The Synthesis and Application of a Novel Gold-Cleavable Protecting Group for Alcohols

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## Introduction

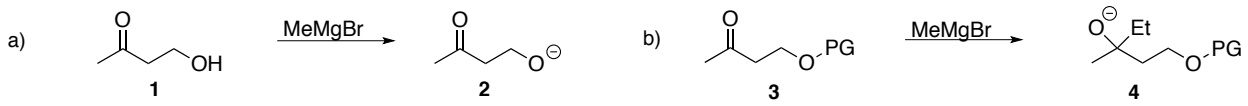
*Protecting Groups*

Protecting groups are important tools for streamlining and simplifying organic synthetic pathways. They are used to temporarily modify reactive functional groups to prevent deleterious side reactions. This allows researchers to develop syntheses that use simpler methods to introduce reactive functional groups and then simply protect them rather than resort to complicated, less efficient processes that add these functional groups in the final steps of the synthesis. In order to be effective, a functional group must meet several conditions:[1]

1. It must be installed and removed selectively in good yields.
2. It must form a protected complex that is stable in the predicted reaction conditions and be easily isolated from other byproducts.
3. It must have minimal additional functionality.

This balance can be surprisingly difficult to achieve when designing a protecting group.

Protecting groups are often used to prevent unwanted reactivity with alcohols. Hydroxyl groups are highly reactive and can act as acids, bases, and nucleophiles under various conditions. For example, Grignard reagents cannot be used when a substrate contains an alcohol, as the Grignard reagent will deprotonate the alcohol (**2**) instead of producing the desired functionality (Scheme 1a). However, the addition of a protecting group allows for nucleophilic addition of the Grignard instead of the deprotonation (Scheme 1b).

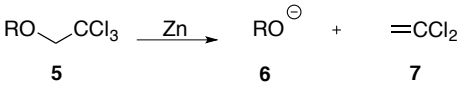



**Scheme 1:** Protecting group effects on Grignard reactions.

Protecting Group Cleavage

Methods of protecting group cleavage are very important in determining their usefulness. If cleavage conditions are too harsh, deleterious side reactions or decomposition of other functional groups can occur. If the conditions are not selective, the overall structure of the molecule could be affected. Other concerns are safety, cost, and practicality of the method. There are three main types of protecting group cleavage: assisted removal, electrolytic cleavage, and photolytic cleavage.[1] Each of these categories of deprotection is broad and encompasses a wide variety of potential reaction conditions.

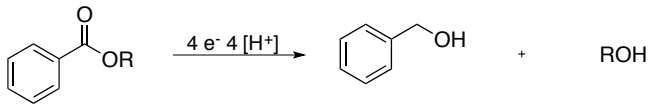
Assisted removal of a protecting group involves a reagent that is mechanistically required for the removal of the group. This additive depends on the cleavage conditions and could include a variety of reagents including acids, bases, or oxidants used stoichiometrically or catalytically. One example of assisted removal is the addition of zinc to facilitate the elimination of the alcohol to form an alkene (**7**) and form ZnCl (Scheme 2).[2] The advantage of assisted deprotection is the potential for specificity; if a protecting group is designed well, it can be removed with a specific reagent that does not affect the rest of the molecule. A possible disadvantage is the need for harsh conditions to attain this specificity. For example, some catalysts can be toxic, making them unsuitable for the synthesis of pharmaceuticals. The majority of protecting groups are cleaved via assisted deprotection.




**Scheme 2:** Assisted deprotection using zinc as a catalyst.

The second type of protecting group removal is electrolytic cleavage. This form of cleavage uses electrolytic oxidation or reduction to remove the protecting group from the substrate.[1] Reductive cleavages are generally more efficient than oxidative cleavages and

produce higher yields. Electrolytic cleavage has been used to remove various protecting groups, such as tosyl, benzoyl, and acetate (**8**) protecting groups (Scheme 3).[3] The substrate is dissolved in an electrolytic solvent, and the electric charge is passed through the solution between a cathode and an anode. In the example shown, a four electron reduction process occurs where the ester (**8**) is dissolved in a 1M solution of tetramethylammonium bromide in methanol and is reduced by the addition of four protons to produce a benzylic alcohol (**9**) and the protected alcohol (**10**). An advantage to electrolytic cleavage is that there is no need to add (and then remove upon completion of the reaction) chemical oxidants or reductants.[1] This is method is used less frequently due to the lack of selectivity and the limitations of the equipment.

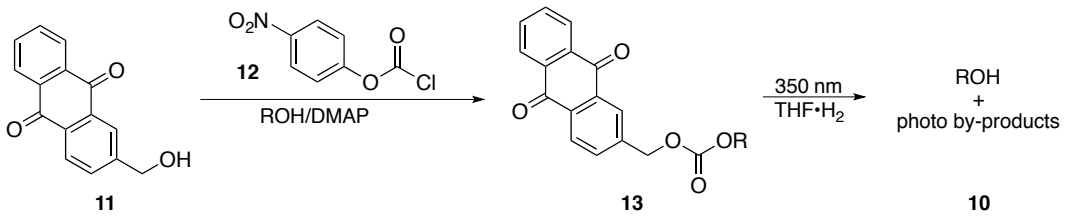



**8** **9** **10**

**Scheme 3:** Electrolytic cleavage of an acetate ester protecting group.

The final type of protecting group removal is photolytic cleavage. Photolytic removal of the protecting group requires irradiation of the protected alcohol with 254–350 nm light, often resulting in high yields of the deprotected alcohol.[1] Anthraquinon-2-methoxycarbonyl (Aqmoc) (**11**) is an example of a relatively novel, photochemically cleavable protecting group for alcohols created by Furuta et. al (Scheme 4).[4] Aqmoc can be cleaved with 350 nm light from galactose derivatives in 1:1 THF/$H_2O$. Experimental evidence indicates that this particular protecting group is cleaved via the triplet excited state. Cleavage of Aqmoc has the advantage yielding byproducts that are not strongly absorbing, making cleavage as simple as monitoring the disappearance of a peak in absorbance around 330 nm and the appearance of a weak peak around 380 nm. Photolytic cleavage requires no additional catalysts, oxidants, or reductants, but suffers from a lack of selectivity. The production of undesired byproducts is nearly impossible to avoid

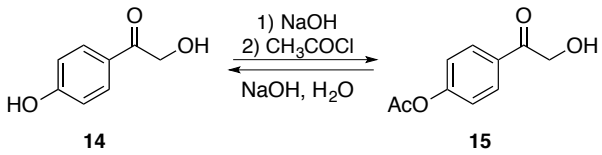
as radiation can form radicals at any position. Though some are more stable than others, it is impossible to completely prevent the formation of undesired radicals and detrimental side-reactions.




**Scheme 4:** Protection and cleavage of an alcohol with Aqmoc.

Historical Examples of Protecting Groups

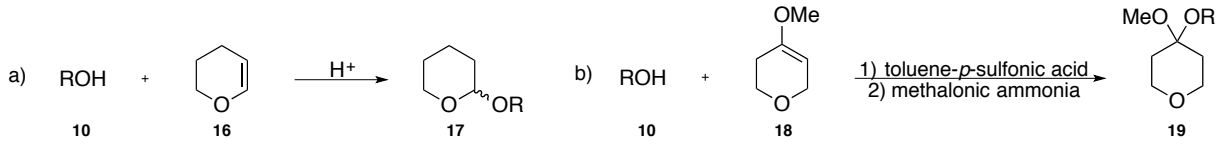
One of the earliest examples of hydroxyl protection was the selective protection of a phenolic hydoxyl group (**14**) as an acetate (**15**) (Scheme 5).[5] This allowed the aliphatic hydroxyl group to undergo further transformations and prevented the formation of byproducts that would be a result of the phenol functional group. The acetate can be removed by saponification. This simple form of deprotection reveals a major disadvantage to acetate and other ester protecting groups: if water is present, the ester can be easily cleaved under mild acidic or basic conditions. As a result, esters are labile and are not very selective or stable protecting groups.




**Scheme 5:** Selective protection of a phenol by formation of an acetate ester.

Another early, commonly used protecting group was the tetrahydropyranyl (THP) protecting group (**16**), which converted the targeted alcohol (**10**) into an acetal (**17**) (Scheme 6). It was first proposed and successfully applied to both phenolic and aliphatic alcohols in 1948 by Parham and Anderson.[6] One notable issue with this protecting group was the formation of a new

chiral center upon the protection of the alcohol (**17**), as the alcohol could add to either face of the double bond. This resulted in the formation of two different stereoisomers of the protected alcohol. The presence of multiple stereoisomers makes isolation and characterization of the product difficult. This problem was addressed by Reese, Saffhill, and Sulston in 1967 with the introduction of the 4-methoxy-5,6,-dihydro-2*H*-pyran protecting group (**18**).[7] This new group still acted as an effective protecting group comparable to THP without producing multiple stereoisomers. The protecting group formed an achiral product upon treatment with the alcohol, resulting in only one stereoisomer of the protected alcohol (**19**).




**Scheme 6:** Evolution of THP-derived protecting groups

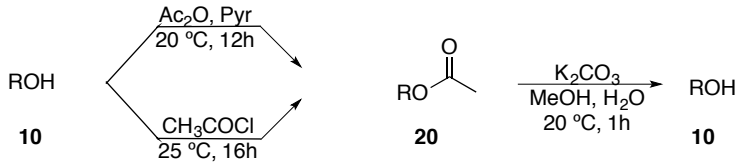
Classes of Protecting Groups

There are four main categories of hydroxyl protecting groups: acetates, silyl ethers, benzyl ethers, and acetals. They vary in overall stability and sensitivity to various reaction conditions. Acetate esters and silyl ethers tend to be less stable, while benzyl ethers are more robust.[8]

*Acetate Protecting Groups*

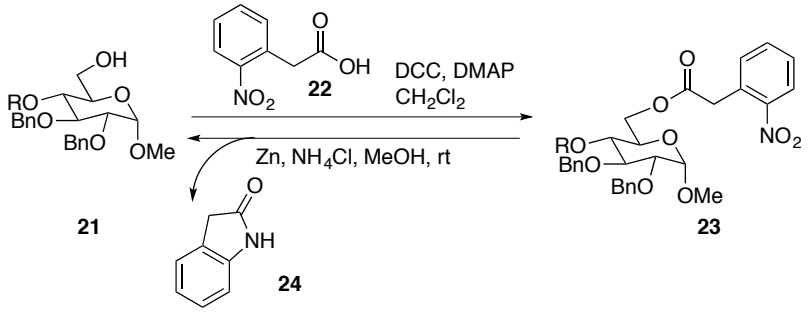
Acetate protecting groups convert the hydroxy functionality into an ester. However, acetate esters are susceptible to hydrolysis and are typically less stable than other types of protecting groups. Simple acetylation of a hydroxyl group is one of the most common forms of acetate protection. Acetate esters (**20**) can be formed in basic or acidic conditions (Scheme 7), as well as a wide variety of other reaction conditions.[1,9,10] Deprotection can be accomplished via hydrolysis with an acid catalyst or an enzyme.[1,11] Cleavage is carried out under mild conditions

that are often not selective. This susceptibility to hydrolysis limits the versatility of these protecting groups, as they are not stable when water is present.




**Scheme 7:** Acetylation (in both basic conditions) and deaceytlation of an alcohol.

(2-Nitrophenyl)acetyl (NPAc) (**22**) is an acetate protecting group developed in 2010 by Fugedi and Daragics.[12] NPAc is stable to a variety of reaction conditions, including acylation and acetylation reactions. It can be removed selectively in the presence of other alcohol protecting groups including various benzyl and silyl protecting groups. It is stable to the cleavage conditions of several other more labile protecting groups. NPAc is selectively cleaved when the nitro group is reduced to an amine, resulting in cleavage and cyclization of the cleaved group (**24**) (Scheme 8). It is still susceptible to acidic and basic conditions

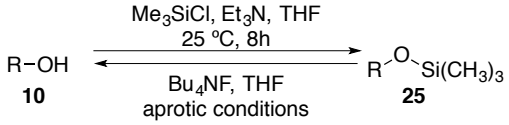



**Scheme 8:** Protection and deprotection of an alcohol using NPAc.

*Silyl Ether Protecting Groups*

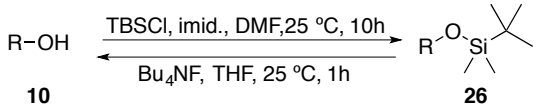
Silyl ethers are a type of hydroxyl protecting group that contain a silicon atom bound to the hydroxyl oxygen atom. Since silicon has a coordination number of four like carbon, silyl ethers typically each contain three additonal R groups bound to the silicon atom. Silyl ethers are modular; changes in the structure and characteristics of these groups change the properties of the

protecting group overall. Bulkier groups can result in steric effects while electron-withdrawing groups make the protected alcohol more susceptible towards basic conditions, but more resistant towards acidic conditions.[1] Like acetate protecting groups, silyl ethers are typically less stable protecting groups and have a tendency to migrate in the presence of a strong base in a protic solvent.[13] Silyl ethers can be cleaved in the presence of fluoride sources such as HF pyridine. This reagent is potentially dangerous and highly impractical because special equipment and safety measures are required: HF•pyridine etches glass and is capable of permeating skin. One of the most common silyl ether protecting groups is trimethylsilyl (TMS) ether (**25**). It is formed by treatment of the alcohol with chlorotrimethylsilane and is easily cleaved by fluoride sources such as HF•pyridine or TBAF (Scheme 9).[1,14] Fluoride forms a strong, energetically favorable bond with silicon, displacing the alcohol. TMS ethers are highly susceptible to acid hydrolysis, limiting their usefulness.[1]




**Scheme 9:** Protection and deprotection of an alcohol using TMS.

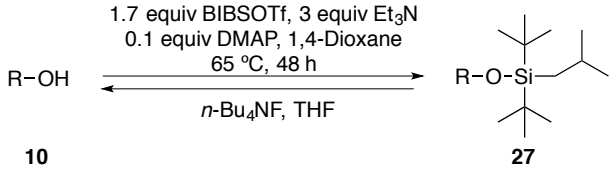
*tert*-Butyldimethylsilyl (TBS) ether (**26**) is a popular silyl ether protecting group due to its flexible protection conditions, stability, and selective removal.[1] It is stable towards basic hydrolysis, particularly in comparison to TMS, high temperatures, and a variety of organic reaction conditions, but it is sensitive to acid and can be metalated with *t*–BuLi.[15,16] It is formed by treating the hydroxyl group with TBSCl and imidazole, forming the protected product in very




**Scheme 10:** Protection and deprotection of an alcohol using TBS.

high yields, and can be selectively cleaved using fluoride ions (Scheme 10).[17] It is an improvement over TMS in stability due to its bulkier substituents, but its susceptibility to acidic conditions and metalation make it unsuitable for many reaction conditions.

Di-*tert*-butylisobutylsilyl (BIBS) (**27**) is a silyl ether protecting group developed in 2011 by Corey et al.[18] This protecting group can be used on a variety of oxygen-containing functional groups, including alcohols and acidic phenols such as 4-nitrophenol. BIBS ethers tend to be more stable than their TBS, triisopropyl silyl ether (TIPS), and *tert*-butyltdiphenyl silyl ether (TBDPS) ether counterparts. BIBS ethers, like other silyl ethers, are also stable to silica gel chromatography and dilute acid. This increased stability comes at the cost of harsher protection conditions requiring heating to 65 ºC and 48 h reaction times (Scheme 11). Like other silyl ethers, it can be selectively cleaved by fluoride sources. It can also be cleaved by hydrolysis, but at a much slower rate than other silyl ethers. This is due to the increased steric bulk of the isopropyl and *tert*-butyl substituents in comparison to the smaller substituents on other silyl ethers.

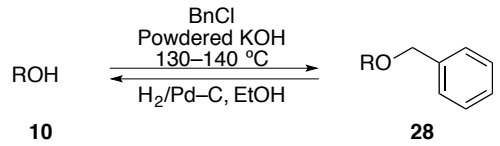



**Scheme 11:** Protection and deprotection of an alcohol using BIBS.

*Benzyl Protecting Groups*

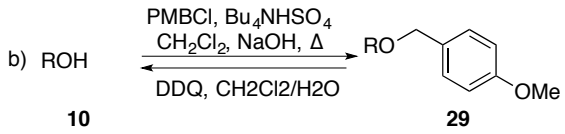
Benzyl protecting groups replace the hydroxyl proton with a benzyl ether. The benzyl group can be substituted a variety of ways which affect the properties of the protecting group. Benzyl ethers are more resilient and are traditionally used for protection throughout an entire synthesis, while less stable, more reactive protecting groups such as acetate esters and silyl ethers are used for a few steps before being cleaved.[8] The simplest benzyl protecting group is a benzyl

ether (**28**), without any substituents (Scheme 12). It is very robust and is orthogonal to other protecting groups, but it can participate in deleterious side reactions.[1] It is formed by treating the alcohol with benzyl chloride and can be cleaved many different ways, though the simplest is hydrogenation with a palladium catalyst.[19,20,21]




**Scheme 12:** Benzyl ether protecting group.

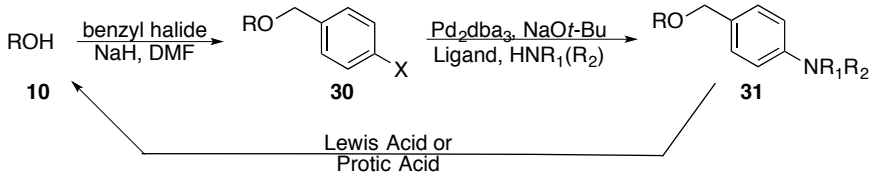
*Para*-methoxybenzyl (PMB) ether (**29**) is a benzyl protecting group containing a methoxy group at the *para* position, which is a strong activator. Similar methods are used to form and cleave PMB ethers as benzyl ethers (Scheme 13).[1] While PMB can also be cleaved by hydrogenation, the electron-donating methoxy group makes it susceptible to oxidative cleavage, making it less robust than its benzyl counterpart. However, this allows it to be selectively cleaved in the presence of benzyl protecting groups.




**Scheme 13:** PMB protecting group.

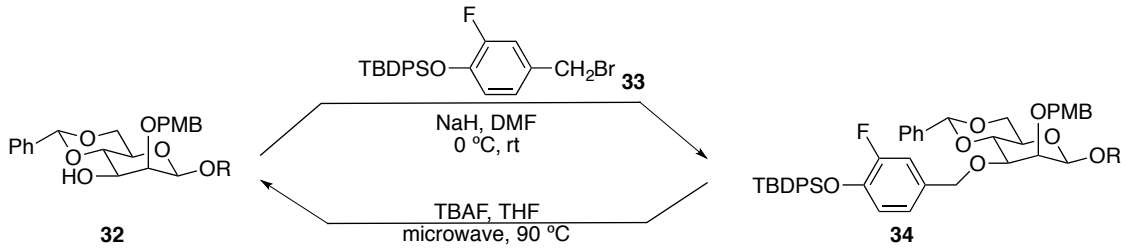
Protecting groups such as 4-bromobenzyl (PBB), 4-iodobenzyl (PIB), or 4-chlorobenzyl (PCB) are examples of another type of benzyl protecting group classified as halobenzyl ethers (**30**) initially proposed by Seeberger and Buchwald et al. in 2000 (Scheme 14).[8] There are a wide variety of such halobenzyl ether protecting groups, characterized by the substituents of the benzyl group. The halogen acts as an electron-withdrawing group and a deactivator of the aromatic ring. The hydroxyl group is protected by treating the compound with the benzyl halide in the presence of a base such as sodium hydride. Deprotection is a two step procedure: first

amination via a Buchwald-Hartwig palladium-catalyzed cross-coupling reaction followed by acidic cleavage. This two-step deprotection improves selectivity and allows deprotection in the presence of other protecting groups, but lengthens the synthesis. PIB has been selectively cleaved in the presence of both PBB and PCC, and PBB has been shown to be orthogonal to both TIPS and PMB.[8]




**Scheme 14:** Formation and cleavage of halobenzyl ether protecting groups.

4-(*tert*-Butyldiphenylsiloxy)-3-fluorobenzyl ether (**34**) was first reported in 2009 by Crich et al. (Scheme 15).[22] This protecting group is formed by treating the hydroxyl group with 4-(*tert*-butyldiphenylsiloxy)-3-fluorobenzyl bromide (**33**) with sodium hydride in DMF and is cleaved using microwave radiation (Scheme 15). Unlike PMB and benzyl ether, this protecting group is stable to hydrogenation conditions and is orthogonal to PMB, which is stable to microwave radiation.



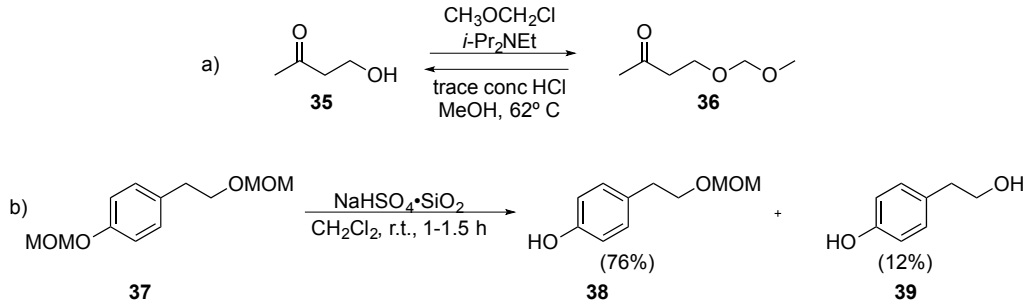

**Scheme 15:** Formation and cleavage of 4-(*tert*-butyldiphenylsiloxy)-3-fluorobenzyl ether protecting groups.

*Acetal Protecting Groups*

Acetal protecting groups form an acetal upon protection and can be removed via hydrolysis, though their stability and removal methods vary greatly. This variety of deprotection

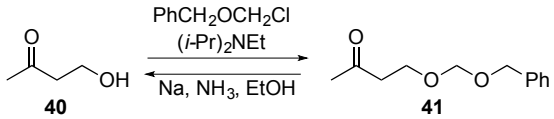
methods allows for tuning to specific reaction conditions. Acetal protecting groups vary in size and are useful for protecting a wide range of alcohols.

Methoxymethyl ether (MOM ether) is one of the most common and most useful protecting groups. It has a wide variety of protection and deprotection methods, making it tunable for various conditions.[1] One of the simplest methods of protection uses chloromethyl methyl ether which, though efficient, is a known DNA alkylator (Scheme 16a).[1,23] It is readily cleaved in acidic conditions in the presence of methanol.[24] Phenolic MOM protecting groups (**37**) can also be selectively cleaved over other protecting groups using silica-supported sodium bisulfate as a catalyst (Scheme 16b).[25] MOM is stable to mild acidic conditions and requires a strong Lewis Acid or hydrochloric acid to be cleaved, making it one of the most versatile, practically useful hydroxyl protecting groups.




**Scheme 16:** Protection using MOM ethers.

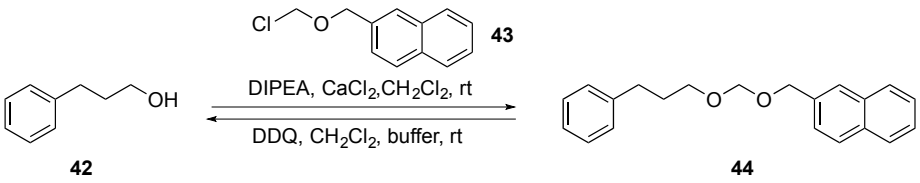
Benzyloxymethyl ether (BOM ether) (**41**) is bulkier than MOM and can provide more steric direction (Scheme17). Treatment of the alcohol with benzyl chloromethyl ether in base at lower temperatures results in production of the protected alcohol in good yields (Scheme 17).[26,27] The protecting group is then readily cleaved in oxidative or reductive conditions, similar to a




**Scheme 17:** Protection and removal of the BOM ether protecting group.

benzyl protecting group.[26,28]

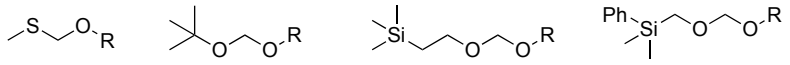
Acetal protecting groups are easily modified to afford different cleavage conditions. For example, 2-naphthylmethoxymethyl (NAPOM) (**31**) is a recently developed acetal-type hydroxyl protecting group proposed in 2015 by Torikai et al. (Scheme 18).[29] This protecting group is very large and can be introduced in mild conditions and removed in oxidative or some reductive conditions. It can be used to protect primary, secondary, and tertiary alcohols in good yields, though longer reaction times are required for tertiary alcohols. NAPOM is particularly useful in that it can also be selectively removed in the presence of 2-naphthylmethyl ether (NAP) and *p*-methoxybenzyl ether (PMB) protecting groups, and remains bound in the presence of ceric ammonium nitrate (CAN), which cleaves PMB, and camphorsulfonic acid (CSA), which cleaves TIPS.




**Scheme 18:** The protection and deprotection of a primary alcohol using NAPOM (**31**).

Acetal protecting groups are advantageous due to the fact that they are highly modifiable, yet still retain stability in comparison to other protecting groups. Acetate esters are very susceptible to hydrolysis, and benzyl protecting groups are almost all cleaved by oxidative or reductive conditions. Silyl ethers are also modular, but their tendency to migrate and their sensitivity to hydrolysis make them less versatile. The flexibility of acetals allows for chemists to be creative in their protecting group design and use the acetal model for a variety of reaction conditions and deprotection methods. Table 1 summarizes a variety of commonly used acetal protecting groups.

**Table 1: Acetal-type protecting groups.**

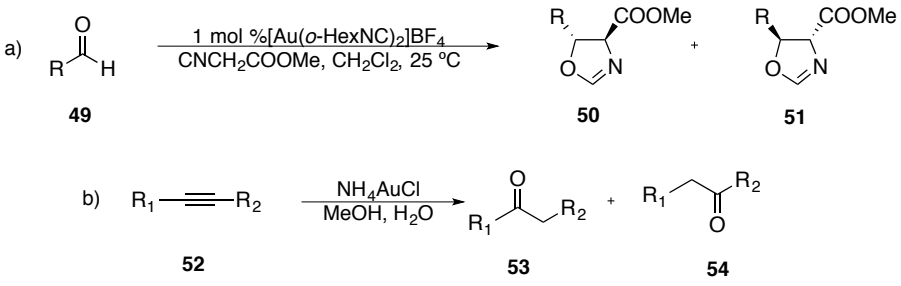


45 46 47 48

| Protecting Group | Protection | Deprotection |
|---|---|---|
| MOM ether (**36**) | MOMCl | Acidic hydrolysis |
| BOM ether (**41**) | BOMCl | Oxidative or reductive conditions |
| NAPOM ether (**44**) | NAPOMCl | Hydrogenation |
| Methylthiomethyl ether (MTM ether) (**45**) | MTMCl[30] | $HgCl_2$, HgS (s) |
| *t*-butoxymethyl ether (*t*-$BuOCH_2OR$) (**46**) | *t*-$BuOCH_2Cl$[31] | $CF_3COOH$ |
| 2-(Trimethylsilyl)ethoxymethyl ether (SEM-OR) (**47**) | SEMCl[32] | $Bu_4NF$, THF, or HMPA[32, 33] |
| (Phenyldimethylsilyl)methoxymethyl Ether (SMOM-OR) (**48**) | SMOMCl[34] | AcOOH, KBR, AcOH, NaOAc |

*Gold Catalysis*

Compared to other forms of catalysis, the development of gold-catalyzed organic transformations is relatively recent. This is in part due to the perception that gold is both inert and expensive.[35] Contrary to these assumptions, gold catalysts are mild and highly selective and the prices of gold catalysts are comparable to other metal catalysts. The first example of a gold-catalyzed reaction was that of Ito, Hayashi, and coworkers in 1986.[36] It was shown that a gold(I) catalyst could facilitate the reaction of an aldehyde (**49**) with isocyanoacetate to form oxazolines

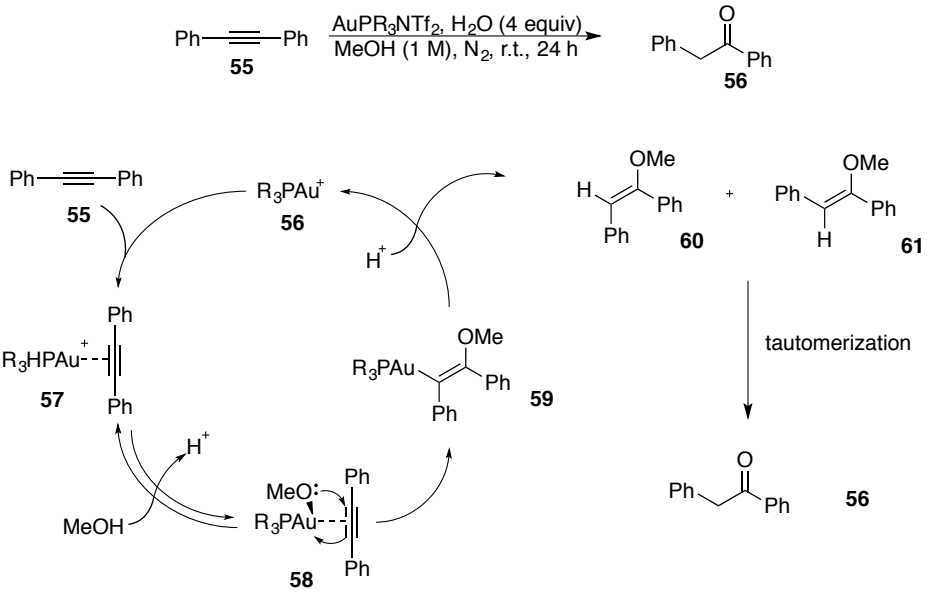



49 50 51 52 53 54

**Scheme 19:** Gold-catalyzed reactions of aldehydes and alkynes.

(**50** and **51**) (Scheme 19a). In 1991, Fukuda and Utimoto demonstrated that gold could catalyze the addition of various nucleophiles across alkynes (**52**) to form useful functional groups, such as ketones (**53** and **54**) from water and methanol (Scheme 19b).[35,37]

Gold (I) and (III) catalysts are electrophilic and act as Lewis acids.[35] The gold ion coordinates with alkynes and alkenes, withdrawing electron density from the bond and activating the system towards nucleophilic attack. Gold catalysts are often used in conjunction with a cocatalyst to increase Lewis acidity by abstracting a ligand from the gold complex, usually a halide. This mechanism is exemplified by the catalytic hydration of an alkyne (**55**) to form a ketone (**56**) as shown by Leyva et al. (Scheme 20).[38] Once the halide is abstracted from the catalyst, the gold(I) species coordinates to the alkyne (**57**), withdrawing electron density. Methanol associaties with the gold(I) catalyst, and the resulting methoxy group (**58**) attacks the alkyne via a migratory insertion to form an alkene (**59**). Protodemetallation results in cleavage of the gold catalyst from the alkene, and both the *cis* and *trans* products are formed (**60** and **61**). Both isomers then tautomerize to the final ketone in the presence of methanol (**56**).




**Scheme 20:** Gold (I)-catalyzed hydration of an alkyne reaction mechanism.[38]

Gold has the unique ability to both withdraw electron density and donate electron density due to the relativistic effects on its 6*s* (the LUMO) and 5*d* (the HOMO) orbitals.[39] Relativistic effects take into account factors that influence bonding and orbital size that were not incorporated into the original Schrödinger equations used to calculate the size and shape of atomic orbitals. The most significant relativistic effect is the increase in the mass of a particle as it approaches the speed of light.[40] In gold atoms, this causes the empty 6*s* orbital to contract and decrease in energy, increasing its acidity (Figure 21a). The filled 5*d* orbital expands and increases in energy, allowing it to stabilize empty *p*-orbitals on the substrate through π back-donation. Therefore, gold is able to act as an acid while also stabilizing adjacent carbocations. There are three ways the gold(I) atom participates in bonding: σ-donation from the substrate to the 6*s* orbital, π-backbonding from the $5d_{xz}$ or $5d_{yz}$ orbital to the *p* orbital of the substrate, and π-backbonding from the remaining 5*d* orbital to the *p*-orbital of the spectator ligand (Figure 21b). The amount of σ bonding is inversely related to the amount of π-backbonding. Spectator ligands that are σ-donating cause the substrate carbon to behave more like a carbene due to the decrease in π back-bonding away from the carbon resulting from the increase in the electron density of the

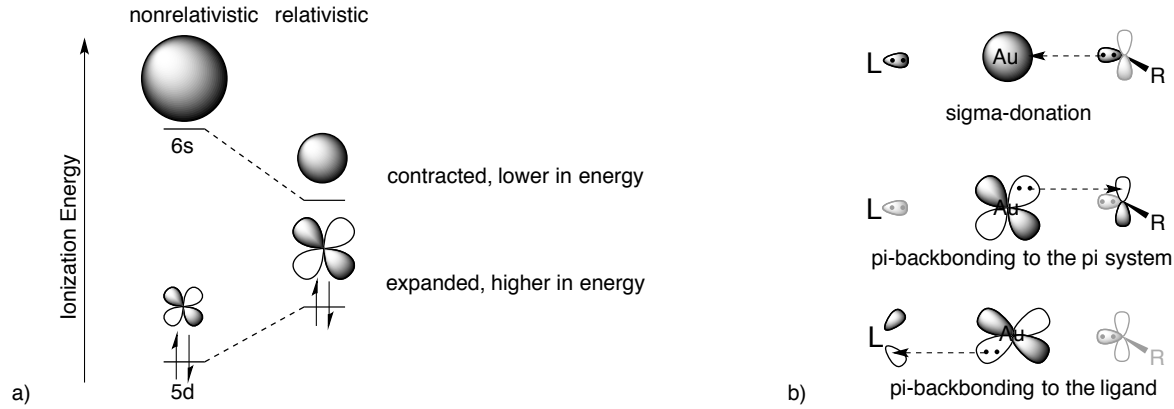


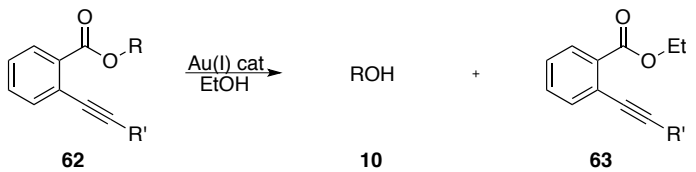

**Figure 21:**[40] a) Relativistic effects on the valence orbitals of gold and b) bonding of gold complexes.

gold, while π-acidic ligands withdraw electron density, shortening the bond between gold and carbon and causing the carbon to behave like a carbocation. The 5*d* orbital participates in π back-donation with both the ligand and the coordinated π system.[39,41] Bonds between gold and the substrate carbon therefore have both π and σ components, but with a total bond order of one.

The unique reactivity of gold catalysts allows them to catalyze a wide variety of reactions, including oxidations and reductions, addition of nucleophiles to electrophiles, cross-coupling reactions, and more.[35] Their selectivity for alkynes and mildness limits deleterious side reactions.

**Proposal**

Finding the balance between selectivity, stability, and practical cleavage conditions is a common issue in protecting group design. Protecting groups such as some silyl ethers and acetate esters are easily cleaved in mild conditions by hydrolysis and are therefore not stable or selective in their cleavage. Silyl ethers can be selectively cleaved with fluoride ions, but these conditions are often too harsh for practical use. Other protecting groups suffer from similar restrictions, seeking the balance between selectivity and practicality. Selective cleavage using a very specific, mild catalyst, such as gold, is a potential solution. Gold selectively coordinates to π systems, yet is also very mild. Previously, Asao et al. proposed a gold-cleavable, acetate-type protecting group (**62**) for alcohols, selectively cleaved by a gold(I) catalyst in the presence of ethanol (Scheme 22).[42] Benefits to the protecting group include selectivity and regeneration of the protecting group (**63**). However, as an acetate-type protecting group, it suffers from

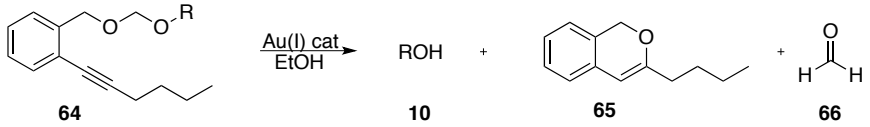



**62** **10** **63**

**Scheme 22:** Protecting group proposed by Asao et al.[42]

susceptibility to removal by hydrolysis as well as by reduction.[1]

Therefore, a novel, selective, gold-cleavable, aryloxymethyl acetal protecting group (**64**) for primary alcohols based on the acetate protecting group designed by Asao et al. is proposed (Scheme 23). This protecting group contains an acetal instead of an acetate, making it less susceptible to hydrolysis and more robust under acidic conditions. This protecting group is formed by an optimized, copper-free Sonogashira coupling followed by a chloromethyl ether formation. Byproducts of the deprotection include a nonpolar, aryl byproduct (**65**) and formaldehyde (**66**).

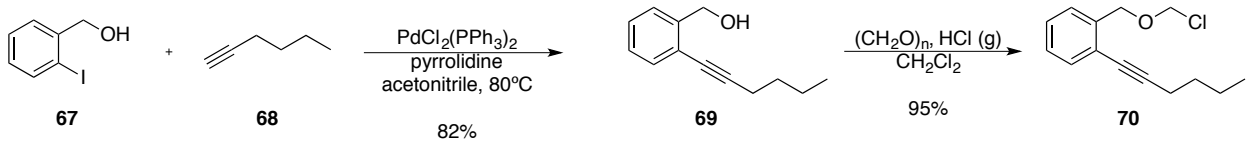



**Scheme 23:** The proposed gold-cleavable, acetal-type protecting group for hydroxyl groups.

**Results and Discussion**

*Synthesis of the Protecting Group*

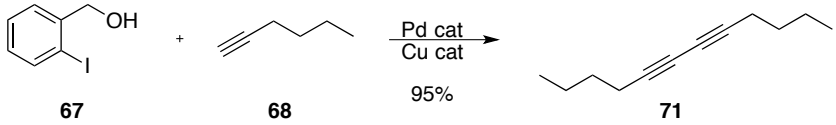
The proposed protecting group was synthesized in two steps: the first step was a Sonogashira coupling between 2-iodobenzyl alcohol (**67**) and 1-hexyne (**68**) (any monosubstituted alkyne with an alkyl functional group is suitable, 1-hexyne was selected for its availability) followed by a chloromethyl ether formation to form the protecting group (**70**) (Scheme 24).



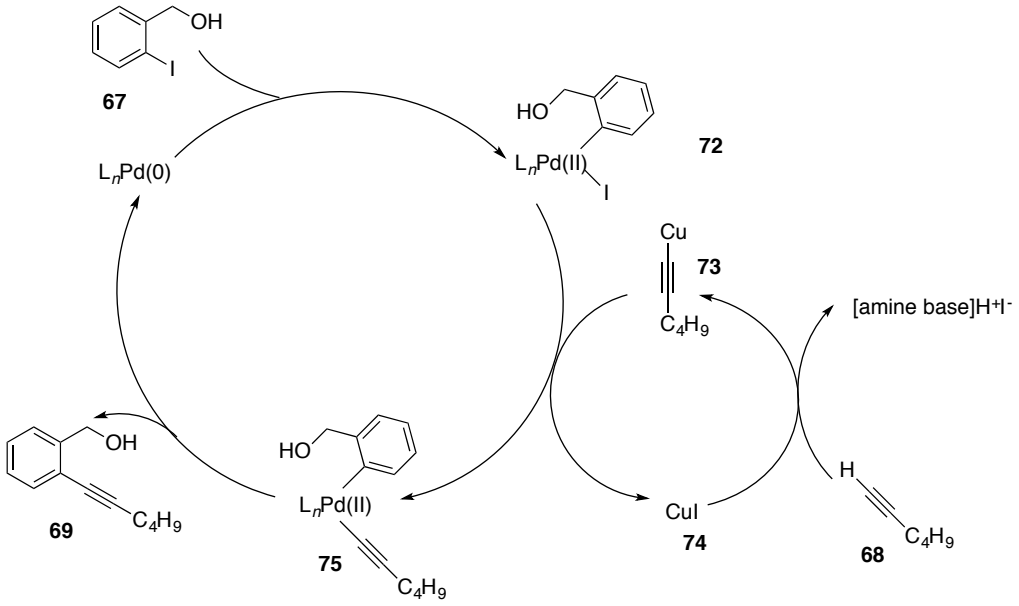

**Scheme 24:** Synthetic plan for the proposed protecting group.

Initial attempts to perform a traditional Sonogashira coupling between 2-iodobenzyl alcohol (**67**) and 1-hexyne (**68**) using both a palladium catalyst and a copper co-catalyst resulted

in a Glaser homocoupling (**71**) between two 1-hexyne molecules instead of the desired Sonogashira coupling (Scheme 25). This is likely due to the presence of oxygen gas which, in addition to the copper catalyst, is known to catalyze the Glaser coupling.[43] In a Sonogashira coupling, copper (I) is used as a cocatalyst to facilitate coordination of the alkyne to palladium (Scheme 26).[43] The Glaser coupling can be catalyzed using a variety of conditions involving copper (I), including one method that uses a palladium and a copper catalyst, similar to the conditions for a Sonogashira coupling.[44] The mechanism of the Glaser coupling is not fully elucidated and depends greatly on the reaction conditions.[43] A current theory suggests that the intermediate contains two copper centers (**79**) (Scheme 27). Isolation of the Glaser product (**71**)

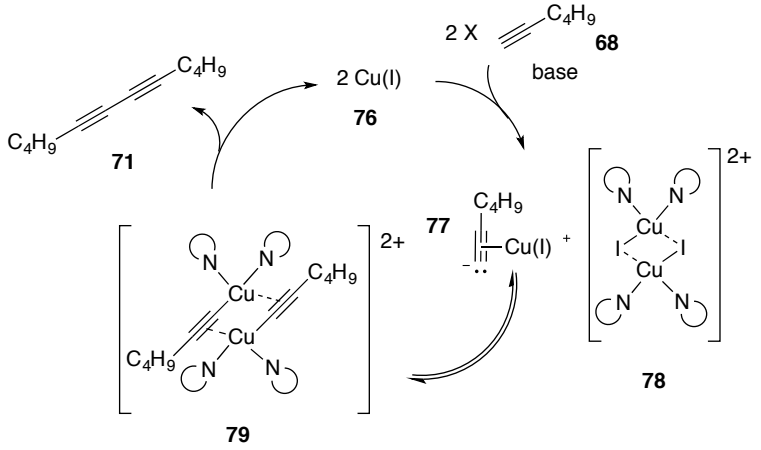



**Scheme 25:** Competing copper-catalyzed Glaser coupling.




**Scheme 26:** Copper-catalyzed Sonogashira coupling mechanism.[43]

was difficult due to the extremely nonpolar nature of the compound. Therefore, a copper-free Sonogashira coupling was developed to eliminate the competing Glaser coupling.

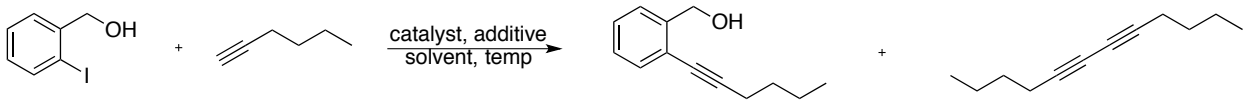



**Scheme 27:** Hypothesized Glaser coupling mechanism.[43]

The Sonogashira coupling was optimized by varying the solvent, additive, and temperature of the reaction (Table 2). Efficiency was determined by comparing the ratios of product (**69**) to starting material, which were determined by comparing the integrations of corresponding peaks in the $^{1}$H NMR spectra of the crude oil after extraction and concentration. The first method attempted was a traditional Sonogashira coupling with a copper co-catalyst and diisopropylamine in DMF (entry 1).[45] This resulted in a 3:5 ratio of product to starting material in addition to the copper-catalyzed Glaser coupling discussed above. Results were similar for a solvent-free, palladium and copper catalyzed Sonogashira coupling with triethylamine as an additive (entry 2).[46] A copper-free Sonogashira coupling developed by Li et al. using TBAF in THF was attempted because of its high rate of success with a variety of substrates without the use of copper (entry 3).[47] However, it produced a similar ratio of product to starting material as the conditions from entry 2. A reaction with silver (I) oxide as an additive instead of copper (I) iodide as proposed by Mori et al. was then attempted (entry 4).[48] Silver (I) was considered a good potential replacement for copper (I) as it has similar properties as copper and is known to

activate alkynes. In this case, it resulted in a less favorable conversion ratio. Changing the additive from silver to pyrrolidine and the solvent to water increased the ratio of product to starting material significantly (entries 5–7).[49] The catalyst was changed to $PdCl_2$ to determine catalyst effect, and it was found that $PdCl_2(PPh_3)_2$ was the better catalyst (entries 5–6). With the addition of pyrrolidine in water using the original catalyst, the reaction became reasonably effective, resulting in a 65% yield and a 4:1 ratio of the desired product to the starting material (entry 6). Increasing the equivalents of 1-hexyne did not improve the yield (entry 7). However, changing the solvent to acetonitrile and heating the reaction mixture to reflux resulted in high yields with almost complete conversion of the starting material to the product (entry 8). Due to the sensitivity of the catalyst to water, it became necessary to use distilled pyrrolidine to ensure successful reactivity, as pyrrolidine is easily contaminated with water over time.

**Table 2: Sonogashira coupling method development.**

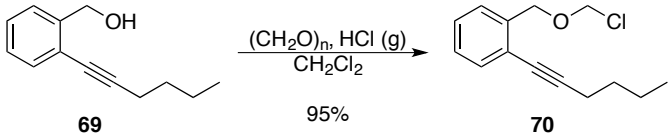



**67** **68** **69** **71**

| Entry | Catalyst | Additive | Solvent | Temp (°C) | 69:67 | Yield |
|---|---|---|---|---|---|---|
| 1[45] | $PdCl_2(PPh_3)_2$ | CuI, DIPA | DMF | 70 | 3:5 | ND |
| 2[46] | $PdCl_2(PPh_3)_2$ | CuI, $NEt_3$ | none | rt | 2:3 | ND |
| 3[47] | $PdCl_2(PPh_3)_2$ | TBAF | THF | 60 | 2:3 | ND |
| 4[48] | $PdCl_2(PPh_3)_2$ | $Ag_2O$ | THF | 60 | 1:4 | ND |
| 5[49] | $PdCl_2$ | Pyrrolidine | $H_2O$ | 50 | 5:2 | ND |
| 6 | $PdCl_2(PPh_3)_2$ | Pyrrolidine | $H_2O$ | 50 | 4:1 | 65% |
| 7 | $PdCl_2(PPh_3)_2$ | Pyrrolidine, 50 eq hexyne | $H_2O$ | 50 | 4:1 | 65% |
| 8 | $PdCl_2(PPh_3)_2$ | Pyrrolidine | $CH_3CN$ | 80 | >99:1 | 82% |

With a successful method for the synthesis of the coupled alkyne (**69**) developed, attempts at the last step of the protecting group synthesis, a chloromethyl ether formation, were made. Initial attempts using paraformaldehyde in TMSCl appeared successful according to $^1H$

NMR spectra of the crude oil.[50] However, further attempts failed to successfully repeat the process. Therefore, a different method using paraformaldehyde and HCl gas was used successfully with reproducibility (Scheme 28).[51] Gaseous hydrochloric acid was generated by treating calcium chloride with concentrated hydrochloric acid.[52] $^1$H NMR spectroscopy indicated that the crude oil was produced cleanly, precluding the need for column chromatography. This was advantageous, as attempts at purification revealed that the protecting group decomposed on silica gel. One disadvantage to this method is the corrosive nature of the gaseous hydrochloric acid, however, the simplicity, short reaction time, and near-complete conversion of the starting material to the desired product make this reaction ideal. Overall, the proposed protecting group (**70**) was synthesized in two steps with a 78% total yield.

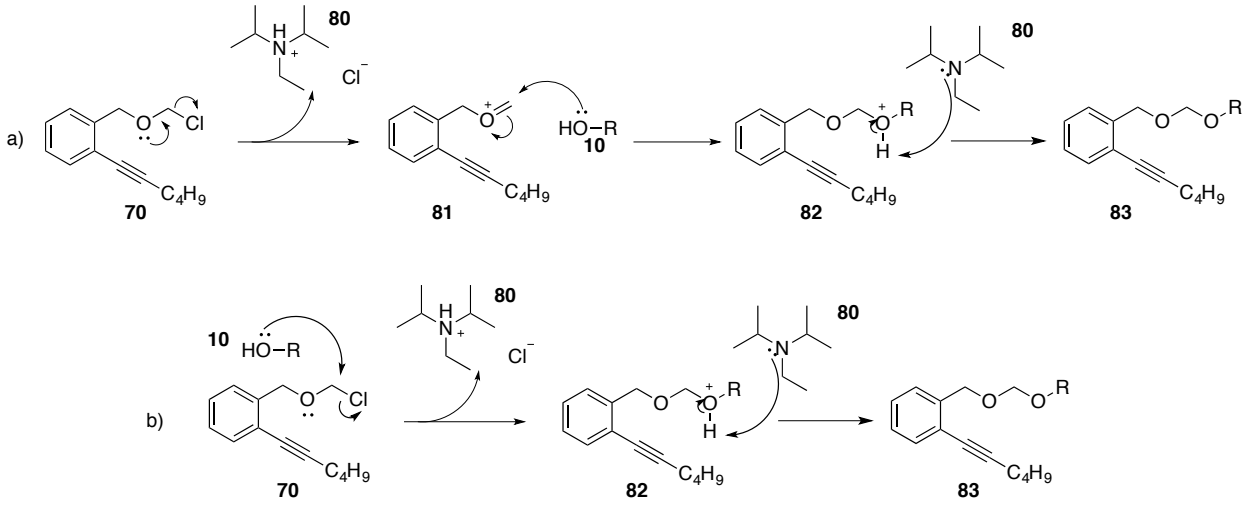



**Scheme 28:** Chloromethyl ether formation.

*Protection*

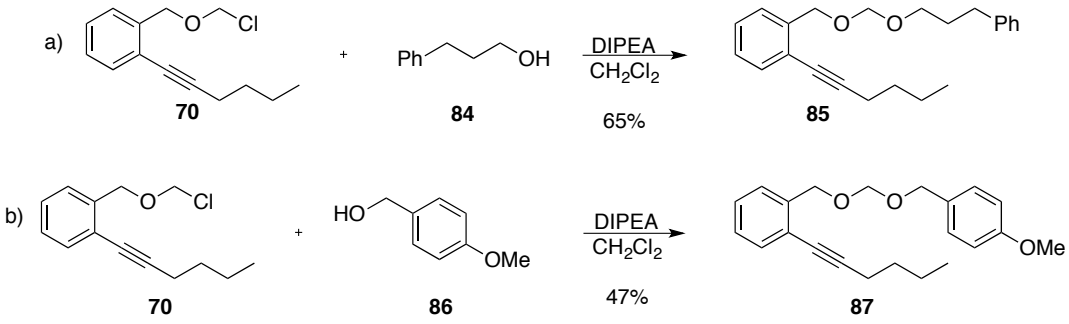
Protection of primary alcohols using the synthesized protecting group was straightforward, requiring only the addition of an ammine base in dichloromethane.[53] The reaction likely proceeds by either an $S_N2$ or $S_N1$ mechanism (Scheme 29). The proposed $S_N1$ mechanism involves the production of an oxocarbenium intermediate (**81**). $S_N1$ reactions do not normally occur at primary positions, but the stability of the oxocarbenium may facilitate cation formation. The $S_N2$ mechanism is also likely, but could suffer from steric effects depending on the bulk of the alcohol substituents. An $S_N2$ mechanism is more likely for a primary position and is thus the most probable mechanism in this situation. The presence of the base (**80**) stabilizes the free chlorine atoms in both cases. These reaction conditions are very similar to potential

protection conditions for BOM-ether protecting groups. Purification of the protected alcohol (**83**) was difficult due to the polarity of the product, resulting in overlap with other byproducts. One potential byproduct was the coupling of the protecting group with the benzylic alcohol of any Sonogashira product remaining from the chloromethyl ether formation that could not be extracted.




**Scheme 29:** a) $S_N1$ and b) $S_N2$ potential protection mechanisms.

Protection of 3-phenyl-1-propanol (**84**) to form the protected product (**85**) proceeded with 65% yields (Scheme 30a). However, switching to 4-methoxybenzyl alcohol (**86**) to aid with visualization and isolation in the deprotection step resulted in significantly lower yields of the protected product (**87**) (Scheme 30b). This could be due to steric hindrance, as the alcohol is at

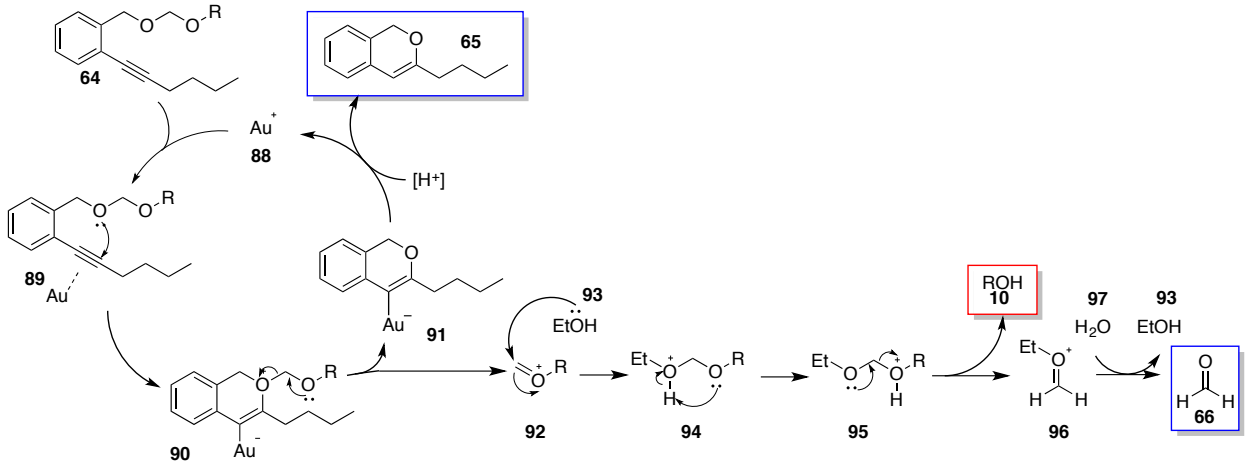



**Scheme 30:** Protection of a) 3-phenyl-1-propanol and b) 4-methoxybenzyl alcohol.

the benzylic position, putting the alkyl chain of the protecting group closer to the aromatic ring of the alcohol than if 3-phenyl-1-propanol was used. Dry diisopropylethylamine and dry dichloromethane were used, as the reaction is water-sensitive.

*Deprotection*

Once the alcohols were protected, gold (I)-catalyzed deprotection conditions were investigated. Conditions were chosen based on those used by Asao et al.[46] Cleavage of the protecting group from the alcohol was thought to proceed by the mechanism shown in Scheme 31**.** The proposed mechanism employs gold (I) (**88**) as a Lewis acid that selectively activates the alkyne to intramolecular nucleophilic attack (**89**). This results in a 6-*endo*-dig cyclization forming an oxocarbenium ion (**92**) as well as a new aryl side product (**65**). This cyclization follows Baldwin's Rules, a set of guidelines used to predict favored and disfavored ring-closing reactions.[54] A nucleophile such as ethanol or water must be present in order to reform the alcohol (**10**) from the oxocarbenium ion (**92**). The silver(I) catalyst was necessary to abstract the halogen from the gold catalyst to form the activated gold species.

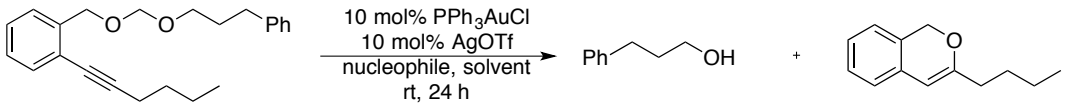



**Scheme 31:** Proposed mechanism of the gold-catalyzed cleavage of the protecting group.

3-phenyl-1-propanol (**84**) was chosen as the first substrate for protection and deprotection (Table 3). Initially, ethanol was used as both the solvent and nucleophile (entry 1). However, this

produced no detectable amounts of alcohol or aryl side product (**65**), so benzene was added as a solvent and the nucleophile was added in varying amounts (entries 2–5). The best conditions employed a 1:1 ratio of ethanol to benzene (entry 3), producing a 19% yield of 3-phenyl-1-propanol (**84**) and a 90% yield of the aryl side product (**65**). The use of water as a proton source was also mildly successful, with a 17% yield of the alcohol (entry 4). Undistilled benzene was found to contain sufficient amounts of water to cleave the protecting group from 3-phenyl-1-propanol (entry 5). Low yields of the alcohol for the deprotection coupled with good yields of the aryl side-product as characterized by $^1$H NMR spectroscopy indicated that the deprotection was successful, but there were issues with isolation of the alcohol. 3-Phenyl-1-propanol could only be visualized on TLC plates using a potassium permanganate or a CAM stain unless the concentration was sufficiently high, so the substrate for protection and deprotection was changed to the more easily visualized 4-methoxybenzyl alcohol.

**Table 3: Method development for the deprotection of 3-phenyl-1-propanol.**



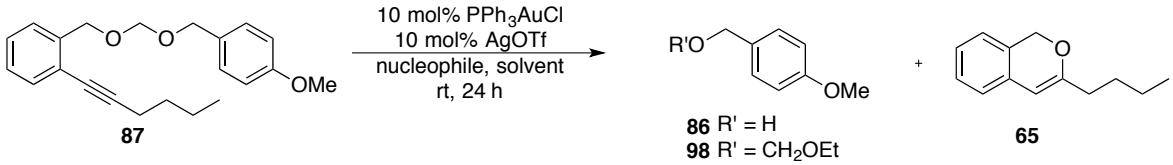

**85** **84** **65**

| Entry | Nucleophile | Solvent | Amount of Nucleophile | % yield alcohol | % yield aryl byproduct |
|---|---|---|---|---|---|
| 1 | EtOH | EtOH | - | NR | NR |
| 2 | EtOH | benzene | 1.5 equiv | 5 | 25 |
| 3 | EtOH | benzene | 0.5 M | 19 | 90 |
| 4 | $H_2O$ | benzene | 1.5 equiv | 17 | >100 |
| 5 | - | benzene | - | 12 | ND |

Protected 4-methoxybenzyl alcohol (**87**) was exposed to similar conditions as the 3-phenyl-1-propanol. Again, ethanol was ineffective as a both a solvent and a proton source, producing no discernible yield of the alcohol (Table 4, entry 1). A 1:1 ratio of ethanol and benzene produced higher yields of the cleaved product (59%). However, this was later determined to be a new acetal (**98**) rather than the desired alcohol. Water proved to be an

effective proton source that produced the desired alcohol (**86**), though with lower yields (entry 3). Dry benzene resulted in no production of the alcohol, but the solution turned a bright red color early in the reaction (entry 4). This is indicative of the formation of a benzyl cation.[55] The formation of this cation has implications on the hypothesized mechanism of the deprotection for this benzyl alcohol.

**Table 4: Method development for the deprotection of 4-methoxybenzyl alcohol.**




**87**

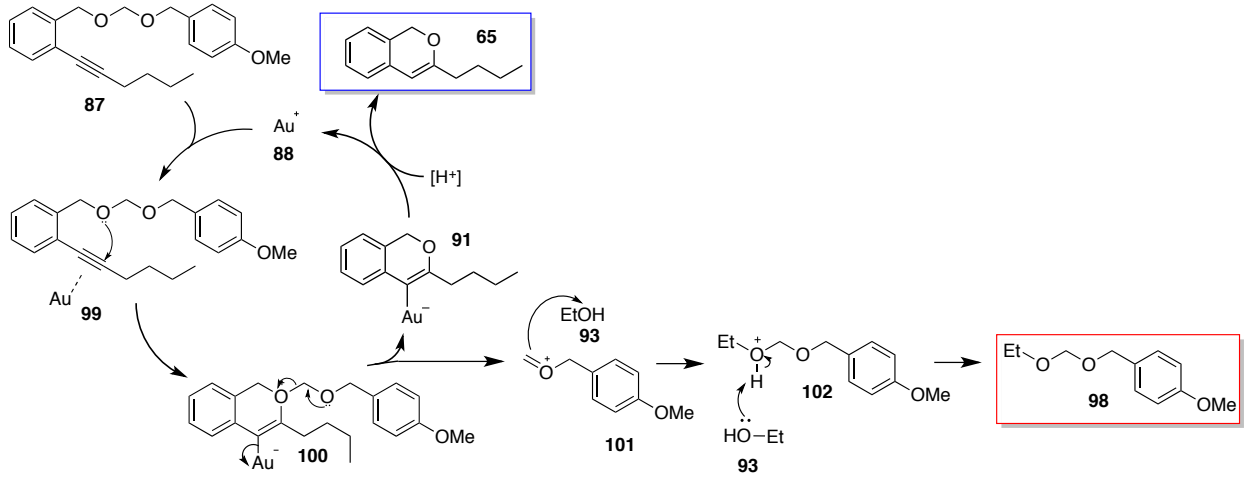
**86** R' = H
**98** R' = $CH_2OEt$

**65**

| Entry | Nucleophile | Solvent | Amount of Nucleophile | % yield alcohol (86) | % yield acetal (98) | % yield aryl byproduct |
|---|---|---|---|---|---|---|
| 1 | EtOH | EtOH | - | NR | NR | NR |
| 2 | EtOH | benzene | 0.5 M | 0 | 59 | 63 (impure) |
| 3 | $H_2O$ | dry benzene | 1.5 equiv | 32 | 0 | ND |
| 4 | - | dry benzene | - | NR | NR | NR |

It was found that 4-methoxybenzyl alcohol was being cleaved from the protecting group by a different mechanism than 3-phenyl-1-propanol when ethanol was used as an additive. Instead of 4-methoxybenzyl alcohol, a new product (**98**) was formed as the result of the attack of ethanol by the oxocarbenium ion intermediate (**101**) (Scheme 32). In this mechanism, no formaldehyde is produced after the aryl byproduct (**65**) leaves. Instead, the carbon remains and the oxocarbenium attacks the ethanol to form a new acetal (**98**), which is essentially an ethyloxymethyl protecting group bound to 4-methoxybenzyl alcohol. It was initially thought that the oxygen from 4-methoxybenzyl alcohol left to form a benzylic cation which was then attacked by water or ethanol. However, both proton and carbon NMR spectra contained peaks that indicated the formation of an acetal. These peaks are absent for entry 3, which contains no

ethanol. The formation of a new acetal is preferable, as the formation of a benzylic cation would mean loss of the original oxygen atom and loss of chirality for chiral alcohols.




**Scheme 32:** Proposed mechanism for the deprotection of 4-methoxybenzyl alcohol.

**Conclusion and Future Studies**

A novel, gold(I)-cleavable protecting group for hydroxyl groups was successfully synthesized in good yields and was applied to two different primary alcohols. Synthesis of the protecting group necessitated the development of a copper-free Sonogashira coupling and a chloromethyl ether formation, resulting in a 78% total yield of the protecting group. Two primary alcohols were protected using this novel protecting group, and these two alcohols were both successfully cleaved from the protecting group using a gold(I) catalyst. It was found that the benzylic alcohol had a different mechanism of cleavage than the other primary alcohol, which led to the cleavage of the initial protecting group and the formation of an ethyloxymethyl protecting group.

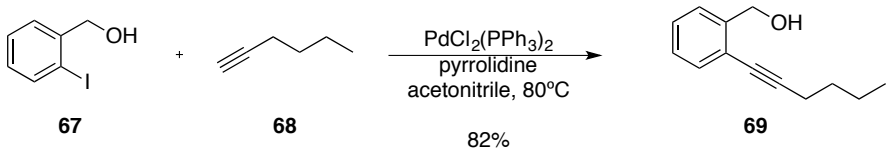
Future studies will involve continued optimization of both the protection and deprotection steps. Other alcohols will be tested, such as secondary and tertiary alcohols as well as other primary alcohols. The deprotection mechanism for benzylic alcohols will be further

investigated, particularly ways to cleave the protecting group without forming a new acetal. The protecting group structure itself will be further developed by modifying the alkyne substituent. The effects of electron-donating and electron-withdrawing groups on the alkyne could also be investigated. Finally, the robustness of the protected alcohol will be investigated by exposure to various reaction conditions, such as acidic, basic, oxidizing, and reducing reagents.

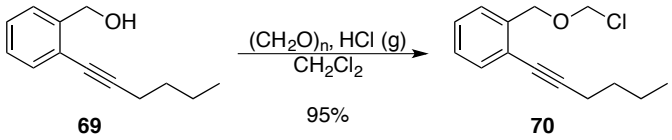
**General Experimental Details.** All reactions were run in flame-dried glassware under an intert atmosphere of nitrogen using standard syringe and septa techniques unless otherwise specified. All commercially available reagents were used as received unless otherwise stated. Pyrrolidine, dichloromethane ($CH_2Cl_2$), diisopropyethylamine (DIPEA), and benzene were distilled over calcium hydride when indicated. Column chromatography was performed using forced flow (flash chromatography) of the indicated eluent on silica gel. Thin layer chromatography (TLC) was performed on silica gel plates and developed plates were visualized with potassium permangangate or CAM stain.

$^{1}H$ and $^{13}C$ NMR spectra were recorded with a Varian Oxford 300 spectrometer (300 MHz for $^{1}H$ and 75 MHz for $^{13}C$) and were referenced to residual solvent peaks. Data are presented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants (in Hertz), and integration. Infrared spectra were recorded on a Nicolet iS5-IR spectrometer.

**Experimental**

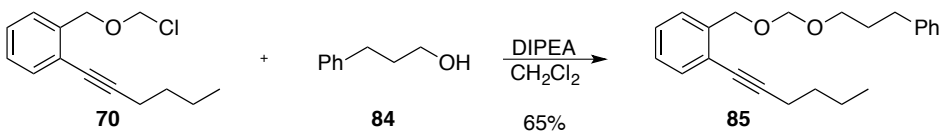



**2-(1-hexyn-1-yl)-benzenemethanol (69).** 2-iodobenzyl alcohol **67** (1.0 g, 4.27 mmol) was dissolved in 8.54 mL acetonitrile in a dry flask under nitrogen. Once it was dissolved, 1-hexyne **68** (0.613 mL, 5.34 mmol), pyrrolidine (0.713 ml, 8.54 mmol), and $PdCl_2(PPh_3)_2$ (60.0 mg, 0,0854 mmol) were added. The reaction mixture was heated to reflux and allowed to stir for 2 h 20 min. Once cooled, the reaction mixture was washed with 20 mL saturated aqueous $NH_4Cl$ and 20 mL $H_2O$ and was then extracted with ethyl acetate (3 x 20 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the crude residue by column chromatography (15% EtOAc/hexanes) yielded the title compound as an orange oil (0.658 g, 83%): $R_f$= 0.17 (15% EtOAc/hexanes); $^1$H NMR (300 MHz, $CDCl_3$) δ 7.46–7.35 (m, 2H), 7.30–7.18 (m, 2H) 4.78 (s, 2H), 2.45 (t, $J$ = 6.9, 2H), 1.65–1.42 (m, 4H), 0.95 (t, $J$ = 7.2, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 144.5, 139.2, 132.3, 128.0, 127.4, 127.2, 95.6, 78.2, 64.2, 30.9, 22.1, 19.3, 13.7; IR (thin film) 3331, 3065, 2956, 2929, 2871, 2227, 1600 cm$^{-1}$.



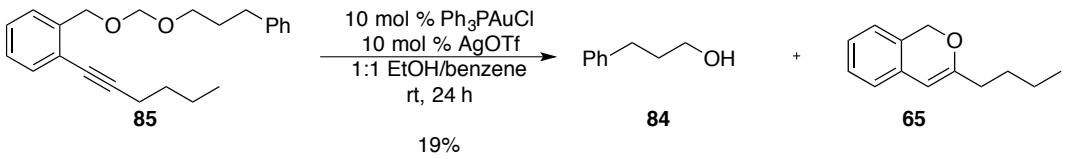

**Chloromethyl Ether (70).** 2-(1-hexyn-1-yl)-benzenemethanol **69** (200 mg, 1.06 mmol) and paraformaldehyde (35.1 mg, 1.17 mmol) were dissolved in 5 mL $CH_2Cl_2$. Concentrated HCl was added dropwise via addition flask into solid $CaCl_2$ to produce HCl gas, which was allowed to bubble through the reaction mixture for 1 h. After 1 h, HCl gas production was stopped and 10 mL pentane was added to the reaction mixture. The mixture was dried over $MgSO_4$ and

concentrated *in vacuo*, yielding a brown oil (0.2385 g, 95%); $^{1}$H NMR (300 MHz, $CDCl_3$) δ 7.47–7.25 (m, 4H), 5.60 (s, 2H), 4.91 (s, 2H), 2.48 (t, $J$ = 6.9, 2H), 1.66–1.44 (m, 4H), 1.00–0.91 (m, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 137.4, 132.4, 132.3, 128.5, 128.2, 128.0, 95.8, 82.6, 78.1, 70.3, 31.0, 22.3, 19.5, 13.9; IR (thin film) 2956, 2930, 2871, 2229, 1601, 1116, 756 cm$^{-1}$.

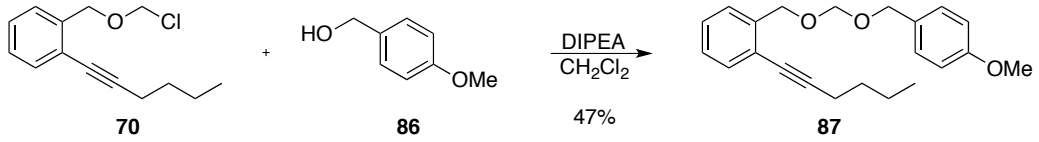



**70** **84** 65% **85**

**Acetal 1 (85).** To a solution of 3-phenyl-1-propanol **84** (0.088 mL, 0.647 mmol) in 1.65 mL $CH_2Cl_2$ in a dry flask under nitrogen was added DIPEA (0.170 mL, 0.971 mmol). The solution was stirred at 0 ºC for 10 min. Chloromethyl ether **70** (191.5 mg, 0.809 mmol) dissolved in 5 mL $CH_2Cl_2$ was added. The reaction mixture was allowed to stir at 0 ºC under nitrogen for 1 h. The reaction mixture was then removed from the ice bath and was allowed to stir at room temperature for 18 h under nitrogen. The reaction mixture was then diluted with 10 mL $CH_2Cl_2$ and washed with 10 mL sat aq $NaHCO_3$, 10 mL distilled water, and 10 mL sat aq sodium chloride. The organic layer was dried over $MgSO_4$ and the mixture was concentrated *in vacuo*. Purification of the crude residue by column chromatography (10% EtOAc/hexanes) yielded the title compound as a yellow oil (0.1426 g, 65%): $R_f$ = 0.20 (10% EtOAc/hexanes); $^{1}$H NMR (300 MHz, $CDCl_3$) δ 7.48–7.39 (m, 2H), 7.29–7.15 (m, 5H), 4.82 (s, 2H), 4.78 (s, 2H), 3.63 (t, $J$ = 6.3, 2H), 2.72 (t, $J$ = 7.5, 2H), 2.43 (t, $J$ = 6.9, 2H), 1.98–1.88 (m, 2H), 1.64–1.41 (m, 2H), 0.96–0.90 (m, 5H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 141.9, 139.6, 132.1, 128.5 (2), 128.4 (2), 127.7, 127.6, 127.5, 127.2, 125.9, 122,7, 95.2, 78.2, 67.9, 67.3, 32.5, 31.5, 31.0, 22.1, 19.3, 13.7; IR (thin film) 3027, 2956, 2930, 2872, 10366 cm$^{-1}$.

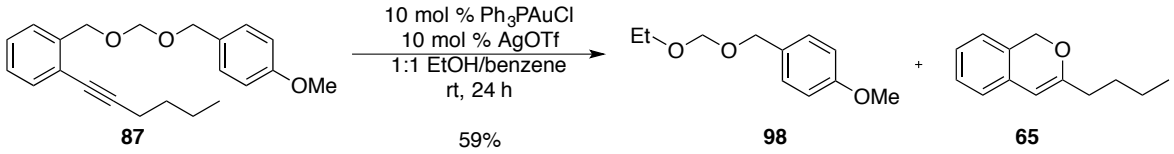



**3-Phenyl-1-propanol (84).** To a mixture of acetal 1 **85** (100. mg, 0.297 mmol) in 50% EtOH/benzene (1.188 mL) was added $Ph_3PAuCl$ (14.7 mg, 0.0297 mmol) and AgOTf (7.63 mg, 0.0297 mmol). The mixture was allowed to stir at room temperature under nitrogen for 24 h. The reaction mixture was washed with 5 mL sat aq $NaHCO_3$ and was extracted with $Et_2O$ (3 x 5 mL). The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the crude residue by column chromatography (30% EtOAc/hexanes) yielded the title compound as a pale yellow oil (0.0075 g, 19%): $R_f$ = 0.26 (30% EtOAc/hexanes); NMR and IR spectroscopy were found to correspond to known spectra for 3-phenyl-1-propanol.




**Acetal 2 (87).** To a solution of 4-methoxylbenzyl alcohol **86** (0.227 mL, 1.830mmol) in 4.576 mL dry $CH_2Cl_2$ in a dry flask under nitrogen was added dry DIPEA (0.478 mL, 2.746). The solution was stirred at 0 ºC for 10 min. Chloromethyl ether **70** (191.5 mg, 0.809 mmol) dissolved in 5 mL $CH_2Cl_2$ was added. The reaction mixture was allowed to stir at 0 ºC under nitrogen for 1 h. The reaction mixture was then removed from the ice bath and was allowed to stir at room temperature for 18 h under nitrogen. The reaction mixture was then diluted with 10 mL $CH_2Cl_2$ and washed with 10 mL sat aq $NaHCO_3$, 10 mL distilled water, and 10 mL sat aq sodium chloride. The organic layer was dried over $MgSO_4$ and the mixture was concentrated *in vacuo*. Purification of the crude residue by column chromatography (5% EtOAc/hexanes) yielded the title compound as a yellow oil (0.2901 g, 47%): $R_f$ = 0.78 (20% EtOAc/hexanes); $^1$H NMR (300

MHz, $CDCl_3$) δ 7.46 (t, *J* = 9.6, 2H), 7.33–7.24 (m, 4H), 6.91 (d, *J* = 6.9, 2H), 4.90 (s, 2H), 4.82 (s, 2H), 4.64 (s, 2H), 3.82 (s, 3H), 2.45 (t, *J* = 7.2, 3H), 1.60 (q, *J* = 7.2, 2H), 1.50 (q, *J* = 7.5, 2H), 0.96 (t, *J* = 7.2, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 159.5, 139.7, 132.4, 130.2, 129.9 (2), 127.9, 127.8, 127.5, 123.1, 114.1 (2), 95.4, 94.4, 78.4, 69.3, 68.3, 55.5, 31.1, 22.3, 19.5, 13.9; IR (thin film) 2931, 2872, 1032 cm$^{-1}$.




**4-Methoxybenzyl ethyloxymethyl ether (98).** To a mixture of protected 4-methoxybenzyl alcohol **87** (0.2732 g, 0.8073 mmol) in 50% EtOH/benzene (3.230 mL, 0.25 M) was added $Ph_3PAuCl$ (33.9 mg, 0.0807 mmol) and AgOTf (20.7 mg, 0.0807 mmol). The mixture was allowed to stir at room temperature under nitrogen for 24 h. The reaction mixture was washed with 10 mL saturated aqueous $NaHCO_3$ and was extracted with diethyl ether (3 x 15 mL). The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the crude residue by column chromatography (30% EtOAc/hexanes) yielded the title compound as a pale yellow oil (0.0935 g, 70%): $R_f$ = 0.58 (15-30% EtOAc/hexanes); $^1$H NMR (300 MHz, $CDCl_3$) δ 7.28 (d, *J* = 8.4, 2H), 6.88 (d, *J* = 8.4, 2H), 4.75 (s, 2H), 4.55 (s, 2H), 3.82 (s, 3H), 3.66 (t, *J* = 7.2, 3H), 1.25 (q, *J* = 7.2, 2H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 159.4, 130.2, 129.8 (2), 114.0 (2), 94.3, 69.1, 63.5, 55.5, 15.4; IR (thin film) 2931, 1725, 1032 cm$^{-1}$.

**Isochromeme (65)** $R_f$ = 0.87 $^1$H NMR (300 MHz, $CDCl_3$) δ 7.17 (t, *J* = 7.5, 1H), 7.07, (t, *J* = 6.6, 1H), 6.96 ( d, *J* = 7.2, 1H), 6.90 (d, *J* = 7.2, 1H), 5.64 (s, 1H), 5.03 (s, 2H), 2.19 (t, *J* = 7.5, 2H), 1.55 (quint, *J* = 6.3, 2H), 1.38 (sext, *J* = 7.5, 2H), 0.93 (t, *J* = 7.2, 3H); $^{13}$C NMR (75 MHz,

$CDCl_3$) δ 159.1, 132.3, 128.3, 127.4, 125.8, 123.9, 122.6, 101.1, 68.9, 33.6, 29.4, 22.6, 14.2 ; IR (thin film) 3021, 2956, 2928, 2859, 1642 $cm^{-1}$.

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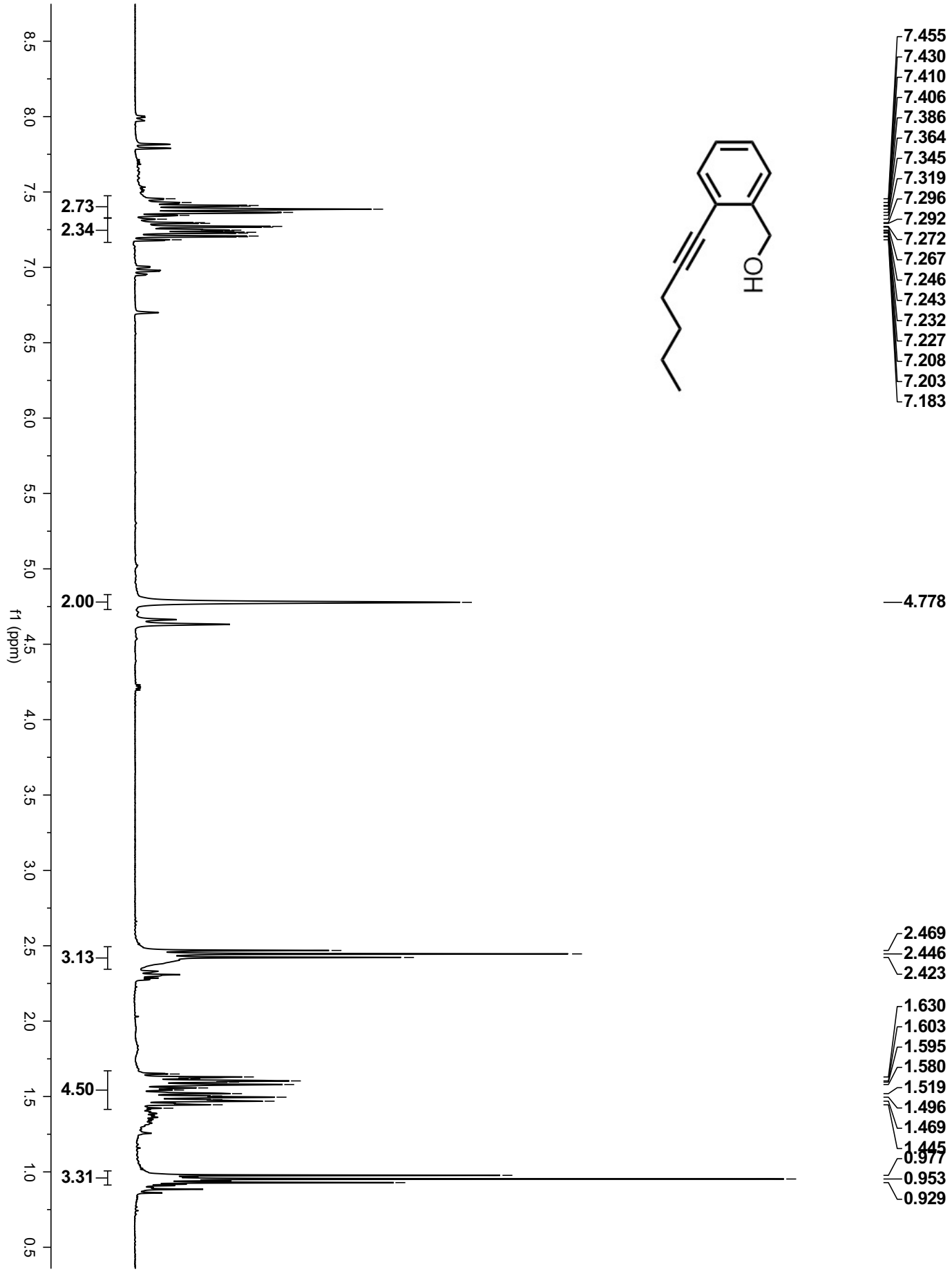
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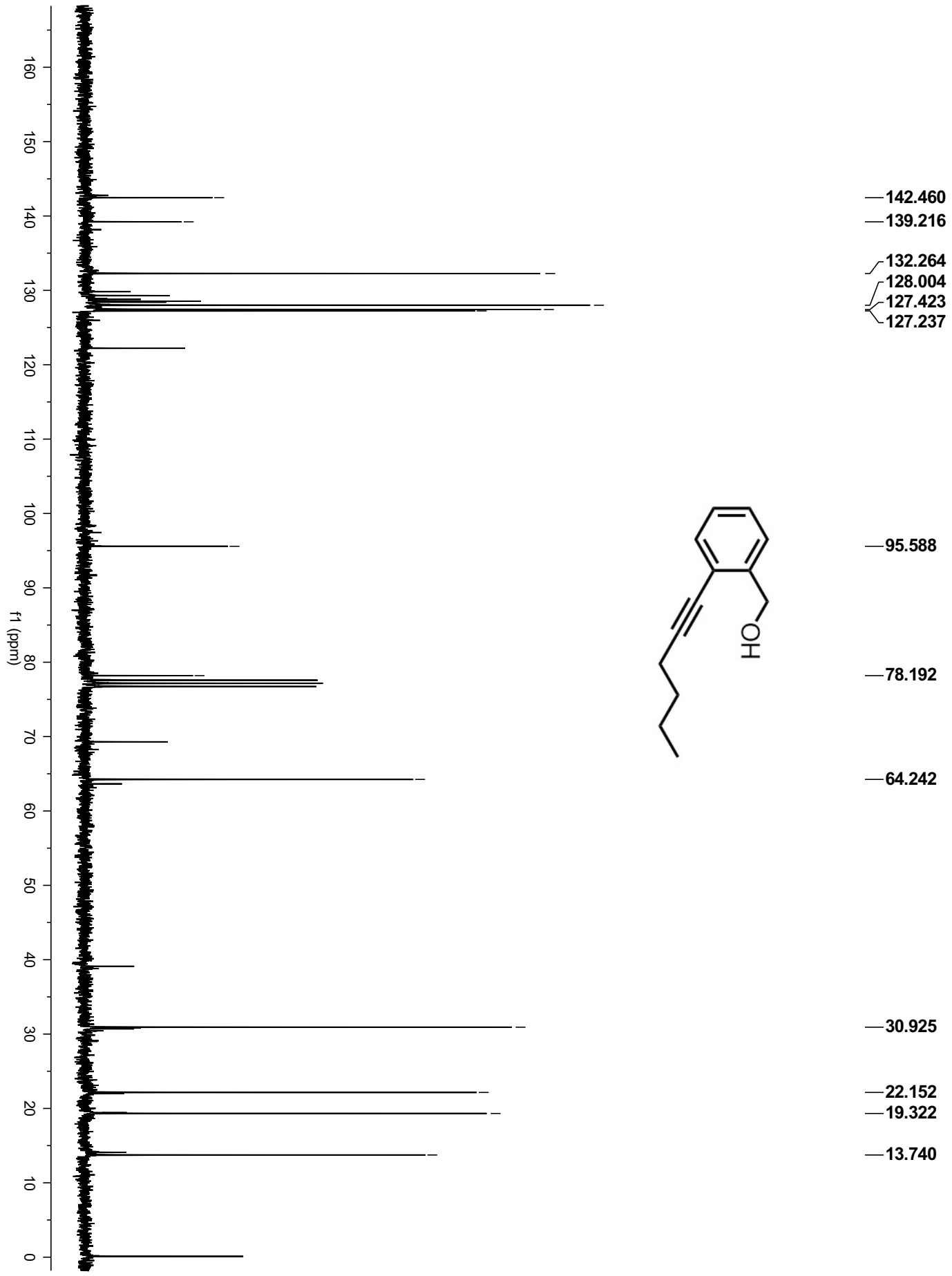
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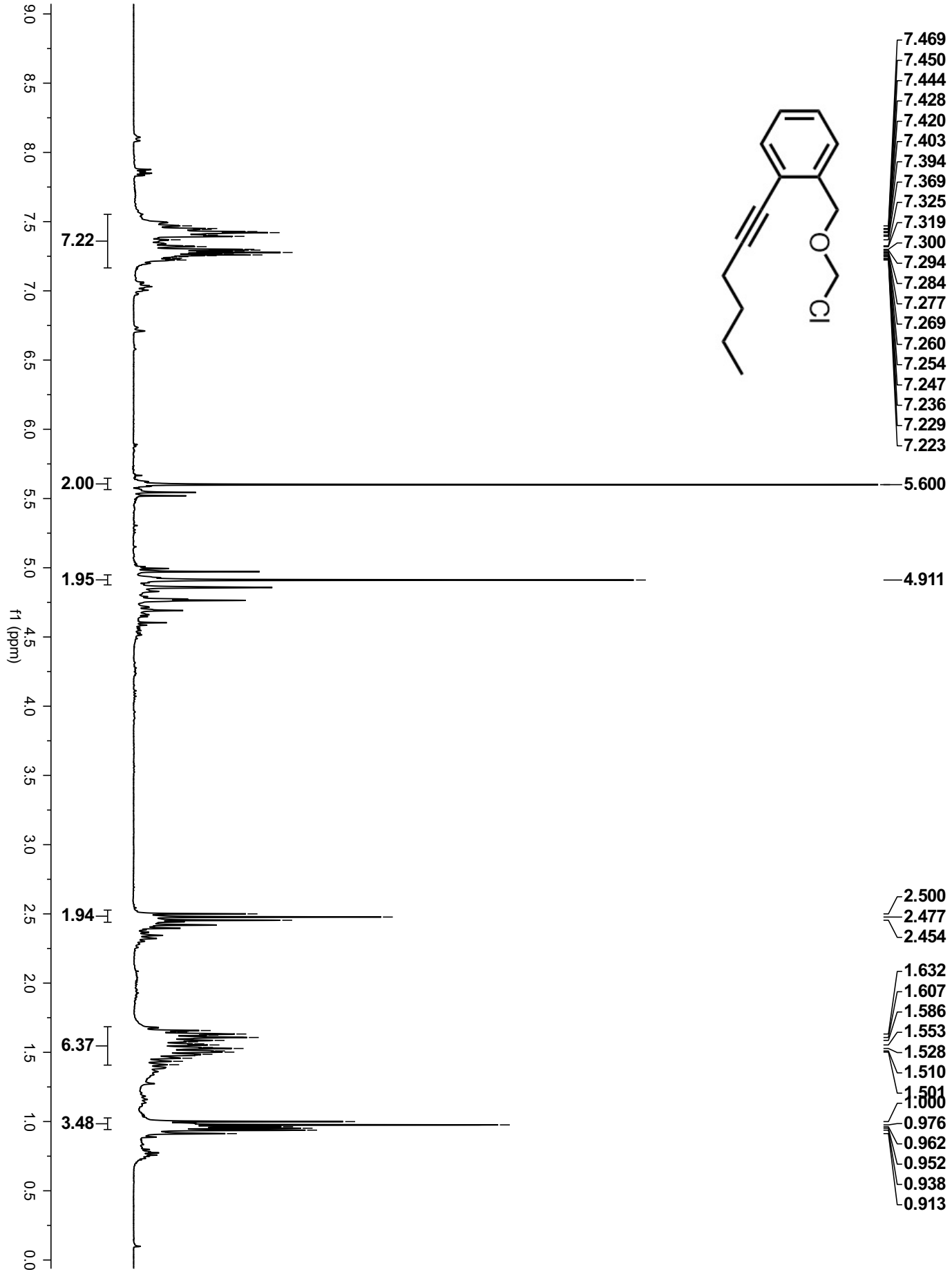
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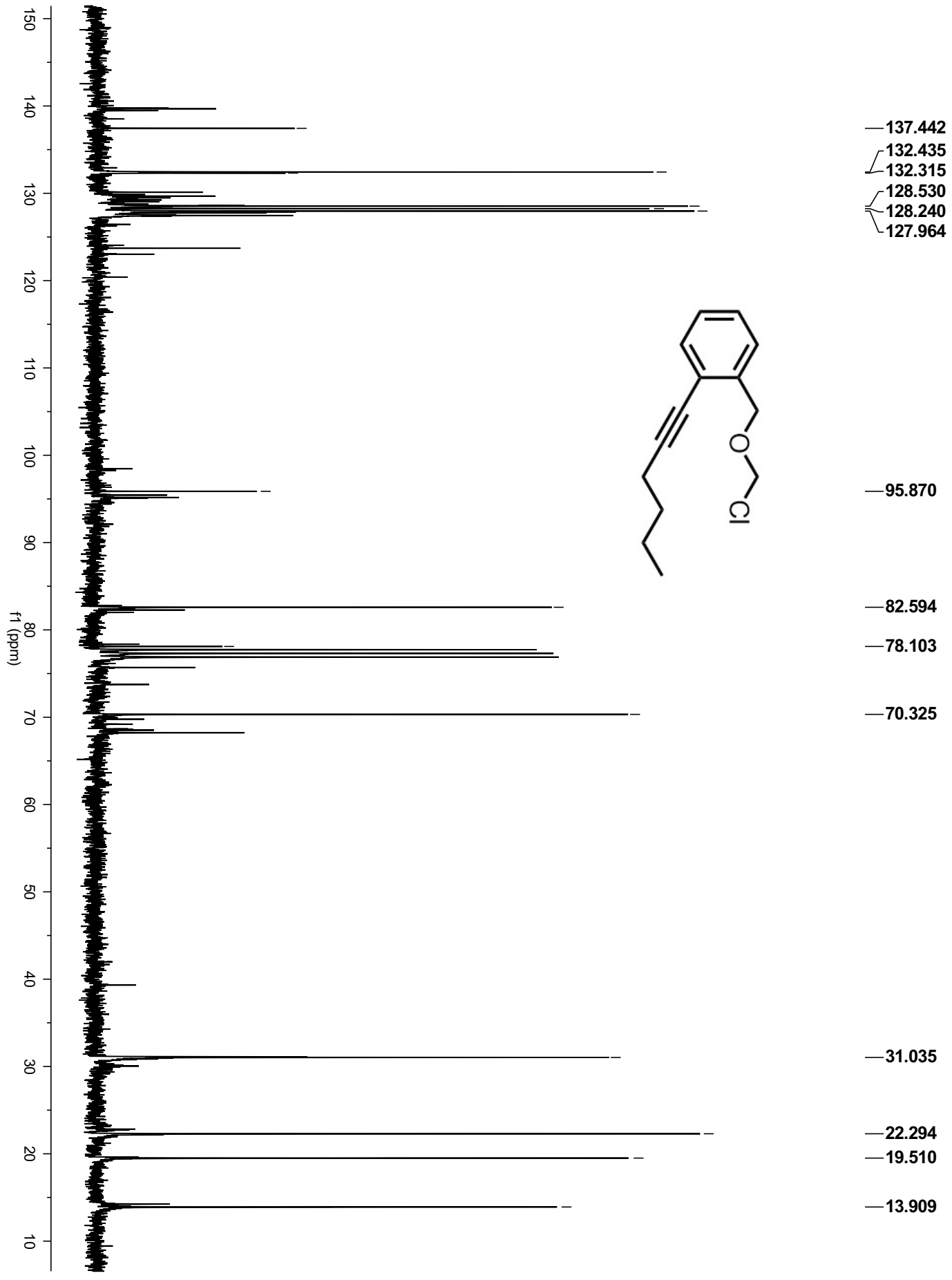
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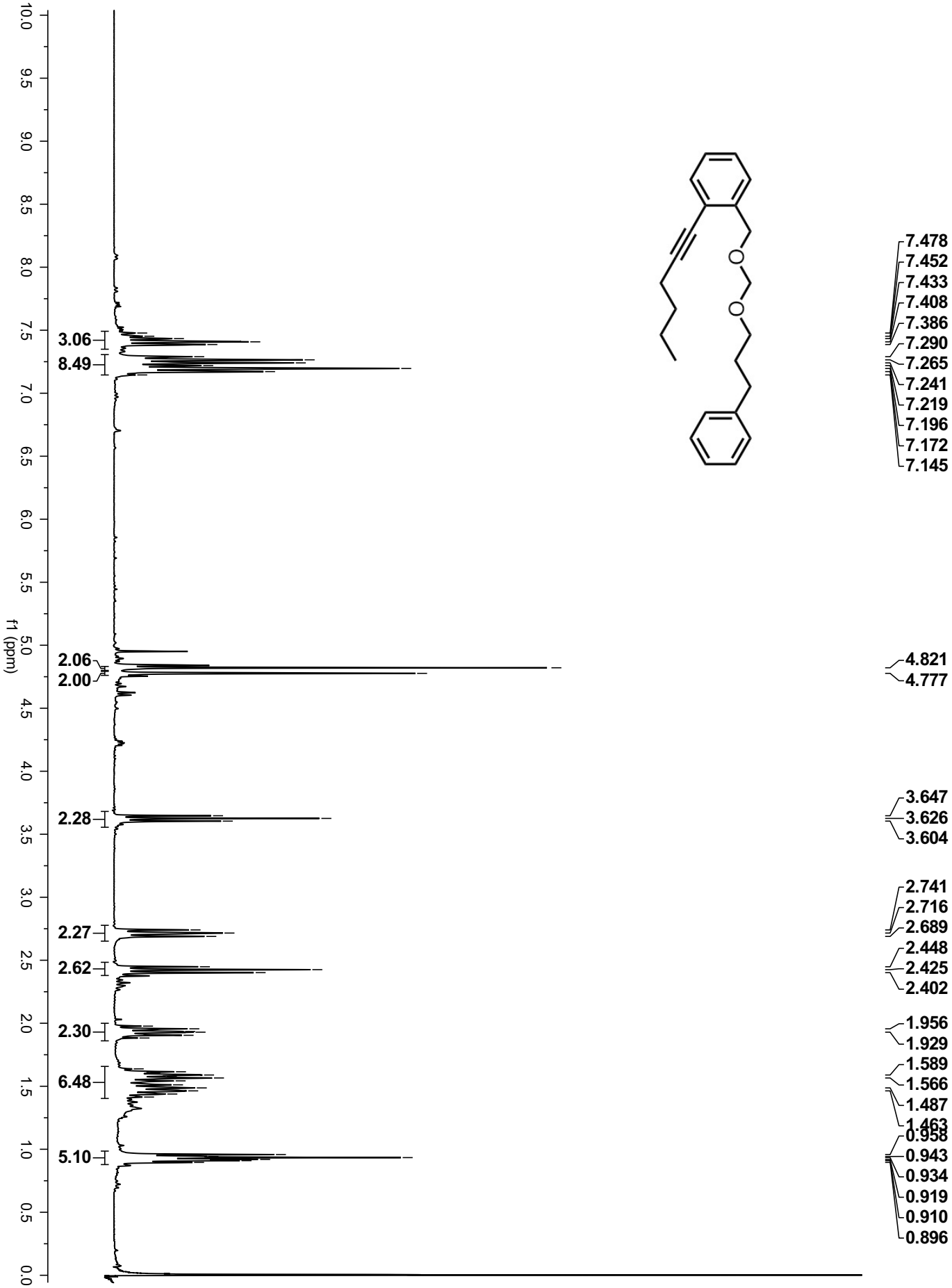
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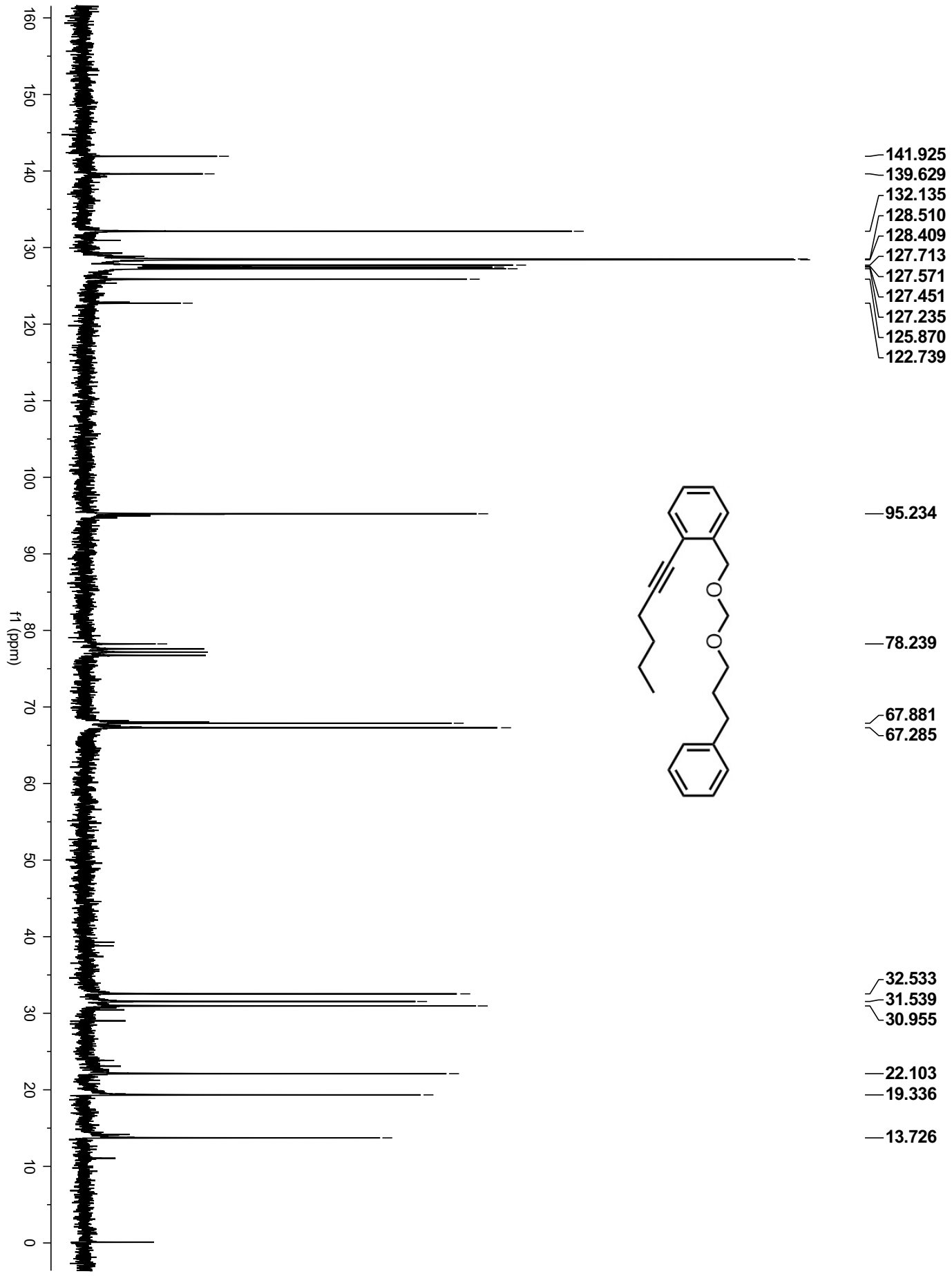

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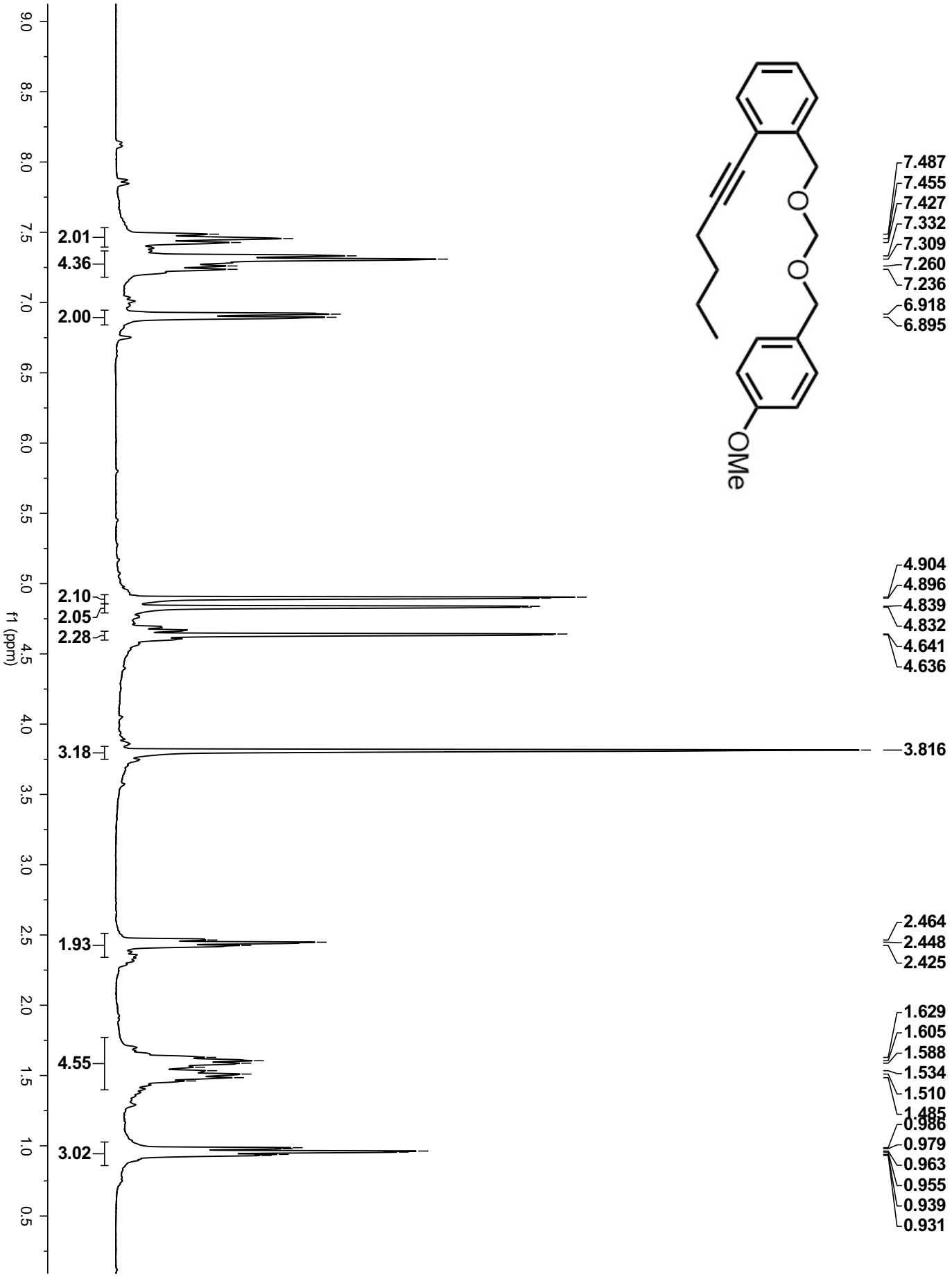

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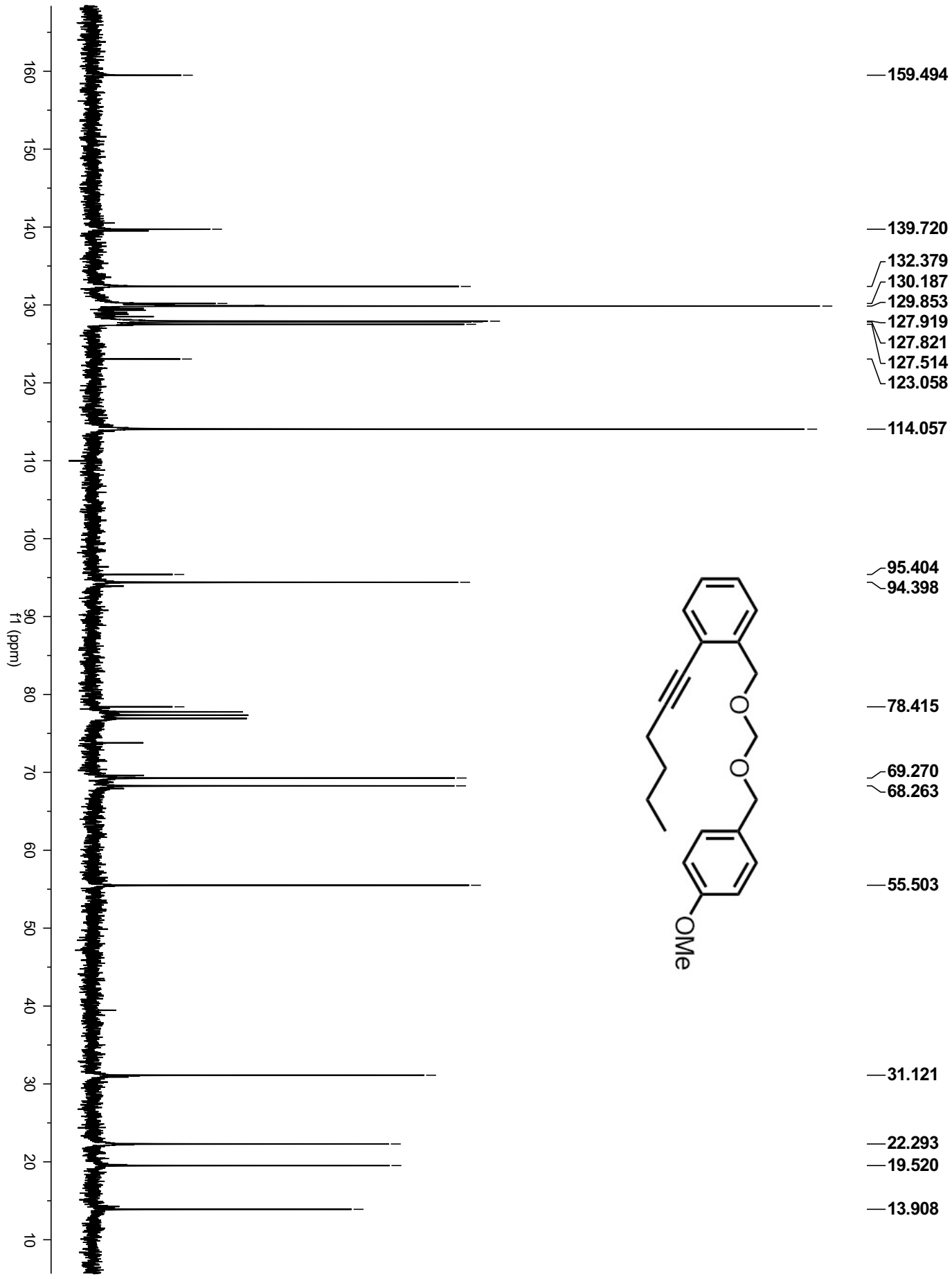

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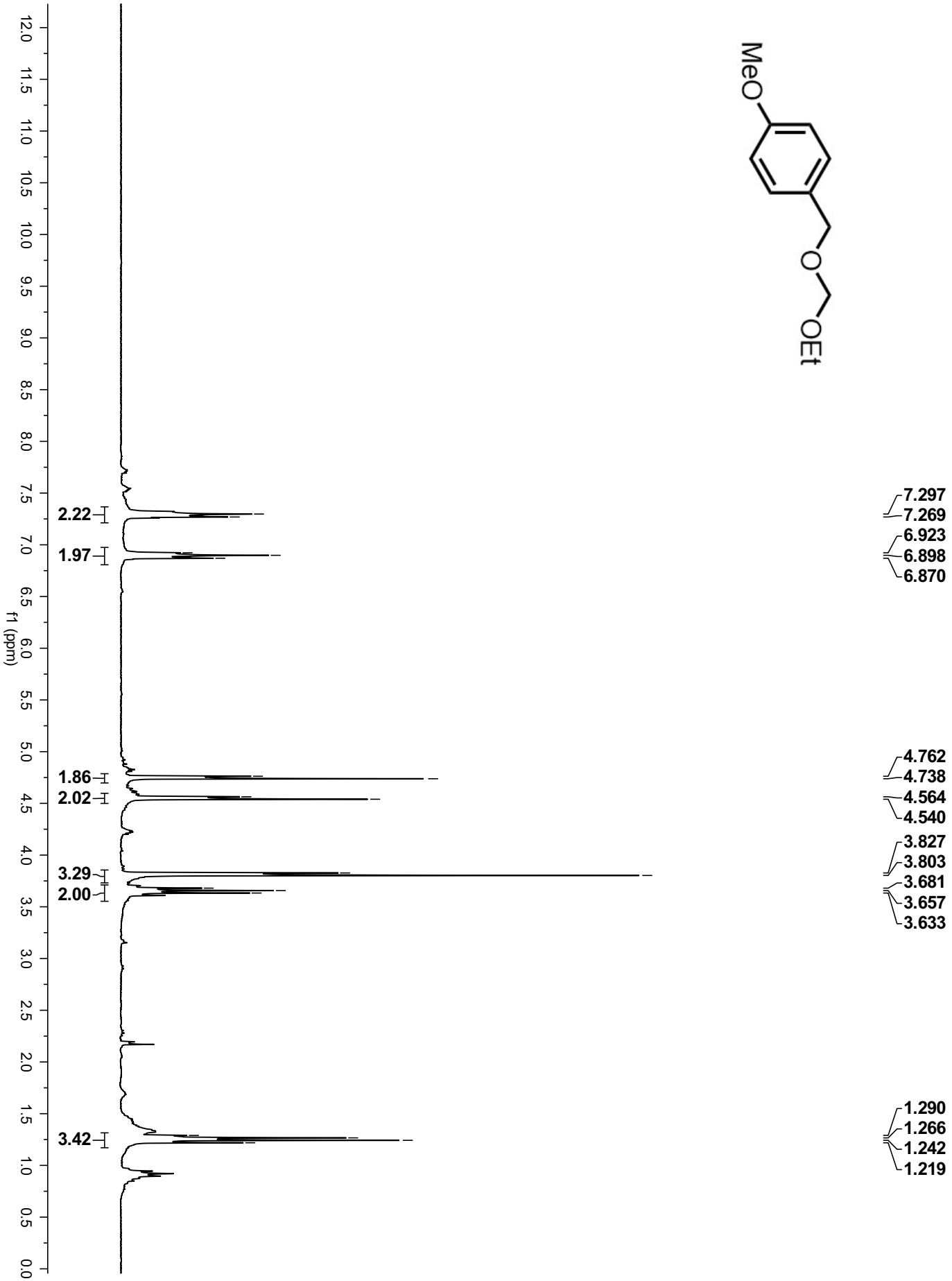

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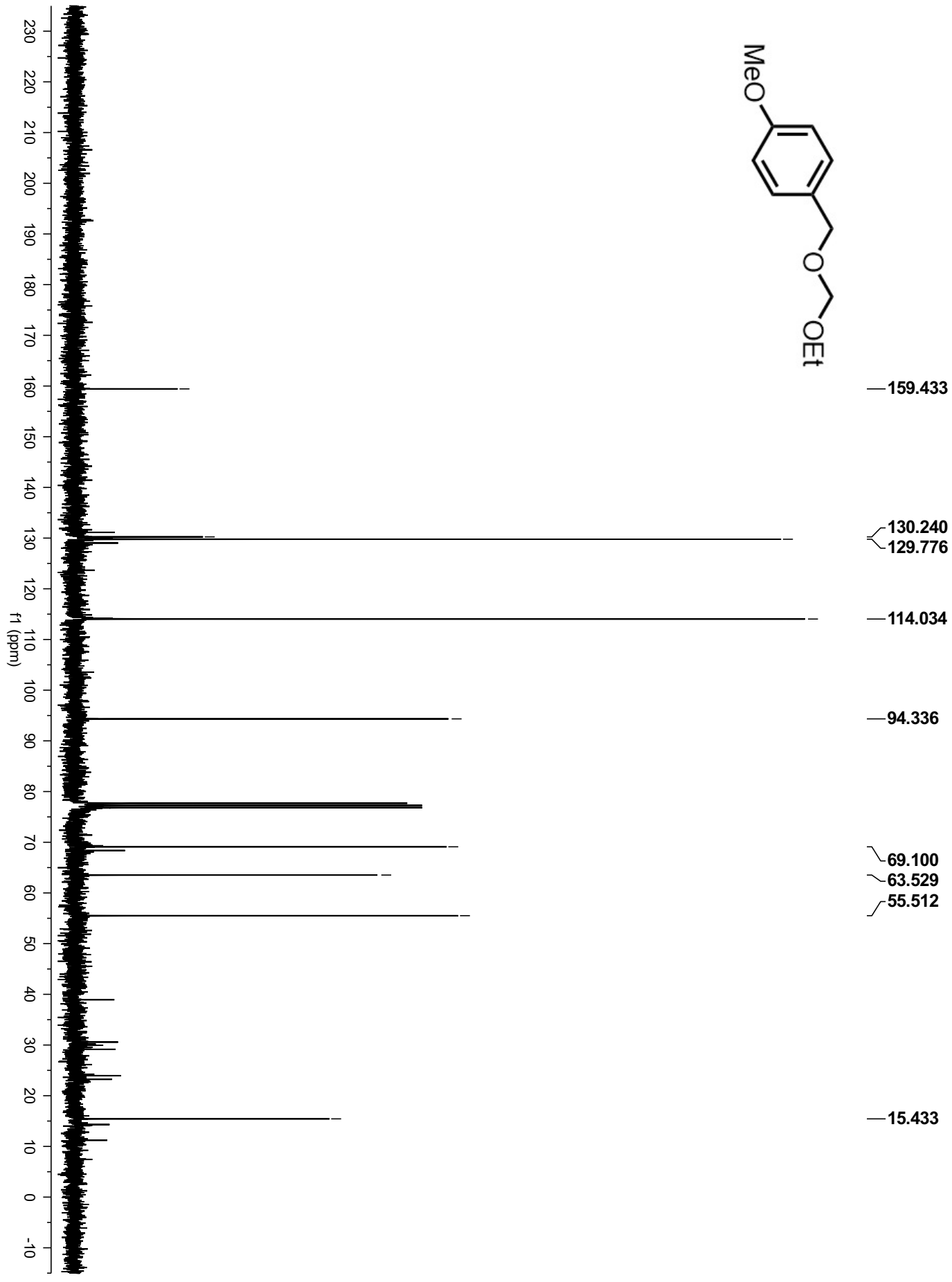

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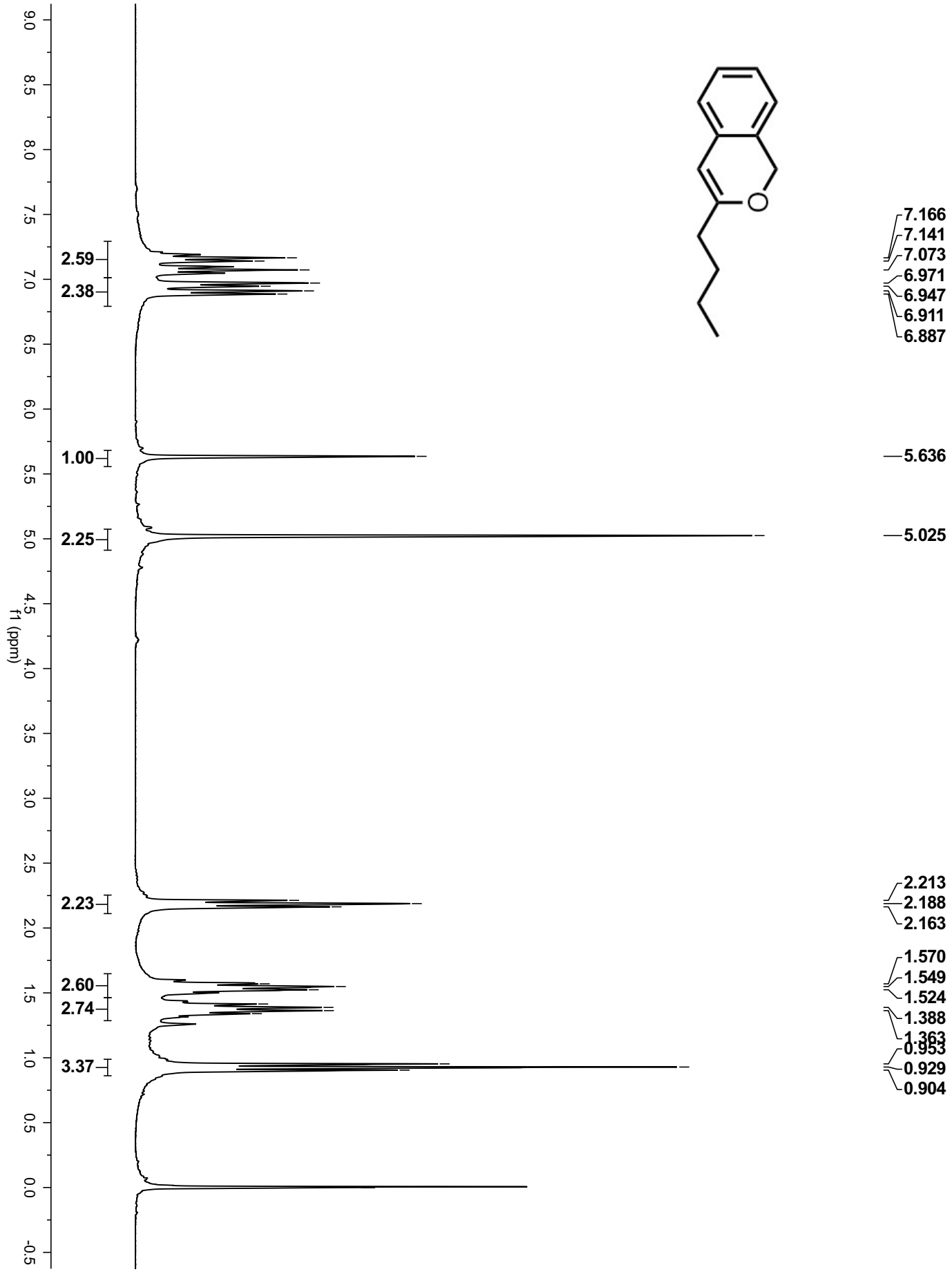

f1 (ppm)
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
141.925
139.629
132.135
128.510
128.409
127.713
127.571
127.451
127.235
125.870
122.739
95.234
78.239
67.881
67.285
32.533
31.539
30.955
22.103
19.336
13.726

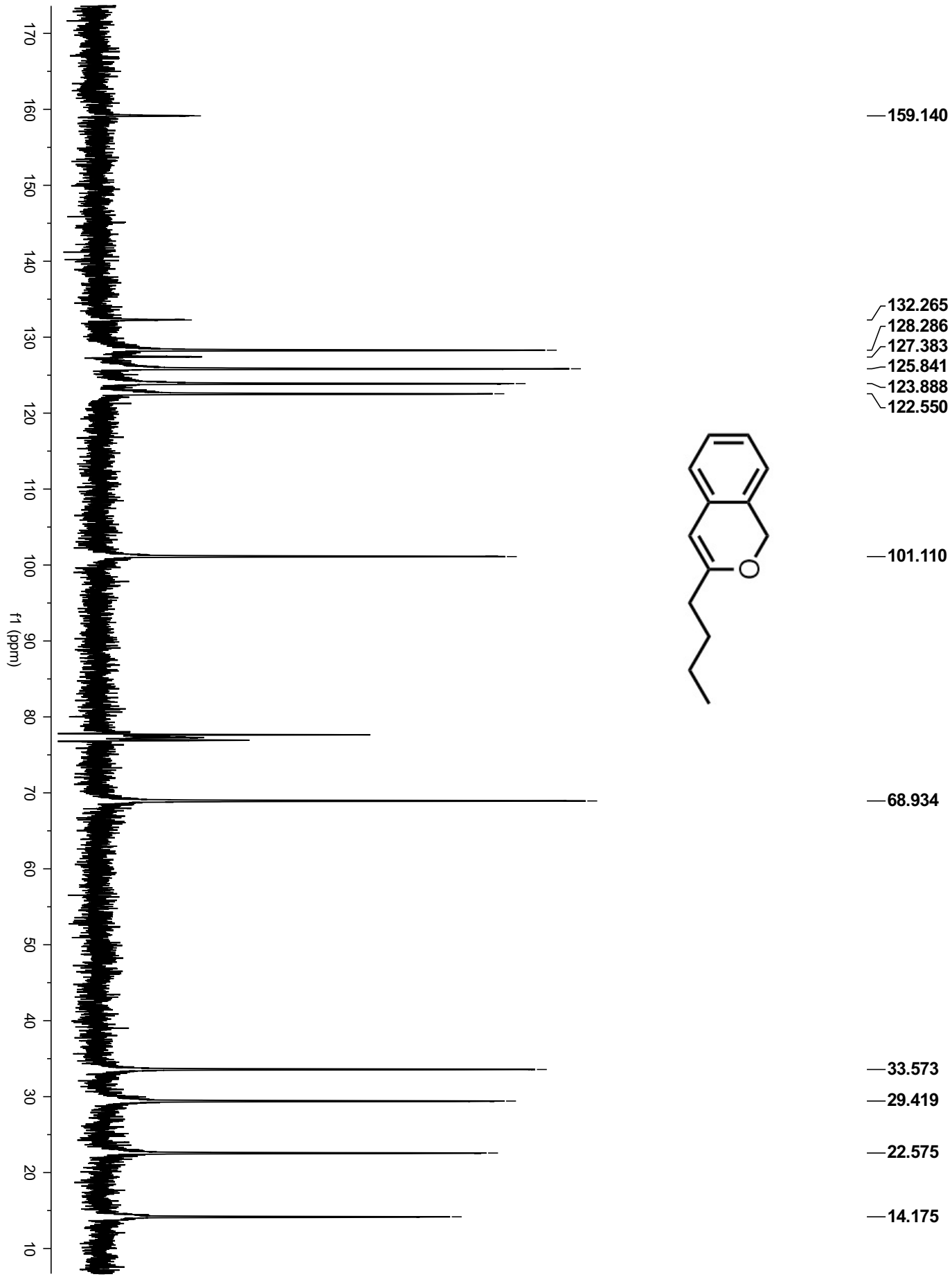

f1 (ppm)
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
2.01
4.36
2.00
2.10
2.05
2.28
3.18
1.93
4.55
3.02
OMe
7.487
7.455
7.427
7.332
7.309
7.260
7.236
6.918
6.895
4.904
4.896
4.839
4.832
4.641
4.636
3.816
2.464
2.448
2.425
1.629
1.605
1.588
1.534
1.510
1.485
0.986
0.979
0.963
0.955
0.939
0.931


159.494
139.720
132.379
130.187
129.853
127.919
127.821
127.514
123.058
114.057
95.404
94.398
78.415
69.270
68.263
55.503
31.121
22.293
19.520
13.908
OMe
f1 (ppm)


MeO
O
OEt
f1 (ppm)
12.0
11.5
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
2.22
1.97
1.86
2.02
3.29
2.00
3.42
7.297
7.269
6.923
6.898
6.870
4.762
4.738
4.564
4.540
3.827
3.803
3.681
3.657
3.633
1.290
1.266
1.242
1.219


MeO
O
OEt
159.433
130.240
129.776
114.034
94.336
69.100
63.529
55.512
15.433
f1 (ppm)


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
f1 (ppm)
2.59
2.38
1.00
2.25
2.23
2.60
2.74
3.37
7.166
7.141
7.073
6.971
6.947
6.911
6.887
5.636
5.025
2.213
2.188
2.163
1.570
1.549
1.524
1.388
1.363
0.953
0.929
0.904
O


159.140
132.265
128.286
127.383
125.841
123.888
122.550
101.110
68.934
33.573
29.419
22.575
14.175
f1 (ppm)