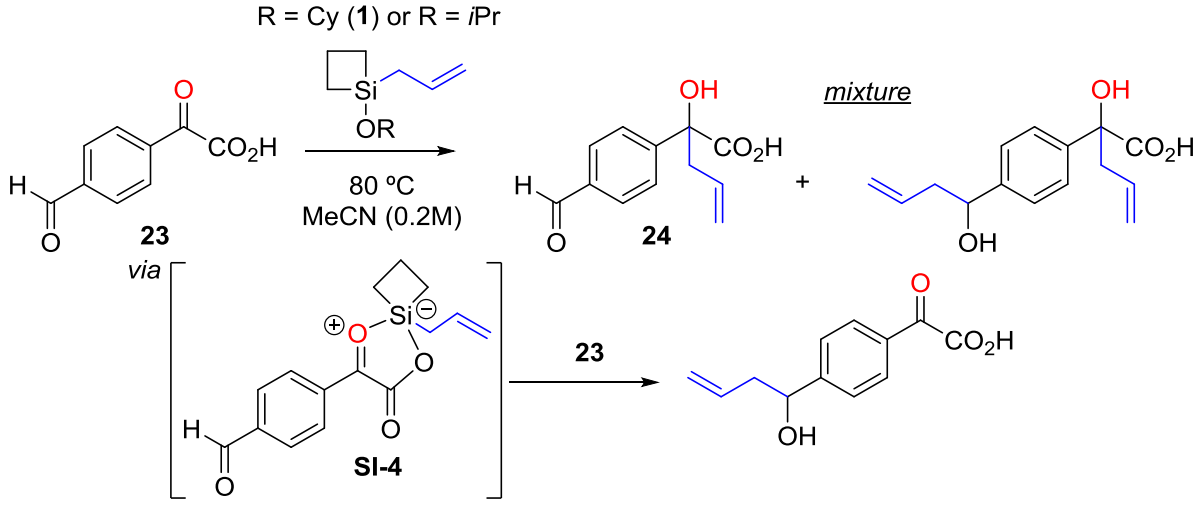


Scheme 3-11. Allylation of **21**.



Scheme 3-12. Synthesis of compound **23**.

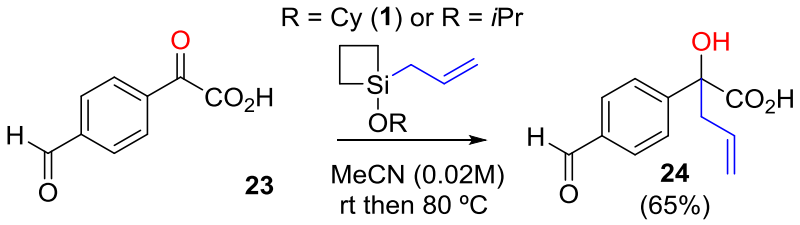
To the same end, compound **23** was also prepared (Scheme 3-12). Curiously, the reaction of this simpler substrate (with only four electrophilic sites) proceeded *less* chemoselectively. Desired product (**24**) was indeed formed, but with significant amounts of aldehyde addition products as well. It was thought that allylation at the aldehyde resulted from an *intermolecular* reaction with allylsilanide **SI-4** (Scheme 3-13). Upon treating **23** with **1**, the reaction mixture became bright orange that we have attributed to the charged complex of **SI-4**. Moreover, rapid release of cyclohexanol was observed (< 15 min.) when monitoring the reaction by ^{1}H NMR in MeCN (d-6). This was indicative of exchange with the substrate hydroxyl prior to the allylation event.



Scheme 3-13. Allylation of aldehyde α-oxocarboxylic acid **23** - first attempts.

Arguably, the ketone of compound **23** is more sterically hindered than that of compound **21**. It is thought that this may slow down the intramolecular process, allowing for the intermolecular allylation of

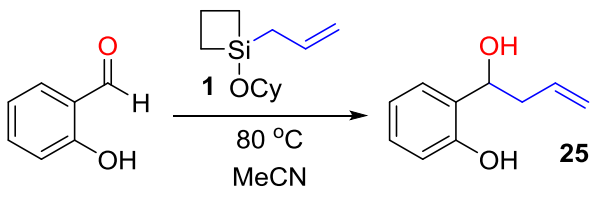
the aldehyde of **23** to compete. Therefore, to promote intramolecular allylation of the ketone, the reaction of **23** and **1** was performed under more dilute conditions (0.02M), and the mixture was allowed to react at room temperature to allow for the exchange of the alkoxy substituents, followed by heating to promote allylation (Scheme 3-14). Using these conditions, chemoselective ketone allylation product **24** was isolated in 65% yield.



Scheme 3-14. Chemoselective allylation of **23**.

3.4 Allylation of Salicylaldehyde and Similar Substrates

In thinking about other substrates to investigate, we saw promise in salicylaldehyde. Experiments had shown that benzaldehyde was unreactive when treated with **1** in MeCN at 80 °C. However, we wondered if by having a nearby hydroxyl group, we could promote the nucleophilic addition as we had seen with previous substrates. In fact, treating salicylaldehyde with **1** in MeCN at 80 °C produced clean allylation of the aldehyde, yielding compound **25** (Scheme 3-15). Moreover, in a 1:1 mixture with benzaldehyde, **25** was recovered in > 90% yield, along with the unreacted benzaldehyde. The results from this experiment are represented graphically in Figure 3-5.



Scheme 3-15. Allylation of salicylaldehyde.

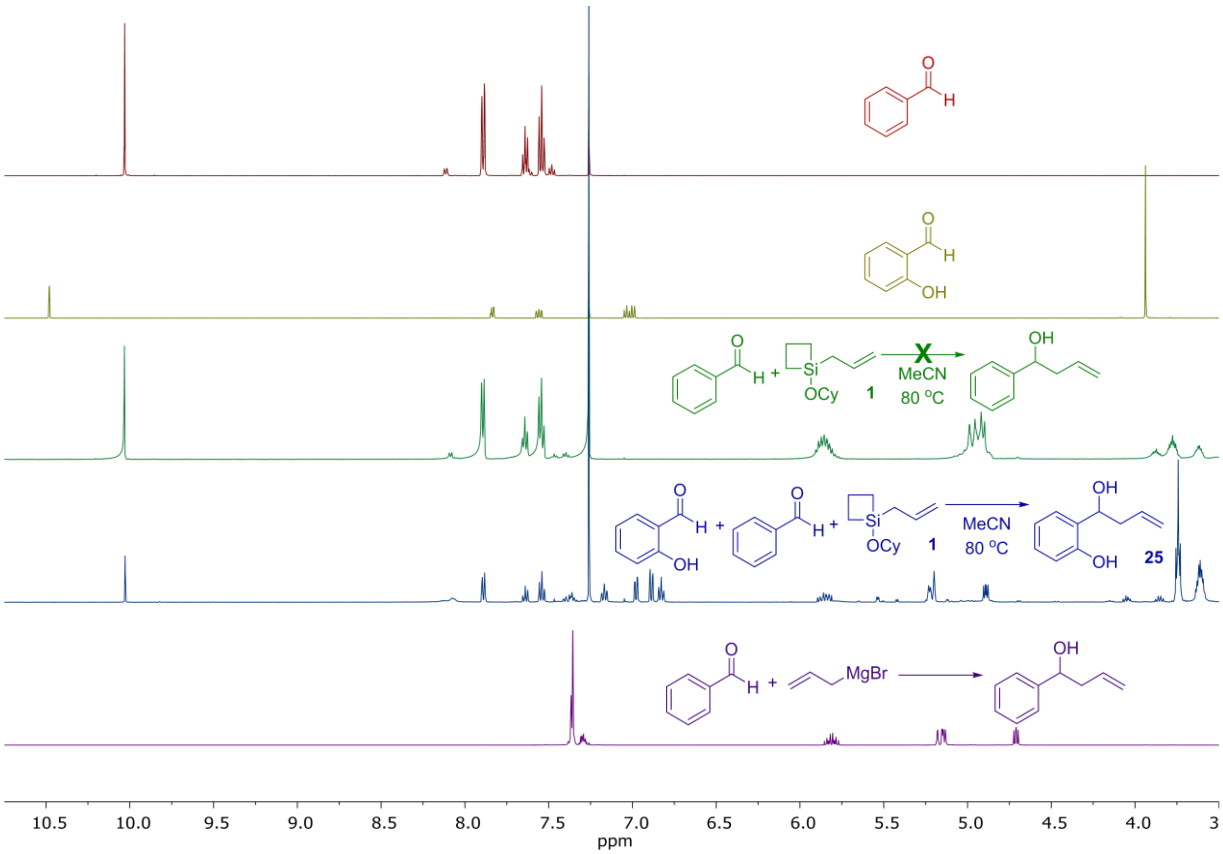
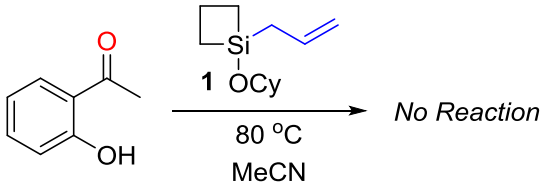


Figure 3-5. ^{1}H NMR – Comparison of reactions of **1** with benzaldehyde and salicylaldehyde.

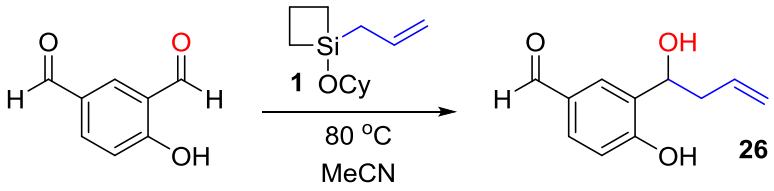
The bottom trace of Figure 3-5 (purple) shows the deliberate synthesis of allylated benzaldehyde using allyl Grignard. As can be seen in the figure, the reaction of **1** and benzaldehyde under our reaction conditions showed no allylated product (green); only starting silane and benzaldehyde (red) were present in the reaction mixture. The blue trace shows the reaction mixture of **1** with 1:1 benzaldehyde and salicylaldehyde (yellow). Noticeably, the aldehyde peak corresponding to salicylaldehyde is no longer present, and the peaks corresponding to compound **25** are slightly shifted from the starting material. Also of importance, is free cyclohexanol visible at 3.60 ppm, indicating exchange with salicylaldehyde occurred.

Interestingly, 2'-hydroxyacetophenone (the corresponding ketone equivalent of salicylaldehyde) failed to react under these conditions (Scheme 3-16). It is hypothesized that the lower electrophilicity of ketones vs. aldehydes plays a role.



Scheme 3-16. Attempted allylation of 2'-hydroxyacetophenone.

Similar to α-oxocarboxylic acids, chemoselectivity could be achieved with salicylaldehyde-based substrates. For example, the allylation of 4-hydroxyisophthalaldehyde and **1** proceeded cleanly, and after treatment with TBAF, compound **26** was isolated in 58% yield (Scheme 3-17). Ito and coworkers were also able to perform the allylation of 4-hydroxyisophthalaldehyde using allyltributyltin.[43] They explained their result as an intramolecular hydrogen bond between the phenol and *ortho*-aldehyde, thereby causing this aldehyde to be more electrophilic. While this phenomenon may contribute to what we observed, based on the understanding of our proposed mechanism, we argue that it is the intramolecular reaction of compound **1** that is most important for the chemoselectivity observed.



Scheme 3-17. Allylation of 4-hydroxyisophthalaldehyde.

Conclusion

To summarize, siletanes are easily activated silane compounds. This arises from the relief of ring strain when the silane goes from tetracoordinate to pentacoordinate. The groups of Matsumoto and Fujimoto confirmed the enhanced Lewis acidity of siletanes by comparing allylsiletane to allyldimethylsilane, a similar compound. Computations carried out by Fujimoto fully characterize the enhanced reactivity of siletane compounds relative to their non-cyclized counterparts. Due to Matsumoto's success with allylalkoxysiletane **1**, we set out to use **1** in our own investigations. Because Matsumoto's reported synthesis did not work in our hands, we turned to Sakurai's method of silyletherification of alcohols to obtain useful amounts of **1.** During this process, a rearrangement product was observed in the ^{1}H NMR. It is thought that this product arises from an initial carbocation intermediate that is formed. We continued to explore these rearrangement products by preparing dimethyl-, diisopropyl-, and diphenyl-rearranged products. We then compared the amount of rearranged product to non-rearranged product and discovered that silanes with bulkier groups tended to have more rearranged product, while smaller groups, such as the dimethyl- and siletane products showed smaller amounts of rearranged product. This result has been rationalized by the fact that bulkier groups do not allow the initial iodine to attach to silicon, thereby releasing allyliodide. Instead, the second allyl group attacks the carbocation that is formed, leaving an empty space on silicon for either iodine or an alcohol to bind. These rearranged products were proven to be useful. Diphenyl- rearranged product **5** was alkylated with dimethylmalonate, producing **6** in high yield. Compound **5** was also treated with methyl acrylate and Grubb's catalyst to afford **7**, also in high yield. Finally, **7** was treated with benzylamine to form substituted pyrrolidine **8**.

We then focused our attention to the allylation of α-oxocarboxylic acids. It was thought that by having a more active silane, and proceeding through Matsumoto's exchange mechanism, no additives would needed for the reaction to proceed. Indeed, allylation of α-oxocarboxylic acids and salicylaldehyde

derivatives can be achieved by reacting these compounds in the presence of **1** at 80 °C in MeCN. The reaction can achieve high yields with good chemoselectivity. The reaction does not occur unless both the siletane and substrate contain exchangeable groups, i.e. hydroxyls, near the reactive carbonyl. To demonstrate this, the reaction was attempted with **1** and benzaldehyde, as well as acetophenone. Furthermore, the reaction of diallylsiletane and 2-hydroxyacetophenone showed no allylation product. The reaction is proposed to proceed by alkoxyexchange between the substrate and siletane alcohol, followed by intramolecular coordination of the carbonyl to silicon, and finally allylation. The α-hydroxycarboxylic acid products were purified via a basic extraction procedure, while salicylaldehyde derivatives were treated with TBAF to afford the diol. These reactions occur without the presence of an added silicon activator, such as DMF, and it is presumed that MeCN plays no role in the allylation process. The results presented are presumed to arise from the Lewis acidity of siletanes like **1** and similar compounds (e.g. HO^{i}Pr instead of HOCy). The reactions were shown to be chemoselective for carbonyls near hydroxyl groups like that of α-oxocarboxylic acids or salicylaldehyde. In addition, it was shown that β-oxocarboxylic acid **20** decomposes to acetophenone when treated with the same reaction conditions. Moreover, it was shown that salicylaldehyde reacts fully with **1** even in the presence of benzaldehyde, leaving the latter unreacted. Sterics may also play a role in the allylation of aldehyde containing substrates. Compounds that are less sterically hindered around the carbonyl tend to have better chemoselectivity towards allylation of the ketone over the aldehyde. More sterically hindered substrates required more dilute conditions in order for preferential allylation at the ketone to occur. In these cases, it was also necessary to allow exchange of the alkoxy groups to occur before heating. Future experiments may focus on the manipulation of steroids or natural products such as hydrocortisone and honokiol derivatives to provide a simple, greener process to transform more complex structures with multiple exchangeable hydroxyl groups, yet only one active carbonyl.

Supporting Information

General: All reactions were carried out in an N_2 atmosphere in flame-dried glassware unless otherwise specified. All solvents were dried via a column of activated alumina under nitrogen immediately prior to use. All reagents were purchased and used as received unless otherwise noted. All TLC analysis used 0.25 mm silica layer fluorescence UV_{254} plates. Flash chromatography: SilaCycle silica gel P60 (230-400 mesh). NMR: Spectra were obtained on a Bruker Avance III 500 MHz FT-NMR Spectrometer in the solvents indicated; chemical shifts (δ) are given in ppm, coupling constants (*J*) are given in Hz. MestreNova 10.0 software was used to determine yield of select substrates. Solvent signals were used as references ($CDCl_3$: $\delta_C \equiv 77.00$ ppm; residual $CHCl_3$ in $CDCl_3$ $\delta_H \equiv 7.26$ ppm)

Experimentals

Compound 1: 1-Allyl-1-cyclohexyloxysiletane

Method 1: Iodine Catalyzed Monoetherification of Diallylsiletane

To a Schlenk flask containing a solution of diallylsiletane (**2**) (1.1 g, 6.9 mmol, 1.0 eq.) in DCM (35 mL) was added I_2 (180 mg, 10 mol %) at room temperature, and the solution was stirred for 10 min. The solution turned deep red. HOCy (0.72 mL, 6.9 mmol, 1.0 eq.) was then added and the solution was heated to 35 °C for 30 min. The solution turned deep orange. After 30 min. a drop of pyridine was added, and the solution was concentrated *in vacuo*. Purification by chromatography on silica (20:1 to 10:1 Hex:EtOAc) gave **1** as a pale yellow oil (0.44 g, 30%, R_f = .98 in 10:1 Hex:EtOAc).

Method 2: Direct Synthesis from 1,1-Dichlorosilacyclobutane

To a Schlenk flask was added neat 1,1-dichlorosilacyclobutane (1.0 mL, 8.4 mmol, 1.0 eq.) at 0 °C. Allyl Grignard (1.0 M in diethyl ether, 8.4 mL, 8.4 mmol, 1.0 eq.) was added dropwise over 15 min. and the solution was stirred for 1 h at 0 °C, then filtered through a Schlenk filter under N_2, using Et_2O to rinse, and the solution was brought to 0.20 M in silane. The solution was cooled back to 0 °C, and

diisopropylethylamine (Hünig's base, 2.2 mL, 13 mmol, 1.5 eq.) was added, followed by HOCy (0.92 mL, 8.9 mmol, 1.1 eq.). The solution was stirred and warmed to room temperature over 3 h. The resulting product was filtered through cotton using Et_2O, and concentrated *in vacuo*. The resulting mixture was triturated in Et_2O overnight, and was again filtered through cotton with Et_2O. The mixture was again concentrated *in vacuo* and used without any further purification. (1.9 g, 54.1% pure in **1** along with small amounts of **2**, **3**, and Hünig's base).

Spectral data matched that of Matsumoto.[17]

Compound 1-*i*Pr: 1-Allyl-1-isopropoxysiletane

To a Schlenk flask was added neat 1,1-dichlorosilacyclobutane (2.0 mL, 17 mmol, 1.0 eq.) at 0 °C. Allyl Grignard (1.0 M in diethyl ether, 17.0 mL, 17 mmol, 1.0 eq.) was added dropwise over 15 min. and the solution was stirred for 1 h at 0 °C, then filtered through a Schlenk filter under N_2, using Et_2O to rinse, and the solution was brought to 0.20 M in silane. The solution was cooled back to 0 °C, and Hünig's base (4.4 mL, 25 mmol, 1.5 eq.) was added, followed by HO*i*Pr (1.4 mL, 18 mmol, 1.1 eq.). The solution was stirred and warmed to room temperature over 3 h. The resulting product was filtered through cotton using Et_2O, and concentrated *in vacuo*. The resulting mixture was triturated in Et_2O overnight, and was again filtered through cotton with Et_2O. The mixture was again concentrated *in vacuo* and used without any further purification. (2.9 g, 57.3% pure in **1-*i*Pr**, along with small amounts of **2**, diisopropylsiletane, and Hünig's base).

Spectral Data: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.86 (ddt, *J* = 17.3, 10.0, 7.9 Hz, 1H), 4.97 (dq, *J* = 16.9, 1.5 Hz, 1H), 4.91 (ddt, *J* = 8.8, 2.1, 1.1 Hz, 1H), 4.18 (sept., *J* = 6.1 Hz, 1H), 1.96 (m, 1H), 1.75 (dt, *J* = 8.1, 1.1 Hz, 2H), 1.54 (m, 1H), 1.34-1.22 (m, 4H), 1.21 (d, *J* = 6.0 Hz, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 133.0, 113.9, 65.9, 25.7, 23.3, 17.8, 13.4.

Compound 2: Diallylsiletane

To a Schlenk flask was added pentane (17 mL) and 1,1-dichlorosilacyclobutane (1.0 mL, 8.4 mmol, 1.0 eq.) at -78 °C. Allyl Grignard (1.0 M in diethyl ether, 21 mL, 21 mmol, 2.5 eq.) was added slowly. The mixture was stirred at -78 °C for 1 h, then warmed to room temperature for an additional hour. The mixture was filtered through Celite ®545, and concentrated *in vacuo* (1.3 g, 98%).

Spectral Data: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.86 (ddt, *J* = 16.9, 10.1, 8.1 Hz, 2H), 4.95 (dq, *J* = 17.1, 1.8 Hz, 2H), 4.91 (dt, *J* = 10.1, 1.1 Hz, 2H) 2.05 (pent., *J* = 8.2 Hz, 2H), 1.79 (dt, *J* = 8.0, 1.2 Hz, 4H), 1.04 (t, *J* = 8.5 Hz, 4H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 133.7, 113.7, 22.5, 18.0, 11.9.

Compound 3: Dicyclohexyloxysiletane

To a Schlenk flask was added DCM (42 mL) and 1,1-dichlorosilacyclobutane (1.0 mL, 8.4 mmol, 1.0 eq.) at 0 °C. Triethylamine (5.9 mL, 42 mmol, 5.0 eq.) was added, followed by HOCy (1.8 mL, 17 mmol, 2.5 eq.). The mixture was stirred and allowed to warm to room temperature overnight. The reaction was quenched with NH_4Cl solution (15 mL), and the product was extracted with DCM (10 mL x 3). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo.* The product was passed through silica using 10:1 Hex:EtOAc to remove excess HOCy (2.0 g, 95%).

Spectral Data: ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.90 (sept. *J* = 4.7 Hz, 1H), 1.92-1.84 (m, 4H), 1.80-1.66 (m, 6H), 1.57-1.35 (m, 10H), 1.34-1.16 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 71.3, 35.8, 25.5, 24.2, 21.6, 11.9.

Compound 4: 1-Cyclohexyloxy-1-(2-(iodomethyl)pent-4-en-1-yl)siletane

To a Schlenk flask containing diallylsiletane (**2**) (150 mg, 1.0 mmol, 1.0 eq.) and DCM (10 mL) at room temperature was added I_2 (130 mg, 1.0 mmol, 1.0 eq.) and the mixture was stirred for 3 h. The reaction was cooled to 0 °C and Et_3N (0.42 mL, 3.0 mmol, 3.0 eq.) followed by HOCy (0.21 mL, 2.0 mmol, 2.0 eq.) were added. The solution was allowed to slowly warm to room temperature over 3 h, and was then

quenched with water (25 mL) and extracted with DCM (20 mL x 2). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by chromatography on silica (20:1 Hex:MTBE) gave the alkyl iodide **4** as a clear, colorless oil. (0.20 g, 54%)

Spectral Data: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.75 (ddt, *J* = 17.3, 10.1, 7.2 Hz, 1H), 5.16 (m, 1H), 5.10 (ddt, *J* = 10.1, 2.1, 1.0 Hz, 1H) 3.83 (tt, *J* = 9.5, 4.0 Hz, 1H), 3.39 (dd, *J* = 9.5, 4.5 Hz, 1H) 3.34 (dd, *J* = 9.9, 5.5 Hz, 1H), 2.25 (m, 1H) 2.04 (m, 1H), 1.99 (m, 1H), 1.87-1.80 (m, 2H), 1.78-1.72 (m, 2H), 1.72-1.66 (m, 2H), 1.61 (m, 1H), 1.55 (m, 1H), 1.48 (m, 1H), 1.43-1.14 (m, 6H), 0.87 (d, *J* = 6.8 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.6, 117.3, 71.6, 40.9, 35.7, 35.1, 25.5, 24.0, 21.3, 19.0, 18.7, 18.6, 13.7.

Compound 5: (Cyclohexyloxy)(2-(iodomethyl)pent-4-en-1-yl)diphenylsilane

To a Schlenk flask containing diallyldiphenylsilane (0.27 mL, 1.0 mmol, 1.0 eq.) and DCM (10 mL) at room temperature was added I_2 (130 mg, 1.0 mmol, 1.0 eq.) and the mixture was stirred for 3 h. The reaction was cooled to 0 °C and Et_3N (0.42 mL, 3.0 mmol, 3.0 eq.) followed by HOCy (0.21 mL, 2.0 mmol, 2.0 eq.) were added. The solution was allowed to slowly warm to room temperature over 3 h, and was then quenched with water (25 mL) and extracted with DCM (20 mL x 2). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by chromatography on silica (20:1 Hex:MTBE) gave the alkyl iodide **5** as a clear, colorless oil. (0.35 g, 72%)

Spectral Data: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67-7.57 (m, 4H), 7.45-7.41 (m, 2H), 7.41-7.35 (m, 4H), 5.61 (ddt, *J* = 17.2, 10.2, 7.2 Hz, 1H) 5.07-5.00 (m, 2H), 3.72 (ddt, *J* = 9.2, 5.1, 3.5 Hz, 1H), 3.30 (dd, *J* = 9.5, 4.2 Hz, 1H), 3.24 (dd, J = 9.5, 5.0 Hz, 1H), 2.14 (m, 1H), 2.07 (m, 1H), 1.70 (m, 4H), 1.52 (m, 1H), 1.48-1.33 (m, 4H), 1.29-1.11 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.6, 135.3, 117.3, 71.6, 40.9, 35.7, 35.1, 25.5, 24.0, 21.3, 19.0, 18.7, 18.6, 18.5, 13.7.

Compound 6: Propanedioic acid, 2-[2-[[(cyclohexyloxy)diphenylsilyl]methyl]-4-penten-1-yl-1,3-dimethylester

To a solution of dimethyl malonate (0.050 mL, 0.40 mmol, 1.0 eq.) in DMF (0.2 mL) at 0 °C was added NaH (16 mg, 0.40 mmol, 1.0 eq.) and the mixture was stirred for 20 min. Iodide **5** (50 mg, 0.10 mmol, 0.25 eq.) was then added and the mixture was allowed to slowly warm to room temperature for 24 h. The reaction was quenched with water (10 mL) and extracted with MTBE (10 mL x 2). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by chromatography on silica (10:1 to 4:1 Hex:EtOAc, R_f = 0.45 in 4:1 Hex:EtOAc) afforded **6** as an oil. (37 mg, 76%)

Spectral Data: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.58 – 7.55 (m, 4H), 7.42 – 7.38 (m, 2H), 7.38 – 7.33 (m, 4H), 5.64 (ddt, *J* = 17.2, 10.2, 7.1 Hz, 1H), 4.97 (m, 1H), 4.91 (m, 1H), 3.68 (tt, *J* = 9.0, 3.4 Hz, 1H), 3.63 (s, 6H), 3.46 (dd, *J* = 8.1, 7.2 Hz, 1H), 2.12 (m, 1H), 2.02 – 1.94 (m, 2H), 1.85 (dt, *J* = 14.0, 7.1 Hz, 1H), 1.72 – 1.60 (m, 5H), 1.46 – 1.40 (m, 2H), 1.40 – 1.29 (m, 4H), 1.16 (d, *J* = 5.8 Hz, 1H), 1.15 (d, *J* = 4.2 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.0, 169.9, 136.0, 135.9, 135.8, 129.7, 127.7, 116.8, 71.6, 52.4, 52.3, 49.6, 40.0, 35.6, 35.5, 31.5, 25.6, 23.9, 19.3.

Compound 7: 2-Hexenoic acid, 6-[(cyclohexyloxy)diphenylsilyl]-5-(iodomethyl)-,methyl ester, (2*E*)

To a solution of **5** (50 mg, 0.10 mmol, 1.0 eq.) in DCM (1 mL) was added methyl acrylate (0.05 mL, 0.5 mmol, 5 eq.) followed by Grubbs' 2nd generation catalyst (2 mg, 0.02 mmol, 0.2 eq.) and the mixture was stirred for 15 h before concentrating *in vacuo*. Purification by chromatography on silica (10:1 to 4:1 Hex:EtOAc, R_f = 0.6 in 4:1 Hex:EtOAC) afforded **7** as an oil. (53 mg, 98%)

Spectral Data: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60 – 7.56 (m, 4H), 7.46 – 7.41, (m, 2H), 7.41 – 7.36 (m, 4H), 6.76 (ddd, *J* = 15.3, 7.9, 7.2 Hz, 1H), 5.83 (d, *J* = 15.6 Hz, 1H), 3.72 (s, 3H), 3.70 (m, 1H), 3.25 (dd, *J* = 9.8, 4.2 Hz, 1H), 3.21 (dd, *J* = 9.8, 5.1 Hz, 1H), 2.36 – 2.27 (m, 2H), 2.22 (m, 1H), 1.74 – 1.60 (m, 4H), 1.47 – 1.33 (m, 4H), 1.27 (dd, *J* = 15.1, 6.6 Hz, 1H), 1.19 (dd, *J* = 15.2, 6.6 Hz, 1H), 1.22 – 1.13 (m, 2H). ^{13}C NMR (125 MHz,

$CDCl_3$) δ 166.7, 146.1, 135.2, 135.1, 134.7, 134.6, 130.0, 129.9, 128.0, 127.9, 127.8, 123.2, 71.8, 51.4, 39.5, 35.6, 35.5, 34.3, 25.5, 23.9, 20.6, 19.0.

Compound 8: 2-Pyrrolidineacetic acid, 4-[[(cyclohexyloxy)diphenylsilyl]methyl]-1-(phenylmethyl)-, methyl ester

To a solution of **12** (50 mg, 0.090 mmol, 1.0 eq.) in MeOH (1 mL) was added benzylamine (12 µL, 0.11 mmol, 1.2 eq.) and the mixture was heated to reflux for 24 h. The solution was cooled to room temperature and MeOH was removed on a rotary evaporator. The residue was redissolved in MTBE (15 mL) and washed with water (10 mL) and brine (10 mL). The organic phase was dried over $MgSO_4$, filtered, and concentrated *in vacuo.* Purification by chromatography on silica (1:1 to 0:1 Hex:EtOAc) afforded **8** as an oil. (30 mg, 64%)

Spectral data for the mixture of stereoisomers: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.58 – 7.53 (m, 8H), 7.43 – 7.38 (m, 4H), 7.38 – 7.32 (m, 8H), 7.32 – 7.20 (m, 10H), 3.87 (d, *J* = 12.4 Hz, 1H), 3.67 (m, 2H), 3.64 (s, 6H), 3.50 (s, 1H), 3.46 (s, 1H), 3.25 (d, *J* = 12.5 Hz, 1H), 2.96 (m, 1H), 2.90 (m, 1H), 2.66 (dd, (*J* = 14.9, 4.0 Hz, 1H), 2.56 (m, 1H), 2.55 (dd, *J* = 13.7, 3.5 Hz, 1H), 2.41 (m, 1H), 2.35 (m, 2H), 2.31 – 2.13 (m, 4H), 1.84 (t, *J* = 9.0 Hz, 1H), 1.76 – 1.59 (m, 11H), 1.47 – 1.40 (m, 4H), 1.26 (m, 8H), 1.24 – 1.09 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.7, 135.9, 134.8, 134.7, 134.6, 134.6, 129.9, 129.6, 129.1, 128.8, 128.2, 128.1, 127.9, 127.7, 126.9, 76.8, 76.7, 71.4, 63.4, 60.3, 60.0, 58.6, 51.4, 42.1, 40.7, 40.4, 35.6, 35.5, 31.4, 31.2, 29.7, 29.6, 29.4, 25.6, 25.5, 23.9, 22.7, 19.9, 14.1.

Compound 9: 2-Phenylpent-4-ene-1,2-diol

To a Schlenk flask was added 2-hydroxyacetophenone (50 mg, 0.37 mmol, 1.0 eq.) and **1** (84 mg, 0.40 mmol, 2.0 eq.) in MeCN (1.2 mL). The mixture was heated to 80 °C and stirred overnight. The solvent was removed *in vacuo*, then the product was washed with water (10 mL), and extracted with EtOAc (15 mL x 3). (0.52 mg, 80%)

Spectral data matched that reported by Agami.[44]

Compound 10: α-Oxo-β-methyl-benzenepropanoic acid

To a Schlenk flask was added phenylpyruvic acid (1.0 g, 6.1 mmol, 1.0 eq.) in THF (6.1 mL) at 0 °C. Iodomethane (0.38 mL, 6.1 mmol, 1.0 eq.) and 1 M NaOH (18 mL, 18 mmol, 3.0 eq.) were added and the solution was slowly warmed to room temperature and stirred for 48 h. The volatile solvent was removed *in vacuo*, and the impurities were extracted with EtOAc (20 mL x 3). The aqueous layer was cooled to 0 °C and acidified with 10% HCl to pH 1. The product was extracted with EtOAc (20 mL x 3), then washed with brine (10 mL x 3). The organic layers were combined, dried with $MgSO_4$, and concentrated *in vacuo.* (1.0 g, 92%)

Spectral Data: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35-7.32 (m, 2H), 7.30-7.27 (m, 3H), 4.70 (q, *J* = 6.9 Hz, 1H), 1.51 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.9, 129.2, 128.5, 127.9, 46.2, 25.2, 16.9.

Compound 11: 2-Oxo-4-phenyl-3-butenoic acid

To a Schlenk flask containing MeOH (0.64 mL) at 0 °C was added pyruvic acid (0.80 mL, 11 mmol, 1.0 eq.) and benzaldehyde (1.2 mL, 11 mmol, 1.0 eq.). A solution of KOH (950 mg, 17 mmol, 1.5 eq.) in MeOH (3.2 mL) was added slowly. After 1 h stirring in an ice bath, the solution was moved to a refrigerator, and stored overnight. The resulting crystals were collected by filtration, and washed with cold MeOH and Et_2O. The crystals were dissolved in DI H_2O, and acidified to pH 1 with 10% HCl. The solid crystals that formed were dissolved in EtOAc, and the product was extracted (15 mL x 3). The resulting combined organics were washed with H_2O and brine. The final organic layer was dried with $MgSO_4$, filtered, and concentrated *in vacuo.* (1.7 g, 85%)

Spectral data: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.14 (dd, *J* = 16.6, 4.4 Hz, 1H), 7.72-7.68 (m, 2H), 7.60 (dd, *J* = 16.2, 3.4 Hz, 1H), 7.53-7.44 (m, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 182.3, 160.5, 151.3, 133.8, 132.4, 129.5, 129.2, 117.7.

Compound 12: 4-(2-Furanyl)-2-oxo-3-butenoic acid

To a Schlenk flask containing MeOH (0.64 mL) at 0 °C was added pyruvic acid (0.80 mL, 11 mmol, 1.0 eq.) and furfural (0.94 mL, 11 mmol, 1.0 eq.). A solution of KOH (954 mg, 17.0 mmol, 1.5 eq.) in MeOH (3.2 mL) was added slowly. After 1 h stirring in an ice bath, the solution was moved to a refrigerator, and stored overnight. The resulting crystals were collected by filtration, and washed with cold MeOH and Et_2O. The crystals were dissolved in DI H_2O, and acidified to pH 1 with 10% HCl. The solid crystals that formed were dissolved in EtOAc, and the product was extracted (15 mL x 3). The resulting combined organics were washed with H_2O and brine. The final organic layer was dried with $MgSO_4$, filtered, and concentrated *in vacuo.* (1.6 g, 83%)

Spectral data: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.92 (d, *J* = 15.8 Hz, 1H), 7.64 (d, *J* = 1.6 Hz, 1H), 7.40 (d, *J* = 15.7 Hz, 1H), 6.95 (d, *J* = 3.6 Hz, 1H), 6.59 (dd, *J* = 3.6, 1.8 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 181.8, 160.1, 151.0, 147.3, 136.1, 120.3, 115.2, 113.6.

General Procedure for Allylations of α-Oxocarboxylic Acids (Compounds 13-19)

To a Schlenk flask containing MeCN (0.3 M in α-oxocarboxylic acid) was added the α-oxocarboxylic acid (1.0 eq.) and **1** (1.1 eq.). The solution was heated to 80 °C and stirred overnight. The solution was concentrated via rotary evaporator to remove MeCN. The resulting product was washed with 1 M NaOH (15 mL x 2), and the silane byproducts were removed with Et_2O (15 mL x 2). The aqueous layer was acidified to pH 1 with 1 M HCl, and extracted with EtOAc (20 mL x 3). The combined organic layers were dried with $MgSO_4$, filtered, and concentrated *in vacuo*.

Compound 13: 2-Hydroxy-2-methyl-4-pentenoic acid

The general procedure was followed with pyruvic acid (100 mg, 1.1 mmol, 1.0 eq.) and **1** (210 mg, 1.3 mmol, 1.1 eq.). (97 mg, 65%)

Spectral data: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.80 (ddt, *J* = 18.1, 9.3, 7.3 Hz, 1H), 5.20-5.13 (m, 1H), 4.97-4.86 (m, 1H), 2.57 (dd, *J* = 13.6, 7.7 Hz, 1H), 2.43 (dd, 13.9, 7.3 Hz, 1H), 1.47 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 180.9, 131.6, 119.9, 74.5, 44.3, 25..

Compound 14: 2-Ethyl-2-hydroxy-4-pentenoic acid

The general procedure was followed with 2-oxobutyric acid (50 mg, 0.49 mmol, 1.0 eq.) and **1** (111 mg, 0.53 mmol, 1.1 eq.). (49 mg, 70%)

For purification and characterization purposes, compound **14** was converted to **14-OMe**: To a round bottom containing MeOH (2 mL) was added **14** (50 mg, 0.34 mmol, 1.0 eq.) and pTSA (7 mg, 0.03 mmol, 0.1 eq.). The solution was refluxed for 4 h, then cooled and diluted with EtOAc (10 mL), washed with $NaHCO_3$ (10 mL x 3) and brine (10 mL x 1). The organics were collected, dried with $MgSO_4$, and concentrated *in vacuo.* Purification by chromatography on silica (10:1 to 0:1 Hex:EtOAc) afforded **14-OMe** as an oil (R_f = 0.24 in 10:1 Hex:EtOAc).

*Spectral data for **14-OMe:*** ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.77 (ddt, *J* = 18.2, 9.5, 6.8 Hz, 1H), 5.13-5.07 (m, 2H), 3.77 (s, 3H), 2.47 (ddt, *J* = 13.8, 7.7, 1.2 Hz, 1H), 2.41 (ddt, *J* = 13.8, 7.8, 1.1 Hz, 1H), 1.79 (dq, *J* = 14.0, 7.2 Hz, 1H), 1.70 (dq, *J* = 14.9, 7.6 Hz, 1H) 0.87 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 132.4, 118.8, 52.6, 43.6, 31.7, 29.7, 22.6, 7.9.

Compound 15: α-Hydroxy-α-2-propen-1-yl-benzeneacetic acid

The general procedure was followed with phenyl glyoxylic acid (50 mg, 0.33 mmol, 1.0 eq.) and **1** (76 mg, 0.36 mmol, 1.1 eq.). (56 mg, 88%)

Spectral Data: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64 (d, *J* = 7.6 Hz, 2H), 7.37 (t, *J* = 7.8 Hz, 2H), 7.32 (t, *J* = 7.3 Hz, 1H), 5.79 (ddt, *J* = 17.2, 10.3, 7.0 Hz, 1H), 5.23 (d, *J* = 17 Hz, 1H), 5.18 (d, *J* = 10.0 Hz, 1H) 3.02 (dd, *J* =

13.8 Hz, 7.1 Hz, 1H), 2.81 (dd, *J* = 14.3, 6.7 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.9, 140.3, 131.8, 128.4, 128.0, 125.6, 120.1, 44.0.

Compound 16: α-Hydroxy-α-2-propen1-yl-benzenepropanoic acid

The general procedure was followed with phenyl pyruvic acid (50 mg, 0.30 mmol, 1.0 eq.) and **1** (69 mg, 0.33 mmol, 1.1 eq.). (46 mg, 73%)

For purification and characterization purposes, compound **16** was converted to **16-OMe**: To a round bottom containing MeOH (1 mL) was added **16** (46 mg, 0.22 mmol, 1.0 eq.) and pTSA (4 mg, 0.02 mmol, 0.1 eq.). The solution was refluxed for 4 hr, then cooled and diluted with EtOAc (10 mL), washed with $NaHCO_3$ (10 mL x 3) and brine (10 mL x 1). The organics were collected, dried with $MgSO_4$, and concentrated *in vacuo.* Purification by chromatography on silica (20:1 to 10:1 Hex:EtOAc) gave **16-OMe** as a pale yellow oil (R_f = 0.31 in 10:1 Hex:EtOAc).

Spectral data: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30-7.23 (m, 3H), 7.18 (m, 2H), 5.82 (dddd, *J* = 17.1, 10.3, 7.7, 6.8 Hz, 1H), 5.16-5.11 (m, 2H), 3.72 (s, 3H), 3.06 (d, *J* = 13.2 Hz, 1H), 2.95 (d, *J* = 13.6 Hz, 1H), 2.62 (ddt, *J* = 13.9, 7.6, 1.0 Hz, 1H), 2.50 (ddt, *J* = 13.8, 7.1, 1.4 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.5, 135.6, 132.3, 129.9, 128.2. 126.9, 118.9, 78.2, 52.5, 45.1, 43.5.

Compound 17: α-Allyl-α-hydroxy-β-methyl-benzenepropanoic acid

The general procedure was followed with **10** (50 mg, 0.28 mmol, 1.0 eq.) and **1** (64 mg, 0.30 mmol, 1.1 eq.). (32 mg, 51%; d.r. 2.1)

For purification and characterization purposes, compound **17** was converted to **17-OMe**: To a round bottom containing MeOH (1 mL) was added **17** (32 mg, 0.14 mmol, 1.0 eq.) and pTSA (3 mg, 0.02 mmol, 0.1 eq.). The solution was refluxed for 4 h, then cooled and diluted with EtOAc (10 mL), washed with $NaHCO_3$ (10 mL x 3) and brine (10 mL x 1). The organics were collected, dried with $MgSO_4$, and concentrated *in vacuo.*

Purification by chromatography on silica (20:1 to 10:1 Hex:EtOAc) gave **17-OMe** as a pale yellow oil (R_f = 0.35 in 10:1 Hex:EtOAc).

Spectral data for mixture of diastereomers: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35-7.18 (m, 10H), 5.76 (ddt, *J* = 21.3, 8.4, 6.4 Hz, 1H), 5.66 (ddt, *J* = 20.6, 8.3, 6.5 Hz, 1H), 5.15-5.07 (m, 2H), 5.04-4.96 (m, 2H), 3.81 (s, 3H), 3.57 (s, 3H), 3.16-3.10 (m, 2H) 2.69 (ddt, *J* = 13.8, 6.3, 1.5 Hz, 1H), 2.49 (ddq, *J* = 13.9, 8.3, 1.1 Hz, 1H), 2.35 (ddd, *J* = 13.9, 8.3, 0.81 Hz, 1H), 2.03 (ddt, *J* = 13.9, 6.3, 1.4 Hz, 1H), 1.40 (d, *J* = 7.2 Hz, 3H), 1.24 (d, *J* = 7.1 Hz, 3H) ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.5, 175.7, 142.1, 141.5, 132.9, 132.8, 130.1, 129.2, 128.6, 128.3, 128.1, 127.6, 127.5, 127.0, 126.9, 118.7, 118.6, 80.3, 80.2, 52.9, 52.3, 46.7, 46.6, 42.8, 41.7, 16.5, 14.6.

Compound 18: 2-Allyl-2-hydroxy-4-phenyl-3-butenoic acid

The general procedure was followed with **11** (50 mg, 0.28 mmol, 1.0 eq.) and **1** (64 mg, 0.30 mmol, 1.1 eq.). (45 mg, 72%)

Spectral data: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 (d, *J* = 7.9 Hz, 2H), 7.32 (t, *J* = 7.9 Hz, 2H), 7.27 (t, *J* = 7.3 Hz, 1H), 6.87 (d, 16.1 Hz, 1H), 6.37 (d, 15.7 Hz, 1H), 5.84 (ddt, *J* = 16.4, 9.7, 7.5 Hz, 1H), 5.26-5.18 (m, 2H), 2.75 (dd, *J* = 13.9, 8.1 Hz, 1H), 2.60 (dd, *J* = 14.6, 7.0 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.7, 135.9, 131.4, 130.8, 128.7, 128.6, 128.0, 126.8, 120.2, 77.1, 43.8.

Compound 19: 2-Allyl-[4-(2-Furanyl)]-2-hydroxy-3-butenoic acid

The general procedure was followed with **12** (50 mg, 0.30 mmol, 1.0 eq.) and **1** (69 mg, 0.33 mmol, 1.1 eq.). (36 mg, 58%)

For purification and characterization purposes, compound **19** was converted to **19-OTBDPS**: To a Schlenk flask was added DCM (2 mL) and **19** (37 mg, .18 mmol, 1.0 eq.) at 0 °C. Hünig's base (57 mg, 0.44 mmol, 2.5 eq.) was added followed by *tert*-butyl(chloro)diphenylsilane (53 mg, 0.19 mmol, 1.1 eq.). The solution was allowed to warm to room temperature overnight. The reaction was quenched with DI H_2O (10 mL) and

extracted with DCM (10 mL x 3). Purification by chromatography on silica (20:1 to 10:1 Hex:EtOAc) gave **19-OTBDPS** as a clear oil (R_f = 0.68 in 10:1 Hex:EtOAc).

Spectral data: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64 (dd, *J* = 8.0, 1.2 Hz, 2H), 7.56 (dd, *J* = 8.0, 1.4 Hz, 2H), 7.45-7.37 (m, 3H), 7.35-7.27 (m, 2H), 7.25-7.19 (m, 2H), 6.33 (dd, *J* = 3.2, 1.8 Hz, 1H), 6.29 (d, *J* = 16.0 Hz, 1H), 6.24 (d, *J* = 16.0 Hz, 1H), 6.01 (d, *J* = 3.3 Hz, 1H), 5.97 (m, 1H), 5.12-5.06 (m, 2H), 2.74 (ddt, *J* = 14.0, 7.4, 1.0 Hz, 1H), 2.68 (ddt, *J* = 13.9, 6.3, 1.5 Hz, 1H)1.04, 1.04 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.7, 152.1, 142.2, 136.2, 135.4, 132.8, 130.0, 129.0, 127.6, 127.0, 119.8, 118.8, 111.2, 108.6, 81.0, 44.0, 26.9, 19.1.

Compound 20: Benzoylacetic acid

To a round bottom flask was added ethyl benzoylacetate (1 mL, 5.8 mmol, 1 eq.) and 1 M NaOH (6 mL, 1.0 eq.) at room temperature. The mixture was allowed to stir overnight, then washed with Et_2O (10 mL x 4). The aqueous layer was acidified to pH 1 with 1 M HCl. The resulting white solids were collected by filtration. (0.92 g, 98%)

Spectral data matched that reported by Tirpak.[45]

Compound 21: (3*E*)-4-(4-formylphenyl)-2-oxo-3-butenoic acid

To a Schlenk flask containing MeOH (0.70 mL) at 0 °C was added pyruvic acid (0.40 mL, 5.7 mmol, 1.0 eq.) and terephthalaldehyde (1.5 g, 11 mmol, 2.0 eq.). A solution of KOH (0.48 g, 8.5 mmol, 1.5 eq.) in MeOH (1.6 mL) was slowly added dropwise. An additional 1 mL MeOH was added for solubility. The solution was stirred for 1 h at 0 °C, then refrigerated overnight. The resulting crystals were collected by filtration and washed with cold MeOH and Et_2O. The crystals were dissolved in 1 M NaOH, and the solution was acidified to pH 1 with 10% HCl. The product was extracted with EtOAc (15 mL x 3). The combined organic layers were washed with H_2O and brine (15 mL x 3), then dried with $MgSO_4$, filtered, and concentrated *in vacuo*. (0.88 g, 88%)

Spectral data matched that report by Sello.[46]

Compound 22: (3*E*)-2-Allyl-4-(4-formylphenyl)-2-hydroxy-3-butenoic acid

To a Schlenk flask containing MeCN (2.5 mL) was added **21** (0.10 g, 0.49 mmol, 1.0 eq.) and **1** (0.22 g, 1.1 mmol, 2.1 eq.). The solution was heated to 80 °C and stirred overnight. The solution was concentrated via rotary evaporator to remove MeCN. The resulting product was washed with 1 M NaOH (15 mL x 2), and the silane byproducts were removed with Et_2O (15 mL x 2). The aqueous layer was acidified to pH 1 with 1 M HCl, and extracted with EtOAc (20 mL x 3). The combined organic layers were dried with $MgSO_4$, filtered, and concentrated *in vacuo*. (110 mg, 89%)

For purification and characterization purposes, compound **22** was converted to **22-OMe**. To a Schlenk flask containing MeOH/DCM (8.4 mL, 1:1) was added **22** at room temperature. $TMSCHN_2$ (0.51 mL, 1.02 mmol, 1.2 eq.), was added dropwise over 10 min. After stirring for 20 min, additional $TMSCHN_2$ (0.25 mL, 0.51 mmol, 0.6 eq.) was added. After stirring an additional 10 min, a third addition of $TMSCHN_2$ (0.13 mL, 0.25 mmol, 0.3 eq.) was added, and the solution stirred for 5 min. The reaction was quenched with AcOH (0.10 mL) and diluted with toluene (0.38 mL). The solvent was removed *in vacuo.* Purification by chromatography on silica (10:1 to 4:1 Hex:EtOAc) gave **22-OMe** as a pale yellow oil (R_f = 0.28 in 4:1 Hex:EtOAc).

Spectral data: ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.97 (s, 1H), 7.83 (d, *J* = 8.7, 2H), 7.53 (d, *J* = 8.7 Hz, 2H), 6.91 (d, *J* = 15.5 Hz, 1H), 6.49 (d, *J* = 14.6 Hz, 1H), 5.79 (dddd, *J* = 14.5, 9.7, 7.7, 6.8 Hz, 1H), 5.19-5.13 (m, 2H) 3.82 (s, 3H), 2.68 (ddt, *J* = 13.9, 7.9, 1.1 Hz, 1H), 2.54 (ddt, *J* = 13.5, 6.9, 1.2 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.7, 174.5, 142.3, 135.6, 132.9, 131.6, 130.1, 129.2, 127.2, 119.7, 53.3, 44.0.

Compound 23: 4-Formyl-α-oxo-benzeneacetic acid

Prepared according to He, et. al.[47] *To* a Schlenk flask containing THF (10 mL) was added Mg° (290 mg, 12 mmol, 2.0 eq.), and a small crystal of I_2. An aliquot (0.25 mL) of 4-bromobenzaldehyde dimethyl acetal (1.0 mL total, 6.0 mmol, 1.0 eq.) was added and the solution was stirred vigorously. At this point the reaction flask was heated via heat gun until the solution became lighter in color. The remainder of the bromide was added somewhat slowly and the solution was allowed to stir for 30 min. In a separate Schlenk flask containing THF (13 mL) was added diethyl oxalate (0.85 mL, 6.3 mmol, 1.1 eq.) at -78 °C. To this solution, the Grignard solution was added via syringe at -78 °C. The reaction was allowed to stir at -78 °C for 2 h, then 0 °C for an additional 2 h The reaction was quenched with NH_4Cl, and extracted with EtOAc (15 mL x 3). The combined organic layers were additionally washed with brine (15 mL x 3). The organic layer was dried with $MgSO_4$, filtered, and concentrated *in vacuo* in a round bottom. To this round bottom was then added KOH (2.5 M, 9.6 mL, 24 mmol, 4.0 eq.). The reaction was tracked by TLC. When complete, the solution was acidified to pH 1 with 1 M HCl, and stirred for 30 min. The product was extracted with EtOAc (15 mL x 3), dried, filtered, and concentrated *in vacuo.* Finally, the product recrystallized in DCM, affording **23** as a yellow solid.

Spectral data: ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.16 (s, 1H), 8.53 (d, *J* = 9.6 Hz, 2H), 8.05 (d, *J* = 10.3 Hz, 2H).

Compound 24: α-Allyl-4-formyl-α-hydroxy-benzeneacetic acid

To a Schlenk flask containing MeCN (14 mL) was added **1-*i*Pr** (0.11 g, 0.31 mmol, 1.1 eq.) and **23** (50 mg, 0.28 mmol, 1.0 eq.). The mixture was allow to stir for 5 h at room temperature before being heated to 80 °C overnight. The solvent was removed by rotary evaporator. The resulting product was redissolved in THF (2.8 mL) and TBAF (0.90 mL, 0.90 mmol, 3.0 eq.) was added. The mixture was allowed to stir 1 h at room temperature. The reaction was quenched with NH_4Cl (10 mL) and extracted with EtOAc (15 m x 2). The combined organic layers were dried over $MgSO_4$, and concentrated *in vacuo.* (41.5 mg, 65%)

For purification and characterization purposes, **24** was converted to **24-OMe.** To a Schlenk flask was added **24** in DCM/MeOH (3.0 mL, 1:1) at room temperature. $TMSCHN_2$ (0.56 mL, 0.34 mmol, 1.2 eq.) was added dropwise over 10 min. After stirring for 20 min, additional $TMSCHN_2$ (0.28 mL, 0.17 mmol, 0.60 eq.) was added. After stirring for an additional 10 min, a third addition of $TMSCHN_2$ (0.17 mL, 0.085 mmol, 0.30 eq.) was added, and the solution stirred for 5 min. The reaction was quenched with AcOH (0.03 mL), and diluted with toluene (0.01 mL) before concentrating *in vacuo.* Purification by chromatography on silica (4:1 to 1:1 Hex:EtOAc) gave **24-OMe** as a clear oil (R_f = 0.6 in 1:1 Hex:EtOAc).

Spectral data: ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.02 (s, 1H), 7.89-7.86 (m, 2H), 781-7.78 (m, 2H), 5.76 (ddt, *J* = 20.5, 7.5, 6.8 Hz, 1H), 5.20-5.13 (m, 2H), 3.8 (s, 3H), 2.98 (dd, *J* = 14.3, 7.2 Hz, 1H), 2.77 (ddt, *J* = 11.7, 6.9, 1.1 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.8, 174.3, 147.6, 135.8, 131.6, 129.6, 126.4, 119.9, 78.1, 53.6, 44.3.

Compound 25: 2-(1-hydroxybut-3-en-1-yl)phenol

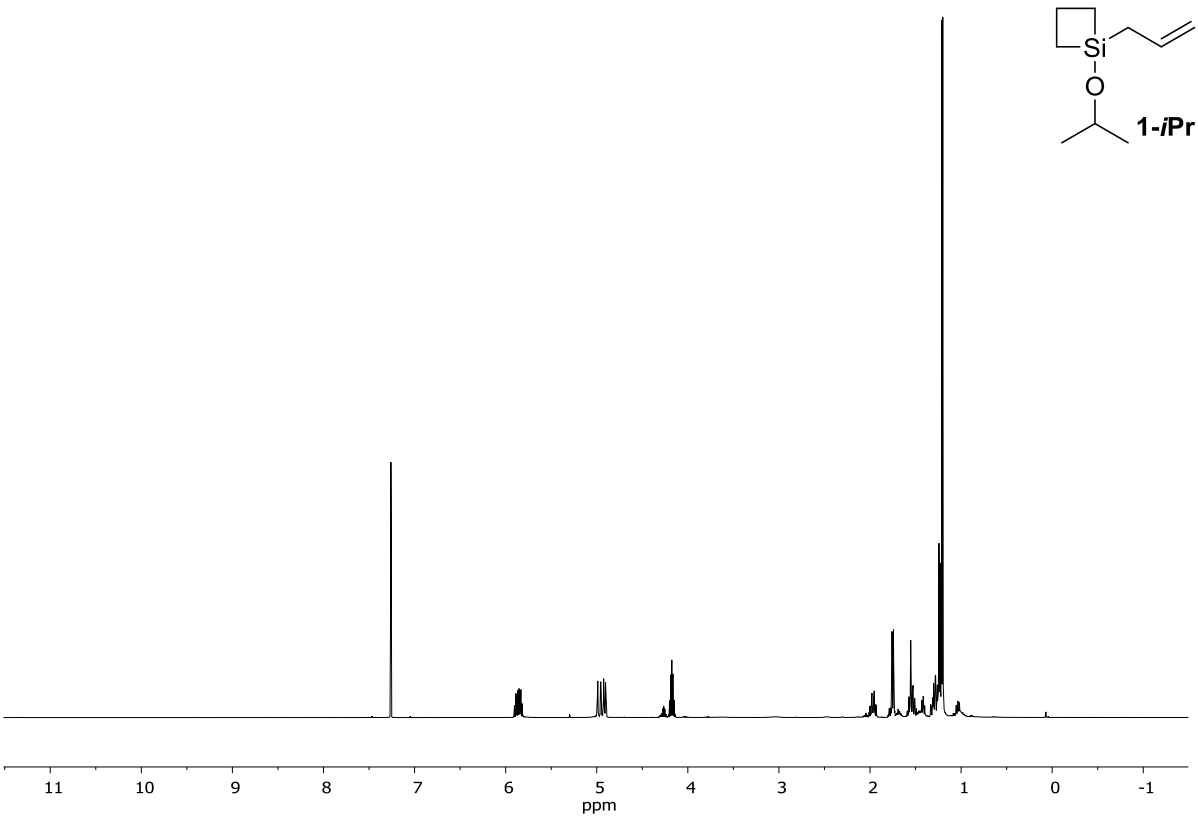
To a Schlenk flask containing MeCN (1.4 mL) was added salicylaldehyde (50 mg, 0.41 mmol, 1.0 eq.) and **1** (93 mg, 0.44 mmol, 1.1 eq.). The mixture was stirred and heated to 80 °C overnight. The solvent was removed via rotary evaporator, and the resulting product was redissolved in THF (4 mL) in a new Schlenk flask. The flask was cooled to 0 °C, and TBAF (2.5 mL, 2.5 mmol, 6.0 eq.) was added slowly. The mixture was stirred and warmed to room temperature over 30 min. The reaction was quenched with NH_4Cl (10 mL) and the product was extracted with EtOAc (15 mL x 2). Purification by chromatography on silica (4:1 to 1:1 Hex:MTBE) gave **25** as a clear oil. (R_f = 0.26 in 4:1 Hex:MTBE) (29 mg, 43%)

Spectral data: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98 (s,br., 1H), 7.20-7.16 (m, 1H), 6.98 (dd, *J* = 7.6, 1.6 Hz, 1H), 6.88 (dd, *J* = 8.2, 1.0 Hz, 1H), 6.84 (td, *J* = 7.6, 1.2 Hz, 1H), 5.85 (ddt, *J* = 21.0, 7.9, 6.4 Hz, 1H), 5.25-5.20 (m, 2H), 4.88 (dd, *J* = 8.6, 5.2 Hz, 1H), 2.68-2.55 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.5, 133.9, 129.0, 127.1, 126.3, 119.8, 119.5, 117.3, 74.7, 42.1.

Compound 26: 4-Hydroxy-3-(1-hydroxybut-3-en-1-yl)benzaldehyde

To a Schlenk flask containing MeCN (3.5 mL) was added 4-hydroxyisophthalaldehyde (0.10 g, 0.67 mmol, 1.0 eq.) and **1** (0.30 g, 1.4 mmol, 2.2 eq.). The mixture was heated to 80 °C and stirred overnight. The solution turned from white to yellow to orange, and finally to red. The solvent was removed via rotary evaporator. Purification by chromatography on silica (10:1 Hex:MTBE to 0:1 Hex:MTBE) gave **26** as a yellow solid. (R_f = 0.33 in 1:1 Hex:MTBE) (75 mg, 58%).

Spectral data: ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.81 (s, 1H), 7.70 (dd, *J* = 8.5, 2.2 Hz, 1H), 7.54 (d, *J* = 2.1 Hz, 1H), 6.98 (d, *J* = 8.4 Hz, 1H), 5.84 (ddt, *J* = 17.0, 10.3, 7.2 Hz, 1H), 5.26-5.20 (m, 2H), 4.99 (t, *J* = 7.1 Hz, 1H), 2.64-2.60 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.9, 161.7, 133.1, 132.0, 129.0, 128.9, 126.8, 120.1, 17.9, 74.3, 42.3.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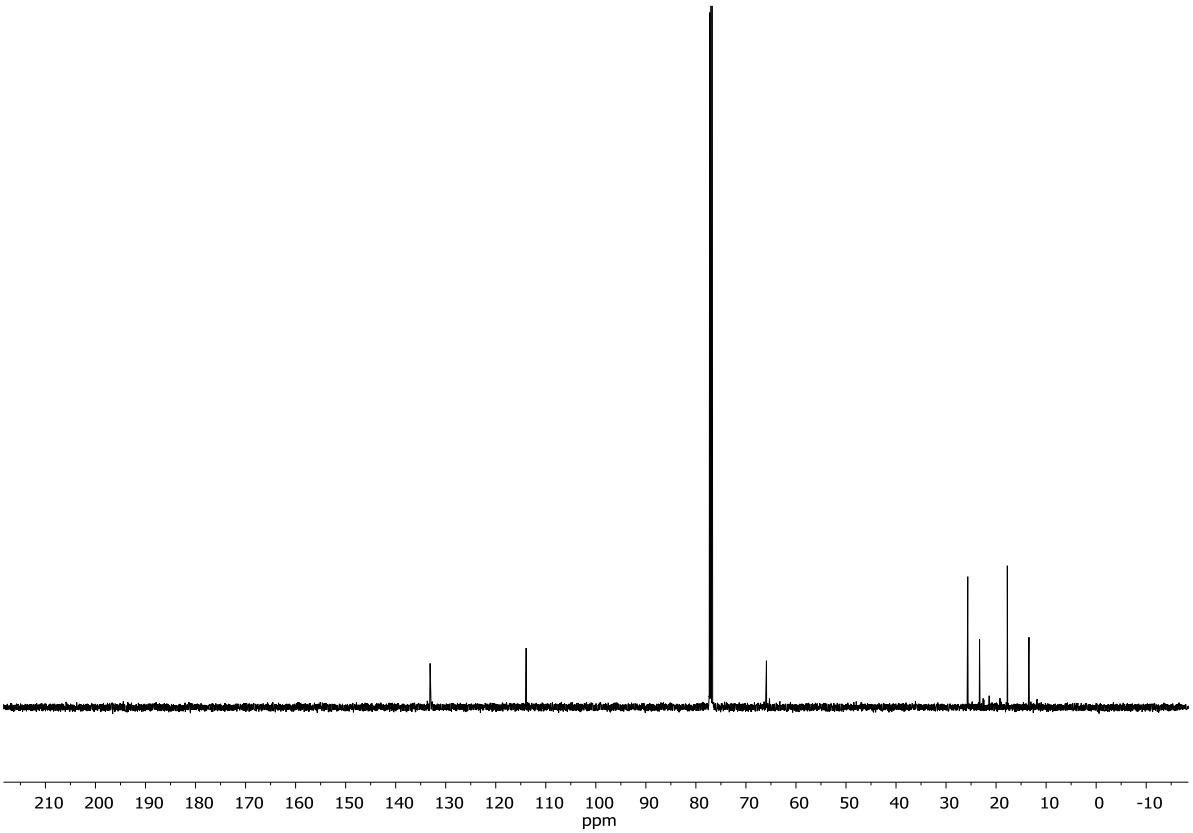
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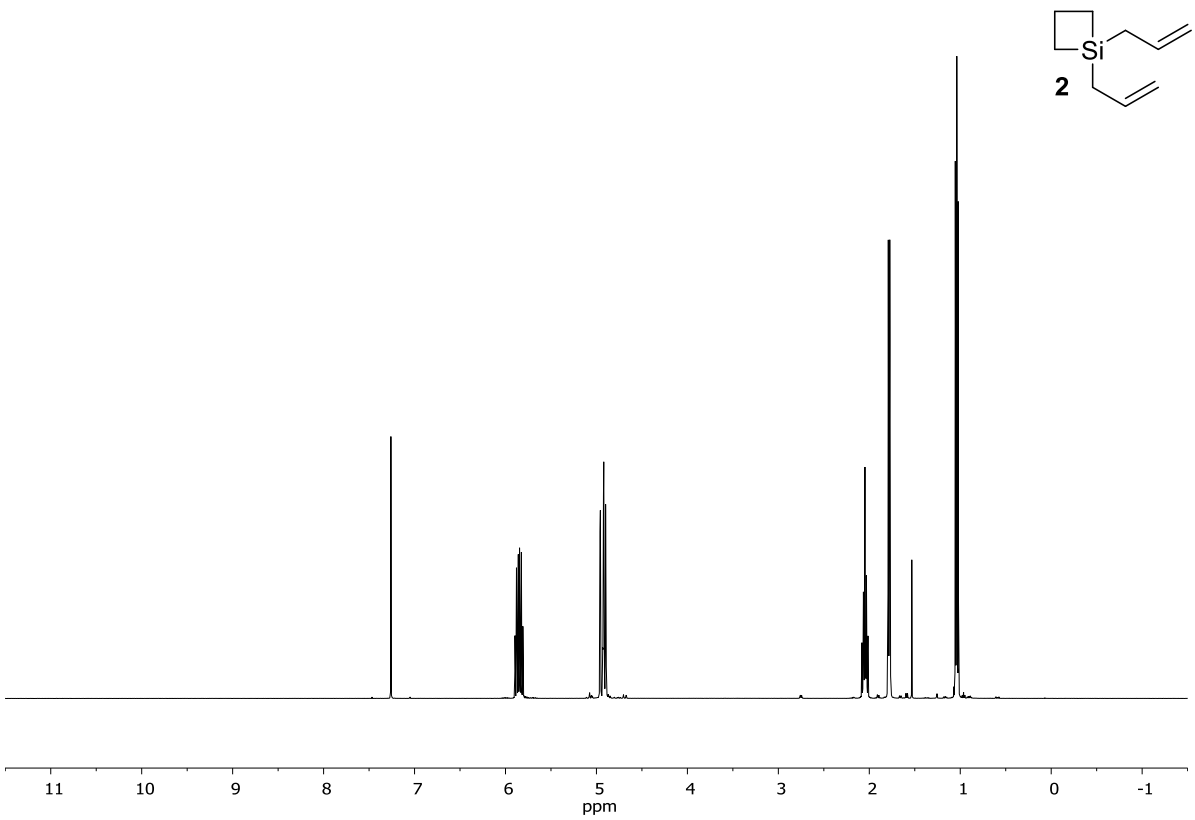
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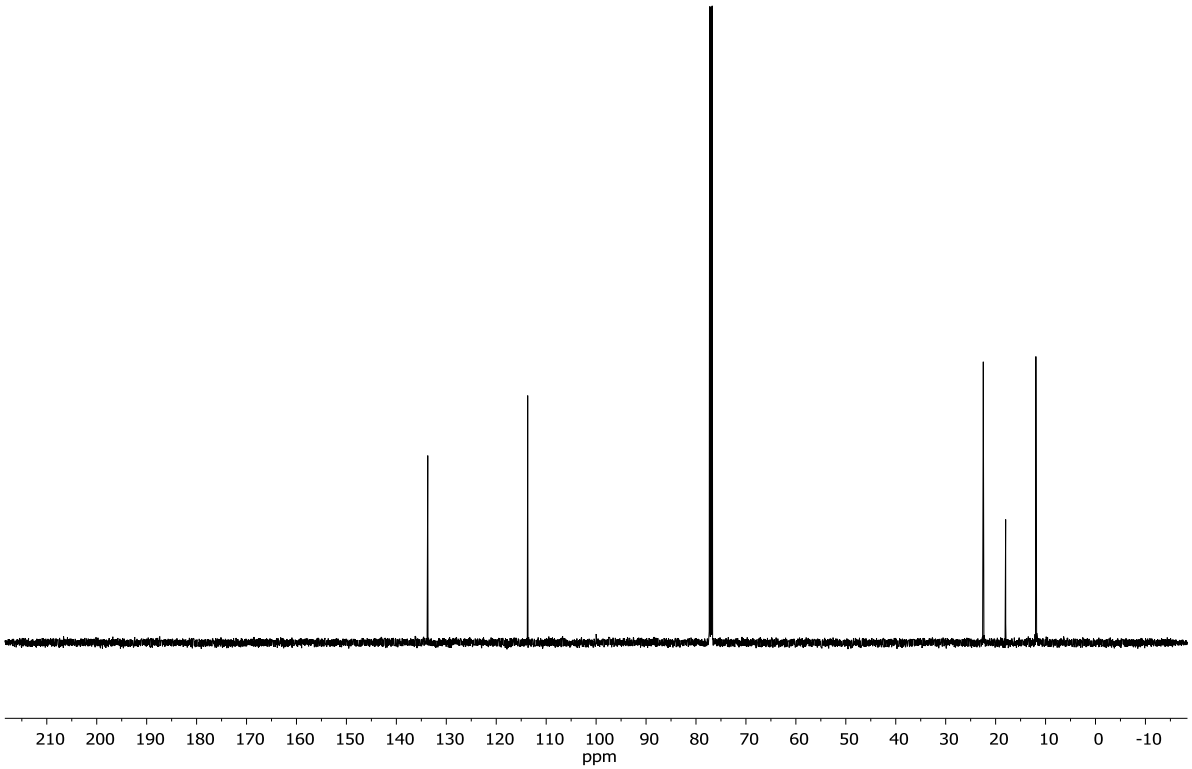
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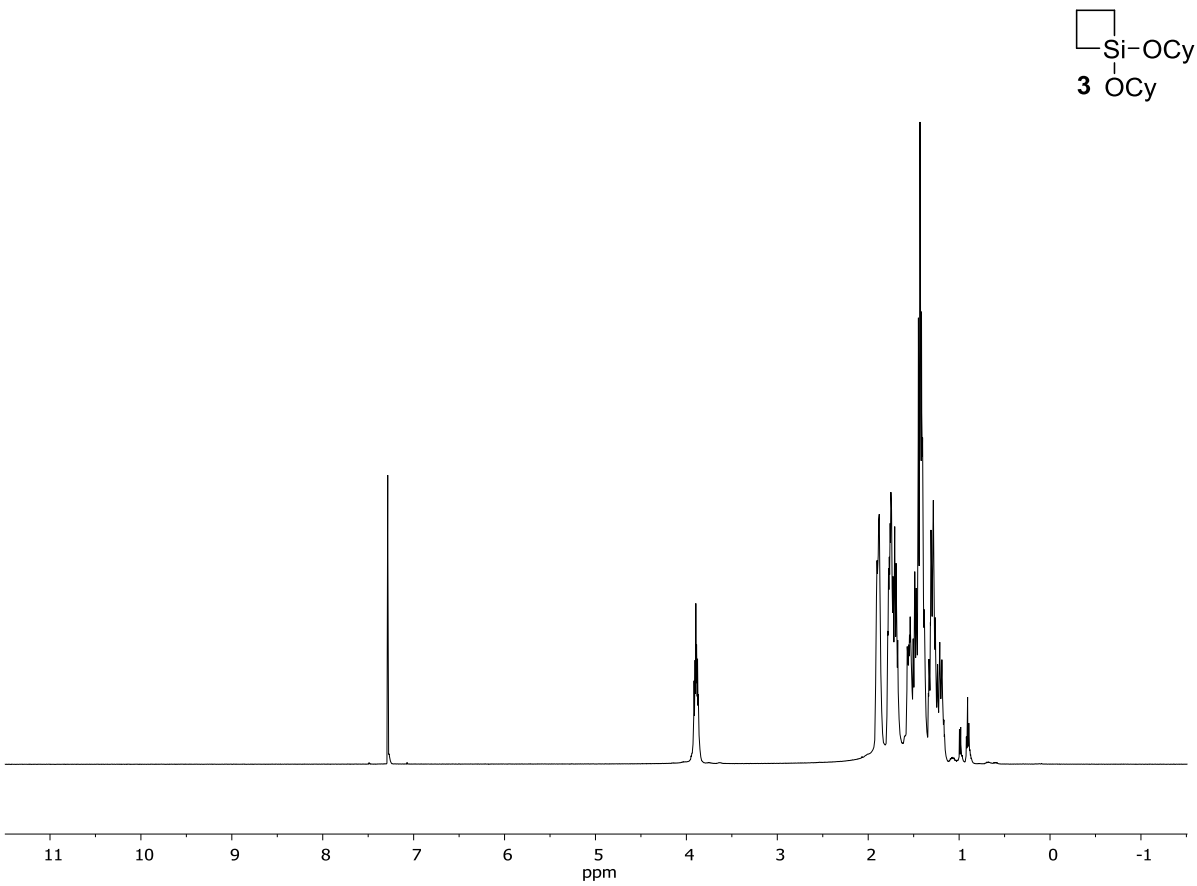
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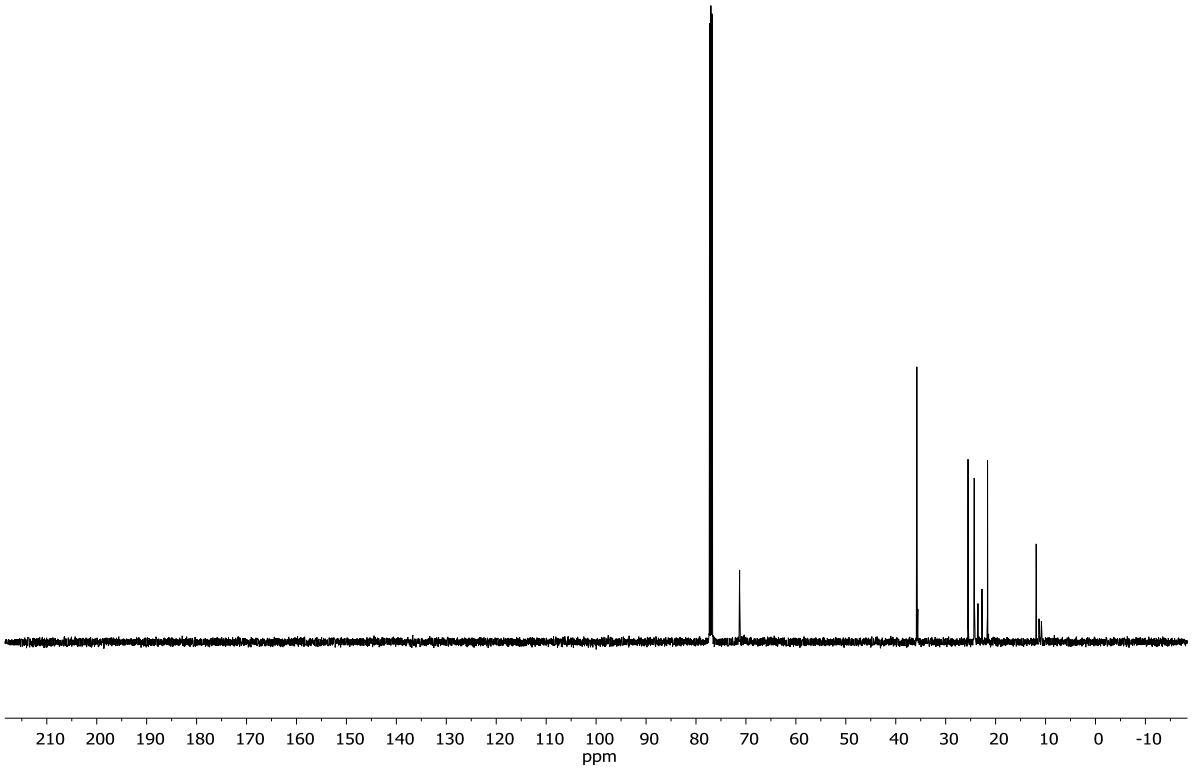
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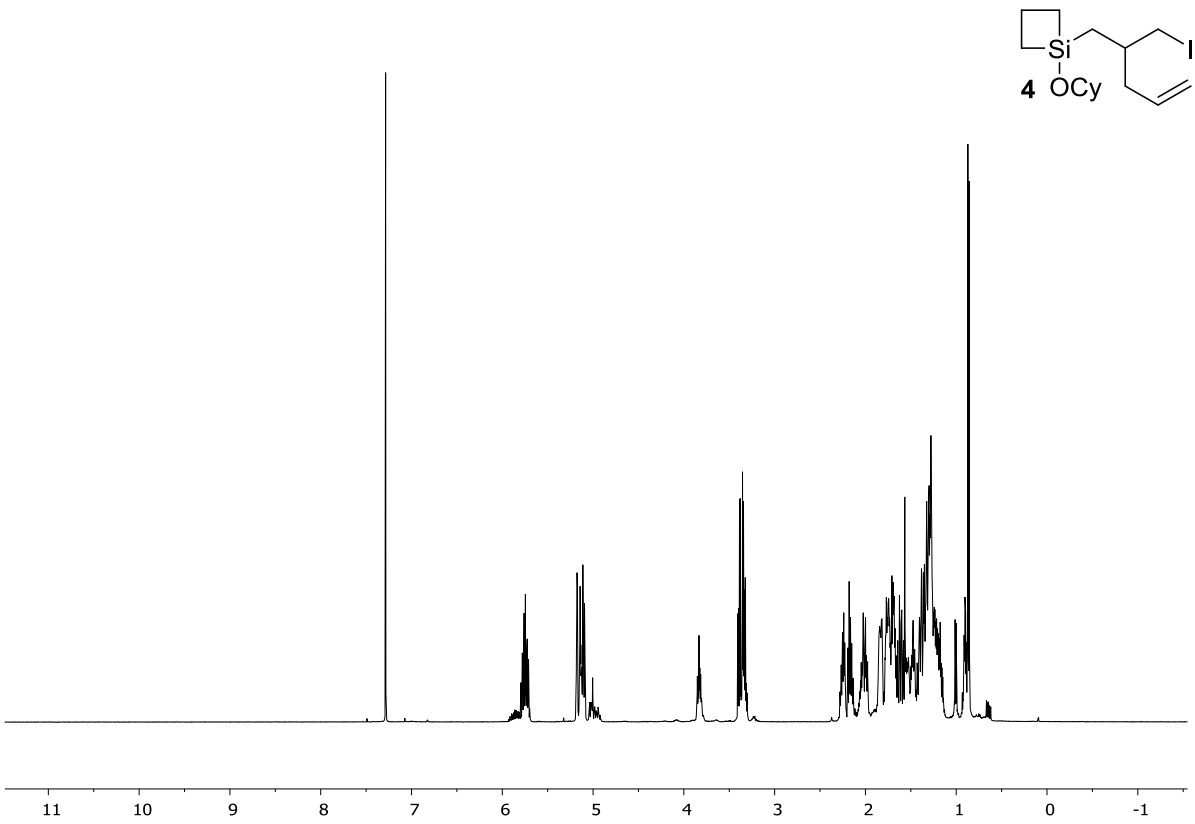
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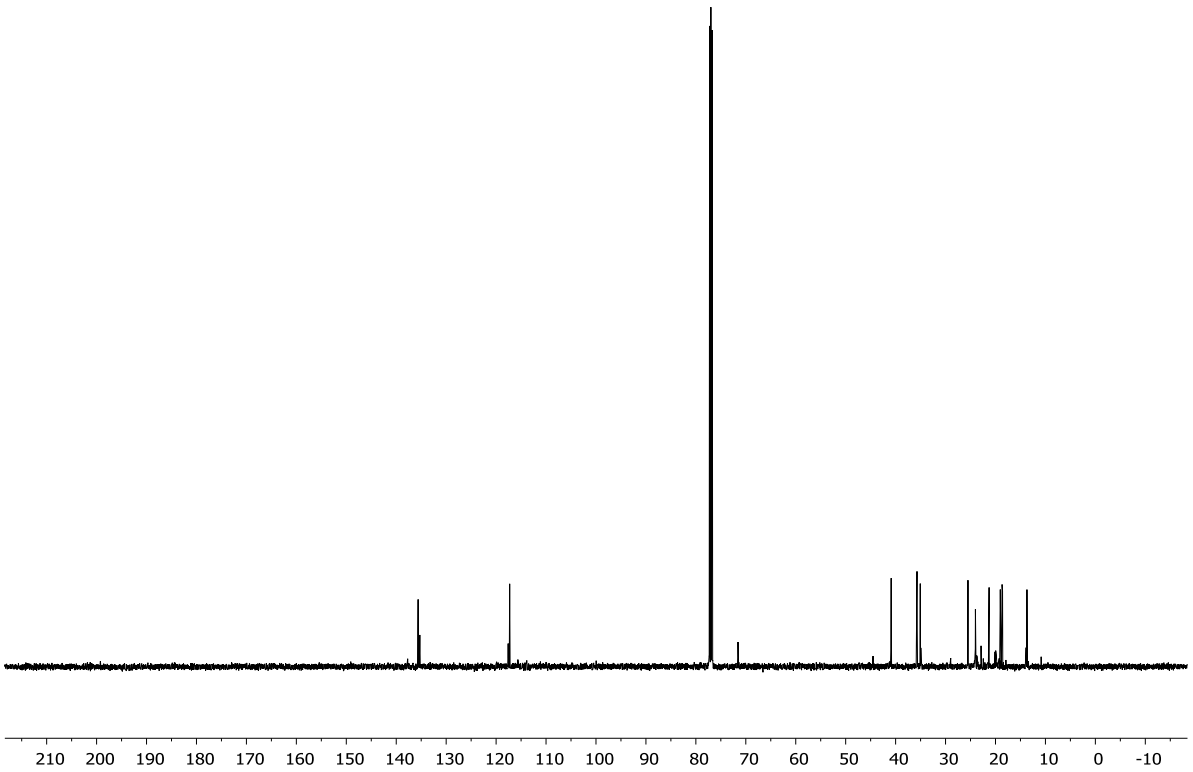
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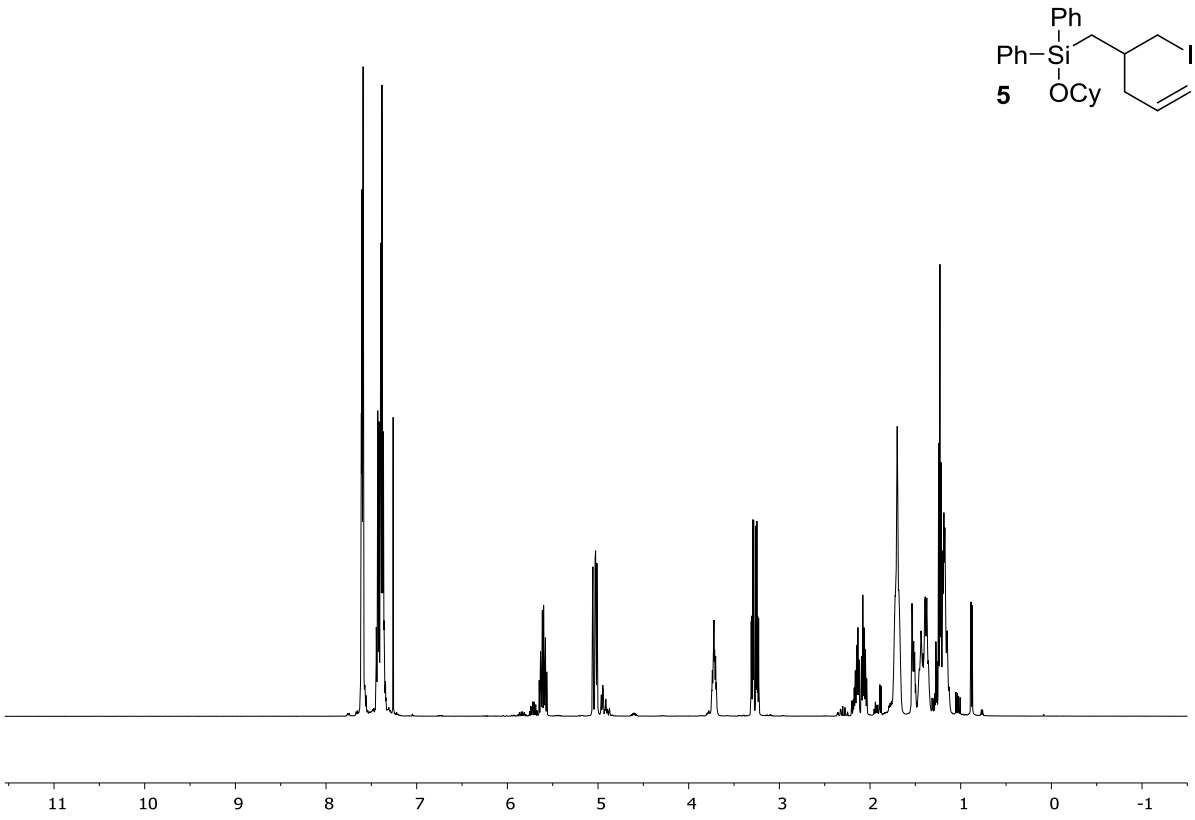
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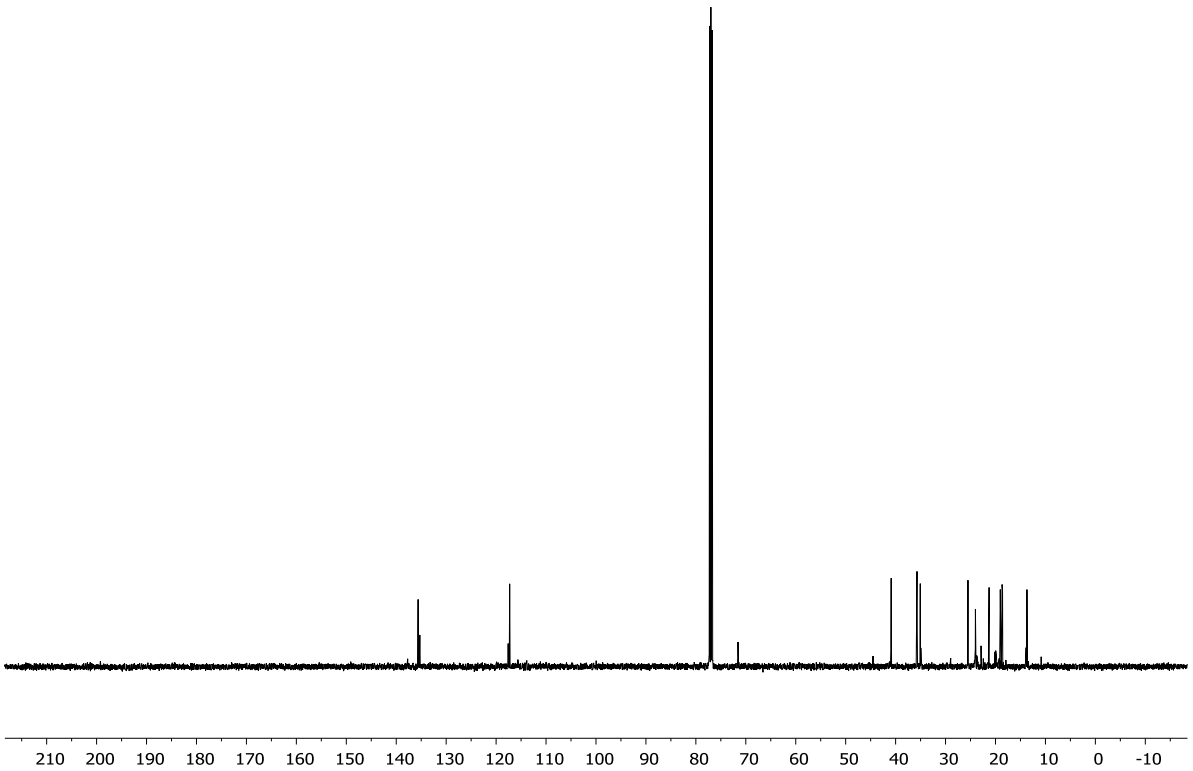
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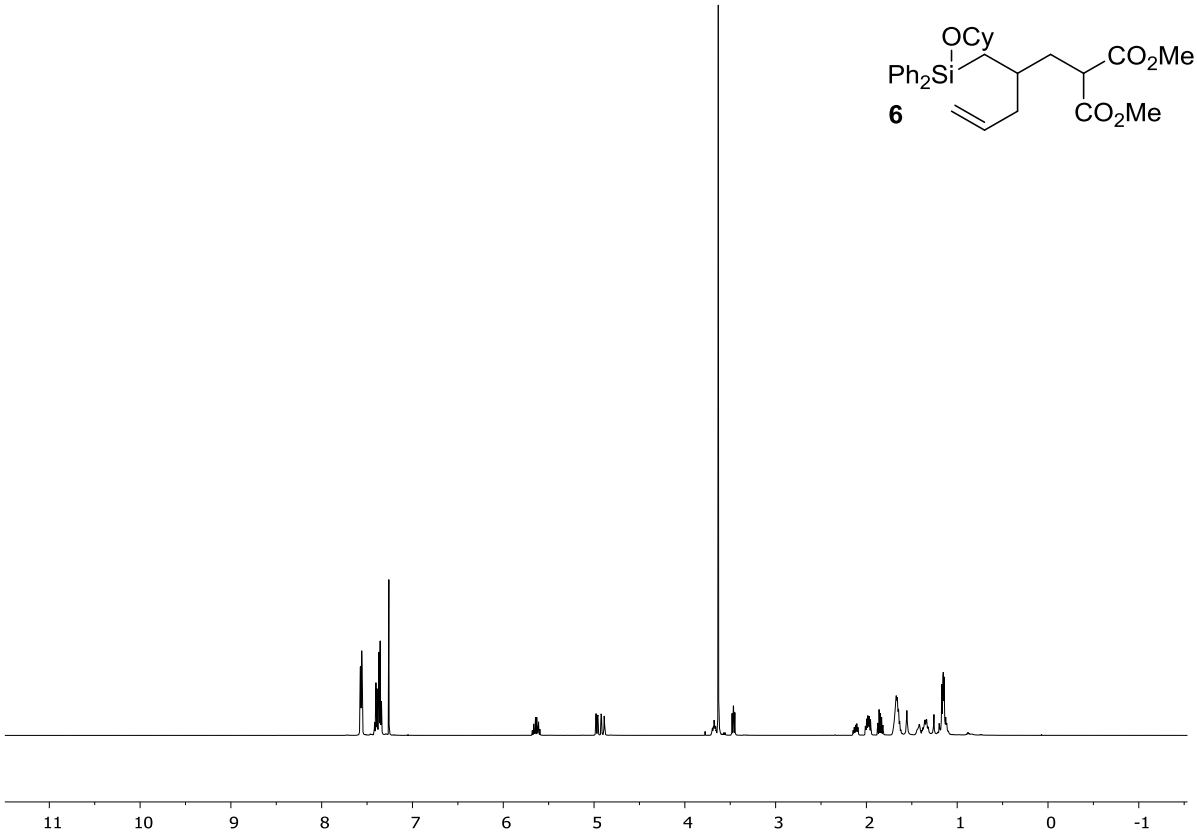
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Ph2Si
CO2Me
CO2Me
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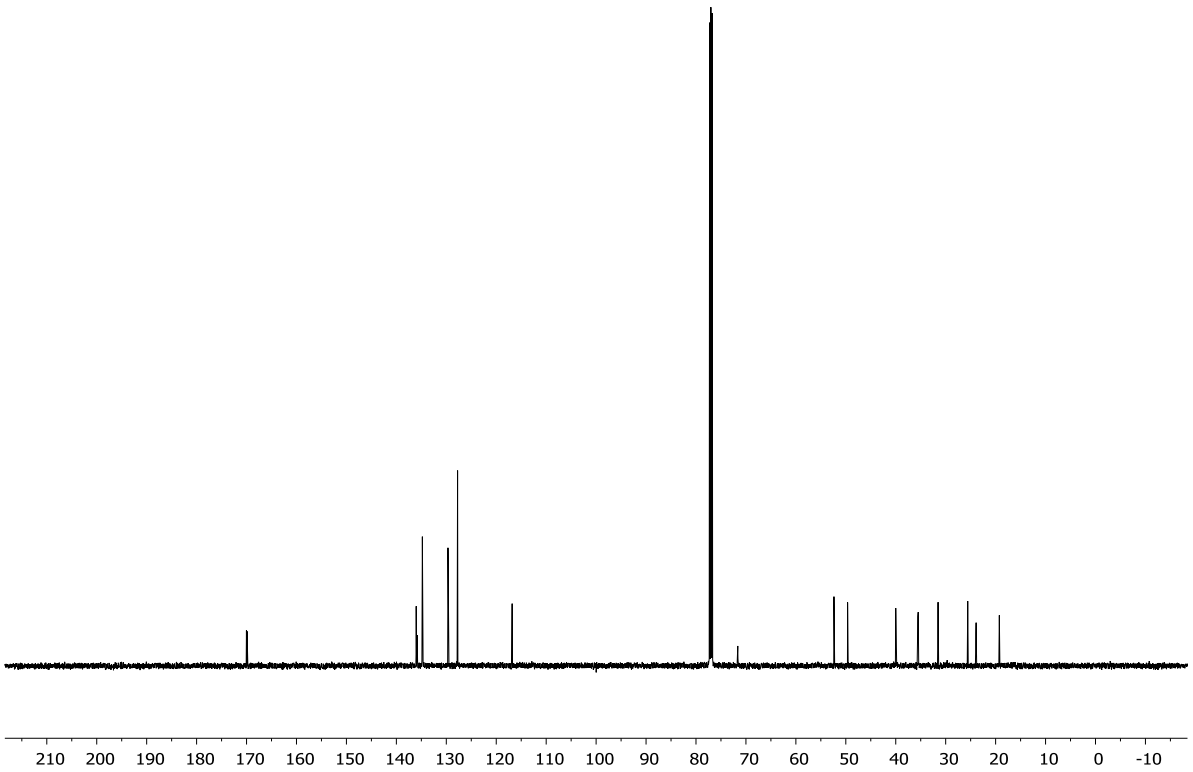
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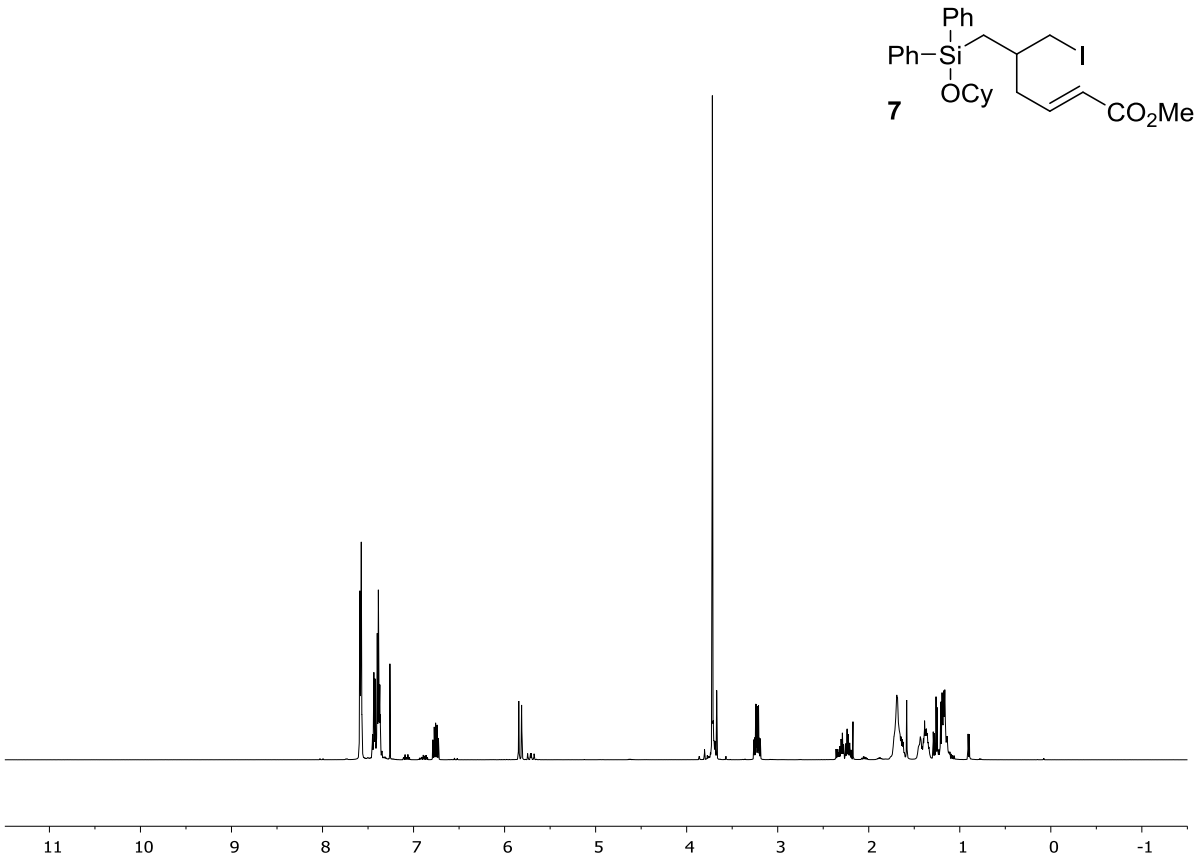
Ph
Ph–Si
OCy
I
CO2Me
7
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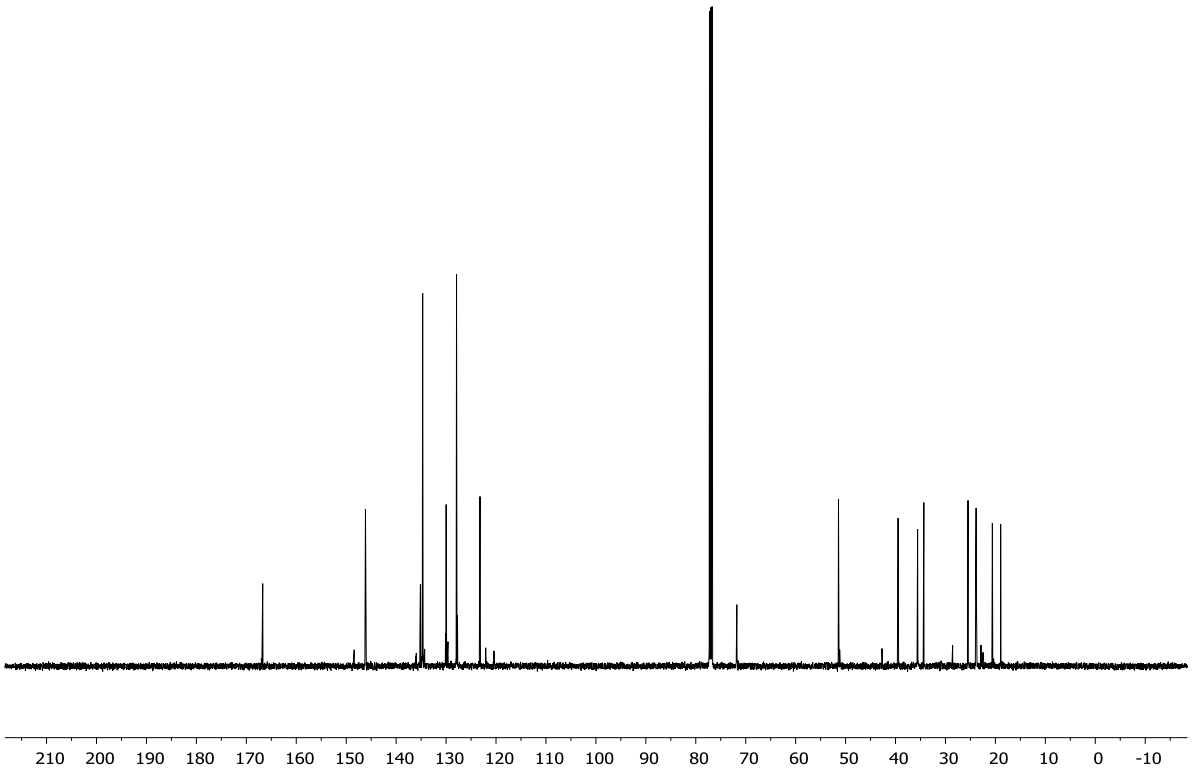
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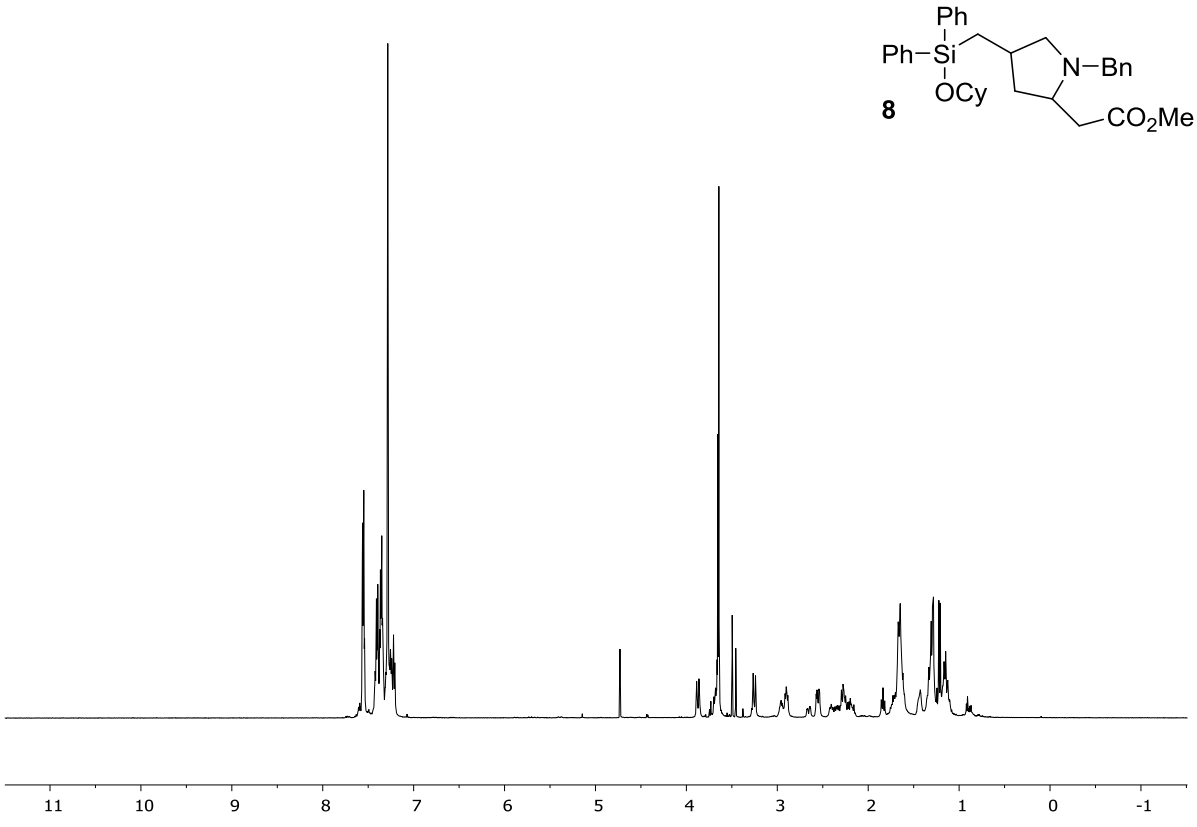
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Ph–Si
OCy
N–Bn
CO2Me
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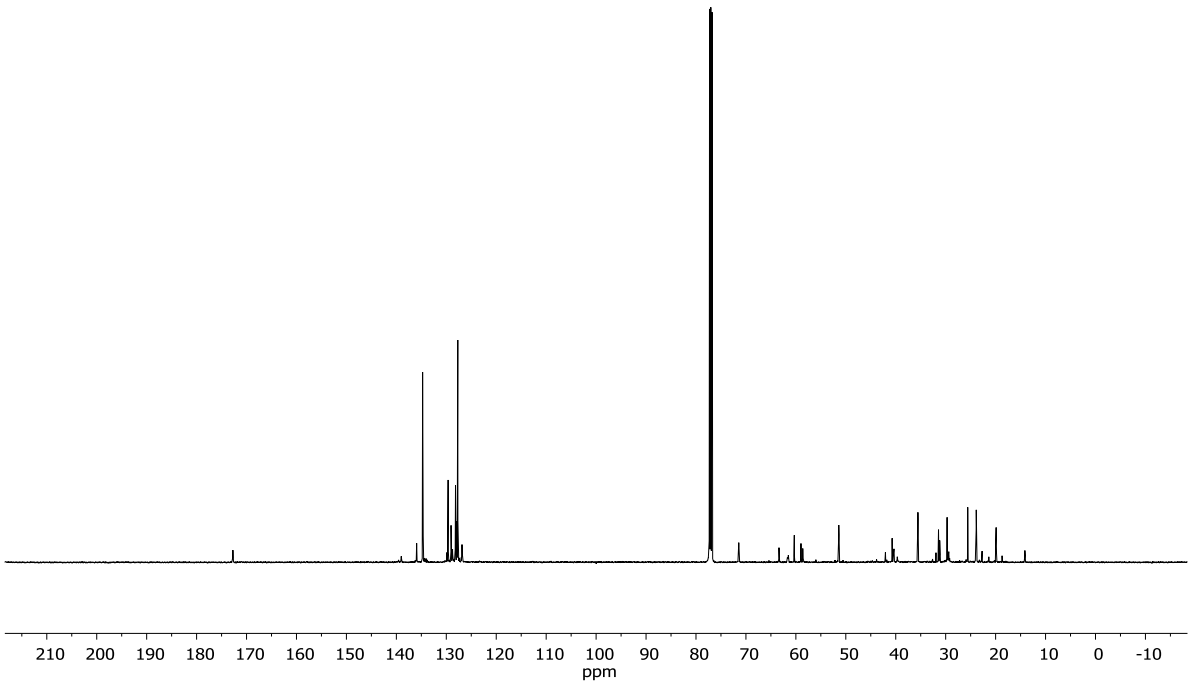
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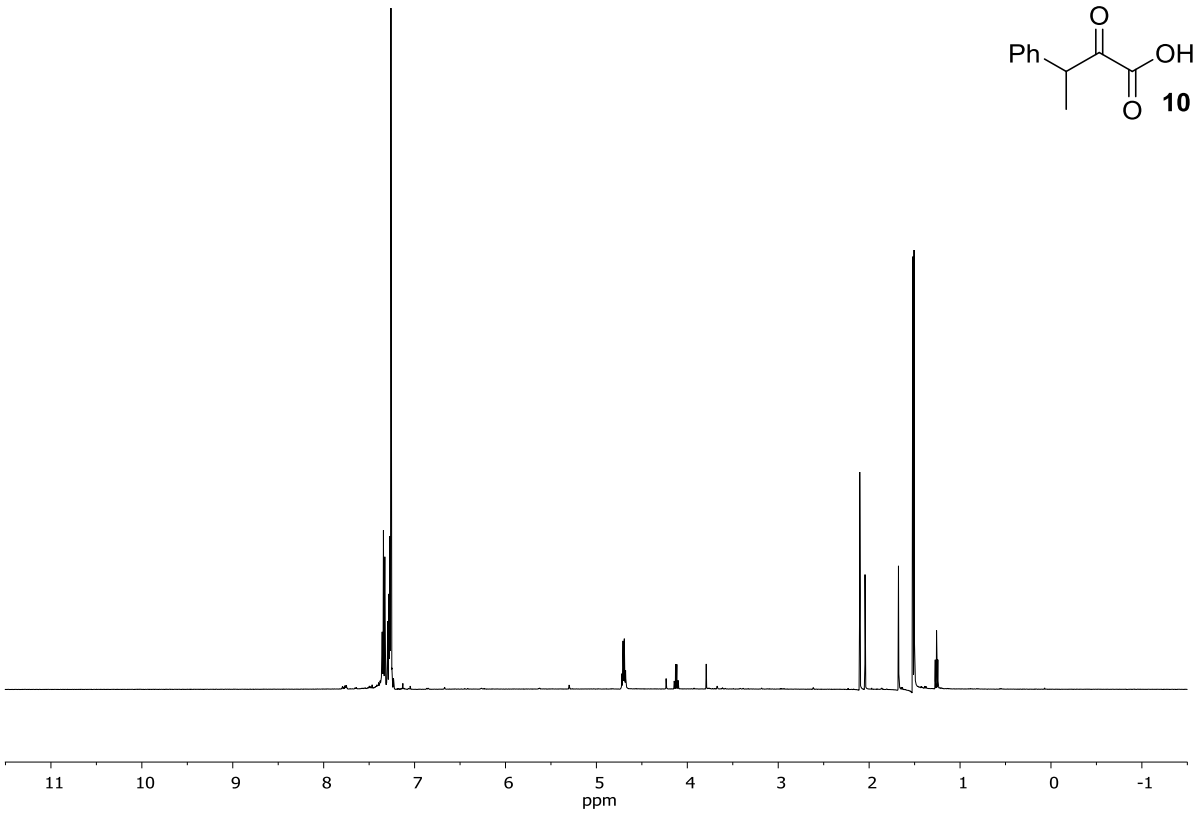
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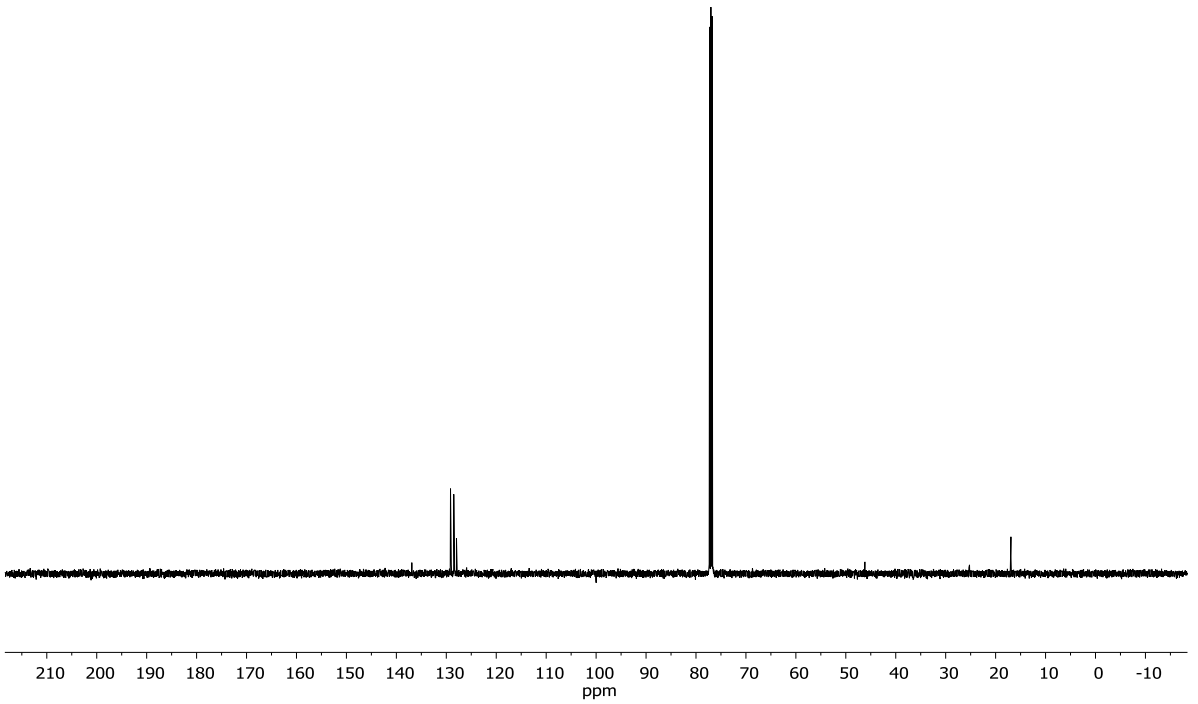
ppm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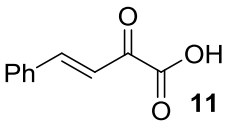
O
OH
Ph
O

11

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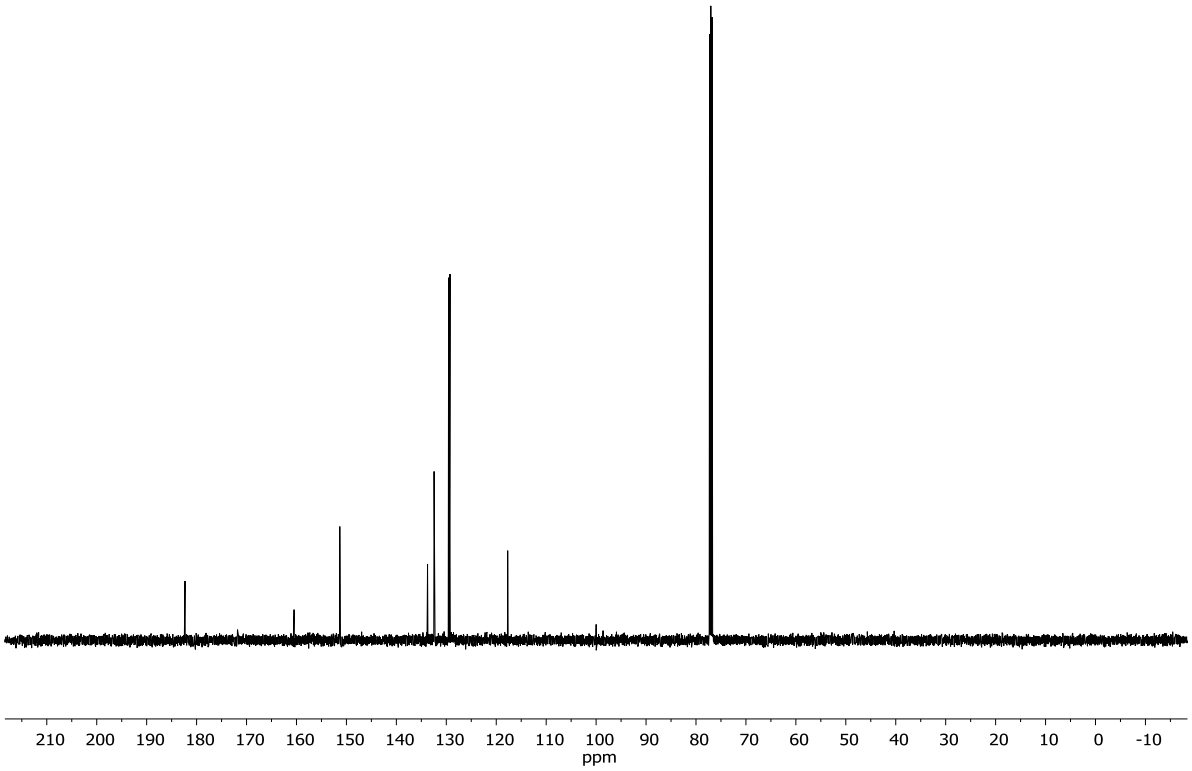
ppm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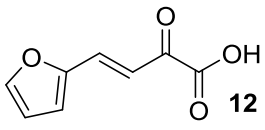
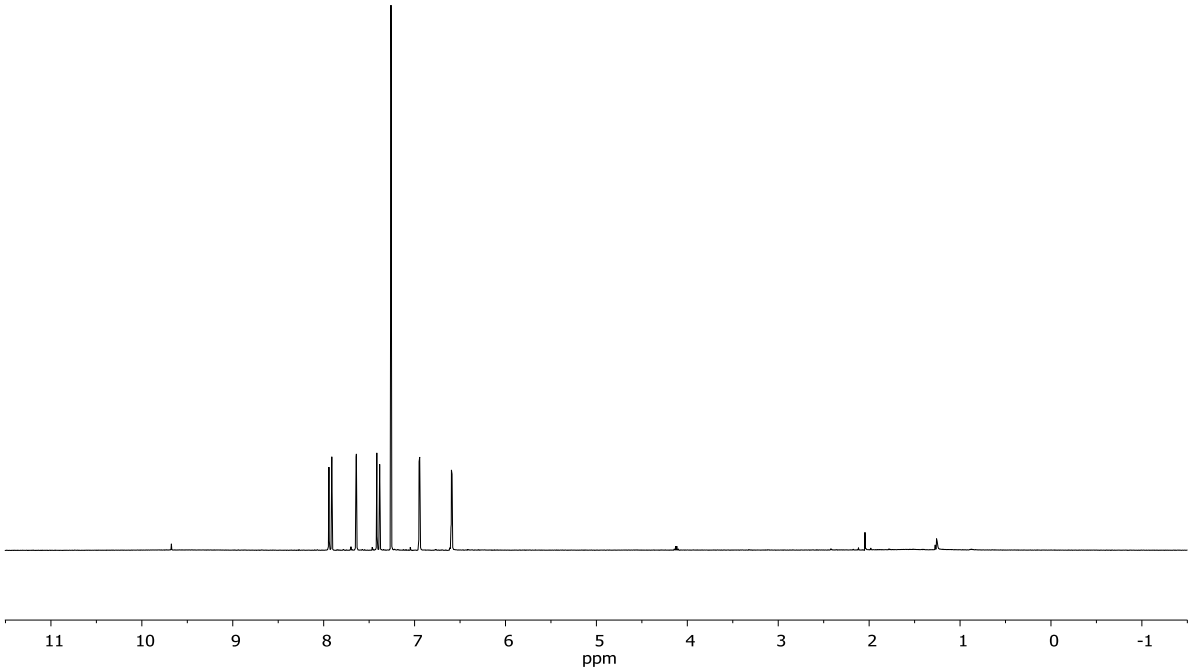

O
OH
O
O

12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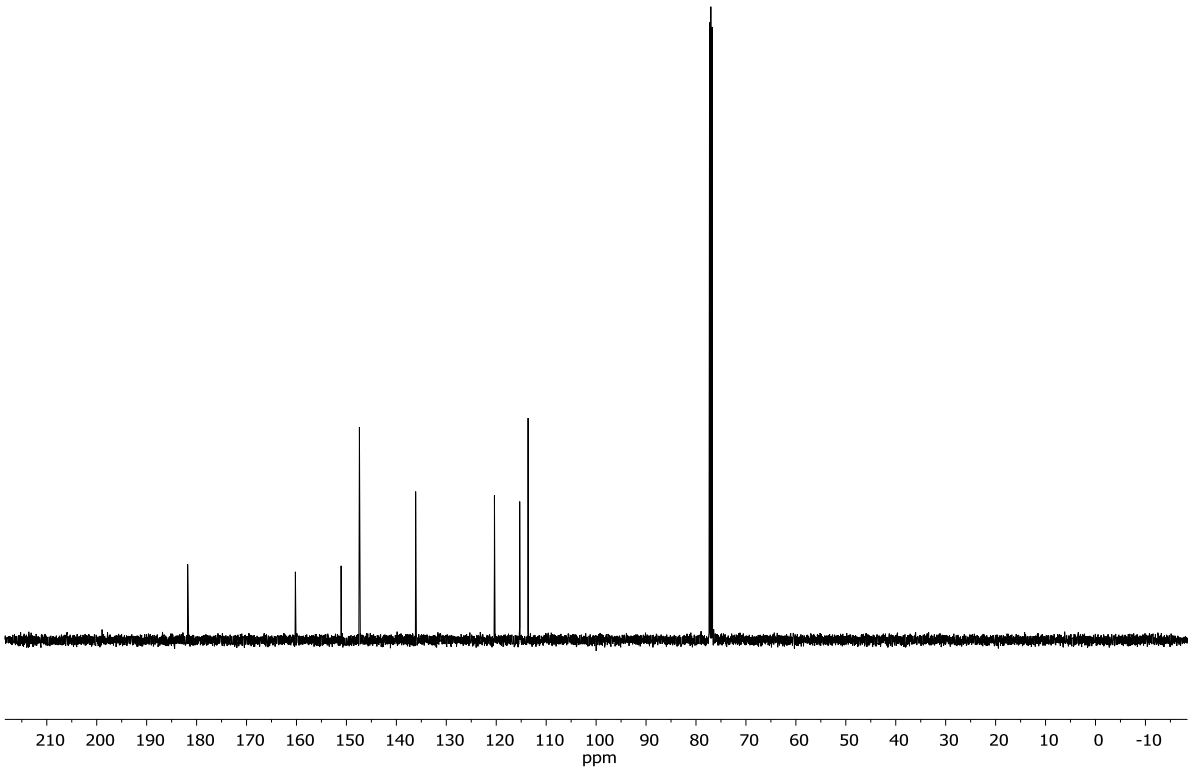
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10
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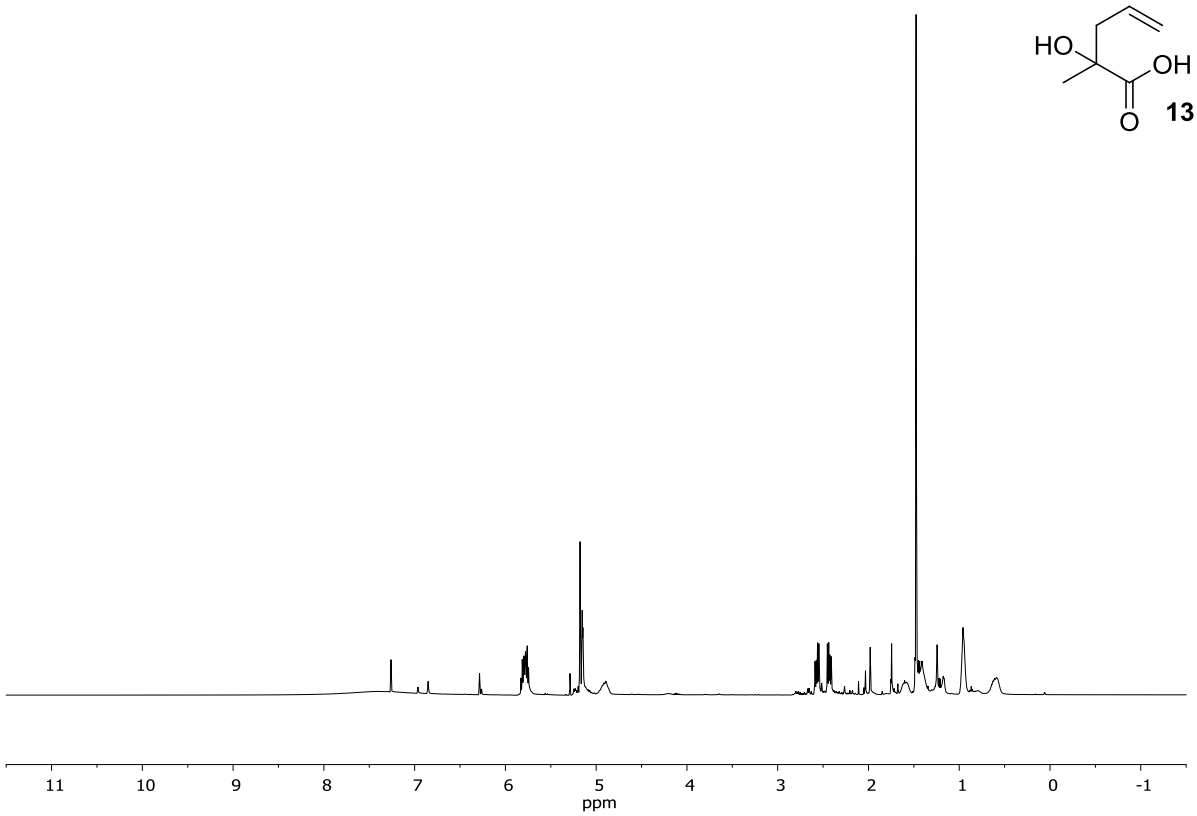
-10
ppm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OH
O
13
11
10
9
8
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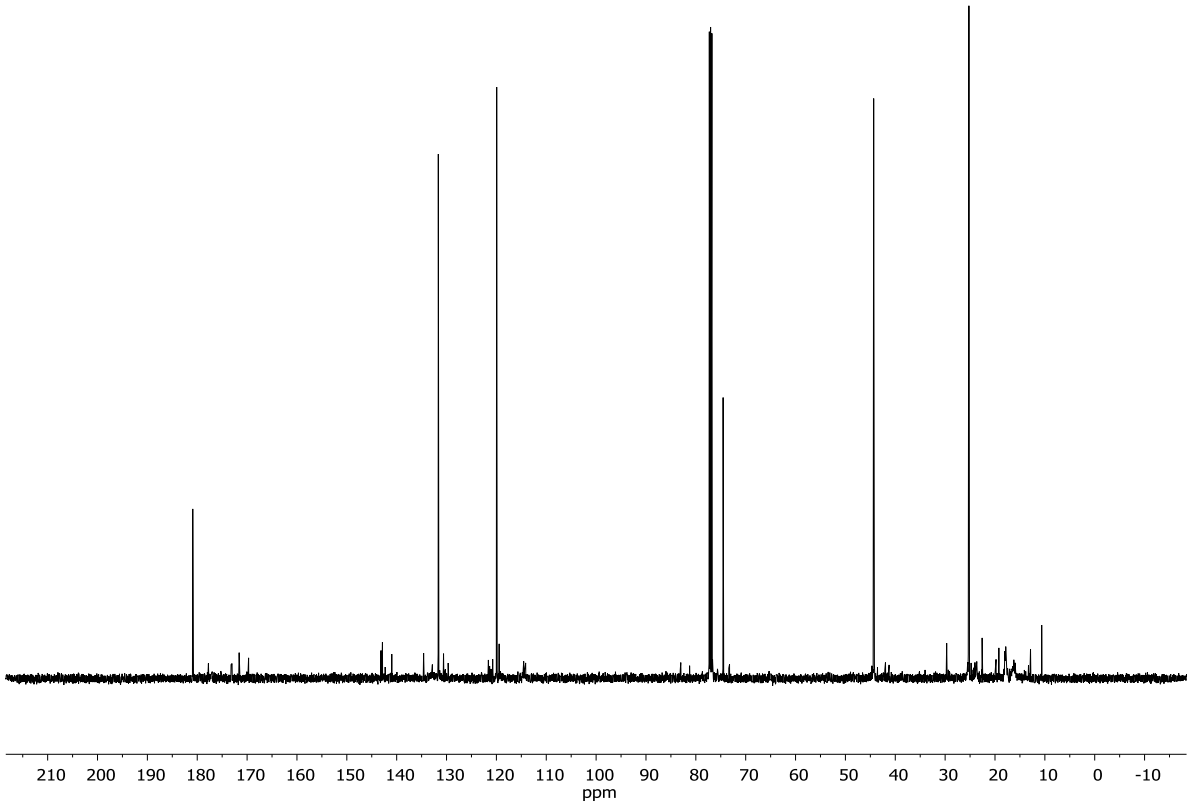
5
4
3
2
1
0
-1
ppm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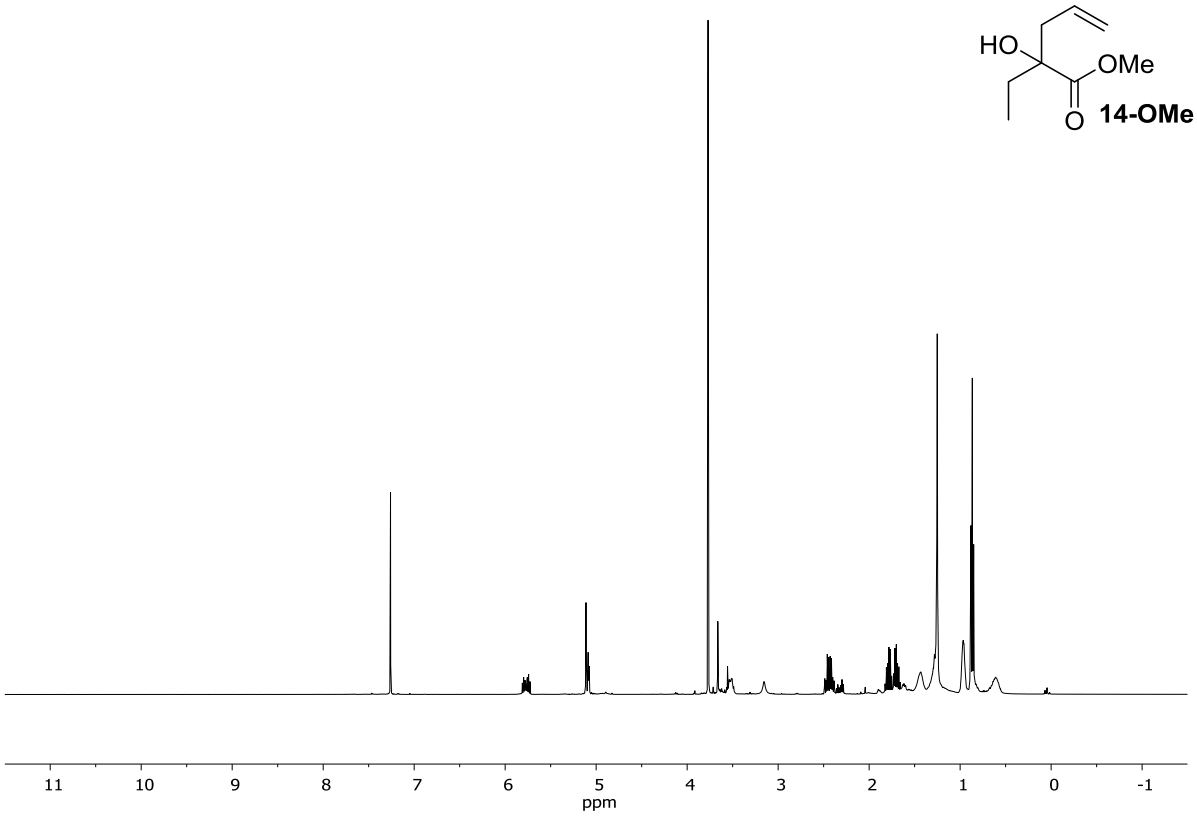
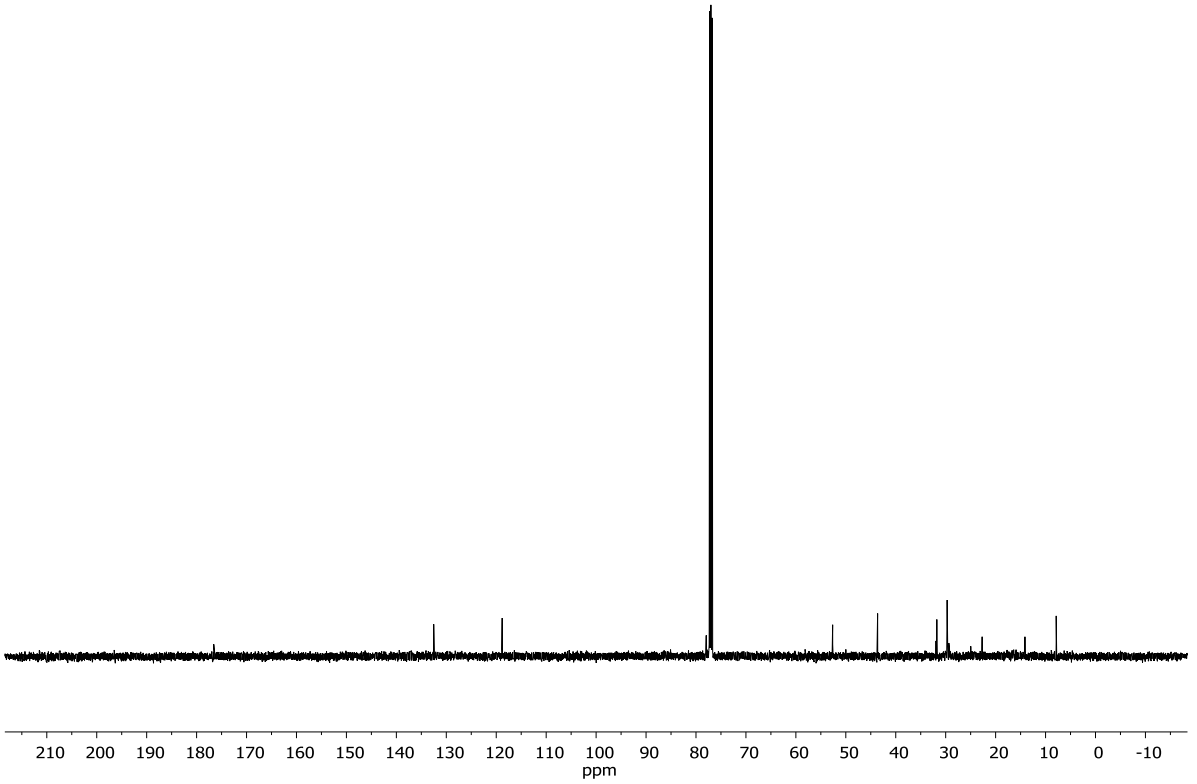

HO
OMe
O
14-OMe
11 10 9 8 7 6 5 4 3 2 1 0 -1
ppm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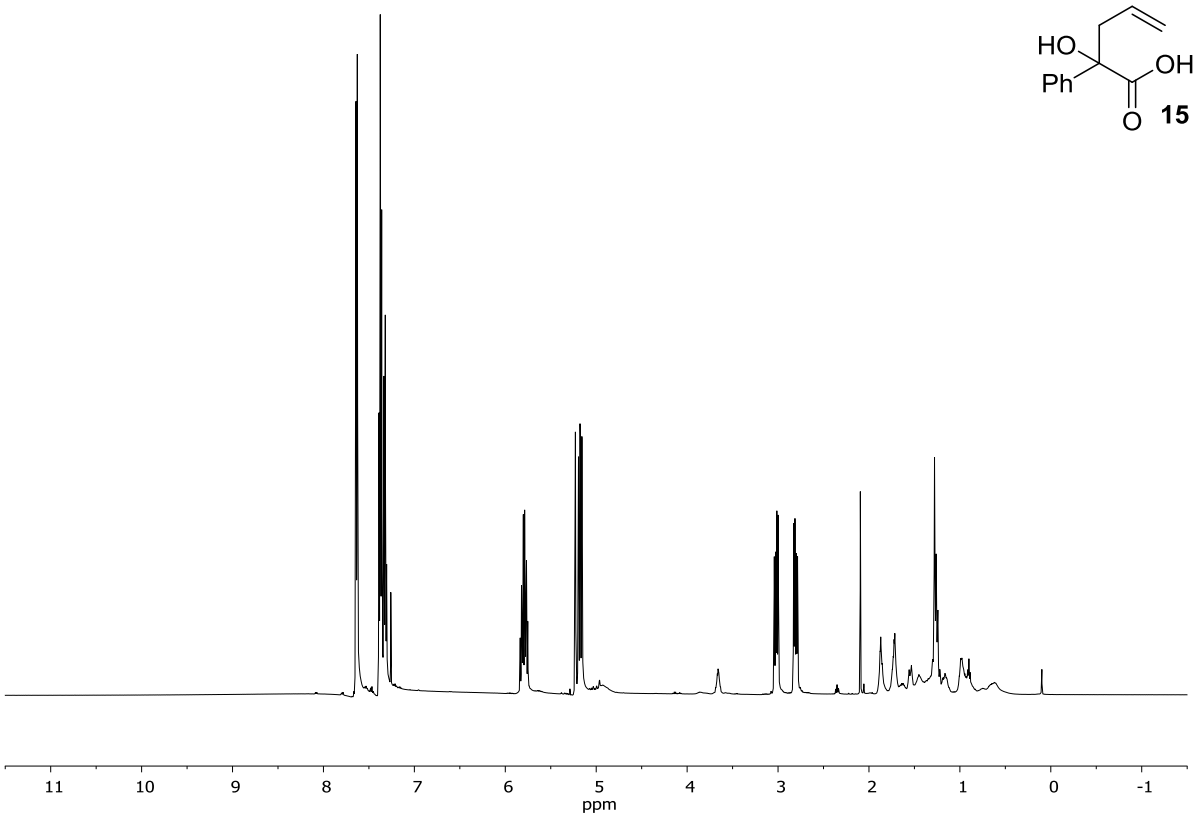
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OH
Ph
O
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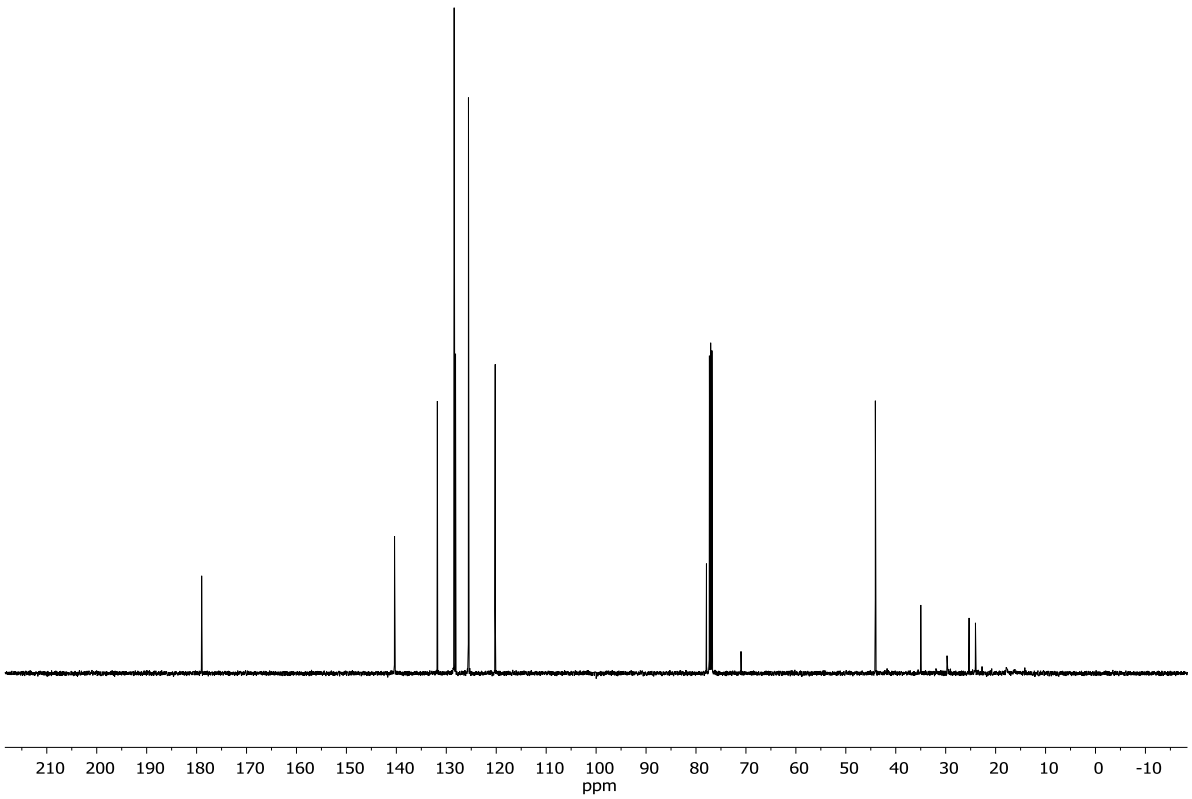
10
9
8
7
6
5
4
3
2
1
0
-1
ppm

15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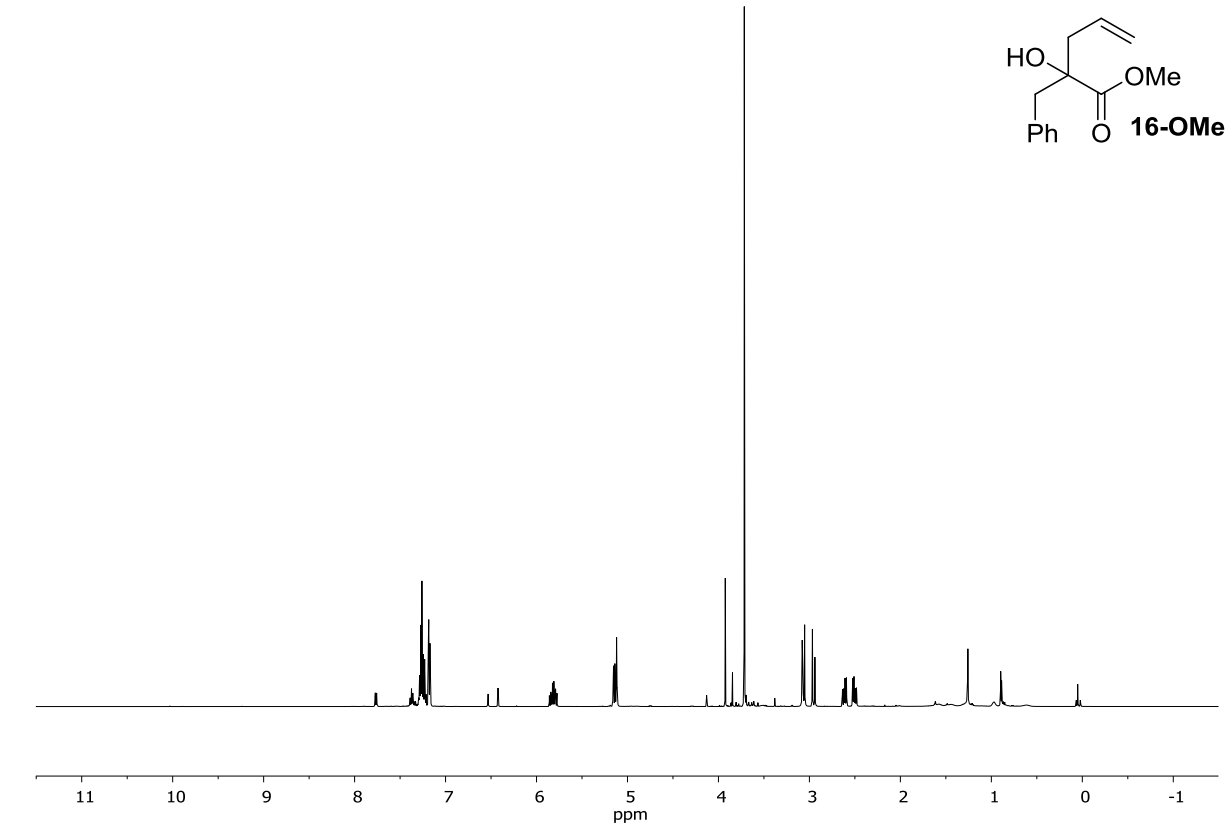
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OMe
Ph
O
16-OMe
11
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9
8
7
6
5
4
3
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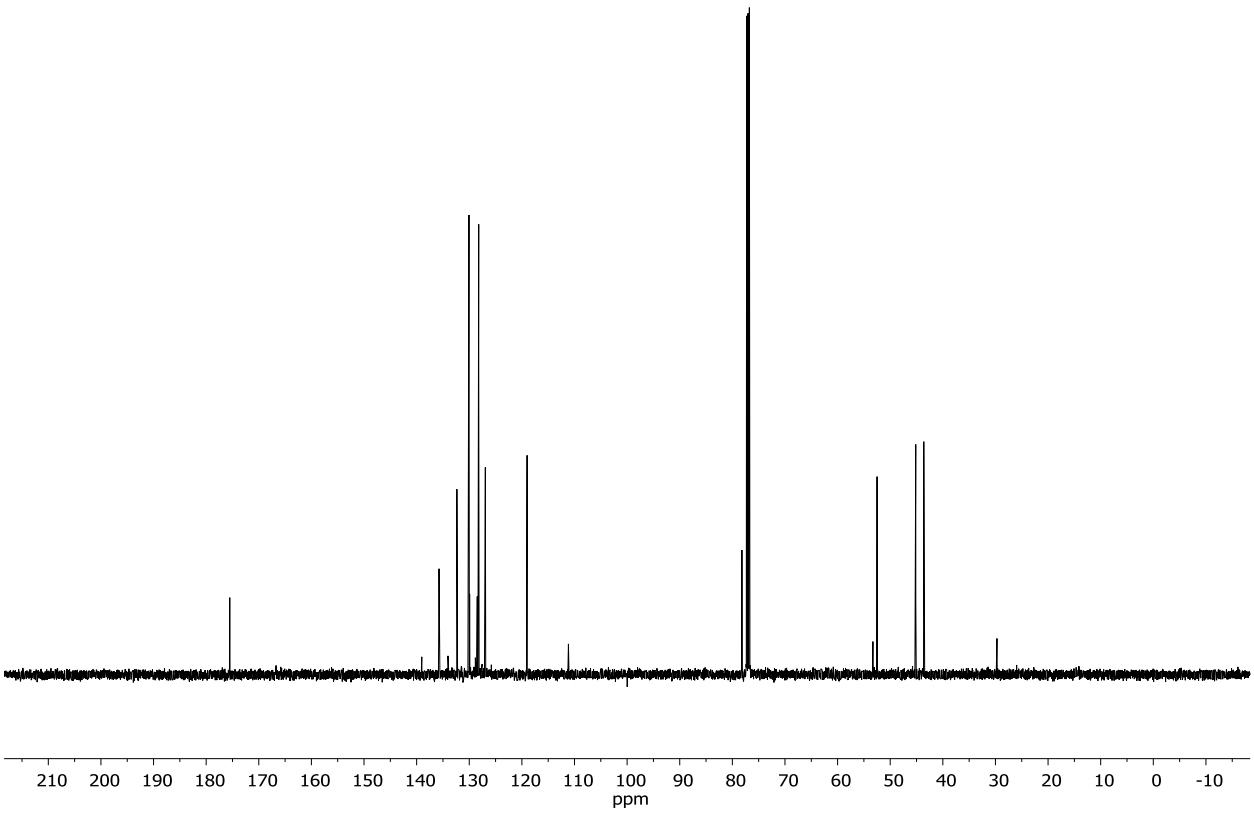
1
0
-1
ppm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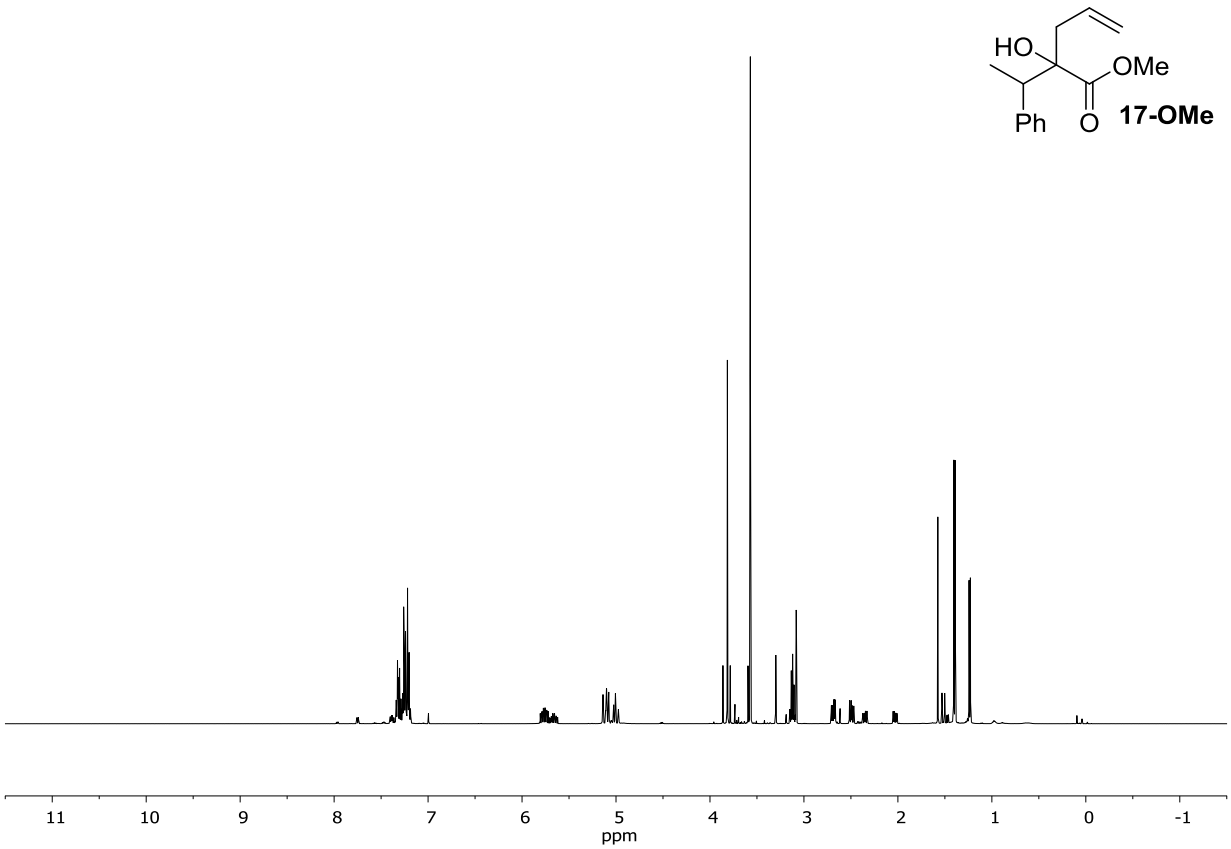
-10
ppm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OMe
Ph
O
17-OMe
11
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9
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7
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5
4
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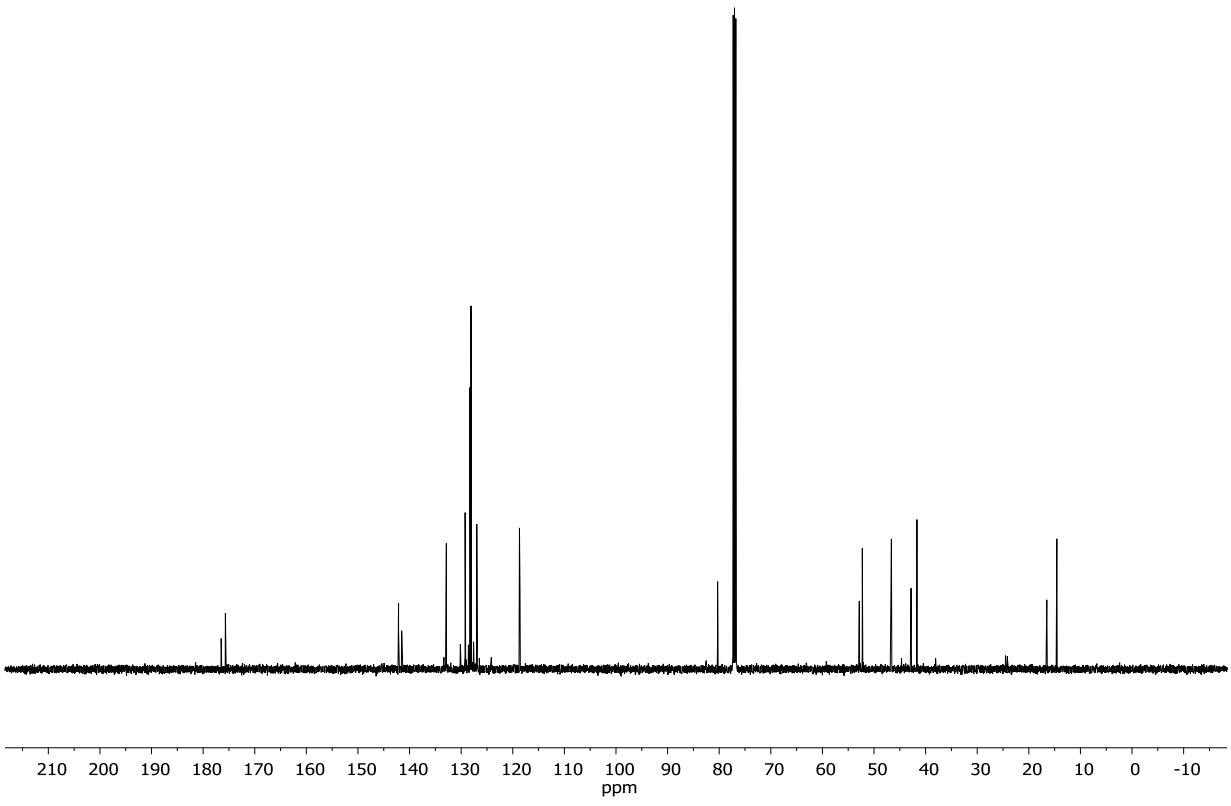
2
1
0
-1
ppm


210
200
190
180
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70
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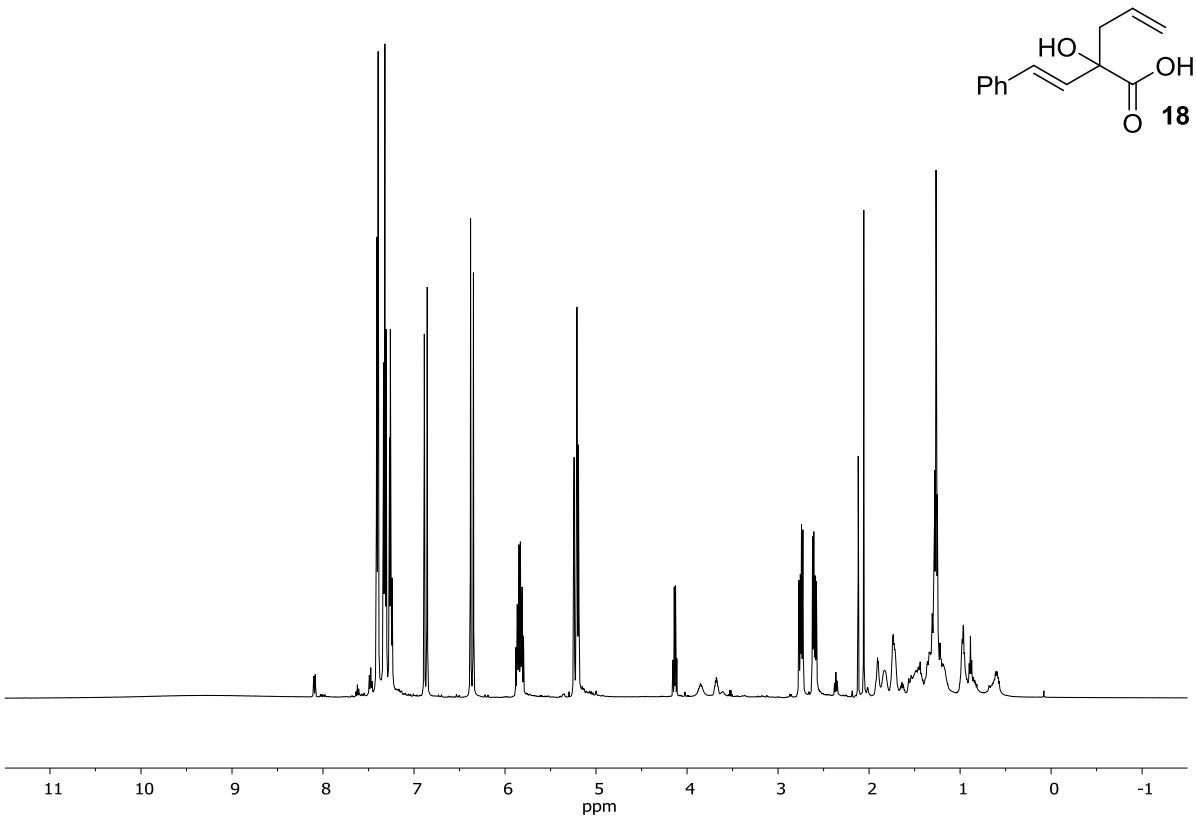
-10
ppm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OH
Ph
O
18
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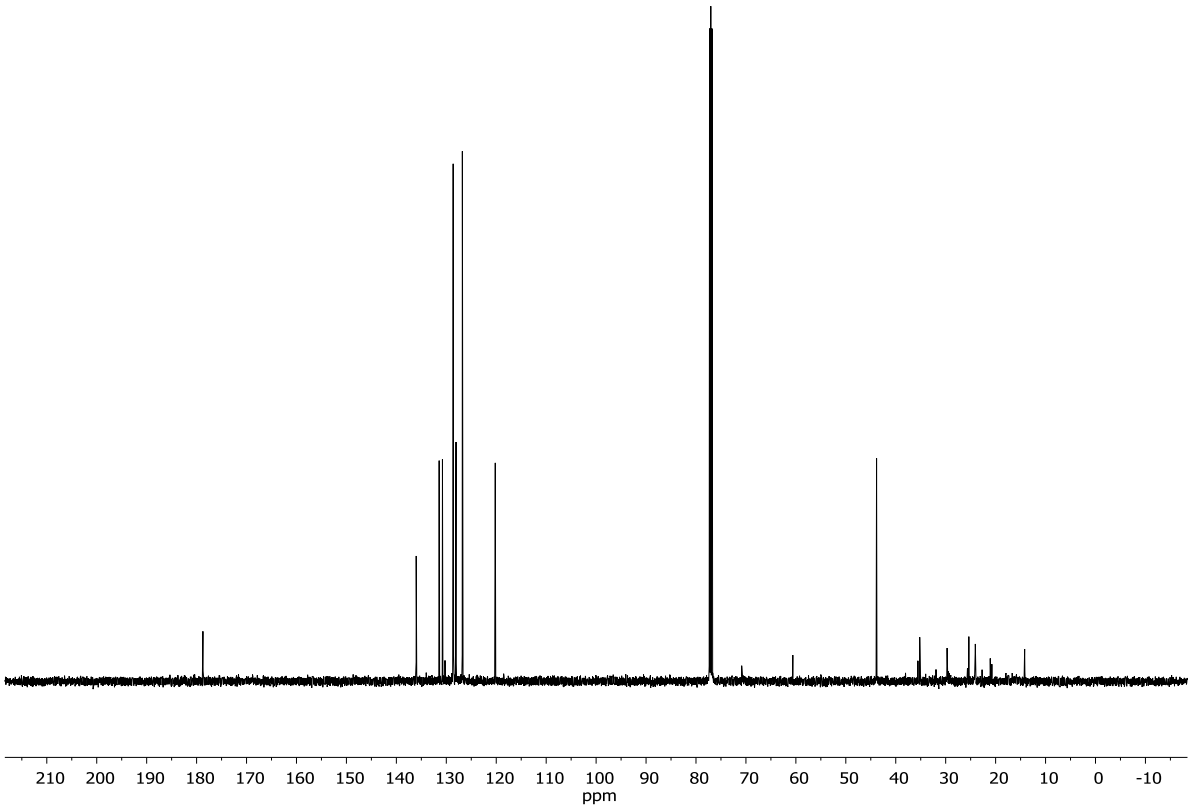
ppm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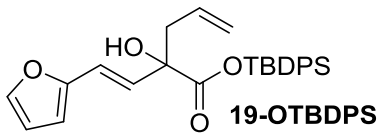
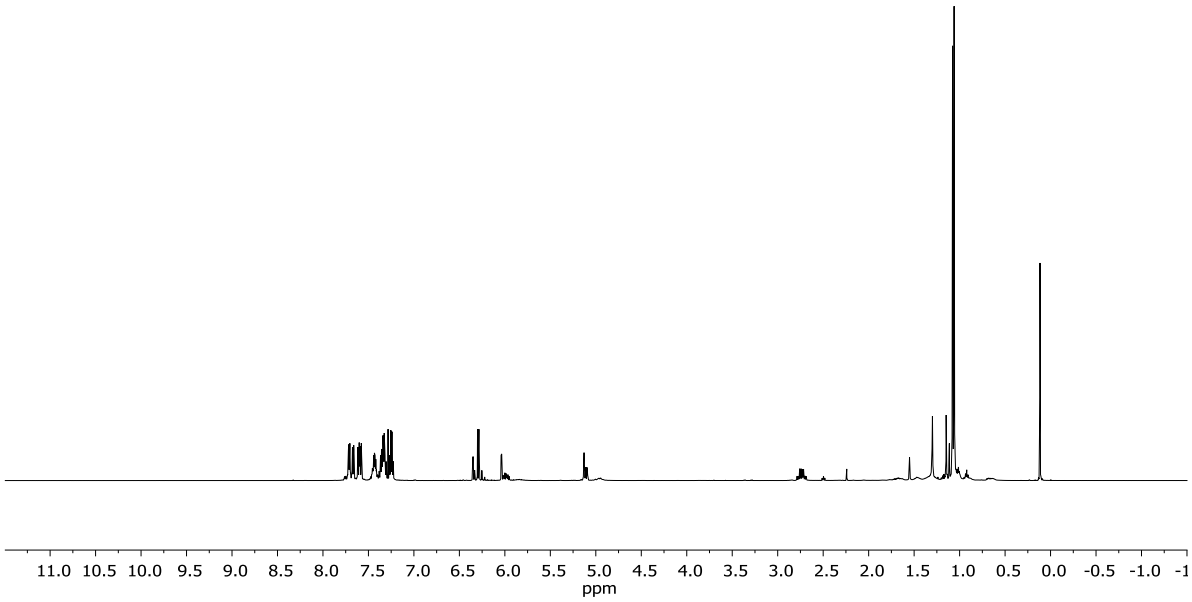

HO
O
OTBDPS
O

19-OTBDPS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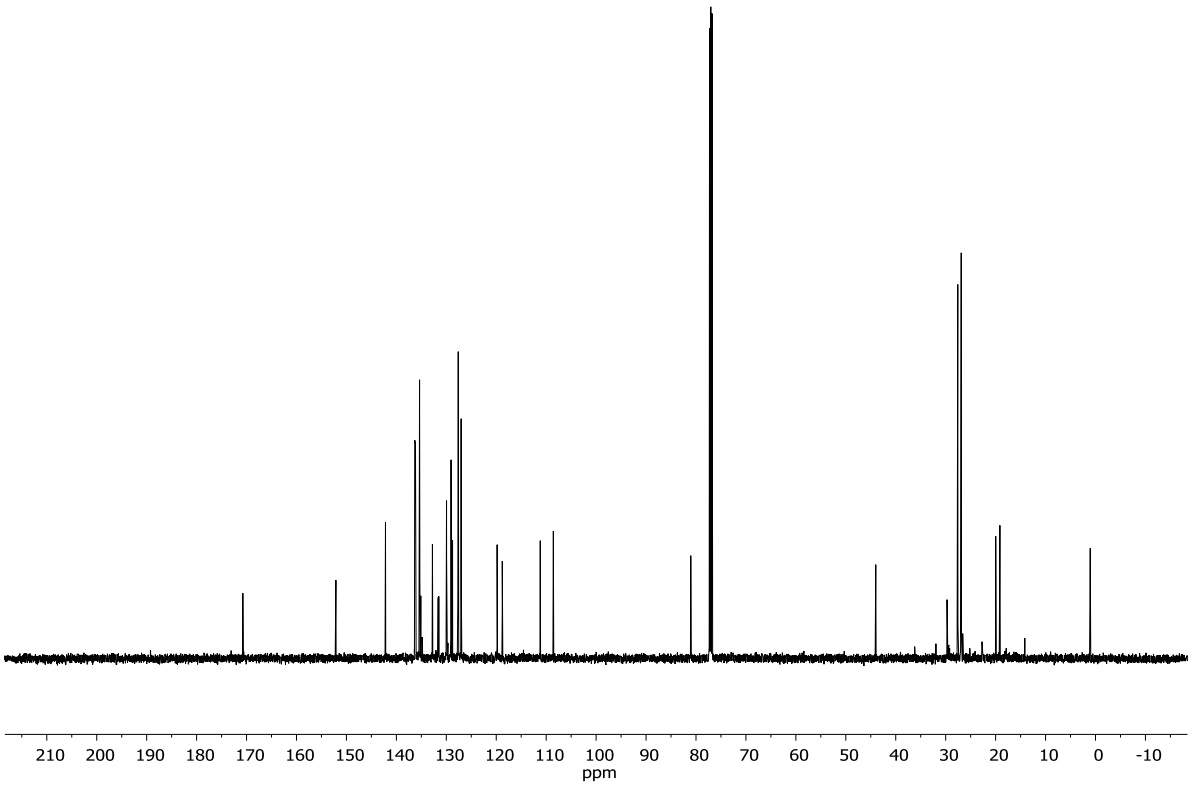
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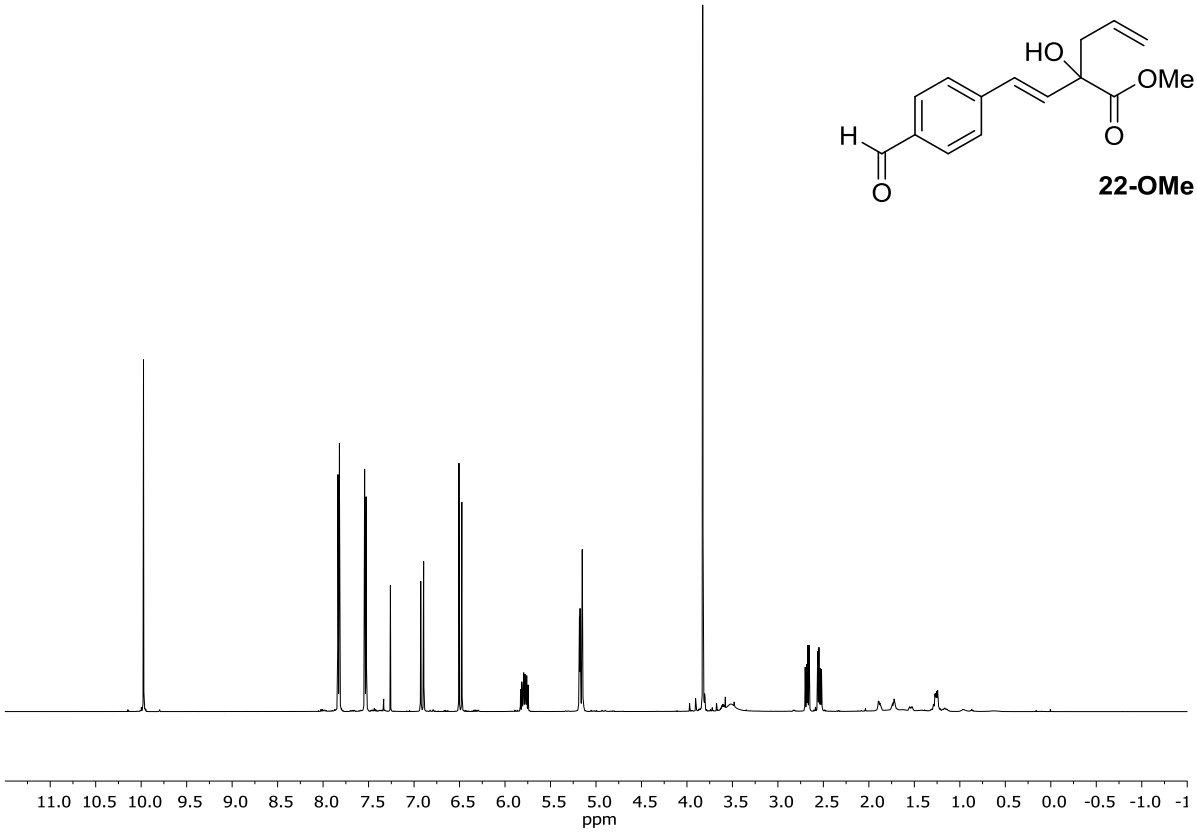
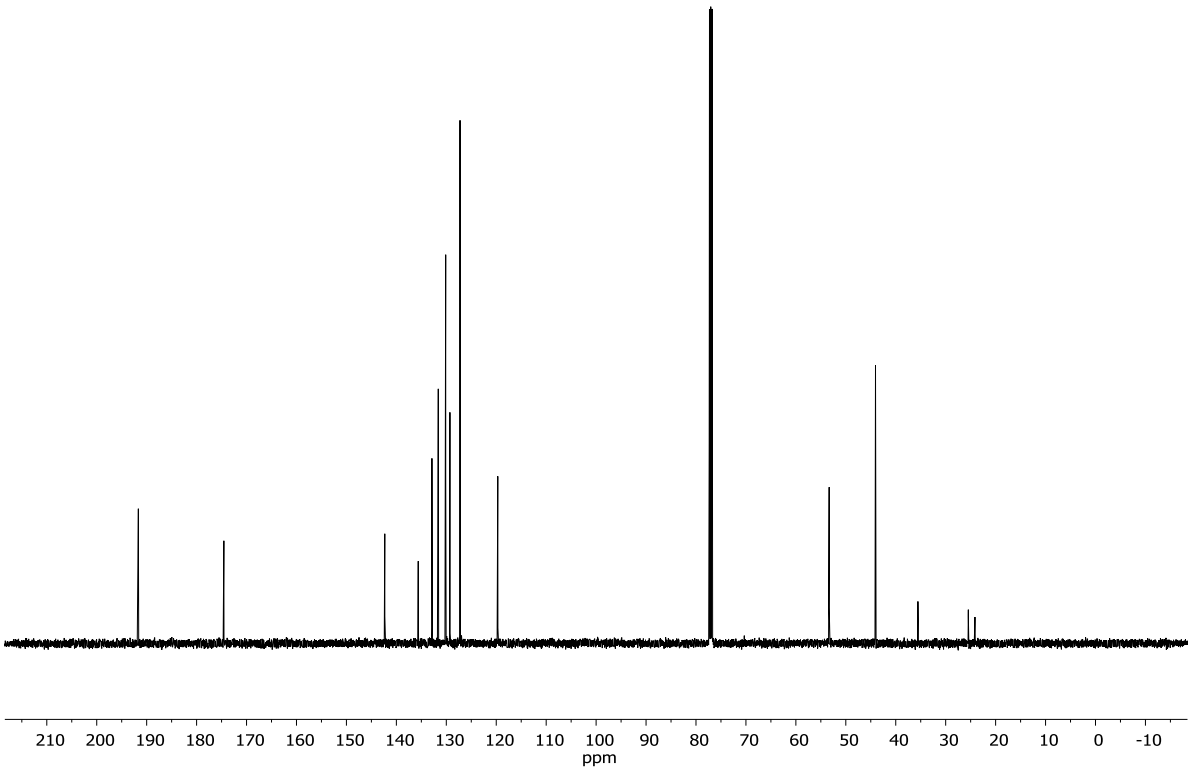

HO
OMe
H
O
O
22-OMe
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0 -1
ppm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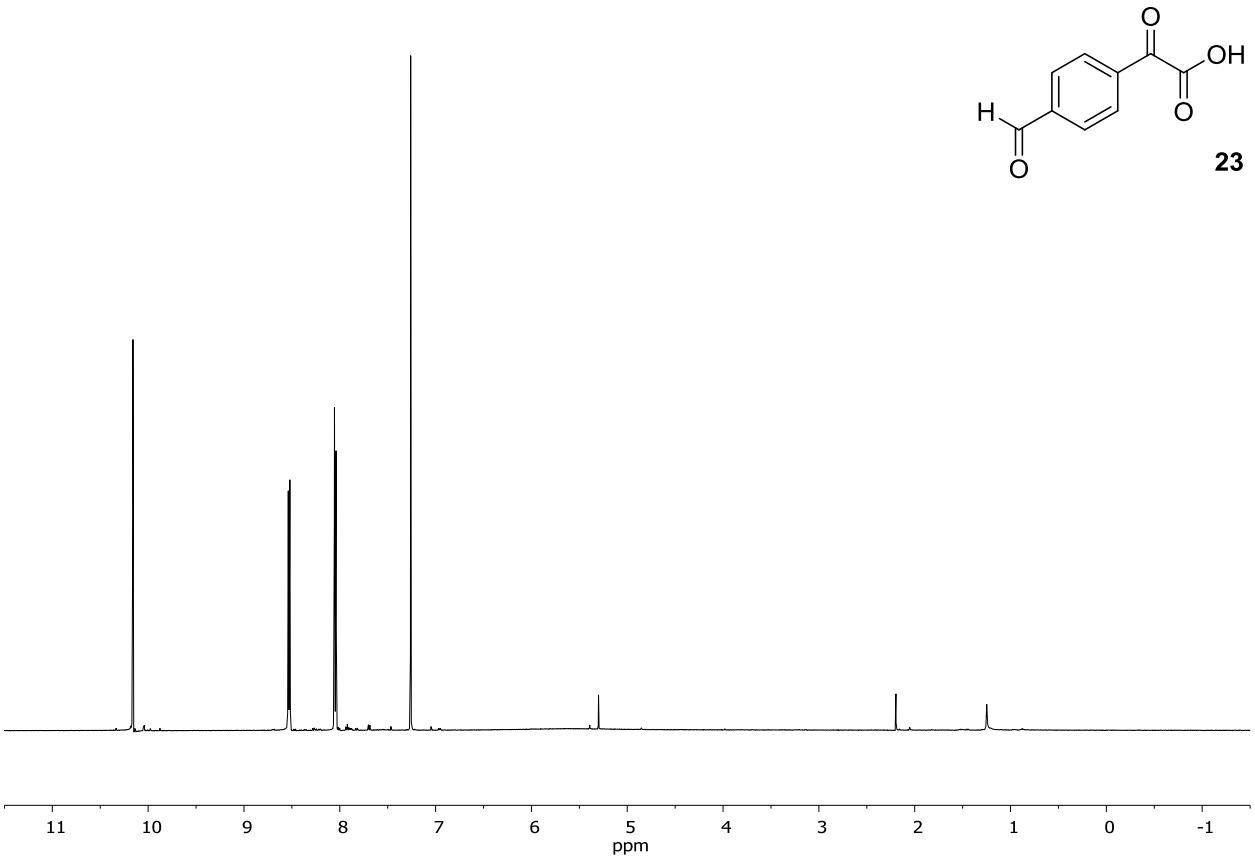
ppm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OH
H
O
O
23
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10
9
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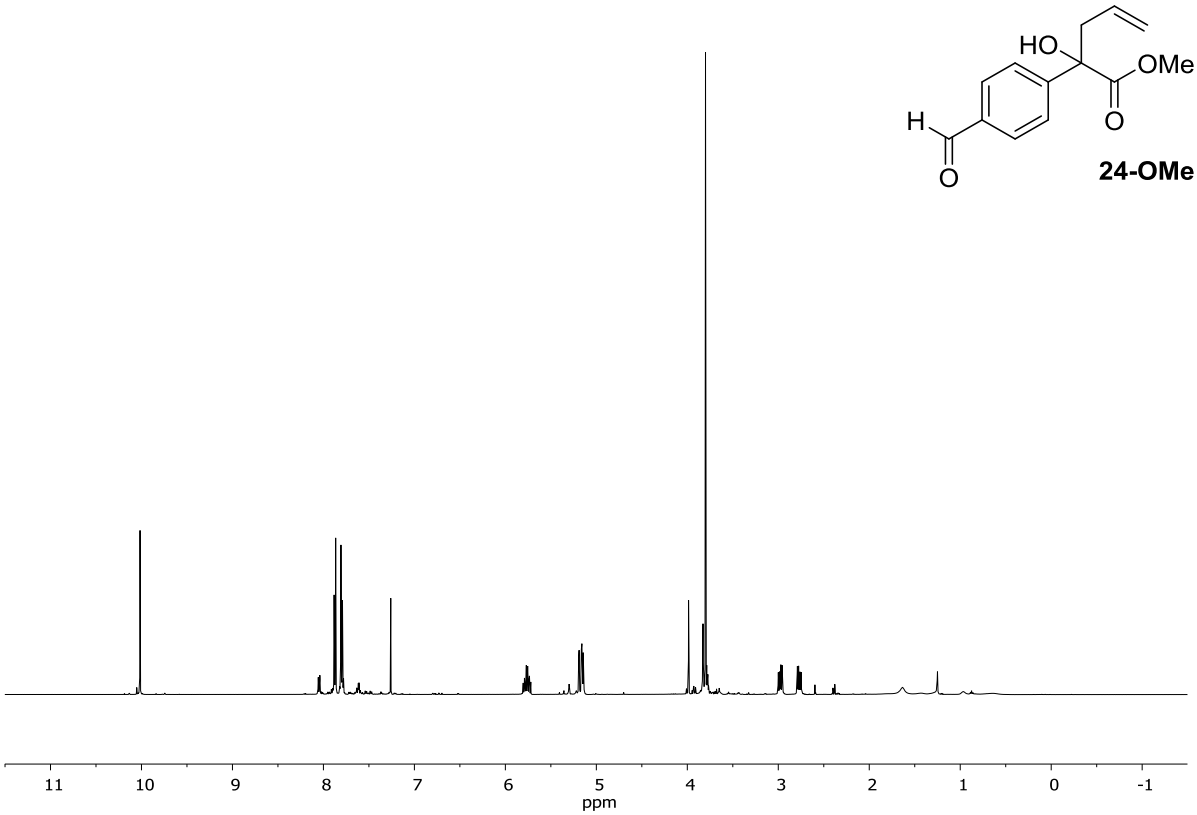
5
4
3
2
1
0
-1
ppm


HO
OMe
O
H
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3
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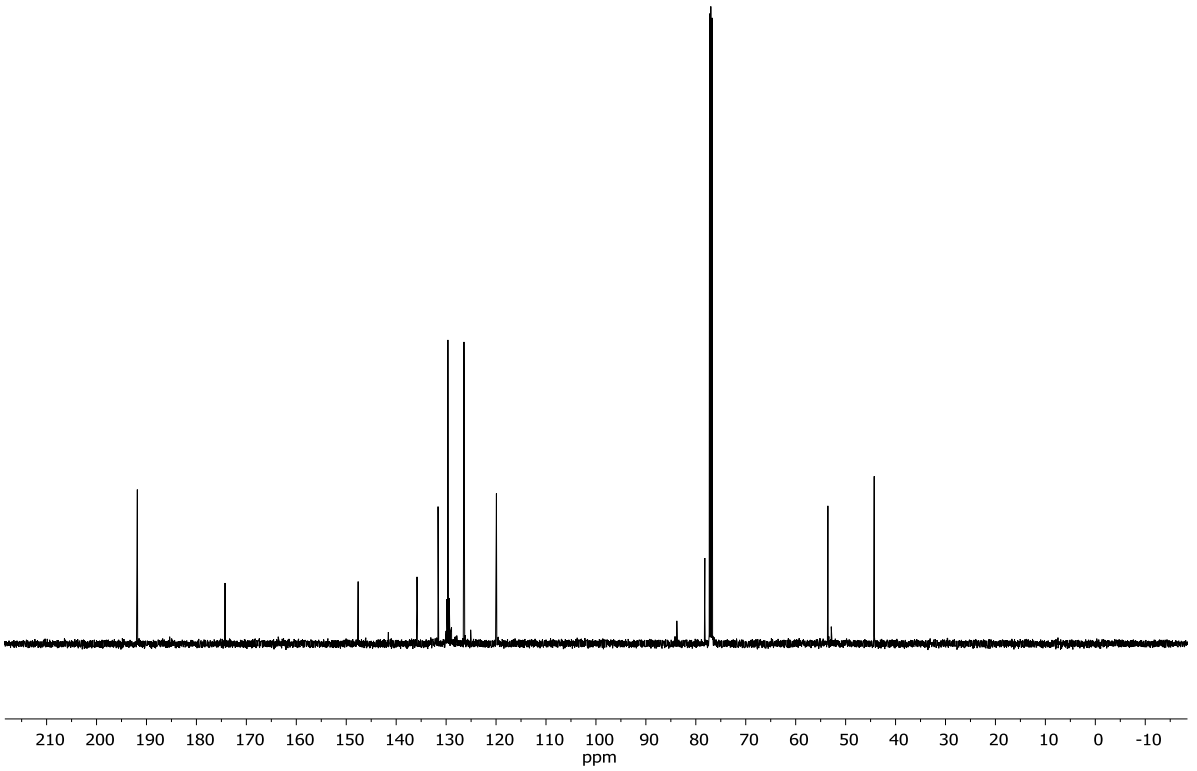
-1
ppm

24-OMe


210
200
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180
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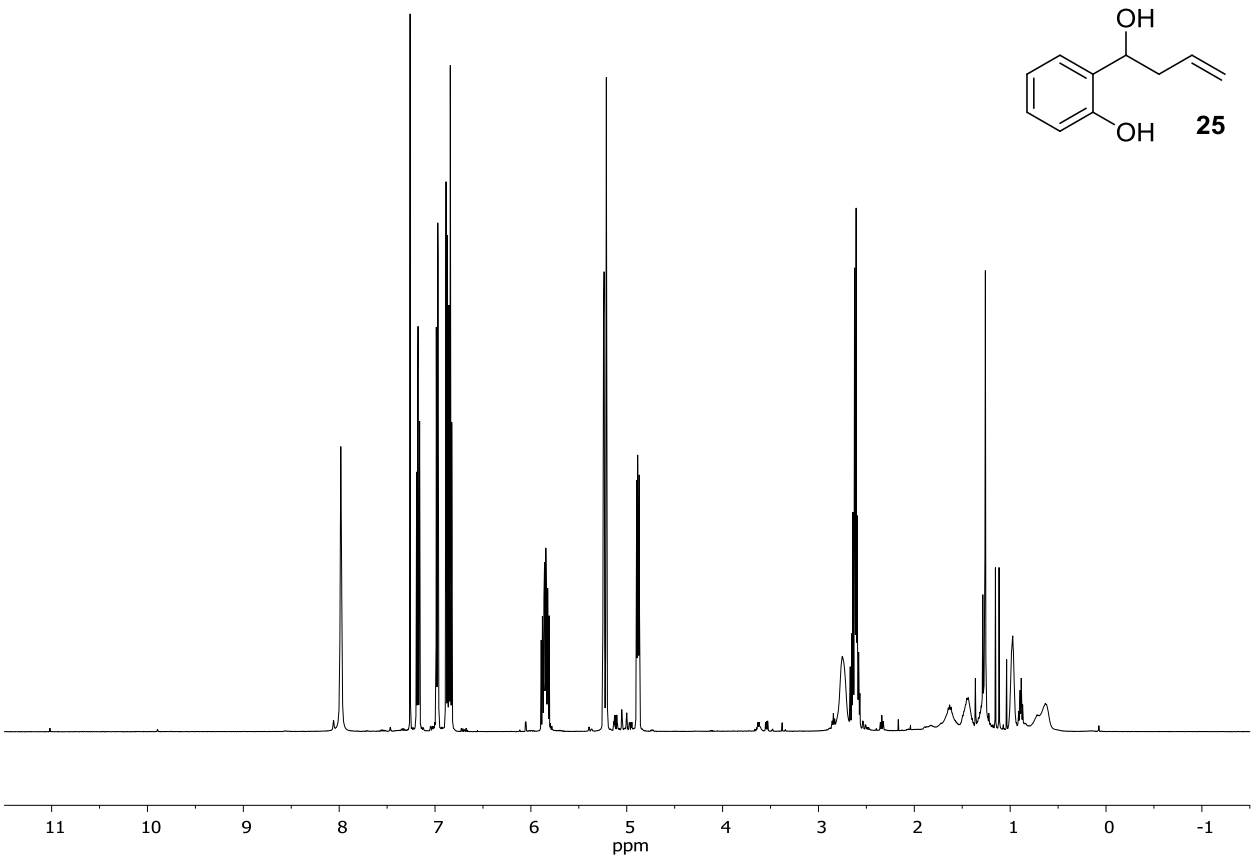
10
0
-10
ppm


OH
OH
25
11
10
9
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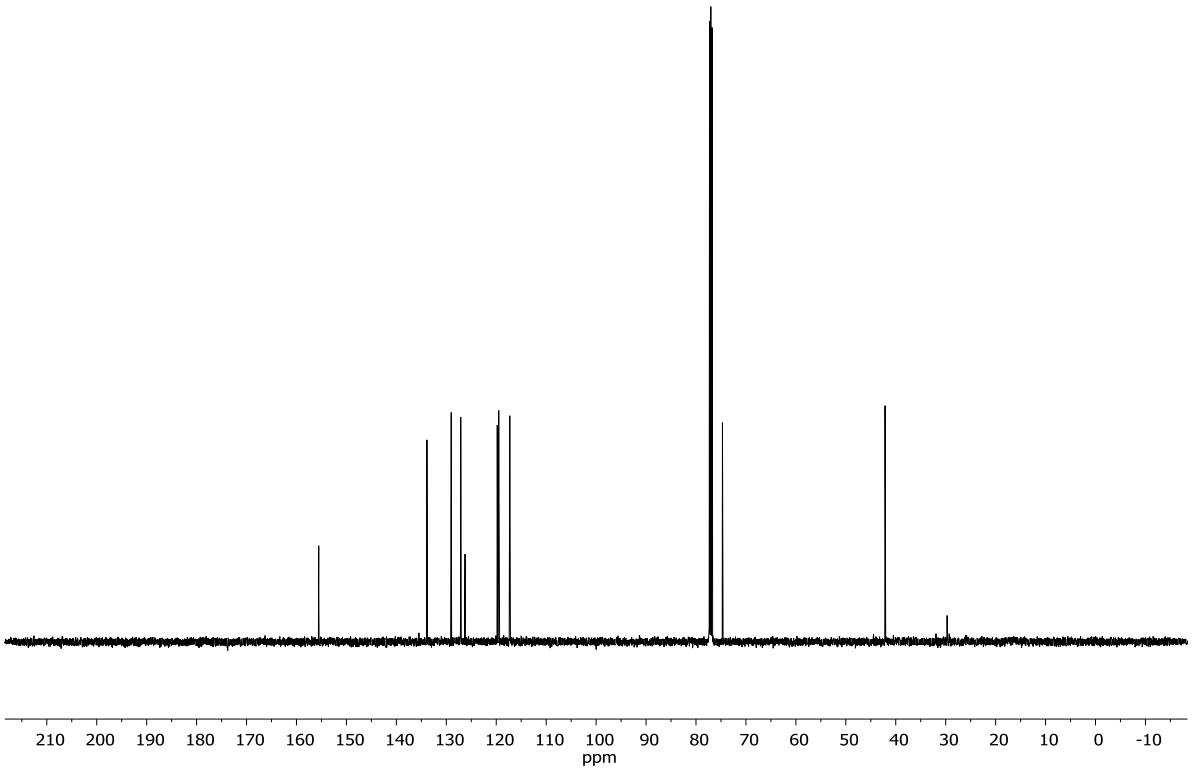
4
3
2
1
0
-1
ppm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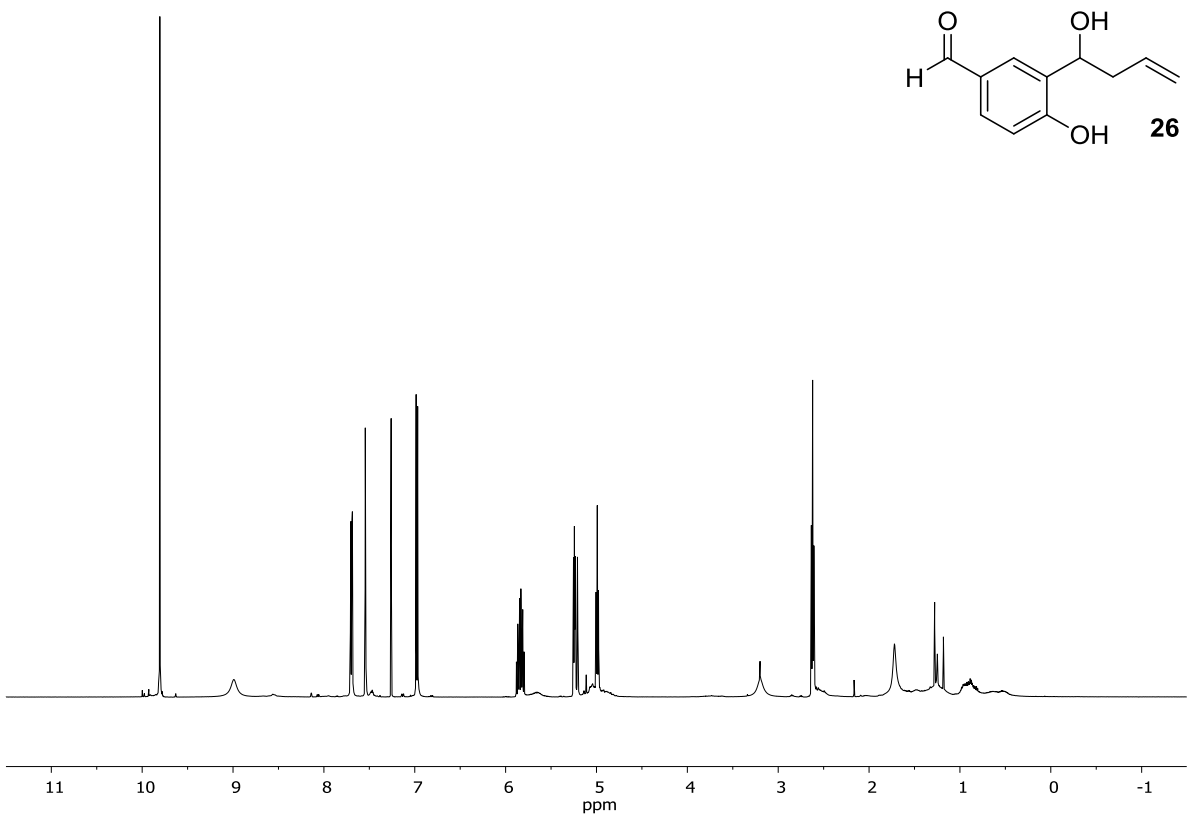
0
-10
ppm


O
OH
H
OH
26
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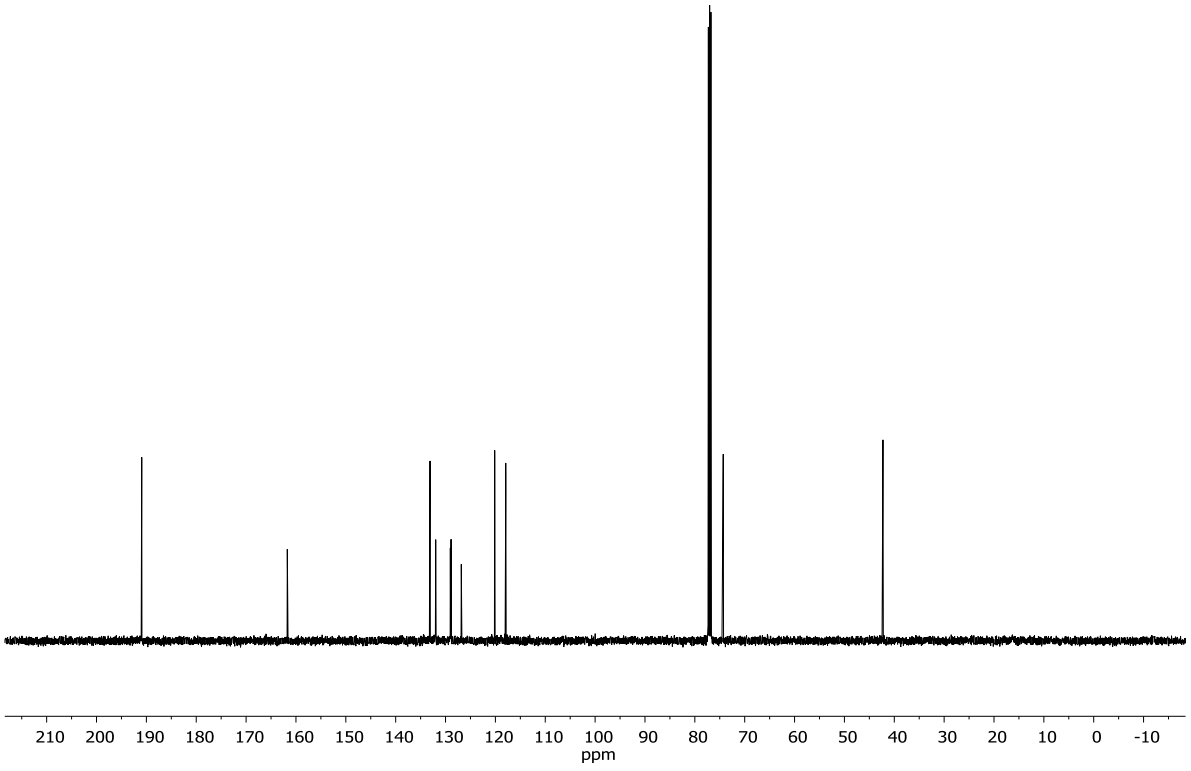
ppm


210
200
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140
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120
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100
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80
70
60
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30
20
10
0
-10
ppm

Works Cited

(1) Imamoto, T.; Takiyama, N.; Nakamura, K.; Hatajima, T.; and Kamiya, Y. Reactions of Carbonyl Compounds with Grignard Reagents in the Presence of Cerium Chloride. *Journal of the American Chemical Society* 1989, 111 (12), 4392-4398.

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