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Toward Biologically Active 2,6-Disubstituted Dihydropyran Ring Systems Using an Environmentally Benign Bismuth Catalyst and Mukaiyama Aldol Reaction

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Toward Biologically Active 2,6-Disubstituted Dihydropyran Ring Systems Using an Environmentally Benign Bismuth Catalyst and Mukaiyama Aldol Reaction

A thesis submitted in partial fulfillment of the requirement
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by

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Abstract

Herein are described optimization studies on the first step of a one-pot, three-component reaction towards biologically active 2,6-disubstituted dihydropyrans (DHPs). Bismuth tribromide proves to be a satisfactory catalyst for a Mukaiyama aldol reaction between an aldehyde or ketone and a silylated enol ether or ketene acetal. This environmentally benign catalyst establishes the viability of a three-component, one-pot reaction toward DHP ring systems, present in anti-cancer, anti-fungal, and anti-osteoporosis agents, among others.

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Introduction

Toward 2,6-Disubstituted Dihydropyrans via Three-Component, One-Pot Synthesis

Cyclic ethers are a distinct class of molecules that are highly prevalent in nature. Many such compounds, specifically those containing 2,6-disubstituted dihydropyran ring systems, have been produced by microscopic living organisms.[1] A variety of dihydropyran ring systems, hereafter DHPs, have been isolated, slightly modified, and recognized as potential aids in the clinical world. One such molecule, Scytophycin C, has been isolated from the terrestrial blue-green alga *Scytonema pseudohofmanni* and has been demonstrated to exhibit potent activity against a variety of human carcinoma cell lines including solid tumors.[2] In addition, the DHP-containing molecule abruticine 1 has been proven an effective anti-fungal agent.[3]

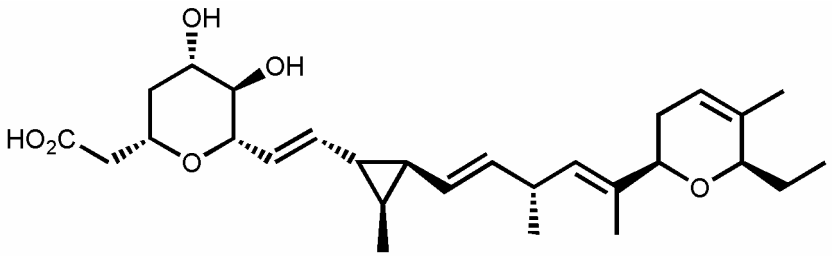
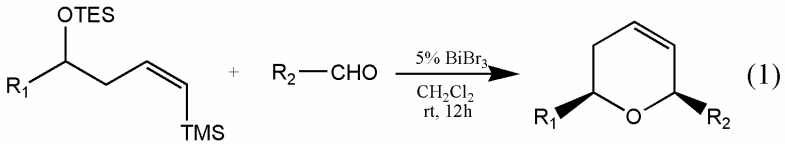


Figure 1 Abruticine 1, a 2,6-disubstituted DHP ring system

2,6-Disubstituted DHPs are also synthetically useful intermediates in the production of polysubstituted tetrahydropyran ring systems, such as those found in the pseudomonic acids which are commonly used in skin antibiotics to fight infections including *Staphylococcus epidermidis*.[4] The wide variety of important applications of dihydropyran systems in the biomedical world has made their synthesis a widely explored topic of research.

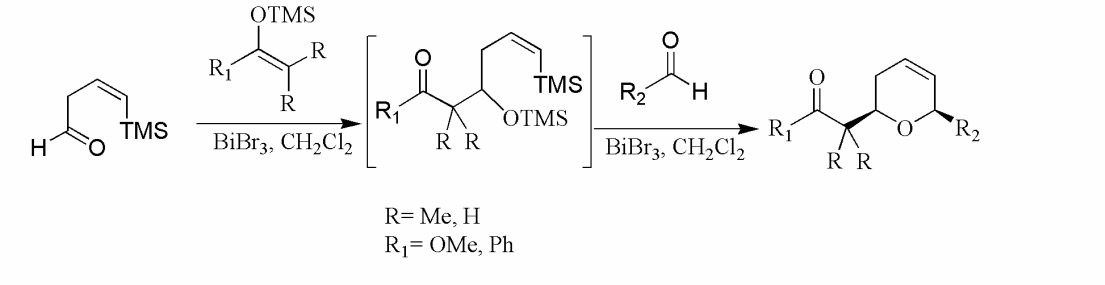
While 2,6-disubstituted DHPs can be synthesized by living organisms, their production in a lab would allow for large scale, industrial applications such as those in the biomedical world. Initial investigation by Hinkle et al. led to the development of a two-component tandem addition/silyl-Prins reaction to afford *cis*-2,6-disubstituted DHPs using 5 mol % bismuth (III) bromide in methylene chloride (**eq 1**).[5] Hinkle et al. report *cis*-DHP products in good to excellent isolated yields after flash column chromatography.



(1)

Equation 1. Two-component tandem addition/silyl-Prins reaction towards 2,6-disubstituted DHPs

After further analysis, Hinkle et al. devised a three-component, one-pot synthesis to achieve an expedient laboratory synthesis of these valuable molecules. The proposed synthesis depicted in **Scheme 1** would allow for rapid construction of the biologically active *cis*-diastereomer of DHP-containing molecules. The synthetic scheme consists of an initial Mukaiyama aldol reaction to a β,γ-unsaturated aldehyde, which is followed by an intermolecular addition and terminated by an intramolecular silyl-Prins cyclization to afford *cis*-2,6-disubstituted dihydropyrans. One unoptimized example was reported and this product was isolated in good chemical yield and high diastereoselectivity for the *cis*- isomer.



Scheme 1 Proposed sequence for one-pot synthesis of DHP ring systems

The diastereoselectivity of the cyclization reaction is particularly important because only certain diastereomers can be utilized by enzymes found in the human body. In the case of Abruticine 1 (see **Figure 1**), the *cis*- diastereomer is biologically active, whereas the *trans*- is not. Another example of a biologically active cyclic ether, diospongin, can be utilized in both the *cis*- and *trans*- conformations.

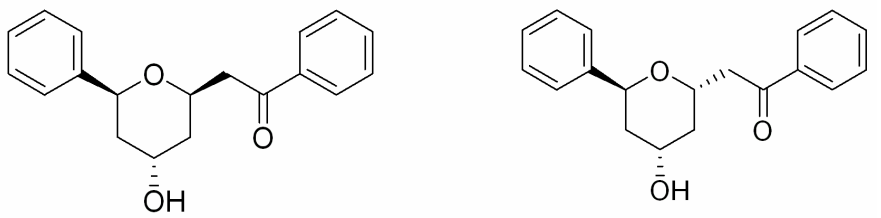


Figure 2 Biologically active diospongin molecules

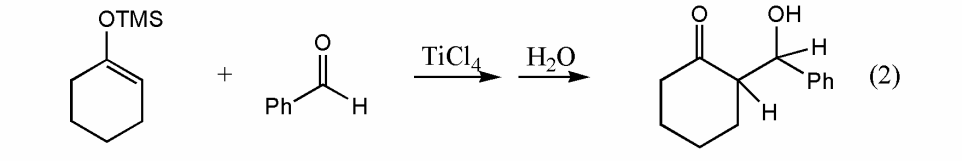
Both conformations of this natural product can be used to fight decay of bone density in those suffering from osteoporosis.[6] Since the body reacts to specific diastereomers, a synthetic scheme producing diastereoselective cyclic ethers is ideal.

This report focuses primarily on the first step of the one-pot, three-component reaction, which creates the intermediate that can be cyclized to form a diastereoselective 2,6-disubstituted DHP ring system. Since the ultimate goal is to eliminate the isolation and purification of the intermediate, as well as increase the

yield of the overall reaction, studies on the yield and purity of the putative aldol adduct are inherent to the synthesis of this class of biologically important molecules.

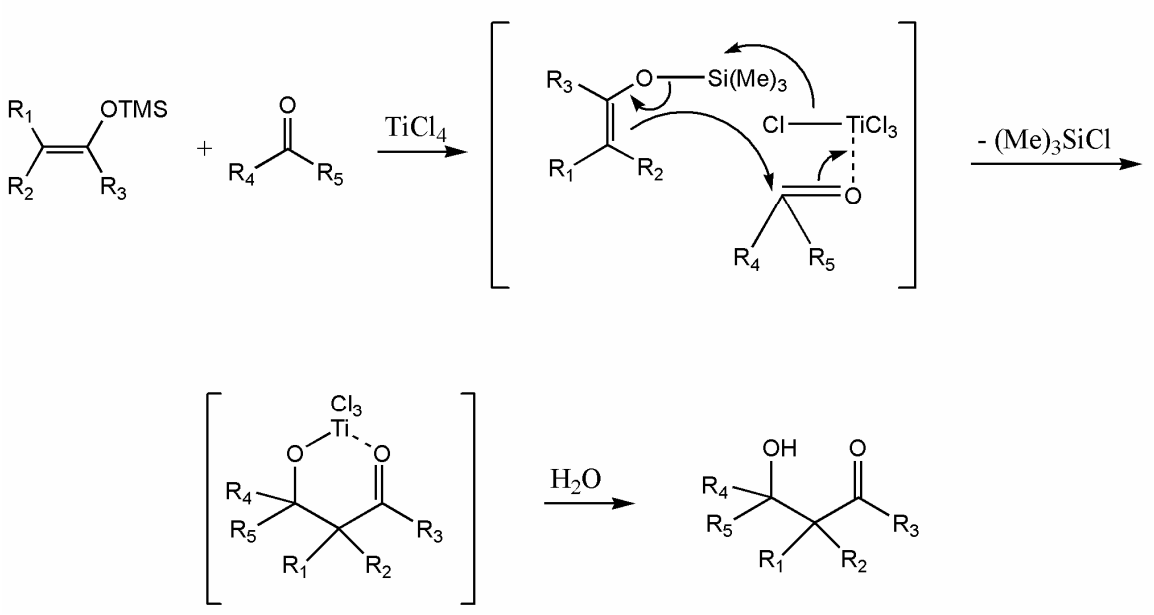
The Mukaiyama Aldol Reaction and Bismuth Catalysis

The first step of the three component, one-pot synthesis can be carried out efficiently using the Mukaiyama aldol reaction, a type of aldol reaction between a trimethylsilyl enol ether of ketones and an aldehyde or ketone catalyzed by a Lewis acid. The archetypal reaction published by Teruki Mukaiyama in 1973 is that of the silyl enol ether of cyclohexanone with benzaldehyde using one equivalent of titanium tetrachloride in dichloromethane at room temperature (**eq 2**).[7]



Equation 2. General Mukaiyama Reaction

Mukaiyama reported that the cross-aldol addition type products were obtained in good yields, and that none of the self-addition or condensation product of ketone or aldehyde was detected. Mukaiyama later reported a generalized mechanism for this reaction (**Scheme 2**).[8]



Scheme 2 Mukaiyama aldol proposed mechanism

Since Mukaiyama's initial report of this reaction, many syntheses of macromolecules have utilized the aldol reaction bearing his name. Yokokawa et al. utilized the diastereoselective Mukaiyama aldol reaction with β–alkoxy aldehyde to construct the tetrahydropyran segment as part of a convergent approach towards synthesis of the marine natural product hennoxazole A, which has been found to be active against herpes simplex virus type 1 and displays peripheral analgesic activity.[9]

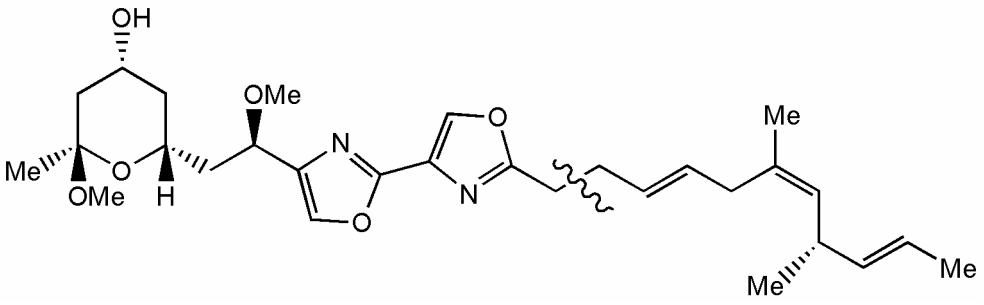
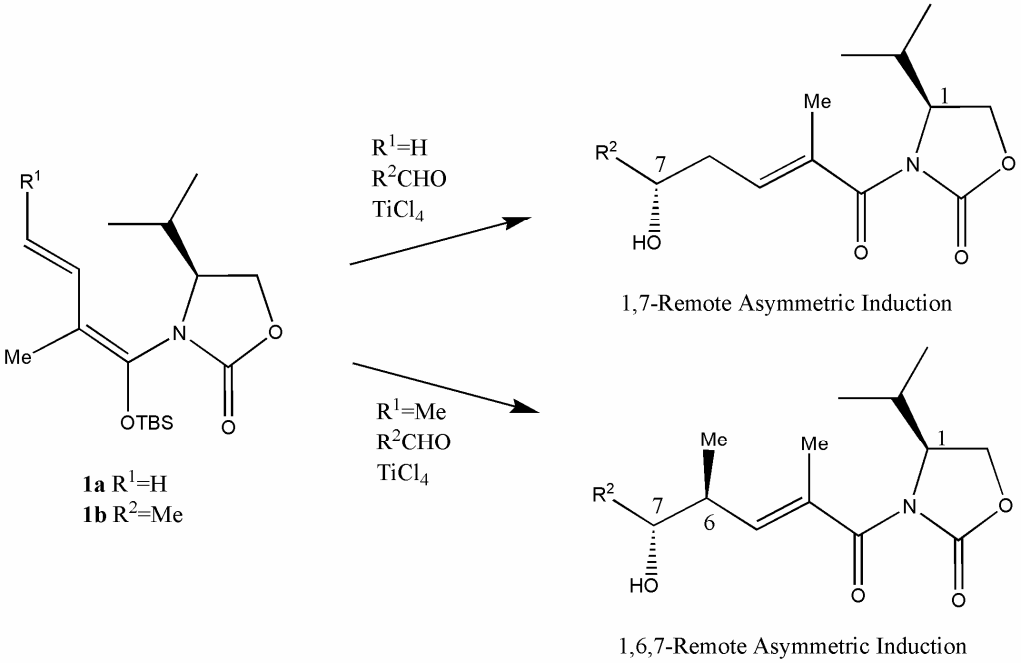


Figure 3 Hennoxazole A

In addition, Kobayashi et al.[10] achieved a convergent total synthesis of khafrefungin on the basis of the highly stereoselective $TiCl_4$-mediated vinylogous Mukaiyama

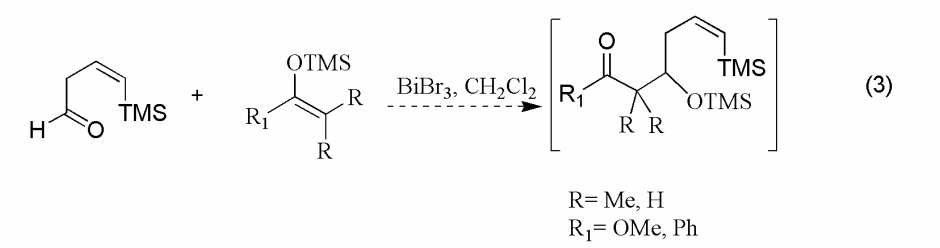
aldol reaction using vinylketene silyl N,O-acetal in conjunction with other methods (**Scheme 3**).



Scheme 3 Remote Asymmetric Induction

Khafrefungin, an antifungal agent cultured by a Merck group in 1997, has a specific biologically active enantiomer and therefore highly benefits from the catalytic enantioselective Mukaiyama aldol reaction.

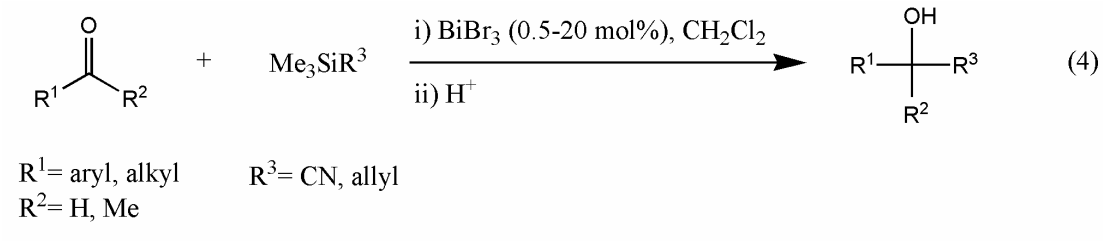
Hinkle et al. used the Mukaiyama aldol reaction to synthesize the intermediate in the three-component reaction to synthesize 2,6 DHP ring systems (**eq 3**).[5]



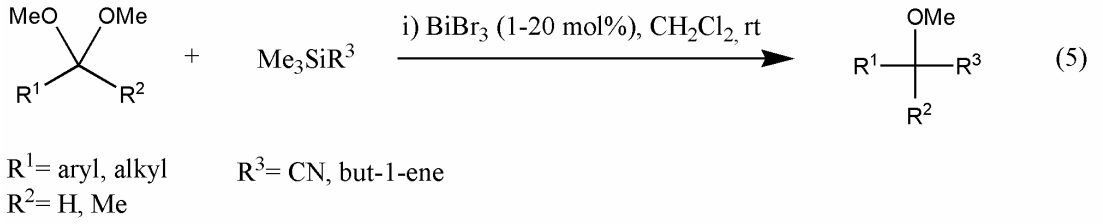
Equation 3. Synthesis of intermediate in three-component reaction

One unique feature of this application is the use of bismuth (III) bromide as the Lewis acid catalyst instead of titanium tetrachloride. The enhancement of organic synthesis using bismuth derivatives has become a widely explored area of chemistry in the past 20 years.[11, 12] Both organic and inorganic bismuth compounds have been increasingly used as catalysts for addition, substitution, and rearrangement reactions. Bismuth, the least toxic of the heavy, non-radioactive main group elements, is also inexpensive and easy to handle. Several bismuth compounds act as Lewis acids, and are desirable in comparison to many commonly used Lewis acids because they work efficiently under milder conditions while still providing high yields. Two commonly used bismuth complexes used in synthetic organic reactions are $BiBr_3$ and $Bi(OTf)_3$. Bismuth (III) bromide has been utilized to synthesize alcohols and ethers, whereas bismuth triflate tends to be used for alkylation, amination, and other reactions involving amines/amides. The many academic and industrial applications of these and other bismuth-catalyzed processes have made bismuth-catalyzed organic synthesis a hot topic of research.

Bismuth bromide is highly efficient and versatile, as it catalyzes a variety of ether-forming reactions. Popular uses for bismuth bromide as a catalyst include cyanation, allylation, and coupling of carbonyl compounds as well as tandem addition/silyl-Prins reactions to 2,6-disubstituted DHPs. Komatsu et al.[13] employed bismuth (III) bromide for the cyanation and allylation of aldehydes, ketones, and acetals with organosilicon reagents (**eqs 4, 5**).



Equation 4. Komatsu et al. cyanation and allylation of aldehydes, ketones

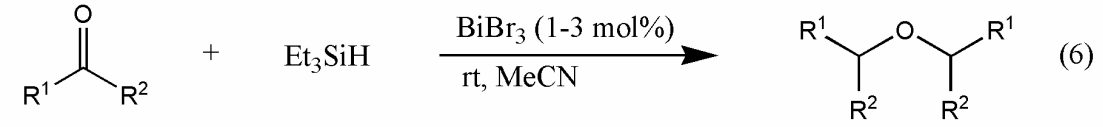


Equation 5. Komatsu et al. cyanation of acetals

Bismuth (III) bromide acted as an efficient catalyst, allowing for short reaction times on the order of one hour and yields up to 90%. The group also attempted to use bismuth trichloride, bismuth triiodide, and antimony trichloride as catalysts for these reactions, but these provided little or less catalytic activity. This shows that bismuth is superior to other metals in its capability as a catalyst in the cyanation and allylation of aldehydes and ketones under the reaction conditions described by Komatsu et al. Bismuth was also compared with previously reported achiral Lewis acid catalysts, such as TMSOTf and TMSI, but the bismuth reagent was found to have the highest activity rate at the lowest cost and was easiest to handle.

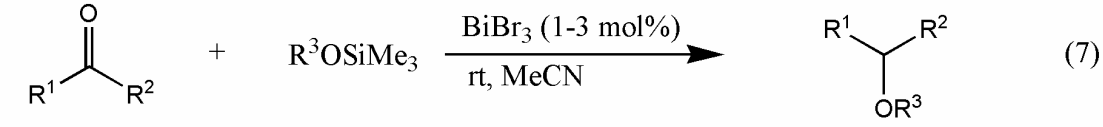
Komatsu et al.[14] also explored bismuth bromide as a catalyst in reductive coupling of carbonyl compounds. Bismuth bromide successfully and efficiently catalyzed reductive homocoupling of carbonyl compounds and heterocoupling of a

carbonyl compound with an alkoxysilane to afford the corresponding symmetrical and unsymmetrical ethers, respectively (**eqs 6, 7**).



R^1= aryl, alkyl
R^2= H, Me, Et, Ph

Equation 6. Komatsu et al. reductive homocoupling of carbonyl compounds

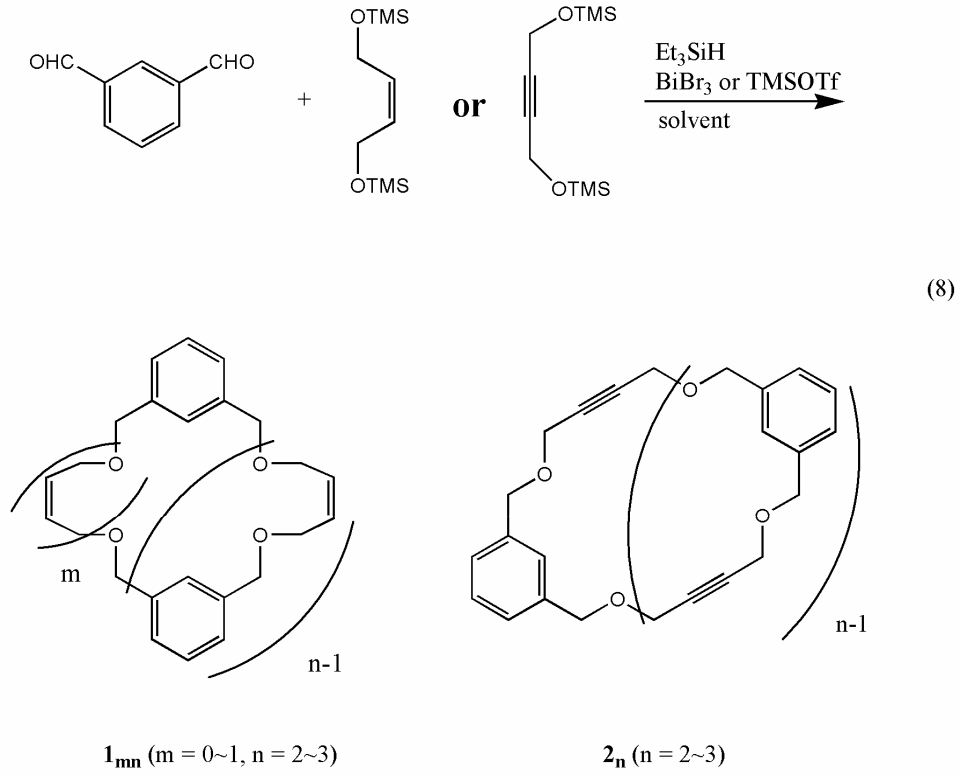


R^1= aryl, alkyl
R^2= H, Me, Et, Ph
R^3= aryl

Equation 7. Komatsu et al. heterocoupling of a carbonyl compound

Only 1-3 mol% of the catalyst was needed for these reactions. With bismuth (III) bromide, the reaction proceeded under non-basic conditions and did not form elimination products, which is an advantage over the classical method for these reactions (the Williamson method). The reaction with bismuth (III) bromide is also advantageous because hindered substrates, such as ketones with bulky R groups, can successfully react, whereas they do not react according to the Williamson method. Acyclic ketones, aliphatic ketones, benzaldehyde, and derivatives of benzaldehyde bearing an electron-withdrawing group at the *ortho* or *para* position afforded the homocoupling products in good to excellent yields (ranging from 83-93%). Benzyl and 2-octyl trimethylsilyl ethers coupled with various aldehydes and acyclic and aliphatic ketones, while acetophenone was unreactive under the same conditions.

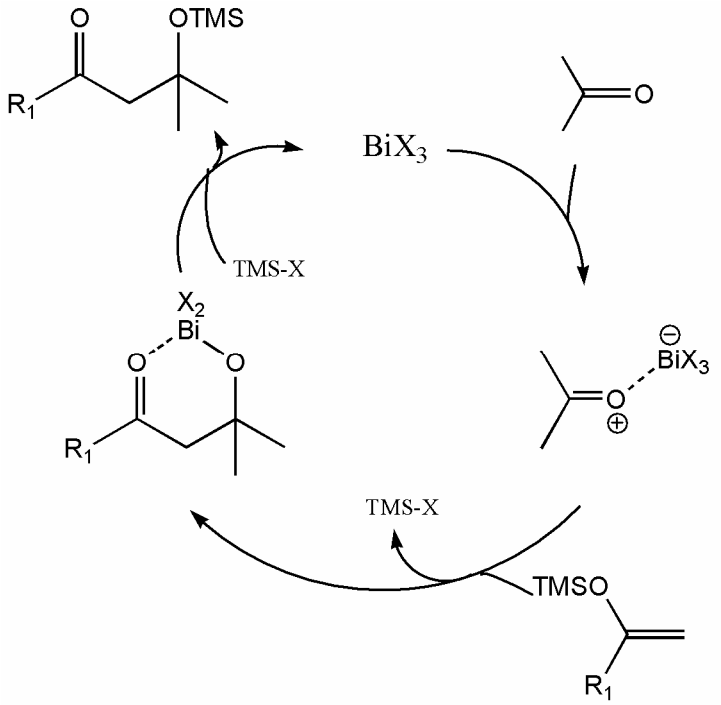
This indicates that bismuth tribromide can discriminate phenyl ketones from acyclic and aliphatic ones, which is a characteristic that other previously reported Lewis acids, such as TMSOTf, do not have. The reductive coupling of carbonyl compounds was extended to preparation of macrocyclic ethers with multiple benzyl allyl or benzyl propargyl ether linkages in a single step (**eq 8**).



Equation 8. Komatsu et al. macrycycle preparation

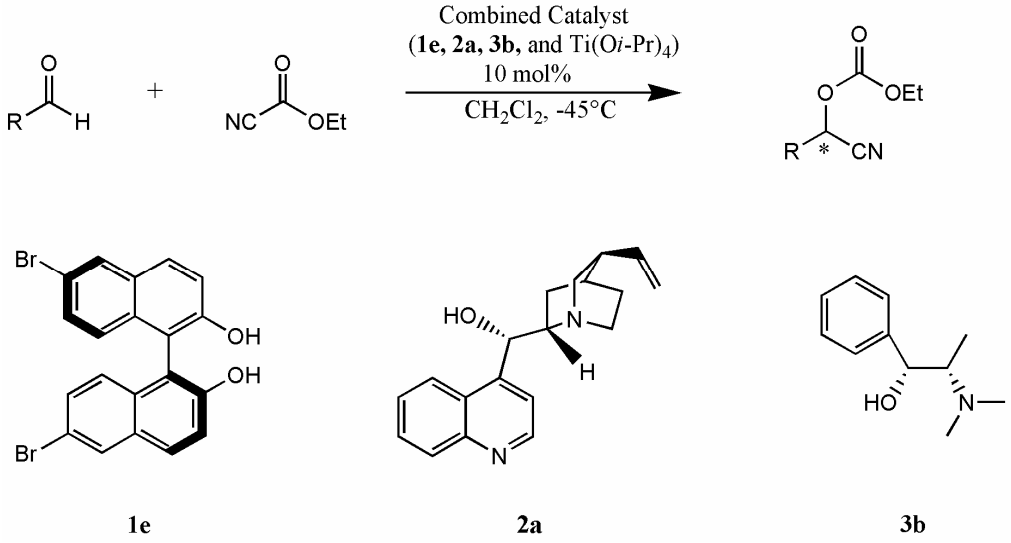
Larger macrocycles were obtained in better yield with bismuth tribromide than with TMSOTf, again showing that $BiBr_3$ is a better catalytic agent than other common Lewis acids. The Komatsu group continues to explore the utility of bismuth bromide-catalyzed reductive carbonyl coupling to synthesize novel crownophanes in a one-pot procedure.

These few examples indicate the wide variety of reactions that bismuth (III) bromide is capable of successfully catalyzing, in many cases better than other, more commonly used Lewis acids that are more difficult to work with. While it is demonstrated that bismuth (III) bromide is an efficient and useful catalyst, the exact role of bismuth is unclear. There are several roles which the bismuth halides could play in these reactions, including the role of a metallic Lewis acid, a progenitor of R_3Si-X, or a progenitor of H-X. If bismuth is acting as a metallic Lewis acid, the mechanism of the Mukaiyama aldol reaction would be that proposed by Mukaiyama (**Scheme 2**). According to **Scheme 2**, the metallic Lewis acid (titanium or bismuth) would activate the carbonyl carbon on the aldehyde or ketone by forming a covalent bond to the corresponding oxygen, forming an oxocarbenium ion. The carbonyl carbon is then susceptible to attack by the nucleophilic silylated ketene acetal. A suggested catalytic cycle for the Mukaiyama aldol reaction catalyzed by bismuth is depicted in **Scheme 4**.[15]



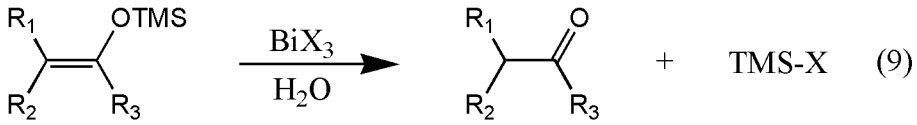
Scheme 4 Catalytic cycle for the aldol reaction catalyzed by the BiX_3-metal iodide system

If bismuth is, in fact, the catalyst, an enantioselective Mukaiyama aldol reaction may be possible by combining BiX_3 with one or multiple diastereomeric species. Feng et al.[16] report a multicomponent bifunctional catalytic system based on a titanium complex to afford efficient enantioselective cyanation of aldehydes (up to 99% ee). The catalyst was readily prepared from tetraisopropyl titanate (Ti(O*i*-Pr)$_4$), (*S*)-6,6′-dibromo-1,1′-bi-2-naphthol (**1e**), cinchonine (**2a**), and (1*R*,2*S*)-(-)-*N*-methylephedrine (**3b**) (**Scheme 5**).



Scheme 5 Feng et al. multicomponent bifunctional catalytic system based on a titanium complex

While the mechanism involving bismuth as a metallic Lewis acid catalyst is viable, there are also publications which claim that R_3Si-X is actually the catalyst. Yamamoto et al.[17] state that Me_3SiX-induced Mukaiyama aldol reaction proceeds through each catalytic cycle under the influence of X^-. This would indicate that the silyl group from a silyl ketene acetal or a silyl enol ether would coordinate to X^- and become the Lewis acid, which would in turn catalyze the Mukaiyama aldol reaction (**eq 9**).



Equation 9. TMS-X as Mukaiyama aldol catalyst

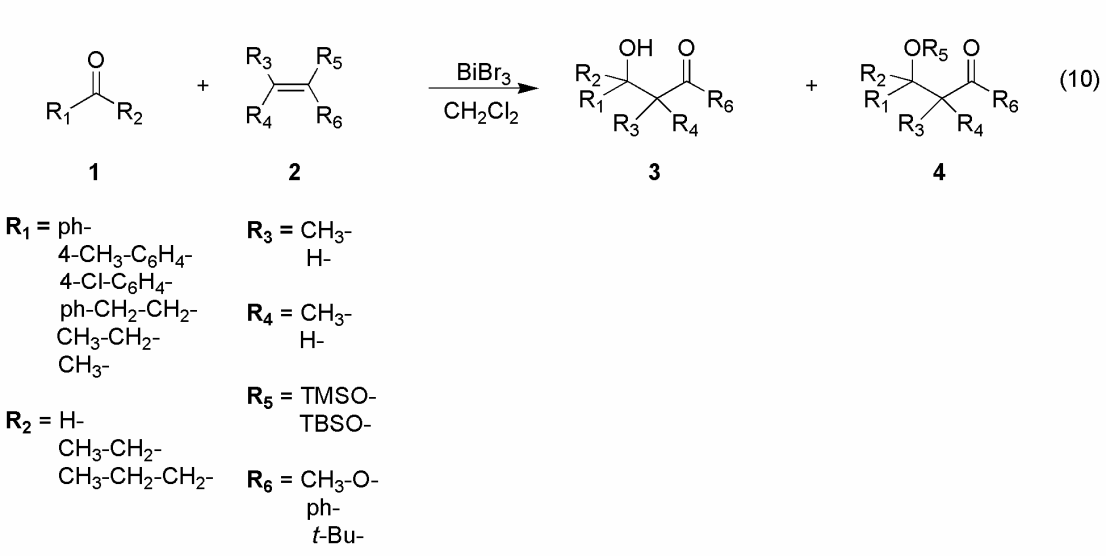
Still another proposed mechanism argues that H-X acts as the actual catalyst of the Mukaiyama aldol reaction. Evans et al. [18] indicate that bismuth (III) salts provide a convenient, inexpensive, and environmentally benign source of the corresponding Brønsted acid. Evans et al. claim that the hydrolysis of bismuth (III)

bromide is known to afford two equivalents of hydrogen bromide and insoluble bismuth oxybromide, and that the former is responsible for the observed catalysis. While the role of bismuth, if any, in the Mukaiyama aldol reaction is not currently understood, bismuth (III) salts do serve as excellent catalysts. Further research needs to be conducted to determine the exact role of bismuth in this and similar reactions.

Both steps of the one-pot, three-component reaction proposed by Hinkle et al. (**Scheme 1**), an initial Mukaiyama aldol reaction to a β,γ-unsaturated aldehyde followed by an intermolecular addition and termination by an intramolecular silyl-Prins cyclization, are catalyzed by bismuth (III) bromide.

Results and Discussion

In order to further understand the mechanism involved with the bismuth (III) bromide catalyst as well as the general nature of the products formed from the Mukaiyama aldol reaction as it pertains to the synthesis of the intermediate of the one-pot, three-component reaction towards 2,6-disubstituted DHP ring systems, we conducted studies using a variety of electrophiles and nucleophiles. Both aldehydes and ketones were used as electrophiles, and ketene acetals as well as enol ethers were used as nucleophiles. The general reaction in **Equation 10** was followed for all reactions described:



Equation 10. General Mukaiyama aldol reaction used for synthesis

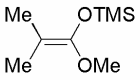
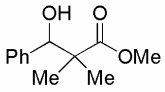
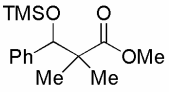
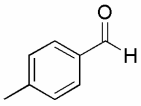
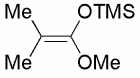
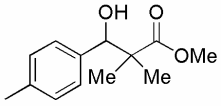
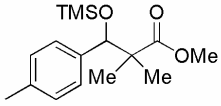
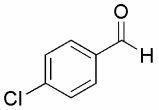
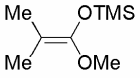
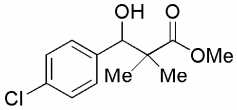
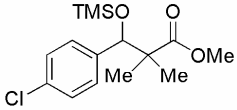
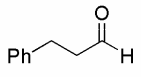
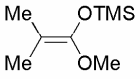
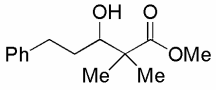
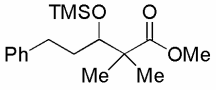
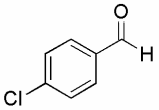
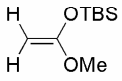
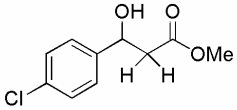
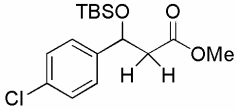
Reactions were generally conducted by weighing $BiBr_3$ (5%) in a clean, dry round bottom flask, which was immediately capped and put under argon pressure. Solvent (methylene chloride) was added via syringe, followed by 1 equivalent of electrophile, **1**, and 2.2 equivalents of nucleophile, **2**. The reaction was then left to stir at room temperature for 30-60 minutes, although TLC indicated that all aldehyde

had been consumed in a matter of seconds. After 30-60 minutes, the solution was concentrated *in vacuo* and then was subject to flash chromatography in chloroform to eliminate the bismuth catalyst. Column chromatography using a mixture of hexanes and ethyl acetate was then carried out to separate the silylated and desilylated aldol products.

In an attempt to determine the kinetic rate of reaction, the reaction was carried out at a temperature of approximately -35 °C. However, the reaction was completed almost instantaneously as indicated by ^{1}H NMR, hindering the ability to monitor the progression of the reaction. To ensure that bismuth (III) bromide was in fact acting as a catalyst, the reaction was also carried out in the absence of bismuth (III) bromide using reagents **1a** and **2a** (see **Table 1**). The yield of this reaction was 3%, indicating that the bismuth (III) bromide does indeed act as a catalyst.

Using the general procedure, the following results were obtained for the addition of silylated ketene acetyls to aldehydes:

Table 1. Mukaiyama aldol type addition: aldehyde reacted with silylated ketene acetal

	Electrophile	Nucleophile	Alcohol Product	Silylated Product	Overall Yield[a,b]
A					
	1a	**2a**	**3aa** (-)	**4aa** (81%)	81%
B					
	1b	**2a**	**3ba** (27%)	**4ba** (58%)	85%
C					
	1c	**2a**	**3ca** (77%)	**4ca** (7%)	84%
D					
	1d	**2a**	**3da** (41%)	**4da** (11%)	52%
E					
	1c	**2b**	**3cb** (12%)	**4cb** (16%)	28%

a Yield based upon isolated materials purified by column chromatography
b Overall yield indicates the combined yields of silylated and desylated aldol products

Of the nucleophiles used, the commercially available β,β-dimethyl ketene silyl acetal **2a** gave highest yields, ranging from 52% to 85%. The result reported in **Table 1** are consistent with the nucleophilicity scales developed by Mayr et al., [19] who defined a set of parameters that describe electrophilicity and nucleophilicity.

According to these parameters, β,β-dimethyl ketene silyl acetal **2a** has an *N* (nucleophilicity parameter) value of 9.49, while β,β-unsubstituted ketene silyl acetals have an *N* value ranging from 4-5. While the origin of *N*, or nucleophilicity parameter, is not fully understood, the introduction of methyl groups at the position of nucleophilic attack leads to an increase of *N*, indicating increased nucleophilicity. This is in accord with the results reported in entry **C** of **Table 1**, where the overall yield obtained with electrophile **1c** and nucleophile **2a,** which contains two methyl groups at the position of electrophilic attack, was 84%. This was much higher than the overall yield reported in entry **E**, 28%, in which β,β-unsubstituted ketene silyl acetal **2b** was used as the nucleophile with the same electrophile, **1c**.

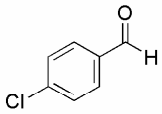
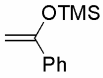
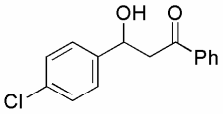
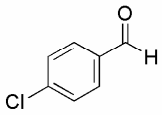
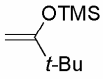
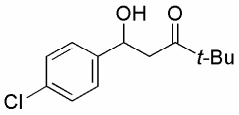
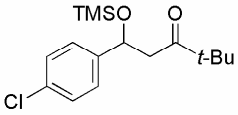
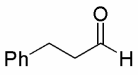
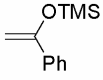
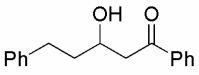
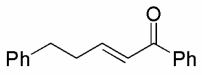
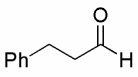
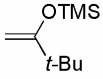
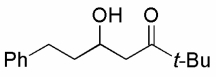
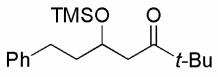
In addition to the nucleophilicity of the silylated ketene acetal, the electrophilicity of the aldehyde also contributed to the overall yield. The phenyl group adjacent to the carbonyl carbon in benzaldehyde (**1a**) can stabilize the putative cation resulting from Lewis acid activation of the carbonyl moiety, making the aldehyde less reactive than one without a highly electron-donating substituent, such as formaldehyde. *p*-Tolualdehyde (**1b**) is comparatively less reactive[19] than benzaldehyde because the methyl group at the *para* position further contributes to the electron donating capability of the aromatic ring on the aldehyde. In contrast to the methyl group on *p*-tolualdehyde, the chlorine on 4-chlorobenzaldehyde (**1c**) is electron withdrawing *via* induction, and therefore destabilizes the oxocarbenium ion slightly. Therefore, 4-chlorobenzaldehyde is more reactive than benzaldehyde. Phenylpropionaldehyde (**1d**) is another example of an aldehyde that is more reactive than benzaldehyde. Since the phenyl group is two carbons away from the

electrophilic carbonyl carbon, it cannot donate electrons *via* resonance. Therefore, phenylpropionaldehyde behaves as an aliphatic aldehyde in its reactivity.

Despite the differences in reactivity of the electrophiles used with nucleophile **2a**, all reactions went to completion and the overall yields were all above 50%, indicating the strong nucleophilicity of **2a**. The yields with aromatic aldehydes, entries **A, B,** and **C** in **Table 1**, were all >80%, while the yield with the aliphatic aldehyde, entry **D**, was markedly lower at 52%. This difference may be due to the fact that the aliphatic electrophiles are more prone to self-addition or condensation as well as elimination reactions, leading to a lower yield of the desired aldol products.

To further explore the Mukaiyama aldol reaction as it pertains to producing an intermediate in good yield towards the synthesis of 2,6-disubstituted DHP ring systems, aldehydes **1c** and **1d** were also reacted with commercially available β,β-saturated silylated enol ethers **2d** and **2e**. The results are shown in **Table 2**.

Table 2. Mukaiyama aldol type addition: aldehyde reacted with silylated enol ether

	Electrophile	Nucleophile	Alcohol Product	Silylated Product	Overall Yield
A				Unidentified Product	
	1c	**2d**	**3cd** (76%)	**4cd** (13%)	89%
B					
	1c	**2e**	**3ce** (54%)	**4ce** (21%)	75%
C					
	1d	**2d**	**3dd** (77%)	**4dd** (-)	77%
D					
	1d	**2e**	**3de** (68%)	**4de** (32%)	100%

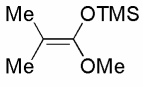
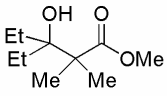
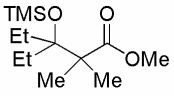
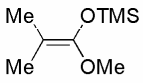
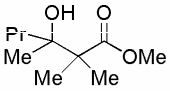
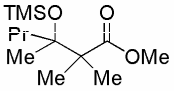
The nucleophiles used in the reactions described in **Table 2**, **2d** and **2e**, have *N* values of 6.66 and 4.47, respectively.[19] Yields with both aromatic electrophile **1c** and aliphatic electrophile **1d** were all >75%, showing no favor towards nucleophile **2d** despite its higher *N* value.

In contrast with entry **E** in **Table 1**, where β,β-unsubstituted ketene silyl acetal gave a very low yield of 28% when reacted with aromatic aldehyde **1c**, entries

A and **B** in **Table 2** indicate that β,β-unsubstituted silyl enol ethers give yields >75% when reacted with **1c**. This calls attention to the discrepancy between ketene acetals and enol ethers. The –OMe group present on the ketene silyl acetal may make the β-carbon more basic than that on the silylated enol ether, thus making the enol ether more prone to initiating undesired aldol reactions.

Finally, in an effort to continue exploration of the Mukaiyama aldol reaction, ketones were utilized as the electrophile instead of aldehydes. The results are indicated in **Table 3**.

Table 3. Mukaiyama aldol type addition: ketone reacted with silylated ketene acetal

	Electrophile	Nucleophile	Alcohol Product	Silylated Product	Overall Yield
A					
	1e	**2a**	**3ea** (4%)	**4ea** (75%)	79%
B					
	1f	**2a**	**3fa** (7%)	**4fa** (53%)	60%

Since ketones are generally less reactive than aldehydes due to increased steric hindrance as well as increased electron density donation from the two R groups adjacent to the carbonyl carbon, a lower overall yield for reactions using a ketone as the electrophile using the same nucleophile (**2a**) would be expected compared to the reactions using an aldehyde as the electrophile. The data reported in **Table 1** and **Table 3** is consistent with this fact, as the overall yields for reactions using aldehydes

with nucleophile **2a** were mostly above 80%, whereas the overall yields for reactions using ketones with nucleophile **2a** were 60% and 79%. However, the reaction between aldehyde **1d** and **2a**, giving a 52% yield, is lower than both reactions using ketones, encouraging further investigation.

Shibasaki et al.[20] conducted studies on the Mukaiyama aldol reaction similar to those shown in **Figure 3** using ketones as electrophiles. Shibasaki et al. described reactions using a variety of ketones, including those with an electron donating group such as phenyl adjacent to the carbonyl carbon, with β,β-dimethyl ketene silyl acetal **2a**, and reported all yields >90%. Instead of using a bismuth compound as a catalyst, CuCl-TBAT (tetrabutylammoniumtriphenyldifluorosilicate) was used. Similar to the $BiBr_3$-catalyzed Mukaiyama aldol reaction, the detailed reaction mechanism involving the copper catalyst is not clear. However, Shibasaki et al. propose that the initial generation of copper fluoride from CuCl and TBAT induces a dynamic ligand exchange between silicon and copper atoms, which appears to be the key for generation of a highly active copper enolate nucleophile. Shibasaki et al. continue to conduct detailed mechanistic studies of the CuCl-TBAT-catalyzed Mukaiyama aldol reaction.

While all three series of reactions described in **Table 1, Table 2,** and **Table 3** show little to no consistency with respect to the ratio of isolated β-hydroxy:β-siloxy products (e.g., **Table 1**, **3aa:4aa**), studies using gas chromatography/mass spectrometry before separation of products *via* silica gel chromatography indicate that the silica gel interacts with the products and alters this ratio (**Table 4**).

Table 4. Alcohol:silylsted product ratios before and after column chromatography

Molecules/mixtures	Alcohol:Silylated product ratio before column chromatography	Alcohol:Silylated product ratio before column chromatography
3ca, 4ca	2.72:1	5.67:1
3da, 4da	1.46:1	3.73:1

In both cases studied, there was more alcohol product after column chromatography. This is likely due to an interaction between the trimethylsilyl group and the silica gel. Since the trimethylsilylated product is desired as the intermediate for the one-pot, three component reaction, this is a significant finding and will be explored further.

Initial studies were also conducted on the optimization of the ratio of electrophile to nucleophile used in the Mukaiyama aldol reaction. While the general procedure indicates 1 equivalent of electrophile and 2.2 equivalents of nucleophile, some reactions were found to proceed to completion (as indicate by the absence of an aldehydic peak on ^{1}H NMR spectra) with comparable yields using a smaller amount of the nucleophile. The reaction to produce the mixture of **3da** and **4da** (**Table 1**) required only 1.4 equivalents of the nucleophile **2a** with 1.0 equivalent of **1d**. In addition, only 1.3 equivalents of nucleophile **2d** was required to react with 1.0 equivalent of **1d** to afford **3dd**, and 1.2 equivalents of nucleophile **2e** was required to react with 1.0 equivalent of **1d** to afford a mixture of **3de** and **4de**. **Table 5** summarizes these findings.

Table 5. Relative equivalents of electrophile, nucleophile to afford certain molecules/mixtures

Molecules/mixtures produced	Electrophile; relative equivalents	Nucleophile; relative equivalents
3da, 4da	**1d**, 1.0 eq	**2a**, 1.4 eq
3dd	**1d**, 1.0 eq	**2d**, 1.3 eq
3de, 4de	**1d**, 1.0 eq	**2e**, 1.2 eq

Reducing the amount of starting material would prevent waste as well as contamination of the product and allow for a more efficient three-component, one-pot reaction shown in **Scheme 1**. Further studies to optimize the relative equivalents of electrophile to nucleophile will be necessary in order to maximize yields in this reaction.

Future Directions

Both steps of the one-pot, three-component reaction devised by Hinkle et al. (**Scheme 1**), the Mukaiyama aldol reaction and the tandem addition/silyl-Prins reaction, are currently being explored. While bismuth (III) bromide catalyzes the Mukaiyama aldol reaction as indicated by >80% yield in the presence of the catalyst compared to the 3% yield of the same reaction in the absence of the catalyst (the reaction between **1a** and **2a**), the mechanism of the reaction is not clear. Further kinetic studies by slowing the reaction *via* temperature and reagent addition control may help to determine the mechanism, but are beyond the scope of this paper. In addition, carrying out the reaction in the presence of a strong base to eliminate the possibility of a Brønsted acid-catalyzed reaction should be conducted to determine whether the catalytic cycle involves a Brønsted acid or a Lewis acid.

In addition, the utilization of the Mukaiyama aldol reaction product as a viable intermediate in the subsequent tandem addition/silyl-Prins reaction needs to be further investigated. While **eq 1** indicates that a reactant similar to the Mukaiyama aldol product can successfully afford 2,6-disubstituted DHPs, studies using the exact product of the Mukaiyama aldol reaction as the reagent in the tandem addition/silyl-Prins reaction will need to be optimized.

Conclusions

Bismuth (III) bromide proves to be a convenient, inexpensive, and environmentally benign catalyst for both reactions involved in the devised one-pot, three-component synthetic scheme devised by Hinkle et al., which are the Mukaiyama aldol and the tandem addition/silyl-Prins reactions. While BiX_3 is a viable metallic Lewis acid catalyst, further exploration of the true catalytic cycle will provide further insight into whether bismuth derivatives can ultimately be used to produce enantioselective aldol products.

The choice of both electrophile and nucleophile is important role to the yield of the Mukaiyama aldol reaction. β,β-Disubstituted ketene silyl acetals tend to give highest yields with aromatic as opposed to aliphatic aldehydes, while β,β-unsubstituted silylated enol ethers give high yields with both aliphatic and aromatic aldehydes. β,β-Disubstituted ketene silyl acetals also react efficiently with ketones to form the desired aldol product in good yield.

The synthesis of 2,6-disubstituted dihydropyran ring systems is vital to the large scale production of a variety of anti-fungal, anti-osteoporosis, and anti-cancer agents, among others. Given the efficiency of the bismuth-initiated Mukaiyama aldol reaction, the one-pot, three-component reaction proposed by Hinkle al. proves to be a viable synthetic scheme towards these biologically active molecules.

Experimental Section

General Methods

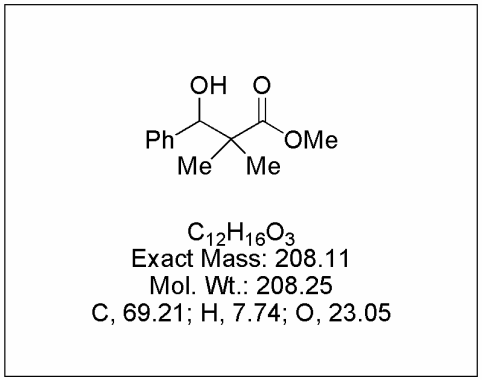
All reagents were used as received unless otherwise noted. Dichloromethane and acetonitrile were distilled from CaH_2.

NMR spectra were recorded using a Varian Mercury 400 MHz instrument. ^{13}C NMR spectra were recorded with the aid of an ATP sequence in which methylene and quaternary carbons = e (even) and methyl and methane carbons = o (odd). All ^{1}H NMR spectra are referenced according to a chloroform peak at 7.27 ppm and all ^{13}C H NMR are referenced to the chloroform triplet at 77.23 ppm. Complex coupling constants were calculated according to the method of Hoye.

General Procedure for Aldol Reactions:

All reactions were performed under anhydrous conditions and under argon gas pressure at room temperature. $BiBr_3$ or $Bi(OTf)_3$ was added to an oven-dried round bottom flask equipped with a stir bar. Distilled solvent was added *via* syringe, followed by the addition of the aldehyde or ketone stubstrate. Finally, the silyl ketene acetal or silyl enol ether was added rapidly *via* syringe.

Methyl 3-hydroxy-2,2-dimethyl-3-phenylpropanoate (3aa):

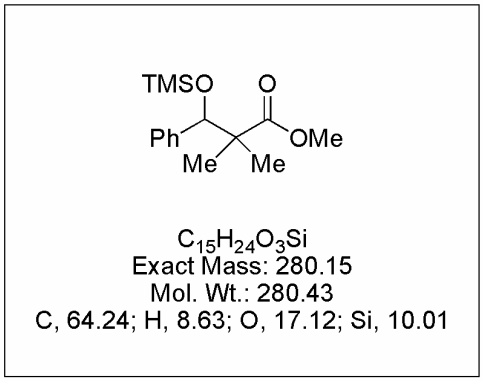


This compound was prepared following the general procedure using $Bi(OTf)_3$ (0.062 g, 0.094 mmol, 0.15 eq), CH_2Cl_2 (2.0 mL), C_6H_5CHO (0.096 mL,

0.942 mmol, 1.0 eq), $(CH_3)_2C=C(OSiMe_3)OMe$ (0.229 mL, 1.304 mmol, 1.2 eq), and (R)-(+)-2-methyl-CBS-oxazaborolidine (0.026 g, 0.094 mmol, 0.1 eq). The solution was stirred for 30 minutes and subsequently purified in a silica gel plug using $MeCl_2$. The crude product was purified by column chromatography (8:2 Hexanes:EtOAc, R_f=0.25 in 8:2 Hexanes:EtOAc). The fractions were concentrated *in vacuo* to afford 0.047 g white solid, 24% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29-7.34 (m, 5H), 4.91 (d, *J* = 4.4, 1H), 3.72 (s, 3H), 3.04 (d, *J* = 4.03, 1H), 1.15 (s, 3H), 1.19 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.0(e), 127.9(o), 127.8(o), 88.3(o, 78.9(o), 66.0(e), 52.4(o), 48.0(e), 23.5(o), 19.4(o).

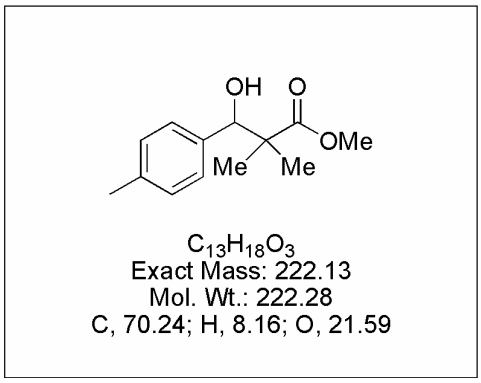
Methyl 3-phenyl-2,2-dimethyl-3-trimethylsiloxypropanoate (4aa):



This compound was prepared following the general procedure using $BiBr_3$ (0.095 g, 0.212 mmol, 0.151 eq), CH_2Cl_2 (4.0 mL), C_6H_5CHO (0.14 mL, 1.4 mmol, 1.0 eq), and $(CH_3)_2C=C(OSiMe_3)OMe$ (0.63 mL, 3.1 mmol, 2.2 eq). The solution was stirred for 30 minutes and subsequently purified in a silica gel plug using $MeCl_2$. The crude product was purified by column chromatography (95:5 Hexanes:EtOAc, R_f=0.33 in 95:5 Hexanes:EtOAc). The fractions were concentrated *in vacuo* to afford 0.316 g colorless oil, 80% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31-7.33 (m, 5H), 5.02 (s, 1H), 3.72 (s, 3H), 1.17 (s, 3H), 1.04 (s, 3H), 0.005 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.3(e), 140.8(e), 127.9(o), 127.5(o), 127.4(o), 79.3(o), 52.0(o), 49.3(e), 22.1(o), 19.4(o), 0.4(o).

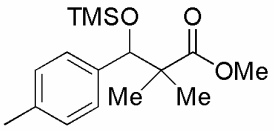
Methyl 3-hydroxy-2,2-dimethyl-3-*p*-tolylpropanoate (3ba):



This compound was prepared following the general procedure using $BiBr_3$ (0.031 g, 0.068 mmol, 0.1 eq), CH_2Cl_2 (2.0 mL), *p*-tolualdehyde (0.081 mL, 0.680 mmol, 1.0 eq), and $(CH_3)_2C{=}C(OSiMe_3)OMe$ (0.304 mL, 1.495 mmol, 2.2 eq). The solution was stirred for 30 minutes and subsequently purified in a silica gel plug using $MeCl_2$. The crude product was purified by column chromatography using gradient elution (9:1, 8:2 Hexanes:EtOAc, R_f=0.1 in 9:1 Hexanes:EtOAc). The fractions were concentrated *in vacuo* to afford 0.040 g white solid, 26% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.12-7.20 (aparent doublet d, 4H), 4.87 (d, J = 4.4, 1H), 3.72 (s, 3H), 2.96 (d, J = 5.5, 1H), 2.34 (s, 3H), 1.41 (s, 3H), 1.11 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.5(e), 137.0(e), 128.6(o), 127.6(o), 78.8(o), 52.4(o), 48.0(e), 23.4(o), 21.5(o), 19.4(o).

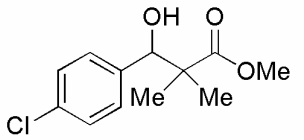
Methyl 3-*p*-tolyl-2,2-dimethyl-3-trimethylsiloxypropanoate (4ba):



$C_{16}H_{26}O_3Si$
Exact Mass: 294.17
Mol. Wt.: 294.46
C, 65.26; H, 8.90; O, 16.30; Si, 9.54

Exact procedure for **3ba** followed to afford 0.116 g white solid, 58% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.10-7.16 (aparent doublet d, 4H), 4.94 (s, 1H), 3.67 (s, 3H), 2.33 (s, 3H), 1.12 (s, 3H), 0.99 (s, 3H), 0.34 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.5(e), 137.0(e), 128.6(o), 127.6(o), 78.8(o), 52.4(o), 48.0(e), 23.4(o), 21.5(o), 19.4(o).

Methyl 3-(4-chlorophenyl)-3-hydroxy-2,2-dimethylpropanoate (3ca):



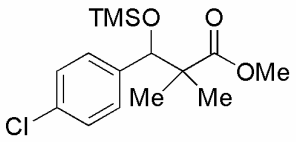
$C_{12}H_{15}ClO_3$
Exact Mass: 242.07
Mol. Wt.: 242.7
C, 59.39; H, 6.23; Cl, 14.61; O, 19.78

This compound was prepared following the general procedure using $BiBr_3$ (0.049 g, 0.109 mmol, 0.1 eq), CH_2Cl_2 (2.5 mL), 4-chlorobenzaldehyde (0.15 mL, 1.092 mmol, 1.0 eq), and $(CH_3)_2C{=}C(OSiMe_3)OMe$ (0.488 mL, 2.402 mmol, 2.2 eq). The solution was stirred for 30 minutes and subsequently purified in a silica gel plug using $MeCl_2$. The crude product was purified by column chromatography using gradient elution (9:1, 8:2 Hexanes:EtOAc). The fractions were concentrated *in vacuo* to afford 0.205 g white solid, 77% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21-7.30 (aparent doublet d, 4H), 4.86 (d, J = 4.0, 1H), 3.71 (s, 3H), 3.24 (d, J = 4.0, 1H), 1.12 (s, 3H), 1.09 (s, 3H); ^{13}C NMR (100

MHz, $CDCl_3$) δ 178.0(e), 138.5(e), 133.6(e), 129.1(o), 128.0(o), 78.1(o), 52.5(o), 47.9(e), 23.2(o), 19.3(o).

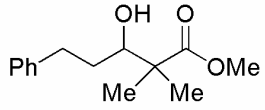
Methyl 3-(4-chlorophenyl)-2,2-dimethyl-3-trimethylsiloxypropanoate (4ca):



$C_{15}H_{23}ClO_3Si$
Exact Mass: 314.11
Mol. Wt.: 314.88
C, 57.22; H, 7.36; Cl, 11.26; O, 15.24; Si, 8.92

Exact procedure for **3ca** followed to afford 0.022 g colorless oil, 7% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24-7.30 (aparent doublet d, 4H), 3.71 (s, 3H), 2.22 (s, 1H), 1.15 (s, 3H), 1.02 (s, 3H), 0.00 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.0(e), 139.5(e), 133.2(e), 129.1(o), 127.8(o), 78.7(o), 52.0(o), 49.2(e), 21.8(o), 19.6(o), 0.3(o).

Methyl 3-hydroxy-2,2-dimethyl-5-phenylpentanoate (3da):

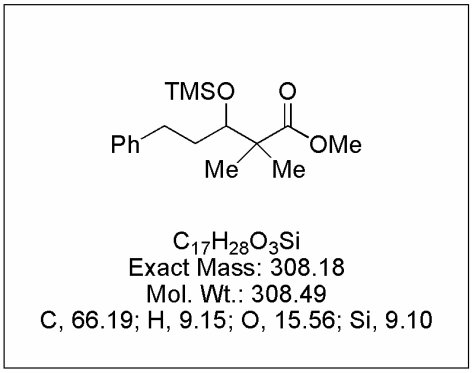


$C_{14}H_{20}O_3$
Exact Mass: 236.14
Mol. Wt.: 236.31
C, 71.16; H, 8.53; O, 20.31

This compound was prepared following the general procedure using $BiBr_3$ (0.069 g, 0.155 mmol, 0.1 eq), CH_2Cl_2 (5.0 mL), 3-phenylpropionaldehyde (0.208 g, 1.549 mmol, 1.0 eq), and $(CH_3)_2C{=}C(OSiMe_3)OMe$ (0.378 mL, 2.168 mmol, 1.4 eq). The solution was stirred for 30 minutes and subsequently purified in a silica gel plug using $MeCl_2$. The crude product was purified by column chromatography using gradient elution (95:5, 9:1, 8:2 Hexanes:EtOAc). The fractions were concentrated *in vacuo* to afford 0.149 g colorless oil, 41% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20-7.29 (m, 5H), 3.69 (s, 3H), 3.59-3.64 (m, 1H), 2.92-2.99 (m, 1H), 2.61-2.69 (m, 1H), 2.57 (d, 1H), 1.72-1.80 (m, 1H), 1.55-1.65 (m, 1H), 1.84 (s, 3H), 1.16 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.0(e), 142.2(e), 128.6(o), 128.5(o), 125.9(o), 76.3(o), 52.2(o), 47.4(e), 33.9(e), 33.3(e), 22.9(o), 20.7(o).

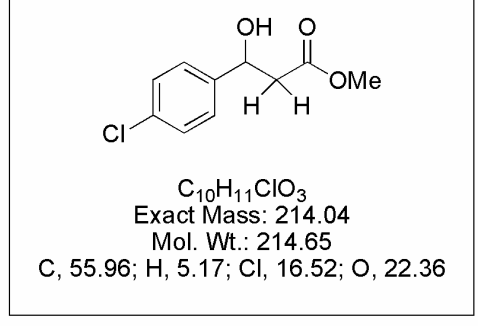
Methyl 5-phenyl-2,2-dimethyl-3-trimethylsilyloxypropanoate (4da):



$C_{17}H_{28}O_3Si$
Exact Mass: 308.18
Mol. Wt.: 308.49
C, 66.19; H, 9.15; O, 15.56; Si, 9.10

Exact procedure for **3da** followed to afford 0.054 g colorless oil, 11% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27-7.28 (m, 2H), 7.17-7.19 (m, 3H), 3.96-3.99 (m, 1H), 3.65 (s, 3H), 2.74-2.85 (m, 1H), 2.44-2.52 (m, 1H), 1.62-1.68 (m, 2H), 1.16 (s, 3H), 1.09 (s, 3H), 0.15 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.6(e), 142.3(e), 128.5(o), 128.4(o), 125.9(o), 77.7(o), 52.0(o), 48.5(e), 35.4(e), 33.9(e), 21.8(o), 20.7(o), 1.3(o).

Methyl 3-(4-chlorophenyl)-3-hydroxypropanoate (3cb):



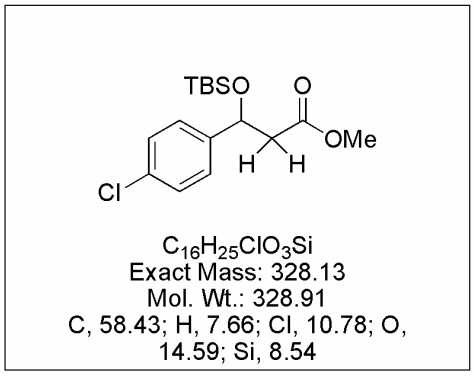
$C_{10}H_{11}ClO_3$
Exact Mass: 214.04
Mol. Wt.: 214.65
C, 55.96; H, 5.17; Cl, 16.52; O, 22.36

This compound was prepared following the general procedure using $BiBr_3$ (0.066 g, 0.148 mmol, 0.1 eq), CH_2Cl_2 (5.0 mL), 4-chlorobenzaldehyde (0.208 mL, 1.478 mmol, 1.0 eq), and 1-(*tert*-butyldimethlsilyloxy)-1-methoxyethene (0.710 mL, 3.252 mmol, 2.2 eq). The solution was stirred for 60 minutes and

subsequently purified in a silica gel plug using $MeCl_2$. The crude product was purified by column chromatography (9:1 Hexanes:EtOAc). The fractions were concentrated *in vacuo* to afford 0.038 g orange oil, 12% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27-7.35 (m, 4H), 5.11-5.14 (m, 1H), 3.74 (s, 3H), 3.32 (s, 1H), 2.71-2.74 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.6(e), 141.0(e), 133.6(e), 128.8(o), 127.1(o), 69.9(o), 52.3(o), 43.3(e).

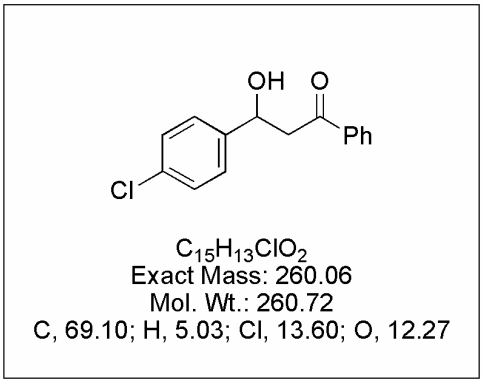
Methyl 3-(4-chlorophenyl)-3-*tert*-butyldimethylsiloxypropanoate (4cb):



$C_{16}H_{25}ClO_3Si$
Exact Mass: 328.13
Mol. Wt.: 328.91
C, 58.43; H, 7.66; Cl, 10.78; O, 14.59; Si, 8.54

Exact procedure for **3cb** followed to afford 0.068 g colorless oil, 16 % yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29-7.32 (m, 4H), 5.24 (dd, *J* = 9.2, 4.4, 1H), 3.68 (s, 3H), 2.71 (dd, *J* = 14.7, 9.2, 1H), 2.53 (dd, *J* = 16.6, 4.0, 1H), 0.85 (s, 9H), 0.01 (s, 3H), -0.16 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.0(o), 171.3(e), 142.7(e), 133.2(e), 128.6(o), 127.3(o), 71.8(o), 51.9(o), 46.5(e), 26.0(o), 18.4(e).

3-(4-chlorophenyl)-3-hydroxy-1-phenylpropan-1-one (3cd):



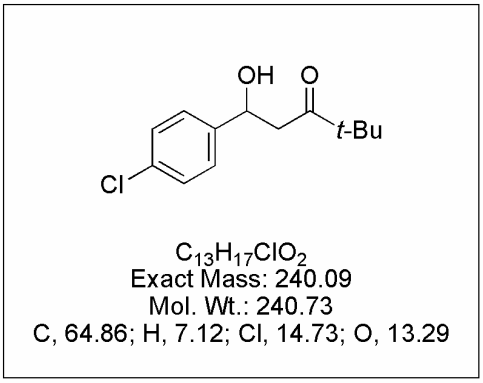
$C_{15}H_{13}ClO_2$
Exact Mass: 260.06
Mol. Wt.: 260.72
C, 69.10; H, 5.03; Cl, 13.60; O, 12.27

This compound was prepared following the general procedure using $BiBr_3$ (0.068 g, 0.15 mmol, 0.1 eq), CH_2Cl_2 (5.0 mL), 4-chlorobenzaldehyde (0.212 g, 1.50 mmol, 1.0 eq), and 1-phenyl-1-(trimethylsiloxy)ethylene (0.683 g, 3.30

mmol, 2.2 eq). The solution was stirred for 30 minutes and subsequently purified in a silica gel plug using $MeCl_2$. The crude product was purified by column chromatography (9:1 Hexanes:EtOAc). The fractions were concentrated *in vacuo* to afford 0.296 g white solid, 76% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, *J* = 7.323, 2H), 7.59-7.63 (m, 1H), 7.47-7.51 (m, 2H), 7.35-7.41 (m, 4H), 5.32-5.36 (m, 1H), 3.66 (s, 1H), 3.34-3.36 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.9(e), 141.5(e), 136.4(e), 133.9(o), 133.4(e), 128.8(o), 128.7(o), 128.2(o), 127.2(o), 69.6(o), 47.5(e).

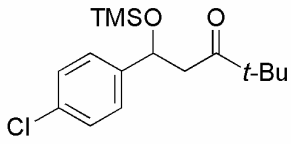
1-(4-chlorophenyl)-1-hydroxy-4,4-dimethylpentan-3-one (3ce):



This compound was prepared following the general procedure using $BiBr_3$ (0.070 g, 0.156 mmol, 0.1 eq), CH_2Cl_2 (5.0 mL), 4-chlorobenzaldehyde (0.219 g, 1.56 mmol, 1.0 eq), and (2,2-dimethyl-1-methylene-propoxy) trimethylsilane (0.742 mL, 3.43 mmol, 2.2 eq). The solution was stirred for 60 minutes and subsequently purified in a silica gel plug using $MeCl_2$. The crude product was purified by column chromatography using gradient elution (95:5, 9:1 Hexanes:EtOAc). The fractions were concentrated *in vacuo* to afford 0.201 g white solid, 54% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (s, 4H), 5.08-5.12 (m, 1H), 3.63-3.64 (m, 1H), 2.83-2.85 (m, 1H), 1.13 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.0(o), 141.6(e), 133.3(e), 128.7(o), 127.2(o), 69.7(o), 45.6(e), 44.7(e), 26.5(o).

1-(4-chlorophenyl)-4,4-dimethyl-1-trimethylsiloxypentan-3-one (4ce):

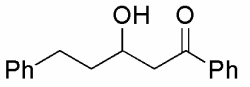


$C_{16}H_{25}ClO_2Si$
Exact Mass: 312.13
Mol. Wt.: 312.91
C, 61.41; H, 8.05; Cl, 11.33; O, 10.23; Si, 8.98

Exact procedure followed for **3ce** to afford 0.103 g colorless oil, 21% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (s, 4H), 5.23-5.26 (m, 1H), 3.01-3.08 (m, 1H), 2.46-2.52 (m, 1H), 1.07 (s, 9H), 0.00 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.8(e), 143.5(e), 132.8(e), 128.5(o), 127.2(o), 70.7(o), 48.0(e), 44.4(e), 26.1(o), 0.4(o).

3-hydroxy-1,5-diphenylpentan-1-one (3dd):



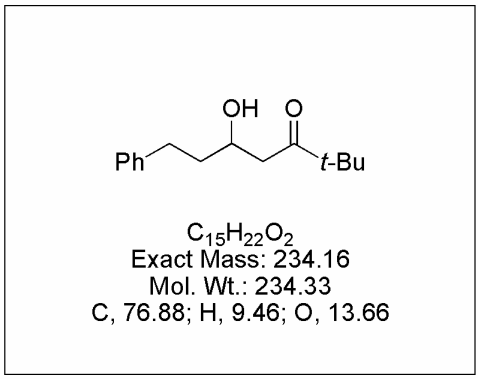
$C_{17}H_{18}O_2$
Exact Mass: 254.13
Mol. Wt.: 254.32
C, 80.28; H, 7.13; O, 12.58

This compound was prepared following the general procedure using $BiBr_3$ (0.064 g, 0.143 mmol, 0.1 eq), CH_2Cl_2 (5.0 mL), 3-phenylpropionaldehyde (0.193 g, 1.44 mmol, 1.0 eq), and 1-phenyl-1-(trimethylsiloxy)ethylene (0.359 mL, 1.87 mmol, 1.3 eq). The solution was stirred for 60 minutes and subsequently purified in a silica gel plug using $MeCl_2$. The crude product was purified by column chromatography (9:1 Hexanes:EtOAc). The fractions were concentrated *in vacuo* to afford 0.282 g colorless oil, 77% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92-7.95 (m, 2H), 7.56-7.60 (m, 1H), 7.45-7.49 (m, 2H), 7.17-7.31 (m, 5H), 4.21-4.27 (m, 1H), 3.33-3.36 (m, 1H), 3.04-3.20 (m, 2H), 2.86-2.93 (m, 1H), 2.72-2.80 (m, 1H), 1.91-1.99 (m, 1H), 1.77-1.85 (m, 1H); ^{13}C

NMR (100 MHz, $CDCl_3$) δ 142.0(e), 136.8(e), 133.7(o), 128.8(o), 128.6(o), 128.5(o), 128.1(o), 126.0(o), 67.3(o), 45.3(e), 38.4(e), 32.2(e).

5-hydroxy-2,2-dimethyl-7-phenylheptan-3-one (3de):

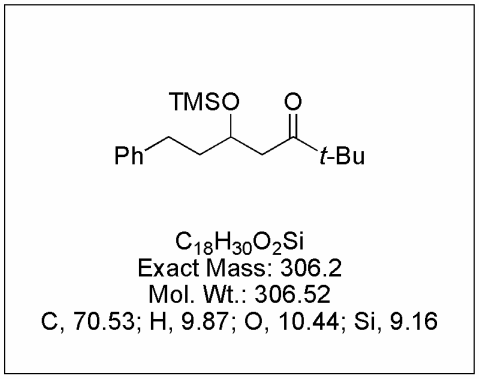


$C_{15}H_{22}O_2$
Exact Mass: 234.16
Mol. Wt.: 234.33
C, 76.88; H, 9.46; O, 13.66

This compound was prepared following the general procedure using $BiBr_3$ (0.074 g, 0.165 mmol, 0.1 eq), CH_2Cl_2 (5.0 mL), 3-phenylpropionaldehyde (0.221 g, 1.65 mmol, 1.0 eq), and (2,2-dimethyl-1-methylene-propoxy) trimethylsilane (0.341 mL, 1.98 mmol, 1.2 eq). The solution was stirred for 60 minutes and subsequently purified in a silica gel plug using $MeCl_2$. The crude product was purified by column chromatography using gradient elution (9:1, 8:2 Hexanes:EtOAc). The fractions were concentrated *in vacuo* to afford 0.097 g colorless oil, 68% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26-7.30 (m, 2H), 7.18-7.21 (m, 3H), 4.01 (s, 1H), 3.37 (s, 1H), 2.80-2.87 (m, 1H), 2.64-2.73 (m, 2H), 2.53-2.60 (m, 1H), 1.79-1.88 (m, 1H), 1.66-1.73 (m, 1H), 1.13 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.0(e), 128.5(o), 128.4(o), 125.9(o), 67.3(o), 44.6(e), 43.4(e), 38.3(e), 32.1(e), 26.6(o).

2,2-dimethyl-7-phenyl-5-trimethylsiloxyheptan-3-one (4de):



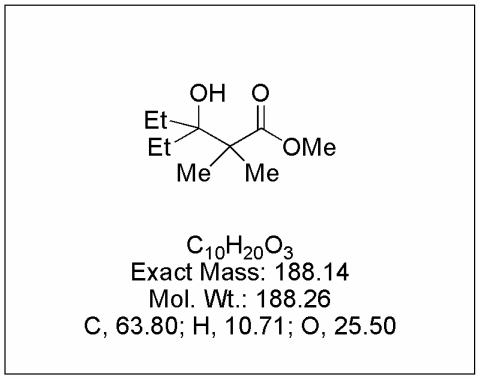
$C_{18}H_{30}O_2Si$
Exact Mass: 306.2
Mol. Wt.: 306.52
C, 70.53; H, 9.87; O, 10.44; Si, 9.16

Exact procedure followed for **3de** to afford 0.162 g colorless oil, 32% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14-7.18 (m, 2H), 7.05-7.08 (m, 3H), 4.18-4.20 (m, 1H),

2.67-2.73 (m, 1H), 2.57-2.61 (m, 1H), 2.47-2.50 (m, 1H), 2.35-2.41 (m, 1H), 1.61-1.68 (m, 2H), 1.00 (s, 9H), 0.00 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 213.9(e), 142.2(e), 128.5(o), 128.4(o), 125.9(o), 68.7(o), 44.8(e), 44.5(e), 39.8(e), 32.4(e), 26.4(o), 0.8(o).

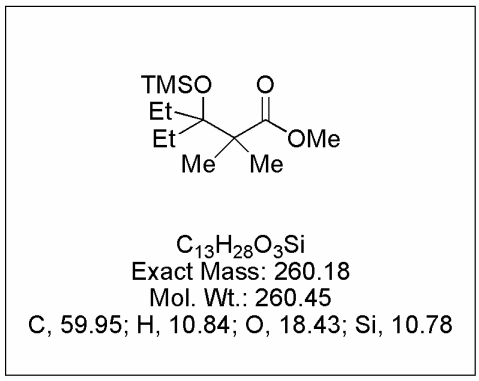
Methyl-3-ethyl-3-hydroxy-2,2-dimethylpentanoate (3ea):



This compound was prepared following the general procedure using $BiBr_3$ (0.073 g, 0.162 mmol, 0.15 eq), CH_2Cl_2 (4.0 mL), 3-pentanone (0.112 mL, 1.105 mmol, 1.0 eq), and $(CH_3)_2C{=}C(OSiMe_3)OMe$ (0.494 mL, 2.43 mmol, 2.2 eq). The solution was stirred for 60 minutes and subsequently purified in a silica gel plug using $MeCl_2$. The crude product was purified by column chromatography using gradient elution (95:5, 9:1 Hexanes:EtOAc). The fractions were concentrated *in vacuo* to afford 0.008 g colorless oil, 4% yield.

Not fully characterized.

Methyl-3-ethyl-2,2-dimethyl-3-trimethylsiloxypentanoate (4ea):

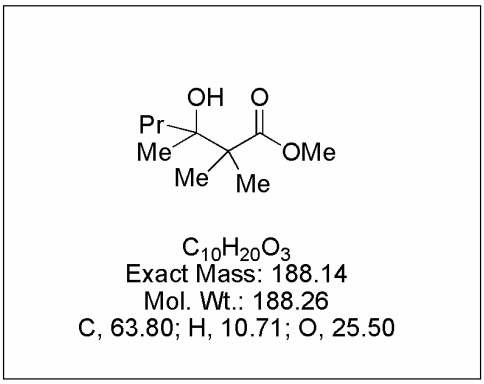


Exact procedure for **3ea** followed to afford 0.215 g colorless oil, 75% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.62 (s, 3H), 1.71-1.76 (m, 4H), 1.20 (s, 6H), 0.82-0.86 (m,

6H), 0.11 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.3(e), 82.9(e), 51.8(e), 51.7(o), 27.9(e), 27.9(e), 22.7(o), 9.8(o), 3.3(o).

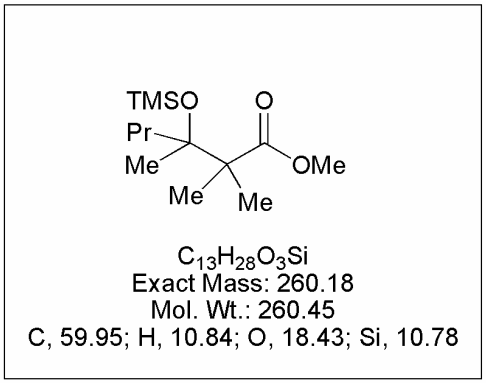
Methyl-3-hydroxy-2,2,3-trimethylhexanoate (3fa):



This compound was prepared following the general procedure using $BiBr_3$ (0.075 g, 0.167 mmol, 0.15 eq), CH_2Cl_2 (4.0 mL), 2-pentanone (0.119 mL, 1.114 mmol, 1.0 eq), and $(CH_3)_2C{=}C(OSiMe_3)OMe$ (0.498 mL, 2.451 mmol, 2.2 eq). The solution was stirred for 60 minutes and subsequently purified in a silica gel plug using $MeCl_2$. The crude product was purified by column chromatography (95:5 Hexanes:EtOAc). The fractions were concentrated *in vacuo* to afford 0.021 g colorless oil, 7% yield.

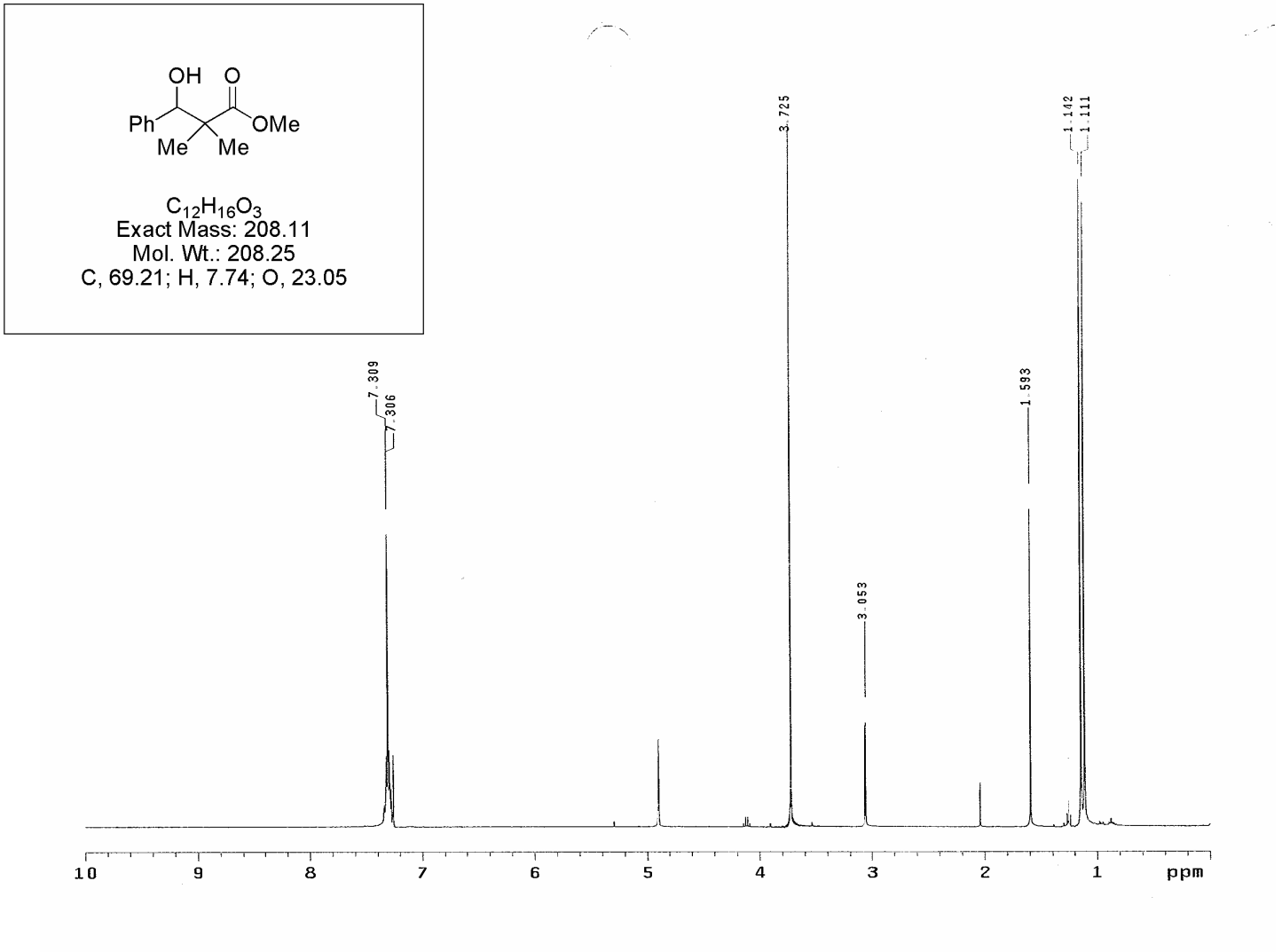
Not fully characterized.

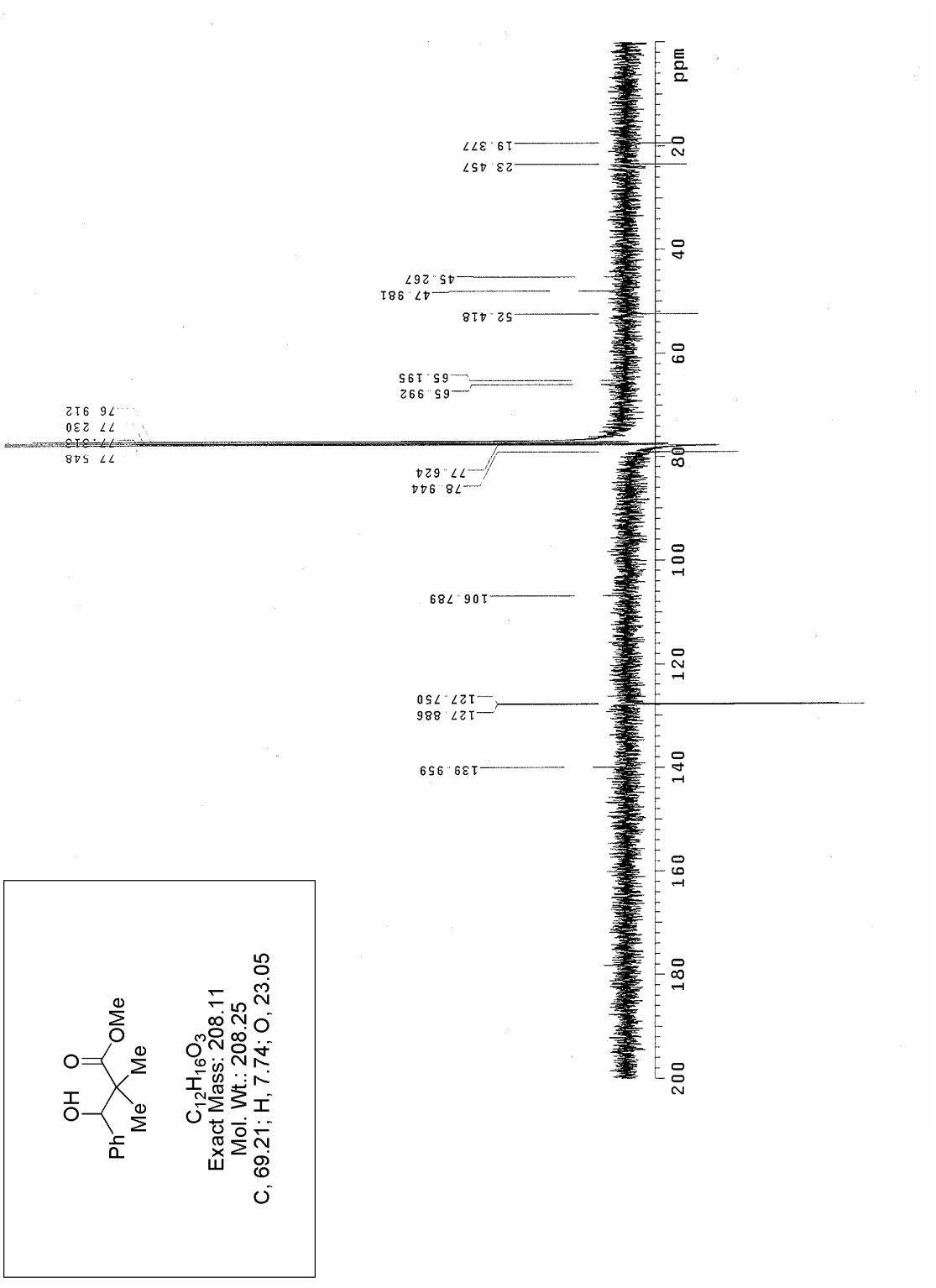
Methyl-2,2,3-trimethyl-3-trimethylsiloxyhexanoate (4fa):

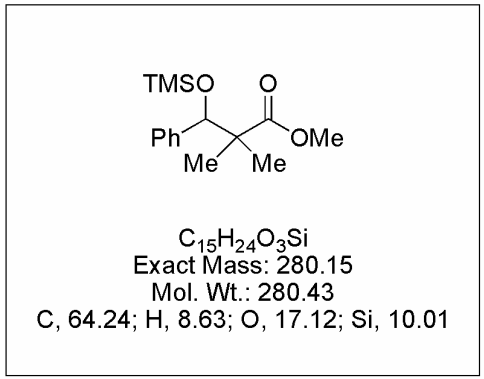


Exact procedure for **3fa** followed to afford 0.154 g colorless oil, 53% yield.

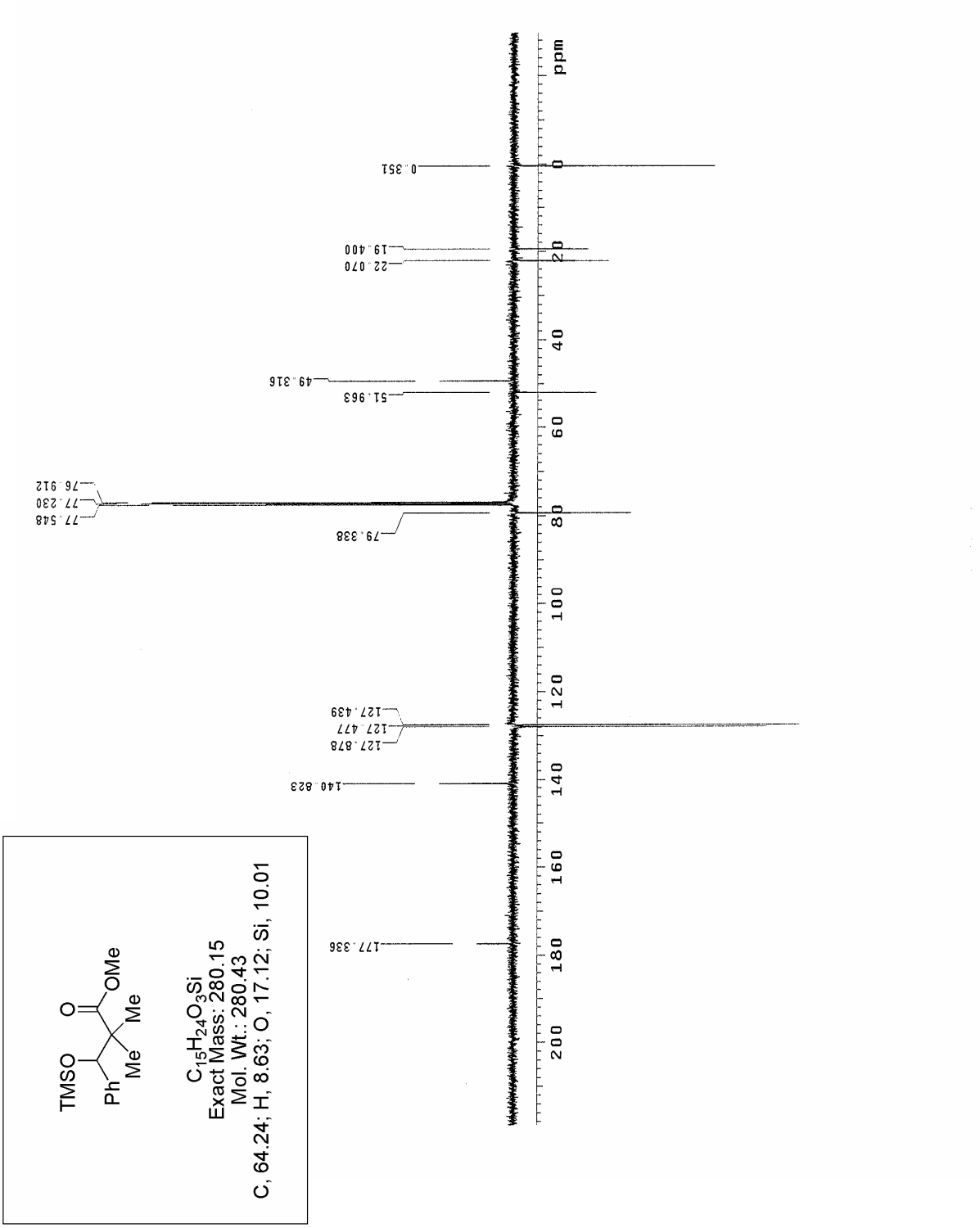
^{1}H NMR (400 MHz, $CDCl_3$) δ 3.53 (s, 3H), 1.46-1.53 (m, 2H), 1.17-1.33 (m, 2H), 1.15 (s, 3H), 1.08 (s, 6H), 0.73-0.81 (m, 3H), 0.00 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.2(e), 79.6(e), 51.9(e), 51.7(o), 41.2(e), 22.6(o), 22.1(o), 21.7(o), 18.0(e), 15.1(o), 3.1(o).

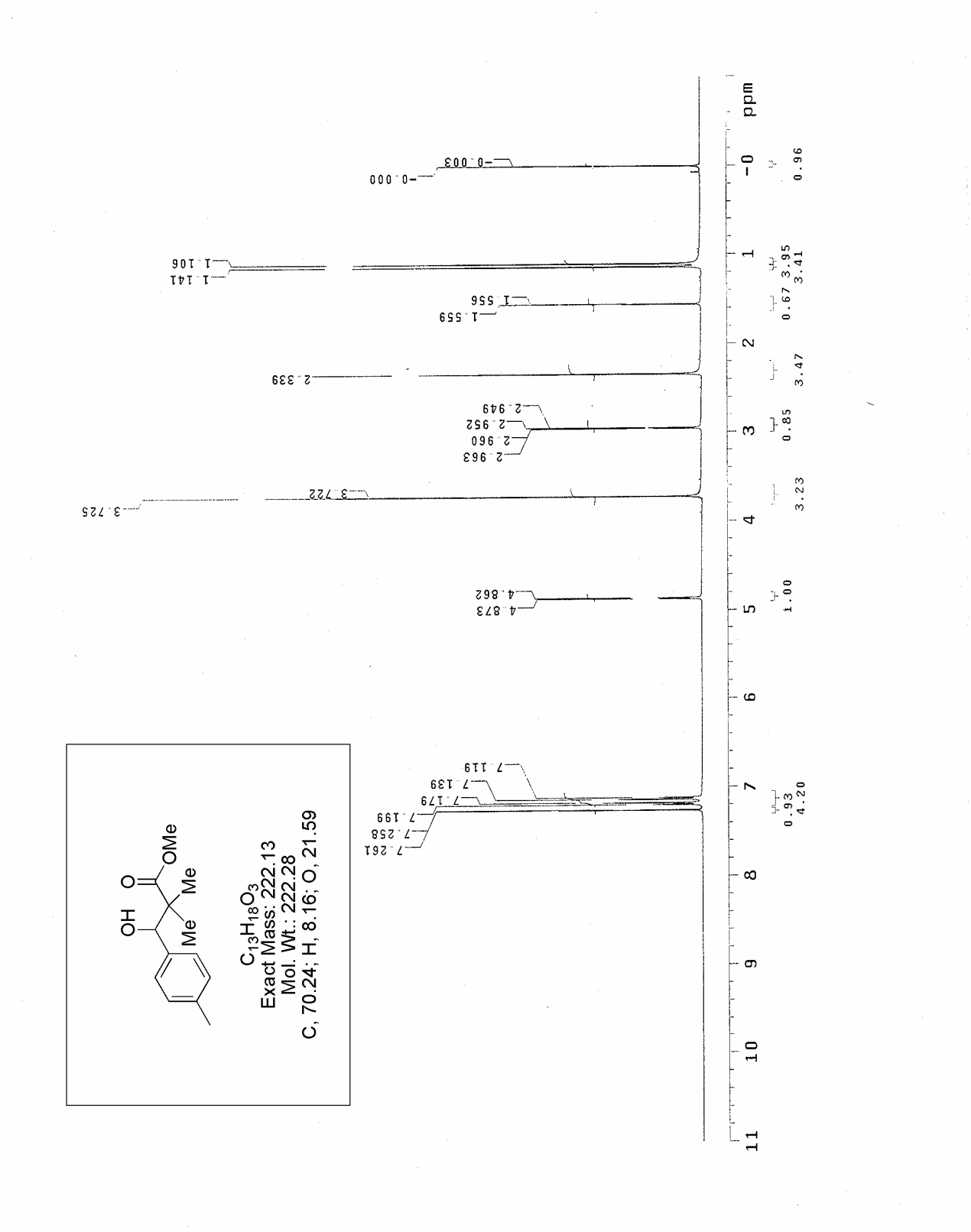

OH
O
Ph
OMe
Me
Me
C12H16O3
Exact Mass: 208.11
Mol. Wt.: 208.25
C, 69.21; H, 7.74; O, 23.05
7.309
7.306
3.725
3.053
1.593
1.142
1.111
10
9
8
7
6
5
4
3
2
1
ppm

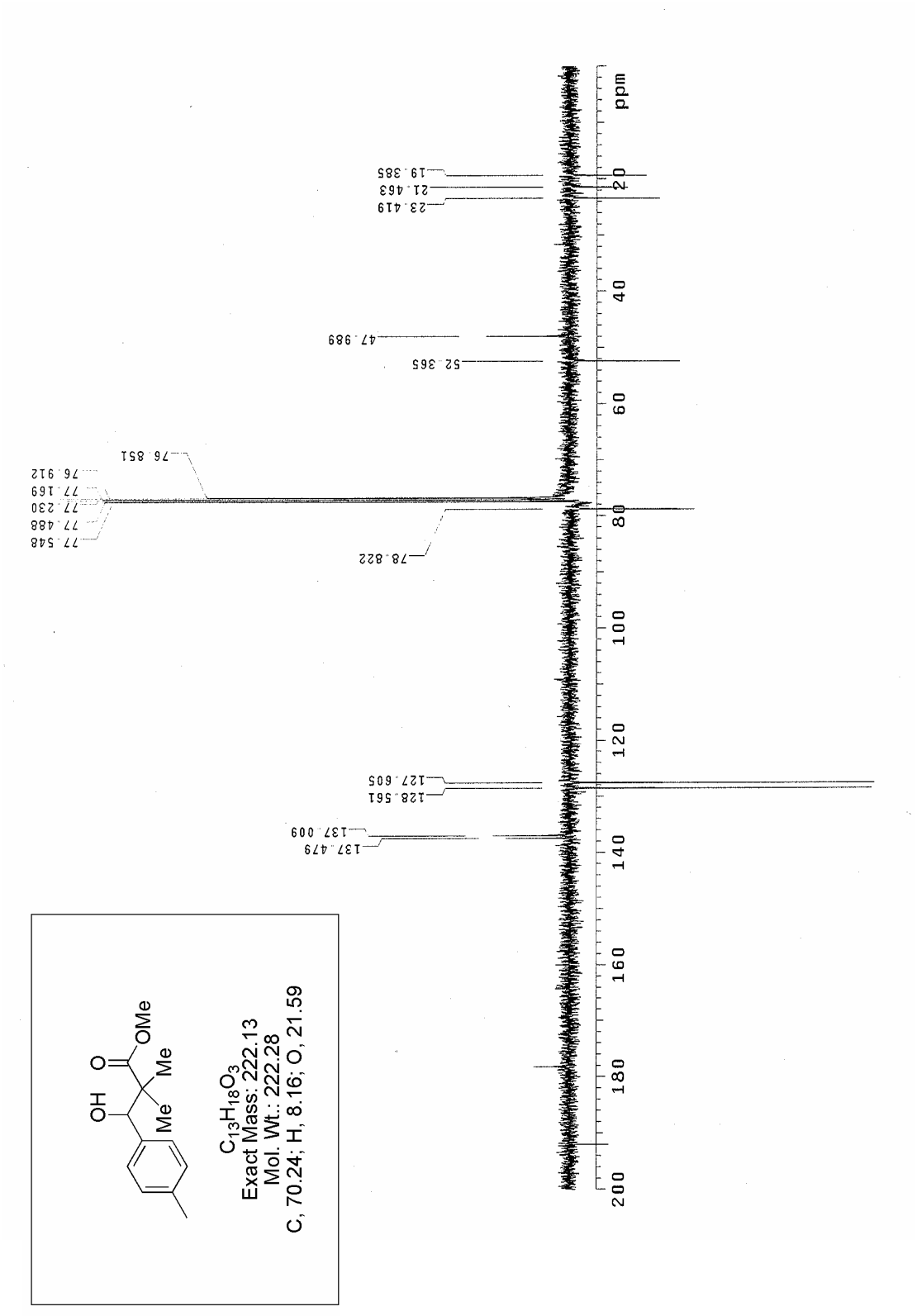

OH O
OMe
Me
Me
Ph
C12H16O3
Exact Mass: 208.11
Mol. Wt.: 208.25
C, 69.21; H, 7.74; O, 23.05
ppm
19.377
23.457
45.267
47.981
52.418
65.195
65.992
76.912
77.230
77.548
77.624
78.944
106.789
127.750
127.886
139.959



$C_{15}H_{24}O_3Si$
Exact Mass: 280.15
Mol. Wt.: 280.43
C, 64.24; H, 8.63; O, 17.12; Si, 10.01


TMSO
O
OMe
Ph
Me
Me
C15H24O3Si
Exact Mass: 280.15
Mol. Wt.: 280.43
C, 64.24; H, 8.63; O, 17.12; Si, 10.01
177.336
140.823
127.878
127.477
127.439
79.338
77.548
77.230
76.912
51.963
49.316
22.070
19.400
0.351
ppm
200
180
160
140
120
100
80
60
40
20
0


OH
O
OMe
Me
Me
$C_{13}H_{18}O_3$
Exact Mass: 222.13
Mol. Wt.: 222.28
C, 70.24; H, 8.16; O, 21.59
7.261
7.258
7.199
7.179
7.139
7.119
4.873
4.862
3.725
3.722
2.963
2.960
2.952
2.949
2.339
1.559
1.556
1.141
1.106
0.003
0.000
ppm
0.93
4.20
1.00
3.23
0.85
3.47
0.67
3.95
3.41
0.96


OH
O
OMe
Me
Me
$C_{13}H_{18}O_3$
Exact Mass: 222.13
Mol. Wt.: 222.28
C, 70.24; H, 8.16; O, 21.59
19.385
21.463
23.419
47.989
52.365
76.851
76.912
77.169
77.230
77.488
77.548
78.822
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137.009
137.479
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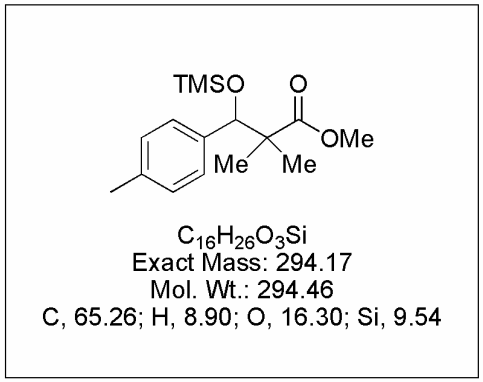
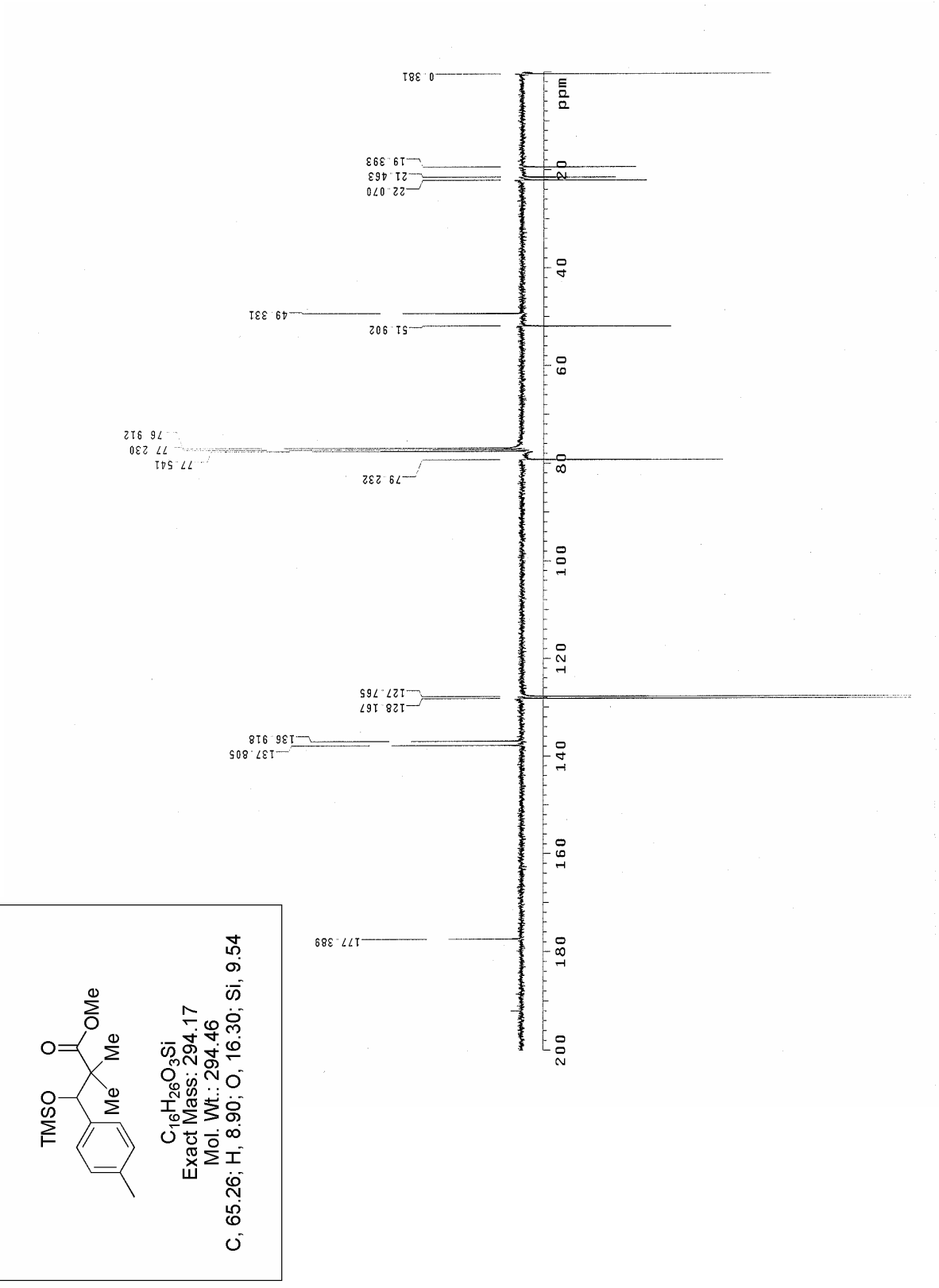
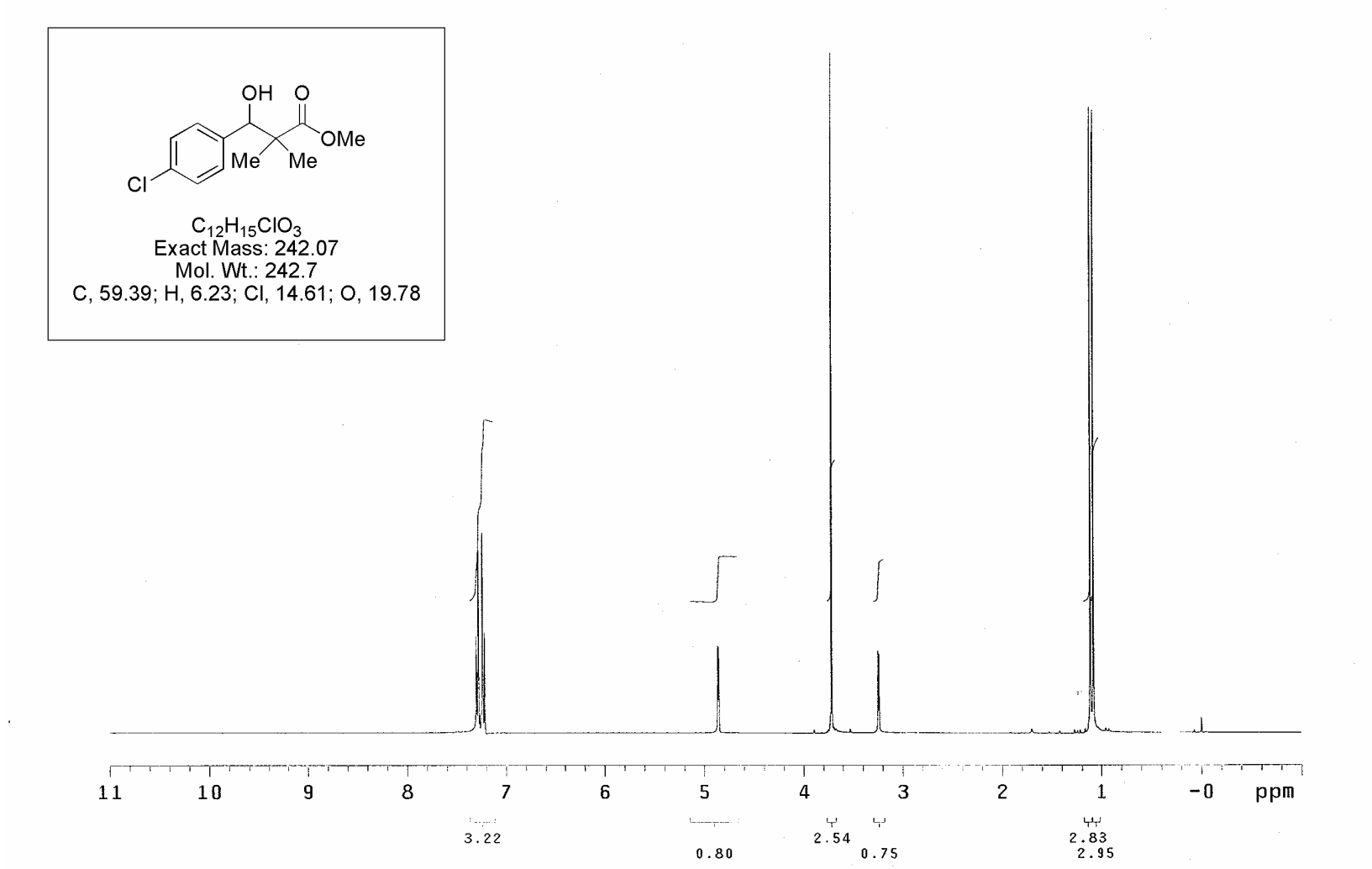
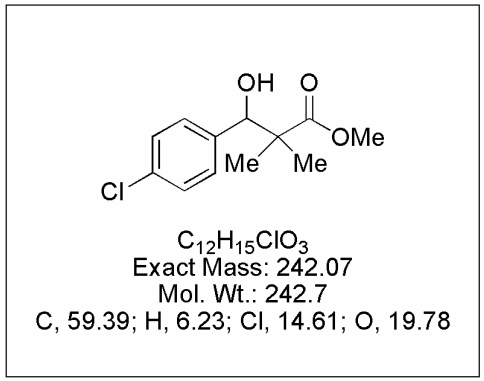
20
40
60
80
100
120
140
160
180
200



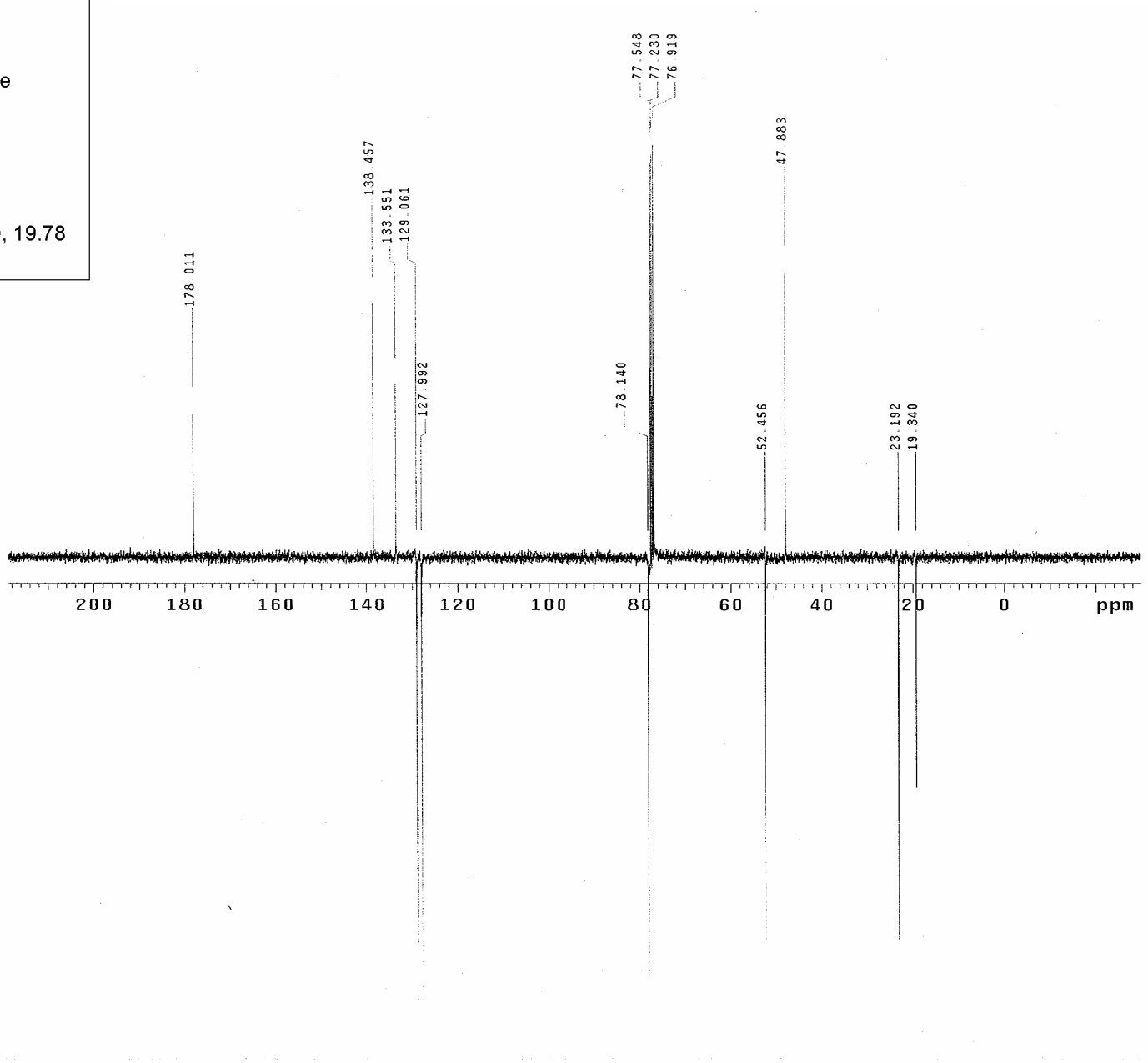
$C_{16}H_{26}O_3Si$
Exact Mass: 294.17
Mol. Wt.: 294.46
C, 65.26; H, 8.90; O, 16.30; Si, 9.54

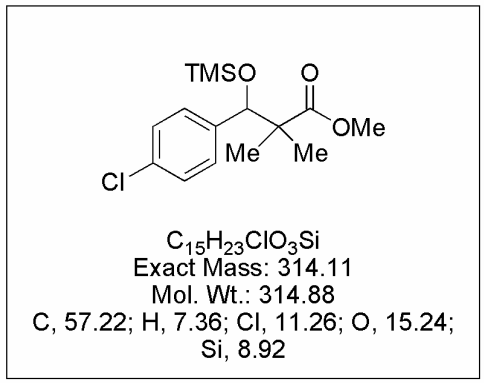

0.381
19.393
21.463
22.070
49.331
51.902
76.912
77.230
77.541
79.232
126.167
127.765
136.918
137.805
177.389
ppm
20
40
60
80
100
120
140
160
180
200
TMSO
O
OMe
Me
Me
C16H26O3Si
Exact Mass: 294.17
Mol. Wt.: 294.46
C, 65.26; H, 8.90; O, 16.30; Si, 9.54


OH
O
OMe
Me
Me
Cl
C12H15ClO3
Exact Mass: 242.07
Mol. Wt.: 242.7
C, 59.39; H, 6.23; Cl, 14.61; O, 19.78
11
10
9
8
7
6
5
4
3
2
1
-0
ppm
3.22
0.80
2.54
0.75
2.83
2.95

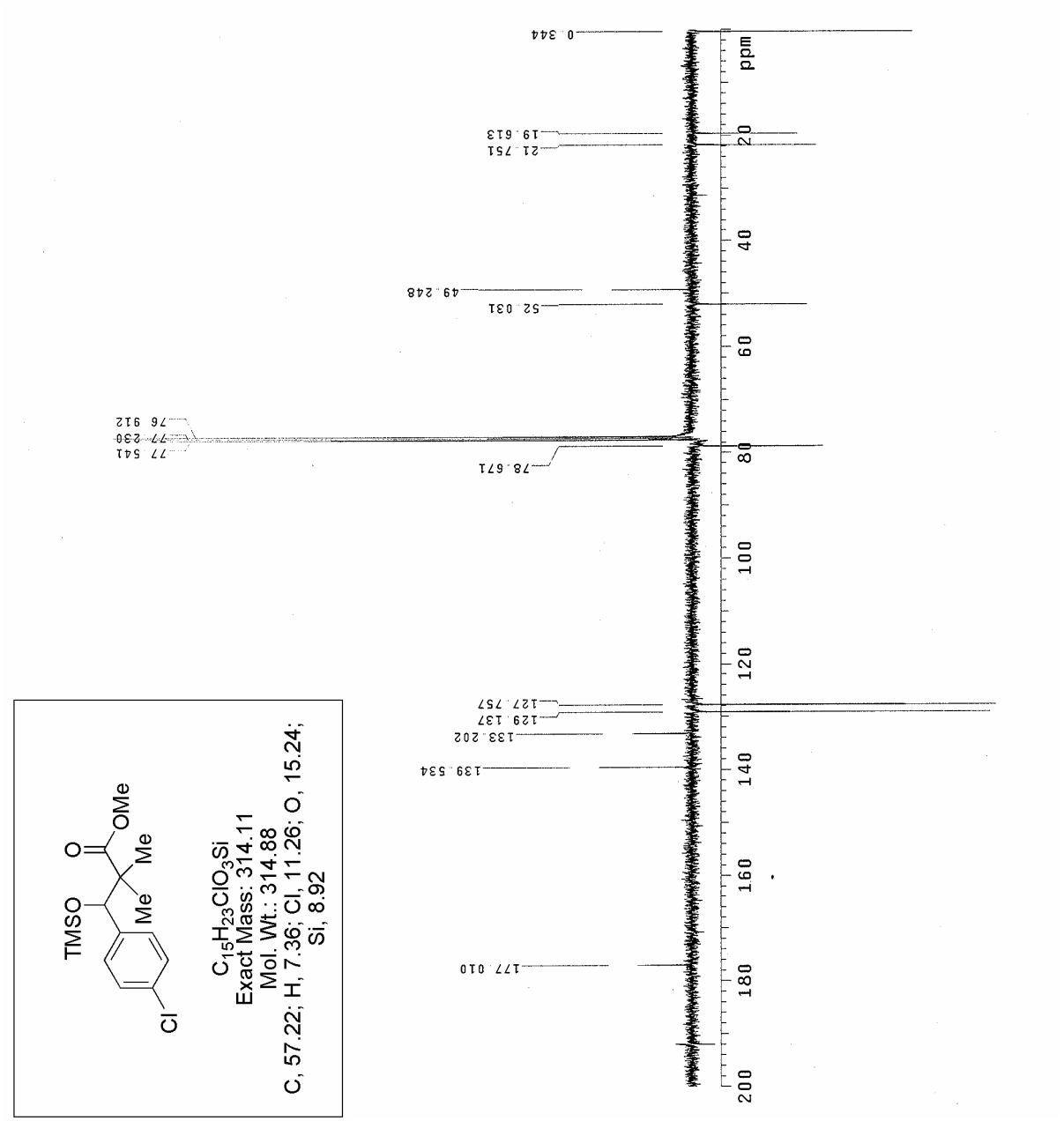


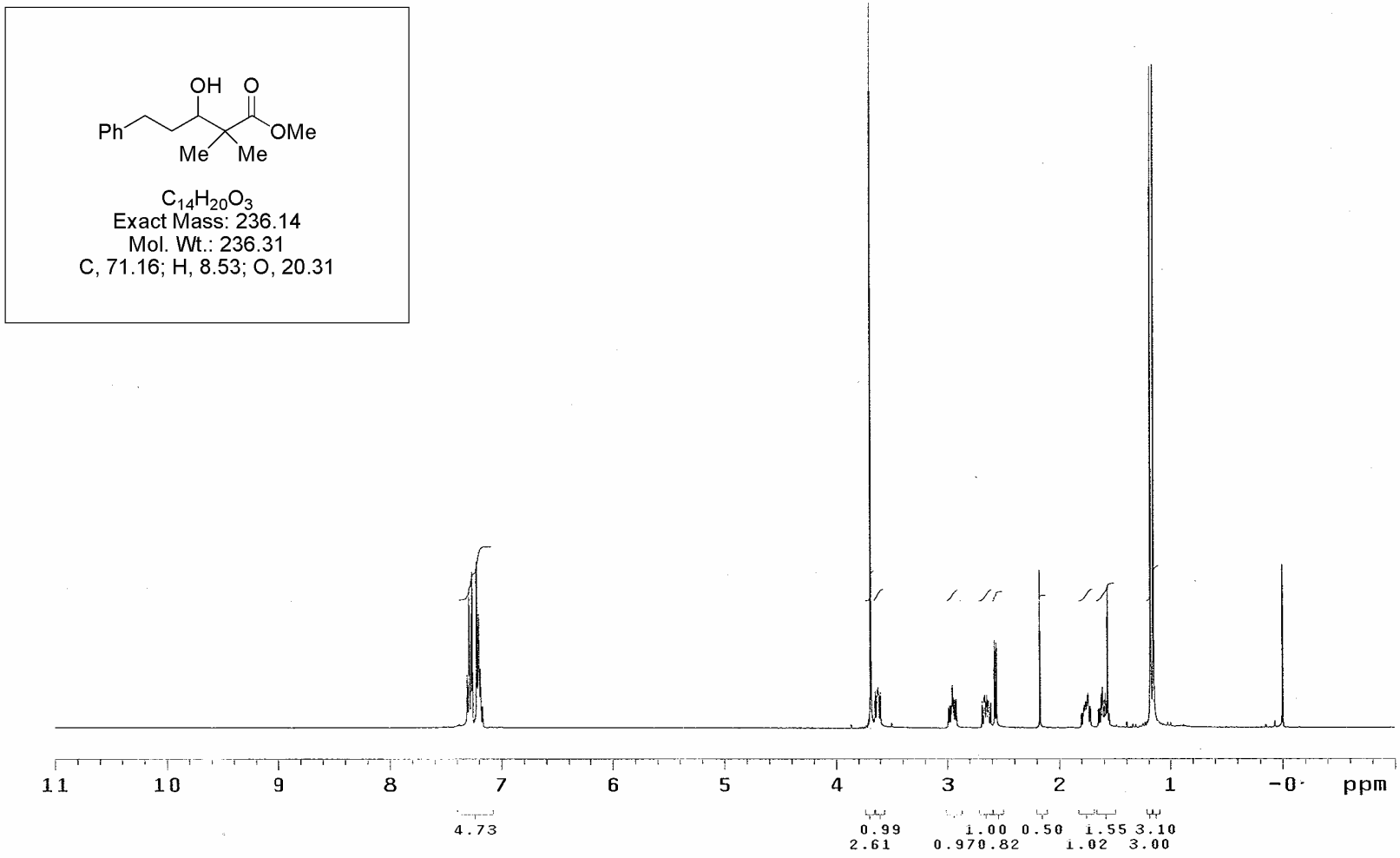
$C_{12}H_{15}ClO_3$
Exact Mass: 242.07
Mol. Wt.: 242.7
C, 59.39; H, 6.23; Cl, 14.61; O, 19.78

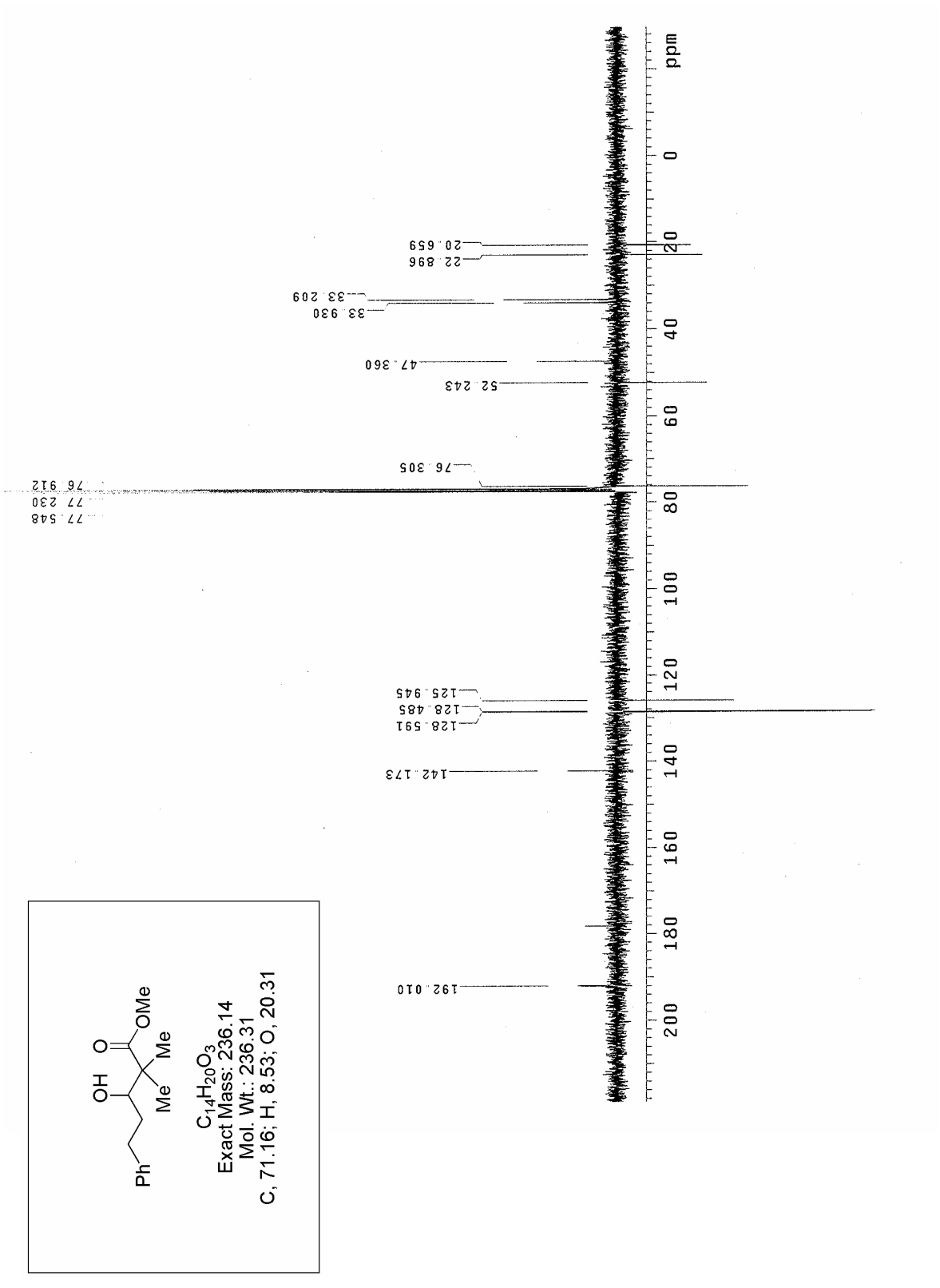




$C_{15}H_{23}ClO_3Si$
Exact Mass: 314.11
Mol. Wt.: 314.88
C, 57.22; H, 7.36; Cl, 11.26; O, 15.24;
Si, 8.92


TMSO
O
OMe
Me
Me
Cl
C15H23ClO3Si
Exact Mass: 314.11
Mol. Wt.: 314.88
C, 57.22; H, 7.36; Cl, 11.26; O, 15.24;
Si, 8.92
0.344
19.613
21.751
49.248
52.031
76.912
77.230
77.541
78.671
127.757
129.137
133.202
139.534
177.010
ppm


OH
O
Ph
OMe
Me
Me
C14H20O3
Exact Mass: 236.14
Mol. Wt.: 236.31
C, 71.16; H, 8.53; O, 20.31
11
10
9
8
7
6
5
4
3
2
1
-0
ppm
4.73
0.99
2.61
1.00
0.97
0.50
0.82
1.55
1.02
3.10
3.00


ppm
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20
40
60
80
100
120
140
160
180
200
192.010
142.173
128.591
128.485
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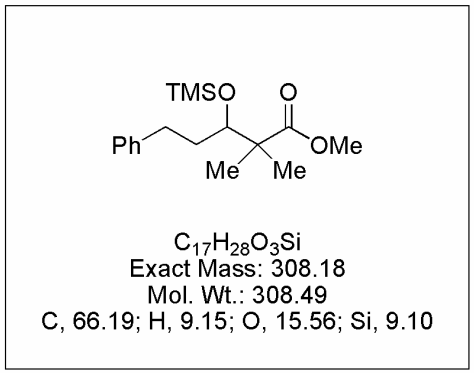
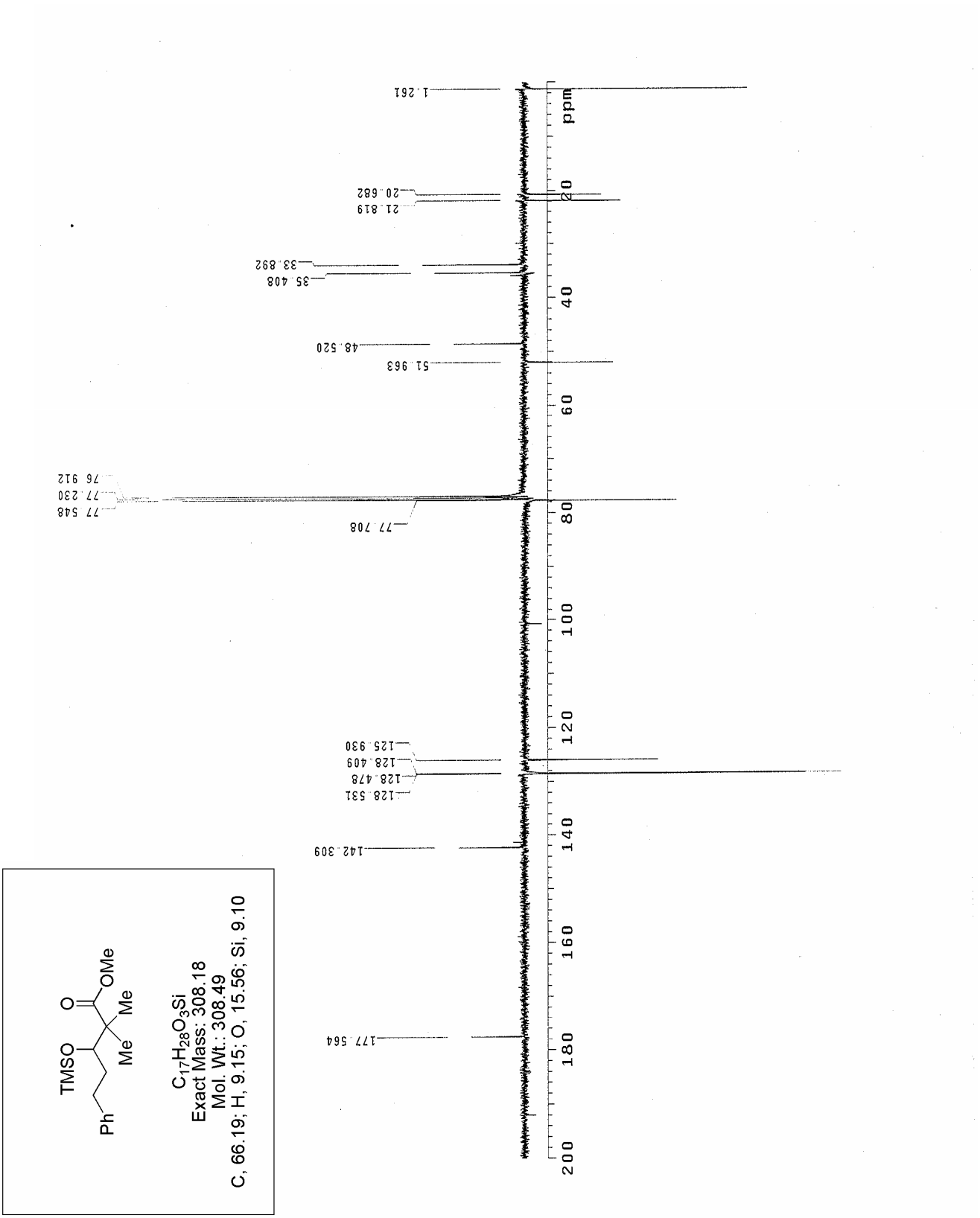
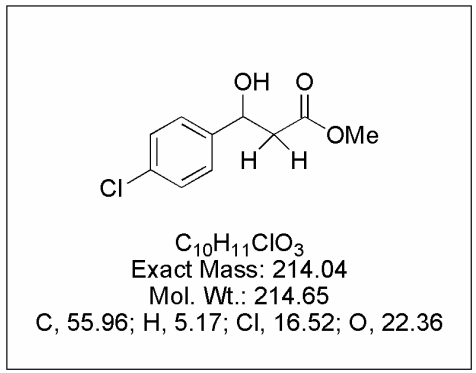
76.912
77.230
77.548
76.305
52.243
47.360
33.930
33.209
22.896
20.659
OH
O
OMe
Me
Me
Ph
C14H20O3
Exact Mass: 236.14
Mol. Wt.: 236.31
C, 71.16; H, 8.53; O, 20.31



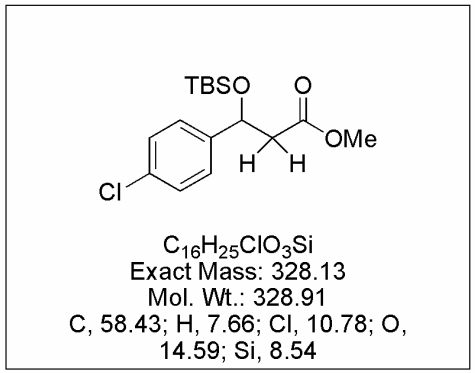
$C_{17}H_{28}O_3Si$
Exact Mass: 308.18
Mol. Wt.: 308.49
C, 66.19; H, 9.15; O, 15.56; Si, 9.10


TMSO
O
OMe
Me
Me
Ph
$C_{17}H_{28}O_3Si$
Exact Mass: 308.18
Mol. Wt.: 308.49
C, 66.19; H, 9.15; O, 15.56; Si, 9.10
1.261
20.682
21.819
33.892
35.408
48.520
51.963
76.912
77.230
77.548
77.708
125.930
128.409
128.478
128.531
142.309
177.564
ppm
200
180
160
140
120
100
80
60
40
20

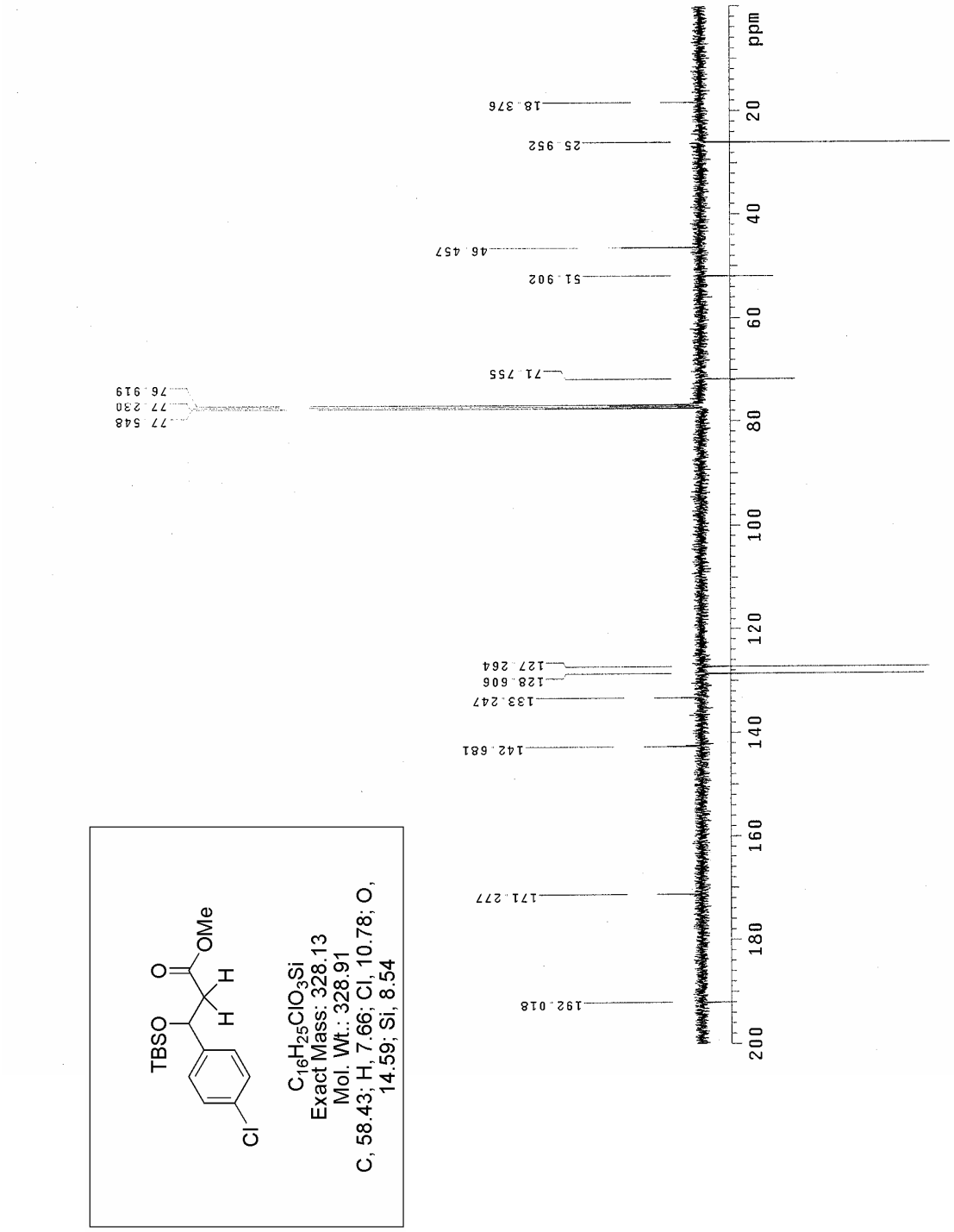


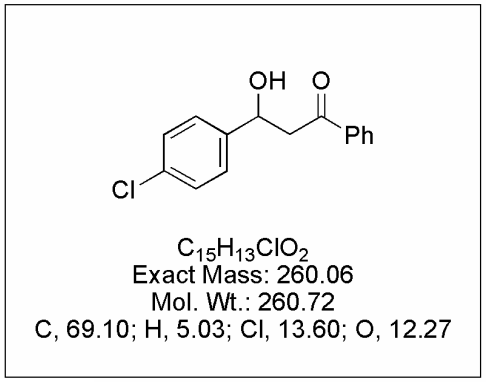
$C_{10}H_{11}ClO_3$
Exact Mass: 214.04
Mol. Wt.: 214.65
C, 55.96; H, 5.17; Cl, 16.52; O, 22.36

OH
O
OMe
H
H
Cl
C10H11ClO3
Exact Mass: 214.04
Mol. Wt.: 214.65
C, 55.96; H, 5.17; Cl, 16.52; O, 22.36
172.642
140.952
133.611
128.811
127.143
77.548
77.230
76.919
69.852
52.281
43.265
ppm
200
180
160
140
120
100
80
60
40
20

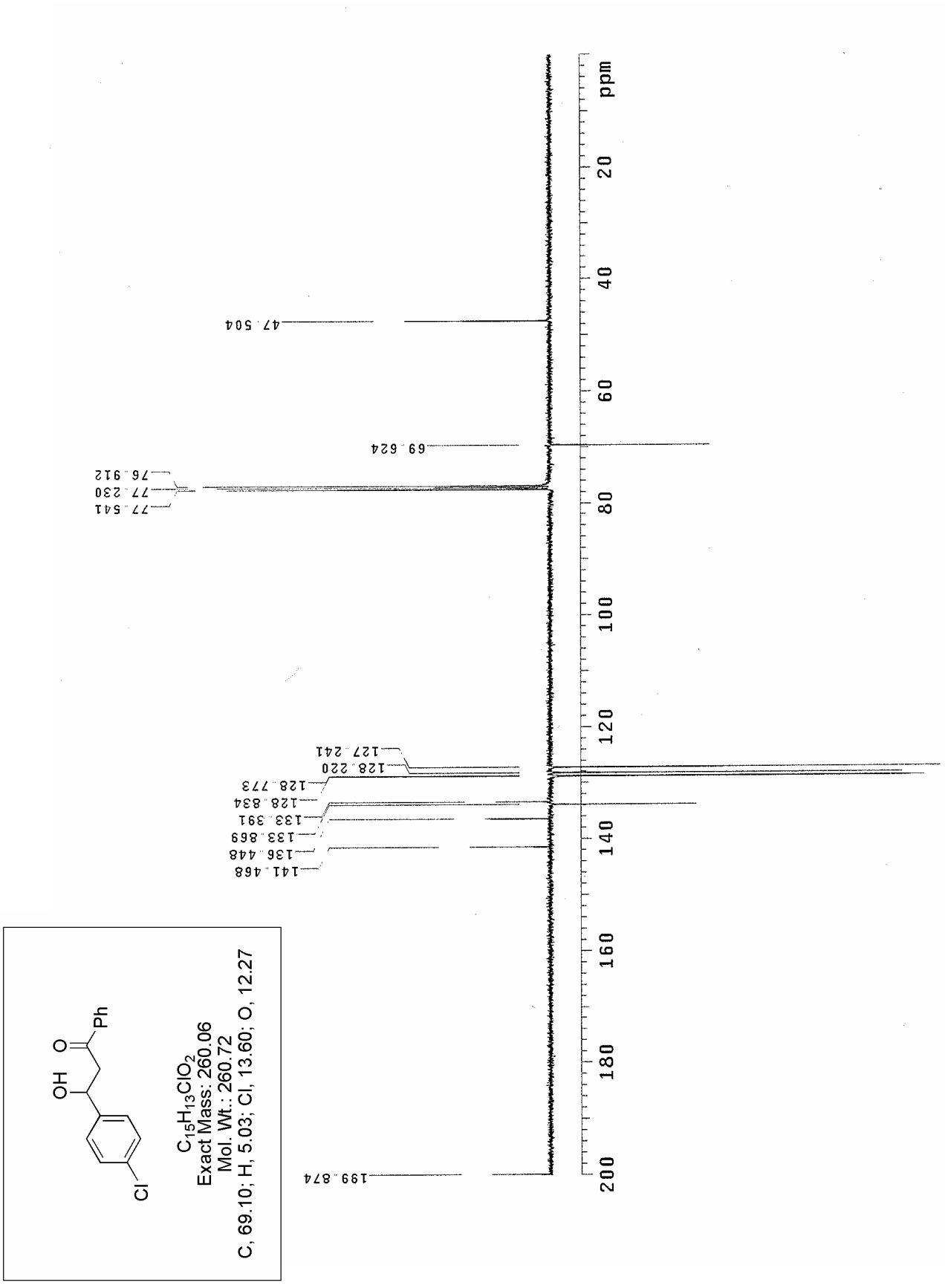


$C_{16}H_{25}ClO_3Si$
Exact Mass: 328.13
Mol. Wt.: 328.91
C, 58.43; H, 7.66; Cl, 10.78; O, 14.59; Si, 8.54


TBSO
O
OMe
H
H
Cl
C16H25ClO3Si
Exact Mass: 328.13
Mol. Wt.: 328.91
C, 58.43; H, 7.66; Cl, 10.78; O,
14.59; Si, 8.54
ppm
18.376
25.952
46.457
51.902
71.755
76.919
77.230
77.548
127.264
128.606
133.247
142.681
171.277
192.018



$C_{15}H_{13}ClO_2$
Exact Mass: 260.06
Mol. Wt.: 260.72
C, 69.10; H, 5.03; Cl, 13.60; O, 12.27


Ph
O
OH
Cl
$C_{15}H_{13}ClO_2$
Exact Mass: 260.06
Mol. Wt.: 260.72
C, 69.10; H, 5.03; Cl, 13.60; O, 12.27
199.874
141.468
136.448
133.869
133.391
128.834
128.773
128.220
127.241
77.541
77.230
76.912
69.624
47.504
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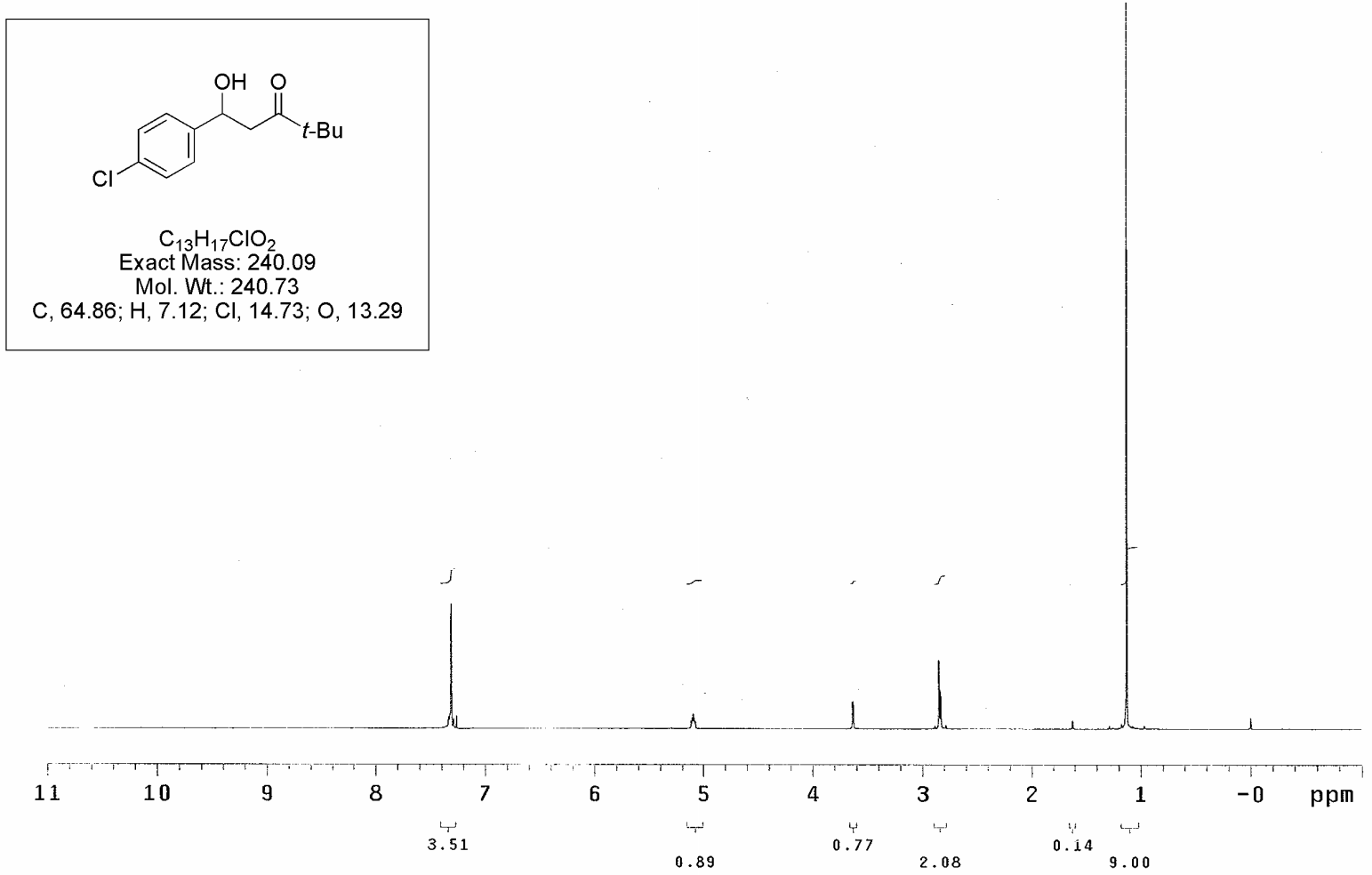
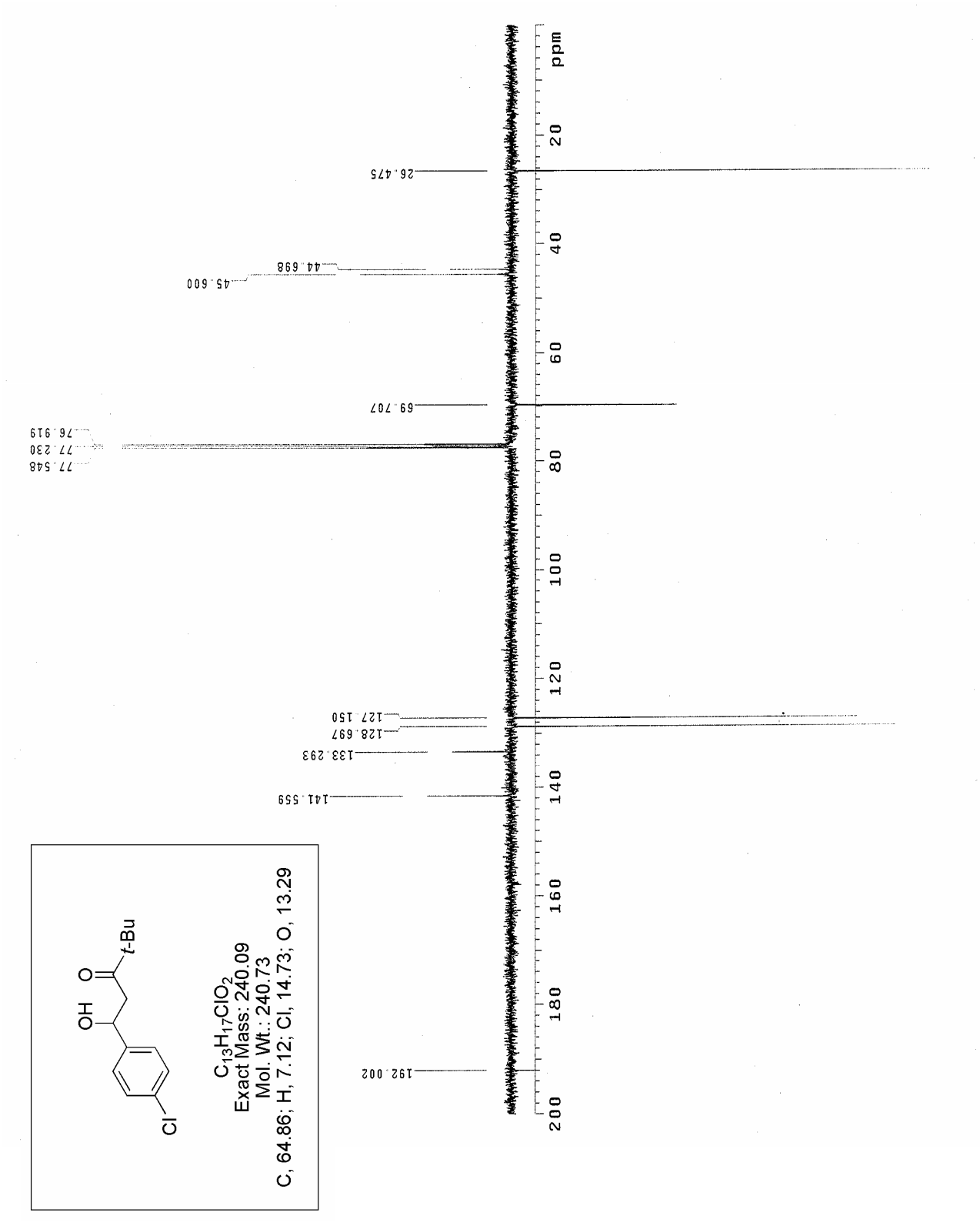
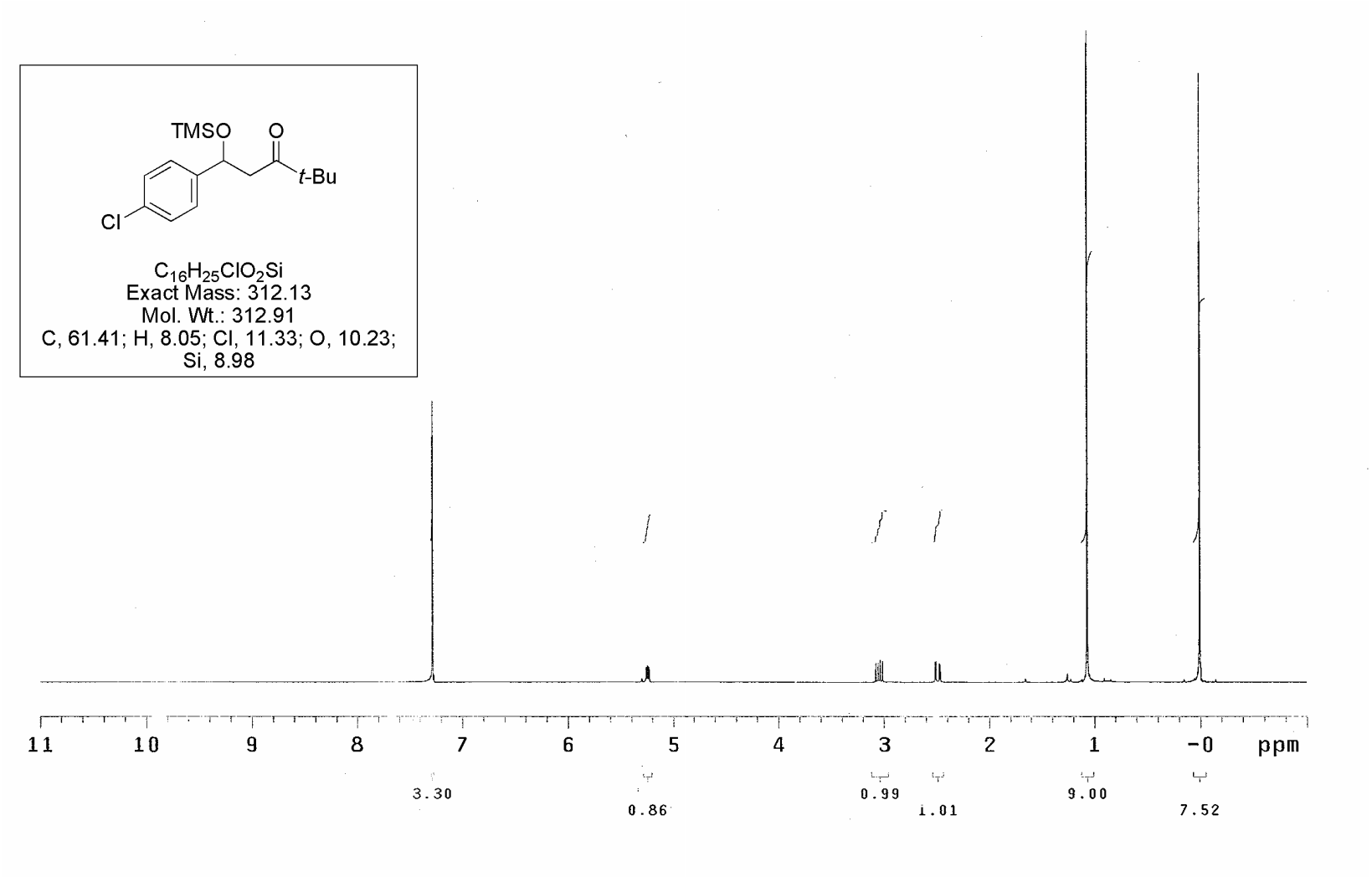
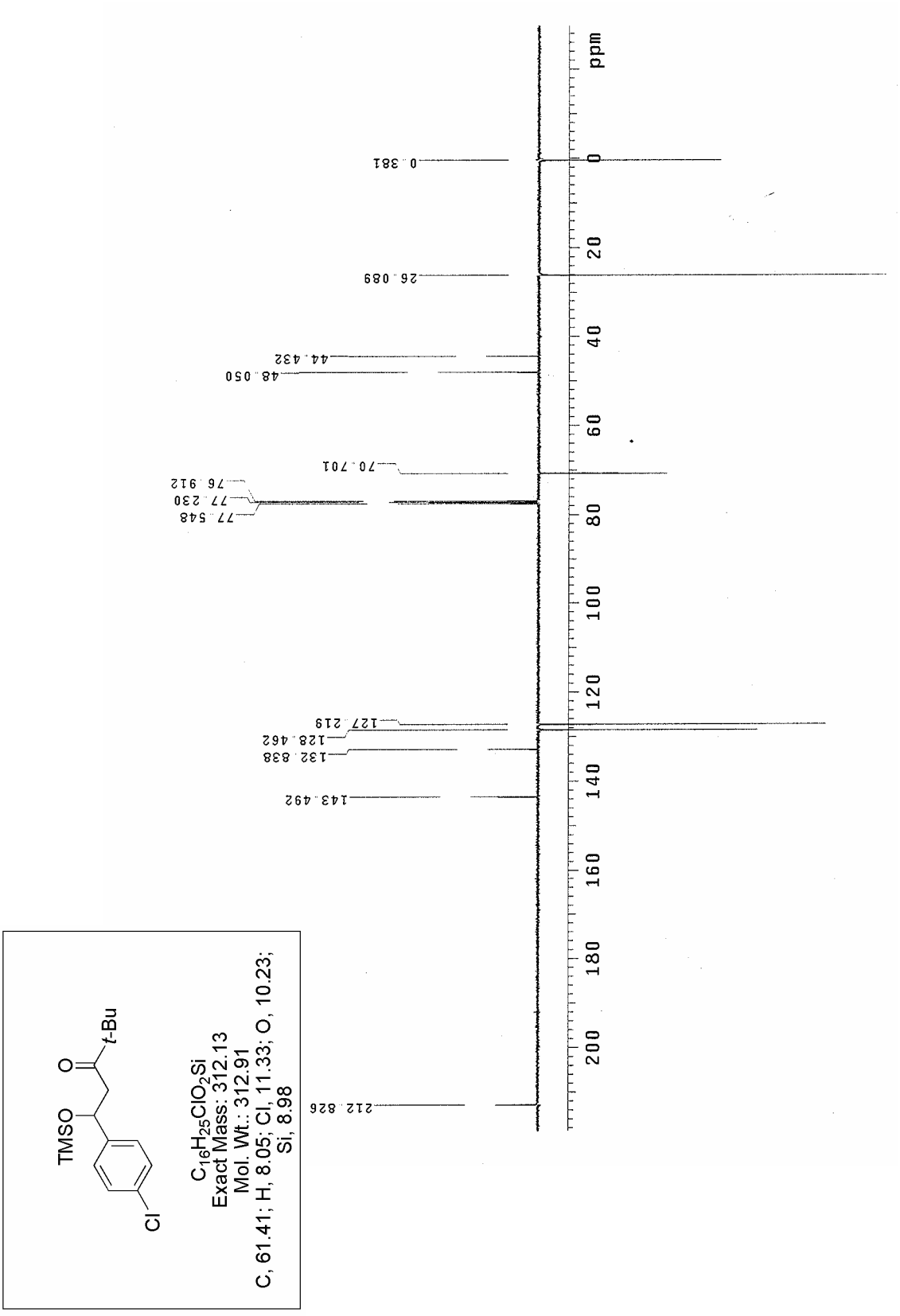
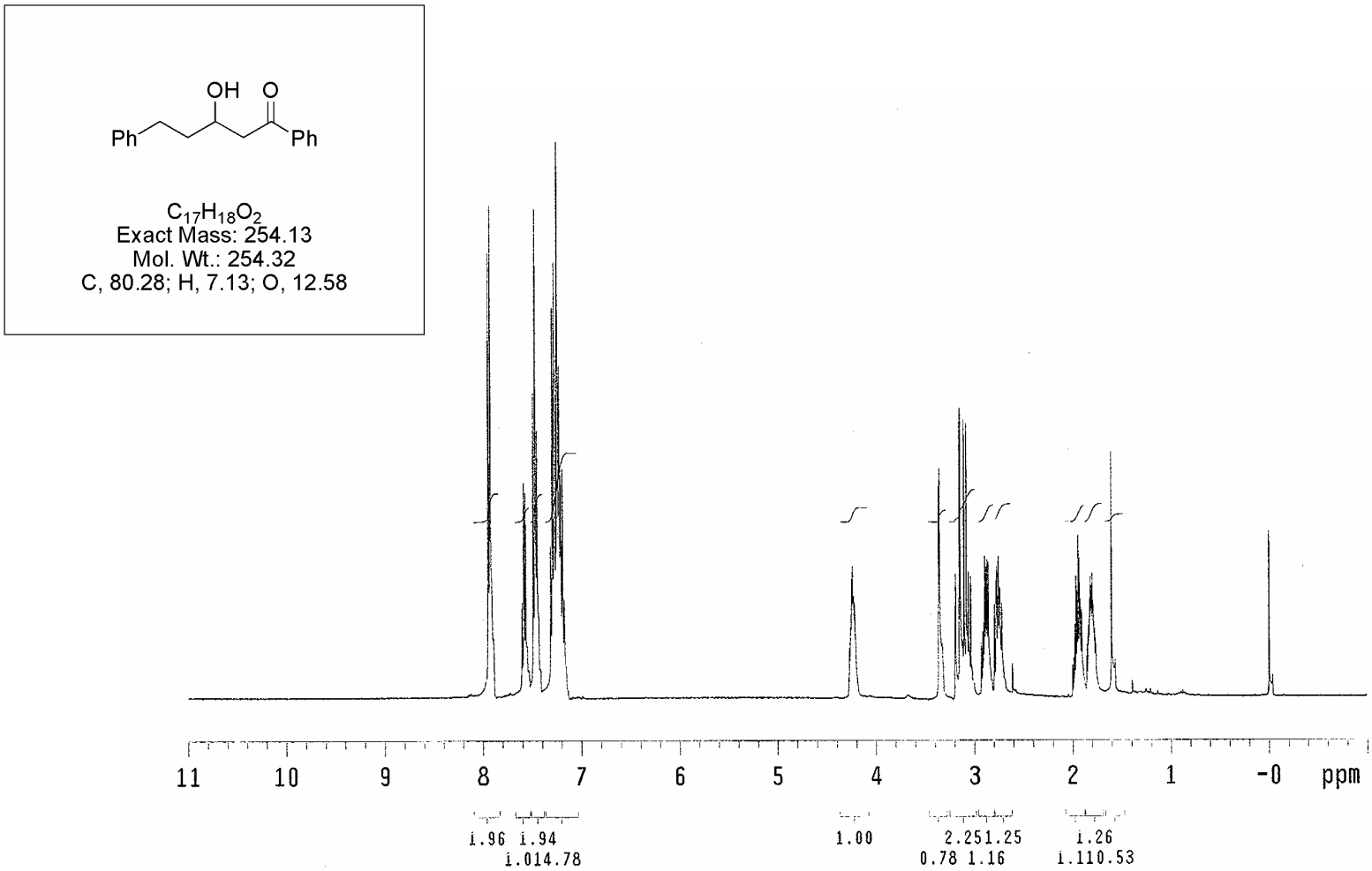
200
180
160
140
120
100
80
60
40
20

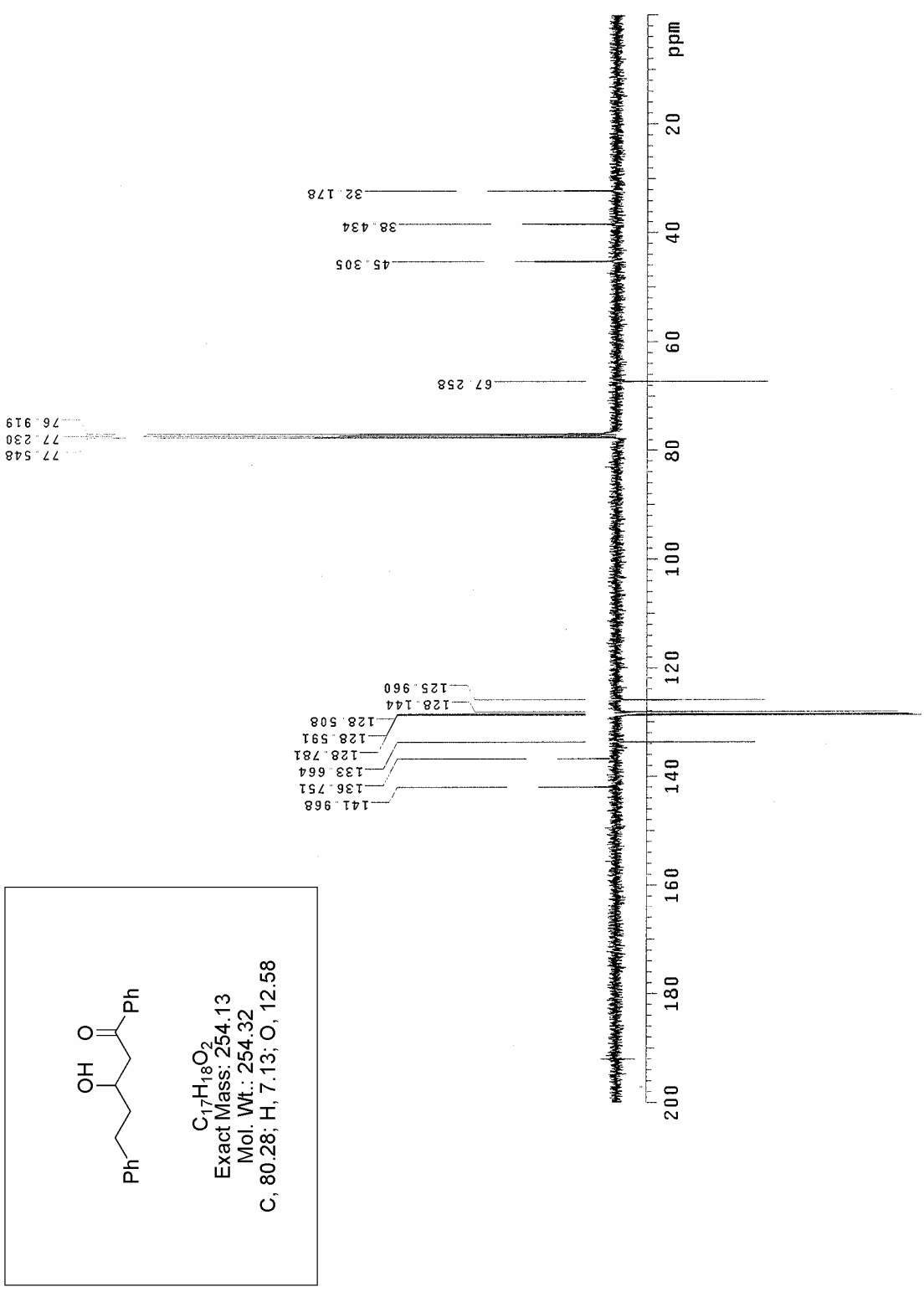

OH
O
t-Bu
Cl
C13H17ClO2
Exact Mass: 240.09
Mol. Wt.: 240.73
C, 64.86; H, 7.12; Cl, 14.73; O, 13.29
11
10
9
8
7
6
5
4
3
2
1
-0
ppm
3.51
0.89
0.77
2.08
0.14
9.00

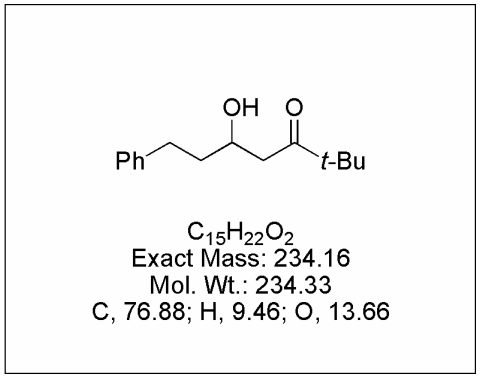

OH O
t-Bu
Cl
C13H17ClO2
Exact Mass: 240.09
Mol. Wt.: 240.73
C, 64.86; H, 7.12; Cl, 14.73; O, 13.29
192.002
141.559
133.293
128.697
127.150
77.548
77.230
76.919
69.707
45.600
44.698
26.475
ppm
200
180
160
140
120
100
80
60
40
20


TMSO
O
t-Bu
Cl
C16H25ClO2Si
Exact Mass: 312.13
Mol. Wt.: 312.91
C, 61.41; H, 8.05; Cl, 11.33; O, 10.23;
Si, 8.98
11
10
9
8
7
6
5
4
3
2
1
-0
ppm
3.30
0.86
0.99
1.01
9.00
7.52

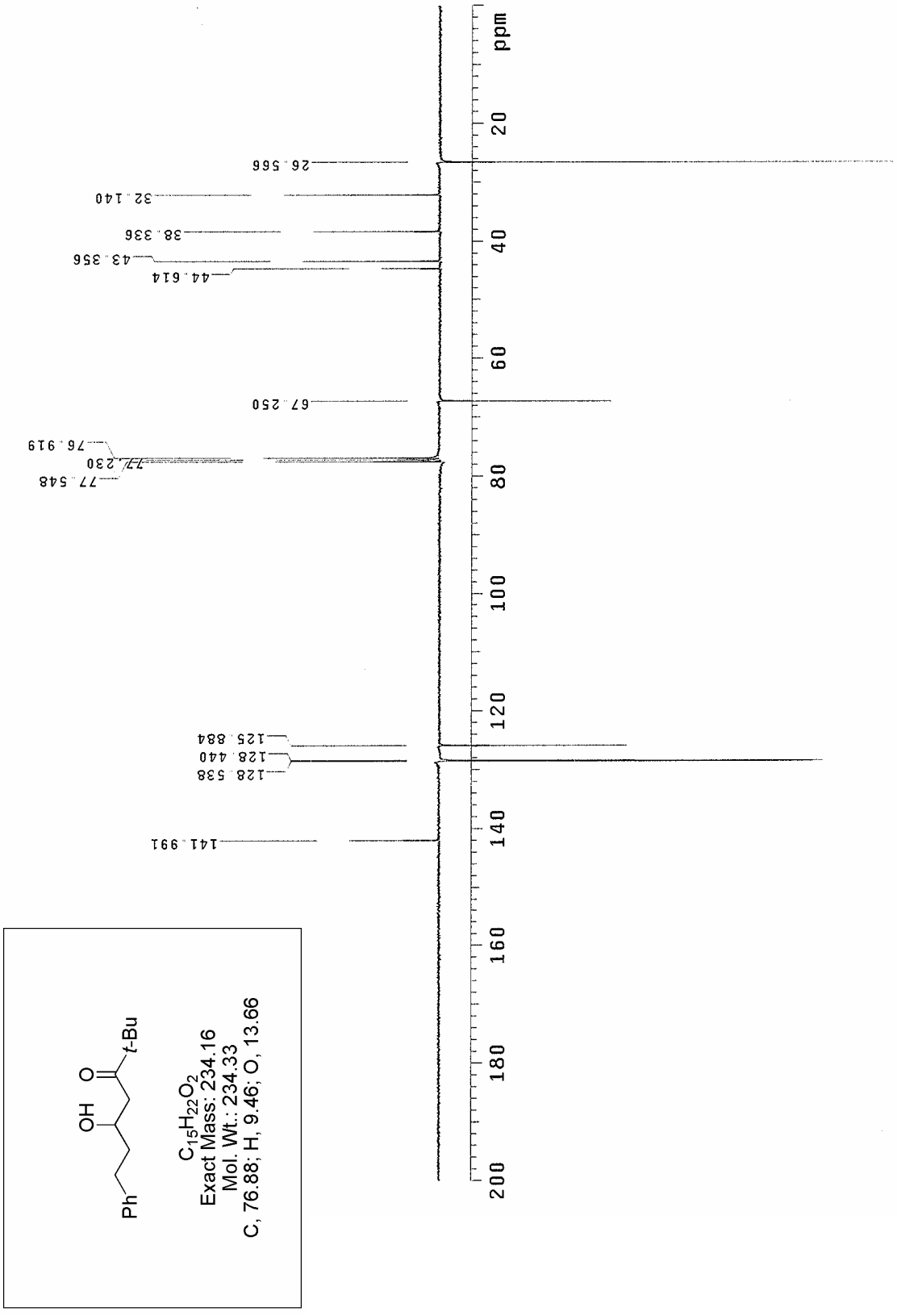

TMSO
O
t-Bu
Cl
C16H25ClO2Si
Exact Mass: 312.13
Mol. Wt.: 312.91
C, 61.41; H, 8.05; Cl, 11.33; O, 10.23;
Si, 8.98
212.826
143.492
132.838
128.462
127.219
77.548
77.230
76.912
70.701
48.050
44.432
26.089
0.381
ppm
0
20
40
60
80
100
120
140
160
180
200

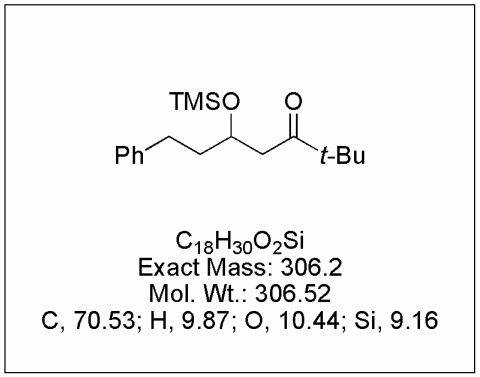

OH
O
Ph
Ph
C17H18O2
Exact Mass: 254.13
Mol. Wt.: 254.32
C, 80.28; H, 7.13; O, 12.58
11
10
9
8
7
6
5
4
3
2
1
-0
ppm
1.96
1.94
1.014.78
1.00
2.251.25
0.78
1.16
1.26
1.110.53


OH O
Ph
Ph
C17H18O2
Exact Mass: 254.13
Mol. Wt.: 254.32
C, 80.28; H, 7.13; O, 12.58
ppm
20
40
60
80
100
120
140
160
180
200
32.178
38.434
45.305
67.258
76.919
77.230
77.548
125.960
128.144
128.508
128.591
128.781
133.664
136.751
141.968

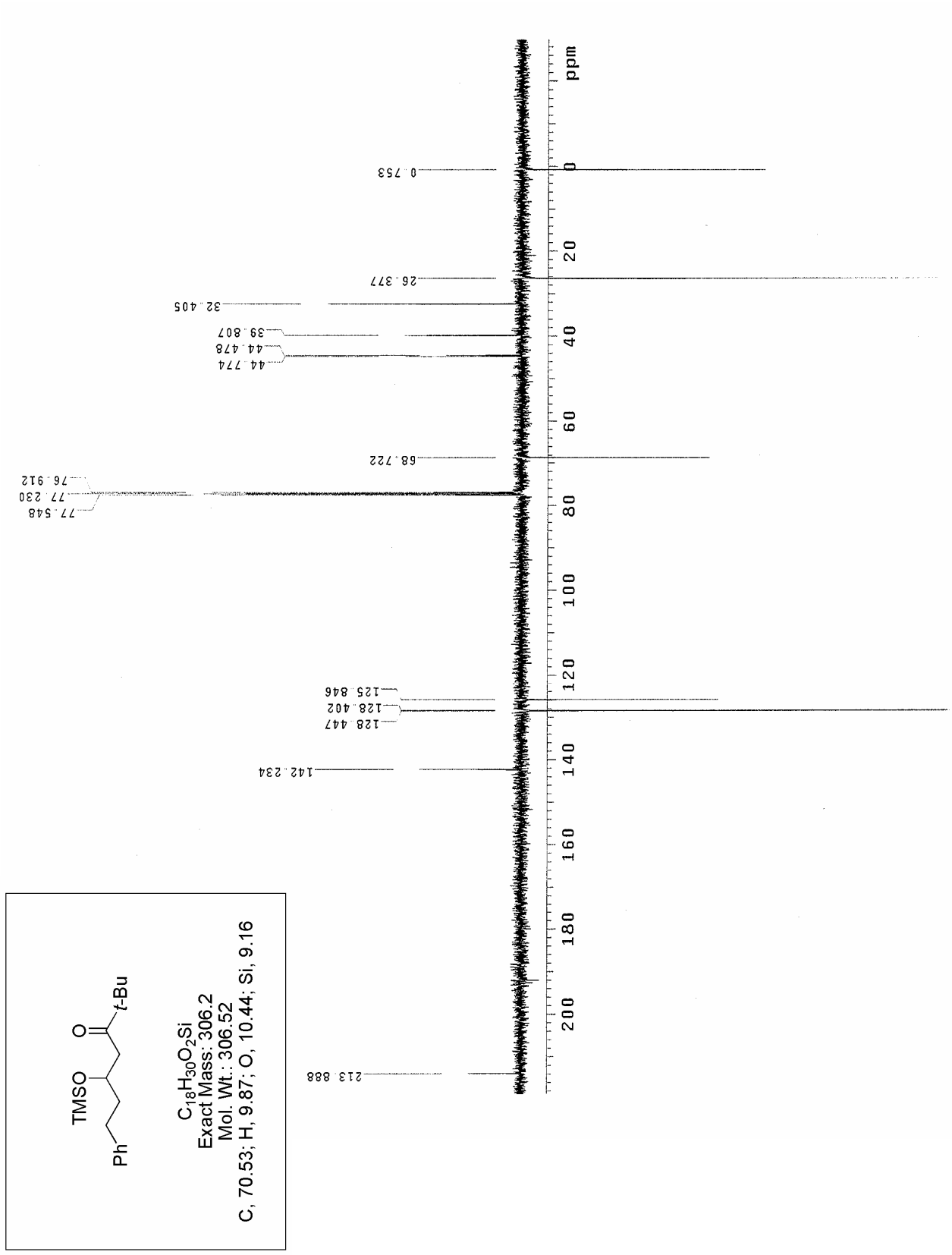


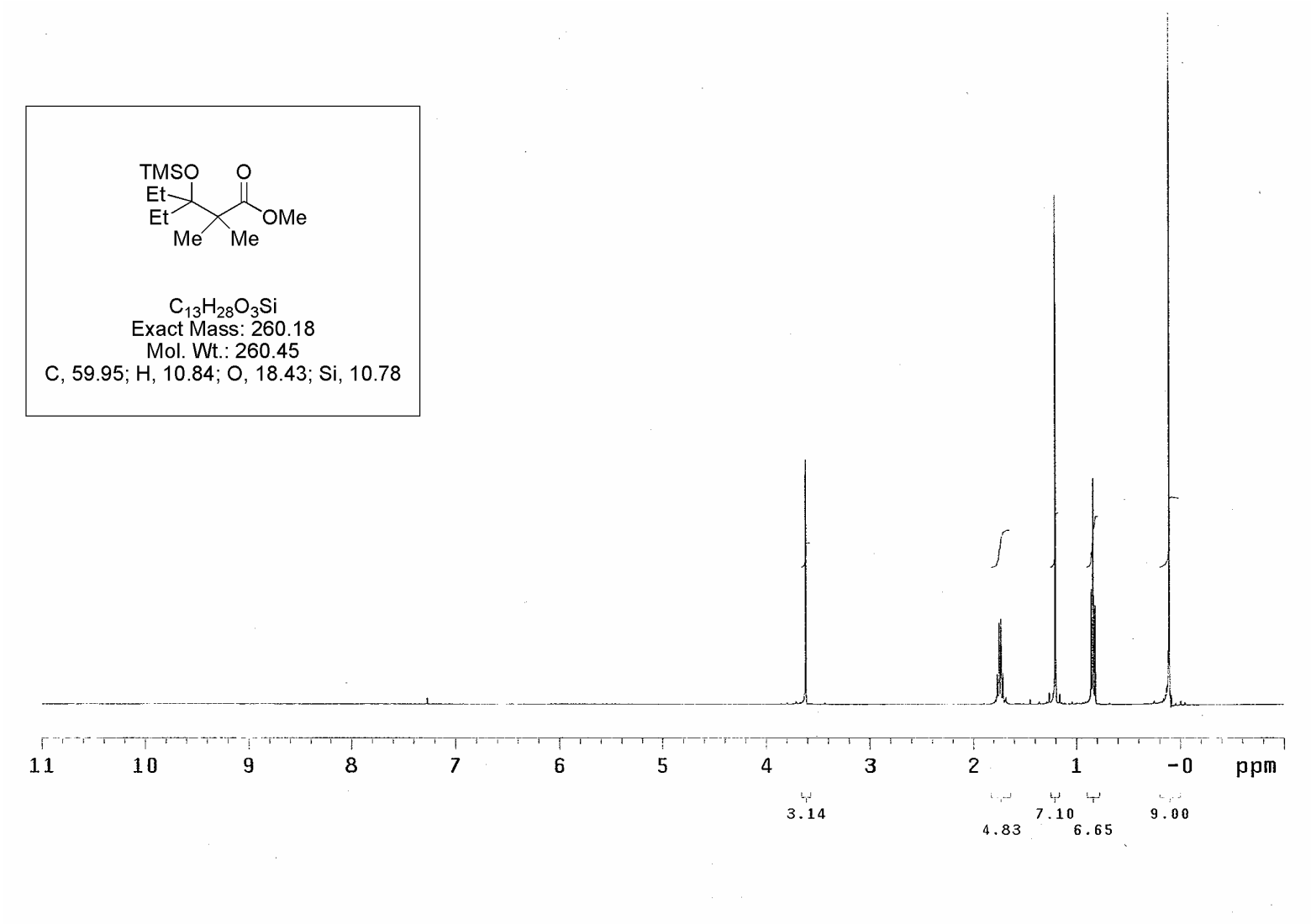
$C_{15}H_{22}O_2$
Exact Mass: 234.16
Mol. Wt.: 234.33
C, 76.88; H, 9.46; O, 13.66

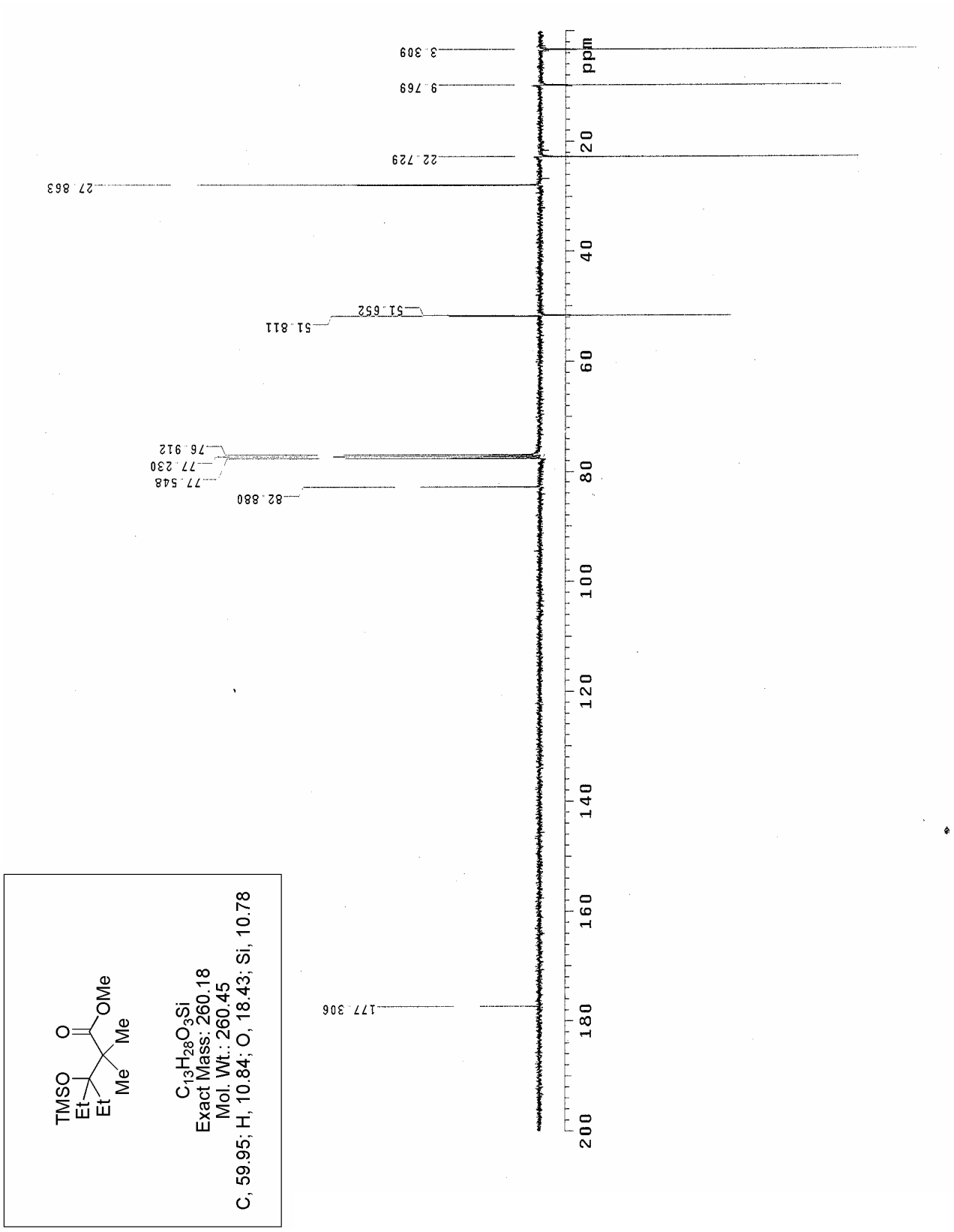

OH O t-Bu
Ph
C15H22O2
Exact Mass: 234.16
Mol. Wt.: 234.33
C, 76.88; H, 9.46; O, 13.66
ppm
20
40
60
80
100
120
140
160
180
200
26.566
32.140
38.336
43.356
44.614
67.250
76.919
77.230
77.548
125.884
128.440
128.538
141.991

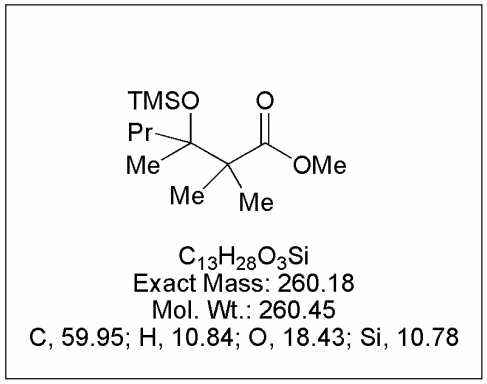


$C_{18}H_{30}O_2Si$
Exact Mass: 306.2
Mol. Wt.: 306.52
C, 70.53; H, 9.87; O, 10.44; Si, 9.16

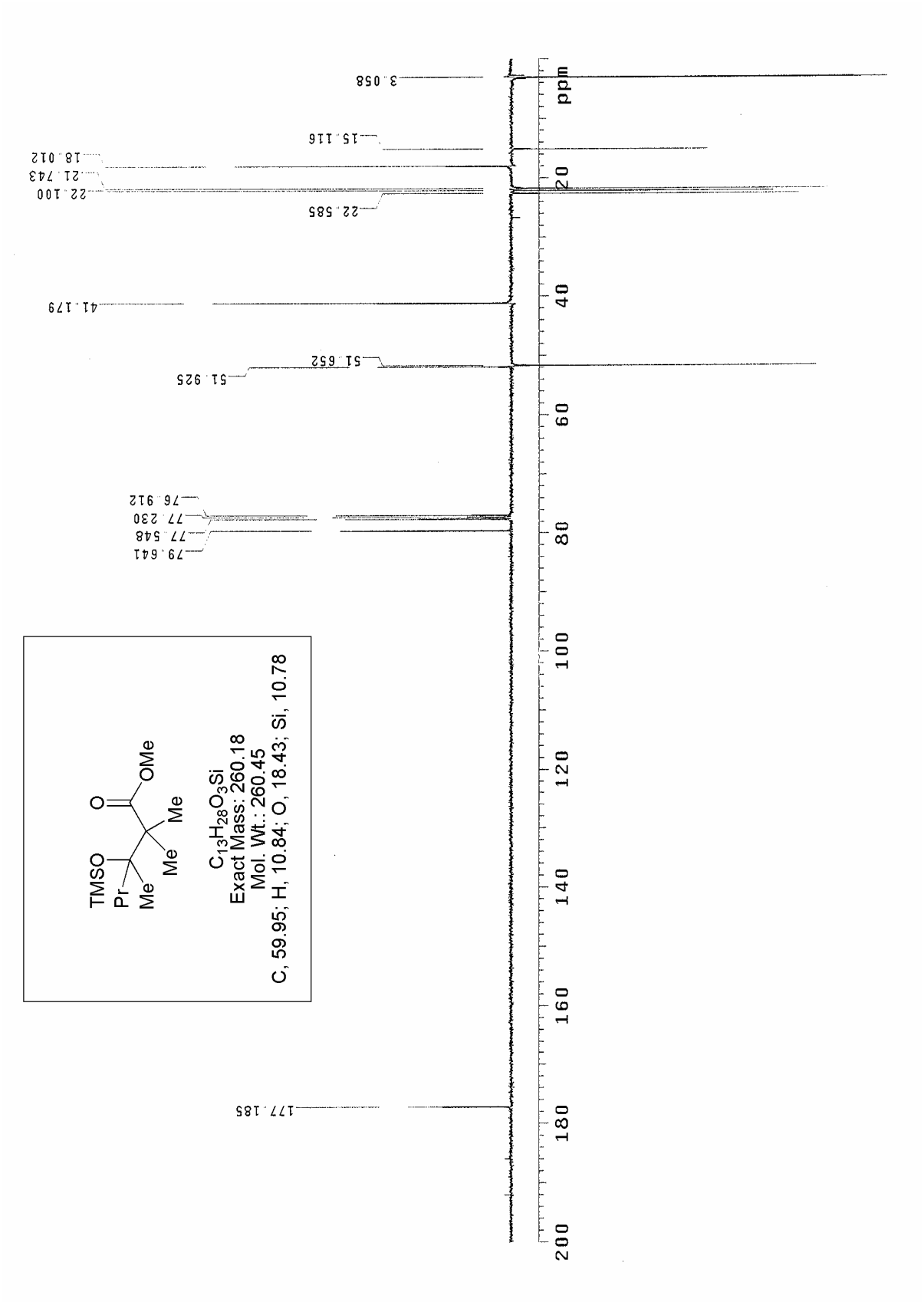

TMSO
O
t-Bu
Ph
$C_{18}H_{30}O_2Si$
Exact Mass: 306.2
Mol. Wt.: 306.52
C, 70.53; H, 9.87; O, 10.44; Si, 9.16
213.888
142.234
128.447
128.402
125.846
77.548
77.230
76.912
68.722
44.774
44.478
39.807
32.405
26.377
0.753
ppm
200
180
160
140
120
100
80
60
40
20
0


TMSO
O
Et
Et
OMe
Me
Me
C13H28O3Si
Exact Mass: 260.18
Mol. Wt.: 260.45
C, 59.95; H, 10.84; O, 18.43; Si, 10.78
11
10
9
8
7
6
5
4
3
2
1
-0
ppm
3.14
4.83
7.10
6.65
9.00


TMSO
Et
Et
O
OMe
Me
Me
C13H28O3Si
Exact Mass: 260.18
Mol. Wt.: 260.45
C, 59.95; H, 10.84; O, 18.43; Si, 10.78
177.306
82.880
77.548
77.230
76.912
51.811
51.652
27.863
22.729
9.769
3.309
ppm
200
180
160
140
120
100
80
60
40
20



$C_{13}H_{28}O_3Si$
Exact Mass: 260.18
Mol. Wt.: 260.45
C, 59.95; H, 10.84; O, 18.43; Si, 10.78


3.058
15.116
18.012
21.743
22.100
22.585
41.179
51.652
51.925
76.912
77.230
77.548
79.641
177.185
ppm
TMSO
Pr
Me
Me
Me
O
OMe
C13H28O3Si
Exact Mass: 260.18
Mol. Wt.: 260.45
C, 59.95; H, 10.84; O, 18.43; Si, 10.78

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