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New Iron-Mediated Synthetic Reactions: Grignard Addition to Enynoates and C–H Bond Peroxygenation

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March, 2014

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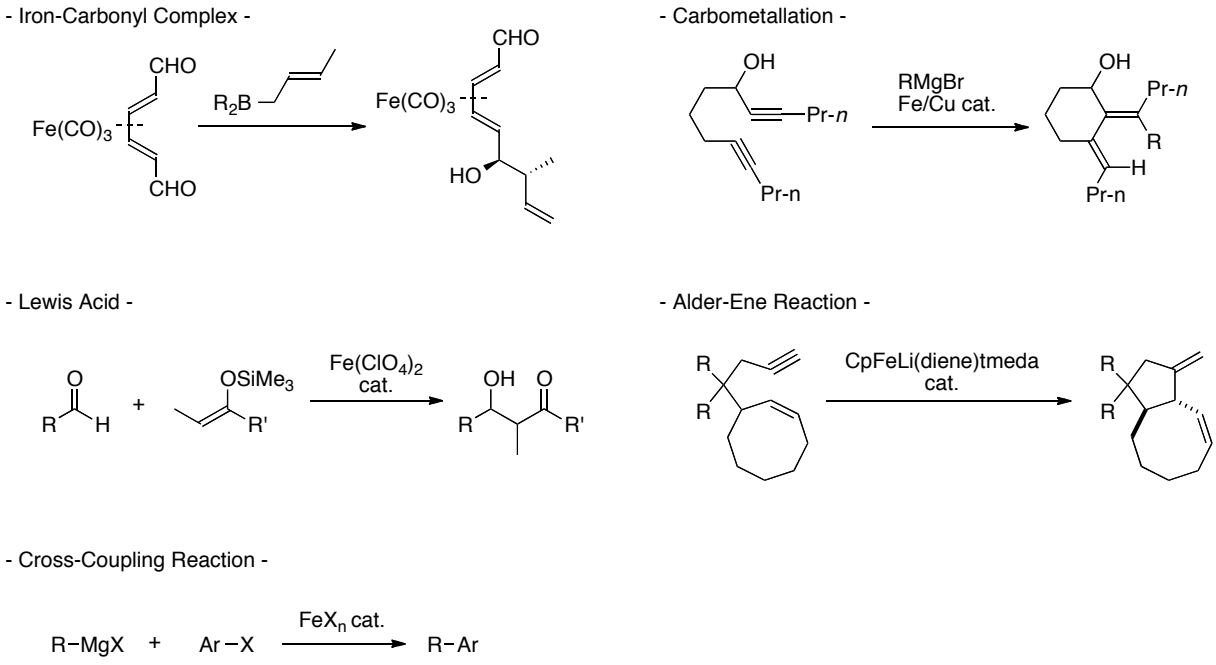
Chapter 1
Introduction

Iron-catalyzed or -mediated reactions in organic synthesis

Organic synthesis has played an essential role in invention of novel pharmaceuticals, agrochemicals, and materials that are all indispensable in modern human life. Although one can design and synthesize various target organic compounds, including those with high complexity, utilizing various types of organic reactions, there still remain many problems to be solved for realization of truly efficient and environmentally benign organic synthesis. One of the most important problems in organic synthesis is development of new efficient carbon-carbon or carbon-heteroatom bond forming reactions particularly for the construction of frameworks of target molecules. To this end, organometallic reagents together with catalytic amount of transition metals have been shown powerful and useful, because they exhibit a wide variety of reactivity toward diverse kinds of electrophiles, depending on metal elements, to form various types of carbon-carbon or carbon-heteroatom bonds. Though noble transition metals like palladium, rhodium, and nickel are usually valuable for this purpose, these transition metal salts and their derivatives are often expensive and have toxicity. Therefore, it is a worthwhile endeavor to search for possible alternatives in a quest for more affordable and sustainable metals.

Iron catalysis seems to provide many chances in this regard, because salts of this metal are cheap, generally nontoxic, benign, and readily available.[1] Despite these favorable attributes, applications in organic synthesis were largely confined, for a long time, to Lewis acid chemistry[2] as well as to the stoichiometric use of iron-carbonyl complexes as shown in Scheme 1.[3] More recently, however, a rapidly growing number of examples have highlighted how iron catalysis may fertilize fields not commonly associated with this particular metal, such as cross coupling chemistry[4], carbometallation[5], and Alder-ene reactions[6] (Scheme 1). Despite these important advances, the field is still in its infancy, not least because the exact nature of the catalytically competent iron species is often unknown and/or subject to somewhat controversial debate.

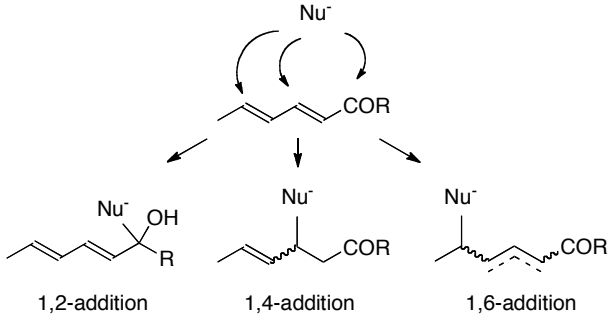
Scheme 1. Iron-catalyzed or -mediated reactions in organic synthesis.



Conjugate addition

Although many synthetic methods using transition metal-catalyzed or -mediated reactions are developed, transition metal-catalyzed conjugate addition of organometallic reagents to electron-deficient olefins is one of the most versatile methods for the selective carbon-carbon bond formation. Especially, copper salts are exclusively used as an excellent catalyst to effect this transformation, and their broad applicability has been firmly established.[7] Though there are numerous reports on the nucleophilic addition to electron-deficient olefins as mentioned above, similar reactions to the corresponding dienes or enynes have been rarely reported.[8,9] For example, the selective addition to α,β,γ,δ-unsaturated carbonyl compounds has not been amply solved, because they have multiple reaction sites (e.g., 1,2-, 1,4-, and 1,6-addition) and the stereoselection (*E* or *Z*) of the remaining olefinic bond as illustrated in Scheme 2.

Scheme 2. Conjugate addition to α,β,γ,δ-unsaturated carbonyl compounds.



As shown in Scheme 3, because conjugated enynes like 2-alken-4-ynoates also have multiple reaction sites, there are again issues on the regioselection (β- and δ-addition). An allene, obtained from the δ-addition (or 1,6-addition) shown in Scheme 3,[10] is a compound in which one carbon atom has double bonds with each of its two adjacent carbons[11] and is contained in natural organic compounds[12] (Figure 1). As allenes have cumulative double bonds, of which the center carbon trends to electron-deficiency and less steric repulsion, they are more reactive than normal olefins. Thus, they are used as synthetic intermediates for heterocyclic compounds and natural products as shown in Scheme 4.[13]

Scheme 3. Selective addition to conjugated enynes.

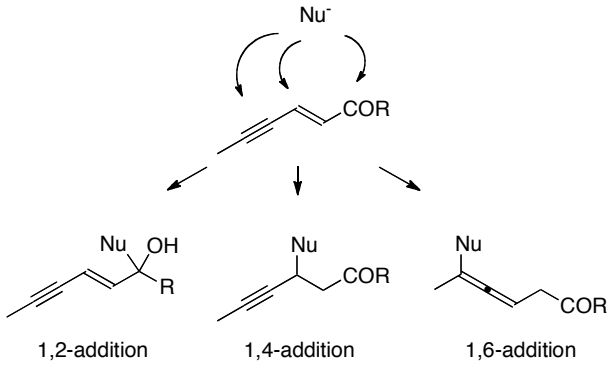
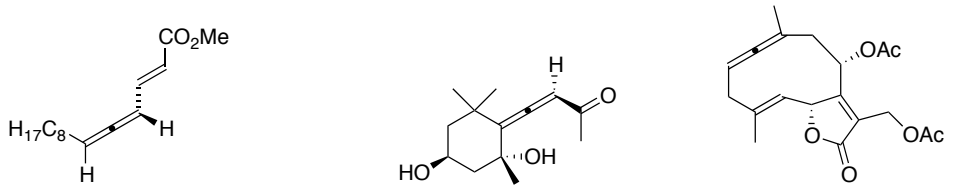


Figure 1. Allenes in natural organic compounds.

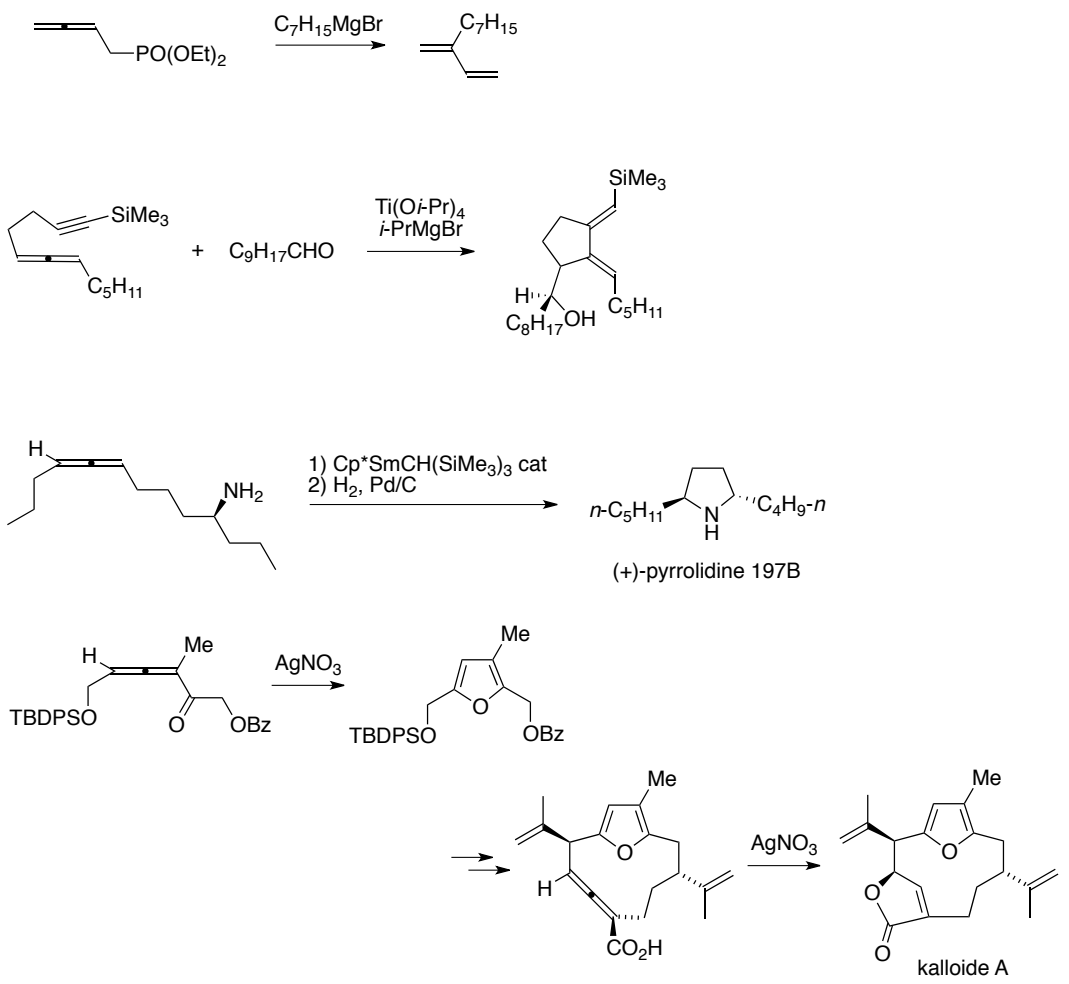


insect pheromone
(isolated from *Acanthosclides obtectus*)

glasshopper ketone
(isolated from *Romalea microptera*)

vernoallenolide
(isolated from *Vernonia sp.*)

Scheme 4. Synthetic utility of allenes.

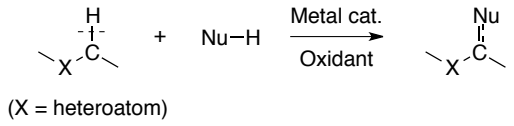


C–H bond functionalization

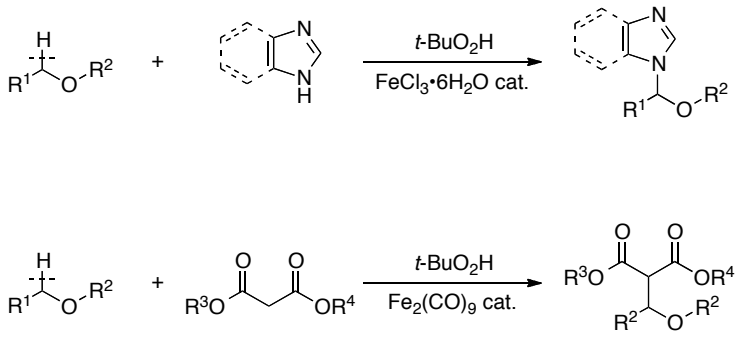
Carbon-hydrogen bonds (abbreviated to C–H bonds hereafter) are ubiquitous in organic compounds. If the C–H bonds could be used as a functional group, similar to a carbon-halogen bond, it would become one of the most powerful, valuable, straightforward methods for producing complex molecules and for the construction of C–C bond frameworks. Thus, many types of C–H bond functionalization have been developed all over the world.[14]

α-Oxidation is one of the useful C–H bond functionalizations for not only introducing a functional group but also making a new carbon–carbon bond on a carbon next to a heteroatom by oxidant under a catalytic amount of transition metals (Scheme 5).[15,16] Although oxygen is a most inexpensive and environment-friendly agent as oxidant for α-oxidation, *t*-BuO_2H is more useful from the stand point of safety and economical oxidation in organic synthesis as illustrated in Scheme 6.[17]

Scheme 5. Transition metal-catalyzed α-oxidation.

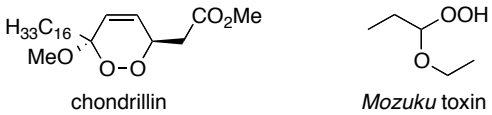


Scheme 6. Examples of iron-catalyzed α-oxidation of ethers by using *t*-BuO_2H.



Although a variety of nucleophiles are applied to this process, it has not been amply explored that the oxidant itself is incorporated into the substrate to give a synthetically useful product. While a peroxyacetal, which is formed by the direct introduction of hydroperoxy group at α-position of an ether by treatment with RO_2H, is one of the useful synthetic intermediates, its synthetic method is limited and its reactivity is still unclear.[18] Furthermore, the structures of peroxyacetals are included in natural products as shown in Figure 2.[19]

Figure 2. Peroxyacetals in natural organic compounds.

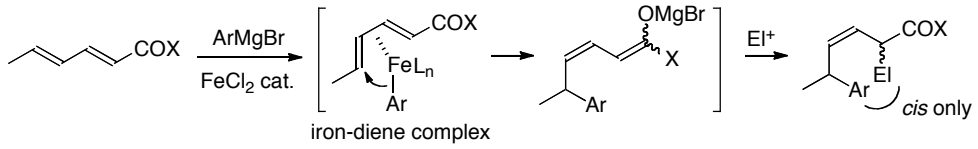


Iron-catalyzed reactions developed in our laboratory

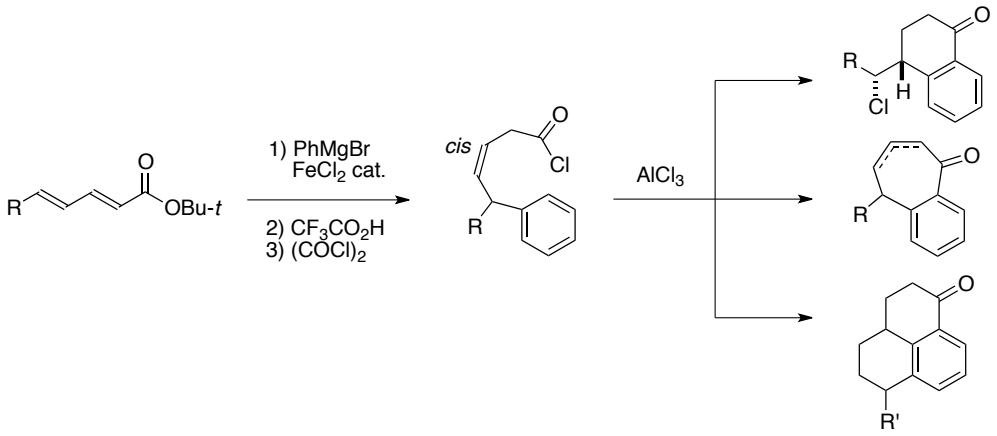
Recently, we focused our attention on the development of new iron-catalyzed or -mediated reactions and reported an iron-catalyzed selective conjugate addition of aryl Grignard reagents to α,β,γ,δ-unsaturated dienoates or -amides (Scheme 7).[9a,20] This reaction gives stereo-defined *cis*-4-aryl-2-alkenoates or -amides, which has not been achieved by other metal reagents. This may come from the intermediary formation of iron-diene complex, which effects the aryl transfer from iron to the terminal position of the dienoate to give the *cis*-product after hydrolysis ($El^+ = H^+$).

The magnesium dienolate could be utilized in the reactions with other electrophiles (El^+ = alkyl halides) to give α-alkylated *cis*-4-aryl-2-alkenoates. The above *cis*-alignment of the incoming aryl group and the carbonyl group on the other side of the allylic system was readily applied to the preparation of cyclic products of various ring systems via the Friedel-Crafts reaction as shown in Scheme 8.[21]

Scheme 7. Iron-catalyzed 1,6-addition of aryl Grignard reagents to α,β,γ,δ-unsaturated dienoate or dienamide.

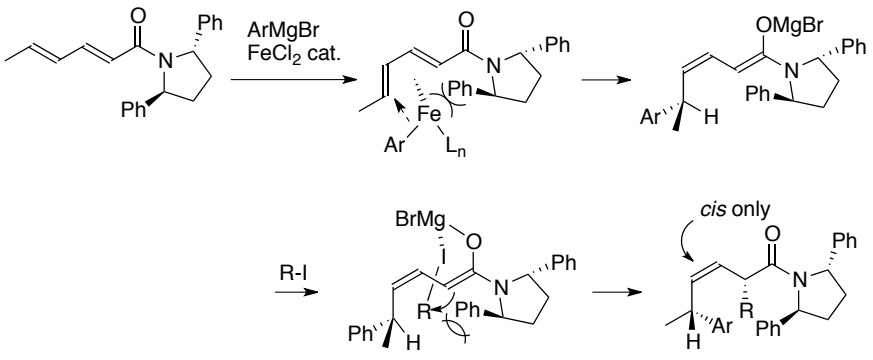


Scheme 8. Application to the preparation of bicyclic products.



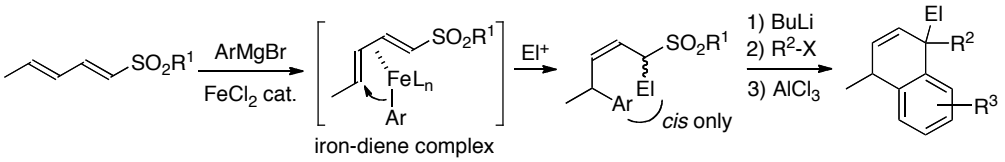
Another application is a highly efficient asymmetric δ-addition as shown in Scheme 9, where the *s-cis*-diene-iron intermediate appears to play an important role to control the stereochemistry of the first aryl addition at the remote position from the chiral auxiliary.[9a]

Scheme 9. Application to the asymmetric multi-component coupling.



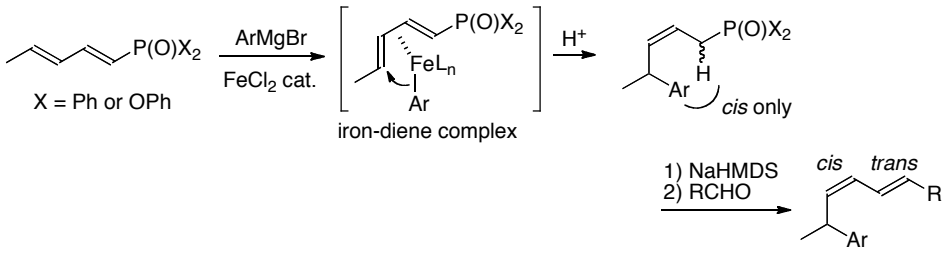
We have also found that this system could be applied to α,β,γ,δ-unsaturated sulfones. In addition, the resulting allylic sulfones having *cis*-olefin geometry could be utilized to the intramolecular Friedel-Crafts reaction to give bicyclic compounds (Scheme 10).[22]

Scheme 10. Iron-catalyzed δ-addition of aryl Grignard reagents to α,β,γ,δ-unsaturated sulfones.



Other applications were the addition to α,β,γ,δ-unsaturated phosphine oxides or phosphonates (Scheme 11). These electron-withdrawing groups are good precursors of Wittig reagents. Actually, these products could be applied to the Wittig reaction to afford dienes with high stereoselectivities.[23]

Scheme 11. Iron-catalyzed δ-addition of aryl Grignard reagents to α,β,γ,δ-unsaturated phosphorus compounds.



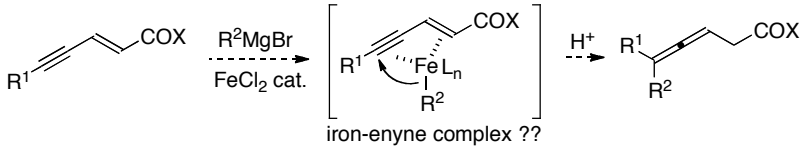
Contents in this Thesis

Seeing this successful iron-catalyzed selective addition to various functionalized 2,4-alkadienes, we turned our attention to other α,β,γ,δ-unsaturated compounds, hoping to develop different valuable reactions. Meanwhile, we have also investigated new reactions using iron reagents. The following chapters will show our study along this line.

Chapter 2 of this thesis describes an iron-catalyzed synthesis of allenes from 2-alken-4-ynoates and Grignard reagents. As already shown in eqs 1-3, the iron-catalyzed selective conjugate addition of aryl Grignard reagents to 2,4-alkadienoates and -amides, and 1,3-alkadienyl sulfones, phosphine oxides, or phosphonates has been reported from our laboratory. While all of these reactions may involve the intermediary formation of the iron-diene complex, it is interesting whether the similar complex could be formed between iron salts and other α,β,γ,δ-unsaturated compounds or not. In order to expand the applicability of this reaction system, we planned to use a new α,β,γ,δ-unsaturated carbonyl compound, 2-alken-4-ynoate, hopefully

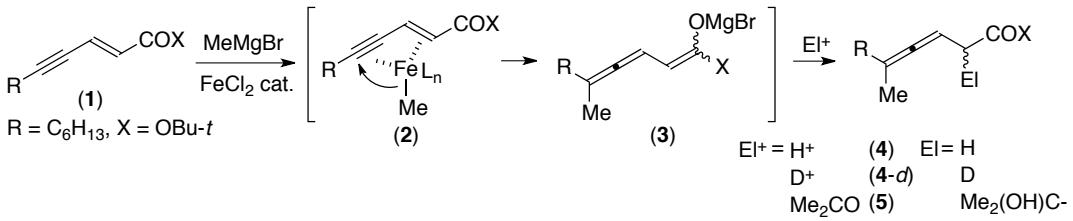
giving the corresponding allene (Scheme 12).

Scheme 12. Extension to conjugated enynes.

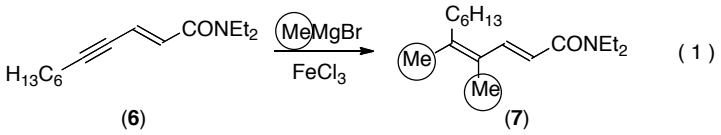


When 2-alken-4-ynoate **1** was treated with MeMgBr in the presence of a catalytic amount of $FeCl_2$, the addition proceeded in 1,6-selective manner to give allene **4** as shown in Scheme 13. Deuteriolysis afforded the corresponding product **4**-*d*, showing the presence of the intermediate magnesiated allene **3**. This intermediate **3** could be actually utilized in an aldol-type reaction with acetone to give homo-allenyl alcohol **5**. Thus, the 1,6-selective conjugate addition to 2-alken-4-ynoates has been achieved.[24]

Scheme 13. Iron-catalyzed 1,6-addition of aryl or methyl Grignard reagents to enynoates and -amides.



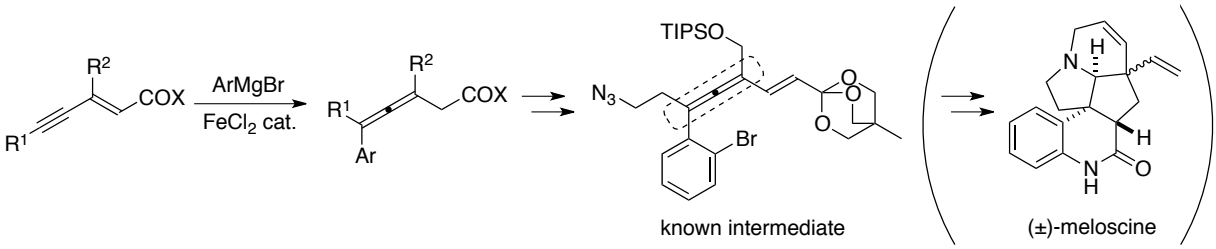
In addition, when 2-alken-4-ynamide **6** was treated with excess MeMgBr in the presence of a stoichiometric amount of $FeCl_3$, an usual double addition of methyl groups unexpectedly proceeded to give dimethyldiene **7**, which will be shown in chapter 2 (eq 1).



(1)

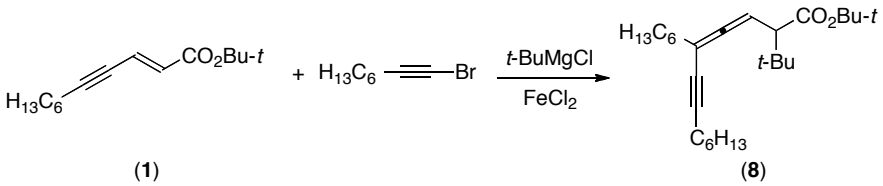
In this chapter, a synthetic study of a natural product based on the above 1,6-addition is also described (Scheme 14).

Scheme 14. Application aiming at the synthesis of natural product.

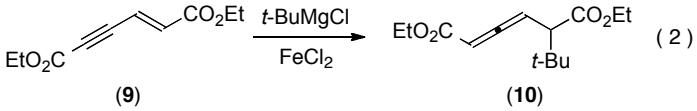


Chapter 3 describes an iron-mediated α-addition of Grignard reagents to 2-alken-4-ynoates. When we continued the investigation on other Grignard reagents for the aforementioned 1,6-addition, we found *t*-BuMgCl is unsuitable for this addition not to give a desired product. However, we found that the simultaneous addition of 1-bromo-1-octyne to the same reaction unexpectedly affords the three-component coupling product **8** via α-addition of *t*-BuMgCl (Scheme 15).[25] We were interested in this three-component coupling reaction and decided to start ample examination.

Scheme 15. Iron-mediated three-component coupling reaction of 2-alken-4-ynoate, *t*-BuMgCl, and 1-bromo-1-alkyne.

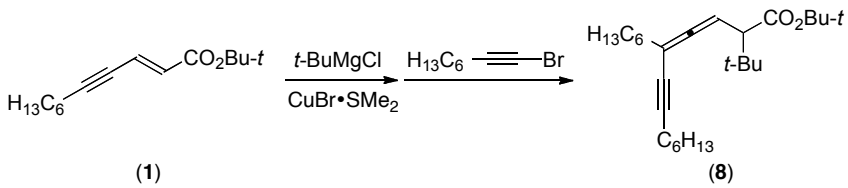


We also found the α-addition of *t*-BuMgCl to 2-alken-4-ynedioate **9** possible in the presence of a stoichiometric amount of $FeCl_2$ (eq 2).



Alternatively, a copper-mediated addition of a *tert*- or *sec*-alkyl Grignard reagent to 2-alken-4-ynoates **1** proceeded in an *anti*-Michael manner, which was followed by alkylation with 1-bromo-1-alkynes, to give a same product **8** as shown in Scheme 16. These Fe- or Cu-mediated reactions could be used complementarily.

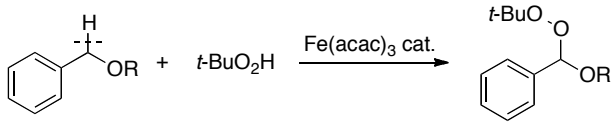
Scheme 16. Copper-mediated three-component coupling reaction of 2-alken-4-ynoate, *t*-BuMgCl, and 1-bromo-1-alkyne.



(**1**) (**8**)

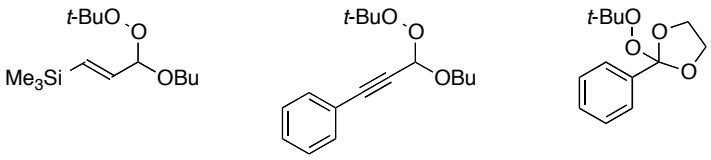
Chapter 4 describes iron-catalyzed synthesis of peroxyacetals. We have also examined a new iron-catalyzed reaction, C–H bond functionalization. As part of our challenging study to develop a new reaction using iron reagents, we examined iron-catalyzed C–H bond oxidation. When benzyl ether **9** was treated with *t*-BuO_2H in the presence of a catalytic amount of $Fe(acac)_3$, C–H bond functionalization accompanied with the uptake of a *t*-BuO_2– residue to the substrate took place to give mixed peroxyacetals **10**, which are otherwise tedious to prepare (Scheme 17).[26] This reaction is also valid for the preparation of olefinic or acetylenic peroxyacetals and unsaturated peroxyorthoesters shown in Figure 3.

Scheme 17. Iron-catalyzed selective synthesis of peroxyacetals from benzyl ethers and *tert*-butyl hydroperoxide.



(**9**) (**10**)

Figure 3. Various types of peroxyacetals.



Chapter 5 describes the summary of this thesis.

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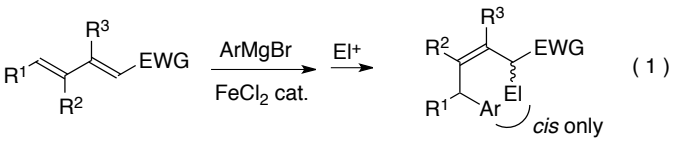
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Chapter 2
Iron-Catalyzed Synthesis of Allenes from 2-Alken-4-ynoates and Grignard Reagents

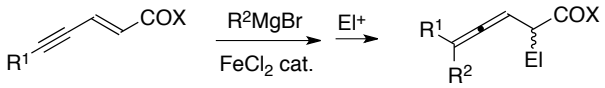
1. Introduction

Conjugate addition of Grignard reagents to α,β,γ,δ-unsaturated carbonyl compounds is a convenient method for the preparation of unsaturated building blocks, under the assumption that both regioselectivity of the addition and stereoselectivity of the newly-generated olefin moiety reach very high levels.[1] Recently, we achieved a 1,6-addition of aryl Grignard reagents to 2,4-alkadienoates and -amides and δ-addition to 1,3-alkadienyl sulfones, 1,3-alkadienyl phosphine oxides, and 1,3-alkadienyl phosphonates satisfying these two requirements, by introducing an iron catalyst as shown in eq 1.[2,3] After our continuing study to broaden the application of this reaction to other α,β,γ,δ-unsaturated compounds, we report here that Grignard reagents undergo 1,6-addition to 2-alken-4-ynoates in the presence of the similar iron catalyst to give allenes[4] as formulated in eq 2.[5]



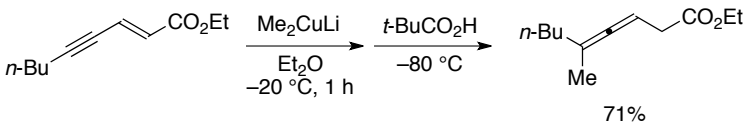
(1)

EWG = COX Urabe, H. *et al. Tetrahedron Lett.* **2005**, *46*, 603-606.
COX Urabe, H. *et al. Angew. Chem. Int. Ed.* **2008**, *47*, 6860-6864.
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$P(O)Ph_2$, $P(O)(OEt)_2$ Oh, Y. T., Ph.D. Thesis, Tokyo Institute of Technology, **2013**.



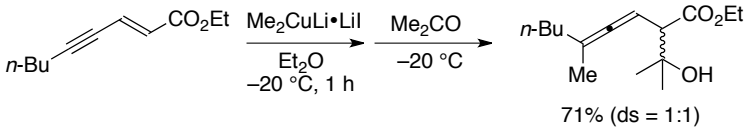
(2)

Although the similar 1,6-addition to 2-alken-4-ynoates has been already performed with organolithium reagents in the presence of a stoichiometric (eqs 3 and 4) or catalytic (eqs 5 and 6) copper species,[6] they suffer from the limitation of the applicable substrates and tedious experimental operation especially in the case of catalytic reactions with respect to copper. Moreover, their extension to more convenient and economical Grignard reagents has proved unsuccessful.[7]



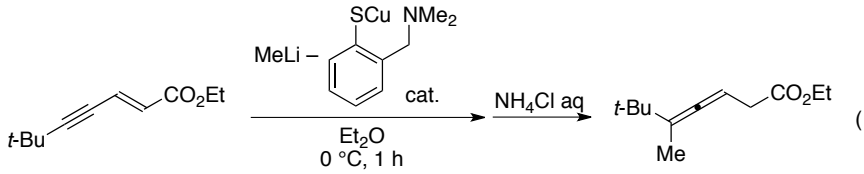
(3)

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Krause, N.; Gerold, A. *Angew. Chem., Int. Ed.* **1997**, *36*, 186-204.



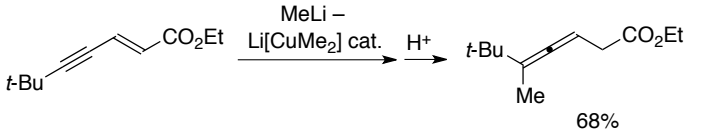
71% (ds = 1:1) (4)

Arndt, S.; Handke, G.; Krause, N. *Chem. Ber.* **1993**, *126*, 251-259.



64% (5)

Haubrich, A.; Van Klaveren, M.; Van Koten, G.; Handke, G.; Krause, N. *J. Org. Chem.* **1993**, *58*, 5849-5852.
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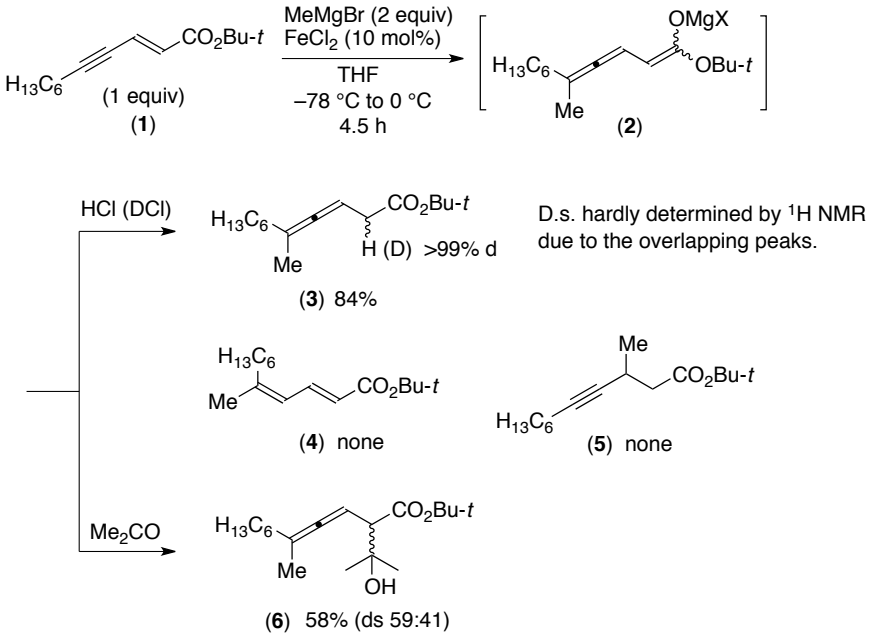
68% (6)

Krause, N.; Gerold, A. *Angew. Chem., Int. Ed.* **1997**, *36*, 186-204.
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2. Results and Discussion

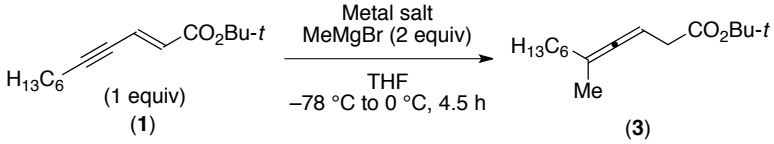
We examined the feasibility of the iron-catalyzed conjugate addition of Grignard reagents to 2-alken-4-ynoates. Thus, *tert*-butyl 2-undecen-4-ynoate (**1**) was treated with MeMgBr in the presence of a catalytic amount of $FeCl_2$ (10 mol%, 99.9% purity) to give allene **3** in 84% yield after aqueous workup (Scheme 1). Both isomeric diene **4** and acetylene **5** was not detected in the crude reaction mixture by careful ^{1}H NMR analysis. Instead of hydrolysis, deuteriolysis gave a mono-deuterated product **3**-*d* with high deuterium incorporation, showing the presence of the metal enolate species **2**[8] before workup. This intermediate **2** could be also utilized in an aldol-type reaction with acetone to give the adduct **6**.[9]

Scheme 1. Fe-catalyzed conjugate addition in a highly regioselective manner.



Recent reports addressed that certain iron-catalyzed reactions might be actually catalyzed by copper impurities contained in the iron reagents.[10] The effect of iron as the actual catalyst in the present reaction is obvious by the following data shown in Table 1. The use of $FeCl_2$ of 99.998% purity did not change the reaction course and gave actually the same yield and regio- and stereoselectivities of the 1,6-adduct (entry 3). On the other hand, while copper catalysts (10 mol%) such as $CuCl_2$, CuI, CuBr, $CuBr{\cdot}SMe_2$, CuCN, and Li_2CuCl_4 furnished the desired product **3** in the yields between 0–65% (entries 1-4, 6, 8-11) less than that in Scheme 1,[7] the 1,6-addition no longer proceeded with 0.01 mol% of an effective catalyst ($CuCl_2$ or CuI, entries 5 and 7), which is a 50 times more amount than that existing as impurities in 99.998% pure $FeCl_2$.

Table 1. The effect of the purity of $FeCl_2$ on the reaction.

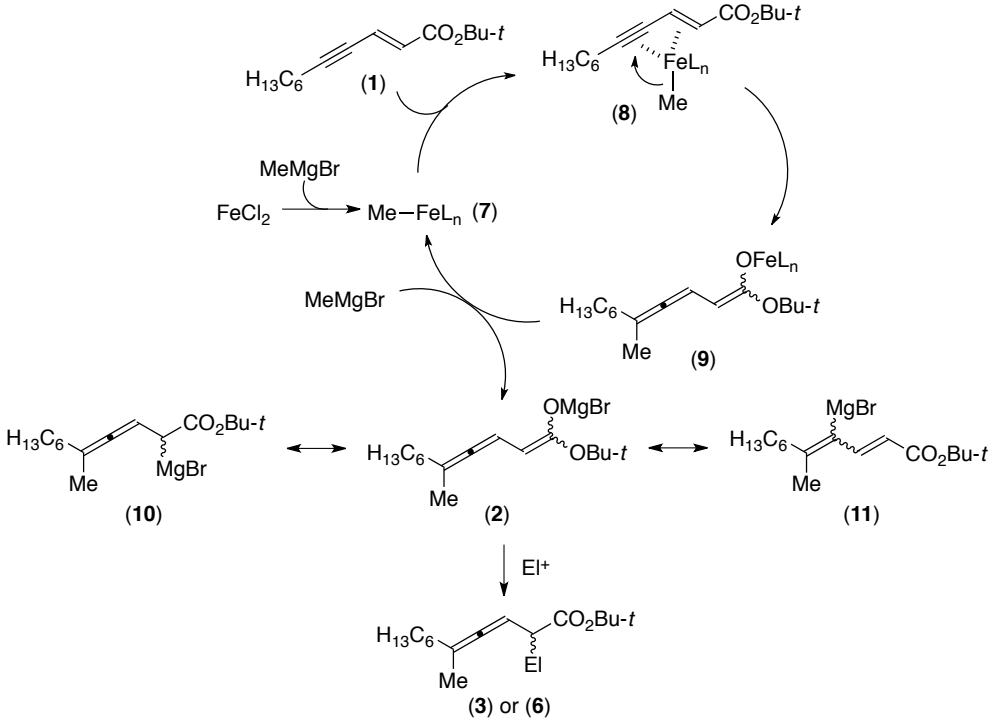


Entry	Metal salt	(mol%)	Yield (%)[a]
1	none	-	0
2	$FeCl_2$ (99.9%)	10	84
3	$FeCl_2$ (99.998%)	10	86
4	$CuCl_2$	10	(47)
5		0.01	(0)
6	CuI	10	(40)
7		0.01	(0)
8	CuBr	10	(54)
9	$CuBr•SMe_2$	10	(65)
10	CuCN	10	(0)
11	Li_2CuCl_4	10	(0)

[a]Isolated yields. Yields determined by ^1H NMR are shown in parentheses.

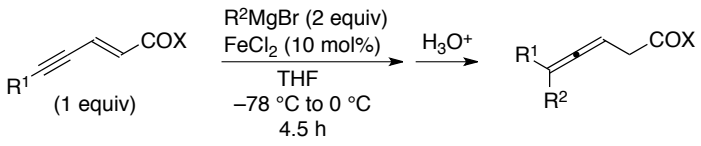
A mechanism of this reaction is proposed in Scheme 2. The Fe catalyst first reacts with MeMgBr to form methyliron intermediate such as **7** (L = Me, Cl, or Br),[11] which plays an important role for the methyl transfer to the δ-position to the carbonyl group in **8** to yield **9**.[8] Transmetallation of **9** with Grignard reagent affords the magnesium enolate **2**[8] and the starting organoiron reagent **7**, which makes the catalytic cycle completed. Finally, the resultant enolate **2** reacted with an electrophile again in a regioselective manner to give exclusively allene **3** or **6** as the observed product.

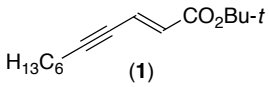
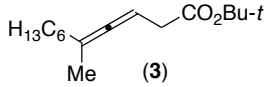
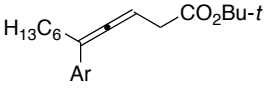
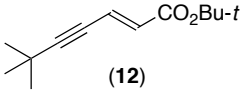
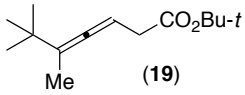
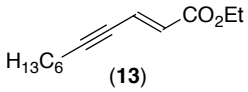
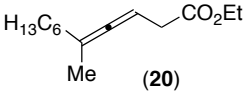
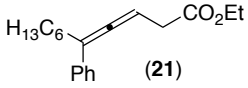
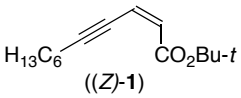
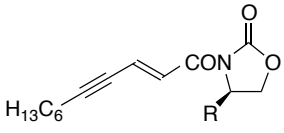
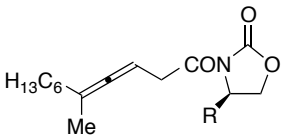
Scheme 2. Proposed catalytic cycle for this reaction.



Other results obtained from various 2-alken-4-ynoates and Grignard reagents are summarized in Table 2. The above reaction is also found valid for aryl Grignard reagents to give arylallenes, where somewhat hindered aryl groups such as *ortho*-substituted ones gave products in better yields (entries 2 and 3 vs. 4 and 5). This perhaps comes from the steric protection of the allene moiety against dual nucleophilic addition (see the structure **28** below) or the suppression of the homocoupling process of aryl Grignard reagents. However, other alkyl Grignard reagents, such as ethyl-, isopropenyl-, allyl-, and benzylmagnesium bromide were not good reagents for this reaction to give the desired products in poor yields (0-39%). The iron-controlled regioselectivity appears to prevail over the steric congestion at the reacting position, because sterically demanding *t*-Bu-substituted 2-penten-4-ynoate **12** still gave exclusively the expected allene **19** in a good yield (entry 6). Ethyl ester **13**, instead of **1** with *tert*-butyl ester, survived the reaction conditions to give desired allenes **20** and **21** in good product yields (entries 7 and 8). *tert*-Butyl (*Z*)-2-undecen-4-ynoate ((*Z*)-**1**), which is an olefinic isomer of **1**, gave the same product **3** in a similar yield (entries 1 vs. 9). As further extension of the substrates, (2-alken-4-ynoyl)oxazolidinones **14a–c** (entries 10-12) were also suitable for this reaction to give expected allenes **22a–c**.[12,13] When optically active oxazolidinones **14b** and **c** were used, they showed moderate chiral induction in products **22b** and **c** (entries 11 and 12).

Table 2. Preparation of various allenes from enynoates and enynoyloxazolidinones.

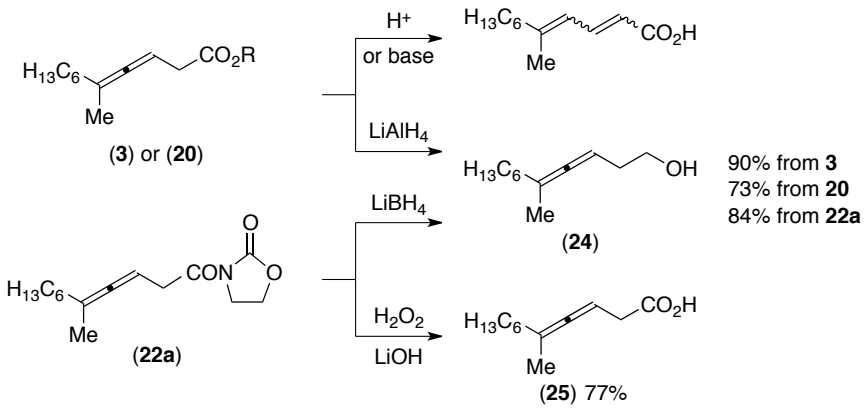


Entry	Substrate	R^2MgBr	Product	Yield (%)[a]	Ds
1	 (**1**)	MeMgBr	 (**3**)	84	
	1	ArMgBr			
2			Ar = Ph (**15**)	60	
3			*p*-MeC_6H_4- (**16**)	48	
4			*o*-MeC_6H_4- (**17**)	80	
5			*o*-$(MeO)C_6H_4$- (**18**)	74	
6	 (**12**)	MeMgBr	 (**19**)	68	
7	 (**13**)	MeMgBr	 (**20**)	72	
8	**13**	PhMgBr	 (**21**)	66	
9	 ((*Z*)-**1**)	MeMgBr	**3**	73	
		MeMgBr			
10	R = H (**14a**)		R = H (**22a**)	75	
11	Ph (**14b**)		Ph (**22b**)	74	67:33[b]
12[c]	Bn (**14c**)		Bn (**22c**)	85	67:33[b]

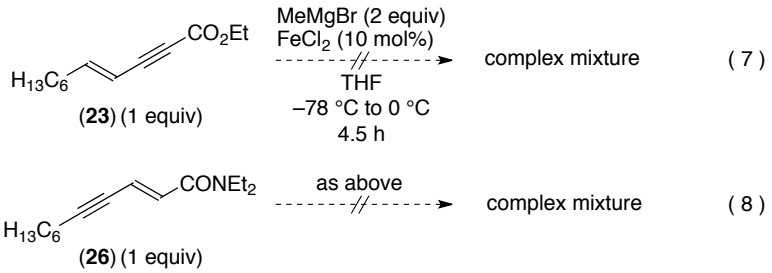
[a]Isolated yield. [b]Absolute stereochemistry of the allene part has not been determined. [c]This reaction was performed at –78 °C for 3 h.

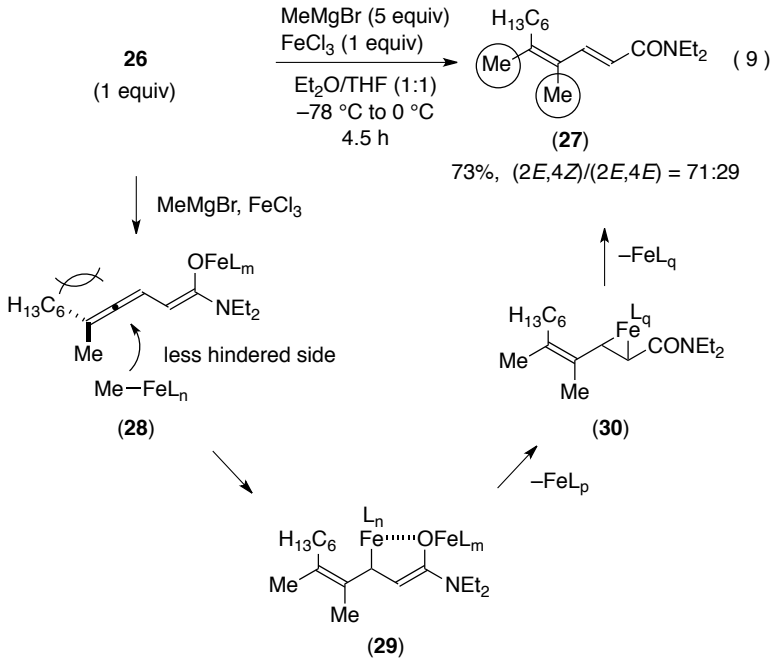
Ester and oxazolidinone groups in the products may serve for the subsequent synthetic manipulation with the allene moiety being intact, as shown in Scheme 3. While the hydrolysis of ethyl or *tert*-butyl esters **3** and **20** under the acidic or basic conditions was unsuccessful only to give the corresponding 2,4-alkadienoic acid, the reduction of **3** and **20** with $LiAlH_4$ afforded the alcohol **24**.[14] In this regard, oxazolidinone **22a** was found to be more versatile, because its reduction to alcohol **24** could be carried out with milder $LiBH_4$ and even its hydrolysis to carboxylic acid **25** was readily achieved,[12d] without accompanying any trace amount of the isomeric 2,4-alkadienoic acid.

Scheme 3. Transformations of the allene adducts.



Contrary to 2-undecen-4-ynoate **13** shown above, isomeric 4-undecen-2-ynoate **23** (eq 7) or amide **26** (eq 8) was not a good substrate for this transformation to give an intractable mixture. However, under forcing conditions using a stoichiometric amount of $FeCl_3$ and excess methyl Grignard reagent (eq 9), amide **26** underwent an unusual double addition of methyl groups to the acetylenic bond to give dimethyldiene **27**.[15] A proposed reaction course is shown in eq 9, which consists of (i) carbometallation of allene-substituted enolate **28** with methyliron species to give **29**, (ii) ligand exchange on the iron of **29** to form **30**, and (iii) the extrusion of a lower-valent iron FeL_q to give **27**. Thus, the whole understanding of eq 9 is the oxidative addition of Me anion to acetylene and, at the same time, one equiv of Fe^{III} (or Fe^{II}) should be reduced to Fe^{I} (or Fe^{0}) during this process. This mechanism could account for the fact that deuterium uptake to the product was not detected after workup with deuteriochloric acid.

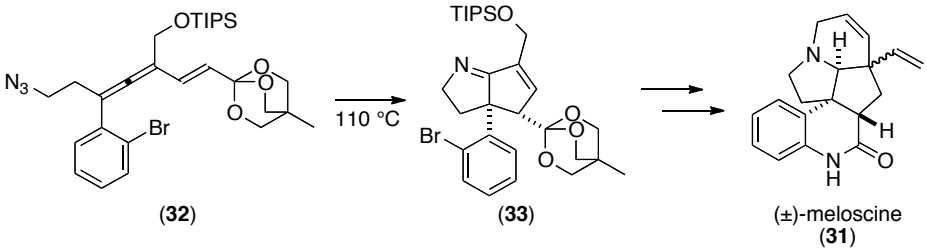




Preliminary Synthetic Study towards an Alkaloid, Meloscine

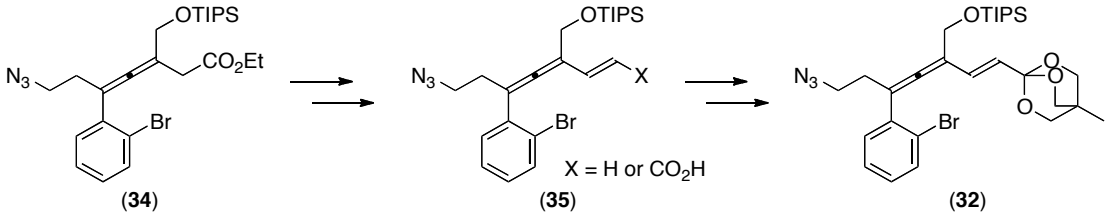
The above iron-catalyzed 1,6-addition was planned to apply to the synthesis of (±)-meloscine (**31**) in Scheme 4. (+)-Meloscine was isolated from the New Caledonian plant *Melodinus Scandens* Forst. and is structurally related to the *Aspidosperma* alkaloids.[16] Some species of genus *Melodinus* have been used in Chinese folk medicine to improve meningitis in children and rheumatic heart diseases. Recently, meloscine (**31**)[17] was synthesized from the key allenic intermediate **32** via its cyclization to **33** (Scheme 4).[17a]

Scheme 4. Synthetic study of (±)-meloscine**.**

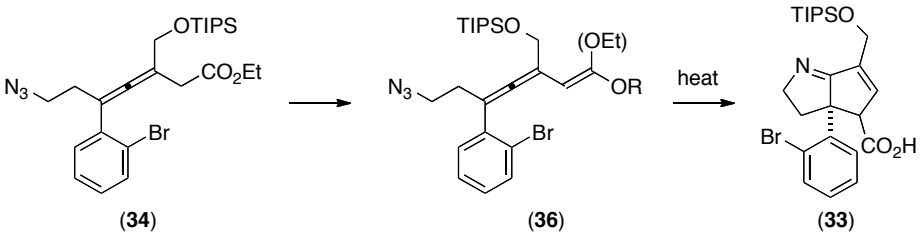


We conceived that the transformations shown in Scheme 5 or 6 would achieve the preparation of the same or a similar intermediates such as **32** or **33** leading to the total synthesis of **31** according to Scheme 4. To obtain **32** or **33**, we, in turn, chose the common allene **34** as an important key intermediate, which may be readily prepared by the present iron-catalyzed Grignard addition to enynoates.

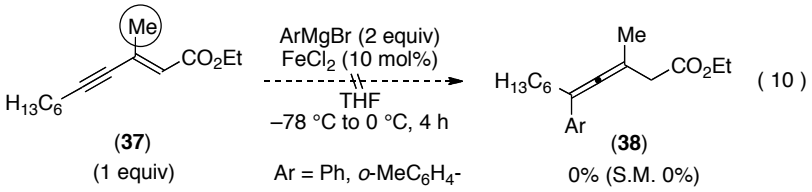
Scheme 5. Synthetic plan A to the same intermediate.



Scheme 6. Synthetic plan B to the similar intermediate.

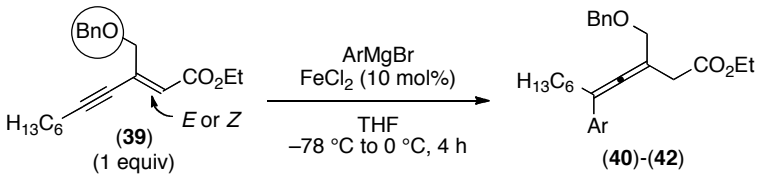


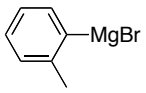
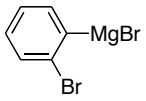
As the first model experiment, we attempted the addition of ArMgBr to a 2-alken-4-ynoate **37** having a methyl substituent at its β-position, but the desired adduct was not obtained (eq 10).



Although we were discouraged by this result, we did choose a more realistic model, i.e. a β-benzyloxymethyl-substituted 2-alken-4-ynoate such as **39** (Table 3) to make a final decision on the suitability of this project. To our surprise and gratifying, we were pleased to see that the addition of PhMgBr to this substrate **39** proceeded albeit in a moderate yield (entry 1, Table 3). This yield was not improved by changing the stereochemistry of the starting enyne **39** (entry 2). We conceived that the moderate yield would be further improved by switching PhMgBr to *o*-substituted aryl Grignard reagent, based on the previous observation regarding entries 2-5 of Table 2. In fact, *o*-tolylmagnesium bromide gave the corresponding adduct **41** in a better yield with decreasing the equivalents of the Grignard reagent from three to two (entry 3). This tendency was still sound for 2-bromophenylmagnesium halide (prepared from 2-bromo(iodo)benzene and isopropylmagnesium chloride *in situ*), affording the desired tetrasubstituted allene **42** with the halogen moiety on its aromatic ring remaining unattacked in a good yield (entry 4).

Table 3. 1,6-Addition of ArMgBr to model compound.

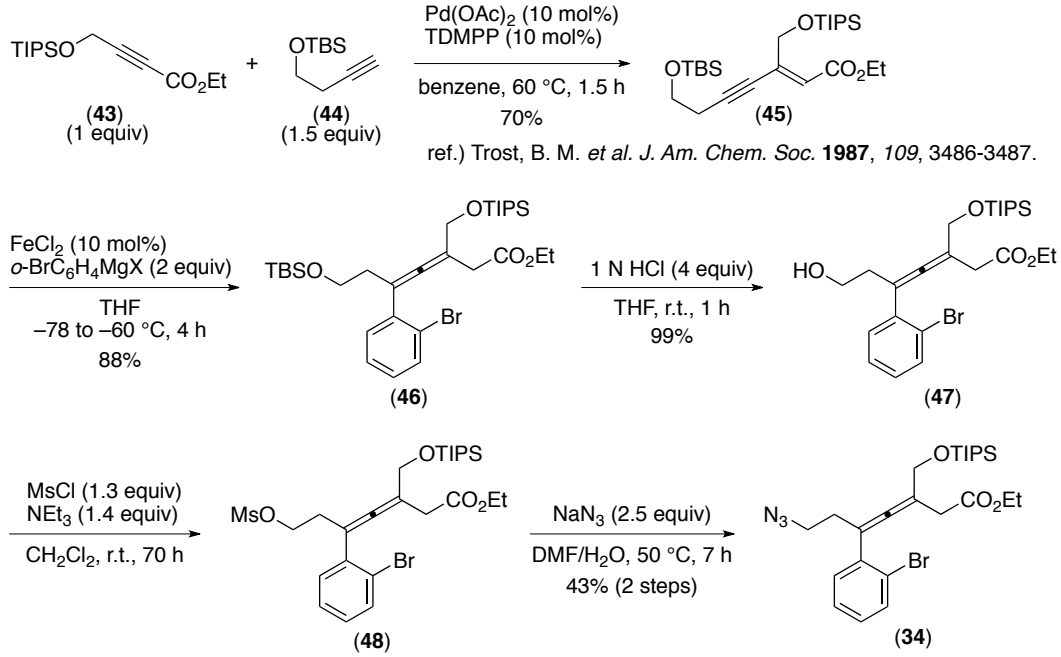


Entry	**39** (*E* or *Z*)	ArMgBr	(equiv)	Product	Yield (%)[a]
1	*Z*	PhMgBr	3	(**40**)	44
2	*E*	PhMgBr	3	(**40**)	32
3	*Z*		2	(**41**)	75
4	*Z*		2	(**42**)	77

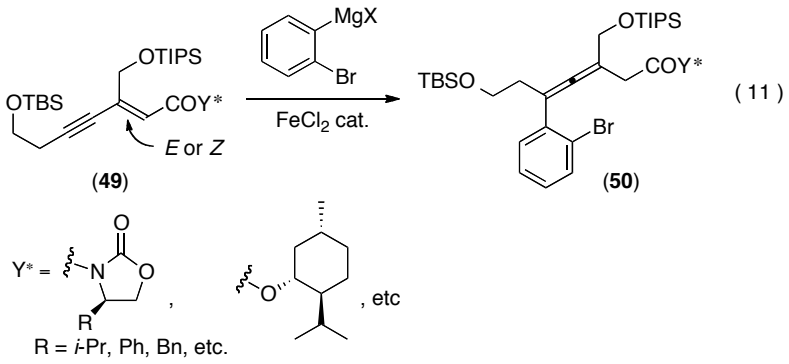
[a]Isolated yields.

Achieving the successful preparation of the model compound **42**, we turned out attention to the synthesis of the key intermediate **34**, which was straightforward as shown in Scheme 7. The Pd-catalyzed coupling of acetylenes **43** and **44** according to the Trost protocol gave 2-alken-4-ynoate **45**. When the iron-catalyzed addition of the aryl Grignard reagent to **45** was performed according to entry 4 in Table 3, the desired allene **46** was isolated in 88% yield. Selective deprotection of the TBS group in **46** with 1 N HCl solution,[19] mesylation of the resulting alcohol **47**,[20] and the substitution with NaN_3[21] proceeded with the allene portion intact to afford the key tetrasubstituted allene **34** in a good yield.

Scheme 7. Synthesis of key allene intermediate **31**.



Further transformation of **34** to the advanced intermediate **32** or **33** as shown in Scheme 5 or 6, and the preparation of optically active allene **50** from a chiral starting material **49** (*cf.* entries 11 and 12 in Table 2) according to eq 11 are now in progress.



Conclusion

In conclusion, the highly selective remote addition of Grignard reagents to α,β,γ,δ-unsaturated carbonyl compounds has been realized with the iron catalyst to provide a new synthetic method of allenes. Further investigation of this method directed to asymmetric synthesis or the total synthesis of naturally occurring products is in progress in our laboratory.

3. References and Notes

1. For recent reports of conjugate addition to α,β,γ,δ-unsaturated carbonyl compounds, see the followings. Under Fe catalysis: (a) Okada, S.; Arayama, K.; Murayama, R.; Ishizuka, T.; Hara, K.; Hirone, N.; Hata, T.; Urabe, H. *Angew. Chem., Int. Ed.* **2008**, *47*, 6860-6864. Cu: (b) den Hartog, T.; Harutyunyan, S. R.; Font, D.; Minnaard, A. J.; Feringa, B. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 398-401. (c) Hénon, H.; Mauduit, M.; Alexakis, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 9122-9124. (d) Lee, K.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2010**, *132*, 2898-2900. (e) Wencel-Delord, J.; Alexakis, A.; Crévisy, C.; Mauduit, M. *Org. Lett.* **2010**, *12*, 4335-4337. (f) Tissot, M.; Hernández, A. P.; Müller, D.; Mauduit, M.; Alexakis, A. *Org. Lett.* **2011**, *13*, 1524-1527. Rh or Ir: (g) De la Herrán, G.; Csákÿ, A. G. *Synlett* **2009**, 585-588. (h) Nishimura, T.; Yasuhara, Y.; Sawano, T.; Hayashi, T. *J. Am. Chem. Soc.* **2010**, *132*, 7872-7873. –Metal-free: (i) Ocejo, M.; Carrillo, L.; Badía, D.; Vicario, J. L.; Fernández, N.; Reyes, E. *J. Org. Chem.* **2009**, *74*, 4404-4407.
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3. For reviews on iron-mediated or -catalyzed reactions, see: (a) Plietker, B., Ed. *Iron Catalysis in Organic Chemistry*; Wiley-VCH: Weinheim, 2008. (b) Correa, A.; Mancheño, O. G.; Bolm, C. *Chem. Soc. Rev.* **2008**, *37*, 1108-1117. (c) Bauer, E. B. *Curr. Org. Chem.* **2008**, *12*, 1341-1369. (d) Enthaler, S.; Junge, K.; Beller, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 3317-3321. (e) Bolm, C.; Legros, J.; Le Paih, J.; Zani, L. *Chem. Rev.* **2004**, *104*, 6217-6254. For enyne cyclization: (f) Michelet, V.; Toullec, P. Y.; Genêt, J.-P. *Angew. Chem., Int. Ed.* **2008**, *47*, 4268-4315. Coupling reactions: (g) Plietker, B. *Synlett* **2010**, 2049-2058. (h) Plietker, B.; Dieskau, A. *Eur. J. Org. Chem.* **2009**, 775-787. (i) Czaplik, W. M.; Mayer, M.; Cvengros, J.; Jacobi von Wangelin, A. *ChemSusChem* **2009**, *2*, 396-417. (j) Sherry, B. D.; Fürstner, A. *Acc. Chem. Res.* **2008**, *41*, 1500-1511. (k) Fürstner, A.; Martin, R. *Chem. Lett.* **2005**, *34*, 624-629. Iron carbonyl complexes: (l) Semmelhack, M. F. In *Organometallics in Organic Synthesis. A Manual*, 2nd ed.; Schlosser, M., Ed.; John Wiley & Sons: Chichester, 2002; pp 1006-1121. (m) Wilkinson, G., Stone, F. G. A., Abel, E. W., Eds. *Comprehensive Organometallic Chemistry*; Pergamon Press: Oxford, 1982; Vol. 4, pp 243-649.
4. Krause, N.;, Hashmi, A. S. K., Eds. *Modern Allene Chemistry*; Wiley-VCH: Weinheim, 2004; Vols. 1 and 2.
5. For preparations of allenes, see the followings. Via substitution or addition with organometallic reagents: (a) Krause, N.; Hoffmann-Röder, A. *Tetrahedron* **2004**, *60*, 11671-11694. Via a 1,6-addition of organocopper reagents derived alkyllithiums to 2-alken-4-ynoates, -amides, or -ones: (b) Krause, N.; Gerold, A. *Angew. Chem., Int. Ed.* **1997**,

36, 186-204. (c) Krause, N.; Thorand, S. *Inorg. Chim. Acta* **1999**, *296*, 1-11. (d) Yoshikai, N.; Nakamura, E. *Chem. Rev.* **2012**, *112*, 2339-2372.

6. (a) Krause, N. *Chem. Ber.* **1990**, *123*, 2173-2180. (b) Krause, N. *Chem. Ber.* **1991**, *124*, 2633-2635. (c) Krause, N.; Handke, G. *Tetrahedron Lett.* **1991**, *32*, 7229-7232. (d) Krause, N. *J. Org. Chem.* **1992**, *57*, 3509-3512. (e) Handke, G.; Krause, N. *Tetrahedron Lett.* **1993**, *34*, 6037-6040. (f) Krause, N. *Liebigs Ann. Chem.* **1993**, 521-525. (g) Arndt, S.; Handke, G.; Krause, N. *Chem. Ber.* **1993**, *126*, 251-259. (h) Krause, N.; Arndt, S. *Chem. Ber.* **1993**, *126*, 261-263. (i) Gerold, A.; Krause, N. *Chem. Ber.* **1994**, *127*, 1547-1549. (j) Krause, N.; Wagner, R.; Gerold, A. *J. Am. Chem. Soc.* **1994**, *116*, 381-382. (k) Hohmann, M.; Krause, N. *Chem. Ber.* **1995**, *128*, 851-860. (l) Koop, U.; Handke, G.; Krause, N. *Liebigs Ann.* **1996**, 1487-1499. (m) Laux, M.; Krause, N.; Koop, U. *Synlett* **1996**, 87-88. (n) Krause, N.; Hohmann, M. *Synlett* **1996**, 89-91. (o) Becker, M.; Krause, N. *Liebigs Ann./Recueil* **1997**, 725-728. (p) Canisius, J.; Gerold, A.; Krause, N. *Angew. Chem., Int. Ed.* **1999**, *38*, 1644-1646. (q) Canisius, J.; Mobley, T. A.; Berger, S.; Krause, N. *Chem. Eur. J.* **2001**, *7*, 2671-2675. (r) Mori, S.; Uerdingen, M.; Krause, N.; Morokuma, K. *Angew. Chem., Int. Ed.* **2005**, *44*, 4715-4719. (s) Haubrich, A.; van Klaveren, M.; van Koten, G.; Handke, G.; Krause, N. *J. Org. Chem.* **1993**, *58*, 5849-5852.

7. That the similar addition of Grignard reagents to enynoates under Cu catalysis led to low product yields is shown in references 5b and c.

8. Metal enolates such as **2** or **9** have their resonance isomers like **10** and **11**, but the latter two structures are totally or partially abbreviated to make simplification in Schemes 1 and 2, and eq 9.

9. The similar 1,6-addition of organocuprates generated from alkyllithiums and the subsequent aldol reaction have been reported, see: reference 6g.

10. (a) Buchwald, S. L.; Bolm, C. *Angew. Chem., Int. Ed.* **2009**, *48*, 5586-5587. (b) Larsson, P.-F.; Correa, A.; Carril, M.; Norrby, P.-O.; Bolm, C. *Angew. Chem., Int. Ed.* **2009**, *48*, 5691-5693.

11. For related discussion on the iron species in this addition of Grignard reagents, see: (a) reference 1a. (b) Hata, T.; Sujaku, S.; Hirone, N.; Nakano, K.; Imoto, J.; Imade, H.; Urabe, H. *Chem.-Eur. J.* **2011**, *17*, 14593-14602. (c) Fürstner, A.; Krause, H.; Lehmann, C. W. *Angew. Chem., Int. Ed.* **2006**, *45*, 440-444. (d) Fürstner, A.; Martin, R.; Krause, H.; Seidel, G.; Goddard, R.; Lehmann, C. W. *J. Am. Chem. Soc.* **2008**, *130*, 8773-8787.

12. For reviews on the reactions of acyloxazolidinones, see: (a) Evans, D. A. *Aldrichimica Acta* **1982**, *15*, 23-32. (b) Ager, D. J.; Prakash, I.; Schaad, D. R. *Chem. Rev.* **1996**, *96*, 835-875. (c) Ager, D. J.; Prakash, I.; Schaad, D. R. *Aldrichimica Acta* **1997**, *30*, 3-12. The hydrolysis to

carboxylic acid was performed according to the following literature: (d) Evans, D. A.; Britton, T. C.; Ellman, J. A. *Tetrahedron Lett*. **1987**, *28*, 6141-6144.

13. The similar 1,6-addition of organocuprates generated from alkyllithiums to achiral (2-alken-4-ynoyl)oxazolidinones has been reported, see: reference 6k.
14. The similar $LiAlH_4$ reduction of ethyl 3,4-alkadienoates has been precedented, see: reference 6g.
15. A related double addition of organocuprates to enynone (hence, containing carbometallation to the electron-rich allene intermediates) is known, but the regioselection and the oxidation state of the product are not similar: Lee, S.-H.; Hulce, M. *Tetrahedron Lett*. **1990**, *31*, 311-314.
16. (a) Bernauer, K.; Englert, G.; Vetter, W.; Weiss, E. *Helv*. *Chim*. *Acta* **1969**, *52*, 1886-1905. (b) Oberhansi, W.E. *Helv*. *Chim*. *Acta* **1969**, *52*, 1905-1911.
17. Previous synthesis of meloscine, see: (a) Feldman, K. S.; Antoline, J. F. *Tetrahedron* **2013**, *69*, 1434-1445. (b) Overman, L. E.; Robertson, G. M.; Robichaud, A. J. *J*. *Am*. *Chem*. *Soc*. **1991**, *113*, 2598-2610. (c) Selig, P.; Bach, T. *Angew*. *Chem., Int*. *Ed*. **2008**, *47*, 5082-5084. (d) Selig, P.; Herdtweck, E.; Bach, T. *Chem.-Eur*. *J*. **2009**, *15*, 3509-3525. (e) Hayashi, Y.; Inagaki, F.; Mukai, C. *Org*. *Lett*. **2011**, *13*, 1778-1780. (f) Zhang, H.; Curran, D. P. *J*. *Am*. *Chem*. *Soc*. **2011**, *133*, 10376-10378.
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19. (a) Crouch, R. D. *Tetrahedron* **2013**, *69*, 2383-2417. (b) Becker, M. H.; Chua, P.; Downham, R.; Douglas, C. J.; Garg, N. K.; Hiebert, S.; Jaroch, S.; Matsuoka, R. T.; Middleton, J. M.; Ng, F. W.; Overmann, L. E. *J*. *Am*. *Chem*. *Soc*. **2007**, *129*, 11987-12002.
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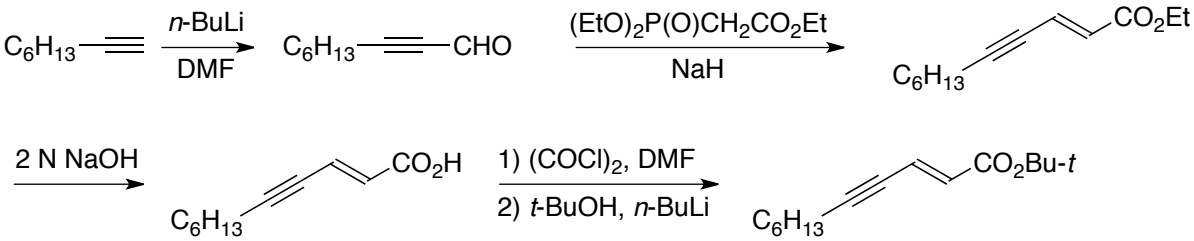
Experimental Section (Chapter 2)

General. ^{1}H and ^{13}C NMR spectra were taken on a Varian Gemini-300 spectrometer at 300 and 75 MHz or Agilent 400-MR spectromer at 400 and 100 MHz, respectively. Unless otherwise specified in spectral data, the former was always used. $CDCl_3$ was used as the solvent. Chemical shifts are reported in parts per million shift (δ value) from Me_4Si (δ 0 ppm for ^{1}H) or based on the middle peak of the solvent ($CDCl_3$) (δ 77.00 ppm for ^{13}C NMR) as an internal standard. Signal patterns are indicated as br, broad; s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. Coupling constants (*J*) are given in Hertz. Infrared (IR) spectra were recorded on a JASCO A-100 spectrometer and are reported in wave numbers (cm^{-1}). Optical rotation was measured on JASCO DIP-370 digital polarimeter. $FeCl_2$ (purity: 99.9%) was purchased from Soekawa Chemicals Co. Methylmagnesium bromide in THF was purchased from Kanto Chemicals Co. Other aryl Grignard reagents were prepared in THF as a 1.02-1.11 M solution from the corresponding bromides and magnesium turnings by the usual procedure, titrated, and stored under an argon atmosphere. Dry solvents (THF, diethyl ether, and CH_2Cl_2) were purchased from Kanto Chemicals Co. (Japan). Chemicals were purified or dried in a standard manner, if necessary.

***tert*-Butyl (*E*)-2-undecen-4-ynoate (1).**



This was prepared as follows.



To a solution of 1-octyne (0.840 mL, 6.00 mmol) in Et_2O (20 mL) was added BuLi (1.65 M in hexane, 4.36 mL, 7.20 mmol) at –78 ºC under argon. After stirring at –78 °C for 0.5 h, DMF (0.700 mL, 9.00 mmol) was introduced to the mixture at –78 °C and the solution was stirred at that temperature for 2 h. The reaction was terminated by the addition of aqueous saturated NH_4Cl solution. The organic products were extracted with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo* to afford 2-nonynal (887 mg, *ca*. 100%), which was directly used in the next step.

To a suspension of sodium hydride (334 mg of a 60% suspension in mineral oil, 8.34 mmol) in THF (6 mL) was added triethyl phosphonoacetate (1.55 mL, 7.70 mmol) at 0 °C under argon. After the

mixture was stirred for 10 min at room temperature, it was again cooled to 0 °C. Then, 2-nonynal (887 mg, *ca*. 6.00 mmol) was added and the mixture was warmed to room temperature and was stirred for 1 h. The reaction was terminated by the slow addition of water. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed successively with water and brine, dried over Na_2SO_4, and concentrated *in vacuo* to a crude oil, which was chromatographed on silica gel (hexane-ethyl acetate) to afford ethyl (*E*)-2-undecen-4-ynoate (676 mg, 54% over 2 steps) exclusively with *E*-olefinic bond as an oil.

A mixture of ethyl (*E*)-2-undecen-4-ynoate (618 mg, 2.97 mmol) and 2 N NaOH solution (10 mL) was refluxed for 2.5 h without a co-solvent. The reaction mixture was cooled to room temperature, diluted with ethyl acetate, and acidified with 1 N HCl. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were dried over Na_2SO_4, and concentrated *in vacuo* to give a crude oil, which was chromatographed on silica gel (hexane-ethyl acetate) to afford (*E*)-2-undecen-4-ynoic acid (448 mg, 84%) as an oil.

To a stirred solution of the above (*E*)-2-undecen-4-ynoic acid (448 mg, 2.49 mmol) in CH_2Cl_2 (2.5 mL) were successively added DMF (1 drop) and oxalyl chloride (0.430 mL, 4.97 mmol) at room temperature. After the mixture was stirred for 2 h, the solvent and the excess oxalyl chloride were removed *in vacuo* to afford the desired (*E*)-2-undecen-4-ynoic acid chloride as a crude oil, which was directly used in the next step.

To a solution of *t*-BuOH (0.240 mL, 2.49 mmol) in THF (2.5 mL) was added BuLi (1.65 M in hexane, 1.51 mL, 2.49 mmol) at 0 °C under argon. After the mixture was stirred at room temperature for 1 h, the above (*E*)-2-undecen-4-ynoic acid chloride in THF (3.5 mL) was added at 0 °C. After the mixture was stirred at room temperature for 1.5 h, the reaction was quenched by the addition of water. The organic layer was separated and the aqueous layer was extracted with AcOEt. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo* to give a crude oil, which was chromatographed on silica gel (hexane-ethyl acetate) to afford the title compound (267 mg, 38% overall yield from the carboxylic acid) exclusively with *E*-olefinic bond as an oil.

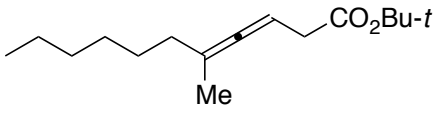
^{1}H NMR δ 0.89 (t, *J* = 6.6 Hz, 3H, alkyl-Me), 1.18-1.62 (m, 8H, alkyl H), 1.48 (s, 9H, -C(C$\underline{H}_3$)$_3$), 2.36 (dt, *J* = 2.1, 6.9 Hz, 2H, $C_5H_{11}C\underline{H}_2C{\equiv}C$-), 6.07 (d, *J* = 15.9 Hz, 1H, -CH=C$\underline{H}$CO$_2$Bu-*t*), 6.66 (dt, *J* = 15.9, 2.1 Hz, 1H, -C$\underline{H}$=CHCO$_2$Bu-*t*).

^{13}C NMR δ 14.02, 19.70, 22.50, 28.04 (3 carbons, -C($\underline{C}$H$_3$)$_3$), 28.29, 28.50, 31.26, 77.93, 80.66 (C≡C), 100.08 (C≡C), 124.99 (C=C), 131.11 (C=C), 165.42 (C=O).

IR (neat) 3070 (C=C-H), 2931, 2860, 2216 (C≡C), 1712 (C=O), 1620 (C=C), 1458, 1367, 1308, 1149, 962, 862 cm^{-1}.

Anal. Calcd for $C_{15}H_{24}O_2$: C, 76.23; H, 10.24. Found: C, 75.97; H, 10.06.

Typical procedure for the addition of Grignard reagent to functionalized enyne. *tert*-Butyl 5-methyl-3,4-undecadienoate (3) from *tert*-butyl (*E*)-2-undecen-4-ynoate (1).



To a solution of *tert*-butyl (*E*)-2-undecen-4-ynoate (**1**) (47.3 mg, 0.200 mmol) and $FeCl_2$ (2.5 mg, 0.020 mmol, reagent of 99.9% purity purchased from Soekawa Chemicals Co. (Japan)) in 1 mL of THF was added MeMgBr (0.380 mL, 1.06 M solution in THF, 0.400 mmol) at –78 °C under argon. Then, the solution was slowly warmed to 0 °C over 4.5 h. The reaction was terminated by the addition of 1 N HCl solution (1 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with aqueous saturated $NaHCO_3$ solution and brine, dried over Na_2SO_4, and concentrated *in vacuo* to give a crude oil, ^{1}H NMR analysis of which did not show the presence of other regioisomers. The crude product was chromatographed on silica gel (hexane-ethyl acetate) to afford the title compound (43.2 mg, 84%) as an oil.

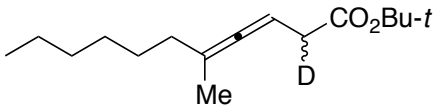
^{1}H NMR δ 0.88 (t, *J* = 6.9 Hz, 3H, alkyl-Me), 1.16-1.60 (m, 8H, alkyl H), 1.45 (s, 9H, -C(C$\underline{H}_3$)$_3$), 1.67 (d, *J* = 2.7 Hz, 3H, C_6H_{13}C($\underline{Me}$)-), 1.92 (dt, *J* = 2.7, 7.8 Hz, 2H, $C_5H_{11}C\underline{H}_2$C(Me)-), 2.88 (d, *J* = 7.2 Hz, 2H, -C$\underline{H}_2$CO$_2$Bu-*t*), 5.12 (m, 1H, -C=C=C$\underline{H}$-).

^{13}C NMR δ 14.07, 19.00, 22.62, 27.27, 28.00 (3 carbons, -C($\underline{C}$H$_3$)$_3$), 28.88, 31.69, 33.78, 36.63, 80.33, 83.64, 100.50, 171.21 (C=O), 202.26 (C=$\underline{C}$=C).

IR (neat) 2929, 2858, 1969 (C=C=C), 1734 (C=O), 1633, 1458, 1367, 1257, 1147, 847 cm^{-1}.

Anal. Calcd for $C_{16}H_{28}O_2$: C, 76.14; H, 11.18. Found: C, 76.16; H, 10.88.

A diastereomeric mixture of *tert*-butyl 2-deuterio-5-methyl-3,4-undecadienoate (3-*d*).



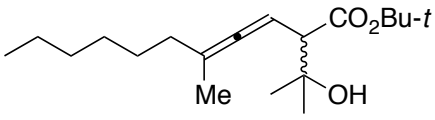
To a solution of *tert*-butyl (*E*)-2-undecen-4-ynoate (**1**) (47.3 mg, 0.200 mmol) and $FeCl_2$ (2.5 mg, 0.020 mmol) in 1 mL of THF was added MeMgBr (0.36 mL, 1.12 M solution in THF, 0.40 mmol) at –78 °C under argon. Then, the solution was slowly warmed to 0 °C over 4.5 h. The reaction was terminated by the addition of 1 N DCl solution (0.2 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with aqueous saturated $NaHCO_3$ solution and brine, dried over Na_2SO_4, and concentrated *in vacuo* to give a crude oil, ^{1}H NMR analysis of which did not show the presence of other regioisomers. The crude product was chromatographed on silica gel (hexane-ethyl acetate) to afford the title compound (40.0 mg, 79%) as an oil.

^{1}H NMR δ 0.88 (t, *J* = 6.9 Hz, 3H, alkyl-Me), 1.20-1.55 (m, 8H, alkyl H), 1.45 (s, 9H, -C(C$\underline{H}_3$)$_3$), 1.67 (d, *J* = 2.7 Hz, 3H, C_6H_{13}C($\underline{Me}$)-), 1.92 (dt, *J* = 2.7, 7.8 Hz, 2H, $C_5H_{11}C\underline{H}_2$C(Me)-), 2.86 (m, *J* = 7.2 Hz, 1H, -C$\underline{H}$DCO$_2$Bu-*t*), 5.11 (m, 1H, -C=C=C$\underline{H}$-).

^{13}C NMR δ 14.09, 19.03, 22.64, 27.29, 28.03 (3 carbons, -C(<u>C</u>H$_3$)$_3$), 28.90, 31.71, 33.80, 36.39 (t, *J* = 19.9 Hz, C-D coupling), 80.36, 83.59, 100.53, 171.26 (C=O), 202.28 (C=<u>C</u>=C).

The integration of peak areas at δ 2.86 (m, 1H, -C<u>H</u>DCO$_2$Bu-*t*) showed total 1.00H as compared to the original value of **3** (2H) to show >99% deuterium incorporation at this position. However, the diastereoselectivity of this compound was hardly determined by ^{1}H NMR spectroscopy.

A 59:41 diastereomeric mixture of *tert*-butyl 5-methyl-(1-methyl-1-hydroxyethyl)-3,4-undecadienoate (6) prepared by methyl Grignard addition to enyne 1, followed by *in situ* carbonyl addition.



To a solution of *tert*-butyl (*E*)-2-undecen-4-ynoate (**1**) (47.3 mg, 0.200 mmol) and $FeCl_2$ (2.5 mg, 0.020 mmol) in 1 mL of THF was added MeMgBr (0.380 mL, 1.06 M solution in THF, 0.400 mmol) at –78 °C under argon. After the mixture was warmed up to 0 ºC over 4.5 h, acetone (0.070 mL, 0.950 mmol, dehydrated reagent purchased from Kanto Chemicals Co. (Japan)) was added and the reaction mixture was stirred at 0 °C for 5 h. The reaction was terminated at room temperature by the addition of 1 N HCl solution (1 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed successively with aqueous saturated $NaHCO_3$ solution and brine, dried over Na_2SO_4, and concentrated *in vacuo* to give a crude oil, ^{1}H NMR analysis of which revealed that other regioisomer(s) were absent and that the diastereoselectivity of the product was 59:41. The crude oil was chromatographed on silica gel (hexane-ethyl acetate) to afford the title compound (36.1 mg, 58%) as an oil and of the same diastereomeric composition observed for a crude sample.

Major isomer: ^{1}H NMR δ 0.88 (t, *J* = 6.9 Hz, 3H, alkyl-Me), 1.27 (s, 6H, -C(OH)<u>Me</u>$_2$), 1.23-1.57 (m, 8H, alkyl H), 1.48 (s, 9H, -CO$_2$C(C<u>H</u>$_3$)$_3$), 1.68 (d, *J* = 2.7 Hz, 3H, C$_6$H$_{13}$C(<u>Me</u>)-), 1.92 (m, 2H, C$_5$H$_{11}$C<u>H</u>$_2$C(Me)-), 2.82 (d, *J* = 9.3 Hz, 1H, -C<u>H</u>CO$_2$Bu-*t*), 3.53 (s, 1H, -O<u>H</u>), 5.19 (m, 1H, -C=C=C<u>H</u>-).

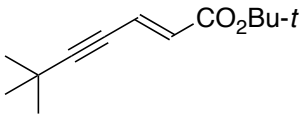
Minor isomer: ^{1}H NMR (characteristic peaks are shown) δ 2.83 (d, *J* = 9.3 Hz, 1H, -C<u>H</u>CO$_2$Bu-*t*), 3.58 (s, 1H, -O<u>H</u>).

^{13}C NMR δ 14.06, 18.97, 19.09, 22.59, 22.62, 26.50, 26.65, 27.27, 27.46, 27.98 (3 carbons, -C(<u>C</u>H$_3$)$_3$), 28.63, 28.70, 28.94, 31.71, 33.63, 33.86, 56.95, 57.28, 71.12, 71.29, 81.44, 81.49, 85.74, 86.04, 100.55, 100.61, 173.84 (C=O), 173.86 (C=O), 203.17 (C=<u>C</u>=C), 203.21 (C=<u>C</u>=C) for a 59:41 mixture of diastereomers. As this sample is an almost 1:1 mixture of isomers, some peaks may be overlapping.

IR (neat) 3510 (OH), 2960, 2929, 2858, 1967 (C=C=C), 1705 (C=O), 1612, 1458, 1369, 1255, 1146, 955, 852 cm^{-1} for a 59:41 mixture of diastereoisomers.

Anal. Calcd for $C_{19}H_{34}O_3$: C, 73.50; H, 11.04. Found: C, 73.48; H, 10.84 for a 59:41 mixture of diastereoisomers.

***tert*-Butyl (*E*)-6,6-dimethyl-2-hepten-4-ynoate (12).** This is a known compound [Hadi, V.; Yoo, K. S.; Jeong, M.; Jung, K. W. *Tetrahedron Lett*. **2009**, *50*, 2370-2373].



To a suspension of $Pd(tfa)_2$ (33.2 mg, 0.100 mmol) and K_2CO_3 (1.38 g, 9.98 mmol) in DMF (15 mL) was added 3,3-dimethyl-1-butyne (0.620 mL, 5.03 mmol) and *tert*-butyl acrylate (2.93 mL, 20.0 mmol) at room temperature under oxygen. After the mixture was stirred for 4 h at room temperature, the reaction was terminated by the addition of water. The organic layer was separated and the aqueous layer was extracted with hexane. The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo* to give a crude oil, which was chromatographed on silica gel (hexane-ethyl acetate) to afford the pure title compound (419 mg, 40%) exclusively with *E*-olefinic bond as an oil.

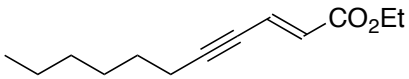
^{1}H NMR δ 1.25 (s, 9H, -C(C$\underline{H}_3$)$_3$), 1.47 (s, 9H, -C(C$\underline{H}_3$)$_3$), 6.07 (d, *J* = 15.9 Hz, 1H, -C$\underline{H}$=CHCO$_2$Bu-*t*), 6.66 (d, *J* = 15.9 Hz, 1H, -CH=C$\underline{H}$CO$_2$Bu-*t*).

^{13}C NMR δ 28.06 (3 carbons, -C($\underline{C}$H$_3$)$_3$), 28.26, 30.59 (3 carbons, -C($\underline{C}$H$_3$)$_3$), 76.49, 80.57 (C≡C), 107.74 (C≡C), 124.95 (C=C), 131.04 (C=C), 165.38 (C=O).

IR (neat) 3066 (C=C-H), 2972, 2931, 2870, 2224 (C≡C), 1712 (C=O), 1618 (C=C), 1458, 1367, 1257, 1155, 962, 862, 771 cm^{-1}.

Anal. Calcd for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68. Found: C, 75.07; H, 9.84.

Ethyl (*E*)-2-undecen-4-ynoate (13).



The preparation of ethyl (*E*)-2-undecen-4-ynoate (**13**) exclusively with *E*-olefinic bond has been already shown in that of *tert*-butyl (*E*)-2-undecen-4-ynoate (**1**).

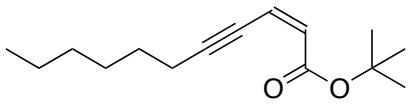
^{1}H NMR δ 0.90 (t, *J* = 6.9 Hz, 3H, alkyl-Me), 1.19-1.46 (m, 6H, alkyl H), 1.29 (t, *J* = 6.9 Hz, 3H, -CO$_2$CH$_2$C$\underline{H}_3$), 1.49-1.60 (m, 2H, alkyl H), 2.37 (dt, *J* = 2.1, 6.6 Hz, 2H, C$_5$H$_{11}$C$\underline{H}_2$C≡C-), 4.20 (q, *J* = 6.9 Hz, 2H, -CO$_2$C$\underline{H}_2$CH$_3$), 6.14 (d, *J* = 15.9 Hz, 1H, -CH=C$\underline{H}$CO$_2$Et), 6.76 (dt, *J* = 15.9, 2.1 Hz, 1H, -C$\underline{H}$=CHCO$_2$Et).

^{13}C NMR δ 13.97, 14.15, 19.69, 22.46, 28.22, 28.47, 31.22, 60.50, 77.87 (C≡C), 100.79 (C≡C), 126.07 (C=C), 129.16 (C=C), 166.10 (C=O).

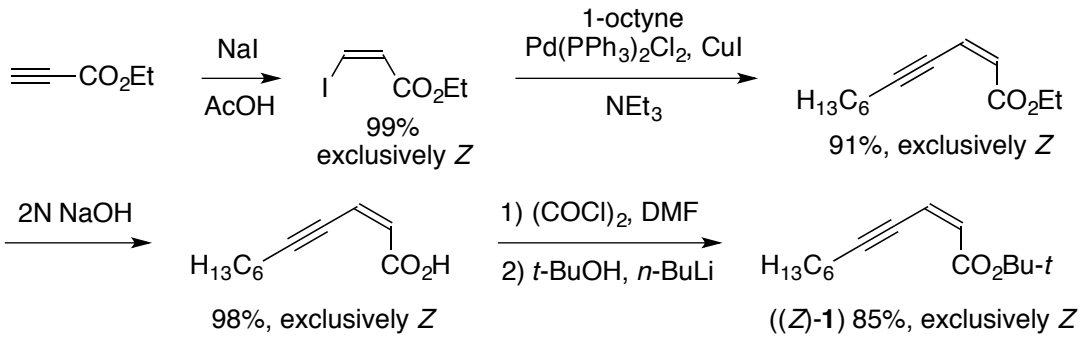
IR (neat) 3070 (C=C-H), 2933, 2860, 2216 (C≡C), 1718 (C=O), 1620 (C=C), 1466, 1367, 1302, 1157, 1041, 962, 862, 721 cm^{-1}.

Anal. Calcd for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68. Found: C, 74.85; H, 9.65.

***tert*-Butyl (*Z*)-2-undecen-4-ynoate ((*Z*)-1).**



This was prepared according to the following scheme [(a) Piers, E.; Wong, T.; Coish, P. D.; Rogers, C. *Can. J. Chem.* **1994**, *72*, 1816-1819. (b) Rubina, M.; Conley, M.; Gevorgyan, V. *J. Am. Chem. Soc.* **2006**, *128*, 5818-5827].



To a suspension of sodium iodide (2.40 g, 16.0 mmol) in AcOH (3.70 mL, 64.6 mmol) was added ethyl propiolate (1.01 mL, 9.97 mmol) under argon. After the reaction mixture was stirred in an oil bath maintained at 115 °C for 1.5 h, it was cooled to room temperature and the reaction was terminated by the addition of water. The organic products were extracted with Et_2O. The combined organic layers were washed successively with aqueous saturated $NaHCO_3$ solution, aqueous saturated $Na_2S_2O_3$ solution, and brine, dried over Na_2SO_4, and concentrated *in vacuo* to afford ethyl (*Z*)-3-iodoacrylate (2.24 g, 99%, exclusively *Z*), which was directly used in the next step.

To a suspension of $Pd(PPh_3)_2Cl_2$ (70.2 mg, 0.100 mmol) and CuI (38.1 mg, 0.200 mmol) in triethylamine (15 mL) was added ethyl (*Z*)-3-iodoacrylate (2.24 g, 9.91 mmol) in triethylamine (5 mL), followed by 1-octyne (1.42 mL, 10.0 mmol), under argon. After the mixture was stirred for 12 h at room temperature, it was quenched with aqueous saturated NH_4Cl solution. The organic products were extracted with ethyl acetate. The combined organic layers were washed successively with 1 N HCl, water, and brine, dried over Na_2SO_4, and concentrated *in vacuo* to a crude oil, which was chromatographed on silica gel (hexane-ethyl acetate) to afford ethyl (*Z*)-2-undecen-4-ynoate (1.88 g, 91%, exclusively *Z*) as an oil.

A mixture of ethyl (*Z*)-2-undecen-4-ynoate (1.88 g, 9.03 mmol) and aqueous 2 N NaOH solution (10 mL) was refluxed for 1.5 h without a co-solvent. The reaction mixture was cooled to room temperature, diluted with ethyl acetate, and acidified with 1 N HCl. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo* to give a crude oil, which was chromatographed on silica gel (hexane-ethyl acetate) to afford (*Z*)-2-undecen-4-ynoic acid (1.60 g, 98%, exclusively *Z*) as an oil.

To a stirred solution of the above (*Z*)-2-undecen-4-ynoic acid (901 mg, 5.00 mmol) in CH_2Cl_2 (20 mL) were successively added DMF (1 drop) and oxalyl chloride (0.860 mL, 10.0 mmol) at room temperature. After the mixture was stirred for 2 h, the solvent and the excess oxalyl chloride were removed *in vacuo* to afford the desired (*Z*)-2-undecen-4-ynoyl chloride as a crude oil, which was directly used in the next step.

To a solution of *t*-BuOH (0.480 mL, 5.02 mmol) in THF (10 mL) was added BuLi (1.60 M in hexane, 3.15 mL, 5.04 mmol) at 0 °C under argon. After the mixture was stirred at room temperature for 1 h, the above (*Z*)-2-undecen-4-ynoyl chloride (*ca*. 990 mg, 4.98 mmol) in THF (5 mL) was added at 0 °C. After stirring at room temperature for 1.5 h, the reaction was quenched with water. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo* to give a crude oil, which was chromatographed on silica gel (hexane-ethyl acetate) to afford the title compound (999 mg, 85% overall yield from the carboxylic acid, exclusively *Z*) as an oil.

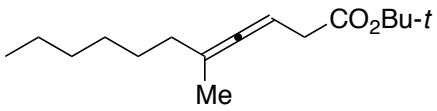
^{1}H NMR δ 0.89 (t, *J* = 6.8 Hz, 3H, alkyl-Me), 1.22-1.63 (m, 8H, alkyl H), 1.50 (s, 9H, -C(C$\underline{H}_3$)$_3$), 2.43 (dt, *J* = 2.4, 7.2 Hz, 2H, $C_5H_{11}C\underline{H}_2C{\equiv}C$-), 5.93 (d, *J* = 11.6 Hz, 1H, -CH=C$\underline{H}$CO$_2$Bu-*t*), 6.07 (td, *J* = 2.4, 11.6 Hz, 1H, -C$\underline{H}$=CHCO$_2$Bu-*t*).

^{13}C NMR δ 14.00, 20.08, 22.50, 28.13 (3 carbons, -C($\underline{C}H_3$)$_3$), 28.38, 28.61, 31.32, 77.71, 80.52 (C≡C), 103.35 (C≡C), 122.53 (C=C), 129.27 (C=C), 164.21 (C=O).

IR (neat) 3004 (C=C-H), 2957, 2859, 2208 (C≡C), 1722 (C=O), 1607 (C=C), 1457, 1367, 1303, 1152, 967, 819 cm^{-1}.

HRMS (ESI) Calcd for $C_{15}H_{24}O_2Na$ [M+Na]$^+$: 259.1669. Found: 259.1666.

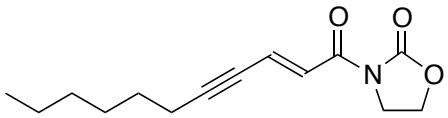
***tert*-Butyl 5-methyl-3,4-undecadienoate (3) from *tert*-butyl (*Z*)-2-undecen-4-ynoate ((*Z*)-1).**



To a solution of *tert*-butyl (*Z*)-2-undecen-4-ynoate ((*Z*)-**1**) (47.3 mg, 0.200 mmol) and $FeCl_2$ (2.5 mg, 0.020 mmol) in 1 mL of THF was added MeMgBr (0.400 mL, 0.99 M solution in THF, 0.396 mmol) at –78 °C under argon. Then, the solution was slowly warmed to 0 °C over 4.5 h. The reaction was terminated by the addition of 1 N HCl solution (1 mL). The organic layer was

separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with aqueous saturated $NaHCO_3$ solution and brine, dried over Na_2SO_4, and concentrated *in vacuo* to give a crude oil, ^{1}H NMR analysis of which did not show the presence of other regioisomers. The crude product was chromatographed on silica gel (hexane-ethyl acetate) to afford the title compound (36.9 mg, 73%) as an oil.
For the spectroscopic data, see: *tert*-butyl 5-methyl-3,4-undecadienoate (**3**) from *tert*-butyl (*E*)-2-undecen-4-ynoate (**1**).

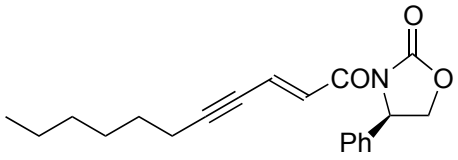
(*E*)-3-(2-Undecen-4-ynoyl)oxazolidin-2-one (14a).



A mixture of ethyl (*E*)-2-undecen-4-ynoate (**13**) (460 mg, 2.21 mmol) and 2 N NaOH solution (10 mL) was refluxed for 1.5 h without a co-solvent. The reaction mixture was cooled to room temperature, diluted with ethyl acetate, and acidified with 1 N HCl. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were dried over Na_2SO_4, and concentrated *in vacuo* to give a crude oil, which was chromatographed on silica gel (hexane-ethyl acetate) to afford (*E*)-2-undecen-4-ynoic acid (369 mg, 93%) as an oil.
To a stirred solution of the above (*E*)-2-undecen-4-ynoic acid (369 mg, 2.05 mmol) in CH_2Cl_2 (10 mL) were successively added DMF (1 drop) and oxalyl chloride (0.350 mL, 4.10 mmol) at room temperature. After the mixture was stirred for 2 h, the solvent and the excess oxalyl chloride were removed *in vacuo* to afford the desired (*E*)-2-undecen-4-ynoic acid chloride as a crude oil, which was directly used in the next step.
To a solution of 2-oxazolidone (179 mg, 2.06 mmol) in THF (5 mL) was added BuLi (1.65 M in hexane, 1.24 mL, 2.05 mmol) at 0 °C under argon. After the mixture was stirred at room temperature for 1 h, the above (*E*)-2-undecen-4-ynoic acid chloride (*ca*. 2.05 mmol) in THF (10 mL) was added at 0 °C. After the mixture was stirred at room temperature for 1.5 h, the reaction was quenched by the addition of water. The organic layer was separated and the aqueous layer was extracted with AcOEt. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo* to give a crude oil, which was chromatographed on silica gel (hexane-ethyl acetate) to afford the title compound (300 mg, 59% overall yield from the carboxylic acid) exclusively with *E*-olefinic bond as an oil.
^{1}H NMR δ 0.90 (t, *J* = 7.2 Hz, 3H, alkyl-Me), 1.19-1.48 (m, 6H, alkyl H), 1.56 (quintet, *J* = 7.2 Hz, 2H, alkyl H), 2.39 (dt, *J* = 2.1, 7.2 Hz, 2H, $C_5H_{11}C\underline{H}_2C{\equiv}C$-), 4.08 (t, *J* = 8.4 Hz, 2H, -$NCH_2C\underline{H}_2O$-), 4.45 (t, *J* = 8.4 Hz, 2H, -$NC\underline{H}_2CH_2O$-), 6.92 (dt, *J* = 15.6, 2.1 Hz, 1H, -$C\underline{H}$=$CHCONR_2$), 7.55 (d, *J* = 15.6 Hz, 1H, -CH=$C\underline{H}CONR_2$).
^{13}C NMR δ 13.96, 19.81, 22.42, 28.15, 28.49, 31.19, 42.60, 62.05, 78.65 (C≡C), 102.71 (C≡C), 127.32 (C=C), 127.73 (C=C), 153.25 (NC(=O)O), 165.42 (C=O).

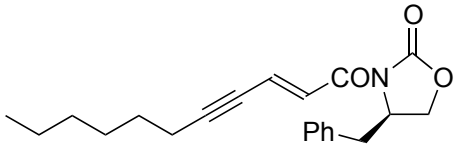
IR (neat) 3097 (C=C-H), 2931, 2858, 2214 (C≡C), 1778 (carbamate C=O), 1680 (amide C=O), 1604 (C=C), 1350, 1221, 1109, 1034, 966, 860, 758, 698 cm^{-1}.
Anal. Calcd for $C_{14}H_{19}NO_3$: C, 67.45; H, 7.68. Found: C, 67.23; H, 7.65.

(*R*,*E*)-3-(2-Undecen-4-ynoyl)-4-phenyloxazolidin-2-one (14b).



To a stirred solution of the above (*E*)-2-undecen-4-ynoic acid (541 mg, 3.00 mmol) in CH_2Cl_2 (3 mL) were successively added DMF (1 drop) and oxalyl chloride (0.510 mL, 5.95 mmol) at room temperature. After the mixture was stirred for 2 h, the solvent and the excess oxalyl chloride were removed *in vacuo* to afford the desired (*E*)-2-undecen-4-ynoic acid chloride as a crude oil, which was directly used in the next step.
To a solution of (*R*)-4-phenyloxazolidin-2-one (490 mg, 3.03 mmol) in THF (5 mL) was added BuLi (1.62 M in hexane, 1.85 mL, 3.00 mmol) at 0 °C under argon. After the mixture was stirred at room temperature for 1 h, the above (*E*)-2-undecen-4-ynoic acid chloride in THF (3 mL) was added at 0 °C. After the mixture was stirred at room temperature overnight, the reaction was quenched by the addition of water. The organic layer was separated and the aqueous layer was extracted with AcOEt. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo to give a crude oil, which was chromatographed on silica gel (hexane-ethyl acetate) to afford the title compound (697 mg, 71% overall yield from the carboxylic acid) exclusively with *E*-olefinic bond as an oil.
^{1}H NMR δ 0.89 (t, *J* = 7.2 Hz, 3H, alkyl-Me), 1.17-1.60 (m, 8H, alkyl H), 2.38 (dt, *J* = 2.4, 7.2 Hz, 2H, $C_5H_{11}C\underline{H}_2C{\equiv}C$-), 4.30 (dd, *J* = 3.6, 9.0 Hz, 1H, PhHC$\underline{H}_2$O-), 4.72 (t, *J* = 9.0 Hz, 1H, PhHC$\underline{H}_2$O-), 5.49 (dd, *J* = 3.6, 9.0 Hz, 1H, PhC$\underline{H}$-), 6.85 (dt, *J* = 15.6, 2.4 Hz, 1H, -C$\underline{H}$=CHCONR$_2$), 7.27-7.44 (m, 5H, Ph-H), 7.59 (d, *J* = 15.6 Hz, 1H, -CH=C$\underline{H}$CONR$_2$).
^{13}C NMR δ 14.13, 20.01, 22.59, 28.32, 28.65, 31.35, 57.81, 70.01, 78.78 (C≡C), 102.94 (C≡C), 125.83 (2 carbons), 127.60, 128.14, 128.65, 129.10 (2 carbons), 138.71, 153.35 (NC(=O)O), 163.96 (C=O).
IR (neat) 3090 (C=C-H), 3060 (Ar), 3035 (Ar), 2931, 2858, 2212 (C≡C), 1780 (carbamate C=O), 1680 (amide C=O), 1604 (C=C), 1468, 1300, 1209, 1117, 1086, 1068, 955, 856, 781, 755, 697 cm^{-1}.
Anal. Calcd for $C_{20}H_{23}NO_3$: C, 73.82; H, 7.12. Found: C, 73.89; H, 7.24.
$[\alpha]_D^{27}$ –7.9 (*c* 1.02, $CHCl_3$).

(*R*,*E*)-3-(2-Undecen-4-ynoyl)-4-benzyloxazolidin-2-one (14c).



To a stirred solution of the above (*E*)-2-undecen-4-ynoic acid (541 mg, 3.00 mmol) in CH_2Cl_2 (3 mL) were successively added DMF (1 drop) and oxalyl chloride (0.510 mL, 5.95 mmol) at room temperature. After the mixture was stirred for 2 h, the solvent and the excess oxalyl chloride were removed *in vacuo* to afford the desired (*E*)-2-undecen-4-ynoic acid chloride as a crude oil, which was directly used in the next step.

To a solution of (*R*)-4-benzyloxazolidin-2-one (532 mg, 3.00 mmol) in THF (5 mL) was added BuLi (1.62 M in hexane, 1.85 mL, 3.00 mmol) at 0 °C under argon. After the mixture was stirred at room temperature for 1 h, the above (*E*)-2-undecen-4-ynoic acid chloride in THF (3 mL) was added at 0 °C. After the mixture was stirred at room temperature overnight, the reaction was quenched by the addition of water. The organic layer was separated and the aqueous layer was extracted with AcOEt. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo to give a crude oil, which was chromatographed on silica gel (hexane-ethyl acetate) to afford the title compound (756 mg, 74% overall yield from the carboxylic acid) exclusively with *E*-olefinic bond as an oil.

^{1}H NMR δ 0.90 (t, *J* = 6.9 Hz, 3H, alkyl-Me), 1.18-1.63 (m, 8H, alkyl H), 2.41 (dt, *J* = 2.4, 7.2 Hz, 2H, $C_5H_{11}C\underline{H}_2C{\equiv}C$-), 2.81 (dd, *J* = 9.6, 13.2 Hz, 1H, benzyl H), 3.33 (dd, *J* = 3.3, 13.2 Hz, 1H, benzyl H), 4.19 (dd, *J* = 3.3, 9.0 Hz, 1H, BnCHC$\underline{H}_2$O-), 4.23 (dd, *J* = 7.2, 9.0 Hz, 1H, BnCHC$\underline{H}_2$O-), 4.74 (ddt, *J* = 7.2, 9.6, 3.3 Hz, 1H, BnC$\underline{H}$-), 6.99 (dt, *J* = 15.3, 2.4 Hz, 1H, -C$\underline{H}$=CHCONR$_2$), 7.16-7.39 (m, 5H, Ph-H), 7.59 (d, *J* = 15.3 Hz, 1H, -CH=C$\underline{H}$CONR$_2$).

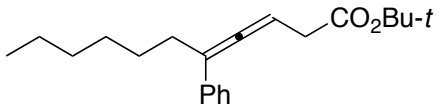
^{13}C NMR δ 14.14, 20.03, 22.60, 28.34, 28.67, 31.36, 37.87, 55.35, 66.19, 78.81 (C≡C), 102.87 (C≡C), 127.26, 127.74, 127.91, 128.87 (2 carbons), 129.34 (2 carbons), 135.08, 153.07 (NC(=O)O), 164.40 (C=O).

IR (neat) 3096 (Ar, C=C-H), 3029 (Ar), 3007 (Ar), 2926, 2855, 2215 (C≡C), 1790 (carbamate C=O), 1671 (amide C=O), 1605 (C=C), 1457, 1388, 1358, 1297, 1206, 1117, 1052, 1029, 1003, 963, 861, 705 cm^{-1}.

Anal. Calcd for $C_{21}H_{25}NO_3$: C, 74.31; H, 7.42. Found: C, 74.23; H, 7.43.

$[\alpha]_D^{27}$ –59.5 (*c* 0.99, $CHCl_3$).

***tert*-Butyl 5-phenyl-3,4-undecadienoate (15).**



To a solution of *tert*-butyl (*E*)-2-undecen-4-ynoate (**1**) (47.3 mg, 0.200 mmol) and $FeCl_2$ (2.5 mg, 0.020 mmol) in 1 mL of THF was added PhMgBr (0.380 mL, 1.06 M solution in THF, 0.400 mmol) at –78 °C under argon. Then, the solution was slowly warmed to 0 °C over 4.5 h. The reaction was terminated by the addition of 1 N HCl solution (1 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with aqueous saturated $NaHCO_3$ solution and brine, dried over Na_2SO_4, and concentrated *in vacuo* to give a crude oil, ^{1}H NMR analysis of which did not show the presence of other regioisomers. The crude product was chromatographed on silica gel (hexane-ethyl acetate) to afford the title compound (37.8 mg, 60%) as an oil.

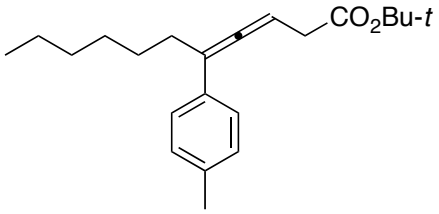
^{1}H NMR δ 0.89 (t, *J* = 6.9 Hz, 3H, alkyl-Me), 1.16-1.64 (m, 8H, alkyl H), 1.46 (s, 9H, -C(C<u>H</u>$_3$)$_3$), 2.41 (dt, *J* = 3.0, 7.5 Hz, 2H, $C_5H_{11}C\underline{H}_2C$(Ph)-), 3.03 (d, *J* = 7.5 Hz, 2H, -C<u>H</u>$_2$CO$_2$Bu-*t*), 5.61 (tt, *J* = 3.0, 7.5 Hz, 1H, -C=C=C<u>H</u>-), 7.14-7.48 (m, 5H, Ar-H).

^{13}C NMR δ 14.09, 22.65, 27.72, 28.01 (3 carbons, -C(<u>C</u>H$_3$)$_3$), 29.08, 29.67, 31.71, 36.26, 80.97, 87.97, 106.72, 126.07 (2 carbons), 126.65, 128.27 (2 carbons), 136.67, 170.75 (C=O), 204.86 (C=<u>C</u>=C).

IR (neat) 3059 (Ar), 3030 (Ar), 2929, 2858, 1952 (C=C=C), 1732 (C=O), 1616, 1456, 1367, 1257, 1149, 804, 700 cm^{-1}.

Anal. Calcd for $C_{21}H_{30}O_2$: C, 80.21; H, 9.62. Found: C, 79.97; H, 9.87.

***tert*-Butyl 5-(4-methylphenyl)-3,4-undecadienoate (16).**



To a solution of *tert*-butyl (*E*)-2-undecen-4-ynoate (**1**) (47.3 mg, 0.200 mmol) and $FeCl_2$ (2.5 mg, 0.020 mmol) in 1 mL of THF was added (4-methylphenyl)magnesium bromide (0.360 mL, 1.11 M solution in THF, 0.400 mmol) at –78 °C under argon. Then, the solution was slowly warmed to 0 °C over 4.5 h. The reaction was terminated by the addition of 1 N HCl solution (1 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with aqueous saturated $NaHCO_3$ solution and brine, dried over Na_2SO_4, and concentrated *in vacuo* to give a crude oil, ^{1}H NMR analysis of which did not show the presence of other regioisomers. The crude product was chromatographed on silica gel (hexane-ethyl acetate) to afford the title compound (31.6 mg, 48%) as an oil.

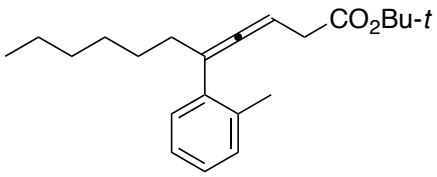
^{1}H NMR δ 0.88 (t, *J* = 6.6 Hz, 3H, alkyl-Me), 1.14-1.64 (m, 8H, alkyl H), 1.46 (s, 9H, -C(C<u>H</u>$_3$)$_3$), 2.24-2.46 (m, 2H, $C_5H_{11}C\underline{H}_2C$(Ar)), 2.33 (s, 3H, Ar-Me), 3.02 (d, *J* = 7.2 Hz, 2H, -C<u>H</u>$_2$CO$_2$Bu-*t*), 5.58 (m, 1H, -C=C=C<u>H</u>-), 7.12 (d, *J* = 8.7 Hz, 2H, Ar-H), 7.30 (d, *J* = 8.7 Hz, 2H, Ar-H).

^{13}C NMR δ 14.09, 21.05, 22.66, 27.74, 28.03 (3 carbons, -C(<u>C</u>H$_3$)$_3$), 29.09, 29.75, 31.71, 36.36, 80.71, 87.80, 106.54, 125.97 (2 carbons), 128.97 (2 carbons), 133.68, 136.36, 170.83 (C=O), 204.63 (C=<u>C</u>=C).

IR (neat) 3078 (Ar), 3051 (Ar), 3024 (Ar), 2927, 2858, 1952 (C=C=C), 1732 (C=O), 1610, 1512, 1456, 1367, 1255, 1149, 820 cm^{-1}.

Anal. Calcd for $C_{22}H_{32}O_2$: C, 80.44; H, 9.82. Found: C, 80.37; H, 9.91.

***tert*-Butyl 5-(2-methylphenyl)-3,4-undecadienoate (17).**



To a solution of *tert*-butyl (*E*)-2-undecen-4-ynoate (**1**) (47.3 mg, 0.200 mmol) and $FeCl_2$ (2.5 mg, 0.020 mmol) in 1 mL of THF was added (2-methylphenyl)magnesium bromide (0.380 mL, 1.05 M solution in THF, 0.400 mmol) at –78 °C under argon. Then, the solution was slowly warmed to 0 °C over 4.5 h. The reaction was terminated by the addition of 1 N HCl solution (1 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with aqueous saturated $NaHCO_3$ solution and brine, dried over Na_2SO_4, and concentrated *in vacuo* to give a crude oil, ^{1}H NMR analysis of which did not show the presence of other regioisomers. The crude product was chromatographed on silica gel (hexane-ethyl acetate) to afford the title compound (52.6 mg, 80%) as an oil.

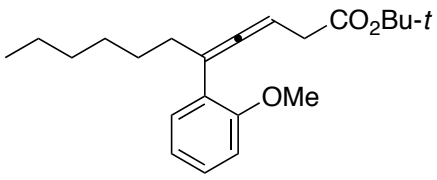
^{1}H NMR δ 0.87 (t, *J* = 7.2 Hz, 3H, alkyl-Me), 1.16-1.55 (m, 8H, alkyl H), 1.44 (s, 9H, -C(C<u>H</u>$_3$)$_3$), 2.26-2.36 (m, 2H, $C_5H_{11}C\underline{H}_2C$(Ar)-), 2.33 (s, 3H, Ar-Me), 2.98 (d, *J* = 7.5 Hz, 2H, -C<u>H</u>$_2$CO$_2$Bu-*t*), 5.33 (tt, *J* = 3.0, 7.5 Hz, 1H, -C=C=C<u>H</u>-), 7.12-7.26 (m, 4H, Ar-H).

^{13}C NMR δ 14.08, 20.46, 22.63, 27.59, 28.00 (3 carbons, -C(<u>C</u>H$_3$)$_3$), 28.93, 31.68, 33.75, 36.10, 80.64, 85.08, 105.32, 125.69, 126.75, 127.81, 130.39, 135.81, 137.57, 170.79 (C=O), 203.33 (C=<u>C</u>=C).

IR (neat) 3100 (Ar), 3060 (Ar), 3010 (Ar), 2927, 2856, 1959 (C=C=C), 1734 (C=O), 1628, 1458, 1367, 1147, 847, 756, 727 cm^{-1}.

Anal. Calcd for $C_{22}H_{32}O_2$: C, 80.44; H, 9.82. Found: C, 80.42; H, 9.68.

***tert*-Butyl 5-(2-methoxyphenyl)-3,4-undecadienoate (18).**



To a solution of *tert*-butyl (*E*)-2-undecen-4-ynoate (**1**) (94.5 mg, 0.400 mmol) and $FeCl_2$ (5.1 mg, 0.040 mmol) in 2 mL of THF was added [(2-methoxy)phenyl]magnesium bromide (0.780 mL, 1.02 M solution in THF, 0.800 mmol) at –78 °C under argon. Then, the solution was slowly warmed to 0 °C over 4.5 h. The reaction was terminated by the addition of 1 N HCl solution (1 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with aqueous saturated $NaHCO_3$ solution and brine, dried over Na_2SO_4, and concentrated *in vacuo* to give a crude oil, ^{1}H NMR analysis of which did not show the presence of other regioisomers. The crude product was chromatographed on silica gel (hexane-ethyl acetate) to afford the title compound (102 mg, 74%) as an oil.

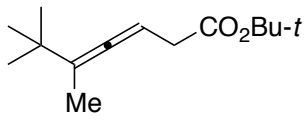
^{1}H NMR δ 0.87 (t, *J* = 6.9 Hz, 3H, alkyl-Me), 1.18-1.54 (m, 8H, alkyl H), 1.45 (s, 9H, -C(C$\underline{H}_3$)$_3$), 2.39 (m, 2H, $C_5H_{11}C\underline{H}_2C$(Ar)-), 3.01 (d, *J* = 7.5 Hz, 2H, -C$\underline{H}_2CO_2$Bu-*t*), 3.81 (s, 3H, -O$\underline{Me}$), 5.36 (tt, *J* = 2.7, 7.5 Hz, 1H, -C=C=C$\underline{H}$-), 6.86 (d, *J* = 7.5 Hz, 1H, Ar-H), 6.91 (t, *J* = 7.5 Hz, 1H, Ar-H), 7.19 (d, *J* = 7.5 Hz, 1H, Ar-H), 7.21 (t, *J* = 7.5 Hz, 1H, Ar-H).

^{13}C NMR δ 14.08, 22.63, 27.79, 28.03 (3 carbons, -C($\underline{C}H_3$)$_3$), 28.88, 31.69, 32.16, 36.41, 55.45, 80.51, 84.59, 104.36, 111.11, 120.49, 127.14, 128.11, 129.74, 156.80, 170.97 (C=O), 204.86 (C=$\underline{C}$=C).

IR (neat) 3068 (Ar), 3024 (Ar), 2956, 2929, 2856, 1957 (C=C=C), 1732 (C=O), 1624, 1597, 1579, 1491, 1464, 1367, 1250, 1147, 1030, 947, 847, 752 cm^{-1}.

Anal. Calcd for $C_{22}H_{32}O_3$: C, 76.70; H, 9.36. Found: C, 76.56; H, 9.33.

***tert*-Butyl 5,6,6-trimethyl-3,4-heptadienoate (19).**



To a solution of *tert*-butyl (*E*)-6,6-dimethyl-2-hepten-4-ynoate (**12**) (41.7 mg, 0.200 mmol) and $FeCl_2$ (2.5 mg, 0.020 mmol) in 1 mL of THF was added MeMgBr (0.360 mL, 1.12 M solution in THF, 0.400 mmol) at –78 °C under argon. Then, the solution was slowly warmed to 0 °C over 4.5 h. The reaction was terminated by the addition of 1 N HCl solution (1 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with aqueous saturated $NaHCO_3$ solution and brine, dried over Na_2SO_4, and concentrated *in vacuo* to give a crude oil, ^{1}H NMR analysis of which did not show the presence of other regioisomers. The crude product was chromatographed on silica gel (hexane-ethyl acetate) to afford the title compound (30.6 mg, 68%) as an oil.

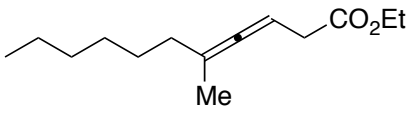
^{1}H NMR δ 1.04 (s, 9H, -C(C$\underline{H}_3$)$_3$), 1.45 (s, 9H, -C(C$\underline{H}_3$)$_3$), 1.68 (d, *J* = 2.7 Hz, 3H, *t*-BuC($\underline{Me}$)-), 2.88 (d, *J* = 6.9 Hz, 2H, -C$\underline{H}_2CO_2$Bu-*t*), 5.11 (tq, *J* = 6.9, 2.7 Hz, 1H, -C=C=C$\underline{H}$-).

^{13}C NMR δ 14.89, 28.05 (3 carbons, -C($\underline{C}H_3$)$_3$), 28.99 (3 carbons, -C($\underline{C}H_3$)$_3$), 33.32, 36.92, 80.38, 83.92, 109.30, 171.27 (C=O), 201.48 (C=$\underline{C}$=C).

IR (neat) 2966, 2868, 1965 (C=C=C), 1734 (C=O), 1458, 1367, 1259, 1147, 849, 804 cm^{-1}.

Anal. Calcd for $C_{14}H_{24}O_2$: C, 74.95; H, 10.78. Found: C, 74.72; H, 10.42.

Ethyl 5-methyl-3,4-undecadienoate (20).



To a solution of ethyl (*E*)-2-undecen-4-ynoate (**13**) (41.7 mg, 0.200 mmol) and $FeCl_2$ (2.5 mg, 0.020 mmol) in 1 mL of THF was added MeMgBr (0.290 mL, 1.40 M solution in THF, 0.410 mmol) at –78 °C under argon. Then, the solution was slowly warmed to 0 °C over 4.5 h. The reaction was terminated by the addition of 1 N HCl solution (1 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with aqueous saturated $NaHCO_3$ solution and brine, dried over Na_2SO_4, and concentrated *in vacuo* to give a crude oil, ^{1}H NMR analysis of which did not show the presence of other regioisomers. The crude product was chromatographed on silica gel (hexane-ethyl acetate) to afford the title compound (32.1 mg, 72%) as an oil.

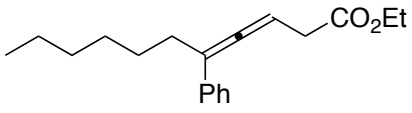
^{1}H NMR δ 0.88 (t, *J* = 6.9 Hz, 3H, alkyl-Me), 1.18-1.46 (m, 8H, alkyl H), 1.27 (t, *J* = 6.9 Hz, 3H, -$CO_2CH_2C\underline{H}_3$), 1.67 (d, *J* = 3.0 Hz, 3H, $C_6H_{13}C(\underline{Me})$-), 1.92 (dt, *J* = 3.0, 8.1 Hz, 2H, $C_5H_{11}C\underline{H}_2C(Me)$-), 2.97 (d, *J* = 6.9 Hz, 2H, -$C\underline{H}_2CO_2Et$), 4.15 (q, *J* = 6.9 Hz, 2H, -$CO_2C\underline{H}_2CH_3$), 5.13 (m, 1H, -C=C=C$\underline{H}$-).

^{13}C NMR δ 14.06, 14.15, 18.90, 22.61, 27.26, 28.86, 31.68, 33.75, 35.43, 60.52, 83.13, 100.77, 171.93 (C=O), 202.40 (C=$\underline{C}$=C).

IR (neat) 2960, 2927, 2856, 1969 (C=C=C), 1739 (C=O), 1464, 1367, 1317, 1157, 1097, 1036, 804 cm^{-1}.

Anal. Calcd for $C_{14}H_{24}O_2$: C, 74.95; H, 10.78. Found: C, 74.63; H, 10.88.

Ethyl 5-phenyl-3,4-undecadienoate (21).



To a solution of ethyl (*E*)-2-undecen-4-ynoate (**13**) (41.7 mg, 0.200 mmol) and $FeCl_2$ (2.5 mg, 0.020 mmol) in 1 mL of THF was added PhMgBr (0.370 mL, 1.09 M solution in THF, 0.400 mmol) at –78 °C under argon. Then, the solution was slowly warmed to 0 °C over 4.5 h. The reaction was terminated by the addition of 1 N HCl solution (1 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with aqueous saturated $NaHCO_3$ solution and brine, dried over Na_2SO_4, and concentrated *in vacuo* to give a crude oil, ^{1}H NMR analysis of which did not show the presence of other regioisomers.

The crude product was chromatographed on silica gel (hexane-ethyl acetate) to afford the title compound (37.7 mg, 66%) as an oil.

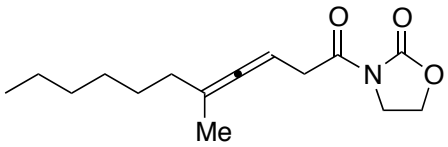
^{1}H NMR δ 0.89 (t, *J* = 7.2 Hz, 3H, alkyl-Me), 1.18-1.60 (m, 8H, alkyl H), 1.27 (t, *J* = 6.9 Hz, 3H, -$CO_2CH_2C\underline{H}_3$), 2.42 (dt, *J* = 3.0, 8.4 Hz, 2H, $C_5H_{11}C\underline{H}_2C$(Ph)-), 3.12 (d, *J* = 7.2 Hz, 2H, -$C\underline{H}_2CO_2Et$), 4.17 (q, *J* = 6.9 Hz, 2H, -$CO_2C\underline{H}_2CH_3$), 5.63 (tt, *J* = 3.0, 7.2 Hz, 1H, -C=C=C<u>H</u>-), 7.15-7.44 (m, 5H, Ar-H).

^{13}C NMR δ 14.09, 14.17, 22.66, 27.73, 29.07, 29.71, 31.71, 34.99, 60.77, 87.43, 106.96, 126.08 (2 carbons), 126.73, 128.30 (2 carbons), 136.52, 171.51 (C=O), 205.03 (C=<u>C</u>=C).

IR (neat) 3059 (Ar), 3028 (Ar), 2927, 2856, 1951 (C=C=C), 1738 (C=O), 1454, 1259, 1161, 1036, 760, 694 cm^{-1}.

Anal. Calcd for $C_{19}H_{26}O_2$: C, 79.68; H, 9.15. Found: C, 79.76; H, 9.49.

3-(5-Methyl-3,4-undecadienoyl)oxazolidin-2-one (22a).



To a solution of (*E*)-3-(2-undecen-4-ynoyl)oxazolidin-2-one (**14a**) (49.9 mg, 0.200 mmol) and $FeCl_2$ (2.5 mg, 0.020 mmol) in 1 mL of THF was added MeMgBr (0.360 mL, 1.12 M solution in THF, 0.400 mmol) at –78 °C under argon. Then, the solution was slowly warmed to 0 °C over 4.5 h. The reaction was terminated by the addition of 1 N HCl solution (1 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with aqueous saturated $NaHCO_3$ solution and brine, dried over Na_2SO_4, and concentrated *in vacuo* to give a crude oil, ^{1}H NMR analysis of which did not show the presence of other regioisomers. The crude product was chromatographed on silica gel (hexane-ethyl acetate) to afford the title compound (39.6 mg, 75%) as an oil.

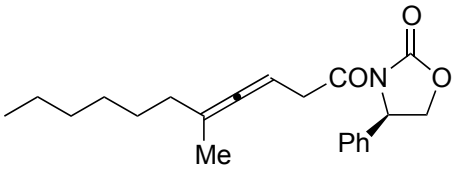
^{1}H NMR δ 0.88 (t, *J* = 6.9 Hz, 3H, alkyl-Me), 1.16-1.46 (m, 8H, alkyl H), 1.67 (d, *J* = 2.7 Hz, 3H, $C_6H_{13}C(\underline{Me})$-), 1.92 (dt, *J* = 2.4, 8.1 Hz, 2H, $C_5H_{11}C\underline{H}_2C$(Me)-), 3.62 (d, *J* = 6.9 Hz, 2H, -$C\underline{H}_2CONR_2$), 4.03 (t, *J* = 8.1 Hz, 2H, -$NC\underline{H}_2CH_2O$-), 4.42 (t, *J* = 8.1 Hz, 2H, -$NCH_2C\underline{H}_2O$-), 5.22 (m, 1H, -C=C=C<u>H</u>-).

^{13}C NMR δ 14.02, 18.79, 22.56, 27.26, 28.85, 31.63, 33.70, 36.18, 42.44, 62.02, 82.41, 100.95, 153.31 (NC(=O)O), 171.47 (C=O), 202.53 (C=<u>C</u>=C).

IR (neat) 2927, 2856, 1969 (C=C=C), 1782 (carbamate C=O), 1703 (amide C=O), 1389, 1225, 1111, 1039, 1009, 958, 760 cm^{-1}.

Anal. Calcd for $C_{15}H_{23}NO_3$: C, 67.90; H, 8.74. Found: C, 67.89; H, 8.81.

A 67:33 diastereomeric mixture of (4*R*)-3-(5-methyl-3,4-undecadienoyl)-4-phenyloxazolidin-2-one (22b).



To a solution of (*R*,*E*)-3-(2-undecen-4-ynoyl)-4-phenyloxazolidin-2-one (**14b**) (48.8 mg, 0.150 mmol) and $FeCl_2$ (1.9 mg, 0.015 mmol) in 1 mL of THF was added MeMgBr (0.270 mL, 1.12 M solution in THF, 0.302 mmol) at –78 °C under argon. Then, the solution was slowly warmed to 0 °C over 4.5 h. The reaction was terminated by the addition of 1 N HCl solution (1 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with aqueous saturated $NaHCO_3$ solution and brine, dried over Na_2SO_4, and concentrated *in vacuo* to give a crude oil, ^{1}H NMR analysis of which revealed that the diastereoselectivity of the product was 67:33 and did not show the presence of other regioisomers. The crude product was chromatographed on silica gel (hexane-ethyl acetate) to afford the title compound (38.0 mg, 74%) as an oil and of a 67:33 diastereomeric mixture.

Major isomer: ^{1}H NMR (400 MHz) δ 0.88 (t, *J* = 7.2 Hz, 3H, alkyl-Me), 1.18-1.48 (m, 8H, alkyl H), 1.64 (d, *J* = 2.8 Hz, 3H, $C_6H_{13}C(\underline{Me})$-), 1.88 (m, 2H, $C_5H_{11}C\underline{H_2}C(Me)$-), 3.59 (d, *J* = 6.8, 17.2 Hz, 1H, -$C\underline{H_2}CONR_2$), 3.65 (d, *J* = 6.8, 17.2 Hz, 1H, -$C\underline{H_2}CONR_2$), 4.29 (dd, *J* = 3.2, 8.8 Hz, 1H, PhCHC$\underline{H_2}$O-), 4.68 (t, *J* = 8.8 Hz, 1H, PhCHC$\underline{H_2}$O-), 5.16 (m, 1H, -C=C=C$\underline{H}$-), 5.42 (dd, *J* = 3.2, 8.8 Hz, 1H, PhC$\underline{H}$-), 7.24-7.44 (m, 5H, Ph-H).

^{13}C NMR δ 14.07, 18.79, 22.61, 27.28, 28.87, 31.64, 33.76, 36.64, 57.52, 70.00, 82.32, 100.95, 125.93, 128.65 (2 carbons), 129.11 (2 carbons), 138.96, 153.52 (NC(=O)O), 170.75 (C=O), 202.64 (C=$\underline{C}$=C).

Minor isomer: ^{1}H NMR (400 MHz, only characteristic peaks are shown) δ 0.87 (t, *J* = 7.2 Hz, 3H, alkyl-Me), 1.62 (d, *J* = 3.2 Hz, 3H, $C_6H_{13}C(\underline{Me})$-), 3.58 (dd, *J* = 6.8, 17.6 Hz, 1H, -$C\underline{H_2}CONR_2$), 3.66 (dd, *J* = 6.8, 17.6 Hz, 1H, -$C\underline{H_2}CONR_2$), 4.28 (dd, *J* = 3.6, 8.8 Hz, 1H, PhCHC$\underline{H_2}$O-), 4.69 (t, *J* = 8.8 Hz, 1H, PhCHC$\underline{H_2}$O-).

^{13}C NMR (100 MHz, only characteristic peaks are shown) δ 18.84, 22.57, 33.71, 36.60, 82.30, 100.97, 202.70.

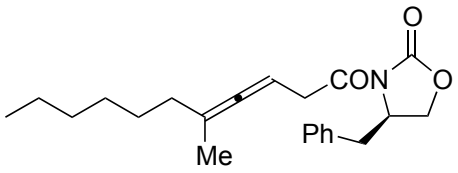
IR (neat) 3065 (Ar, C=C-H), 3034 (Ar), 2954, 2925, 2854, 1965 (C=C=C), 1783 (carbamate C=O), 1709 (amide C=O), 1621, 1594, 1457, 1385, 1330, 1233, 1200, 1060, 762, 699 cm^{-1} for a 67:33 mixture of diastereoisomers.

Anal. Calcd for $C_{21}H_{27}NO_3$: C, 73.87; H, 7.97. Found: C, 73.57; H, 8.27 for a 67:33 mixture of diastereoisomers.

$[\alpha]_D^{23}$ –92.9 (*c* 1.04, $CHCl_3$) for a 67:33 mixture of diastereoisomers.

The absolute stereochemistry of the allene was not determined.

A 67:33 diastereomeric mixture of (4*R*)-3-(5-methyl-3,4-undecadienoyl)-4-benzyloxazolidin-2-one (22c).



To a solution of (*R*,*E*)-3-(2-undecen-4-ynoyl)-4-benzyloxazolidin-2-one (**14c**) (33.9 mg, 0.100 mmol) and $FeCl_2$ (1.3 mg, 0.010 mmol) in 0.5 mL of THF was added MeMgBr (0.180 mL, 1.12 M solution in THF, 0.202 mmol) at –78 °C under argon for 3 h. The reaction was terminated by the addition of 1 N HCl solution (1 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with aqueous saturated $NaHCO_3$ solution and brine, dried over Na_2SO_4, and concentrated *in vacuo* to give a crude oil, ^{1}H NMR analysis of which revealed that the diastereoselectivity of the product was 67:33 and did not show the presence of other regioisomers. The crude product was chromatographed on silica gel (hexane-ethyl acetate) to afford the title compound (30.2 mg, 85%) as an oil and of a 67:33 diastereomeric mixture.

Major isomer: ^{1}H NMR (400 MHz) δ 0.874 (t, *J* = 7.2 Hz, 3H, alkyl-Me), 1.20-1.46 (m, 8H, alkyl H), 1.68 (d, *J* = 2.8 Hz, 3H, $C_6H_{13}C(\underline{Me})$-), 1.93 (dt, *J* = 2.8, 8.0 Hz, 2H, $C_5H_{11}C\underline{H_2}C(Me)$-), 2.76 (dd, *J* = 9.6, 13.2 Hz, 1H, benzyl-H), 3.32 (dd, *J* = 3.6, 13.2 Hz, 1H, benzyl-H), 3.60 (dd, *J* = 6.4, 20.8 Hz, 1H, -$C\underline{H_2}CONR_2$), 3.66 (dd, *J* = 6.4, 20.8 Hz, 1H, -$C\underline{H_2}CONR_2$), 4.17 (dd, *J* = 3.6, 9.2 Hz, 1H, BnCHC$\underline{H_2}$O-), 4.20 (dd, *J* = 6.8, 9.2 Hz, 1H, BnCHC$\underline{H_2}$O-), 4.67 (ddt, *J* = 6.8, 9.6, 3.6 Hz, 1H, BnCH-), 5.25 (m, 1H, -C=C=C$\underline{H}$-), 7.19-7.37 (m, 5H, Ph-H).

^{13}C NMR δ 14.07, 18.93, 22.61, 27.36, 28.93, 31.70, 33.82, 36.66, 37.81, 55.17, 66.15, 82.54, 101.10, 127.31, 128.93 (2 carbons), 129.40 (2 carbons), 135.24, 153.23 (NC(=O)O), 171.36 (C=O), 202.65 (C=$\underline{C}$=C).

Minor isomer: ^{1}H NMR (400 MHz, only characteristic peaks are shown) δ 0.870 (t, *J* = 7.2 Hz, 3H, alkyl-Me), 3.61 (dd, *J* = 7.2, 13.6 Hz, 1H, -$C\underline{H_2}CONR_2$), 3.65 (dd, *J* = 7.2, 13.6 Hz, 1H, -$C\underline{H_2}CONR_2$).

^{13}C NMR (100 MHz, only characteristic peaks are shown) δ 18.89, 27.34, 28.91, 33.79, 36.61, 37.80, 82.53, 101.08, 202.66.

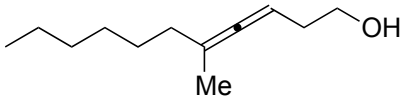
IR (neat) 3062 (Ar, C=C=H), 3028 (Ar), 2926, 2855, 1966 (C=C=C), 1784 (carbamate C=O), 1701 (amide C=O), 1454, 1386, 1357, 1212, 1108, 1051, 807, 761, 702 cm^{-1} for a 67:33 mixture of diastereoisomers.

Anal. Calcd for $C_{22}H_{29}NO_3$: C, 74.33; H, 8.22. Found: C, 74.06; H, 8.38 for a 67:33 mixture of diastereoisomers.

$[\alpha]_D^{27}$ –55.4 (*c* 2.03, $CHCl_3$) for a 67:33 mixture of diastereoisomers.

The absolute stereochemistry of the allene was not determined.

5-Methyl-3,4-undecadienol (24) from *tert*-butyl 5-methyl-3,4-undecadienoate (3).



To a suspension of $LiAlH_4$ (56.9 mg, 1.50 mmol) in THF (2 mL) was added *tert*-butyl 5-methyl-3,4-undecadienoate (**3**) (75.7 mg, 0.300 mmol) in THF (1 mL) at 0 °C under argon. After the mixture was allowed to warm to room temperature and was stirred for 1 h, it was again cooled in an ice bath. Then, H_2O (0.100 mL), 15% aqueous NaOH solution (0.100 mL), and H_2O (0.300 mL) were added carefully to the mixture in this order. After the organic layer was stirred together with Na_2SO_4, the heterogeneous mixture was filtrated. The filtrate was concentrated *in vacuo* to give a crude oil, ^1H NMR analysis of which did not show the presence of other olefins. The crude product was chromatographed on silica gel (hexane-ethyl acetate) to afford the title compound (49.0 mg, 90%) as an oil.

^1H NMR (400 MHz) δ 0.88 (t, *J* = 7.2 Hz, 3H, alkyl-Me), 1.20-1.46 (m, 8H, alkyl H), 1.54 (t, *J* = 6.0 Hz, 1H, -OH), 1.69 (d, *J* = 2.8 Hz, 3H, -C=C=C(Me)-), 1.93 (dt, *J* = 2.8, 7.2 Hz, 2H, $C_5H_{11}CH_2C$=C=C(Me)-), 2.23 (q, *J* = 6.0 Hz, 2H, -CH_2CH_2OH), 3.69 (q, *J* = 6.0 Hz, 2H, -CH_2CH_2OH), 5.01 (m, 1H, -C=C=CH-).

^{13}C NMR (100 MHz) δ 14.07, 19.24, 22.62, 27.49, 28.92, 31.70, 32.60, 33.96, 62.14, 86.17, 100.24, 202.06 (C=C=C).

IR (neat) 3342 (OH), 2956, 2926, 2856, 1965 (C=C=C), 1458, 1378, 1049, 801, 758 cm^{-1}

Anal. Calcd for $C_{12}H_{22}O$: C, 79.06; H, 12.16. Found: C, 79.36; H, 12.18.

5-Methyl-3,4-undecadienol (24) from ethyl 5-methyl-3,4-undecadienoate (20).

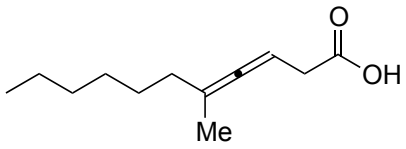
To a suspension of $LiAlH_4$ (94.9 mg, 2.50 mmol) in THF (3 mL) was added ethyl 5-methyl-3,4-undecadienoate (**20**) (112 mg, 0.500 mmol) in THF (2 mL) at 0 °C under argon. After the mixture was allowed to warm to room temperature and was stirred for 12 h, it was again cooled in an ice bath. Then, H_2O (0.100 mL), 15% aqueous NaOH solution (0.100 mL), and H_2O (0.300 mL) were added carefully to the mixture in this order. After the organic layer was stirred together with Na_2SO_4, the heterogeneous mixture was filtrated. The filtrate was concentrated *in vacuo* to give a crude oil, ^1H NMR analysis of which did not show the presence of other olefins. The crude product was chromatographed on silica gel (hexane-ethyl acetate) to afford the title compound (66.8 mg, 73%) as an oil.

5-Methyl-3,4-undecadienol (24) from 3-(5-methyl-3,4-undecadienoyl)oxazolidin-2-one (22a).

To a suspension of $LiBH_4$ (18.6 mg, 0.854 mmol) in THF (1 mL) was added 3-(5-methyl-3,4-undecadienoyl)oxazolidin-2-one (**22a**) (75.4 mg, 0.285 mmol) in THF (2 mL) at room temperature under argon. After the reaction mixture was stirred for 2 h, it was quenched by the addition of water. The organic layer was separated and the aqueous layer was extracted with AcOEt. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo* to give a crude oil, ^1H NMR analysis of which did not show the presence of other olefins. The crude

product was chromatographed on silica gel (hexane-ethyl acetate) to afford the title compound (43.4 mg, 84%) as an oil.

5-Methyl-3,4-undecadienoic acid (25)



A solution of 3-(5-methyl-3,4-undecadienoyl)oxazolidin-2-one (**22a**) (106 mg, 0.400 mmol) in THF (1 mL) and water (0.3 mL) was cooled 0 °C. In a separate flask, LiOH (19.2 mg, 0.802 mmol) was dissolved in H_2O_2 (0.210 mL, 35% in water, *ca*. 2.41 mmol) and this solution was slowly added to the above THF solution of oxazolidinone. After the mixture was stirred for 1 h at 0 °C, the reaction was terminated by the addition of a solution of Na_2SO_3 (315 mg, 2.50 mmol) in water (1.5 mL) over 15 min, followed by 1 N HCl. The organic layer was separated and the aqueous layer was extracted with AcOEt. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo* to give a crude oil, ^{1}H NMR analysis of which did not show the presence of other olefins. The crude product was chromatographed on silica gel (hexane-ethyl acetate) to afford the title compound (60.5 mg, 77%) as an oil.

^{1}H NMR (400 MHz) δ 0.88 (t, *J* = 6.8 Hz, 3H, alkyl-Me), 1.21-1.42 (m, 8H, alkyl H), 1.68 (d, *J* = 2.4 Hz, 3H, -C=C=C(Me)-), 1.94 (m, 2H, $C_5H_{11}CH_2C$=C=C(Me)-), 3.04 (d, *J* = 7.2 Hz, 2H, -CH_2CO_2H), 5.14 (m, 1H, -C=C=CH-). Peak of carboxylic proton was not seen.

^{13}C NMR (100 MHz) δ 14.09, 18.86, 22.63, 27.29, 28.88, 31.70, 33.77, 35.17, 82.44, 101.17, 178.08 (C=O), 202.70 (C=C=C).

IR (neat) 3360 (COOH), 2956, 2927, 2856, 1969 (C=C=C), 1713 (C=O), 1633, 1457, 1412, 1289, 1217, 1156, 938, 801 cm^{-1}

Anal. Calcd for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27. Found: C, 73.59; H, 10.48.

(*E*)-*N*,*N*-Diethyl-2-undecen-4-ynamide (26).



To a solution of 1-octyne (0.420 mL, 2.97 mmol) in Et_2O (10 mL) was added BuLi (1.65 M in hexane, 2.20 mL, 3.63 mmol) at –78 ºC under argon. After stirring at –78 °C for 0.5 h, DMF (0.350 mL, 4.55 mmol) was introduced to the mixture at –78 °C and the solution was stirred at that temperature for 2 h. The reaction was terminated by the addition of aqueous saturated NH_4Cl solution. The organic products were extracted with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo* to afford 2-nonynal (414 mg, *ca*. 100%), which was directly used in the next step.

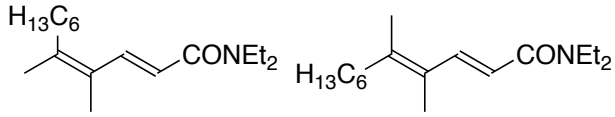
To a suspension of sodium hydride (160 mg of a 60% suspension in mineral oil, 4.00 mmol) in THF (15 mL) was added *N*,*N*-diethyl(diethylphosphono)acetamide (580 mg, 3.60 mmol) in THF (5 mL) at 0 °C under argon. After the mixture was stirred for 10 min at room temperature, it was again cooled to 0 °C. Then, 2-nonynal (414 mg, *ca*. 3.00 mmol) was added and the mixture was warmed to room temperature and was stirred for 1 h. The reaction was terminated by the slow addition of water. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed successively with water and brine, dried over Na_2SO_4, and concentrated *in vacuo* to a crude oil, which was chromatographed on silica gel (hexane-ethyl acetate) to afford the title compound (559 mg, 79%) exclusively with *E*-olefinic bond as an oil.

^{1}H NMR δ 0.90 (t, *J* = 6.9 Hz, 3H, alkyl-Me), 1.15 (t, *J* = 6.9 Hz, 3H, -CON($CH_2C\underline{H}_3$)$_2$), 1.21 (t, *J* = 6.9 Hz, 3H, -CON($CH_2C\underline{H}_3$)$_2$), 1.24-1.46 (m, 6H, alkyl H), 1.56 (quintet, *J* = 6.9 Hz, 2H, alkyl H), 2.36 (dt, *J* = 2.4, 6.9 Hz, 2H, $C_5H_{11}C\underline{H}_2C{\equiv}C$-), 3.37 (q, *J* = 6.9 Hz, 2H, -CON($C\underline{H}_2CH_3$)$_2$), 3.44 (q, *J* = 6.9 Hz, 2H, -CON($C\underline{H}_2CH_3$)$_2$), 6.59 (d, *J* = 15.3 Hz, 1H, -CH=C<u>H</u>CONEt$_2$), 6.79 (dt, *J* = 15.3, 2.4 Hz, 1H, -C<u>H</u>=CHCONEt$_2$).

^{13}C NMR δ 13.01, 13.94, 14.92, 19.62, 22.42, 28.31, 28.47, 31.19, 40.90, 42.02, 78.62 (C≡C), 98.36 (C≡C), 123.51 (C=C), 128.41 (C=C), 164.69 (C=O).

IR (neat) 3070 (C=C-H), 2960, 2931, 2858, 2214 (C≡C), 1641 (C=O), 1603 (C=C), 1431, 1282, 1134, 958, 733 cm^{-1}.

A 71:29 mixture of (2*E*,4*Z*)- and (2*E*,4*E*)-*N*,*N*-diethyl-4,5-dimethyl-2,4-undecadienamide (27).



To a solution of (*E*)-*N*,*N*-diethyl-2-undecen-4-ynamide (**26**) (47.1 mg, 0.200 mmol) and $FeCl_3$ (32.4 mg, 0.200 mmol, reagent of 97% purity purchased from Sigma-Aldrich Co. (USA)) in 1 mL of Et_2O was added MeMgBr (0.890 mL, 1.12 M solution in THF, 1.00 mmol) at –78 °C under argon. Then, the solution was slowly warmed to 0 °C over 4.5 h. The reaction was terminated by the addition of 1 N HCl solution (1 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with aqueous saturated $NaHCO_3$ solution and brine, dried over Na_2SO_4, and concentrated *in vacuo* to give a crude oil, ^{1}H NMR analysis of which revealed that the (2*E*,4*Z*)/(2*E*,4*E*) ratio of the product was 71:29. The crude product was chromatographed on silica gel (hexane-ethyl acetate) to afford the title compound (39.0 mg, 73%) as an oil of a 71:29 mixture of (2*E*,4*Z*)- and (2*E*,4*E*)-isomers.

Major isomer: ^{1}H NMR (400 MHz) δ 0.88 (m, 3H, alkyl-Me), 1.08-1.46 (m, 14H, alkyl H and -CON($CH_2C\underline{H}_3$)$_2$), 1.81 (br s, 3H, $C_6H_{13}C$(Me)=C(<u>Me</u>)-), 1.85 (br s, 3H, $C_6H_{13}C$(<u>Me</u>)=C(Me)-), 2.33 (t, *J* = 8.0 Hz, 2H, $C_5H_{11}C\underline{H}_2C$=C-), 3.44 (m, 4H, -CON($C\underline{H}_2CH_3$)$_2$), 6.17 (d, *J* = 15.2 Hz, 1H, -CH=C<u>H</u>CONEt$_2$), 7.89 (d, *J* = 15.2 Hz, 1H, -C<u>H</u>=CHCONEt$_2$).

^{13}C NMR (100 MHz) δ 13.22, 14.05, 14.51, 14.87, 20.60, 22.59, 29.09, 29.38, 31.76, 34.66, 40.92, 42.13, 114.81 (C=C), 125.77 (C=C), 140.97 (C=C), 144.13 (C=C), 166.82 (C=O).

Minor isomer: ^{1}H NMR (400 MHz) (characteristic peaks are shown) δ 1.81 (br s, 3H, $C_6H_{13}C(Me)=C(\underline{Me})$-), 1.94 (q, *J* = 1.2 Hz, 3H, $C_6H_{13}C(\underline{Me})=C(Me)$-), 2.18 (t, *J* = 8.0 Hz, 2H, $C_5H_{11}C\underline{H_2}C=C$-), 6.16 (d, *J* = 15.2 Hz, 1H, -CH=C$\underline{H}$CONEt$_2$), 7.88 (d, *J* = 15.2 Hz, 1H, -C$\underline{H}$=CHCONEt$_2$).

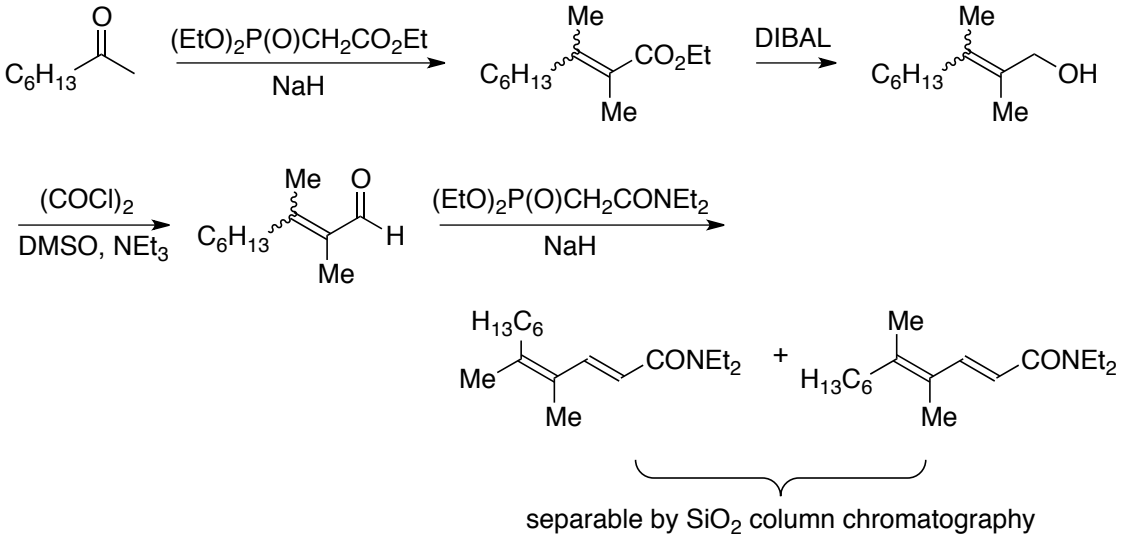
^{13}C NMR (100 MHz) (characteristic peaks are shown) δ 19.01 (2 peaks), 29.35, 36.13, 115.00 (C=C), 125.62 (C=C), 141.66 (C=C), 144.00 (C=C).

IR (neat) 3080 (C=C-H), 2960, 2929, 2858, 1643 (C=O), 1595 (C=C), 1427, 1379, 1281, 1136, 976, 845 cm^{-1} for a 71:29 mixture of (2*E*,4*Z*)- and (2*E*,4*E*)-isomers.

Anal. Calcd for $C_{17}H_{31}NO$: C, 76.92; H, 11.77. Found: C, 77.31; H, 11.91 for a 71:29 mixture of (2*E*,4*Z*)- and (2*E*,4*E*)-isomers.

Authentic samples of (2*E*,4*Z*)-*N*,*N*-diethyl-4,5-dimethyl-2,4-undecadienamide (27) and (2*E*,4*E*)-*N*,*N*-diethyl-4,5-dimethyl-2,4-undecadienamide (27).

This was prepared as follows.



To a suspension of sodium hydride (520 mg of a 60% suspension in mineral oil, 13.0 mmol) in THF (30 mL) was added triethyl 2-methylphosphonoacetate (2.57 mL, 12.0 mmol) at 0 °C under argon. After the mixture was stirred for 10 min at room temperature, it was again cooled to 0 °C. Then, 2-octanone (1.57 mL, 10.0 mmol) was added and the mixture was stirred in an oil bath maintained at 60 °C and was stirred for 12 h. The reaction was terminated by the slow addition of water. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed successively with water and brine, dried over Na_2SO_4, and concentrated *in vacuo* to a crude oil, which was chromatographed on silica gel (hexane-ethyl acetate) to afford a 1:1 mixture of (*E*)- and (*Z*)-ethyl 2,3-dimethyl-2-nonenoate (1.63 g, 77%) as an oil.

To a solution of the above 1:1 mixture of (*E*)- and (*Z*)-ethyl 2,3-dimethyl-2-nonenoate (1.63 g, 7.68 mmol) in CH_2Cl_2 (30 mL) was added DIBAL (18.4 mL, 1.04 M solution in hexane, 19.2 mmol) at –78 °C. After the solution was allowed to warm up to room temperature over 2 h, it was quenched with 1 N HCl. The organic phase was separated and the aqueous phase was extracted with ethyl acetate. The combined organic extracts were successively washed with 1 N HCl solution and with $NaHCO_3$ solution, dried over Na_2SO_4, and concentrated *in vacuo* to a crude oil, which was chromatographed on silica gel (hexane-ethyl acetate) to afford a 1:1 mixture of (*E*)- and (*Z*)-2,3-dimethyl-2-nonenol (1.29 g, 99%) as an oil.

To a solution of oxalyl chloride (0.860 mL, 10.0 mmol) in CH_2Cl_2 (20 mL) was added DMSO (1.42 mL, 20.0 mmol) at –78 °C under argon, followed 10 min later by the above 1:1 mixture of (*E*)- and (*Z*)-2,3-dimethyl-2-nonenol (851 mg, 5.00 mmol) in CH_2Cl_2 (10 mL). After stirring for 15 min, triethylamine (4.16 mL, 30.0 mmol) was added to the mixture, which was then warmed to 0 °C and stirred for 2 h at the same temperature. After the mixture was warmed to room temperature and stirred for an additional 1 h, the reaction was terminated by the addition of water. The organic layer was separated and the aqueous layer was extracted with dichloromethane. The combined organic layers were washed with water and brine, dried over Na_2SO_4, and concentrated *in vacuo* to a crude oil, which was chromatographed on silica gel (hexane-ethyl acetate) to afford a 1:1 mixture of (*E*)- and (*Z*)-2,3-dimethyl-2-nonenal (704 mg, 84%) as an oil.

To a suspension of sodium hydride (217 mg of a 60% suspension in mineral oil, 5.43 mmol) in THF (5 mL) was added *N,N*-diethyl(diethylphosphono)acetamide (808 mg, 5.01 mmol) in THF (5 mL) at 0 °C under argon. After the mixture was stirred for 10 min at room temperature, it was again cooled to 0 °C. Then, a 1:1 mixture of (*E*)- and (*Z*)-2,3-dimethyl-2-nonenal (704 mg, 4.18 mmol) in THF (5 mL) was added and the mixture was warmed to room temperature and was stirred overnight. The reaction was terminated by the slow addition of water. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with water and brine, dried over Na_2SO_4, and concentrated *in vacuo* to a crude oil, which was chromatographed on silica gel (hexane-ethyl acetate) to afford a pure portion of (2*E*,4*Z*)-*N,N*-diethyl-4,5-dimethyl-2,4-undecadienamide (**27**) (266 mg, 24%), an inseparable portion of both isomers of **27** (360 mg, 32%), and a pure portion of (2*E*,4*E*)-*N,N*-diethyl-4,5-dimethyl-2,4-undecadienamide (**27**) (150 mg, 14%) as oils in the order of elusion.

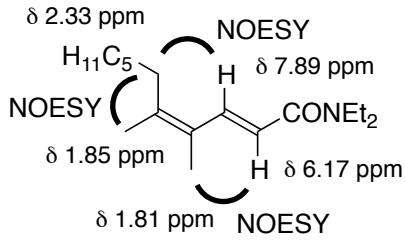
(2*E*,4*Z*)-*N,N*-Diethyl-4,5-dimethyl-2,4-undecadienamide (27).

^{1}H NMR (400 MHz) δ 0.87 (t, *J* = 7.2 Hz, 3H, alkyl-Me), 1.10-1.48 (m, 14H, alkyl H and -CON($CH_2C\underline{H}_3$)$_2$), 1.81 (br s, 3H, $C_6H_{13}C(Me)=C(\underline{Me})$-), 1.85 (br s, 3H, $C_6H_{13}C(\underline{Me})=C(Me)$-), 2.33 (t, *J* = 8.0 Hz, 2H, $C_5H_{11}C\underline{H}_2C$=C-), 3.42 (q, *J* = 6.6 Hz, 2H, -CON($C\underline{H}_2CH_3$)$_2$), 3.46 (q, *J* = 6.6 Hz, 2H, -CON($C\underline{H}_2CH_3$)$_2$), 6.17 (d, *J* = 15.2 Hz, 1H, -CH=C$\underline{H}$CONEt$_2$), 7.89 (d, *J* = 15.2 Hz, 1H, -C$\underline{H}$=CHCONEt$_2$).

^{13}C NMR (100 MHz) δ 13.22, 14.03, 14.50, 14.86, 20.59, 22.58, 29.07, 29.37, 31.74, 34.65, 40.89, 42.13, 114.82 (C=C), 125.76 (C=C), 140.97 (C=C), 144.13 (C=C), 166.78 (C=O).

IR (neat) 3078 (C=C-H), 2960, 2929, 2850, 1639 (C=O), 1604 (C=C), 1427, 1381, 1282, 1138, 1097, 976, 845 cm^{-1}.

NOESY experiments showed the correlation between the peaks at δ 1.81 ppm ($C_6H_{13}C(Me)=C(\underline{Me})$) and δ 6.17 ppm ($CH=C\underline{H}CONEt_2$), at δ 1.85 ppm ($C_6H_{13}C(\underline{Me})=C(Me)$) and δ 2.33 ppm ($C_5H_{11}C\underline{H_2}C(Me)=C(Me)$), and at δ 2.33 ppm ($C_5H_{11}C\underline{H_2}C(Me)=C(Me)$) and δ 7.89 ppm ($C\underline{H}=CHCONEt_2$). Thus, the stereochemistry of the diene bond has been confirmed.



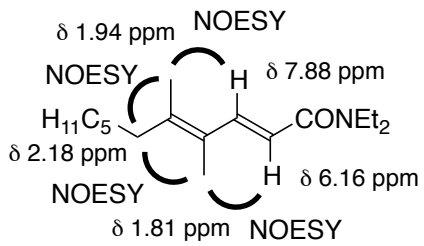
(2*E*,4*E*)-*N*,*N*-Diethyl-4,5-dimethyl-2,4-undecadienamide (27).

^1H NMR (400 MHz) δ 0.89 (t, *J* = 6.8 Hz, 3H, alkyl-Me), 1.16 (t, *J* = 6.8 Hz, 3H, $-CON(CH_2C\underline{H_3})_2$), 1.22 (t, *J* = 6.8 Hz, 3H, $-CON(CH_2C\underline{H_3})_2$), 1.26-1.46 (m, 8H, alkyl H), 1.81 (q, *J* = 1.2 Hz, 3H, $C_6H_{13}C(Me)=C(\underline{Me})-$), 1.94 (q, *J* = 1.2 Hz, 3H, $C_6H_{13}C(\underline{Me})=C(Me)-$), 2.18 (t, *J* = 8.0 Hz, 2H, $C_5H_{11}C\underline{H_2}C=C-$), 3.42 (q, *J* = 6.8 Hz, 2H, $-CON(C\underline{H_2}CH_3)_2$), 3.46 (q, *J* = 6.8 Hz, 2H, $-CON(C\underline{H_2}CH_3)_2$), 6.16 (d, *J* = 15.2 Hz, 1H, $-CH=C\underline{H}CONEt_2$), 7.88 (d, *J* = 15.2 Hz, 1H, $-C\underline{H}=CHCONEt_2$).

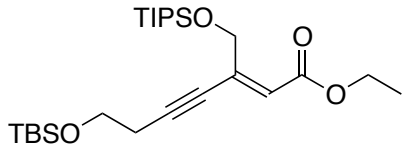
^{13}C NMR (100 MHz) δ 13.21, 14.03, 14.86, 18.99 (2 peaks), 22.57, 27.90, 29.33, 31.73, 36.12, 40.92, 42.16, 115.00 (C=C), 125.62 (C=C), 141.62 (C=C), 143.98 (C=C), 166.78 (C=O).

IR (neat) 3068 (C=C-H), 2958, 2929, 2858, 1641 (C=O), 1595 (C=C), 1425, 1379, 1279, 1136, 1097, 976, 843 cm^{-1}.

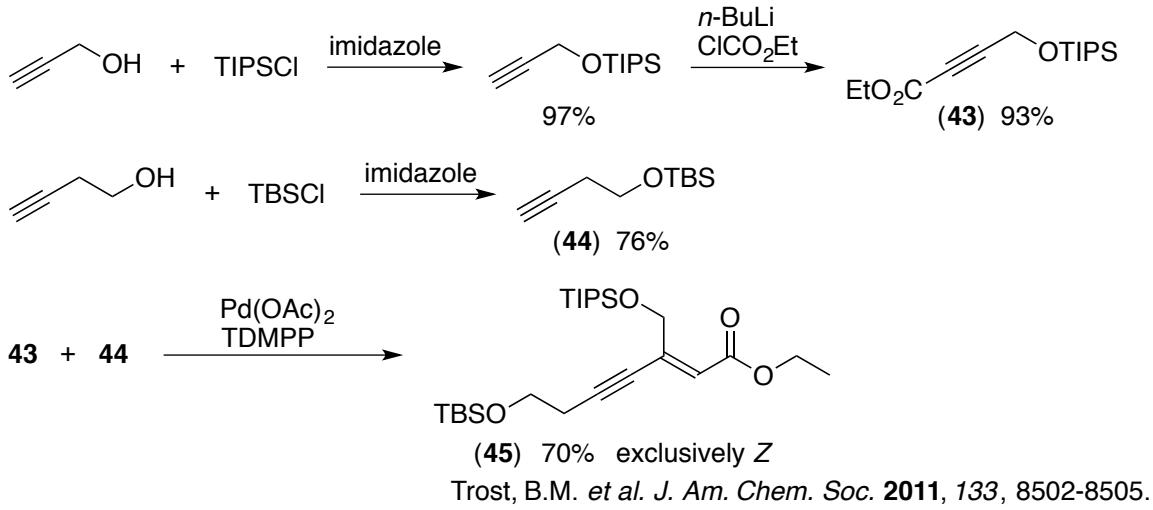
NOESY experiments showed the correlation between the peaks at δ 1.81 ppm ($C_6H_{13}C(Me)=C(\underline{Me})$) and δ 2.18 ($C_5H_{11}C\underline{H_2}C(Me)=C(Me)$), at δ 1.81 ppm ($C_6H_{13}C(Me)=C(\underline{Me})$) and δ 6.16 ($CH=C\underline{H}CONEt_2$), at δ 1.94 ppm ($C_6H_{13}C(\underline{Me})=C(Me)$) and δ 2.18 ($C_5H_{11}C\underline{H_2}C(Me)=C(Me)$), and at δ 1.94 ppm ($C_6H_{13}C(\underline{Me})=C(Me)$) and δ 7.88 ($C\underline{H}=CHCONEt_2$). Thus, the stereochemistry of the diene bond has been confirmed.



Ethyl (*Z*)-7-(*tert*-butyldimethylsilyloxy)-3-[(triisopropylsilyloxy)methyl]-2-hepten-4-ynoate (45).



This was prepared according to the following scheme.



Trost, B.M. *et al. J. Am. Chem. Soc.* **2011**, *133*, 8502-8505.

To a solution of propargyl alcohol (1.74 mL, 30.2 mmol) and imidazole (5.11 g, 75.0 mmol) in 90 mL of CH_2Cl_2 was slowly added triisopropylsilyl chloride (6.42 mL, 30.0 mmol) at 0 °C under argon. After the mixture was stirred at 0 °C for 2 h, the reaction was terminated by addition of 1 N HCl solution. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed successively with aqueous saturated $NaHCO_3$ solution and brine, dried over Na_2SO_4, and concentrated *in vacuo* to afford 1-(triisopropylsilyloxy)-2-propyne (6.19 g, 97%) as an oil, which was directly used in the next step.

To a solution of the above 1-(triisopropylsilyloxy)-2-propyne (6.19 g, 29.0 mmol) in 49 mL of THF was added *n*-BuLi (20.0 mL, 1.60 M in hexane, 32.0 mmol) at –78 °C under argon. After the mixture was stirred at –78 °C for 1 h, ethyl chloroformate (3.05 mL, 32.0 mmol) was added at –78 °C. Then, the solution was slowly warmed to 0 °C over 3 h. The reaction was terminated by addition of aqueous saturated NH_4Cl solution. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo* to give a crude oil, which was chromatographed on silica gel (hexane-ethyl acetate) to afford ethyl 5-(triisopropylsilyloxy)-2-butynoate (**43**) (7.74 g, 93%) as an oil.

To a solution of 3-butyn-1-ol (1.50 mL, 19.8 mmol) and imidazole (3.41 g, 50.1 mmol) in 60 mL of CH_2Cl_2 was added *tert*-butyldimethylsilyl chloride (3.01 g, 20.0 mmol) at 0 °C under argon. After

the mixture was stirred at room temperature for 2 h, the reaction was terminated by the addition of water. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed successively with aqueous saturated $NaHCO_3$ solution and brine, dried over Na_2SO_4, and concentrated *in vacuo* to give a crude oil, which was chromatographed on silica gel (hexane) to afford 1-(*tert*-butyldimethylsilyloxy)-3-butyne (**44**) (2.78 g, 76%) as an oil.

A mixture of $Pd(OAc)_2$ (44.9 mg, 0.200 mmol) and tris(2,6-dimethoxyphenyl)phosphine (88.5 mg, 0.200 mmol) in 1 mL of benzene was stirred at room temperature for 15 min under argon. A solution of ethyl 5-(triisopropylsilyloxy)-2-butynoate (**43**) (569 mg, 2.00 mmol) and 1-(*tert*-butyldimethylsilyloxy)-3-butyne (**44**) (553 mg, 3.00 mmol) in 1 mL of benzene was then added at room temperature. The mixture was stirred in an oil bath maintained at 60 °C for 1.5 h. After being cooled to room temperature, the reaction mixture was concentrated *in vacuo* to give a crude oil, which was chromatographed on silica gel (hexane-ethyl acetate) to afford the title compound (654 mg, 70%, exclusively *Z*) as an oil.

^{1}H NMR δ 0.07 (s, 6H, -Si(CH_3)$_2$), 0.89 (s, 9H, -SiC($C\underline{H}_3$)$_3$), 1.08 (d, *J* = 5.6 Hz, 18H, -SiCH($C\underline{H}_3$)$_2$), 1.10 (m, 3H, -SiC$\underline{H}$(CH_3)$_2$), , 1.26 (t, *J* = 6.8 Hz, 3H, -$CO_2CH_2C\underline{H}_3$), 2.59 (t, *J* = 7.6 Hz, 2H, -$C\underline{H}_2CH_2$OTBS), 3.75 (t, *J* = 7.6 Hz, 2H, -$CH_2C\underline{H}_2$OTBS), 4.14 (q, *J* = 6.8 Hz, 2H, -$CO_2C\underline{H}_2CH_3$), 4.81 (d, *J* = 2.0 Hz, 2H, -CH_2OTIPS), 5.99 (t, *J* = 2.0 Hz, 1H, -C=C$\underline{H}CO_2$Et).

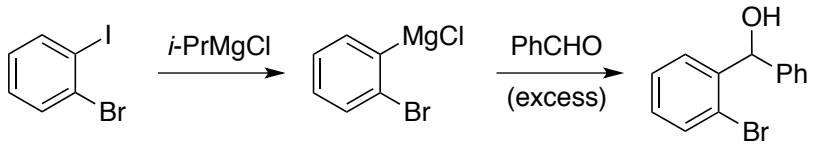
The assignment of *Z* olefinic stereochemistry to this compound was temporarily done based on the stereochemical outcome reported in this literature [Trost, B. M.; Taft, B. R.; Masters, J. T.; Lumb, J.-P. *J. Am. Chem. Soc.* **2011**, *133*, 8502-8505].

^{13}C NMR δ –5.35 (2 carbons, -Si($\underline{C}H_3$)$_2$), 11.96 (3 carbons, -Si$\underline{C}$H(CH_3)$_2$), 14.21, 17.94 (6 carbons, -SiCH($\underline{C}H_3$)$_2$), 18.31, 24.11, 25.85 (3 carbons, -SiC($\underline{C}H_3$)$_3$), 60.15, 61.58, 61.69, 80.69 (C≡C), 95.24 (C≡C), 122.24 (C=C), 144.58 (C=C), 165.71 (C=O).

IR (neat) 2943, 2866, 2222 (C≡C), 1710 (C=O), 1606 (C=C), 1464, 1373, 1333, 1255, 1161, 1109, 1039, 917, 882, 838, 751, 666 cm^{-1}.

HRMS (ESI) Calcd for $C_{25}H_{48}O_4Si_2Na$ $[M+Na]^+$: 491.2983. Found: 491.2973.

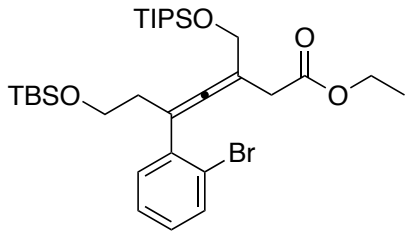
Preparation of 2-bromophenylmagnesium halide. This was prepared according to the following scheme [(a) Boymond, L.; Rottländer, M.; Chahiez, G.; Knochel, N. *Angew. Chem. Int. Ed.* **1998**, *37*, 1701-1703. (b) Cvengroš, J.; Stolz, D.; Togni, A. *Synthesis* **2009**, 2818-2824].



To a solution of 2-bromo(iodo)benzene (113.2 mg, 0.400 mmol) in 0.8 mL of THF was added isopropylmagnesium chloride (1.88 M in THF, 0.210 mL, 0.400 mmol) at –25 °C under argon. After the mixture was stirred at –25 °C for 1 h, benzaldehyde (46.7 mg, 0.440 mmol) in 1 mL of

THF was added at –25 °C under argon. After the mixture was stirred at room temperature for 3 h, the reaction was terminated by the addition of 1 N HCl solution. The organic layer was separated and the aqueous layer was extracted with Et_2O. The combined organic layers were washed successively with aqueous saturated $NaHCO_3$ solution and brine, dried over Na_2SO_4, and concentrated *in vacuo* to give a crude oil, ^{1}H NMR analysis of which revealed that the yield of (2-bromophenyl)(phenyl)methanol (δ 6.21 ppm, d, J = 3.6 Hz, ArC<u>H</u>(OH)Ph) was 81% by using trichloroethylene (0.36 μL, 0.400 mmol) as an internal standard.
Thus, the yield of 2-bromophenylmagnesium halide was estimated to be 81% based on 2-bromo (iodo)benzene.

Ethyl 5-(2-bromophenyl)-7-(*tert*-butyldimethylsilyloxy)-3-[(triisopropylsilyloxy)methyl]-3,4-heptadienoate (46).

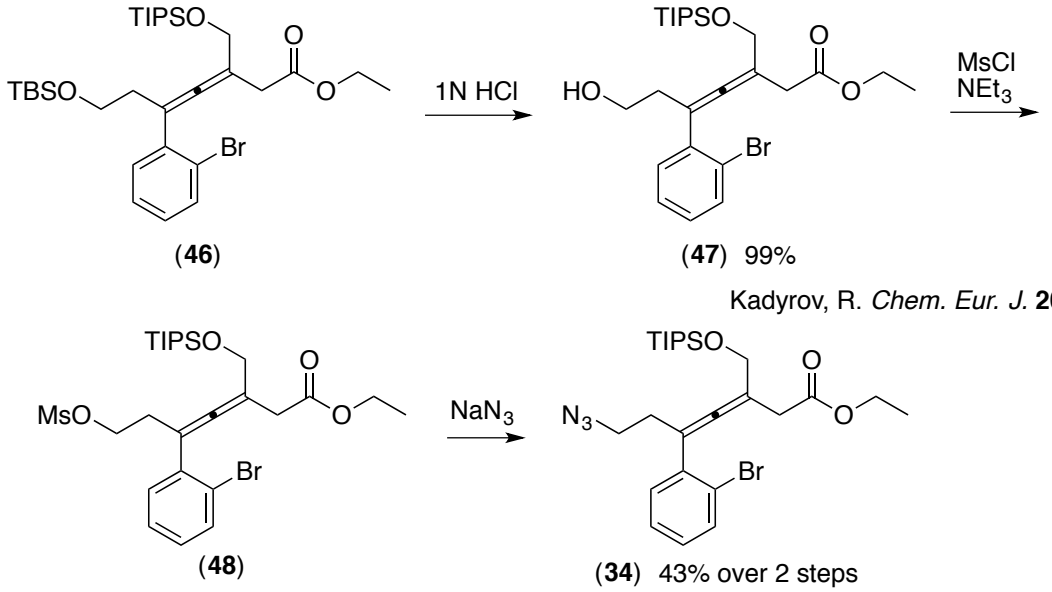


(**46**)

To a solution of ethyl (*Z*)-7-(*tert*-butyldimethylsilyloxy)-3-[(triisopropylsilyloxy)methyl]-2-hepten-4-ynoate (**45**) (234.4 mg, 0.500 mmol) and $FeCl_2$ (6.3 mg, 0.050 mmol) in 2.5 mL of THF was added 2-bromophenylmagnesium halide (ca. 1.0 mmol, prepared from isopropylmagnesium chloride (1.88 M in THF, 0.660 mL, 1.25 mmol) and 2-bromo(iodo)benzene (353.6 mg, 1.25 mmol) in 3.32 mL of THF as above) at –78 °C under argon. After the mixture was stirred at –78 °C for 3 h, the solution was slowly warmed to –60 °C over 1 h. The reaction was terminated by the addition of a 1:1 mixture of THF and water. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were filtered through a short pad of silica gel with the aid of ethyl acetate. The combined filtrates were concentrated *in vacuo* to give a crude oil, ^{1}H NMR analysis of which did not show the presence of other regioisomers. The crude product was chromatographed on silica gel (hexane-ethyl acetate) to afford the title compound (275.6 mg, 88%) as an oil.
^{1}H NMR δ 0.02 (s, 6H, -Si(C<u>H</u>$_3$)$_2$), 0.86 (s, 9H, -SiC(C<u>H</u>$_3$)$_3$), 0.97-1.13 (m, 21H, -SiC<u>H</u>(C<u>H</u>$_3$)$_2$), 1.23 (t, J = 7.2 Hz, 3H, -CO$_2$CH$_2$C<u>H</u>$_3$), 2.59 (t, J = 7.6 Hz, 1H, -C<u>H</u>$_2$CH$_2$OTBS), 2.60 (t, J = 7.6 Hz, 1H, -C<u>H</u>$_2$CH$_2$OTBS), 3.15 (d, J = 15.6 Hz, 1H, -C<u>H</u>$_2$CO$_2$Et), 3.20 (d, J = 15.6 Hz, 1H, -C<u>H</u>$_2$CO$_2$Et), 3.71 (t, J = 7.6 Hz, 2H, -CH$_2$C<u>H</u>$_2$OTBS), 4.13 (q, J = 7.2 Hz, 2H, -CO$_2$C<u>H</u>$_2$CH$_3$), 4.33 (d, J = 14.8 Hz, 1H, -C<u>H</u>$_2$OTIPS), 4.36 (d, J = 14.8 Hz, 1H, -C<u>H</u>$_2$OTIPS), 7.08 (dt, J = 2.0, 7.6 Hz, 1H, 4-Ar-H), 7.24 (dt, J = 0.8, 7.6 Hz, 1H, 5-Ar-H), 7.26 (dd, J = 2.0, 7.6 Hz,1H, 6-Ar-H), 7.53 (dd, J = 0.8, 7.6 Hz, 1H, 3-Ar-H).

^{13}C NMR δ –5.34 (2 peaks, -Si(<u>C</u>H$_3$)$_2$), 11.93 (3 carbons, -Si<u>C</u>H(CH$_3$)$_2$), 14.16, 17.93 (3 carbons, -SiCH(<u>C</u>H$_3$)$_2$), 17.95 (3 carbons, -SiCH(<u>C</u>H$_3$)$_2$), 18.21, 25.88 (3 carbons, -SiC(<u>C</u>H$_3$)$_3$), 34.84, 36.75, 60.55, 61.65, 63.67, 99.60 (<u>C</u>=C=C), 104.02 (<u>C</u>=C=C), 122.84, 127.11, 128.35, 130.52, 132.89, 138.85, 171.12 (C=O), 200.93 (C=<u>C</u>=C).
IR (neat) 3065 (Ar), 2943, 2865, 1970 (C=C=C), 1738 (C=O), 1470, 1385, 1322, 1255, 1147, 1097, 882, 837, 776, 683 cm^{-1}.
HRMS (ESI) Calcd for $C_{31}H_{53}{}^{79}BrO_4Si_2Na$ [M+Na]$^+$: 647.2558. Found: 647.2569.

Ethyl 7-azido-5-(2-bromophenyl)-3-[(triisopropylsilyloxy)methyl]-3,4-heptadienoate (34).
This was prepared according to the following scheme.



(**46**) (**47**) 99%

Kadyrov, R. *Chem. Eur. J.* **2013**, *19*, 1002-1012.

(**48**) (**34**) 43% over 2 steps

Pei, D. *et al. J. Med. Chem.* **2004**, *47*, 4941-4949.

To a solution of ethyl 5-(2-bromophenyl)-7-(*tert*-butyldimethylsilyloxy)-3-[(triisopropylsilyloxy)methyl]-3,4-heptadienoate (**46**) (125 mg, 0.200 mmol) in 2 mL of THF was added 1 N HCl solution (0.800 mL, 0.800 mmol) at room temperature. After the mixture was stirred at room temperature for 1 h, the reaction was terminated by the addition of aqueous saturated $NaHCO_3$ solution. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo* to give a crude oil, which was chromatographed on silica gel (hexane-ehtyl acetate) to afford ethyl 5-(2-bromophenyl)-7-hydroxy-3-[(triisopropylsilyloxy)methyl]-3,4-heptadienoate (**47**) (101.3 mg, 99%) as an oil.
To a solution of the above ethyl 5-(2-bromophenyl)-7-hydroxy-3-[(triisopropylsilyloxy)methyl]-3,4-heptadienoate (**47**) (49.5 mg, 0.100 mmol) and triethylamine (0.020 mL, 0.140 mmol) in 1 mL of CH_2Cl_2 was added methanesulfonyl chloride (0.010 mL, 0.130 mmol) at 0 °C. After the mixture was warmed to room temperature and was stirred for 70 h, the reaction was terminated by the addition of water. The organic layer was separated and the aqueous layer was extracted with

CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo* to give crude ethyl 5-(2-bromophenyl)-7-(methanesulfonyloxy)-3-[(triisopropylsilyloxy)methyl]-3,4-heptadienoate (**48**) (43.8 mg, ca. 77%) as an oil, which was directly used in the next step.

To a solution of the above ethyl 5-(2-bromophenyl)-7-(methanesulfonyloxy)-3-[(triisopropylsilyloxy)methyl]-3,4-heptadienoate (**48**) (43.8 mg, ca. 0.074 mmol) in an 8:1 (v/v) mixture of DMF and water (0.45 mL) was added sodium azide (12.0 mg, 0.185 mmol) at room temperature under argon. The mixture was stirred in an oil bath maintained at 50 °C for 7 h. After being cooled to room temperature, the reaction was terminated by the addition of water. The organic products were extracted with ethyl acetate. The combined organic layers were washed successively with water and brine, dried over Na_2SO_4, and concentrated *in vacuo* to give a crude oil, which was chromatographed on silica gel (hexane-ethyl acetate) to afford the title compound (22.5 mg, 43% over 2 steps from ethyl 5-(2-bromophenyl)-7-hydroxy-3-[(triisopropylsilyloxy)methyl]-3,4-heptadienoate (**46**)) as an oil.

^{1}H NMR δ 0.98-1.13 (m, 21H, -Si(C$\underline{H}$(C$\underline{H}_3$)$_2$)$_3$), 1.25 (t, *J* = 7.2 Hz, 3H, -$CO_2CH_2C\underline{H}_3$), 2.62 (dt, *J* = 15.2, 7.2 Hz, 1H, $N_3CH_2C\underline{H}_2$-), 2.67 (dt, *J* = 15.2, 7.2 Hz, 1H, $N_3CH_2C\underline{H}_2$-), 3.18 (d, *J* = 16.0 Hz, 1H, -C$\underline{H}_2CO_2$Et), 3.23 (d, *J* = 16.0 Hz, 1H, -C$\underline{H}_2CO_2$Et), 3.38-3.49 (m, 2H, $N_3C\underline{H}_2CH_2$-), 4.15 (q, *J* = 7.2 Hz, 2H, -$CO_2C\underline{H}_2CH_3$), 4.35 (d, *J* = 16.8 Hz, 1H, -C$\underline{H}_2$OTIPS), 4.38 (d, *J* = 16.8 Hz, 1H, -C$\underline{H}_2$OTIPS), 7.11 (t, 1H, *J* = 8.0 Hz, 4-Ar-H), 7.12 (t, 1H, *J* = 8.0 Hz, 5-Ar-H), 7.24 (m, 1H, 6-Ar-H), 7.56 (d, *J* = 8.0 Hz, 1H, 3-Ar-H).

^{13}C NMR δ 11.93 (3 carbons, -Si($\underline{C}$HMe$_2$)$_3$), 14.16, 17.91 (3 carbons, -CH($\underline{C}$H$_3$)$_2$), 17.93 (3 carbons, -CH($\underline{C}$H$_3$)$_2$), 32.62, 34.75, 49.31, 60.72, 63.49, 101.13 ($\underline{C}$=C=C), 104.09 (C=$\underline{C}$=C), 122.80, 127.37, 128.77, 130.45, 133.05, 138.22, 171.01 (C=O), 200.76 (C=$\underline{C}$=C).

IR (neat) 3056 (Ar), 2942, 2866, 2098 (C=C=C), 1736 (C=O), 1467, 1367, 1322, 1259, 1145, 1092, 1028, 911, 882, 803, 735, 684 cm^{-1}.

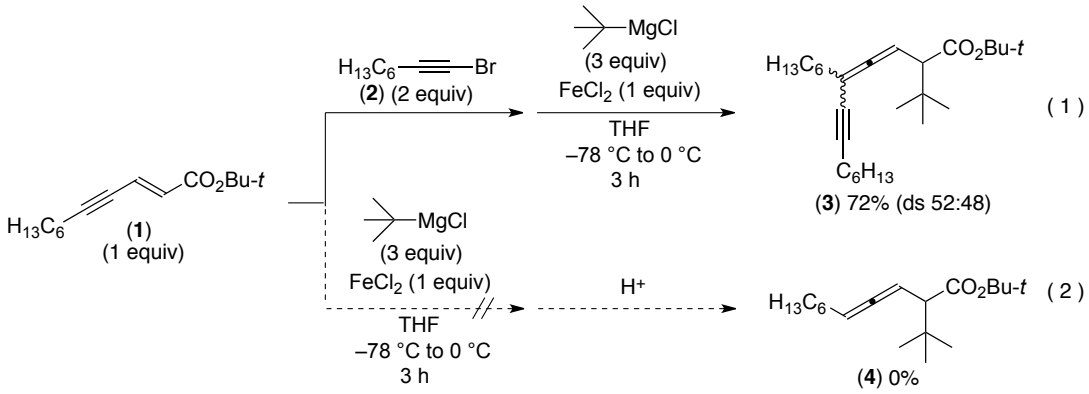
HRMS (ESI) Calcd for $C_{25}H_{38}{}^{79}BrN_3O_3SiNa$ $[M+Na]^+$: 558.1758. Found: 558.1756.

Chapter 3
Iron-Mediated Three-Component Coupling Reaction between 2-Alken-4-ynoates, *tert*-Alkyl Grignard Reagent, and 1-Bromo-1-alkyne

1. Introduction

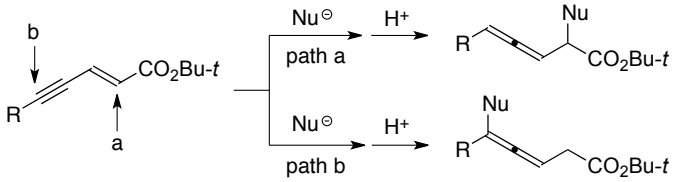
In Chapter 2, we described iron-catalyzed 1,6-addition of Grignard reagents to 2-alken-4-ynoates,[1] in which the Grignard reagents are limited to methyl or aryl Grignard reagents. During the course of our study on this reaction, aiming at the expansion of its applicability, we happened to find that *t*-BuMgCl did add to enyne **1** in the presence of 1-bromo-1-octyne (**2**) to give the three-component coupling product **3** in good yield (eq 1, Scheme 1). This reaction is quite unusual, because the *tert*-butyl group is present at the α-position of the ester, showing that an *anti*-Michael-type addition[2] may occur, and more importantly, the addition of *t*-BuMgCl itself did not proceed at all if the 1-bromo-1-alkyne is absent from the reaction media as in eq 2 in Scheme 1. While a more detailed reaction course will be discussed later, this is an interesting and new three-component coupling reaction, incorporating both *tert*-alkyl and alkynyl groups on the enynoate template.

Scheme 1. Iron-mediated *tert*-alkyl Grignard addition.



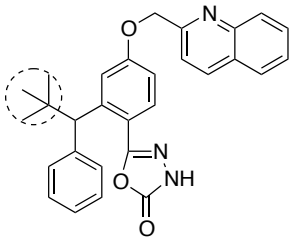
Actually, the carbon nucleophile, *t*-BuMgCl, was introduced to the α,β,γ,δ-unsaturated esters in an '*anti*-Michael' fashion (path a, Scheme 2), i.e. α-addition of *t*-BuMgCl, which is a quite unusual pattern of the conjugate addition as compared to the normal Michael-type addition (path b) amply discussed in Chapter 2. Thus, in this chapter, the scope and limitation of this new reaction will be discussed.

Scheme 2. Michael vs *anti*-Michael addition to enynoate.

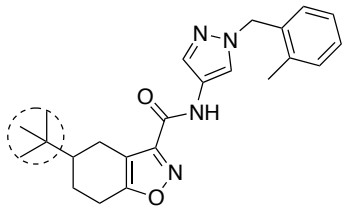


The introduction of *tert*-alkyl group often provides a useful tool for a drug design as shown in Fig. 1.[3,4] While a few examples of the *tert*-butyl substitutions can be seen in the structures **5**-**7**, a more effective *tert*-alkyl group such as the adamantyl group is also representative (structure **8**). For these reasons, we considered that the above three-component coupling reaction provides a new tool for the introduction of a *tert*-alkyl group, possibly contributing to drug design.

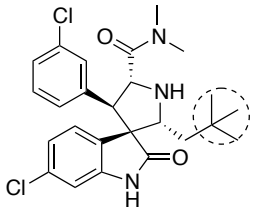
Figure 1. Drug design with *tert*-alkyl groups.



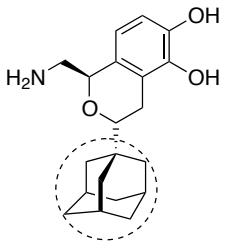
(**5**)
FLAP inhibitor



(**6**)
Inhibitor of Mtb



(**7**)
MDM2 inhibitor



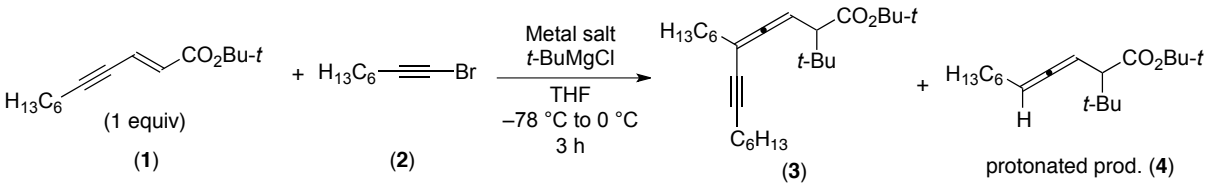
(**8**)
D_1 dopamine receptor agonist

2. Results and Discussion

As described in the previous section, the simple addition of *t*-BuMgCl to enyne **1** in the presence of $FeCl_2$ failed (Scheme 1, eq 2). However, the same reaction in the presence of 1-bromo-1-octyne (**2**) did proceed to give an unexpected adduct of these three components **3** (eq 1). As the reaction conditions listed in eq 1, Scheme 1 are optimized ones, the process to reach this best set of reaction conditions is summarized in Table 1. When an equimolar mixture of *tert*-butyl (*E*)-2-undecen-4-ynoate (**1**) and 1-bromo-1-octyne (**2**) was treated with *t*-BuMgCl (1 equiv), the three-component coupling reaction[5] did not occur at all, resulting in the recovery of the starting material **1** (entry 1). However, increasing the equivalents of *t*-BuMgCl led to the increase in the

product yield (entries 2 and 3). Thus the excess Grignard reagent seems to be necessary for the progress of this reaction, due perhaps to its consumption by the oxidation with the iron salt. After further optimization (entries 4 and 5), the best result was achieved with $FeCl_2$ (1 equiv), excess 1-bromo-1-octyne (**2**) (2 equiv), and again excess *t*-BuMgCl (3 equiv) (entry 5), where the desired product **3** was obtained in high yield. Some attempts to make this reaction catalytic regarding the iron salt were undertaken (entries 6-8). However, the product yields decreased, showing that the stoichiometric iron salts is essential at least for now. In addition, other metal salts were examined whether the similar reaction took place or not (entries 9-13). In most cases, the desired product **3** was not obtained (entries 11-13), but CuBr•SMe_2 was found effective for this reaction, which will be discussed later.

Table 1. Optimization of reaction conditions.

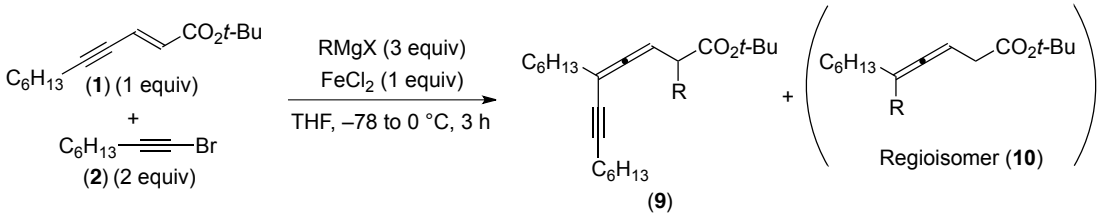


Entry	Metal salt (equiv)	$H_{13}C_6$—≡—Br (equiv)	*t*-BuMgCl (equiv)	Yield (%)[a] by ^{1}H NMR		
				3	**4**	**1**
1	$FeCl_2$ (1)	1	1	0	0	100
2	$FeCl_2$ (1)	1	2	23	0	61
3	$FeCl_2$ (1)	1	3	35	0	19
4	$FeCl_2$ (1)	2	2	15	0	79
5	$FeCl_2$ (1)	2	3	82 (72)	0	0
6	$FeCl_2$ (0.5)	2	3	55	0	0
7	$FeCl_2$ (0.1)	2	3	21	0	28
8	$FeCl_2$ (0.1)	1	2	36	0	39
9	$CoCl_2$ (1)	2	3	3	0	37
10	$MnCl_2$ (1)	2	3	0	21	0
11	$NiCl_2$ (1)	2	3	0	0	68
12	CuBr•SMe_2 (1)	2	3	62	0	0
13	$CuCl_2$ (1)	2	3	40	0	33

[a]Isolated yield is shown in parentheses.

In conjunction with the Scheme 1, *tert*-butyl Grignard reagent was pointed out to be an essential constituent for this reaction. In fact, we attempted the similar reaction with other Grignard reagents, such as those shown in entries 2-7, Table 2, and found that these all did not participate in the reaction.

Table 2. Choice of Grignard reagents.

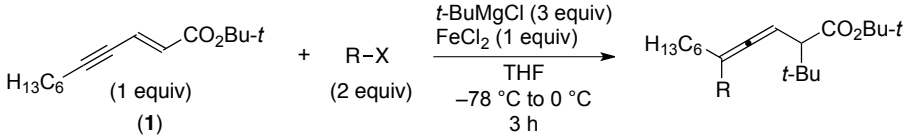


Entry	RMgX	Yield (%) by ^{1}H NMR		
		9	**1**	**10**
1	*t*-BuMgCl	82 (72)[a]	0	0
2	*i*-PrMgCl	0	93	0
3	MeMgBr	0	100	0
4	allyl-MgCl	0	50	7
5	BnMgCl	0	100	0
6	PhMgBr	0	86	0
7	≡—MgBr	0	100	0

[a]Isolated yield.

The similar situation was also observed for another starting material, 1-bromo-1-octyne, as switching this bromine to other ones shown in Table 3 only resulted in the no or low-yield reactions.

Table 3. Possible alternatives for 1-bromo-1-alkyne.



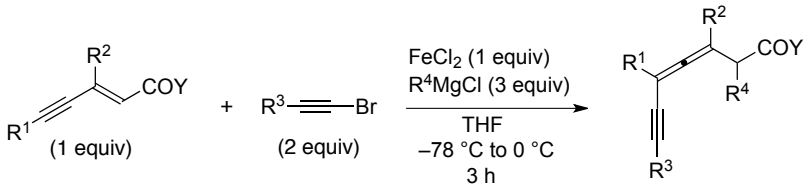
Entry	R-X	Yield (%) by ^{1}H NMR	
		Prod.	**1**
1	$H_{13}C_6$—≡—Br	82 (72)[a]	0
2	$H_{13}C_6$—≡—Cl	24	5
3	$H_{13}C_6$—≡—I	17	54
4	PhBr	0	0
5	allyl-Br	0	72
6	BnBr	0	0
7	$C_6H_{13}Br$	0	0

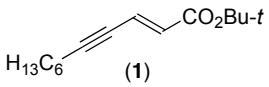
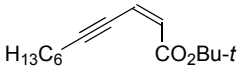
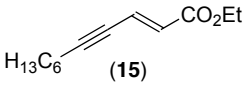
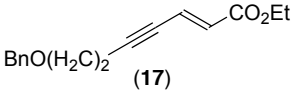
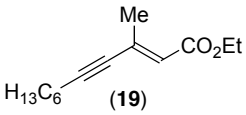
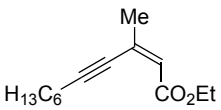
[a]Isolated yield.

The investigation shown above revealed that the transformation of eq 1 in Scheme 1 requires **1**, **2**, and **3** as the essential constituents. Under these conditions, other results were obtained to show the applicability of this reaction, which was summarized in Table 4. 1-Bromo-1-alkynes other than 1-bromo-1-octyne (**2**), even having a terminal olefin, gave the corresponding coupling

products **11** and **12** in good yields (entries 2 and 3). More importantly, this reaction would be generally applicable to *tert*-alkyl Grignard reagents, because *t*-amyl Grignard reagent nicely gave the desired adduct **13** in a good yield (entry 4). (*Z*)-2-Alken-4-ynoate **14** as well as (*E*)-2-alken-4-ynoate **1** could be utilized equally well to give product **3** (entry 5). The enynoates also show reasonable generality, as ethyl ester **15** rather than *tert*-butyl ester **1** and ethyl ester **17** having a benzyloxy-substituted side chain gave the desired products **16** and **18** in good yields (entries 6 and 7). Analogously, from isomeric enynoates with a tri-substituted olefin **19** and **21**, tetra-substituted allene **20** was obtained in good yields (entries 8 and 9). In these cases, the olefinic stereochemistry of the starting materials did not affect the efficiency of this reaction, which was already pointed out also in the entries 1 and 5. The variation of starting materials shown in Table 4 indicates that this transformation is a new method to achieve a three-component coupling reaction, both incorporating a *tert*-alkyl group and giving functionalized conjugated ynallenes.

Table 4. Preparation of various allenes.

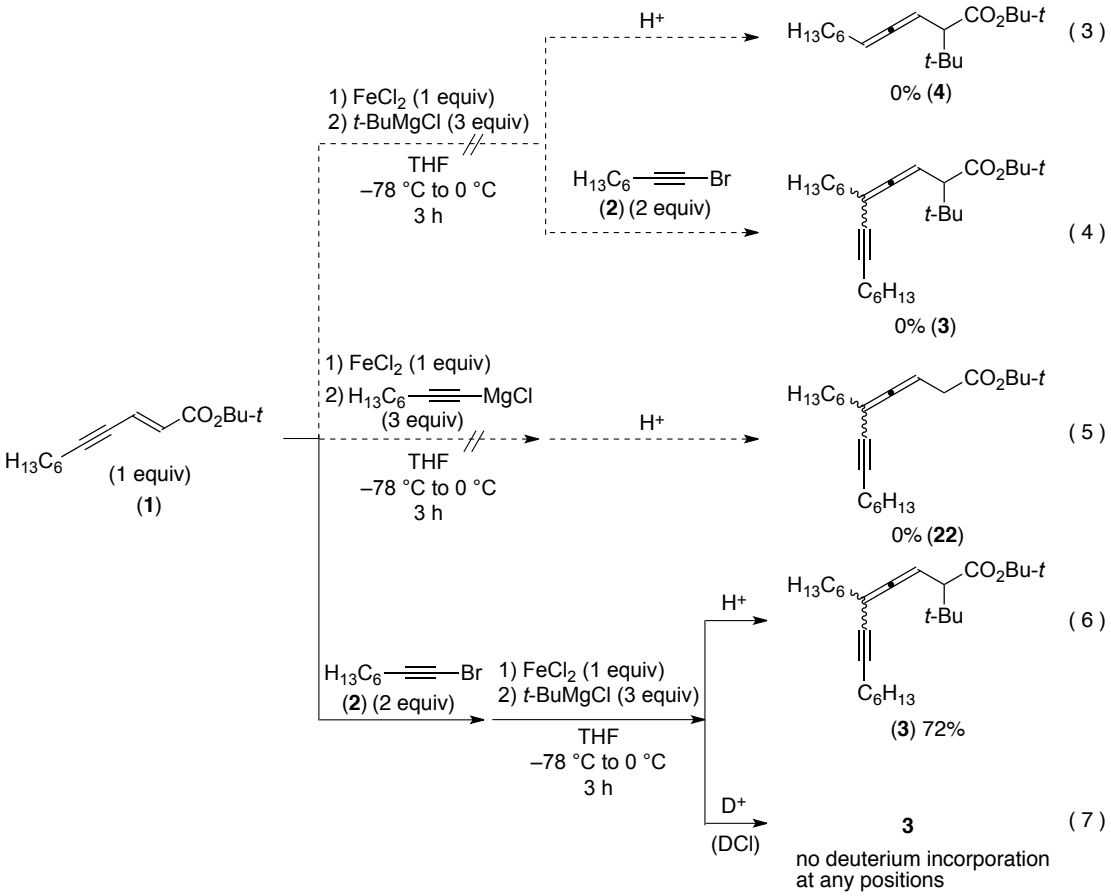


Entry	Substrate	R^3	R^4	Product	Yield (%)[a]	Ds
1	 (**1**)	C_6H_{13}	*t*-Bu	(**3**)	72	52:48
2	**1**	$CH_2{=}CH(CH_2)_8$	*t*-Bu	(**11**)	66	58:42
3	**1**	$Ph(CH_2)_3$	*t*-Bu	(**12**)	74	57:43
4	**1**	C_6H_{13}		(**13**)	64	54:46
5	 (**14**)	C_6H_{13}	*t*-Bu[b]	(**3**)	65	58:42
6	 (**15**)	C_6H_{13}	*t*-Bu	(**16**)	62	52:48
7	 (**17**)	C_6H_{13}	*t*-Bu	(**18**)	61	51:49
8	 (**19**)	C_6H_{13}	*t*-Bu	(**20**)	77	52:48
9	 (**21**)	C_6H_{13}	*t*-Bu[b]	(**20**)	69	51:49

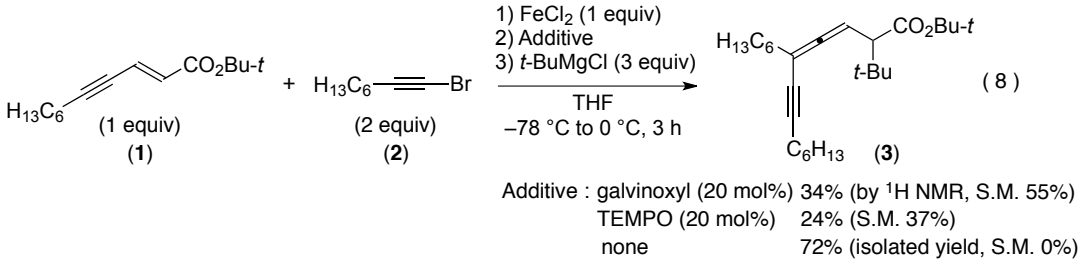
[a]Isolated yields. [b]*t*-BuMgCl (4 equiv) was used.

This three-component coupling reaction is quite interesting in the following three points: (i) incorporation of a sterically demanding *tert*-alkyl group, (ii) that *tert*-alkyl Grignard reagent formally attacks the conjugated enynoate in an *anti*-Michael fashion, and (iii) that as the bromide, only 1-bromo-1-alkyne is so far acceptable and, without it, even the simple addition of *tert*-butyl Grignard reagent does not occur. To get some insight into its reaction course, the following experiments in Scheme 3 were executed. The fundamental addition of *t*-BuMgCl did not proceed without 1-bromo-1-octyne (**2**) so that the *tert*-butylated product **4** was not detected after hydrolysis (eq 3). If protonation is replaced with the alkylation with 1-bromo-1-octyne (**2**), alkylated product **3** was not formed (eq 4), which is a natural outcome. This clearly negates that the reaction consists of the *t*-BuMgCl addition in an *anti*-Michael addition (i.e. carbomagnesiation) followed by the interception of the allenylmetal species with 1-halo-1-alkyne (or proton) as an electrophile. In eq 5, octynyl Grignard reagent (prepared from 1-octyne and isopropylmagnesium chloride *in situ*) was allowed to react with **1** in the presence of the iron salt, but the product **22** resulting form the normal conjugate adduct was not detected, either, suggesting that the reaction of **1** → **3** does not involve the halogen-metal exchange to generate the alkynyl Grignard reagent (and *t*-BuBr) *in situ*. In contrast to these experiments, when a mixture of **1**, **2**, and $FeCl_2$ was treated with *t*-BuMgCl, the desired product **3** was produced in a good yield (eq 6). Finally, deuteriolysis of the reaction of eq 6 shows no deuterium incorporation at any positions in the product (eq 7), showing the absence of the metallated derivative of **3** before workup.

Scheme 3. Examinations for reaction mechanism study.



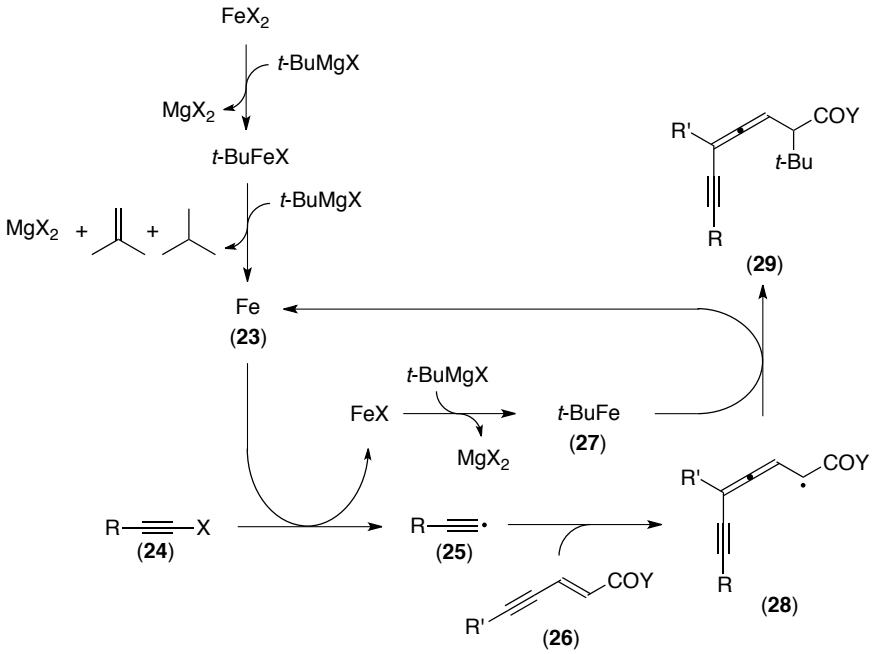
These experiments in Scheme 3 clearly exclude that this transformation is based on the nucleophilic addition of *t*-BuMgCl (eqs 3 and 4) or R–C≡C–MgCl generated *in situ* (eq 5) in an *anti*- or normal Michael fashion. Thus, we conceived that a radical reaction may be involved. In order to probe this possibility, we carried out the reactions in the presence of a radical scavenger as shown in eq 8. In fact, a radical scavenger (galvinoxyl or TEMPO) suppressed the progress of the reaction to some extent.



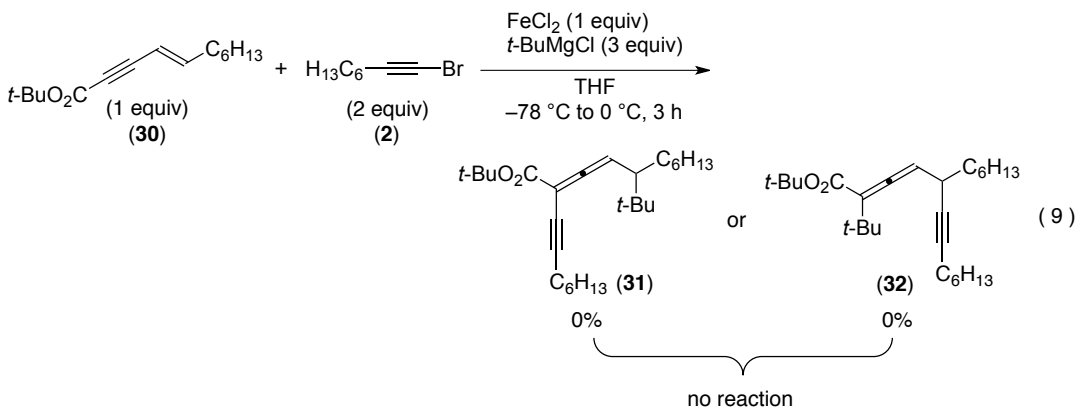
Thus, considering these experimental facts in eqs 3-8 together, we propose a reaction course involving radical species rather than anionic ones as shown in Scheme 4. First, a stoichiometric amount of $FeCl_2$ and *t*-BuMgCl generate a low-valent iron **23**, which effects single-electron

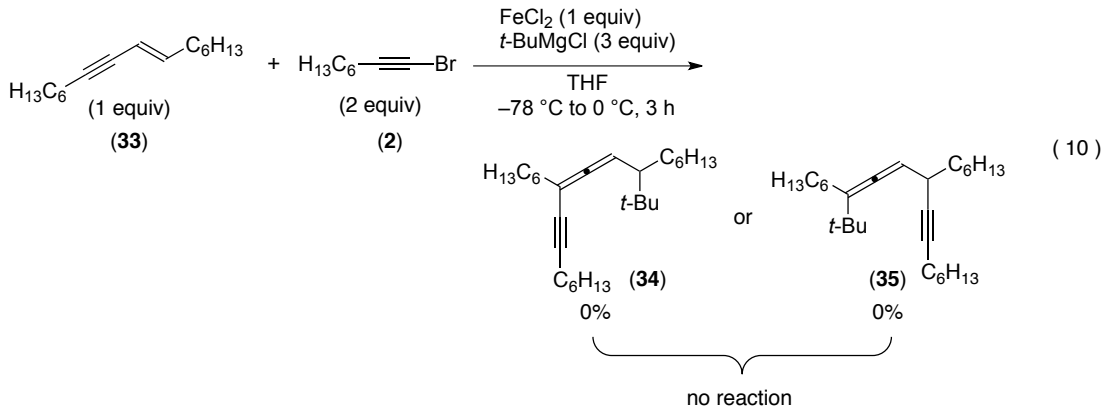
reduction of 1-bromo-1-alkyne **24** to generate alkynyl radical **25**. Then, this radical **25** adds to 2-alken-4-ynoates **26** to produce a radical α to ester **28**, which abstracts *tert*-butyl group from *t*-BuFe species **27**, generated from **23** and 1-bromo-1-alkyne in the reaction media, to give the observed product **29**.

Scheme 4. Proposed reaction course.



Having established the iron-mediated three-component coupling reaction, we studied the feasibility of the same reaction for other types of functionalized enynes. Enyne **30** with an ester group at the acetylenic terminus rather than the olefinic one **1** afforded no isolable products (eq 9). Enyne **33** lacking functional group(s) did not give adducts **34** and **35**, either (eq 10), reconfirming that the reaction of **1** → **3** may not be classified into usual carbometallation of enynes with *t*-BuMgCl.

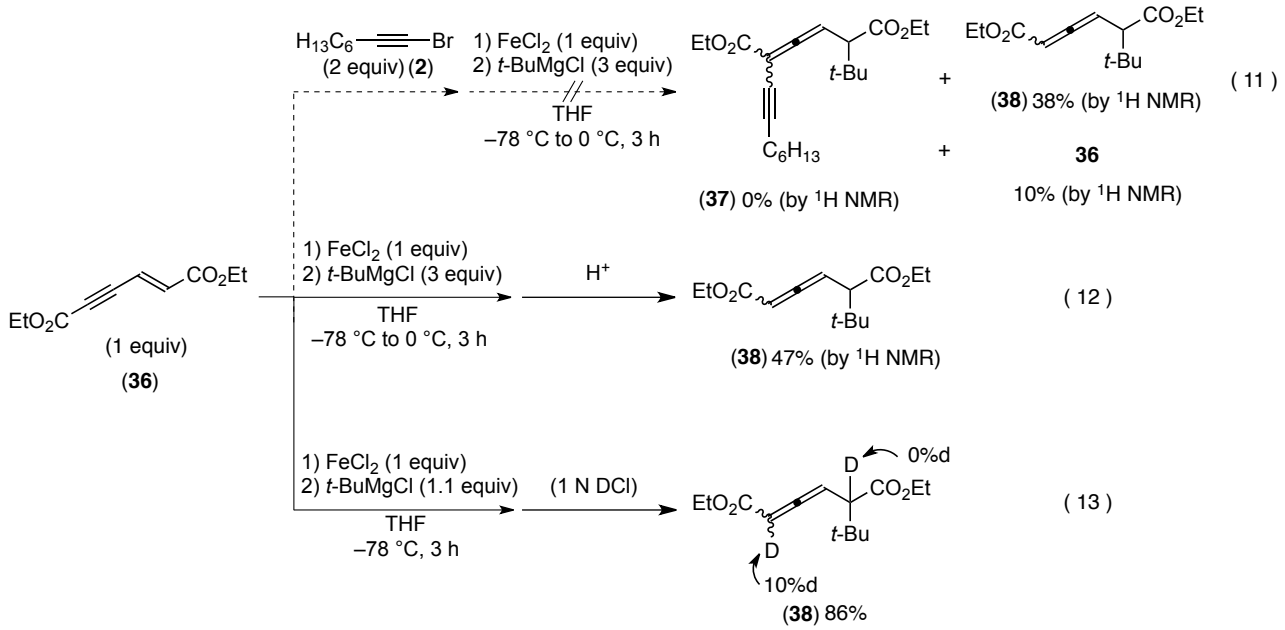




(10)

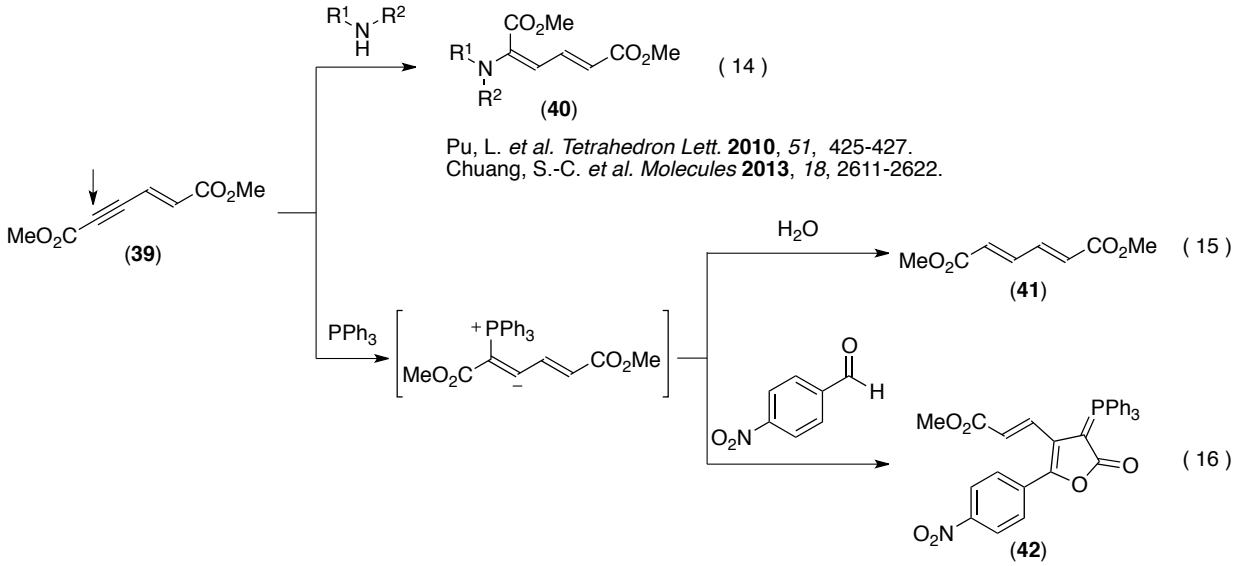
Finally, an enyne **36** carrying two ester groups at its both termini was subjected to the three-component coupling reaction as shown in Scheme 5. This starting enyne **36** has six reaction sites in the same molecule. Although the desired product **37** was not detected, *t*-Bu-adduct **38** was detected albeit in a moderate yield (eq 11). This yield of **38** was increased by omission of 1-bromo-1-octyne (**2**) (eq 12), and was further increased through optimization of the stoichiometry of *t*-BuMgCl (eq 13). It should be emphasized that as deuteriolysis afforded the deuterated product of a very low deuterium content (eq 13), this reaction course could not be explained by simple Grignard addition as the case of **1** → **3**.

Scheme 5. Grignard addition to 2-alken-4-ynedioate

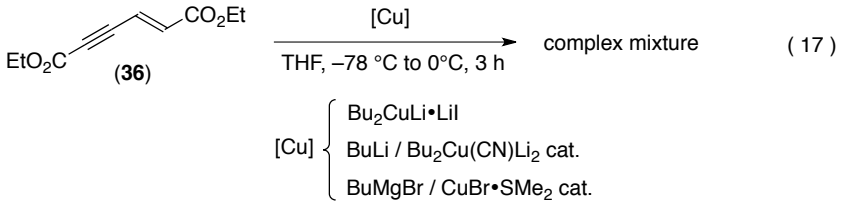


A few examples of the nucleophilic addition to 2-alken-4-ynedioate **39** have been reported (Scheme 6),[6] but the nucleophiles are limited to amine or phosphine and the addition always proceeds at the acetylene moiety in a regioselective manner.

Scheme 6. Nucleophilic addition to 2-alken-4-ynedioates.



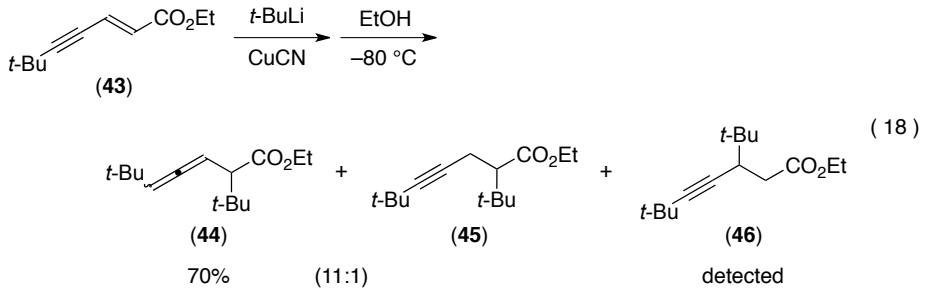
Thus, to see the reactivity of representative carbon nucleophiles such as organometallic reagents toward this class of compounds, we attempted the addition of alkyllithium or alkyl Grignard reagents to 2-alken-4-ynedioate **36** in the presence of copper salts (eq 17). However, these reactions furnished a mixture of messy products. Thus, the reaction of eq 13 should be a new entry to the nucleophilic addition to those enynedioates and should find use to provide a building block containing a *tert*-alkyl group.



Comparison with New Copper-Mediated *anti*-Michael Addition of Grignard Reagents to 2-Alken-4-ynoates

During the course of our study on iron-mediated coupling reaction, we noticed the similar three-component coupling reaction between enynoates, *t*-BuMgCl, and 1-bromo-1-alkyne in the presence of $CuBr•SMe_2$ as shown in entry 12 of Table 1. However, the protocol of α-addition of *t*-BuLi in the presence of a copper salt has been reported as shown in eq 18 twenty years ago.[7,8] However, this reaction has been limited to alkyllithiums and its α-selection is not always high so that the synthetic utility should be rather diminished. In addition, extension of this reaction to the corresponding Grignard reagents has not been reported. As Grignard reagents are less expensive, easier to be prepared, and more convenient (higher functional group compatibility, etc.) than

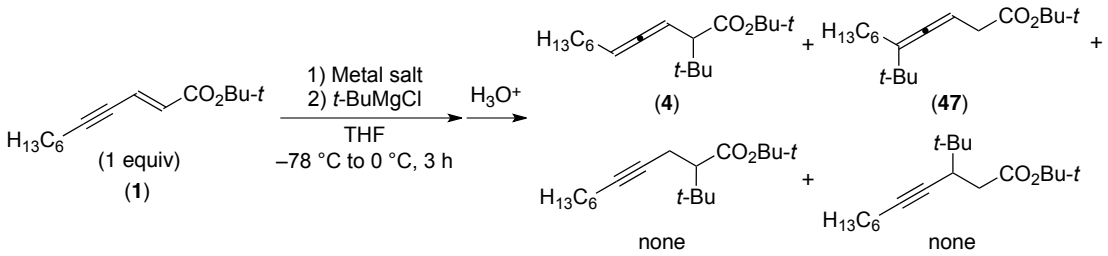
organolithium reagents and the regioselectivity found in entry 12 of Table 1 is more dependable than that in eq 18, we stated to investigate the copper-promoted reactions in conjunction with the iron-promoted ones.



N. Krause *et al. Chem. Ber.* **1994**, *127*, 1547-1549.

The outcome of the preliminary investigation is shown in Table 5, in which enynoate **1** was allowed to react with *t*-BuMgCl in the presence of copper salts. As described previously (eq 3), $FeCl_2$ did not assist the *anti*-Michael addition to furnish a mixture of messy products (entry 1, Table 5). In contrast to the iron-mediated reaction, copper salts such as $CuCl_2$, CuCl, CuBr, and CuI are effective for the α-addition (entries 2-6). Among these copper salts, CuBr•SMe_2 was found particularly effective for this reaction (entries 8-14). After optimization of the stoichiometry of the substrates, the conditions of entry 10 (CuBr•SMe_2 (1 equiv) and *t*-BuMgCl (1.5 equiv)) proved marginally best. Under these conditions, virtually the single regioisomer **4** was produced. An attempt to decrease the amount of CuBr•SMe_2 was not successful because of the poor product yields (entries 12-14).

Table 5. Copper-mediated *anti*-Michael addition.

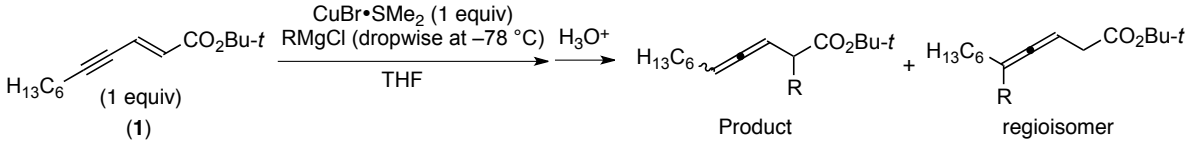


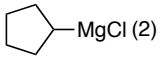
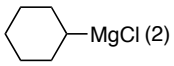
Entry	Metal salt (equiv)	*t*-BuMgCl (equiv)	Yield (%)[a] by ^{1}H NMR		
			4	**47**	**1**
1	$FeCl_2$ (1.25)	4	0	0	0
2	$CuCl_2$ (1.25)	4	50	25	0
3	CuCl (1.25)	4	37	6	0
4	CuBr (1.25)	4	29	8	0
5	CuI (1.25)	4	47	8	0
6	CuCN (1.25)	4	16	0	0
7	Li_2CuCl_4 (1.25)	4	0	0	100
8	CuBr•SMe_2 (1.25)	4	78	0	0
9	CuBr•SMe_2 (1)	3	99	0	0
10	CuBr•SMe_2 (1)	1.5	100 (99)	0	0
11	CuBr•SMe_2 (1)	1	65	0	35
12	CuBr•SMe_2 (0.2)	1.5	40	0	40
13	CuBr•SMe_2 (0.2)	2	40	0	13
14	CuBr•SMe_2 (0.5)	1.5	79	0	11

[a]Isolated yield is shown in parentheses.

Table 6 summarizes the variation of Grignard reagents applicable to the copper-mediated reaction. In addition to *tert*-alkyl Grignard reagent (entries 1 and 2), *sec*-alkyl counterparts such as *i*-Pr, cyclopentyl, and cyclohexyl Grignard reagents could be used as well (entries 6-8). In the latter reactions, the reaction temperature should be maintained at –78 °C and a Grignard reagent should be slowly added over 60 min (entries 6-8). Other types of Grignard reagents such as *n*-butyl, benzyl, or phenyl Grignard reagents did not give the desired adduct, resulting in the recovery of the starting material **1** (entries 9-11).

Table 6. Variation in Grignard reagents.

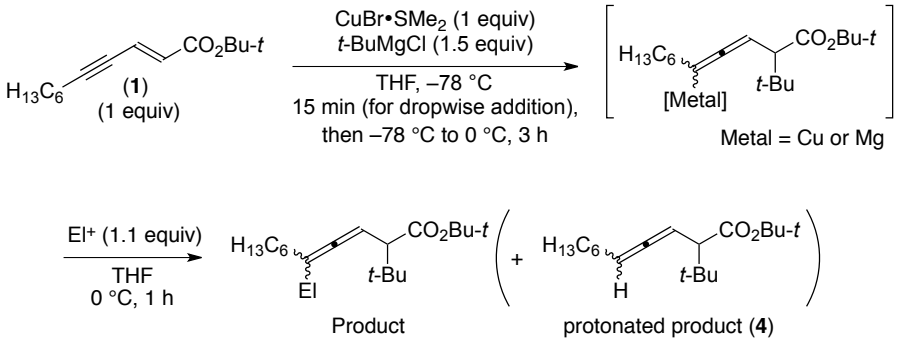


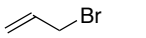
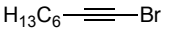
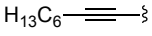
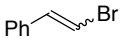
Entry	RMgCl (equiv)	Period for dropwise addition at–78 °C (min)	After dropwise addition		Yield (%)[a]			
			Period (h)	Temp. (°C)	Product	Ds	Regioisomer	**1**
1	*t*-BuMgCl (1.5)	15	3	–78 to 0	99	54:46	(0)	(0)
2	*t*-AmylMgCl (1.5)	15	3	–78 to 0	90	55:45	(0)	(0)
3	*i*-PrMgCl (1.5)	15	3	–78 to 0	(19)		(48)	(0)
4	(1.5)	15	3	–78	(62)		(0)	(31)
5	(2)	15	3	–78	(81)		(5)	(0)
6	(2)	60	3	–78	78	55:45	(0)	(5)
7	 (2)	60	4	–78	78	55:45	(0)	(0)
8	 (2)	60	4	–78	84	54:46	(0)	(0)
9	BuMgCl (2)	15	3	–78 to 0	(0)		(0)	(100)
10	BnMgCl (2)	15	3	–78 to 0	(0)		(0)	(100)
11	PhMgCl (2)	15	3	–78 to 0	(0)		(0)	(100)

[a]Isolated yield. Yields in parentheses and diastereoselectivities were determined by ^{1}H NMR analysis using an internal standard (trichloroethylene).

When the above reaction was terminated by deuteriolysis as shown in entry 2 of Table 7, mono-deuterated product **4**-*d* with high deuterium incorporation was recovered, showing the presence of the allenylmetal intermediate (in square brackets) before aqueous work up. This is in stark contract to the iron-mediated reaction. In addition to 1-bromo-1-octyne mentioned in entry 12 of Table 1, allyl bromide works well to afford the desired product **48** in an excellent yield (entry 3, Table 7). However, aryl, vinyl, primary-alkyl halides, and even an aldehyde or a carboxylic acid halide did not react with the intermediate allenylmetal species at all (entries 5-10).

Table 7. Variation in electrophiles.

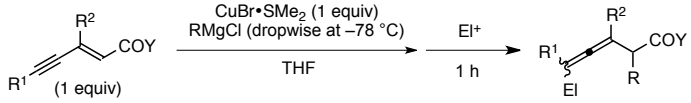


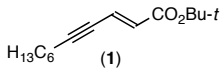
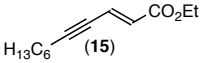
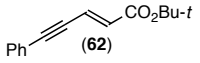
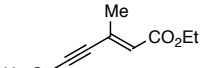
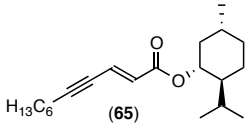
Entry	El+	El	Yield (%)[a] Product		Ds	4
1	HCl	H	(**4**)	99	54:46	-
2	DCl	D	(**4**-*d*)	98 (93%d)	52:48	-
3			(**48**)	93	54:46	(0)
4			(**3**)	92	54:46	(0)
5	PhBr			(0)		(97)
6	PhI			(0)		(100)
7				(0)		(86)
8	$C_6H_{13}I$			(0)		(64)
9	$C_6H_{13}CHO$			(0)		(0)
10	C_3H_7COCl			(0)		(28)

[a]Isolated yields. Yields in parentheses were determined by ^{1}H NMR analysis using an internal standard (trichloroethylene).

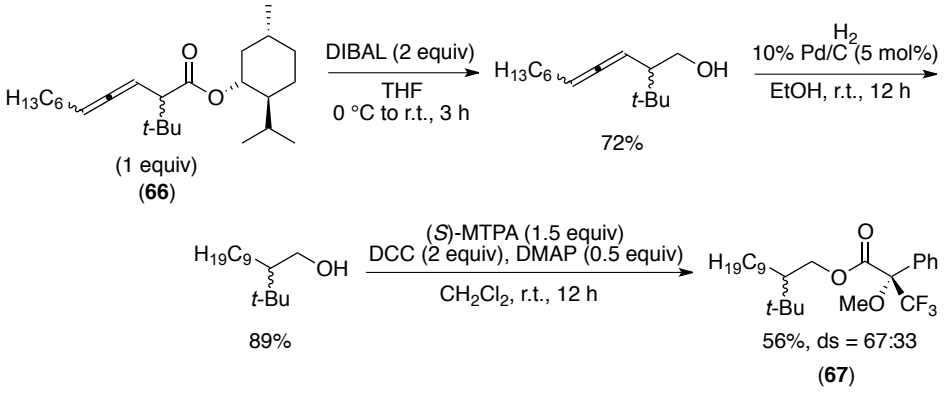
Based on the above studies, we performed more experiments to show the scope and limitation of this copper-mediated reaction. Table 8 summarizes a variety of products that can be obtained by this method. As the 1-bromo-1-alkyne, phenyl- or methoxylcabonyl-substituted ones could be used (entry 5 and 6). This transformation is valid for *sec*-alkyl Grignard reagents such as *i*-Pr, cyclopentyl, and cyclohexyl Grignard reagents to afford the corresponding allenes **52**-**60** (entries 8-16). Besides *tert*-butyl ester **1**, ethyl ester **15** and phenyl-substituted enynoate **62** participated in the addition as well to give **61** and **63** (entries 17 and 18). Furthermore, β-substituted enynoate **19** could be utilized equally well to give the *anti*-Michael adduct **64** (entry 19). In addition, (-)-menthyl ester **65** reacted smoothly with *t*-BuMgCl to afford the allene **66** as a mixture of diasteroisomers (entry 20), albeit with a moderate asymmetric induction from the chiral auxiliary to the α-carbon of the enynoate (see eq 19).

Table 8. Preparation of various allenes.



Entry	Substrate	RMgCl R	RMgCl (equiv)	Period for dropwise addition at –78 °C (min)	After dropwise addition Period (h)	After dropwise addition Temp. (°C)	EI+ (equiv)	Temp. for the reaction with eletrophile (°C)	EI		Yield (%)[a]	Ds
1	 (**1**)	*t*-Bu	1.5	15	3	–78 to 0	HCl	0	H	(**4**)	99	54:46
2	**1**		1.5	15	3	–78 to 0	DCl	0	D	(**4**-*d*)	98 (93%*d*)	52:48
3	**1**		1.5	15	3	–78 to 0	 (1.1)	0		(**48**)	93	54:46
4	**1**		1.5	15	3	–78 to 0	$H_{13}C_6C{\equiv}CBr$ (1.1)	0	$H_{13}C_6C{\equiv}C$–	(**3**)	92	54:46
5	**1**		1.5	15	3	–78 to 0	$PhC{\equiv}CBr$ (1.1)	0	$PhC{\equiv}C$–	(**49**)	91	57:43
6	**1**		1.5	15	3	–78 to 0	$MeO_2CC{\equiv}CBr$ (1.1)	0	$MeO_2CC{\equiv}C$–	(**50**)	86	55:45
7	**1**		1.5	15	3	–78 to 0	HCl	0	H	(**51**)	90	55:45
8	**1**	*i*-Pr	2	60	3	–78	HCl	–78	H	(**52**)	78	55:45
9	**1**		2	60	3	–78	 (2)	–78		(**53**)	77	52:48
10	**1**		2	60	3	–78	$H_{13}C_6C{\equiv}CBr$ (2)	–78	$H_{13}C_6C{\equiv}C$–	(**54**)	65	55:45
11	**1**		2	60	4	–78	HCl	–78	H	(**55**)	78	55:45
12	**1**		2	60	4	–78	 (2)	–78		(**56**)	75	52:48
13	**1**		2	60	4	–78	$H_{13}C_6C{\equiv}CBr$ (2)	–78	$H_{13}C_6C{\equiv}C$–	(**57**)	68	55:45
14	**1**		2	60	4	–78	HCl	–78	H	(**58**)	84	54:46
15	**1**		2	60	4	–78	 (2)	–78		(**59**)	78	50:50
16	**1**		2	60	4	–78	$H_{13}C_6C{\equiv}CBr$ (2)	–78	$H_{13}C_6C{\equiv}C$–	(**60**)	65	55:45
17	 (**15**)	*t*-Bu	1.5	15	3	–78 to 0	HCl	0	H	(**61**)	82	57:43
18	 (**62**)	*t*-Bu	1.5	15	3	–78 to 0	HCl	0	H	(**63**)	94	53:47
19	 (**19**)	*t*-Bu	1.5	15	3	–78 to 0	HCl	0	H	(**64**)	87	51:49
20	 (**65**)	*t*-Bu	1.5	15	3	–78 to 0	HCl	0	H	(**66**)	98	–[b]

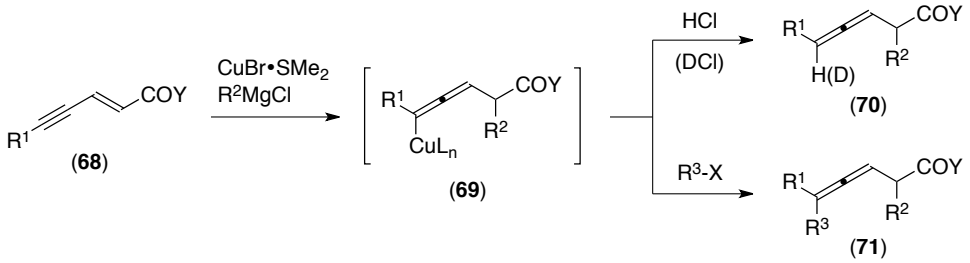
[a]Isolated yield. [b]This product is most likely a mixture of 4 diastereoisomers. The diastereoselectivity between the carbon α to carbonyl group and the chiral auxiliary was 67:33 as determined by eq 19.

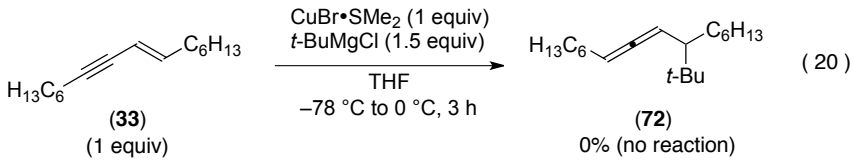


(19)

A mechanism of this reaction is already proposed by Krause *et al*. in conjunction with the result of eq 18 and shown in Scheme 7.[7,8] Thus, it involves an *anti*-Michael addition of Grignard reagents to enynoates **68** to give allenylmetal intermediate **69** which suggests that the electron-withdrawing groups (i.e., ester) do not have an enough influence on the direction of the reaction and that the simple carbometallation to the enyne structure is a prevailing driving force. However, the latter interpretation should not be overestimated, because an unfunctionalized enyne represented by 7-hexadecen-9-yne (**33**) did not undergo the carbomatallation under the same reaction conditions (eq 20).

Scheme 7. Proposed reaction course.





(20)

Conclusion

In conclusion, we developed the iron-mediated three-component coupling reaction of 2-alken-4-ynoates, 1-bromo-1-alkynes, and *tert*-alkyl Grignard reagents and, alternatively, α-addition of *t*-BuMgCl to 2-alken-4-ynedioates. These reactions have quite unusual aspects: (i) clean incorporation of a sterically demanding *tert*-alkyl group, (ii) formal addition of *tert*-alkyl Grignard reagents in an *anti*-Michael fashion, and (iii) that the reaction course does not involve an anionic addition, but most likely consists of a radical pathway. These characteristics are unique in the stand point of the role of iron reagents in organic synthesis. In conjunction with these iron-mediated reaction, we also disclosed a copper-mediated *anti*-Michael addition of a *tert*- or *sec*-alkyl Grignard reagent to 2-alken-4-ynoates to give an allenylmetal species, which was then alkylated with 1-bromo-1-alkynes to give the same product as those of the aforementioned iron-mediated reactions. These Fe- or Cu-mediated reactions could be used complementarily: iron reagents are less toxic and expensive than copper reagents and the laboratory operation of the iron-mediated reactions is simpler, while the copper-mediated reaction covers somewhat wider product variation. Further investigation on the utility of these reactions is now in progress.

3. References and Notes

1. Hata, T.; Iwata, S.; Seto, S.; Urabe, H. *Adv. Synth. Catal.* **2012**, *354*, 1885-1889.
2. The α-addition to α,β-unsaturated carbonyl compounds having a strong electron-withdrawing group, such as a trifluoromethyl, nitro, or carbonyl group, at their β-position is of course quite common and has been reported for various nucleophiles such as carbon, nitrogen, oxygen, or sulfur nucleophiles. For examples, see: (a) Lewandowska, E. *Tetrahedron* **2007**, *63*, 2107–2122. Carbon nucleophiles: (b) Ballini, R.; Bosica, G.; Palmieri, A.; Bakhtiari, K. *Synlett* **2009**, *2009*, 268–270. (c) Shim, J.-G.; Park, J. C.; Cho, C. S.; Shim, S. C.; Yamamoto, Y. *Chem. Commun.* **2002**, *2002*, 852–853. (d) Klumpp, G. W.; Mierop, A. J. C.; Vrielink, J. J.; Brugman, A.; Schakel, M. *J. Am. Chem. Soc.* **1985**, *107*, 6740–6742. (e) Aurell, M. J.; Bañuls, M. J.; Mestres, R.; Muñoz, E. *Tetrahedron* **2001**, *57*, 1067–1074. Nitrogen nucleophiles: (f) Ballini, R.; Bazán, N. A.; Bosica, G.; Palmieri, A. Uncatalyzed, *Tetrahedron Lett.* **2008**, *49*, 3865–3867. (g) Yuan, H.; Zheng, Y.; Zhang, J. *J. Org. Chem.* **2012**, *77*, 8744–8749. (h) Trost, B. M.; Dake, G. R. *J. Am. Chem. Soc.* **1997**, *119*, 7595–7596. Oxygen nucleopliles: (i) Bumgardner, C. L.; Bunch, J. E.; Whangbo, M. H. *Tetrahedron* **1986**, *27*, 1883-1886. Sulfur nucleophiles: (j) Ponticello, G. S.; Freedman, M. B.; Habecker, Ch. N.; Holloway, M. K.; Amato, J. S.; Conn, R. S.; Baldwin, J. J. *J. Org. Chem.* **1988**, *53*, 9-13. (k) Chatfield, D. C.; Augsten, A.; Cunha, C. D.; Lewandowska, E.; Wnuk, S. F. *Eur. J. Org. Chem.* **2004**, 313-322.
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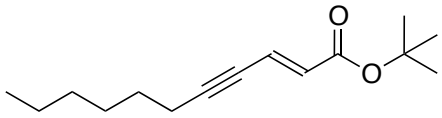
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Experimental Section (Chapter 3)

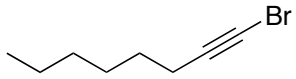
General. ^{1}H and ^{13}C NMR spectra were taken on an Agilent 400-MR spectrometer at 400 and 100 MHz, respectively. $CDCl_3$ was used as the solvent. Chemical shifts are reported in parts per million shift (δ value) from Me_4Si (δ 0 ppm for ^{1}H) or based on the middle peak of the solvent ($CDCl_3$) (δ 77.00 ppm for ^{13}C NMR) as an internal standard. Signal patterns are indicated as br, broad; s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. Coupling constants (*J*) are given in Hertz. Infrared (IR) spectra were recorded on a JASCO A-100 spectrometer and are reported in wave numbers (cm^{-1}). High resolution mass spectra (HRMS) were obtained on a Bruker micrOTOF II in positive electrospray ionization (ESI) method calibrated with sodium formate at the Suzukake-dai Material Analysis Center, Technical Department, Tokyo Institute of Technology. *tert*-Butylmagnesium chloride (1.02 ~ 1.03 M in THF) was purchased from Kanto Chemicals Co. (Japan). Silica gel for flash chromatography (Catalog No. 233-00077, 75-150 μm) was purchased from Wako Pure Chemical Industries, Ltd. (Japan). Dry solvents (THF, Et_2O, CH_2Cl_2, and toluene) were purchased from Kanto Chemicals Co. (Japan). Chemicals were purified or dried in a standard manner, if necessary.

Iron-Mediated Three-Component Coupling Reaction

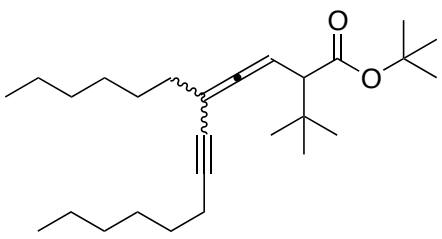
***tert*-Butyl (*E*)-2-undecen-4-ynoate (1).** This is a known compound [Hata, T.; Iwata, S.; Seto, S.; Urabe, H. *Adv. Synth. Catal.* **2012**, *354*, 1885-1889]. The olefin is exclusively *E*.



1-Bromo-1-octyne (2). This is a known compound and was prepared by a literature method [Yamagishi, M.; Nishigai, K.; Hata, T.; Urabe, H. *Org. Lett.* **2011**, *13*, 4873-4875].



***tert*-Butyl 2-(*tert*-butyl)-5-hexyl-3,4-tridecadien-6-ynoate (3) from *tert*-butyl (*E*)-2-undecen-4-ynoate (1).**



To a suspension of *tert*-butyl (*E*)-2-undecen-4-ynoate (**1**) (47.3 mg, 0.200 mmol), 1-bromo-1-octyne

(**2**) (75.6 mg, 0.400 mmol), and $FeCl_2$ (25.4 mg, 0.200 mmol) in 1 mL of THF was added *tert*-butylmagnesium chloride (0.590 mL, 1.02 M solution in THF, 0.602 mmol) at –78 ºC under argon. After the solution was slowly warmed to 0 ºC over 3 h, the reaction was terminated by the addition of 1 N HCl solution (1 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed successively with aqueous saturated $NaHCO_3$ solution and brine, dried over Na_2SO_4, and concentrated *in vacuo* to give a crude oil, ^{1}H NMR analysis of which revealed that other regioisomers were absent and that the diastereoselectivity of the product was 52:48. The crude product was chromatographed on silica gel (hexane-ethyl acetate) to afford the title compound (57.8 mg, 72%) as an oil and of the same diastereomeric composition observed for a crude sample.

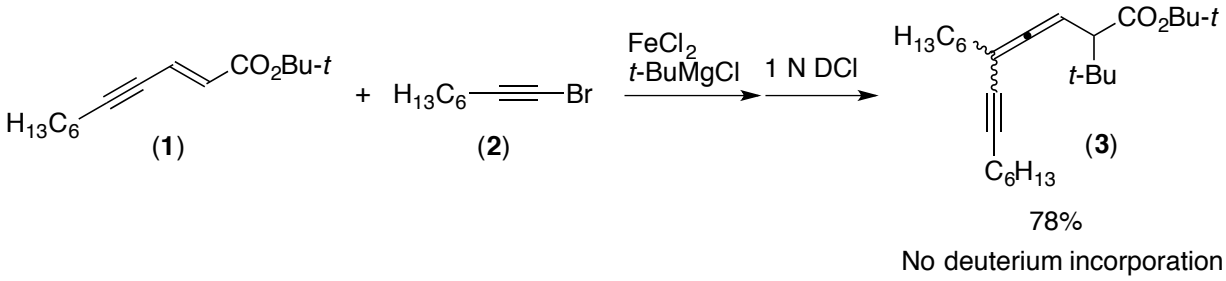
^{1}H NMR δ 0.85-0.91 (m, 6H, alkyl-Me), 0.99 (s, 9H × 0.48, -C(C$\underline{H}_3$)$_3$), 1.01 (s, 9H × 0.52, -C(C$\underline{H}_3$)$_3$), 1.20-1.56 (m, 16H, alkyl H), 1.457 (s, 9H × 0.52, -CO$_2$C(C$\underline{H}_3$)$_3$), 1.462 (s, 9H × 0.48, -CO$_2$C(C$\underline{H}_3$)$_3$), 2.06 (m, 2H, $C_5H_{11}C\underline{H}_2$-), 2.29 (dt, J = 1.2, 6.8 Hz, 2H × 0.52, -C≡CC$\underline{H}_2C_5H_{11}$), 2.30 (dt, J = 1.2, 6.8 Hz, 2H × 0.48, -C≡CC$\underline{H}_2C_5H_{11}$), 2.68 (d, J = 9.6 Hz, 1H × 0.52, -C$\underline{H}$CO$_2$Bu-*t*), 2.71 (d, J = 9.6 Hz, 1H × 0.48, -C$\underline{H}$CO$_2$Bu-*t*), 5.38 (dm, J = 9.6 Hz, 1H, $C_6H_{13}C$=C=C$\underline{H}$-).

^{13}C NMR δ 14.02, 14.05, [19.51 (major), 19.58 (minor)], 22.55, 22.59, [27.58 (3 carbons, -C(C$\underline{H}_3$)$_3$, major), 27.66 (minor)] 28.09 (3 carbons, -C(C$\underline{H}_3$)$_3$), [28.45 (major), 28.53 (minor)], [28.57 (major), 28.63 (minor)], [28.75 (minor), 28.79 (major)], 31.35, 31.63, 33.78, 33.99, [34.31 (minor), 34.41 (major)], [57.43 (minor), 57.62 (major)], [75.74 (C≡C, major), 75.89 (minor)], [80.45 (major), 80.52 (minor)], [88.84 (C=C=C, minor), 89.31 (major)], [90.50 (minor), 90.67 (major)], [92.16 (major), 92.42 (minor)], [172.10 (C=O, major), 171.87 (minor)], [209.50 (C=C=C, minor), 209.62 (major)]. A pair of diastereomeric peaks are shown in square brackets.

IR (neat) 2958, 2931, 2859, 2220 (C≡C), 1955 (C=C=C), 1726 (C=O), 1467, 1368, 1334, 1142, 1034, 968, 850, 730 cm^{-1} for a 52:48 mixture of diastereoisomers.

HRMS (ESI) Calcd for $C_{27}H_{46}O_2Na$ [M+Na]$^+$: 425.3390. Found: 425.3400 for a 52:48 mixture of diastereoisomers.

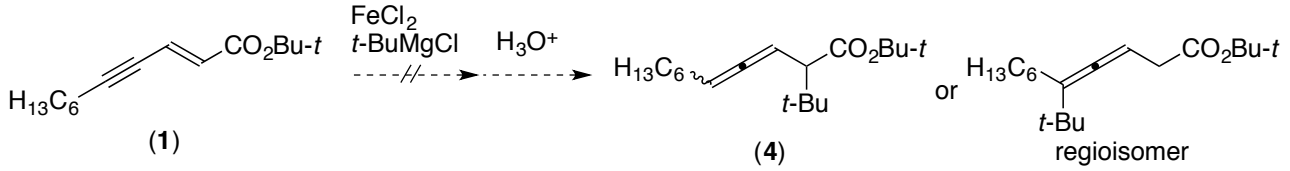
Control experiment for 1 → 3. Deuteriolysis in place of hydrolytic work-up.



To a suspension of *tert*-butyl (*E*)-2-undecen-4-ynoate (**1**) (47.3 mg, 0.200 mmol), 1-bromo-1-octyne (**2**) (75.6 mg, 0.400 mmol), and $FeCl_2$ (25.4 mg, 0.200 mmol) in 1 mL of THF was added *tert*-butylmagnesium chloride (0.590 mL, 1.02 M solution in THF, 0.602 mmol) at –78 ºC under argon. After the solution was slowly warmed to 0 ºC over 3 h, the reaction was terminated by the addition of 1 N DCl solution (0.5 mL). The organic layer was separated and the aqueous layer was extracted

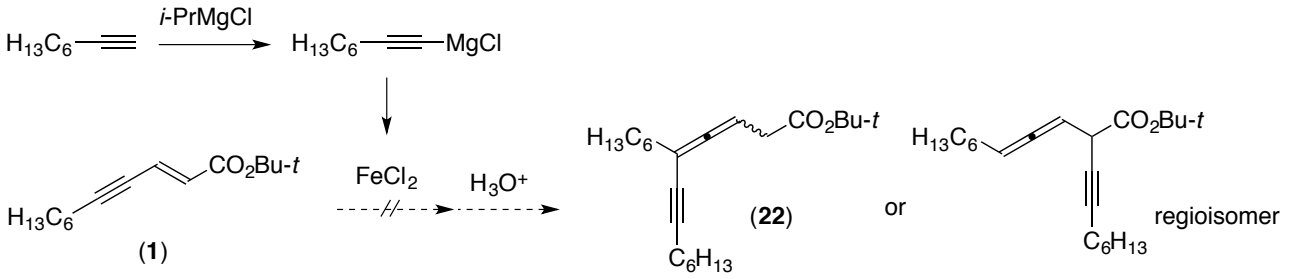
with ethyl acetate. The combined organic layers were washed successively with aqueous saturated $NaHCO_3$ solution and brine, dried over Na_2SO_4, and concentrated *in vacuo* to give a crude oil. The crude product was analyzed by ^1H NMR with trichloroethylene as an internal standard to show that *tert*-butyl 2-(*tert*-butyl)-5-hexyl-3,4-tridecadien-6-ynoate (**3**) was formed in 78% yield and obvious incorporation of deuterium was not observed at any positions.

Control experiment for 1 → 3. The reaction in the absence of 1-bromo-1-octyne (2).



To a suspension of *tert*-butyl (*E*)-2-undecen-4-ynoate (**1**) (47.3 mg, 0.200 mmol) and $FeCl_2$ (25.4 mg, 0.200 mmol) in 1 mL of THF was added *tert*-butylmagnesium chloride (0.590 mL, 1.02 M solution in THF, 0.602 mmol) at –78 ºC under argon. After the solution was slowly warmed to 0 ºC over 3 h, the reaction was terminated by the addition of 1 N HCl solution (1 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed successively with aqueous saturated $NaHCO_3$ solution and brine, dried over Na_2SO_4, and concentrated *in vacuo* to give a crude oil, ^1H NMR analysis of which revealed that *tert*-butyl 2-(*tert*-butyl)-3,4-undecadienoate (**4**) or its regioisomer was not formed.

Control experiment for 1 → 3. The reaction with 1-octynyl Grignard reagent in place of *t*-BuMgCl.

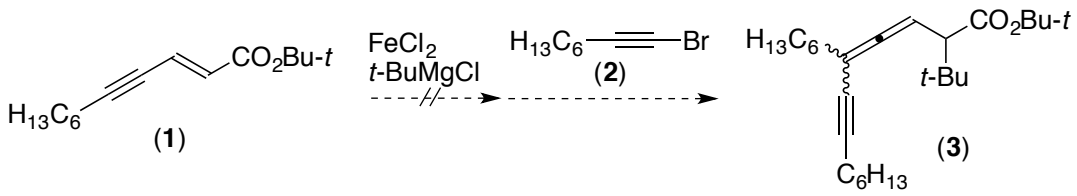


To a solution of 1-octyne (66.2 mg, 0.600 mmol) in 0.5 mL of THF was added isopropylmagnesium chloride (0.540 mL, 1.22 M solution in THF, 0.659 mmol) at 0 °C under argon. After the mixture was stirred at room temperature for 1.5 h, the reaction mixture was directly used in the following reaction.

To a suspension of *tert*-butyl (*E*)-2-undecen-4-ynoate (**1**) (47.3 mg, 0.200 mmol) and $FeCl_2$ (25.4 mg, 0.200 mmol) in 1 mL of THF was added the above 1-octynylmagnesium chloride at –78 ºC under argon. After the solution was slowly warmed to 0 ºC over 3 h, the reaction was terminated by the addition of 1 N HCl solution (1 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed successively with aqueous saturated $NaHCO_3$ solution and brine, dried over Na_2SO_4, and concentrated *in vacuo* to give a crude oil,

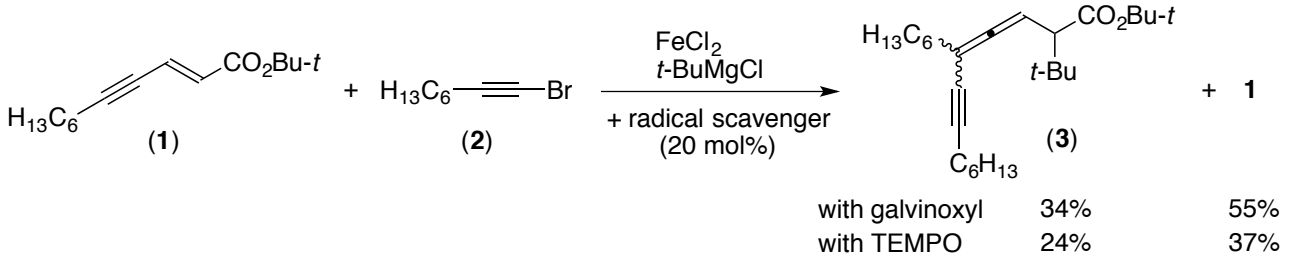
^{1}H NMR analysis of which revealed that *tert*-butyl 5-hexyl-3,4-tridecadien-6-ynoate (**6**) or its regioisomer was not formed.

Control experiment for 1 → 3. Stepwise addition / alkynylation.



To a suspension of *tert*-butyl (*E*)-2-undecen-4-ynoate (**1**) (47.3 mg, 0.200 mmol) and $FeCl_2$ (25.4 mg, 0.200 mmol) in 1 mL of THF was added *tert*-butylmagnesium chloride (0.590 mL, 1.02 M solution in THF, 0.602 mmol) at –78 ºC under argon. After the mixture was slowly warmed to 0 ºC over 3 h, 1-bromo-1-octyne (**2**) (75.6 mg, 0.400 mmol) in 0.5 mL of THF was added. Then, the mixture was stirred at 0 °C for 1 h. The reaction was terminated by the addition of 1 N HCl solution (1 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed successively with aqueous saturated $NaHCO_3$ solution and brine, dried over Na_2SO_4, and concentrated *in vacuo* to give a crude oil, ^{1}H NMR analysis of which revealed that *tert*-butyl 2-(*tert*-butyl)-5-hexyl-3,4-tridecadien-6-ynoate (**3**) was not formed.

Control experiment for 1 → 3. The reaction in the presence of a radical scavenger.



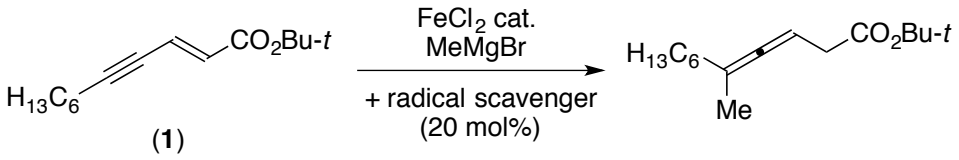
With galvinoxyl

To a suspension of *tert*-butyl (*E*)-2-undecen-4-ynoate (**1**) (23.6 mg, 0.100 mmol), 1-bromo-1-octyne (**2**) (37.8 mg, 0.200 mmol), $FeCl_2$ (12.7 mg, 0.100 mmol), and galvinoxyl (8.4 mg, 0.020 mmol) in 0.5 mL of THF was added *tert*-butylmagnesium chloride (0.290 mL, 1.03 M solution in THF, 0.299 mmol) at –78 ºC under argon. After the solution was slowly warmed to 0 ºC over 3 h, the reaction was terminated by the addition of 1 N HCl solution (1 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed successively with aqueous saturated $NaHCO_3$ solution and brine, dried over Na_2SO_4, and concentrated *in vacuo* to give a crude oil, ^{1}H NMR analysis of which revealed that the yields of *tert*-butyl 2-(*tert*-butyl)-5-hexyl-3,4-tridecadien-6-ynoate (**3**) and recovered starting material **1** were 34% and 55%, respectively, by using trichloroethylene as an internal standard.

With TEMPO

To a suspension of *tert*-butyl (*E*)-2-undecen-4-ynoate (**1**) (23.6 mg, 0.100 mmol), 1-bromo-1-octyne (**2**) (37.8 mg, 0.200 mmol), $FeCl_2$ (12.7 mg, 0.100 mmol), and TEMPO (3.1 mg, 0.020 mmol) in 1 mL of THF was added *tert*-butylmagnesium chloride (0.290 mL, 1.03 M solution in THF, 0.299 mmol) at –78 ºC under argon. After the solution was slowly warmed to 0 ºC over 3 h, the reaction was terminated by the addition of 1 N HCl solution (1 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed successively with aqueous saturated $NaHCO_3$ solution and brine, dried over Na_2SO_4, and concentrated *in vacuo* to give a crude oil, ^{1}H NMR analysis of which revealed that the yields of *tert*-butyl 2-(*tert*-butyl)-5-hexyl-3,4-tridecadien-6-ynoate (**3**) and recovered starting material **1** were 24% and 37%, respectively, by using trichloroethylene as an internal standard.

Control experiment. Normal 1,6-addition of MeMgBr in the presence of a radical scavenger.



With galvinoxyl

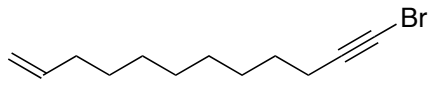
To a suspension of *tert*-butyl (*E*)-2-undecen-4-ynoate (**1**) (23.6 mg, 0.100 mmol), $FeCl_2$ (1.3 mg, 0.010 mmol), and galvinoxyl (8.4 mg, 0.020 mmol) in 1 mL of THF was added methylmagnesium bromide (0.200 mL, 0.99 M solution in THF, 0.198 mmol) at –78 ºC under argon. After the solution was slowly warmed to 0 ºC over 4.5 h, the reaction was terminated by the addition of 1 N HCl solution (1 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed successively with aqueous saturated $NaHCO_3$ solution and brine, dried over Na_2SO_4, and concentrated *in vacuo* to give a crude oil, ^{1}H NMR analysis of which revealed that the yields of *tert*-butyl 5-methyl-3,4-undecadienoate and recovered starting material **1** were 33% and 11%, respectively, by using trichloroethylene as an internal standard.

With TEMPO

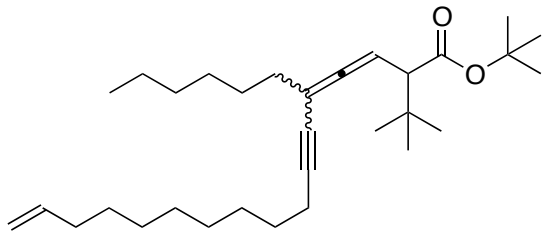
To a suspension of *tert*-butyl (*E*)-2-undecen-4-ynoate (**1**) (23.6 mg, 0.100 mmol), $FeCl_2$ (1.3 mg, 0.010 mmol), and TEMPO (3.1 mg, 0.020 mmol) in 1 mL of THF was added methylmagnesium bromide (0.200 mL, 0.99 M solution in THF, 0.198 mmol) at –78 ºC under argon. After the solution was slowly warmed to 0 ºC over 4.5 h, the reaction was terminated by the addition of 1 N HCl solution (1 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed successively with aqueous saturated $NaHCO_3$ solution and brine, dried over Na_2SO_4, and concentrated *in vacuo* to give a crude oil, ^{1}H NMR analysis of which revealed that the yields of *tert*-butyl 5-methyl-3,4-undecadienoate and recovered starting material **1** were 0% and 93%, respectively, by using trichloroethylene as an internal standard.

1-Bromo-11-dodecen-1-yne. This is a known compound and was prepared by a literature method

[Yamagishi, M.; Nishigai, K.; Hata, T.; Urabe, H. *Org. Lett.* **2011**, *13*, 4873-4875].



***tert*-Butyl 2-(*tert*-butyl)-5-hexyl-3,4,16-heptadecatrien-6-ynoate (11).**



To a suspension of *tert*-butyl (*E*)-2-undecen-4-ynoate (**1**) (47.3 mg, 0.200 mmol), 1-bromo-11-dodecen-1-yne (91.7 mg, 0.400 mmol), and $FeCl_2$ (25.4 mg, 0.200 mmol) in 1 mL of THF was added *tert*-butylmagnesium chloride (0.590 mL, 1.02 M solution in THF, 0.602 mmol) at –78 ºC under argon. After the solution was slowly warmed to 0 ºC over 3 h, the reaction was terminated by the addition of 1 N HCl solution (1 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed successively with aqueous saturated $NaHCO_3$ solution and brine, dried over Na_2SO_4, and concentrated *in vacuo* to give a crude oil, ^{1}H NMR analysis of which revealed that other regioisomers were absent and that the diastereoselectivity of the product was 58:42. The crude product was chromatographed on silica gel (hexane-ethyl acetate) to afford the title compound (60.0 mg, 66%) as an oil and of the same diastereomeric composition observed for a crude sample.

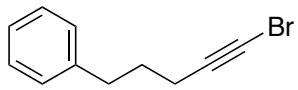
^{1}H NMR δ 0.88 (t, *J* = 7.2 Hz, 3H, alkyl-Me), 0.99 (s, 9H × 0.42, -C(C$\underline{H}_3$)$_3$), 1.01 (s, 9H × 0.58, -C(C$\underline{H}_3$)$_3$), 1.22-1.55 (m, 20H, alkyl H), 1.457 (s, 9H × 0.58, -CO_2C(C$\underline{H}_3$)$_3$), 1.462 (s, 9H × 0.42, -CO_2C(C$\underline{H}_3$)$_3$), 2.00-2.10 (m, 4H, -C$\underline{H}_2$C$_5$H$_{11}$ and -C$\underline{H}_2$CH=CH$_2$), 2.29 (dt, *J* = 1.2, 7.2 Hz, 2H × 0.58, -C≡CC$\underline{H}_2$-), 2.30 (dt, *J* = 1.2, 7.2 Hz, 2H × 0.42, -C≡CC$\underline{H}_2$-), 2.68 (d, *J* = 10.0 Hz, 1H × 0.58, -C$\underline{H}$CO$_2$Bu-*t*), 2.71 (d, *J* = 10.0 Hz, 1H × 0.42, -C$\underline{H}$CO$_2$Bu-*t*), 4.93 (tdd, *J* = 1.2, 2.0, 10.4 Hz, 1H, -CH=C$\underline{H}_2$), 4.99 (tdd, *J* = 1.6, 2.0, 17.2 Hz, 1H, -CH=C$\underline{H}_2$), 5.38 (dm, *J* = 10.0 Hz, 1H, C$_6$H$_{13}$C=C=C$\underline{H}$-), 5.81 (tdd, *J* = 6.8, 10.4, 17.2 Hz, 1H, -C$\underline{H}$=CH$_2$).

^{13}C NMR δ 14.06, [19.50 (major), 19.58 (minor)], 22.60, [27.58 (3 carbons, -C(C$\underline{H}_3$)$_3$, major), 27.67 (minor)], 28.10 (3 carbons, -C(C$\underline{H}_3$)$_3$), [28.57 (major), 28.63 (minor)], 28.77, [28.81 (major), 28.85 (minor)], 28.93, 29.09 (2 peaks), 29.38, 31.64, 33.79 (2 peaks), 33.99, [34.31(major), 34.41 (minor)], [57.43 (minor), 57.62 (major)], [75.75 (C≡C, minor), 75.90 (major)], [80.45 (major), 80.52 (minor)], [88.86 (C=C=C, minor), 89.32 (major)], [90.50 (minor), 90.67 (major)], [92.13 (major), 92.40 (minor)], [114.08 (C=C, minor), 114.11 (major)], 139.18 (C=C), [171.86 (C=O, minor), 172.09 (major)], [209.50 (C=C=C, minor), 209.62 (major)]. A pair of diastereomeric peaks are shown in square brackets.

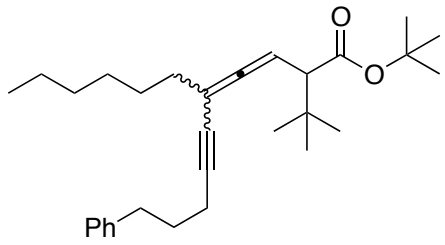
IR (neat) 3077, 2957, 2928, 2856, 2219 (C≡C), 1952 (C=C=C), 1726 (C=O), 1641, 1466, 1367, 1255, 1141, 993, 909, 848, 761 cm^{-1} for a 58:42 mixture of diastereoisomers.

HRMS (ESI) Calcd for $C_{31}H_{52}O_2Na$ $[M+Na]^+$: 479.3860. Found: 479.3848 for a 58:42 mixture of diastereoisomers.

1-Bromo-5-phenyl-1-pentyne. This is a known compound and was prepared by a literature method [Yamagishi, M.; Nishigai, K.; Hata, T.; Urabe, H. *Org. Lett.* **2011**, *13*, 4873-4875].



***tert*-Butyl 2-(*tert*-butyl)-5-hexyl-10-phenyl-3,4-decadien-6-ynoate (12).**



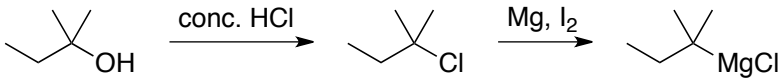
To a suspension of *tert*-butyl (*E*)-2-undecen-4-ynoate (**1**) (47.3 mg, 0.200 mmol), 1-bromo-5-phenyl-1-pentyne (89.2 mg, 0.400 mmol), and $FeCl_2$ (25.4 mg, 0.200 mmol) in 1 mL of THF was added *tert*-butylmagnesium chloride (0.590 mL, 1.02 M solution in THF, 0.602 mmol) at –78 ºC under argon. After the solution was slowly warmed to 0 ºC over 3 h, the reaction was terminated by the addition of 1 N HCl solution (1 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed successively with aqueous saturated $NaHCO_3$ solution and brine, dried over Na_2SO_4, and concentrated *in vacuo* to give a crude oil, ^{1}H NMR analysis of which revealed that other regioisomers were absent and that the diastereoselectivity of the product was 57:43. The crude product was chromatographed on silica gel (hexane-ethyl acetate) to afford the title compound (64.5 mg, 74%) as an oil and of the same diastereomeric composition observed for a crude sample.

^{1}H NMR δ 0.88 (t, *J* = 6.8 Hz, 3H, alkyl-Me), 1.00 (s, 9H × 0.43, -C(C$\underline{H}_3$)$_3$), 1.01 (s, 9H × 0.57, -C(C$\underline{H}_3$)$_3$), 1.21-1.54 (m, 8H, alkyl H), 1.45 (s, 9H × 0.43, -CO_2C(C$\underline{H}_3$)$_3$), 1.46 (s, 9H × 0.57, -CO_2C(C$\underline{H}_3$)$_3$), 1.82 (quintet, *J* = 6.8 Hz, 2H, -C$\underline{H}_2$$CH_2$Ph), 2.09 (dt, *J* = 2.8, 7.6 Hz, 2H, C_5H_{11}C$\underline{H}_2$-), 2.315 (dt, *J* = 0.8, 6.8 Hz, 2H × 0.57, -C$\underline{H}_2$(CH_2)$_2$Ph), 2.322 (dt, *J* = 0.8, 6.8 Hz, 2H × 0.43, -C$\underline{H}_2$(CH_2)$_2$Ph), 2.70 (d, *J* = 10.0 Hz, 1H × 0.57, -C$\underline{H}$$CO_2$Bu-*t*), 2.72 (t, *J* = 6.8 Hz, 2H, -C$\underline{H}_2$Ph), 2.73 (d, *J* = 10.0 Hz, 1H × 0.43, -C$\underline{H}$$CO_2$Bu-*t*), 5.41 (dm, *J* = 10.0 Hz, 1H, C_6H_{13}C=C=C$\underline{H}$-), 7.12-7.31 (m, 5H, Ar-H).

^{13}C NMR δ 14.06, 18.93, 22.60, 27.59 (3 carbons, -C(C$\underline{H}_3$)$_3$), 27.67, 28.10 (3 carbons, -C(C$\underline{H}_3$)$_3$), [28.58 (major), 28.64 (minor)], [30.38 (minor), 30.43 (major)], 31.64, [33.79 (major), 34.02 (minor)], [34.34 (major), 34.39 (minor)], [34.69 (major), 34.78 (minor)], [57.43 (minor), 57.62 (major)], 76.68 (C≡C), [80.49 (major), 80.55 (minor)], 89.41 (C=C=C), 90.57, 91.49, 125.83 (Ph), 128.31 (2 carbons, Ph), 128.53 (2 carbons, Ph), 141.73 (Ph), 172.08 (C=O), [209.55 (C=C=C, minor), 209.63 (major)].

A pair of diastereomeric peaks are shown in square brackets.
IR (neat) 3086 (Ar), 3063 (Ar), 3027 (Ar), 2958, 2931, 2871, 2215 (C≡C), 1952 (C=C=C), 1725 (C=O), 1456, 1368, 1255, 1143, 1032, 848, 747, 700 cm^{-1} for a 57:43 mixture of diastereoisomers.
HRMS (ESI) Calcd for $C_{30}H_{44}O_4Na$ $[M+Na]^+$: 459.3234. Found: 459.3226 for a 57:43 mixture of diastereoisomers.

Preparation of *tert*-amylmagnesium chloride. This was prepared according the following scheme [(a) Reetz, M. T.; Chatziiosifidis, I.; Hübner, F.; Heimbach, H. *Org. Synth. Coll.* **1990**, *7*, 424. (b) Norris, J. F.; Olmsted, A. W. *Org. Synth. Coll.* **1941**, *1*, 144. (c) Puntambeker, S. V.; Zoellner, E.A. *Org. Synth. Coll.* **1941**, *1*, 524. (d) Whitmore, F. C.; Badertscher, D. E. *J. Am. Chem. Soc.* **1933**, *55*, 1559-1567].

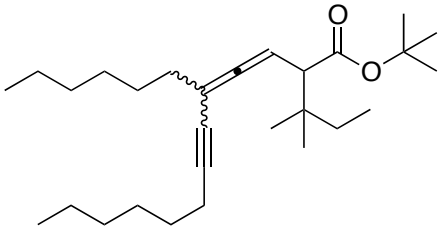


A mixture of 2-methyl-2-butanol (5.3 mL, 49.0 mmol) and concentrated HCl (25 mL) was stirred vigorously at room temperature for 10 min. The organic layer was separated, washed with cold water several times, dried over $CaCl_2$, and distilled at an atmospheric pressure to afford 2-chloro-2-methylbutane (3.65 g, 70%, bp 85 °C).
To a suspension of magnesium turnings (534 mg, 22.0 mmol) and iodine (*ca.* 5 mg) in 1 mL of THF was added 2-chloro-2-methylbutane (0.860 mL, 6.98 mmol) at room temperature under argon. The suspension was stirred in an oil bath maintained at 50 °C until the reaction started. Then, a solution of 2-chloro-2-methylbutane (1.60 mL, 13.00 mmol) in 7 mL of THF was slowly added to the above mixture warmed in an oil bath maintained at 50 °C. After the addition was completed, the mixture was warmed in an oil bath maintained at 60 °C. After stirring at 60 °C for 3 h, the solution was cooled to room temperature. The resulting THF solution of *tert*-amylmagnesium chloride was titrated as shown below to indicate its concentration being 1.00 M.

Titration

A 0.300-mL aliquot of the Grignard solution was quenched with an exactly known, excess volume of a 1.002 M HCl solution (purchased from Yoneyama Chemical, Inc. (Japan)) and the mixture was then back-titrated with a 0.5005 M NaOH solution (purchased from Yoneyama Yakuhin Kogyo, Co., Ltd. (Japan)) with methyl orange as an indicator, determining its concentration to be 1.00 M.

***tert*-Butyl 2-(*tert*-amyl)-5-hexyl-3,4-tridecadien-6-ynoate (13).**



To a suspension of *tert*-butyl (*E*)-2-undecen-4-ynoate (**1**) (47.3 mg, 0.200 mmol), 1-bromo-1-octyne (75.6 mg, 0.400 mmol), and $FeCl_2$ (25.4 mg, 0.200 mmol) in 1 mL of THF was added *tert*-amylmagnesium chloride (0.600 mL, 1.00 M solution in THF, 0.600 mmol) at –78 ºC under argon. After the solution was slowly warmed to 0 ºC over 3 h, the reaction was terminated by the addition of 1 N HCl solution (1 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed successively with aqueous saturated $NaHCO_3$ solution and brine, dried over Na_2SO_4, and concentrated *in vacuo* to give a crude oil, ^{1}H NMR analysis of which revealed that other regioisomers were absent and that the diastereoselectivity of the product was 54:46. The crude product was chromatographed on silica gel (hexane-ethyl acetate) to afford the title compound (53.2 mg, 64%) as an oil and of the same diastereomeric composition observed for a crude sample.

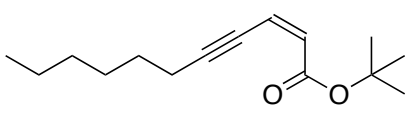
^{1}H NMR δ 0.81-0.92 (m, 9H, alkyl-Me and -$CMe_2CH_2C\underline{H}_3$), 0.93 (s, 3H × 0.46, -$C(C\underline{H}_3)_2Et$), 0.95 (s, 6H × 0.54, -$C(C\underline{H}_3)_2Et$), 0.96 (s, 3H × 0.46, -$C(C\underline{H}_3)_2Et$), 1.20-1.56 (m, 18H, alkyl H and -$CMe_2C\underline{H}_2CH_3$), 1.46 (s, 9H, -$CO_2C(C\underline{H}_3)_3$), 2.06 (dt, *J* = 2.8, 7.2 Hz, 2H, $C_5H_{11}C\underline{H}_2$-), 2.30 (dt, *J* = 2.8, 7.2 Hz, 2H, -$C{\equiv}CC\underline{H}_2C_5H_{11}$), 2.79 (d, *J* = 10.0 Hz, 1H × 0.54, -$C\underline{H}CO_2$Bu-*t*), 2.82 (d, *J* = 10.0 Hz, 1H × 0.46, -$C\underline{H}CO_2$Bu-*t*), 5.38 (dm, *J* = 10.0 Hz, 1H, $C_6H_{13}C{=}C{=}C\underline{H}$-).

^{13}C NMR δ [8.10 (minor), 8.14 (major)], 14.04, 14.06, [19.50 (minor), 19.58 (major)], [22.54 (minor), 22.56 (major)], 22.59, 24.04, [24.11 (major), 24.21(minor)], [27.53 (minor), 27.89 (major)], 28.08 (3 carbons, -$C(\underline{C}H_3)_3$), [28.46 (minor), 28.53 (major)], [28.56 (minor), 28.66 (major)], [28.74 (major), 28.78 (minor)], [31.34 (major), 31.35 (minor)], [31.63 (minor), 31.65 (major)], [33.12 (major), 33.72 (minor)], 34.38, [36.64 (major), 36.91 (minor)], [55.20 (major), 55.42 (minor)], [75.70 (C≡C, major), 75.81 (minor)], [80.42 (minor), 80.51 (major)], [88.67 ($\underline{C}$=C=C, major), 89.14 (minor)], [90.39 (major), 90.57 (minor)], [92.11 (major), 92.42 (minor)], [171.19 (C=O, minor), 171.94 (major)], [209.36 (C=$\underline{C}$=C, major), 209.49 (minor)]. A pair of diastereomeric peaks are shown in square brackets.

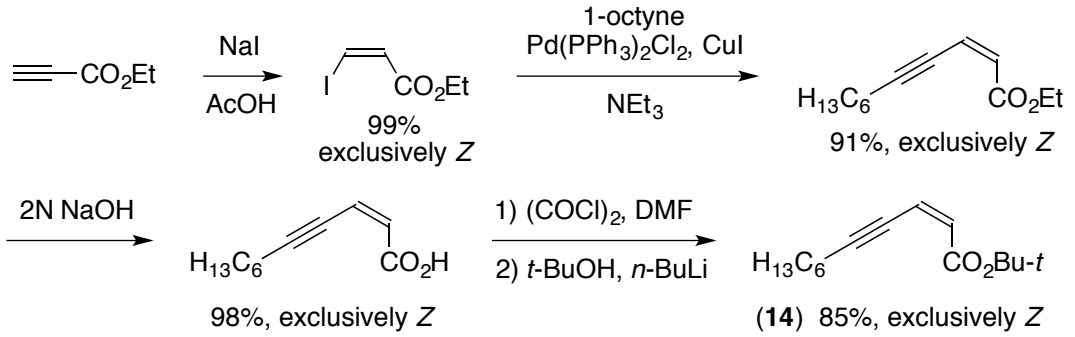
IR (neat) 2960, 2930, 2859, 2215 (C≡C), 1951 (C=C=C), 1725 (C=O), 1466, 1368, 1254, 1140, 916, 847, 734 cm^{-1} for a 54:46 mixture of diastereoisomers.

HRMS (ESI) Calcd for $C_{28}H_{48}O_2Na$ $[M+Na]^+$: 439.3547. Found: 425.3547 for a 54:46 mixture of diastereoisomers.

tert-Butyl (*Z*)-2-undecen-4-ynoate (14).



This was prepared according to the following scheme [(a) Piers, E.; Wong, T.; Coish, P. D.; Rogers, C. *Can. J. Chem.* **1994**, *72*, 1816-1819. (b) Rubina, M.; Conley, M.; Gevorgyan, V. *J. Am. Chem. Soc.* **2006**, *128*, 5818-5827].



To a suspension of sodium iodide (2.40 g, 16.0 mmol) in AcOH (3.70 mL, 64.6 mmol) was added ethyl propiolate (1.01 mL, 9.97 mmol) under argon. After the reaction mixture was stirred in an oil bath maintained at 115 °C for 1.5 h, it was cooled to room temperature and the reaction was terminated by the addition of water. The organic products were extracted with Et_2O. The combined organic layers were washed successively with aqueous saturated $NaHCO_3$ solution, aqueous saturated $Na_2S_2O_3$ solution, and brine, dried over Na_2SO_4, and concentrated *in vacuo* to afford ethyl (*Z*)-3-iodoacrylate (2.24 g, 99%, exclusively *Z*), which was directly used in the next step.

To a suspension of $Pd(PPh_3)_2Cl_2$ (70.2 mg, 0.100 mmol) and CuI (38.1 mg, 0.200 mmol) in triethylamine (15 mL) was added ethyl (*Z*)-3-iodoacrylate (2.24 g, 9.91 mmol) in triethylamine (5 mL), followed by 1-octyne (1.42 mL, 10.0 mmol), under argon. After the mixture was stirred for 12 h at room temperature, it was quenched with aqueous saturated NH_4Cl solution. The organic products were extracted with ethyl acetate. The combined organic layers were washed successively with 1 N HCl, water, and brine, dried over Na_2SO_4, and concentrated *in vacuo* to a crude oil, which was chromatographed on silica gel (hexane-ethyl acetate) to afford ethyl (*Z*)-2-undecen-4-ynoate (1.88 g, 91%, exclusively *Z*) as an oil.

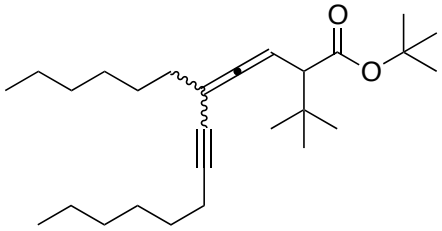
A mixture of ethyl (*Z*)-2-undecen-4-ynoate (1.88 g, 9.03 mmol) and aqueous 2 N NaOH solution (10 mL) was refluxed for 1.5 h without a co-solvent. The reaction mixture was cooled to room temperature, diluted with ethyl acetate, and acidified with 1 N HCl. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo* to give a crude oil, which was chromatographed on silica gel (hexane-ethyl acetate) to afford (*Z*)-2-undecen-4-ynoic acid (1.60 g, 98%, exclusively *Z*) as an oil.

To a stirred solution of the above (*Z*)-2-undecen-4-ynoic acid (901 mg, 5.00 mmol) in CH_2Cl_2 (20 mL) were successively added DMF (1 drop) and oxalyl chloride (0.860 mL, 10.0 mmol) at room temperature. After the mixture was stirred for 2 h, the solvent and the excess oxalyl chloride were removed *in vacuo* to afford the desired (*Z*)-2-undecen-4-ynoyl chloride as a crude oil, which was directly used in the next step.

To a solution of *t*-BuOH (0.480 mL, 5.02 mmol) in THF (10 mL) was added BuLi (1.60 M in hexane, 3.15 mL, 5.04 mmol) at 0 °C under argon. After the mixture was stirred at room temperature for 1 h, the above (*Z*)-2-undecen-4-ynoyl chloride (*ca*. 990 mg, 4.98 mmol) in THF (5 mL) was added at 0 °C. After stirring at room temperature for 1.5 h, the reaction was quenched with water. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo* to give a crude oil, which was chromatographed on silica gel (hexane-ethyl acetate) to afford the title compound (999 mg, 85%

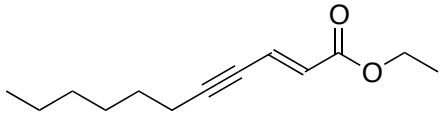
overall yield from the carboxylic acid, exclusively *Z*) as an oil.
^{1}H NMR δ 0.89 (t, *J* = 6.8 Hz, 3H, alkyl-Me), 1.22-1.63 (m, 8H, alkyl H), 1.50 (s, 9H, -C(C$\underline{H}_3$)$_3$), 2.43 (dt, *J* = 2.4, 7.2 Hz, 2H, $C_5H_{11}C\underline{H}_2C{\equiv}C$-), 5.93 (d, *J* = 11.6 Hz, 1H, -CH=C$\underline{H}CO_2$Bu-*t*), 6.07 (td, *J* = 2.4, 11.6 Hz, 1H, -C$\underline{H}$=CHCO$_2$Bu-*t*).
^{13}C NMR δ 14.00, 20.08, 22.50, 28.13 (3 carbons, -C($\underline{C}H_3$)$_3$), 28.38, 28.61, 31.32, 77.71, 80.52 (C≡C), 103.35 (C≡C), 122.53 (C=C), 129.27 (C=C), 164.21 (C=O).
IR (neat) 3004 (C=C-H), 2957, 2859, 2208 (C≡C), 1722 (C=O), 1607 (C=C), 1457, 1367, 1303, 1152, 967, 819 cm^{-1}.
HRMS (ESI) Calcd for $C_{15}H_{24}O_2Na$ [M+Na]$^+$: 259.1669. Found: 259.1666.

***tert*-Butyl 2-(*tert*-butyl)-5-hexyl-3,4-tridecadien-6-ynoate (3) from *tert*-butyl (*Z*)-2-undecen-4-ynoate (14).**

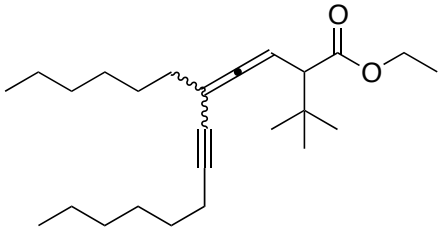


To a suspension of *tert*-butyl (*Z*)-2-undecen-4-ynoate (**14**) (47.3 mg, 0.200 mmol), 1-bromo-1-octyne (**2**) (75.6 mg, 0.400 mmol), and $FeCl_2$ (25.4 mg, 0.200 mmol) in 1 mL of THF was added *tert*-butylmagnesium chloride (0.780 mL, 1.03 M solution in THF, 0.803 mmol) at –78 ºC under argon. After the solution was slowly warmed to 0 ºC over 3 h, the reaction was terminated by the addition of 1 N HCl solution (1 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed successively with aqueous saturated $NaHCO_3$ solution and brine, dried over Na_2SO_4, and concentrated *in vacuo* to give a crude oil, ^{1}H NMR analysis of which revealed that other regioisomers were absent and that the diastereoselectivity of the product was 58:42. The crude product was chromatographed on silica gel (hexane-ethyl acetate) to afford the title compound (52.0 mg, 65%) as an oil and of the same diastereomeric composition observed for a crude sample.
For the spectroscopic data, see: *tert*-butyl 2-(*tert*-butyl)-5-hexyl-3,4-tridecadien-6-ynoate (**3**) from *tert*-butyl (*E*)-2-undecen-4-ynoate (**1**).

Ethyl (*E*)-2-undecen-4-ynoate (15). This is a known compound [Hata, T.; Iwata, S.; Seto, S.; Urabe, H. *Adv. Synth. Catal.* **2012**, *354*, 1885-1889]. The olefin is exclusively *E*.



Ethyl 2-(*tert*-butyl)-5-hexyl-3,4-tridecadien-6-ynoate (16)



To a suspension of ethyl (*E*)-2-undecen-4-ynoate (**15**) (41.7 mg, 0.200 mmol), 1-bromo-1-octyne (**2**) (75.6 mg, 0.400 mmol), and $FeCl_2$ (25.4 mg, 0.200 mmol) in 1 mL of THF was added *tert*-butylmagnesium chloride (0.580 mL, 1.03 M solution in THF, 0.597 mmol) at –78 ºC under argon. After the solution was slowly warmed to 0 ºC over 3 h, the reaction was terminated by the addition of 1 N HCl solution (1 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with aqueous saturated $NaHCO_3$ solution and brine, dried over Na_2SO_4, and concentrated *in vacuo* to give a crude oil, ^{1}H NMR analysis of which revealed that other regioisomers were absent and that the diastereoselectivity of the product was 52:48. The crude product was chromatographed on silica gel (hexane-ethyl acetate) to afford the title compound (46.5 mg, 62%) as an oil and of the same diastereomeric composition observed for a crude sample.

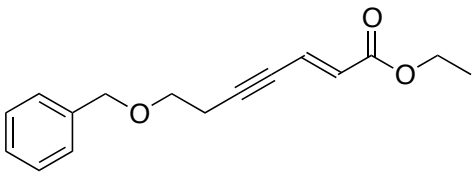
^{1}H NMR δ 0.84-0.93 (m, 6H, alkyl-Me), 0.99 (s, 9H × 0.52, -C(C$\underline{H}_3$)$_3$), 1.01 (s, 9H × 0.48, -C(C$\underline{H}_3$)$_3$), 1.20-1.56 (m, 19H, alkyl H and –$CO_2CH_2C\underline{H}_3$), 2.07 (m, 2H, $C_5H_{11}C\underline{H}_2$-), 2.30 (t, *J* = 6.4 Hz, 2H, -C≡C$C\underline{H}_2C_5H_{11}$), 2.79 (d, *J* = 10.0 Hz, 1H × 0.48, -C$\underline{H}CO_2$Et), 2.82 (d, *J* = 10.0 Hz, 1H × 0.52, -C$\underline{H}CO_2$Et), 4.14 (q, *J* = 7.2 Hz, 2H, -$CO_2C\underline{H}_2CH_3$), 5.41 (dm, *J* = 10.0 Hz, 1H, C_6H_{13}C=C=C$\underline{H}$-).

^{13}C NMR δ 14.02, 14.05, [14.22 (major), 14.24 (minor)], [19.48 (major), 19.56 (minor)], 22.57, 22.63, [27.51 (3 carbons, -C($\underline{C}H_3$)$_3$, minor), 27.59 (major)], 27.89, 28.43, [28.52 (major), 28.60 (minor)], [28.70 (major), 28.74 (minor)], [31.32 (major), 31.33 (minor)], [31.57 (minor), 31.63 (major)], [33.72 (minor), 34.10 (major)], 34.43, [56.60 (major), 56.74 (minor)], 60.21, [75.45 (major, C≡C), 75.67 (minor)], [88.48 (major, $\underline{C}$=C=C), 88.89 (minor)], [90.63 (major), 90.85 (minor)], [92.33 (minor), 92.68 (major)], [171.86 (C=O, minor), 172.63 (major)], [209.50 (C=$\underline{C}$=C, major), 209.70 (minor)]. A pair of diastereomeric peaks are shown in square brackets.

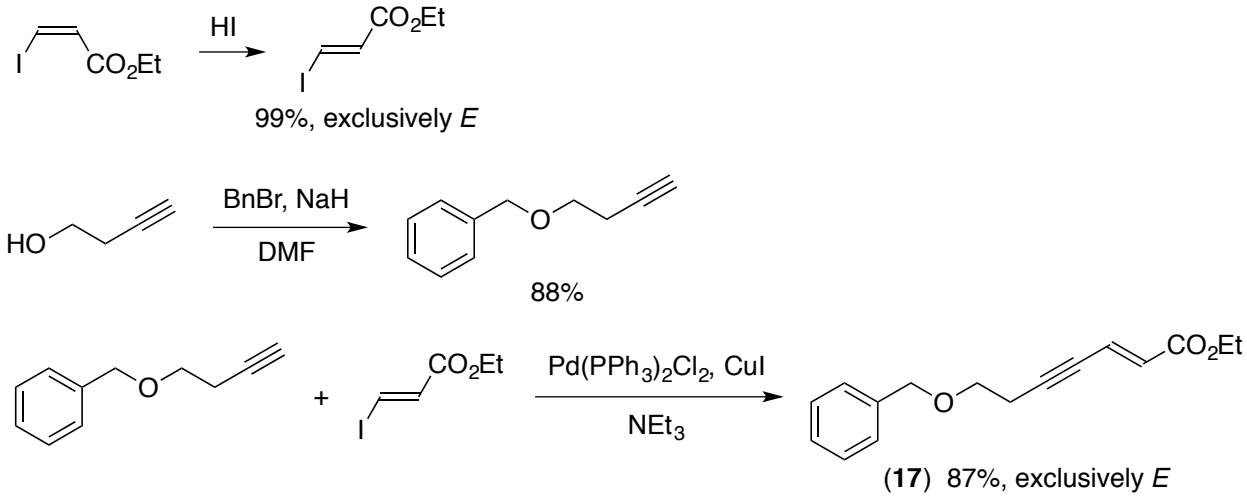
IR (neat) 2956, 2928, 2858, 2221 (C≡C), 1951 (C=C=C), 1738 (C=O), 1466, 1366, 1331, 1200, 1144, 1046, 965, 869, 726 cm^{-1} for a 52:48 mixture of diastereoisomers.

HRMS (ESI) Calcd for $C_{25}H_{42}O_2Na$ $[M+Na]^+$: 397.3077. Found: 397.3077 for a 52:48 mixture of diastereoisomers.

Ethyl (*E*)-7-benzyloxy-2-hepten-4-ynoate (17)



This was prepared according to the following scheme [(a) Zhang, W.; Xu, H.; Xu, H.; Tang, W. *J. Am. Chem. Soc.* **2009**, *131*, 3832-3833. (b) Rubina, M.; Conley, M.; Gevorgyan, V. *J. Am. Chem. Soc.* **2006**, *128*, 5818-5827].



The preparation of ethyl (*Z*)-3-iodoacrylate was already described in that of *tert*-butyl (*Z*)-2-undecen-4-ynoate (**14**).

To a solution of ethyl (*Z*)-3-iodoacrylate (2.26 g, 10.0 mmol) in toluene (2 mL) was added 57% hydroiodic acid (0.170 mL, 0.10 mmol). The mixture was stirred in an oil bath maintained at 80 °C for 8 h. After being cooled to room temperature, the reaction was terminated by the addition of aqueous saturated $NaHCO_3$ solution. The organic layer was separated and the aqueous layer was extracted with Et_2O. The combined organic layers were washed with aqueous saturated $Na_2S_2O_3$ solution and brine, dried over Na_2SO_4, and concentrated *in vacuo* to afford ethyl (*E*)-3-iodoacrylate (2.22 g, 98%, exclusively *E*), which was directly used in the next step.

To a solution of 3-butyn-1-ol (0.760 mL, 10.0 mmol) in DMF (10 mL) was added NaH (0.440 g of a 60% suspension in mineral oil, 11.0 mmol) at 0 °C under argon. After the mixture was stirred at 0 °C for 30 min, benzyl bromide (1.20 mL, 10.0 mmol) was added. After stirring at room temperature for 2 h, the reaction was quenched by the addition of water. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo* to give a crude oil, which was chromatographed on silica gel (hexane-ethyl acetate) to afford 4-benzyloxy-1-butyne (1.40 g, 88%) as an oil.

To a suspension of $Pd(PPh_3)_2Cl_2$ (14.0 mg, 0.020 mmol) and CuI (7.6 mg, 0.040 mmol) in NEt_3 (2 mL) were added ethyl (*E*)-3-iodoacrylate (452 mg, 2.00 mmol) and 4-benzyloxy-1-butyne (320 mg, 2.00 mmol) in NEt_3 (2 mL) at room temperature under argon. After the mixture was stirred for 12 h, the reaction was quenched by the addition of aqueous saturated NH_4Cl solution. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed successively with 1 N HCl, aqueous saturated $NaHCO_3$ solution, and brine, dried over Na_2SO_4, and concentrated *in vacuo* to give a crude oil, which was chromatographed on silica gel (hexane-ethyl acetate) to afford the title compound (449 mg, 87%, exclusively *E*) as an oil.

^{1}H NMR δ 1.29 (t, *J* = 6.8 Hz, 3H, -$CO_2CH_2C\underline{H}_3$), 2.69 (dt, *J* = 2.4, 6.8 Hz, 2H, Bn$OCH_2C\underline{H}_2$-), 3.62 (t, *J* = 6.8 Hz, 2H, Bn$OC\underline{H}_2CH_2$-), 4.21 (q, *J* = 6.8 Hz, 2H, -$CO_2C\underline{H}_2CH_3$), 4.57 (s, 2H, Ph$C\underline{H}_2$O-), 6.16 (d,

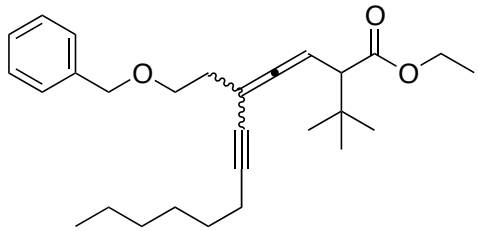
J = 15.6 Hz, 1H, -CH=C<u>H</u>CO$_2$Et), 6.75 (td, *J* = 2.4, 15.6 Hz, 1H, -C<u>H</u>=CHCO$_2$Et), 7.26-7.39 (m, 5H, Ph-H).

^{13}C NMR δ 14.20, 21.20, 60.65, 67.82, 73.03, 78.71 (C≡C), 96.98 (C≡C), 125.64, 127.70 (2 carbons, Ph), 127.75, 128.44 (2 carbons, Ph), 129.86, 137.89, 166.03 (C=O).

IR (neat) 3088 (Ar), 3064 (Ar), 3031 (Ar), 2980, 2934, 2906, 2865, 2219 (C≡C), 1714 (C=O), 1621 (C=C), 1454, 1366, 1304, 1268, 1158, 1101, 1031, 962, 862, 738 cm^{-1}.

HRMS (ESI) Calcd for $C_{16}H_{18}O_3Na$ [M+Na]$^+$: 281.1148. Found: 281.1142.

Ethyl 5-(2-benzyloxyethyl)-2-(*tert*-butyl)-3,4-tridecadien-6-ynoate (18).



To a suspension of ethyl (*E*)-7-benzyloxy-2-hepten-4-ynoate (**17**) (51.7 mg, 0.200 mmol), 1-bromo-1-octyne (**2**) (75.6 mg, 0.400 mmol), and $FeCl_2$ (25.4 mg, 0.200 mmol) in 1 mL of THF was added *tert*-butylmagnesium chloride (0.590 mL, 1.02 M solution in THF, 0.602 mmol) at –78 ºC under argon. After the solution was slowly warmed to 0 ºC over 3 h, the reaction was terminated by the addition of 1 N HCl solution (1 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed successively with aqueous saturated $NaHCO_3$ solution and brine, dried over Na_2SO_4, and concentrated *in vacuo* to give a crude oil, ^{1}H NMR analysis of which revealed that other regioisomers were absent and that the diastereoselectivity of the product was 51:49. The crude product was chromatographed on silica gel (hexane-ethyl acetate) to afford the title compound (51.5 mg, 61%) as an oil and of the same diastereomeric composition observed for a crude sample.

^{1}H NMR δ 0.89 (t, *J* = 7.2 Hz, 3H, alkyl-Me), 0.96 (s, 9H × 0.51, -C(C<u>H</u>$_3$)$_3$), 1.00 (s, 9H × 0.49, -C(C<u>H</u>$_3$)$_3$), 1.20-1.42 (m, 6H, alkyl H), 1.27 (t, *J* = 6.0 Hz, 3H, -CO$_2$CH$_2$C<u>H</u>$_3$), 1.49 (m, 2H, alkyl H), 2.28 (t, *J* = 7.2 Hz, 2H, -C<u>H</u>$_2$C$_5$H$_{11}$), 2.40 (m, 2H, BnOCH$_2$C<u>H</u>$_2$-), 2.82 (d, *J* = 10.0 Hz, 1H, -C<u>H</u>CO$_2$Et), 3.61 (t, *J* = 6.8 Hz, 2H × 0.51, BnOC<u>H</u>$_2$CH$_2$-), 3.64 (t, *J* = 6.8 Hz, 2H × 0.49, BnOC<u>H</u>$_2$CH$_2$-), 4.13 (q, *J* = 6.0 Hz, 2H, -CO$_2$C<u>H</u>$_2$CH$_3$), 4.53 (s, 2H, PhC<u>H</u>$_2$O-), 5.46 (m, 1H, C$_6$H$_{13}$C=C=C<u>H</u>-), 7.24-7.37 (m, 5H, Ph-H).

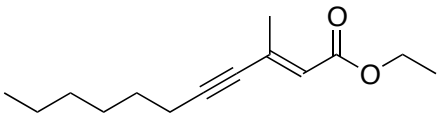
^{13}C NMR δ 14.03, [14.23 (major), 14.26 (minor)], [19.48 (minor), 19.56 (major)], [22.52 (major), 22.53 (minor)], [27.51 (3 carbons, -C(<u>C</u>H$_3$)$_3$, minor), 27.58 (major)], [28.44 (minor), 28.54 (major)], [28.64 (major), 28.68 (minor)], [31.29 (major), 31.32 (minor)], 34.14, [34.53 (minor), 34.76 (major)], [56.45 (major), 56.56 (minor)], 60.25, [68.27 (minor), 68.36 (major)], [72.87 (minor), 72.92 (major)], [74.93 (C≡C, major), 75.15 (minor)], [87.45 (major), 87.78 (minor)], [88.97 (<u>C</u>=C=C, major), 89.35 (minor)], [92.76 (minor), 93.11 (major)], [127.46 (minor), 127.49 (major)], [127.58 (2 carbons, Ph, minor), 127.60 (major)], 128.30 (2 carbons, Ph), [138.41 (major), 138.44 (minor)], [172.51 (C=O, major), 172.72 (minor)], [210.11 (C=<u>C</u>=C, major), 210.16 (minor)]. A pair of diastereomeric peaks

are shown in square brackets.

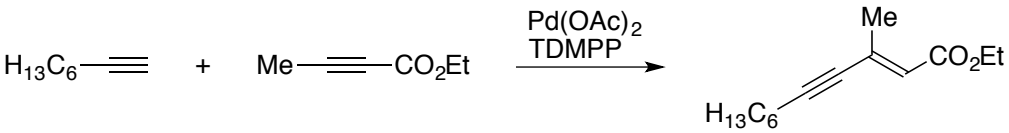
IR (neat) 3088 (Ar), 3064 (Ar), 3030 (Ar), 2958, 2931, 2859, 2220 (C≡C), 1953 (C=C=C), 1730 (C=O), 1455, 1149, 1099, 1028, 912, 855, 736 cm^{-1} for a 51:49 mixture of diastereoisomers.

HRMS (ESI) Calcd for $C_{28}H_{40}O_3Na$ $[M+Na]^+$: 447.2870. Found: 447.2869 for a 51:49 mixture of diastereoisomers.

Ethyl (*E*)-3-methyl-2-undecen-4-ynoate (19). This was prepared by a literature method [Trost, B. M.; Sorum, M. T.; Chan, C.; Harms, A. E.; Rühter, G. *J. Am. Chem. Soc.* **1997**, *119*, 698-708].



This was prepared according to the following scheme.



(**19**) 87%, exclusively *E*

A mixture of $Pd(OAc)_2$ (33.7 mg, 0.150 mmol) and tris(2,6-dimethoxyphenyl)phosphine (66.4 mg, 0.150 mmol) in 10 mL of toluene was stirred at room temperature for 15 min under argon. To the mixture was added a solution of 1-octyne (0.710 mL, 5.01 mmol) and ethyl 2-butynoate (0.580 mL, 4.98 mmol) in 5 mL of toluene. After stirring at room temperature for 18 h, the reaction mixture was concentrated *in vacuo* to give a crude oil, which was chromatographed on silica gel (hexane-ethyl acetate) to afford the title compound (0.970 g, 87%, exclusively *E*) as an oil.

^{1}H NMR δ 0.90 (t, *J* = 7.2 Hz, 3H, alkyl-Me), 1.27 (t, *J* = 7.6 Hz, 3H, $-CO_2CH_2C\underline{H}_3$), 1.24-1.46 (m, 6H, alkyl H), 1.54 (quintet, *J* = 7.2 Hz, 2H, alkyl H), 2.27 (d, *J* = 1.2 Hz, 3H, $-CH=CC\underline{H}_3$), 2.34 (t, *J* = 7.2 Hz, 2H, $C_5H_{11}C\underline{H}_2-$), 4.16 (q, *J* = 7.6 Hz, 2H, $-CO_2C\underline{H}_2CH_3$), 5.98 (q, *J* = 1.2 Hz, 1H, $-C=C\underline{H}CO_2Et$).

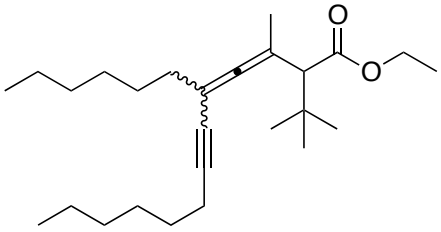
Although NOE experiments cannot be performed to this compound, the stereochemistry of its stereoisomer, ethyl (*Z*)-3-methyl-2-undecen-4-ynoate (**21**), was firmly assigned to *Z* by NOE experiments (see **21**). Accordingly, this compound was then deduced to be *E*, which is consistent with the stereochemical outcome reported in this literature.

^{13}C NMR δ 14.00, 14.26, 19.47, 20.17, 22.50, 28.37, 28.49, 31.26, 59.81, 82.99 (C≡C), 95.80 (C≡C), 123.08 (C=C), 138.85 (C=C), 166.30 (C=O).

IR (neat) 2957, 2932, 2859, 2219 (C≡C), 1715 (C=O), 1616 (C=C), 1466, 1375, 1338, 1257, 1156, 1042, 871, 737 cm^{-1}.

HRMS (ESI) Calcd for $C_{14}H_{22}O_2Na$ $[M+Na]^+$: 245.1512. Found: 245.1517.

Ethyl 2-(*tert*-butyl)-5-hexyl-3-methyl-3,4-tridecadien-6-ynoate (20) from ethyl (*E*)-3-methyl-2-undecen-4-ynoate (19).



To a suspension of ethyl (*E*)-3-methyl-2-undecen-4-ynoate (**19**) (44.5 mg, 0.200 mmol), 1-bromo-1-octyne (**2**) (75.6 mg, 0.400 mmol), and $FeCl_2$ (25.4 mg, 0.200 mmol) in 1 mL of THF was added *tert*-butylmagnesium chloride (0.580 mL, 1.03 M solution in THF, 0.597 mmol) at –78 ºC under argon. After the solution was slowly warmed to 0 ºC over 3 h, the reaction was terminated by the addition of 1 N HCl solution (1 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed successively with aqueous saturated $NaHCO_3$ solution and brine, dried over Na_2SO_4, and concentrated *in vacuo* to give a crude oil, ^{1}H NMR analysis of which revealed that other regioisomers were absent and that the diastereoselectivity of the product was 52:48. The crude product was chromatographed on silica gel (hexane-ethyl acetate) to afford the title compound (60.2 mg, 77%) as an oil and of the same diastereomeric composition observed for a crude sample.

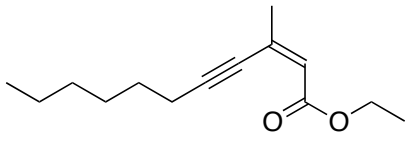
^{1}H NMR δ 0.85-0.92 (m, 6H, alkyl-Me), 1.05 (s, 9H, -C(C$\underline{H}_3$)$_3$), 1.22-1.56 (m, 19H, alkyl H and -$CO_2CH_2C\underline{H}_3$), 1.79 (s, 3H, -C=C=CC$\underline{H}_3$), 2.05 (m, 2H, $C_5H_{11}C\underline{H}_2$-), 2.28 (t, J = 6.8 Hz, 2H × 0.48, -C≡CC$\underline{H}_2C_5H_{11}$), 2.30 (t, J = 6.8 Hz, 2H × 0.52, -C≡CC$\underline{H}_2C_5H_{11}$), 2.66 (s, 1H × 0.52, -C$\underline{H}CO_2$Et), 2.77 (s, 1H × 0.48, -C$\underline{H}CO_2$Et), 4.11 (q, J = 6.8 Hz, 2H, -$CO_2C\underline{H}_2CH_3$).

^{13}C NMR δ 14.03, 14.06, [14.23 (minor), 14.26 (major)], [19.55 (major), 20.13 (minor)], 21.63, [22.56 (major), 22.62 (minor)], [27.58 (major), 27.61 (minor)], [28.06 (3 carbons, -C($\underline{C}H_3$)$_3$, major), 28.19 (minor)], [28.44 (major), 28.50 (minor)], [28.64 (minor), 28.74 (major)], 28.85, 29.56, 31.35, [31.65 (minor), 31.69 (major)], [34.16 (major), 34.34 (minor)], [34.49 (minor), 34.63 (major)], 59.88, [60.04 (major), 60.07 (minor)], [76.29 (C≡C, minor), 76.54 (major)], [89.48 (minor), 90.67 (major)], [91.20 (minor), 91.80 (major)], [96.59 (minor), 96.66 (major)], [172.23 (C=O, minor), 172.33 (major)], [208.46 (C=$\underline{C}$=C, major), 208.92 (minor)]. A pair of diastereomeric peaks are shown in square brackets.

IR (neat) 2956, 2930, 2858, 2220 (C≡C), 1950 (C=C=C), 1738 (C=O), 1466, 1366, 1331, 1143, 1046, 759 cm^{-1} for a 52:48 mixture of diastereoisomers.

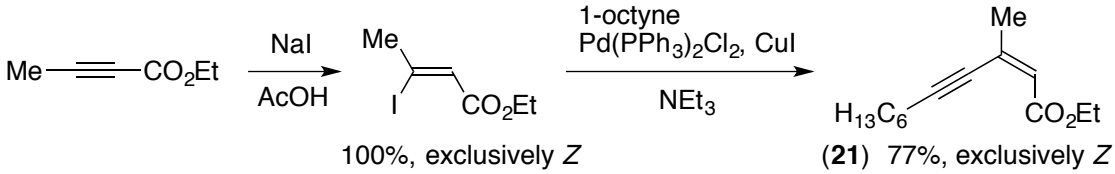
HRMS (ESI) Calcd for $C_{26}H_{44}O_2Na$ [M+Na]$^+$: 411.3234. Found: 411.3227 for a 52:48 mixture of diastereoisomers.

Ethyl (*Z*)-3-methyl-2-undecen-4-ynoate (21).



This was prepared according to the following scheme [(a) Piers, E.; Wong, T.; Coish, P. D.; Rogers, C.

Can. J. Chem. **1994**, *72*, 1816-1819. (b) Rubina, M.; Conley, M.; Gevorgyan, V. *J. Am. Chem. Soc.* **2006**, *128*, 5818-5827].

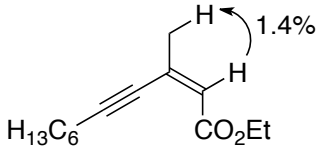


To a suspension of sodium iodide (1.20 g, 8.01 mmol) in AcOH (1.83 mL, 31.97 mmol) was added ethyl 2-butynoate (0.580 mL, 4.98 mmol) under argon. After the mixture was stirred in an oil bath maintained at 115 °C for 1.5 h and cooled to room temperature, the reaction was terminated by the addition of water. The organic products were extracted with Et_2O. The combined organic layers were washed successively with aqueous saturated $NaHCO_3$ solution, aqueous saturated $Na_2S_2O_3$ solution, and brine, dried over Na_2SO_4, and concentrated *in vacuo* to afford ethyl (*Z*)-3-iodo-2-butenoate (1.20 g, 100%, exclusively *Z*), which was directly used -C=C<u>H</u>CO_2Et n the next step.

To a suspension of $Pd(PPh_3)_2Cl_2$ (35.1 mg, 0.050 mmol) and CuI (19.0 mg, 0.100 mmol) in triethylamine (10 mL) was added ethyl (*Z*)-3-iodo-2-butenoate (1.20 g, 5.00 mmol) in triethylamine (2 mL), followed by 1-octyne (0.710 mL, 5.01 mmol), under argon. After the mixture was stirred at room temperature for 12 h, the reaction was terminated by the addition of aqueous saturated NH_4Cl solution. The organic products were extracted with ethyl acetate. The combined organic layers were washed successively with 1 N HCl, water, and brine, dried over Na_2SO_4, and concentrated *in vacuo* to a crude oil, which was chromatographed on silica gel (hexane-ethyl acetate) to afford the title compound (856 mg, 77%, exclusively *Z*) as an oil.

^{1}H NMR δ 0.89 (t, *J* = 7.2 Hz, 3H, alkyl-Me), 1.28 (t, *J* = 7.2 Hz, 3H, -CO_2CH_2C<u>H</u>$_3$), 1.24-1.48 (m, 6H, alkyl H), 1.60 (quintet, *J* = 7.2 Hz, 2H, alkyl H), 2.02 (d, *J* = 1.2 Hz, 3H, -CH=CC<u>H</u>$_3$), 2.44 (t, *J* = 7.2 Hz, 2H, $C_5H_{11}C$<u>H</u>$_2$-), 4.19 (q, *J* = 7.2 Hz, -CO_2C<u>H</u>$_2CH_3$), 5.92 (q, *J* = 1.2 Hz, 1H, -C=C<u>H</u>CO_2Et).

NOE experiments showed the correlation between the peaks at δ 2.02 ppm (-CH=CC<u>H</u>$_3$) and at δ 5.92 ppm (-C=C<u>H</u>CO_2Et). Thus, the stereochemistry of the olefin was assigned to *E*.

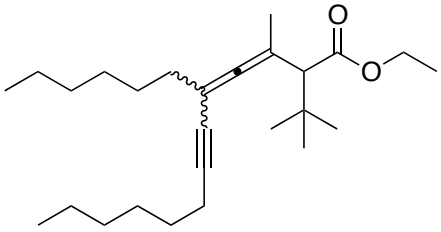


^{13}C NMR δ 14.01, 14.25, 19.98, 22.50, 25.82, 28.41, 28.57, 31.28, 59.86, 79.74 (C≡C), 103.12 (C≡C), 123.17 (C=C), 135.78 (C=C), 165.25 (C=O).

IR (neat) 2956, 2932, 2859, 2222 (C≡C), 1727 (C=O), 1620 (C=C), 1446, 1376, 1278, 1221, 1152, 1050, 851, 758 cm^{-1}.

HRMS (ESI) Calcd for $C_{14}H_{22}O_2Na$ $[M+Na]^+$: 245.1512. Found: 245.1512.

Ethyl 2-(*tert*-butyl)-5-hexyl-3-methyl-3,4-tridecadien-6-ynoate (20) from ethyl (*Z*)-3-methyl-2-undecen-4-ynoate (21).

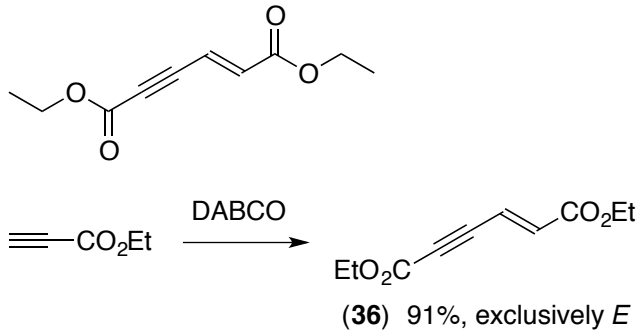


To a suspension of ethyl (*Z*)-3-methyl-2-undecen-4-ynoate (**21**) (44.5 mg, 0.200 mmol), 1-bromo-1-octyne (**2**) (75.6 mg, 0.400 mmol), and $FeCl_2$ (25.4 mg, 0.200 mmol) in 1 mL of THF was added *tert*-butylmagnesium chloride (0.780 mL, 1.03 M solution in THF, 0.803 mmol) at –78 ºC under argon. After the solution was slowly warmed to 0 ºC over 3 h, the reaction was terminated by the addition of 1 N HCl solution (1 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed successively with aqueous saturated $NaHCO_3$ solution and brine, dried over Na_2SO_4, and concentrated *in vacuo* to give a crude oil, ^1H NMR analysis of which revealed that other regioisomers were absent and that the diastereoselectivity of the product was 51:49. The crude product was chromatographed on silica gel (hexane-ethyl acetate) to afford the title compound (51.7 mg, 69%) as an oil and of the same diastereomeric composition observed for a crude sample.

For the spectroscopic data, see: ethyl 2-(*tert*-butyl)-5-hexyl-3-methyl-3,4-tridecadien-6-ynoate (**20**) from ethyl (*E*)-3-methyl-2-undecen-4-ynoate (**19**).

Iron-Mediated Regioselective Conjugate Addition of Grignard Reagents to 2-Alken-4-ynedioates

Diethyl *(E)*-2-hexen-4-ynedioate (36). This is a known compound and was prepared by a literature method [(a) Ramachandran, P. V.; Rudd, M. T.; Reddy, M. V. R. *Tetrahedron Lett*. **2005**, *46*, 2547-2549. (b) Slugovc, C.; Doberer, D.; Gemel, C.; Schmid, R.; Kirchner, K.; Winkler, B.; Stelzer, F. *Monatsh. Chem*. **1998**, *129*, 221-233].



(**36**) 91%, exclusively *E*

To a suspension of 1,4-diazabicyclo[2.2.2]octane (DABCO) (11.2 mg, 0.100 mmol) in CH_2Cl_2 (20 mL) was added ethyl propiolate (1.01 mL, 9.97 mmol) at room temperature under argon. After the mixture was stirred for 5 min, the solvent was removed *in vacuo* to give a crude oil, which was chromatographed on silica gel (hexane-ethyl acetate) to afford the title compound (896 mg, 91%, exclusively *E*) as an oil.

^{1}H NMR δ 1.31 (t, *J* = 7.2 Hz, 3H, -$CO_2CH_2C\underline{H}_3$), 1.33 (t, *J* = 7.2 Hz, 3H, -$CO_2CH_2C\underline{H}_3$), 4.24 (q, *J* = 7.2 Hz, 2H, -$CO_2C\underline{H}_2CH_3$), 4.28 (q, *J* = 7.2 Hz, 2H, -$CO_2C\underline{H}_2CH_3$), 6.46 (d, *J* = 16.0 Hz, 1H, -CH=C$\underline{H}CO_2$Et), 6.78 (d, *J* = 16.0 Hz, 1H, -C$\underline{H}$=CHCO_2Et).

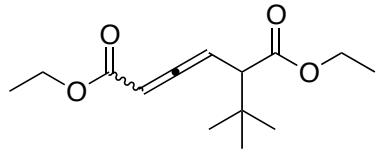
^{13}C NMR δ 13.92, 14.06, 61.24, 62.37, 81.44 (C≡C), 87.00 (C≡C), 121.45 (C=C), 135.35 (C=C), 153.05 (C=O), 164.61 (C=O).

IR (neat) 3070, 2984, 2939, 2908, 2223 (C≡C), 1716 (C=O), 1623 (C=C), 1467, 1367, 1245, 1181, 1098, 1029, 961, 860, 748 cm^{-1}.

HRMS (ESI) Calcd for $C_{10}H_{12}O_4Na$ $[M+Na]^+$: 219.0628. Found: 219.0625.

These spectral properties were in good agreement with those reported in the above literature.

Diethyl 5-(*tert*-butyl)-2,3-hexadienedioate (38)



To a suspension of diethyl (*E*)-2-hexen-4-ynedioate (**36**) (39.2 mg, 0.200 mmol) and $FeCl_2$ (25.4 mg, 0.200 mmol) in 2 mL of THF was added *tert*-butylmagnesium chloride (0.22 mL, 1.02 M solution in THF, 0.224 mmol) at –78 °C under argon. After stirring at –78 °C for 3 h, the reaction was terminated by the addition of a 1:1 mixture of THF and 1 N HCl solution (1 mL) at –78 °C. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined

organic layers were washed successively with aqueous saturated $NaHCO_3$ solution and brine, dried over Na_2SO_4, and concentrated *in vacuo* to give a crude oil, ^{1}H NMR analysis of which revealed that other regioisomers were absent and that the diastereoselectivity of the product was 53:47. The crude product was chromatographed on silica gel (hexane-ethyl acetate) to afford the title compound (43.7 mg, 86%) as an oil and of the same diastereomeric composition observed for a crude sample.

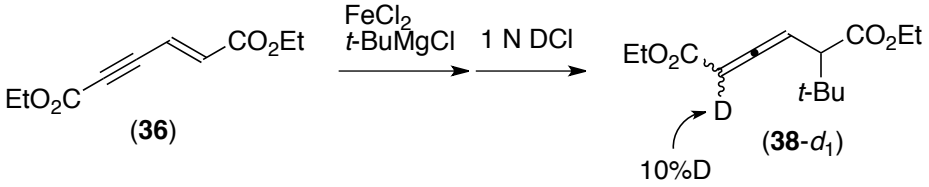
^{1}H NMR δ 1.01 (s, 9H × 0.47, -C(C$\underline{H}_3$)$_3$), 1.05 (s, 9H × 0.53, -C(C$\underline{H}_3$)$_3$), 1.26 (t, *J* = 7.2 Hz, 3H, -$CO_2CH_2C\underline{H}_3$), 1.28 (t, *J* = 7.2 Hz, 3H, -$CO_2CH_2C\underline{H}_3$), 2.93 (d, *J* = 10.8 Hz, 1H × 0.53, -C$\underline{H}CO_2$Et), 2.95 (d, *J* = 10.0 Hz, 1H × 0.47, -C$\underline{H}CO_2$Et), 4.11-4.26 (m, 4H, -$CO_2C\underline{H}_2CH_3$ and –$CHCO_2C\underline{H}_2CH_3$), 5.61 (d, *J* = 6.4 Hz, 1H × 0.53, $EtO_2CC\underline{H}$=C=), 5.62 (d, *J* = 6.0 Hz, 1H × 0.47, $EtO_2CC\underline{H}$=C=), 5.77 (dd, *J* = 6.0, 10.0 Hz, 1H × 0.47, EtO_2CCH=C=C$\underline{H}$-), 5.78 (dd, *J* = 6.4, 10.8 Hz, 1H × 0.53, EtO_2CCH=C=C$\underline{H}$-).

^{13}C NMR δ 14.17, 14.23, [27.52 (3 carbons, -C($\underline{C}H_3$)$_3$, minor), 27.55 (major)], [34.43 (major), 34.56 (minor)], [55.36 (minor), 55.81 (major)], [60.53 (minor), 60.58 (major)], [60.53 (minor), 60.84 (major)], [88.34 ($\underline{C}$=C=C, major), 88.46 (minor)], [92.05 ($\underline{C}$=C=C, minor), 92.15 (major)], [165.66 (C=O, minor), 165.75 (major)], [171.69 (C=O, minor), 171.95 (major)], [212.03 (C=$\underline{C}$=C, major), 212.18 (minor)]. A pair of diastereomeric peaks are shown in square brackets.

IR (neat) 2963, 2873, 1965 (C=C=C), 1725 (C=O), 1467, 1368, 1256, 1152, 1096, 1039, 875, 814 cm^{-1} for a 53:47 mixture of diastereoisomers.

HRMS (ESI) Calcd for $C_{14}H_{22}O_4Na$ [M+Na]$^+$: 277.1410. Found: 277.1416 for a 53:47 mixture of diastereoisomers.

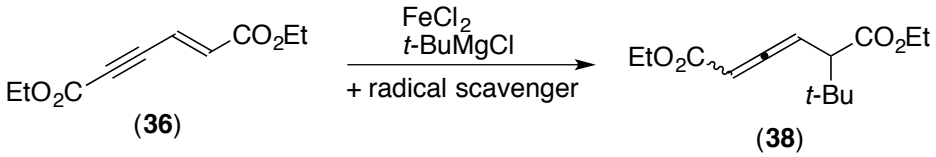
Control experiment for 36 → 38. Deuteriolysis in place of hydrolytic work-up.



To a suspension of diethyl (*E*)-2-hexen-4-ynedioate (**36**) (39.2 mg, 0.200 mmol) and $FeCl_2$ (25.4 mg, 0.200 mmol) in 2 mL of THF was added *tert*-butylmagnesium chloride (0.22 mL, 1.02 M solution in THF, 0.224 mmol) at –78 °C under argon. After stirring at –78 °C for 3 h, the reaction was terminated by the addition of a 1:1 mixture of THF and 1 N DCl solution (1 mL) at –78 °C. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed successively with aqueous saturated $NaHCO_3$ solution and brine, dried over Na_2SO_4, and concentrated *in vacuo* to give a crude oil, ^{1}H NMR analysis of which revealed that other regioisomers were absent and that the diastereoselectivity of the product was 55:45. The crude product was chromatographed on silica gel (hexane-ethyl acetate) to afford the title compound (41.6 mg, 82%) as an oil and of the same diastereomeric composition observed for a crude sample.

The integration of peak areas at δ 5.61 (d, $EtO_2CC\underline{H}$=C=) and 5.62 (d, $EtO_2CC\underline{H}$=C=) was total 0.90H as compared to the original value of **38** (1H) to show 10% deuterium incorporation at this position.

Control experiment for 36 → 38. The Reaction in the presence of a radical scavenger.



With galvinoxyl (20 mol%)

To a suspension of diethyl (*E*)-2-hexen-4-ynedioate (**36**) (19.6 mg, 0.100 mmol), $FeCl_2$ (12.7 mg, 0.100 mmol), and galvinoxyl (8.4 mg, 0.020 mmol) in 1 mL of THF was added *tert*-butylmagnesium chloride (0.11 mL, 1.03 M solution in THF, 0.113 mmol) at –78 °C under argon. After stirring at –78 °C for 3 h, the reaction was terminated by the addition of a 1:1 mixture of THF and 1 N HCl solution (1 mL) at –78 °C. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed successively with aqueous saturated $NaHCO_3$ solution and brine, dried over Na_2SO_4, and concentrated *in vacuo* to give a crude oil, ^1H NMR analysis of which revealed that the yields of diethyl 5-(*tert*-butyl)-2,3-hexadienedioate (**38**) and recovered starting material **36** were 53% and 23%, respectively, by using trichloroethylene as an internal standard.

With galvinoxyl (100 mol%)

To a suspension of diethyl (*E*)-2-hexen-4-ynedioate (**36**) (9.8 mg, 0.050 mmol), $FeCl_2$ (6.3 mg, 0.050 mmol), and galvinoxyl (21.1 mg, 0.050 mmol) in 0.5 mL of THF was added *tert*-butylmagnesium chloride (0.055 mL, 1.02 M solution in THF, 0.056 mmol) at –78 °C under argon. After stirring at –78 °C for 3 h, the reaction was terminated by the addition of a 1:1 mixture of THF and 1 N HCl solution (1 mL) at –78 °C. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed successively with aqueous saturated $NaHCO_3$ solution and brine, dried over Na_2SO_4, and concentrated *in vacuo* to give a crude oil, ^1H NMR analysis of which revealed that the yields of diethyl 5-(*tert*-butyl)-2,3-hexadienedioate (**38**) and recovered starting material **36** were 33% and 67%, respectively, by using trichloroethylene as an internal standard.

With TEMPO (20 mol%)

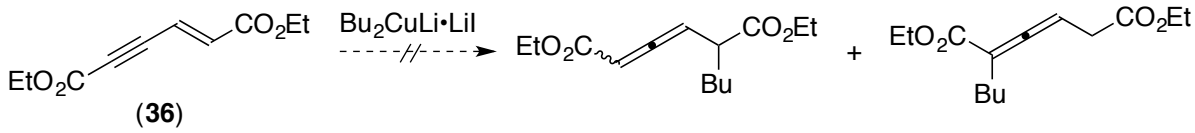
To a suspension of diethyl (*E*)-2-hexen-4-ynedioate (**36**) (19.6 mg, 0.100 mmol), $FeCl_2$ (12.7 mg, 0.100 mmol), and TEMPO (3.1 mg, 0.020 mmol) in 1 mL of THF was added *tert*-butylmagnesium chloride (0.110 mL, 1.03 M solution in THF, 0.113 mmol) at –78 °C under argon. After stirring at –78 °C for 3 h, the reaction was terminated by the addition of a 1:1 mixture of THF and 1 N HCl solution (1 mL) at –78 °C. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed successively with aqueous saturated $NaHCO_3$ solution and brine, dried over Na_2SO_4, and concentrated *in vacuo* to give a crude oil, ^1H NMR analysis of which revealed that the yields of diethyl 5-(*tert*-butyl)-2,3-hexadienedioate (**38**) and recovered starting material **36** were 85% and 10%, respectively, by using trichloroethylene as an internal standard.

With TEMPO (100 mol%)

To a suspension of diethyl (*E*)-2-hexen-4-ynedioate (**36**) (9.8 mg, 0.050 mmol), $FeCl_2$ (6.3 mg, 0.050 mmol), and TEMPO (7.8 mg, 0.050 mmol) in 0.5 mL of THF was added *tert*-butylmagnesium chloride (0.055 mL, 1.02 M solution in THF, 0.056 mmol) at –78 °C under argon. After stirring at –78 °C for 3 h, the reaction was terminated by the addition of a 1:1 mixture of THF and 1 N HCl solution (1 mL) at –78 °C. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed successively with aqueous saturated $NaHCO_3$ solution and brine, dried over Na_2SO_4, and concentrated *in vacuo* to give a crude oil, ^1H NMR analysis of which revealed that the yields of diethyl 5-(*tert*-butyl)-2,3-hexadienedioate (**38**) and recovered starting material **36** were 23% and 53%, respectively, by using trichloroethylene as an internal standard.

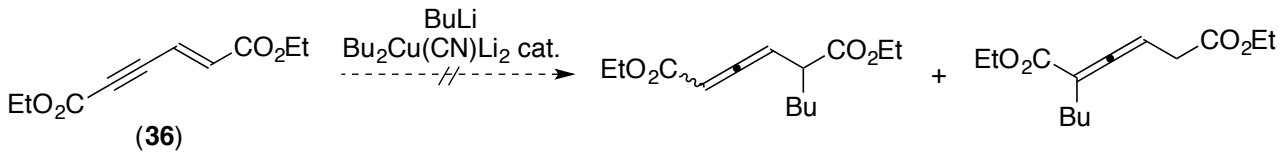
Control experiment for the nucleophilic addition of representative copper reagents to diethyl (*E*)-2-hexen-4-ynedioate (36). [Uerdingen, M.; Krause, N. *Tetrahedron*, **2000**, *56*, 2799-2804]**.**

With Bu_2CuLi•LiI



To a suspension of CuI (19.0 mg, 0.100 mmol) in 0.5 mL of THF was added BuLi (0.130 mL, 1.60 M in hexane, 0.208 mmol) at –30 °C under argon. After the mixture was stirred at –30 °C for 15 min, the resulting solution was cooled to –78 °C. A solution of diethyl (*E*)-2-hexen-4-ynedioate (**36**) (19.6 mg, 0.100 mmol) in 0.5 mL of THF slowly added at –78 °C. After the solution was slowly warmed to 0 °C over 3 h, the reaction was terminated by the addition of aqueous saturated NH_4Cl solution (1 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo* to give a crude oil, ^1H NMR analysis of which revealed that any notable adducts were not formed.

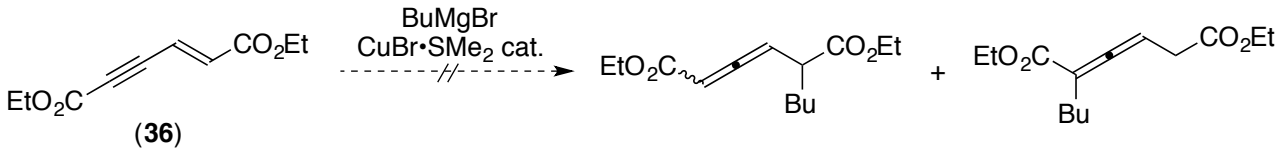
With BuLi / $Bu_2Cu(CN)Li_2$ cat.



To a suspension of CuCN (0.9 mg, 0.010 mmol) in 0.5 mL of THF was added BuLi (0.015 mL, 1.60 M in hexane, 0.024 mmol) at –30 °C under argon. After the mixture was stirred at –30 °C for 15 min, the resulting solution was cooled to –78 °C. A solution of diethyl (*E*)-2-hexen-4-ynedioate (**36**) (19.6 mg, 0.100 mmol) in 0.5 mL of THF slowly added at –78 °C, followed by BuLi (0.13 mL, 1.60 M in hexane, 0.208 mmol) was slowly added at –78 °C. After the solution was slowly warmed to 0 °C

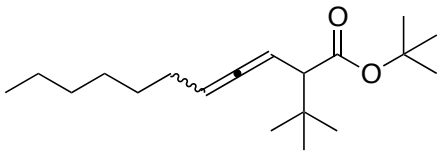
over 3 h, the reaction was terminated by the addition of aqueous saturated NH_4Cl solution (1 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo* to give a crude oil, ^1H NMR analysis of which revealed that any notable adducts were not formed.

With BuMgBr / CuBr•SMe_2 cat.



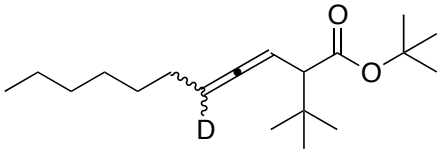
To a suspension of CuBr•SMe_2 (2.1 mg, 0.010 mmol) and diethyl (*E*)-2-hexen-4-ynedioate (**36**) (19.6 mg, 0.100 mmol) in 1 mL of THF was added BuMgBr (0.220 mL, 0.900 M in hexane, 0.198 mmol) at –78 °C under argon. After the solution was slowly warmed to 0 °C over 3 h, the reaction was terminated by the addition of aqueous saturated NH_4Cl solution (1 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo* to give a crude oil, ^1H NMR analysis of which revealed that any notable adducts were not formed.

Copper-Mediated *anti*-Michael Addition
***tert*-Butyl 2-(*tert*-butyl)-3,4-undecadienoate (4).**



To a suspension of *tert*-butyl (*E*)-2-undecen-4-ynoate (**1**) (47.3 mg, 0.200 mmol) and CuBr•SMe_2 (41.1 mg, 0.200 mmol) in 2 mL of THF was slowly added *tert*-butylmagnesium chloride (0.290 mL, 1.02 M solution in THF, 0.296 mmol) at –78 ºC over 15 min under argon. After the solution was slowly warmed to 0 ºC over 3 h, the reaction was terminated by the addition of 1 N HCl solution (1 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed successively with aqueous saturated $NaHCO_3$ solution and brine, dried over Na_2SO_4, and concentrated *in vacuo* to give a crude oil, ^{1}H NMR analysis of which revealed that other regioisomers were absent and that the diastereoselectivity of the product was 54:46. The crude product was chromatographed on silica gel (hexane-ethyl acetate) to afford the title compound (58.4 mg, 99%) as an oil and of the same diastereomeric composition observed for a crude sample.
^{1}H NMR δ 0.88 (t, *J* = 6.8 Hz, 3H, alkyl-Me), 0.98 (s, 9H × 0.46, -C(C$\underline{H}_3$)$_3$), 0.99 (s, 9H × 0.54, -C(C$\underline{H}_3$)$_3$), 1.22-1.44 (m, 8H, alkyl H), 1.46 (s, 9H, -CO_2C(C$\underline{H}_3$)$_3$), 1.97 (m, 2H, $C_5H_{11}C\underline{H}_2$-), 2.648 (dd, *J* = 1.2, 10.0 Hz, 1H × 0.54, -C$\underline{H}CO_2$Bu-*t*), 2.652 (dd, *J* = 1.2, 10.0 Hz, 1H × 0.46, -C$\underline{H}CO_2$Bu-*t*), 5.11 (dq, *J* = 1.2, 6.0 Hz, 1H × 0.46, $C_6H_{13}C\underline{H}$=C=CH-), 5.12 (dq, *J* = 1.2, 6.0 Hz, 1H × 0.54, $C_6H_{13}C\underline{H}$=C=CH-), 5.19 (tdd, *J* = 3.2, 6.0, 10.0 Hz, 1H, C_6H_{13}CH=C=C$\underline{H}$-).
^{13}C NMR δ 14.06, 22.60, [27.55 (3 carbons, -C($\underline{C}H_3$)$_3$, minor), 27.63 (major)], 28.13 (3 carbons, -C($\underline{C}H_3$)$_3$), 28.48, [28.78 (major), 28.83 (minor)], [28.93 (major), 29.34 (minor)], 31.66, [33.81 (major), 34.07 (minor)], [57.87 (minor), 58.05 (major)], [80.24 (minor), 80.36 (major)], [87.63 (C$\underline{C}$=C=C, major), 87.94 (minor)], 91.06 (C$\underline{C}$=C=C), [172.51 (C=O, major), 172.54 (minor)], [204.78 (C=C$\underline{C}$=C, major), 204.93 (minor)]. A pair of diastereomeric peaks are shown in square brackets.
IR (neat) 2960, 2930, 2858, 1963 (C=C=C), 1727 (C=O), 1466, 1367, 1337, 1257, 1140, 1031, 968, 849, 759 cm^{-1} for a 54:46 mixture of diastereoisomers.
HRMS (ESI) Calcd for $C_{19}H_{34}O_2Na$ $[M+Na]^+$: 317.2451. Found: 317.2443 for a 54:46 mixture of diastereoisomers.

***tert*-Butyl 2-(*tert*-butyl)-5-deuterio-3,4-undecadienoate (4-*d*).**



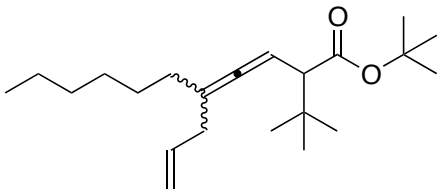
To a suspension of *tert*-butyl (*E*)-2-undecen-4-ynoate (**1**) (47.3 mg, 0.200 mmol) and CuBr•SMe_2 (41.1 mg, 0.200 mmol) in 2 mL of THF was slowly added *tert*-butylmagnesium chloride (0.29 mL, 1.02 M solution in THF, 0.296 mmol) at –78 ºC over 15 min under argon. After the solution was

slowly warmed to 0 ºC over 3 h, the reaction was terminated by the addition of 1 N DCl solution (0.2 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed successively with aqueous saturated $NaHCO_3$ solution and brine, dried over Na_2SO_4, and concentrated *in vacuo* to give a crude oil, ^{1}H NMR analysis of which revealed that other regioisomers were absent and that the diastereoselectivity of the product was 52:48. The crude product was chromatographed on silica gel (hexane-ethyl acetate) to afford the title compound (58.2 mg, 98%) as an oil and of the same diastereomeric composition observed for a crude sample.

^{1}H NMR δ 0.88 (t, *J* = 6.8 Hz, 3H, alkyl-Me), 0.98 (s, 9H × 0.48, -C(C$\underline{H}_3$)$_3$), 0.99 (s, 9H × 0.52, -C(C$\underline{H}_3$)$_3$), 1.20-1.50 (m, 8H, alkyl H), 1.46 (s, 9H, -CO_2C(C$\underline{H}_3$)$_3$), 1.98 (m, 2H, $C_5H_{11}C\underline{H}_2$-), 2.649 (d, *J* = 10.0 Hz, 1H × 0.52, -C$\underline{H}CO_2$Bu-*t*), 2.653 (d, *J* = 10.0 Hz, 1H × 0.48, -C$\underline{H}CO_2$Bu-*t*), 5.19 (dm, *J* = 10.0 Hz, 1H, C_6H_{13}CD=C=C$\underline{H}$-).

The integration of peak areas at δ 5.12 (dq, $C_6H_{13}C\underline{H}$=C=CH-) was total 0.07H as compared to the original value of **4** (1H) to show 93% deuterium incorporation at this position.

***tert*-Butyl 2-(*tert*-butyl)-5-hexyl-3,4,7-octatrienoate (48).**



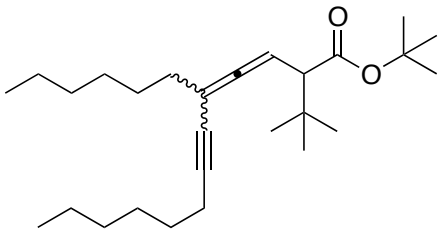
To a suspension of *tert*-butyl (*E*)-2-undecen-4-ynoate (**1**) (47.3 mg, 0.200 mmol) and CuBr•SMe_2 (41.1 mg, 0.200 mmol) in 1 mL of THF was slowly added *tert*-butylmagnesium chloride (0.290 mL, 1.02 M solution in THF, 0.296 mmol) at –78 ºC over 15 min under argon. After the mixture was slowly warmed to 0 ºC over 3 h, allyl bromide (26.6 mg, 0.220 mmol) was added. After the mixture was stirred at 0 ºC for 1 h, the reaction was terminated by the addition of aqueous saturated NH_4Cl solution (1 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed successively with water and brine, dried over Na_2SO_4, and concentrated *in vacuo* to give a crude oil, ^{1}H NMR analysis of which revealed that other regioisomers were absent and that the diastereoselectivity of the product was 54:46. The crude product was chromatographed on silica gel (hexane-ethyl acetate) to afford the title compound (62.0 mg, 93%) as an oil and of the same diastereomeric composition observed for a crude sample.

^{1}H NMR δ 0.87 (t, *J* = 6.8 Hz, 3H × 0.46, alkyl-Me), 0.88 (t, *J* = 6.8 Hz, 3H × 0.54, alkyl-Me), 0.988 (s, 9H × 0.46, -C(C$\underline{H}_3$)$_3$), 0.99 (s, 9H × 0.54, -C(C$\underline{H}_3$)$_3$), 1.21-1.50 (m, 8H, alkyl H), 1.45 (s, 9H, -CO_2C(C$\underline{H}_3$)$_3$), 1.92 (m, 2H, $C_5H_{11}C\underline{H}_2$-), 2.62 (d, *J* = 10.0 Hz, 1H × 0.46, -C$\underline{H}CO_2$Bu-*t*), 2.63 (d, *J* = 10.0 Hz, 1H × 0.54, -C$\underline{H}CO_2$Bu-*t*), 2.69 (m, 2H, -C$\underline{H}_2$CH=CH_2), 5.02 (m, 2H, -CH=C$\underline{H}_2$), 5.20 (m, 1H, C_6H_{13}C=C=CH-), 5.79 (m, 1H, -C$\underline{H}$=CH_2).

^{13}C NMR δ 14.06, 22.60, 27.30, 27.66 (3 carbons, -C($\underline{C}H_3$)$_3$), 28.10 (3 carbons, -C($\underline{C}H_3$)$_3$), [28.98 (minor), 29.03 (major)], [31.72 (major), 31.83 (minor)], 32.40, [33.55 (major), 33.57 (minor)], [37.32 (major), 37.88 (minor)], [58.38 (major), 58.48 (minor)], [80.05 (major), 80.08 (minor)], [88.77 ($\underline{C}$=C=C, major), 88.86 (minor)], [102.87 ($\underline{C}$=C=C, major), 103.09 (minor)], [115.55 (C=C, major),

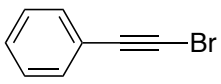
115.72 (minor)], 136.09 (C=C), 172.71 (C=O), [202.32 (C=C=C, minor), 202.39 (major)]. A pair of diastereomeric peaks are shown in square brackets.
IR (neat) 3078, 2959, 2930, 2872, 1964 (C=C=C), 1726 (C=O), 1638, 1467, 1367, 1255, 1140, 991, 912, 850 cm^{-1} for a 54:46 mixture of diastereoisomers.
HRMS (ESI) Calcd for $C_{22}H_{38}O_2Na$ $[M+Na]^+$: 357.2764. Found: 357.2767 for a 54:46 mixture of diastereoisomers.

***tert*-Butyl 2-(*tert*-butyl)-5-hexyl-3,4-tridecadien-6-ynoate (3).**



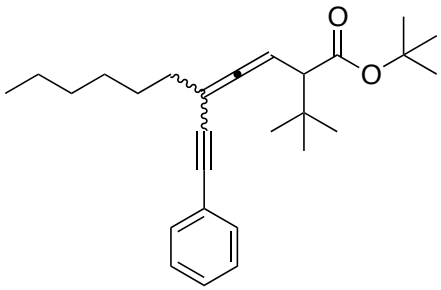
To a suspension of *tert*-butyl (*E*)-2-undecen-4-ynoate (**1**) (47.3 mg, 0.200 mmol) and $CuBr•SMe_2$ (41.1 mg, 0.200 mmol) in 1 mL of THF was slowly added *tert*-butylmagnesium chloride (0.290 mL, 1.02 M solution in THF, 0.296 mmol) at –78 ºC over 15 min under argon. After the mixture was slowly warmed to 0 ºC over 3 h, 1-bromo-1-octyne (**2**) (41.6 mg, 0.220 mmol) in THF (1 mL) was added. After the mixture was stirred at 0 ºC for 1 h, the reaction was terminated by the addition of aqueous saturated NH_4Cl solution (1 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed successively with water and brine, dried over Na_2SO_4, and concentrated *in vacuo* to give a crude oil, ^1H NMR analysis of which revealed that other regioisomers were absent and that the diastereoselectivity of the product was 54:46. The crude product was chromatographed on silica gel (hexane-ethyl acetate) to afford the title compound (74.4 mg, 92%) as an oil and of the same diastereomeric composition observed for a crude sample.
For the spectroscopic data, see: *tert*-butyl 2-(*tert*-butyl)-5-hexyl-3,4-tridecadien-6-ynoate (**3**) from *tert*-butyl (*E*)-2-undecen-4-ynoate (**1**).

(Bromoethynyl)benzene. This is a known compound and was prepared by a literature method [Mu, Z.; Shu, L.; Fuchs, H.; Mayor, M.; Chi, L. *J. Am. Chem. Soc.* **2008**, *130*, 10840-10841].



^1H NMR δ 7.28-7.37 (m, 3H, Ph-H), 7.43-7.47 (m, 2H, Ph-H).
^{13}C NMR δ 49.71 (C≡C), 80.03 (C≡C), 122.69, 128.31 (2 carbons, Ar), 128.66, 131.99 (2 carbons, Ar).
IR (neat) 3086 (Ar), 3061 (Ar), 3034 (Ar), 2201 (C≡C), 1596, 1574, 1486, 1443, 1069, 1026, 915, 752, 689 cm^{-1}.
These spectral properties were in good agreement with those reported in the above literature.

***tert*-Butyl 2-(*tert*-butyl)-5-hexyl-7-phenyl-3,4-heptadien-6-ynoate (49).**



To a suspension of *tert*-butyl (*E*)-2-undecen-4-ynoate (**1**) (47.3 mg, 0.200 mmol) and CuBr•SMe_2 (41.1 mg, 0.200 mmol) in 1 mL of THF was slowly added *tert*-butylmagnesium chloride (0.290 mL, 1.02 M solution in THF, 0.296 mmol) at –78 ºC over 15 min under argon. After the mixture was warmed up to 0 ºC over 3 h, (bromoethynyl)benzene (39.8 mg, 0.220 mmol) in THF (1 mL) was added. After the mixture was stirred at 0 ºC for 1 h, the reaction was terminated by the addition of aqueous saturated NH_4Cl solution (1 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed successively with water and brine, dried over Na_2SO_4, and concentrated *in vacuo* to give a crude oil, ^{1}H NMR analysis of which revealed that other regioisomers were absent and that the diastereoselectivity of the product was 57:43. The crude product was chromatographed on silica gel (hexane-ethyl acetate) to afford the title compound (71.9 mg, 91%) as an oil and of the same diastereomeric composition observed for a crude sample.

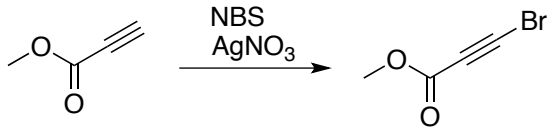
^{1}H NMR δ 0.89 (t, *J* = 6.8 Hz, 3H, alkyl-Me), 1.02 (s, 9H × 0.57, -C(C$\underline{H}_3$)$_3$), 1.04 (s, 9H × 0.43, -C(C$\underline{H}_3$)$_3$), 1.22-1.62 (m, 8H, alkyl H), 1.48 (s, 9H, -CO_2C(C$\underline{H}_3$)$_3$), 2.19 (m, 2H, $C_5H_{11}C\underline{H}_2$-), 2.75 (d, *J* = 10.0 Hz, 1H × 0.43, -C$\underline{H}CO_2$Bu-*t*), 2.77 (d, *J* = 10.0 Hz, 1H × 0.57, -C$\underline{H}CO_2$Bu-*t*), 5.50 (dm, *J* = 10.0 Hz, 1H, $C_6H_{13}C$=C=C$\underline{H}$-), 7.27-7.33 (m, 3H, Ph-H), 7.37-7.44 (m, 2H, Ph-H).

^{13}C NMR δ 14.07, 22.60, [27.60 (3 carbons, -C($\underline{C}H_3$)$_3$, minor), 27.68 (major)], 27.97, 28.10 (3 carbons, -C($\underline{C}H_3$)$_3$), [28.57 (minor), 28.63 (major)], 31.62, [33.41 (minor), 34.04 (major)], [34.08 (major), 34.44 (minor)], [57.34 (major), 57.52 (minor)], [80.61 (minor), 80.70 (major)], [85.08 (major), 85.15 (minor)], [89.43 ($\underline{C}$=C=C, major), 89.93 (minor)], [90.39 (major), 90.55 (minor)], [91.01 (minor), 91.19 (major)], 123.65, 127.90, 128.20 (2 carbons, Ph), 131.37 (2 carbons, Ph), 171.75 (C=O), [209.78 (C=$\underline{C}$=C, major), 209.88 (minor)]. A pair of diastereomeric peaks are shown in square brackets.

IR (neat) 3107 (Ar), 3086 (Ar), 3063 (Ar), 2959, 2929, 2858, 2208 (C≡C), 1948 (C=C=C), 1725 (C=O), 1598, 1467, 1368, 1256, 1142, 1030, 911, 848, 756 cm^{-1} for a 57:43 mixture of diastereoisomers.

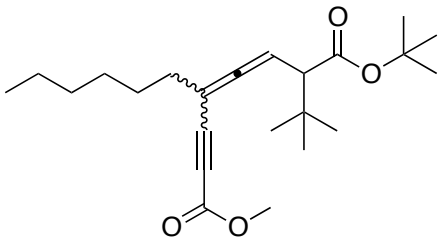
HRMS (ESI) Calcd for $C_{27}H_{38}O_2Na$ [M+Na]$^+$: 417.2764. Found: 417.2763 for a 57:43 mixture of diastereoisomers.

Methyl 3-bromopropiolate. This is a known compound and was prepared by a literature method [Leroy, J. *Synth. Commun.* **1992**, *22*, 567-572].



^{1}H NMR δ 3.79 (s, 3H, -$CO_2C\underline{H}_3$).
^{13}C NMR δ 52.83 (Me), 53.01 (C≡C), 72.45 (C≡C), 152.84 (C=O).
IR (neat) 2956, 2206 (C≡C), 1718 (C=O), 1435, 1252, 1014, 890, 746, 722, 549 cm^{-1}.
These spectral properties were in good agreement with those reported in the above literature.

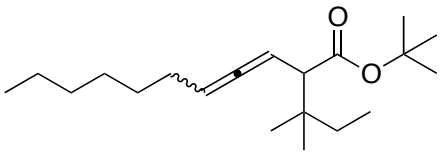
Methyl 4-hexyl-8,8-dimethyl-7-(*tert*-butyloxycarbonyl)-4,5-nonadien-2-ynoate (50).



To a suspension of *tert*-butyl (*E*)-2-undecen-4-ynoate (**1**) (47.3 mg, 0.200 mmol) and CuBr•SMe_2 (41.1 mg, 0.200 mmol) in 1 mL of THF was slowly added *tert*-butylmagnesium chloride (0.290 mL, 1.02 M solution in THF, 0.296 mmol) at –78 ºC over 15 min under argon. After the mixture was slowly warmed to 0 ºC over 3 h, methyl 3-bromopropiolate (35.9 mg, 0.220 mmol) in THF (1 mL) was added. After the mixture was stirred at 0 ºC for 1 h, the reaction was terminated by the addition of aqueous saturated NH_4Cl solution (1 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed successively with water and brine, dried over Na_2SO_4, and concentrated *in vacuo* to give a crude oil, ^{1}H NMR analysis of which revealed that other regioisomers were absent and that the diastereoselectivity of the product was 55:45. The crude product was chromatographed on silica gel (hexane-ethyl acetate) to afford the title compound (65.0 mg, 86%) as an oil and of the same diastereomeric composition observed for a crude sample.
^{1}H NMR δ 0.88 (t, *J* = 6.4 Hz, 3H, alkyl-Me), 1.00 (s, 9H × 0.55, -$C(C\underline{H}_3)_3$), 1.01 (s, 9H × 0.45, -$C(C\underline{H}_3)_3$), 1.22-1.56 (m, 8H, alkyl H), 1.46 (s, 9H × 0.45, -$CO_2C(C\underline{H}_3)_3$), 1.48 (s, 9H × 0.55, -$CO_2C(C\underline{H}_3)_3$), 2.14 (m, 2H, $C_5H_{11}C\underline{H}_2$-), 2.73 (d, *J* = 10.0 Hz, 1H × 0.45, -$C\underline{H}CO_2$Bu-*t*), 2.75 (d, *J* = 10.0 Hz, 1H × 0.55, -$C\underline{H}CO_2$Bu-*t*), 3.77 (s, 3H × 0.45, -$CO_2C\underline{H}_3$), 3.78 (s, 3H × 0.55, -$CO_2C\underline{H}_3$), 5.57 (dm, *J* = 10.0 Hz, 1H, $C_6H_{13}C$=C=C$\underline{H}$-).
^{13}C NMR δ 14.02, 22.54, [27.58 (3 carbons, -$C(\underline{C}H_3)_3$, minor), 27.64 (major)], 27.87, 28.07 (3 carbons, -$C(\underline{C}H_3)_3$), [28.42 (minor), 28.50 (major)], [31.49 (major), 32.48 (minor)], 33.07, [34.14 (major), 34.42 (minor)], 52.60, [56.84 (major), 57.07 (minor)], [80.93 (minor), 81.11 (major)], [81.79 (minor), 81.96 (major)], 83.53, [88.05 (major), 88.21 (minor)], [90.86 ($\underline{C}$=C=C, major), 91.32 (minor)], 154.41 (C=O), [171.13 (C=O, major), 171.34 (minor)], 211.55 (C=$\underline{C}$=C). A pair of diastereomeric peaks are shown in square brackets.
IR (neat) 2958, 2931, 2872, 2215 (C≡C), 1950 (C=C=C), 1719 (C=O), 1458, 1368, 1265, 1142, 1098,

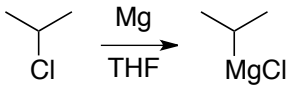
1047, 915, 847, 735 cm^{-1} for a 55:45 mixture of diastereoisomers.
HRMS (ESI) Calcd for $C_{23}H_{36}O_4Na$ $[M+Na]^+$: 399.2506. Found: 399.2495 for a 55:45 mixture of diastereoisomers.

***tert*-Butyl 2-(*tert*-amyl)-3,4-undecadienoate (51).**



To a suspension of *tert*-butyl (*E*)-2-undecen-4-ynoate (**1**) (47.2 mg, 0.200 mmol) and $CuBr•SMe_2$ (41.1 mg, 0.200 mmol) in 1 mL of THF was slowly added *tert*-amylmagnesium chloride (0.600 mL, 1.00 M solution in THF, 0.600 mmol) at –78 ºC over 15 min under argon. After the solution was slowly warmed to 0 ºC over 3 h, the reaction was terminated by the addition of aqueous saturated NH_4Cl solution (1 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed successively with water and brine, dried over Na_2SO_4, and concentrated *in vacuo* to give a crude oil, ^1H NMR analysis of which revealed that other regioisomers were absent and that the diastereoselectivity of the product was 55:45. The crude product was chromatographed on silica gel (hexane-ethyl acetate) to afford the title compound (55.4 mg, 90%) as an oil and of the same diastereomeric composition observed for a crude sample.
^1H NMR δ 0.81-0.91 (m, 6H, alkyl-Me and $–CMe_2CH_2C\underline{H}_3$), 0.92 (s, 3H × 0.45, $-C(C\underline{H}_3)_2CH_2CH_3$), 0.93 (s, 3H × 0.55, $-C(C\underline{H}_3)_2CH_2CH_3$), 0.94 (s, 3H, $-C(C\underline{H}_3)_2Et$), 1.20-1.51 (m, 10H, alkyl H and $-CMe_2C\underline{H}_2CH_3$), 1.45 (s, 9H × 0.55, $-CO_2C(C\underline{H}_3)_3$), 1.46 (s, 9H × 0.45, $-CO_2C(C\underline{H}_3)_3$), 1.99 (m, 2H, $C_5H_{11}C\underline{H}_2-$), 2.76 (d, *J* = 10.0 Hz, 1H, $-C\underline{H}CO_2Bu$-*t*), 5.11 (m, 1H, $C_6H_{13}C\underline{H}$=C=CH-), 5.19 (m, 1H, $C_6H_{13}CH$=C=C$\underline{H}$-).
^{13}C NMR δ 8.12, 14.06, 22.60, [23.95 (minor), 23.99 (major)], [24.01 (minor), 24.15 (major)], 28.12 (3 carbons, $-C(\underline{C}H_3)_3$), [28.46 (major), 28.75 (minor)], [28.81 (major), 28.94 (minor)], 29.35, 31.66, 33.07, [36.44 (major), 36.62 (minor)], 55.78, [80.19 (minor), 80.33 (major)], [87.42 ($\underline{C}$=C=C, major), 87.79 (minor)], 91.03 ($\underline{C}$=C=C), [172.57 (C=O, major), 172.62 (minor)], [204.64 (C=$\underline{C}$=C, major), 204.80 (minor)]. A pair of diastereomeric peaks are shown in square brackets.
IR (neat) 2964, 2929, 2857, 1963 (C=C=C), 1726 (C=O), 1464, 1367, 1342, 1254, 1138, 968, 847, 756 cm^{-1} for a 55:45 mixture of diastereoisomers.
HRMS (ESI) Calcd for $C_{20}H_{36}O_2Na$ $[M+Na]^+$: 331.2608. Found: 331.2607 for a 55:45 mixture of diastereoisomers.

Preparation of isopropylmagnesium chloride.



To a suspension of magnesium turnings (292 mg, 12.0 mmol) in 0.5 mL of THF was added 2-

chloropropane (0.530 mL, 5.80 mmol) at room temperature under argon. The suspension was refluxed in an oil bath maintained at 80 °C until the reaction started. Then, a solution of 2-chloropropane (0.530 mL, 5.80 mmol) in 8.5 mL of THF was slowly added at such a rate as to maintain gentle reflux. After the addition was complete, the mixture was refluxed for another 2 h and allowed to cool to ambient temperature.

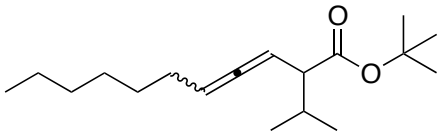
A 0.300-mL aliquot of the Grignard solution was quenched with an exactly known, excess volume of a 1.002 M HCl solution (purchased from Yoneyama Chemical, Inc. (Japan)) and the mixture was then back-titrated with a 0.5005 M NaOH solution (purchased from Yoneyama Yakuhin Kogyo, Co., Ltd. (Japan)) with methyl orange as an indicator, determining its concentration to be 1.12 M.

The above Grignard reagent (5.00 mL, 1.12 M solution in THF, 5.60 mmol) was diluted with THF (6.20 mL) under argon.

A 0.300-mL aliquot of the diluted Grignard solution was again quenched with an exactly known, excess volume of a 1.002 M HCl solution (purchased from Yoneyama Chemical, Inc. (Japan)) and the mixture was then back-titrated with a 0.5005 M NaOH solution (purchased from Yoneyama Yakuhin Kogyo, Co., Ltd. (Japan)) with methyl orange as an indicator, confirming its concentration to be 0.500 M.

Other 0.500 M Grignard reagents (cyclohexyl- and cyclopentylmagnesium chlorides) were also prepared by this procedure.

***tert*-Butyl 2-isopropyl-3,4-undecadienoate (52).**



To a suspension of *tert*-butyl (*E*)-2-undecen-4-ynoate (**1**) (47.3 mg, 0.200 mmol) and CuBr•SMe_2 (41.1 mg, 0.200 mmol) in 1 mL of THF was slowly added isopropylmagnesium chloride (0.80 mL, 0.500 M solution in THF, 0.400 mmol) at –78 ºC over 1 h under argon. After stirring at –78 °C for 3 h, the reaction was terminated by the addition of a 1:1 mixture of THF and 1 N HCl solution (1 mL) at –78 °C. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed successively with aqueous saturated $NaHCO_3$ solution and brine, dried over Na_2SO_4, and concentrated *in vacuo* to give a crude oil, ^{1}H NMR analysis of which revealed that other regioisomers were absent and that the diastereoselectivity of the product was 55:45. The crude product was chromatographed on silica gel (hexane-ethyl acetate) to afford the title compound (43.7 mg, 78%) as an oil and of the same diastereomeric composition observed for a crude sample.

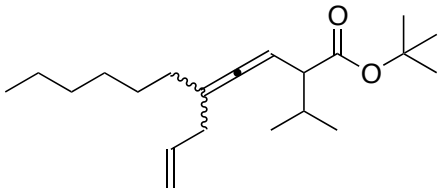
^{1}H NMR δ 0.88 (t, *J* = 6.4 Hz, 3H, alkyl-Me), 0.93 (d, *J* = 6.8 Hz, 3H × 0.45, -CH(C$\underline{H}_3$)$_2$), 0.94 (d, *J* = 6.8 Hz, 6H × 0.55, -CH(C$\underline{H}_3$)$_2$), 0.96 (d, *J* = 6.8 Hz, 3H × 0.45, -CH(C$\underline{H}_3$)$_2$), 1.22-1.48 (m, 8H, alkyl H), 1.45 (s, 9H × 0.45, -CO_2C(C$\underline{H}_3$)$_3$), 1.46 (s, 9H × 0.55, -CO_2C(C$\underline{H}_3$)$_3$), 1.88-2.03 (m, 3H, -C$\underline{H}Me_2$ and $C_5H_{11}C\underline{H}_2$-), 2.55 (dt, *J* = 2.8, 8.8 Hz, 1H × 0.55, -C$\underline{H}CO_2$Bu-*t*), 2.56 (dt, *J* = 2.8, 8.8 Hz, 1H × 0.45, -C$\underline{H}CO_2$Bu-*t*), 5.05-5.18 (m, 2H, $C_6H_{13}C\underline{H}$=C=CH- and C_6H_{13}CH=C=C$\underline{H}$-).

^{13}C NMR δ 14.06, [19.74 (minor), 19.76 (major)], [20.58 (major), 20.61 (minor)], 22.61, 28.08 (3 carbons, -C(<u>C</u>H$_3$)$_3$), 28.57, [28.77 (major), 28.90 (minor)], 29.18, [30.97 (minor), 31.13 (major)], 31.67, [54.87 (major), 54.99 (minor)], [80.22 (major), 80.32 (minor)], [88.72 (<u>C</u>=C=C, minor), 89.11 (major)], 91.62 (<u>C</u>=C=C), [173.20 (C=O, minor), 173.23 (major)], [204.61 (C=<u>C</u>=C, minor), 204.67 (major)]. A pair of diastereomeric peaks are shown in square brackets.

IR (neat) 2961, 2929, 2857, 1964 (C=C=C), 1730 (C=O), 1467, 1367, 1260, 1147, 1019, 978, 843, 805 cm^{-1} for a 55:45 mixture of diastereoisomers.

HRMS (ESI) Calcd for $C_{18}H_{32}O_2Na$ [M+Na]$^+$: 303.2295. Found: 303.2294 for a 55:45 mixture of diastereoisomers.

***tert*-Butyl 5-hexyl-2-isopropyl-3,4,7-octatrienoate (53).**



To a suspension of *tert*-butyl (*E*)-2-undecen-4-ynoate (**1**) (47.3 mg, 0.200 mmol) and CuBr•SMe$_2$ (41.1 mg, 0.200 mmol) in 1 mL of THF was slowly added isopropylmagnesium chloride (0.800 mL, 0.500 M solution in THF, 0.400 mmol) at –78 ºC over 1 h under argon. After stirring at –78 °C for 3 h, allyl bromide (26.6 mg, 0.220 mmol) in THF (1 mL) was added. After the reaction mixture was stirred at –78 ºC for 1 h, the reaction was terminated by the addition of aqueous saturated NH_4Cl solution (1 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed successively with water and brine, dried over Na_2SO_4, and concentrated *in vacuo* to give a crude oil, ^{1}H NMR analysis of which revealed that other regioisomers were absent and that the diastereoselectivity of the product was 52:48. The crude product was chromatographed on silica gel (hexane-ethyl acetate) to afford the title compound (49.1 mg, 77%) as an oil and of the same diastereomeric composition observed for a crude sample.

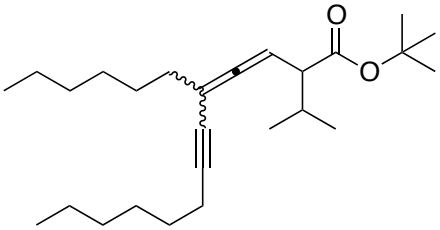
^{1}H NMR δ 0.87 (t, *J* = 7.2 Hz, 3H × 0.52, alkyl-Me), 0.88 (t, *J* = 7.2 Hz, 3H × 0.48, alkyl-Me), 0.94 (d, *J* = 6.4 Hz, 6H × 0.52, -CH(C<u>H</u>$_3$)$_2$), 0.95 (d, *J* = 6.4 Hz, 6H × 0.48, -CH(C<u>H</u>$_3$)$_2$), 1.20-1.50 (m, 8H, alkyl H), 1.45 (s, 9H, -CO$_2$C(C<u>H</u>$_3$)$_3$), 1.87-1.98 (m, 3H, -C<u>H</u>Me$_2$ and $C_5H_{11}C\underline{H}_2$-), 2.50 (t, *J* = 8.8 Hz, 1H, -C<u>H</u>CO$_2$Bu-*t*), 2.70 (d, *J* = 6.4 Hz, 2H, -C<u>H</u>$_2$CH=CH$_2$), 4.96-5.12 (m, 3H, -CH=C<u>H</u>$_2$ and $C_6H_{13}C{=}C{=}C\underline{H}$-), 5.80 (m, 1H, -C<u>H</u>=CH$_2$).

^{13}C NMR δ 14.06, [20.03 (major), 20.08 (minor)], 20.68, 22.63, [27.34 (major), 27.54 (minor)], 28.07 (3 carbons, -C(<u>C</u>H$_3$)$_3$), [29.00 (major), 29.02 (minor)], [30.86 (minor), 30.89 (major)], [31.72 (minor), 31.74 (major)], [31.99 (major), 32.29 (minor)], [37.47 (minor), 37.80 (major)], [55.61 (minor), 55.65 (major)], [80.08 (major), 80.10 (minor)], [90.31 (<u>C</u>=C=C, major), 90.37 (minor)], [103.54 (<u>C</u>=C=C, major), 103.65 (minor)], 115.67 (C=C), 136.11 (C=C), 173.41 (C=O), [202.02 (C=<u>C</u>=C, major), 202.04 (minor)]. A pair of diastereomeric peaks are shown in square brackets.

IR (neat) 3078, 2959, 2929, 2858, 1966 (C=C=C), 1728 (C=O), 1639, 1468, 1367, 1250, 1147, 990, 913, 845 cm^{-1} for a 52:48 mixture of diastereoisomers.

HRMS (ESI) Calcd for $C_{21}H_{36}O_2Na$ [M+Na]$^+$: 343.2608. Found: 343.2599 for a 52:48 mixture of diastereoisomers.

***tert*-Butyl 5-hexyl-2-isopropyl-3,4-tridecadien-6-ynoate (54).**



To a suspension of *tert*-butyl (*E*)-2-undecen-4-ynoate (**1**) (47.3 mg, 0.200 mmol) and $CuBr•SMe_2$ (41.1 mg, 0.200 mmol) in 1 mL of THF was slowly added isopropylmagnesium chloride (0.800 mL, 0.500 M solution in THF, 0.400 mmol) at –78 ºC over 1 h under argon. After stirring at –78 °C for 3 h, 1-bromo-1-octyne (**2**) (41.6 mg, 0.22 mmol) in THF (1 mL) was added. After the reaction mixture was stirred at –78 ºC for 1 h, the reaction was terminated by the addition of aqueous saturated NH_4Cl solution (1 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed successively with water and brine, dried over Na_2SO_4, and concentrated *in vacuo* to give a crude oil, ^{1}H NMR analysis of which revealed that other regioisomers were absent and that the diastereoselectivity of the product was 55:45. The crude product was chromatographed on silica gel (hexane-ethyl acetate) to afford the title compound (50.8 mg, 65%) as an oil and of the same diastereomeric composition observed for a crude sample.

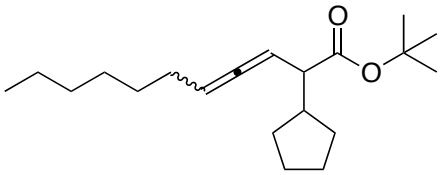
^{1}H NMR δ 0.85-0.92 (m, 6H, alkyl-Me), 0.94 (d, J = 6.4 Hz, 3H × 0.55, -CH(C$\underline{H}_3$)$_2$), 0.95 (d, J = 6.4 Hz, 3H × 0.55, -CH(C$\underline{H}_3$)$_2$), 0.96 (d, J = 6.4 Hz, 3H × 0.45, -CH(C$\underline{H}_3$)$_2$), 0.97 (d, J = 6.4 Hz, 3H × 0.45, -CH(C$\underline{H}_3$)$_2$), 1.22-1.56 (m, 16H, alkyl H), 1.456 (s, 9H × 0.55, -C(C$\underline{H}_3$)$_3$), 1.458 (s, 9H × 0.45, -C(C$\underline{H}_3$)$_3$), 1.98 (m, 1H, -C$\underline{H}$Me$_2$), 2.07 (m, 2H, $C_5H_{11}C\underline{H}_2$-), 2.30 (t, 2H, J = 7.2 Hz, -C≡CC$\underline{H}_2C_5H_{11}$), 2.61 (dd, J = 8.0, 9.2 Hz, 1H × 0.45, -C$\underline{H}$CO$_2$Bu-*t*), 2.62 (dd, J = 8.0, 9.2 Hz, 1H × 0.55, -C$\underline{H}$CO$_2$Bu-*t*), 5.31 (dm, J = 9.2 Hz, 1H, $C_6H_{13}C$=C=C$\underline{H}$-).

^{13}C NMR δ 14.04, 14.07, [19.52 (minor), 19.57 (major)], 19.62, 19.86, 20.59, 22.55, 22.60, [27.59 (major), 27.79 (minor)], 28.04 (3 carbons, -C($\underline{C}$H$_3$)$_3$), [28.47 (minor), 28.54 (major)], [28.59 (minor), 28.61 (major)], 28.75, [30.89 (major), 31.27 (minor)], [31.35 (minor), 31.63 (major)], 34.35, [54.37 (major), 54.55 (minor)], [75.65 (C≡C, major), 75.89 (minor)], [80.45 (major), 80.49 (minor)], [89.96 (major), 90.12 (minor)], [91.07 (minor), 91.14 (major)], [92.15 (minor), 92.45 (major)], [172.58 (C=O, major), 172.75 (minor)], [209.36 (C=$\underline{C}$=C, major), 209.41 (minor)]. A pair of diastereomeric peaks are shown in square brackets.

IR (neat) 2958, 2930, 2858, 2221 (C≡C), 1952 (C=C=C), 1729 (C=O), 1467, 1367, 1329, 1148, 1039, 978, 845, 726 cm^{-1} for a 55:45 mixture of diastereoisomers.

HRMS (ESI) Calcd for $C_{26}H_{44}O_2Na$ [M+Na]$^+$: 411.3234. Found: 411.3232 for a 55:45 mixture of diastereoisomers.

***tert*-Butyl 2-cyclopentyl-3,4-undecadienoate (55).**



To a suspension of *tert*-butyl (*E*)-2-undecen-4-ynoate (**1**) (47.3 mg, 0.200 mmol) and CuBr•SMe_2 (41.1 mg, 0.200 mmol) in 1 mL of THF was slowly added cyclopentylmagnesium chloride (0.800 mL, 0.500 M solution in THF, 0.400 mmol) at –78 ºC over 1 h under argon. After stirring at –78 °C for 4 h, the reaction was terminated by addition of a 1:1 mixture of THF and 1 N HCl solution (1 mL) at –78 °C. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed successively with aqueous saturated $NaHCO_3$ solution and brine, dried over Na_2SO_4, and concentrated *in vacuo* to give a crude oil, ^{1}H NMR analysis of which revealed that other regioisomers were absent and that the diastereoselectivity of the product was 55:45. The crude product was chromatographed on silica gel (hexane-ethyl acetate) to afford the title compound (47.9 mg, 78%) as an oil and of the same diastereomeric composition observed for a crude sample.

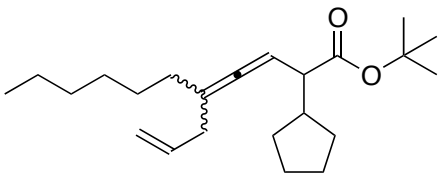
^{1}H NMR δ 0.88 (t, *J* = 6.8 Hz, 3H, alkyl-Me), 1.16-1.66 (m, 16H, alkyl H and cyclopentyl H), 1.44 (s, 9H × 0.55, -$CO_2C(C\underline{H}_3)_3$), 1.45 (s, 9H × 0.45, -$CO_2C(C\underline{H}_3)_3$), 1.98 (m, 2H, $C_5H_{11}C\underline{H}_2$-), 2.13 (m, 1H, cyclopentyl H), 2.626 (t, *J* = 10.0 Hz, 1H × 0.55, -C<u>H</u>CO_2Bu-*t*), 2.630 (t, *J* = 10.0 Hz, 1H × 0.45, -C<u>H</u>CO_2Bu-*t*), 5.08-5.19 (m, 2H, $C_6H_{13}C\underline{H}$=C=CH- and C_6H_{13}CH=C=C<u>H</u>-).

^{13}C NMR δ 14.07, 22.60, [25.04 (major), 25.09 (minor)], 25.31, 28.06 (3 carbons, -C(<u>C</u>$H_3)_3$), [28.63 (minor), 28.78 (major)], 28.89, 29.10, [30.29 (minor), 30.42 (major)], [30.53 (major), 30.59 (minor)], 31.66, [42.47 (major), 42.50 (minor)], [52.99 (minor), 53.19 (major)], [80.21 (major), 80.28 (minor)], [89.66 (<u>C</u>=C=C, major), 89.87 (minor)], [91.89 (<u>C</u>=C=C, major), 91.91 (minor)], [173.36 (C=O, major), 173.40 (minor)], [204.26 (C=<u>C</u>=C, major), 204.36 (minor)]. A pair of diastereomeric peaks are shown in square brackets.

IR (neat) 2955, 2930, 2860, 1964 (C=C=C), 1729 (C=O), 1456, 1367, 1257, 1147, 963, 848, 757 cm^{-1} for a 55:45 mixture of diastereoisomers.

HRMS (ESI) Calcd for $C_{20}H_{34}O_2Na$ $[M+Na]^+$: 329.2451. Found: 329.2458 for a 55:45 mixture of diastereoisomers.

***tert*-Butyl 2-cyclopentyl-5-hexyl-3,4,7-octatrienoate (56).**



To a suspension of *tert*-butyl (*E*)-2-undecen-4-ynoate (**1**) (47.3 mg, 0.200 mmol) and CuBr•SMe_2 (41.1 mg, 0.200 mmol) in 1 mL of THF was slowly added cyclopentylmagnesium chloride (0.800 mL, 0.500 M solution in THF, 0.400 mmol) at –78 ºC over 1 h under argon. After the mixture was stirred at –78 °C for 4 h, allyl bromide (26.6 mg, 0.220 mmol) in THF (1 mL) was added. After the reaction mixture was stirred at –78 ºC for 1 h, the reaction was terminated by the addition of aqueous saturated

NH_4Cl solution (1 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed successively with water and brine, dried over Na_2SO_4, and concentrated *in vacuo* to give a crude oil, ^1H NMR analysis of which revealed that other regioisomers were absent and that the diastereoselectivity of the product was 52:48. The crude product was chromatographed on silica gel (hexane-ethyl acetate) to afford the title compound (51.9 mg, 75%) as an oil and of the same diastereomeric composition observed for a crude sample.

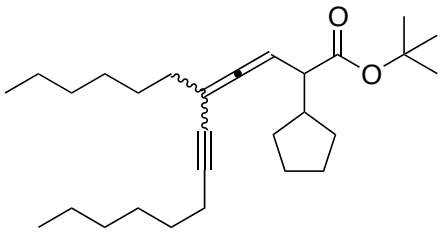
^1H NMR δ 0.87 (t, J = 6.8 Hz, 3H × 0.52, alkyl-Me), 0.88 (t, J = 6.8 Hz, 3H × 0.48, alkyl-Me), 1.18-1.47 (m, 12H, alkyl H and cyclopentyl H), 1.44 (s, 9H, -$CO_2(C\underline{H}_3)_3$), 1.59 (m, 2H, cyclopentyl H), 1.76 (m, 2H, cyclopentyl H), 1.93 (m, 2H, $C_5H_{11}C\underline{H}_2$-), 2.12 (m, 1H, cyclopentyl H), 2.59 (t, J = 9.2 Hz, 1H × 0.52, -$C\underline{H}CO_2$Bu-*t*), 2.60 (t, J = 9.2 Hz, 1H × 0.48, -$C\underline{H}CO_2$Bu-*t*), 2.70 (br d, J = 6.8 Hz, 2H, -$C\underline{H}_2CH=CH_2$), 4.94-5.08 (m, 2H, -CH=$C\underline{H}_2$), 5.12 (td, J = 2.8, 9.2 Hz, 1H, $C_6H_{13}C=C=C\underline{H}$-), 5.79 (tdd, J = 6.8, 10.4, 17.2 Hz, 1H × 0.52, -$C\underline{H}=CH_2$), 5.80 (tdd, J = 6.8, 10.4, 17.2 Hz, 1H × 0.48, -$C\underline{H}=CH_2$).

^{13}C NMR δ 14.08, 22.61, [25.04 (minor), 25.08 (major)], 25.27, [27.30 (minor), 27.47 (major)], 28.03 (3 carbons, -$C(\underline{C}H_3)_3$), 29.02, [30.53 (minor), 30.56 (major)], 30.62, [31.72 (major), 31.73 (minor)], [31.97 (minor), 32.22 (major)], [37.51 (major), 37.81 (minor)], [42.26 (major), 42.40 (minor)], [53.66 (major), 53.70 (minor)], [80.04 (major), 80.05 (minor)], 90.98 ($\underline{C}$=C=C), [103.71 ($\underline{C}$=C=C, minor), 103.85 (major)], [115.61 (C=C, major), 115.66 (minor)], 136.07 (C=C), 173.50 (C=O), [201.63 (C=$\underline{C}$=C, minor), 201.67 (major)]. A pair of diastereomeric peaks are shown in square brackets.

IR (neat) 3077, 2955, 2929, 2870, 1964 (C=C=C), 1728 (C=O), 1641, 1455, 1367, 1256, 1145, 992, 912, 758 cm^{-1} for a 52:48 mixture of diastereoisomers.

HRMS (ESI) Calcd for $C_{23}H_{38}O_2Na$ $[M+Na]^+$: 369.2764. Found: 369.2764 for a 52:48 mixture of diastereoisomers.

***tert*-Butyl 2-cyclopentyl-5-hexyl-3,4-tridecadien-6-ynoate (57).**



To a suspension of *tert*-butyl (*E*)-2-undecen-4-ynoate (**1**) (47.3 mg, 0.200 mmol) and CuBr•SMe_2 (41.1 mg, 0.200 mmol) in 1 mL of THF was slowly added cyclohexylmagnesium chloride (0.800 mL, 0.500 M solution in THF, 0.400 mmol) at –78 ºC over 1 h under argon. After the mixture was stirred at –78 °C for 4 h, 1-bromo-1-octyne (**2**) (41.6 mg, 0.22 mmol) in THF (1 mL) was added. After the reaction mixture was stirred at –78 ºC for 1 h, the reaction was terminated by the addition of aqueous saturated NH_4Cl solution (1 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed successively with water and brine, dried over Na_2SO_4, and concentrated *in vacuo* to give a crude oil, ^1H NMR analysis of which revealed that other regioisomers were absent and that the diastereoselectivity of the product was 55:45. The crude product was chromatographed on silica gel (hexane-ethyl acetate) to afford the title

compound (56.5 mg, 68%) as an oil and of the same diastereomeric composition observed for a crude sample.

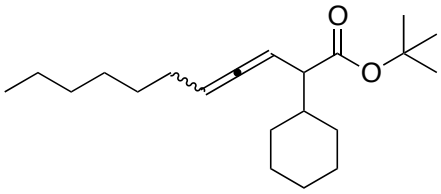
^{1}H NMR δ 0.89 (t, *J* = 7.2 Hz, 6H, alkyl-Me), 1.16-1.86 (m, 24H, alkyl H and cyclopentyl H), 1.44 (s, 9H × 0.45, -$CO_2C(C\underline{H}_3)_3$), 1.45 (s, 9H × 0.55, -$CO_2C(C\underline{H}_3)_3$), 2.07 (m, 2H, $C_5H_{11}C\underline{H}_2$-), 2.15 (m, 1H, cyclopentyl H), 2.30 (t, *J* = 7.2 Hz, 2H, -$C{\equiv}CC\underline{H}_2C_5H_{11}$), 2.68 (t, *J* = 10.0 Hz, 1H × 0.45, -$C\underline{H}CO_2$Bu-*t*), 2.69 (t, *J* = 10.0 Hz, 1H × 0.55, -$C\underline{H}CO_2$Bu-*t*), 5.32 (m, 1H, $C_6H_{13}C{=}C{=}C\underline{H}$-).

^{13}C NMR δ 14.04, 14.06, [19.52 (minor), 19.56 (major)], 22.54, 22.60, 25.10, [25.31 (major), 25.34 (minor)], [27.58 (minor), 27.74 (major)], 28.01 (3 carbons, -$C(\underline{C}H_3)_3$), [28.47 (minor), 28.52 (major)], 28.60, 28.74, [30.25 (major), 30.55 (minor)], [30.56 (major), 30.60 (minor)], 31.34, 31.63, [33.90 (minor), 34.33 (major)], [42.17 (major), 42.67 (minor)], [52.73 (major), 52.80 (minor)], [75.65 (C≡C, major), 75.90 (minor)], [80.40 (minor), 80.44 (major)], [90.86 ($\underline{C}$=C=C, major), 90.95 (minor)], [91.26 (major), 91.44 (minor)], [92.11 (major), 92.49 (minor)], [172.72 (C=O, major), 172.88 (minor)], [209.15 (C=$\underline{C}$=C, minor), 209.22 (major)]. A pair of diastereomeric peaks are shown in square brackets.

IR (neat) 2956, 2929, 2859, 2216 (C≡C), 1951 (C=C=C), 1727 (C=O), 1456, 1367, 1257, 1148, 914, 847, 758 cm^{-1} for a 55:45 mixture of diastereoisomers.

HRMS (ESI) Calcd for $C_{28}H_{46}O_2Na$ $[M+Na]^+$: 437.3390. Found: 437.3388 for a 55:45 mixture of diastereoisomers.

***tert*-Butyl 2-cyclohexyl-3,4-undecadienoate (58).**

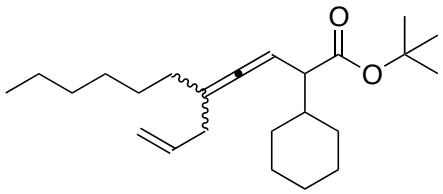


To a suspension of *tert*-butyl (*E*)-2-undecen-4-ynoate (**1**) (47.3 mg, 0.200 mmol) and CuBr•SMe_2 (41.1 mg, 0.200 mmol) in 1 mL of THF was slowly added cyclohexylmagnesium chloride (0.800 mL, 0.500 M solution in THF, 0.400 mmol) at –78 ºC over 1 h under argon. After stirring at –78 °C for 4 h, the reaction was terminated by addition of a 1:1 mixture of THF and 1 N HCl solution (1 mL) at –78 °C. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed successively with aqueous saturated $NaHCO_3$ solution and brine, dried over Na_2SO_4, and concentrated *in vacuo* to give a crude oil, ^{1}H NMR analysis of which revealed that other regioisomers were absent and that the diastereoselectivity of the product was 54:46. The crude product was chromatographed on silica gel (hexane-ethyl acetate) to afford the title compound (53.7 mg, 84%) as an oil and of the same diastereomeric composition observed for a crude sample.

^{1}H NMR δ 0.88 (t, *J* = 6.8 Hz, 3H, alkyl-Me), 0.96-1.50 (m, 14H, alkyl H and cyclohexyl H), 1.46 (s, 9H × 0.46, -$CO_2C(C\underline{H}_3)_3$), 1.45 (s, 9H × 0.54, -$CO_2C(C\underline{H}_3)_3$), 1.52-2.03 (m, 7H, $C_5H_{11}C\underline{H}_2$- and cyclohexyl H), 2.59 (t, *J* = 8.4 Hz, 1H, -$C\underline{H}CO_2$Bu-*t*), 5.06 (m, 1H, $C_6H_{13}C\underline{H}$=C=CH-), 5.14 (m, 1H, C_6H_{13}CH=C=C$\underline{H}$-).

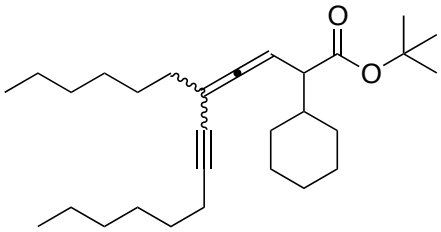
^{13}C NMR δ 14.08, 22.62, 26.10, 26.35, 26.40, 28.10 (3 carbons, -C(<u>C</u>H$_3$)$_3$), 28.57, 28.78, [28.86 (major), 29.14 (minor)], 30.23, 31.04, 31.68, 40.39, [53.99 (major), 54.12 (minor)], [80.24 (major), 80.33 (minor)], [88.92 (<u>C</u>=C=C, minor), 89.14 (major)], 91.58 (<u>C</u>=C=C), 173.26 (C=O), [204.56 (C=<u>C</u>=C, minor), 204.57 (major)]. A pair of diastereomeric peaks are shown in square brackets.
IR (neat) 2927, 2853, 1964 (C=C=C), 1728 (C=O), 1449, 1367, 1256, 1147, 1040, 977, 849, 805, 757 cm^{-1} for a 54:46 mixture of diastereoisomers.
HRMS (ESI) Calcd for $C_{21}H_{36}O_2Na$ [M+Na]$^+$: 343.2608. Found: 343.2599 for a 54:46 mixture of diastereoisomers.

***tert*-Butyl 2-cyclohexyl-5-hexyl-3,4,7-octatrienoate (59).**



To a suspension of *tert*-butyl (*E*)-2-undecen-4-ynoate (**1**) (47.3 mg, 0.200 mmol) and CuBr•SMe$_2$ (41.1 mg, 0.200 mmol) in 1 mL of THF was slowly added cyclohexylmagnesium chloride (0.800 mL, 0.500 M solution in THF, 0.400 mmol) at –78 ºC over 1 h under argon. After the mixture was stirred at –78 °C for 4 h, allyl bromide (26.6 mg, 0.220 mmol) was added. After the reaction mixture was stirred at –78 ºC for 1 h, the reaction was terminated by the addition of aqueous saturated NH_4Cl solution (1 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed successively with water and brine, dried over Na_2SO_4, and concentrated *in vacuo* to give a crude oil, ^{1}H NMR analysis of which revealed that other regioisomers were absent and that the diastereoselectivity of the product was 50:50. The crude product was chromatographed on silica gel (hexane-ethyl acetate) to afford the title compound (56.2 mg, 78%) as an oil and of the same diastereomeric composition observed for a crude sample.
^{1}H NMR δ 0.87 (t, *J* = 7.2 Hz, 3H × 0.50, alkyl-Me), 0.88 (t, *J* = 7.2 Hz, 3H × 0.50, alkyl-Me), 0.94-1.96 (m, 21H, alkyl H and cyclohexyl H), 1.45 (s, 9H, -CO$_2$C(C<u>H</u>$_3$)$_3$), 2.54 (t, *J* = 9.6 Hz, 1H, -C<u>H</u>CO$_2$Bu-*t*), 2.69 (d, *J* = 6.8 Hz, 2H, -C<u>H</u>$_2$CH=CH$_2$), 4.94-5.10 (m, 3H, -CH=C<u>H</u>$_2$, C$_6$H$_{13}$C=C=C<u>H</u>-), 5.79 (tdd, *J* = 6.8, 10.4, 17.2 Hz, 1H, -C<u>H</u>=CH$_2$).
^{13}C NMR δ 14.03, [22.59, 22.61], 26.08 (2 peaks), 26.41, [27.34, 27.57], 28.10 (3 carbons, -C(<u>C</u>H$_3$)$_3$), 29.01, [30.45, 30.53], [31.11, 31.13], 31.74, [32.00, 32.31], [37.50, 37.85], [40.12, 40.16], 54.58, [80.05, 80.07], [90.30 (<u>C</u>=C=C), 90.36], [103.51 (<u>C</u>=C=C), 103.64], [115.55 (C=C), 115.61], [136.10 (C=C), 136.15], 173.36 (C=O), [202.02 (C=<u>C</u>=C), 202.05]. A pair of diastereomeric peaks are shown in square brackets.
IR (neat) 3078, 2927, 2853, 1964 (C=C=C), 1727 (C=O), 1449, 1367, 1255, 1147, 978, 912, 850, 759 cm^{-1} for a 50:50 mixture of diastereoisomers.
HRMS (ESI) Calcd for $C_{24}H_{40}O_2Na$ [M+Na]$^+$: 383.2921. Found: 383.2920 for a 50:50 mixture of diastereoisomers.

***tert*-Butyl 2-cyclohexyl-5-hexyl-3,4-tridecadien-6-ynoate (60).**



To a suspension of *tert*-butyl (*E*)-2-undecen-4-ynoate (**1**) (47.3 mg, 0.200 mmol) and CuBr•SMe_2 (41.1 mg, 0.200 mmol) in 1 mL of THF was slowly added cyclohexylmagnesium chloride (0.800 mL, 0.500 M solution in THF, 0.400 mmol) at –78 ºC over 1 h under argon. After the mixture was stirred at –78 °C for 4 h, 1-bromo-1-octyne (**2**) (41.6 mg, 0.22 mmol) in THF (1 mL) was added. After the reaction mixture was stirred at –78 ºC for 1 h, the reaction was terminated by the addition of aqueous saturated NH_4Cl solution (1 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed successively with water and brine, dried over Na_2SO_4, and concentrated *in vacuo* to give a crude oil, ^{1}H NMR analysis of which revealed that other regioisomers were absent and that the diastereoselectivity of the product was 55:45. The crude product was chromatographed on silica gel (hexane-ethyl acetate) to afford the title compound (50.8 mg, 65%) as an oil and of the same diastereomeric composition observed for a crude sample.

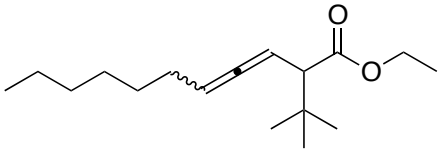
^{1}H NMR δ 0.89 (t, *J* = 7.2 Hz, 6H, alkyl-Me), 0.94-1.90 (m, 27H, alkyl H and cyclohexyl H), 1.45 (s, 9H × 0.55, -C($C\underline{H}_3$)$_3$), 1.46 (s, 9H × 0.45, -C($C\underline{H}_3$)$_3$), 2.07 (m, 2H, $C_5H_{11}C\underline{H}_2$-), 2.30 (t, *J* = 7.2 Hz, 2H, -C≡C$C\underline{H}_2C_5H_{11}$), 2.64 (t, *J* = 9.2 Hz, 1H × 0.45, -$C\underline{H}CO_2$Bu-*t*), 2.66 (t, *J* = 9.2 Hz, 1H × 0.55, -$C\underline{H}CO_2$Bu-*t*), 5.28 (dm, *J* = 9.2 Hz, 1H, $C_6H_{13}C$=C=C$\underline{H}$-).

^{13}C NMR δ 14.03, 14.06, [19.52 (major), 19.55 (minor)], 22.53, 22.59, 26.07, 26.10, 26.31, [27.57 (minor), 27.76 (major)], 28.05 (3 carbons, -C($\underline{C}H_3$)$_3$), [28.46 (minor), 28.52 (major)], 28.58, 28.74, [30.31 (minor), 30.53 (major)], [30.99 (major), 31.01 (minor)], 31.34, 31.63, [33.86 (major), 34.31 (minor)], [40.17 (major), 40.51 (minor)], [53.48 (minor), 53.71 (major)], [75.66 (C≡C, major), 75.92 (minor)], [80.43 (major), 80.48 (minor)], [90.02 ($\underline{C}$=C=C, minor), 90.23 (major)], [91.00 (major), 91.05 (minor)], [92.08 (minor), 92.34 (major)], [172.58 (C=O, minor), 172.75 (major)], [209.29 (C=$\underline{C}$=C, minor), 209.31 (major)]. A pair of diastereomeric peaks are shown in square brackets.

IR (neat) 2955, 2928, 2854, 2216 (C≡C), 1954 (C=C=C), 1728 (C=O), 1450, 1367, 1256, 1147, 978, 849, 760 cm^{-1} for a 55:45 mixture of diastereoisomers.

HRMS (ESI) Calcd for $C_{29}H_{48}O_2Na$ $[M+Na]^+$: 451.3547. Found: 451.3556 for a 55:45 mixture of diastereoisomers.

Ethyl 2-(*tert*-butyl)-3,4-undecadienoate (61).



To a suspension of ethyl (*E*)-2-undecen-4-ynoate (**15**) (41.7 mg, 0.200 mmol) and CuBr•SMe_2 (41.1 mg, 0.200 mmol) in 2 mL of THF was slowly added *tert*-butylmagnesium chloride (0.290 mL, 1.02 M solution in THF, 0.296 mmol) at –78 ºC over 15 min under argon. After the solution was slowly warmed to 0 ºC over 3 h, the reaction was terminated by the addition of 1 N HCl solution (1 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed successively with aqueous saturated $NaHCO_3$ solution and brine, dried over Na_2SO_4, and concentrated *in vacuo* to give a crude oil, ^{1}H NMR analysis of which revealed that other regioisomers were absent and that the diastereoselectivity of the product was 57:43. The crude product was chromatographed on silica gel (hexane-ethyl acetate) to afford the title compound (43.6 mg, 82%) as an oil and of the same diastereomeric composition observed for a crude sample.

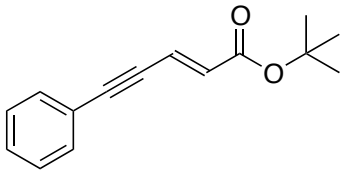
^{1}H NMR δ 0.89 (t, *J* = 7.6 Hz, 3H, alkyl-Me), 0.98 (s, 9H × 0.43, -C(C$\underline{H}_3$)$_3$), 1.00 (s, 9H × 0.57, -C(C$\underline{H}_3$)$_3$), 1.26 (t, *J* = 7.2 Hz, 3H, -$CO_2CH_2C\underline{H}_3$), 1.20-1.46 (m, 8H, alkyl H), 1.98 (m, 2H, $C_5H_{11}C\underline{H}_2$-), 2.76 (d, *J* = 10.0 Hz, 1H, -C$\underline{H}CO_2$Et), 4.13 (q, *J* = 7.2 Hz, 2H × 0.43, -$CO_2C\underline{H}_2CH_3$), 4.14 (q, *J* = 7.2 Hz, 2H × 0.57, -$CO_2C\underline{H}_2CH_3$), 5.11 (q, *J* = 6.4 Hz, 1H × 0.57, $C_6H_{13}C\underline{H}$=C=CH-), 5.13 (q, *J* = 6.4 Hz, 1H × 0.43, $C_6H_{13}C\underline{H}$=C=CH-), 5.22 (tdd, *J* = 2.4, 6.4, 10.0 Hz, 1H, C_6H_{13}CH=C=C$\underline{H}$-).

^{13}C NMR δ 14.03, 14.27, 22.59, [27.53 (3 carbons, -C($\underline{C}H_3$)$_3$, minor), 27.59 (major)], [28.48 (minor), 28.72 (major)], [28.76 (minor), 28.87 (major)], [28.94 (minor), 29.31 (major)], 31.66, [33.82 (major), 34.19 (minor)], [57.02 (minor), 57.26 (major)], [60.03 (minor), 60.08 (major)], [87.36 ($\underline{C}$=C=C, major), 87.60 (minor)], 91.28 ($\underline{C}$=C=C), 173.520 (C=O), [204.91 (C=$\underline{C}$=C, major), 205.07 (minor)]. A pair of diastereomeric peaks are shown in square brackets.

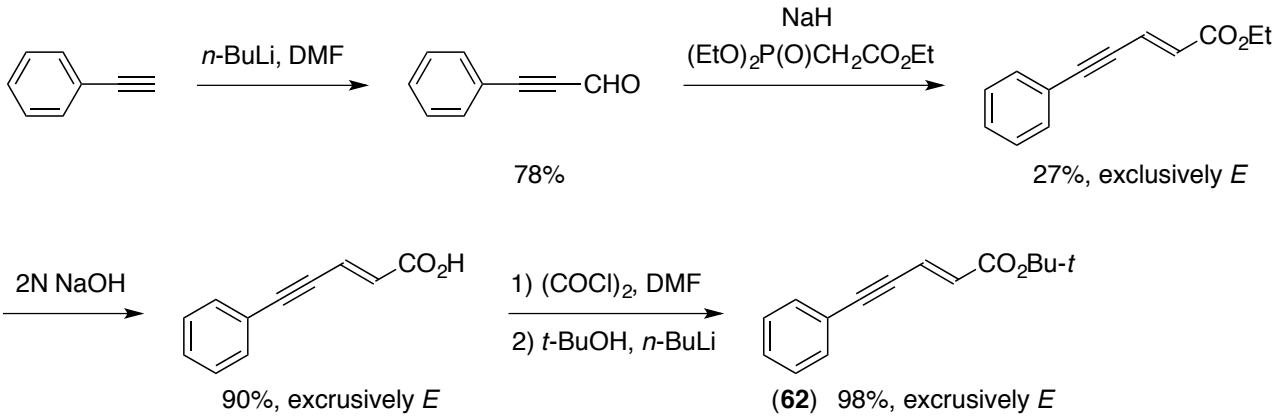
IR (neat) 2958, 2930, 2858, 1963 (C=C=C), 1733 (C=O), 1466, 1367, 1328, 1254, 1148, 1039, 959, 880, 757 cm^{-1} for a 57:43 mixture of diastereoisomers.

HRMS (ESI) Calcd for $C_{17}H_{30}O_2Na$ $[M+Na]^+$: 289.2138. Found: 289.2135 for a 57:43 mixture of diastereoisomers.

tert-Butyl (_E_)-5-phenyl-2-penten-4-ynoate (62)



This was prepared according to the following scheme.



To a solution of phenylacetylene (2.20 mL, 20.0 mmol) in THF (20 mL) was added BuLi (1.65 M in hexane, 12.1 mL, 20.0 mmol) at –40 °C under argon. After stirring at –40 °C for 0.5 h, DMF (3.08 mL, 40.0 mmol) was introduce to the mixture at –40 °C and the solution was stirred at that temperature for 2 h. The reaction was terminated by the addition of aqueous saturated NH_4Cl solution. The organic products were extracted with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo* to afford 3-phenylpropynal (2.04 g, 78%), which was directly used in the next step.

To a suspension of NaH (816 mg of a 60% suspension in mineral oil, 20.4 mmol) in THF (30 mL) was added triethyl phosphonoacetate (3.8 mL, 19.0 mmol) at 0 °C under argon. Then, a solution of 3-phenylpropynal (2.04 g, 15.7 mmol) in THF (10 mL) was added and the mixture was warmed to room temperature. After the stirring was continued for 1 h, the reaction was terminated by the slow addition of water. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed successively with water and brine, dried over Na_2SO_4, and concentrated *in vacuo* to a crude oil, which was chromatographed on silica gel (hexane-ethyl acetate) to afford ethyl (*E*)-5-phenyl-2-penten-4-ynoate (853.8 mg, 27%, exclusively *E*) as an oil.

A mixture of ethyl (*E*)-5-phenyl-2-penten-4-ynoate (853.8 mg, 4.26 mmol) and 2 N NaOH solution (10 mL) was refluxed for 2.5 h without a co-solvent. The reaction mixture was cooled to room temperature, diluted with ethyl acetate, and acidified with 1 N HCl. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo* to give a crude oil, which was chromatographed on silica gel (hexane-ethyl acetate) to afford (*E*)-5-phenyl-2-penten-4-ynoic acid (660.6 mg, 90%, exclusively *E*) as a solid.

To a stirred solution of the above (*E*)-5-phenyl-2-penten-4-ynoic acid (660.6 mg, 3.84 mmol) in CH_2Cl_2 (10 mL) were successively added DMF (1 drop) and oxalyl chloride (0.66 mL, 7.70 mmol) at room temperature. After the mixture was stirred for 2 h, the solvent and the excess oxalyl chloride were removed *in vacuo* to afford the desired (*E*)-5-phenyl-2-penten-4-ynoyl chloride as a crude oil, which was directly used in the next step.

To a solution of *t*-BuOH (0.370 mL, 3.84 mmol) in THF (5 mL) was added BuLi (1.62 M in hexane, 2.37 mL, 3.84 mmol) at 0 °C under argon. After the mixture was stirred at room temperature for 1 h, the above (*E*)-5-phenyl-2-penten-4-ynoyl chloride in THF (5 mL) was added 0 °C. After the mixture was stirred at room temperature for 1.5 h, the reaction was quenched by the addition of water. The

organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo* to give a crude oil, which was chromatographed on silica gel (hexane-ethyl acetate) to afford the title compound (855.6 mg, 98% overall yield from the calboxylic acid, exclusively *E*) as a solid.

^{1}H NMR δ 1.51 (s, 9H, -$CO_2C(C\underline{H}_3)_3$), 6.24 (d, *J* = 15.6 Hz, 1H, -CH=C<u>H</u>CO_2Bu-*t*), 6.88 (d, *J* = 15.6 Hz, 1H, -C<u>H</u>=CHCO_2Bu-*t*), 7.30-7.40 (m, 3H, Ar-H), 7.47 (m, 2H, Ar-H).

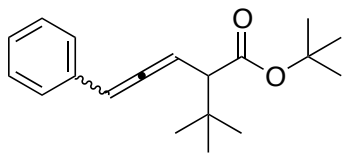
^{13}C NMR δ 28.09 (3 carbons, -C(<u>C</u>$H_3)_3$), 80.99, 86.45 (C≡C), 97.57 (C≡C), 122.34, 123.96, 128.42 (2 carbons, Ar), 129.14, 131.89 (2 carbons, Ar), 132.01, 165.15 (C=O).

IR (KBr) 3100 (Ar), 3080 (Ar), 3060 (Ar), 2978, 2933, 2201 (C≡C), 1703 (C=O), 1618 (C=C), 1444, 1366, 1325, 1254, 1154, 1035, 975, 919, 849, 757 cm^{-1}.

HRMS (ESI) Calcd for $C_{16}H_{18}O_3Na$ $[M+Na]^+$: 251.1043. Found: 251.1043.

M.p. 74-75 °C

***tert*-Butyl 2-(*tert*-butyl)-5-phenyl-3,4-pentadienoate (63).**



To a suspension of *tert*-butyl (*E*)-5-phenyl-2-undecen-4-ynoate (**62**) (45.7 mg, 0.200 mmol) and CuBr•SMe_2 (41.1 mg, 0.200 mmol) in 2 mL of THF was slowly added *tert*-butylmagnesium chloride (0.290 mL, 1.02 M solution in THF, 0.296 mmol) at –78 ºC over 15 min under argon. After the solution was slowly warmed to 0 ºC over 3 h, the reaction was terminated by the addition of aqueous saturated NH_4Cl solution (1 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed successively with water and brine, dried over Na_2SO_4, and concentrated *in vacuo* to give a crude oil, ^{1}H NMR analysis of which revealed that other regioisomers were absent and that the diastereoselectivity of the product was 53:47. The crude product was chromatographed on silica gel (hexane-ethyl acetate) to afford the title compound (53.7 mg, 94%) as an oil and of the same diastereomeric composition observed for a crude sample.

^{1}H NMR δ 1.05 (s, 9H × 0.53, -C(C<u>H</u>$_3)_3$), 1.06 (s, 9H × 0.47, -C(C<u>H</u>$_3)_3$), 1.46 (s, 9H × 0.47, -CO_2C(C<u>H</u>$_3)_3$), 1.47 (s, 9H × 0.53, -CO_2C(C<u>H</u>$_3)_3$), 2.82 (dd, *J* = 1.2, 9.6 Hz, 1H × 0.47, -C<u>H</u>CO_2Bu-*t*), 2.83 (dd, *J* = 1.2, 9.6 Hz, 1H × 0.53, -C<u>H</u>CO_2Bu-*t*), 5.69 (dd, *J* = 6.4, 9.6 Hz, 1H, PhCH=C=C<u>H</u>-), 6.16 (dd, *J* = 1.2, 6.4 Hz, 1H × 0.53, PhC<u>H</u>=C=CH-), 6.19 (dd, *J* = 1.2, 6.4 Hz, 1H × 0.47, PhC<u>H</u>=C=CH-), 7.15-7.33 (m, 5H, Ph-H).

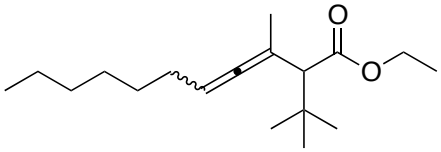
^{13}C NMR δ [27.64 (3 carbons, -C(<u>C</u>$H_3)_3$, minor), 27.82 (major)], 28.13 (3 carbons, -C(<u>C</u>$H_3)_3$), [33.75 (-<u>C</u>Me_3, major), 34.06 (minor)], [57.53 (-<u>C</u>HCO_2Bu-*t*, major), 57.79 (minor)], [80.65 (-CO_2<u>C</u>Me_3, major), 80.72 (minor)], [91.82 (<u>C</u>=C=C, minor), 92.10 (major)], [94.66 (<u>C</u>=C=C, major), 94.85 (minor)], [126.82 (2 carbons, Ph, major), 126.87 (minor)], 126.90 (Ph), [128.53 (2 carbons, Ph, major), 128.56 (minor)], [134.39 (Ph, major), 134.51 (minor)], [171.98 (C=O, major), 172.15 (minor)], [205.79 (C=<u>C</u>=C, minor), 206.10 (major)]. A pair of diastereomeric peaks are shown in square

brackets.

IR (neat) 3084 (Ar), 3063 (Ar), 3032 (Ar), 2964, 2934, 2871, 1952 (C=C=C), 1725 (C=O), 1459, 1367, 1255, 1142, 968, 848, 770 cm^{-1} for a 53:47 mixture of diastereoisomers.

HRMS (ESI) Calcd for $C_{19}H_{26}O_2Na$ $[M+Na]^+$: 309.1825. Found: 309.1821 for a 53:47 mixture of diastereoisomers.

Ethyl 2-(*tert*-butyl)-3-methyl-3,4-undecadienoate (64).



To a suspension of *tert*-butyl (*E*)-3-methyl-2-undecen-4-ynoate (**19**) (44.5 mg, 0.200 mmol) and CuBr•SMe_2 (41.1 mg, 0.200 mmol) in 1 mL of THF was slowly added *tert*-butylmagnesium chloride (0.290 mL, 1.02 M solution in THF, 0.296 mmol) at –78 ºC over 15 min under argon. After the solution was slowly warmed to 0 ºC over 3 h, the reaction was terminated by the addition of aqueous saturated NH_4Cl solution (1 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed successively with water and brine, dried over Na_2SO_4, and concentrated *in vacuo* to give a crude oil, ^{1}H NMR analysis of which revealed that other regioisomers were absent and that the diastereoselectivity of the product was 51:49. The crude product was chromatographed on silica gel (hexane-ethyl acetate) to afford the title compound (49.0 mg, 87%) as an oil and of the same diastereomeric composition observed for a crude sample.

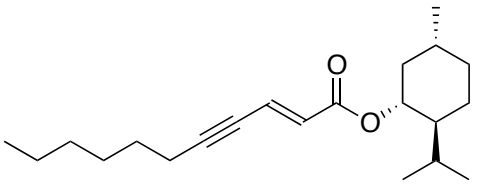
^{1}H NMR δ 0.88 (t, *J* = 6.8 Hz, 3H, alkyl-Me), 1.04 (s, 9H, -C(C$\underline{H}_3$)$_3$), 1.22-1.45 (m, 11H, alkyl H and -$CO_2CH_2C\underline{H}_3$), 1.77 (d, *J* = 2.8 Hz, 3H × 0.49, -C=CC$\underline{H}_3$), 1.78 (d, *J* = 2.8 Hz, 3H × 0.51, -C=CC$\underline{H}_3$), 1.98 (m, 2H, $C_5H_{11}C\underline{H}_2$-), 2.69 (s, 1H, -C$\underline{H}CO_2$Et), 4.12 (m, 2H, -$CO_2C\underline{H}_2CH_3$), 5.05 (qt, *J* = 2.8, 6.4 Hz, 1H, $C_6H_{13}C\underline{H}$=C=C-).

^{13}C NMR δ 14.08, 14.27, [20.96 (major), 21.28 (minor)], 22.64, [28.11 (3 carbons, -C($\underline{C}H_3$)$_3$, minor), 28.19 (major)], [28.81 (minor), 28.86 (major)], [29.00 (major), 29.08 (minor)], [29.12 (minor), 29.16 (major)], [31.68 (minor), 31.71 (major)], [34.45 (minor), 34.61 (major)], [59.57 (major), 59.59 (minor)], [59.87 (minor), 59.91 (major)], [90.69 ($\underline{C}$=C=C, minor), 91.00 (major)], [95.20 ($\underline{C}$=C=C, minor), 95.44 (major)], 172.69 (C=O), [203.91 (C=$\underline{C}$=C, minor), 204.18 (major)]. A pair of diastereomeric peaks are shown in square brackets.

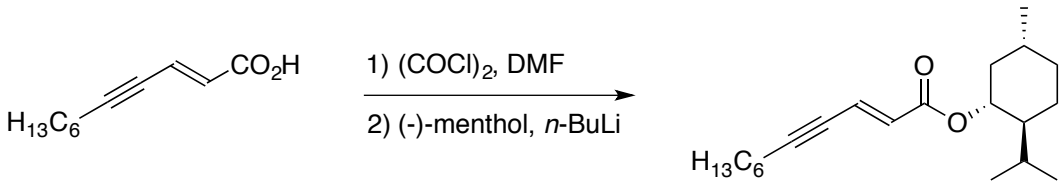
IR (neat) 2957, 2928, 2857, 1962 (C=C=C), 1738 (C=O), 1466, 1367, 1334, 1221, 1143, 1047, 962, 868, 761 cm^{-1} for a 51:49 mixture of diastereoisomers.

HRMS (ESI) Calcd for $C_{19}H_{34}O_2Na$ $[M+Na]^+$: 303.2295. Found: 303.2291 for a 51:49 mixture of diastereoisomers.

(-)-Menthyl (*E*)-2-undecen-4-ynoate (65)



This was prepared according to the following scheme.



(**65**) 57%, excusively *E*

The preparation of (*E*)-2-undecen-4-ynoic acid was already described in that of *tert*-butyl (*E*)-2-undecen-4-ynoate (**1**).

To a stirred solution of (*E*)-2-undecen-4-ynoic acid (1.27 g, 7.05 mmol) in CH_2Cl_2 (20 mL) were successively added DMF (1 drop) and oxalyl chloride (1.20 mL, 13.99 mmol) at room temperature. After the mixture was stirred for 2 h, the solvent and the excess oxalyl chloride were removed *in vacuo* to afford the desired (*E*)-2-undecen-4-ynoyl chloride as a crude oil, which was directly used in the next step.

To a solution of (-)-menthol (1.10 g, 7.04 mmol) in THF (10 mL) was added BuLi (1.58 M in hexane, 4.45 mL, 7.03 mmol) at 0 °C under argon. After the mixture was stirred at room temperature for 1 h, the above (*E*)-2-undecen-4-ynoyl chloride in THF (10 mL) was added 0 °C. After the mixture was stirred at room temperature for 1.5 h, the reaction was quenched by the addition of water. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo* to give a crude oil, which was chromatographed on silica gel (hexane-ethyl acetate) to afford the title compound (1.27 g, 57% overall yield from the carboxylic acid, exclusively *E*) as an oil.

^{1}H NMR δ 0.76 (d, *J* = 7.2 Hz, 3H, cyclohexyl-Me), 0.84-0.93 (m, 9H, alkyl-Me and -CH(C$\underline{H}_3$)$_2$), 0.94-1.14 (m, 4H, cyclohexyl H), 1.24-1.60 (m, 9H, alkyl H and cyclohexyl H), 1.64-1.72 (d-like m, 2H, cyclohexyl H), 1.85 (d/quintet, *J* = 2.4, 6.8 Hz, 1H, -C$\underline{H}$Me$_2$), 2.01 (d-like m, 1H, cyclohexyl H), 2.37 (dt, *J* = 2.0, 6.8 Hz, 2H, $C_5H_{11}C\underline{H}_2$-), 4.74 (dt, *J* = 4.4, 10.8 Hz, 1H, cyclohexyl H), 6.13 (d, *J* = 16.0 Hz, 1H, -CH=C$\underline{H}$CO$_2$(menthyl)), 6.74 (dt, *J* = 16.0, 2.0 Hz, 1H, -C$\underline{H}$=CHCO$_2$(menthyl)).

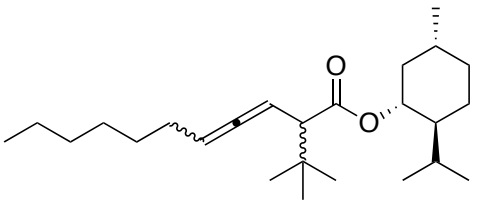
^{13}C NMR δ 13.99, 16.47, 19.75, 20.68, 21.98, 22.50, 23.63, 26.40, 28.33, 28.53, 31.28, 31.41, 34.30, 40.92, 47.17, 74.48, 78.01 (C≡C), 100.66 (C≡C), 125.84 (C=C), 129.80 (C=C), 165.72 (C=O).

IR (neat) 2956, 2930, 2215 (C≡C), 1713 (C=O), 1620 (C=C), 1457, 1370, 1299, 1176, 1096, 1013, 961, 916, 861, 757 cm^{-1}.

HRMS (ESI) Calcd for $C_{21}H_{34}O_2Na$ [M+Na]$^+$: 341.2451. Found: 341.2445.

$[\alpha]_D^{18}$ –85.36 (*c* 1.00, $CHCl_3$).

(-)-Menthyl 2-(*tert*-butyl)-3,4-undecadienoate (66)



To a suspension of (-)-menthyl (*E*)-2-undecen-4-ynoate (**65**) (63.7 mg, 0.200 mmol) and CuBr・SMe_2 (41.1 mg, 0.200 mmol) in 2 mL of THF was slowly added *tert*-butylmagnesium chloride (0.290 mL, 1.02 M solution in THF, 0.296 mmol) at –78 ºC over 15 min under argon. After the solution was slowly warmed to 0 ºC over 3 h, the reaction was terminated by the addition of aqueous saturated NH_4Cl solution (1 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed successively with water and brine, dried over Na_2SO_4, and concentrated *in vacuo* to give a crude oil, ^{1}H NMR analysis of which revealed that other regioisomers were absent and that the diastereoselectivity of the product was hardly determined due to the overlapping peaks. The crude product was chromatographed on silica gel (hexane-ethyl acetate) to afford the title compound (74.0 mg, 98%) as an oil, which is most likely a mixture of 4 diastereomers.

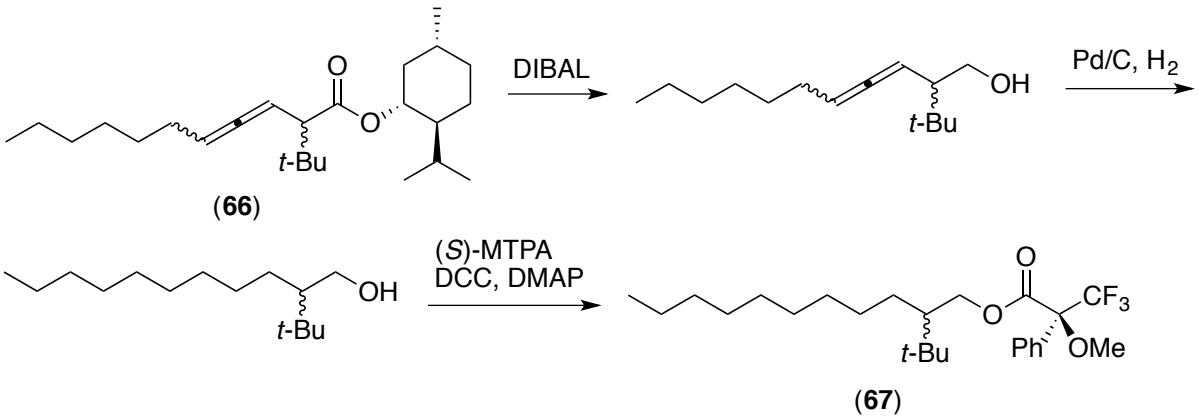
^{1}H NMR δ 0.76 (d, J = 6.8 Hz, 3H, cyclohexyl-Me), 0.84-0.93 (m, 9H, alkyl-Me and –CH($C\underline{H}_3$)$_2$), 0.99 (s, 9H, -C($C\underline{H}_3$)$_3$), 1.20-1.56 (m, 13H, alkyl H and cyclohexyl H), 1.68 (m, 2H, cyclohexyl H), 1.84-2.06 (m, 4H, -$C\underline{H}_2C_5H_{11}$, -$C\underline{H}Me_2$ and cyclohexyl H), 2.76 (d, J = 9.6 Hz, 1H, -$C\underline{H}CO_2$menthyl), 4.71 (m, 1H, cyclohexyl H), 5.06-5.26 (m, 2H, $C_6H_{13}C\underline{H}$=C=CH- and C_6H_{13}CH=C=C$\underline{H}$-).

^{13}C NMR δ 14.04, 15.88, 16.34, 20.69, 20.83, 22.02, 22.64, 23.14, 23.53, 25.95, 26.27, 27.50 (3 carbons, -C($\underline{C}H_3$)$_3$), 27.56 (3 carbons, -C($\underline{C}H_3$)$_3$), 28.46, 28.60, 28.79, 28.87, 28.96, 29.29, 31.43, 31.63, 31.66, 33.84, 34.17, 34.32, 40.87, 41.02, 47.00, 47.10, 57.15, 57.65, 73.94, 73.97, 74.14, 87.79, 91.20, 172.72 (C=O), 172.92 (C=O), 205.03 (C=$\underline{C}$=C), 205.09 (C=$\underline{C}$=C). These peaks are corresponding to a mixture of diastereomers.

IR (neat) 2956, 2928, 2870, 1963 (C=C=C), 1727 (C=O), 1655, 1457, 1367, 1254, 1146, 1096, 987, 878, 758 cm^{-1} for a mixture of diastereoisomers.

HRMS (ESI) Calcd for $C_{25}H_{44}O_2Na$ $[M+Na]^+$: 399.3234. Found: 399.3240 for a mixture of diastereoisomers.

Determination of the diastereoselectivity of 66 between the carbon α to carbonyl group and the chiral auxiliary



To a solution of (-)-menthyl 2-(*tert*-butyl)-3,4-undecadienoate (**66**) (69.6 mg, 0.185 mmol, most likely a mixture of 4 diastereoisomers) in 2 mL of THF was added diisobutylaluminum hydride (0.370 mL, 1.02 M in THF, 0.377 mmol) at –78 °C under argon. After the solution was slowly warmed to 0 °C over 3 h, the reaction was terminated by the addition of aqueous saturated potassium sodium tartrate solution (2 mL). After the mixture was stirred for an additional 1 h, the organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo* to give a crude oil, which was chromatographed on silica gel (hexane-ethyl acetate) to afford 2-(*tert*-butyl)-3,4-undecadien-1-ol (38.8 mg, 72%) as an oil.

A mixture of 2-(*tert*-butyl)-3,4-undecadien-1-ol (38.8 mg, 0.173 mmol) and 10% Pd/C (9.2 mg, 0.009 mmol) in 3 mL of EtOH was stirred at room temperature for 12 h under 1 atm of H_2. Then, the mixture was filtrated through a short pad of Celite with the aid of ethyl acetate. The combined filtrates were concentrated *in vacuo* to give a crude oil, which was chromatographed on silica gel (hexane-ethyl acetate) to afford 2-(*tert*-butyl)-1-undecanol (35.3 mg, 89%) as an oil.

To a solution of 2-(*tert*-butyl)-1-undecanol (11.4 mg, 0.050 mmol) and (*S*)-MTPA (17.6 mg, 0.075 mmol) in 2 mL of CH_2Cl_2 was added *N,N'*-dicyclohexylcarbodiimide (20.6 mg, 0.100 mmol) and 4-(dimethylamino)pyridine (3.1 mg, 0.025 mmol) at room temperature under argon. After the mixture was stirred at room temperature for 12 h, the mixture was filtrated through a short pad of Celite with the aid of ethyl acetate. The combined filtrates were concentrated *in vacuo* to give a crude oil, ^{1}H NMR analysis of which reveal that the diastereoselectivity of the product was 67:33. The crude product was chromatographed on silica gel (hexane-ethyl acetate) to afford MTPA ester of alcohol (12.4 mg, 56%) as an oil and of the same diastereomeric composition observed for crude sample.

^{1}H NMR δ 0.84 (s, 9H × 0.33, -C(C$\underline{H}_3$)$_3$), 0.86 (s, 9H × 0.67, -C(C$\underline{H}_3$)$_3$), 0.89 (t, *J* = 6.4 Hz, 3H, alkyl-Me), 1.04-1.45 (m, 16H, alkyl H), 1.92 (m, 1H, -C$\underline{H}$Bu-*t*), 3.54 (s, 3H × 0.67, -OC$\underline{H}_3$), 3.55 (s, 3H × 0.33, -OC$\underline{H}_3$), 4.19 (dd, *J* = 4.4, 11.2 Hz, 1H × 0.67, -C$\underline{H}_2$OMTPA-(*S*)), 4.26 (dd, *J* = 4.4, 11.2 Hz, 1H × 0.33, -C$\underline{H}_2$OMTPA-(*S*)), 4.36 (dd, *J* = 4.4, 11.2 Hz, 1H × 0.33, -C$\underline{H}_2$OMTPA-(*S*)), 4.45 (dd, *J* = 4.4, 11.2 Hz, 1H × 0.67, -C$\underline{H}_2$OMTPA-(*S*)), 7.34-7.42 (m, 3H, Ar-H), 7.48 (m, 2H, Ar-H).

^{13}C NMR δ 14.06, 22.66, [24.68 (major), 25.48 (minor)], [27.41 (major), 27.54 (minor)], [27.94 (3 carbons, -C(C$\underline{H}_3$)$_3$, minor), 27.98 (major)], [28.71 (major), 28.74 (minor)], [29.30 (major), 29.57 (minor)], [29.60 (major), 29.96 (minor)], 31.89, [32.78 (minor), 32.81 (major)], 34.93, [47.48 (minor), 47.50 (major)], [55.40 (major), 55.76 (minor)], [67.17 (major), 67.27 (minor)], 84.66 (q, *J* = 27.9 Hz,

$\underline{C}$-CF_3), [123.40 (q, J = 287.3 Hz, $\underline{C}F_3$, minor), 123.42 (major)], 127.33 (2 carbons, Ar), 128.32 (2 carbons, Ar), 129.47, [132.47 (major), 132.52 (minor)], 166.85 (C=O). A pair of diastereomeric peaks are shown in square brackets.

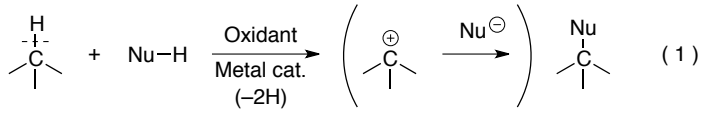
HRMS (ESI) Calcd for $C_{25}H_{39}O_3F_3Na$ $[M+Na]^+$: 467.2744. Found: 467.2743 for a 67:33 mixture of diastereoisomers.

Thus, the diastereoselectivity of **66** between the carbon α to carbonyl group and the chiral auxiliary was determined to 67:33.

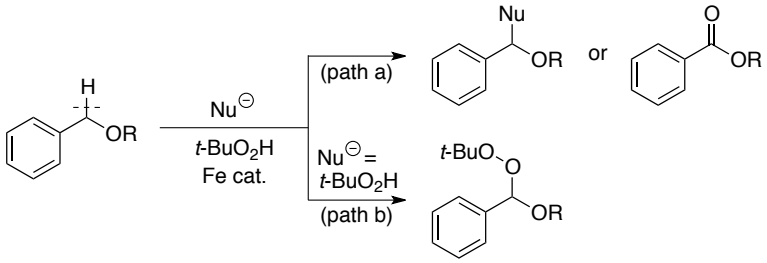
Chapter 4
Synthesis of *tert*-Butyl Peroxyacetals from Benzyl, Allyl, or Propargyl Ethers via Iron-Promoted C–H Bond Functionalization

1. Introduction

Direct functionalization of C–H bond is a useful method to form a new carbon-carbon or -heteroatom bond without any pretreatment of the starting materials. Recently, the substitution of a relatively inactive sp^3-C–H bond adjacent to a heteroatom has attracted much attention.[1,2] In these cases, the reaction has been usually performed in the presence of an oxidant to give a carbocation via the oxidative cleavage of a C–H bond, followed by the addition of a nucleophile. This process is facilitated by an activator such as transition metal catalysts as shown in eq 1. Although a variety of nucleophiles are amenable to this addition (Scheme 1, path a), it has not been amply investigated that the oxidant itself becomes the nucleophile to give a synthetically useful product. Herein we report an example of the latter reaction, where *t*-BuO_2H plays a dual effect as an oxidant of the C–H bond in benzyl ethers and a nucleophile as shown in path b of Scheme 1,[3,4] which is in stark contrast to the reactions with the externally added nucleophiles (path a).[4,5]



Scheme 1. Incorporation of different nucleophiles.

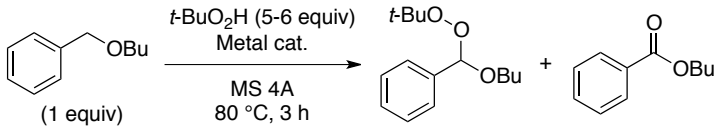


2. Results and Discussion

Table 1 summarizes the variation of metal salts, reaction conditions, and stoichiometry of the substrates and reagents. When benzyl butyl ether (**1**) was treated with *t*-BuO_2H under various transition-metal catalysis (entries 1–8, Table 1), ester **3** was a major product as expected from the previous reports.[3c–f,4a–c,5g–j,6] However, we found that the C–H bond activation with $Fe(acac)_3$[1,7] accompanied the introduction of a *t*-BuO_2– moiety to the substrate, giving mixed peroxyacetal **2**[4d] in good yield, which is the product of path b in Scheme 1 and is otherwise tedious to prepare (entries 9 and 10).[8,9] When the reaction was performed with molecular sieves 4A, the

result was better than that without it (entry 10 *vs*. 11). Among the various conditions and solvents examined, acetonitrile was found optimal to give desired **2** in the highest yield (entries 11-15). After further optimization shown in entries 16–18, the best result was obtained with $Fe(acac)_3$ (10 mol%) and molecular sieves (entry 16). Under these conditions, the formation of by-product **3** could be minimized. While the decomposition of initial product **2** to ester **3** appears a major side path as mentioned above, the yield of a *tert*-butyl acetal derived from the uptake of reduced *t*-BuOH was negligible under these conditions. The reaction could be carried out in the absence of a metal salt, but the reaction rate was lowered (entries 19 and 20). The iron catalyst seems to play a critical role to shorten the reaction period, which then minimizes the opportunity of subsequent decomposition of produced **2** to **3** during the reaction. The reaction system should be kept anhydrous by molecular sieves, otherwise water may cleave the *tert*-butyl peroxide bond to give the less stable hydroperoxide susceptible to decompose to esters. This is consistent with the fact that sterically hindered benzyl ethers show a tendency to give better product yields in this reaction, which will be discussed later.

Table 1. Optimization of the reaction conditions.



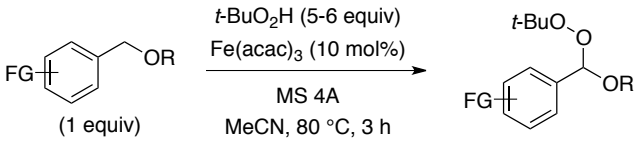
(**1**) (**2**) (**3**)

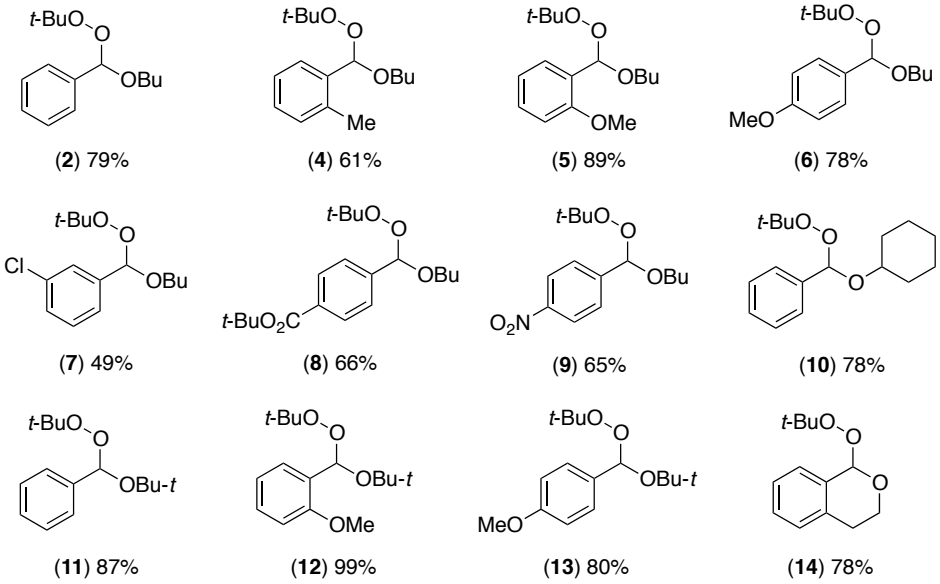
Entry	Metal cat. (mol%)	MS 4A[a]	Solvent	Yield (%)[b] by ^{1}H NMR		
				2	**3**	**1**
1	$MnCl_2$ (20)	–	MeCN	0	46	10
2	$CoCl_2$ (20)	–	MeCN	0	72	6
3	$CuCl_2$ (20)	–	MeCN	0	42	46
4	$NiCl_2$ (20)	–	MeCN	12	76	8
5	$FeCl_2$ (20)	–	MeCN	0	47	53
6	$FeCl_3$ (20)	–	MeCN	0	25	40
7	$FeBr_2$ (20)	–	MeCN	6	44	0
8	$FeBr_3$ (20)	–	MeCN	3	44	0
9	$Fe(OAc)_2$ (20)	–	MeCN	44	7	49
10	$Fe(acac)_3$ (20)	–	MeCN	57	33	10
11	$Fe(acac)_3$ (20)	+	MeCN	81	9	10
12	$Fe(acac)_3$ (20)	+	DCE	57	43	0
13	$Fe(acac)_3$ (20)	+	EtOAc	62	7	30
14	$Fe(acac)_3$ (20)	+	toluene	47	0	53
15	$Fe(acac)_3$ (20)	+	DMSO	2	10	88
16	$Fe(acac)_3$ (10)	+	MeCN	79 (79)	9	12
17[c]	$Fe(acac)_3$ (10)	+	MeCN	56	11	33
18	$Fe(acac)_3$ (5)	+	MeCN	70	7	23
19	–	+	MeCN	48	7	45
20[d]	–	+	MeCN	40	60	0

[a]Abbreviation + or - shows the presense or absence of molecular sieves.
[b]Isolated yield was shown in parentheses. [c]*t*-BuO_2H (3-3.6 equiv) was used.
[d]Reaction period was extended to 6 h.

This transformation is applicable to various benzyl ethers to give desired peroxyacetals as shown in Table 2. Although the undesired formation of esters in small amounts in most cases, they were easily separated by routine flash chromatography on silica gel. Benzyl ethers having an electron-withdrawing group recorded somewhat lower product yields (see products **7**–**9**), because of the increased formation of the corresponding esters. While 2,6-dimethoxybenzyl butyl ether did not afford the desired product, mono-*ortho*-substituents did not block the reaction (products **4**, **5**, and **12**). Interestingly, sterically demanding benzyl *tert*-butyl ethers gave the desired peroxyacetals **11**–**13** in better yields than the corresponding *n*-butyl ethers (**2**, **5**, and **6**). This may arise from the steric protection of the peroxy group against the attack of other reagents in the reaction media. A cyclic ether is also suitable for this reaction to give **14**[4a,b] in good yield. In contrast to the benzyl ethers, benzyl carboxylates and *N*-benzylamines and -amides were not good substrates for this reaction.

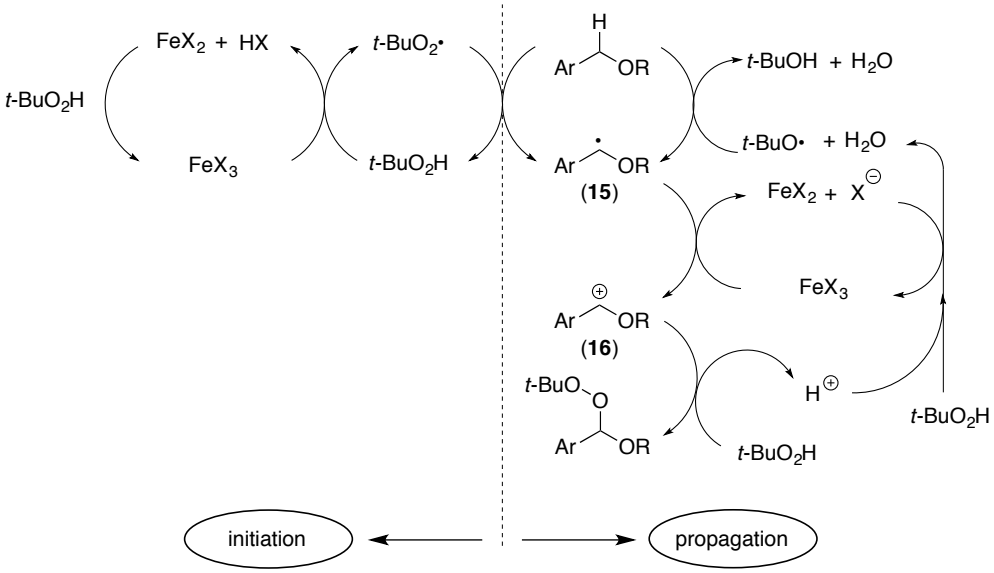
Table 2. Preparation of peroxyacetals.



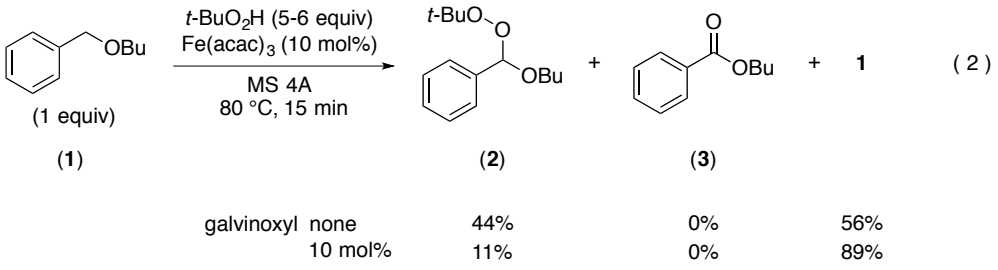


A mechanism of this reaction is proposed in Scheme 2.[10] First, this reaction starts with the generation of *t*-BuO_2• from *t*-BuO_2H, that is the initiation step. This radical abstracts a benzyl hydrogen to give a benzyl radical **15**, which is converted to benzyl cation **16** and *t*-BuO• under the iron catalysis to continue the propagation step. At the final stage, the resultant benzyl cation **16** reacts with *t*-BuO_2H to afford the desired product. As a whole, one equivalent of *t*-BuO_2H is employed as an oxidant (to generate *t*-BuOH and H_2O) and one more as a nucleophile.

Scheme 2. Possible reaction mechanism.

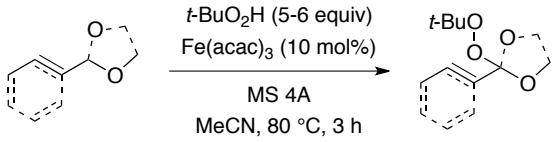


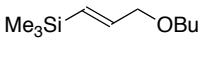
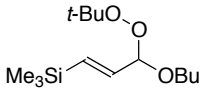
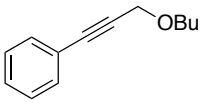
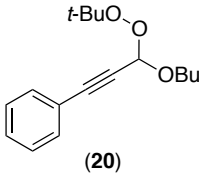
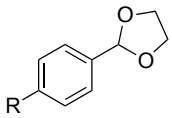
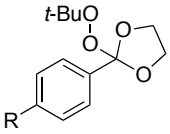
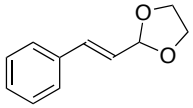
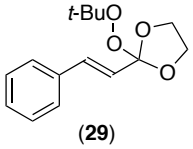
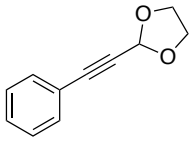
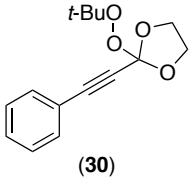
This mechanism involving radical species was evidenced by the fact that the addition of galvinoxyl suppressed the progress of reaction in eq 2. As suggested from the data of Table 1, the reaction could proceed without the iron salt due to the generation of *t*-BuO_2• by the thermal decomposition of *t*-BuO_2H itself, but this is likely promoted by the iron salt as shown in Scheme 2. The higher nucleophilicity[11] and lower steric congestion of *t*-BuO_2H than *t*-BuOH should explain the exclusive uptake of the *t*-BuO_2H in the presence of *t*-BuOH, particularly at the late stage of reaction.



The above mechanism suggests that a radical- or cation-stabilized group instead of the aryl would enable the similar reaction. This proved true, as allyl and propargyl ethers **17** and **19** took part in the same reaction to give olefinic and acetylenic peroxyacetals **18** and **20**, respectively, in good yields (entries 1 and 2, Table 3). In addition, benzylic acetals **21**–**23** were also good substrates for this transformation to afford peroxyorthoesters **26**[4e]–**28** in high yields (entries 3-5). Furthermore, the ethylene acetals of aliphatic unsaturated aldehydes **24** and **25** gave the corresponding peroxyorthoesters **29** and **30** in good yields (entries 6 and 7).

Table 3. Synthesis of various peroxyacetals and peroxyorthoesters.



Entry	Substrate	Product	Yield (%)[a]
1	 (**17**)	 (**18**)	60
2	 (**19**)	 (**20**)	53
3	 R = H (**21**)	 R = H (**26**)	97
4	Cl (**22**)	Cl (**27**)	99
5	OMe (**23**)	OMe (**28**)	90
6	 (**24**)	 (**29**)	97
7	 (**25**)	 (**30**)	84

[a]Isolated yield.

Conclusion

In conclusion, we developed the iron-promoted peroxidation of benzylic C–H bond with *t*-BuO_2H to give various *tert*-butyl peroxyacetals, which are otherwise tedious to obtain. This method is also applicable for the formation of olefinic and acetylenic *tert*-butyl peroxyacetals and unsaturated peroxyorthoesters. Further investigations on the new utilization of this reaction and synthetic applications of the peroxyacetals[12-14] and peroxyorthoesters is in progress in our laboratory.

3. References and Notes

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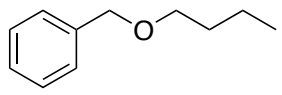
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14. Attempted deprotection of the acetal portion of **26** with CF_3CO_2H (0.3 equiv) in CH_2Cl_2 at room temperature brought about the decomposition of *t*-BuO_2 moiety only to give 2-hydroxyethyl benzoate in quantitative yield after aqueous work up.

Experimental Section (Chapter 4)

General. ^{1}H and ^{13}C NMR spectra were taken on a Varian Gemini-300 spectrometer at 300 and 75 MHz or Agilent 400-MR spectrometer at 400 and 100 MHz, respectively. $CDCl_3$ was used as the solvent. Chemical shifts are reported in parts per million shift (δ value) from Me_4Si (δ 0 ppm for ^{1}H) or based on the middle peak of the solvent ($CDCl_3$) (δ 77.00 ppm for ^{13}C NMR) as an internal standard. Signal patterns are indicated as br, broad; s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. Coupling constants (*J*) are given in Hertz. Infrared (IR) spectra were recorded on a JASCO A-100 spectrometer and are reported in wave numbers (cm^{-1}). High resolution mass spectra (HRMS) were obtained on a Bruker micrOTOF II in positive electrospray ionization (ESI) method calibrated with sodium formate at the Suzukake-dai Material Analysis Center, Technical Department, Tokyo Institute of Technology. $Fe(acac)_3$ (purity: 97%), *t*-butyl hydroperoxide (5.0-6.0 M in decane), and molecular sieves 4A (Catalog No. 688363-500G, powder, activated, 2.5 μm) were purchased from Sigma-Aldrich Co. (USA). Silica gel (Catalog No. 233-00077, 75-150 μm) was purchased from Wako Pure Chemical Industries, Ltd. (Japan). Chromatorex® NH (Cat. No. DM1020, size 100-200 mesh) was purchased from Fuji Silysia Chemical Ltd. (Japan). Dry solvents (THF, diethyl ether, CH_2Cl_2, and CH_3CN) were purchased from Kanto Chemicals Co. (Japan). Chemicals were purified or dried in a standard manner, if necessary.

Caution: Although we have not encountered any dangerous situation during this study, due care must be taken in handling peroxy compounds particularly in a large-scale preparation. *t*-Butyl hydroperoxide in decane should be transferred with a plastic pipette.

Benzyl butyl ether (1). This is a known compound [Ochiai, M.; Ito, T.; Takahashi, H.; Nakanishi, A.; Toyonari, M.; Sueda, T.; Goto, S.; Shiro, M. *J. Am. Chem. Soc.* **1996**, *118*, 7716-7730].



To a suspension of NaH (440 mg of a 60% suspension in mineral oil, 11.0 mmol) in THF (20 mL) was added butanol (0.920 mL, 10.1 mmol) at 0 °C under argon. After the mixture was stirred at room temperature for 1 h, benzyl bromide (1.19 mL, 10.0 mmol) was added at 0 °C. The mixture was stirred at room temperature overnight and was quenched with water. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with water and brine, dried over Na_2SO_4, and concentrated *in vacuo* to give a crude oil, which was chromatographed on silica gel (hexane-ethyl acetate) to afford the title compound (1.28 g, 78%) as an oil.

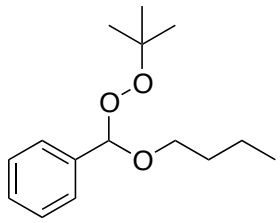
^{1}H NMR (300 MHz) δ 0.92 (t, *J* = 7.2 Hz, 3H, Me), 1.40 (sextet, *J* = 7.2 Hz, 2H, alkyl H), 1.60 (m, 2H, alkyl H), 3.48 (t, *J* = 6.6 Hz, 2H, -OC$\underline{H}_2$$(CH_2)_2CH_3$), 4.50 (s, 2H, benzyl H), 7.24-7.37 (m, 5H, Ar-H).

^{13}C NMR (75 MHz) δ 13.87, 19.34, 31.81, 70.14, 72.79, 127.38, 127.54 (2 carbons), 128.27 (2 carbons), 138.68.

IR (neat) 3090 (Ar), 3070 (Ar), 3030 (Ar), 2958, 2930, 2863, 1454, 1363, 1101, 733, 696 cm^{-1}.

These spectral properties were in good agreement with those reported in the above literature.

Typical procedure for the preparation of peroxyacetals. Butyl (*tert*-butylperoxy)(phenyl)methyl ether (2). This is a known compound [Ochiai, M.; Ito, T.; Takahashi, H.; Nakanishi, A.; Toyonari, M.; Sueda, T.; Goto, S.; Shiro, M. *J. Am. Chem. Soc.* **1996**, *118*, 7716-7730. Chen, L.-A.; Sung, K. *Org. Lett.* **2009**, *11*, 3370-3373].



To a suspension of benzyl butyl ether (**1**) (32.8 mg, 0.200 mmol), $Fe(acac)_3$ (7.1 mg, 0.020 mmol), and MS 4A (100 mg) in 1.0 mL of CH_3CN was added *tert*-butyl hydroperoxide (0.20 mL, 5.0-6.0 M solution in decane, *ca*. 1.0-1.2 mmol) by a plastic pipette at room temperature under argon. The mixture was stirred in an oil bath maintained at 80 °C for 3 h. After being cooled to room temperature, the reaction mixture was filtered through a short pad of silica gel with the aid of ethyl acetate. The combined filtrates were concentrated *in vacuo* to give a crude oil, ^{1}H NMR analysis of which revealed that the yields of the title compound, butyl benzoate (**3**) as a by-product, and recovered starting material **1** are 79%, 17%, and 4%, respectively, by using trichloroethylene as an internal standard. The crude oil was chromatographed on silica gel (hexane-ethyl acetate) to afford the title compound (40.0 mg, 79%) as an oil.

^{1}H NMR (300 MHz) δ 0.92 (t, J = 7.2 Hz, 3H, Me), 1.28 (s, 9H, -C($C\underline{H}_3$)$_3$), 1.42 (m, 2H, alkyl H), 1.65 (m, 2H, alkyl H), 3.66 (dt, J = 9.6, 6.6 Hz, 1H, -O$C\underline{H}_2$(CH$_2$)$_2$CH$_3$), 3.97 (dt, J = 9.6, 6.6 Hz, 1H, -O$C\underline{H}_2$(CH$_2$)$_2$CH$_3$), 5.82 (s, 1H, benzyl H), 7.31-7.39 (m, 3H, Ar-H), 7.44-7.50 (m, 2H, Ar-H).

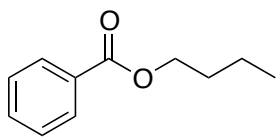
^{13}C NMR (75 MHz) δ 13.88, 19.30, 26.52 (3 carbons, -C($\underline{C}H_3$)$_3$), 32.00, 69.30, 80.78, 106.01, 126.86 (2 carbons), 128.14 (2 carbons), 128.71, 136.84.

IR (neat) 3090 (Ar), 3060 (Ar), 3030 (Ar), 2960, 2930, 2860, 1454, 1363, 1198, 1099 (C-O-O), 1003, 895, 754, 698 cm^{-1}.

Anal. Calcd for $C_{15}H_{24}O_3$: C, 71.39; H, 9.59. Found: C, 71.54; H, 9.52.

These spectral properties were in good agreement with those reported in the above literature.

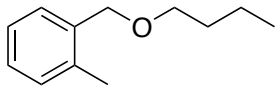
Butyl benzoate (3). This by-product of **2** is a known compound [Ochiai, M.; Ito, T.; Takahashi, H.; Nakanishi, A.; Toyonari, M.; Sueda, T.; Goto, S.; Shiro, M. *J. Am. Chem. Soc.* **1996**, *118*, 7716-7730. Chen, L.-A.; Sung, K. *Org. Lett.* **2009**, *11*, 3370-3373].



^{1}H NMR (300 MHz) δ 0.98 (t, J = 7.2 Hz, 3H, Me), 1.40-1.83 (m, 4H, alkyl H), 4.33 (t, J = 6.6 Hz, 2H,

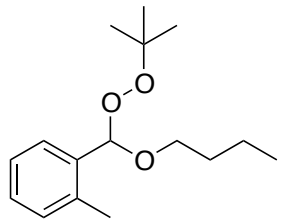
-OC$\underline{H}_2$(CH$_2$)$_2$CH$_3$), 7.38-7.64 (m, 3H, Ar-H), 8.04 (d, *J* = 8.4 Hz, 2H, Ar-H).
These spectral properties were in good agreement with those reported in the above literature.

Butyl (2-methylphenyl)methyl ether.



To a solution of (2-methylphenyl)magnesium bromide [prepared from 1-bromo-2-methylbenzene (0.600 mL, 4.99 mmol) and magnesium turnings (146 mg, 6.00 mmol) in THF (4 mL)] was added a suspension of paraformaldehyde (167 mg, 4.96 mmol) in THF (5 mL) at room temperature. After the mixture was stirred in an oil bath maintained at 50 °C for 1 h, the reaction was terminated by the addition of aqueous saturated NH_4Cl solution. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo* to give a crude oil, which was chromatographed on silica gel (hexane-ethyl acetate) to afford (2-methylphenyl)methanol (582 mg, 95%) as an oil.
To a solution of (2-methylphenyl)methanol obtained above (367 mg, 3.00 mmol) in Et_2O (5 mL) was added phosphorus tribromide (0.110 mL, 1.16 mmol) at 0 °C. After the mixture was stirred at room temperature for 3 h, water was added. The organic products were extracted with ether. The combined organic layers were washed with aqueous saturated $NaHCO_3$ solution, dried over Na_2SO_4, and concentrated *in vacuo* to give a crude oil of 1-(bromomethyl)-2-methylbenzene (317 mg, 57%), which was spectroscopically pure and was directly used in the next step.
To a suspension of NaH (75.2 mg of a 60% suspension in mineral oil, *ca*. 1.88 mmol) in THF (3 mL) was added butanol (0.160 mL, 1.75 mmol) at 0 °C under argon. After the mixture was stirred at room temperature for 1 h, 1-(bromomethyl)-2-methylbenzene (317 mg, 1.71 mmol) in THF (3 mL) was added at 0 °C. The mixture was stirred at room temperature overnight and was quenched with water. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with water and brine, dried over Na_2SO_4, and concentrated *in vacuo* to give a crude oil, which was chromatographed on silica gel (hexane-ethyl acetate) to afford the title compound (189 mg, 62%) as an oil.
^{1}H NMR (300 MHz) δ 0.92 (t, *J* = 7.2 Hz, 3H, alkyl-Me), 1.40 (sextet, *J* = 7.2 Hz, 2H, alkyl H), 1.62 (m, 2H, alkyl H), 2.34 (s, 3H, Ar-Me), 3.49 (t, *J* = 6.6 Hz, 2H, -OC$\underline{H}_2$(CH$_2$)$_2$CH$_3$), 4.49 (s, 2H, benzyl H), 7.13-7.22 (m, 3H, Ar-H), 7.32 (m, 1H, Ar-H).
^{1}H NMR (400 MHz) δ 0.92 (t, *J* = 7.2 Hz, 3H, alkyl-Me), 1.40 (sextet, *J* = 7.2 Hz, 2H, alkyl H), 1.61 (m, 2H, alkyl H), 2.33 (s, 3H, Ar-Me), 3.49 (t, *J* = 6.4 Hz, 2H, -OC$\underline{H}_2$(CH$_2$)$_2$CH$_3$), 4.49 (s, 2H, benzyl H), 7.13-7.22 (m, 3H, Ar-H), 7.32 (m, 1H, Ar-H).
^{13}C NMR (75 MHz) δ 13.92, 18.76, 19.41, 31.85, 70.31, 71.28, 125.70, 127.64, 128.43, 130.14, 136.47, 136.62.
^{13}C NMR (100 MHz) δ 13.91, 18.74, 19.42, 31.87, 70.33, 71.29, 125.70, 127.63, 128.44, 130.15, 136.53, 136.61.
IR (neat) 3068 (Ar), 3021 (Ar), 2958, 2931, 2866, 1462, 1360, 1095, 744 cm^{-1}.
Anal. Calcd for $C_{12}H_{18}O$: C, 80.85; H, 10.18. Found: C, 80.49; H, 10.10.

Butyl (*tert*-butylperoxy)(2-methylphenyl)methyl ether (4).



To a suspension of butyl (2-methylphenyl)methyl ether (35.7 mg, 0.200 mmol), $Fe(acac)_3$ (7.1 mg, 0.020 mmol), and MS 4A (100 mg) in 1.0 mL of CH_3CN was added *tert*-butyl hydroperoxide (0.20 mL, 5.0-6.0 M solution in decane, *ca*. 1.0-1.2 mmol) by a plastic pipette at room temperature under argon. The mixture was stirred in an oil bath maintained at 80 °C for 3 h. After being cooled to room temperature, the reaction mixture was filtered through a short pad of silica gel with the aid of ethyl acetate. The combined filtrates were concentrated *in vacuo* to give a crude oil, ^{1}H NMR analysis of which revealed that the yields of the title compound, butyl 2-methylbenzoate as a by-product, and recovered starting material are 68%, 5%, and 20%, respectively, by using trichloroethylene as an internal standard. The crude oil was chromatographed on silica gel (hexane-ethyl acetate) to afford the title compound (32.4 mg, 61%) as an oil.

^{1}H NMR (300 MHz) δ 0.90 (t, *J* = 6.9 Hz, 3H, alkyl-Me), 1.26 (s, 9H, -C(C$\underline{H}_3$)$_3$), 1.40 (m, 2H, alkyl H), 1.60 (m, 2H, alkyl H), 2.41 (s, 3H, Ar-Me), 3.63 (dt, *J* = 9.6, 6.6 Hz, 1H, -OC$\underline{H}_2$(CH$_2$)$_2$CH$_3$), 3.93 (dt, *J* = 9.6, 6.6 Hz, 1H, -OC$\underline{H}_2$(CH$_2$)$_2$CH$_3$), 5.91 (s, 1H, benzyl H), 7.12-7.24 (m, 3H, Ar-H), 7.50 (d, *J* = 7.5 Hz, 1H, Ar-H).

^{1}H NMR (400 MHz) δ 0.90 (t, *J* = 7.2 Hz, 3H, alkyl-Me), 1.26 (s, 9H, -C(C$\underline{H}_3$)$_3$), 1.39 (m, 2H, alkyl H), 1.61 (m, 2H, alkyl H), 2.41 (s, 3H, Ar-Me), 3.63 (dt, *J* = 9.6, 6.8 Hz, 1H, -OC$\underline{H}_2$(CH$_2$)$_2$CH$_3$), 3.93 (dt, *J* = 9.6, 6.8 Hz, 1H, -OC$\underline{H}_2$(CH$_2$)$_2$CH$_3$), 5.91 (s, 1H, benzyl H), 7.13-7.25 (m, 3H, Ar-H), 7.50 (d, *J* = 7.6 Hz, 1H, Ar-H).

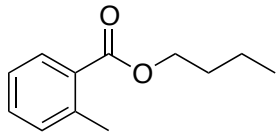
^{13}C NMR (75 MHz) δ 13.88, 19.23, 19.31, 26.55 (3 carbons, -C($\underline{C}$H$_3$)$_3$), 32.04, 69.40, 80.51, 104.51, 125.59, 126.93, 128.58, 130.38, 134.97, 136.14.

^{13}C NMR (100 MHz) δ 13.87, 19.21, 19.32, 26.56 (3 carbons, -C($\underline{C}$H$_3$)$_3$), 32.06, 69.40, 80.50, 104.54, 125.59, 126.96, 128.57, 130.38, 135.02, 136.16.

IR (neat) 3068 (Ar), 3024 (Ar), 2960, 2871, 1462, 1363, 1198, 1092 (C-O-O), 1003, 901, 754 cm^{-1}.

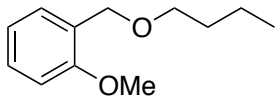
Anal. Calcd for $C_{16}H_{26}O_3$: C, 72.14; H, 9.84. Found: C, 72.28; H, 9.69.

Butyl 2-methylbenzoate. This by-product of **4** is a known compound [Liu, Q.; Li, G.; Liu, J.; Li, P.; Lei, A. *Angew. Chem. Int. Ed.* **2010**, *49*, 3371-3374].



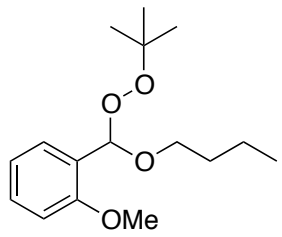
^{1}H NMR (300 MHz) δ 0.98 (t, *J* = 7.2 Hz, 3H, -OCH$_2$(CH$_2$)C$\underline{H}_3$), 1.47 (m, 2H, alkyl H), 1.75 (m, 2H, alkyl H), 2.65 (s, 3H, Ar-Me), 4.40 (t, *J* = 6.4 Hz, 2H, -OC$\underline{H}_2$(CH$_2$)$_2$CH$_3$), 7.23-7.29 (m, 2H, Ar-H), 7.40 (m, 1H, Ar-H), 7.95 (d, *J* = 8.1 Hz, 1H, Ar-H).
These spectral properties were in good agreement with those reported in the above literature.

Butyl (2-methoxyphenyl)methyl ether.



To a solution of 2-methoxybenzaldehyde (1.21 mL, 10.0 mmol) in THF (5 mL) and MeOH (10 mL) was added $NaBH_4$ (585 mg, 15.0 mmol) at 0 °C. After the mixture was stirred at the same temperature for 30 min, the reaction was terminated by the addition of cold 0.5 N HCl solution (5 mL). After the reaction mixture was poured into water, the organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo* to give a crude oil, which was chromatographed on silica gel (hexane-ethyl acetate) to afford (2-methoxyphenyl)methanol (1.30 g, 94%) as an oil.
To a solution of (2-methoxyphenyl)methanol obtained above (1.30 g, 9.41 mmol) in Et_2O (15 mL) was added phosphorus tribromide (0.360 mL, 3.79 mmol) at 0 °C. After the mixture was stirred at room temperature for 3 h, water was added. The organic products were extracted with ether. The combined organic layers were washed with aqueous saturated $NaHCO_3$ solution, dried over Na_2SO_4, and concentrated *in vacuo* to give a crude oil of 1-(bromomethyl)-2-methoxybenzene (1.75 g, 92%), which was spectroscopically pure and was directly used in the next step.
To a suspension of NaH (220 mg of a 60% suspension in mineral oil, *ca*. 5.50 mmol) in THF (5 mL) was added butanol (0.460 mL, 5.03 mmol) at 0 °C under argon. After the mixture was stirred at room temperature for 1 h, 1-(bromomethyl)-2-methoxybenzene (1.01 g, 5.02 mmol) in THF (5 mL) was added at 0 °C. The mixture was stirred at room temperature overnight and was quenched with water. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with water and brine, dried over Na_2SO_4, and concentrated *in vacuo* to give a crude oil, which was chromatographed on silica gel (hexane-ethyl acetate) to afford the title compound (468 mg, 48%) as an oil.
^{1}H NMR (300 MHz) δ 0.92 (t, *J* = 7.2 Hz, 3H, Me), 1.41 (sextet, *J* = 7.2 Hz, 2H, alkyl H), 1.62 (m, 2H, alkyl H), 3.51 (t, *J* = 6.6 Hz, 2H, -OC$\underline{H}_2$(CH$_2$)$_2$CH$_3$), 3.83 (s, 3H, -O$\underline{Me}$), 4.54 (s, 2H, benzyl H), 6.86 (d, *J* = 8.1 Hz, 1H, Ar-H), 6.95 (t, *J* = 6.9 Hz, 1H, Ar-H), 7.25 (m, 1H, Ar-H), 7.38 (d, *J* = 6.9 Hz, 1H, Ar-H).
^{13}C NMR (75 MHz) δ 13.89, 19.34, 31.81, 55.22, 67.42, 70.37, 110.05, 120.33, 127.07, 128.31, 128.59, 156.94.
IR (neat) 3040 (Ar), 3000 (Ar), 2958, 2930, 2868, 1603, 1591, 1495, 1464, 1242, 1095, 1032, 831, 754 cm^{-1}.
Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 74.22; H, 9.33.

Butyl (*tert*-butylperoxy)(2-methoxyphenyl)methyl ether (5).



To a suspension of butyl (2-methoxyphenyl)methyl ether (38.9 mg, 0.200 mmol), $Fe(acac)_3$ (7.1 mg, 0.020 mmol), and MS 4A (100 mg) in 1.0 mL of CH_3CN was added *tert*-butyl hydroperoxide (0.20 mL, 5.0-6.0 M solution in decane, *ca*. 1.0-1.2 mmol) by a plastic pipette at room temperature under argon. The mixture was stirred in an oil bath maintained at 80 °C for 3 h. After being cooled to room temperature, the reaction mixture was filtered through a short pad of silica gel with the aid of ethyl acetate. The combined filtrates were concentrated *in vacuo* to give a crude oil, ^{1}H NMR analysis of which revealed that the yields of the title compound, butyl 2-methoxybenzoate as a by-product, and recovered starting material are 90%, 5%, and 5%, respectively, by using trichloroethylene as an internal standard. The crude oil was chromatographed on silica gel (hexane-ethyl acetate) to afford the title compound (50.4 mg, 89%) as an oil.

^{1}H NMR (300 MHz) δ 0.90 (t, *J* = 6.9 Hz, 3H, alkyl-Me), 1.25 (s, 9H, -C(C$\underline{H}_3$)$_3$), 1.39 (m, 2H, alkyl H), 1.61 (m, 2H, alkyl H), 3.64 (dt, *J* = 9.6, 6.6 Hz, 1H, -OC$\underline{H}_2$(CH$_2$)$_2$CH$_3$), 3.84 (s, 3H, -O$\underline{Me}$), 3.98 (dt, *J* = 9.6, 6.6 Hz, 1H, -OC$\underline{H}_2$(CH$_2$)$_2$CH$_3$), 6.15 (s, 1H, benzyl H), 6.87 (d, *J* = 7.7 Hz, 1H, Ar-H), 6.95 (t, *J* = 7.7 Hz, 1H, Ar-H), 7.31 (t, *J* = 7.7 Hz, 1H, Ar-H), 7.56 (d, *J* = 7.7 Hz, 1H, Ar-H).

^{1}H NMR (400 MHz) δ 0.90 (t, *J* = 7.2 Hz, 3H, alkyl-Me), 1.25 (s, 9H, -C(C$\underline{H}_3$)$_3$), 1.39 (m, 2H, alkyl H), 1.62 (m, 2H, alkyl H), 3.64 (dt, *J* = 9.6, 6.8 Hz, 1H, -OC$\underline{H}_2$(CH$_2$)$_2$CH$_3$), 3.83 (s, 3H, -O$\underline{Me}$), 3.98 (dt, *J* = 9.6, 6.8 Hz, 1H, -OC$\underline{H}_2$(CH$_2$)$_2$CH$_3$), 6.15 (s, 1H, benzyl H), 6.87 (d, *J* = 7.6 Hz, 1H, Ar-H), 6.95 (t, *J* = 7.6 Hz, 1H, Ar-H), 7.30 (t, *J* = 7.6 Hz, 1H, Ar-H), 7.56 (d, *J* = 7.6 Hz, 1H, Ar-H).

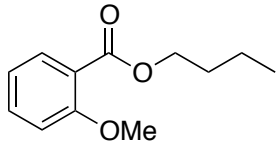
^{13}C NMR (75 MHz) δ 13.87, 19.24, 26.40 (3 carbons, -C($\underline{C}$H$_3$)$_3$), 32.03, 55.22, 69.90, 80.61, 101.44, 110.31, 120.36, 125.12, 127.79, 129.86, 156.63.

^{13}C NMR (100 MHz) δ 13.88, 19.26, 26.44 (3 carbons, -C($\underline{C}$H$_3$)$_3$), 32.04, 55.27, 69.92, 80.63, 101.45, 110.35, 120.39, 125.19, 127.83, 129.87, 156.66.

IR (neat) 3080 (Ar), 3020 (Ar), 2960, 2930, 2880, 1604, 1495, 1466, 1363, 1286, 1248, 1198, 1092 (C-O-O), 895, 754 cm^{-1}.

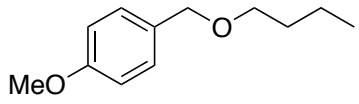
Anal. Calcd for $C_{16}H_{26}O_4$: C, 68.06; H, 9.28. Found: C, 68.06; H, 9.43.

Butyl 2-methoxybenzoate. This by-product of **5** is a known compound [Magerlein, W.; Indolese, A. F.; Beller, M. *J. Organomet. Chem.* **2002**, *641*, 30-40].



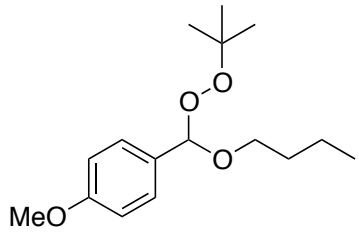
^{1}H NMR (300 MHz) δ 0.95 (t, *J* = 7.4 Hz, 3H, -OCH$_2$(CH$_2$)$_2$C<u>H$_3$</u>), 1.46 (m, 2H, alkyl H), 1.72 (m, 2H, alkyl H), 3.87 (s, 3H, -O<u>Me</u>), 4.28 (t, *J* = 6.6 Hz, 2H, -OC<u>H$_2$</u>(CH$_2$)$_2$CH$_3$), 6.95 (m, 2H, Ar-H), 7.43 (t, *J* = 8.1 Hz, 1H, Ar-H), 7.77 (d, *J* = 7.9 Hz, 1H, Ar-H).
These spectral properties were in good agreement with those reported in the above literature.

Butyl (4-methoxyphenyl)methyl ether. This is a known compound [Ochiai, M.; Ito, T.; Takahashi, H.; Nakanishi, A.; Toyonari, M.; Sueda, T.; Goto, S.; Shiro, M. *J. Am. Chem. Soc.* **1996**, *118*, 7716-7730. Corma, A.; Renz, M. *Angew. Chem. Int. Ed.* **2007**, *46*, 298-300].



To a solution of (4-methoxyphenyl)methanol (1.24 mL, 10.0 mmol) in Et$_2$O (15 mL) was added phosphorus tribromide (0.380 mL, 4.00 mmol) at 0 °C. After the mixture was stirred at room temperature for 3 h, water was added. The organic products were extracted with ether. The combined organic layers were washed with saturated NaHCO$_3$ solution, dried over Na$_2$SO$_4$, and concentrated *in vacuo* to give a crude oil of 1-(bromomethyl)-4-methoxybenzene (1.54 g, 77%), which was spectroscopically pure and was directly used in the next step.
To a suspension of NaH (220 mg of a 60% suspension in mineral oil, 5.50 mmol) in THF (5 mL) was added butanol (0.460 mL, 5.03 mmol) at 0 °C under argon. After the mixture was stirred at room temperature for 1 h, 1-(bromomethyl)-4-methoxybenzene (1.01 g, *ca*. 5.02 mmol) in THF (5 mL) was added at 0 °C. The mixture was stirred at room temperature overnight and was quenched with water. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with water and brine, dried over Na$_2$SO$_4$, and concentrated *in vacuo* to give a crude oil, which was chromatographed on silica gel (hexane-ethyl acetate) to afford the title compound (643 mg, 66%) as an oil.
^{1}H NMR (300 MHz) δ 0.91 (t, *J* = 7.2 Hz, 3H, -OCH$_2$(CH$_2$)$_2$C<u>H$_3$</u>), 1.38 (sextet, *J* = 7.2 Hz, 2H, alkyl H), 1.59 (m, 2H, alkyl H), 3.44 (t, *J* = 6.6 Hz, 2H, -OC<u>H$_2$</u>(CH$_2$)$_2$CH$_3$), 3.80 (s, 3H, -O<u>Me</u>), 4.43 (s, 2H, benzyl H), 6.87 (d, *J* = 8.7 Hz, 2H, Ar-H), 7.26 (d, *J* = 8.7 Hz, 2H, Ar-H).
^{13}C NMR (75 MHz) δ 13.86, 19.32, 31.78, 55.14, 69.83, 72.42, 113.64 (2 carbons), 129.12 (2 carbons), 130.74, 159.01.
IR (neat) 3060 (Ar), 3030 (Ar), 3000 (Ar), 2958, 2930, 2863, 1612, 1514, 1464, 1362, 1302, 1248, 1173, 1097, 1038, 822, 756 cm^{-1}.
Anal. Calcd for C$_{12}$H$_{18}$O$_2$: C, 74.19; H, 9.34. Found: C, 74.27; H, 9.31.
These spectral properties were in good agreement with those reported in the above literature.

Butyl (*tert*-butylperoxy)(4-methoxyphenyl)methyl ether (6).



To a suspension of butyl (4-methoxyphenyl)methyl ether (38.9 mg, 0.200 mmol), $Fe(acac)_3$ (7.1 mg, 0.020 mmol), and MS 4A (100 mg) in 1.0 mL of CH_3CN was added *tert*-butyl hydroperoxide (0.20 mL, 5.0-6.0 M solution in decane, *ca*. 1.0-1.2 mmol) by a plastic pipette at room temperature under argon. The mixture was stirred in an oil bath maintained at 80 °C for 3 h. After being cooled to room temperature, the reaction mixture was filtered through a short pad of silica gel with the aid of ethyl acetate. The combined filtrates were concentrated *in vacuo* to give a crude oil, ^{1}H NMR analysis of which revealed that the yields of the title compound, butyl 4-methoxybenzoate as a by-product, and recovered starting material are 77%, 23%, and 0%, respectively, by using trichloroethylene as an internal standard. The crude oil was chromatographed on silica gel (hexane-ethyl acetate) to afford the title compound (44.0 mg, 78%) as an oil.

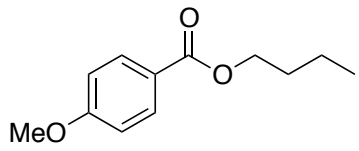
^{1}H NMR (300 MHz) δ 0.92 (t, J = 7.2 Hz, 3H, -OCH$_2$(CH$_2$)$_2$C<u>H</u>$_3$), 1.28 (s, 9H, -C(C<u>H</u>$_3$)$_3$), 1.41 (m, 2H, alkyl H), 1.64 (m, 2H, alkyl H), 3.63 (dt, J = 9.6, 6.6 Hz, 1H, -OC<u>H</u>$_2$(CH$_2$)$_2$CH$_3$), 3.81 (s, 3H, -O<u>Me</u>), 3.95 (dt, J = 9.6, 6.6 Hz, 1H, -OC<u>H</u>$_2$(CH$_2$)$_2$CH$_3$), 5.77 (s, 1H, benzyl H), 6.88 (d, J = 8.7 Hz, 2H, Ar-H), 7.40 (d, J = 8.7 Hz, 2H, Ar-H).

^{13}C NMR (75 MHz) δ 13.89, 19.31, 26.53 (3 carbons, -C(<u>C</u>H$_3$)$_3$), 55.21, 69.24, 80.69, 105.90, 113.50 (2 carbons), 128.14 (2 peaks consisting of 1 carbon and 2 carbons), 129.15, 159.87 .

IR (neat) 3100 (Ar), 3060 (Ar), 3040 (Ar), 2960, 2873, 1614, 1514, 1464, 1363, 1304, 1250, 1198, 1171, 1095 (C-O-O), 1038, 897, 827 cm^{-1}.

Anal. Calcd for $C_{16}H_{26}O_4$: C, 68.06; H, 9.28. Found: C, 68.19; H, 9.29.

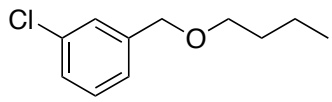
Butyl 4-methoxybenzoate. This by-product of **6** is a known compound [Ochiai, M.; Ito, T.; Takahashi, H.; Nakanishi, A.; Toyonari, M.; Sueda, T.; Goto, S.; Shiro, M. *J. Am. Chem. Soc*. **1996**, *118*, 7716-7730. Neumann, H.; Brennführer, A.; Groβ, P.; Riermeier, T.; Almena, J.; Beller, M. *Adv. Synth. Catal*. **2006**, *348*, 1255-1261].



^{1}H NMR (300 MHz) δ 0.98 (t, J = 7.2 Hz, 3H, -OCH$_2$(CH$_2$)$_2$C<u>H</u>$_3$), 1.36-1.81 (m, 4H, alkyl H), 3.86 (s, 3H, -O<u>Me</u>), 4.30 (t, J = 6.3 Hz, 2H, -OC<u>H</u>$_2$(CH$_2$)$_2$CH$_3$), 6.91 (d, J = 8.7 Hz, 2H, Ar-H), 8.00 (d, J = 8.7 Hz, 2H, Ar-H).

These spectral properties were in good agreement with those reported in the above literature.

Butyl (3-chlorophenyl)methyl ether. This is a known compound [Ochiai, M.; Ito, T.; Takahashi, H.; Nakanishi, A.; Toyonari, M.; Sueda, T.; Goto, S.; Shiro, M. *J. Am. Chem. Soc.* **1996**, *118*, 7716-7730].



To a solution of 3-chlorobenzaldehyde (1.13 mL, 9.98 mmol) in THF (5 mL) and MeOH (10 mL) was added $NaBH_4$ (585 mg, 15.0 mmol) at 0 °C. After the mixture was stirred at the same temperature for 50 min, the reaction was terminated by the addition of cold 0.5 N HCl solution (5 mL). After the reaction mixture was poured into water, the organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo* to give a crude oil, which was chromatographed on silica gel (hexane-ethyl acetate) to afford (3-chlorophenyl)methanol (1.31 g, 92%) as an oil.

To a solution of (3-chlorophenyl)methanol obtained above (1.31 g, 9.19 mmol) in Et_2O (15 mL) was added phosphorus tribromide (0.350 mL, 3.69 mmol) at 0 °C. After the mixture was stirred at room temperature for 3 h, water was added. The organic products were extracted with ether. The combined organic layers were washed with saturated $NaHCO_3$ solution, dried over Na_2SO_4, and concentrated *in vacuo* to give a crude oil of 1-(bromomethyl)-3-chlorobenzene (1.77 g, 94%), which was spectroscopically pure and was directly used in the next step.

To a suspension of NaH (220 mg of a 60% suspension in mineral oil, 5.50 mmol) in THF (5 mL) was added butanol (0.460 mL, 5.03 mmol) at 0 °C under argon. After the mixture was stirred at room temperature for 1 h, 1-(bromomethyl)-3-chlorobenzene (1.03 g, *ca.* 5.01 mmol) in THF (5 mL) was added at 0 °C. The mixture was stirred at room temperature overnight and was quenched with water. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with water and brine, dried over Na_2SO_4, and concentrated *in vacuo* to give a crude oil, which was chromatographed on silica gel (hexane-ethyl acetate) to afford the title compound (482 mg, 49%) as an oil.

^{1}H NMR (300 MHz) δ 0.93 (t, J = 7.2 Hz, 3H, Me), 1.40 (sextet, J = 7.2 Hz, 2H, alkyl H), 1.59 (m, 2H, alkyl H), 3.48 (t, J = 6.6 Hz, 2H, -OC$\underline{H}_2$(CH$_2$)$_2$CH$_3$), 4.47 (s, 2H, benzyl H), 7.18-7.31 (m, 3H, Ar-H), 7.34 (s, 1H, Ar-H).

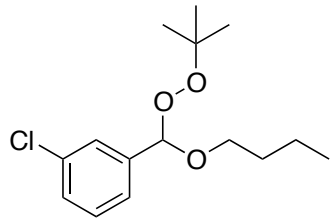
^{13}C NMR (75 MHz) δ 13.87, 19.32, 31.76, 70.42, 72.00, 125.43, 127.49 (2 peaks), 129.56, 134.22, 140.85.

IR (neat) 3070 (Ar), 3020 (Ar), 2958, 2950, 2868, 1601, 1577, 1475, 1430, 1356, 1201, 1109, 779, 683 cm^{-1}.

Anal. Calcd for $C_{11}H_{15}ClO$: C, 66.49; H, 7.61. Found: C, 66.55; H, 7.64.

These spectral properties were in good agreement with those reported in the above literature.

Butyl (*tert*-butylperoxy)(3-chlorophenyl)methyl ether (7).



To a suspension of butyl (3-chlorophenyl)methyl ether (39.7 mg, 0.200 mmol), $Fe(acac)_3$ (7.1 mg, 0.020 mmol), and MS 4A (100 mg) in 1.0 mL of CH_3CN was added *tert*-butyl hydroperoxide (0.20 mL, 5.0-6.0 M solution in decane, *ca*. 1.0-1.2 mmol) by a plastic pipette at room temperature under argon. The mixture was stirred in an oil bath maintained at 80 °C for 3 h. After being cooled to room temperature, the reaction mixture was filtered through a short pad of silica gel with the aid of ethyl acetate. The combined filtrates were concentrated *in vacuo* to give a crude oil, ^{1}H NMR analysis of which revealed that the yields of the title compound, butyl 3-chlorobenzoate as a by-product, and recovered starting material are 56%, 33%, and 0%, respectively, by using trichloroethylene as an internal standard. The crude oil was chromatographed on silica gel (hexane-ethyl acetate) to afford the title compound (56.2 mg, 49%) as an oil.

^{1}H NMR (300 MHz) δ 0.93 (t, *J* = 7.5 Hz, 3H, Me), 1.28 (s, 9H, -C(C$\underline{H}_3$)$_3$), 1.42 (sextet, *J* = 7.5 Hz, 2H, alkyl H), 1.65 (m, 2H, alkyl H), 3.66 (dt, *J* = 9.6, 6.6 Hz, 1H, -OC$\underline{H}_2$(CH$_2$)$_2$CH$_3$), 3.98 (dt, *J* = 9.6, 6.6 Hz, 1H, -OC$\underline{H}_2$(CH$_2$)$_2$CH$_3$), 5.77 (s, 1H, benzyl H), 7.27-7.38 (m, 3H, Ar-H), 7.46 (s, 1H, Ar-H).

^{1}H NMR (400 MHz) δ 0.93 (t, *J* = 7.6 Hz, 3H, Me), 1.27 (s, 9H, -C(C$\underline{H}_3$)$_3$), 1.42 (sextet, *J* = 7.6 Hz, 2H, alkyl H), 1.65 (m, 2H, alkyl H), 3.66 (dt, *J* = 9.6, 6.8 Hz, 1H, -OC$\underline{H}_2$(CH$_2$)$_2$CH$_3$), 3.98 (dt, *J* = 9.6, 6.8 Hz, 1H, -OC$\underline{H}_2$(CH$_2$)$_2$CH$_3$), 5.77 (s, 1H, benzyl H), 7.27-7.37 (m, 3H, Ar-H), 7.47 (s, 1H, Ar-H).

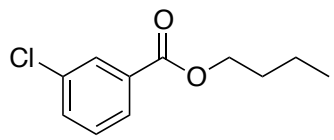
^{13}C NMR (75 MHz) δ 13.86, 19.28, 26.50 (3 carbons, -C($\underline{C}$H$_3$)$_3$), 31.92, 69.52, 80.91, 104.97, 125.09, 127.12, 128.83, 129.43, 134.07, 138.87.

^{13}C NMR (100 MHz) δ 13.86, 19.29, 26.52 (3 carbons, -C($\underline{C}$H$_3$)$_3$), 31.94, 69.52, 80.92, 104.98, 125.10, 127.14, 128.83, 129.44, 134.09, 138.91.

IR (neat) 3072 (Ar), 2960, 2933, 2873, 1577, 1475, 1363, 1198, 1105 (C-O-O), 1003, 874, 786, 719, 687 cm^{-1}.

Anal. Calcd for $C_{15}H_{23}ClO_3$: C, 62.82; H, 8.08. Found: C, 62.86; H, 8.26.

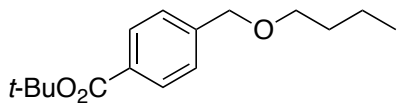
Butyl 3-chlorobenzoate. This by-product of **7** is a known compound [Ochiai, M.; Ito, T.; Takahashi, H.; Nakanishi, A.; Toyonari, M.; Sueda, T.; Goto, S.; Shiro, M. *J. Am. Chem. Soc.* **1996**, *118*, 7716-7730].



^{1}H NMR (300 MHz) δ 0.98 (t, *J* = 7.2 Hz, 3H, Me), 1.38-1.82 (m, 4H, alkyl H), 4.33 (t, *J* = 6.6 Hz, 2H, -OC$\underline{H}_2$(CH$_2$)$_2$CH$_3$), 7.37 (t, *J* = 7.8 Hz, 1H, Ar-H), 7.52 (d, *J* = 7.8 Hz, 1H, Ar-H), 7.92 (d, *J* = 7.8 Hz, 1H, Ar-H), 8.01 (s, 1H, Ar-H).

These spectral properties were in good agreement with those reported in the above literature.

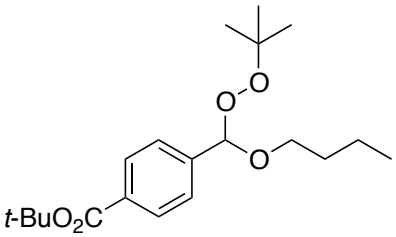
***tert*-Butyl 4-(butoxymethyl)benzoate.**



To a solution of 4-(formyl)benzoic acid (751 mg, 5.00 mmol) in *t*-BuOH (10 mL) were successively added Boc_2O (1.26 mL, 5.48 mmol) and DMAP (403 mg, 3.30 mmol) at room temperature. After the mixture was stirred at room temperature for 7 h, water was added. The organic products were extracted with ether. The combined organic layers were washed with saturated $NaHCO_3$ solution, dried over Na_2SO_4, and concentrated *in vacuo* to give a crude oil, which was chromatographed on silica gel (hexane-ethyl acetate) to afford *tert*-butyl 4-(formyl)benzoate (924 mg, 45%) as an oil.
To a solution of *tert*-butyl 4-(formyl)benzoate (924 mg, 4.48 mmol) in THF (5 mL) and MeOH (10 mL) was added $NaBH_4$ (262 mg, 6.72 mmol) at 0 °C. After the mixture was stirred at the same temperature for 30 min, the reaction was terminated by the addition of cold 0.5 N HCl solution (5 mL). After the reaction mixture was poured into water, the organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo* to give a crude oil, which was chromatographed on silica gel (hexane-ethyl acetate) to afford *tert*-butyl 4-(hydroxymethyl)benzoate (933 mg, 100%) as an oil.
To a solution of *tert*-butyl 4-(hydroxymethyl)benzoate (933 mg, 4.48 mmol) in Et_2O (5 mL) was added phosphorus tribromide (0.170 mL, 1.80 mmol) at 0 °C. After the mixture was stirred at room temperature for 3 h, water was added. The organic products were extracted with ether. The combined organic layers were washed with aqueous saturated $NaHCO_3$ solution, dried over Na_2SO_4, and concentrated *in vacuo* to give a crude oil of *tert*-butyl 4-(bromomethyl)benzoate (868 mg, 71%), which was spectroscopically pure and was directly used in the next step.
To a solution of $AgNO_3$ (3.08 g, 20.0 mmol) in water (20 mL) was added 1 N NaOH (20 mL). After stirring at room temperature for 10 min, the reaction mixture was filtered and washed with water. The solid was dried *in vacuo* to give a dark brown solid of Ag_2O (2.05 g, 88%).
To a suspension of Ag_2O (816 mg, 3.52 mmol) in 10 mL of CH_2Cl_2 was added a mixture of butanol (0.290 mL, 3.17 mmol) and *tert*-butyl 4-(bromomethyl)benzoate (868 mg, *ca*. 3.20 mmol) in CH_2Cl_2 (5 mL) at 0 °C under argon. The mixture was stirred at room temperature overnight and filtered through Celite. The resulting solution was concentrated *in vacuo* to give a crude oil, which was chromatographed on silica gel (hexane-ethyl acetate) to afford the title compound (618 mg, 73%) as an oil.
^{1}H NMR (300 MHz) δ 0.92 (t, J = 7.5 Hz, 3H, Me), 1.40 (sextet, J = 7.5 Hz, 2H, alkyl H), 1.59 (s, 9H, -C(C$\underline{H}_3$)$_3$), 1.63 (m, 2H, alkyl H), 3.47 (t, J = 6.6 Hz, 2H, -OC$\underline{H}_2$(CH$_2$)$_2$CH$_3$), 4.55 (s, 2H, benzyl H), 7.38 (d, J = 8.4 Hz, 2H, Ar-H), 7.96 (d, J = 8.4 Hz, 2H, Ar-H).
^{13}C NMR (75 MHz) δ 13.87, 19.32, 28.13 (3 carbons, -C($\underline{C}$H$_3$)$_3$), 31.77, 70.35, 72.19, 80.81, 126.91 (2 carbons), 129.43 (2 carbons), 131.04, 143.47, 165.60 (C=O).
IR (neat) 3100 (Ar), 3060 (Ar), 3010 (Ar), 2960, 2870, 1714 (C=O), 1614, 1458, 1367, 1292, 1165,

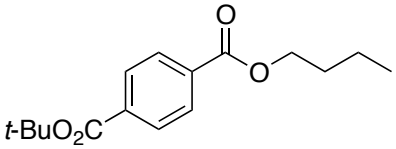
1119, 1020, 850, 758 cm^{-1}.
Anal. Calcd for $C_{16}H_{24}O_3$: C, 72.69; H, 9.15. Found: C, 72.76; H, 9.29.

***tert*-Butyl 4-[butoxy(*tert*-butylperoxy)methyl]benzoate (8).**



To a suspension of *tert*-butyl 4-(butoxymethyl)benzoate (52.9 mg, 0.200 mmol), $Fe(acac)_3$ (7.1 mg, 0.020 mmol), and MS 4A (100 mg) in 1.0 mL of CH_3CN was added *tert*-butyl hydroperoxide (0.20 mL, 5.0-6.0 M solution in decane, *ca*. 1.0-1.2 mmol) by a plastic pipette at room temperature under argon. The mixture was stirred in an oil bath maintained at 80 °C for 3 h. After being cooled to room temperature, the reaction mixture was filtered through a short pad of silica gel with the aid of ethyl acetate. The combined filtrates were concentrated *in vacuo* to give a crude oil, ^{1}H NMR analysis of which revealed that the yields of the title compound, *tert*-butyl butyl terephthalate as a by-product, and recovered starting material are 68%, 20%, and 2%, respectively, by using trichloroethylene as an internal standard. The crude oil was chromatographed on silica gel (hexane-ethyl acetate) to afford the title compound (46.8 mg, 66%) as an oil.
^{1}H NMR (300 MHz) δ 0.92 (t, J = 7.5 Hz, 3H, Me), 1.27 (s, 9H, -C(C$\underline{H}_3$)$_3$), 1.42 (m, 2H, alkyl H), 1.59 (s, 9H, -C(C$\underline{H}_3$)$_3$), 1.63 (m, 2H, alkyl H), 3.66 (dt, J = 9.6, 6.6 Hz, 1H, -OC$\underline{H}_2$(CH$_2$)$_2$CH$_3$), 3.97 (dt, J = 9.6, 6.6 Hz, 1H, -OC$\underline{H}_2$(CH$_2$)$_2$CH$_3$), 5.83 (s, 1H, benzyl H), 7.52 (d, J = 8.1 Hz, 2H, Ar-H), 7.97 (d, J = 8.1 Hz, 2H, Ar-H).
^{13}C NMR (75 MHz) δ 13.85, 19.28, 26.47 (3 carbons, -C($\underline{C}$H$_3$)$_3$), 28.14 (3 carbons, -C($\underline{C}$H$_3$)$_3$), 31.92, 69.36, 80.87, 81.01, 105.33, 126.75 (2 carbons), 129.27 (2 carbons), 132.24, 141.06, 165.44 (C=O).
IR (neat) 3100 (Ar), 3060 (Ar), 2978, 2873, 1716 (C=O), 1614, 1458, 1392, 1365, 1292, 1195, 1165, 1117, 1095 (C-O-O), 1020, 850, 769, 706 cm^{-1}.
Anal. Calcd for $C_{20}H_{32}O_5$: C, 68.15; H, 9.15. Found: C, 67.96; H, 8.98.

***tert*-Butyl butyl terephthalate.** This by-product of **8** was obtained in a separate run in the absence of MS 4A.



To a suspension of *tert*-butyl 4-(butoxymethyl)benzoate (26.5 mg, 0.100 mmol) and $Fe(acac)_3$ (3.5 mg, 0.010 mmol) in 1.0 mL of CH_3CN was added *tert*-butyl hydroperoxide (0.10 mL, 5.0-6.0 M solution

in decane, *ca*. 0.5-0.6 mmol) by a plastic pipette at room temperature under argon. The mixture was heated at 80 °C for 3 h. After being cooled to room temperature, the reaction mixture was filtered through a short pad of silica gel with the aid of ethyl acetate. The combined filtrates were concentrated *in vacuo* to give a crude oil, ^{1}H NMR analysis of which revealed that the yields of the title compound, *tert*-butyl 4-[butoxy(*tert*-butylperoxy)methyl]benzoate (**8**), and recovered starting material are 64%, 36%, and 0%, respectively, by using trichloroethylene as an internal standard. The crude oil was chromatographed on silica gel (hexane-ethyl acetate) to afford the title compound (16.5 mg, 59%) as an oil.

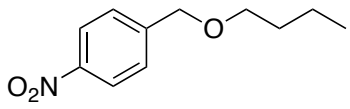
^{1}H NMR (300 MHz) δ 0.99 (t, J = 7.5 Hz, 3H, alkyl-Me), 1.50 (m, 2H, alkyl H), 1.61 (s, 9H, -C(C$\underline{H}_3$)$_3$), 1.77 (quintet, J = 6.6 Hz, 2H, alkyl H), 4.35 (t, J = 6.6 Hz, 2H, -OC$\underline{H}_2$(CH$_2$)$_2$CH$_3$), 8.04 (d, J = 8.4 Hz, 2H, Ar-H), 8.08 (d, J = 8.4 Hz, 2H, Ar-H).

^{13}C NMR (75 MHz) δ 13.75, 19.24, 28.11 (3 carbons, -C($\underline{C}$H$_3$)$_3$), 30.67, 65.20, 81.67, 129.32 (2 peaks of 2 carbons), 133.77, 135.67, 164.93 (C=O), 166.00 (C=O).

IR (neat) 3060 (Ar), 2962, 2873, 1718 (C=O), 1458, 1369, 1275, 1165, 1119, 1018, 849, 731 cm^{-1}.

Anal. Calcd for $C_{16}H_{22}O_4$: C, 69.04; H, 7.97. Found: C, 69.13; H, 8.09.

Butyl (4-nitrophenyl)methyl ether.



For the preparation of Ag_2O, see *tert*-butyl (4-buthoxymethyl)benzoate.

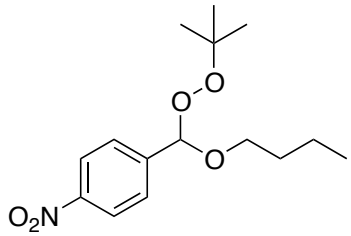
To a solution of 4-nitrobenzaldehyde (1.01 mL, 10.0 mmol) in THF (5 mL) and MeOH (10 mL) was added $NaBH_4$ (585 mg, 15.0 mmol) at 0 °C. After the mixture was stirred at the same temperature for 50 min, the reaction was terminated by the addition of cold 0.5 N HCl solution (10 mL). After the reaction mixture was poured into water, the organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo* to give a crude oil, which was chromatographed on silica gel (hexane-ethyl acetate) to afford (4-nitrophenyl)methanol (1.85 g, 100%) as an oil.

To a solution of (4-nitrophenyl)methanol obtained above (1.53 g, 10.0 mmol) in Et_2O (15 mL) was added phosphorus tribromide (0.380 mL, 4.00 mmol) at 0 °C. After the mixture was stirred at room temperature for 1 h, water was added. The organic products were extracted with ether. The combined organic layers were washed with aqueous saturated $NaHCO_3$ solution, dried over Na_2SO_4, and concentrated *in vacuo* to give a crude oil of 1-(bromomethyl)-4-nitrobenzene (1.85 g, 86%), which was spectroscopically pure and was directly used in the next step.

To a suspension of Ag_2O (765 mg, 3.30 mmol) in 10 mL of CH_2Cl_2 was added a mixture of butanol (0.280 mL, 3.06 mmol) and 1-(bromomethyl)-4-nitrobenzene (648 mg, *ca*. 3.00 mmol) in CH_2Cl_2 (5 mL) at 0 °C under argon. The mixture was stirred at room temperature overnight and filtered through Celite. The resulting solution was concentrated *in vacuo* to give a crude oil, which was chromatographed on silica gel (hexane-ethyl acetate) to afford the title compound (410 mg, 65%) as an oil.

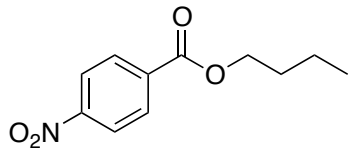
^{1}H NMR (300 MHz) δ 0.94 (t, *J* = 7.2 Hz, 3H, Me), 1.42 (sextet, *J* = 7.2 Hz, 2H, alkyl H), 1.64 (m, 2H, alkyl H), 3.52 (t, *J* = 6.6 Hz, 2H, -OC<u>H</u>$_2$(CH$_2$)$_2$CH$_3$), 4.60 (s, 2H, benzyl H), 7.50 (d, *J* = 8.7 Hz, 2H, Ar-H) , 8.20 (d, *J* = 8.7 Hz, 2H, Ar-H).
^{13}C NMR (75 MHz) δ 13.76, 19.22, 31.63, 70.75, 71.40, 123.39 (2 carbons), 127.45 (2 carbons), 146.46, 147.09.
IR (neat) 3114 (Ar), 3080 (Ar), 2958, 2867, 1522 (NO_2), 1346 (NO_2), 1105, 1014, 843, 739 cm^{-1}.
Anal. Calcd for $C_{11}H_{15}NO_3$: C, 63.14; H, 7.23. Found: C, 63.32; H, 7.16.

Butyl (*tert*-butylperoxy)(4-nitrophenyl)methyl ether (9).



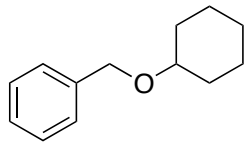
To a suspension of butyl (4-nitrophenyl)methyl ether (41.8 mg, 0.200 mmol), Fe(acac)$_3$ (7.1 mg, 0.020 mmol), and MS 4A (100 mg) in 1.0 mL of CH_3CN was added *tert*-butyl hydroperoxide (0.20 mL, 5.0-6.0 M solution in decane, *ca*. 1.0-1.2 mmol) by a plastic pipette at room temperature under argon. The mixture was stirred in an oil bath maintained at 80 °C for 3 h. After being cooled to room temperature, the reaction mixture was filtered through a short pad of silica gel with the aid of ethyl acetate. The combined filtrates were concentrated *in vacuo* to give a crude oil, ^{1}H NMR analysis of which revealed that the yields of the title compound, butyl 4-nitrobenzoate as a by-product, and the starting material are 62%, 38%, and 0%, respectively, by using trichloroethylene as an internal standard. The crude oil was chromatographed on silica gel (hexane-ethyl acetate) to afford the title compound (38.7 mg, 65%) as an oil and butyl 4-nitrobenzoate (14.8 mg, 33%) as a white solid.
^{1}H NMR (300 MHz) δ 0.94 (t, *J* = 7.2 Hz, 3H, Me), 1.26 (s, 9H, -C(C<u>H</u>$_3$)$_3$), 1.44 (m, 2H, alkyl H), 1.67 (m, 2H, alkyl H), 3.70 (dt, *J* = 9.6, 6.6 Hz, 1H, -OC<u>H</u>$_2$(CH$_2$)$_2$CH$_3$), 4.04 (dt, *J* = 9.6, 6.6 Hz, 1H, -OC<u>H</u>$_2$(CH$_2$)$_2$CH$_3$), 5.85 (s, 1H, benzyl H), 7.66 (d, *J* = 8.4 Hz, 2H, Ar-H), 8.22 (d, *J* = 8.4 Hz, 2H, Ar-H).
^{13}C NMR (75 MHz) δ 13.84, 19.28, 26.46 (3 carbons, -C(<u>C</u>H$_3$)$_3$), 31.85, 69.82, 81.02, 104.29, 123.34 (2 carbons), 127.95 (2 carbons), 143.82, 148.04.
IR (neat) 3113 (Ar), 3082 (Ar), 2960, 2935, 2873, 1608, 1525 (NO_2), 1460, 1350 (NO_2), 1196, 1099 (C-O-O), 1014, 856, 750, 721 cm^{-1}.
Anal. Calcd for $C_{15}H_{23}NO_5$: C, 60.59; H, 7.80. Found: C, 60.73; H, 7.67.

Butyl 4-nitrobenzoate. This by-product of **9** is a known compound [Iwasaki, T.; Maegawa, Y.; Hayashi, Y.; Ohshima, T.; Mashima, K. *J. Org. Chem.* **2008**, *73*, 5147-5150].



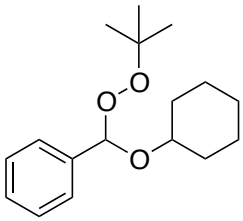
^{1}H NMR (300 MHz) δ 1.00 (t, *J* = 7.2 Hz, 3H, alkyl-Me), 1.49 (sextet, *J* = 7.2 Hz, 2H, alkyl H), 1.79 (m, 2H, alkyl H), 4.38 (t, *J* = 6.6 Hz, 2H, -OC<u>H</u>$_2$(CH$_2$)$_2$CH$_3$), 8.21 (d, *J* = 8.4 Hz, 2H, Ar-H), 8.30 (d, *J* = 8.4 Hz, 2H, Ar-H).
^{13}C NMR (75 MHz) δ 13.72, 19.20, 30.60, 65.81, 123.51 (2 carbons), 130.64 (2 carbons), 135.85, 150.43 (O_2N-<u>C</u>), 164.75 (C=O).
IR (neat) 3114 (Ar), 3080 (Ar), 3057 (Ar), 2962, 2873, 1726 (C=O), 1608, 1529 (NO_2), 1466, 1350 (NO_2), 1279, 1103, 1014, 874, 719 cm^{-1}.
M.p. 34-35 °C.
These spectral properties were in good agreement with those reported in the above literature.

Benzyl cyclohexyl ether. This is a known compound [Ochiai, M.; Ito, T.; Takahashi, H.; Nakanishi, A.; Toyonari, M.; Sueda, T.; Goto, S.; Shiro, M. *J. Am. Chem. Soc.* **1996**, *118*, 7716-7730].



To a suspension of NaH (440 mg of a 60% suspension in mineral oil, 11.0 mmol) in THF (20 mL) was added cyclohexanol (1.04 mL, 9.95 mmol) at 0 °C under argon. After the mixture was stirred at room temperature for 1 h, benzyl bromide (1.32 mL, 11.0 mmol) was added at 0 °C. The mixture was stirred at room temperature overnight and was quenched with water. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with water and brine, dried over Na_2SO_4, and concentrated *in vacuo* to give a crude oil, which was chromatographed on silica gel (hexane-ethyl acetate) to afford the title compound (1.45 g, 76%) as an oil.
^{1}H NMR (300 MHz) δ 1.17-1.43 (m, 5H, alkyl H), 1.53 (m, 1H, alkyl H), 1.68-1.82 (m, 2H, alkyl H), 1.90-2.01 (m, 2H, alkyl H), 3.35 (tt, *J* = 3.6, 9.3 Hz, 1H, -OC<u>H</u>-), 4.55 (s, 2H, benzyl H), 7.25-7.37 (m, 5H, Ar-H).
^{13}C NMR (75 MHz) δ 24.11 (2 carbons), 25.80, 32.22 (2 carbons), 69.61, 76.89, 127.25, 127.45 (2 carbons), 128.26 (2 carbons), 139.27.
IR (neat) 3090 (Ar), 3060 (Ar), 3030 (Ar), 2931, 2856, 1452, 1362, 1097, 1028, 735, 696 cm^{-1}.
Anal. Calcd for $C_{13}H_{18}O$: C, 82.06; H, 9.53. Found: C, 81.88; H, 9.46.
These spectral properties were in good agreement with those reported in the above literature.

(*tert*-Butylperoxy)(phenyl)methyl cyclohexyl ether (10).



To a suspension of benzyl cyclohexyl ether (38.1 mg, 0.200 mmol), $Fe(acac)_3$ (7.1 mg, 0.020 mmol), and MS 4A (100 mg) in 1.0 mL of CH_3CN was added *tert*-butyl hydroperoxide (0.20 mL, 5.0-6.0 M solution in decane, *ca*. 1.0-1.2 mmol) by a plastic pipette at room temperature under argon. The mixture was stirred in an oil bath maintained at 80 °C for 3 h. After being cooled to room temperature, the reaction mixture was filtered through a short pad of silica gel with the aid of ethyl acetate. The combined filtrates were concentrated *in vacuo* to give a crude oil, ^{1}H NMR analysis of which revealed that the yields of the title compound, cyclohexyl benzoate as a by-product, and recovered starting material are 80%, 12%, and 5%, respectively, by using trichloroethylene as an internal standard. The crude oil was chromatographed on silica gel (hexane-ethyl acetate) to afford the title compound (43.6 mg, 78%) as an oil.

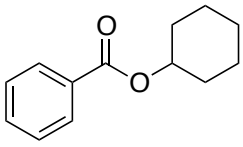
^{1}H NMR (300 MHz) δ 1.14-1.45 (m, 5H, alkyl H), 1.28 (s, 9H, -C(C<u>H</u>$_3$)$_3$), 1.52 (m, 1H, alkyl H), 1.64-1.93 (m, 3H, alkyl H), 2.05 (m, 1H, alkyl H), 3.84 (tt, J = 3.6, 9.3 Hz, 1H, -OC<u>H</u>-), 5.92 (s, 1H, benzyl H), 7.30-7.39 (m, 3H, Ar-H), 7.50 (m, 2H, Ar-H).

^{13}C NMR (75 MHz) δ 24.00, 24.20, 25.71, 26.56 (3 carbons, -C(<u>C</u>H$_3$)$_3$), 32.57, 32.94, 77.21, 80.58, 104.13, 126.98 (2 carbons), 128.08 (2 carbons), 128.62, 137.55.

IR (neat) 3090 (Ar), 3065 (Ar), 3030 (Ar), 2980, 2933, 2850, 1452, 1363, 1198, 1093 (C-O-O), 889, 754, 698 cm^{-1}.

Anal. Calcd for $C_{17}H_{26}O_3$: C, 73.34; H, 9.41. Found: C, 73.39; H, 9.32.

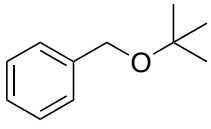
Cyclohexyl benzoate. This by-product of **10** is a known compound [Ochiai, M.; Ito, T.; Takahashi, H.; Nakanishi, A.; Toyonari, M.; Sueda, T.; Goto, S.; Shiro, M. *J. Am. Chem. Soc.* **1996**, *118*, 7716-7730].



^{1}H NMR (300 MHz) δ 1.21-2.04 (m, 10H, alkyl H), 5.02 (m, 1H, -OC<u>H</u>-), 7.36-7.58 (m, 3H, Ar-H), 8.05 (d, J = 7.2 Hz, 2H, Ar-H).

These spectral properties were in good agreement with those reported in the above literature.

Benzyl *tert*-butyl ether. This is a known compound [Ochiai, M.; Ito, T.; Takahashi, H.; Nakanishi, A.; Toyonari, M.; Sueda, T.; Goto, S.; Shiro, M. *J. Am. Chem. Soc.* **1996**, *118*, 7716-7730].



To a suspension of NaH (220 mg of a 60% suspension in mineral oil, 5.50 mmol) in THF (10 mL) was added 2-methyl-2-propanol (0.480 mL, 5.02 mmol) at 0 °C under argon. After the mixture was stirred at room temperature for 1 h, benzyl bromide (0.600 mL, 5.02 mmol) was added at 0 °C. The mixture was stirred at room temperature overnight and was quenched with water. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with water and brine, dried over Na_2SO_4, and concentrated *in vacuo* to give a crude oil, which was chromatographed on silica gel (hexane-ethyl acetate) to afford the title compound (701 mg, 85%) as an oil.

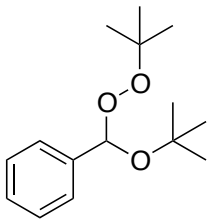
^{1}H NMR (300 MHz) δ 1.30 (s, 9H, -C(C$\underline{H}_3$)$_3$), 4.45 (s, 2H, benzyl H), 7.24-7.38 (m, 5H, Ar-H).

^{13}C NMR (75 MHz) δ 27.65 (3 carbons, -C($\underline{C}H_3$)$_3$), 64.08, 73.35, 127.05, 127.35 (2 carbons), 128.23 (2 carbons), 139.83.

IR (neat) 3090 (Ar), 3060 (Ar), 3030 (Ar), 2974, 1454, 1390, 1363, 1198, 1092, 1065, 887, 733, 696 cm^{-1}.

These spectral properties were in good agreement with those reported in the above literature.

***tert*-Butyl (*tert*-butylperoxy)(phenyl)methyl ether (11).**



To a suspension of benzyl *tert*-butyl ether (32.8 mg, 0.200 mmol), Fe(acac)$_3$ (7.1 mg, 0.020 mmol), and MS 4A (100 mg) in 1.0 mL of CH_3CN was added *tert*-butyl hydroperoxide (0.20 mL, 5.0-6.0 M solution in decane, *ca*. 1.0-1.2 mmol) by a plastic pipette at room temperature under argon. The mixture was stirred in an oil bath maintained at 80 °C for 3 h. After being cooled to room temperature, the reaction mixture was filtered through a short pad of silica gel with the aid of ethyl acetate. The combined filtrates were concentrated *in vacuo* to give a crude oil, ^{1}H NMR analysis of which revealed that the yields of the title compound, *tert*-butyl benzoate as a by-product, and the starting material are 86%, 10%, and 0%, respectively, by using trichloroethylene as an internal standard. The crude oil was chromatographed on silica gel (hexane-ethyl acetate) to afford the title compound (43.7 mg, 87%) as an oil.

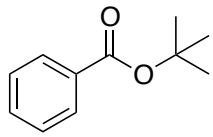
^{1}H NMR (300 MHz) δ 1.26 (s, 9H, -C(C$\underline{H}_3$)$_3$), 1.30 (s, 9H, -C(C$\underline{H}_3$)$_3$), 5.96 (s, 1H, benzyl H), 7.30-7.39 (m, 3H, Ar-H), 7.47-7.53 (m, 2H, Ar-H).

^{13}C NMR (75 MHz) δ 26.56 (3 carbons, -C($\underline{C}H_3$)$_3$), 28.79 (3 carbons, -C($\underline{C}H_3$)$_3$), 74.73, 80.35, 100.38, 127.14 (2 carbons), 128.04 (2 carbons), 128.54, 138.75.

IR (neat) 3091 (Ar), 3066 (Ar), 3032 (Ar), 2977, 2931, 1454, 1363, 1255, 1198, 1092 (C-O-O), 1022, 889, 754, 698 cm^{-1}.

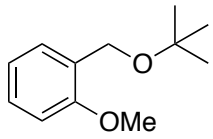
MS (FAB, NBA) *m/z* (rel intensity): 385 ([M+Cs]$^+$, 4), 154 (35), 133 (100).
Anal. Calcd for $C_{15}H_{24}O_3$: C, 71.39; H, 9.59. Found: C, 71.69; H, 9.44.
The MS spectroscopy clearly indicated that this product is *tert*-butyl (*tert*-butylperoxy)(phenyl)methyl ether [M+Cs; 385] (**11**) rather than di-*tert*-butyl acetal of benzaldehyde.

***tert*-Butyl benzoate.** This by-product of **11** is a known compound [Ochiai, M.; Ito, T.; Takahashi, H.; Nakanishi, A.; Toyonari, M.; Sueda, T.; Goto, S.; Shiro, M. *J. Am. Chem. Soc.* **1996**, *118*, 7716-7730].



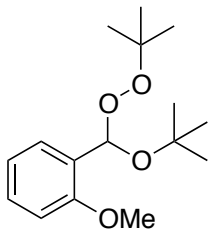
^{1}H NMR (300 MHz) δ 1.60 (s, 9H, -C(CH$_3$)$_3$), 7.30-7.53 (m, 3H, Ar-H), 7.99 (d, *J* = 7.5 Hz, 2H, Ar-H).
These spectral properties were in good agreement with those reported in the above literature.

***tert*-Butyl (2-methoxyphenyl)methyl ether.**



For the preparation of 1-(bromomethyl)-2-methoxybenzene, see butyl (2-methoxyphenyl)methyl ether.
To a suspension of NaH (132 mg of a 60% suspension in mineral oil, 3.30 mmol) in THF (3 mL) was added 2-methyl-2-propanol (0.290 mL, 3.00 mmol) at 0 °C under argon. After the mixture was stirred at room temperature for 1 h, 1-(bromomethyl)-2-methoxybenzene (603 mg, 3.03 mmol) in THF (3 mL) was added at 0 °C. The mixture was stirred at room temperature overnight and was quenched with water. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with water and brine, dried over Na_2SO_4, and concentrated *in vacuo* to give a crude oil, which was chromatographed on silica gel (hexane-ethyl acetate) to afford the title compound (405 mg, 70%) as an oil.
^{1}H NMR (300 MHz) δ 1.30 (s, 9H, -C(C$\underline{H}_3$)$_3$), 3.82 (s, 3H, -O$\underline{Me}$), 4.49 (s, 2H, benzyl H), 6.83 (d, *J* = 7.5 Hz, 1H, Ar-H), 6.95 (t, *J* = 7.5 Hz, 1H, Ar-H), 7.22 (t, *J* = 7.5 Hz, 1H, Ar-H), 7.45 (d, *J* = 7.5 Hz, 1H, Ar-H).
^{13}C NMR (75 MHz) δ 27.63 (3 carbons, -C($\underline{C}$H$_3$)$_3$), 55.17, 58.64, 73.25, 109.82, 120.43, 127.75, 128.15, 128.42, 156.50.
IR (neat) 3060 (Ar), 3050 (Ar), 3040 (Ar), 2974, 1591, 1493, 1389, 1284, 1240, 1198, 1078, 895, 752 cm^{-1}.
Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 73.94; H, 9.04.

***tert*-Butyl (*tert*-butylperoxy)(2-methoxyphenyl)methyl ether (12).**



To a suspension of *tert*-butyl (2-methoxyphenyl)methyl ether (38.9 mg, 0.200 mmol), $Fe(acac)_3$ (7.1 mg, 0.020 mmol), and MS 4A (100 mg) in 1.0 mL of CH_3CN was added *tert*-butyl hydroperoxide (0.20 mL, 5.0-6.0 M solution in decane, *ca*. 1.0-1.2 mmol) by a plastic pipette at room temperature under argon. The mixture was stirred in an oil bath maintained at 80 °C for 3 h. After being cooled to room temperature, the reaction mixture was filtered through a short pad of silica gel with the aid of ethyl acetate. The combined filtrates were concentrated *in vacuo* to give a crude oil, ^{1}H NMR analysis of which revealed that the yields of the title compound, 2-methoxybenzoate as a by-product, and the starting material are 99%, 0%, and 0%, respectively, by using trichloroethylene as an internal standard. The crude oil was chromatographed on silica gel (hexane-ethyl acetate) to afford the title compound (55.8 mg, 99%) as an oil.

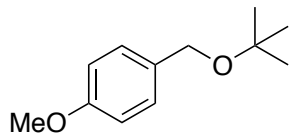
^{1}H NMR (300 MHz) δ 1.25 (s, 9H, -C(C$\underline{H}_3$)$_3$), 1.26 (s, 9H, -C(C$\underline{H}_3$)$_3$), 3.84 (s, 3H, -O$\underline{Me}$), 6.34 (s, 1H, benzyl H), 6.85 (d, *J* = 7.5 Hz, 1H, Ar-H), 6.95 (t, *J* = 7.5 Hz, 1H, Ar-H), 7.29 (t, *J* = 7.5 Hz, 1H, Ar-H), 7.65 (d, *J* = 7.5 Hz, 1H, Ar-H).

^{13}C NMR (75 MHz) δ 26.43 (3 carbons, -C($\underline{C}$H$_3$)$_3$), 28.64 (3 carbons, -C($\underline{C}$H$_3$)$_3$), 55.15, 74.27, 80.33, 95.28, 110.09, 120.39, 127.09, 128.62, 129.67, 156.35.

IR (neat) 3080 (Ar), 3060 (Ar), 3040 (Ar), 2976, 1603, 1493, 1363, 1284, 1246, 1196, 1117, 1075 (C-O-O), 1049, 912, 754 cm^{-1}.

Anal. Calcd for $C_{16}H_{26}O_4$: C, 68.06; H, 9.28. Found: C, 68.22; H, 9.25.

***tert*-Butyl (4-methoxyphenyl)methyl ether.** This is a known compound [Cuenca, A. B.; Mancha, G.; Asensio, G.; Medio-Simón, M. *Chem. Eur. J.* **2008**, *14*, 1518-1523].



For the preparation of 1-(bromomethyl)-4-methoxybenzene, see butyl (4-methoxyphenyl)methyl ether. To a suspension of NaH (220 mg of a 60% suspension in mineral oil, 5.50 mmol) in THF (5 mL) was added 2-methyl-2-propanol (0.480 mL, 5.02 mmol) at 0 °C under argon. After the mixture was stirred at room temperature for 1 h, 1-(bromomethyl)-4-methoxybenzene (1.01 g, 5.02 mmol) in THF (5 mL) was added at 0 °C. The mixture was stirred at room temperature overnight and was quenched with water. The organic layer was separated and the aqueous layer was extracted with ethyl acetate.

The combined organic layers were washed with water and brine, dried over Na_2SO_4, and concentrated *in vacuo* to give a crude oil, which was chromatographed on silica gel (hexane-ethyl acetate) to afford the title compound (532 mg, 55%) as an oil.

^{1}H NMR (300 MHz) δ 1.29 (s, 9H, -C(C$\underline{H}_3$)$_3$), 3.79 (s, 3H, Ar-O$\underline{Me}$), 4.37 (s, 2H, benzyl H), 6.86 (d, *J* = 8.4 Hz, 2H, Ar-H), 7.26 (d, *J* = 8.4 Hz, 2H, Ar-H).

^{1}H NMR (400 MHz) δ 1.28 (s, 9H, -C(C$\underline{H}_3$)$_3$), 3.79 (s, 3H, Ar-O$\underline{Me}$), 4.37 (s, 2H, benzyl H), 6.86 (d, *J* = 8.0 Hz, 2H, Ar-H), 7.26 (d, *J* = 8.0 Hz, 2H, Ar-H).

^{13}C NMR (75 MHz) δ 27.67 (3 carbons, -C($\underline{C}$H$_3$)$_3$), 55.22, 63.73, 73.24, 113.67 (2 carbons), 128.89 (2 carbons), 131.87, 158.76.

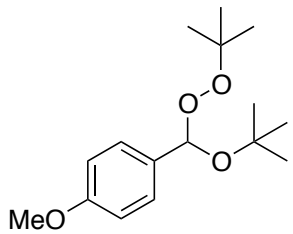
^{13}C NMR (100 MHz) δ 27.70 (3 carbons, -C($\underline{C}$H$_3$)$_3$), 55.25, 63.75, 73.25, 113.70 (2 carbons), 128.88 (2 carbons), 131.94, 158.80.

IR (neat) 3060 (Ar), 3040 (Ar), 2974, 2960, 2900, 2850, 1614, 1514, 1466, 1389, 1362, 1302, 1248, 1196, 1038, 893 cm^{-1}.

Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 74.05; H, 9.24.

These spectral properties were in good agreement with those reported in the above literature.

***tert*-Butyl (*tert*-butylperoxy)(4-methoxyphenyl)methyl ether (13).**



To a suspension of *tert*-butyl (4-methoxyphenyl)methyl ether (38.9 mg, 0.200 mmol), Fe(acac)$_3$ (7.1 mg, 0.020 mmol), and MS 4A (100 mg) in 1.0 mL of CH_3CN was added *tert*-butyl hydroperoxide (0.20 mL, 5.0-6.0 M solution in decane, *ca*. 1.0-1.2 mmol) by a plastic pipette at room temperature under argon. The mixture was stirred in an oil bath maintained at 80 °C for 3 h. After being cooled to room temperature, the reaction mixture was filtered through a short pad of silica gel with the aid of ethyl acetate. The combined filtrates were concentrated *in vacuo* to give a crude oil, ^{1}H NMR analysis of which revealed that the yields of the title compound, *tert*-butyl 4-methoxybenzoate as a by-product, and the starting material are 82%, 12%, and 0%, respectively, by using trichloroethylene as an internal standard. The crude oil was chromatographed on silica gel (hexane-ethyl acetate) to afford the title compound (45.4 mg, 80%) as an oil.

^{1}H NMR (300 MHz) δ 1.26 (s, 9H, -C(C$\underline{H}_3$)$_3$), 1.28 (s, 9H, -C(C$\underline{H}_3$)$_3$), 3.81 (s, 3H, -O$\underline{Me}$), 5.92 (s, 1H, benzyl H), 6.88 (d, *J* = 9.0 Hz, 2H, Ar-H), 7.43 (d, *J* = 9.0 Hz, 2H, Ar-H).

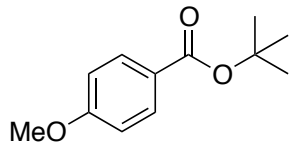
^{1}H NMR (400 MHz) δ 1.26 (s, 9H, -C(C$\underline{H}_3$)$_3$), 1.28 (s, 9H, -C(C$\underline{H}_3$)$_3$), 3.81 (s, 3H, -O$\underline{Me}$), 5.92 (s, 1H, benzyl H), 6.87 (d, *J* = 8.8 Hz, 2H, Ar-H), 7.43 (d, *J* = 8.8 Hz, 2H, Ar-H).

^{13}C NMR (75 MHz) δ 26.58 (3 carbons, -C($\underline{C}$H$_3$)$_3$), 28.79 (3 carbons, -C($\underline{C}$H$_3$)$_3$), 55.20, 74.56, 80.30, 100.14, 113.40 (2 carbons), 128.39 (2 carbons), 131.07, 159.77.

^{13}C NMR (100 MHz) δ 26.60 (3 carbons, -C($\underline{C}$H$_3$)$_3$), 28.82 (3 carbons, -C($\underline{C}$H$_3$)$_3$), 55.22, 74.58, 80.28,

100.15, 113.43 (2 carbons), 128.40 (2 carbons), 131.16, 159.80.
IR (neat) 3100 (Ar), 3068 (Ar), 3033 (Ar), 2976, 1612, 1514, 1464, 1363, 1302, 1250, 1196, 1080 (C-O-O), 1039, 889, 827 cm^{-1}.
Anal. Calcd for $C_{16}H_{26}O_4$: C, 68.06; H, 9.28. Found: C, 68.04; H, 9.14.

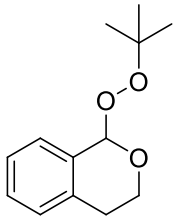
***tert*-Butyl 4-methoxybenzoate.** This by-product of **13** is a known compound [Nishimoto, Y.; Babu, S. A.; Yasuda, M.; Baba, A. *J. Org. Chem.* **2008**, *73*, 9465-9468].



^{1}H NMR (300 MHz) δ 1.58 (s, 9H, -C(C<u>H</u>$_3$)$_3$), 3.85 (s, 3H, -O<u>Me</u>), 6.90 (d, *J* = 8.7 Hz, 2H, Ar-H), 7.94 (d, *J* = 8.7 Hz, 2H, Ar-H).
These spectral properties were in good agreement with those reported in the above literature.

Isochroman. Starting material for 14. This is a known compound and commercially available from Tokyo Chemical Industry Co., Ltd. (Japan).

1-(*tert*-Butylperoxy)isochroman (14). This is a known compound [Nagano, T.; Kobayashi, S. *Chem. Lett.* **2008**, *37*, 1042-1043. Catino, A. J.; Nichols, J. M.; Choi, H.; Gottipamula, S.; Doyle, M. P. *Org. Lett.* **2005**, *7*, 5167-5170].



To a suspension of isochroman (53.7 mg, 0.400 mmol), Fe(acac)$_3$ (14.1 mg, 0.040 mmol), and MS 4A (200 mg) in 2.0 mL of CH_3CN was added *tert*-butyl hydroperoxide (0.40 mL, 5.0-6.0 M solution in decane, *ca*. 2.0-2.4 mmol) by a plastic pipette at room temperature under argon. The mixture was stirred in an oil bath maintained at 80 °C for 3 h. After being cooled to room temperature, the reaction mixture was filtered through a short pad of silica gel with the aid of ethyl acetate. The combined filtrates were concentrated *in vacuo* to give a crude oil, ^{1}H NMR analysis of which revealed that the yields of the title compound, 1-isochromanone as a by-product, and starting material are 65%, 13%, 0%, respectively, by using trichloroethylene as an internal standard. The crude oil was chromatographed on silica gel (hexane-ethyl acetate) to afford the title compound (69.7 mg, 78%) as an oil and 1-isochromanone (12.1 mg, 20%) as an oil.
^{1}H NMR (300 MHz) δ 1.36 (s, 9H, -C(C<u>H</u>$_3$)$_3$), 2.61 (dd, *J* = 3.0, 16.8 Hz, 1H, -OCH$_2$C<u>H</u>$_2$Ar), 3.05 (ddd, *J* = 6.0, 11.7, 16.8 Hz, 1H, -OCH$_2$C<u>H</u>$_2$Ar), 4.02 (dd, *J* = 6.0, 11.7 Hz, 1H, -OC<u>H</u>$_2$CH$_2$Ar), 4.23

(dt, *J* = 3.0, 11.7 Hz, 1H, -OC$\underline{H}_2$CH$_2$Ar), 6.06 (s, 1H, benzyl H), 7.15 (d, *J* = 7.2 Hz, 1H, Ar-H), 7.19-7.33 (m, 2H, Ar-H), 7.36 (d, *J* = 7.2 Hz, 1H, Ar-H).

^{1}H NMR (400 MHz) δ 1.36 (s, 9H, -C(C$\underline{H}_3$)$_3$), 2.61 (dd, *J* = 3.2, 16.4 Hz, 1H, -OCH$_2$C$\underline{H}_2$Ar), 3.04 (ddd, *J* = 6.0, 11.6, 16.4 Hz, 1H, -OCH$_2$C$\underline{H}_2$Ar), 4.01 (dd, *J* = 6.0, 11.6 Hz, 1H, -OC$\underline{H}_2$CH$_2$Ar), 4.23 (dt, *J* = 3.2, 11.6 Hz, 1H, -OC$\underline{H}_2$CH$_2$Ar), 6.05 (s, 1H, benzyl H), 7.15 (d, *J* = 7.2 Hz, 1H, Ar-H), 7.20-7.31 (m, 2H, Ar-H), 7.36 (d, *J* = 7.2 Hz, 1H, Ar-H).

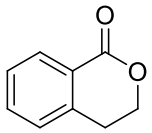
^{13}C NMR (75 MHz) δ 26.60 (3 carbons, -C($\underline{C}$H$_3$)$_3$), 27.72, 58.00, 80.95, 99.16, 126.15, 128.24, 128.61, 128.79, 130.17, 135.52.

^{13}C NMR (100 MHz) δ 26.65 (3 carbons, -C($\underline{C}$H$_3$)$_3$), 27.79, 58.07, 80.98, 99.21, 126.18, 128.29, 128.65, 128.82, 130.27, 135.58.

IR (neat) 3068 (Ar), 3030 (Ar), 2978, 2933, 1456, 1363, 1315, 1198, 1095 (C-O-O), 1003, 906, 746 cm^{-1}.

These spectral properties were in good agreement with those reported in the above literature.

1-Isochromanone. This by-product of **14** is a known compound [Nagano, T.; Kobayashi, S. *Chem. Lett*. **2008**, *37*, 1042-1043].



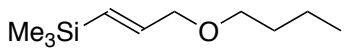
^{1}H NMR (300 MHz) δ 3.07 (t, *J* = 6.0 Hz, 2H, -OCH$_2$C$\underline{H}_2$Ar), 4.55 (t, *J* = 6.0 Hz, 2H, -OC$\underline{H}_2$CH$_2$Ar), 7.28 (d, *J* = 7.5 Hz, 1H, Ar-H), 7.41 (t, *J* = 7.5 Hz, 1H, Ar-H), 7.55 (t, *J* = 7.5 Hz, 1H, Ar-H), 8.11 (d, *J* = 7.5 Hz, 1H, Ar-H).

^{13}C NMR (75 MHz) δ 27.81, 67.28, 125.30, 127.21, 127.69, 130.41, 133.65, 139.52, 165.11 (C=O).

IR (neat) 3072 (Ar), 3033 (Ar), 2978, 2852, 1724 (C=O), 1606, 1460, 1392, 1294, 1244, 1120, 1030, 906, 746, 696 cm^{-1}.

These spectral properties were in good agreement with those reported in the above literature.

Butyl (*E*)-3-(trimethylsilyl)-2-propenyl ether (17).



To a solution of 2-propynol (1.16 mL, 19.9 mmol) in THF (30 mL) was added BuLi (26.7 mL, 1.65 M solution in hexane, 44.1 mmol) dropwise at –78 °C under argon. After the mixture was stirred for 30 min at that temperature, trimethylsilyl chloride (5.60 mL, 44.1 mmol) was added at the same temperature. After the solution was allowed to gradually warm to room temperature and was stirred overnight, the reaction was terminated by the addition of aqueous saturated NH_4Cl solution. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with water and brine, dried over Na_2SO_4, and concentrated *in vacuo* to give a crude oil, which was chromatographed on silica gel (hexane-ethyl acetate) to give 3-

(trimethylsilyl)-2-propynol (1.75 g, 68%) as an oil.

To a stirred solution of the above 3-(trimethylsilyl)-2-propynol (1.28 g, 9.98 mmol) in Et_2O (20 mL) was added Red-Al (65% in toluene, 4.50 mL, 15.0 mmol) at 0 °C dropwise. After the mixture was stirred at room temperature for 2 h, the reaction was terminated by the addition of 1 N HCl solution (10 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with an aqueous saturated $NaHCO_3$ solution, dried over Na_2SO_4, and concentrated *in vacuo* to give a crude oil, which was chromatographed on silica gel (hexane-ethyl acetate) to afford (*E*)-3-(trimethylsilyl)-2-propenol (806 mg, 62%) as an oil.

To a suspension of NaH (220 mg of a 60% suspension in mineral oil, 5.50 mmol) in THF (10 mL) was added (*E*)-3-(trimethylsilyl)-2-propenol (651 mg, 5.00 mmol) in THF (5 mL) at 0 °C under argon. After the mixture was stirred at room temperature for 1 h, butyl iodide (0.630 mL, 5.54 mmol) was added at 0 °C. The mixture was stirred at room temperature overnight and was quenched with water. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with water and brine, dried over Na_2SO_4, and concentrated *in vacuo* to give a crude oil, which was chromatographed on silica gel (hexane-ethyl acetate) to afford the title compound (223 mg, 24%) as an oil.

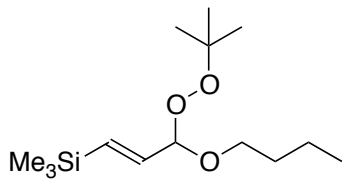
^{1}H NMR (300 MHz) δ 0.07 (s, 9H, -Si$\underline{Me}_3$), 0.93 (t, *J* = 6.9 Hz, 3H, alkyl-Me), 1.38 (sextet, *J* = 6.9 Hz, 2H, alkyl H), 1.59 (m, 2H, alkyl H), 3.43 (t, *J* = 6.6 Hz, 2H, -OC$\underline{H}_2(CH_2)_2CH_3$), 3.99 (dd, *J* = 1.2, 4.5 Hz, 2H, -CH=CHC$\underline{H}_2$O-), 5.91 (dt, *J* = 19.2, 1.2 Hz, 1H, -C$\underline{H}$=CHCH$_2$O-), 6.10 (dt, *J* = 19.2, 4.5 Hz, 1H, -CH=C$\underline{H}$CH$_2$O-).

^{13}C NMR (75 MHz) δ −1.38 (3 carbons, -Si$\underline{Me}_3$), 13.93, 19.32, 31.80, 70.37, 73.72, 131.54, 142.58.

IR (neat) 3000 (C=C-H), 2958, 2871, 1624 (C=C), 1458, 1350, 1248, 1109, 987, 865, 839, 769, 692 cm^{-1}.

Anal. Calcd for $C_{10}H_{22}OSi$: C, 64.45; H, 11.90. Found: C, 64.22; H, 12.10.

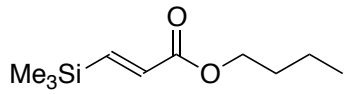
Butyl (*E*)-1-(*tert*-butylperoxy)-3-(trimethylsilyl)-2-propenyl ether (18).



To a suspension of butyl (*E*)-3-(trimethylsilyl)-2-propenyl ether (**17**) (37.3 mg, 0.200 mmol), Fe(acac)$_3$ (7.1 mg, 0.020 mmol), and MS 4A (100 mg) in 1.0 mL of CH_3CN was added *tert*-butyl hydroperoxide (0.20 mL, 5.0-6.0 M solution in decane, *ca*. 1.0-1.2 mmol) by a plastic pipette at room temperature under argon. The mixture was stirred in an oil bath maintained at 80 °C for 3 h. After being cooled to room temperature, the reaction mixture was filtered through a short pad of silica gel with the aid of ethyl acetate. The combined filtrates were concentrated *in vacuo* to give a crude oil, ^{1}H NMR analysis of which revealed that the yields of the title compound, butyl benzoate as a by-product, and recovered starting material **17** are 61%, 8%, and 8%, respectively, by using trichloroethylene as an internal standard. The crude oil was chromatographed on silica gel (hexane-ethyl acetate) to afford

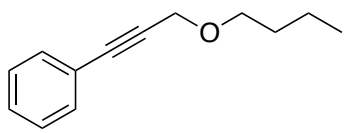
the title compound (33.2 mg, 60%) as an oil.
^{1}H NMR (300 MHz) δ 0.08 (s, 9H, -Si$\underline{Me}_3$), 0.93 (t, *J* = 7.2 Hz, 3H, alkyl-Me), 1.26 (s, 9H, -C(C$\underline{H}_3)_3$), 1.40 (m, 2H, alkyl H), 1.61 (m, 2H, alkyl H), 3.58 (dt, *J* = 9.6, 6.6 Hz, 1H, -OC$\underline{H}_2(CH_2)_2CH_3$), 3.88 (dt, *J* = 9.6, 6.6 Hz, 1H, -OC$\underline{H}_2(CH_2)_2CH_3$), 5.22 (dd, *J* = 1.2, 4.5 Hz, 1H, -CH=CHC$\underline{H}$O-), 5.94 (dd, *J* = 4.5, 18.9 Hz, 1H, -CH=C$\underline{H}$CHO-), 6.12 (dd, *J* = 1.2, 18.9 Hz, 1H, -C$\underline{H}$=CHCHO-).
^{1}H NMR (400 MHz) δ 0.08 (s, 9H, -Si$\underline{Me}_3$), 0.93 (t, *J* = 7.2 Hz, 3H, alkyl-Me), 1.26 (s, 9H, -C(C$\underline{H}_3)_3$), 1.40 (m, 2H, alkyl H), 1.61 (m, 2H, alkyl H), 3.58 (dt, *J* = 9.6, 6.8 Hz, 1H, -OC$\underline{H}_2(CH_2)_2CH_3$), 3.87 (dt, *J* = 9.6, 6.8 Hz, 1H, -OC$\underline{H}_2(CH_2)_2CH_3$), 5.22 (dd, *J* = 1.2, 4.4 Hz, 1H, -CH=CHC$\underline{H}$O-), 5.94 (dd, *J* = 4.4, 18.8 Hz, 1H, -CH=C$\underline{H}$CHO-), 6.11 (dd, *J* = 1.2, 18.8 Hz, 1H, -C$\underline{H}$=CHCHO-).
^{13}C NMR (75 MHz) δ −1.53 (3 carbons, -Si$\underline{Me}_3$), 13.89, 19.25, 26.51 (3 carbons, -C($\underline{C}H_3)_3$), 31.93, 68.60, 80.51, 106.24, 135.05 (C=C), 139.26 (C=C).
^{13}C NMR (100 MHz) δ −1.52 (3 carbons, -Si$\underline{Me}_3$), 13.88, 19.26, 26.53 (3 carbons, -C($\underline{C}H_3)_3$), 31.95, 68.60, 80.50, 106.25, 135.03 (C=C), 139.34 (C=C).
IR (neat) 3020 (C=C-H), 2958, 2871, 1624 (C=C), 1460, 1363, 1313, 1250, 1198, 1111 (C-O-O), 987, 839, 769, 692 cm^{-1}.
Anal. Calcd for $C_{14}H_{30}O_3Si$: C, 61.26; H, 11.02. Found: C, 61.04; H, 10.95.

Butyl (*E*)-3-(trimethylsilyl)-2-propenoate. This by-product of **18** was obtained in a separate run in the absence of MS 4A.



To a suspension of butyl (*E*)-3-(trimethylsilyl)-2-propenyl ether (**17**) (18.6 mg, 0.100 mmol) and Fe(acac)$_3$ (3.5 mg, 0.010 mmol) in 0.5 mL of CH_3CN was added *tert*-butyl hydroperoxide (0.10 mL, 5.0-6.0 M solution in decane, *ca*. 0.5-0.6 mmol) by a plastic pipette at room temperature under argon. The mixture was stirred in an oil bath maintained at 80 °C for 3 h. After being cooled to room temperature, the reaction mixture was filtered through a short pad of silica gel with the aid of ethyl acetate. The combined filtrates were concentrated *in vacuo* to give a crude oil, ^{1}H NMR analysis of which revealed that the yields of the title compound, butyl (*E*)-1-(*tert*-butylperoxy)-3-(trimethylsilyl)-2-propenyl ether (**18**), and recovered starting material **17** are 61%, 39%, and 0%, respectively, by using trichloroethylene as an internal standard. The crude oil was chromatographed on silica gel (hexane-ethyl acetate) to afford the title compound (12.5 mg, 62%) as an oil.
^{1}H NMR (300 MHz) δ 0.14 (s, 9H, -Si$\underline{Me}_3$), 0.95 (t, *J* = 7.5 Hz, 3H, alkyl-Me), 1.41 (sextet, *J* = 7.5 Hz, 2H, alkyl H), 1.66 (m, 2H, alkyl H), 4.15 (t, *J* = 6.9 Hz, 2H, -OC$\underline{H}_2(CH_2)_2CH_3$), 6.24 (d, *J* = 18.9 Hz, 1H, -C$\underline{H}$=CH(C=O)), 7.25 (d, *J* = 18.9 Hz, 1H, -CH=C$\underline{H}$(C=O)).
^{13}C NMR (75 MHz) δ −1.89 (3 carbons, -Si$\underline{Me}_3$), 13.73, 19.16, 30.70, 64.44, 133.96 (C=C), 149.53 (C=C), 166.07 (C=O).
IR (neat) 3040 (C=C-H), 2958, 2924, 2875, 1728 (C=O), 1600 (C=C), 1466, 1306, 1250, 1223, 1167, 997, 866, 839 cm^{-1}.
Anal. Calcd for $C_{10}H_{20}O_2Si$: C, 59.95; H, 10.06. Found: C, 59.72; H, 9.75.

Butyl 3-phenyl-2-propynyl ether (19).



To a solution of phenylacetylene (1.10 mL, 10.0 mmol) in THF (10 mL) was added BuLi (7.27 mL, 1.65 M solution in hexane, 12.0 mmol) dropwise at –78 °C under argon. After the mixture was stirred for 30 min at that temperature, a suspension of paraformaldehyde (400 mg, 12.0 mmol) in THF (10 mL) was added at the same temperature. After the mixture was allowed to gradually warm to room temperature, it was stirred overnight. Then, the reaction was terminated by the addition of aqueous saturated NH_4Cl solution. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with water and brine, dried over Na_2SO_4, and concentrated *in vacuo* to give a crude oil, which was chromatographed on silica gel (hexane-ethyl acetate) to give 3-phenyl-2-propynol (1.32 g, 100%) as an oil.

To a suspension of NaH (440 mg of a 60% suspension in mineral oil, 11.0 mmol) in THF (10 mL) was added 3-phenyl-2-propynol (1.32 g, 9.99 mmol) in THF (5 mL) at 0 °C under argon. After the mixture was stirred at room temperature for 1 h, butyl iodide (1.30 mL, 11.4 mmol) was added at 0 °C. The mixture was stirred at room temperature overnight and was quenched with water. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with water and brine, dried over Na_2SO_4, and concentrated *in vacuo* to give a crude oil, which was chromatographed on silica gel (hexane-ethyl acetate) to afford the title compound (1.10 g, 58%) as an oil.

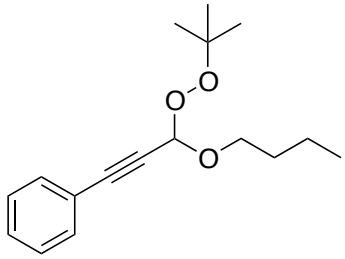
^{1}H NMR (300 MHz) δ 0.94 (t, J = 6.9 Hz, 3H, Me), 1.41 (sextet, J = 6.9 Hz, 2H, alkyl H), 1.62 (m, 2H, alkyl H), 3.58 (t, J = 6.6 Hz, 2H, -OC$\underline{H}_2$(CH$_2$)$_2$CH$_3$), 4.36 (s, 2H, propargyl H), 7.28-7.35 (m, 3H, Ar-H), 7.45 (m, 2H, Ar-H).

^{13}C NMR (75 MHz) δ 13.82, 19.25, 31.57, 58.70, 69.91, 85.42 (C≡C), 85.81 (C≡C), 122.71, 128.19 (2 carbons), 128.27, 131.67 (2 carbons).

IR (neat) 3080 (Ar), 3059 (Ar), 3030 (Ar), 2958, 2920, 2871, 2237 (C≡C), 1599, 1491, 1356, 1099, 756, 690 cm^{-1}.

Anal. Calcd for $C_{13}H_{16}O$: C, 82.94; H, 8.57. Found: C, 82.72; H, 8.63.

Butyl 1-(*tert*-butylperoxy)-3-phenyl-2-propynyl ether (20).



To a suspension of butyl 3-phenyl-2-propynyl ether (**19**) (75.3 mg, 0.400 mmol), $Fe(acac)_3$ (14.1 mg, 0.040 mmol), and MS 4A (200 mg) in 2.0 mL of CH_3CN was added *tert*-butyl hydroperoxide (0.40 mL, 5.0-6.0 M solution in decane, *ca*. 2.0-2.4 mmol) by a plastic pipette at room temperature under argon. The mixture was stirred in an oil bath maintained at 80 °C for 3 h. After being cooled to room temperature, the reaction mixture was filtered through a short pad of silica gel with the aid of ethyl acetate. The combined filtrates were concentrated *in vacuo* to give a crude oil, ^{1}H NMR analysis of which revealed that the yields of the title compound, butyl 3-phenylpropiolate as a by-product, and recovered starting material **19** are 52%, 10%, and 33%, respectively, by using trichloroethylene as an internal standard. The crude oil was chromatographed on silica gel (hexane-ethyl acetate) to afford the title compound (58.6 mg, 53%) as an oil.

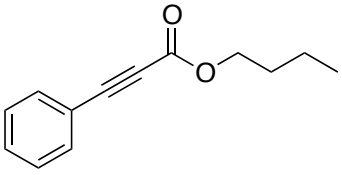
^{1}H NMR (300 MHz) δ 0.94 (t, *J* = 7.5 Hz, 3H, Me), 1.31 (s, 9H, -C($\underline{C}H_3$)$_3$), 1.44 (sextet, *J* = 7.5 Hz, 2H, alkyl H), 1.66 (m, 2H, alkyl H), 3.73 (dt, *J* = 9.6, 6.6 Hz, 1H, -OC$\underline{H}_2$(CH$_2$)$_2$CH$_3$), 3.88 (dt, *J* = 9.6, 6.6 Hz, 1H, -OC$\underline{H}_2$(CH$_2$)$_2$CH$_3$), 5.80 (s, 1H, propargyl H), 7.28-7.39 (m, 3H, Ar-H), 7.48 (m, 2H, Ar-H).

^{13}C NMR (75 MHz) δ 13.84, 19.23, 26.41 (3 carbons, -C($\underline{C}H_3$)$_3$), 31.62, 65.81, 81.18, 81.91, 86.53, 95.65 (acetal), 121.69, 128.26 (2 carbons), 128.94, 131.93 (2 carbons).

IR (neat) 3090 (Ar), 3060 (Ar), 2960, 2930, 2880, 2235 (C≡C), 1491, 1363, 1311, 1196, 1095 (C-O-O), 984, 876, 758, 690 cm^{-1}.

Anal. Calcd for $C_{17}H_{24}O_3$: C, 73.88; H, 8.75. Found: C, 74.25; H, 8.59.

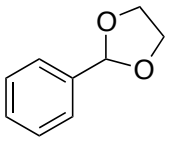
Butyl 3-phenylpropiolate. This by-product of **20** is a known compound [Maki, B. E.; Chan, A.; Phillips, E. M.; Scheidt, K. A. *Org. Lett.* **2007**, *9*, 371-374].



^{1}H NMR (300 MHz) δ 0.95 (t, *J* = 7.2 Hz, 3H, Me), 1.42 (m, 2H, alkyl H), 1.69 (m, 2H, alkyl H), 4.23 (t, *J* = 6.6 Hz, 2H, -OC$\underline{H}_2$(CH$_2$)$_2$CH$_3$), 7.30-7.60 (m, 5H, Ar-H).

These spectral properties were in good agreement with those reported in the above literature.

2-Phenyl-1,3-dioxolane (21). This is a known compound [Gregg, B. T.; Golden, K. C.; Quinn, J. F. *Tetrahedron* **2008**, *64*, 3287-3295. Barbasiewicz, M.; Mąkosza, M. *Org. Lett.* **2006**, *8*, 3745-3748. Lee, A. S.-Y.; Cheng, C.-L. *Tetrahedron* **1997**, *53*, 14255-14262].



A mixture of benzaldehyde (0.880 mL, 8.64 mmol), ethylene glycol (3.00 mL, 53.8 mmol), and a

catalytic amount of *p*-toluenesulfonic acid monohydrate (100 mg, 0.306 mmol) in toluene (15 mL) was heated at reflux for 3 h with azeotropical removal of water by a Dean-Stark trap. Aqueous saturated $NaHCO_3$ solution and AcOEt were added. The organic layer was separated and the aqueous layer was extracted with AcOEt. The combined organic layers were washed successively with water and brine, dried over Na_2SO_4, and concentrated *in vacuo* to give a crude oil, which was chromatographed on silica gel (hexane-ethyl acetate) to afford the title compound (1.17 g, 90%) as an oil.

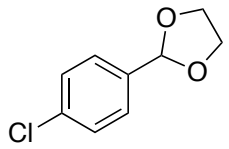
^{1}H NMR (300 MHz) δ 4.01-4.18 (m, 4H, -O(C$\underline{H}_2$)$_2$O-), 5.82 (s, 1H, benzyl H), 7.35-7.43 (m, 3H, Ar-H), 7.45-7.51 (m, 2H, Ar-H).

^{13}C NMR (75 MHz) δ 65.24 (2 carbons), 103.38, 126.38 (2 carbons), 128.30 (2 carbons), 129.14, 137.80.

IR (neat) 3090 (Ar), 3060 (Ar), 3040 (Ar), 2954, 2887, 1458, 1396, 1221, 1093, 1070, 1028, 966, 758, 700 cm^{-1}.

These spectral properties were in good agreement with those reported in the above literature.

2-(4-Chlorophenyl)-1,3-dioxolane (22). This is a known compound [Ranu, B. C.; Jana, R.; Samanta, S. *Adv. Synth. Catal.* **2004**, *346*, 446-450. Goossen, L. J.; Knauber, T. *J. Org. Chem.* **2008**, *73*, 8631-8634].



A mixture of 4-chlorobenzaldehyde (703 mg, 5.00 mmol), ethylene glycol (1.00 mL, 17.9 mmol), and a catalytic amount of *p*-toluenesulfonic acid monohydrate (48.0 mg, 0.250 mmol) in benzene (30 mL) was heated at reflux for 3 h with azeotropical removal of water by a Dean-Stark trap. Aqueous saturated $NaHCO_3$ solution and AcOEt were added. The organic layer was separated and the aqueous layer was extracted with AcOEt. The combined organic layers were washed successively with water and brine, dried over Na_2SO_4, and concentrated *in vacuo* to give a crude oil, which was chromatographed on silica gel (hexane-ethyl acetate) to afford the title compound (500 mg, 54%) as an oil.

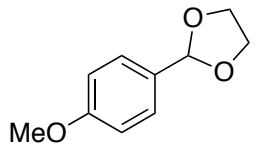
^{1}H NMR (400 MHz) δ 4.02 (m, 2H, -O(C$\underline{H}_2$)$_2$O-), 4.10 (m, 2H, -O(C$\underline{H}_2$)$_2$O-), 5.78 (s, 1H, benzyl H), 7.35 (d, J = 8.8 Hz, 2H, Ar-H), 7.41 (d, J = 8.8 Hz, 2H, Ar-H).

^{13}C NMR (100 MHz) δ 65.29 (2 carbons), 102.99, 127.86 (2 carbons), 128.52 (2 carbons), 134.98, 136.48.

IR (neat) 3058 (Ar), 2955, 2887, 1602, 1492, 1422, 1385, 1298, 1218, 1089, 1015, 972, 821 cm^{-1}.

These spectral properties were in good agreement with those reported in the above literatures.

2-(4-Methoxyphenyl)-1,3-dioxolane (23). This is a known compound [Gregg, B. T.; Golden, K. C.; Quinn, J. F. *Tetrahedron* **2008**, *64*, 3287-3295].



A mixture of 4-methoxybenzaldehyde (0.61 mL, 5.00 mmol), ethylene glycol (1.00 mL, 17.9 mmol), and a catalytic amount of *p*-toluenesulfonic acid monohydrate (48.0 mg, 0.250 mmol) in benzene (30 mL) was heated at reflux for 3 h with azeotropical removal of water by a Dean-Stark trap. Aqueous saturated $NaHCO_3$ solution and AcOEt were added. The organic layer was separated and the aqueous layer was extracted with AcOEt. The combined organic layers were washed successively with water and brine, dried over Na_2SO_4, and concentrated *in vacuo* to give a crude oil, which was chromatographed on silica gel (hexane-ethyl acetate) to afford the title compound (625 mg, 69%) as an oil.

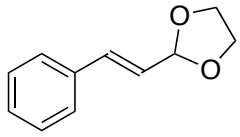
^{1}H NMR (400 MHz) δ 3.80 (s, 3H, -OMe), 4.01 (m, 2H, -O(C$\underline{H}_2$)$_2$O-), 4.12 (m, 2H, -O(C$\underline{H}_2$)$_2$O-), 5.75 (s, 1H, benzyl H), 6.90 (d, J = 8.8 Hz, 2H, Ar-H), 7.40 (d, J = 8.8 Hz, 2H, Ar-H).

^{13}C NMR (100 MHz) δ 55.26, 65.19 (2 carbons), 103.68, 113.72 (2 carbons), 127.82 (2 carbons), 129.98, 160.32.

IR (neat) 3080 (Ar), 3040 (Ar), 3000 (Ar), 2957, 2888, 2839, 1615, 1518, 1464, 1392, 1305, 1250, 1172, 1081, 1033, 966, 830 cm^{-1}.

These spectral properties were in good agreement with those reported in the above literature.

(*E*)-2-Styryl-1,3-dioxolane (24). This is a known compound [Jang, Y.-J.; Shih, Y.-K.; Liu, J.-Y.; Kuo, W.-Y.; Yao, C.-F. *Chem. Eur. J.* **2003**, *9*, 2123-2128].



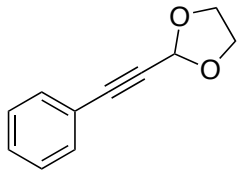
A mixture of *trans*-cinnamaldehyde (0.83 mL, 5.03 mmol), ethylene glycol (1.00 mL, 17.9 mmol), and a catalytic amount of *p*-toluenesulfonic acid monohydrate (48.0 mg, 0.250 mmol) in benzene (30 mL) was heated at reflux for 3 h with azeotropical removal of water by a Dean-Stark trap. Aqueous saturated $NaHCO_3$ solution and AcOEt were added. The organic layer was separated and the aqueous layer was extracted with AcOEt. The combined organic layers were washed successively with water and brine, dried over Na_2SO_4, and concentrated *in vacuo* to give a crude oil, which was chromatographed on silica gel (hexane-ethyl acetate) to afford the title compound (767 mg, 87%) as an oil.

^{1}H NMR (400 MHz) δ 3.96 (m, 2H, -O(C$\underline{H}_2$)$_2$O-), 4.06 (m, 2H, -O(C$\underline{H}_2$)$_2$O-), 5.44 (d, J = 6.0 Hz, 1H, -OC$\underline{H}$O-), 6.17 (dd, J = 6.0, 16.0 Hz, 1H, ArCH=C$\underline{H}$-), 6.78 (d, J = 16.0 Hz, 1H, ArC$\underline{H}$=CH-), 7.24-7.37 (m, 3H, Ar-H), 7.39-7.44 (m, 2H, Ar-H).

^{13}C NMR (100 MHz) δ 65.01 (2 carbons), 103.81, 125.11, 126.89 (2 carbons), 128.30, 128.53 (2 carbons), 134.79, 135.79.

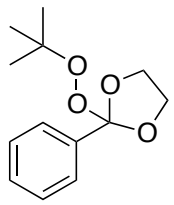
IR (neat) 3083 (Ar), 3060 (Ar), 3029 (Ar), 2954, 2885, 1656 (C=C), 1494, 1451, 1395, 1150, 1063, 959, 831, 750, 693 cm^{-1}.
These spectral properties were in good agreement with those reported in the above literature.

2-(Phenylethynyl)-1,3-dioxolane (25). This is a known compound [Katritzky, A. R.; Odens, H. H.; Voronkov, M. V. *J. Org. Chem.* **2000**, *65*, 1886-1888].



To a solution of phenylacetylene (0.55 mL, 5.01 mmol) in Et_2O (5 mL) was added *n*-BuLi (3.60 mL, 1.65 M solution in hexane, 5.94 mmol) dropwise at –78 °C under argon. After the mixture was stirred for 30 min at that temperature, DMF (0.57 mL, 7.41 mmol) was added at the same temperature. After the solution was allowed to gradually warm to room temperature and was stirred for 3 h, the reaction was terminated by the addition of aqueous saturated NH_4Cl solution. The organic products were extract with ether. The combined organic layers were wash with brine, dried over Na_2SO_4, and concentrated *in vacuo* to afford 3-phenylpropiolaldehyde (650 mg, *ca.* 100%), which was directly used in the next step.
A mixture of 3-phenylpropiolaldehyde (650 mg, *ca.* 5.00 mmol), ethylene glycol (1.00 mL, 17.9 mmol), and a catalytic amount of *p*-toluenesulfonic acid monohydrate (48.0 mg, 0.250 mmol) in benzene (30 mL) was heated at reflux for 3 h with azeotropical removal of water by a Dean-Stark trap. Aqueous saturated $NaHCO_3$ solution and AcOEt were added. The organic layer was separated and the aqueous layer was extracted with AcOEt. The combined organic layers were washed successively with water and brine, dried over Na_2SO_4, and concentrated *in vacuo* to give a crude oil, which was chromatographed on silica gel (hexane-ethyl acetate) to afford the title compound (209 mg, 24% over 2 steps) as an oil.
^{1}H NMR (400 MHz) δ 3.99 (m, 2H, -O(C$\underline{H}_2$)$_2$O-), 4.14 (m, 2H, -O(C$\underline{H}_2$)$_2$O-), 5.89 (s, 1H, propargyl H), 7.28-7.37 (m, 3H, Ar-H), 7.45-7.49 (m, 2H, Ar-H).
^{13}C NMR (100 MHz) δ 64.57 (2 carbons), 84.43, 85.18, 93.44, 121.62, 128.26 (2 carbons), 128.93, 131.91 (2 carbons).
IR (neat) 3099 (Ar), 3080 (Ar), 3059 (Ar), 2958, 2893, 2235 (C≡C), 1599, 1490, 1444, 1389, 1344, 1255, 1100, 1025, 922, 758, 691 cm^{-1}.
These spectral properties were in good agreement with those reported in the above literature.

2-(*tert*-Butylperoxy)-2-phenyl-1,3-dioxolane (26). This is a known compound [Sueda, T.; Fukuda, S.; Ochiai, M. *Org. Lett.* **2001**, *3*, 2387-2390].



To a suspension of 2-phenyl-1,3-dioxolane (**21**) (30.0 mg, 0.200 mmol), $Fe(acac)_3$ (7.1 mg, 0.020 mmol), and MS 4A (100 mg) in 1.0 mL of CH_3CN was added *tert*-butyl hydroperoxide (0.20 mL, 5.0-6.0 M solution in decane, *ca*. 1.0-1.2 mmol) by a plastic pipette at room temperature under argon. The mixture was stirred in an oil bath maintained at 80 °C for 3 h. After being cooled to room temperature, the reaction mixture was filtered through a short pad of Chromatorex^R NH (Cat. No. DM1012, size 100-200 mesh, Fuji Silysia Chemical Ltd., Japan) with the aid of ethyl acetate. The combined filtrates were concentrated *in vacuo* to give a crude oil, which was chromatographed on Chromatorex^R NH (hexane-ethyl acetate) to afford the title compound (46.1 mg, 97%) as an oil.

^{1}H NMR (300 MHz) δ 1.29 (s, 9H, -C(C$\underline{H}_3$)$_3$), 4.13 (m, 2H, -O(C$\underline{H}_2$)$_2$O-), 4.46 (m, 2H, -O(C$\underline{H}_2$)$_2$O-), 7.33-7.40 (m, 3H, Ar-H), 7.64 (m, 2H, Ar-H).

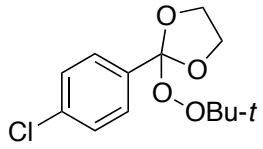
^{13}C NMR (75 MHz) δ 26.53 (3 carbons, -C($\underline{C}$H$_3$)$_3$), 66.68 (2 carbons), 80.83, 122.95, 126.25 (2 carbons), 127.98 (2 carbons), 129.31, 136.04.

IR (neat) 3090 (Ar), 3060 (Ar), 3030 (Ar), 2979, 2940, 2900, 1452, 1365, 1298, 1196, 1099 (C-O-O), 1022, 983, 918, 876, 764, 700 cm^{-1}.

Anal. Calcd for $C_{13}H_{18}O_4$: C, 65.53; H, 7.61. Found: C, 65.82; H, 7.78.

These spectral properties were in good agreement with those reported in the above literature.

2-(*tert*-Butylperoxy)-2-(4-chlorophenyl)-1,3-dioxolane (27).



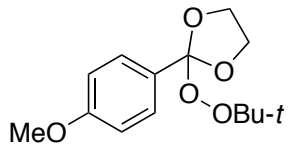
To a suspension of 2-(4-chlorophenyl)-1,3-dioxolane (**22**) (36.9 mg, 0.200 mmol), $Fe(acac)_3$ (7.1 mg, 0.020 mmol), and MS 4A (100 mg) in 1.0 mL of CH_3CN was added *tert*-butyl hydroperoxide (0.20 mL, 5.0-6.0 M solution in decane, *ca*. 1.0-1.2 mmol) by a plastic pipette at room temperature under argon. The mixture was stirred in an oil bath maintained at 80 °C for 3 h. After being cooled to room temperature, the reaction mixture was filtered through a short pad of Chromatorex^R NH with the aid of ethyl acetate. The combined filtrates were concentrated *in vacuo* to give a crude oil, which was chromatographed on Chromatorex^R NH (hexane) to afford the title compound (53.8 mg, 99%) as an oil.

^{1}H NMR (400 MHz) δ 1.27 (s, 9H, -C(C$\underline{H}_3$)$_3$), 4.11 (m, 2H, -O(C$\underline{H}_2$)$_2$O-), 4.44 (m, 2H, -O(C$\underline{H}_2$)$_2$O-), 7.33 (d, J = 8.8 Hz, 2H, Ar-H), 7.57 (d, J = 8.8 Hz, 2H, Ar-H).

^{13}C NMR (100 MHz) δ 26.52 (3 carbons, -C($\underline{C}$H$_3$)$_3$), 66.69 (2 carbons), 80.94, 122.53, 127.83 (2 carbons), 128.17 (2 carbons), 134.66, 135.31.

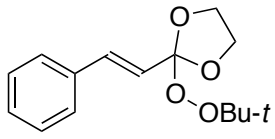
IR (neat) 3074 (Ar), 2980, 2929, 2906, 1602, 1490, 1401, 1364, 1299, 1258, 1196, 1093 (C-O-O), 1049, 1019, 986, 827 cm^{-1}.
HRMS (ESI) Calcd for $C_{13}H_{17}ClO_4Na$ $[M+Na]^+$: 295.0708. Found: 295.0707.

2-(*tert*-Butylperoxy)-2-(4-methoxyphenyl)-1,3-dioxolane (28).



To a suspension of 2-(4-methoxyphenyl)-1,3-dioxolane (**23**) (36.0 mg, 0.200 mmol), $Fe(acac)_3$ (7.1 mg, 0.020 mmol), and MS 4A (100 mg) in 1.0 mL of CH_3CN was added *tert*-butyl hydroperoxide (0.20 mL, 5.0-6.0 M solution in decane, *ca*. 1.0-1.2 mmol) by a plastic pipette at room temperature under argon. The mixture was stirred in an oil bath maintained at 80 °C for 3 h. After being cooled to room temperature, the reaction mixture was filtered through a short pad of Chromatorex^R NH with the aid of ethyl acetate. The combined filtrates were concentrated *in vacuo* to give a crude oil, which was chromatographed on Chromatorex^R NH (hexane) to afford the title compound (48.2 mg, 90%) as an oil.
^{1}H NMR (400 MHz) δ 1.28 (s, 9H, -C(C$\underline{H}_3$)$_3$), 3.80 (s, 3H, -O$\underline{Me}$), 4.10 (m, 2H, -O(C$\underline{H}_2$)$_2$O-), 4.43 (m, 2H, -O(C$\underline{H}_2$)$_2$O-), 6.87 (d, J = 8.8 Hz, 2H, Ar-H), 7.57 (d, J = 8.8 Hz, 2H, Ar-H).
^{13}C NMR (100 MHz) δ 26.58 (3 carbons, -C($\underline{C}$H$_3$)$_3$), 55.27, 66.66 (2 carbons), 80.71, 113.33 (2 carbons), 123.04, 127.71 (2 carbons), 128.48, 160.37.
IR (neat) 3072 (Ar), 3045 (Ar), 3000 (Ar), 2978, 2932, 2905, 2839, 1612, 1515, 1465, 1364, 1311, 1250, 1196, 1173, 1100 (C-O-O), 1035, 984, 832 cm^{-1}.
HRMS (ESI) Calcd for $C_{14}H_{20}O_5Na$ $[M+Na]^+$: 291.1203. Found: 291.1207.

(*E*)-2-(*tert*-Butylperoxy)-2-styryl-1,3-dioxolane (29).



To a suspension of (*E*)-2-styryl-1,3-dioxolane (**24**) (35.2 mg, 0.200 mmol), $Fe(acac)_3$ (7.1 mg, 0.020 mmol), and MS 4A (100 mg) in 1.0 mL of CH_3CN was added *tert*-butyl hydroperoxide (0.20 mL, 5.0-6.0 M solution in decane, *ca*. 1.0-1.2 mmol) by a plastic pipette at room temperature under argon. The mixture was stirred in an oil bath maintained at 80 °C for 3 h. After being cooled to room temperature, the reaction mixture was filtered through a short pad of Chromatorex^R NH with the aid of ethyl acetate. The combined filtrates were concentrated *in vacuo* to give a crude oil, which was

chromatographed on Chromatorex^{R} NH (hexane-ethyl acetate) to afford the title compound (51.2 mg, 97%) as an oil.

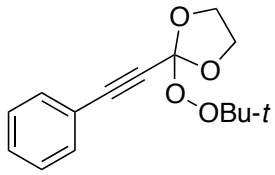
^{1}H NMR (400 MHz) δ 1.29 (s, 9H, -C(C$\underline{H}_3$)$_3$), 4.10 (m, 2H, -O(C$\underline{H}_2$)$_2$O-), 4.36 (m, 2H, -O(C$\underline{H}_2$)$_2$O-), 6.26 (d, *J* = 16.0 Hz, 1H, ArCH=C$\underline{H}$-), 7.00 (d, *J* = 16.0 Hz, 1H, ArC$\underline{H}$=CH-), 7.24-7.37 (m, 3H, Ar-H), 7.39-7.44 (m, 2H, Ar-H).

^{13}C NMR (100 MHz) δ 26.57 (3 carbons, -C(C$\underline{H}_3$)$_3$), 66.30 (2 carbons), 80.67, 121.93, 122.13, 127.08 (2 carbons), 128.41, 128.54 (2 carbons), 133.42, 135.70.

IR (neat) 3084 (Ar), 3061 (Ar), 3028 (Ar), 2978, 2929, 2903, 1656 (C=C), 1495, 1450, 1364, 1199, 1149, 1059 (C-O-O), 1020, 968, 874, 750, 693 cm^{-1}.

HRMS (ESI) Calcd for $C_{15}H_{20}O_4Na$ [M+Na]$^{+}$: 287.1254. Found: 287.1257.

2-(*tert*-Butylperoxy)-2-(phenylethynyl)-1,3-dioxolane (30).



To a suspension of 2-(phenylethynyl)-1,3-dioxolane (**25**) (34.9 mg, 0.200 mmol), Fe(acac)$_3$ (7.1 mg, 0.020 mmol), and MS 4A (100 mg) in 1.0 mL of CH_3CN was added *tert*-butyl hydroperoxide (0.20 mL, 5.0-6.0 M solution in decane, *ca*. 1.0-1.2 mmol) by a plastic pipette at room temperature under argon. The mixture was stirred in an oil bath maintained at 80 °C for 3 h. After being cooled to room temperature, the reaction mixture was filtered through a short pad of Chromatorex^{R} NH with the aid of ethyl acetate. The combined filtrates were concentrated *in vacuo* to give a crude oil, which was chromatographed on Chromatorex^{R} NH (hexane-ethyl acetate) to afford the title compound (44.3 mg, 84%) as an oil.

^{1}H NMR (400 MHz) δ 1.32 (s, 9H, -C(C$\underline{H}_3$)$_3$), 4.19 (m, 2H, -O(C$\underline{H}_2$)$_2$O-), 4.31 (m, 2H, -O(C$\underline{H}_2$)$_2$O-), 7.29-7.38 (m, 3H, Ar-H), 7.49-7.53 (m, 2H, Ar-H).

^{13}C NMR (100 MHz) δ 26.57 (3 carbons, -C(C$\underline{H}_3$)$_3$), 66.30 (2 carbons), 81.42, 81.83, 83.63, 116.41, 121.17, 128.24 (2 carbons), 129.22, 132.15 (2 carbons).

IR (neat) 3106 (Ar), 3083 (Ar), 3063 (Ar), 2980, 2931, 2907, 2241 (C≡C), 1600, 1491, 1444, 1389, 1365, 1305, 1260, 1169, 1046 (C-O-O), 1011, 956, 758, 691 cm^{-1}.

HRMS (ESI) Calcd for $C_{15}H_{18}O_4Na$ [M+Na]$^{+}$: 285.1097. Found: 285.1101.

Chapter 5
Summary

This thesis describes two types of synthetic reactions catalyzed or mediated by iron reagents. In Chapters 2 and 3, new conjugate addition reactions of Grignard reagents to various 2-alken-4-ynoates are described. Synthetic application of their products is also mentioned. In Chapter 4, a direct functionalization of the C–H bond α to ether oxygen giving peroxyacetals and orthoesters is disclosed. These new reactions gave products otherwise tedious to prepare, amply showing the unique role of iron reagents in organic chemistry.

Chapter 1: Introduction

The recent research in the field of conjugate addition of Grignard reagents and C–H bond functionalization in organic synthesis, the development of iron reagents in currently organic chemistry, and the latest contribution from our laboratory are briefly summarized. In addition, the importance of the studies described in this thesis from the scientific and practical point of view is discussed.

Chapter 2: Iron-Catalyzed Synthesis of Allenes from 2-Alken-4-ynoates and Grignard Reagents

Conjugate addition of methyl or aryl Grignard reagents to 2-alken-4-ynoates **1** was nicely catalyzed by $FeCl_2$ to proceed in a 1,6-selective manner, giving 5-methyl(or aryl)-3,4-alkadienoates **2** after workup with electrophiles (eq 1). Tetra-substituted allene **3** prepared by this method would be a good starting material for the synthesis of meloscine (Fig. 1).

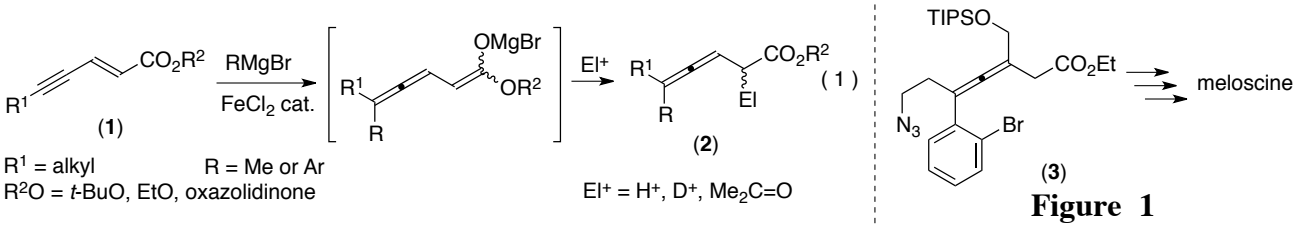
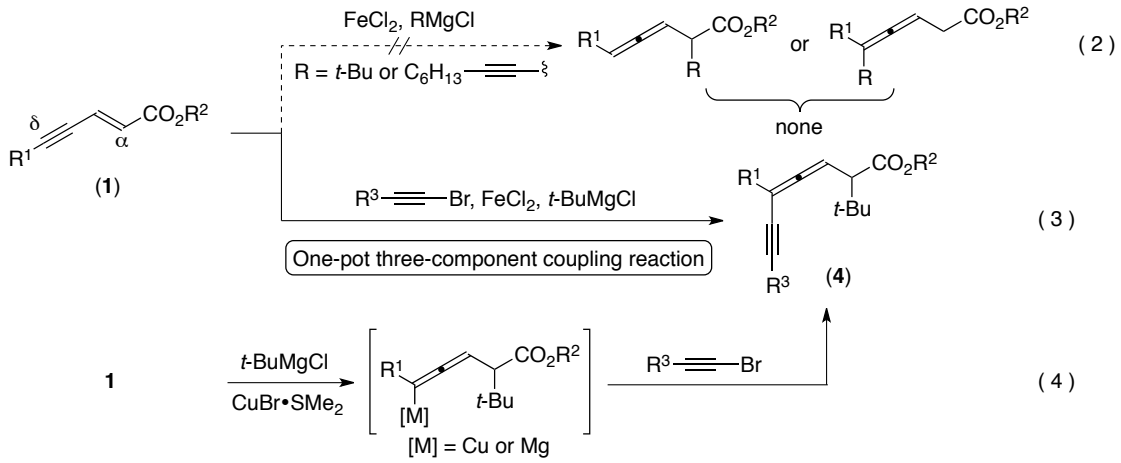


Figure 1

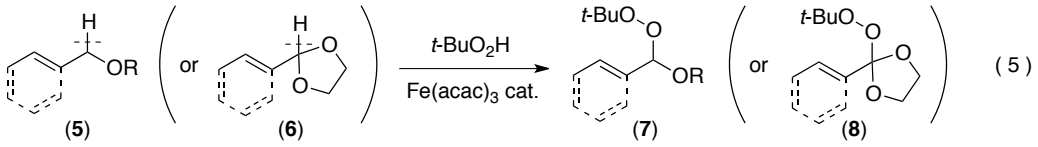
Chapter 3: Iron-Mediated Three-Component Coupling Reaction between 2-Alken-4-ynoates, *tert*-Alkyl Grignard Reagent, and 1-Bromo-1-alkyne

As mentioned in Chapter 2, *t*-BuMgCl or $C_6H_{13}C{\equiv}CMgCl$ did not add to 2-alken-4-ynoate **1** at its α nor δ position in the presence of an iron salt as shown in eq 2. However, when a mixture of **1**, 1-bromo-1-alkynes, and $FeCl_2$ was treated with *t*-BuMgCl, a new one-pot three-component coupling reaction between these starting materials took place to give 2-(*tert*-butyl)-3,4-alkadien-6-ynoates **4** in good yields (eq 3). The results of these equations suggest that this three-component coupling reaction is not a simple anionic process. In conjunction with the transformation of eq 3, we also found a copper-mediated similar three-component coupling reaction (eq 4), which may be different from the aforementioned iron-mediated one from the mechanistic point of view, but could be complementarily used each other.



Chapter 4: Synthesis of *tert*-Butyl Peroxyacetals from Benzyl, Allyl, or Propargyl Ethers *via* Iron-Promoted C–H Bond Functionalization

C–H bond functionalization of benzyl, allyl, or propargyl ethers **5** or acetals **6** with *t*-BuO_2H was achieved with an iron catalyst to give aryl, olefinic, or acetylenic peroxyacetals **7** or peroxyorthoesters **8**, which are otherwise tedious to prepare (eq 5).



In summary, new iron-mediated synthetic reactions, including 1,6- or α-selective conjugate addition of Grignard reagents to enynoates, its extension to three-component coupling reaction between 2-alken-4-ynoates, 1-bromo-1-alkynes, and *tert*-alkyl Grignard reagent, and C–H bond fuctionalization at α position to the ether oxygen, have been disclosed in this thesis. Through these results, the role of iron reagents in organic synthesis and possible synthetic application of the products obtained by these methods are also discussed.

Publications

1. Hata, T.; **Iwata. S.**; Seto, S.; Urabe, H. "Iron-Catalyzed Synthesis of Allenes from 2-Alken-4-ynoates and Grignard Reagents," *Adv. Synth. Catal.* **2012**, *354*, 1885-1889.

2. **Iwata, S.**; Hata, T.; Urabe, H. "Synthesis of *tert*-Butyl Peroxyacetals from Benzyl, Allyl, or Propargyl Ethers *via* Iron-Promoted C–H Bond Functionalization," *Adv. Synth. Catal.* **2012**, *354*, 3480-3484.

Other Publication

3. **Iwata, S.**; Senoo, M.; Hata, T.; Urabe, H. "Synthesis of *S*-Aryl Arenethiosulfonates from *N,N*-Di(arenesulfonyl)hydrazines: Reduction of Sulfonyl Chlorides with an Organic Reagent," *Heteroatom Chem.* **2013**, *24*, 336-344.

Presentation

1. Hata, T.; **Iwata. S.**; Seto, S.; Urabe, H.
   "Iron-Catalyzed Selective Synthesis of Allenes from Functionalized Conjugated Enynes and Grignard Reagents,"
   91st Annual Meeting of the Chemical Society of Japan (March 29, 2011, Kanagawa University, 4C9-33)
   (Oral Presentation)

2. **Iwata. S.**; Hata, T.; Urabe, H.
   "Iron-Catalyzed Selective Synthesis of Peroxyacetals from Benzyl Ethers and *tert*-Butyl Hydroperoxide,"
   91st Annual Meeting of the Chemical Society of Japan (March 29, 2011, Kanagawa University, 4C9-34)
   (Oral Presentation)

3. **Iwata. S.**; Hata, T.; Urabe, H.

"Iron-Catalyzed Selective Synthesis of Peroxyacetals from Unsaturated Ethers and *tert*-Butyl Hydroperoxide,"
16th IUPAC International Symposium on Organometallic Chemistry Directed Towards Organic Synthesis (July 29, 2011, Shanghai, China, P-384)
(Poster Presentation)

4. Hata, T.; **Iwata. S.**; Seto, S.; Urabe, H.
"Iron-Catalyzed Selective Synthesis of Allenes from Functionalized Conjugated Enynes and Grignard Reagents"
58th Symposium on Organometallic Chemistry, Japan (September 8, 2011, Nagoya University, P2A-30)
(Poster Presentation)

5. **Iwata. S.**; Nakagawa, K.; Hata, T.; Urabe, H.
"Iron-Catalyzed Stereoselective 1,6-Conjugate Addition of Heteroaryl Grignard Reagents to 2,4-Alkadienoates,"
92nd Annual Meeting of the Chemical Society of Japan (March 26, 2012, Keio University, 2L2-10)
(Oral Presentation)

6. **Iwata. S.**; Seto, S.; Hata, T.; Urabe, H.
"Iron-Mediated Three-component Coupling Reaction of 2-Alken-4-ynoate, *tert*-Alkyl Grignard Reagent, and 1-Bromo-1-alkyne,"
92nd Annual Meeting of the Chemical Society of Japan (March 26, 2012, Keio University, 2L2-12)
(Oral Presentation)

7. **Iwata. S.**; Ohtani, K.; Hata, T.; Urabe, H.
"Copper- or Iron-Mediated Three-component Coupling of 2-Alken-4-ynoates, Grignard Reagents, and Organic Halides,"
10th International Symposium on Carbanion Chemistry (September 23, 2013, Kyoto, P-51)
(Poster Presentation)

Acknowledgement

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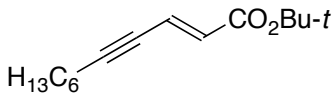
The author would like to express his sincere acknowledgement to his family, especially his parents, Shizuko & Tatsuo Iwata, for their constant assistance and encouragement.

Satoshi Iwata

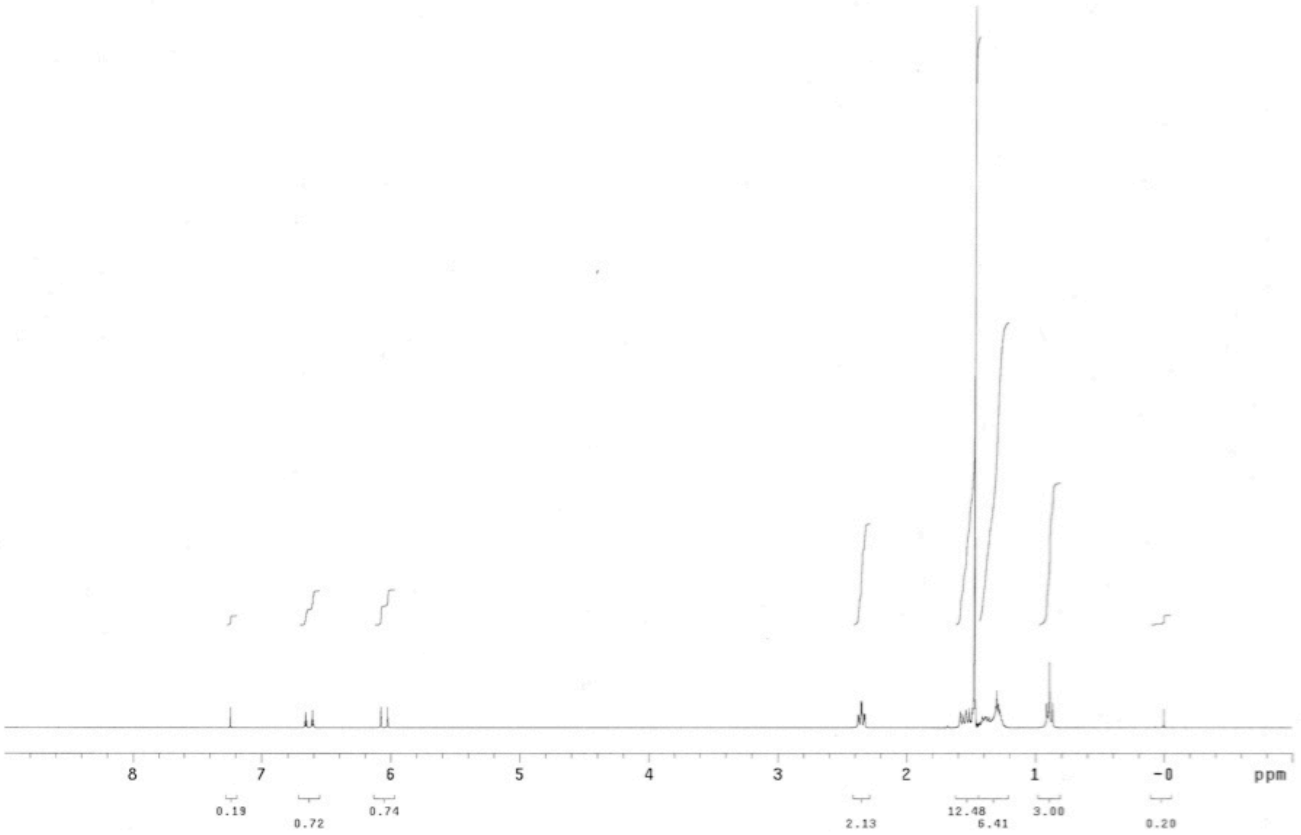
Department of Biomolecular Engineering
Graduate School of Bioscience and Biotechnology
Tokyo Institute of Technology
March 2014

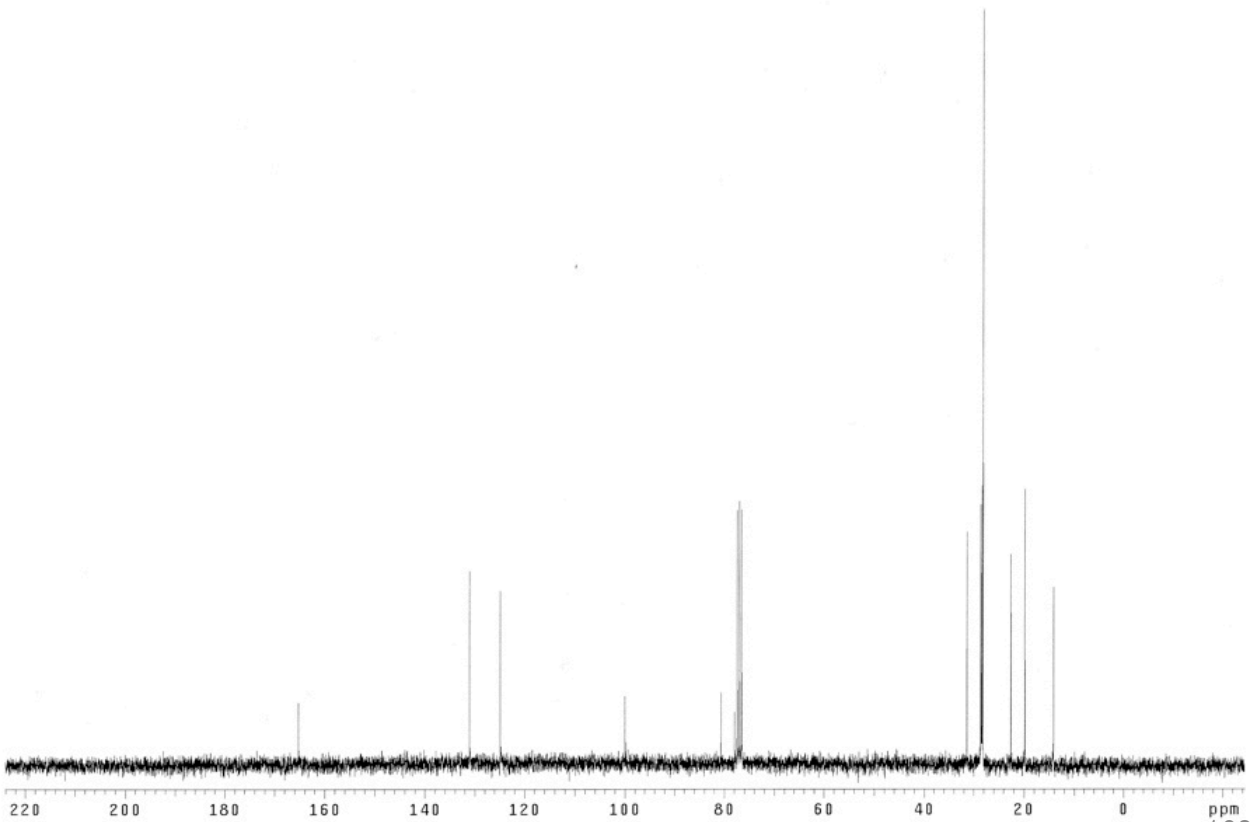
Chapter 2 Supporting Information

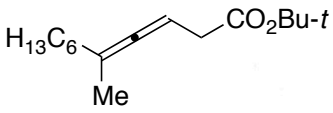
Iron-Catalyzed Synthesis of Allenes from 2-Alken-4-ynoates and Grignard Reagents


CO2Bu-t
H13C6

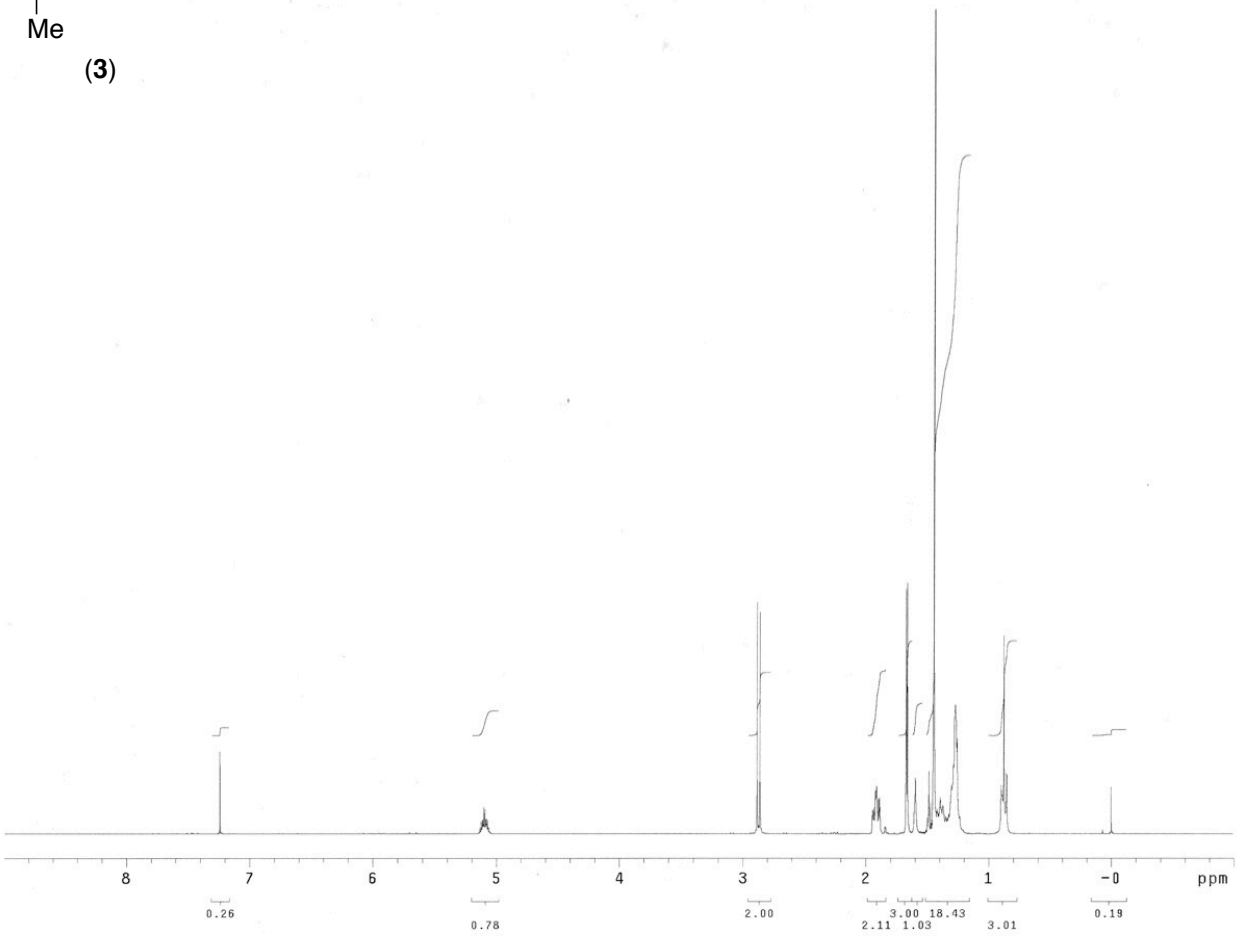
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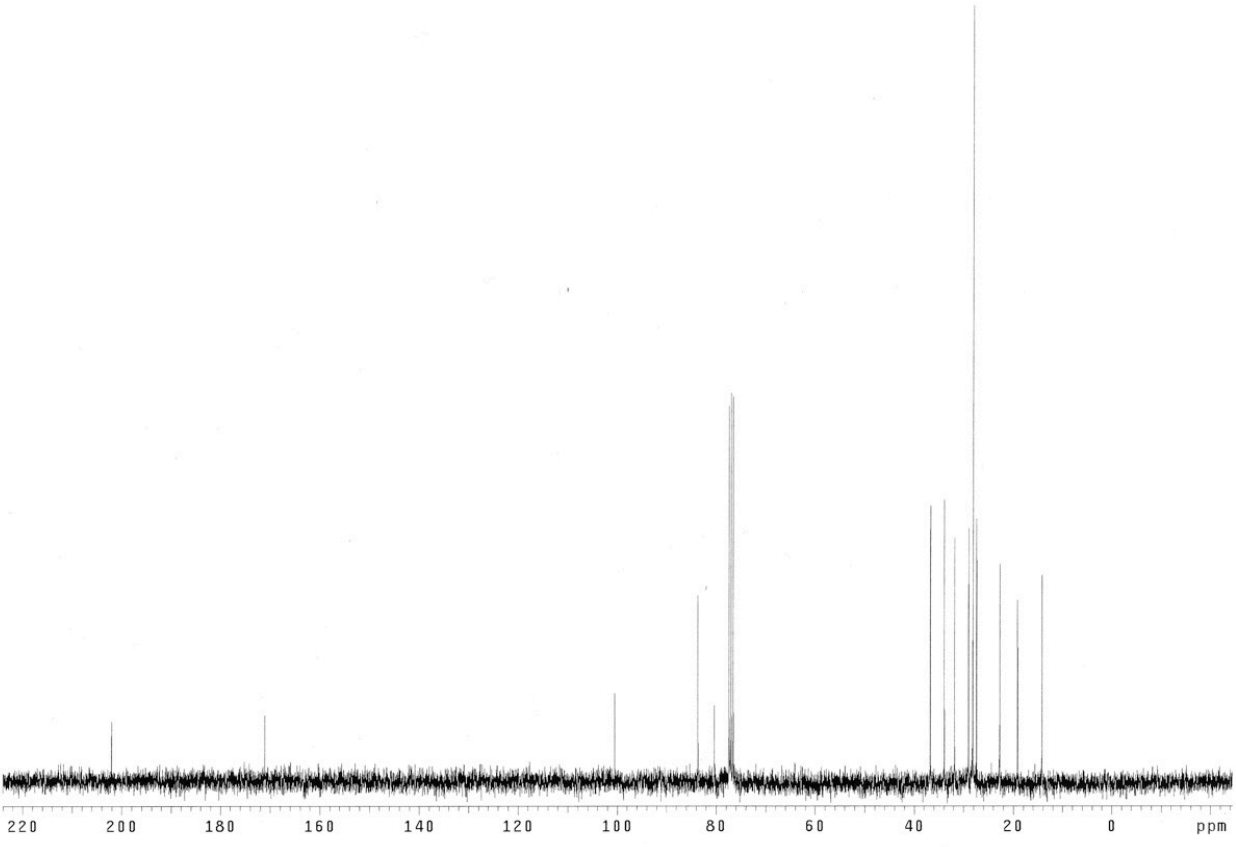

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6
5
4
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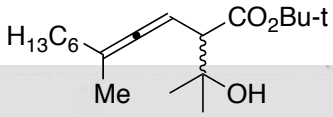

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200
180
160
140
120
100
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60
40
20
0
ppm


$H_{13}C_6$
CO_2Bu-*t*
Me

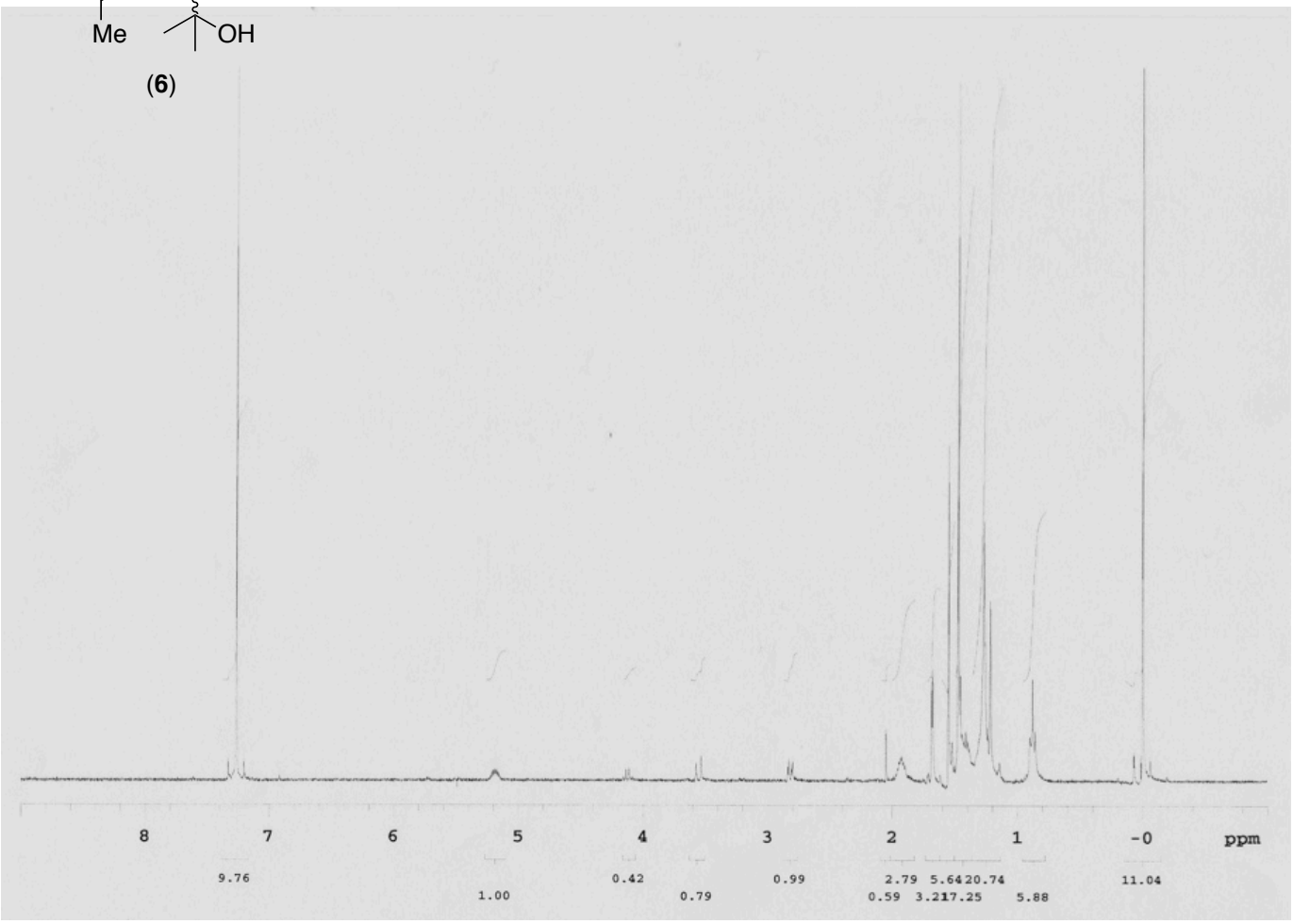
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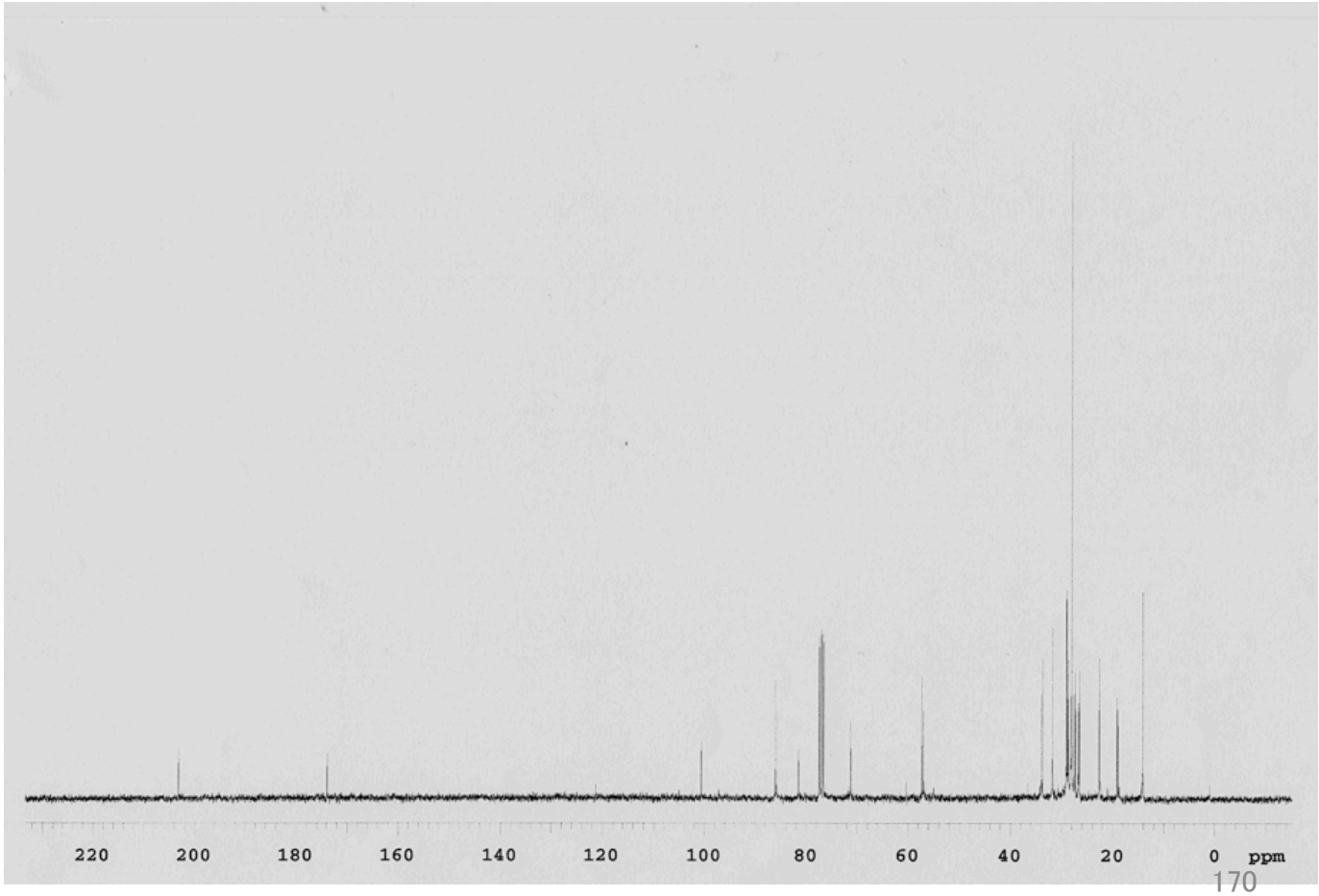

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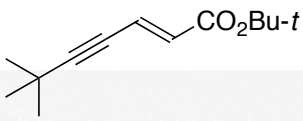

220
200
180
160
140
120
100
80
60
40
20
0
ppm


$H_{13}C_6$
CO_2Bu-t
Me
OH

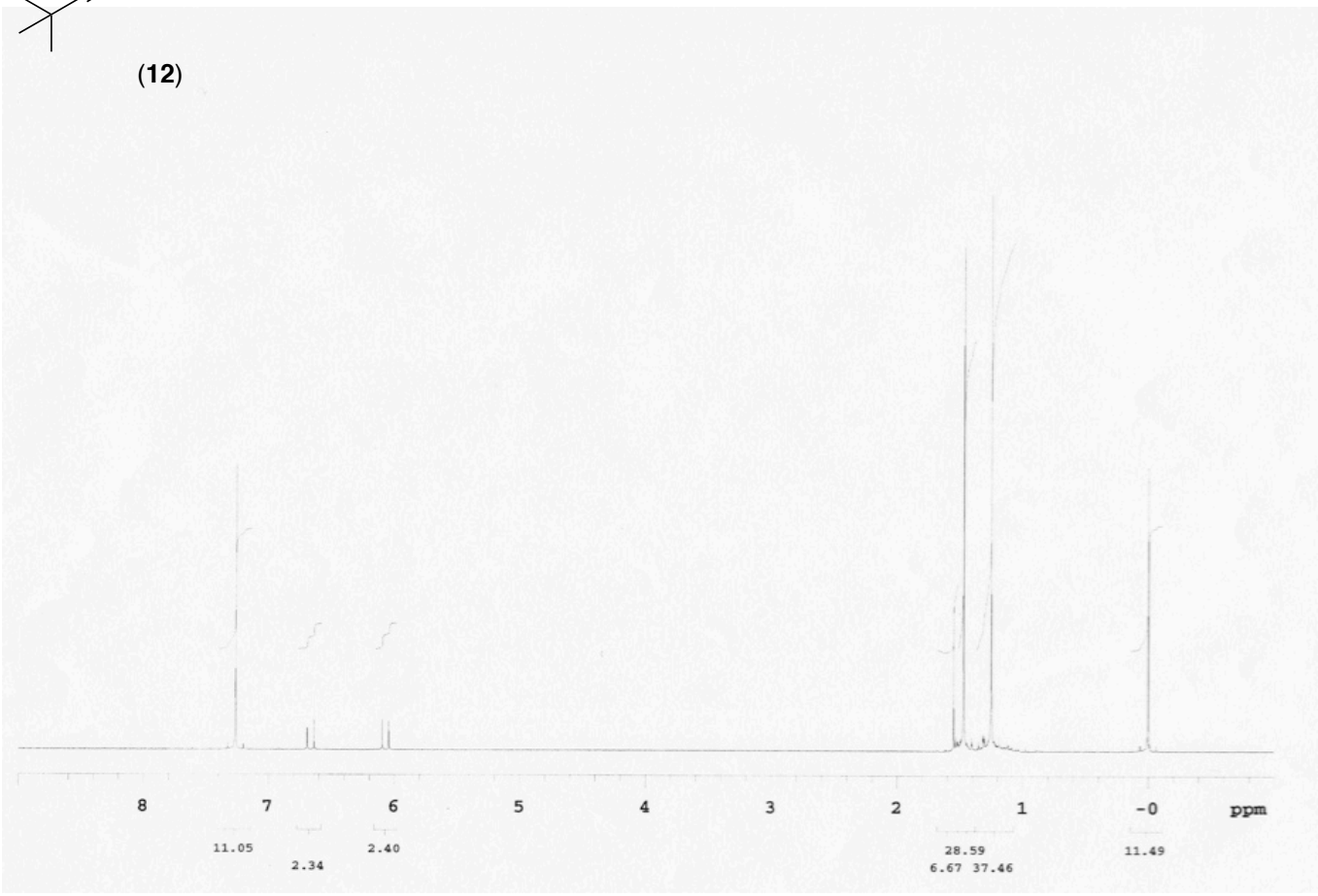
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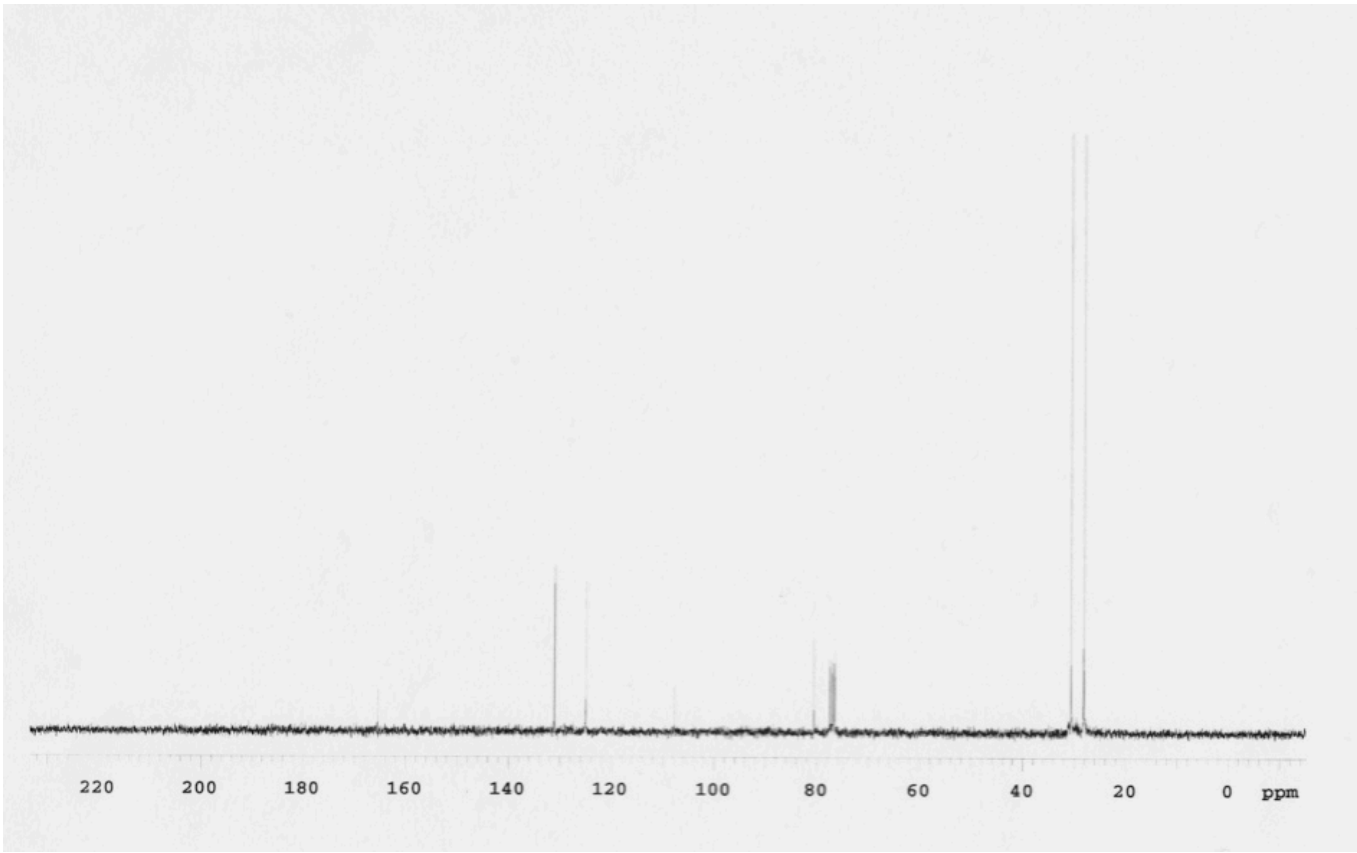

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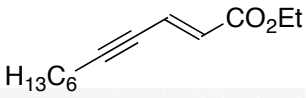

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160
140
120
100
80
60
40
20
0
ppm


CO2Bu-t

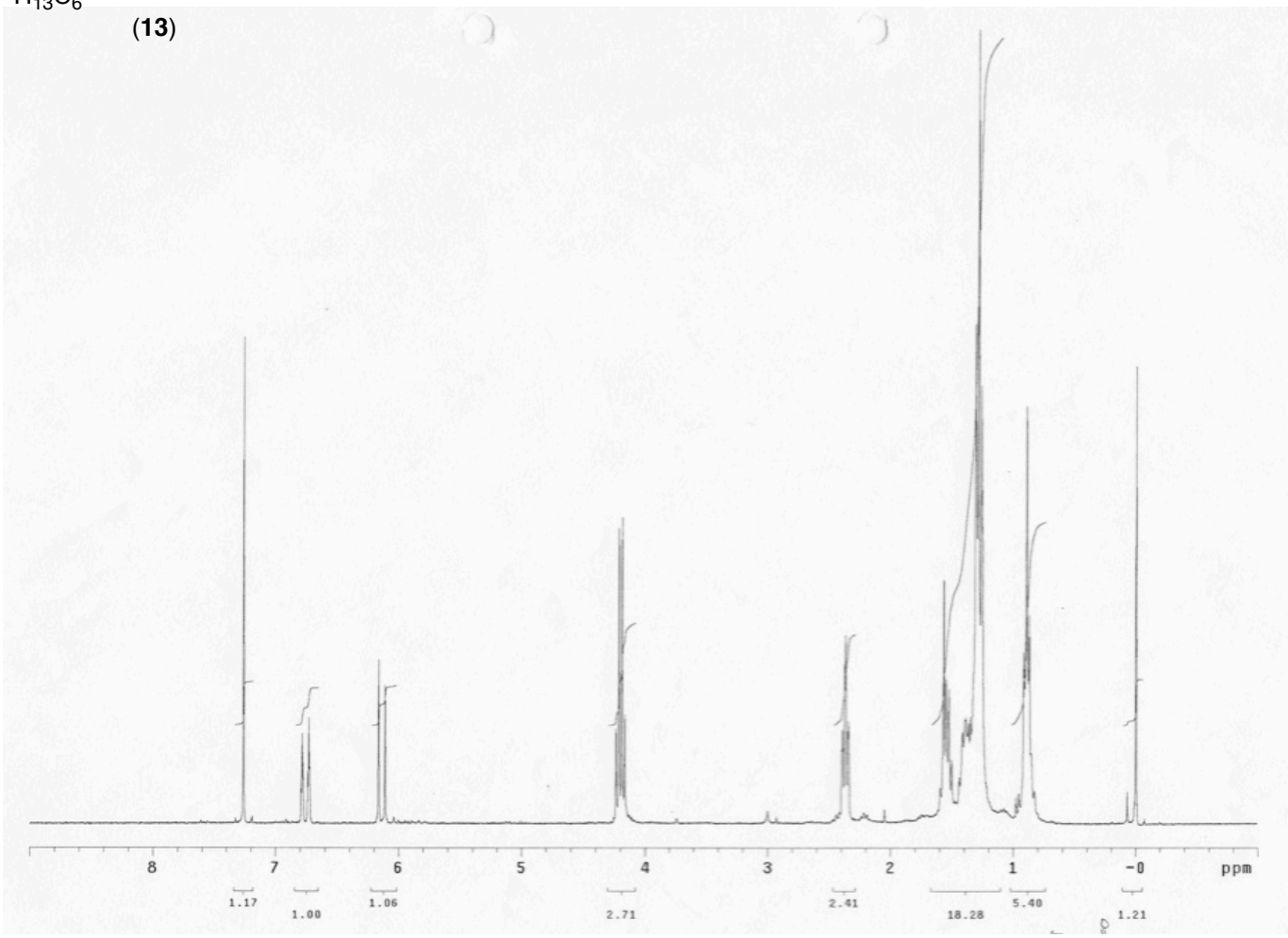
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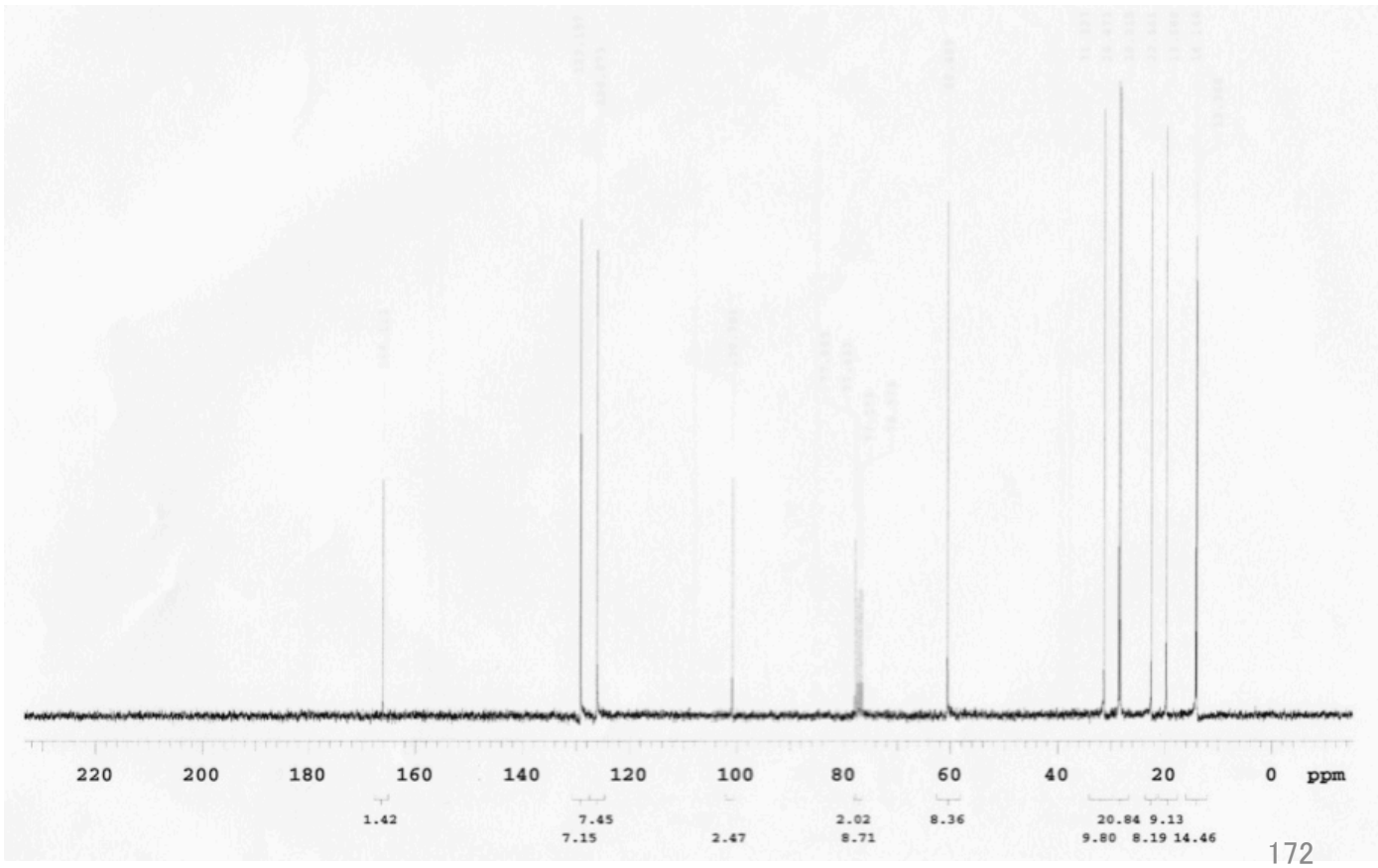

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11.49

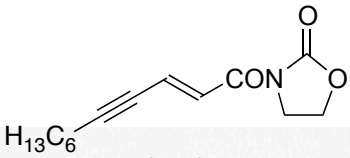

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140
120
100
80
60
40
20
0
ppm


CO_2Et
$H_{13}C_6$

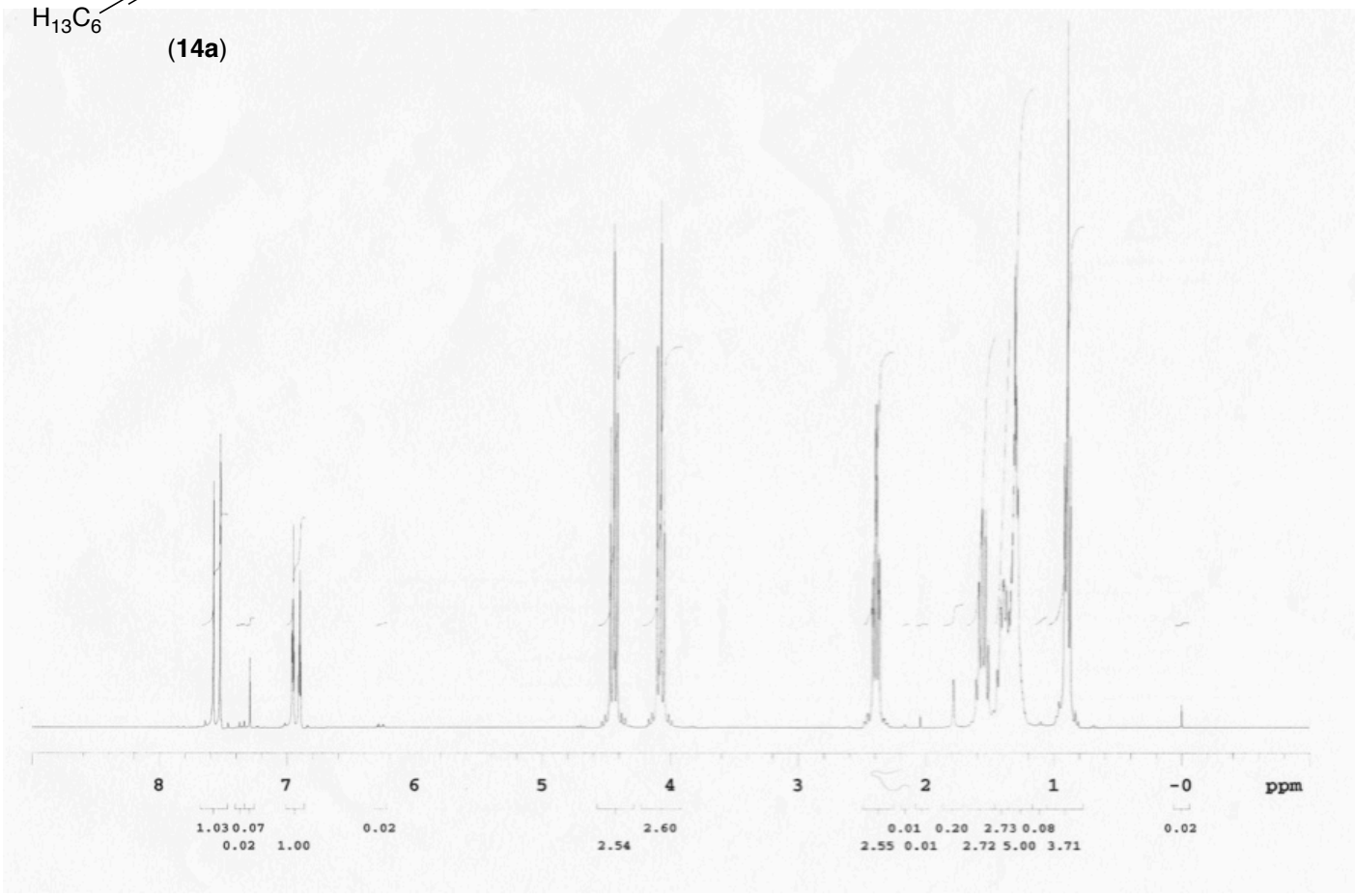
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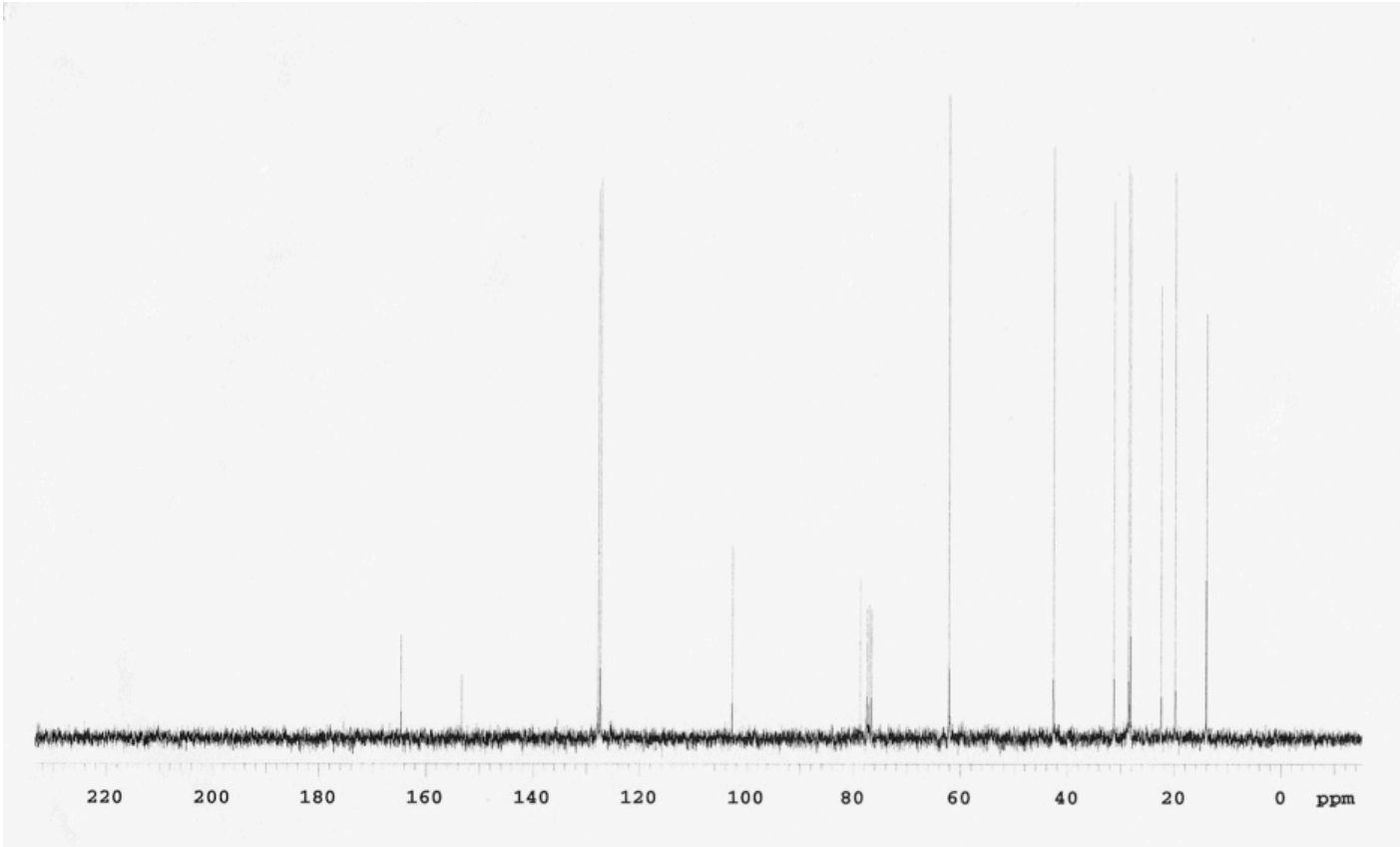

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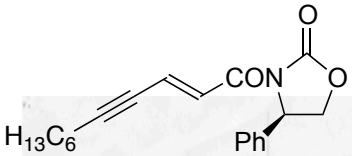

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100
80
60
40
20
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ppm
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2.02
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8.36
20.84
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9.13
8.19
14.46


O
CON
O
$H_{13}C_6$

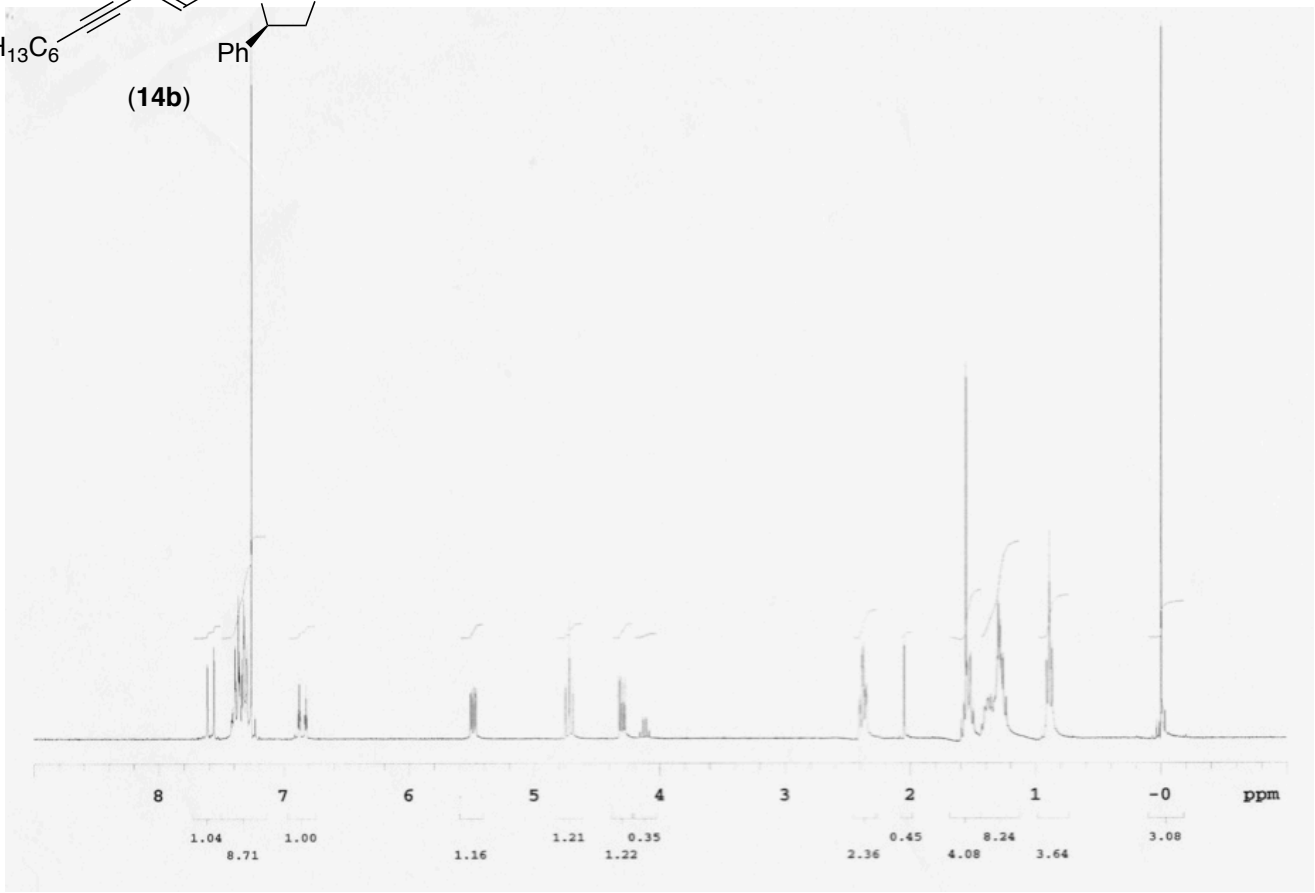
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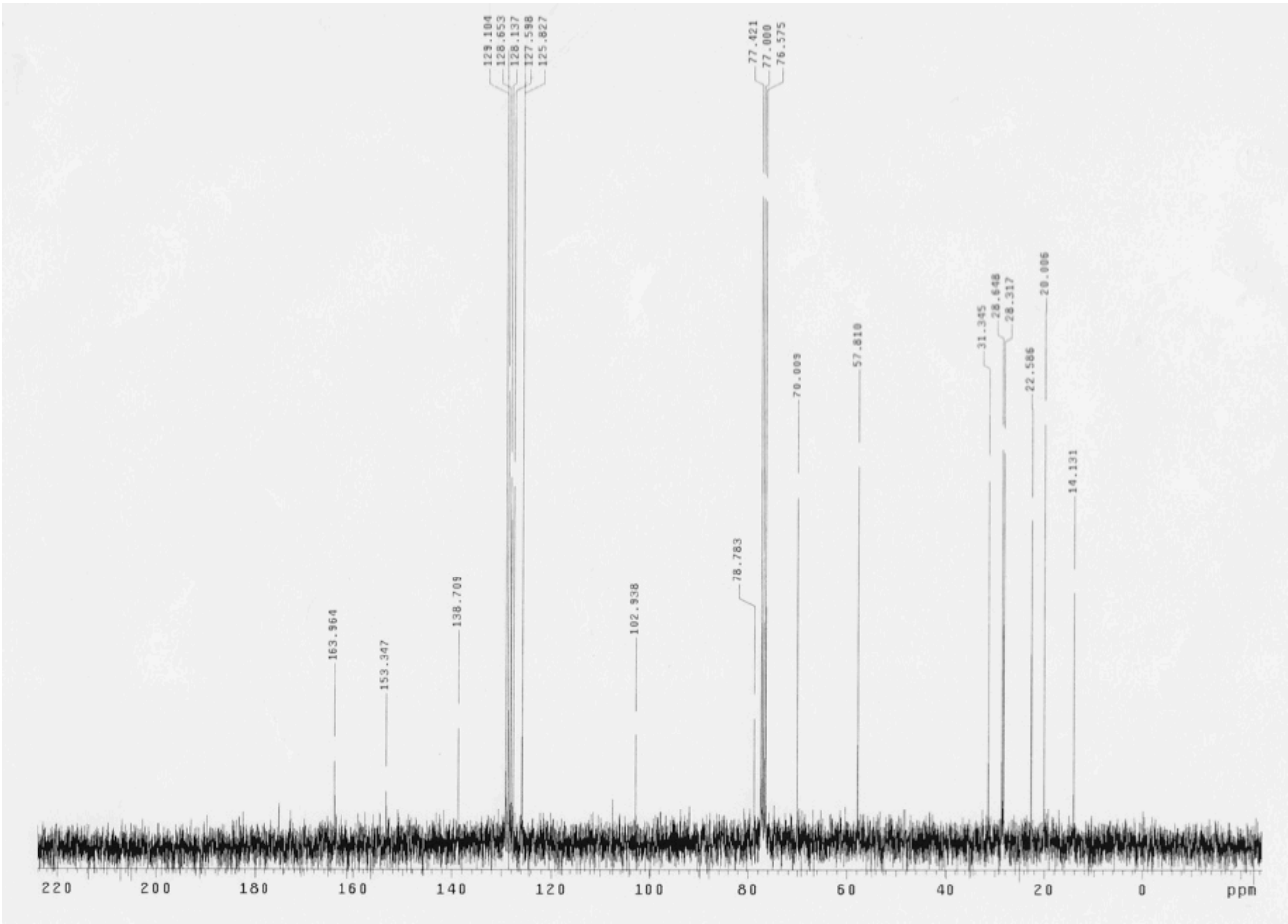

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6
5
4
3
2
1
-0
ppm
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0.02 1.00
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2.60
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0.01 0.20 2.73 0.08
2.55 0.01 2.72 5.00 3.71
0.02

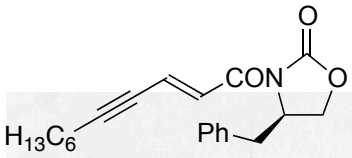

220
200
180
160
140
120
100
80
60
40
20
0
ppm


O
CON
O
$H_{13}C_6$
Ph

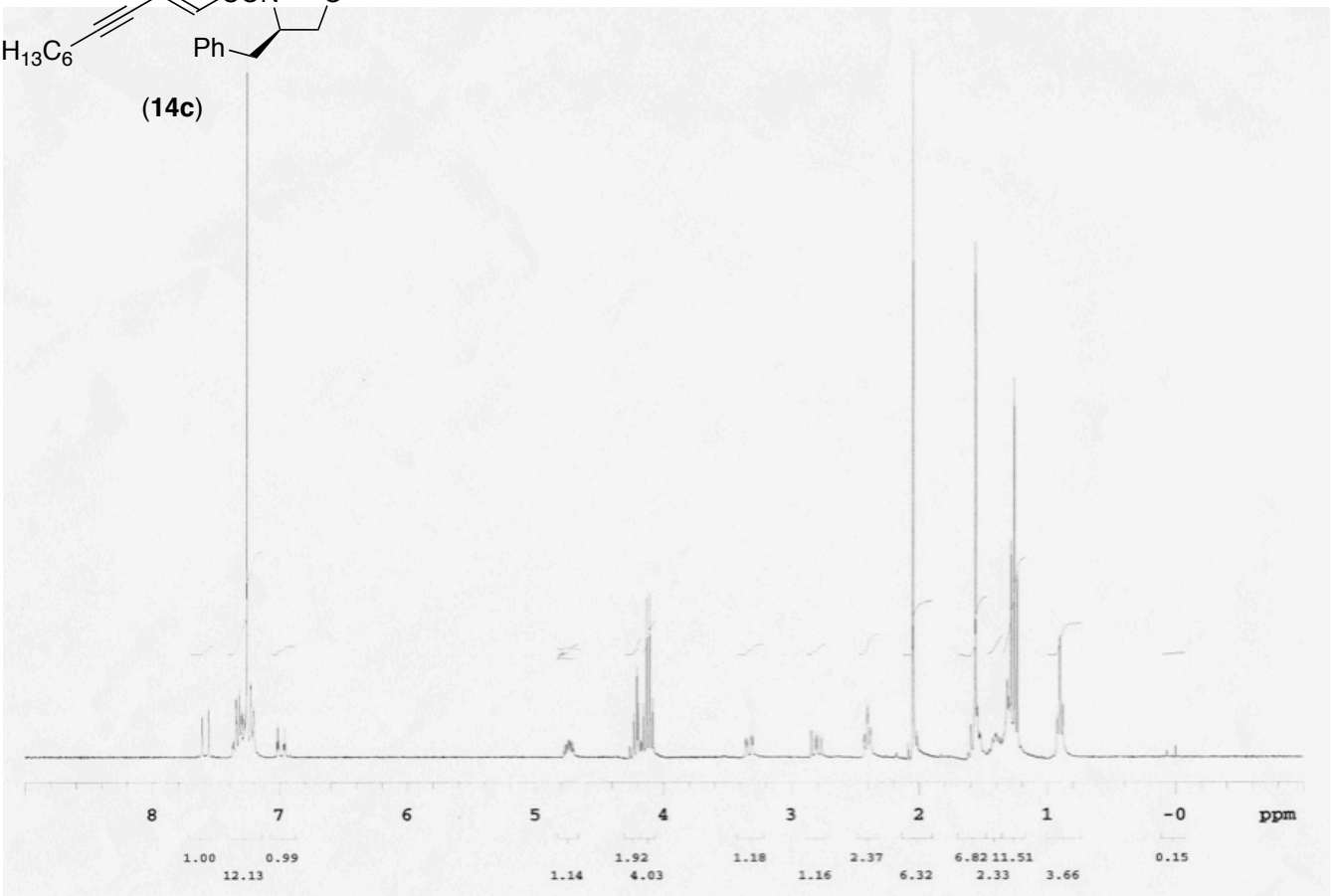
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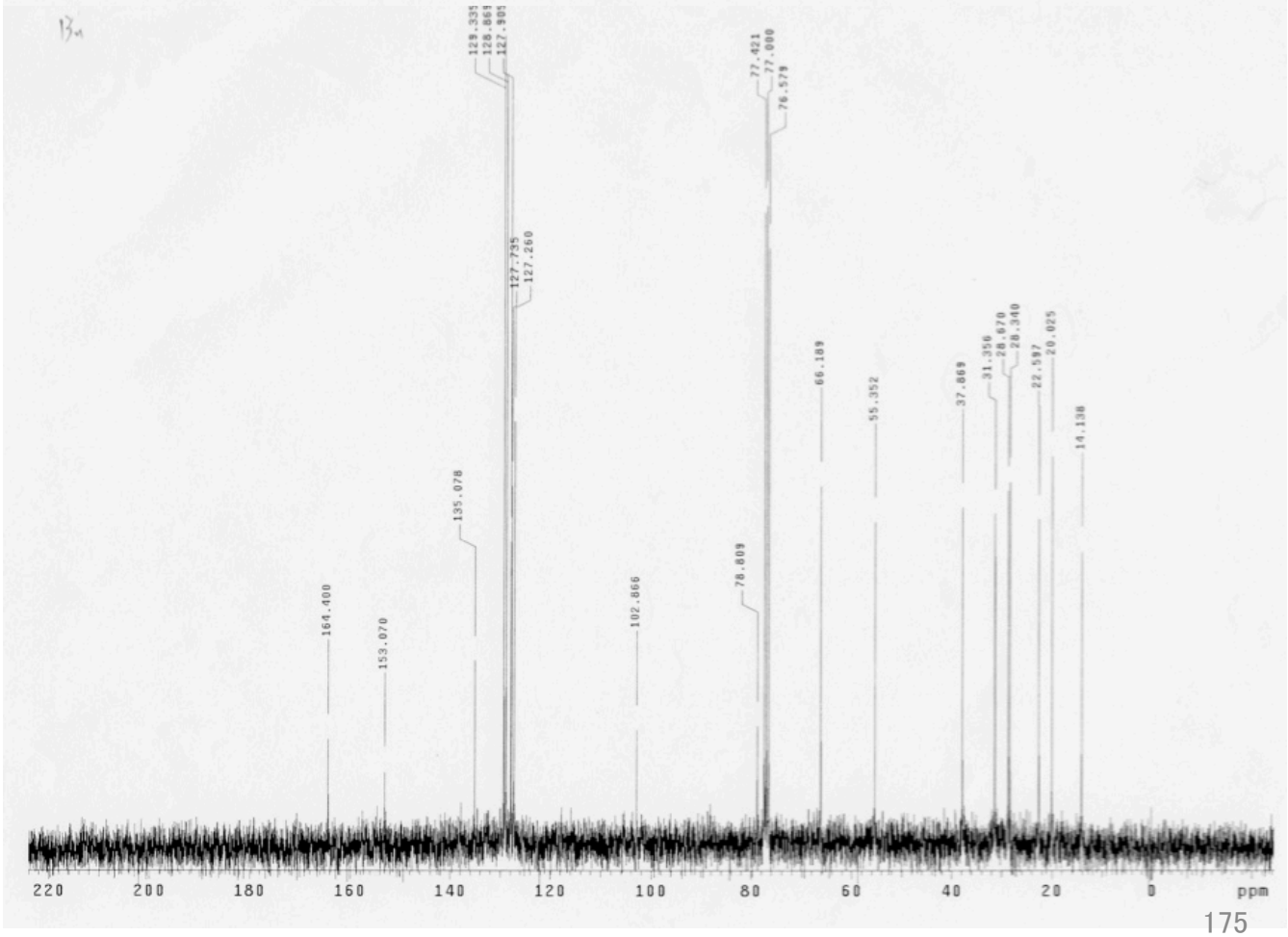

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7
6
5
4
3
2
1
-0
ppm
1.04
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3.64
3.08

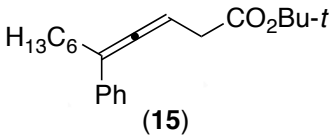

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128.653
128.137
127.598
125.827
77.421
77.000
76.575
70.009
57.810
31.345
28.648
28.317
22.586
20.006
14.131
78.783
102.938
138.709
153.347
163.964
220
200
180
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140
120
100
80
60
40
20
0
ppm


O
CON
O
Ph
$H_{13}C_6$

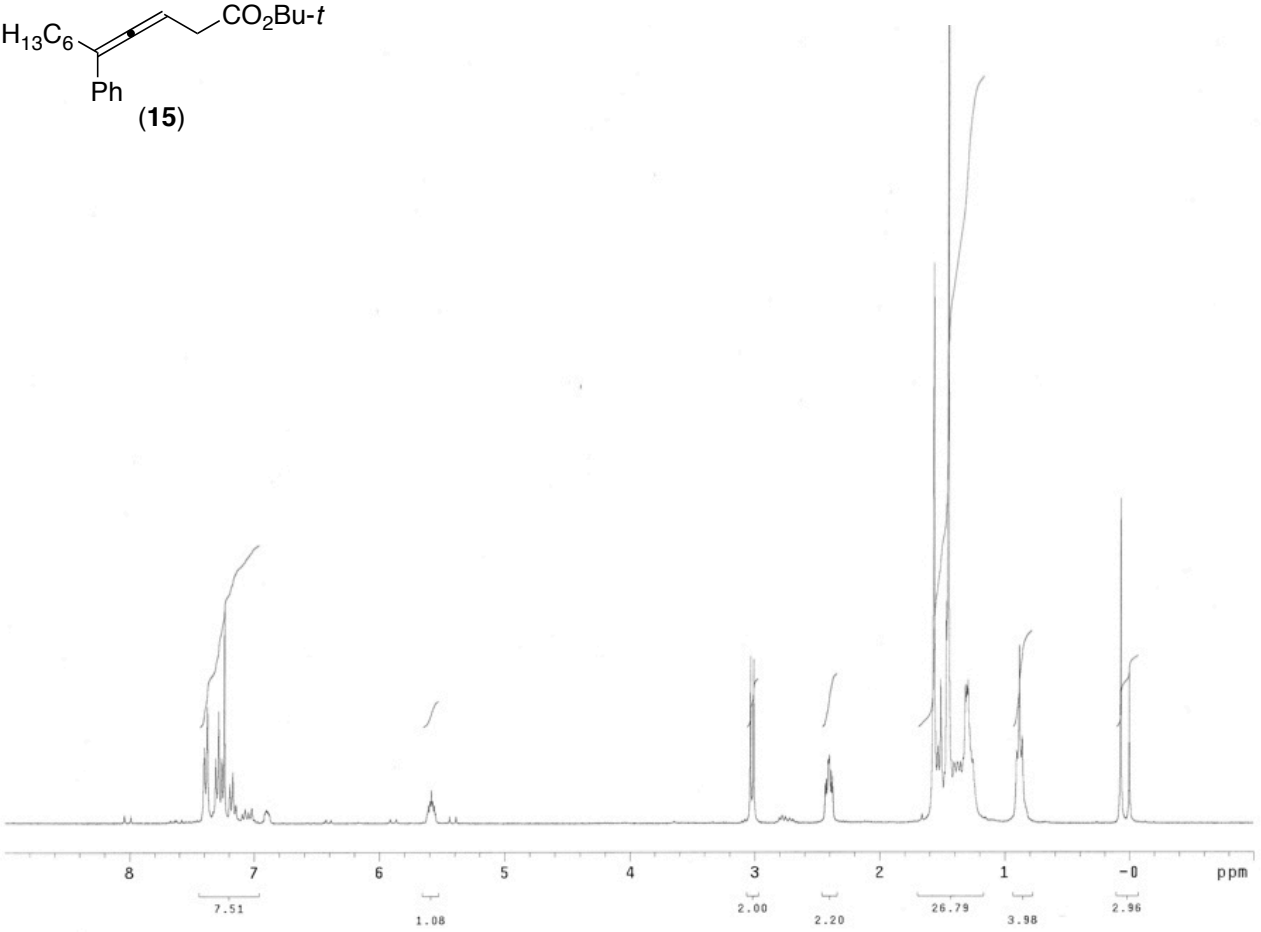
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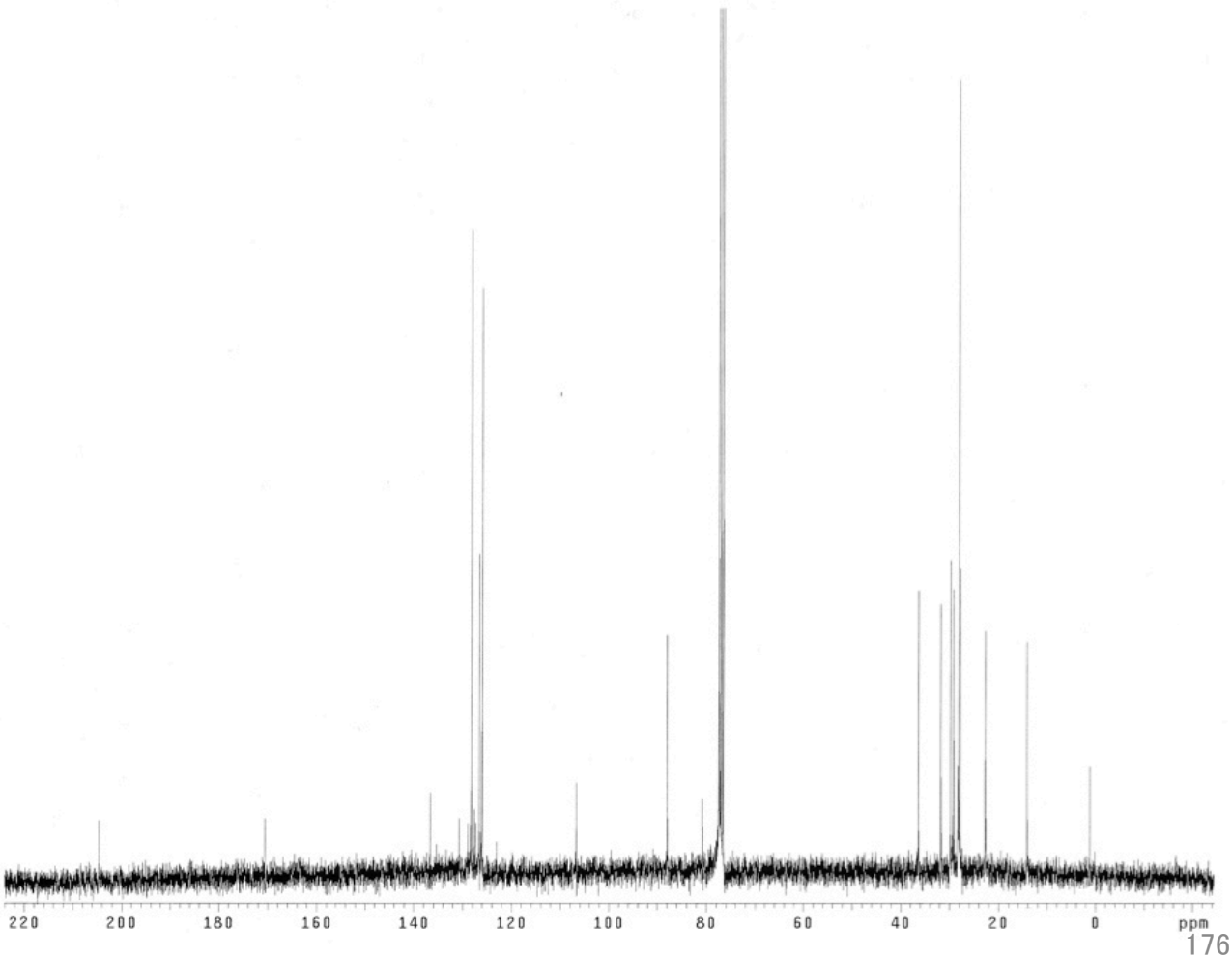

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7
6
5
4
3
2
1
-0
ppm
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0.99
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2.33
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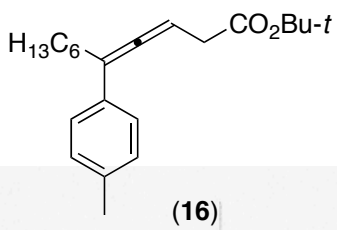

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135.078
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78.809
66.189
55.352
37.869
31.356
28.670
28.340
22.597
20.025
14.138
220
200
180
160
140
120
100
80
60
40
20
0
ppm


$H_{13}C_6$
CO_2Bu-*t*
Ph

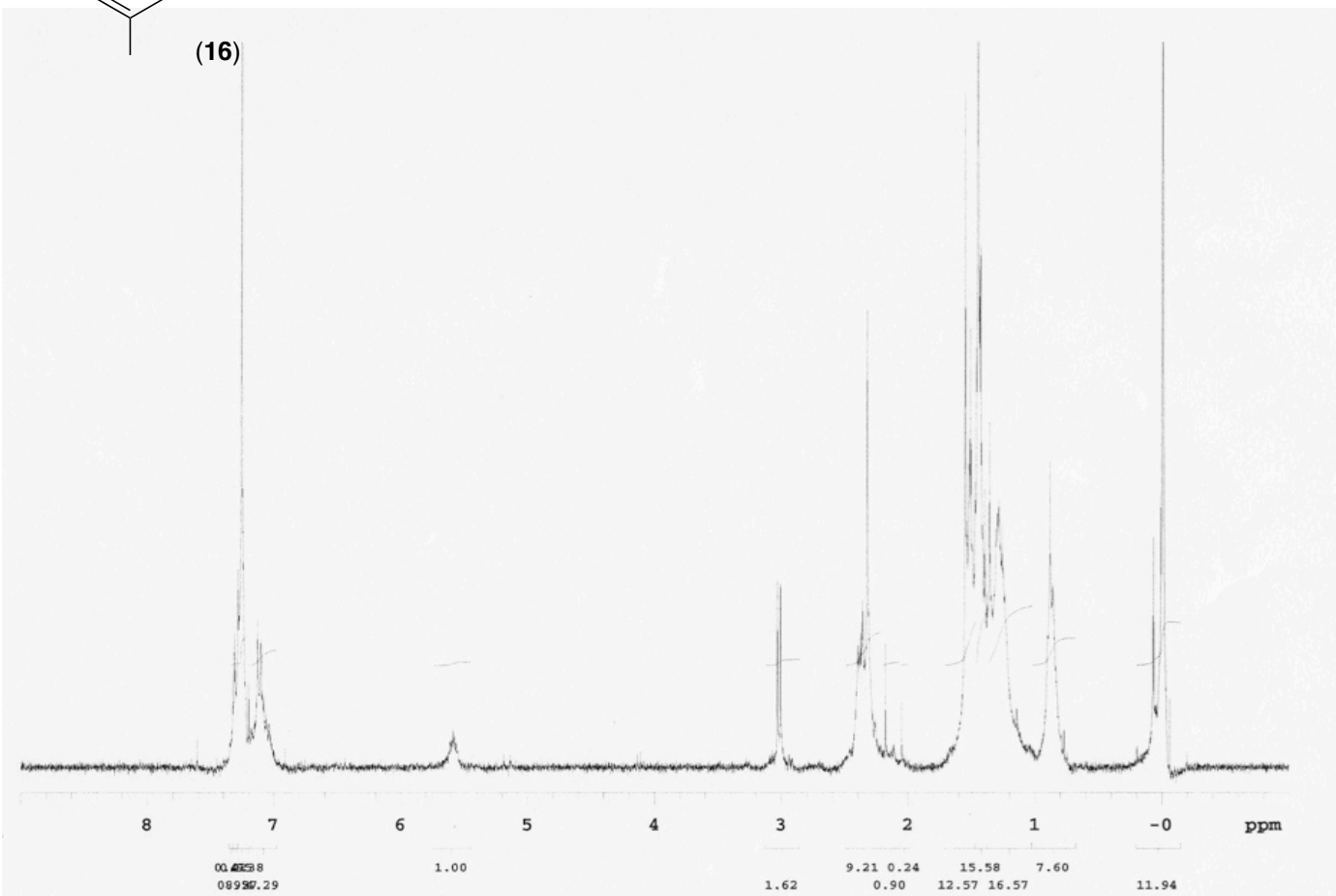
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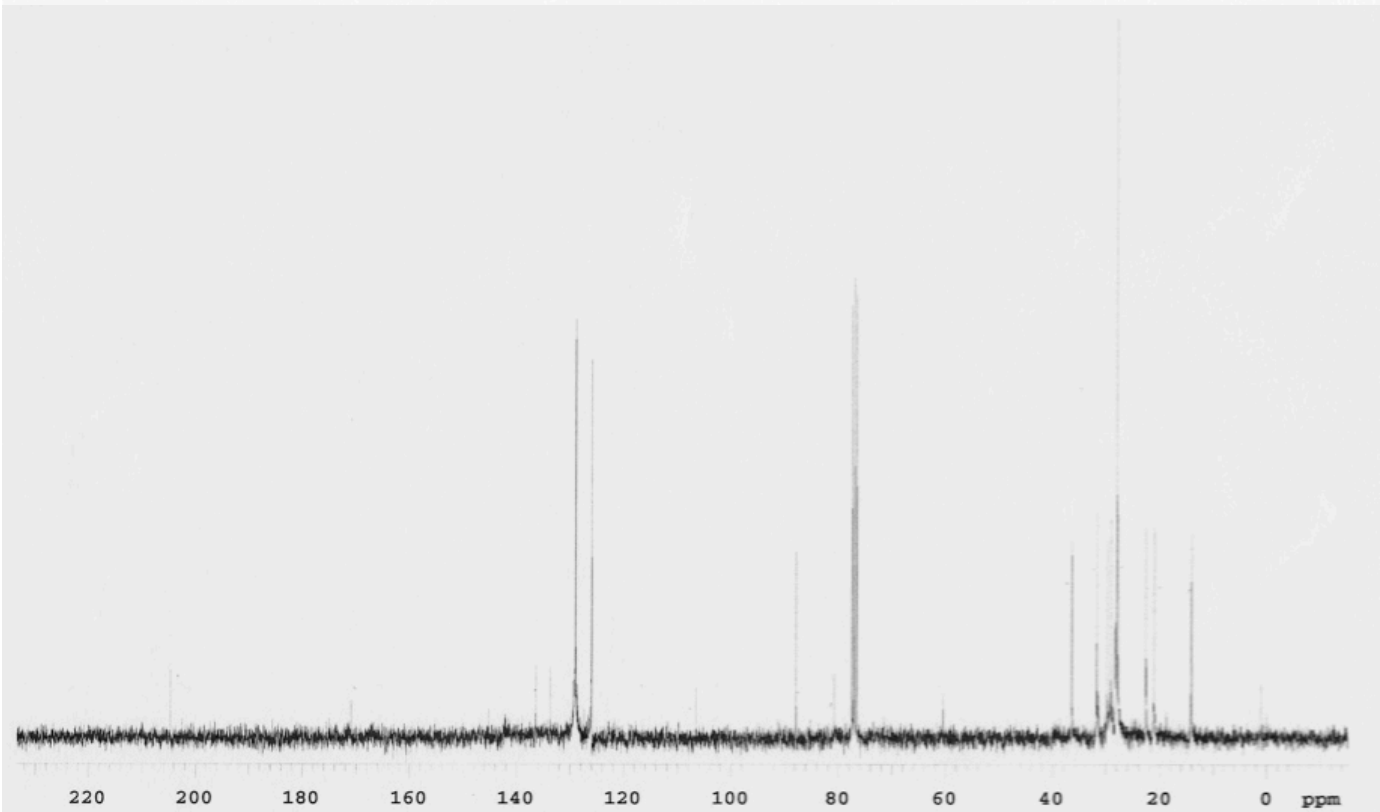

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2.96

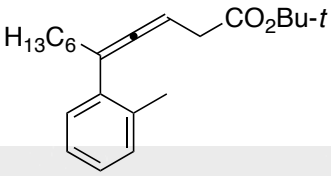

220
200
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160
140
120
100
80
60
40
20
0
ppm


$H_{13}C_6$
CO_2Bu-*t*

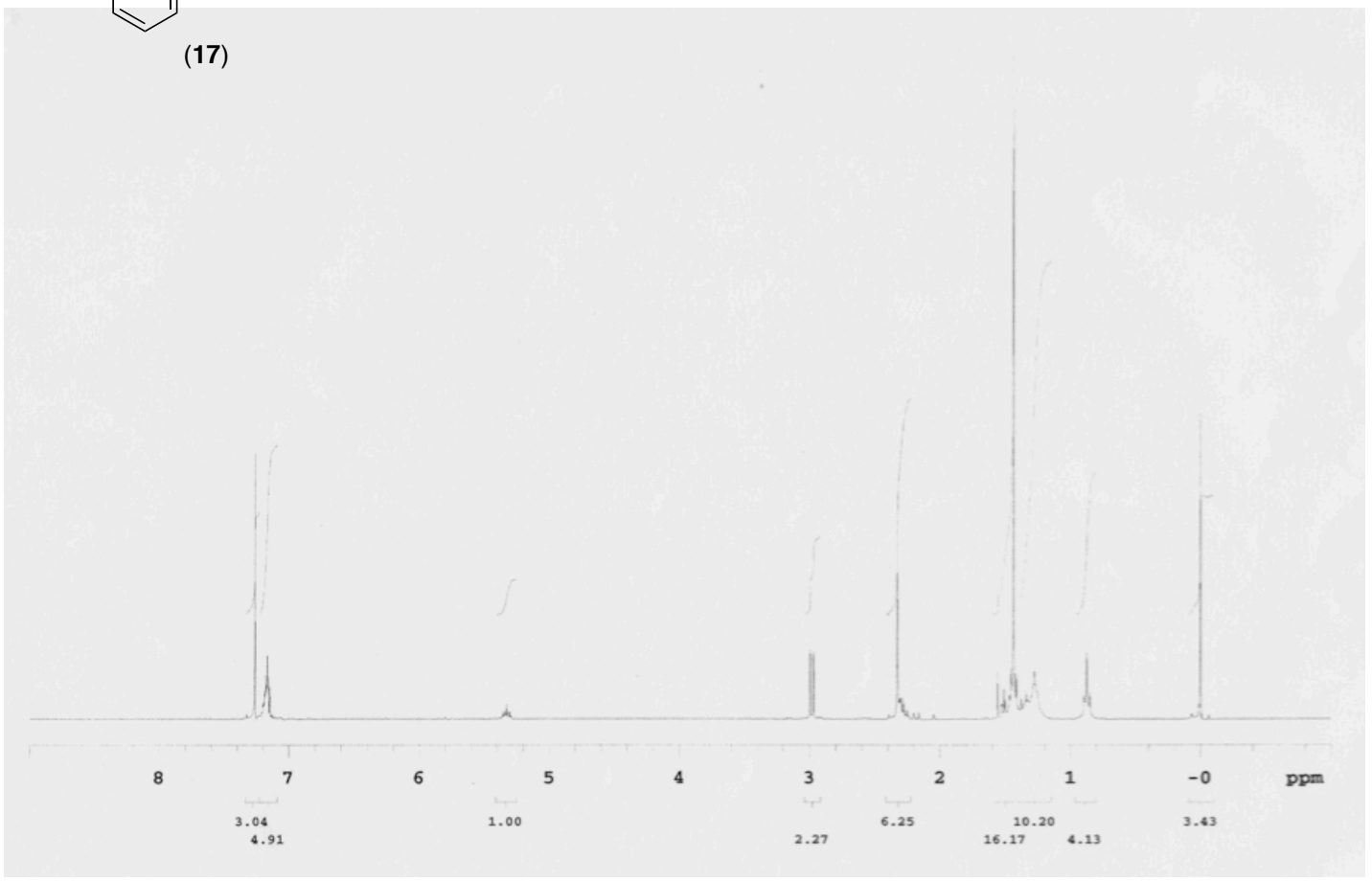
(**16**)

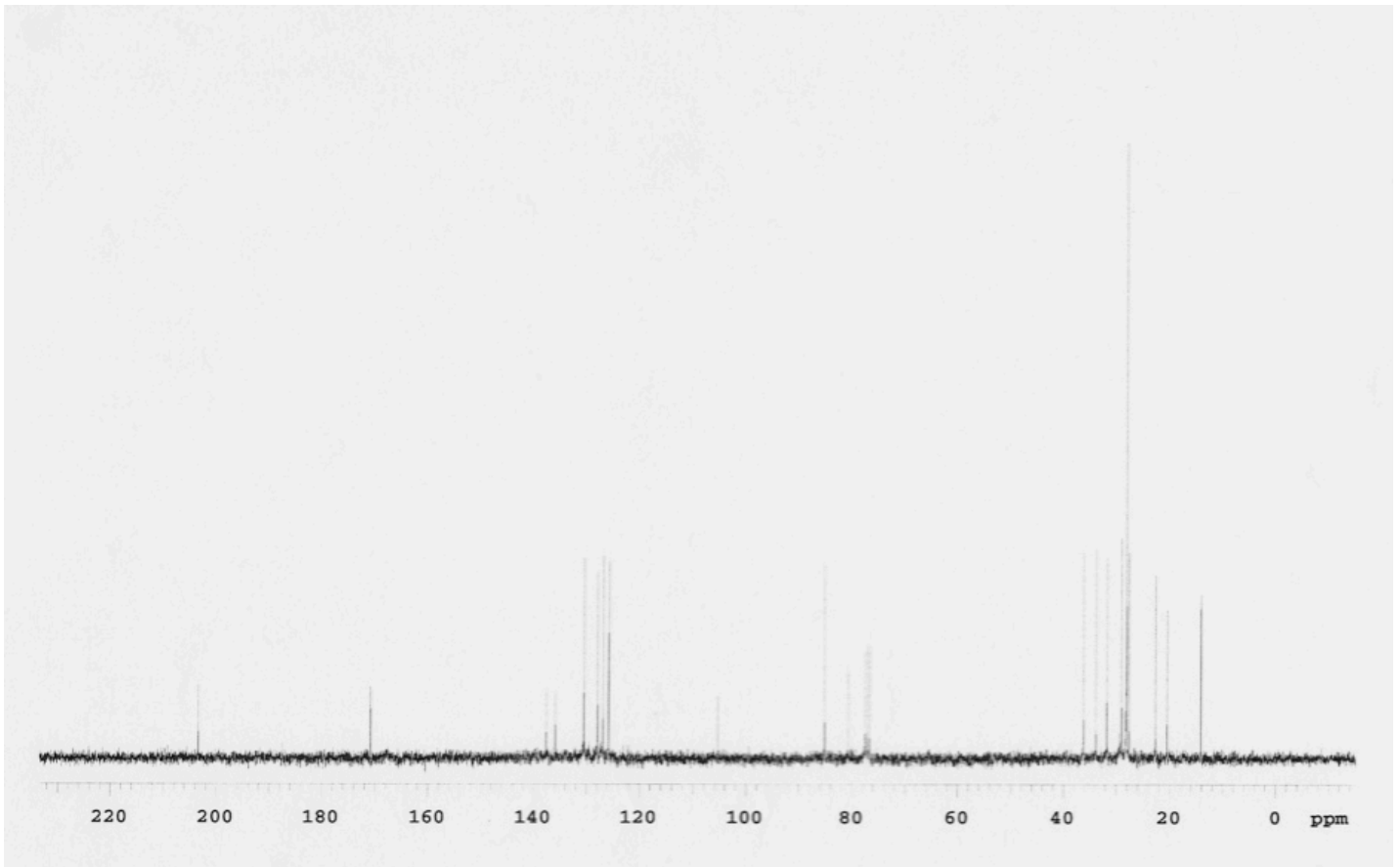

8
7
6
5
4
3
2
1
-0
ppm
1.00
1.62
9.21 0.24
0.90
15.58
12.57 16.57
7.60
11.94

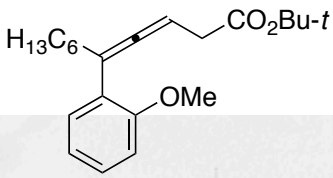

220
200
180
160
140
120
100
80
60
40
20
0
ppm


$H_{13}C_6$
CO_2Bu-*t*

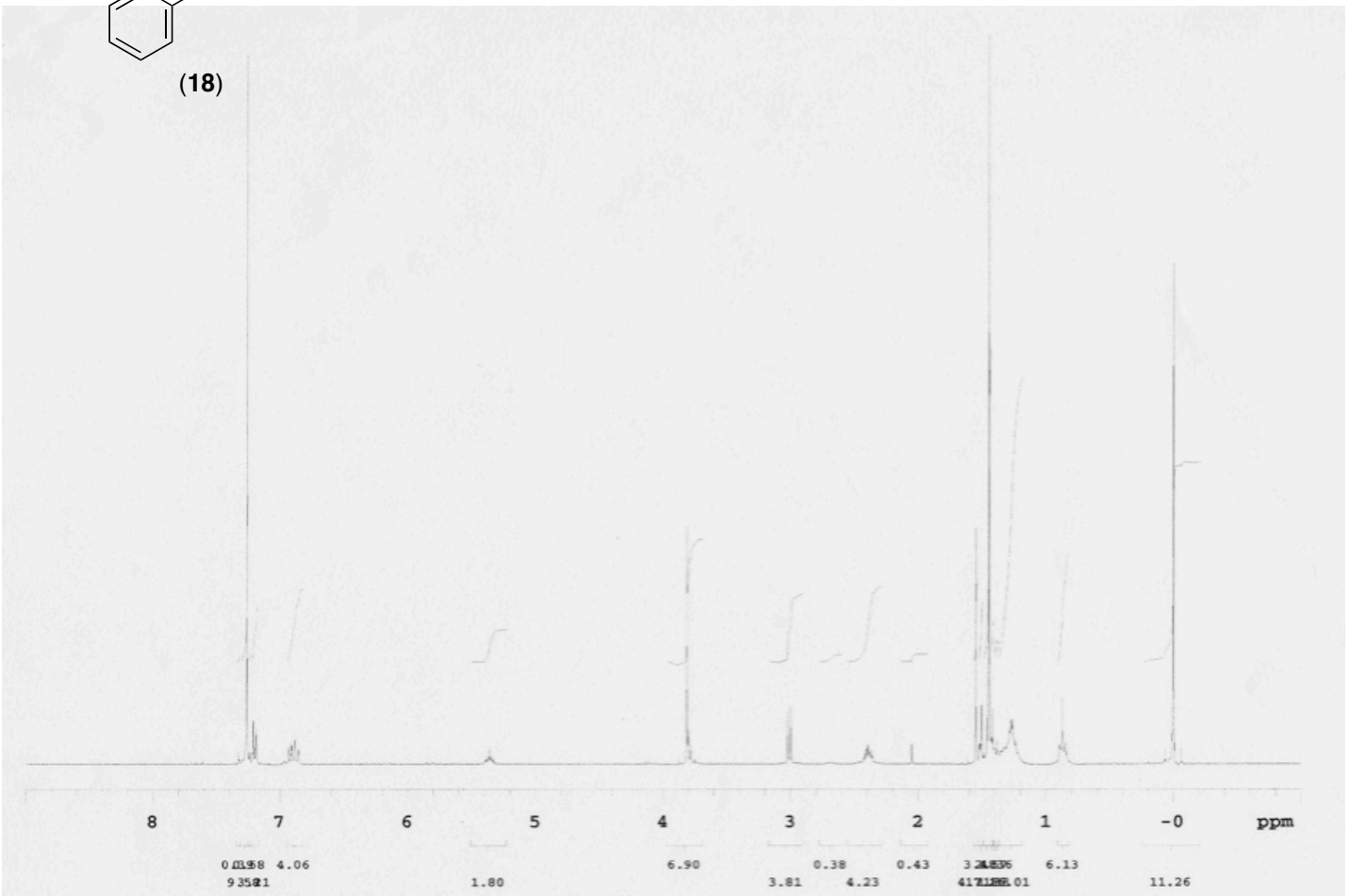
(**17**)

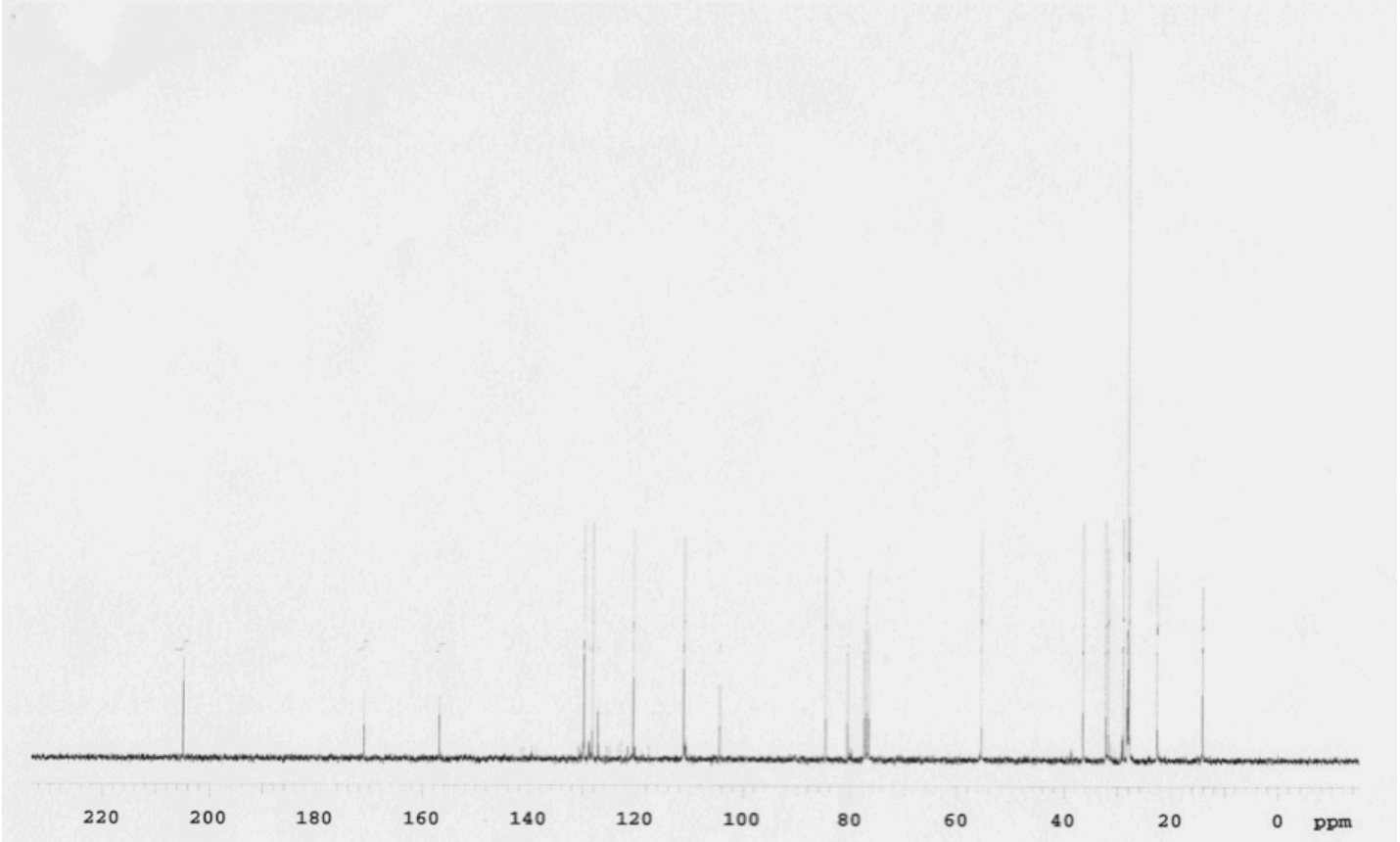

8
7
6
5
4
3
2
1
-0
ppm
3.04
4.91
1.00
2.27
6.25
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16.17
4.13
3.43

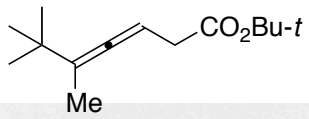

220
200
180
160
140
120
100
80
60
40
20
0
ppm


$H_{13}C_6$
CO_2Bu-*t*
OMe

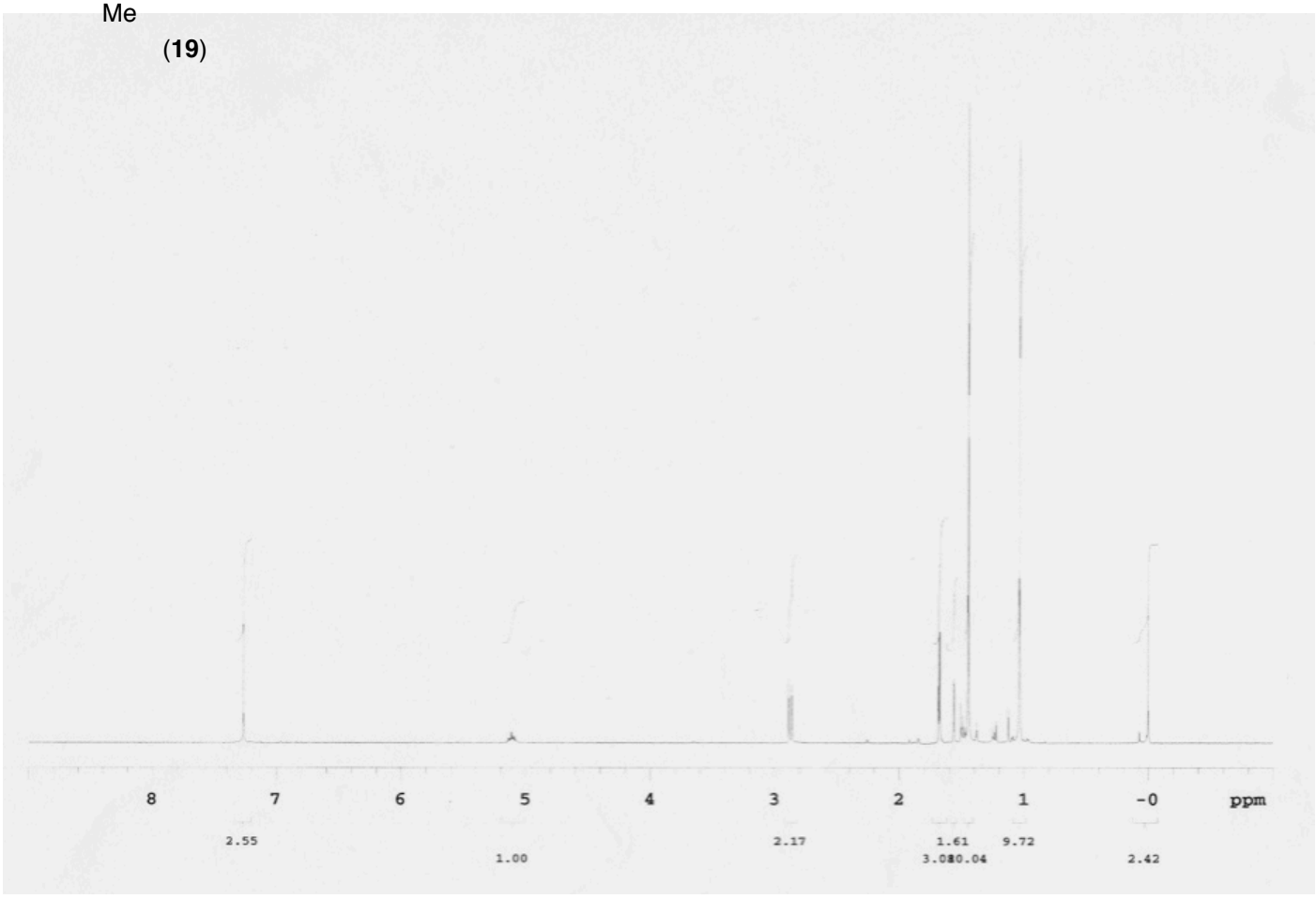
(**18**)

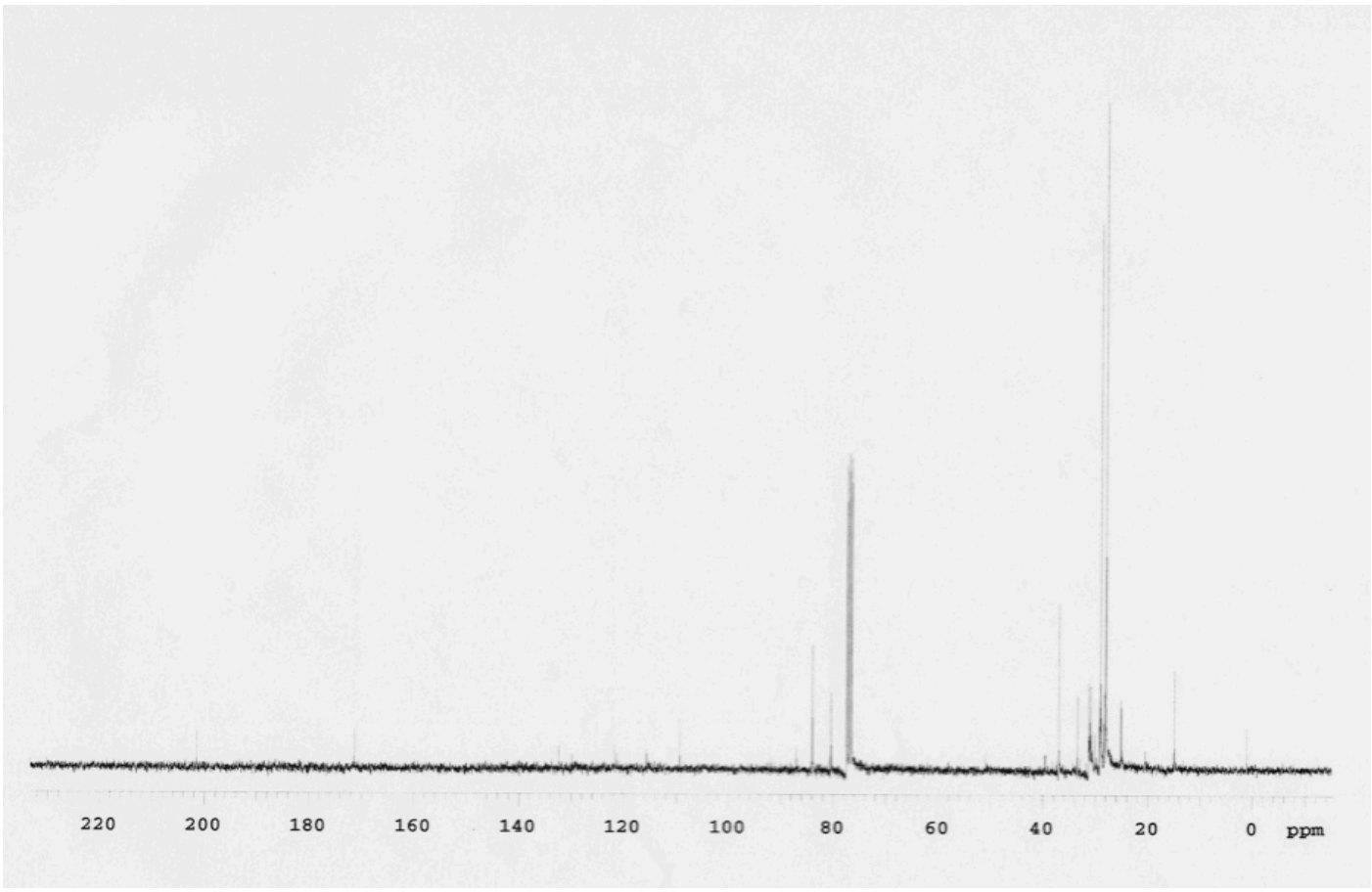

8
7
6
5
4
3
2
1
-0
ppm
4.06
6.90
0.38
0.43
6.13
1.80
3.81
4.23
11.26

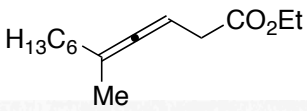

220
200
180
160
140
120
100
80
60
40
20
0
ppm


CO2Bu-t
Me

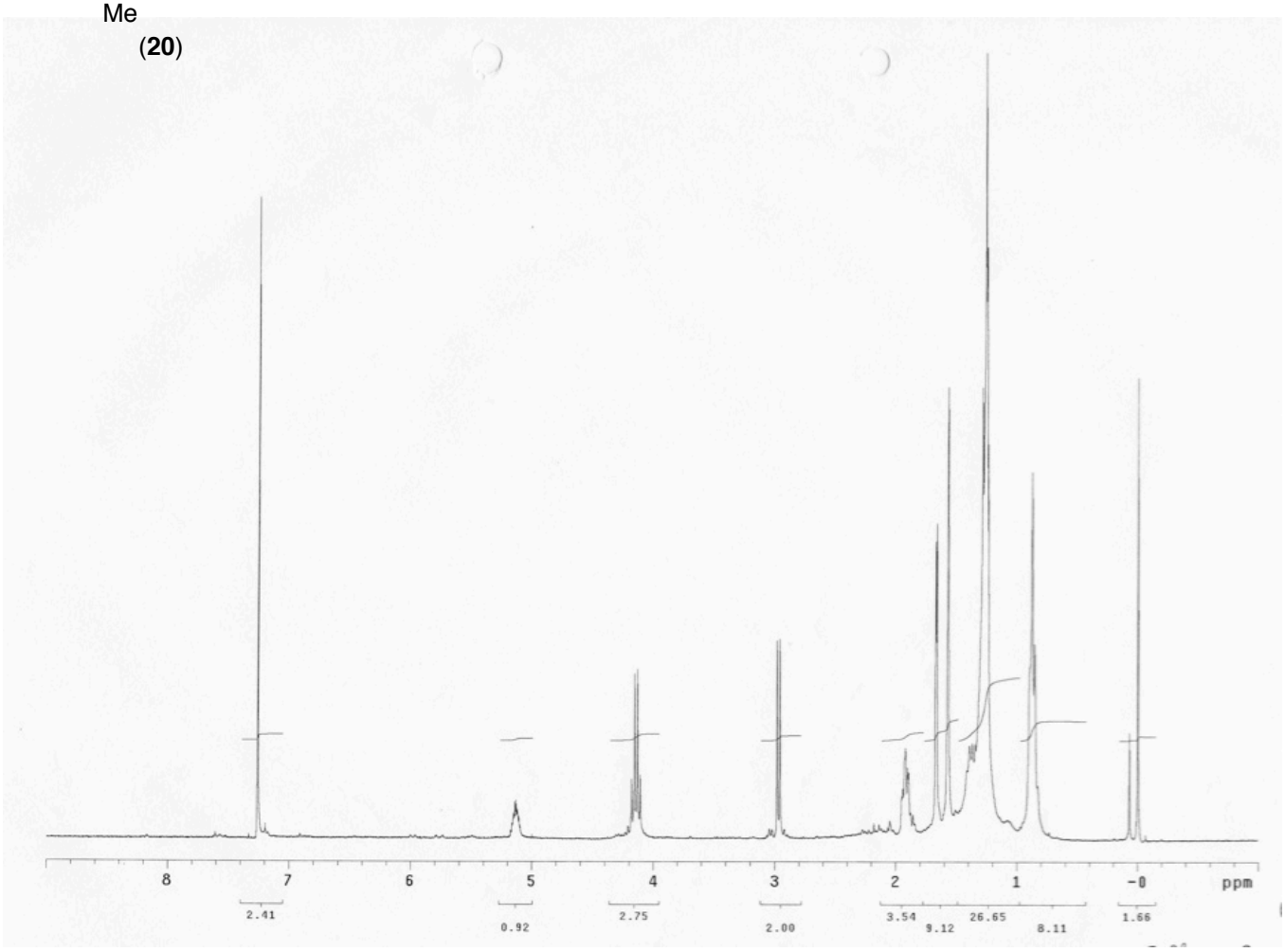
(**19**)

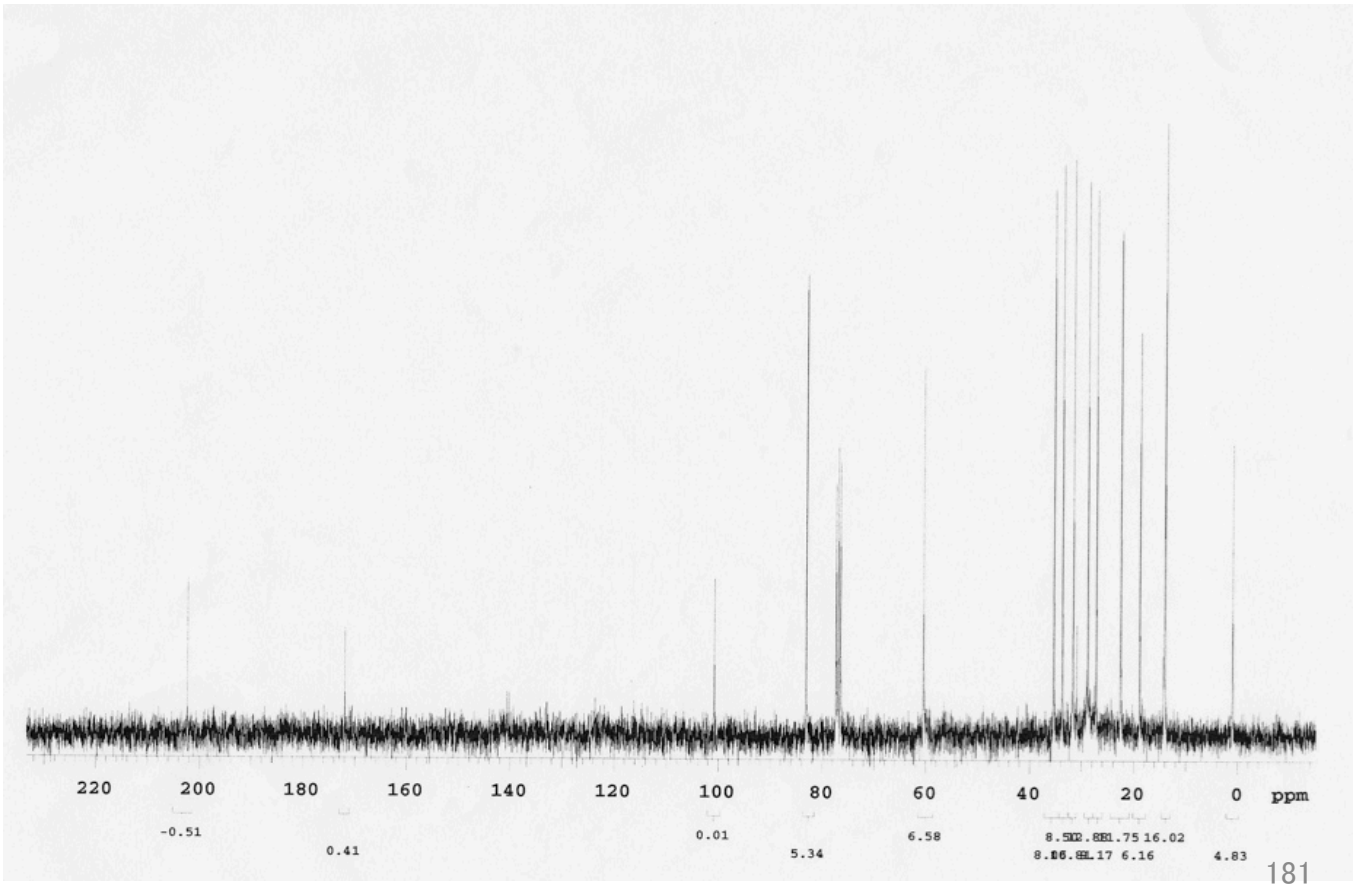

8
7
6
5
4
3
2
1
-0
ppm
2.55
1.00
2.17
1.61
3.08
0.04
9.72
2.42

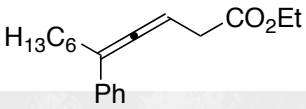

220
200
180
160
140
120
100
80
60
40
20
0
ppm


$H_{13}C_6$
CO_2Et
Me

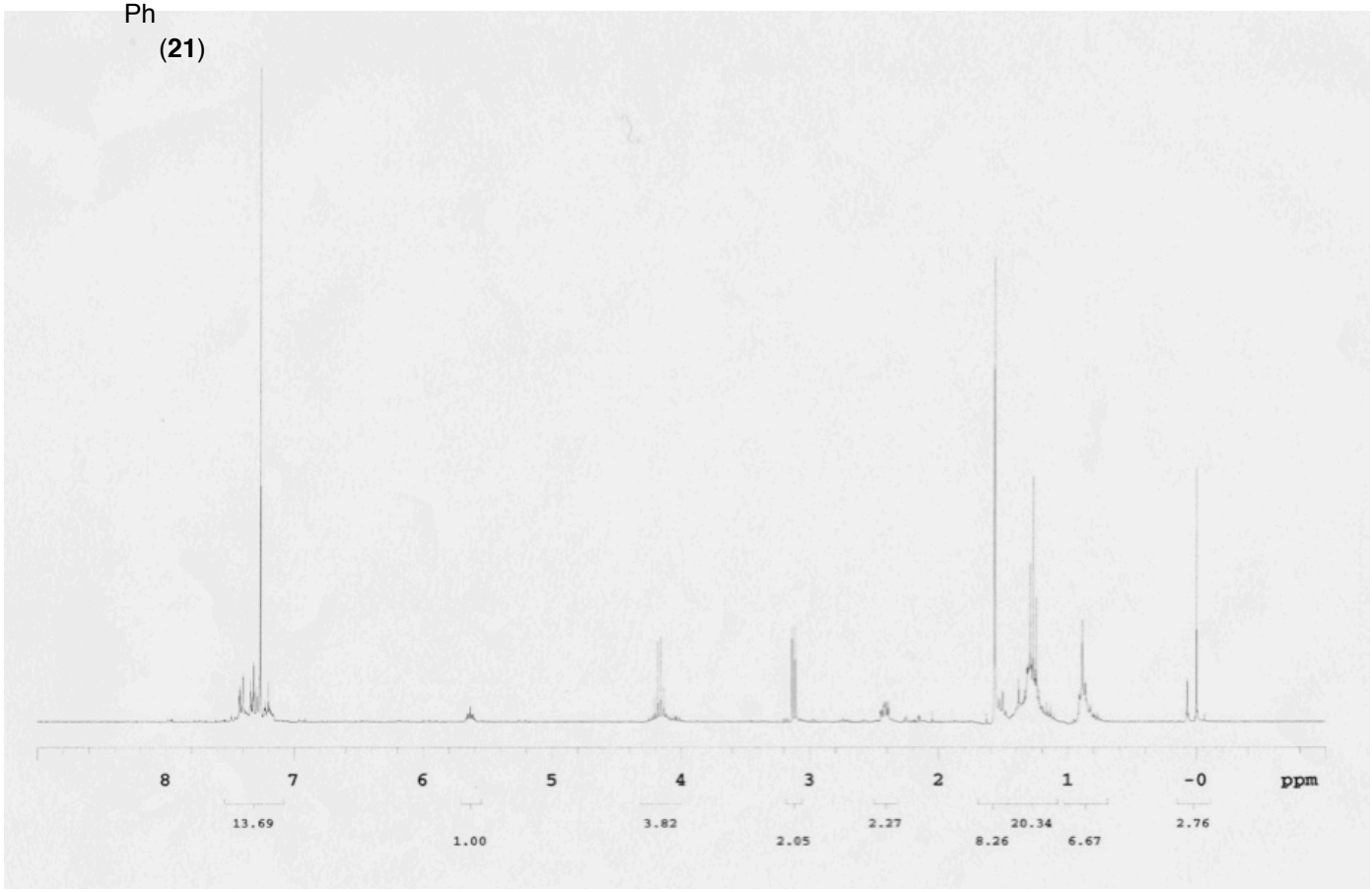
(**20**)

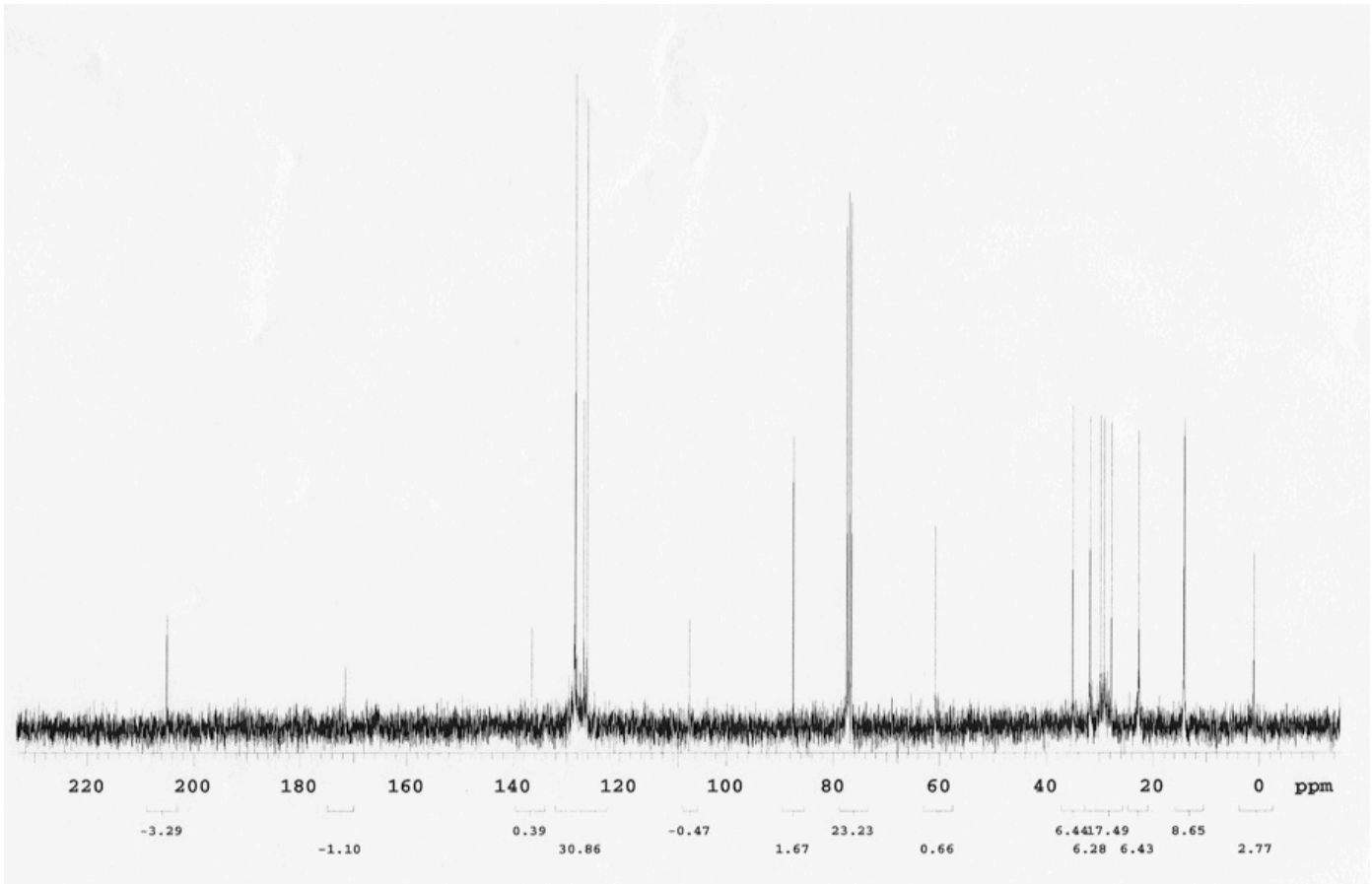

8
7
6
5
4
3
2
1
-0
ppm
2.41
0.92
2.75
2.00
3.54
9.12
26.65
8.11
1.66

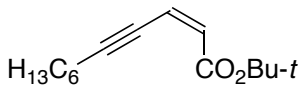

220
200
180
160
140
120
100
80
60
40
20
0
ppm
-0.51
0.41
0.01
5.34
6.58
16.02
6.16
4.83


$H_{13}C_6$
CO_2Et
Ph

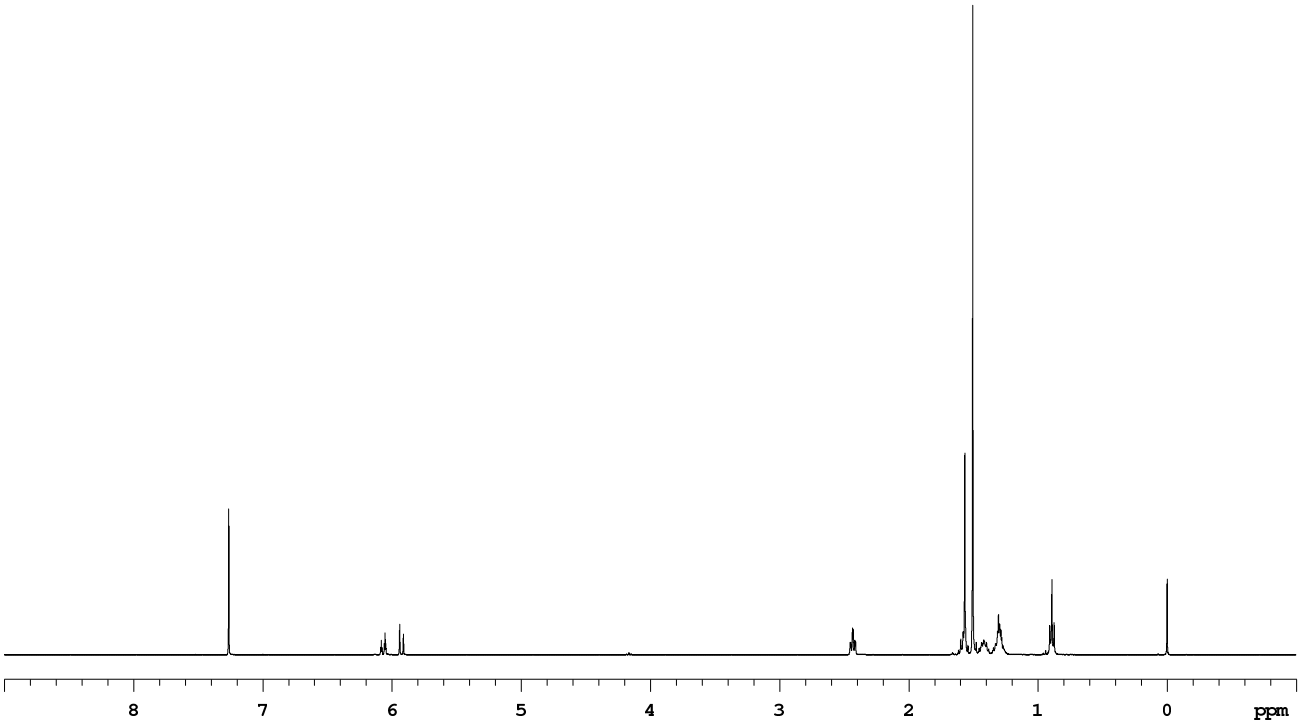
(**21**)

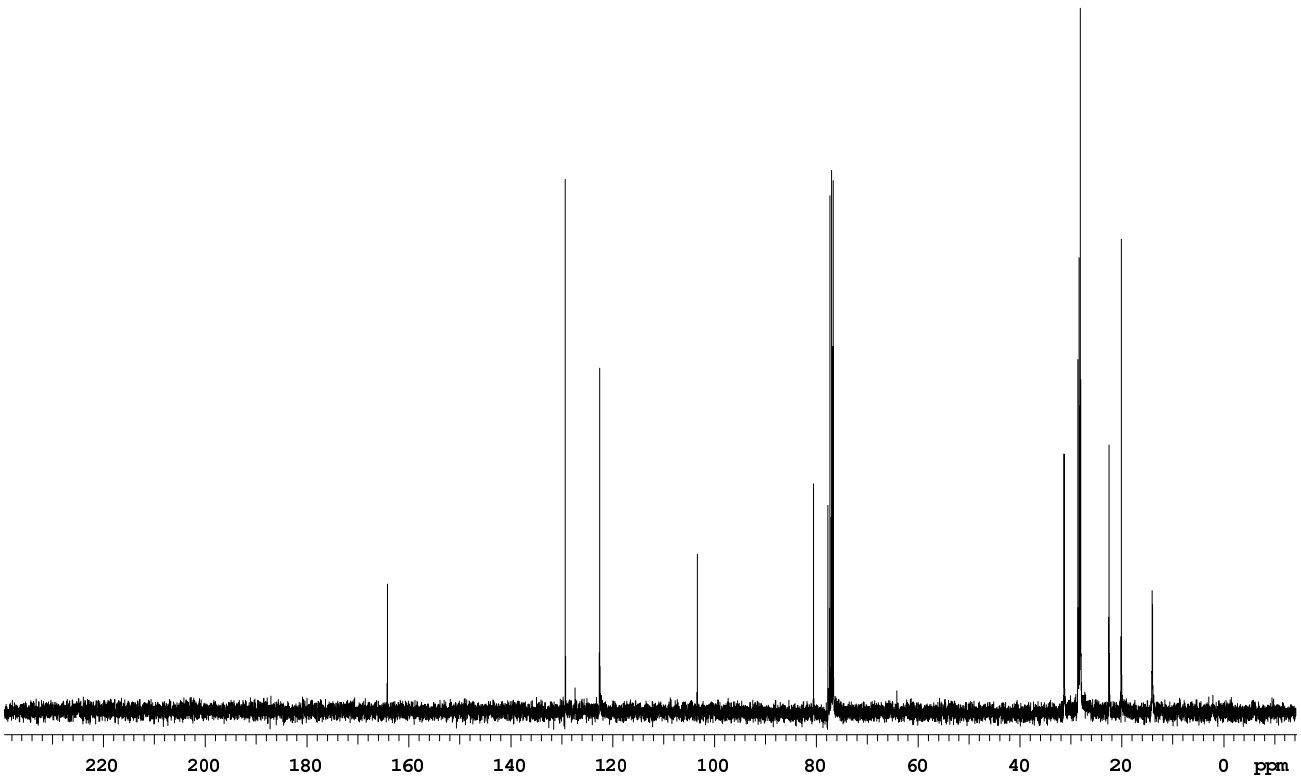

8
7
6
5
4
3
2
1
-0
ppm
13.69
1.00
3.82
2.05
2.27
8.26
20.34
6.67
2.76

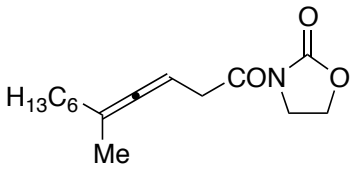

220
200
180
160
140
120
100
80
60
40
20
0
ppm
-3.29
-1.10
0.39
30.86
-0.47
1.67
23.23
0.66
6.44
6.28
17.49
6.43
8.65
2.77


H13C6
CO2Bu-t

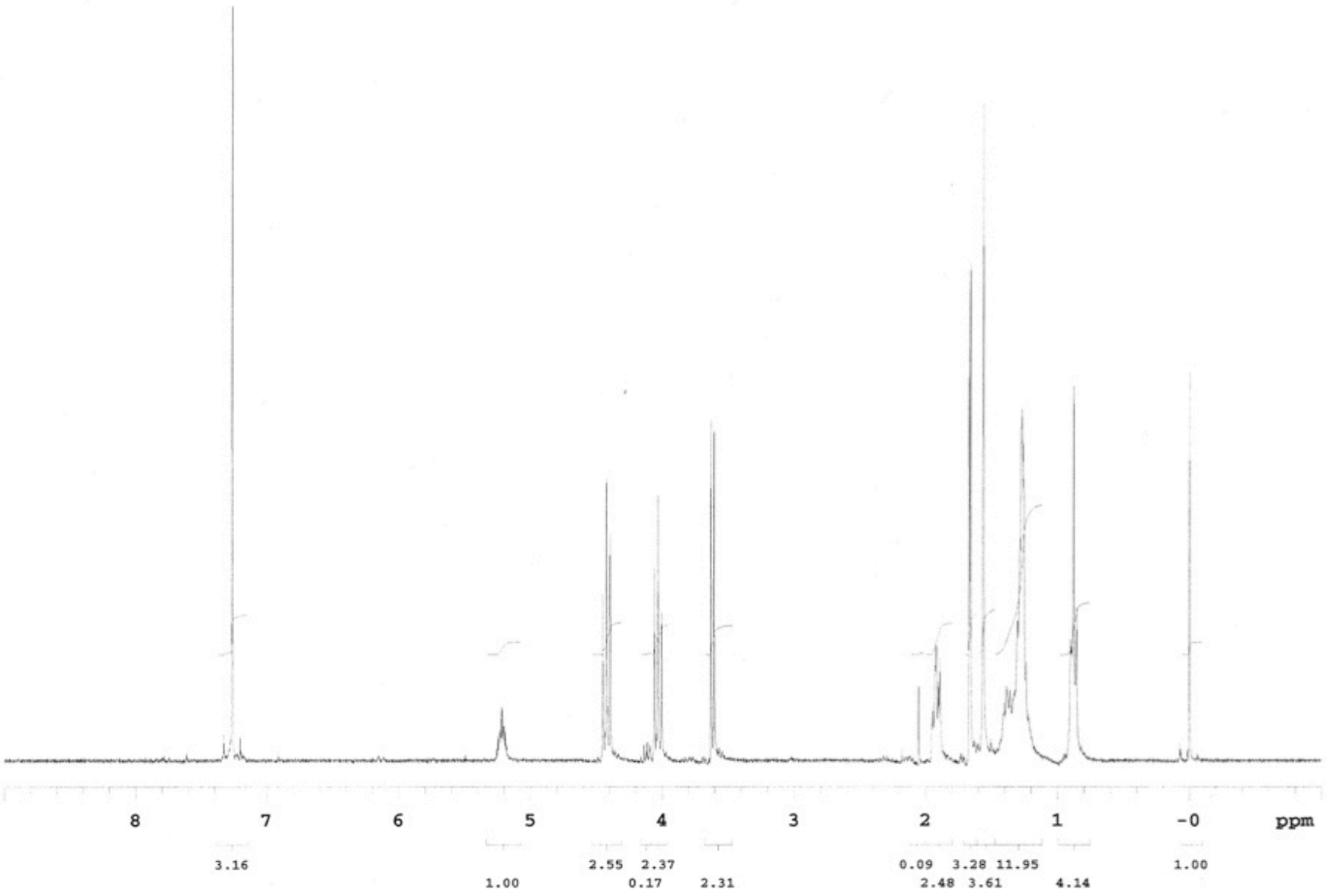
((*Z*)-**1**)

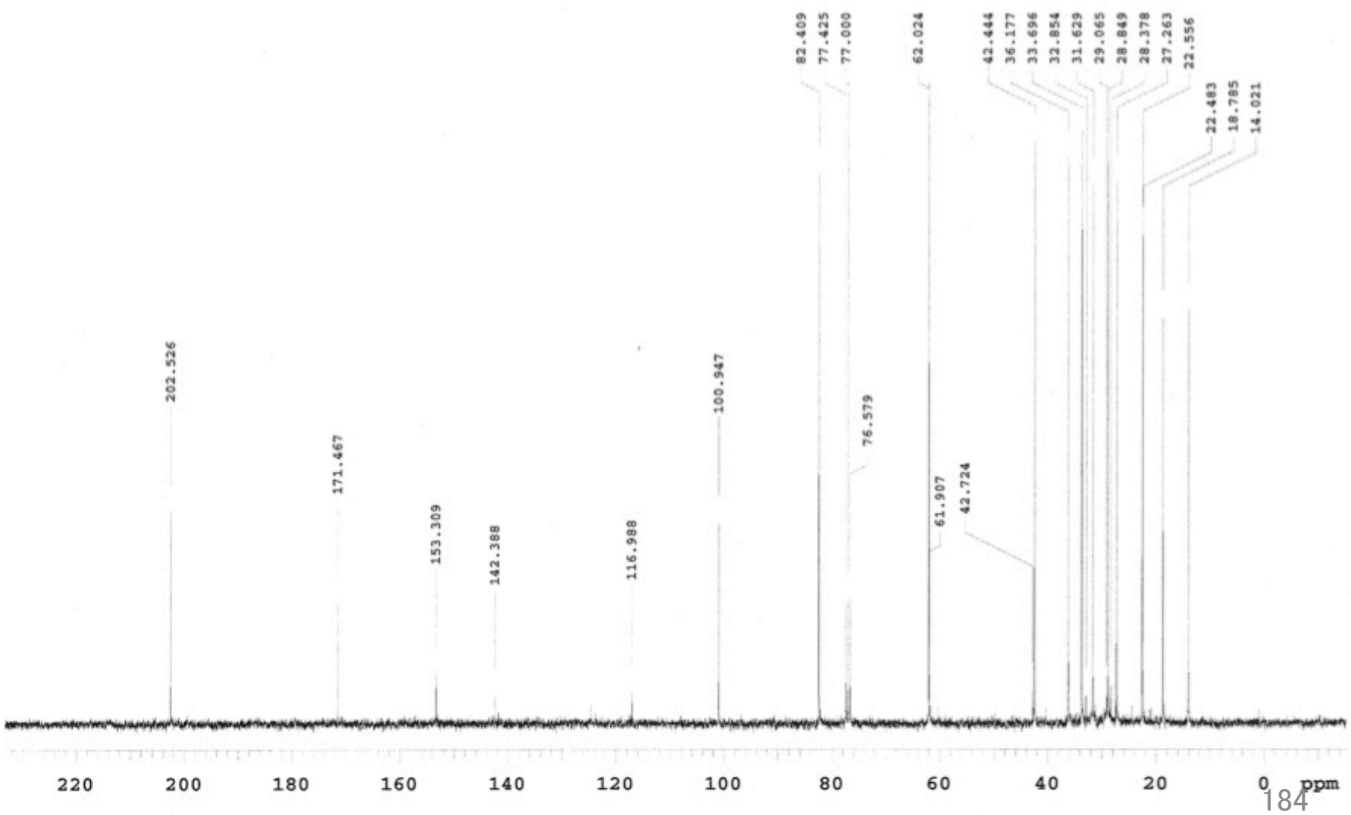

8
7
6
5
4
3
2
1
0
ppm

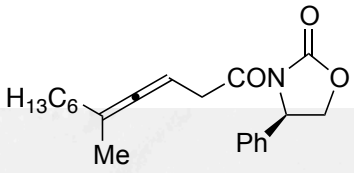

220
200
180
160
140
120
100
80
60
40
20
0
ppm


O
CON
O
$H_{13}C_6$
Me

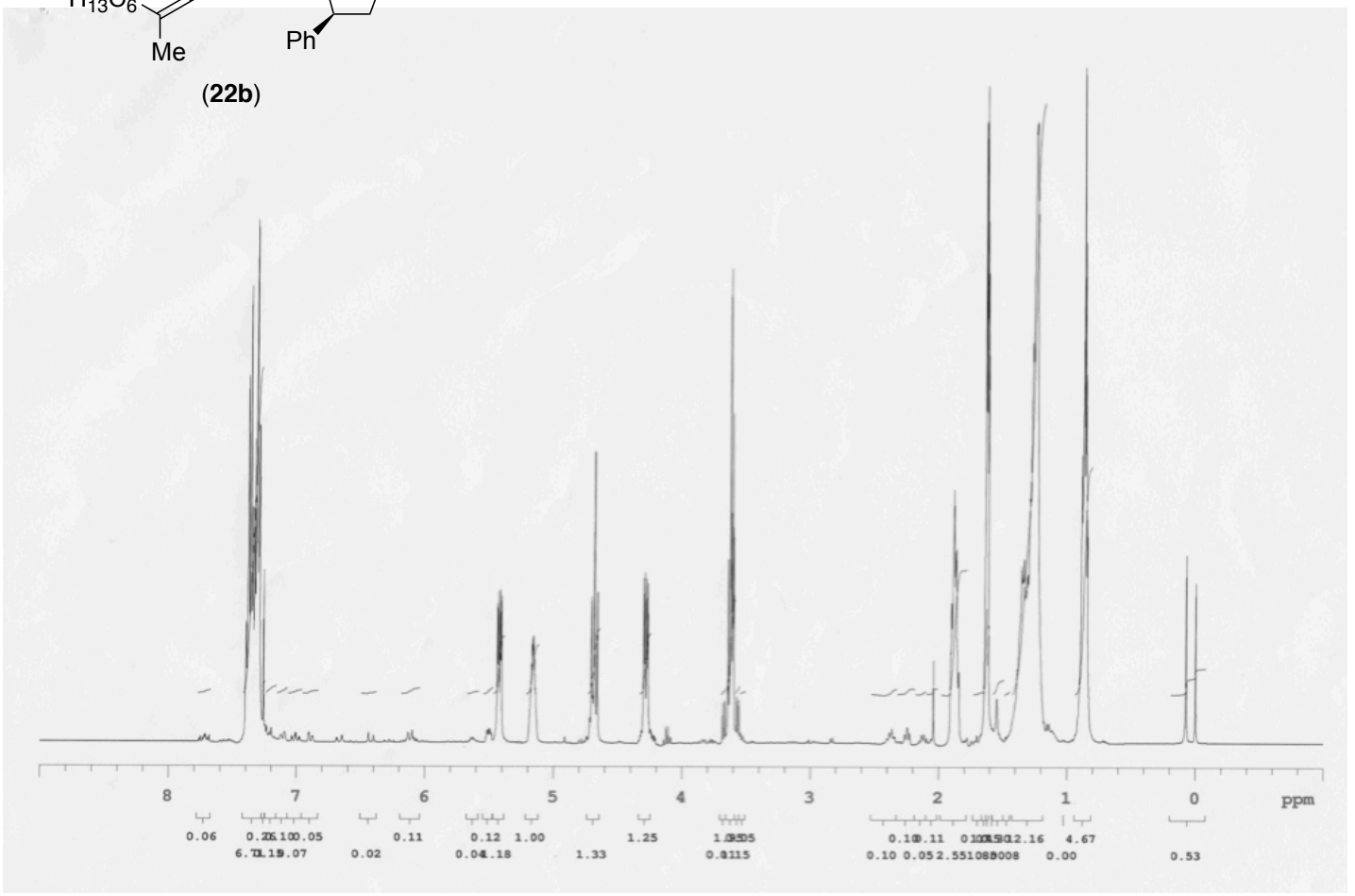
(**22a**)

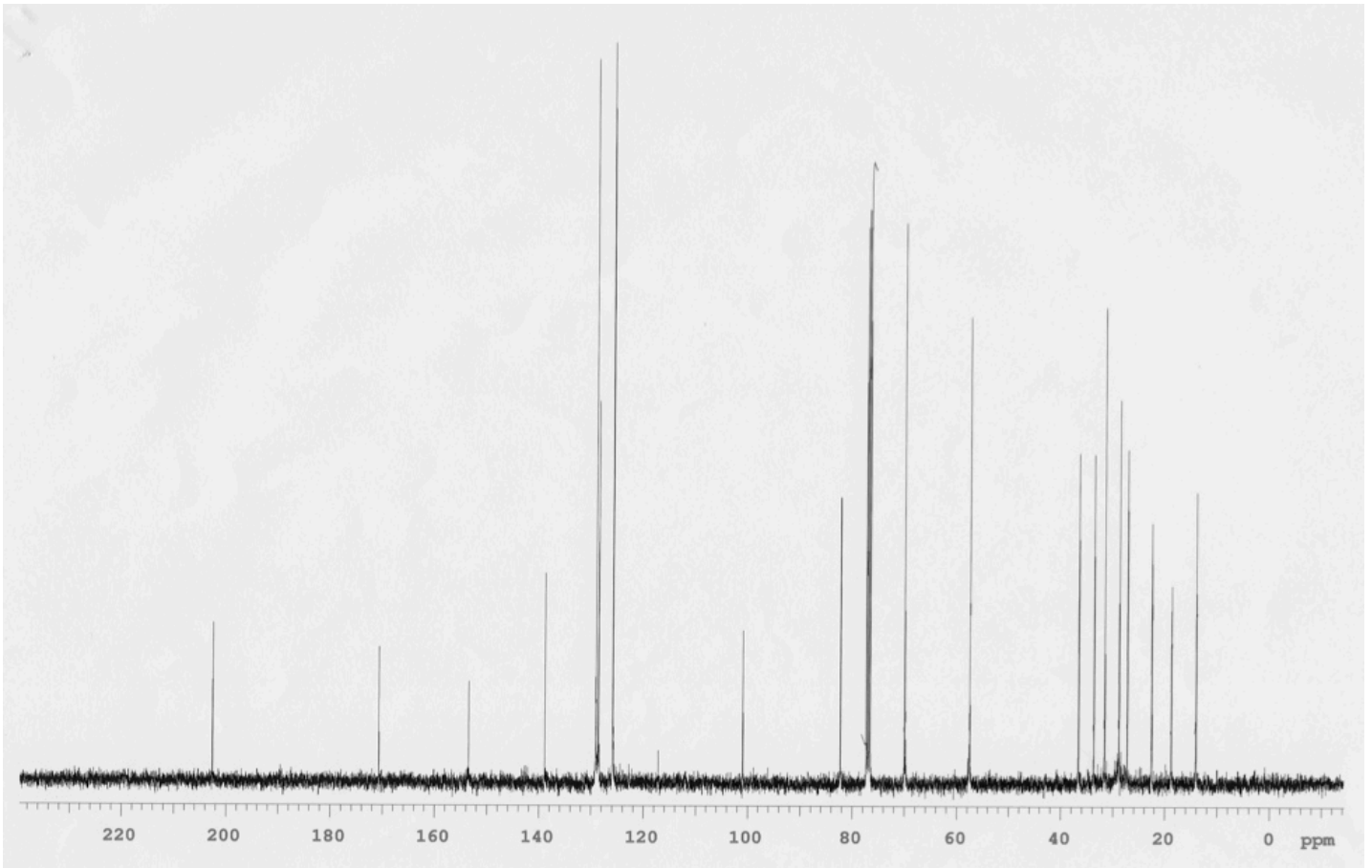

8
7
6
5
4
3
2
1
-0
ppm
3.16
1.00
2.55
2.37
0.17
2.31
0.09
3.28
11.95
2.48
3.61
4.14
1.00

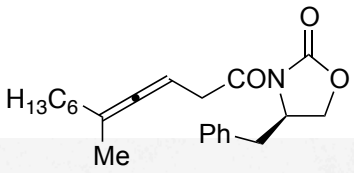

82.409
77.425
77.000
62.024
42.444
36.177
33.696
32.854
31.629
29.065
28.849
28.378
27.263
22.556
22.483
18.785
14.021
202.526
171.467
153.309
142.388
116.988
100.947
76.579
61.907
42.724
220
200
180
160
140
120
100
80
60
40
20
0
ppm


$H_{13}C_6$
CON
O
O
Ph
Me

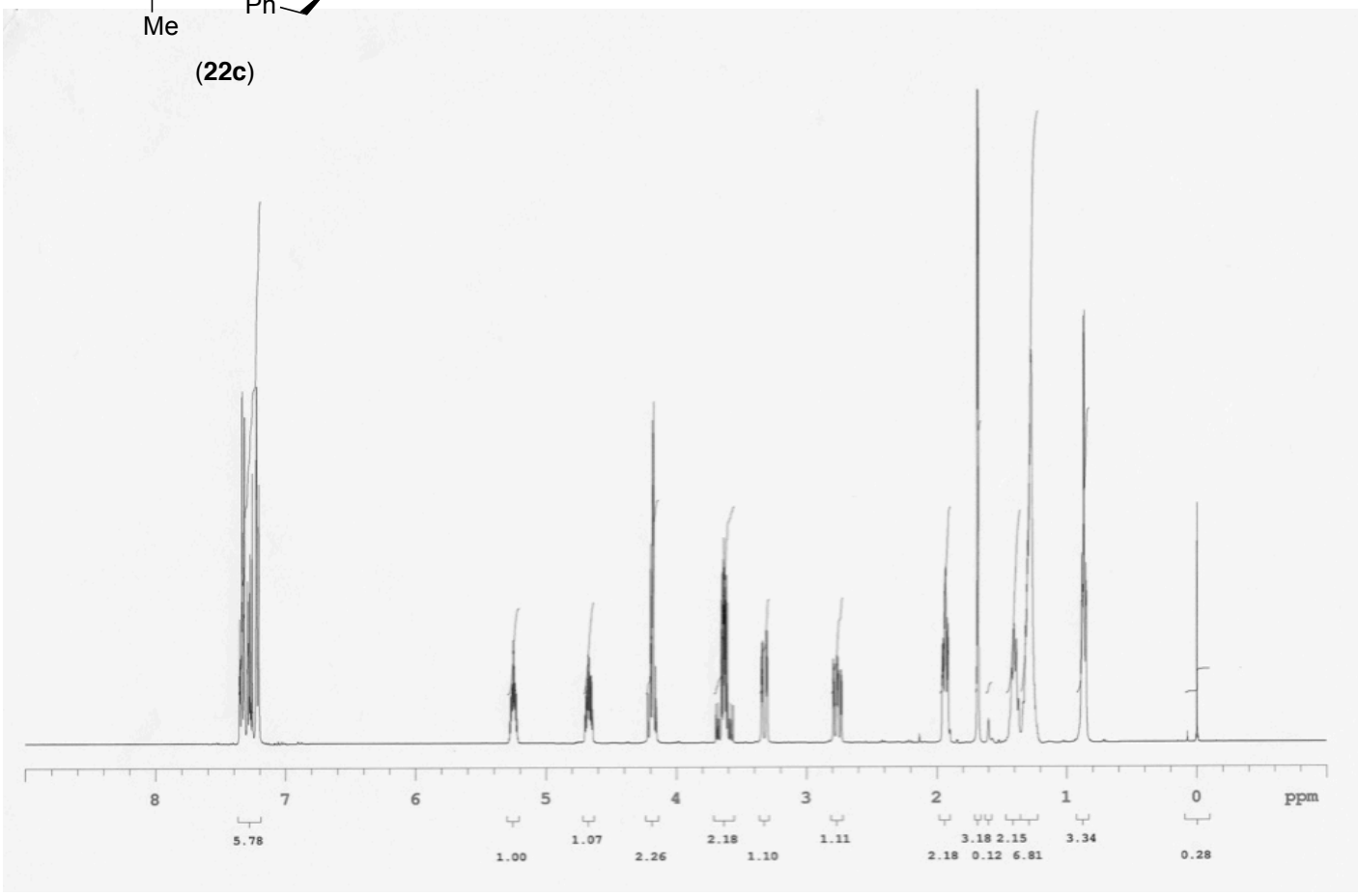
(**22b**)

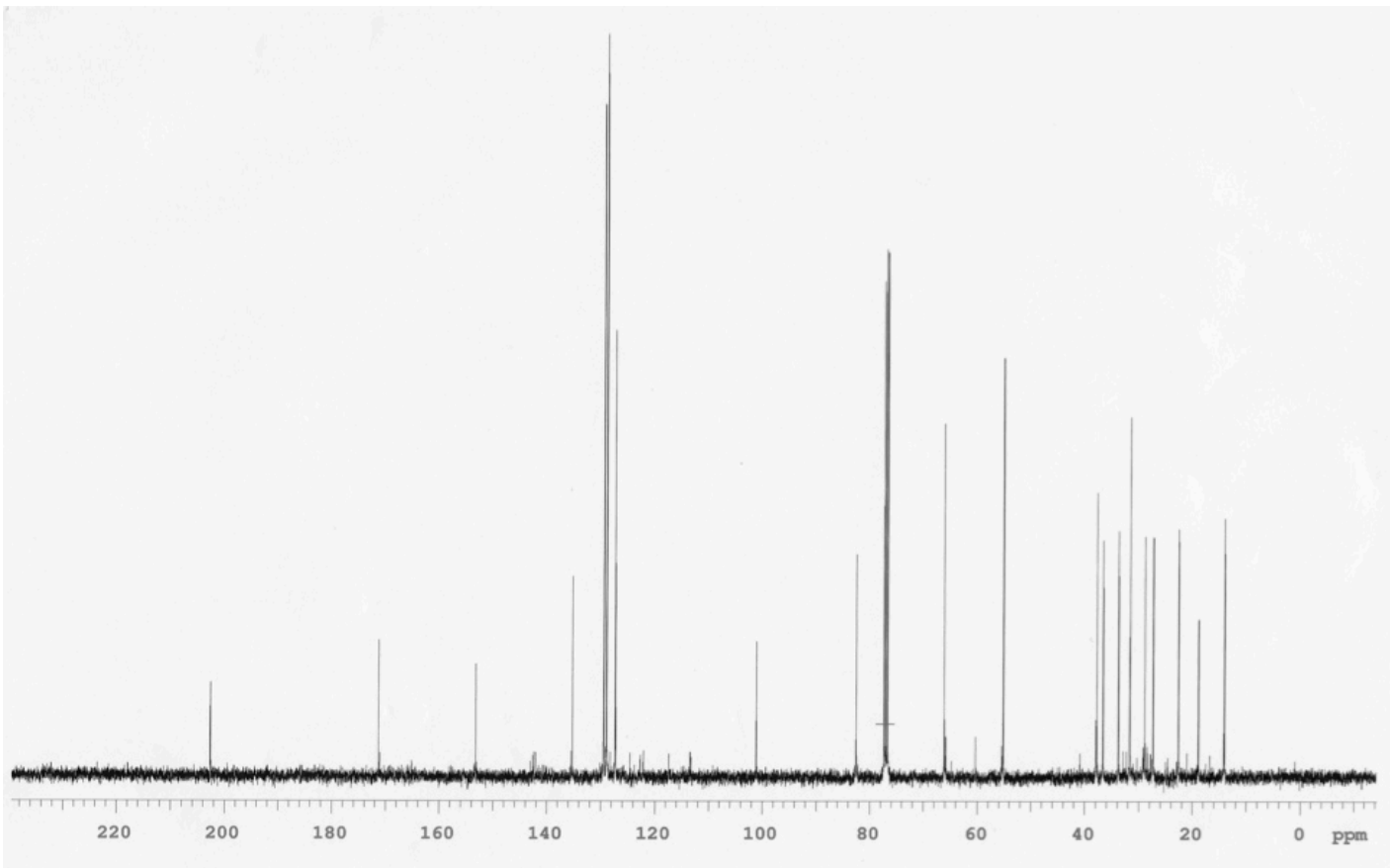

8
7
6
5
4
3
2
1
0
ppm
0.06
0.11
0.12
1.00
1.25
1.33
0.02
0.10
0.05
0.00
0.53
4.67

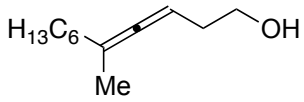

220
200
180
160
140
120
100
80
60
40
20
0
ppm


O
CON
O
$H_{13}C_6$
Ph
Me

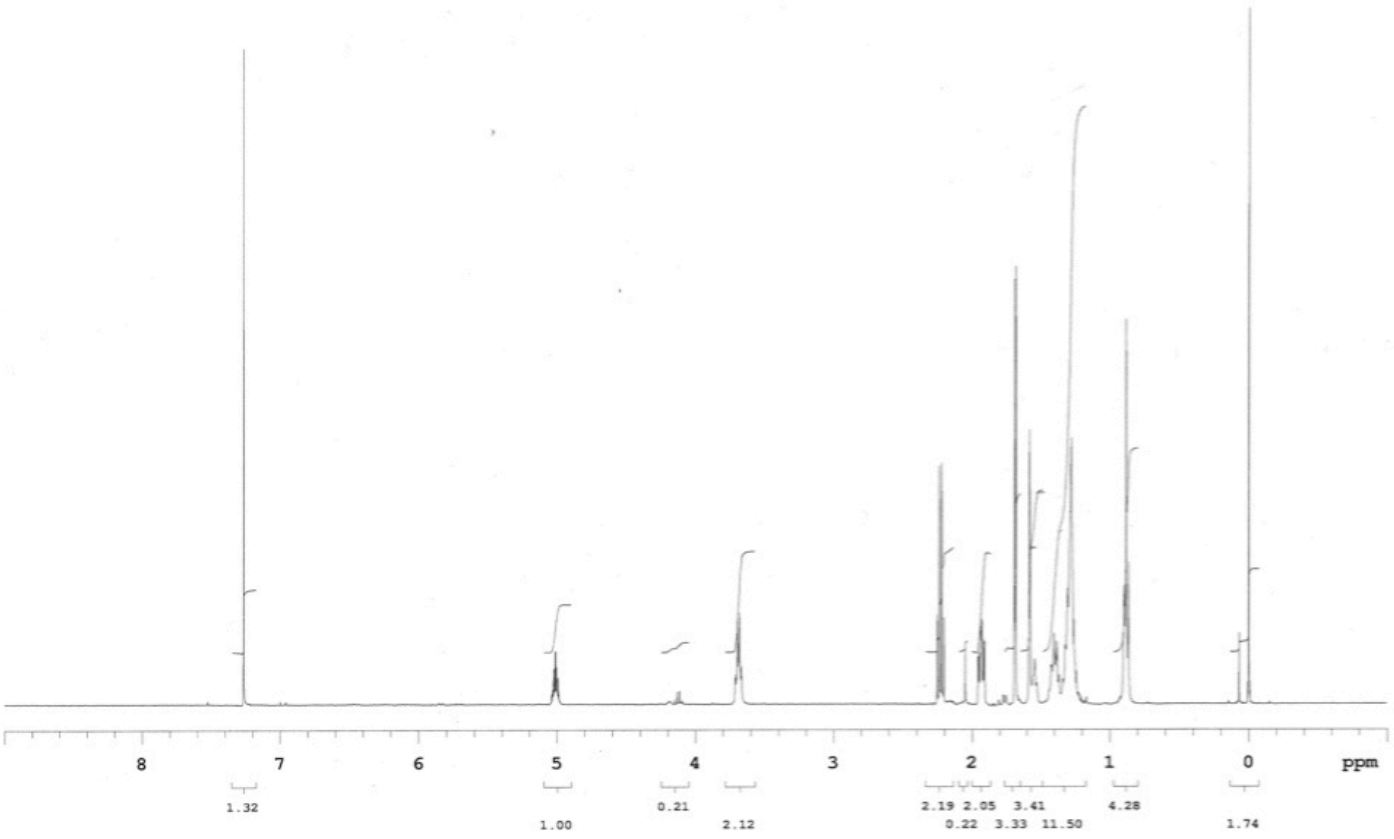
(**22c**)

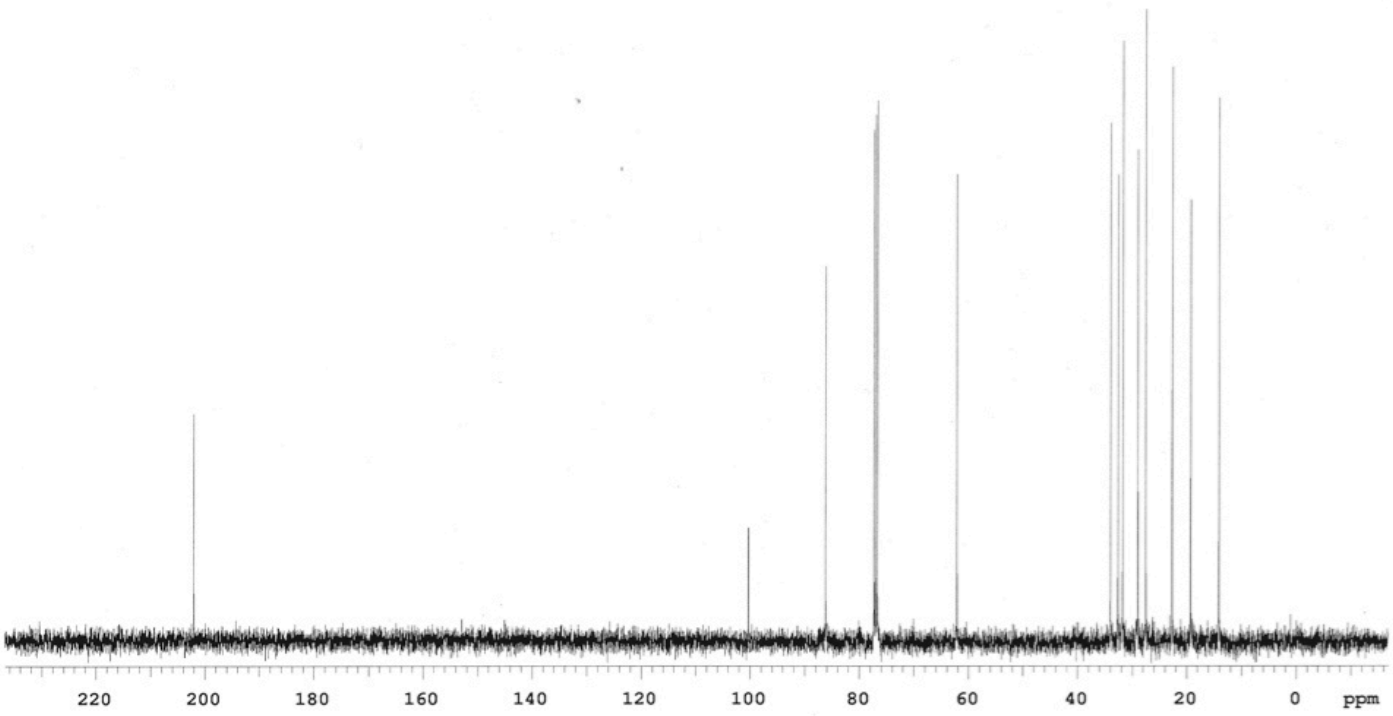

8
7
6
5
4
3
2
1
0
ppm
5.78
1.00
1.07
2.26
2.18
1.10
1.11
2.18
3.18
0.12
2.15
6.81
3.34
0.28

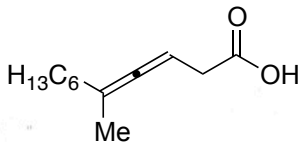

220
200
180
160
140
120
100
80
60
40
20
0
ppm


$H_{13}C_6$
OH
Me

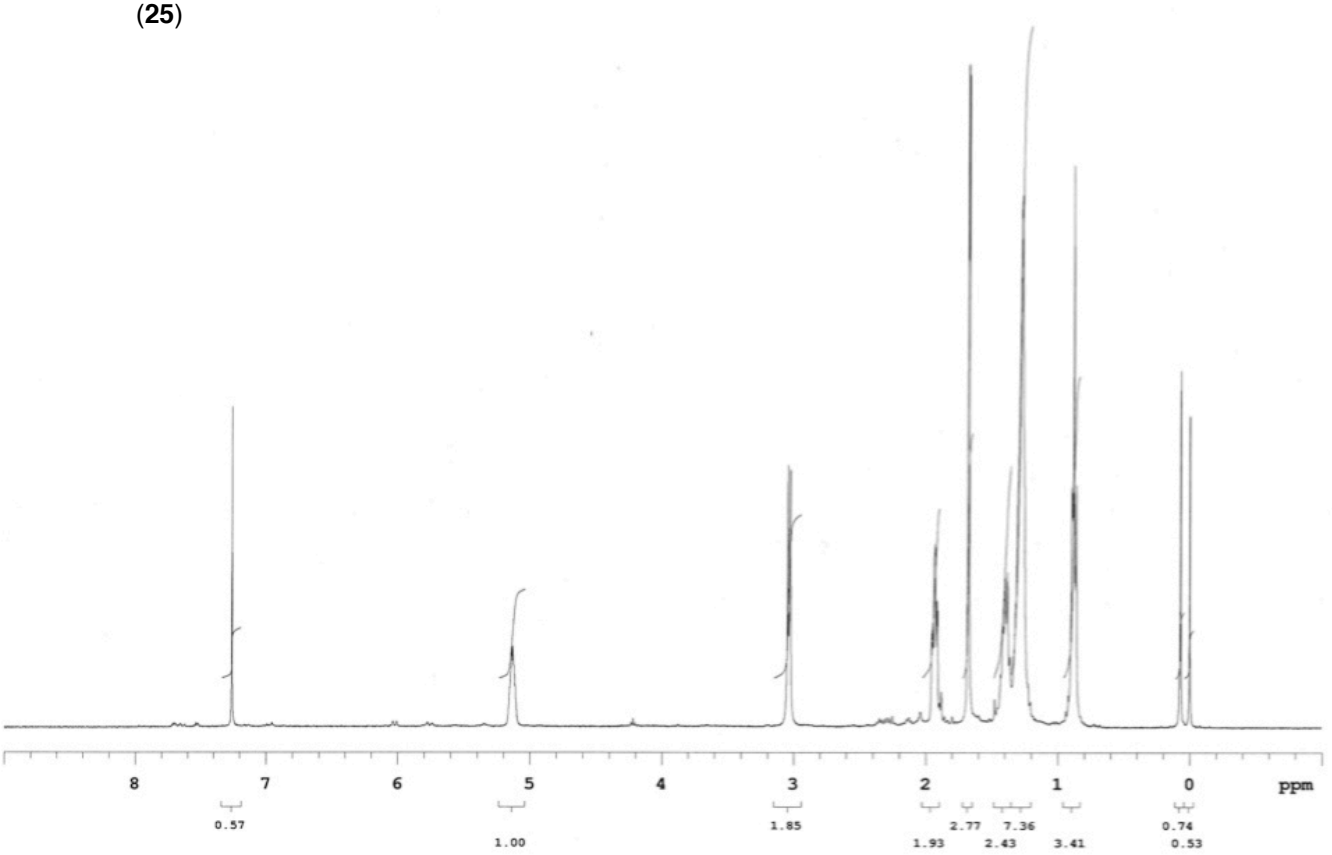
(**24**)

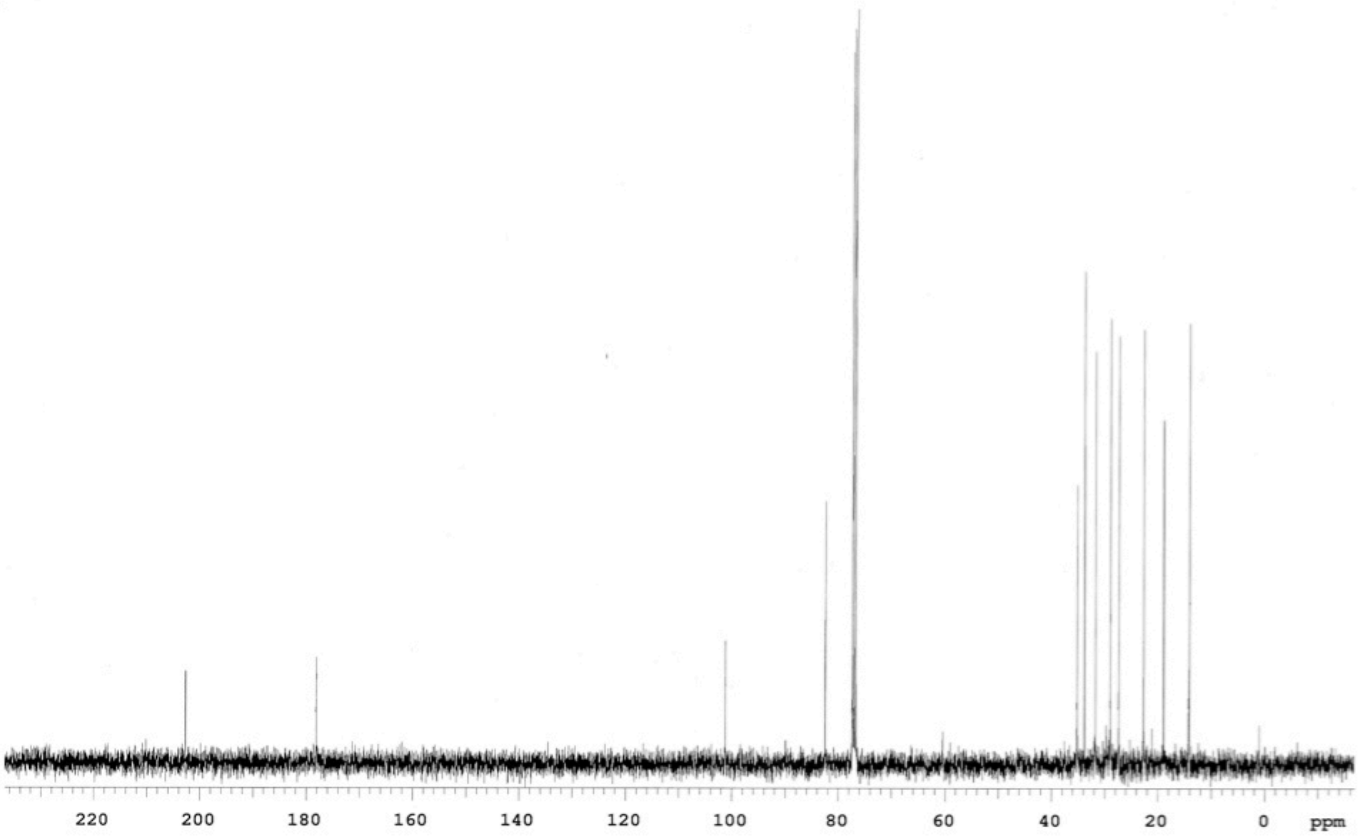

8
7
6
5
4
3
2
1
0
ppm
1.32
1.00
0.21
2.12
2.19
2.05
0.22
3.33
3.41
11.50
4.28
1.74

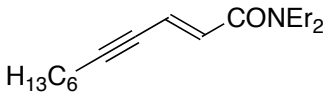

220
200
180
160
140
120
100
80
60
40
20
0
ppm


O
H13C6
OH
Me

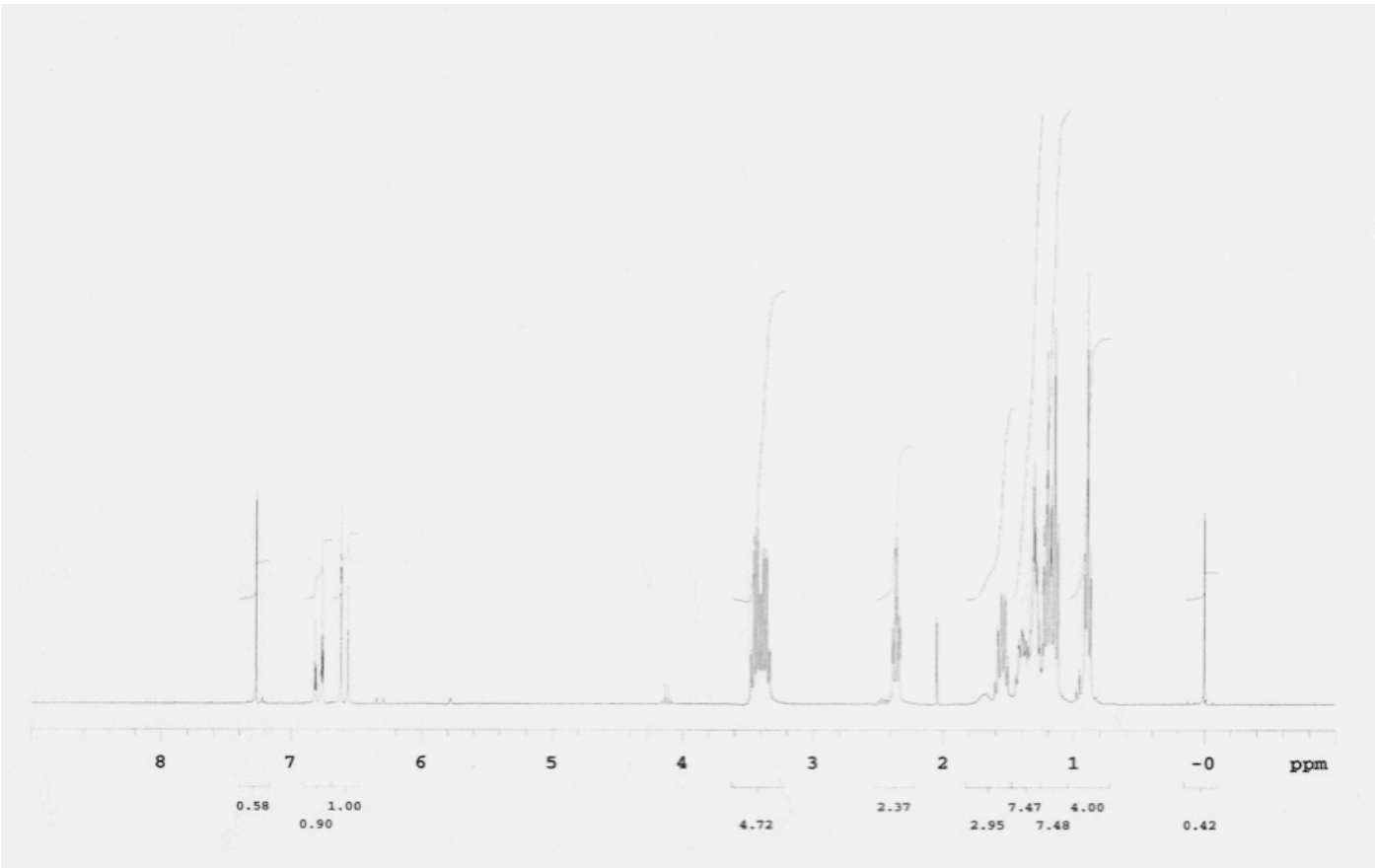
(**25**)

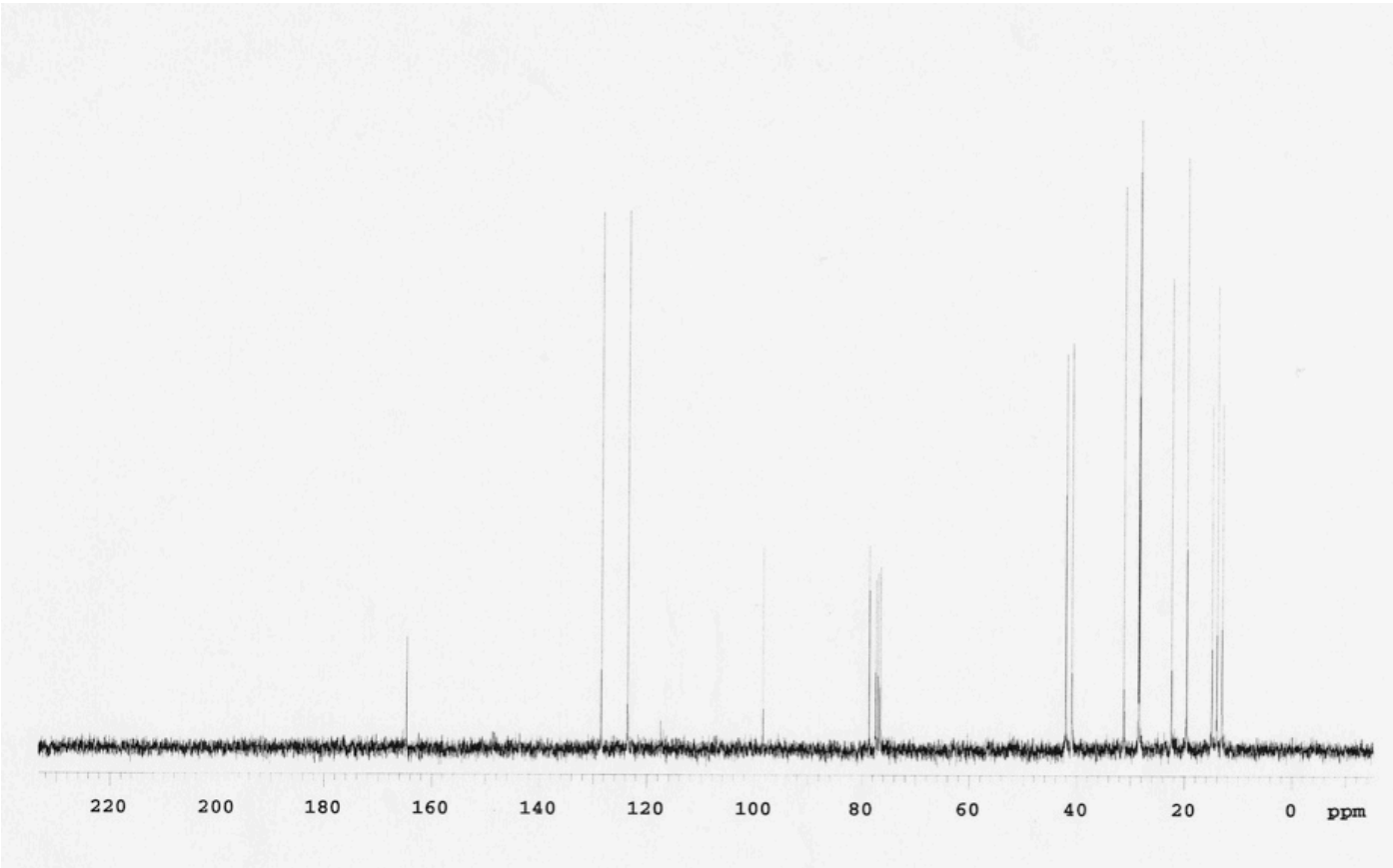

8
7
6
5
4
3
2
1
0
ppm
0.57
1.00
1.85
1.93
2.77
2.43
7.36
3.41
0.74
0.53

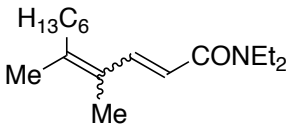

220
200
180
160
140
120
100
80
60
40
20
0
ppm


CONEr2
H13C6

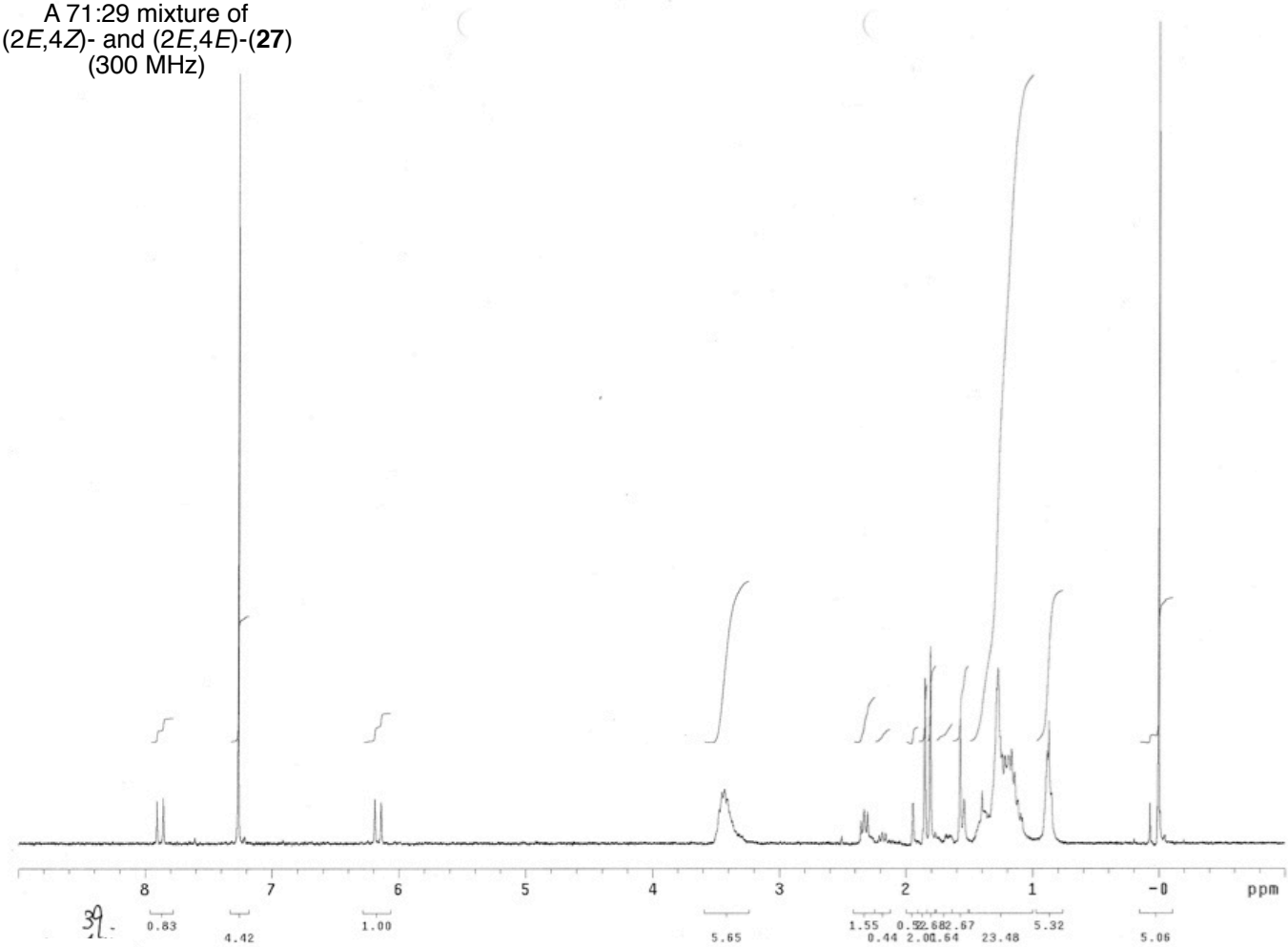
(**26**)

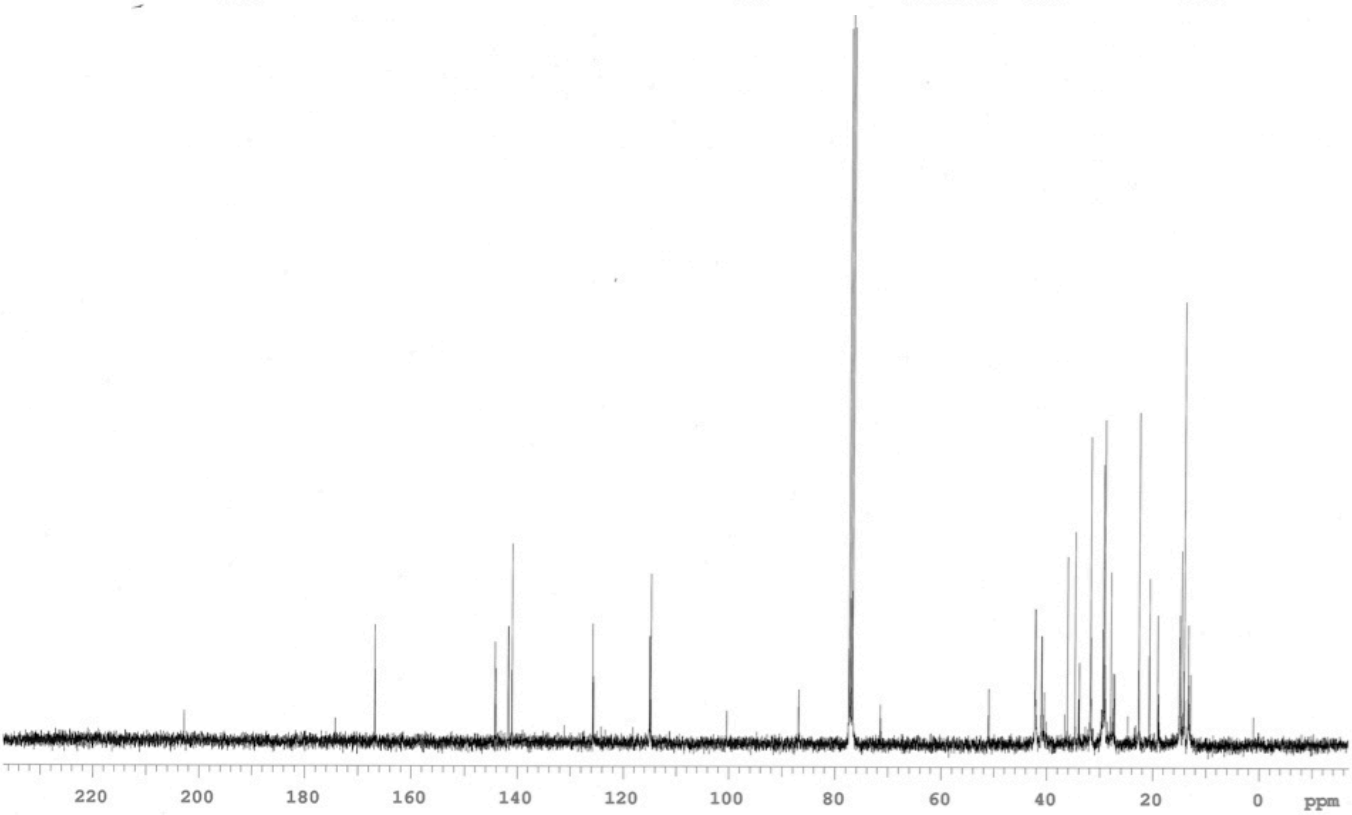

8
7
6
5
4
3
2
1
-0
ppm
0.58
1.00
0.90
4.72
2.37
7.47
4.00
2.95
7.48
0.42

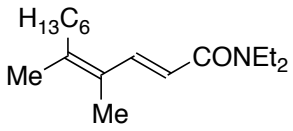

220
200
180
160
140
120
100
80
60
40
20
0
ppm



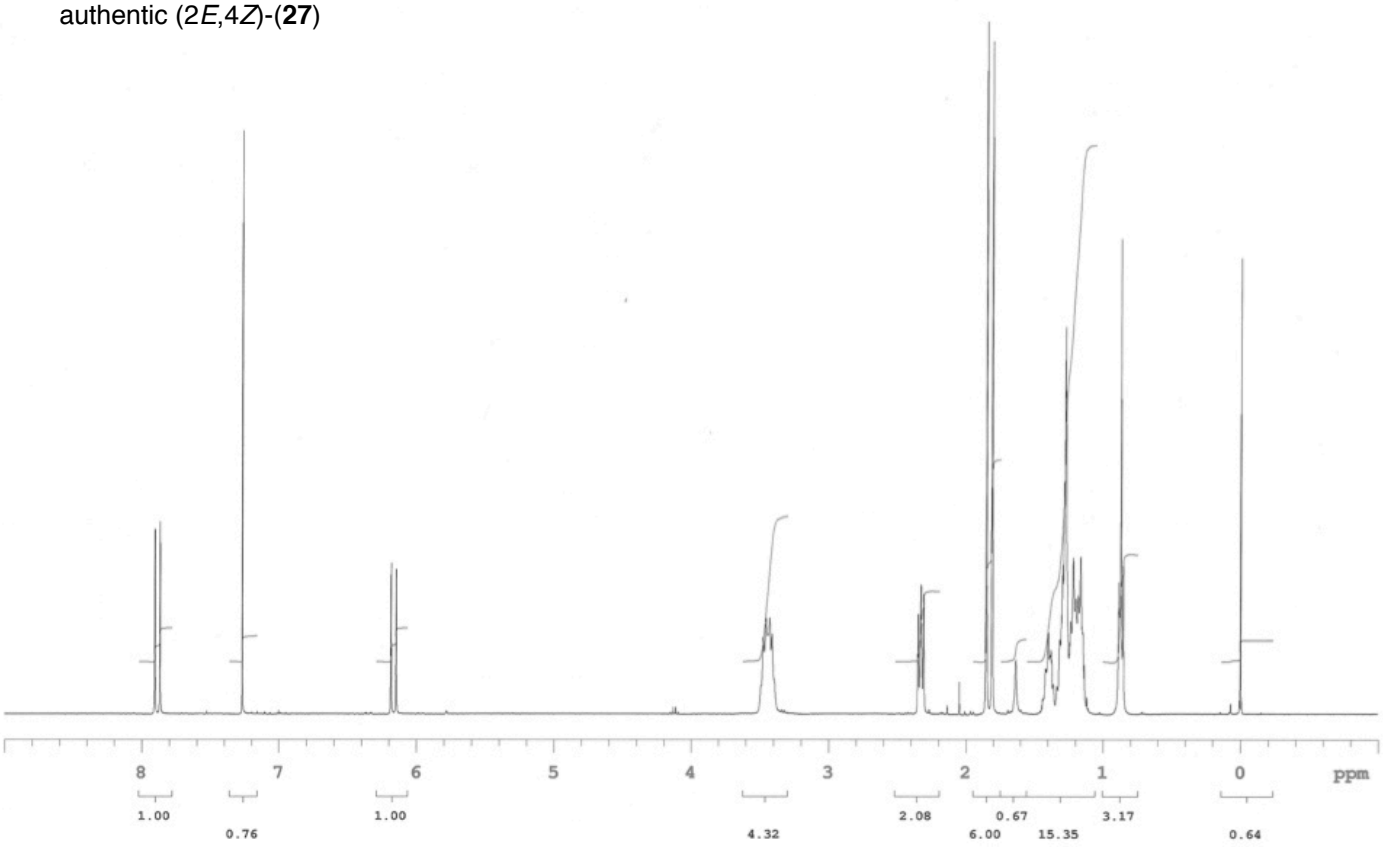
A 71:29 mixture of
(2*E*,4*Z*)- and (2*E*,4*E*)-(**27**)
(300 MHz)

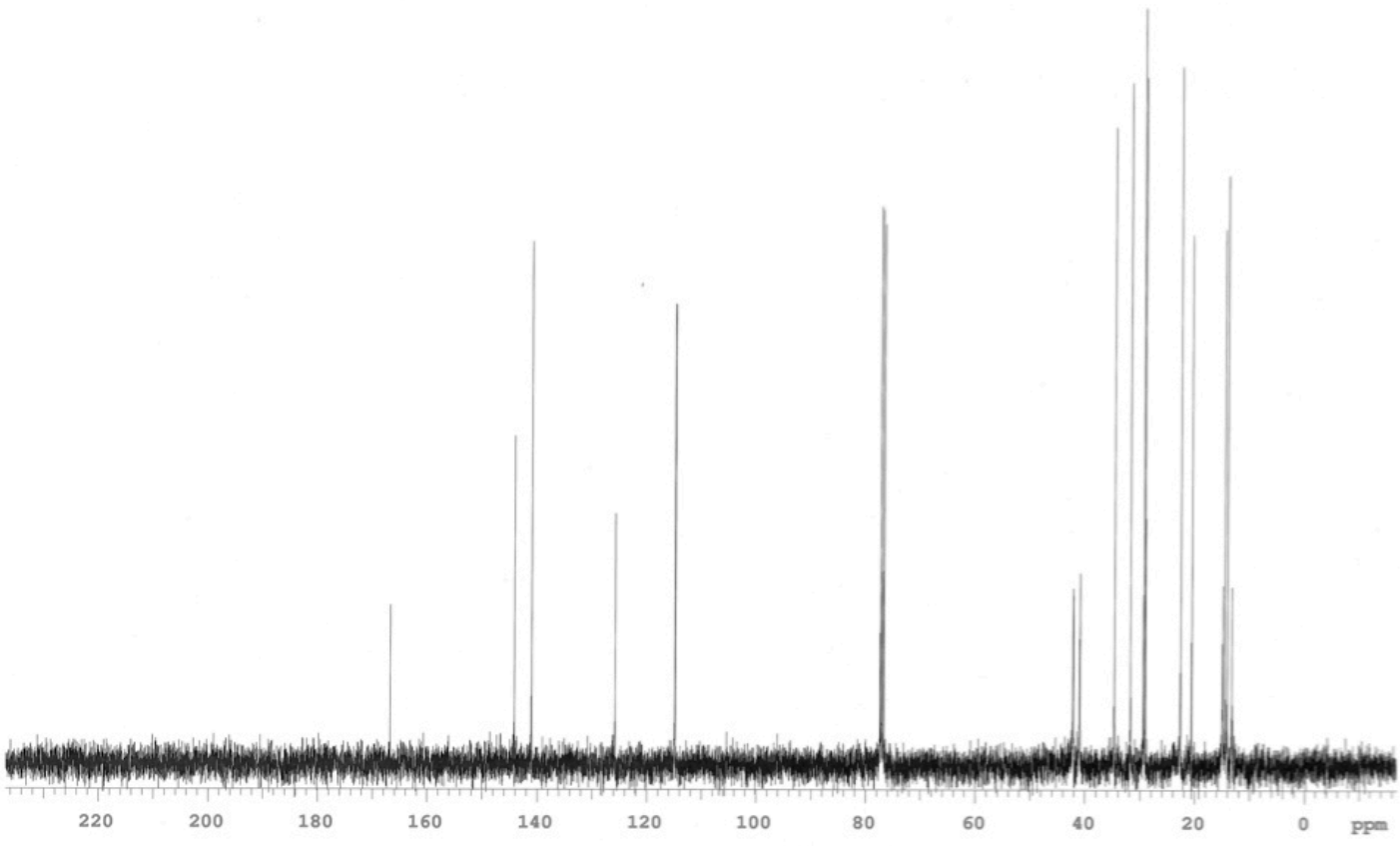


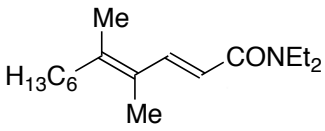




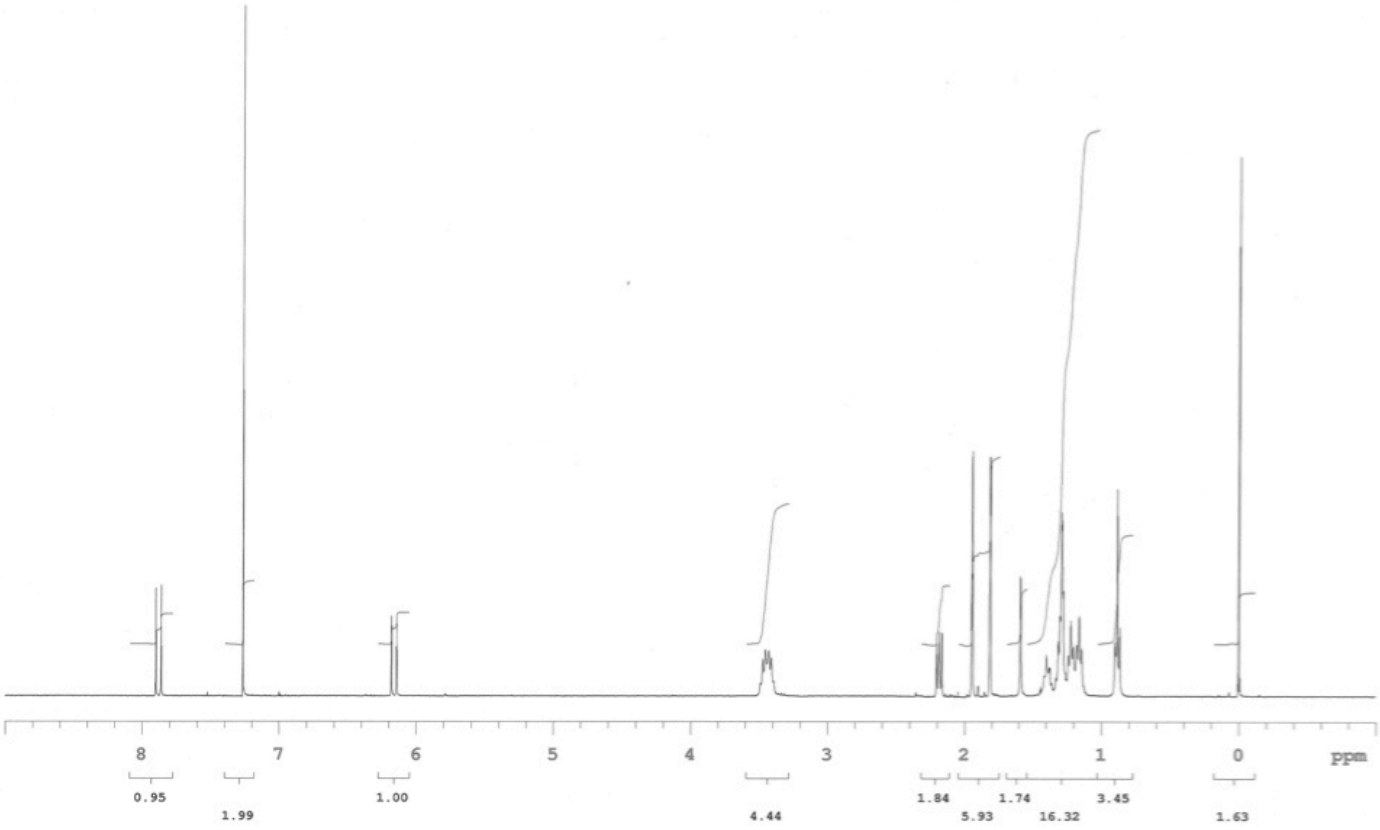
authentic (2*E*,4*Z*)-(**27**)

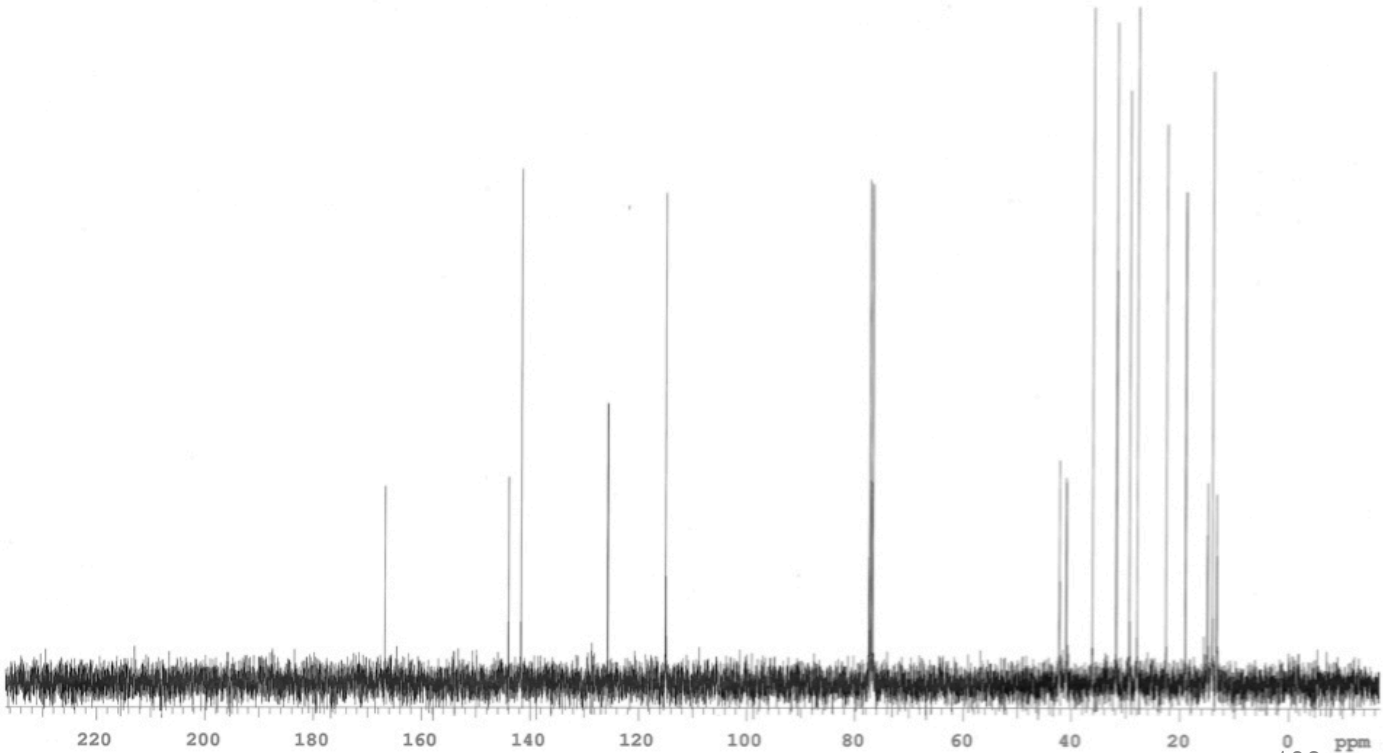


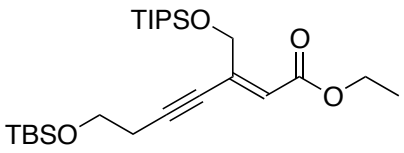




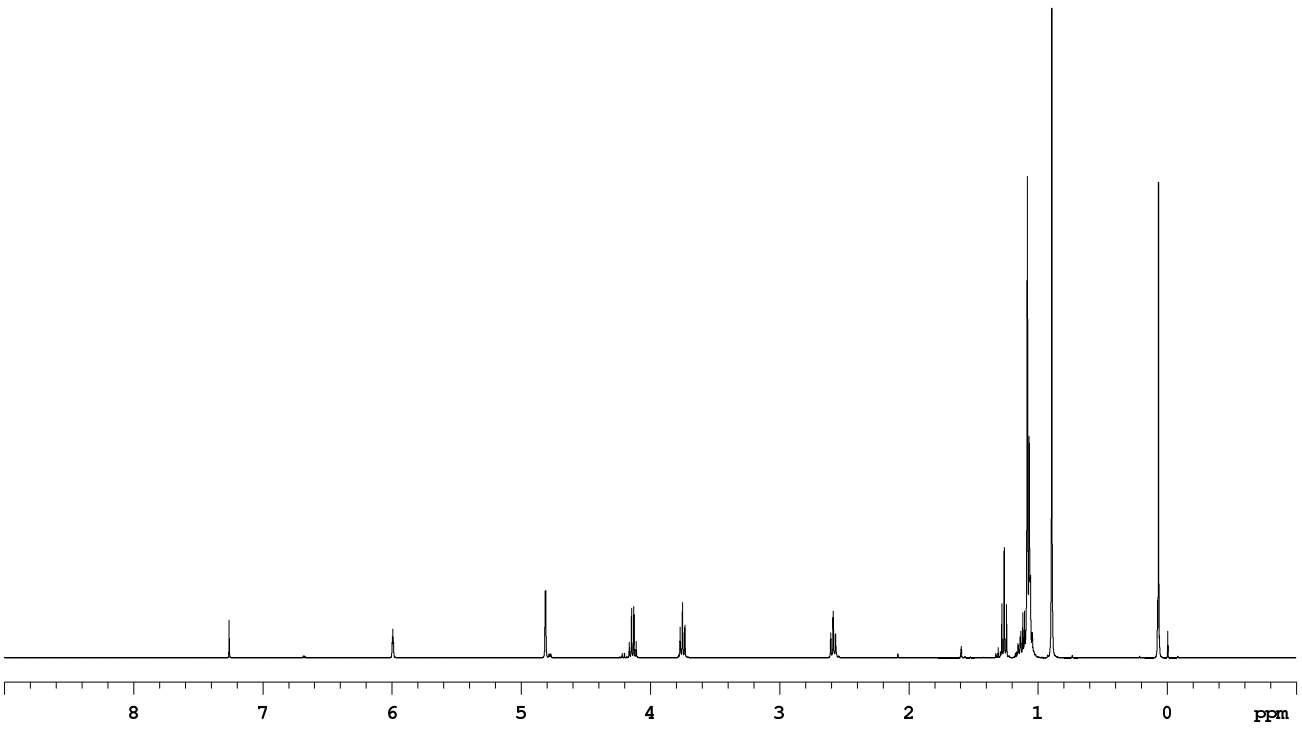
authentic (2*E*,4*E*)-(**27**)

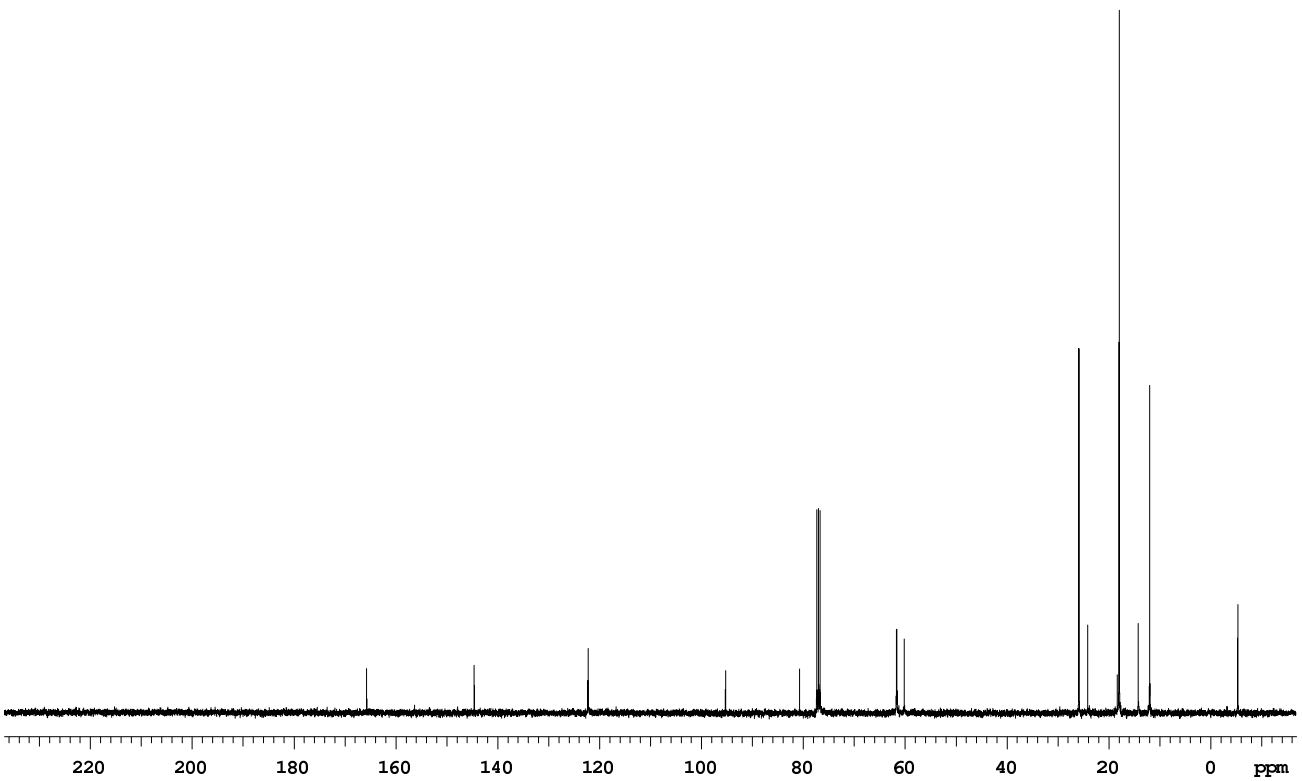


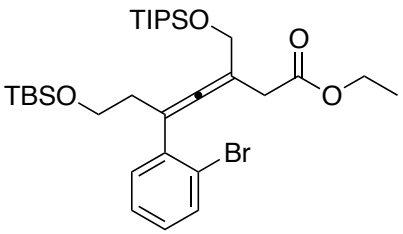



TIPSO
O
O
TBSO

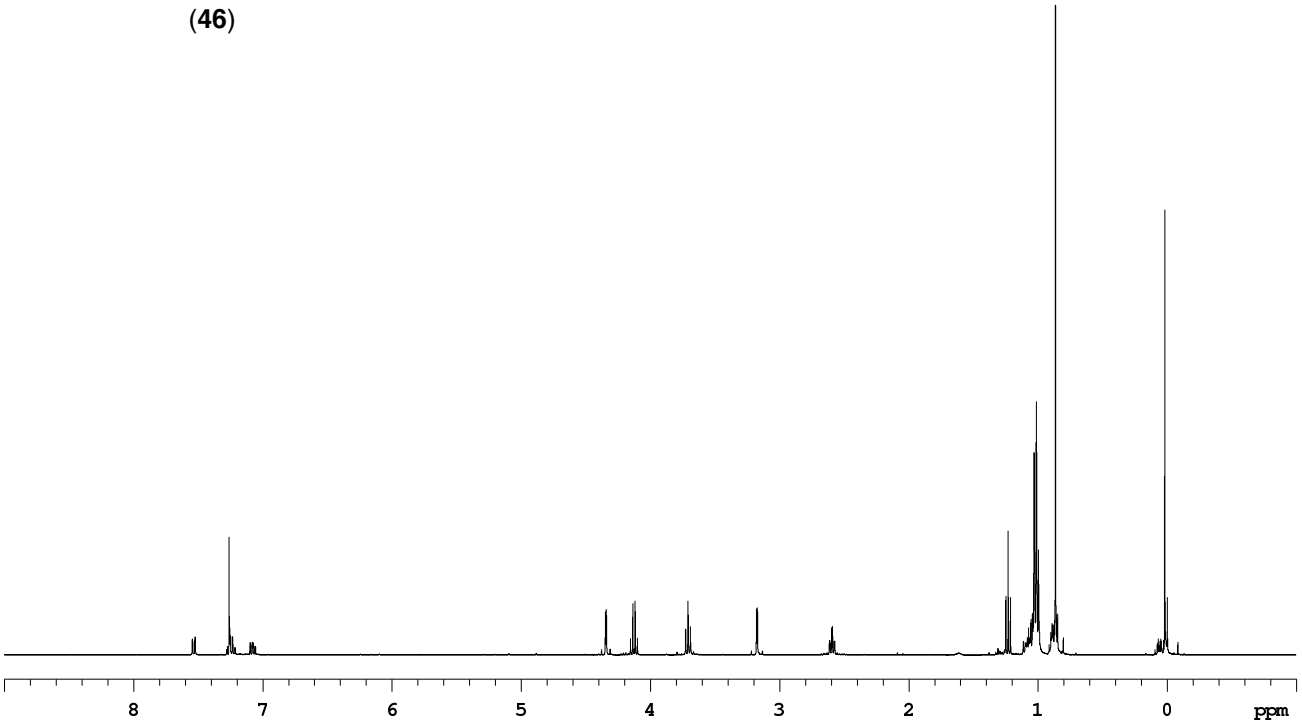
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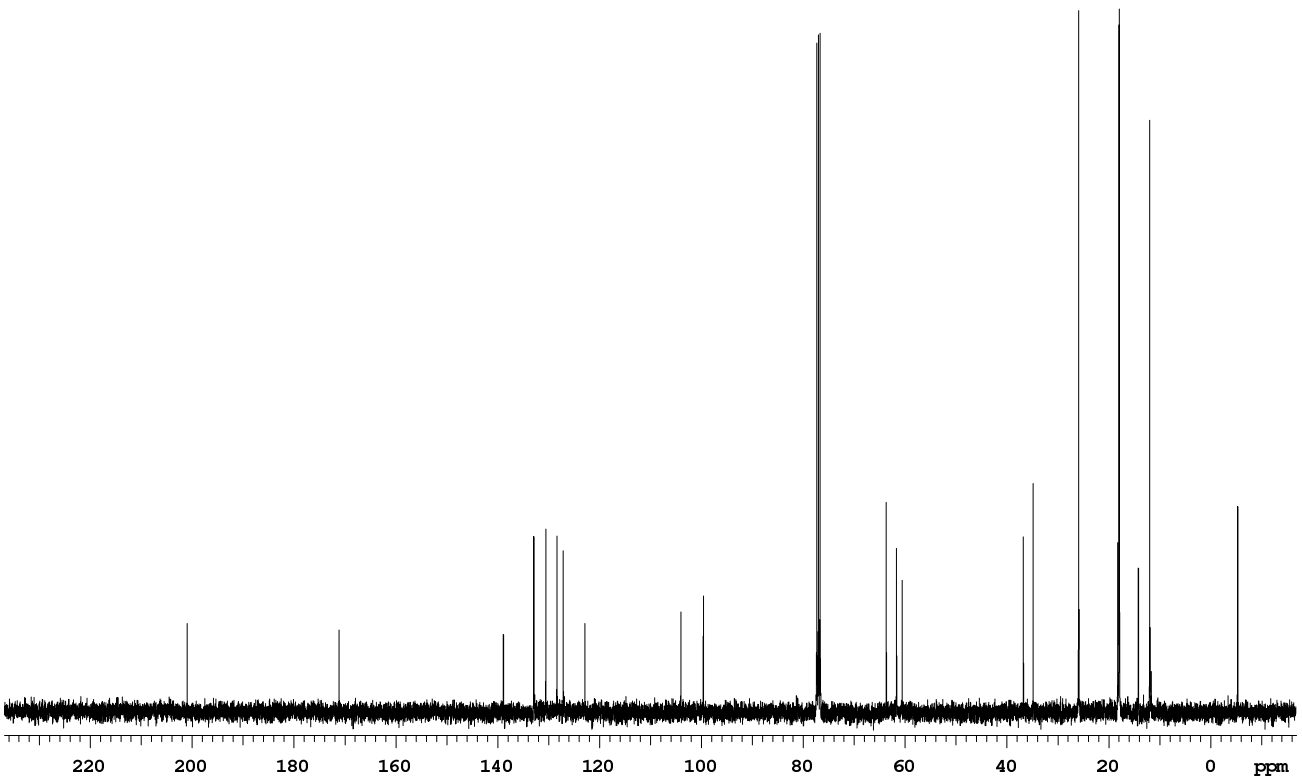

8
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6
5
4
3
2
1
0
ppm

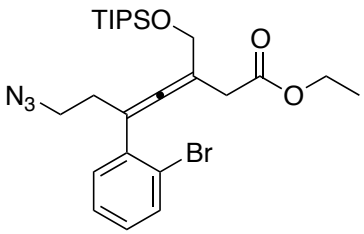

220
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180
160
140
120
100
80
60
40
20
0
ppm


TIPSO
O
TBSO
O
Br

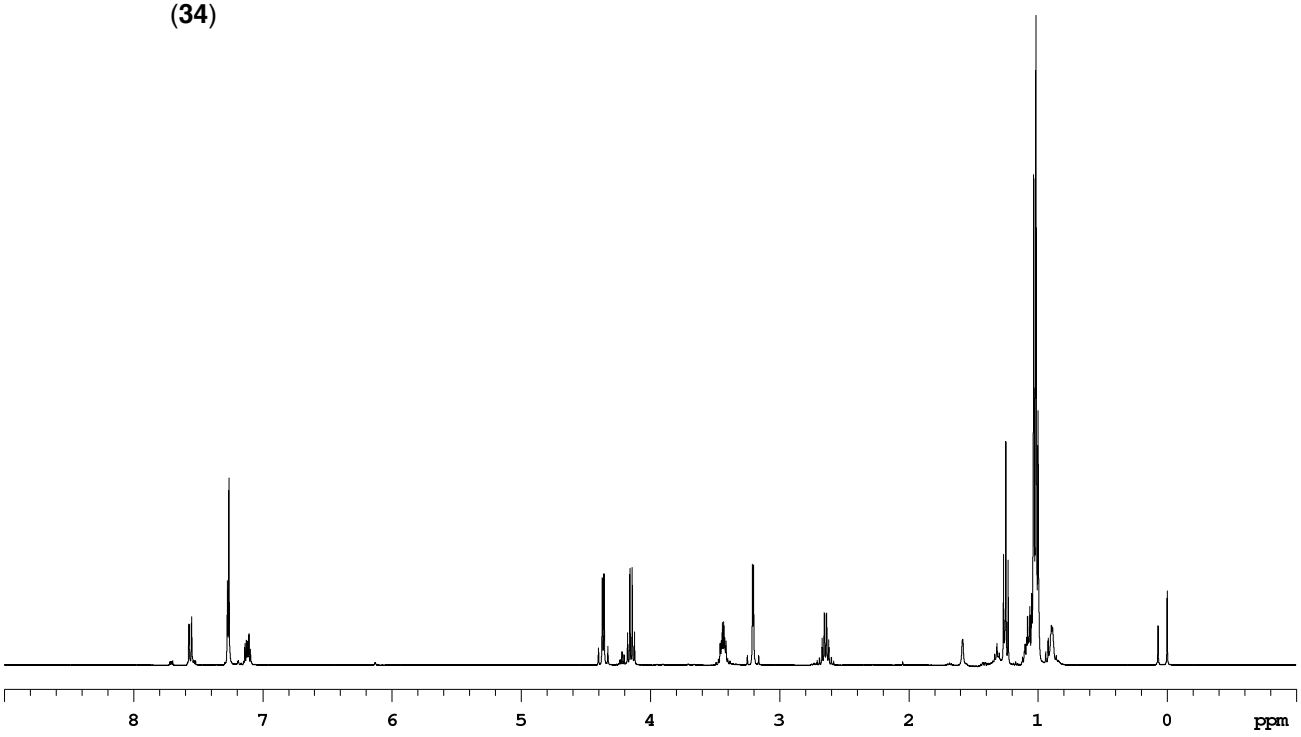
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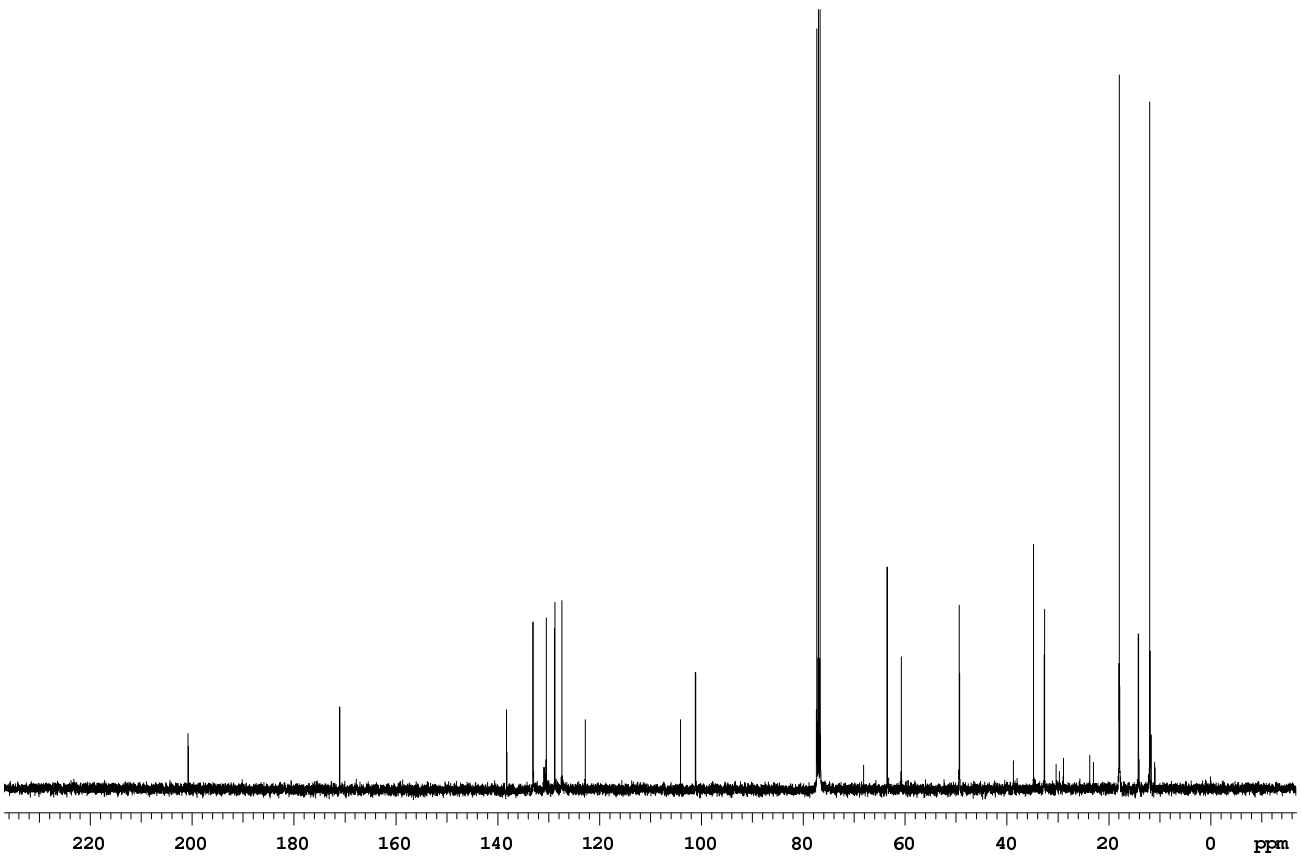

8
7
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5
4
3
2
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ppm


220
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60
40
20
0
ppm


TIPSO
O
N3
O
Br

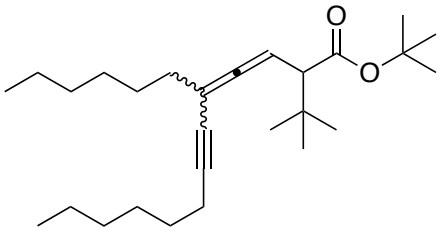
(**34**)


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6
5
4
3
2
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0
ppm

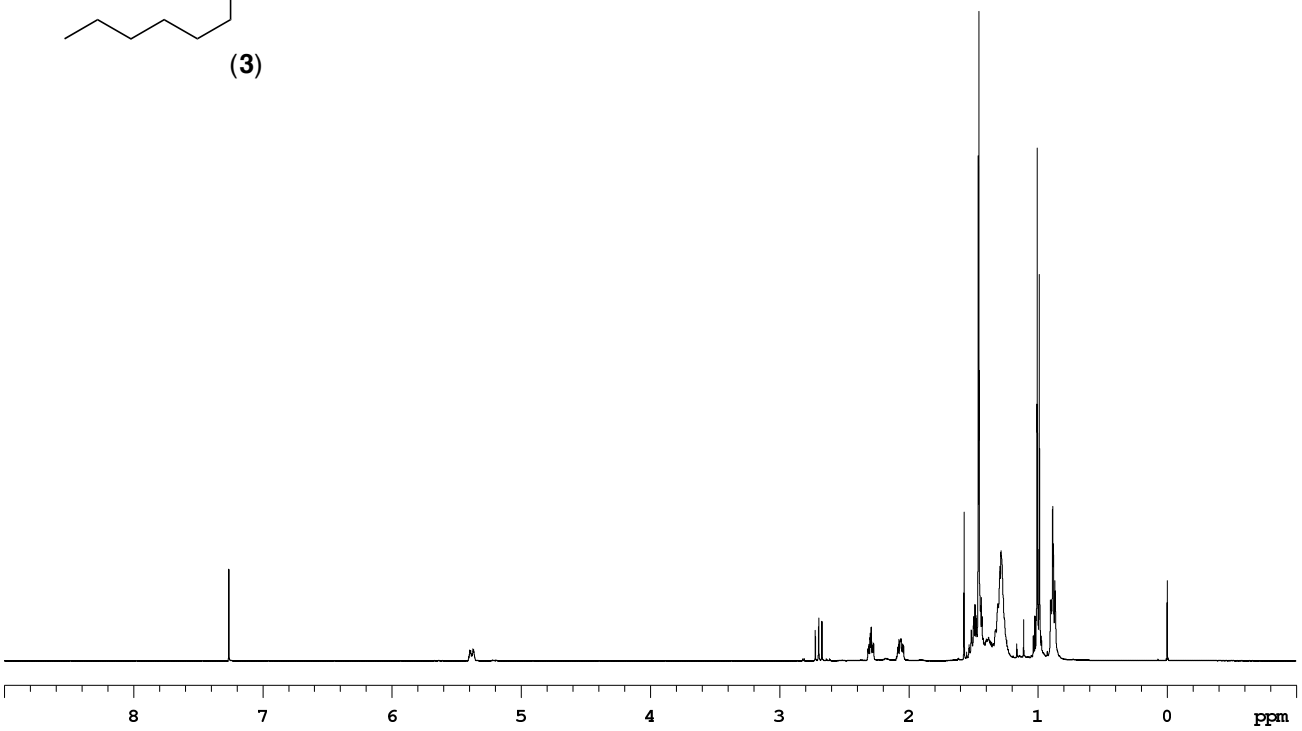

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200
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20
0
ppm

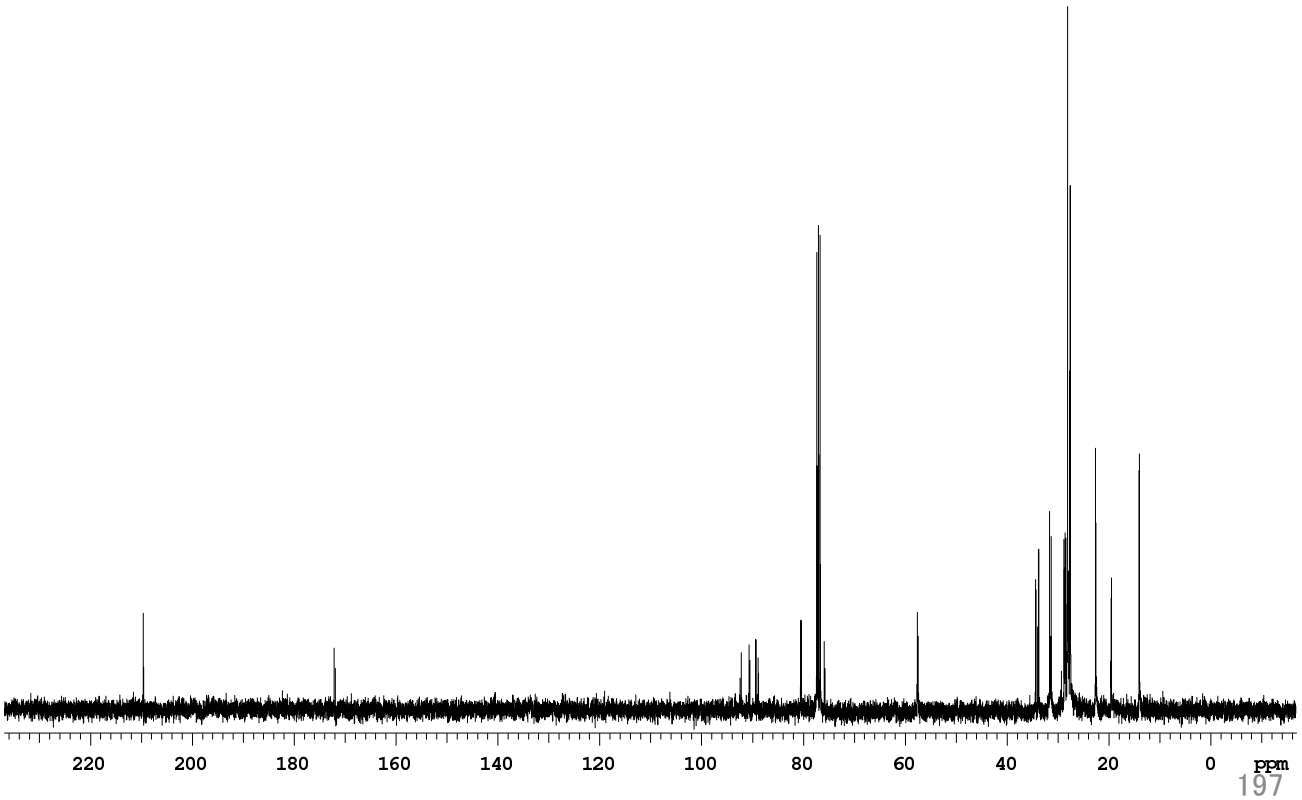
Chapter 3 Supporting Information

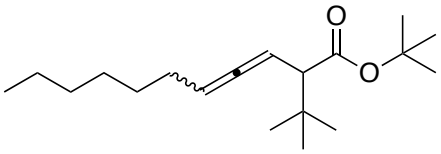
Iron-Mediated Three-Component Coupling Reaction between 2-Alken-4-ynoates, *tert*-Alkyl Grignard Reagent, and 1-Bromo-1-alkyne



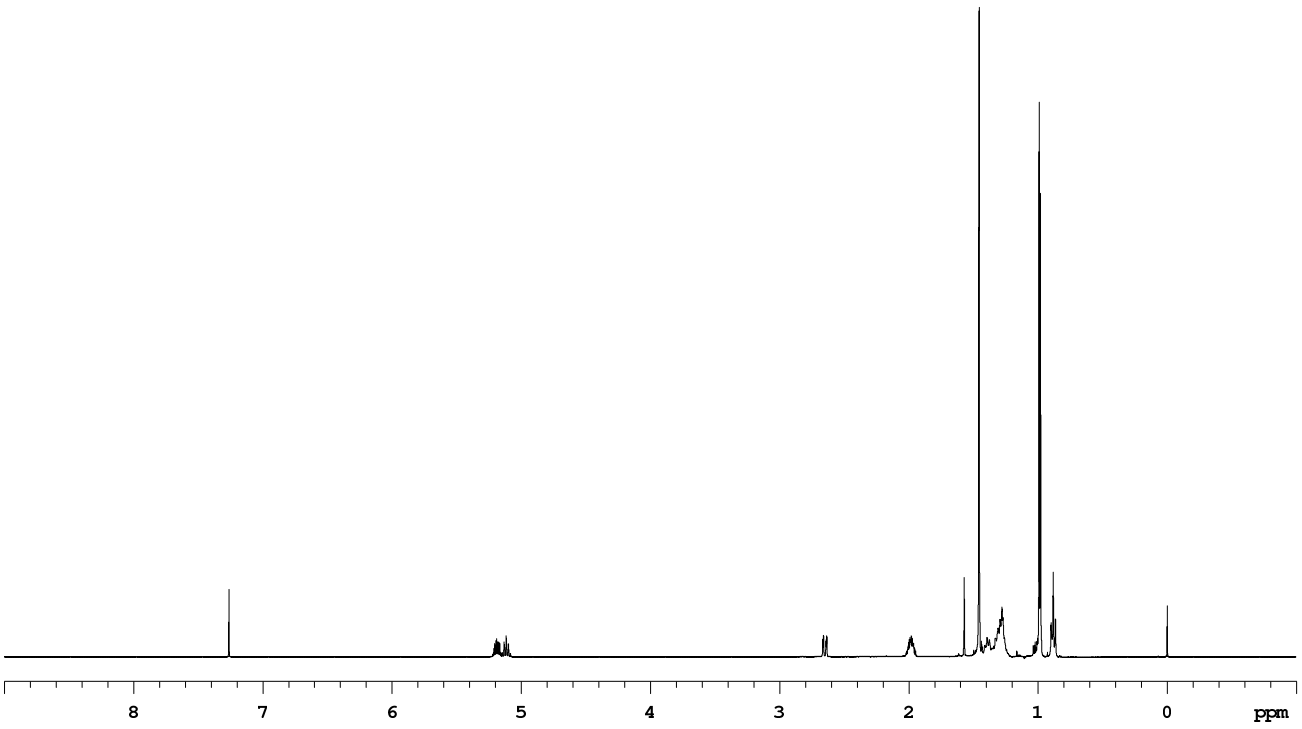
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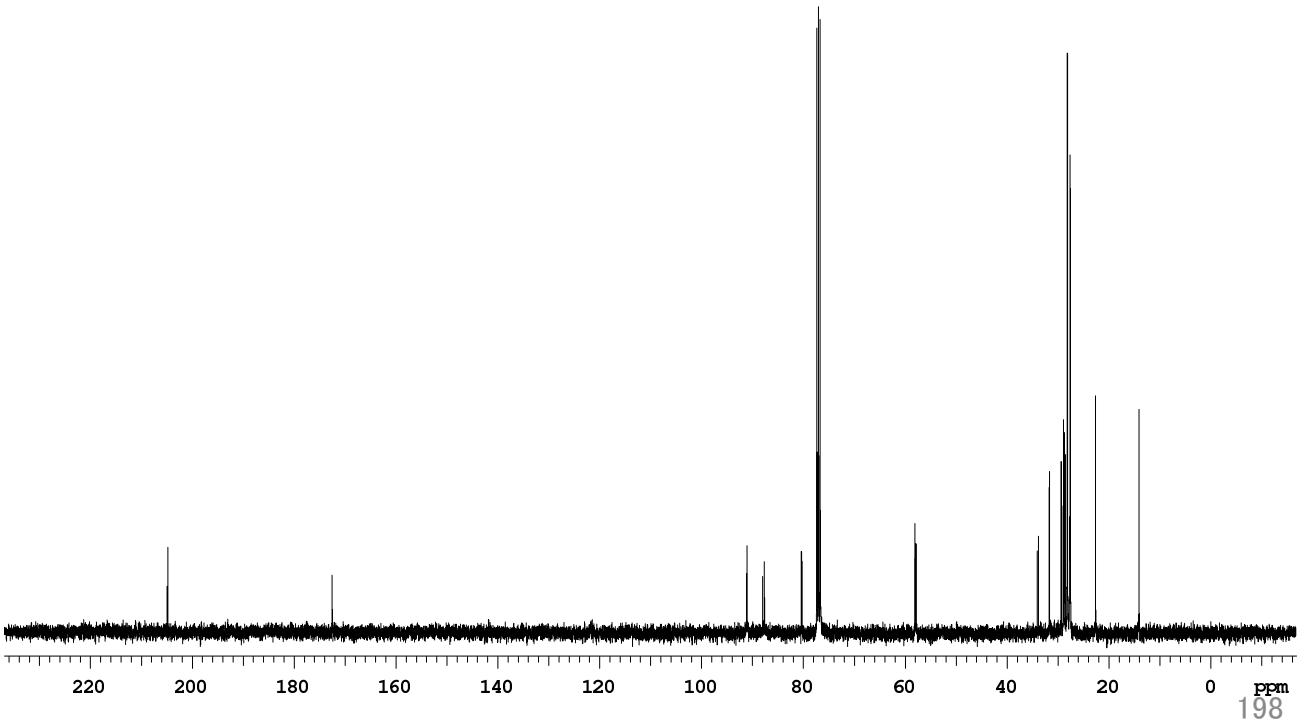


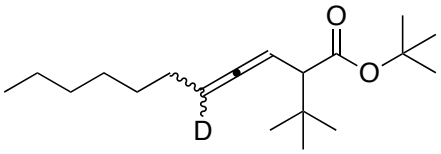




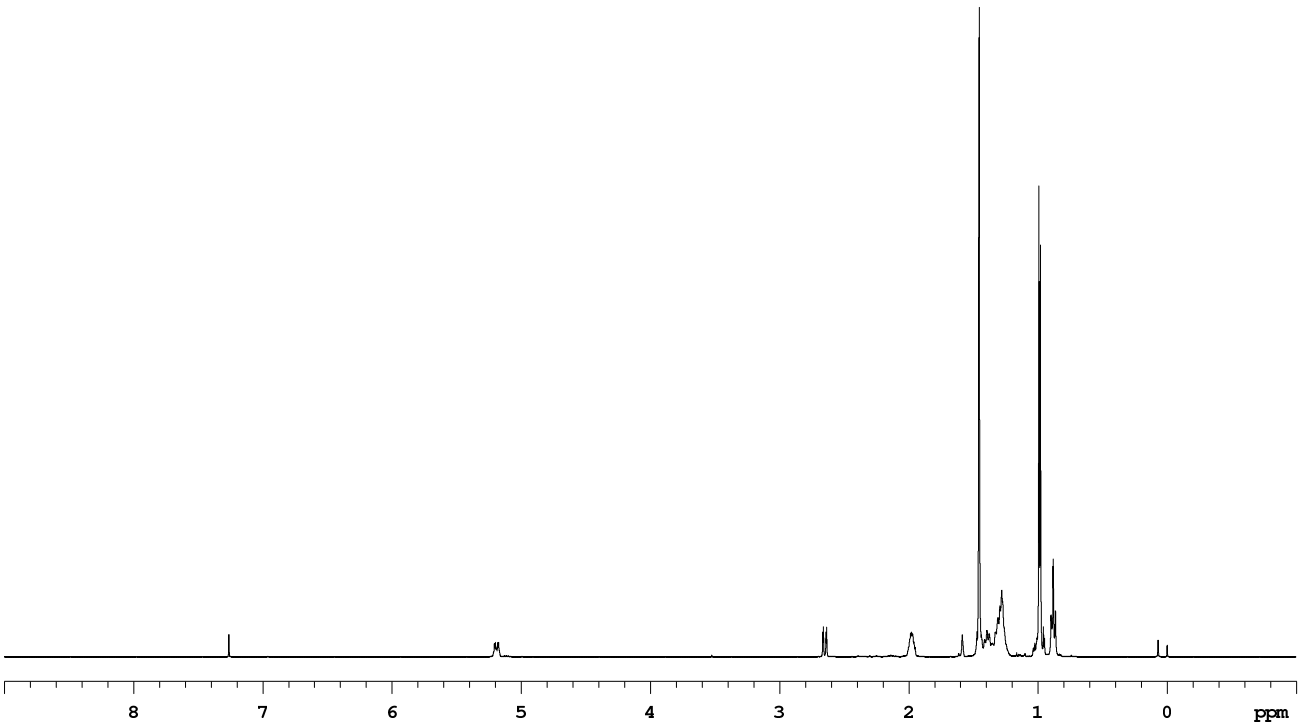
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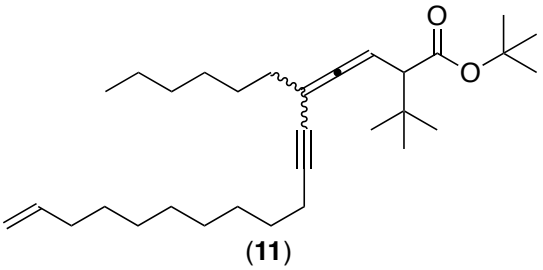




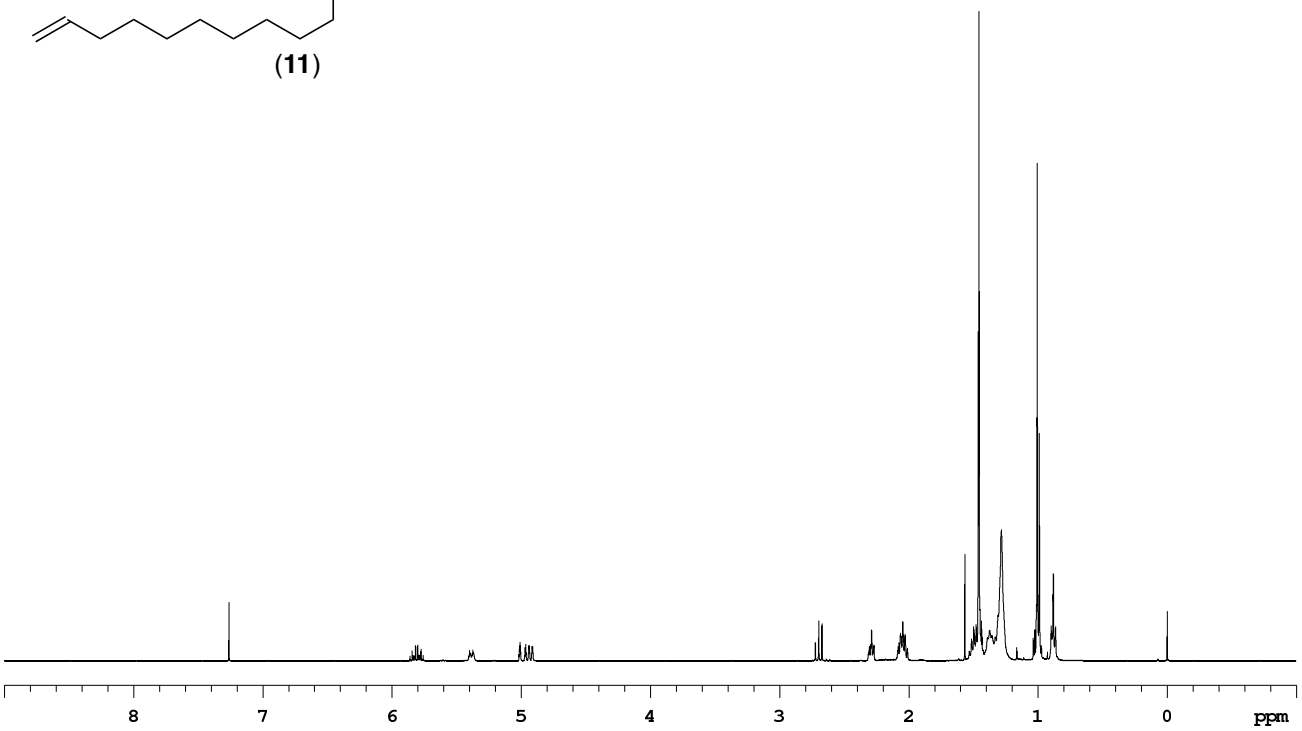


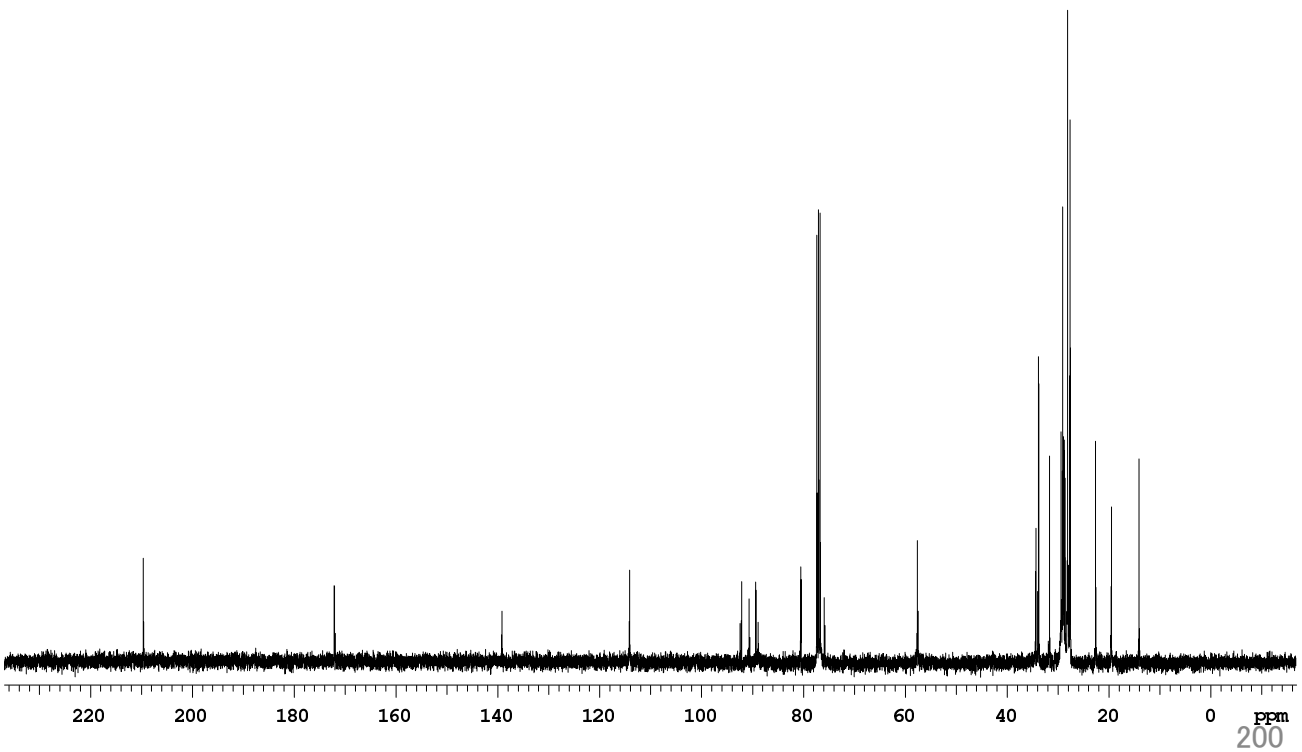
(**4**-*d*)

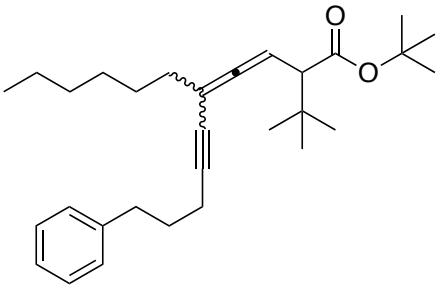




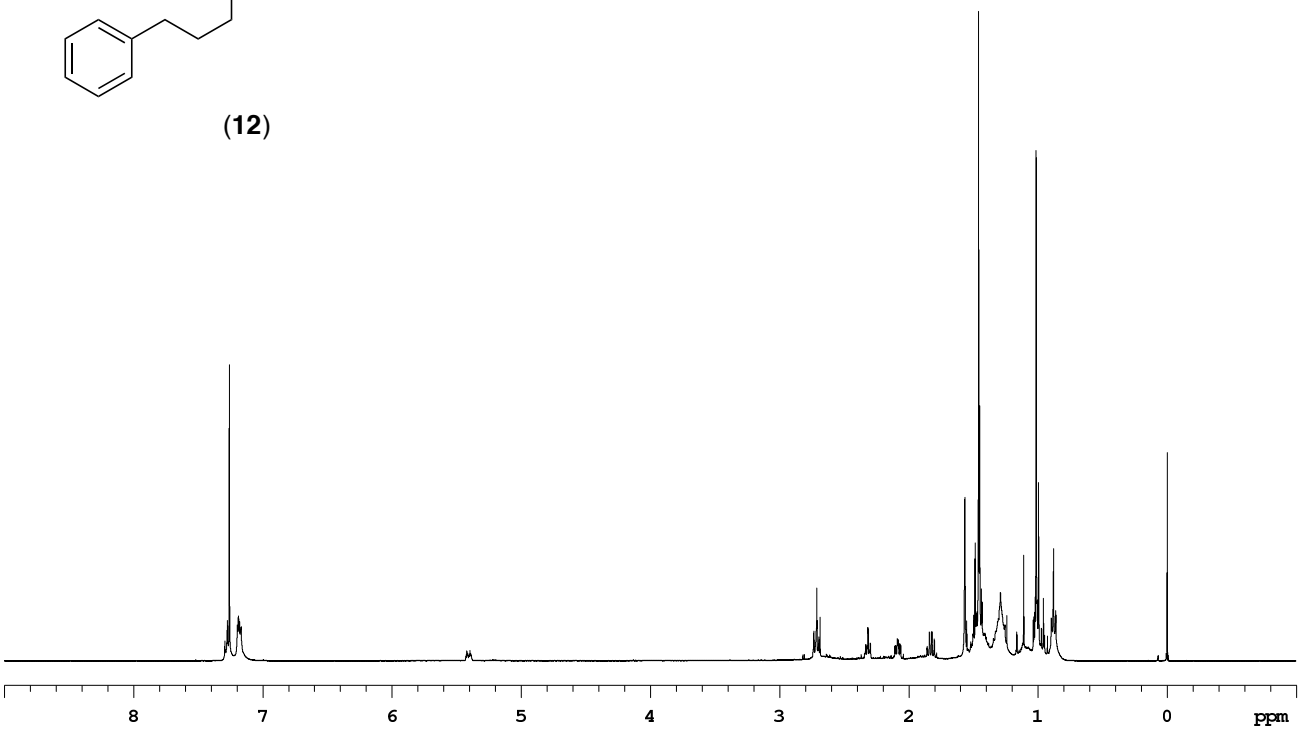
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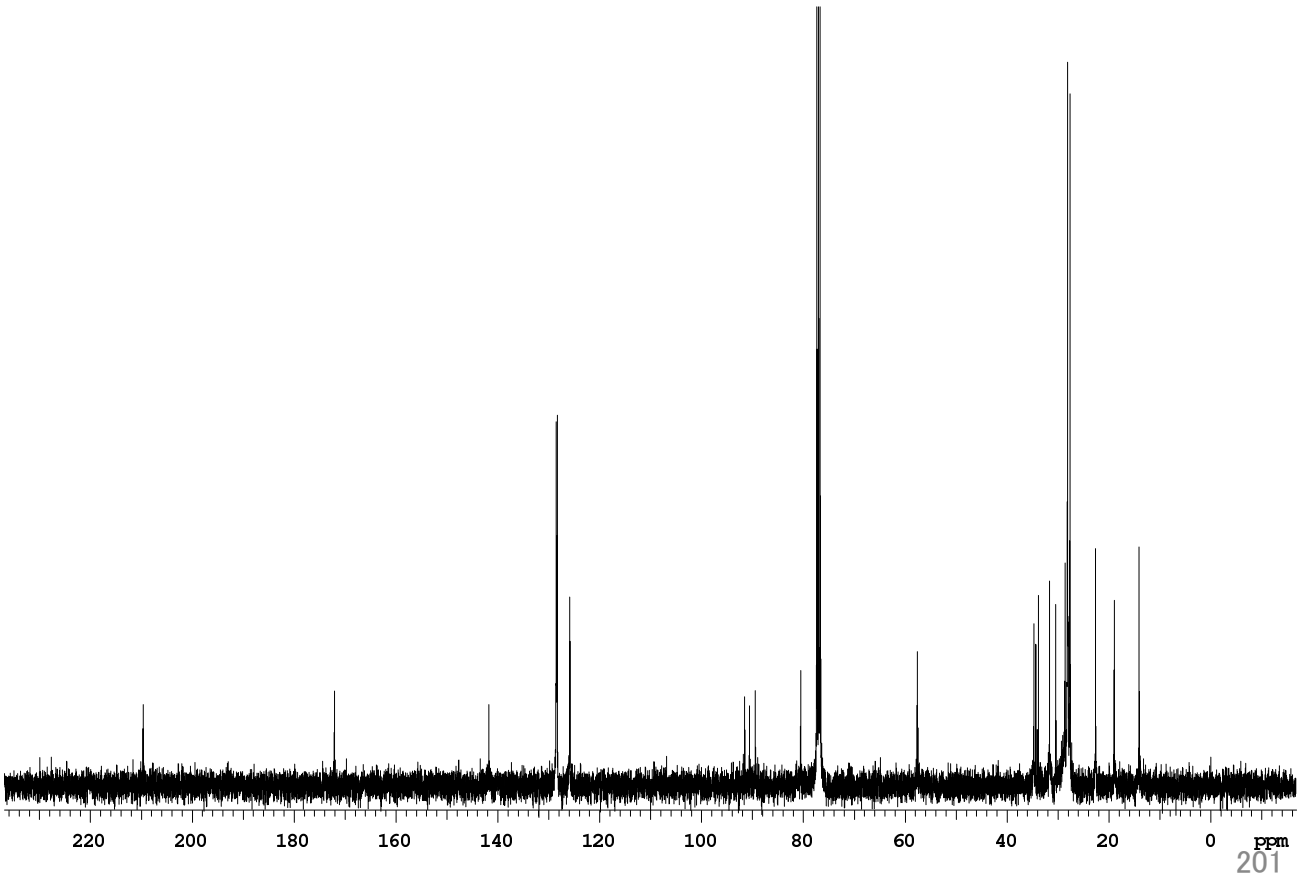


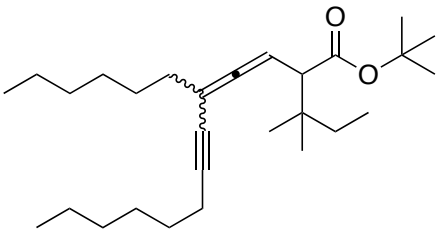




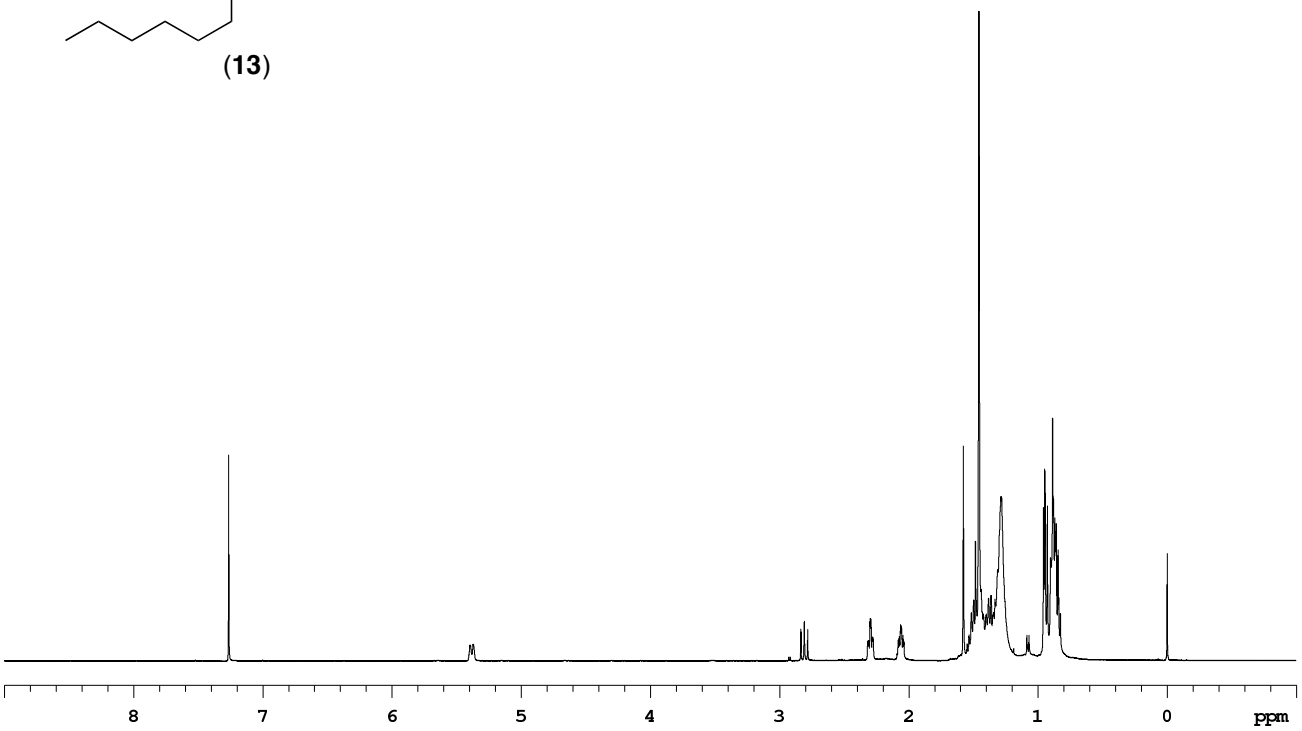
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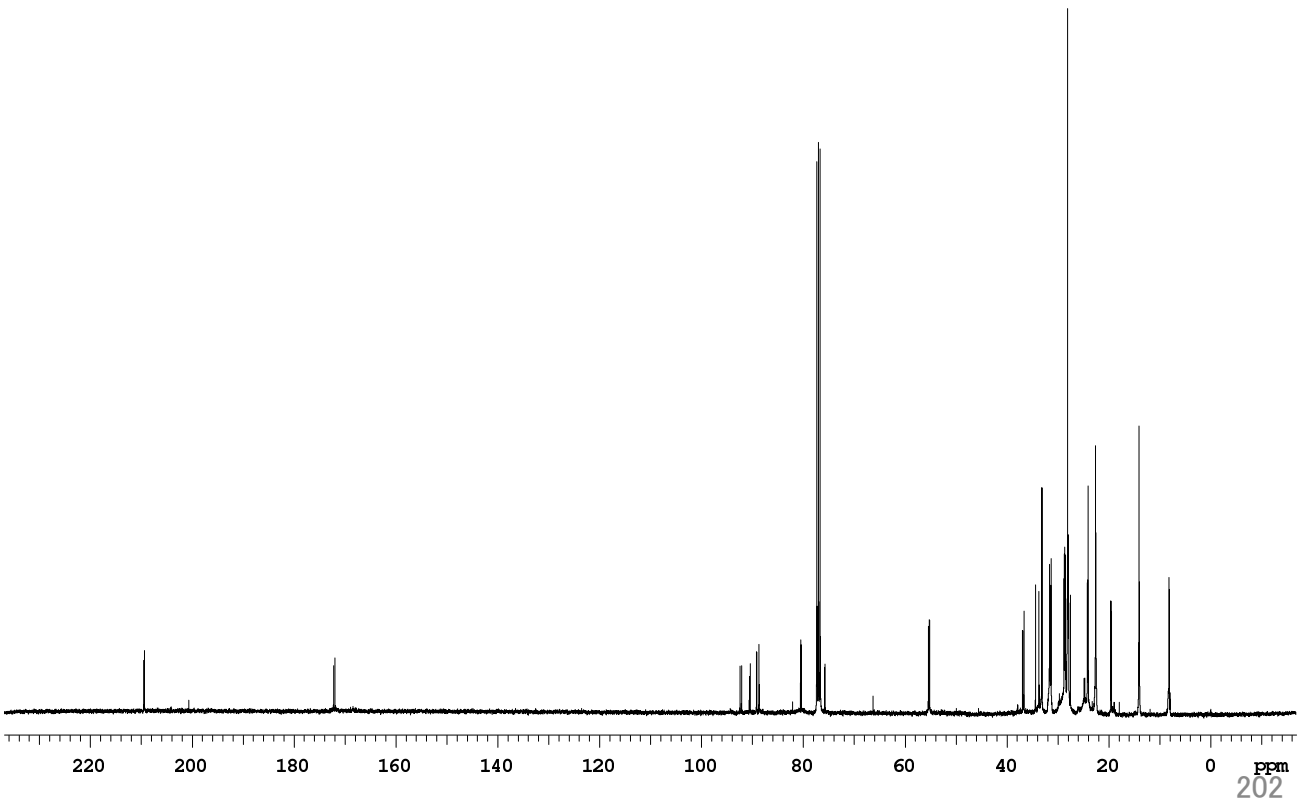


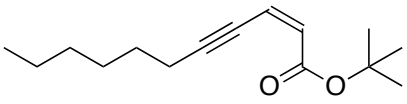




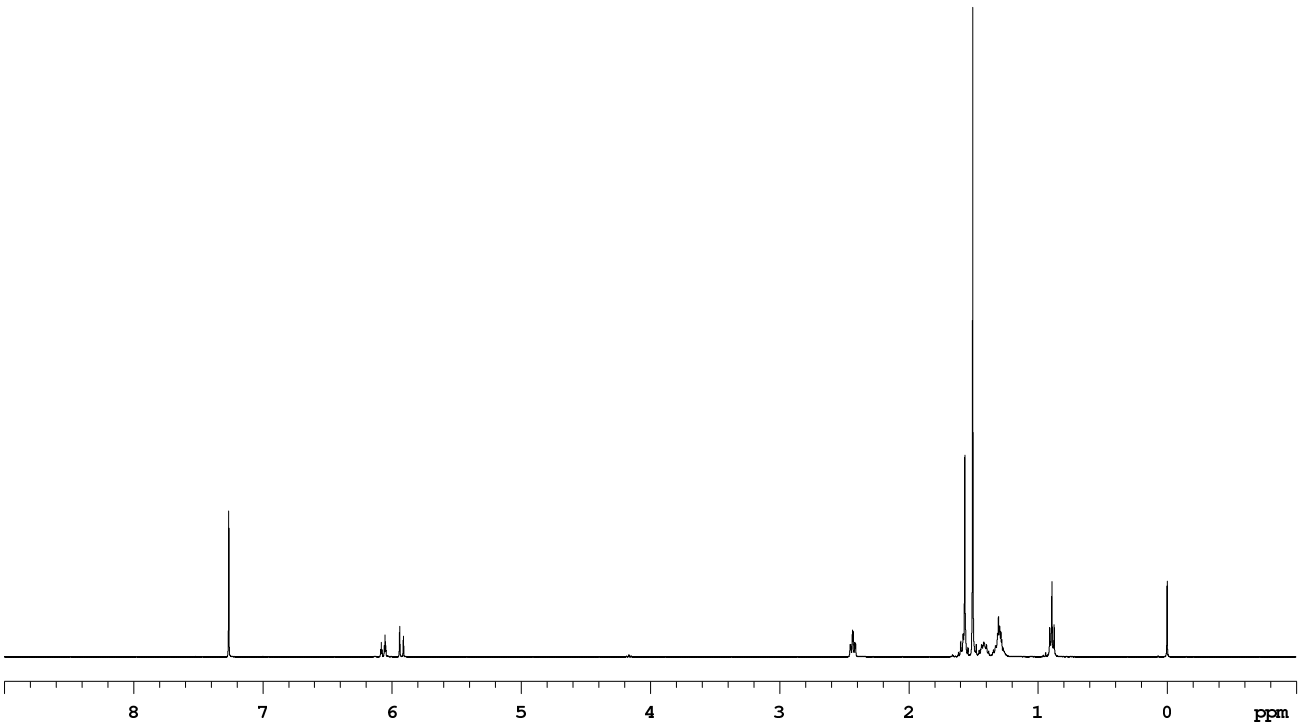
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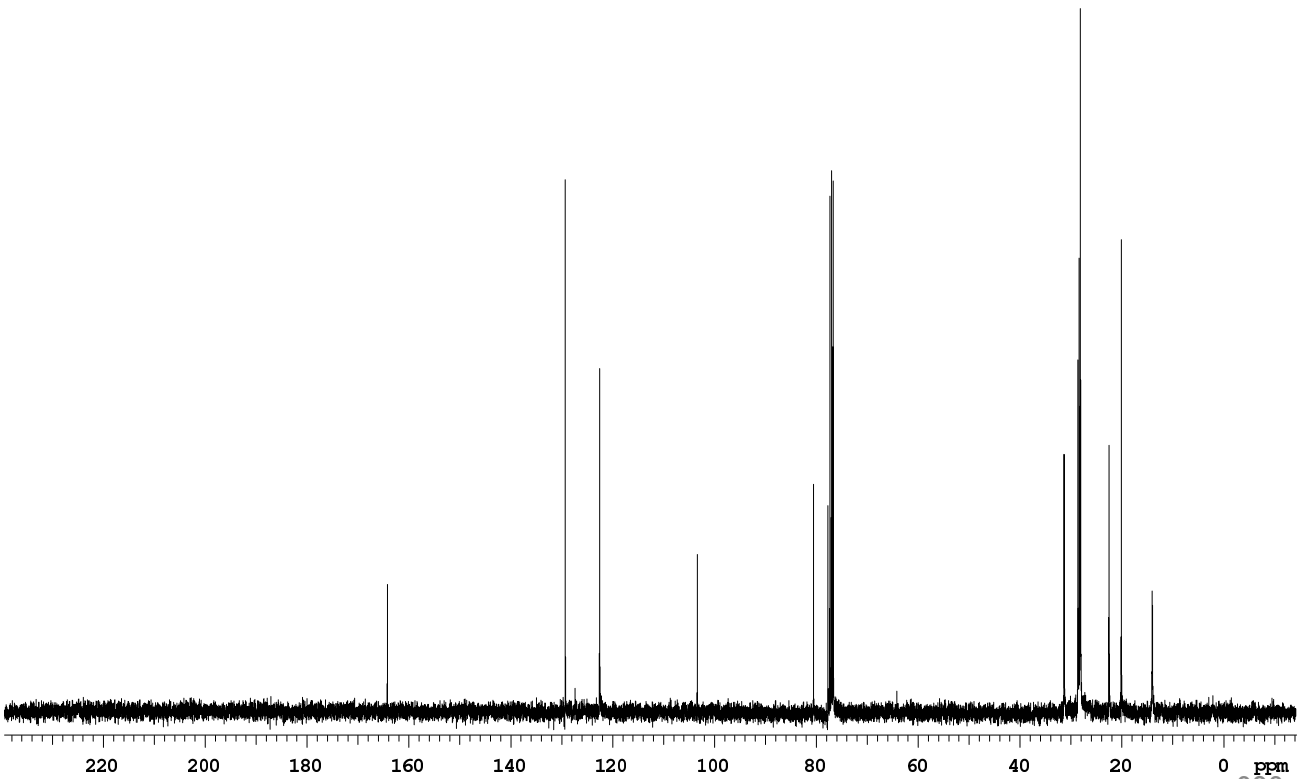


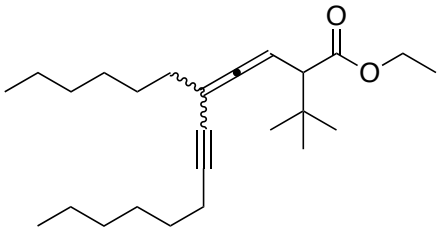




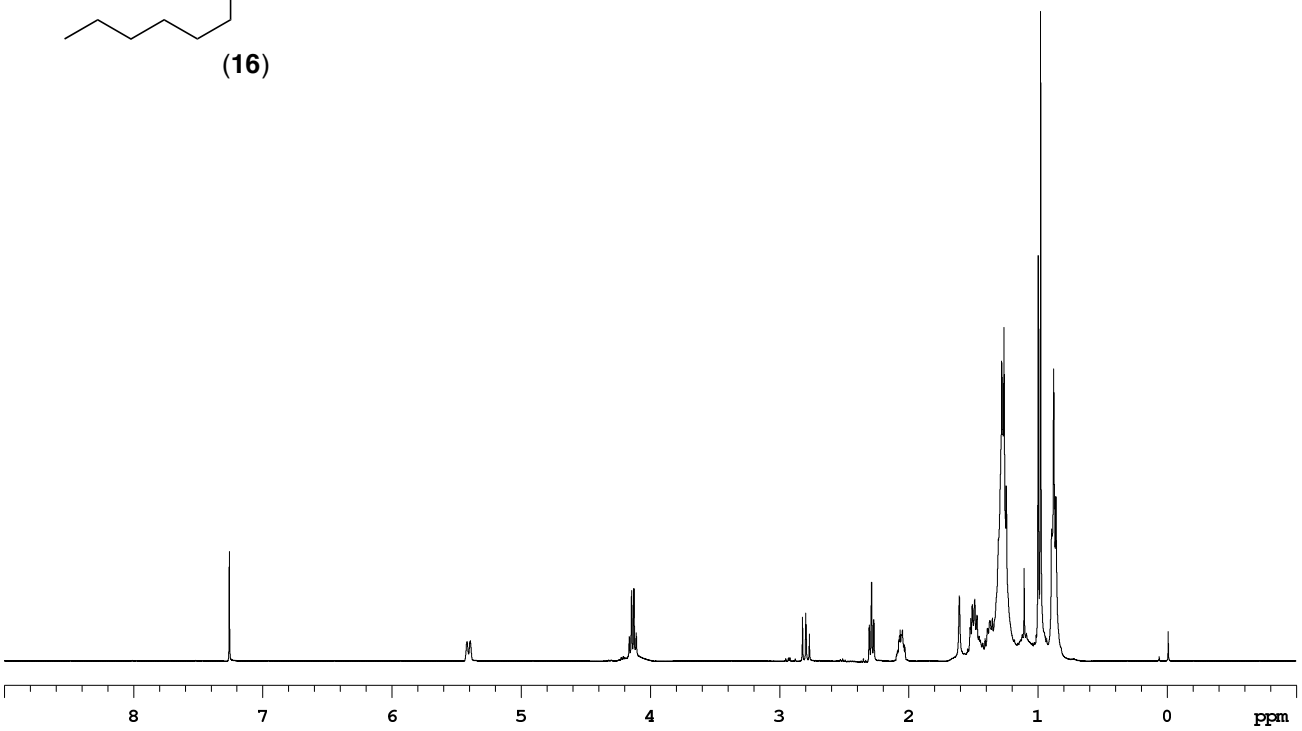
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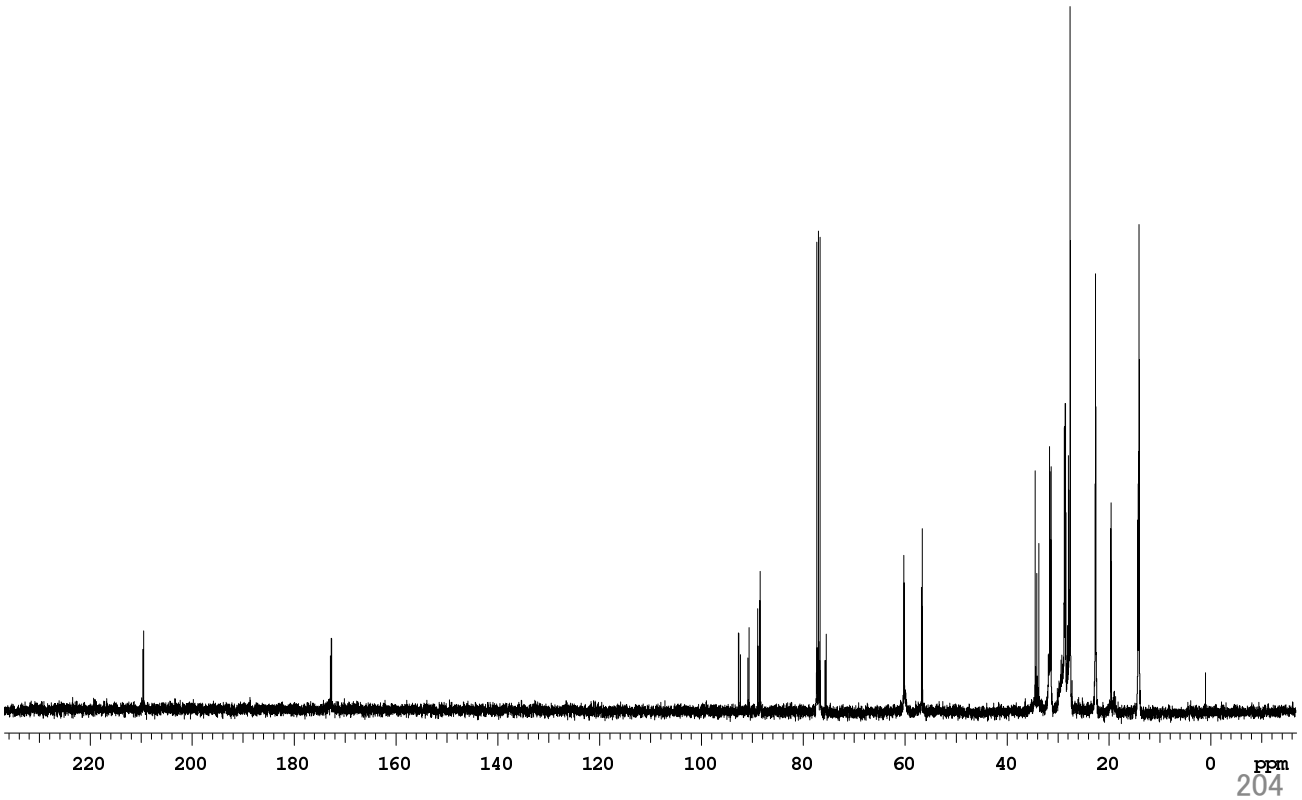


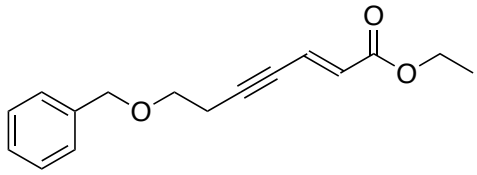




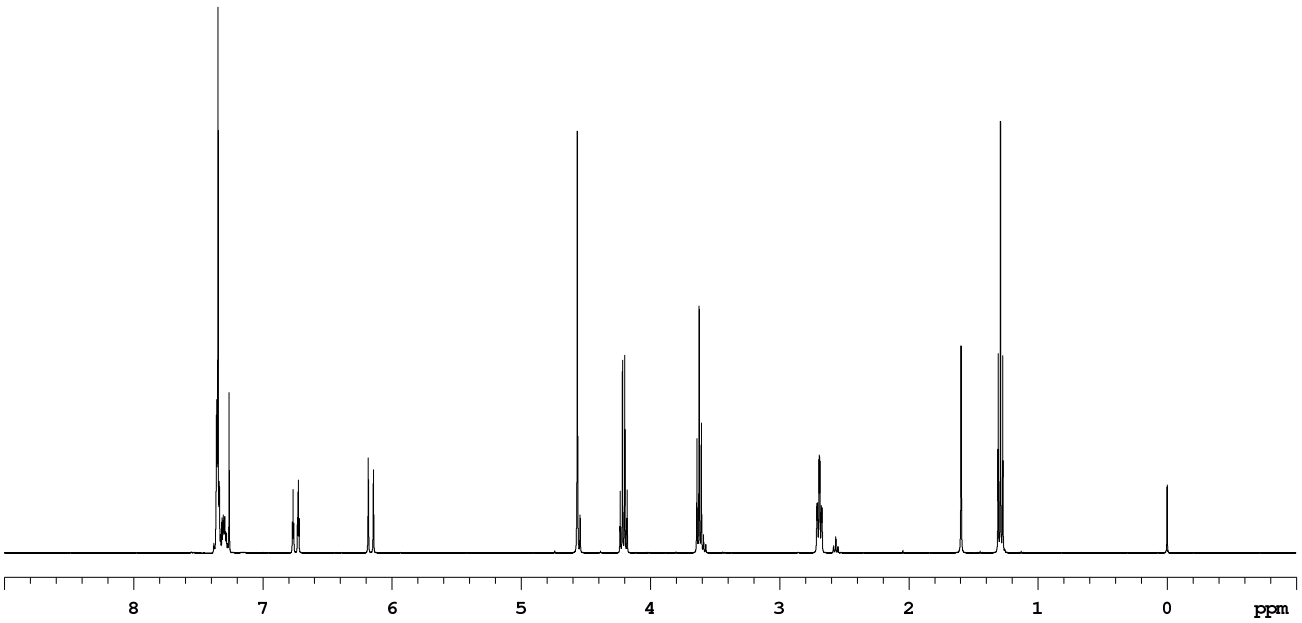
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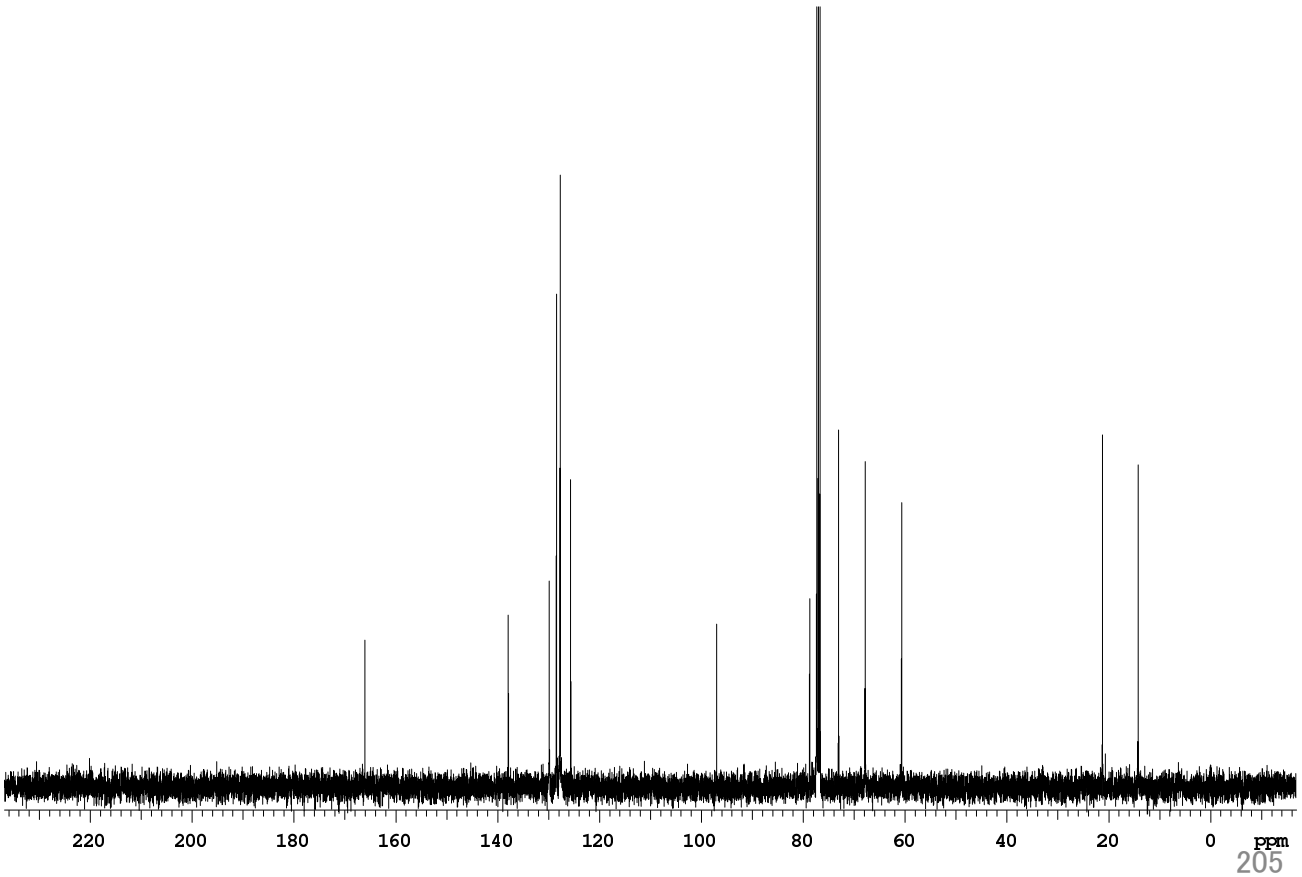


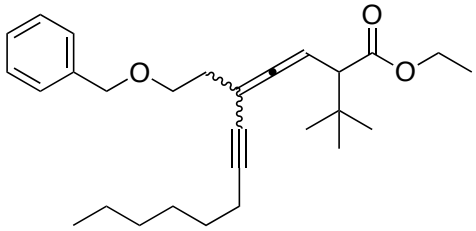




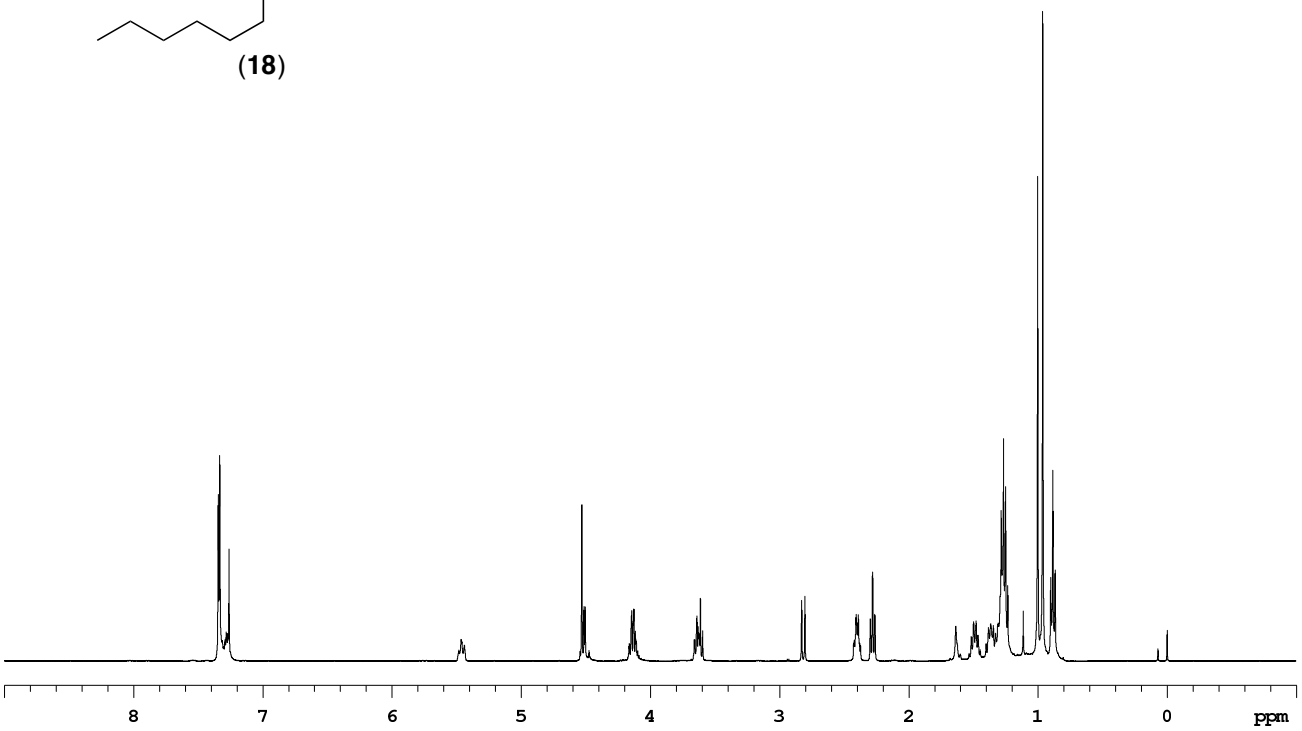
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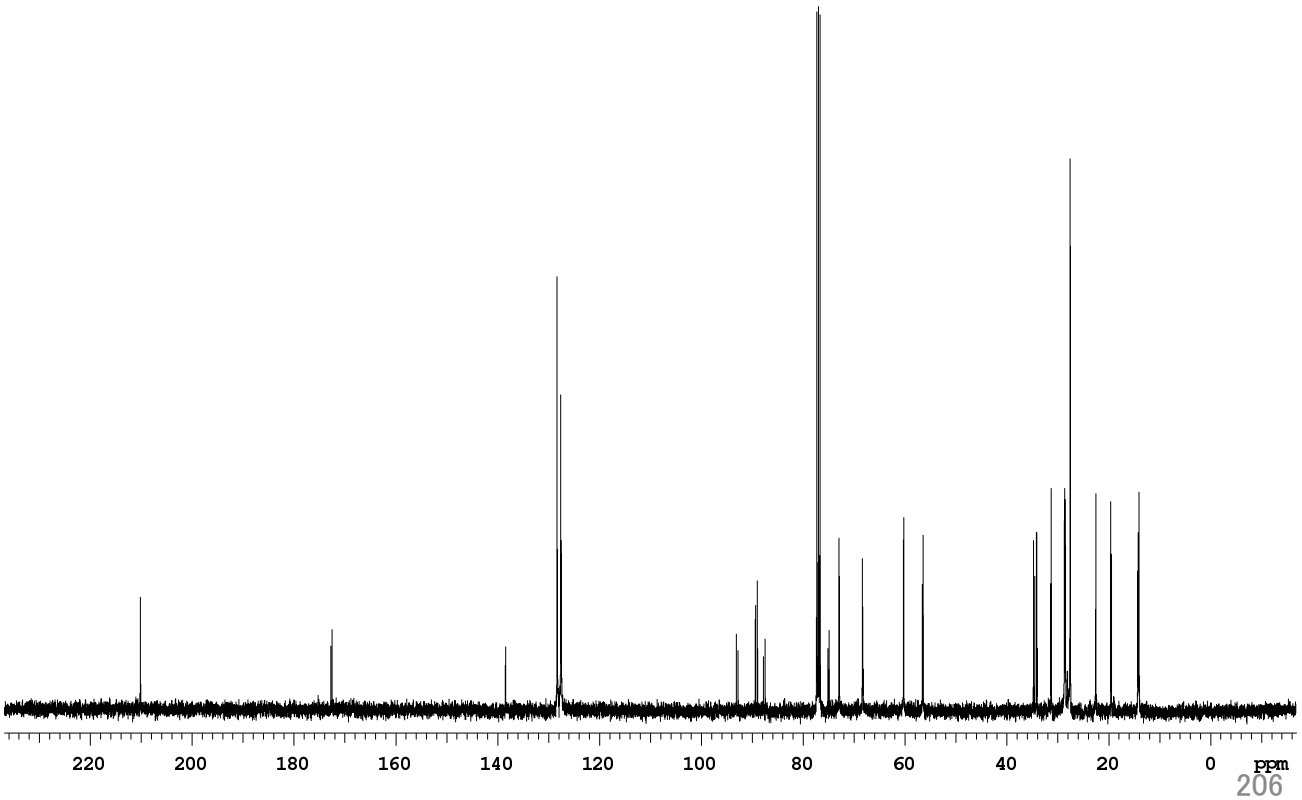


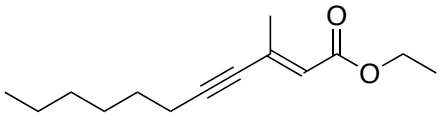




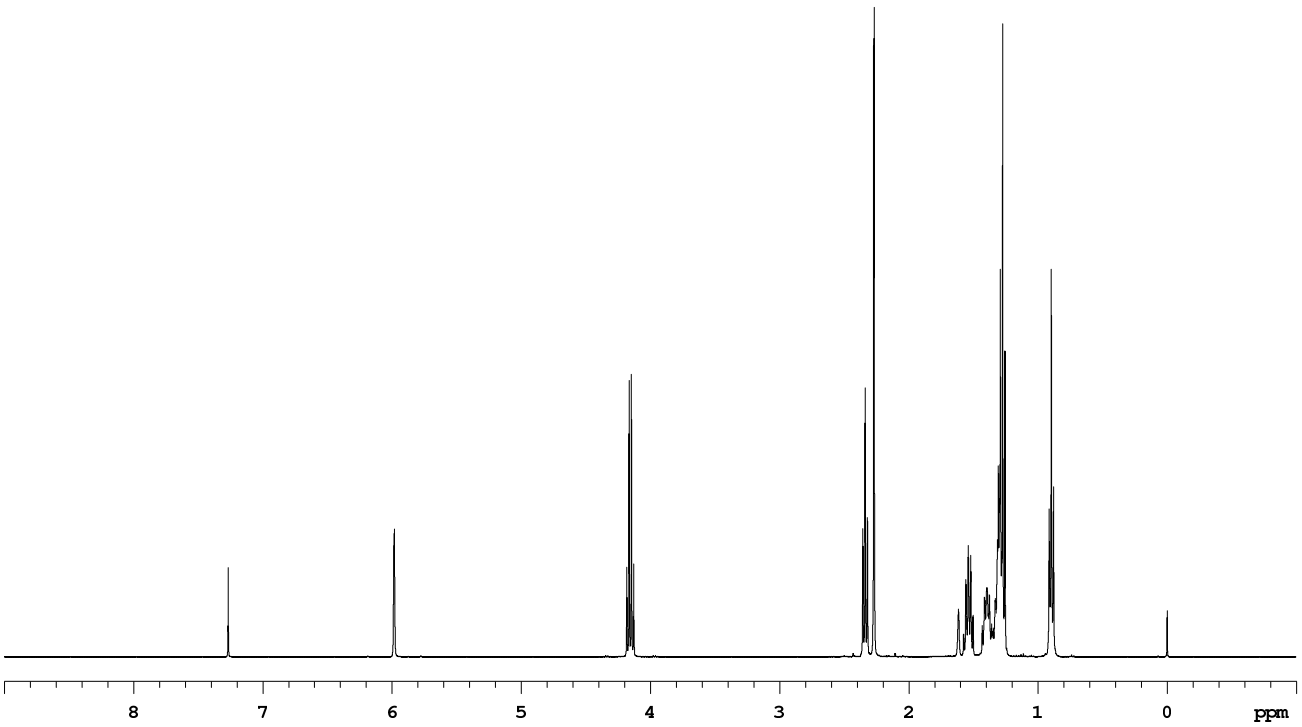
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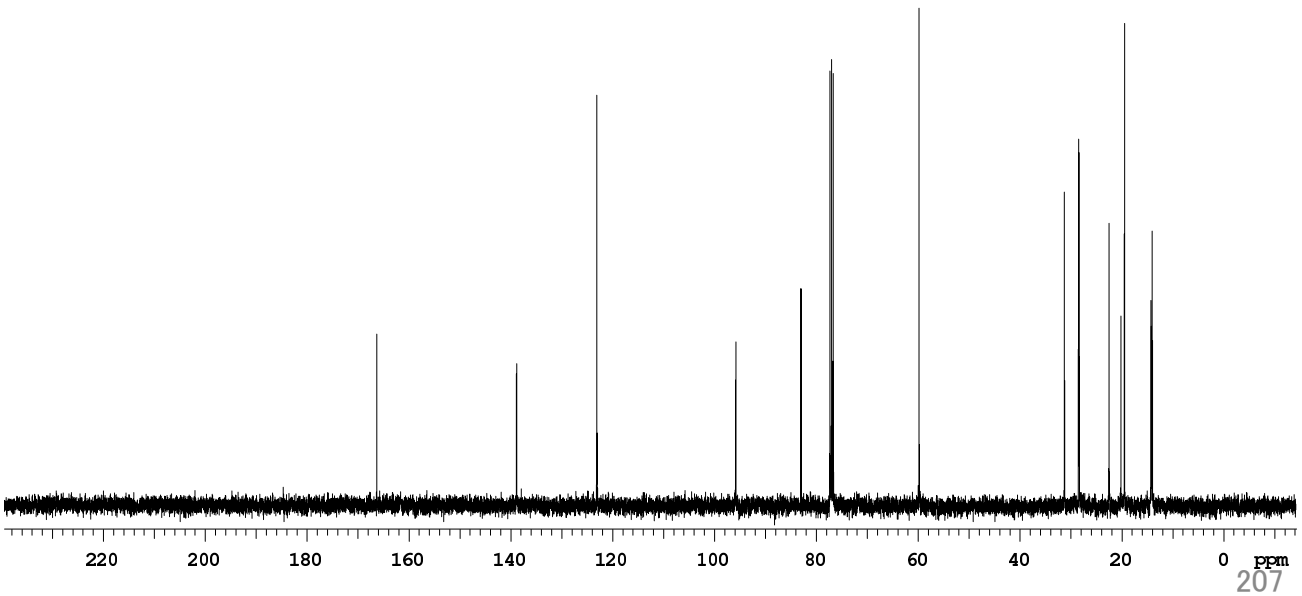


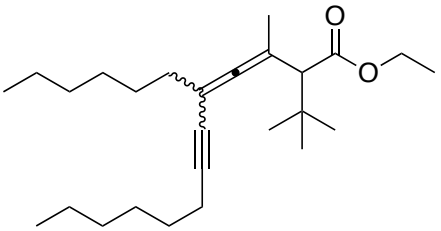




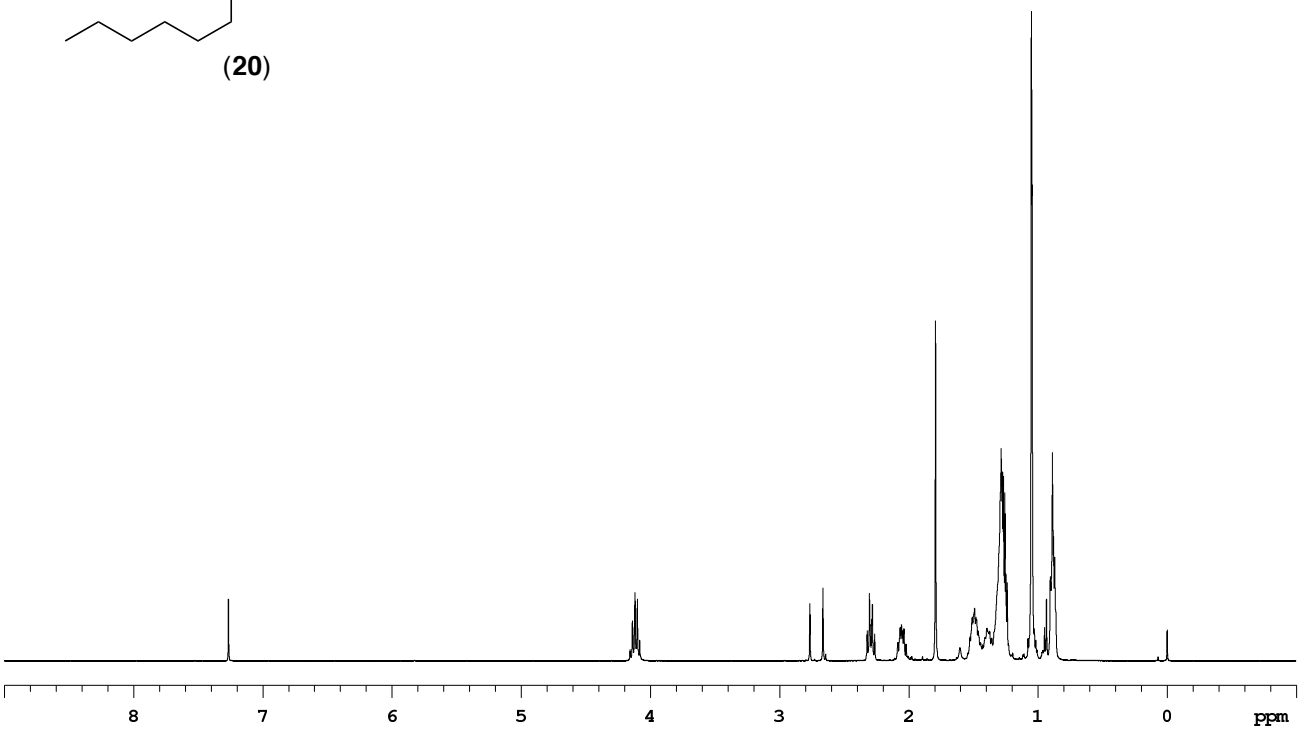
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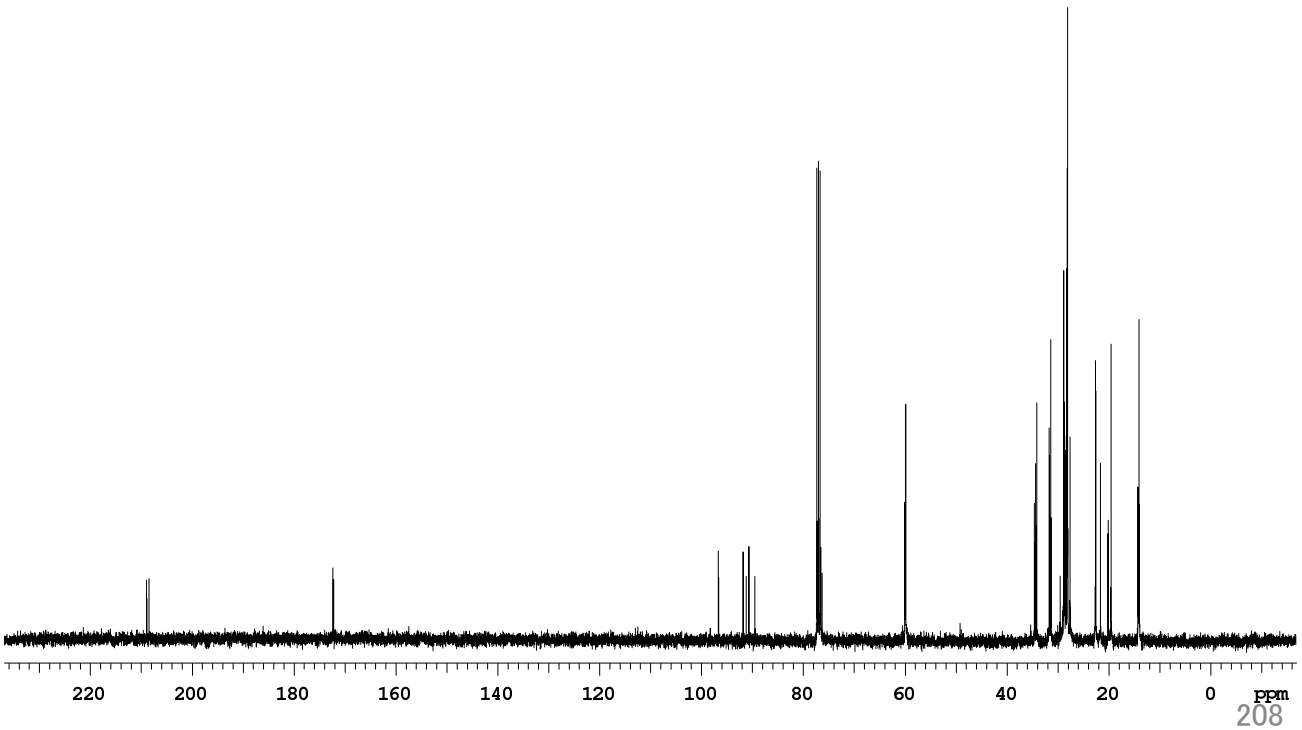


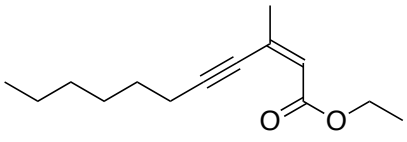




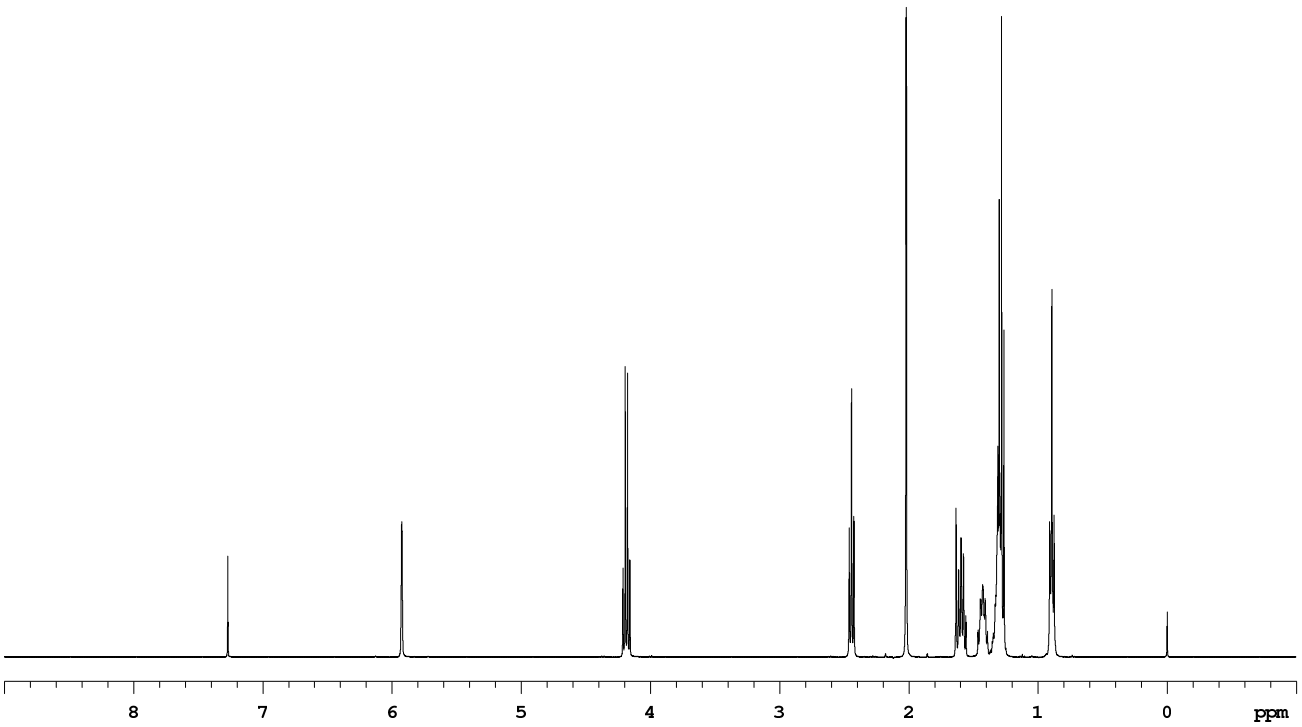
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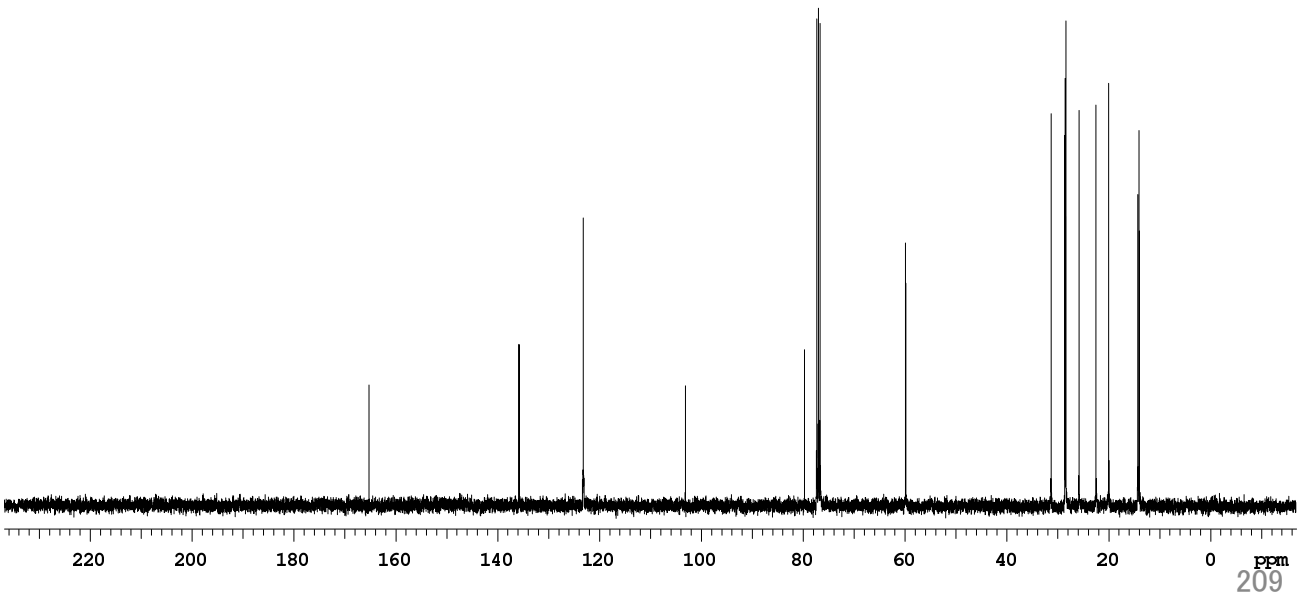


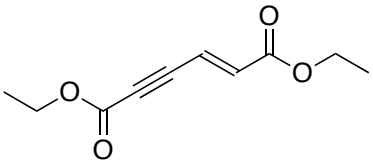




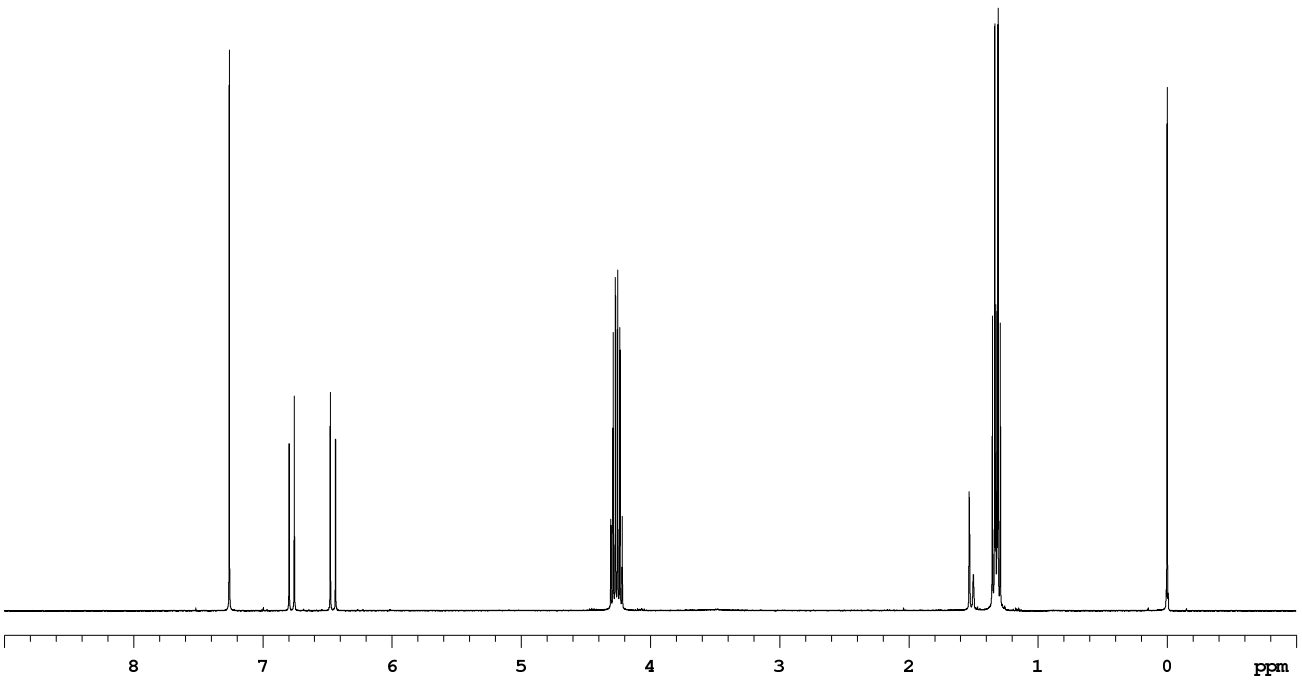
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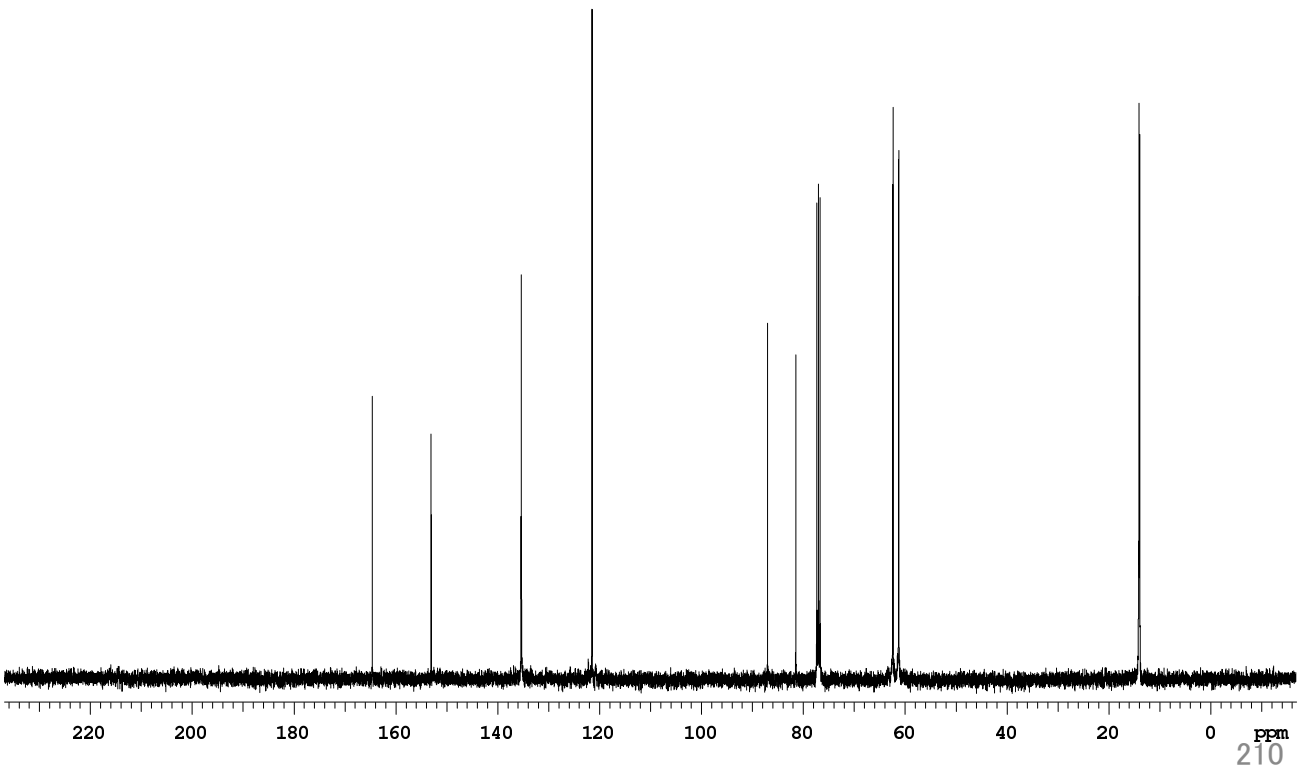


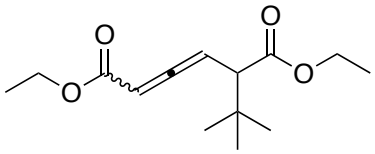




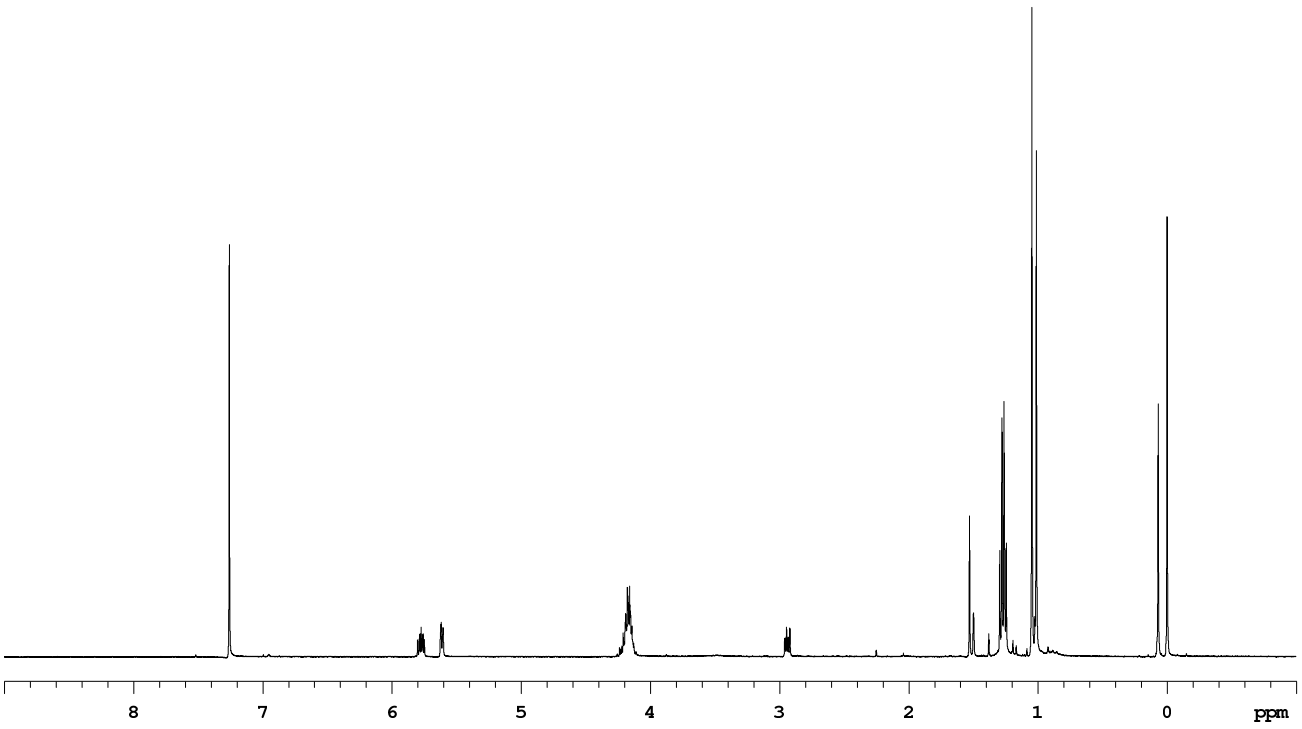
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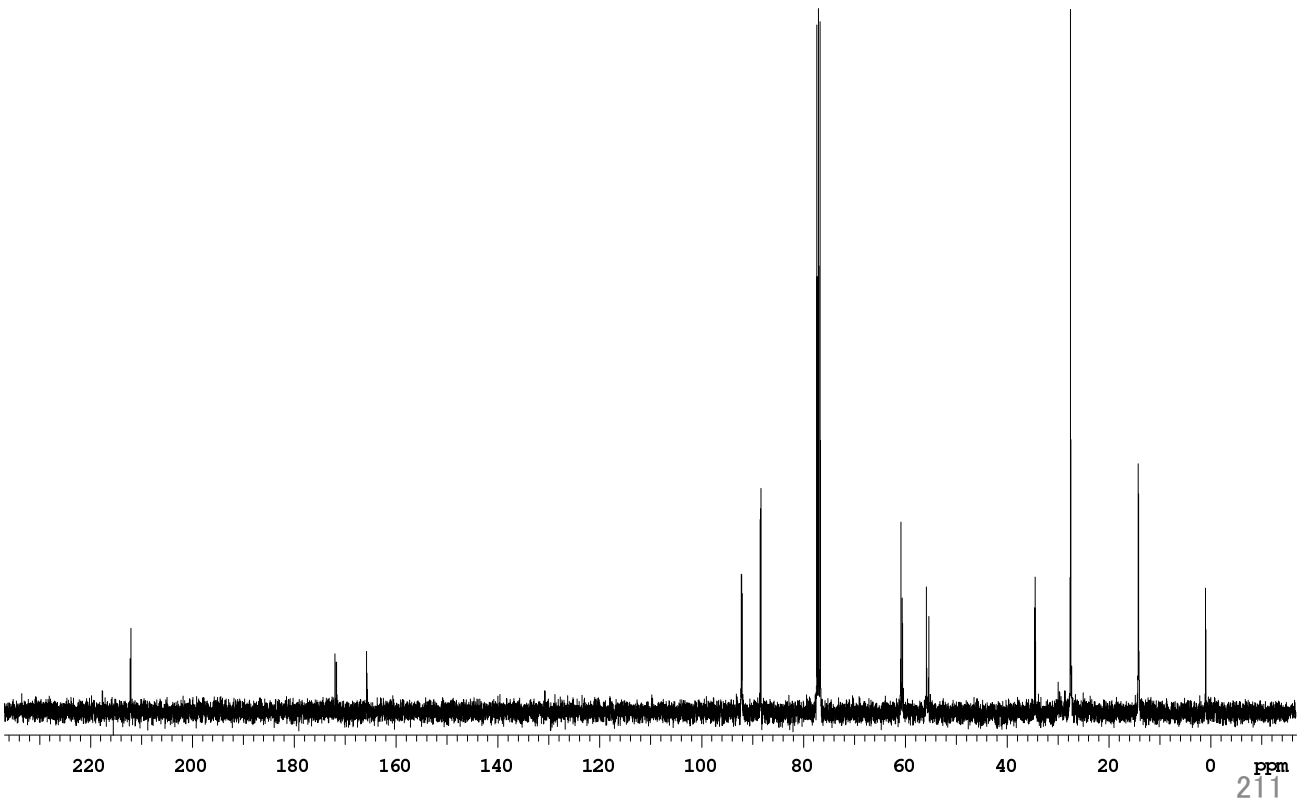


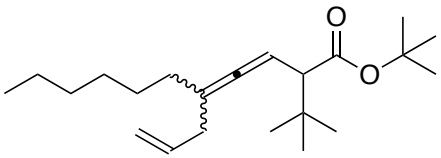




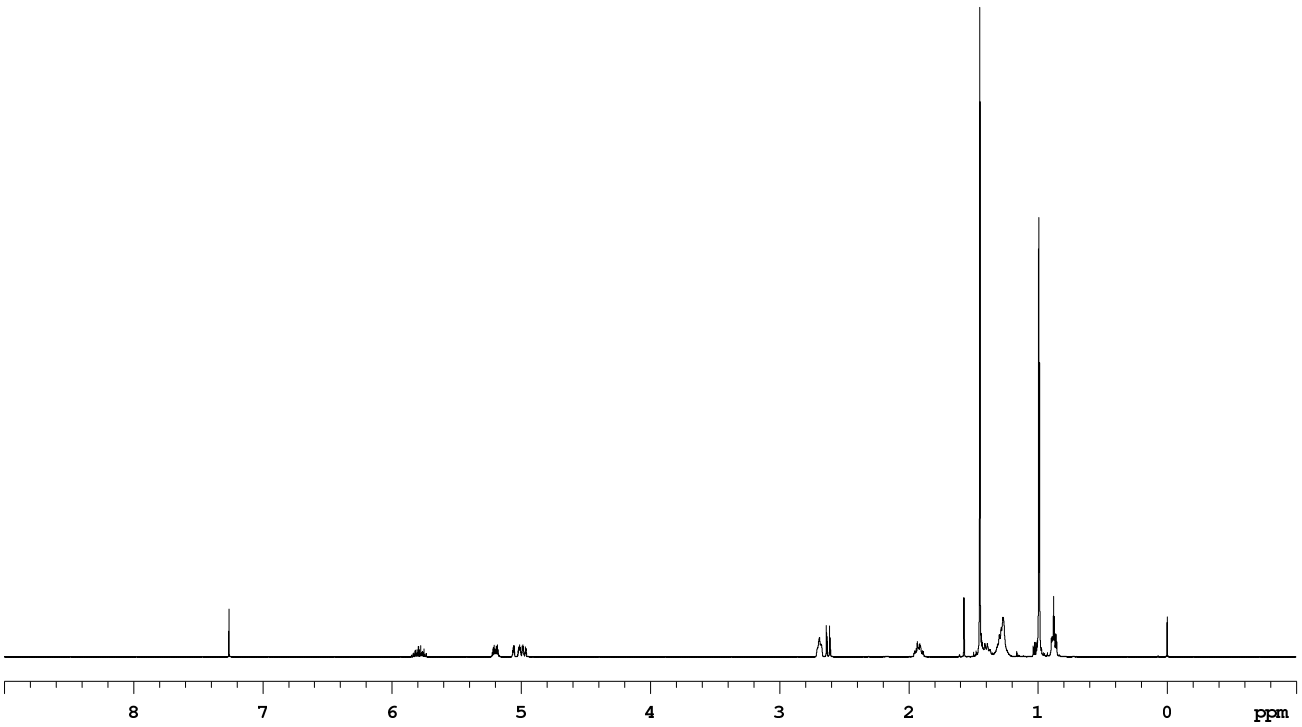
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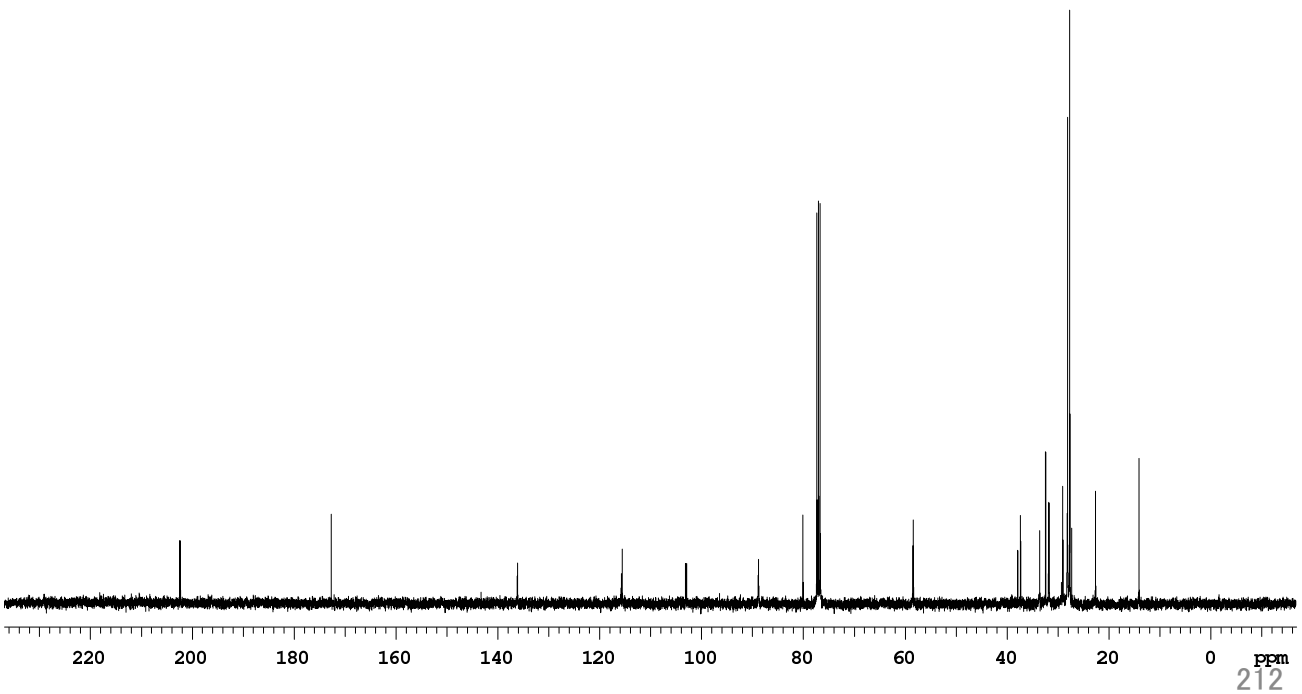


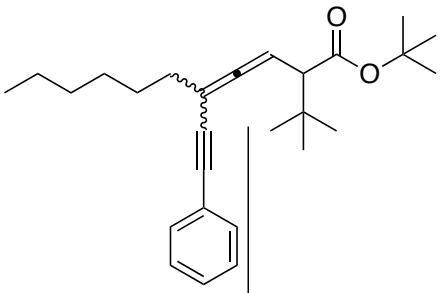




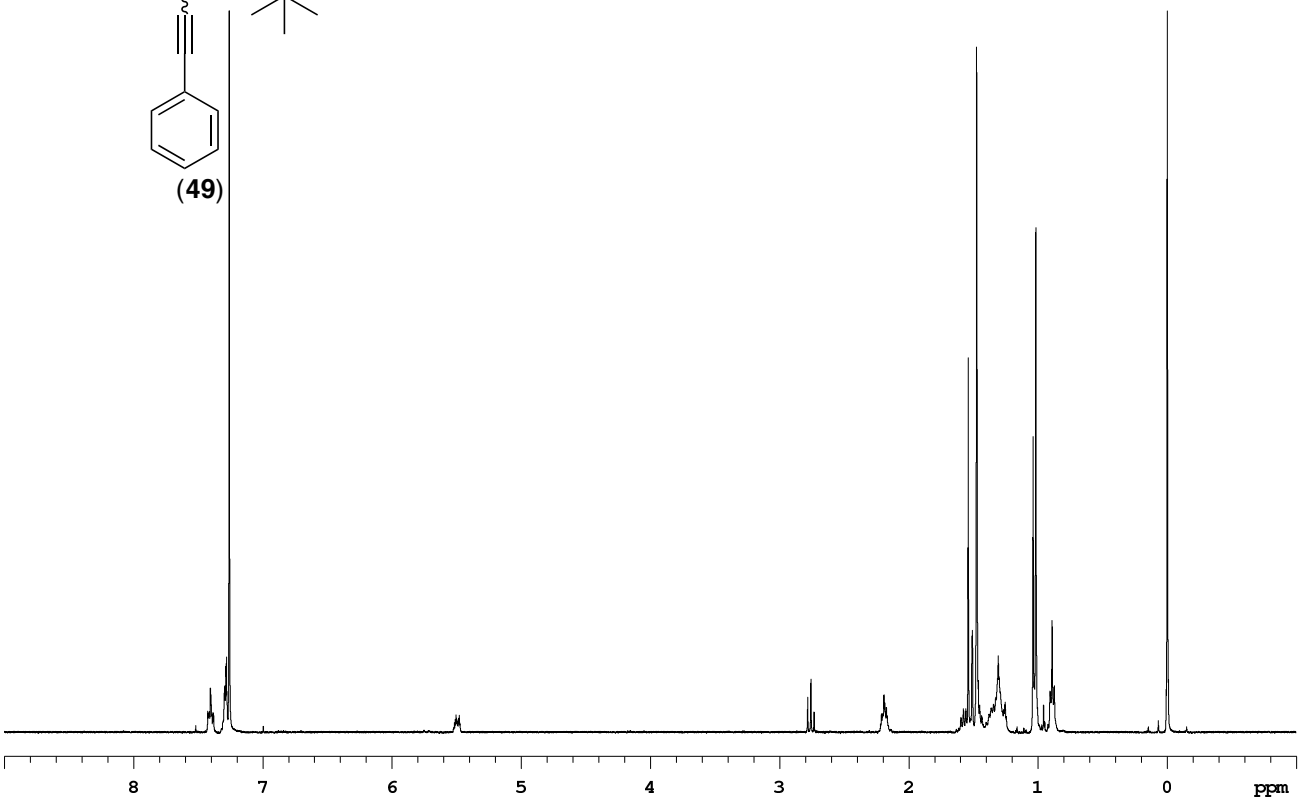
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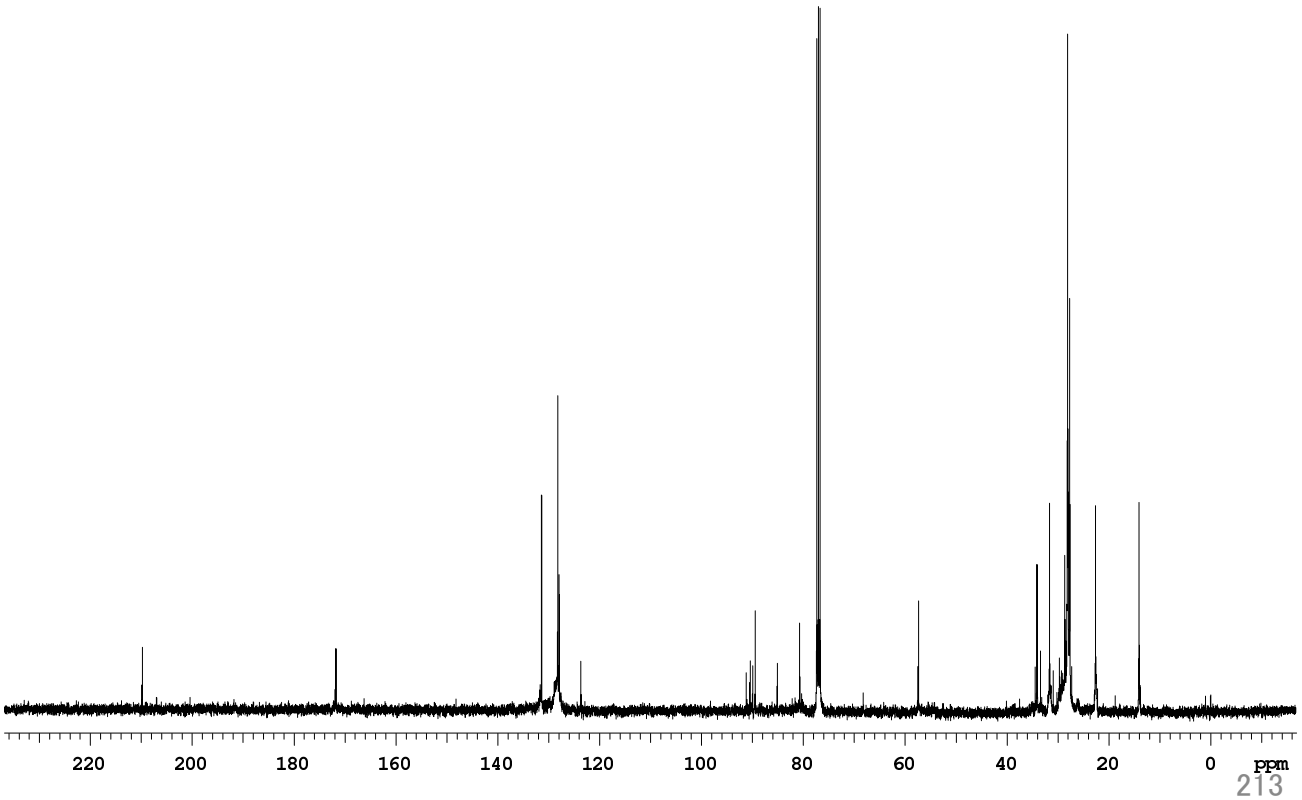


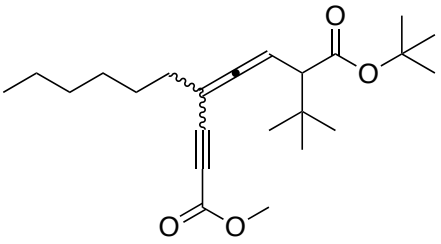




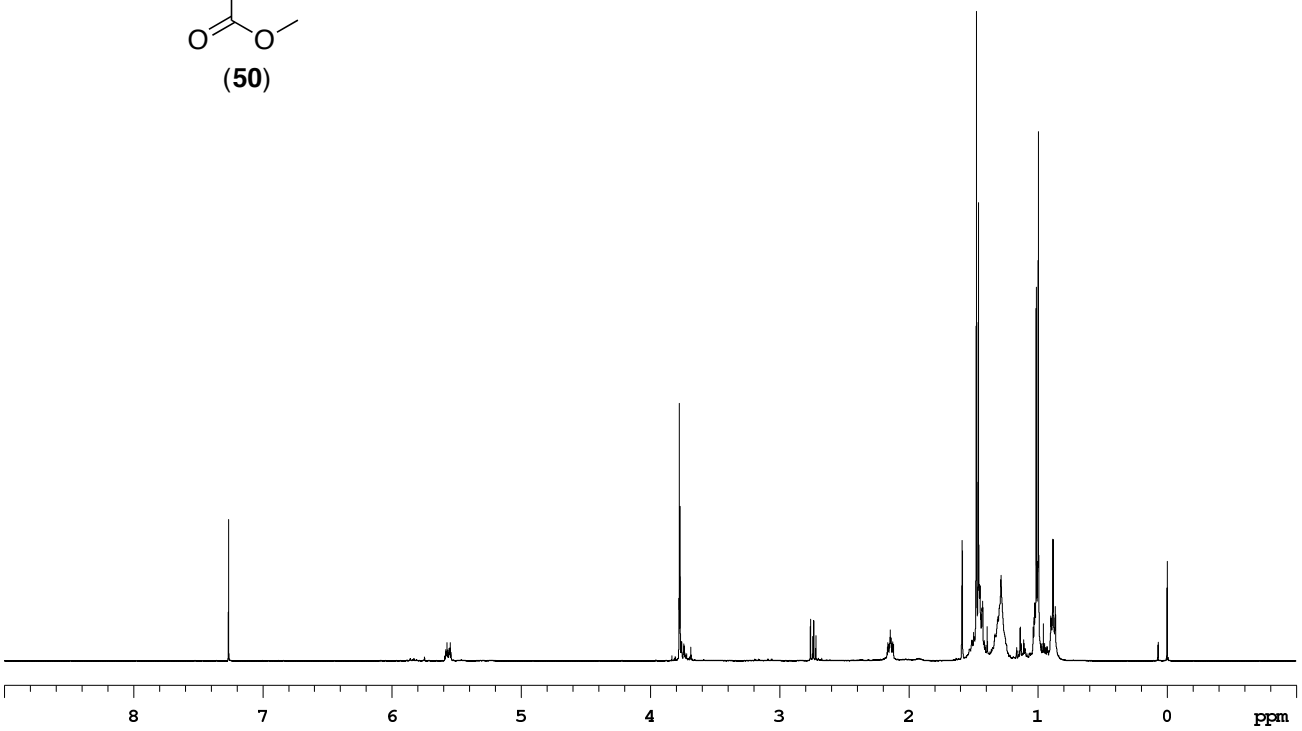
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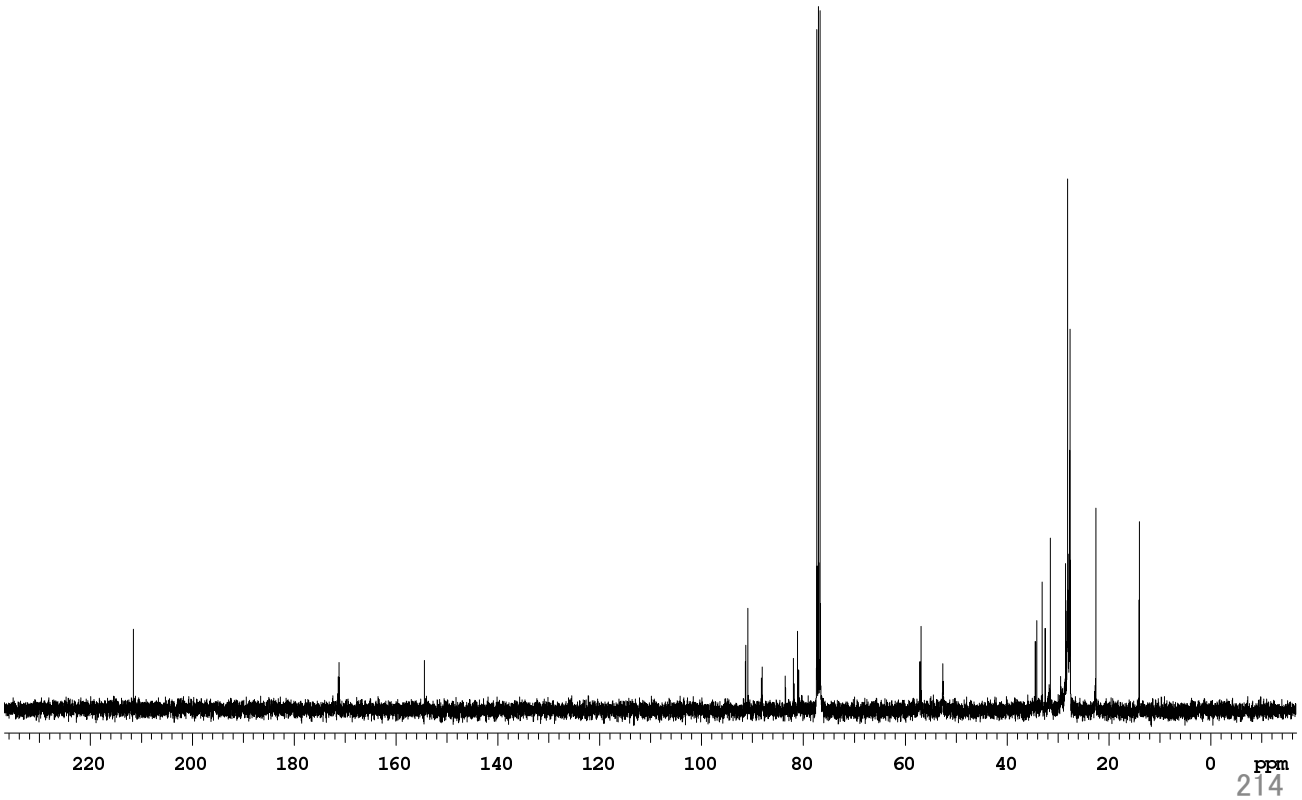


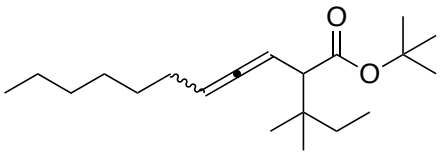




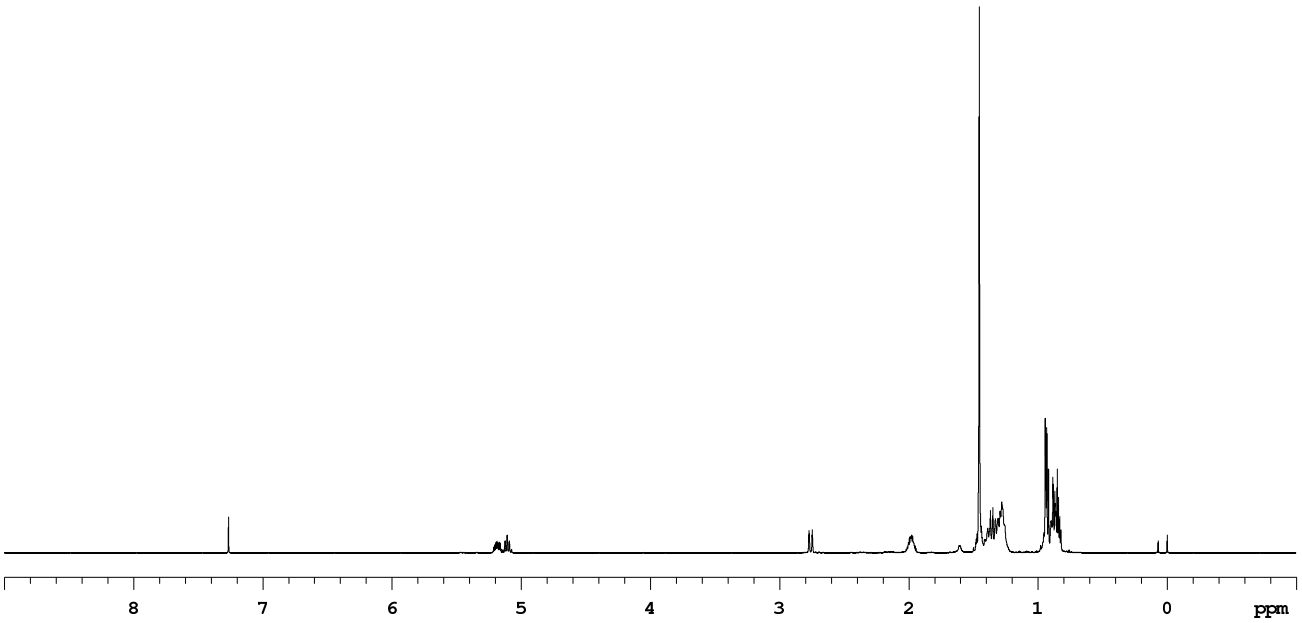
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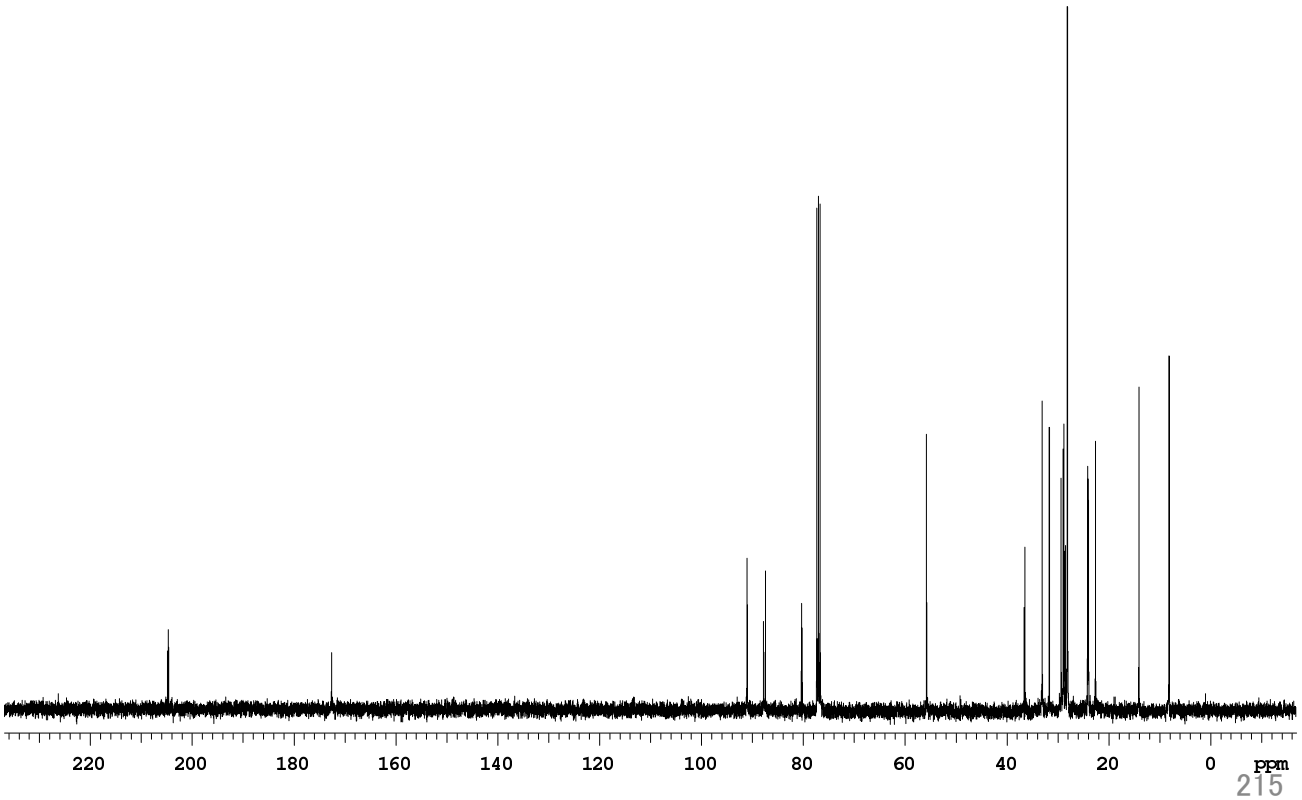


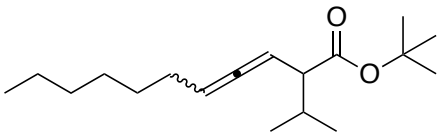




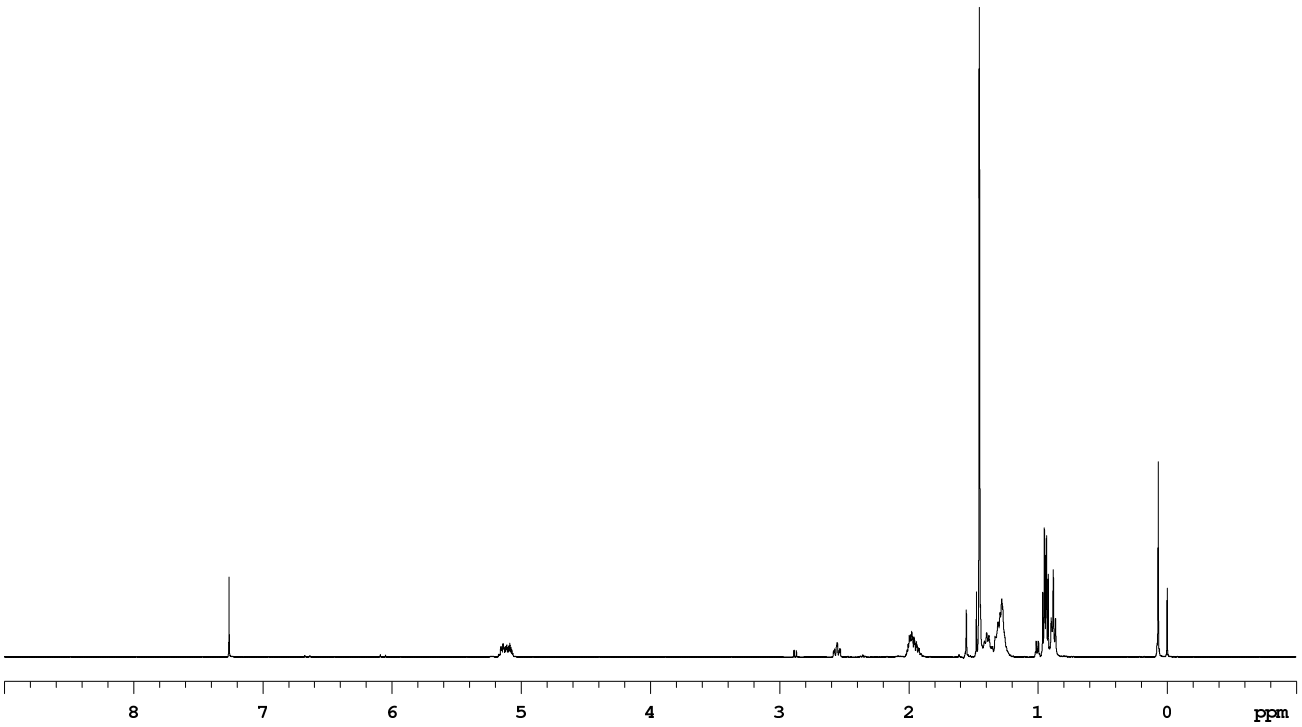
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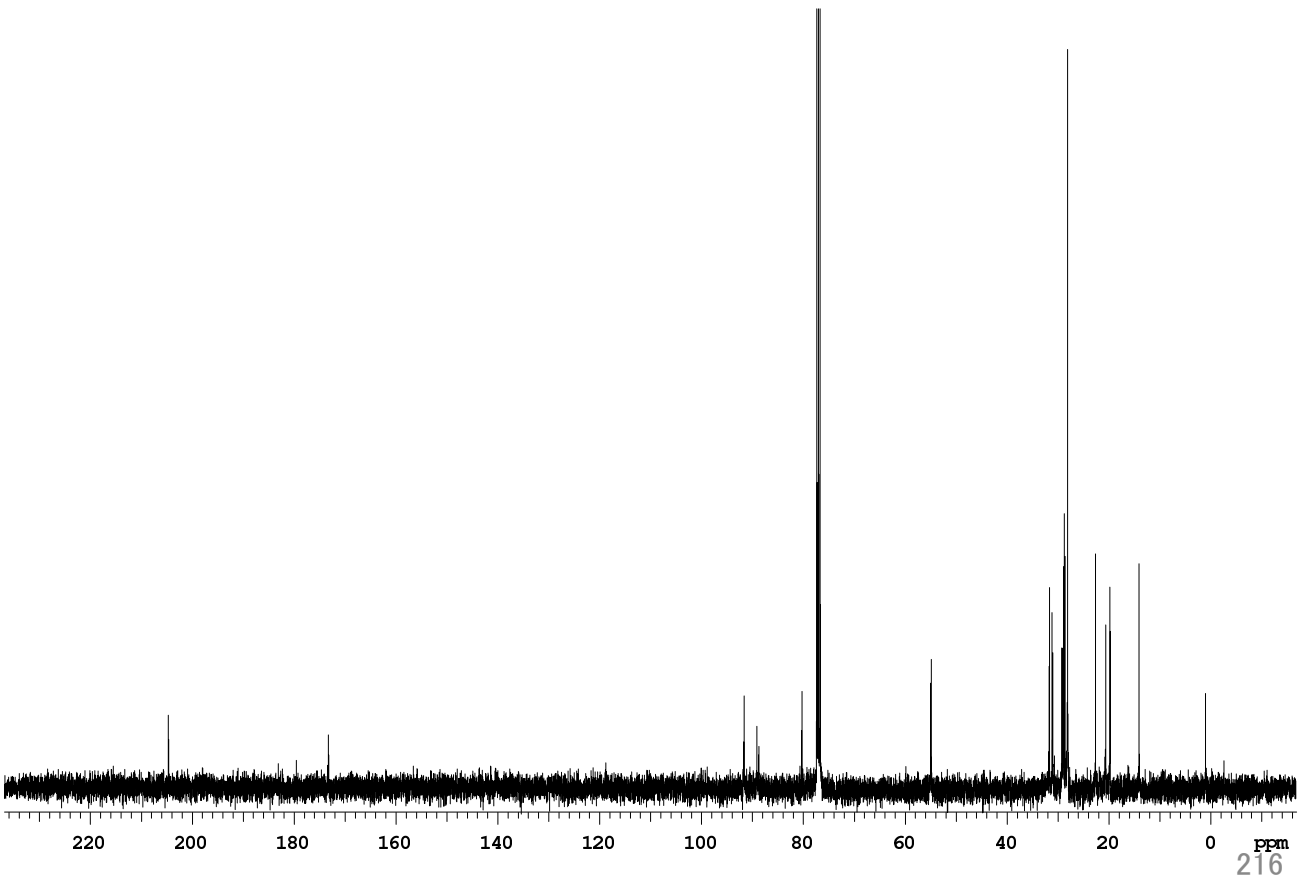


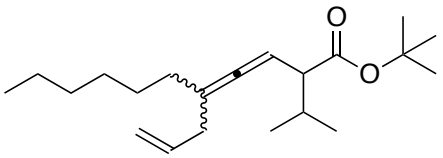




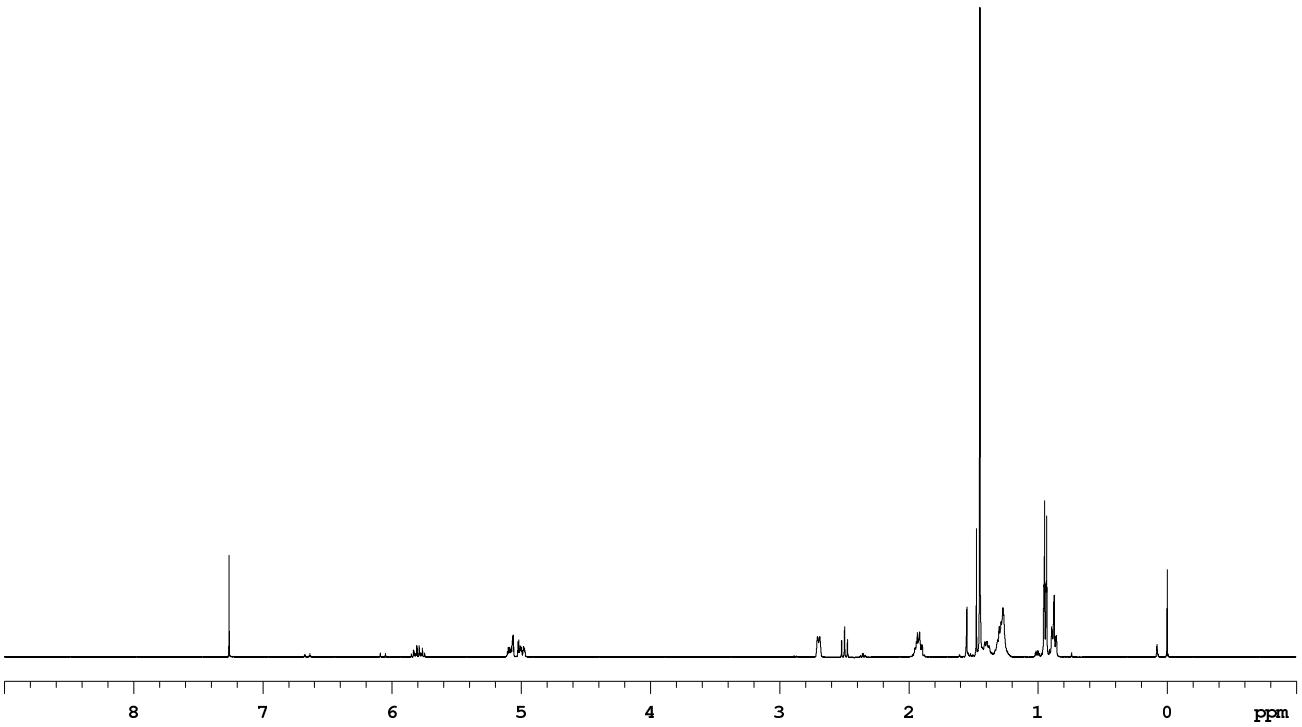
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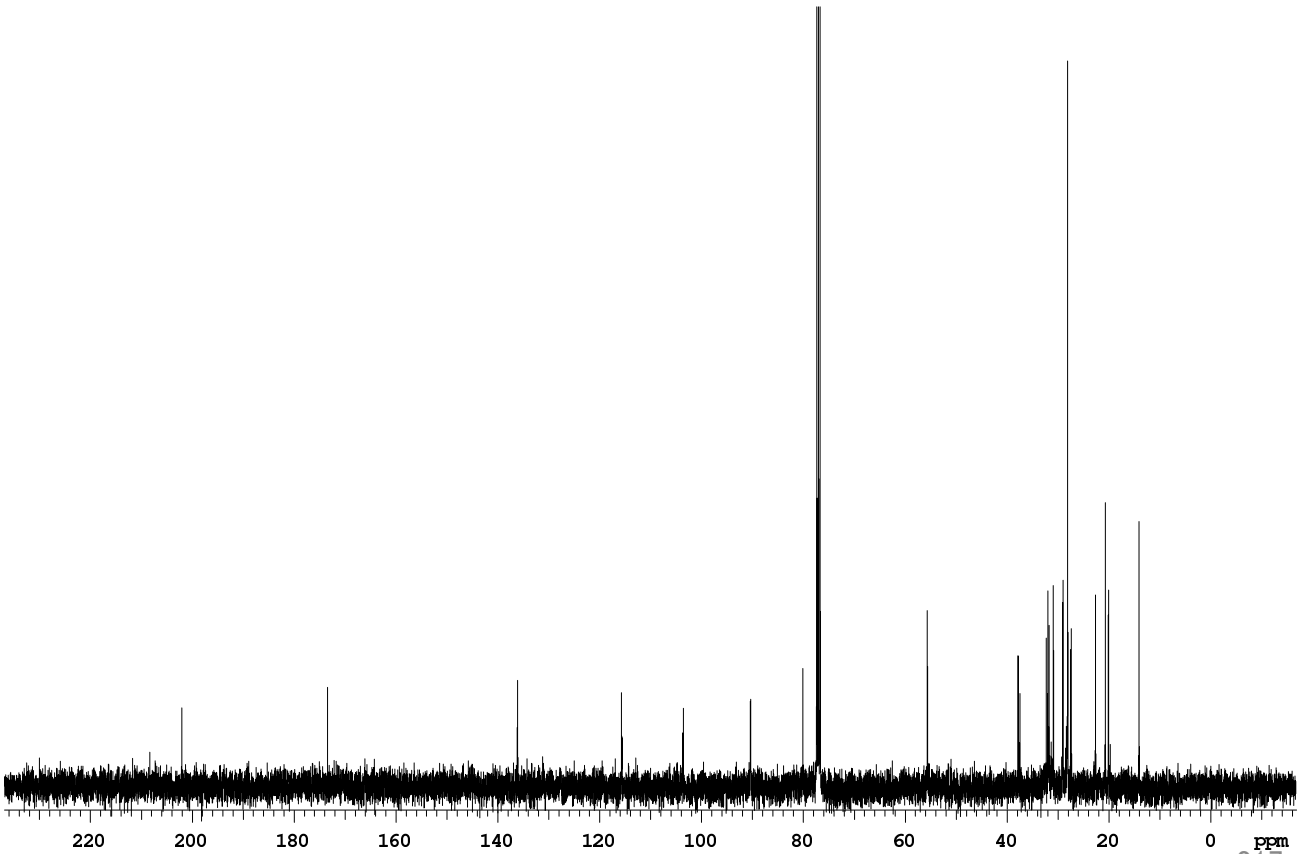


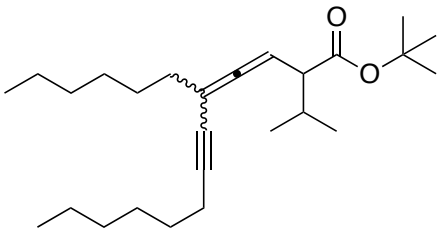




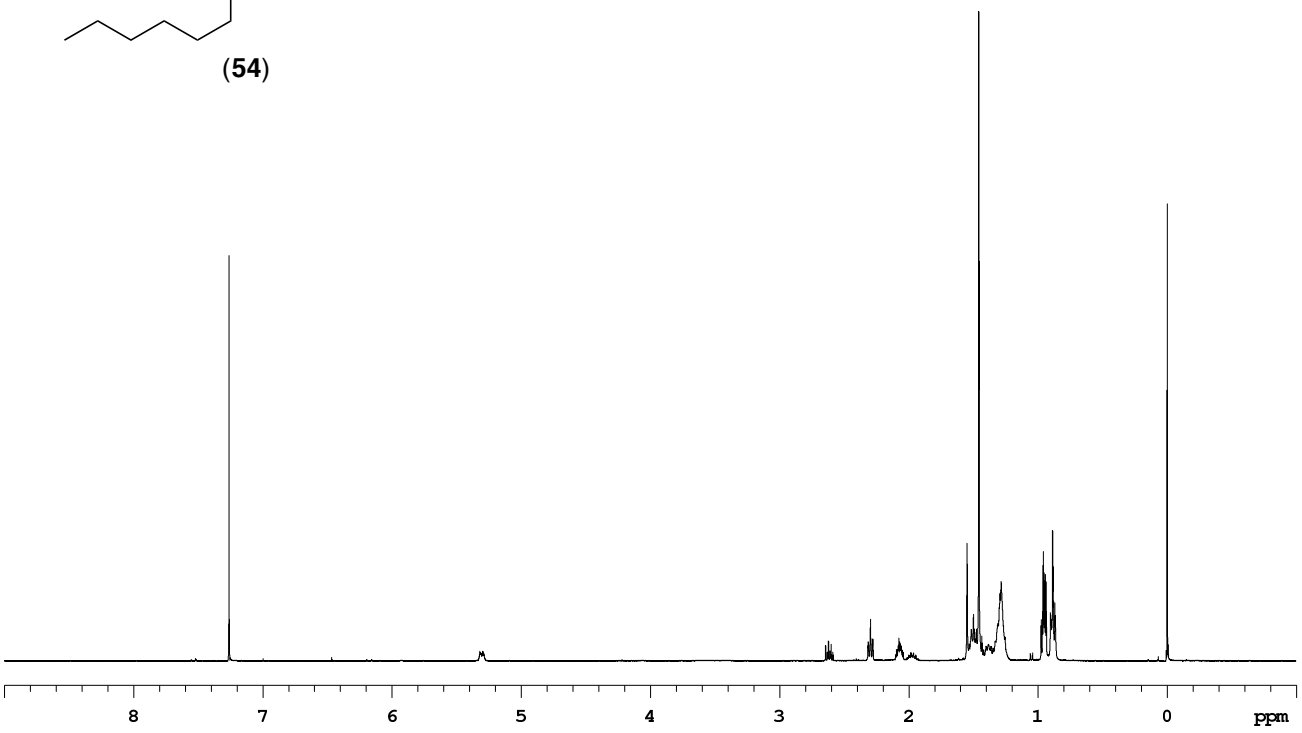
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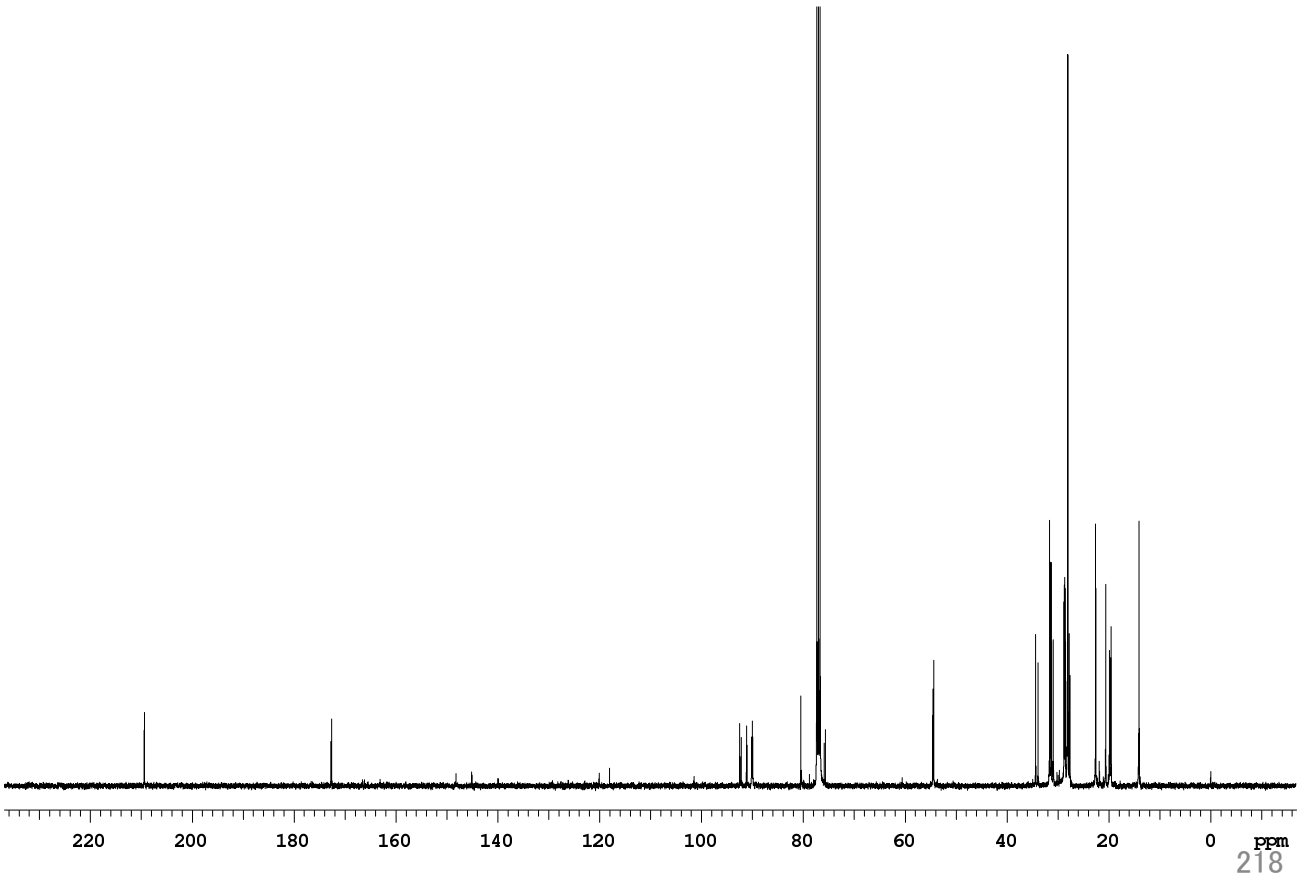


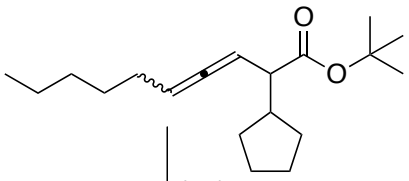




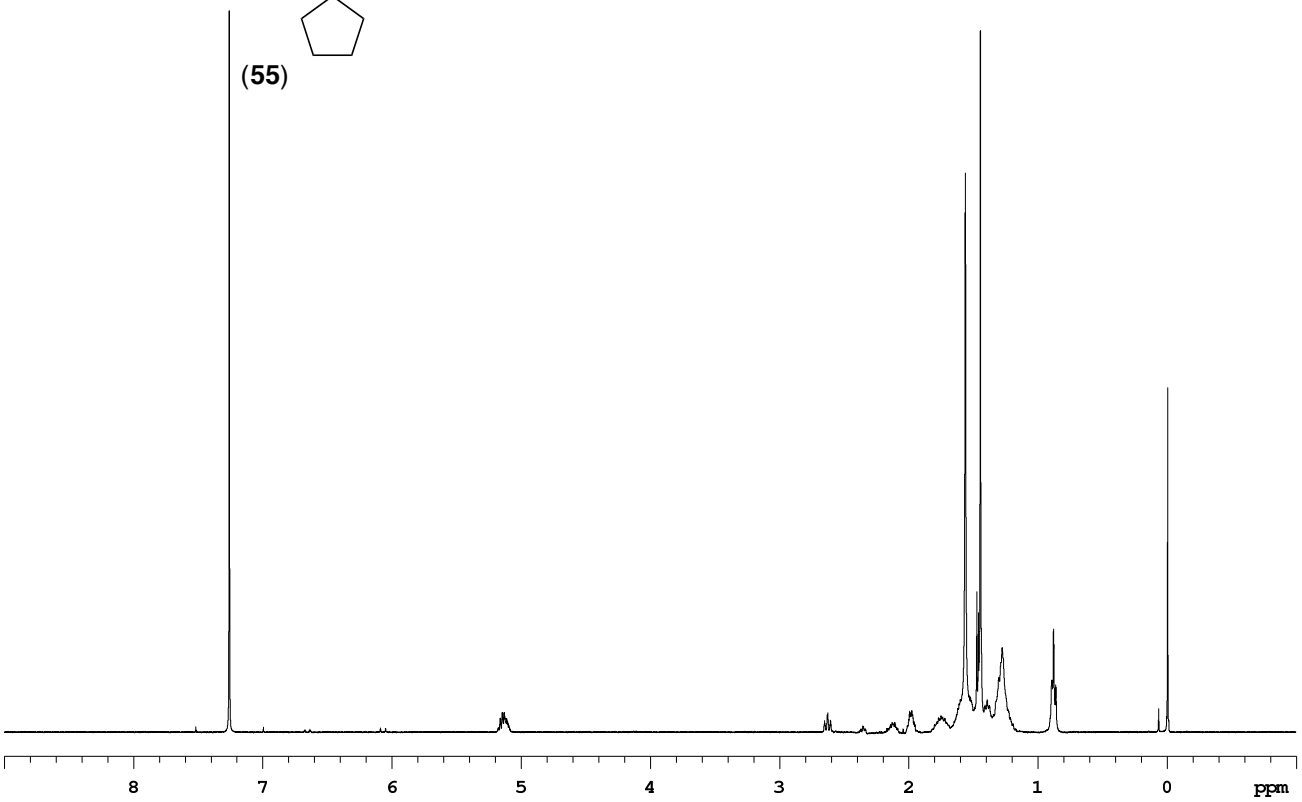
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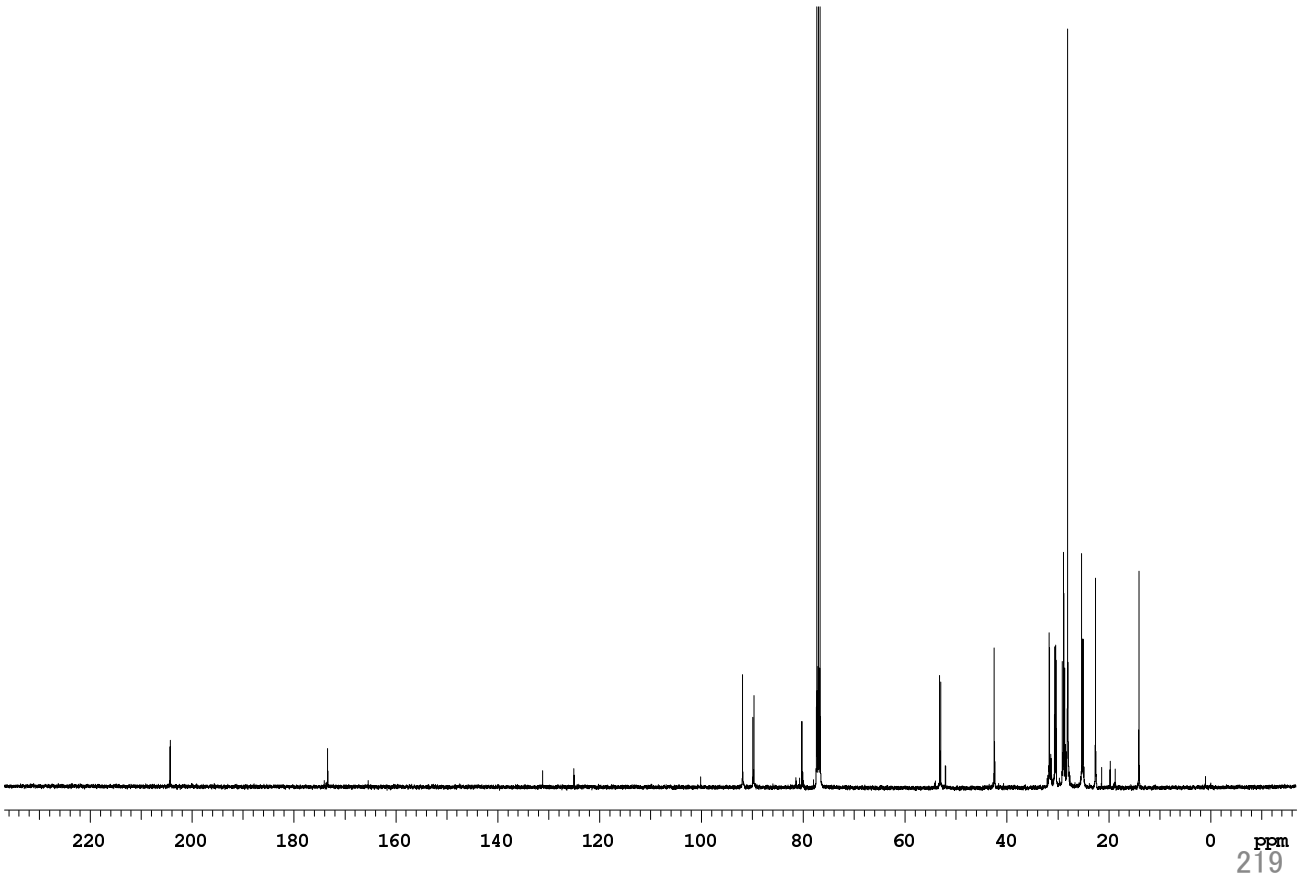


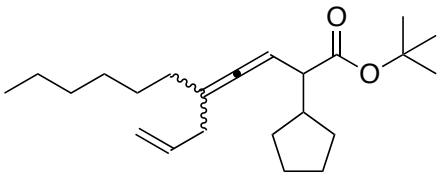




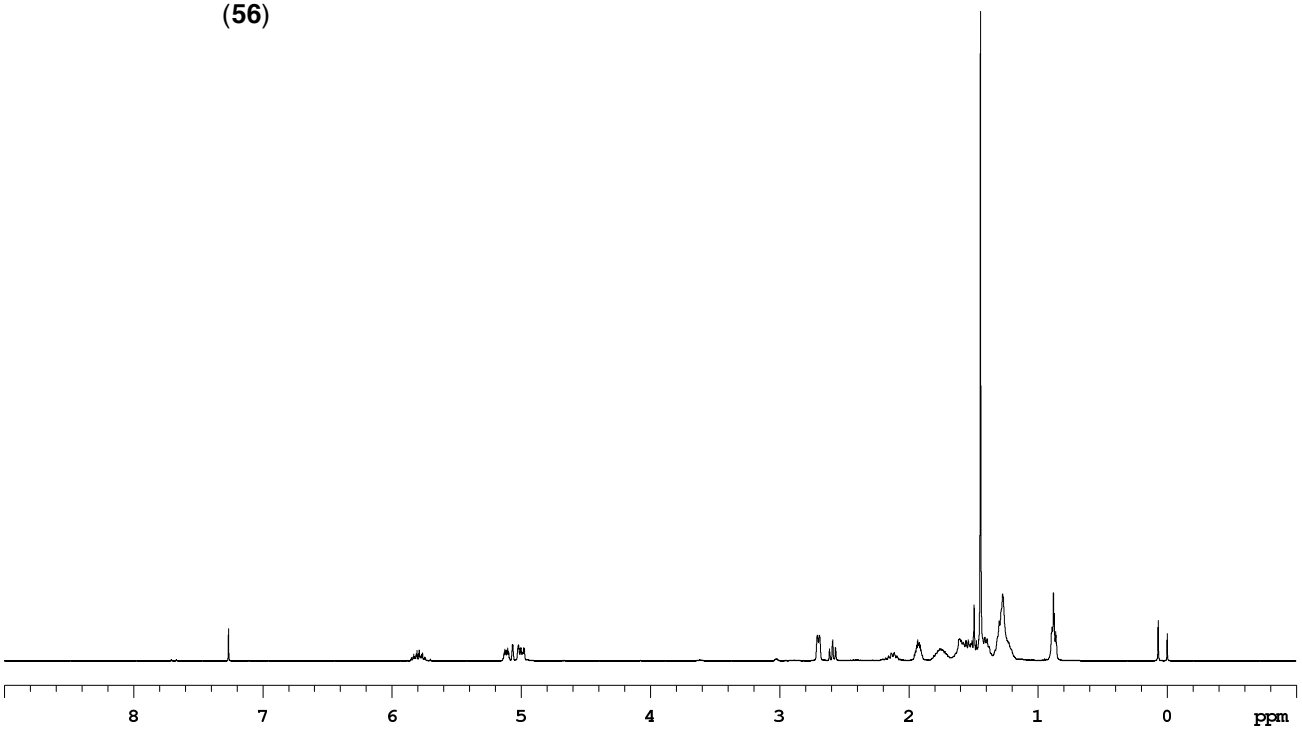
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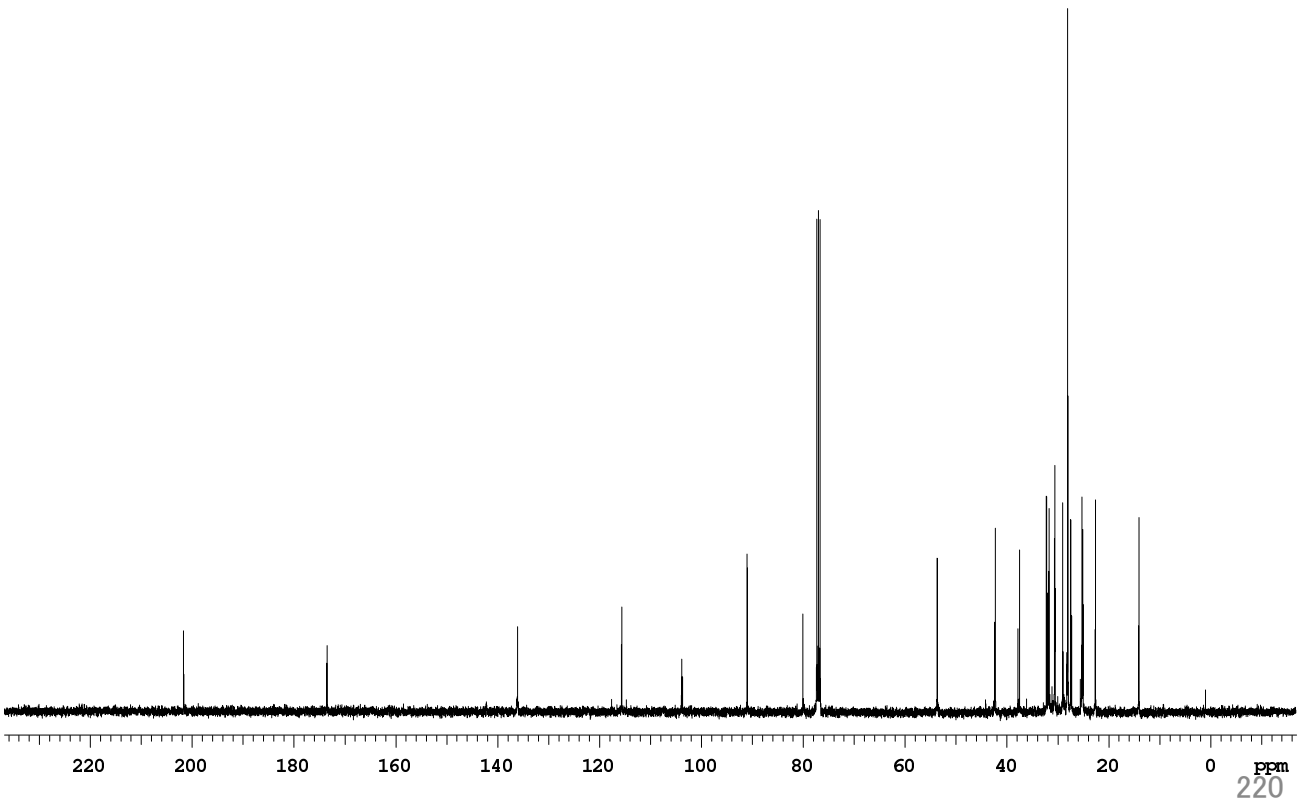


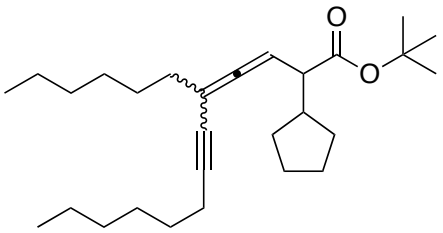




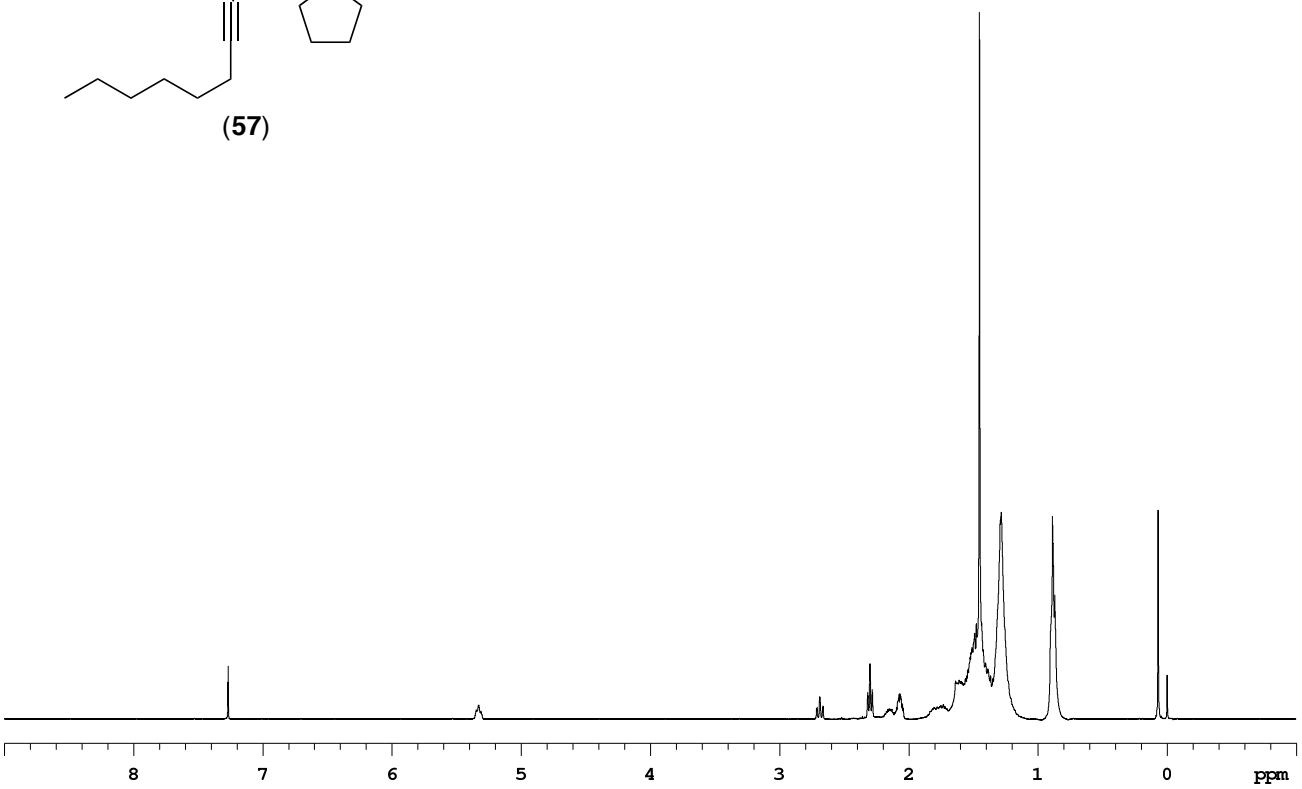
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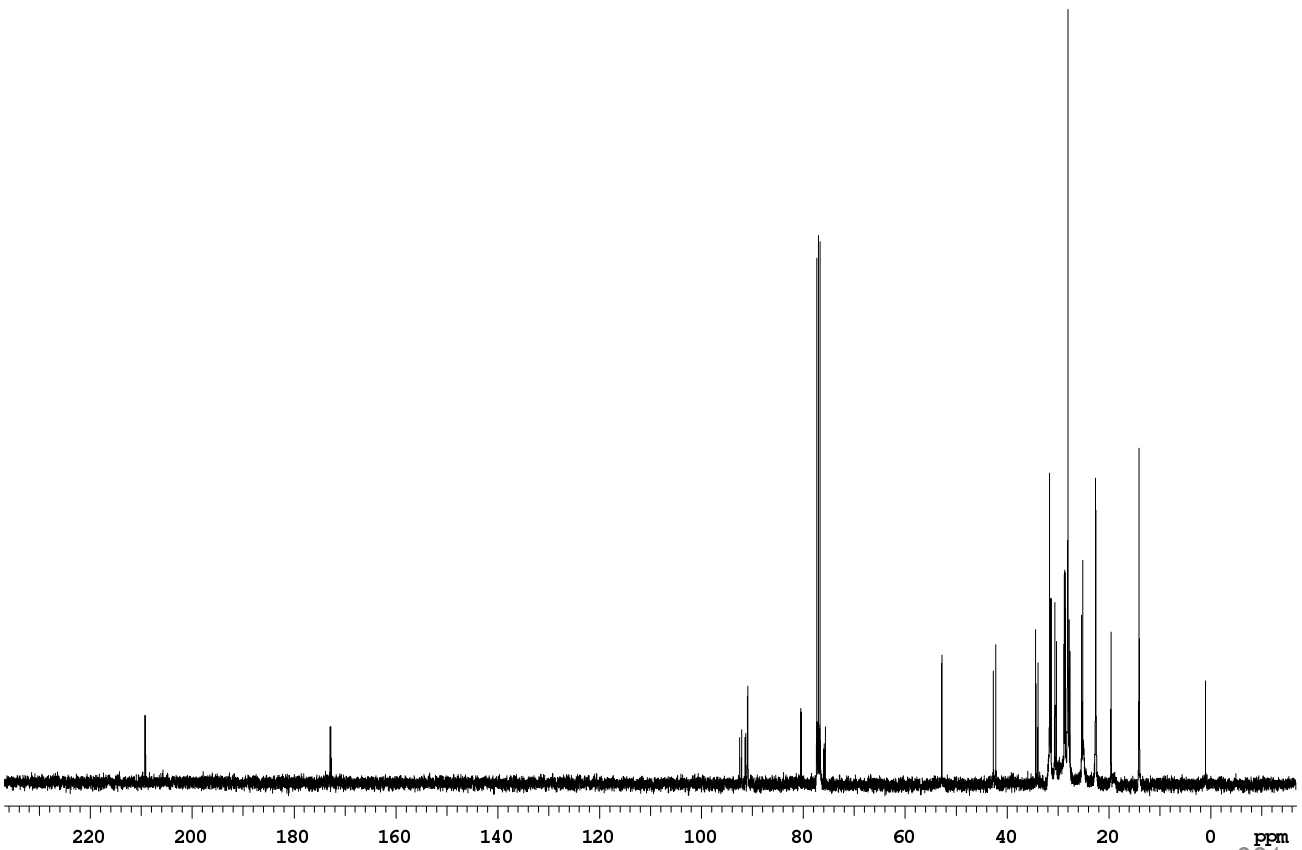


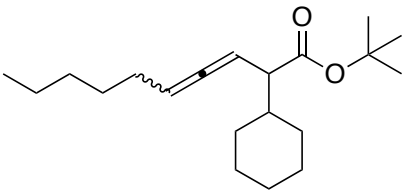




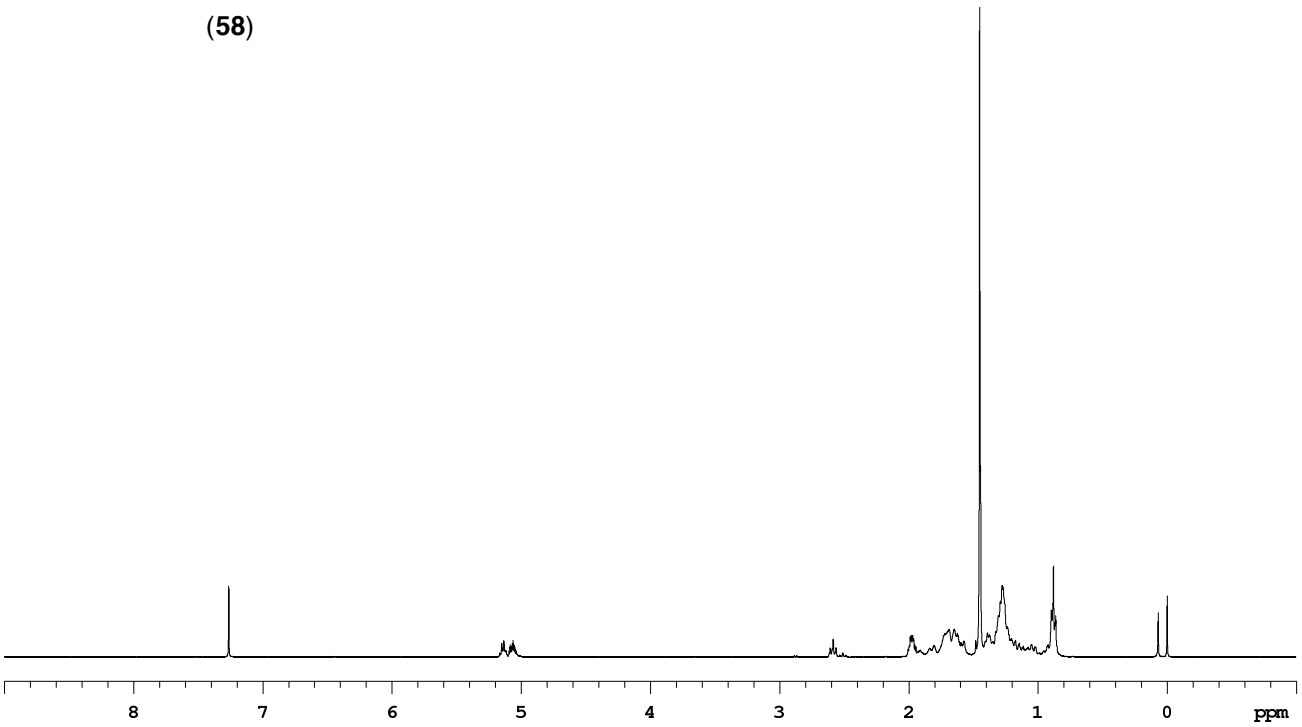
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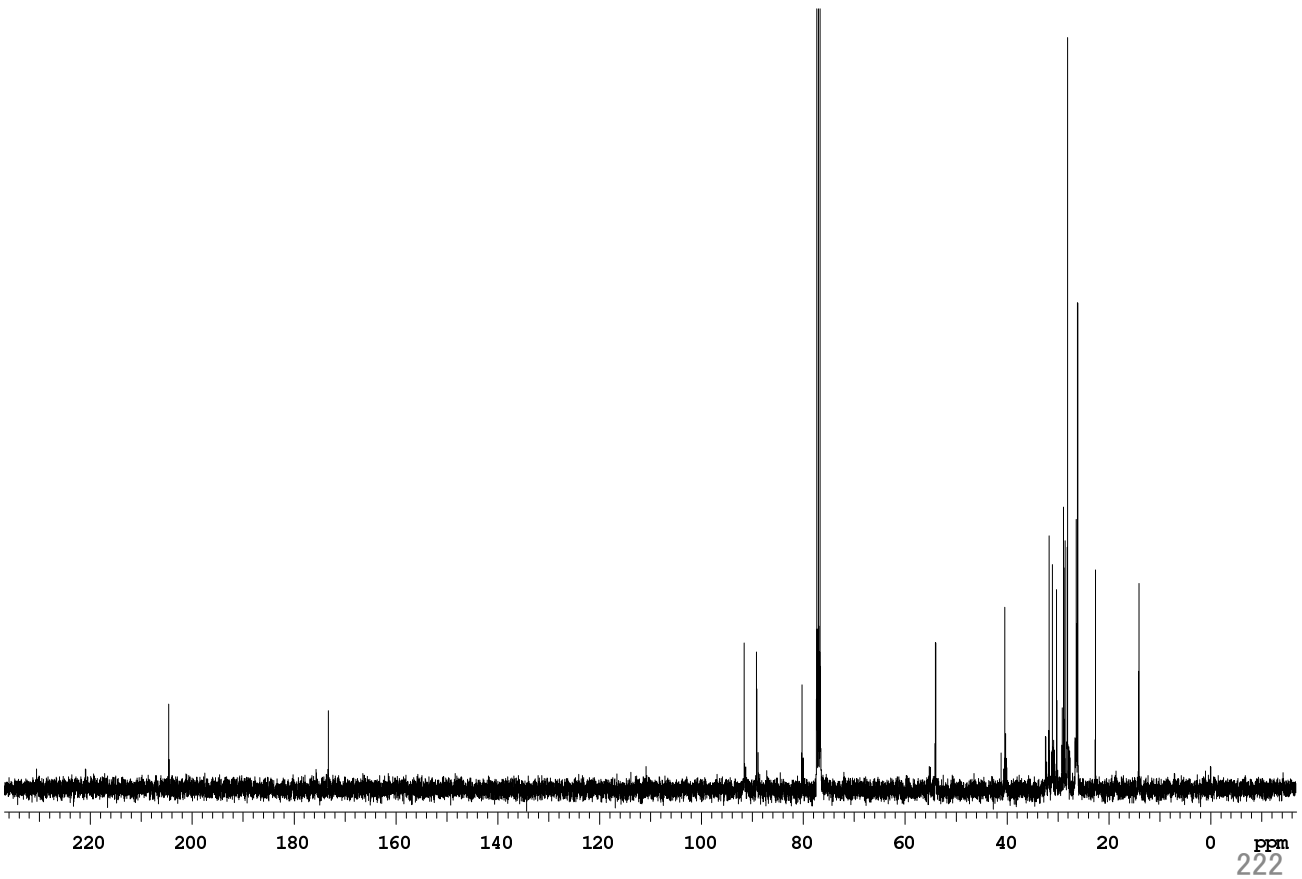


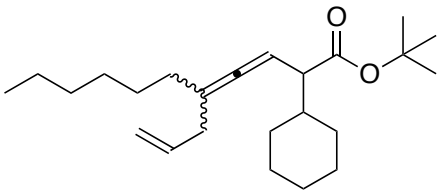




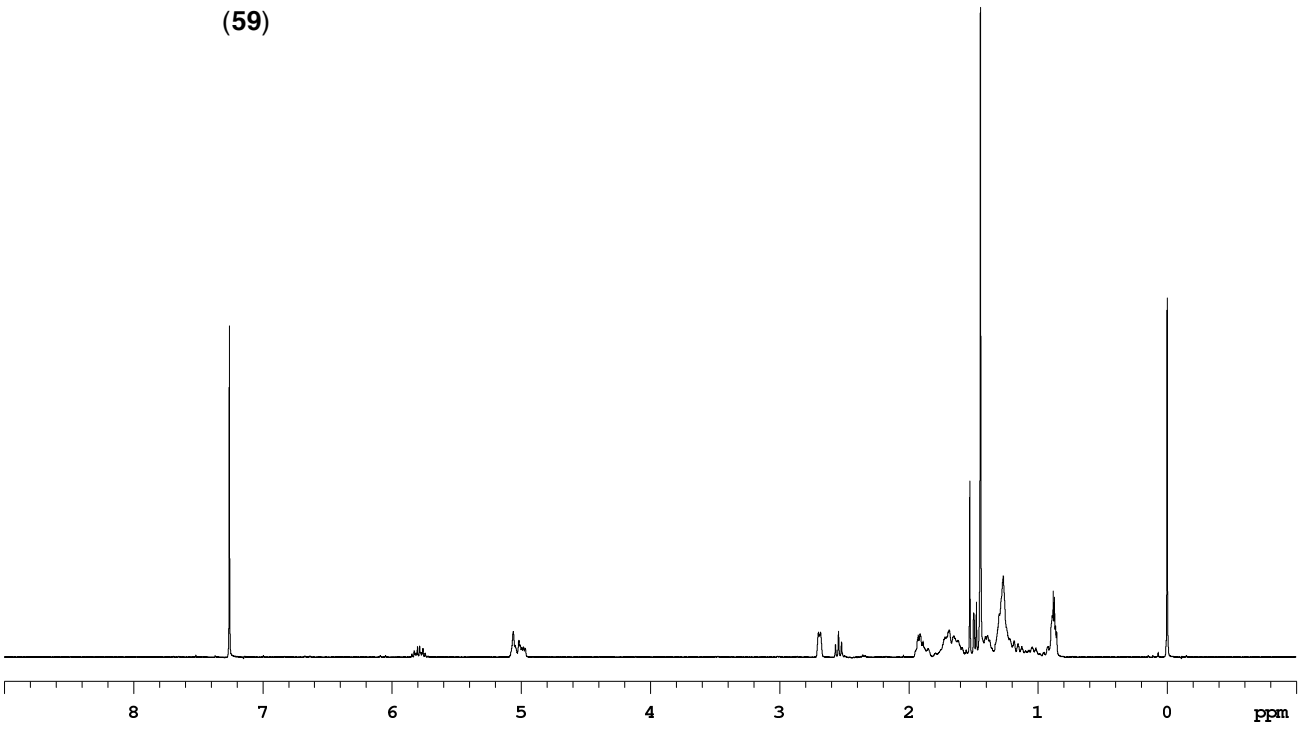
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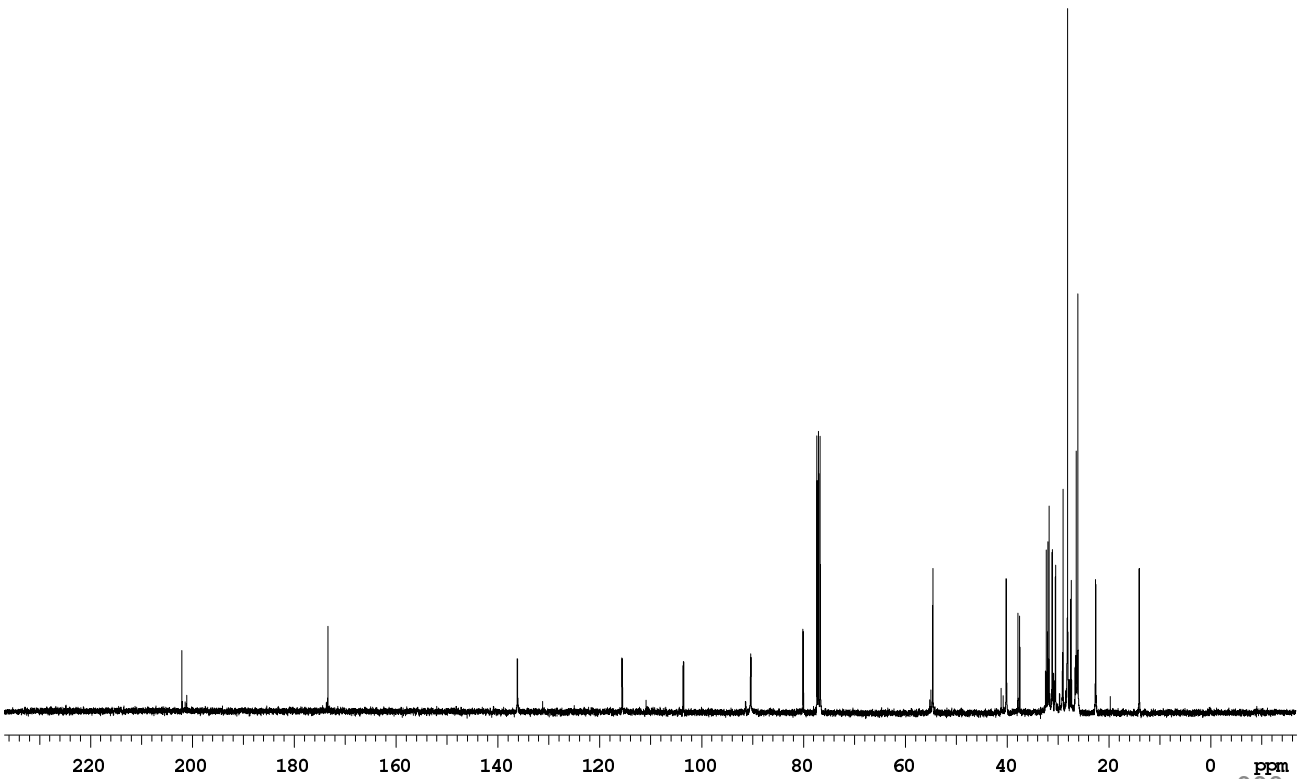


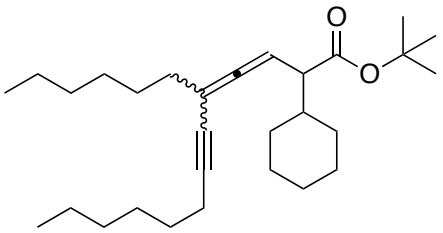




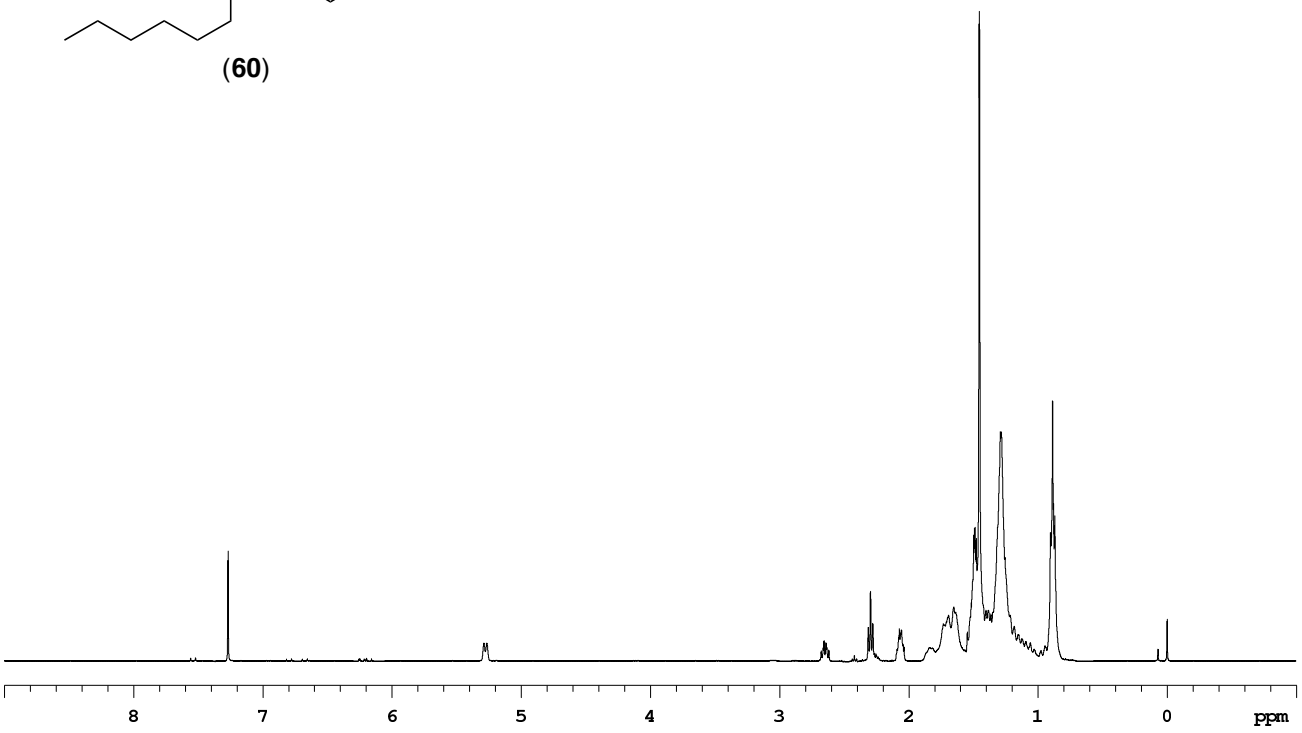
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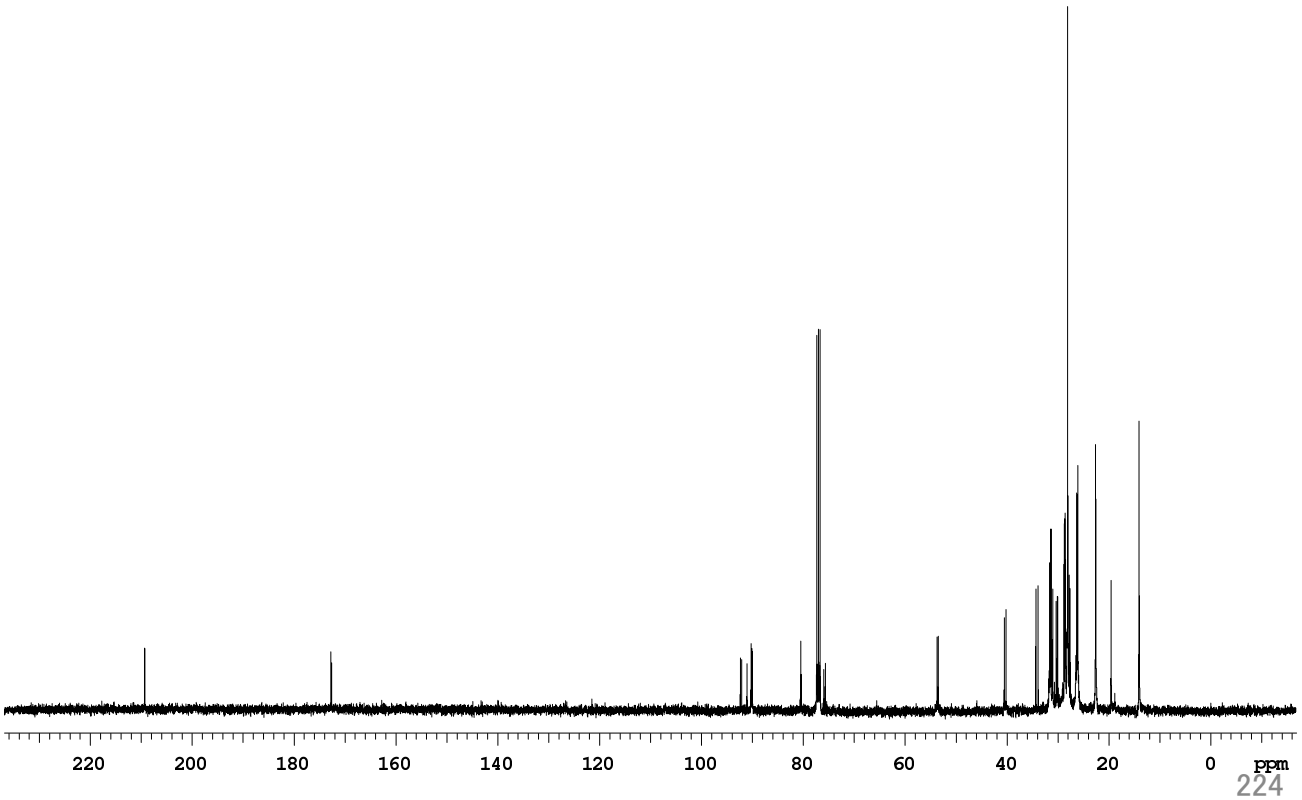


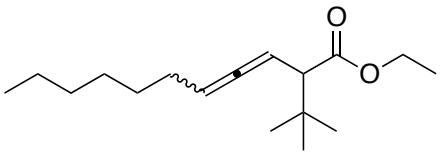




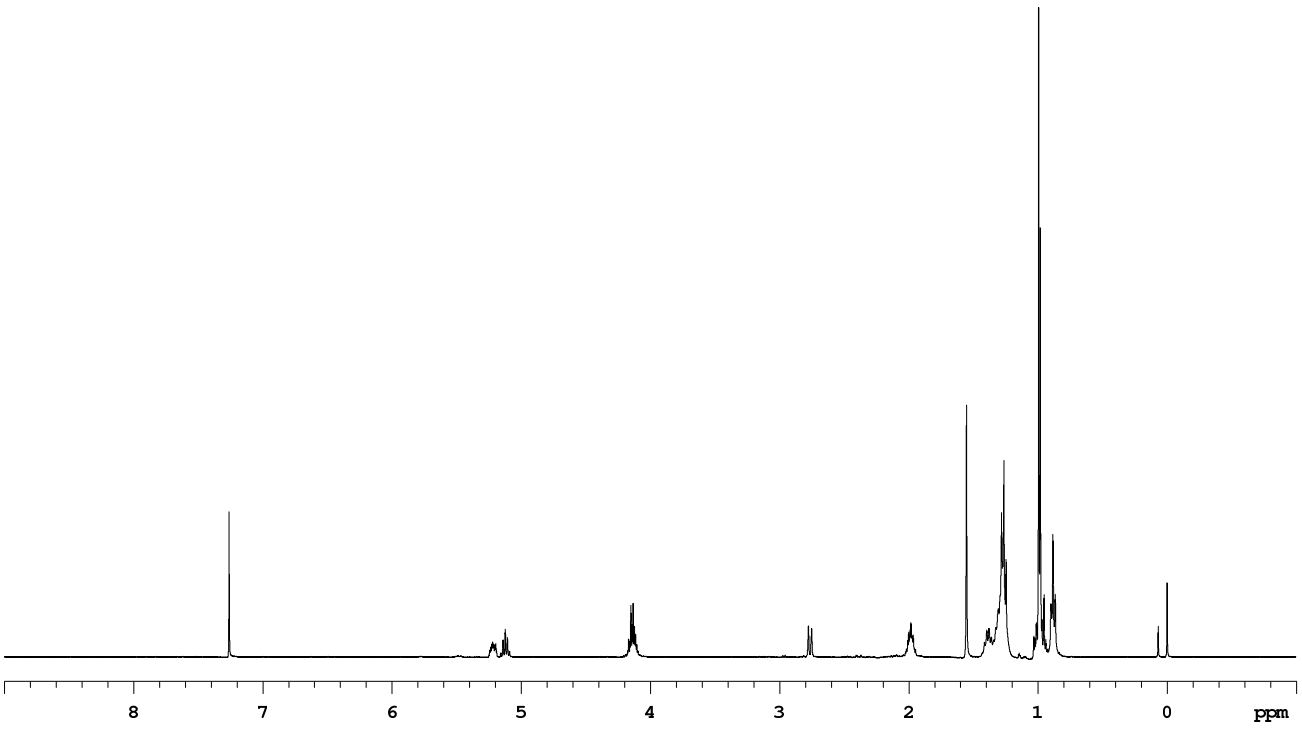
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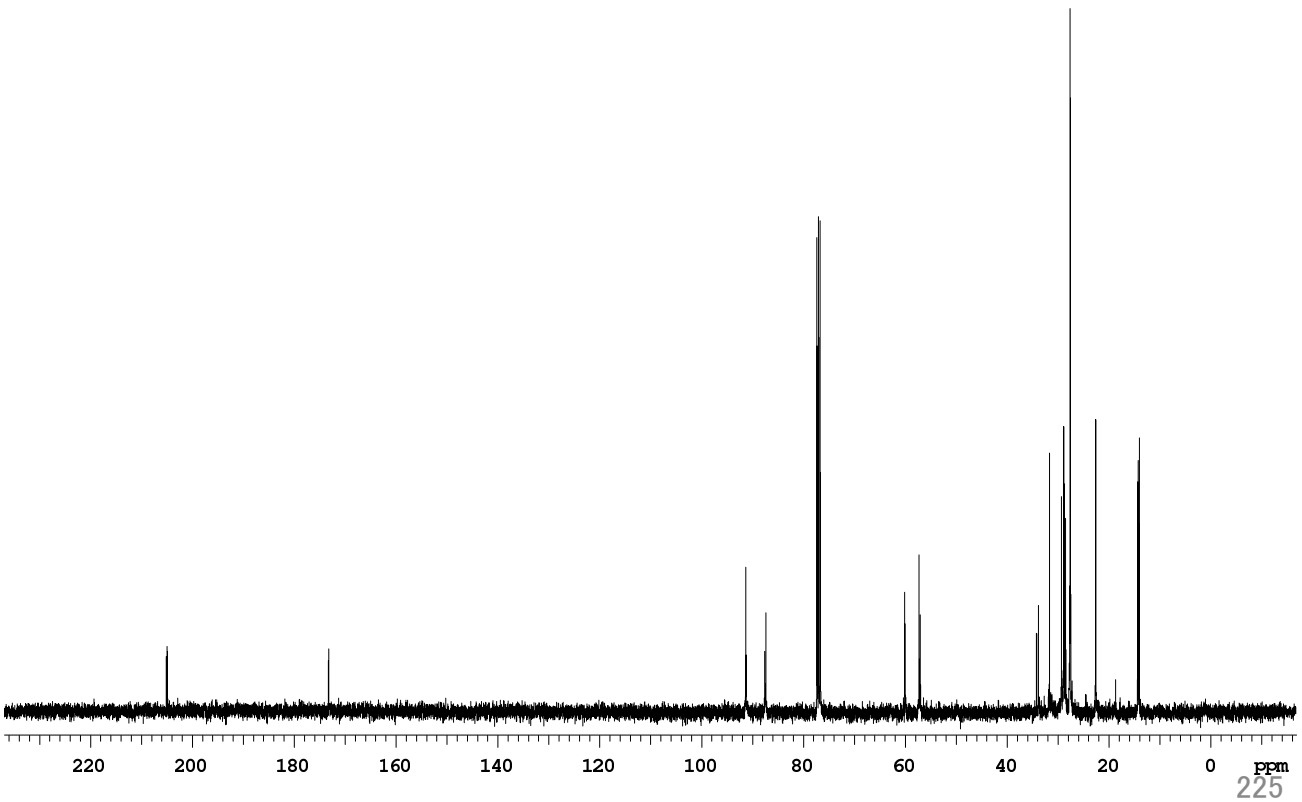


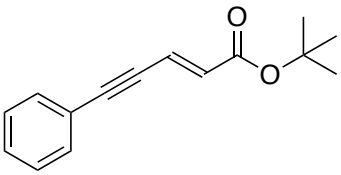




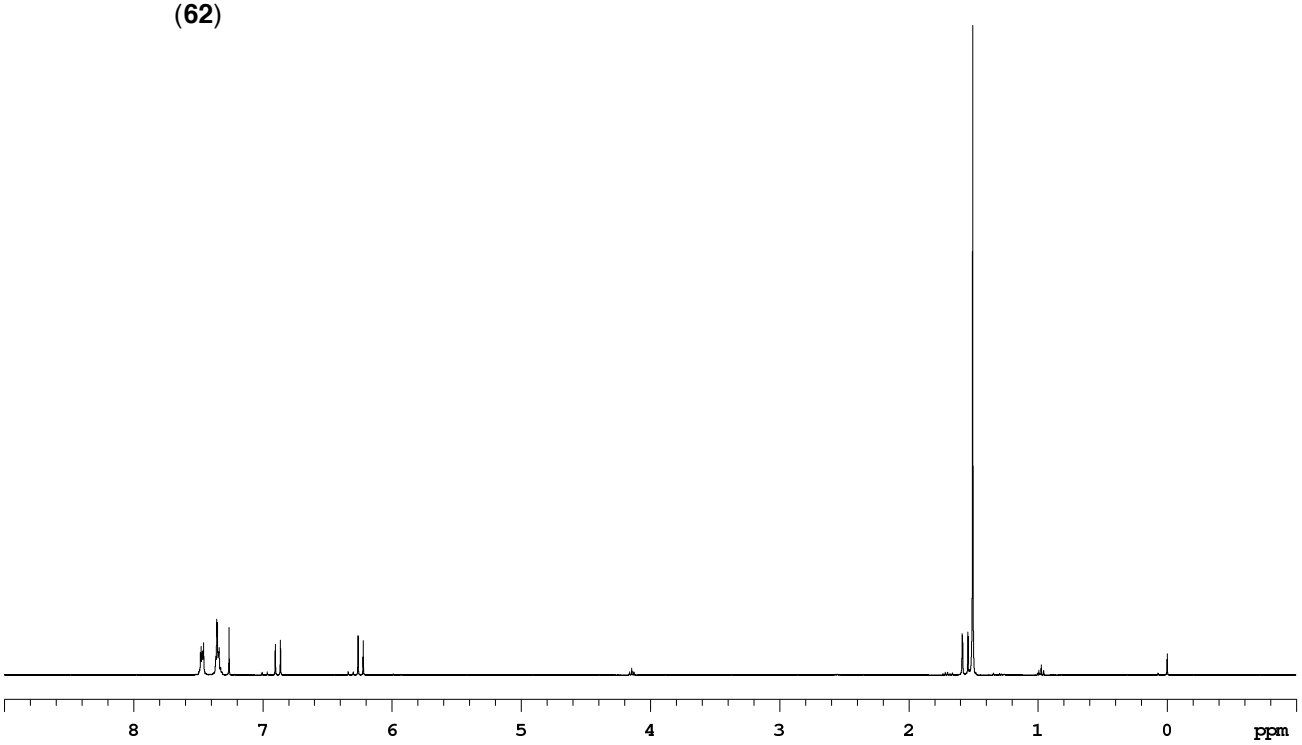
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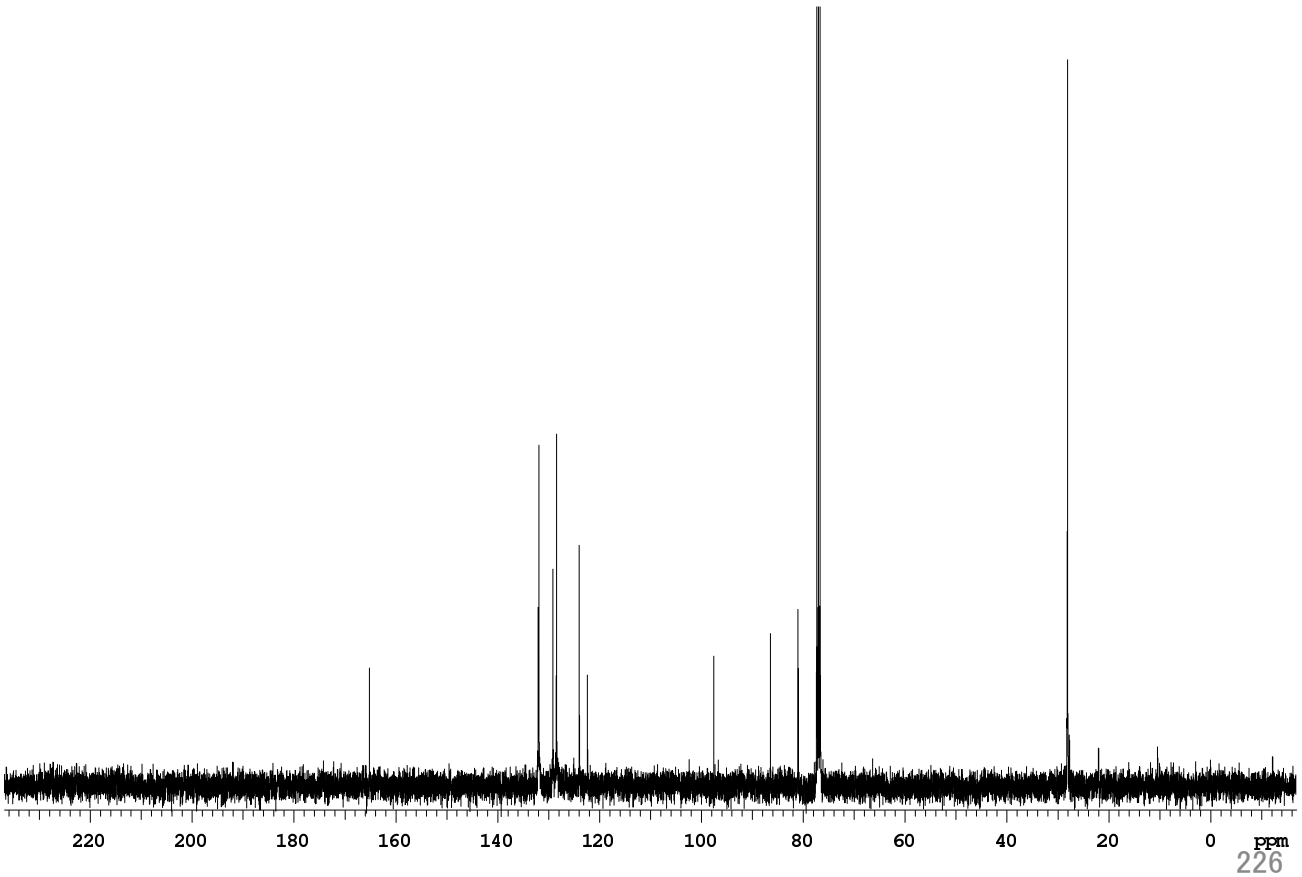


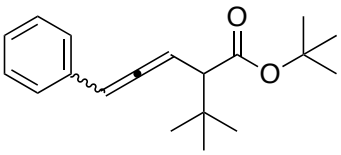




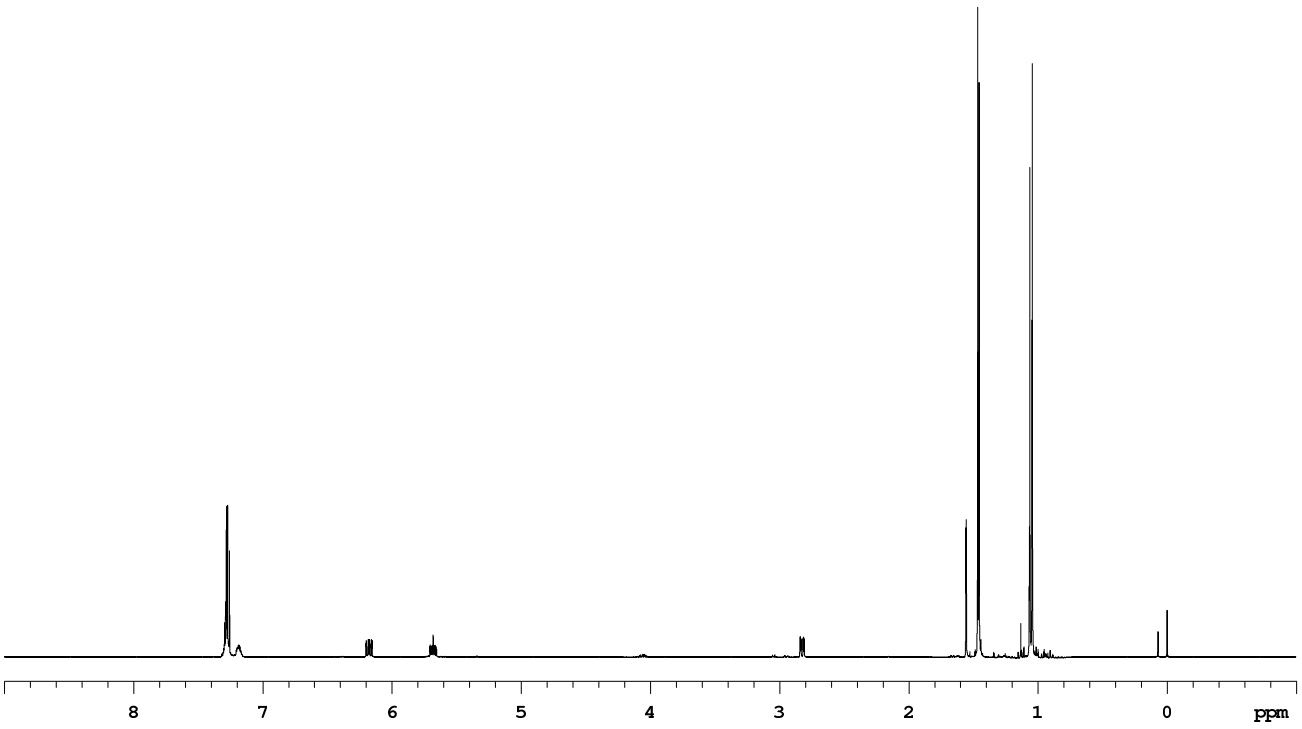
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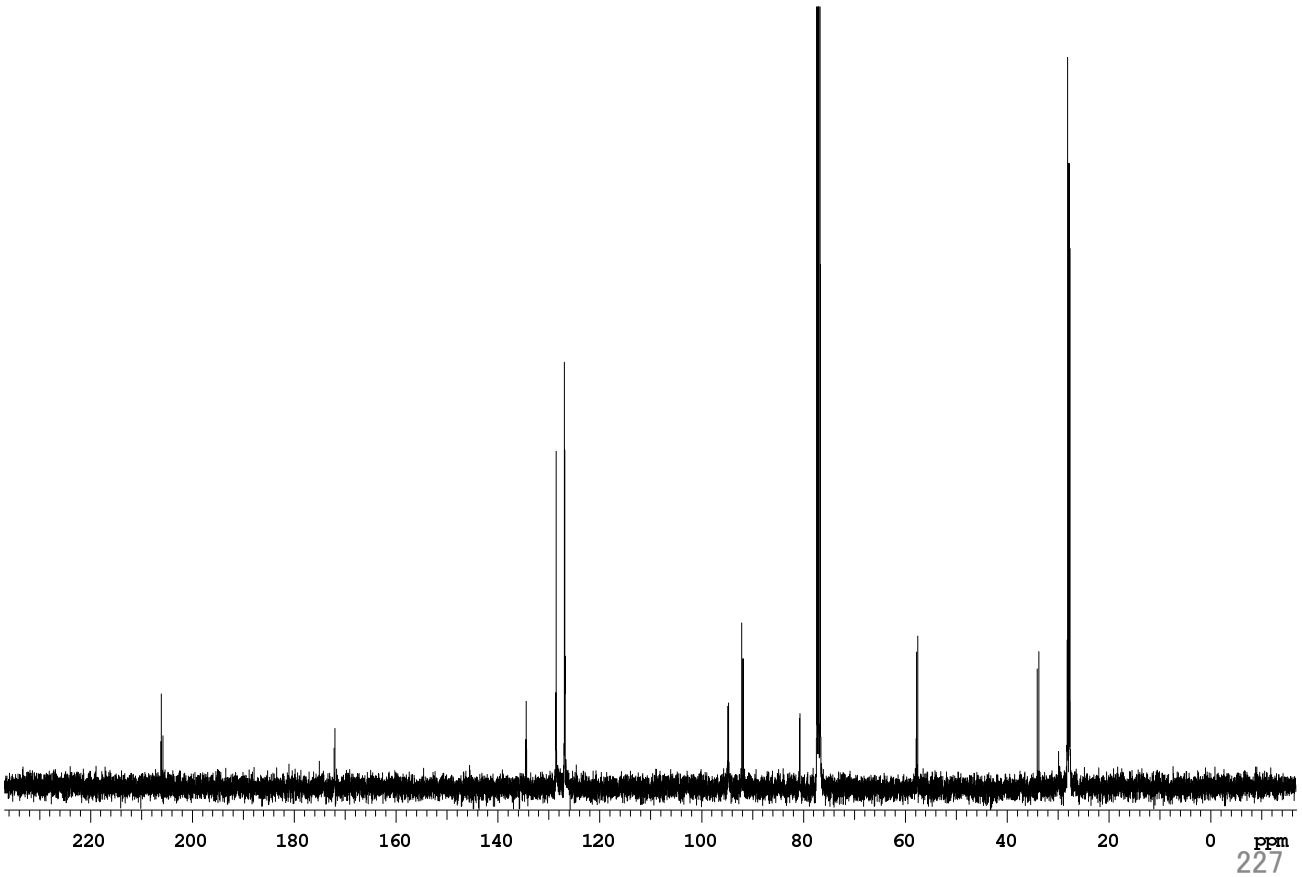


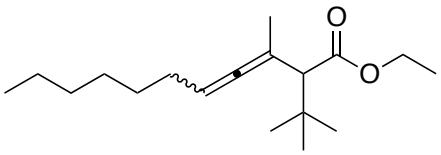




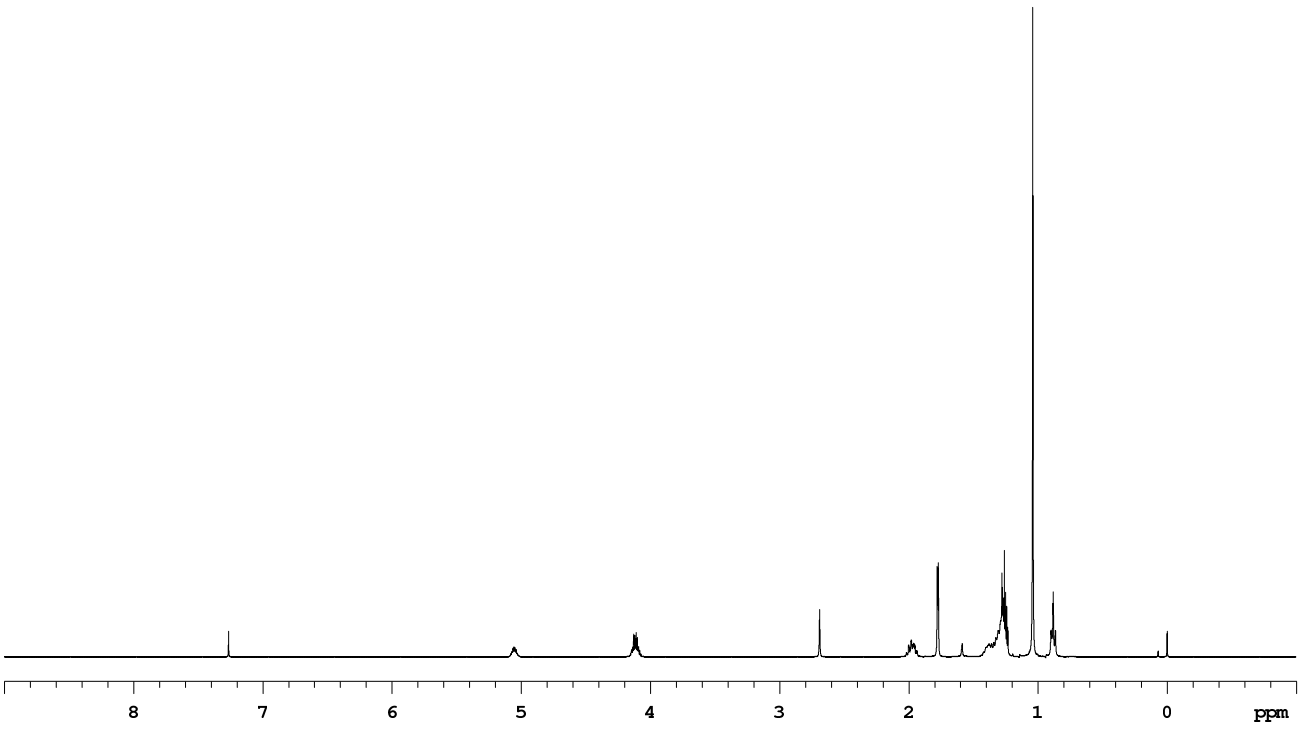
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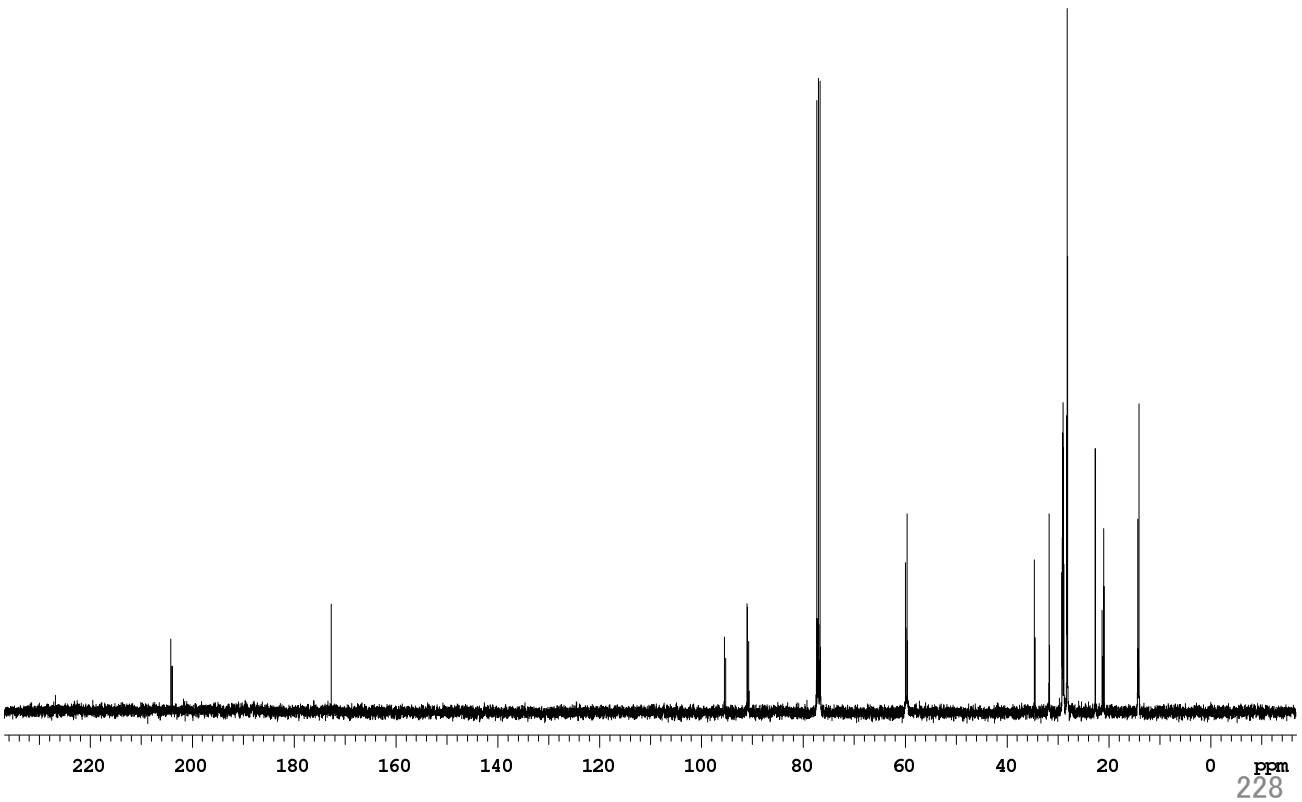


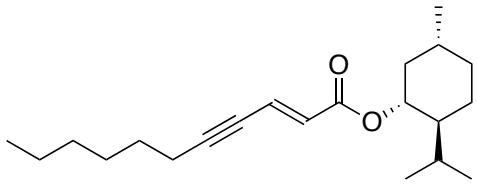




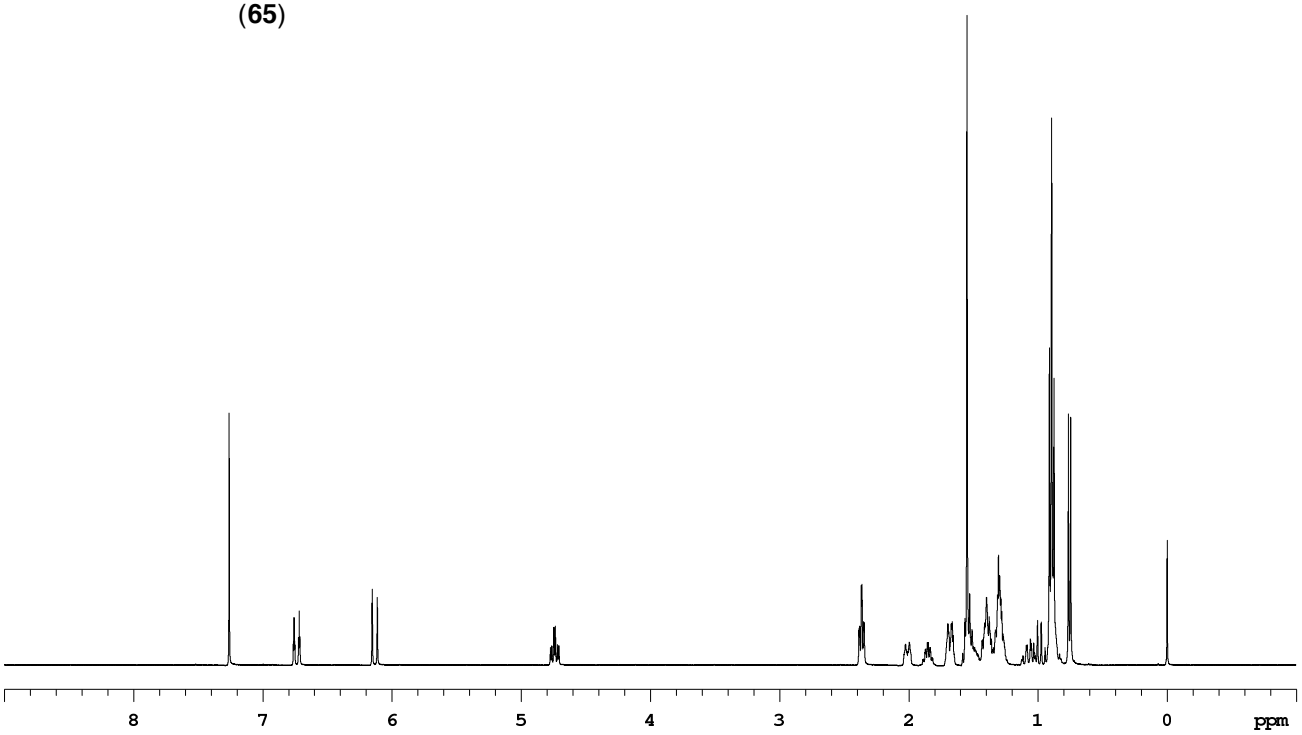
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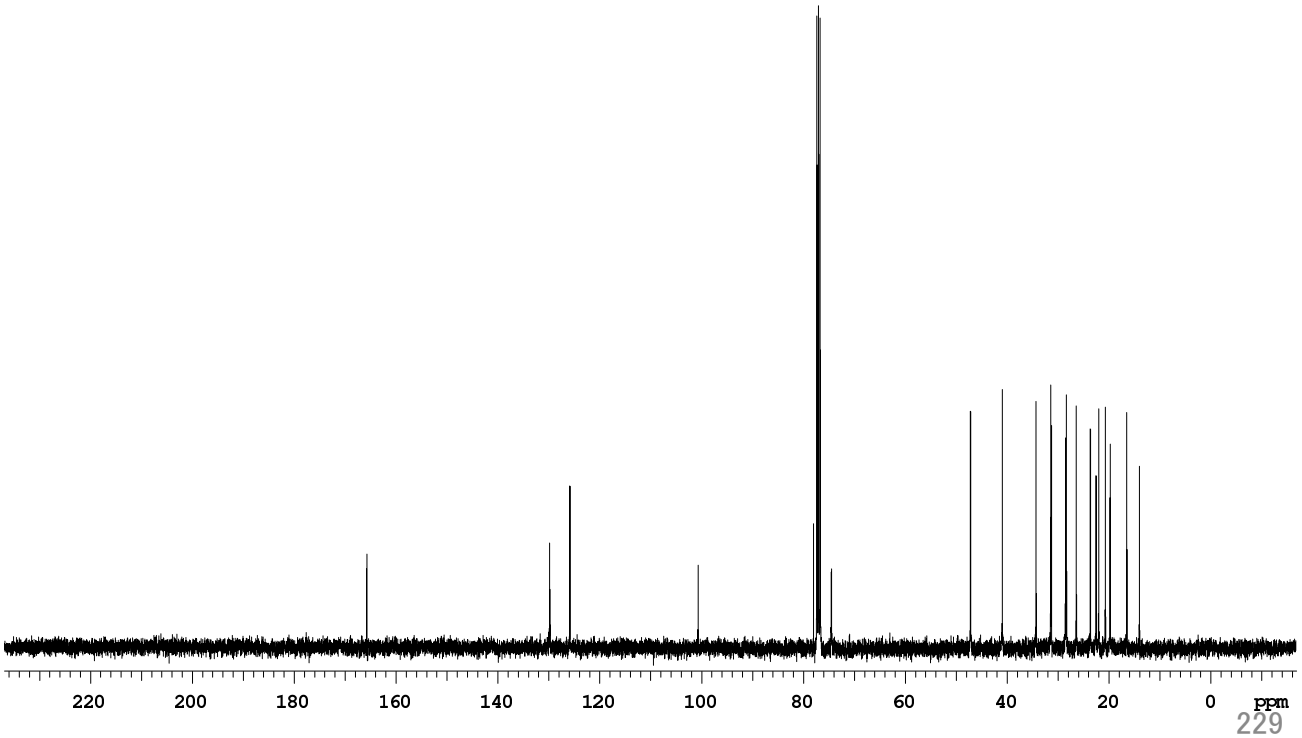


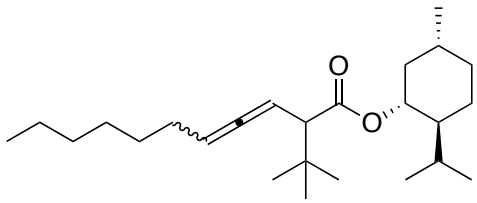




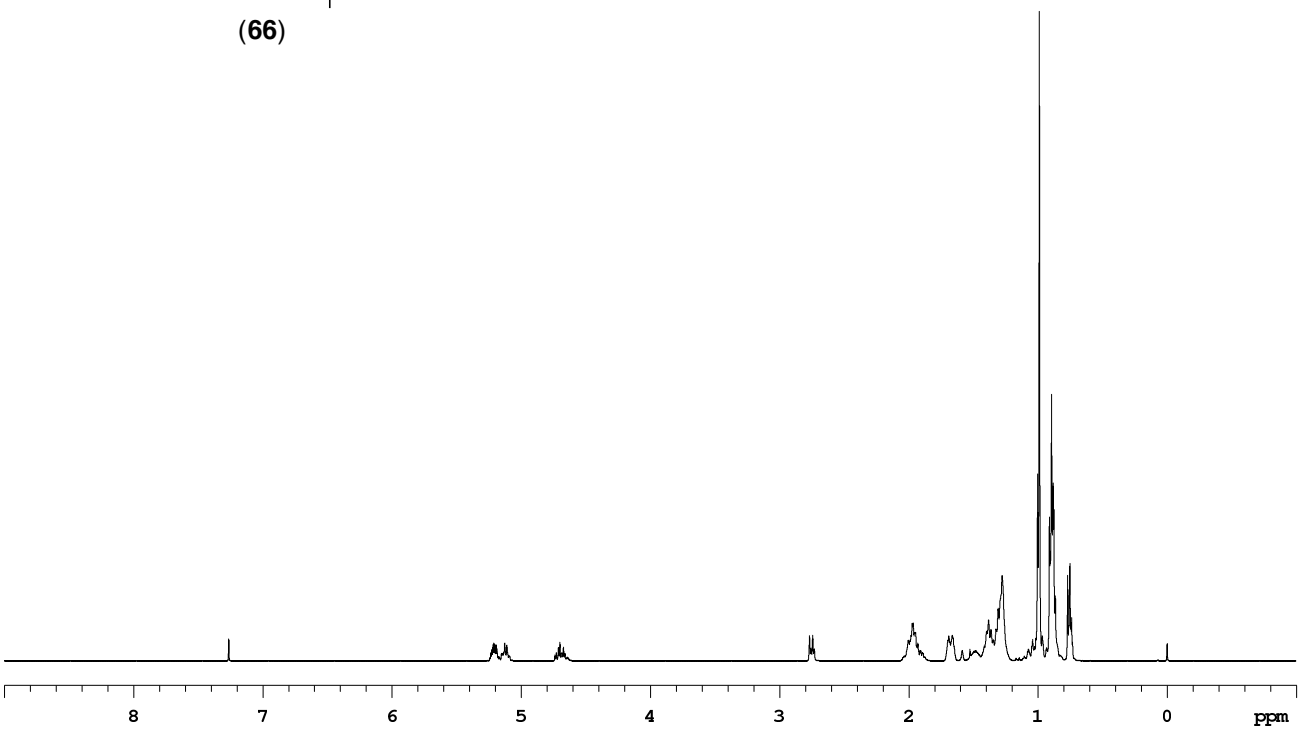
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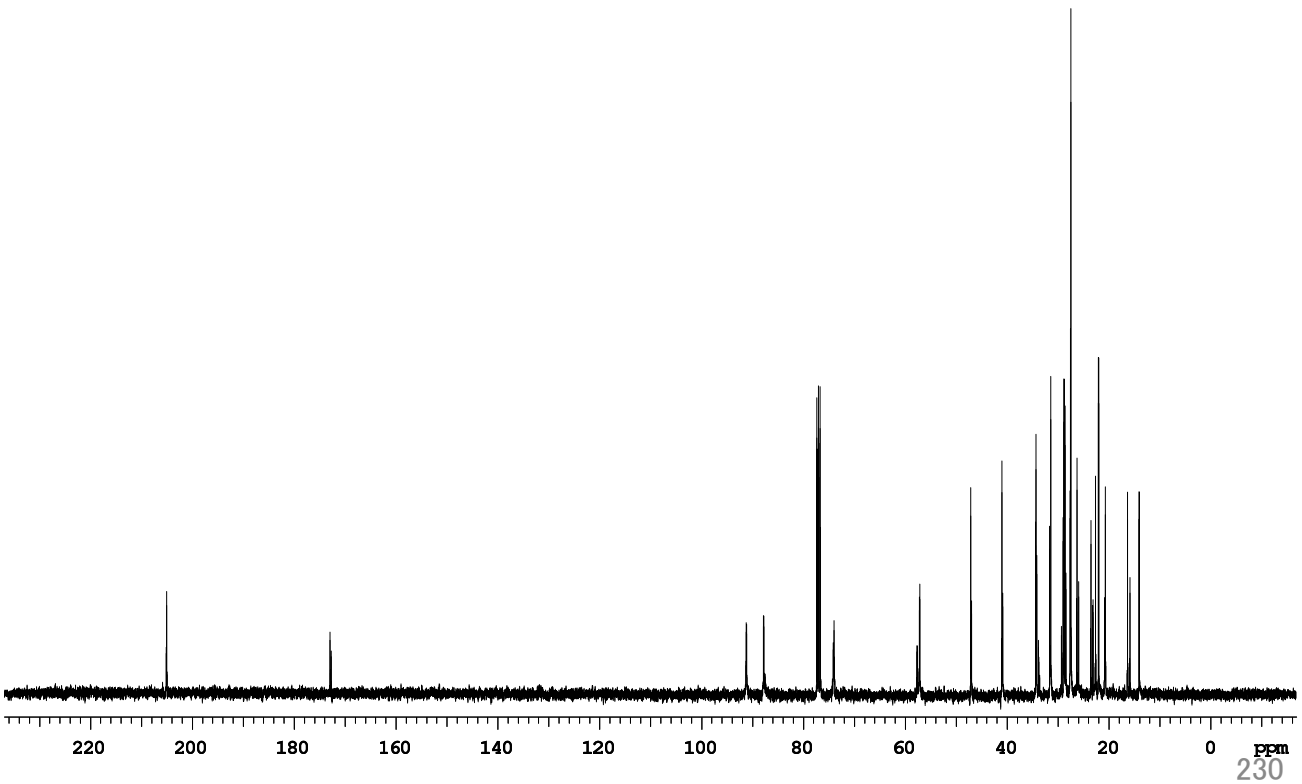


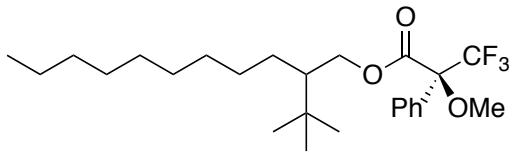




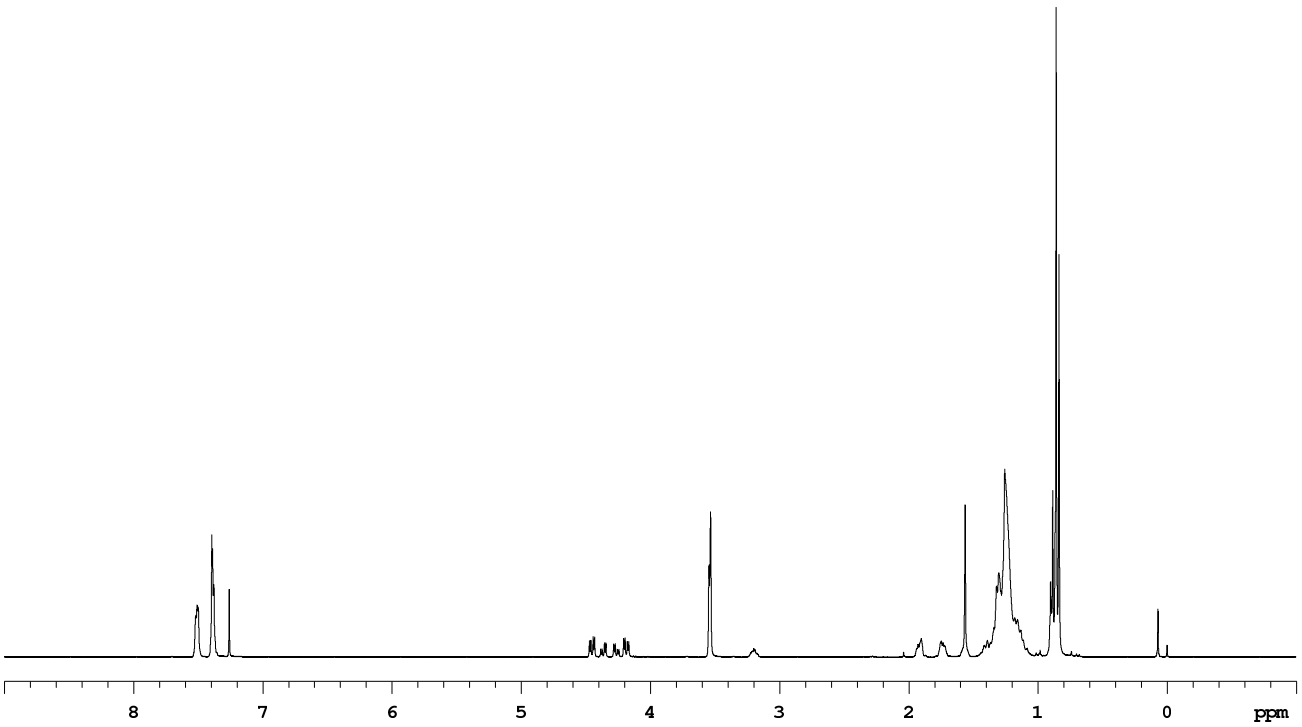
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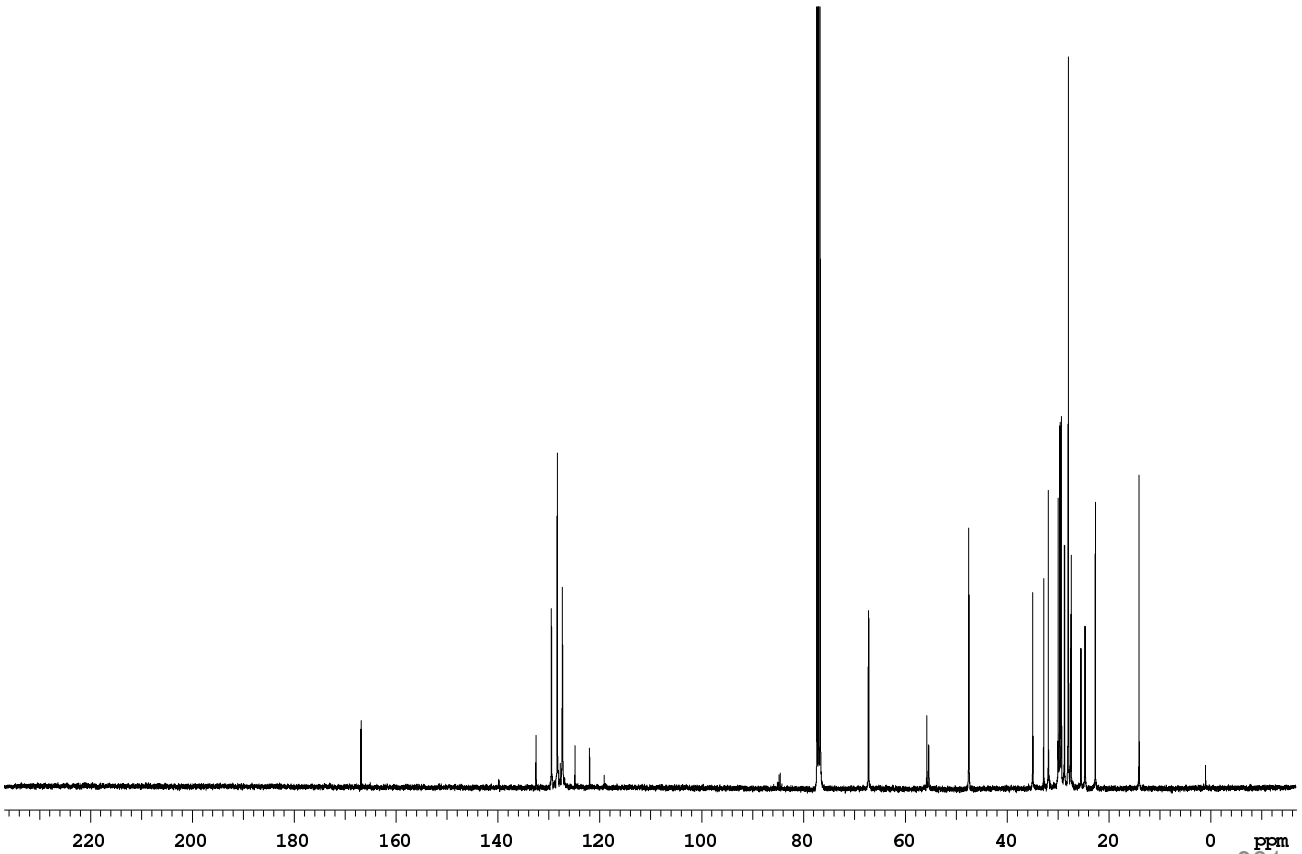





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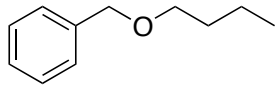
(**67**)


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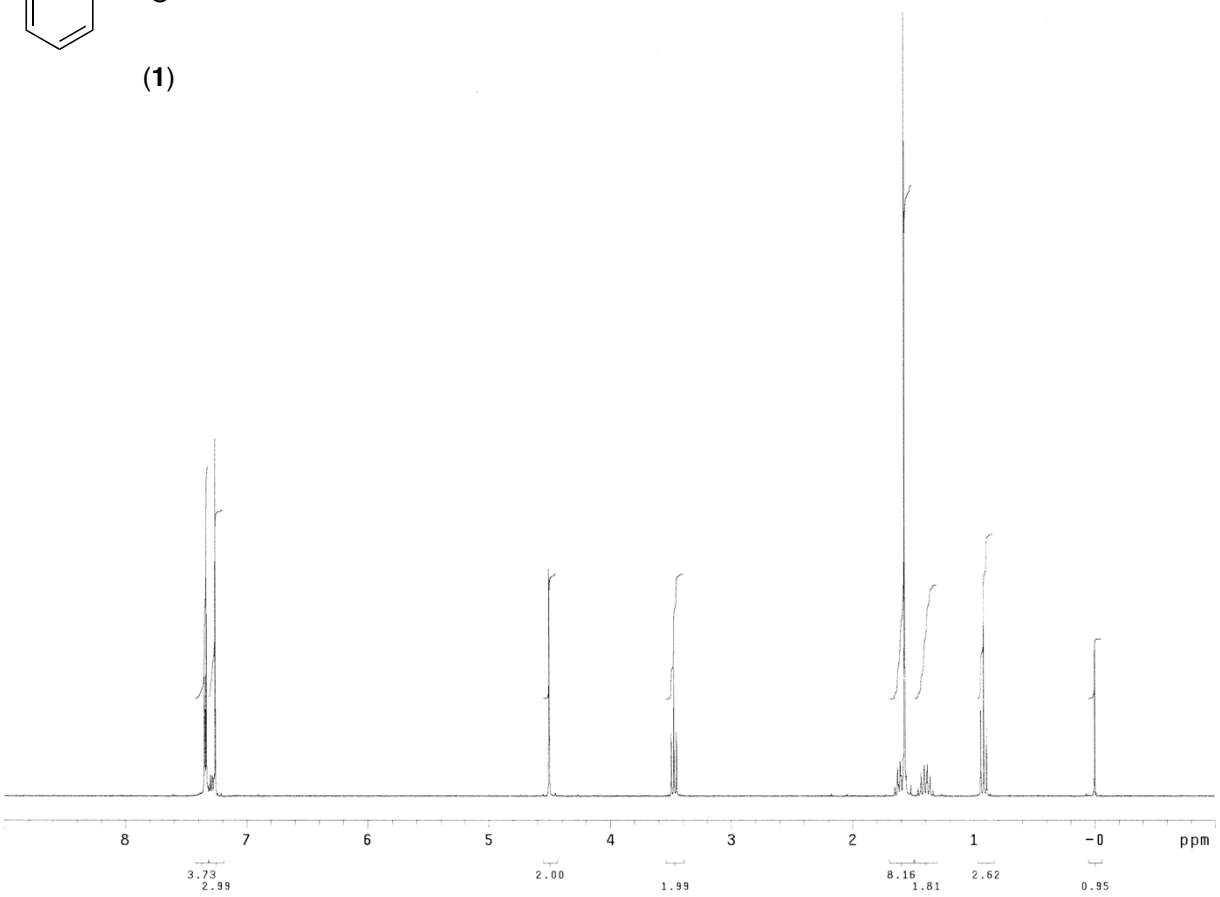

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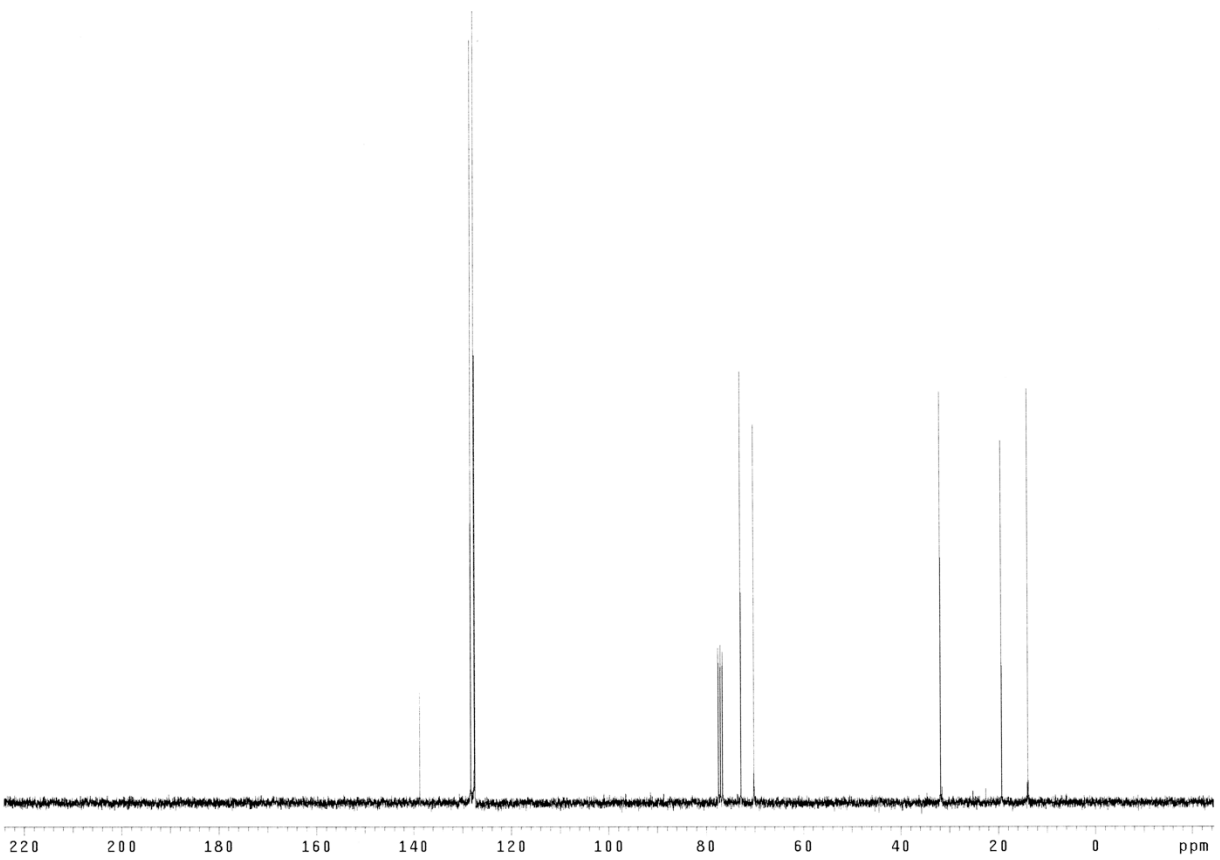
Chapter 4 Supporting Information

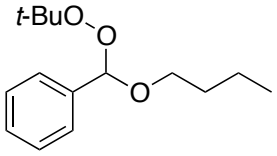
Synthesis of *tert*-Butyl Peroxyacetals from Benzyl, Allyl, or Propargyl Ethers *via* Iron-Promoted C–H Bond Functionalization



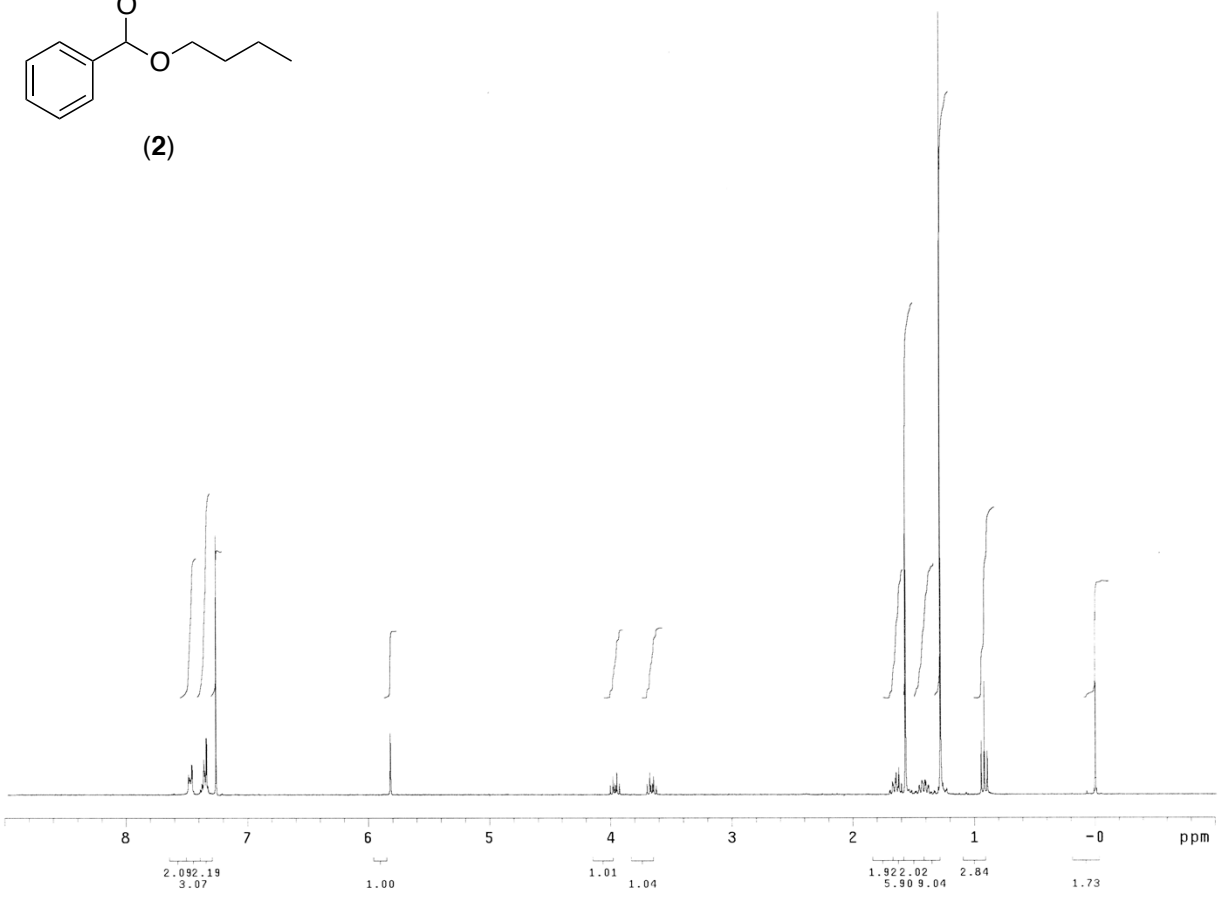
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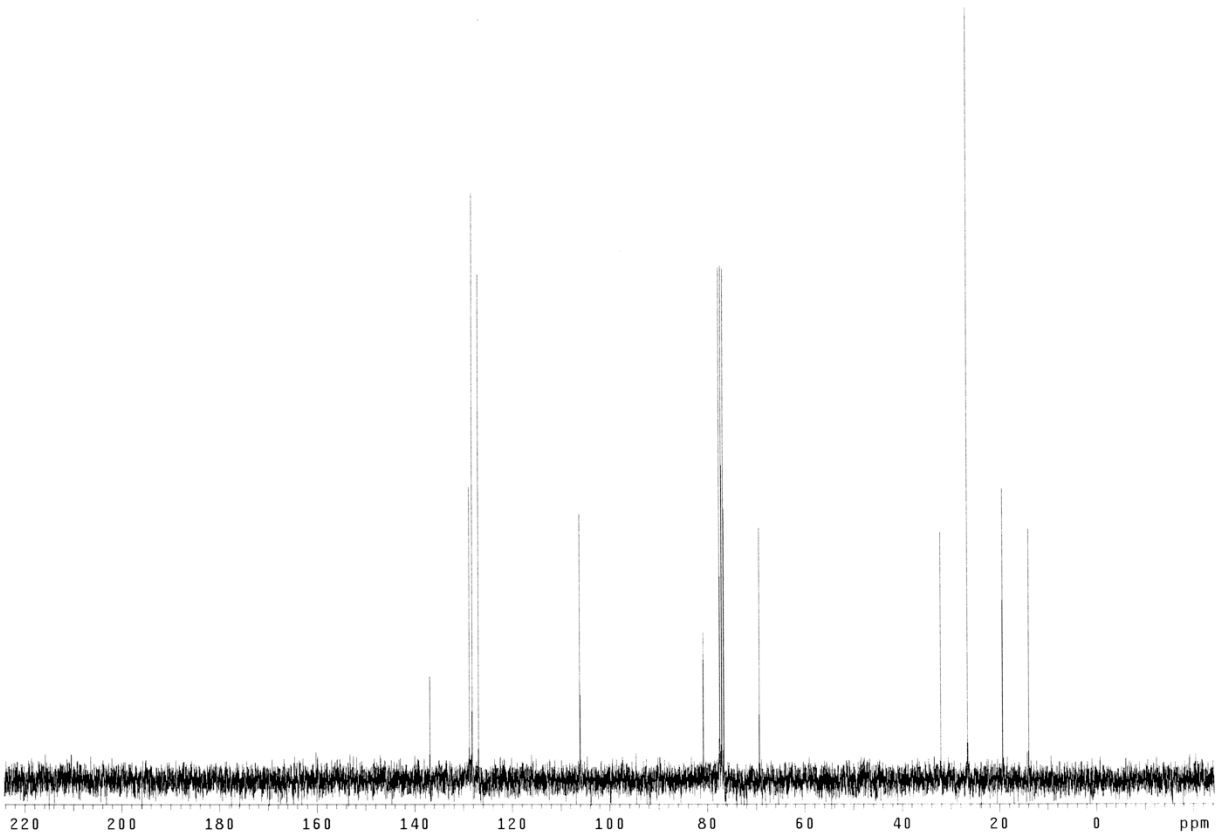

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0.95

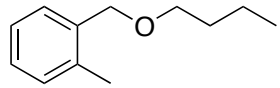

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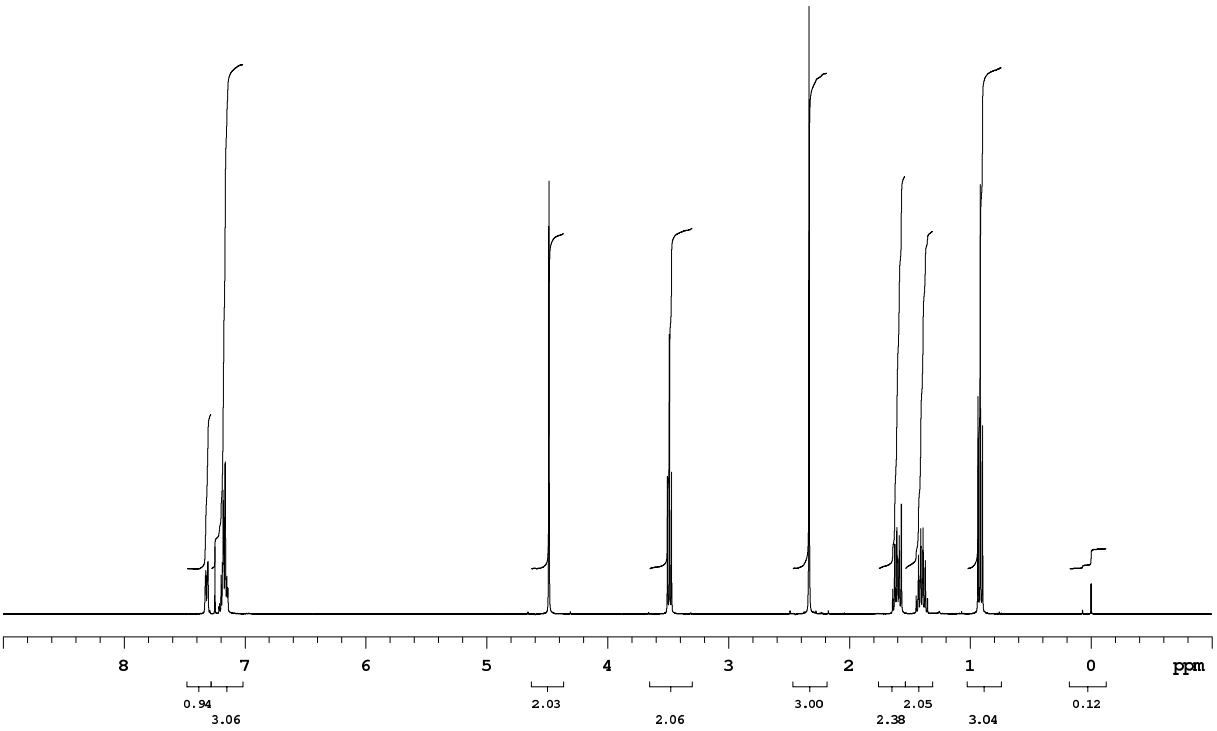

t-BuO
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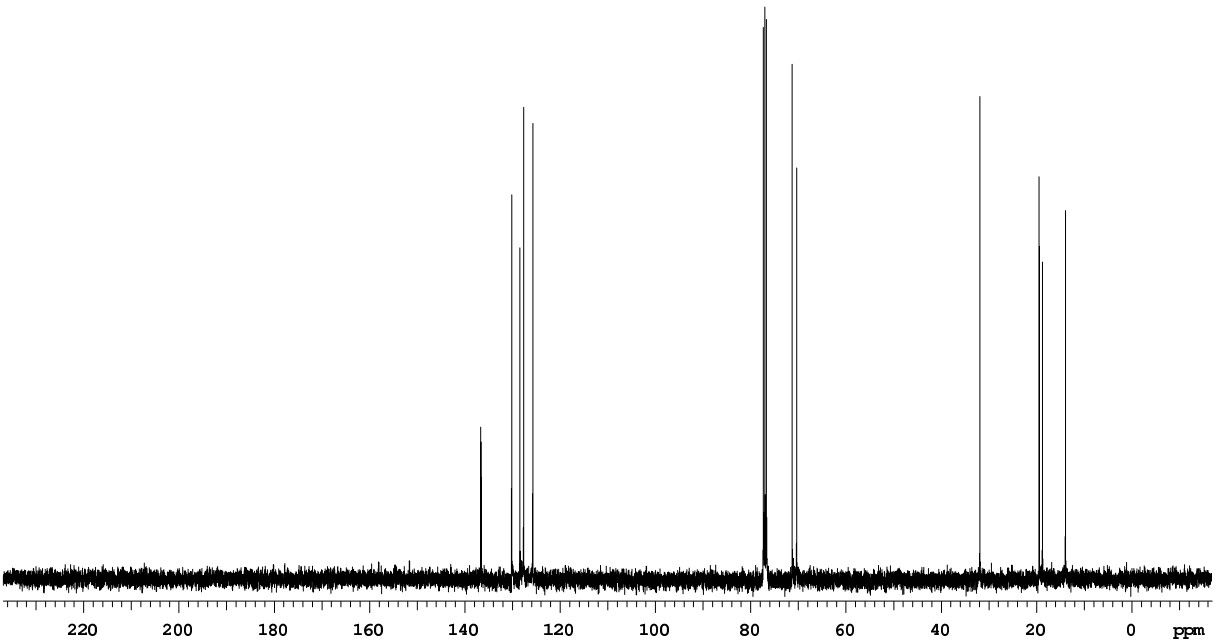
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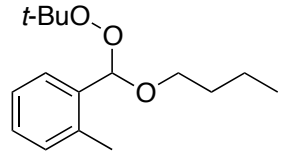

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7
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5
4
3
2
1
-0
ppm
2.09
2.19
3.07
1.00
1.01
1.04
1.92
2.02
5.90
9.04
2.84
1.73


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200
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120
100
80
60
40
20
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ppm

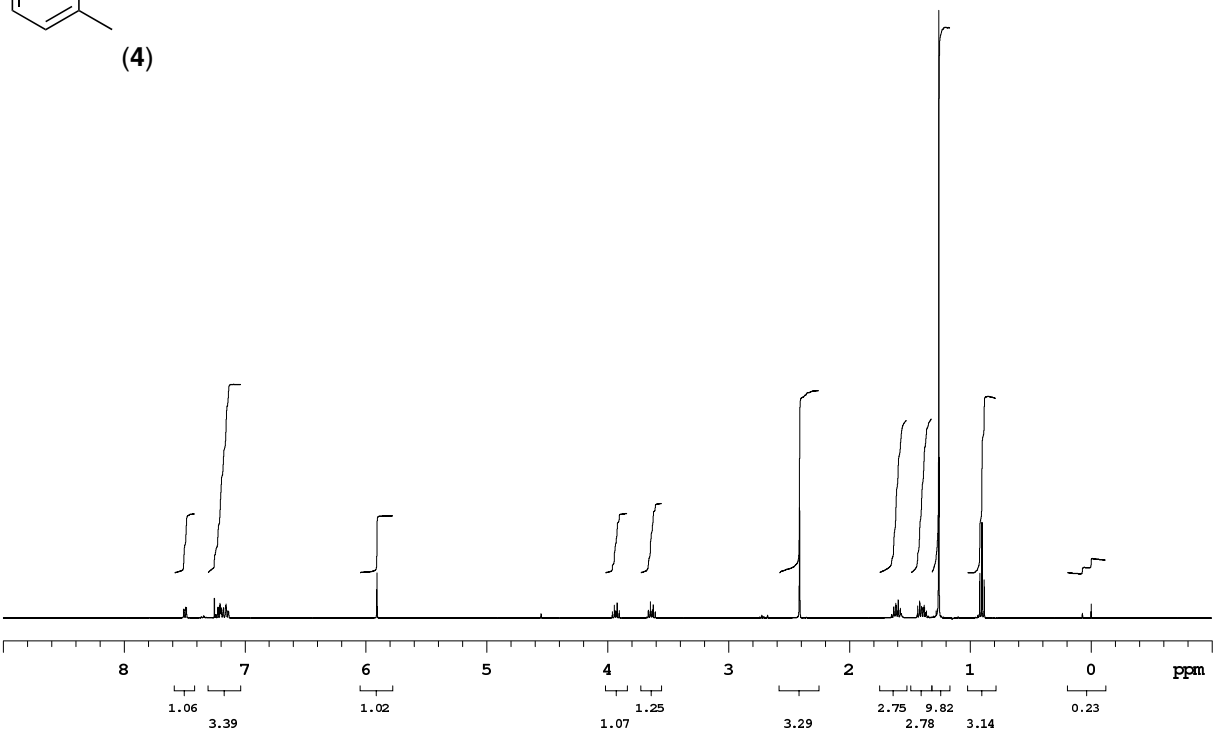

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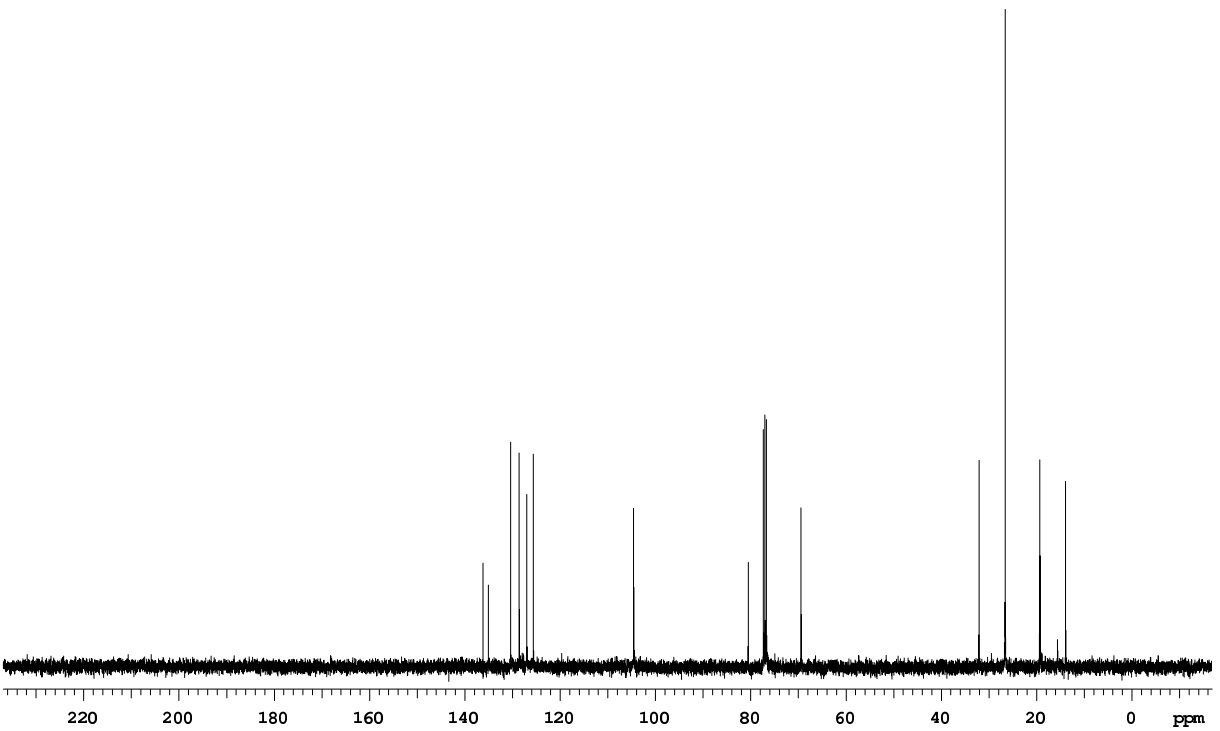

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5
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ppm
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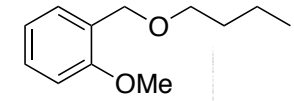

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ppm

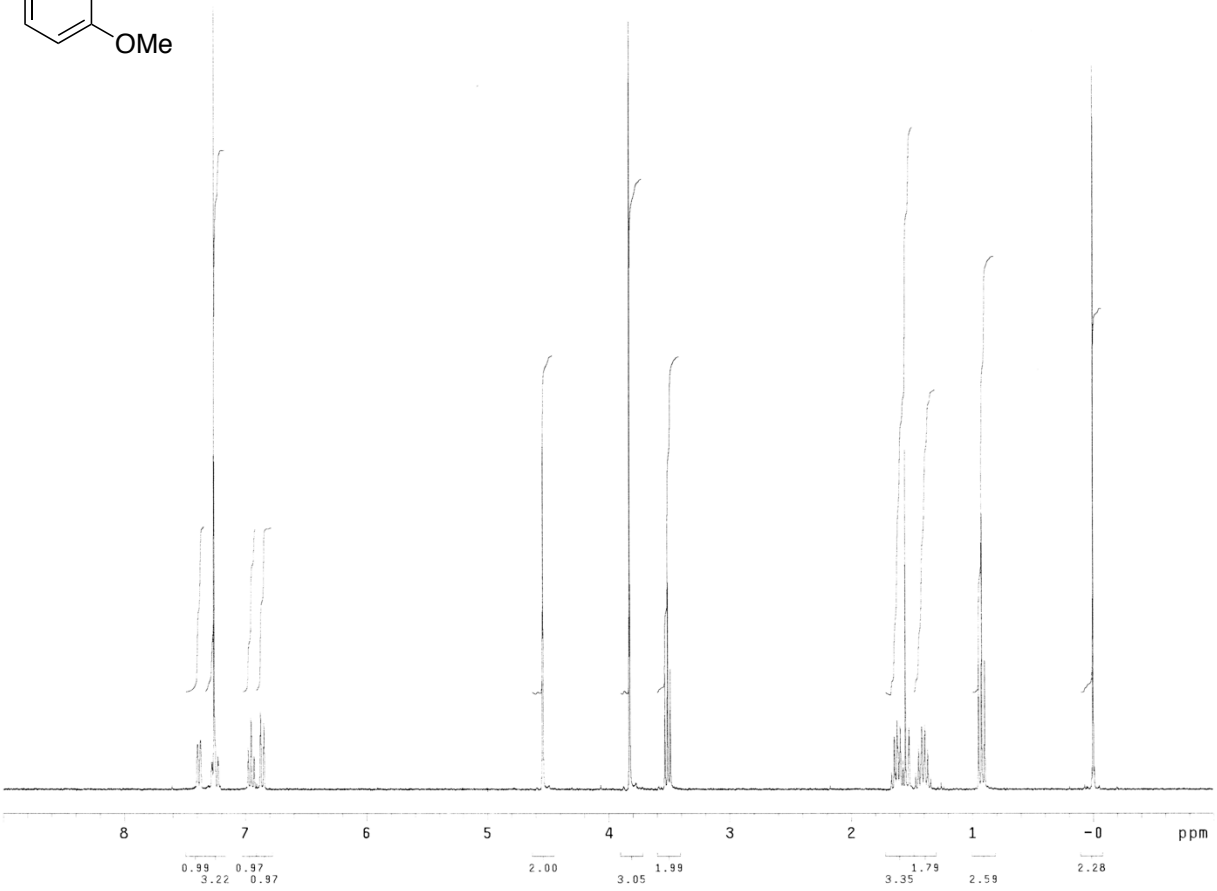

t-BuO
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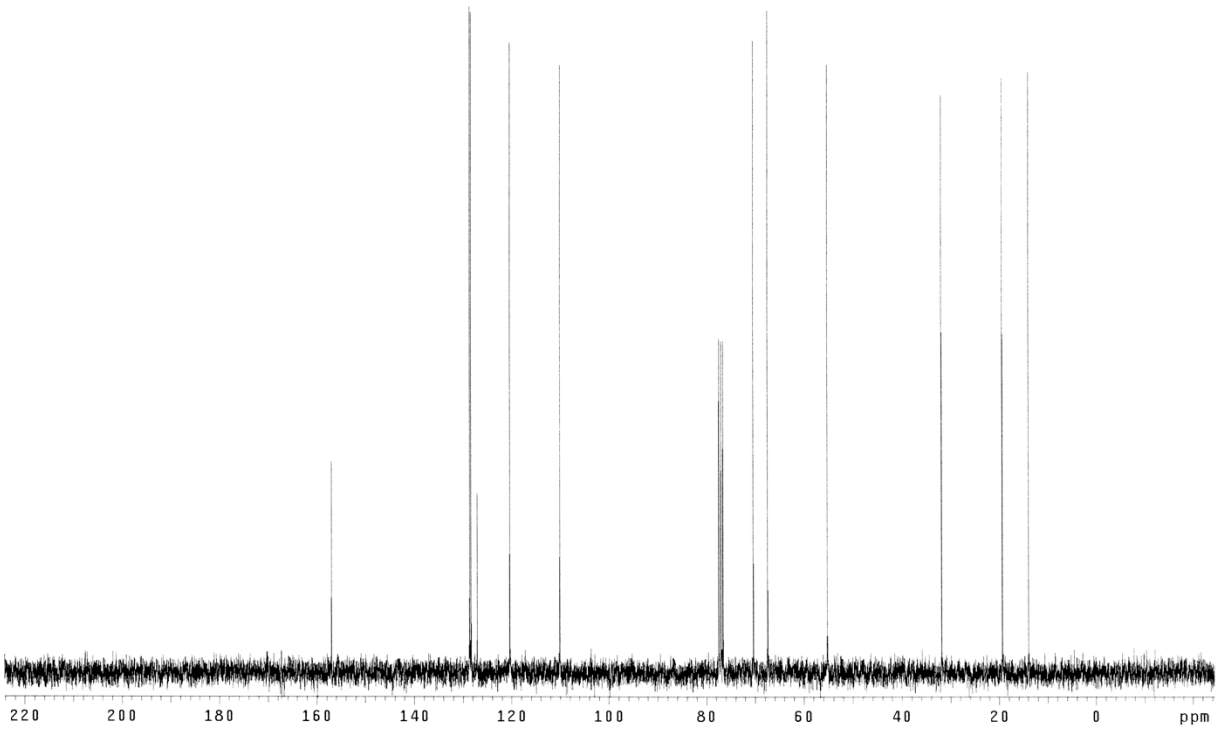
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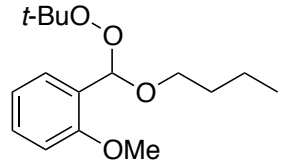

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7
6
5
4
3
2
1
0
ppm
1.06
3.39
1.02
1.07
1.25
3.29
2.75
9.82
2.78
3.14
0.23


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200
180
160
140
120
100
80
60
40
20
0
ppm

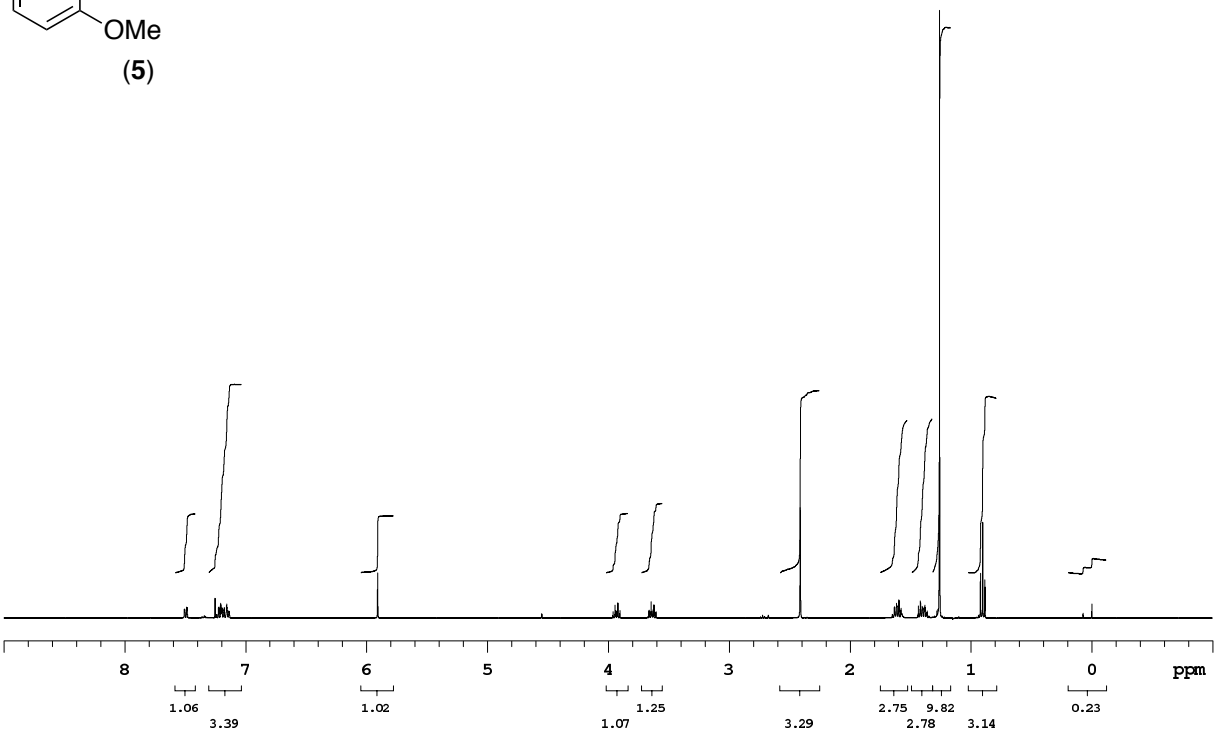

O
OMe

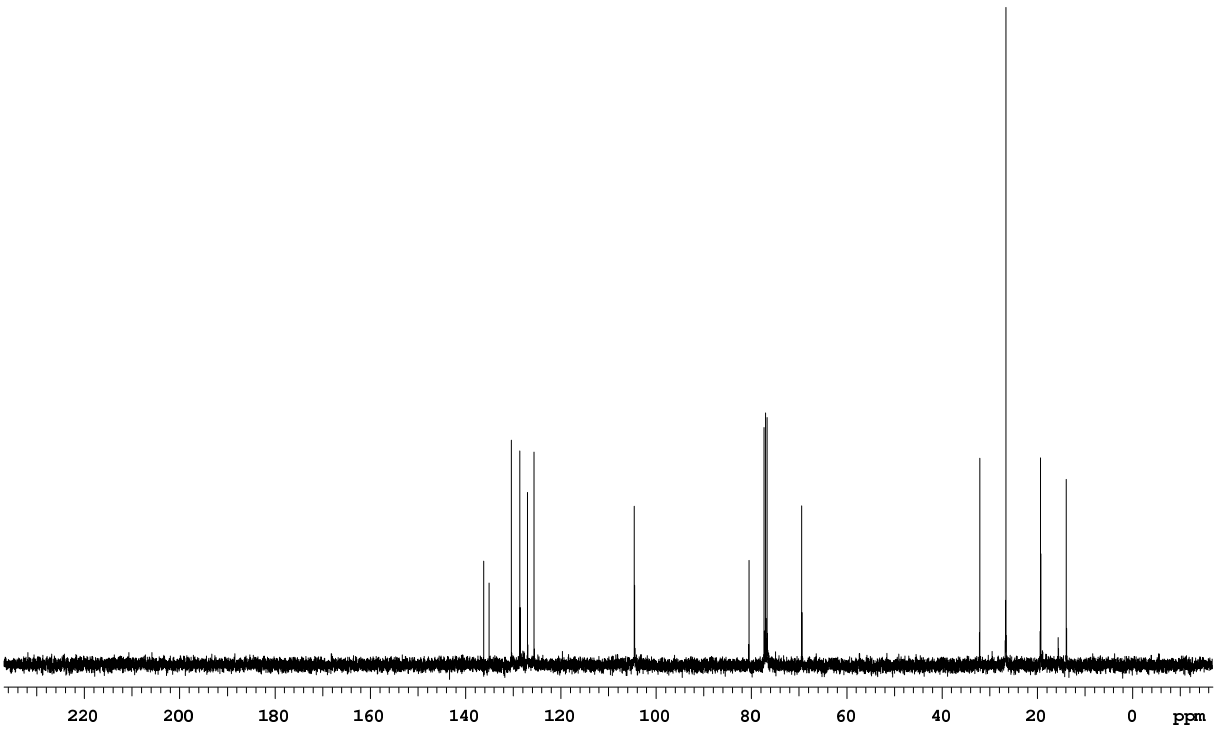

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7
6
5
4
3
2
1
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2.00
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1.99
3.35
1.79
2.59
2.28

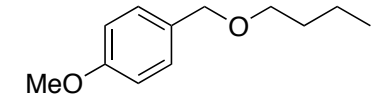

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ppm

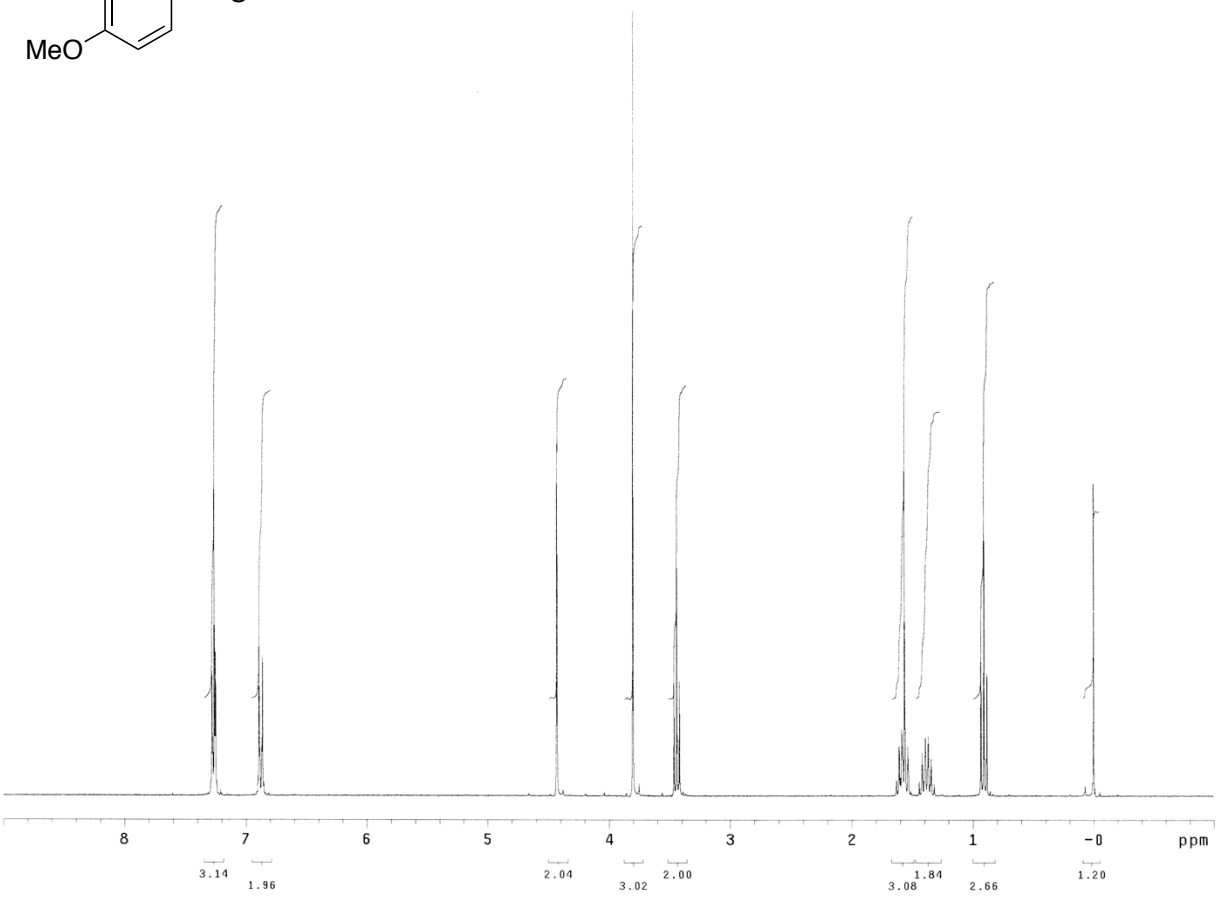

t-BuO
O
O
OMe

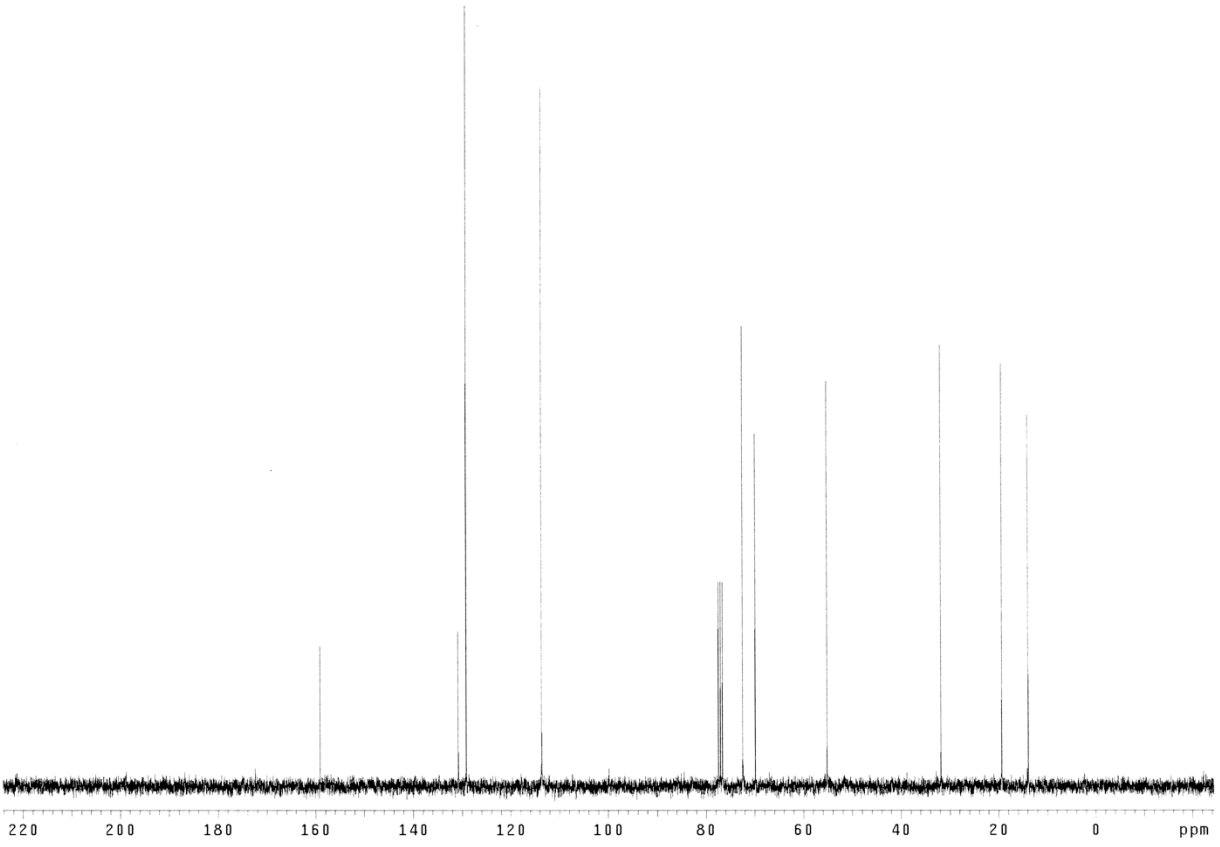
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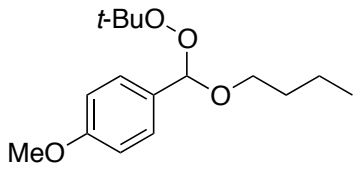

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7
6
5
4
3
2
1
0
ppm
1.06
3.39
1.02
1.07
1.25
3.29
2.75
9.82
2.78
3.14
0.23


220
200
180
160
140
120
100
80
60
40
20
0
ppm

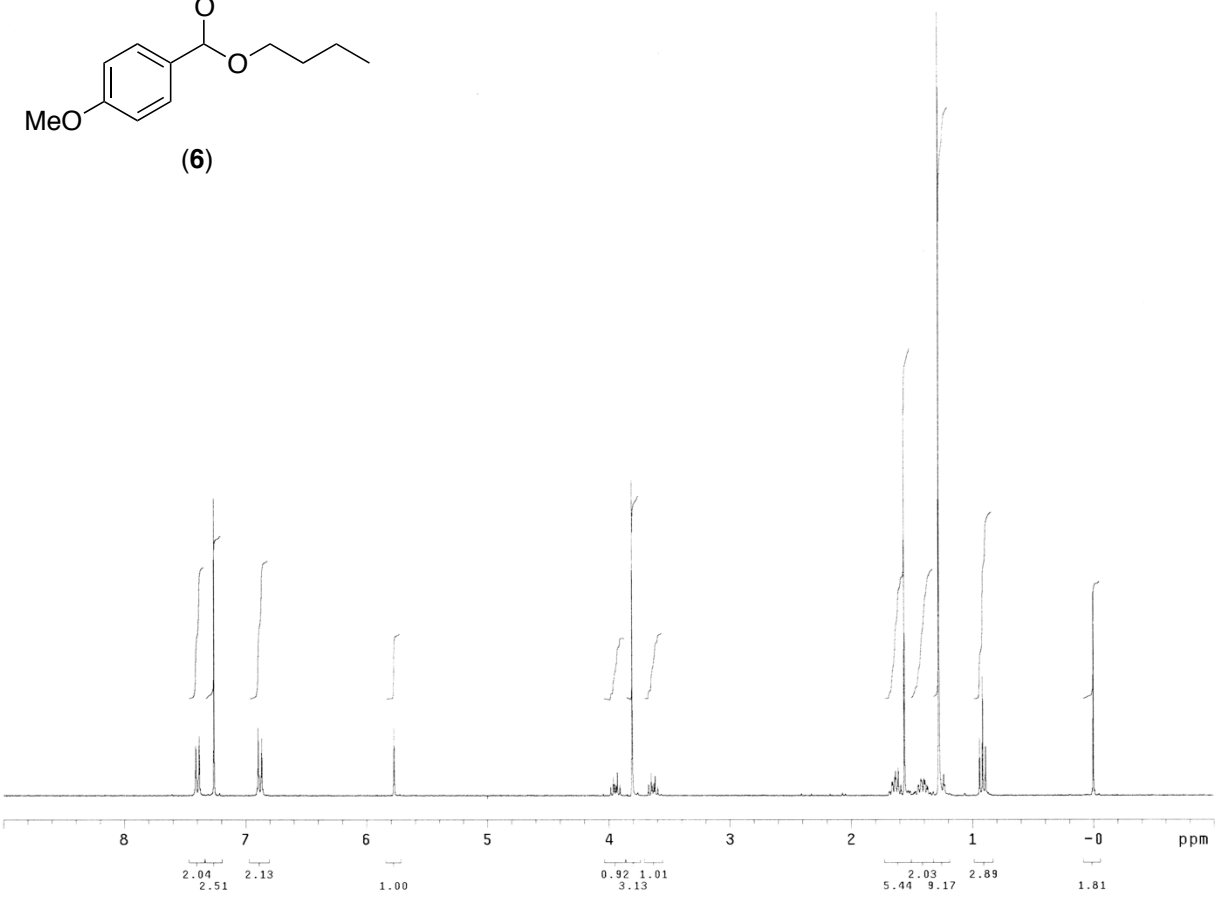

MeO
O

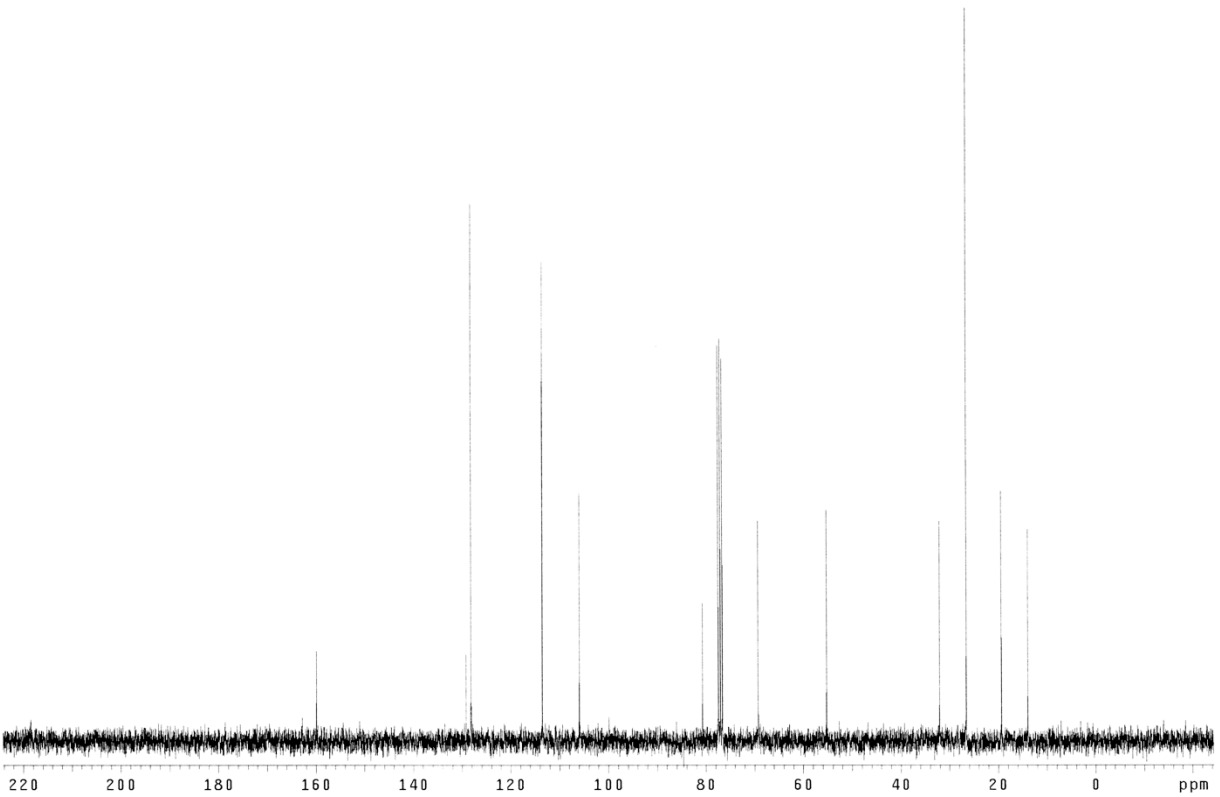

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1.20

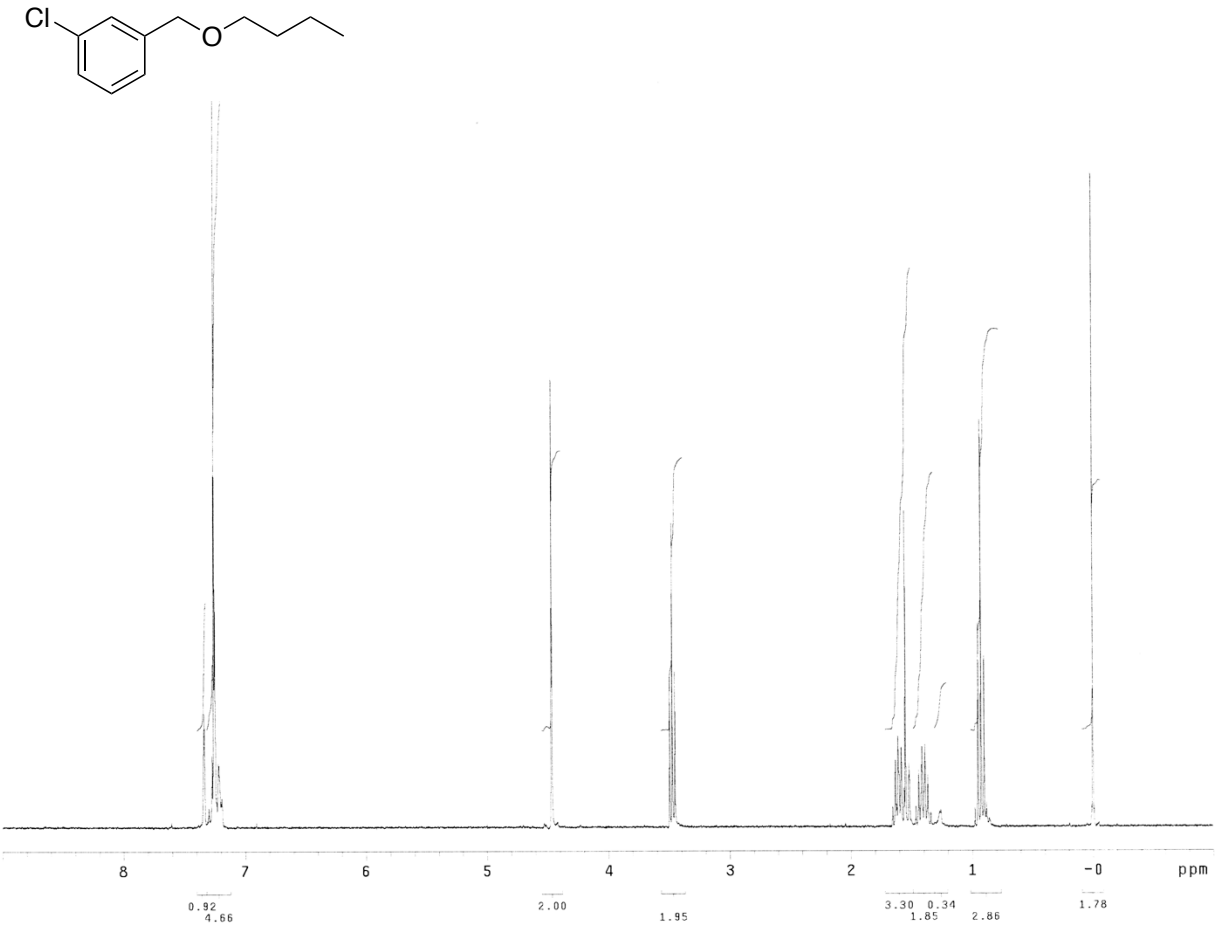

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0
ppm

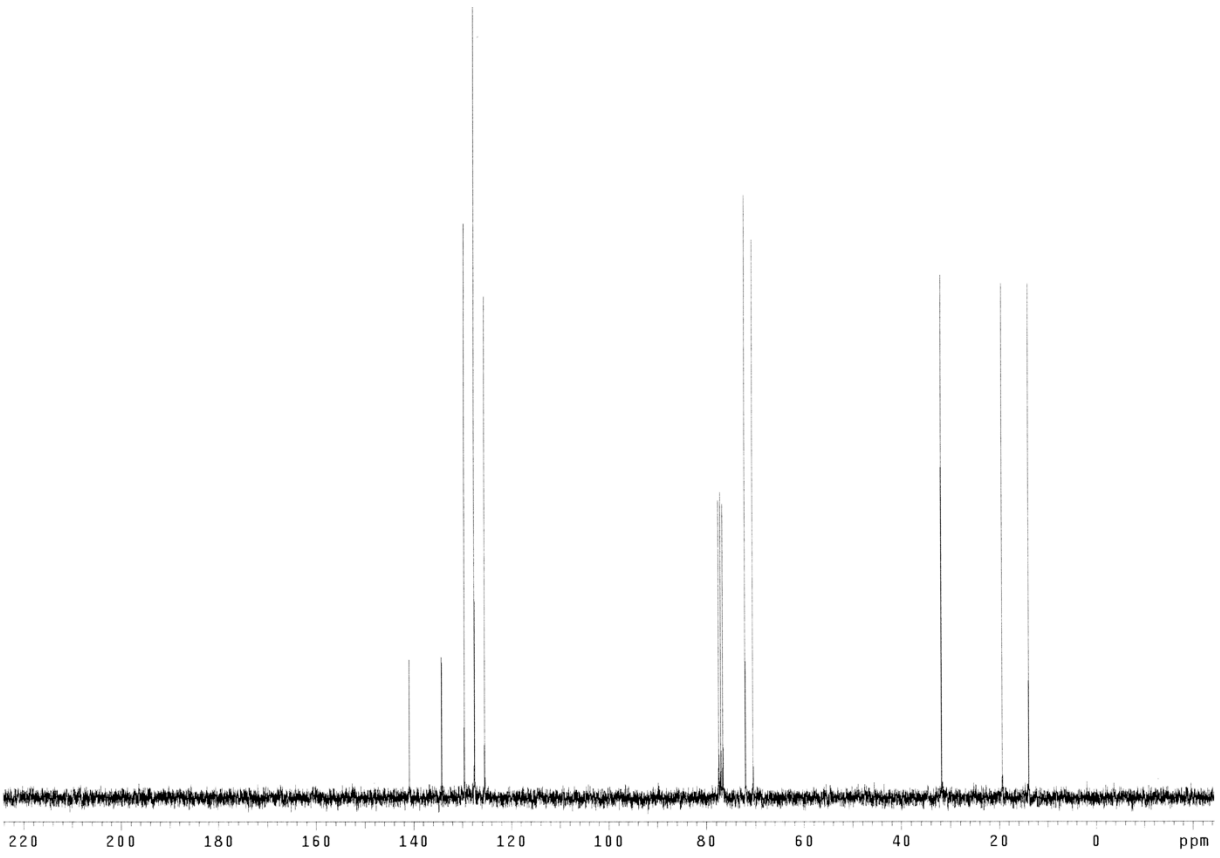

t-BuO
O
O
MeO

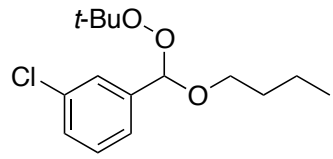
(**6**)


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7
6
5
4
3
2
1
-0
ppm
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1.81

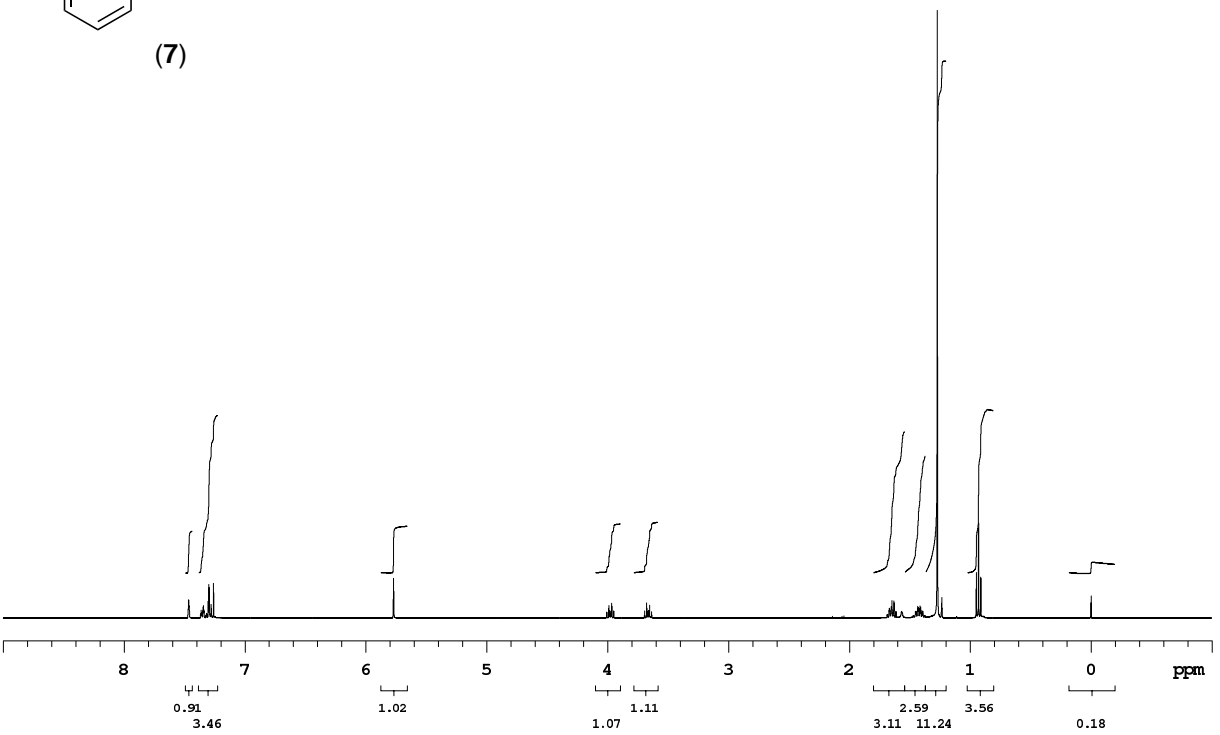

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100
80
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40
20
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ppm

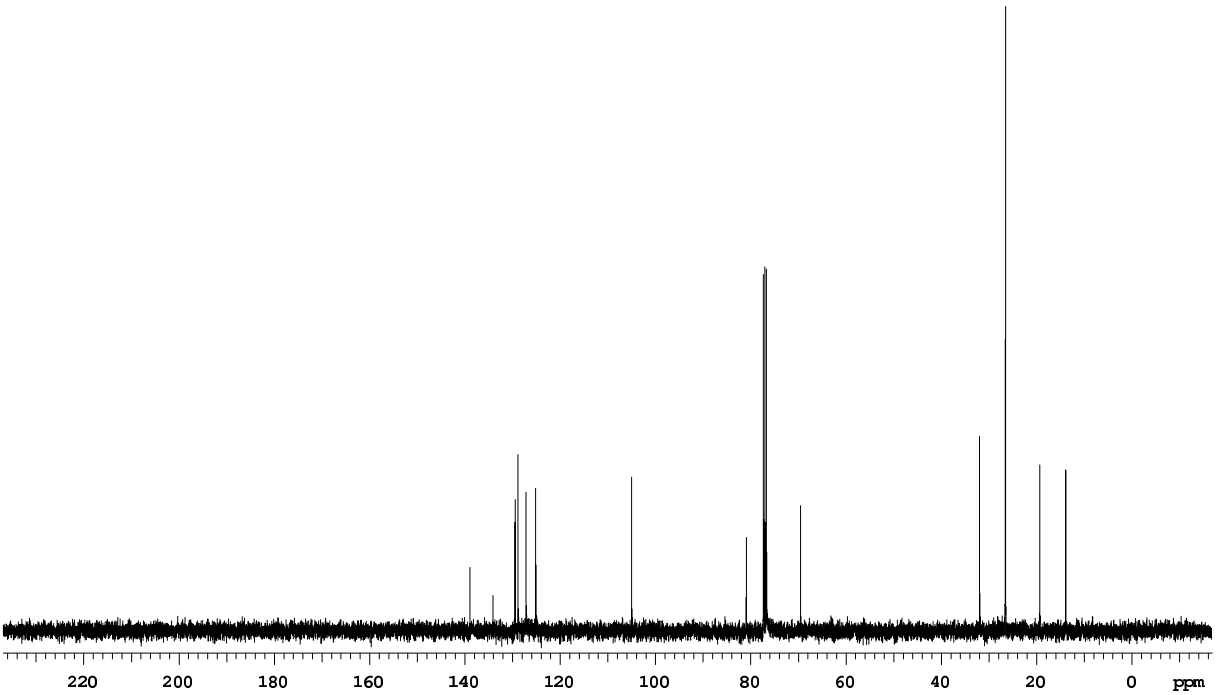

Cl
O
8
7
6
5
4
3
2
1
-0
ppm
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2.00
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1.78

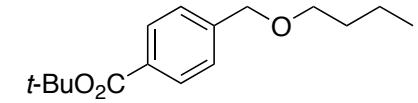

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ppm

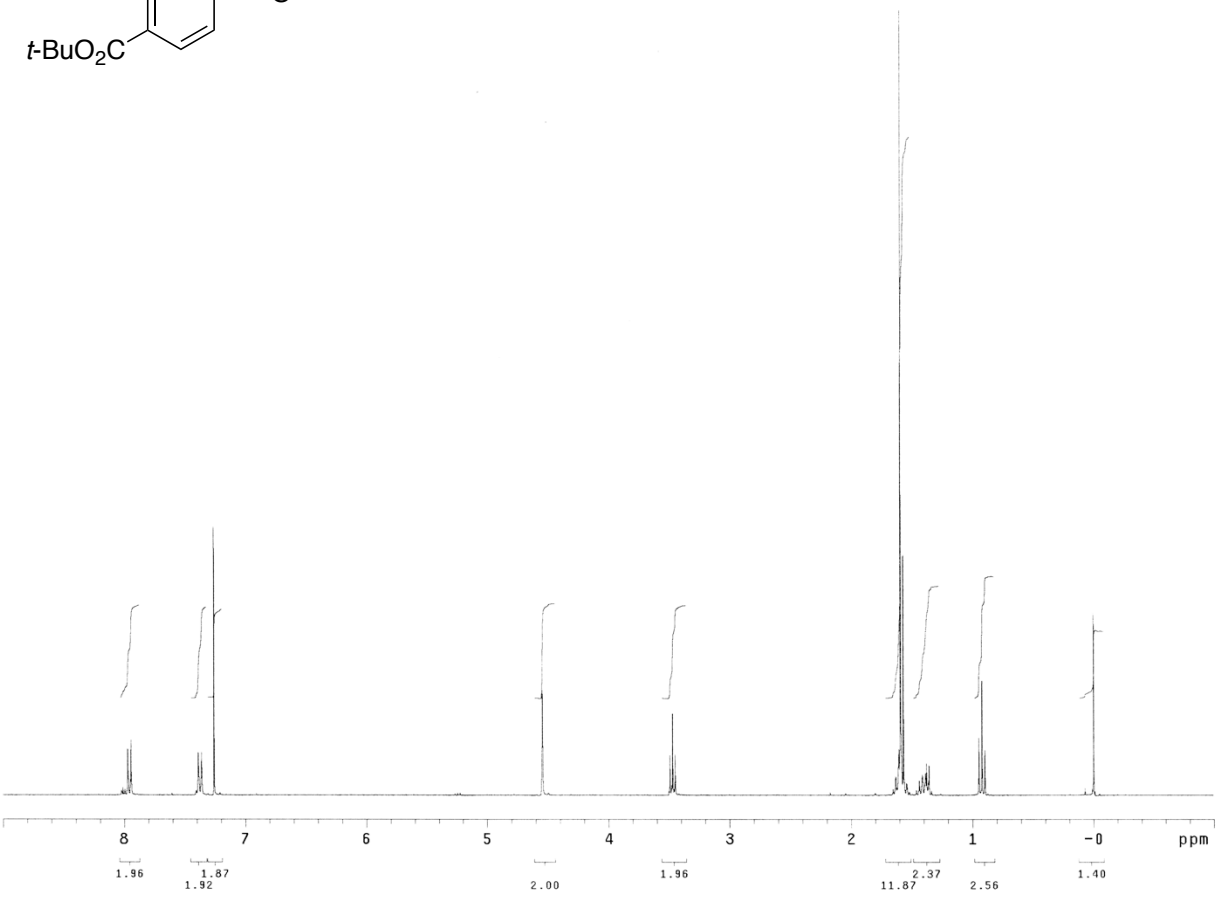

t-BuO
O
Cl
O

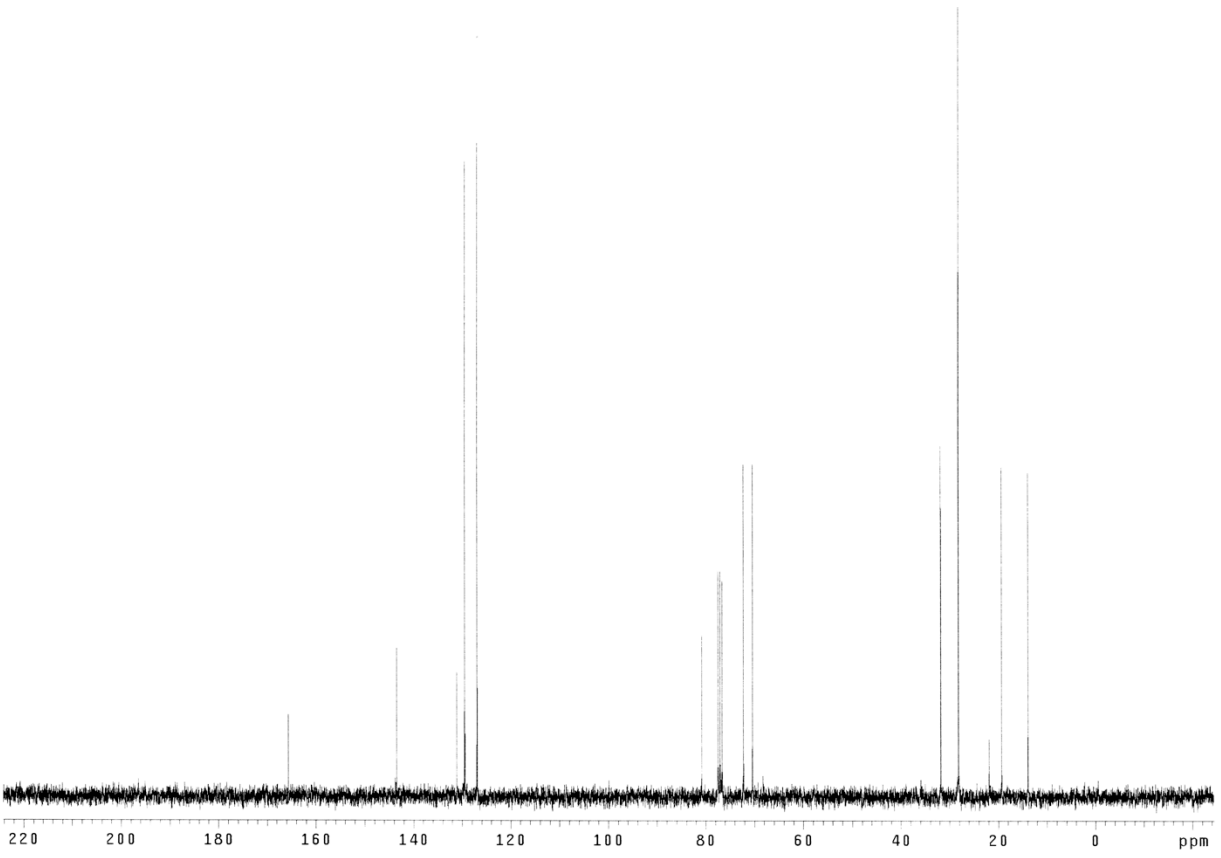
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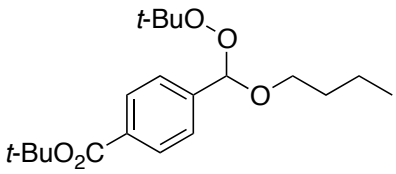

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5
4
3
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1
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ppm
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1.07
1.11
2.59
3.11
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0.18


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120
100
80
60
40
20
0
ppm

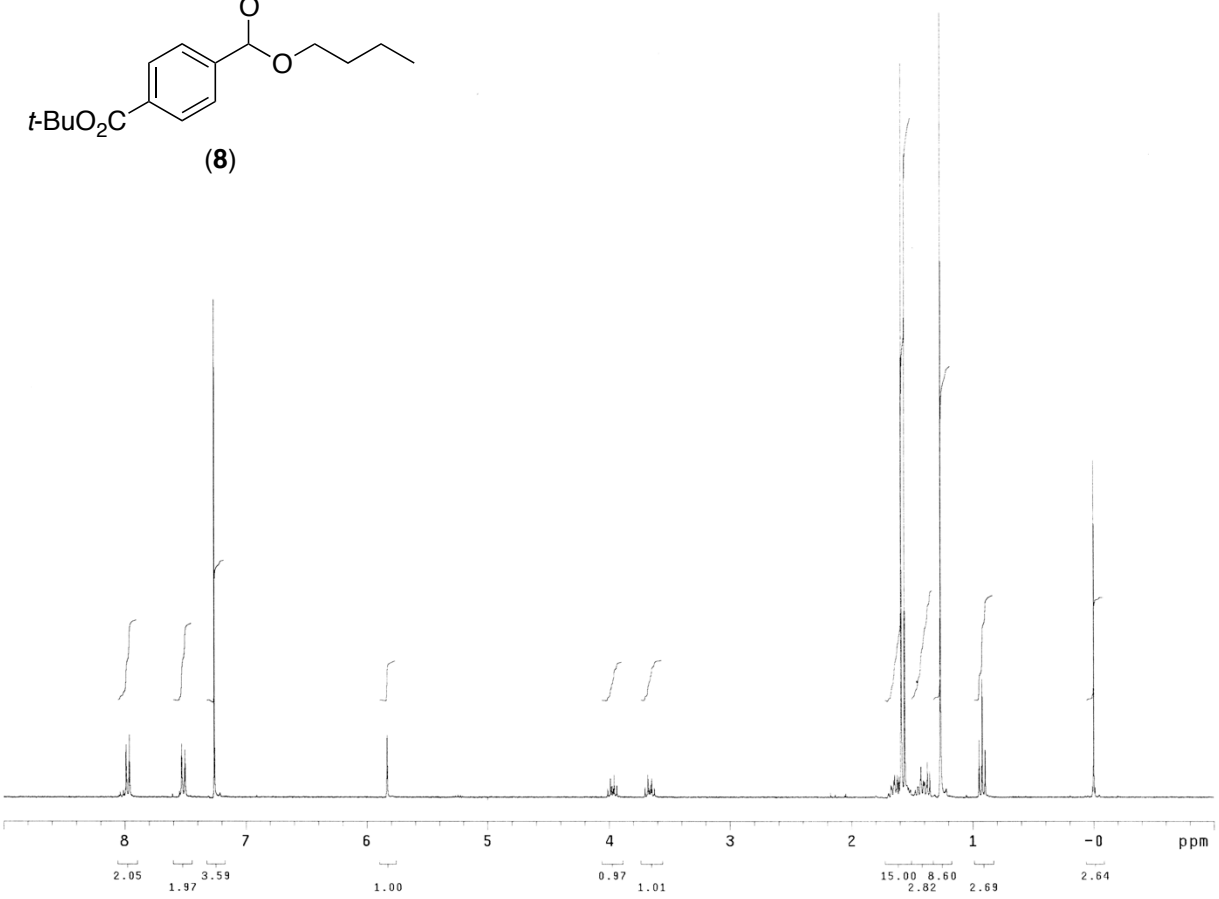

t-BuO2C
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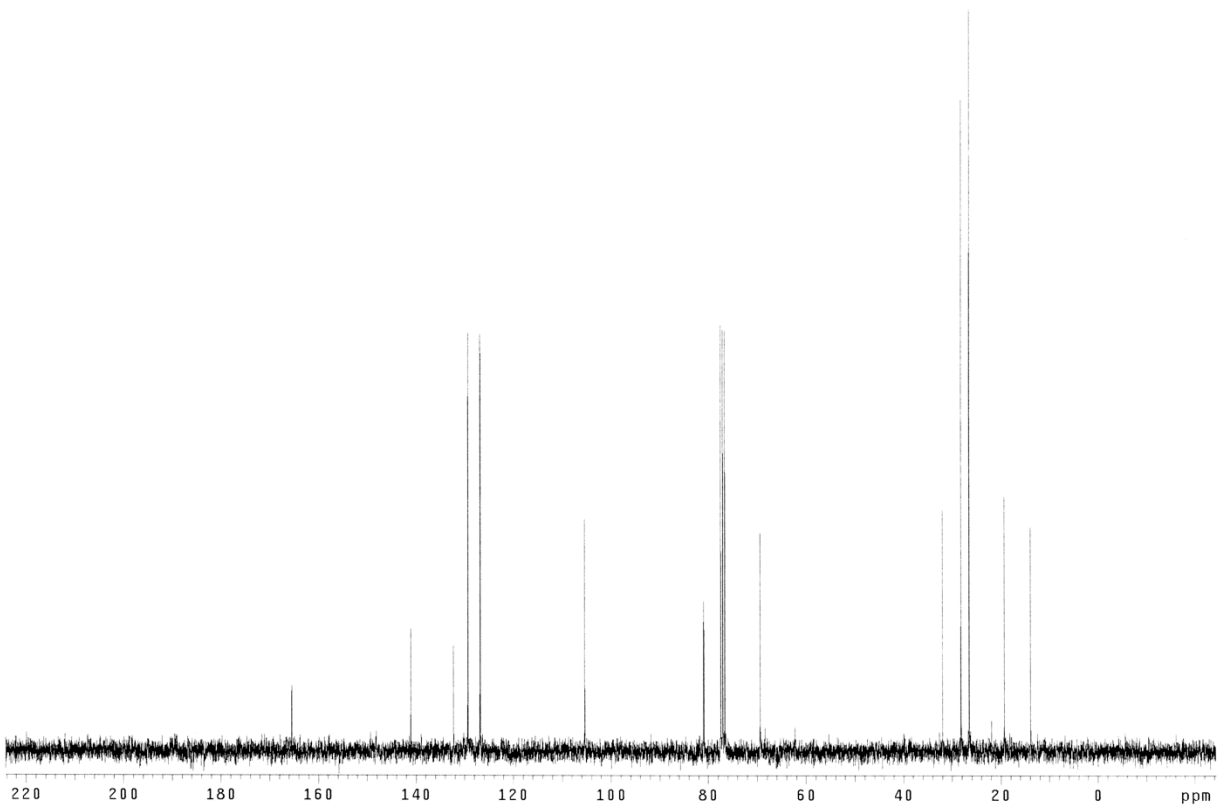

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6
5
4
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ppm
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1.96
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2.37
2.56
1.40

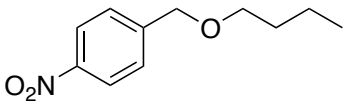

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120
100
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40
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0
ppm

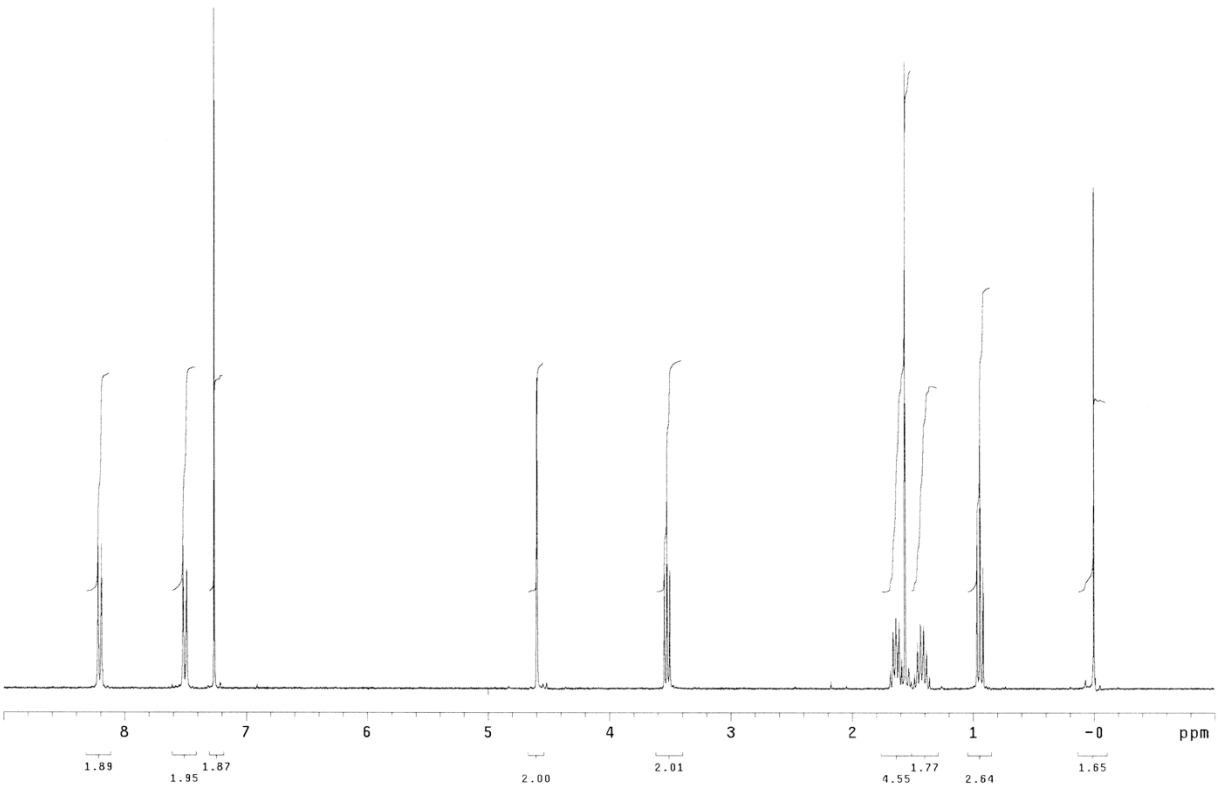

t-BuO
O
O
t-BuO2C

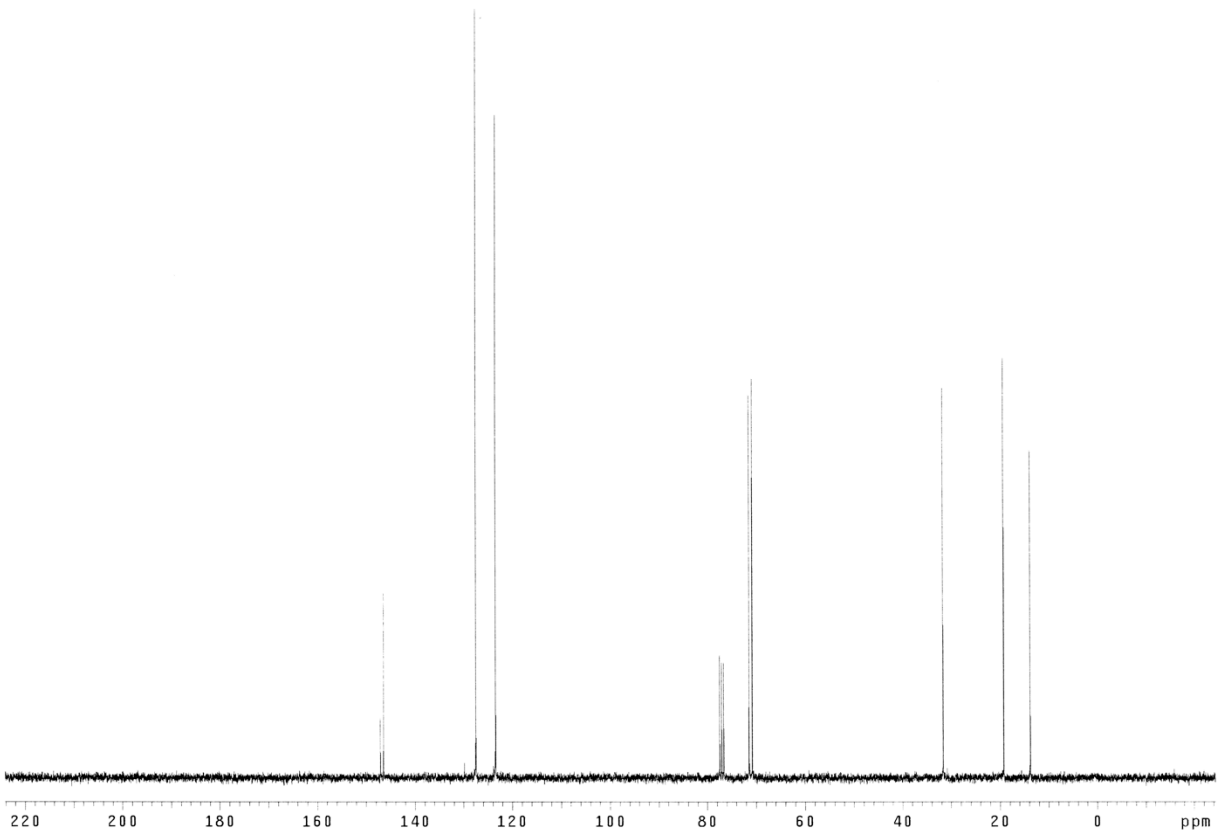
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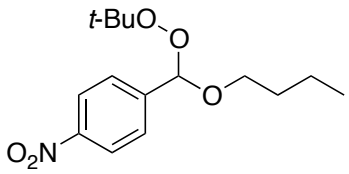

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4
3
2
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-0
ppm
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1.97
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1.00
0.97
1.01
15.00
8.60
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2.69
2.64


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200
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140
120
100
80
60
40
20
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ppm

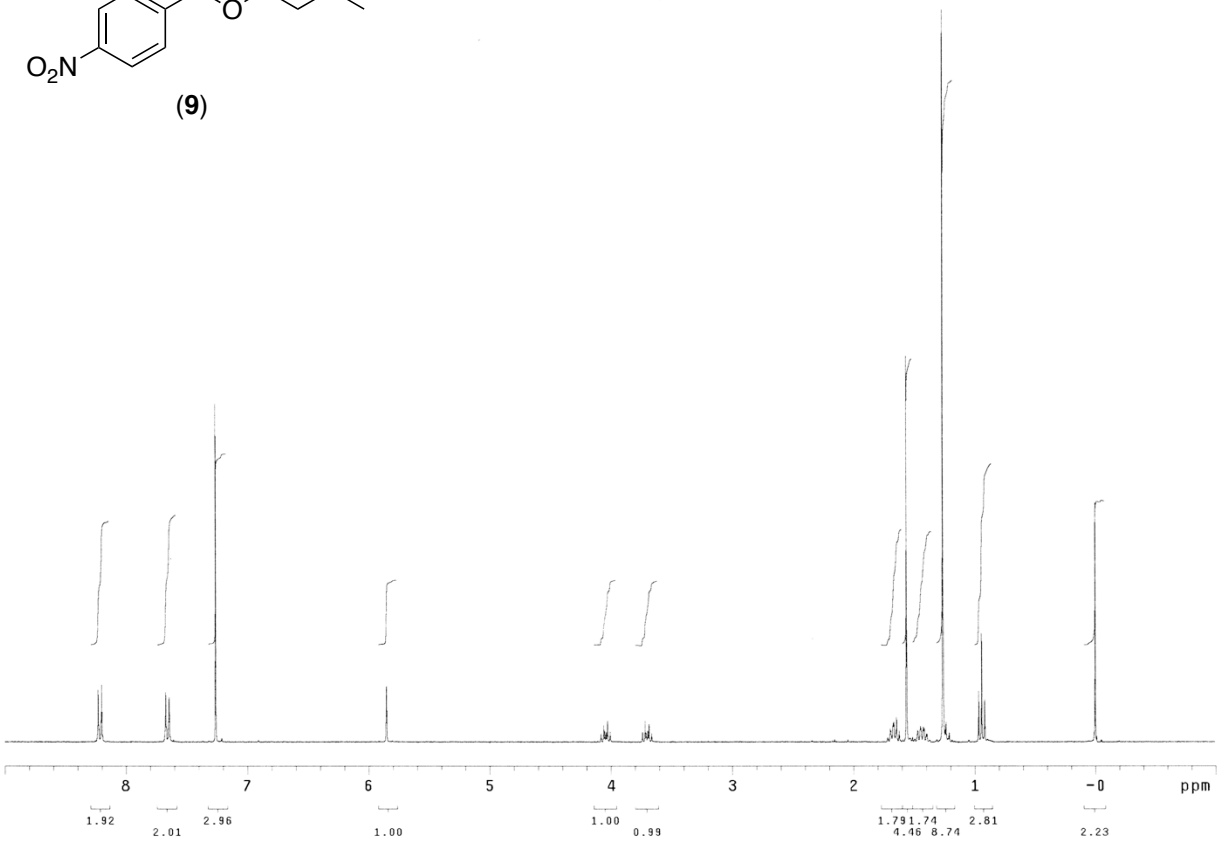

O2N
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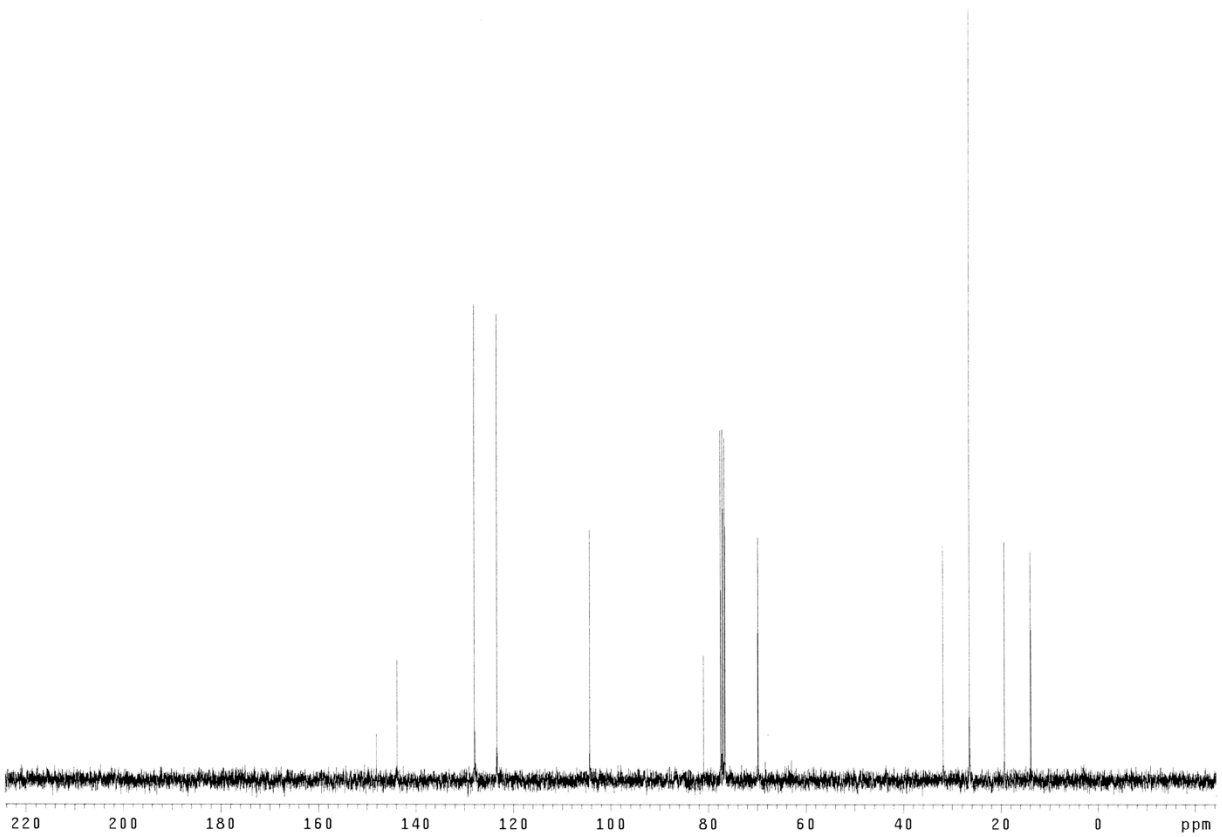

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6
5
4
3
2
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ppm
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1.65

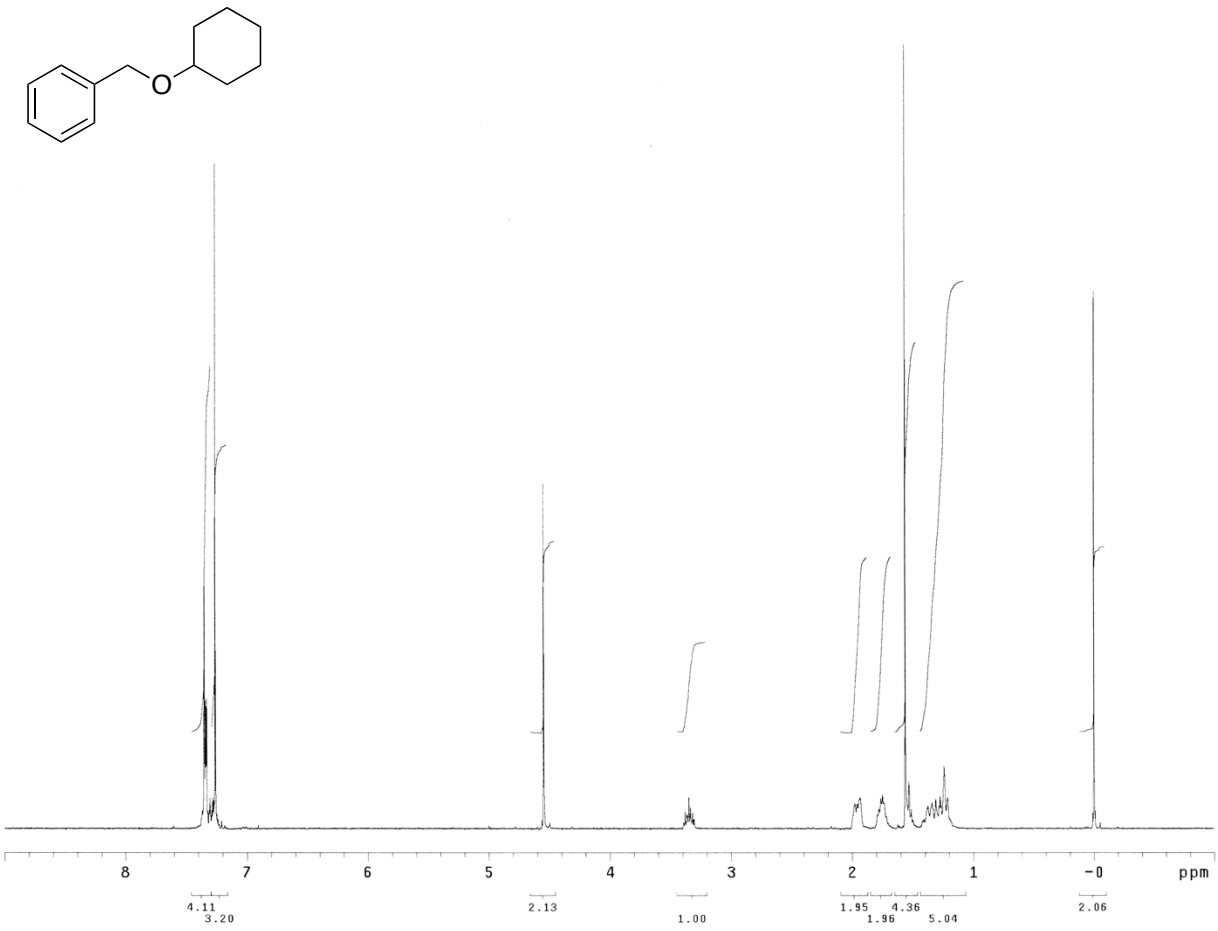

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0
ppm

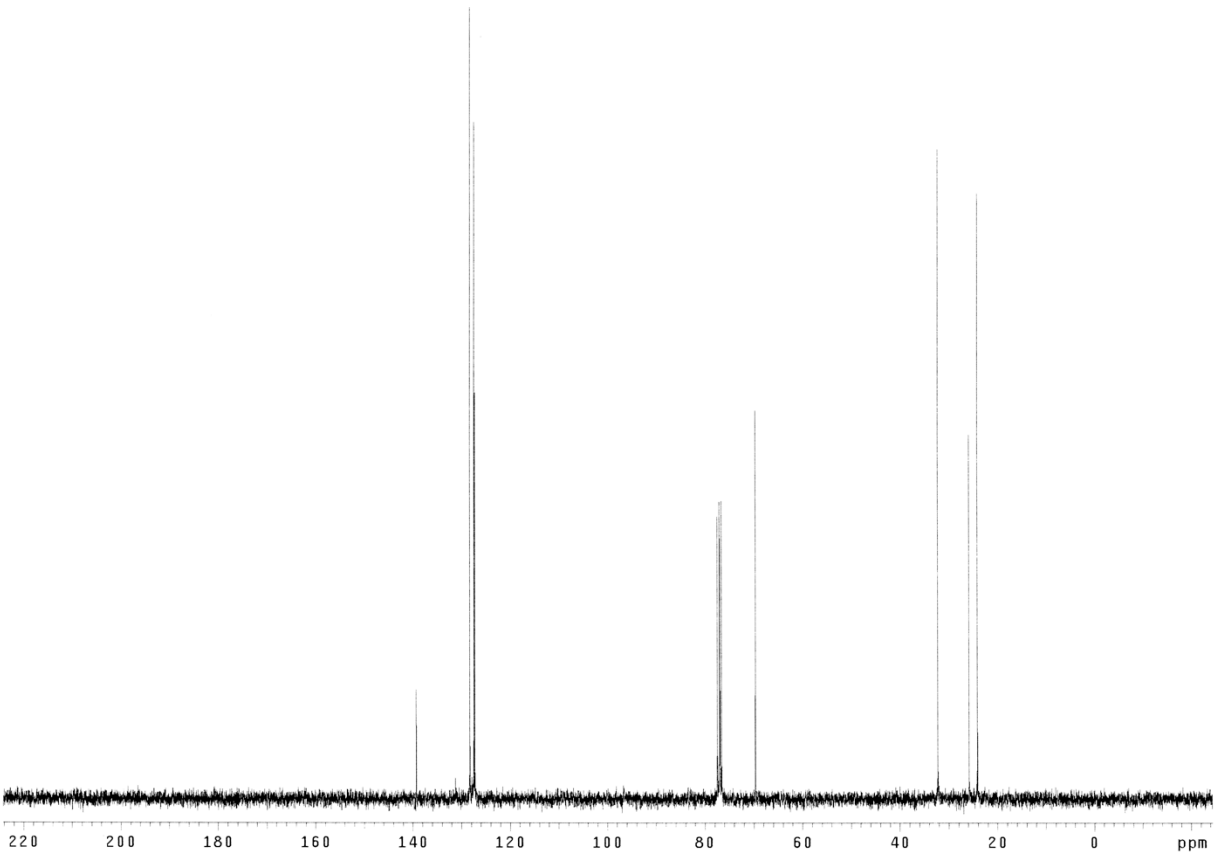

t-BuO
O
O
O2N

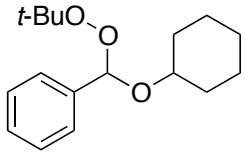
(**9**)


8
7
6
5
4
3
2
1
-0
ppm
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2.01
2.96
1.00
1.00
0.99
1.79
1.74
4.46
8.74
2.81
2.23

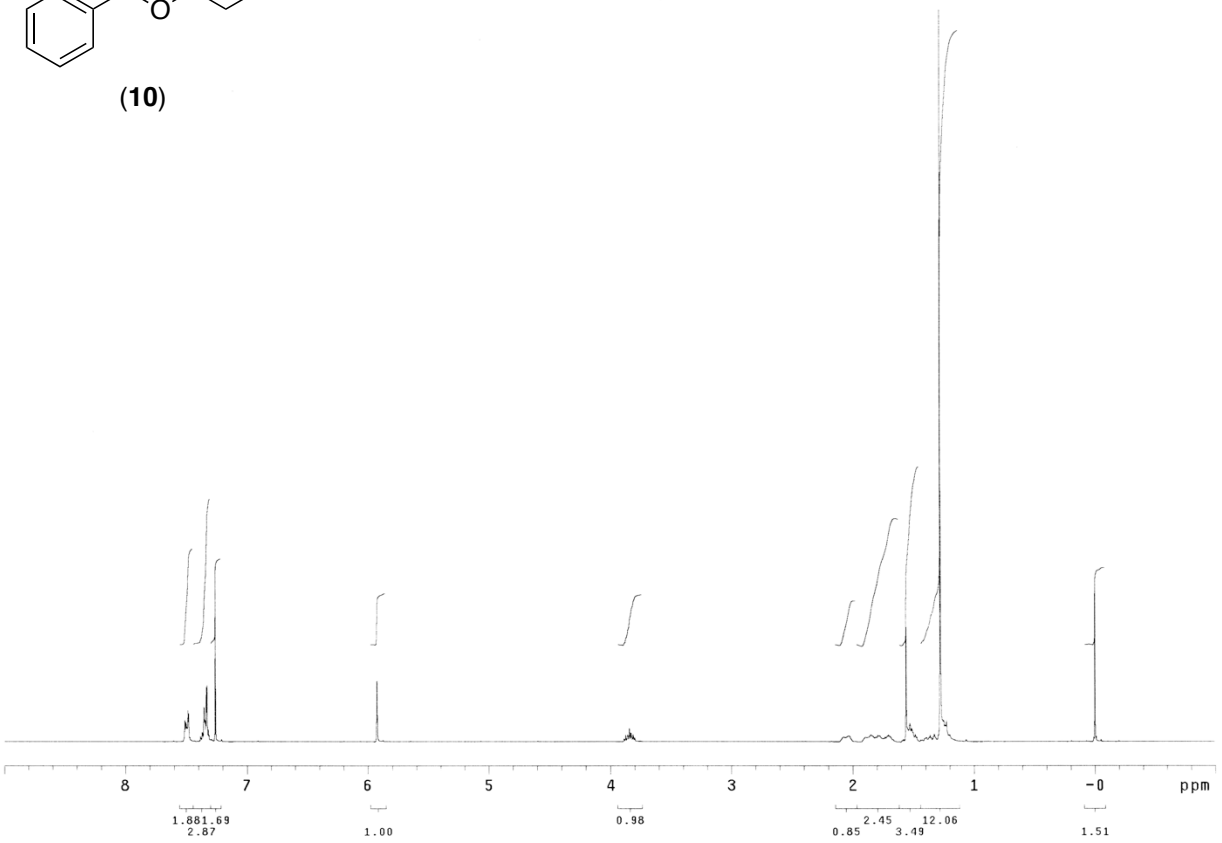

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200
180
160
140
120
100
80
60
40
20
0
ppm

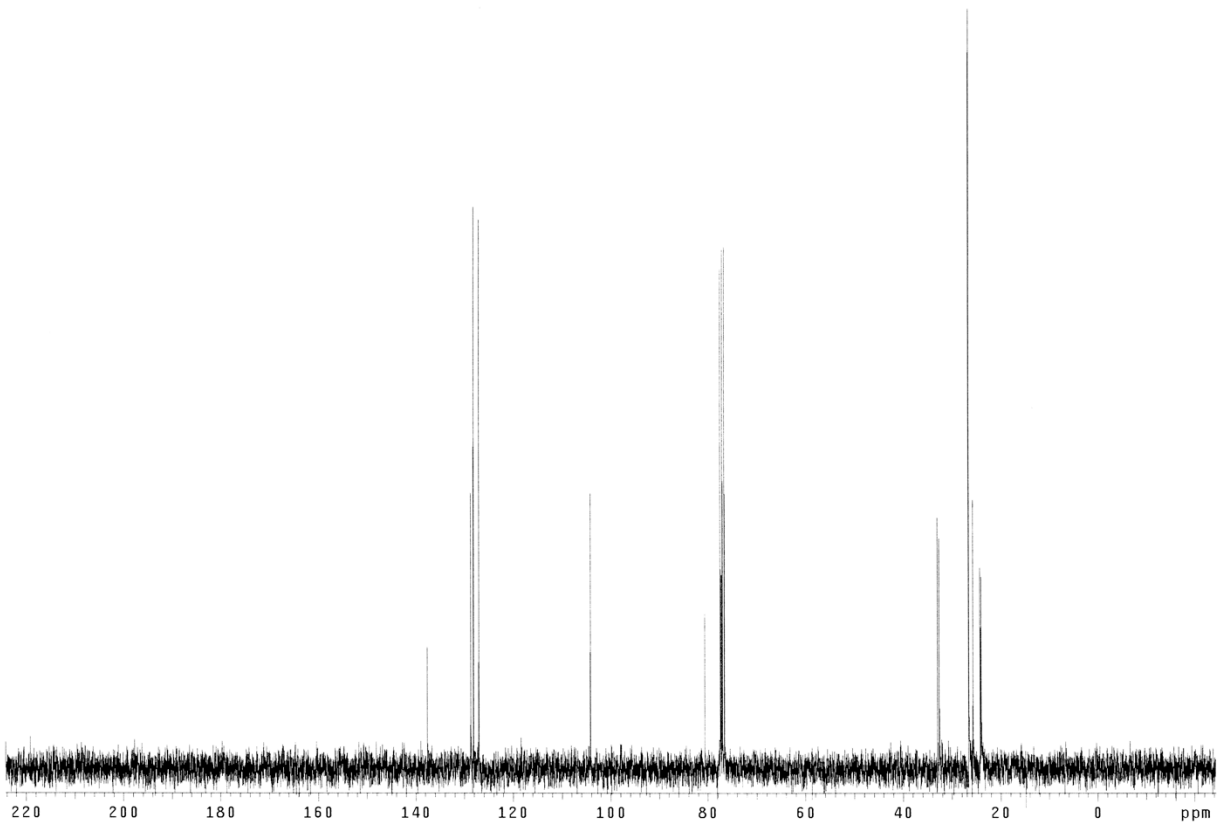

O
8
7
6
5
4
3
2
1
-0
ppm
4.11
3.20
2.13
1.00
1.95
1.96
4.36
5.04
2.06

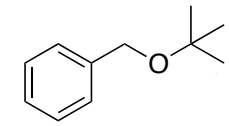

220
200
180
160
140
120
100
80
60
40
20
0
ppm

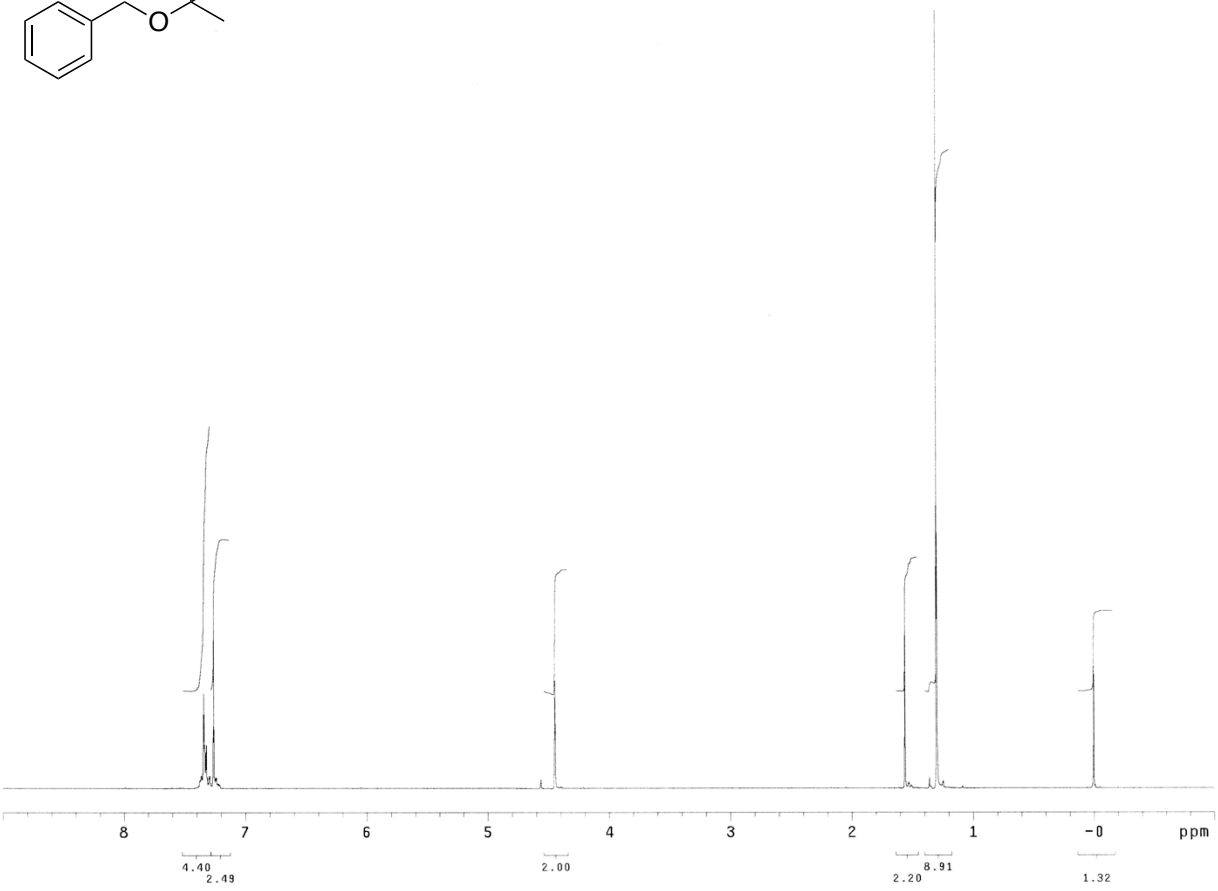

t-BuO
O
O

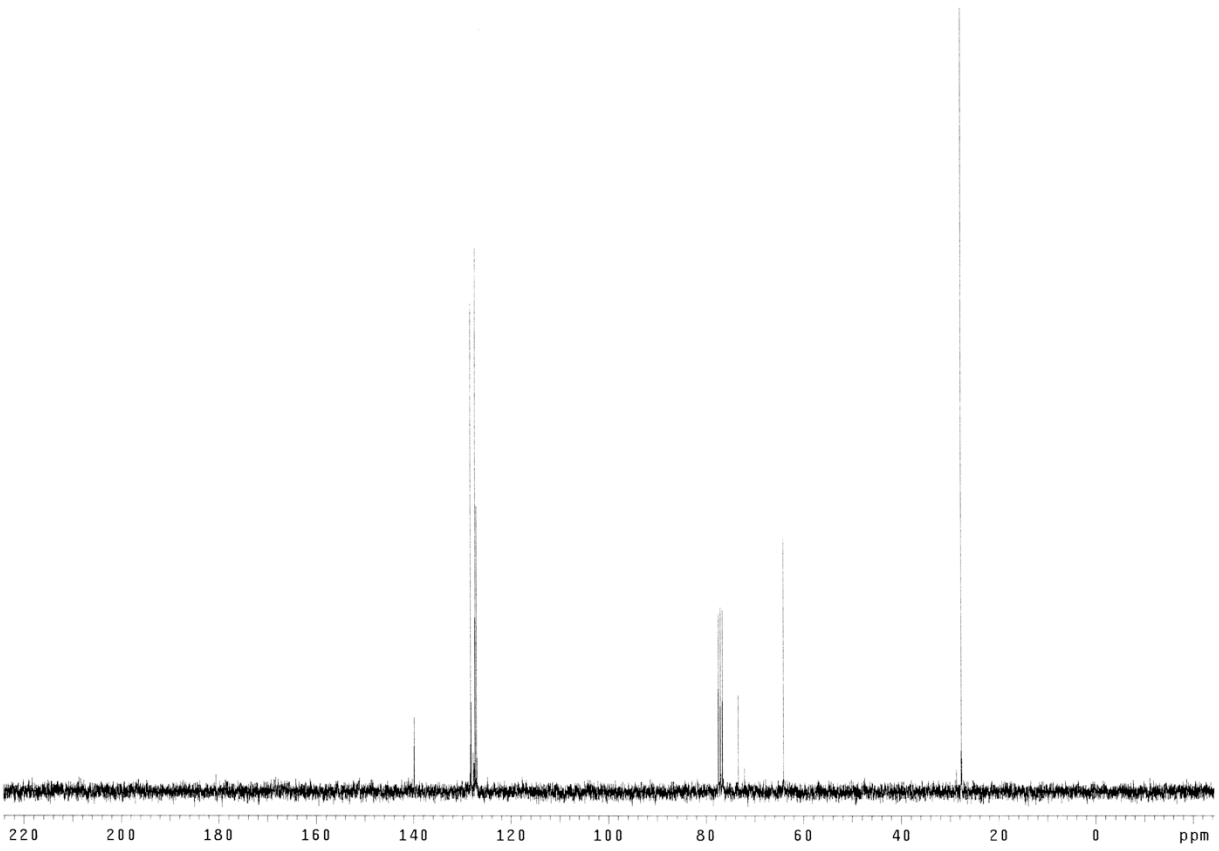
(**10**)

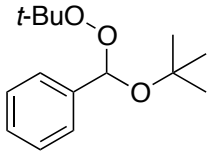

8
7
6
5
4
3
2
1
-0
ppm
1.88
1.69
2.87
1.00
0.98
2.45
12.06
0.85
3.49
1.51


220
200
180
160
140
120
100
80
60
40
20
0
ppm

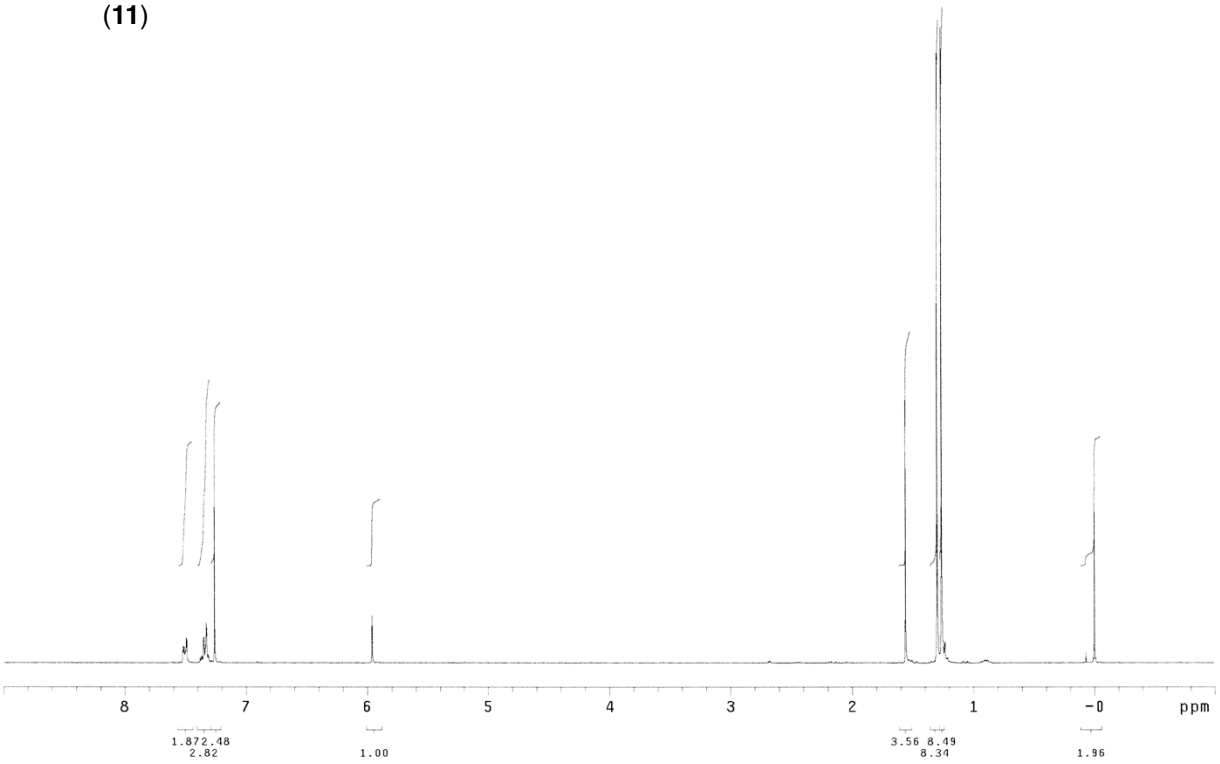


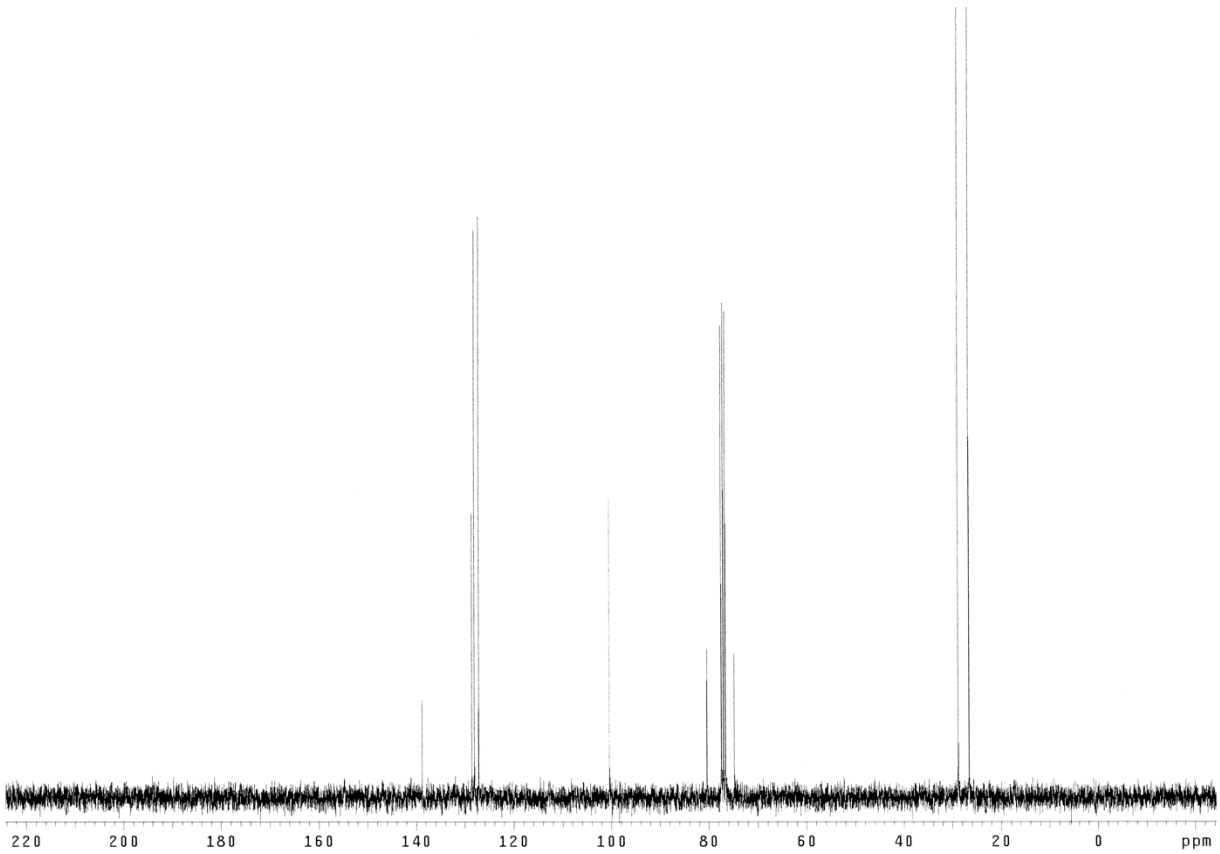

8
7
6
5
4
3
2
1
-0
ppm
4.40
2.49
2.00
2.20
8.91
1.32


220
200
180
160
140
120
100
80
60
40
20
0
ppm

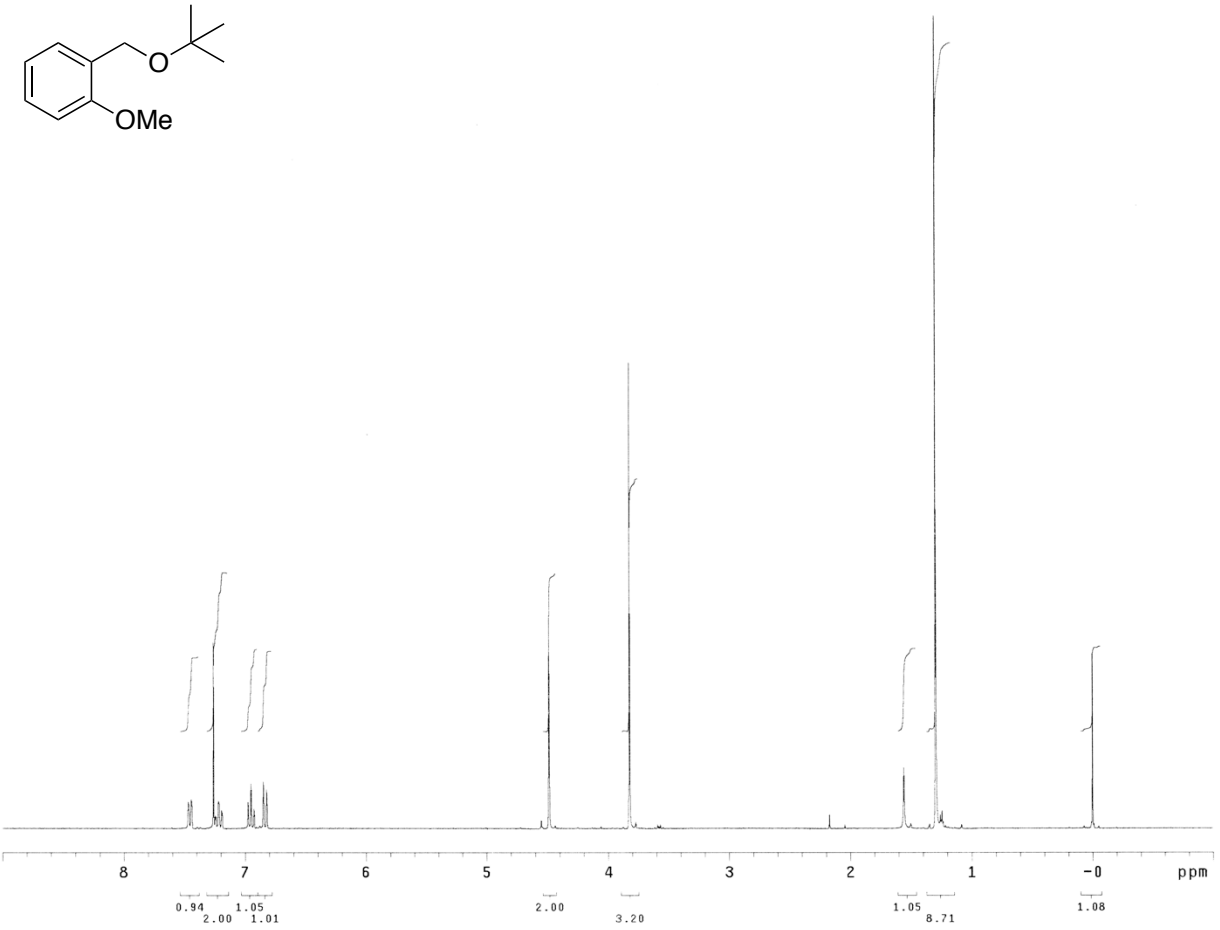

t-BuO
O
O

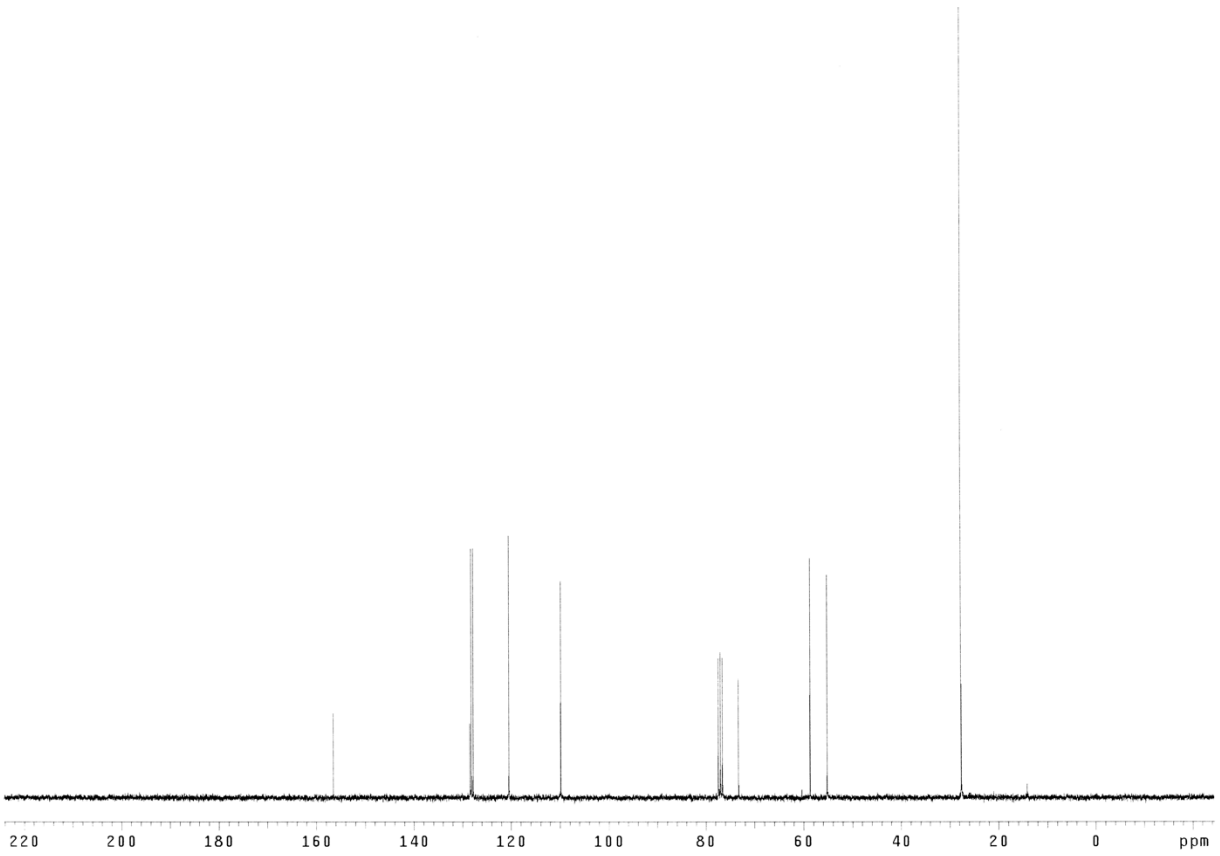
(**11**)

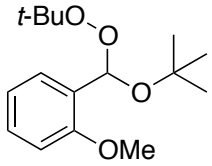

8
7
6
5
4
3
2
1
-0
ppm
1.87
2.48
2.82
1.00
3.56
8.49
8.34
1.96


220
200
180
160
140
120
100
80
60
40
20
0
ppm

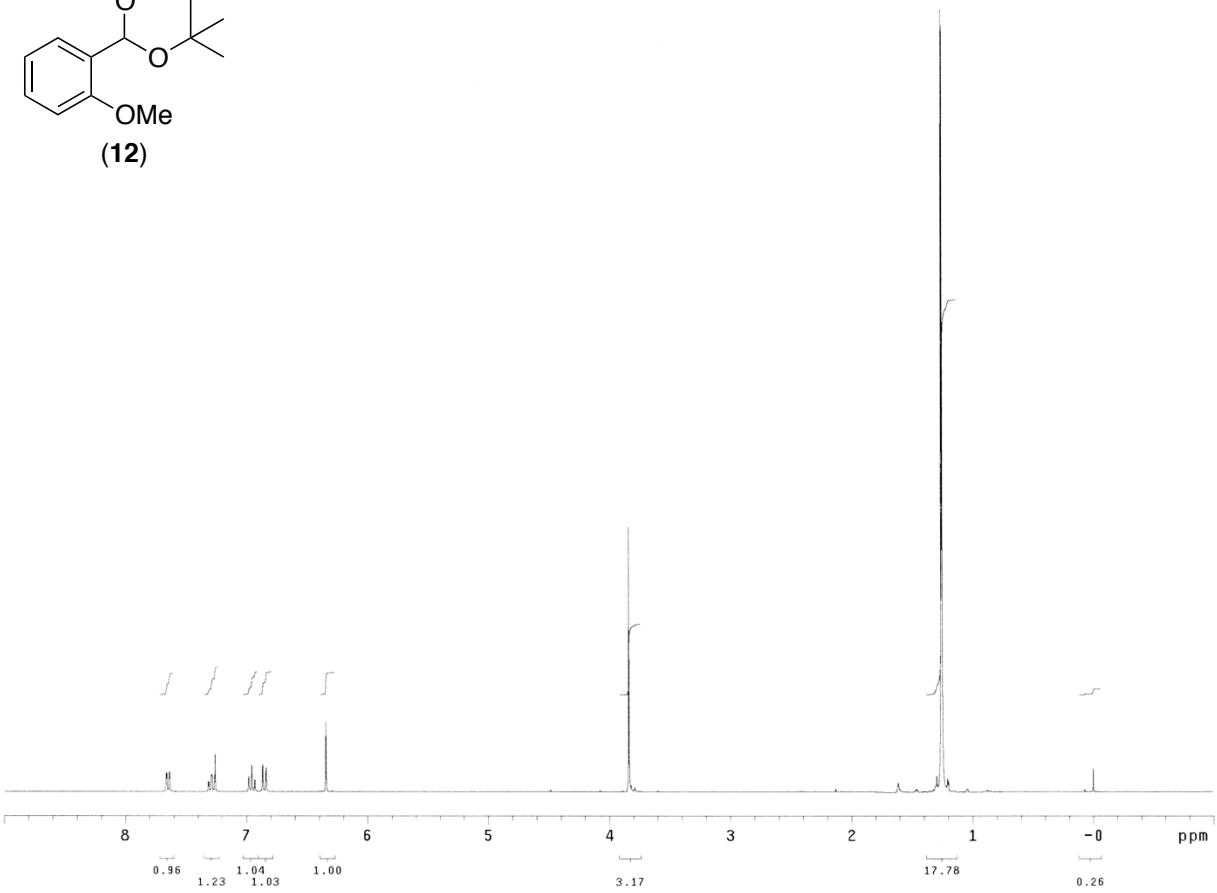
O
OMe

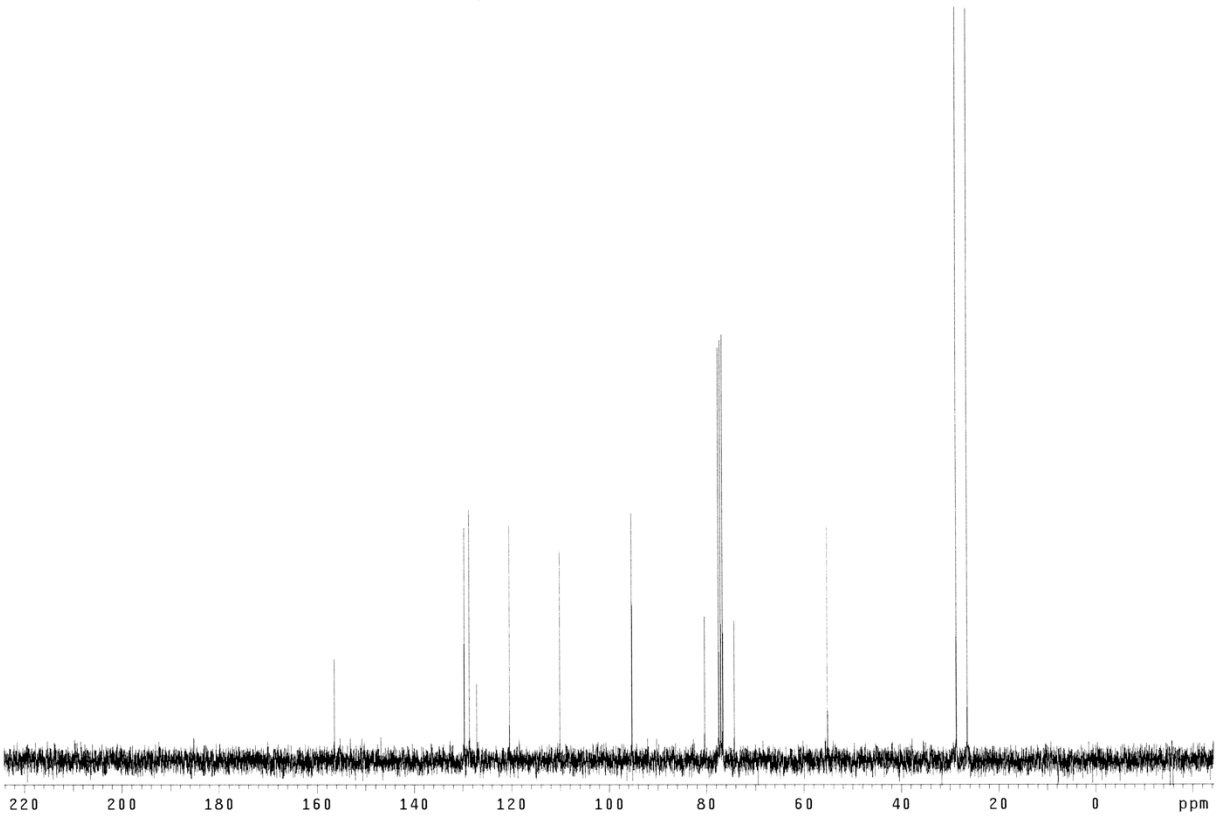

8
7
6
5
4
3
2
1
-0
ppm
0.94
2.00
1.05
1.01
2.00
3.20
1.05
8.71
1.08

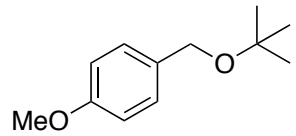

220
200
180
160
140
120
100
80
60
40
20
0
ppm

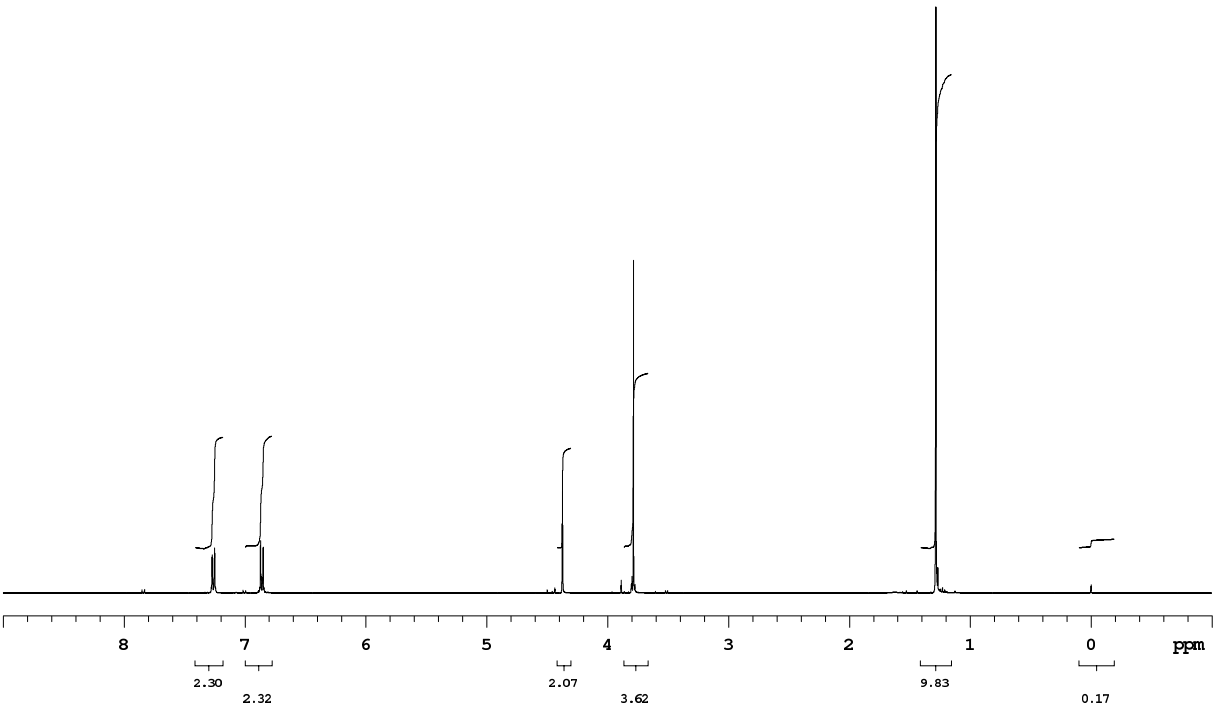

t-BuO
O
O
OMe

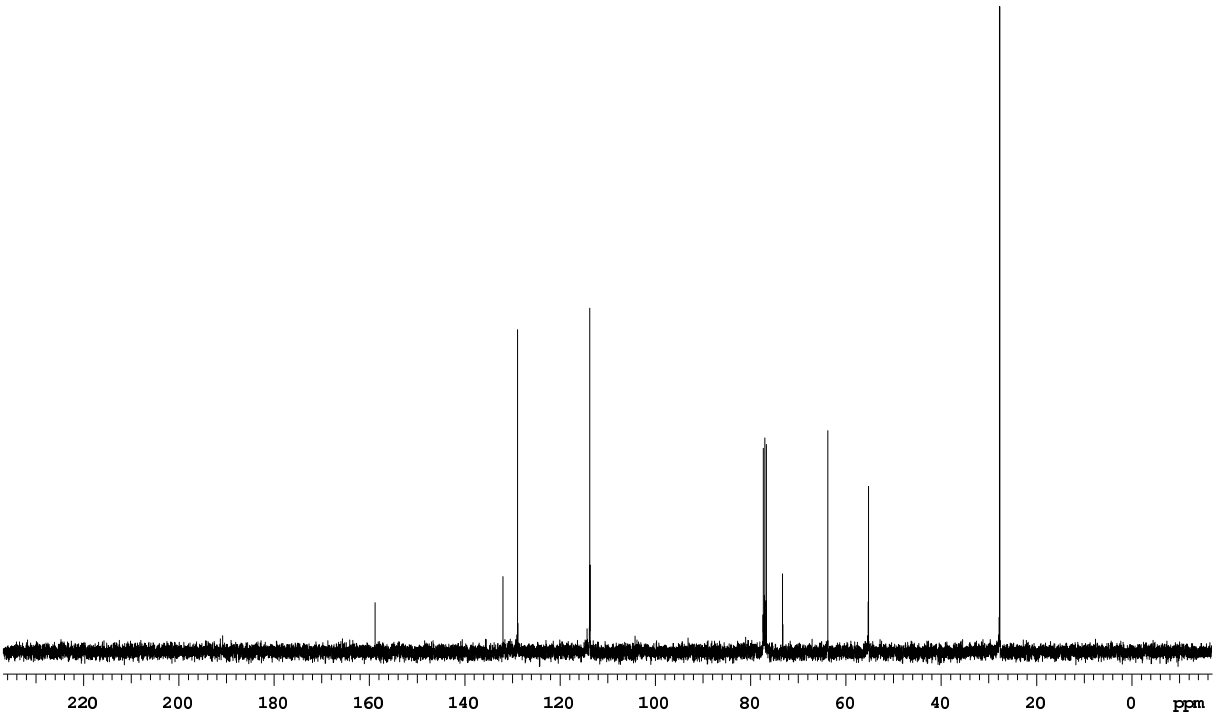
(**12**)

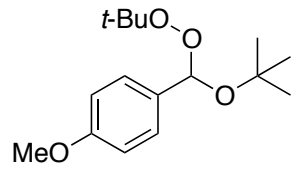

8
7
6
5
4
3
2
1
-0
ppm
0.96
1.23
1.04
1.03
1.00
3.17
17.78
0.26


220
200
180
160
140
120
100
80
60
40
20
0
ppm

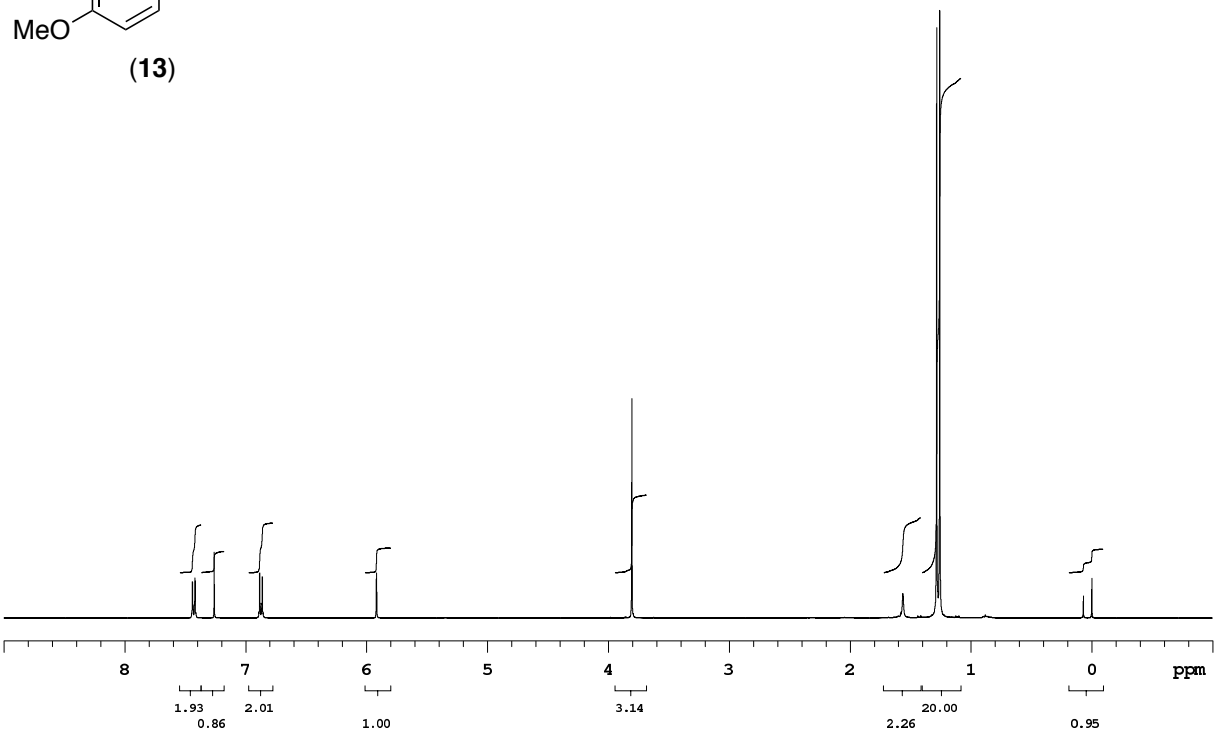

MeO
O

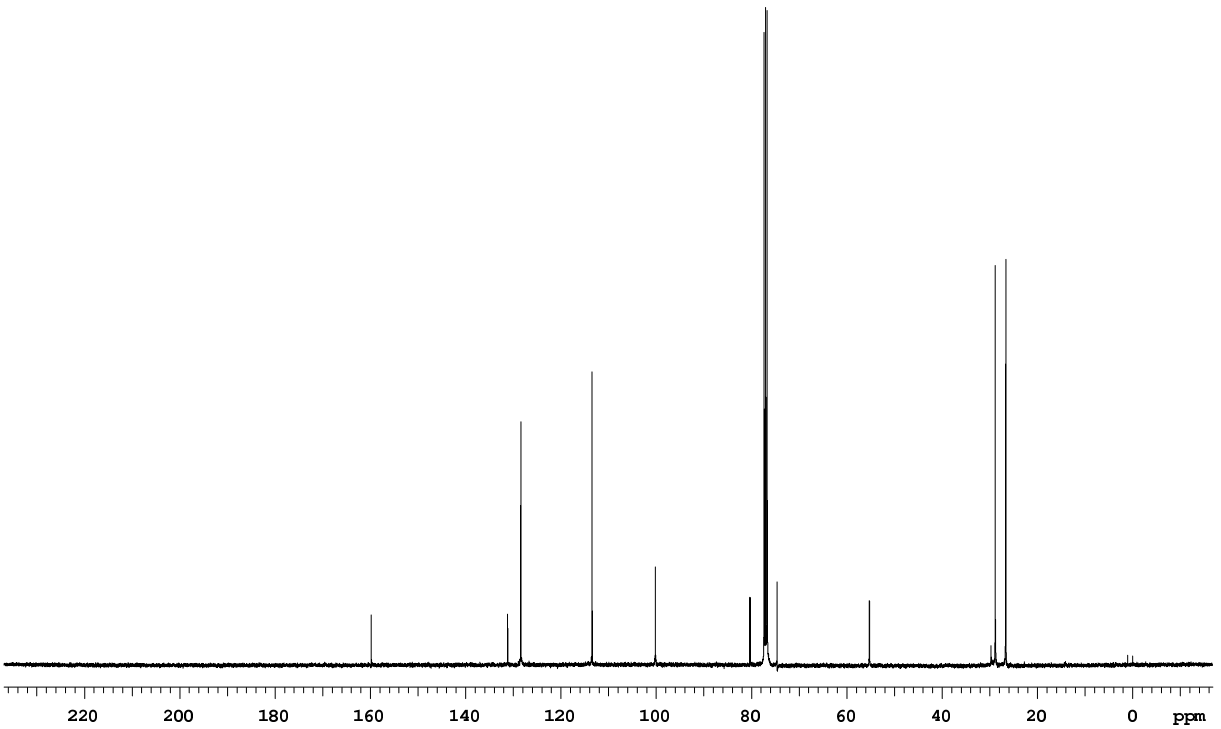

8
7
6
5
4
3
2
1
0
ppm
2.30
2.32
2.07
3.62
9.83
0.17

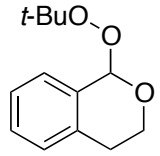

220
200
180
160
140
120
100
80
60
40
20
0
ppm


t-BuO
O
O
MeO

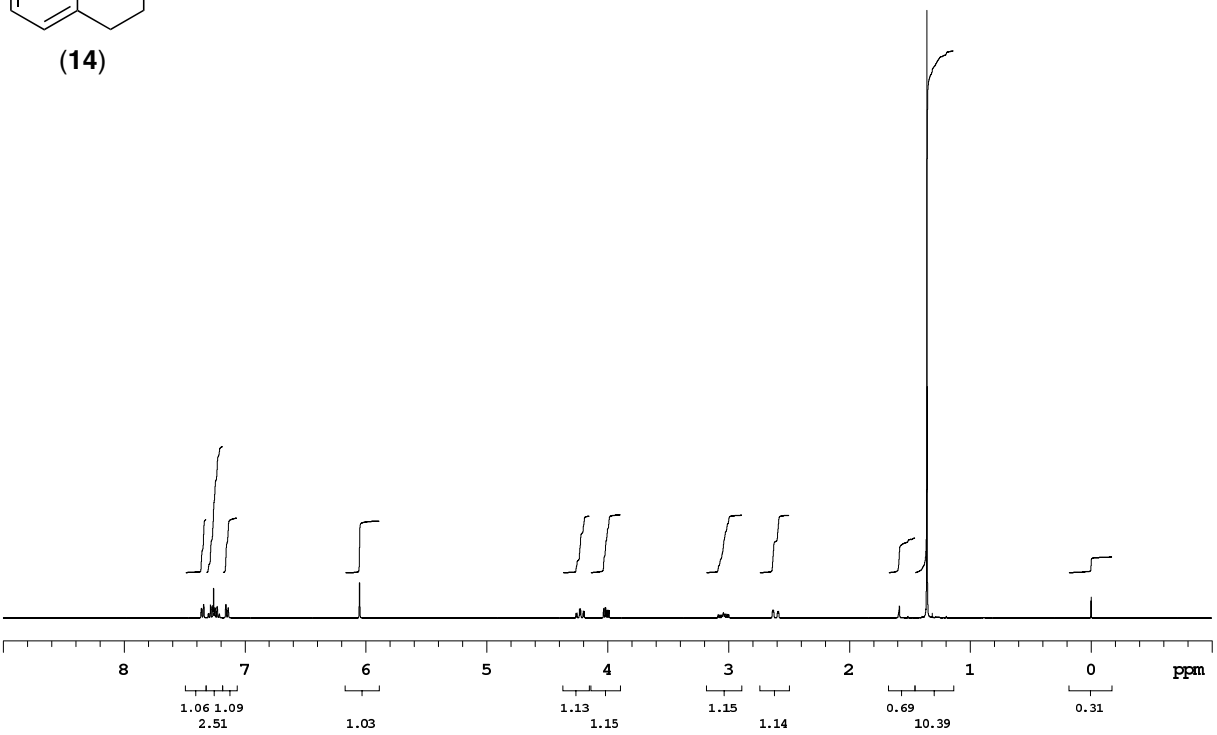
(**13**)

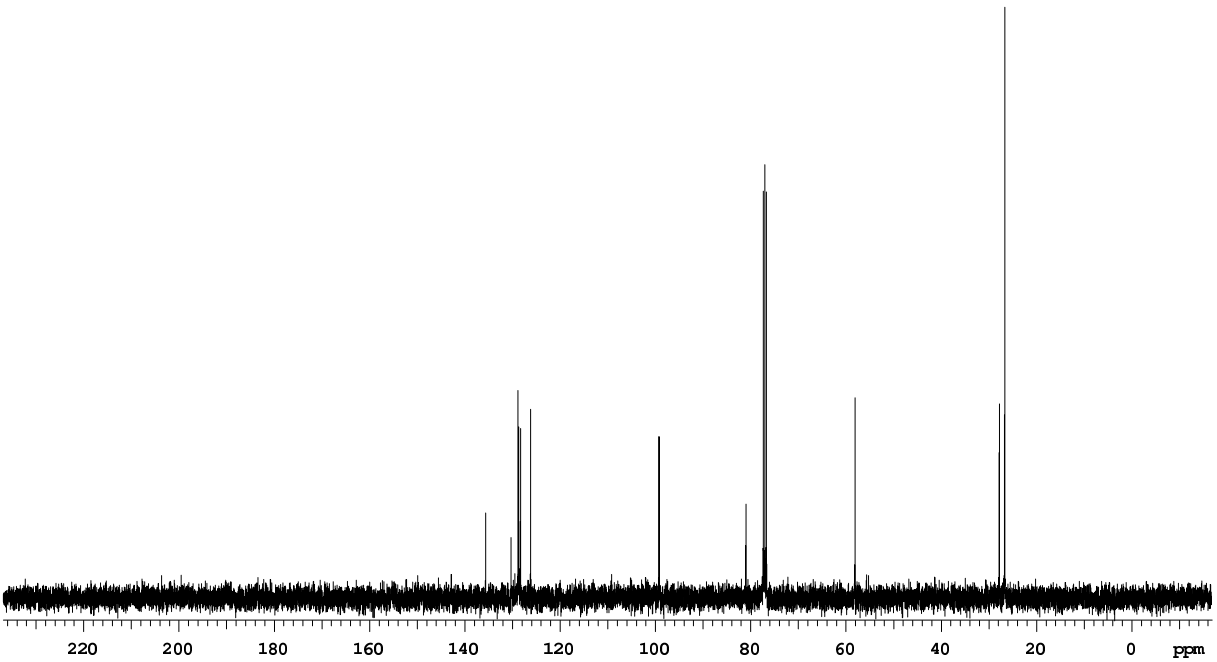

8
7
6
5
4
3
2
1
0
ppm
1.93
0.86
2.01
1.00
3.14
2.26
20.00
0.95

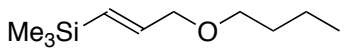

220
200
180
160
140
120
100
80
60
40
20
0
ppm


t-BuO
O
O

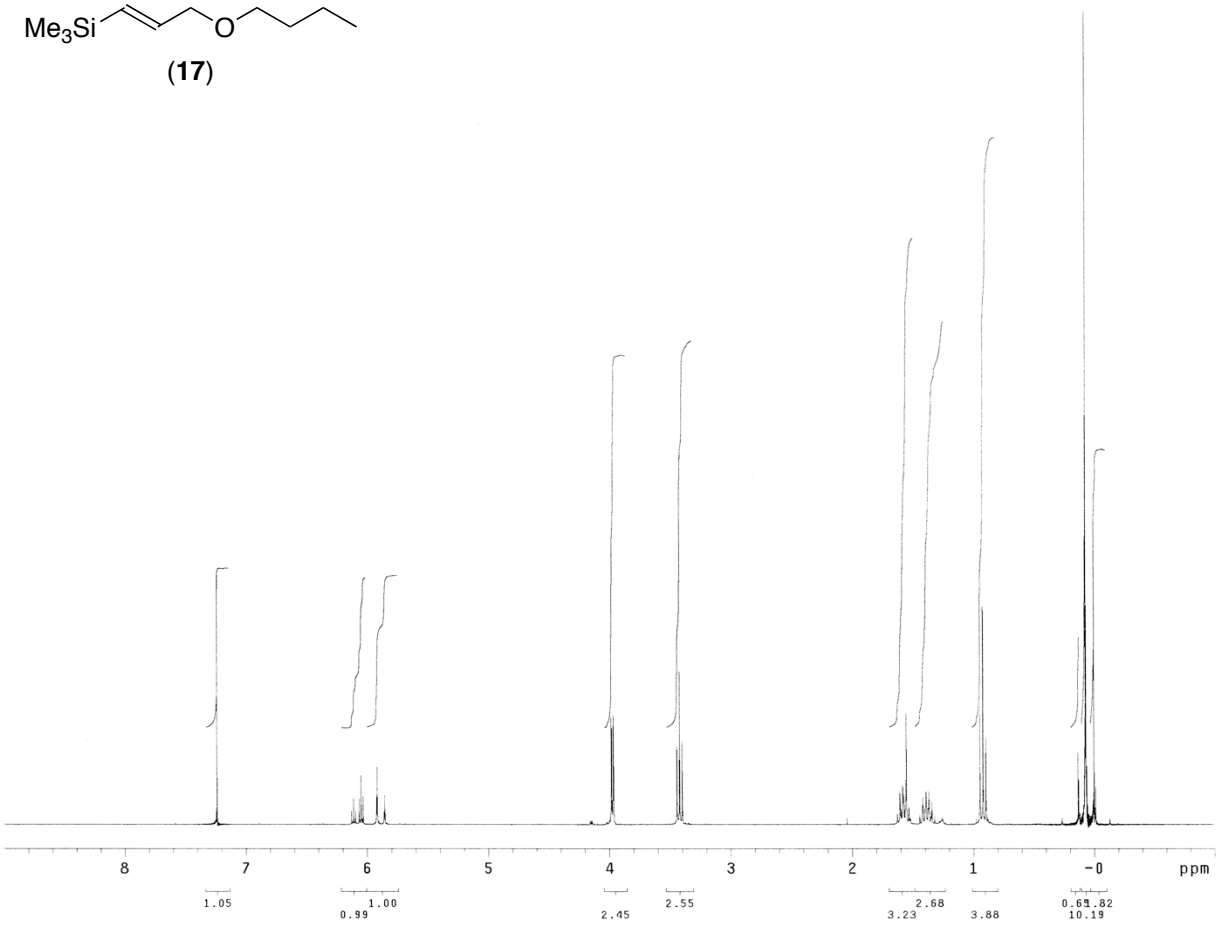
(**14**)

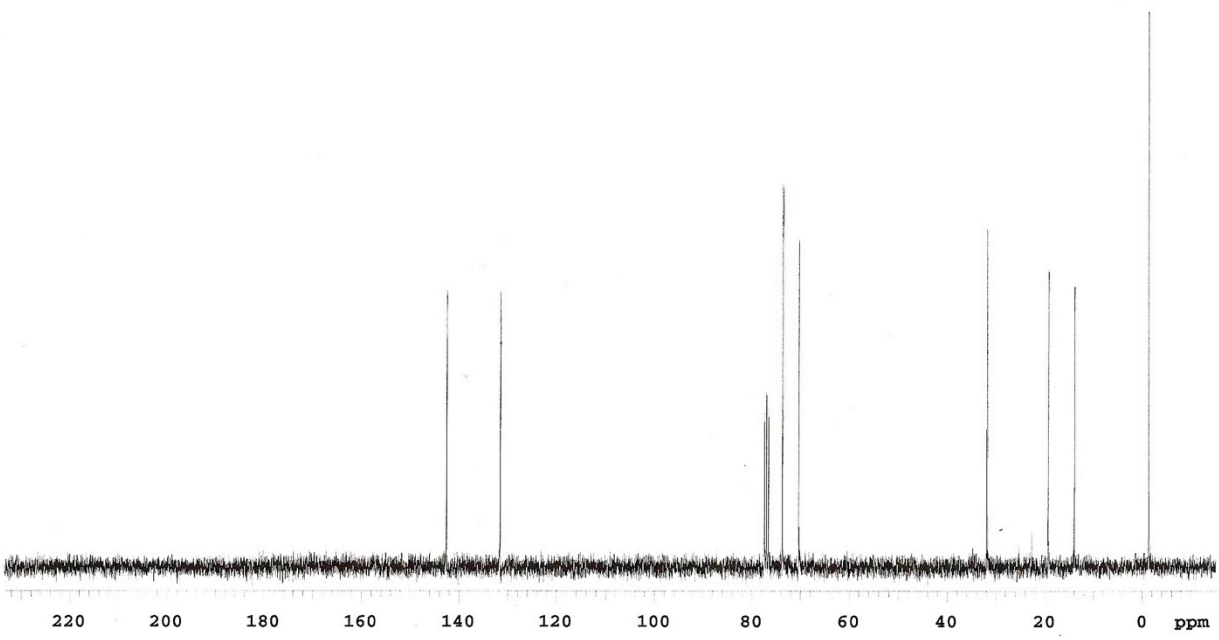

8
7
6
5
4
3
2
1
0
ppm
1.06 1.09
2.51
1.03
1.13
1.15
1.15
1.14
0.69
10.39
0.31

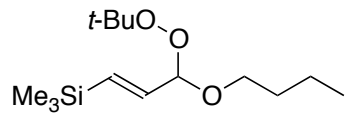

220
200
180
160
140
120
100
80
60
40
20
0
ppm


Me3Si
O

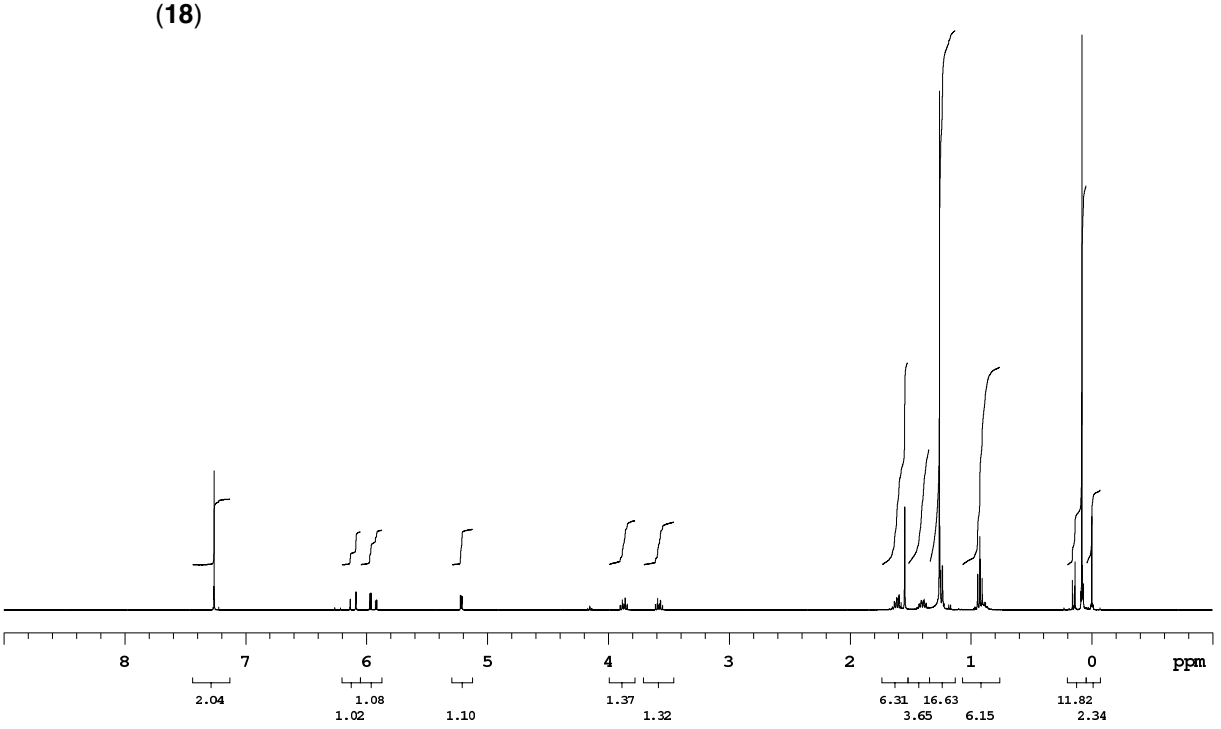
(**17**)

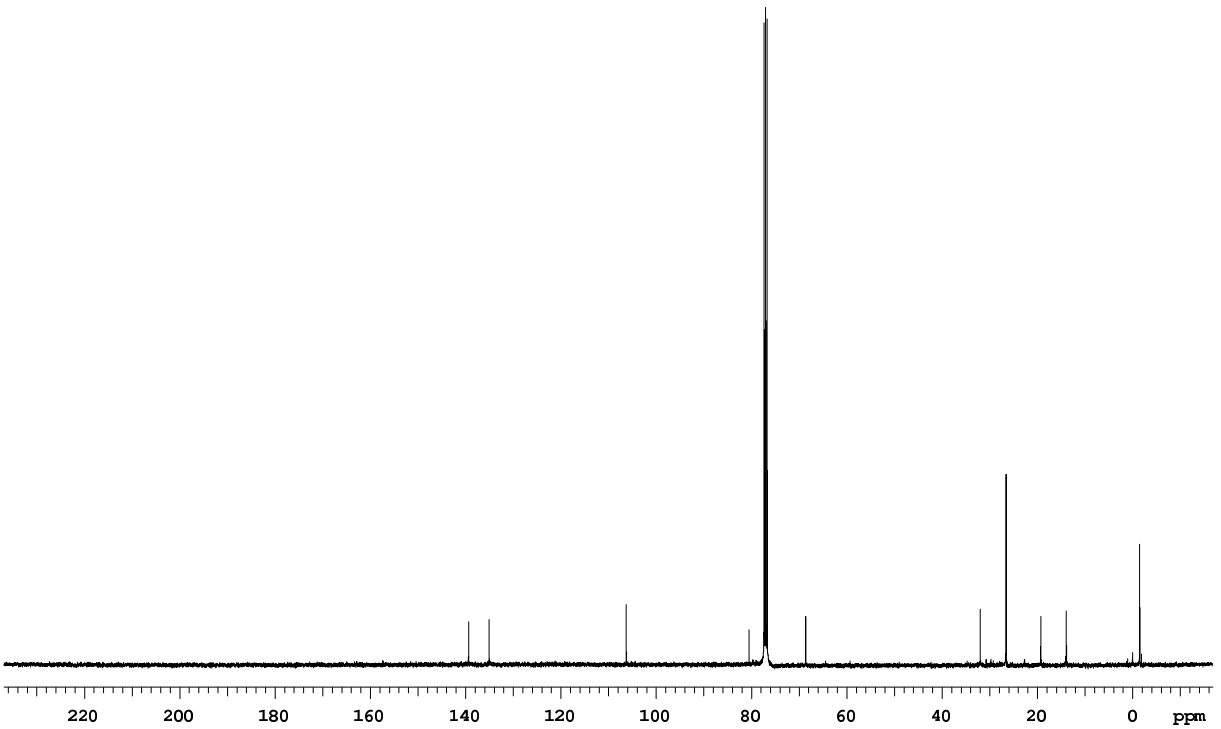

8
7
6
5
4
3
2
1
-0
ppm
1.05
1.00
0.99
2.45
2.55
2.68
3.23
3.88
0.61
1.82
10.19

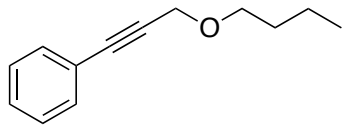

220
200
180
160
140
120
100
80
60
40
20
0
ppm


t-BuO
O
Me3Si
O

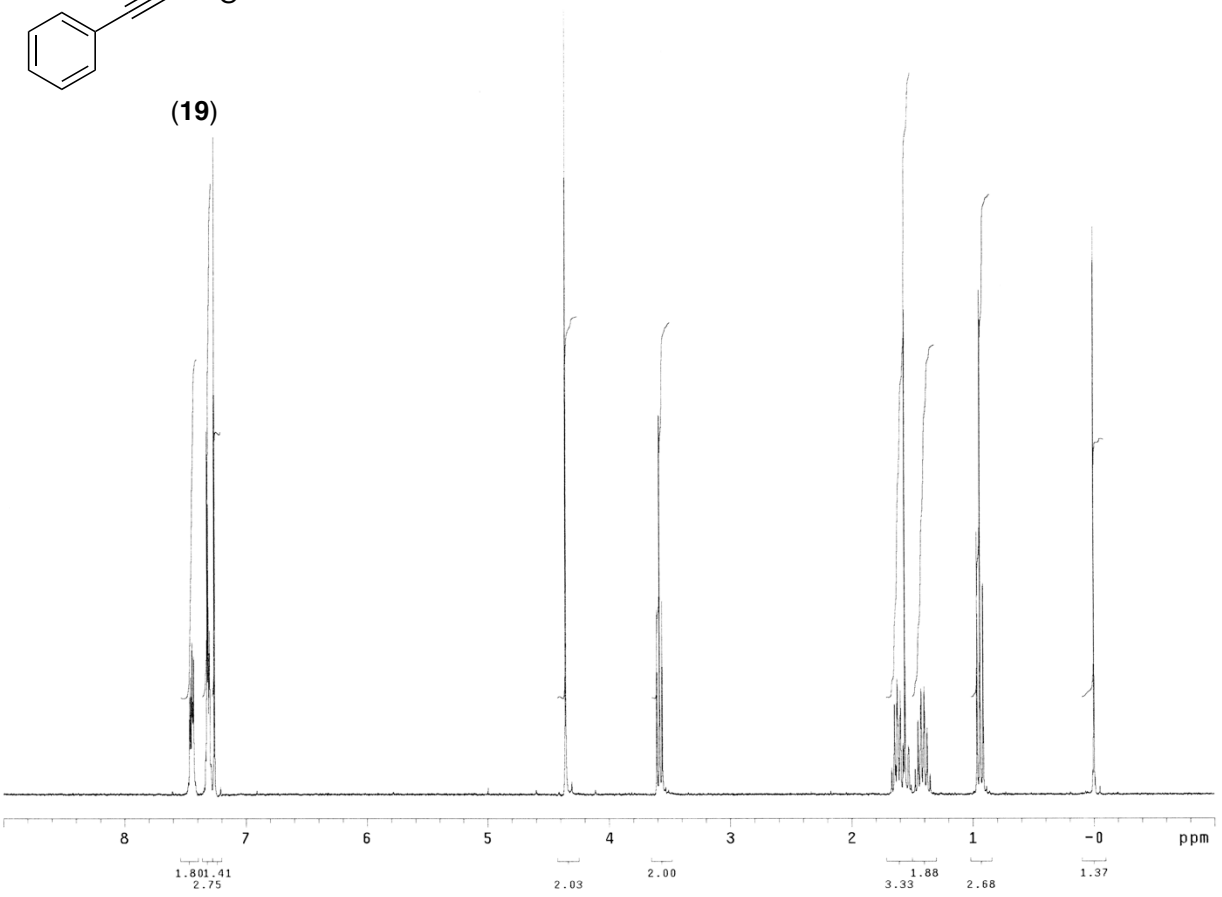
(**18**)

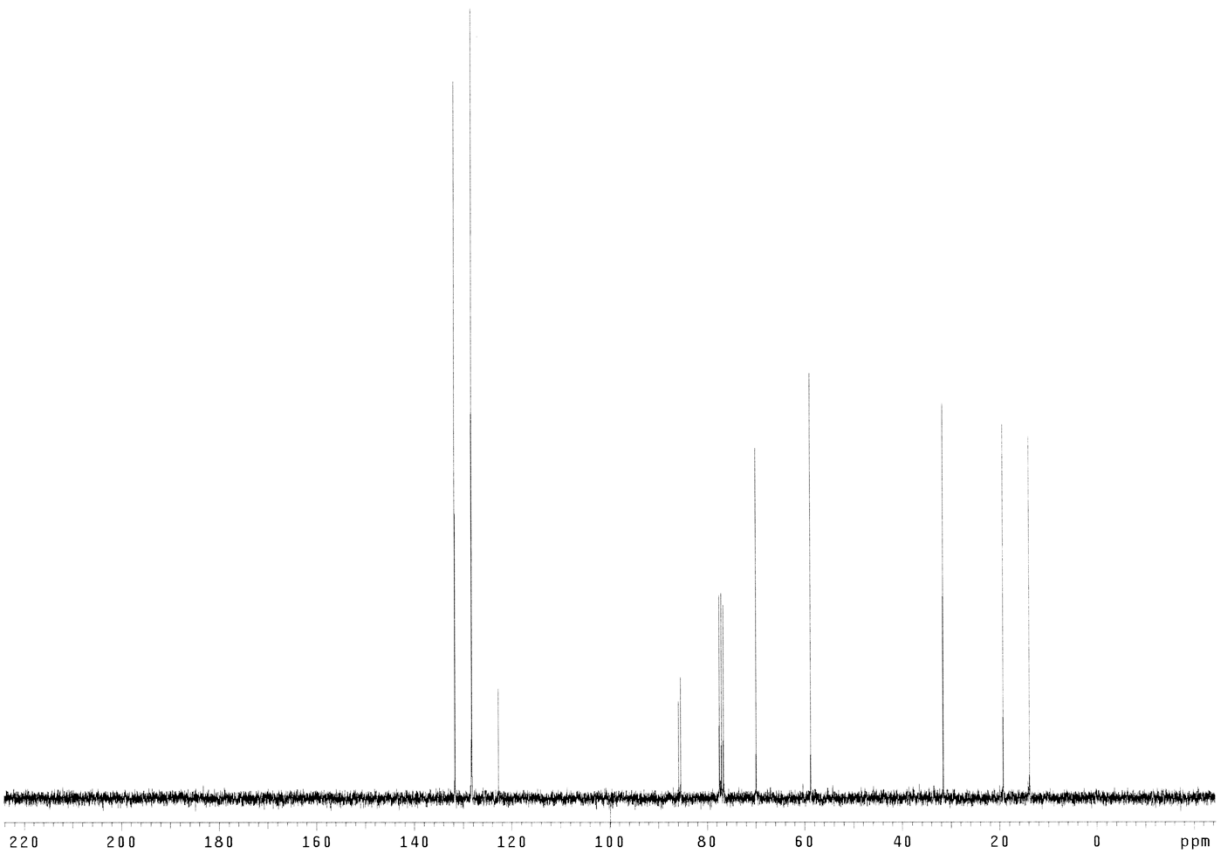

8
7
6
5
4
3
2
1
0
ppm
2.04
1.08
1.02
1.10
1.37
1.32
6.31
16.63
3.65
6.15
11.82
2.34

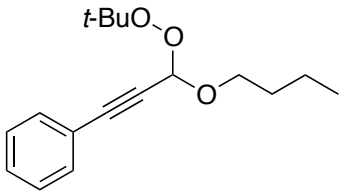

220
200
180
160
140
120
100
80
60
40
20
0
ppm



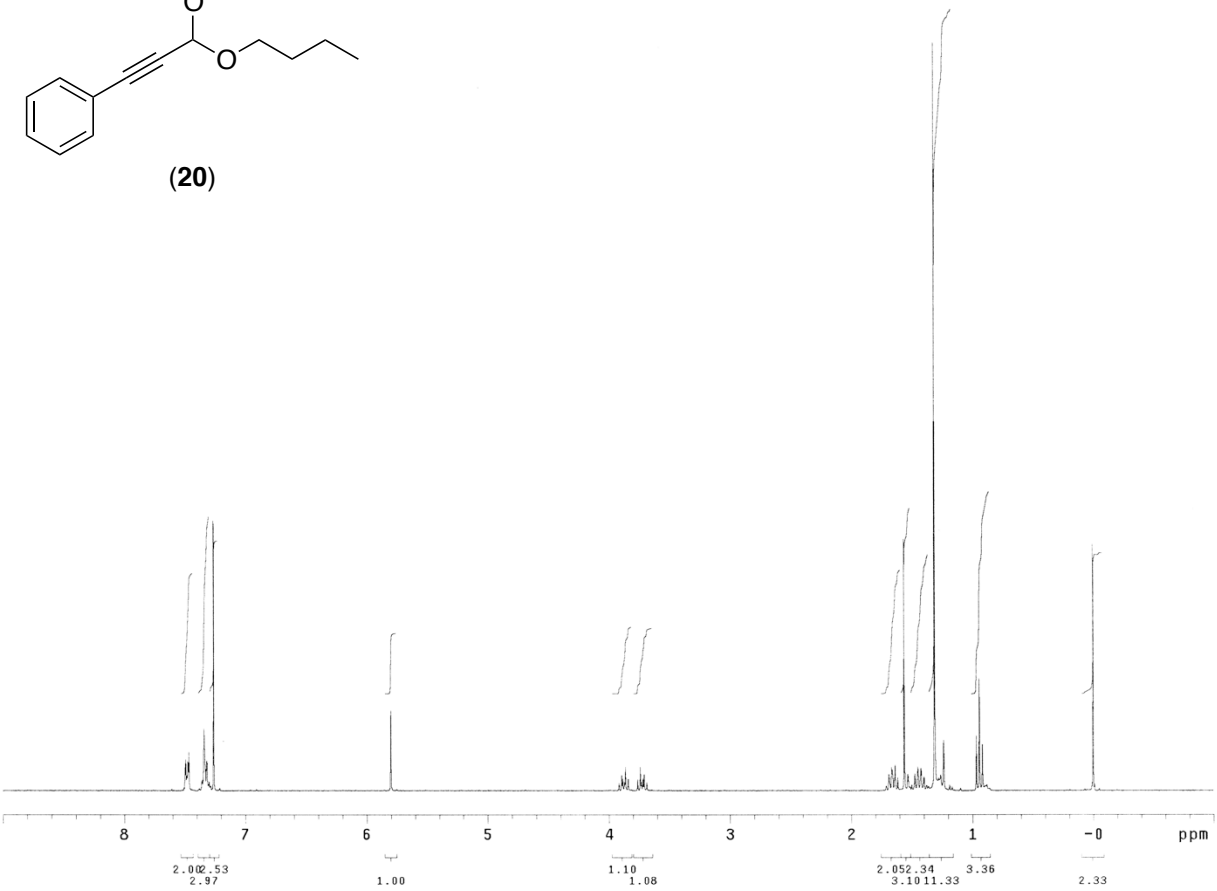
(**19**)

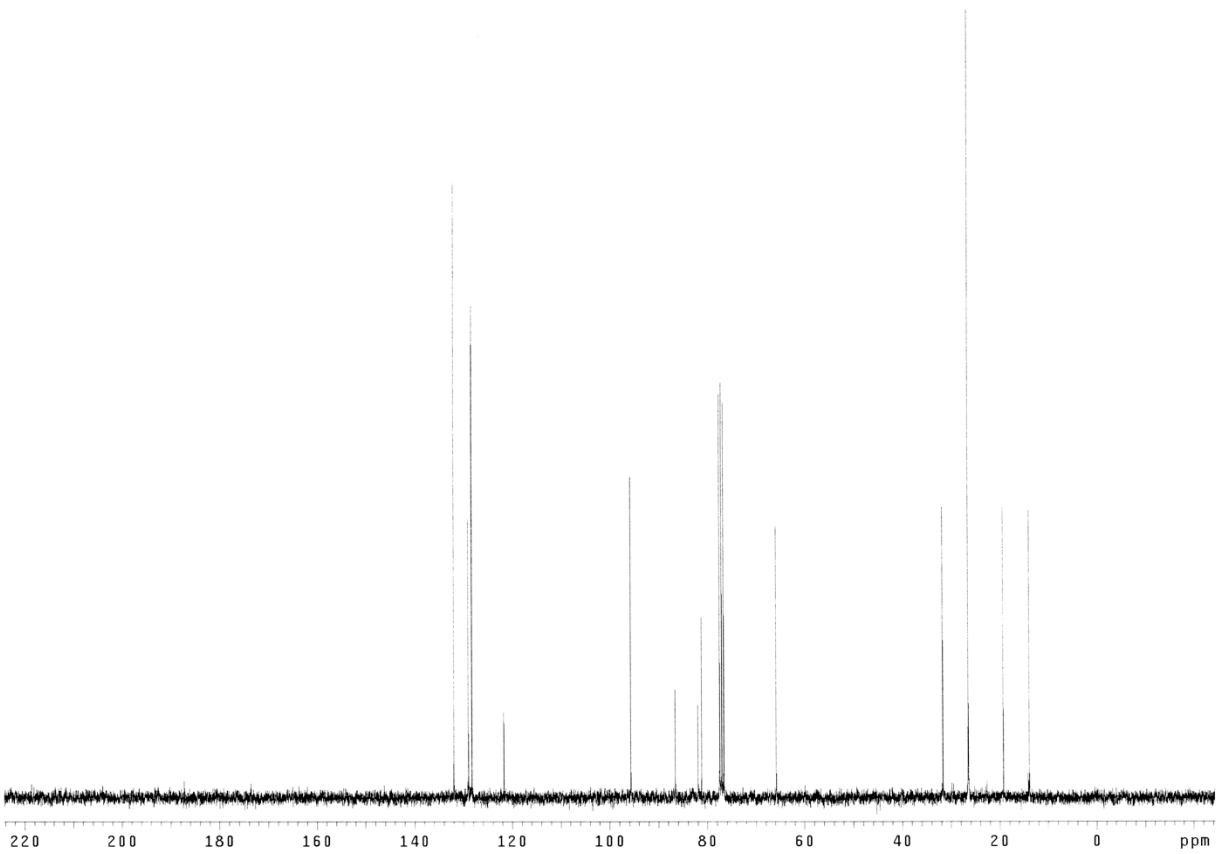

8
7
6
5
4
3
2
1
-0
ppm
1.80
1.41
2.75
2.03
2.00
1.88
3.33
2.68
1.37

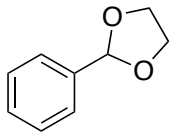

220
200
180
160
140
120
100
80
60
40
20
0
ppm


t-BuO
O
O

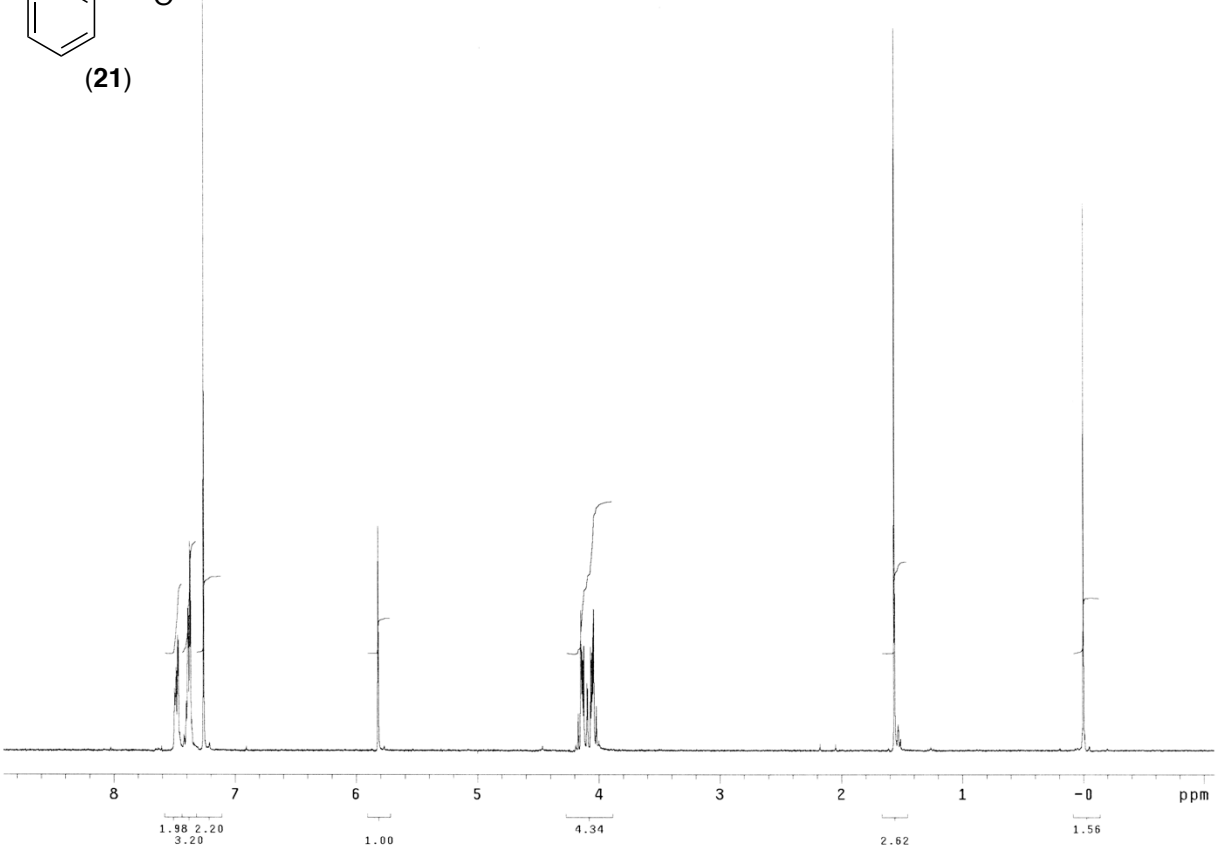
(**20**)

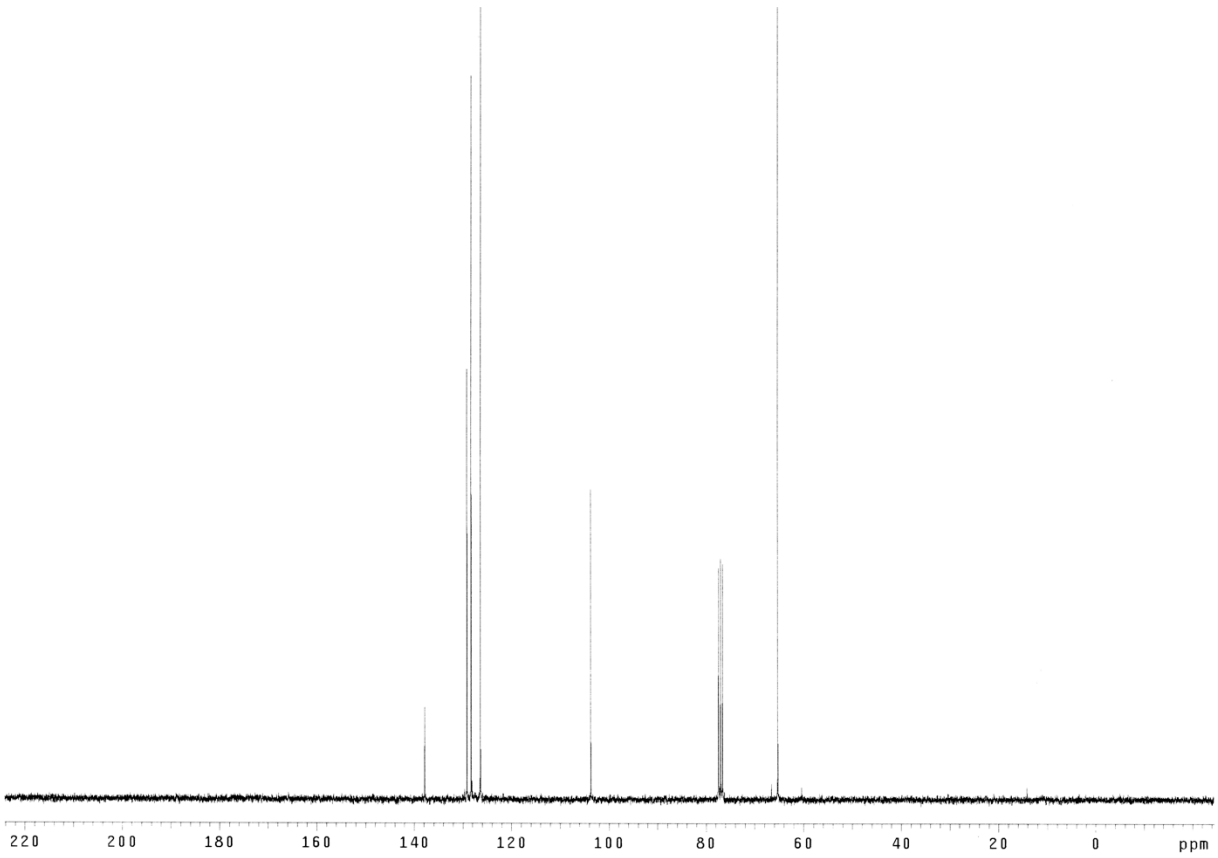

8
7
6
5
4
3
2
1
-0
ppm
2.00
2.53
2.97
1.00
1.10
1.08
2.05
2.34
3.10
11.33
3.36
2.33


220
200
180
160
140
120
100
80
60
40
20
0
ppm



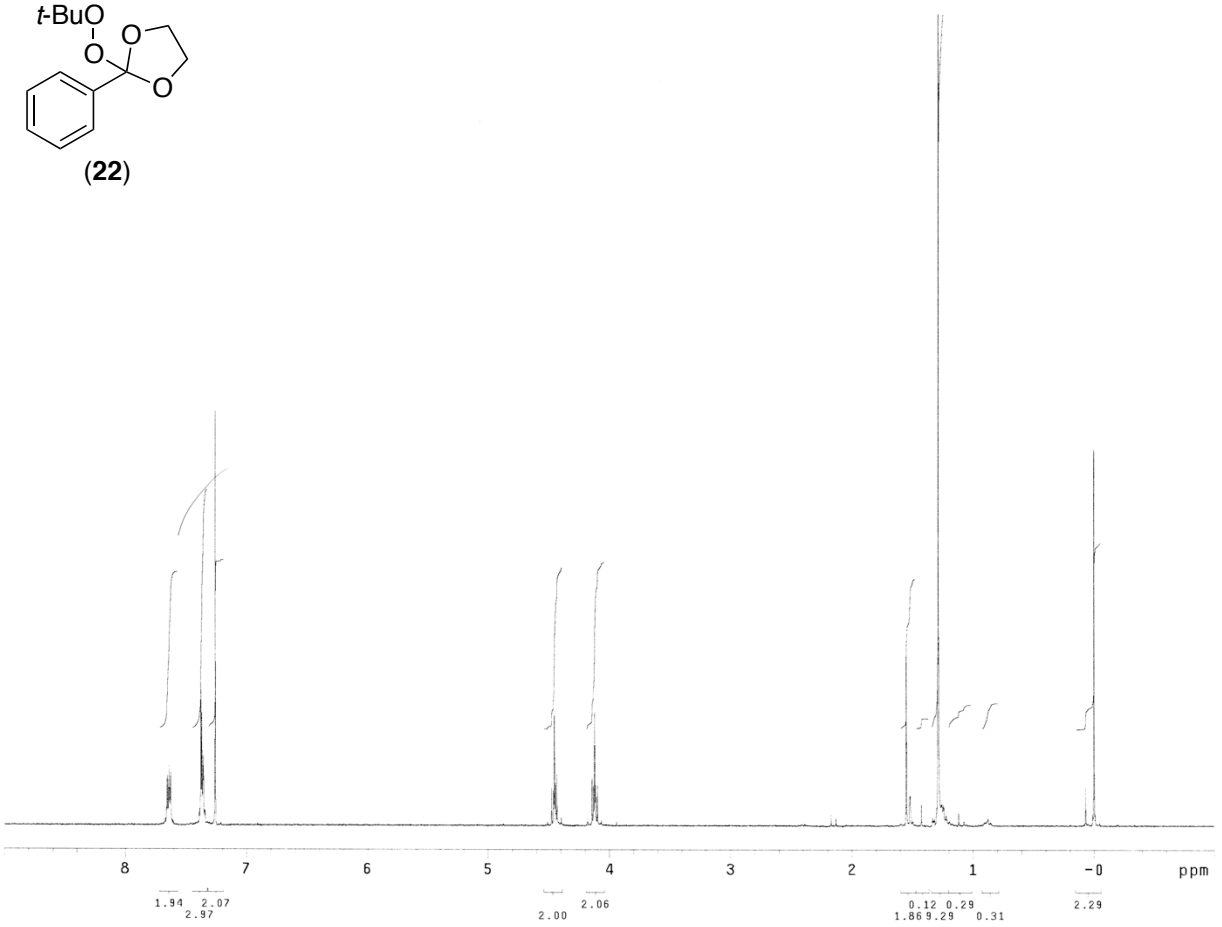
(**21**)

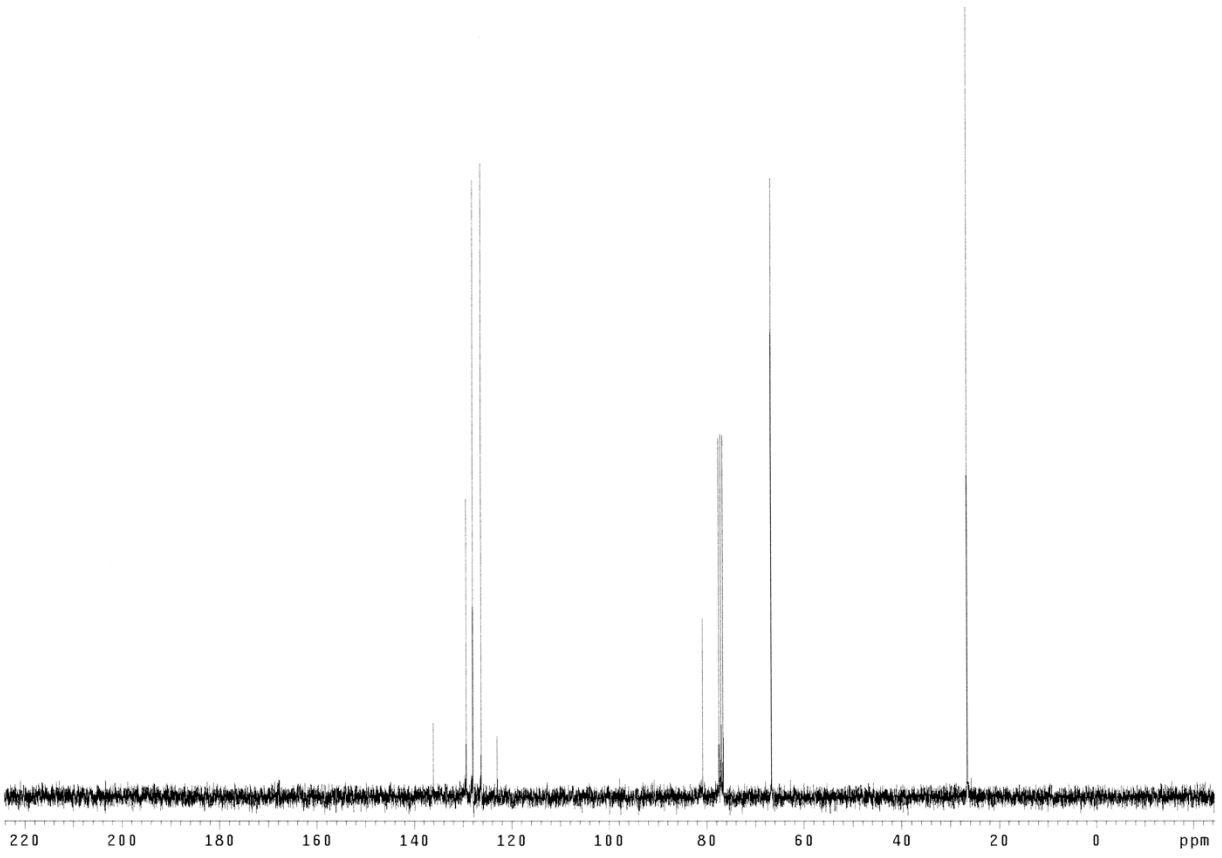

8
7
6
5
4
3
2
1
-0
ppm
1.98 2.20
3.20
1.00
4.34
2.62
1.56


220
200
180
160
140
120
100
80
60
40
20
0
ppm

t-BuO
O
O
O

(**22**)


8
7
6
5
4
3
2
1
-0
ppm
1.94
2.07
2.97
2.00
2.06
0.12
0.29
1.86
9.29
0.31
2.29


220
200
180
160
140
120
100
80
60
40
20
0
ppm