PERICYCLIC REACTIONS IN ORGANIC SYNTHESIS

By

Julia M. Robinson-Surry
B.A. Chemistry
Reed College, 2006

SUBMITTED TO THE
DEPARTMENT OF CHEMISTRY
IN PARTIAL FULFILLMENT
OF THE REQUIREMENTS
FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

at the

MASSACHUSETTS INSTITUTE OF TECHNOLOGY

June 2011

Signature of Author.....

Department of Chemistry
May 2, 2011

Certified by.....

Rick L. Danheiser
Thesis Supervisor

Accepted by.....

Robert W. Field
Chairman, Departmental Committee on Graduate Studies

DISCLAIMER

MISSING PAGE(S)

147

A committee of the Department of Chemistry has examined this doctoral thesis as follows:

Professor Timothy F. Jamison.....
Chairman

Professor Rick L. Danheiser.....
Thesis Supervisor

Professor Gregory C. Fu.....

For my mother,

Mary Kathryn Robinson

PERICYCLIC REACTIONS IN ORGANIC SYNTHESIS

By
Julia M. Robinson-Surry

Submitted to the Department of Chemistry
on May 2, 2011 in partial fulfillment of the
requirements for the degree of Doctor of Philosophy

ABSTRACT

Part I of this thesis describes a formal, metal-free, [2 + 2 + 2] cycloaddition strategy based on a cascade of two pericyclic processes. An intramolecular propargylic ene reaction of a 1,6-diyne is used to generate a vinylallene, which then reacts in an inter- or intramolecular Diels–Alder reaction with an alkenyl or alkynyl dienophile. Reactions involving unsymmetrical alkenyl and alkynyl dienophiles proceed with good to excellent regioselectivity, and endo products are formed exclusively. The mechanism of several earlier fully intramolecular related transformations have been shown to involve an analogous process rather than the diradical-mediated pathways proposed previously.

Part II of this thesis describes a [4 + 4] annulation strategy involving the intramolecular [4 + 2] cycloaddition of conjugated enynes with activated cyclobutene derivatives to access intermediates containing bicyclo[4.2.0]-2,4-octadiene moieties that then undergo electrocyclic ring opening reactions to provide 1,3,5-cyclooctatrienes. Five novel cyclooctatrienes have been prepared using this method.

Part III of this thesis describes the use of supercritical carbon dioxide as an environmentally friendly alternative to conventional solvents for the synthesis of a variety of carboxylic amides. The addition of amines to ketenes generated in situ via the retro-ene reaction of alkynyl ethers provides amides in good yield, in many cases with ethylene as the only byproduct of the reaction. With the exception of primary, unbranched amines, potential side reactions involving addition of the amines to carbon dioxide are not competitive with the desired C–N bond-forming reaction. The amide synthesis is applicable to the preparation of β-hydroxy and β-amino amide derivatives, as well as amides bearing isolated carbon–carbon double bonds.

Thesis Supervisor: Rick L. Danheiser

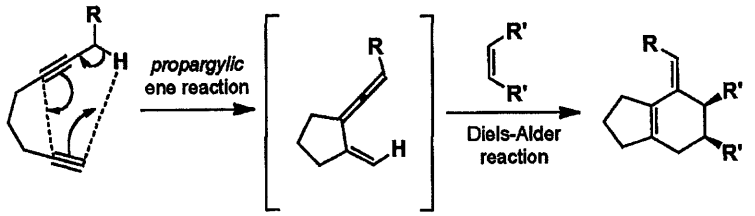
Title: Professor of Chemistry

Table of Contents

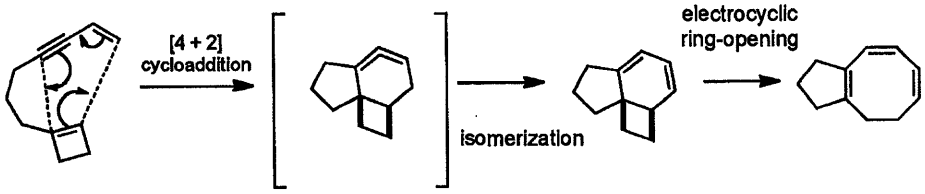
Preface

This thesis covers the general topic of the use of pericyclic reactions to access reactive intermediates for organic synthesis. Three unrelated projects are described that illustrate this strategy. Pericyclic reactions are divided into three general categories: cycloadditions, electrocyclic reactions, and sigmatropic rearrangements. When carried out on suitably functionalized substrates, these reactions can produce transient intermediates that then undergo trapping or rearrangement in situ to form interesting and useful products.

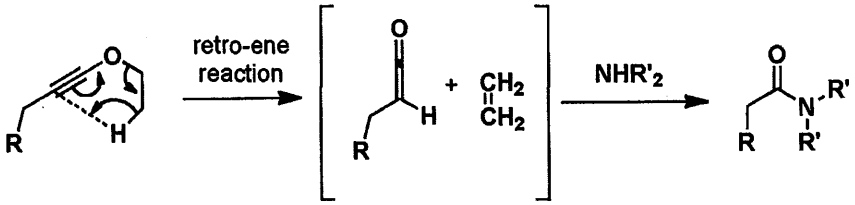
In Part I of this thesis, a formal [2 + 2 + 2] cycloaddition strategy will be discussed in which the reactive intermediate a vinylallene, obtained via a propargylic ene reaction of a 1,6-diyne. The propargylic ene reaction is an unusual variant of the ene reaction wherein the ene component is an alkyne and propargylic hydrogen.



Part II of this thesis discusses a variant of the Diels-Alder reaction where the diene is replaced by a conjugated enyne. In this case, an intramolecular [4 + 2] cycloaddition of a conjugated enyne with cyclobutene derivatives is used to access cyclic allene intermediates that then undergo a cascade of reactions to give eight-membered ring products.



Finally, in Part III of this thesis, a retro-ene reaction of an alkynyl ether is used to produce a ketene in situ that is then trapped with an amine using supercritical carbon dioxide as solvent in a minimal-waste amide synthesis.



Part I

A Formal [2 + 2 + 2] Cycloaddition Strategy Based on an Intramolecular Propargylic Ene Reaction/Diels-Alder Cycloaddition Cascade

Chapter 1 – Introduction and Background

The regioselective preparation of highly substituted aromatic compounds has been an area of active research for many years. Early work in this area focused on successive transformations of an aromatic compound, introducing substituents in a stepwise manner around the ring. Typical methods for appending functional groups onto an existing aryl framework include nucleophilic and electrophilic aromatic substitutions, cross-coupling reactions, and metalation-functionalization reactions. This approach is limited by its inherent inefficiency (many operations) as well as poor regiocontrol in many of the reactions.

An alternative approach to highly substituted aromatic compounds employs annulation methods, in which the ring is prepared from acyclic precursors in a reaction that forms two new bonds.[1] The location of the substituents in the product is determined by the structure and reactivity of the starting materials. In many cases the starting materials are readily available using the well-developed transformations of alkynes. This convergent approach allows for rapid access to highly substituted aryl rings in a regiocontrolled manner.

The Danheiser laboratory has developed several methods for the efficient synthesis of highly substituted aromatic compounds. Previous work in this area focused on benzannulation reactions utilizing cyclobutenones or diazo ketones (as vinylketene[2] precursors) along with an electron-rich alkyne partner to give phenol[3] and aniline[4] derivatives.

The aim of the research described in this section of this thesis was the development of a new annulation process utilizing a 1,6-diyne (as a vinylallene precursor) and an alkene or alkyne partner to give formal [2 + 2 + 2] products. As shown below, the diyne would undergo an unusual variant of the intramolecular ene reaction (which we refer to as the *propargylic* ene reaction) to give a highly reactive s-cis vinylallene that would then be trapped by the alkene or alkyne partner in a Diels-Alder reaction.

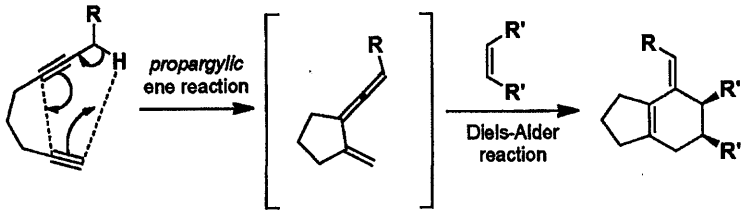
---

[1] Reviewed in: Kotha, S.; Misra, S.; Halder, S. *Tetrahedron* **2008**, *64*, 10775-10790.

[2] For reviews of the chemistry of vinylketenes, see: (a) Danheiser, R. L.; Dudley, G. B.; Austin, W. F. Alkenylketenes. In Science of Synthesis; Danheiser, R. L., Ed.; Thieme: Stuttgart, 2006; Vol. 23; pp 493-568. (b) Tidwell, T. T. Ketenes, 2nd ed.; John Wiley & Sons: Hoboken, NJ, 2006; pp 206-214.

[3] (a) Danheiser, R. L.; Gee, S. K. *J. Org. Chem.* **1984**, *49*, 1672–1674. (b) Danheiser, R. L.; Brisbois, R. G.; Kowalczyk, J. J.; Miller, R. F. *J. Am. Chem. Soc.* **1990**, *112*, 3093–3100. (c) Austin, W. F.; Zhang, Y.; Danheiser, R. L. *Tetrahedron* **2008**, *64*, 915-925.

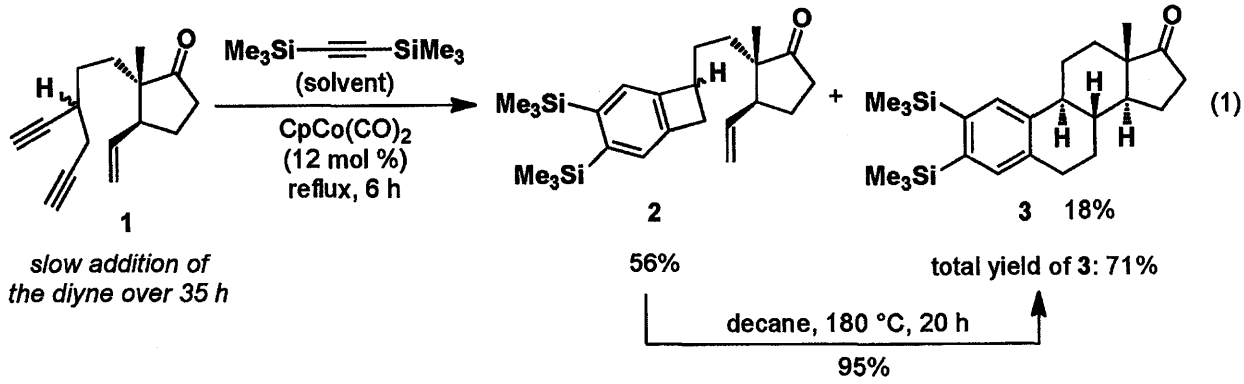
[4] Mak, X. Y.; Crombie, A. L.; Danheiser, R. L. *J. Org. Chem.* **2011**, *76*, 1852-1873.



The impetus for this research was the many limitations of the metal-catalyzed [2 + 2 + 2] cycloaddition reaction. These will be discussed in the next section of this chapter in the context of the use of metal-catalyzed [2 + 2 + 2] cycloadditions in total synthesis.

Metal-Catalyzed [2 + 2 + 2] Cycloaddition Reactions in Total Synthesis

Metal-catalyzed [2 + 2 + 2] cycloadditions have been used extensively to prepare polysubstituted six-membered rings and intermolecular, fully intramolecular, and bimolecular variants have been reported.[5] By far the most synthetically useful variant is the bimolecular method, where a tethered diyne is combined with a third alkyne. Vollhardt was a pioneer in this area with cobalt catalysis in the 1970s and 1980s, illustrated here with the preparation of a key intermediate in the synthesis of estrone (eq 1).[6]



Compound **3** was converted to the natural product via monodesilylation and oxidative cleavage of the remaining TMS group, providing estrone in 5 steps from 2-methylcyclopentenone in 22% overall yield.

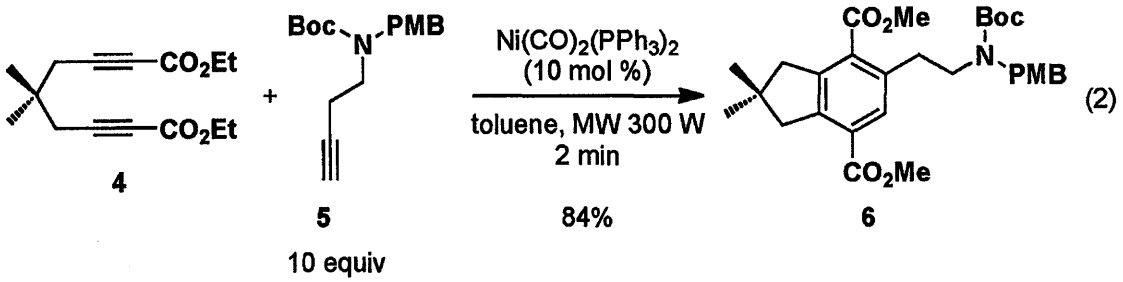
---

[5] For recent reviews, see (a) Agenet, N.; Buisine, O.; Slowinski, F.; Gandon, V.; Aubert, C.; Malacria, M. *Org. React.* **2007**, *68*, 1-302. (b) Kotha, S.; Brahmachary, E.; Lahiri, K. *Eur. J. Org. Chem.* **2005**, 4741-4767. (c) Chopade, P. R.; Louie, J. *Adv. Synth. Catal.* **2006**, *348*, 2307-2327. (d) Galan, B. R.; Rovis, T. *Angew. Chem., Int. Ed.* **2009**, *48*, 2830-2834. (e) Tanaka, K. *Synlett* **2007**, 1977-1993.

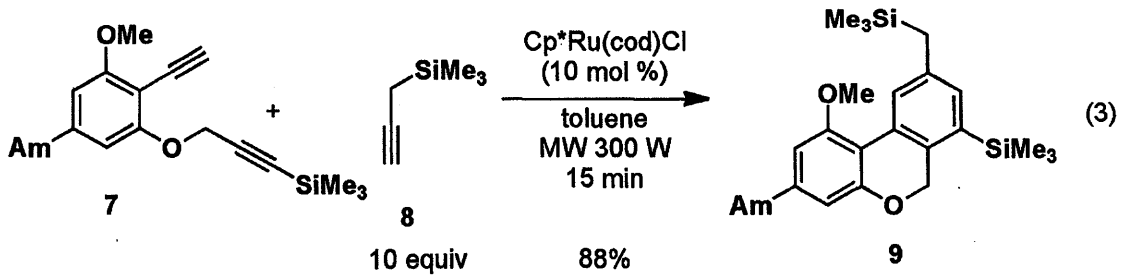
[6] Funk, R. L.; Vollhardt, K. P. C. *J. Am. Chem. Soc.* **1980**, *102*, 5253-5261.

A common problem in these bimolecular reactions is competing cyclotrimerization of the alkyne partner. This can be overcome by using a sterically-encumbered alkyne, such as (bistrimethylsilyl)acetylene, or by utilizing a large excess of the alkyne, commonly 5-10 equivalents, or even by using the alkyne as the solvent, as in the estrone synthesis above.

Another example in which a large excess of the alkyne was employed is shown in eq 2. In his synthesis of illudinine, Dieters prepared advanced intermediate **6** from symmetric diester **4** and protected amino alkyne **5**.[7] In this case nickel catalysis was used under microwave conditions, providing rapid access to the [2 + 2 + 2] product in good yield.



The previous two examples of bimolecular [2 + 2 + 2] cycloadditions involved either a symmetrical alkyne partner or a symmetrical diyne, avoiding the issue of regioselectivity. Many examples of metal-catalyzed [2 + 2 + 2] cycloadditions in the literature give mixtures of isomers. In the bimolecular variant, achieving good regiocontrol is challenging. One case where excellent regioselectivity was obtained was in the synthesis of cannabinol. Dieters and coworkers utilized a [2 + 2 + 2] cycloaddition as the key step to access advanced intermediate **9** (eq 3).[8]



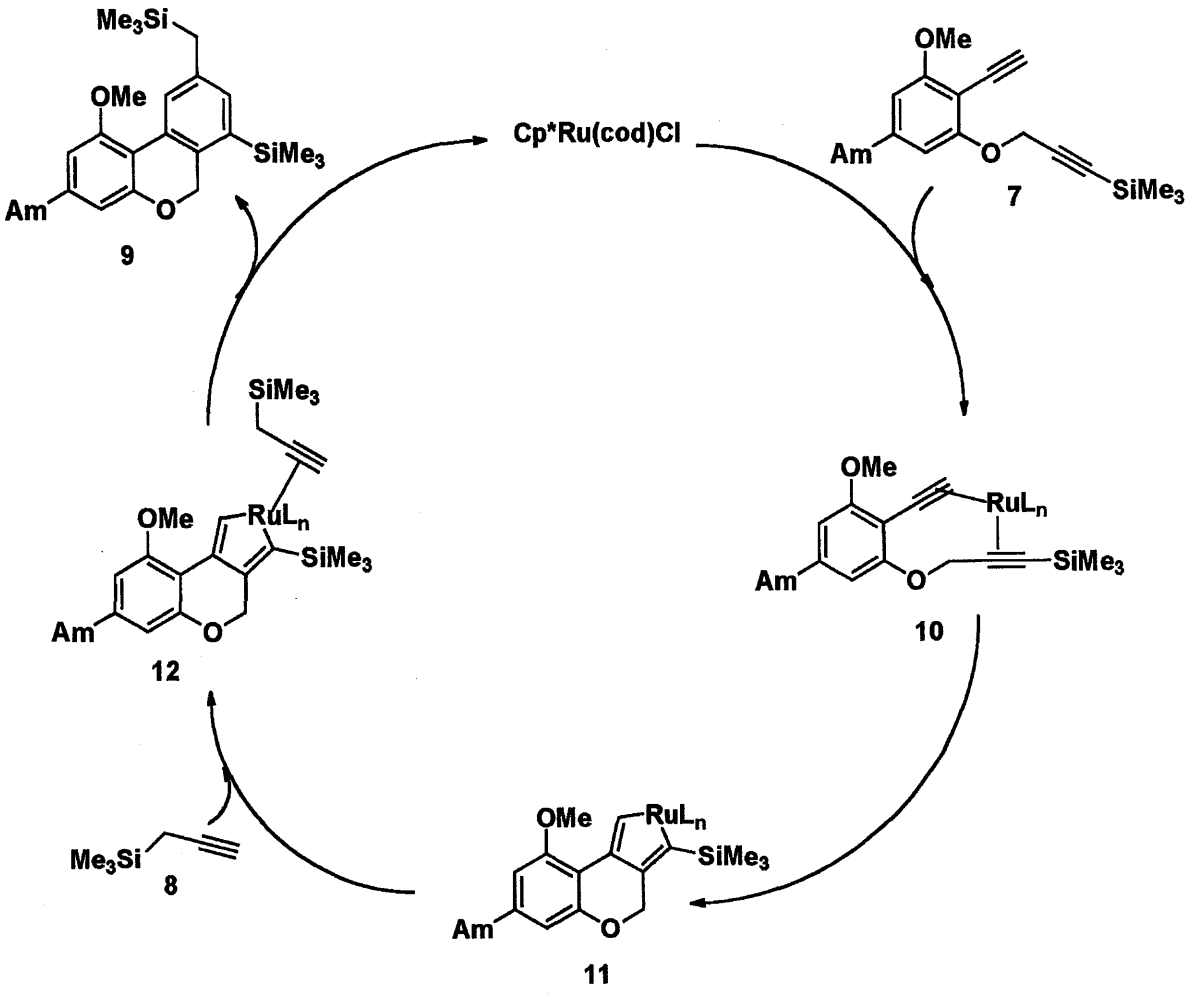
The generally accepted mechanism for metal-catalyzed [2 + 2 + 2] cycloadditions is shown in Scheme 1, using the above cycloaddition as an example. The diyne **7** coordinates to the

---

[7] Teske, J. A.; Dieters, A. *J. Org. Chem.* **2008**, *73*, 342-345.
[8] Teske, J. A.; Dieters, A. *Org. Lett.* **2008**, *10*, 2195-2198.

catalyst, and then undergoes an oxidative coupling reaction to produce intermediate metallocycle **11**. The alkyne partner coordinates to the metal center, giving intermediate **12**. This coordination step is the origin of regioselectivity. In the example shown in the scheme, the trimethylsilyl group that was present on the diyne now serves as a regiodirecting group, resulting in insertion of alkyne **8** in the orientation shown. This trimethylsilyl group is described as a "removable regiodirecting group" because it can be easily cleaved from the product, allowing for selective preparation of a product that could not be obtained otherwise.

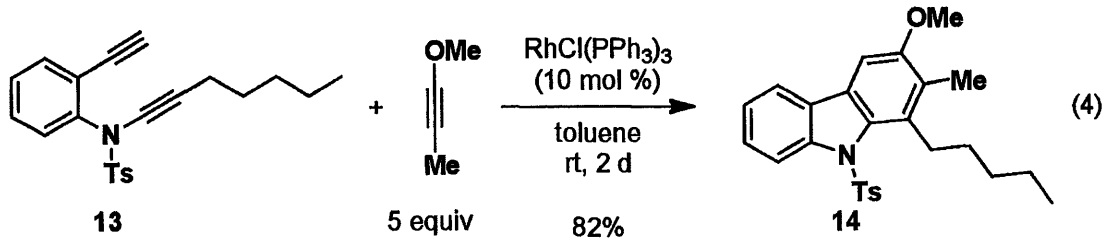
Scheme 1. Mechanism of Metal-Catalyzed [2 + 2 + 2] Cycloaddition Reaction



The mechanism of the conversion of intermediate **12** to the final product **9** is controversial. In the literature on this topic, several mechanisms have been proposed, including insertion followed by reductive elimination as well as a [4 + 2] pathway.[9]

[9] For a discussion of the mechanism of metal-catalyzed [2 + 2 + 2] cycloadditions, see ref. 5a.

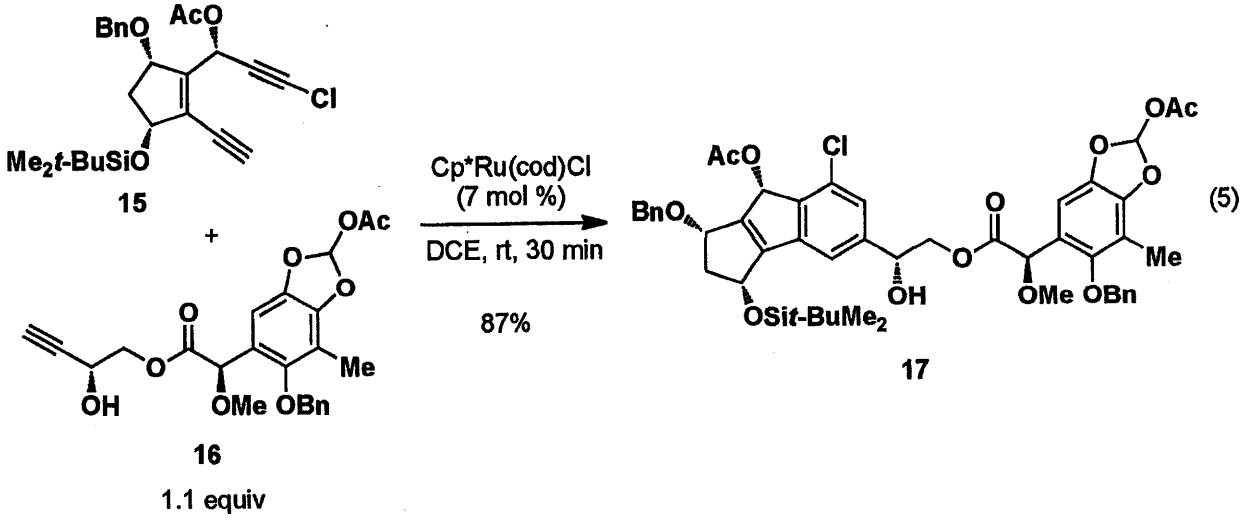
A more recent example of the bimolecular variant with an unsymmetrical alkyne is shown in eq 4. Witulski prepared an intermediate for the synthesis of antiostatin A_1 with excellent regioselectivity using rhodium catalysis.[10]



(4)

With a large excess of methoxypropyne, the highly substituted carbazole was obtained in good yield after prolonged reaction at room temperature. Carbazole **14** was converted to the natural product in four steps, providing antiostatin A_1 in 10 steps from *o*-iodoaniline in 16% overall yield.

Perhaps the most impressive example to date of the bimolecular, metal-catalyzed [2 + 2 + 2] cycloaddition in total synthesis is the preparation of a key intermediate for the preparation of sporolide B by Nicolaou and coworkers (eq 5).[11]



(5)

In this case only a slight excess of the alkyne partner **16** was used, providing an excellent yield of the highly functionalized compound **17**. The high level of regiocontrol is attributed to a

---

[10] Alayrac, C.; Schollmeyer, D.; Witulski, B. *Chem. Commun.* **2009**, 1464-1466.

[11] (a) Nicolaou, K. C.; Wang, J.; Tang, Y.; Botta, L. *J. Am. Chem. Soc.* **2010**, *132*, 11350-11363. (b) Nicolaou, K. C.; Tang, Y.; Wang, J. *Angew. Chem., Int. Ed.* **2009**, *48*, 3449-3453.

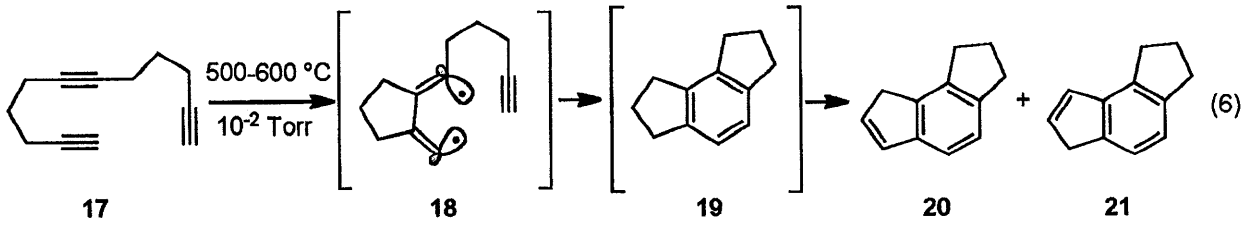
preference, due to steric effects, for only one orientation for the approach of the propargylic alcohol **16** to the initially formed metallocycle.

The examples shown of metal-catalyzed [2 + 2 + 2] cycloadditions in total synthesis illustrate the advantages and limitations of the method. With the exception of the sporolide B synthesis, all of the examples shown (and all of the other examples from the literature not included here) require an excess of alkyne partner and/or slow addition of the diyne via syringe pump, and in many cases the reactions are run at elevated temperature. When the alkyne partner is a complex intermediate that requires many steps for preparation, use of an excess is not feasible.

With all of these factors in mind, it is clear that the synthetic applicability of this bimolecular method is limited and there remains significant room for improvement.

Purely Thermal [2 + 2 + 2] Cycloadditions

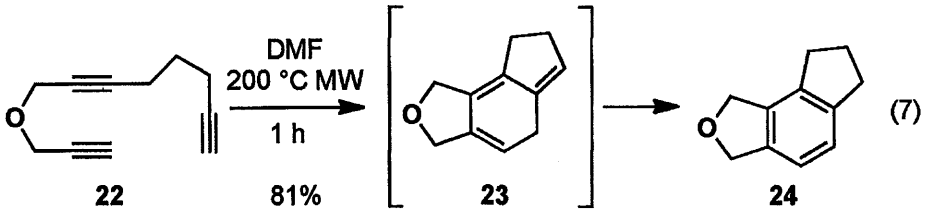
In addition to the metal-catalyzed methods discussed in the previous section, there are a few examples in the literature of purely thermal, fully intramolecular "cyclotrimerization" reactions. In the first report, Johnson showed that heating triyne **17** under flash-vacuum-pyrolysis conditions produced two isomeric arenes (eq 6).[12]



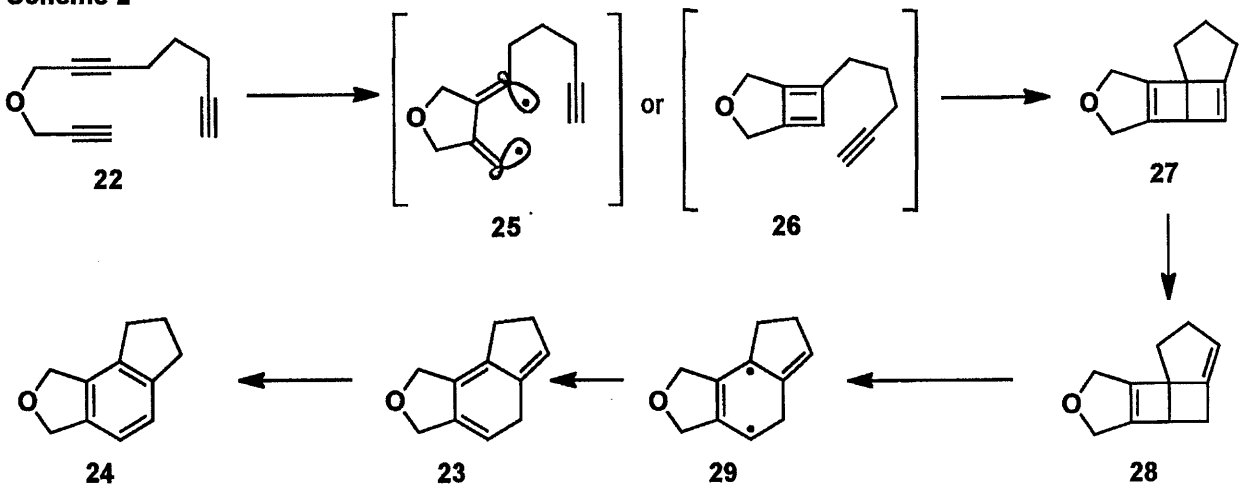
Johnson proposed a stepwise mechanism in which 1,4-diradical **18** is formed and then trapped by the remaining alkyne to give benzenoid product **19**. Under the reaction conditions, **19** undergoes a dehydrogenation reaction to afford a mixture of **20** and **21**.

[12] Kociolek, M. G.; Johnson, R. P. *Tetrahedron Lett.* **1999**, *40*, 4141-4144.

Ley and coworkers have also proposed a stepwise mechanism to account for the "cyclotrimerization" reactions reported by their lab (eq 7).[13] When triyne **22** was heated in DMF, they isolated an intermediate that they identified as **23**, leading to the proposal of a mechanism involving several strained and unusual intermediates (Scheme 2).



Scheme 2

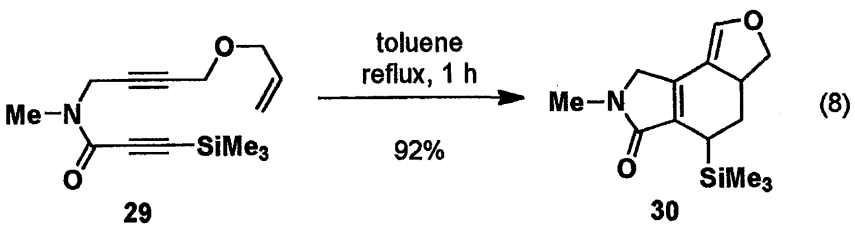


We were intrigued by this mechanism, especially the proposed involvement of cyclobutadiene intermediate **26**, Dewar benzene-type intermediate **27**, as well as anti-Bredt olefin intermediate **28**. As will be discussed in the next chapter, Dr. Takeo Sakai repeated this reaction in our laboratory, and determined via careful ^{1}H NMR experiments that the isolable intermediate is not **23**, but rather an isomeric triene that is consistent with our proposed propargylic ene reaction/Diels-Alder cycloaddition cascade.

Parsons and coworkers have also proposed a radical mechanism for the cyclization reactions observed in their laboratory (e.g. eq 8).[14]

---

[13] Saaby, S.; Baxendale, I. R.; Ley, S. V. *Org. Biomol. Chem.* **2005**, *3*, 3365-3368.
[14] (a) Parsons, P. J.; Board, J.; Faggiani, D.; Hitchcock, P. B.; Preece, L.; Waters, A. J. *Tetrahedron* **2010**, *66*, 6523-6533. (b) Parsons, P. J.; Waters, A. J.; Walter, D. S.; Board, J. *J. Org. Chem.* **2007**, *72*, 1395-1398.

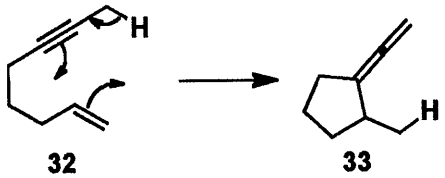


(8)

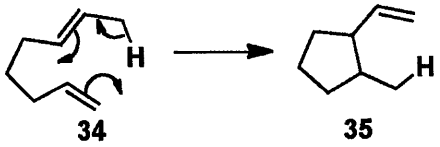
In their most recent publication,[14a] Parsons et al. also mention a concerted pathway involving an ene reaction, among several possible mechanisms to account for the formation of **30**. Deuterium-labeling studies lend support to the ene reaction mechanism.

The Propargylic Ene Reaction

The ene reaction is mechanistically related to the better known and more frequently utilized Diels-Alder reaction, proceeding through a cyclic transition state involving six electrons. It is the thermal reaction of an olefin, containing an allylic hydrogen, with an electron-deficient multiple bond (the enophile), resulting in the formation two new sigma bonds. The intramolecular ene reaction is a well-established process,[15] but there are only a few examples in the literature where the "ene" component is an alkyne with a propargyl hydrogen (eq 10) rather than an alkene with an allylic hydrogen (eq 11).



(10)



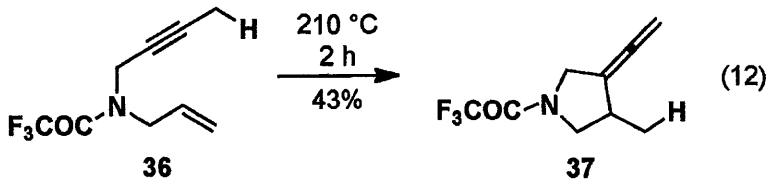
(11)

Oppolzer reported the first propargylic ene reaction in 1973 (eq 12).[16] In the past 38 years, there have been only 5 additional reports of propargylic ene reactions in the literature.

---

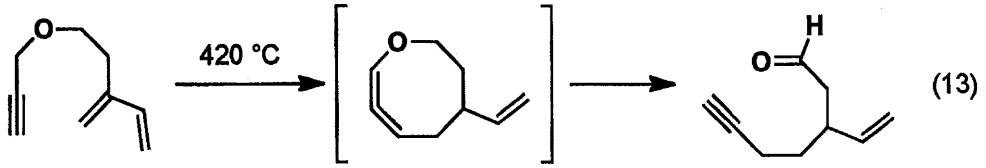
[15] For reviews of the ene reaction, see: (a) Oppolzer, W.; Snieckus, V. *Angew. Chem., Int. Ed.* **1978**, *17*, 476-486. (b) Snider, B. B. Ene Reactions with Alkenes as Enophiles, In *Comprehensive Organic Synthesis*; Paquette, L. A., Ed.; Pergamon Press: Oxford, 191; Vol. 5, pp. 1-28.

[16] Oppolzer, W.; Pfenninger, E.; Keller, K. *Helv. Chim. Acta* **1973**, *56*, 1807-1812.



36 37 (12)

The propargylic ene reaction produces an allene, which may participate in additional reactions in a tandem fashion. In 1988, Shea and coworkers reported an unusual byproduct from the attempted intramolecular Diels-Alder reaction of dienyne **38** (eq 13).[17] They proposed 1,2-cyclooctadiene **39** as the intermediate in this transformation, resulting from a propargylic ene reaction of dienyne **38**. The relatively strained cyclic allene fragments into aldehyde **40** via a retro-hetero-ene process.



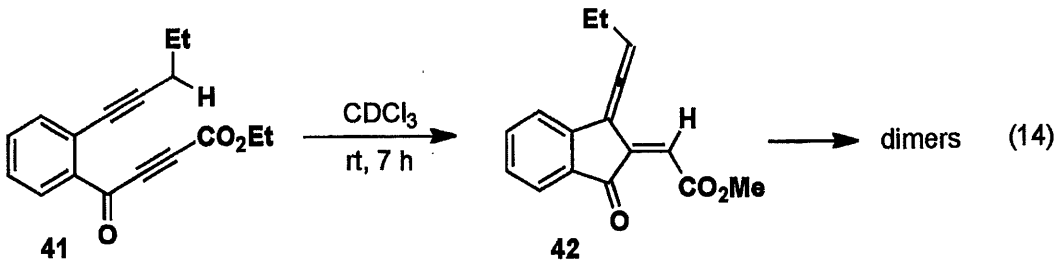
38 39 40 (13)

This mechanism for the conversion of **38** to **40** is supported by deuterium labeling experiments. Interestingly, in this report, Shea calculates the enthalpy change in the parent propargylic ene reaction of propyne with ethylene to be -23 kcal/mol, so even when the product **39** has a calculated strain energy of ca. 14 kcal/mol, the reaction to produce **39** should still be exothermic by 9 kcal/mol!

In 2003, Guitian suggested a propargylic ene reaction as a decomposition pathway for a 1,6-diyne substrate that was being investigated in Pd-catalyzed [2 + 2 + 2] cycloadditions with benzyne.[18] Upon standing at room temperature, **41** was transformed into a compound whose structure was assigned as **42**. The authors did not report any spectral data for **42** and they simply claim that it "finally evolved into a mixture of dimers."

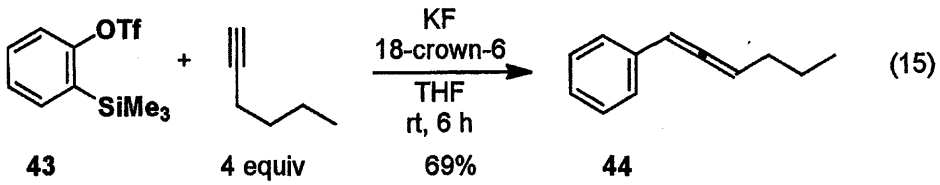
---

[17] Shea, K. J.; Burke, L. D.; England, W. P. *Tetrahedron Lett.* **1988**, *29*, 407-410.
[18] Pena, D.; Perez, D.; Guitan, E.; Castedo, L. *Eur. J. Org. Chem.* **2003**, 1238-1243.

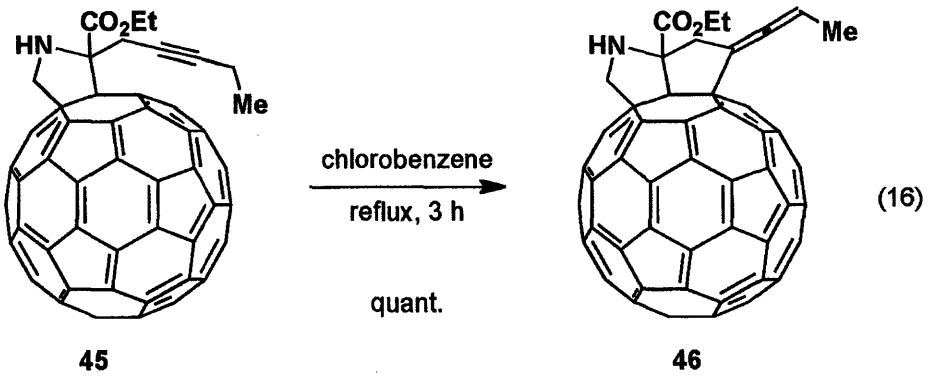


Allene **42** is a highly reactive s-cis vinylallene, so it is not surprising that it could not be isolated. For further discussion of vinylallene reactivity, see the following section in this chapter.

In 2006, Cheng and coworkers reported their studies on ene reactions of arynes with alkynes to give phenylallenes (eq 15).[19] This was the first example of an *intermolecular* propargylic ene reaction.



Also in 2006, an intramolecular ene reaction of 1,6-fullerenynes was reported.[20] Martin and coworkers were attempting to extend the [2 + 2] cycloaddition of 1,6-fullerenynes to form cyclobutene derivatives to include non-terminal alkynes, but they found instead efficient formation of allene derivatives (eq 16).

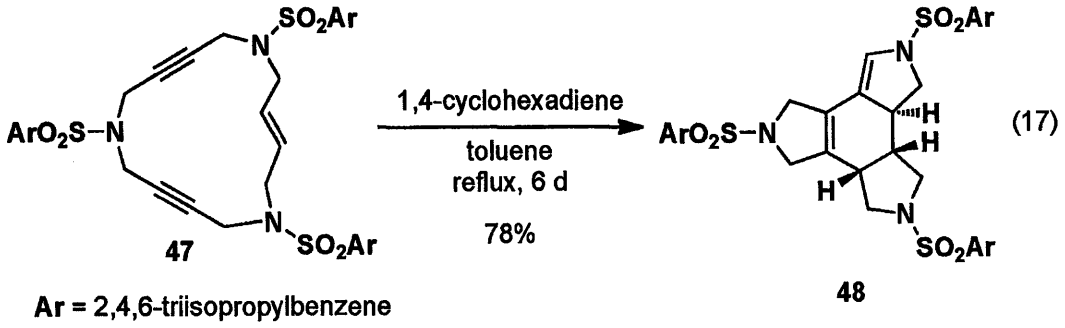


---

[19] Jayanth, T. T.; Jeganmohan, M.; Cheng, M.-J.; Chu, S.-Y.; Cheng, C.-H. *J. Am. Chem. Soc.* **2006**, *128*, 2232-2233.

[20] Altable, M.; Filippone, S.; Martin-Domenech, A.; Guell, M.; Sola, M.; Martin, N. *Org. Lett.* **2006**, *8*, 5959-5962.

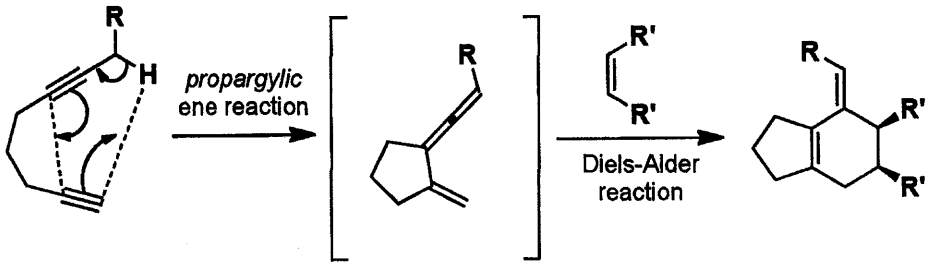
Finally, in 2010, as our study neared completion, Roglans et al. reported three related examples of a fully intramolecular propargylic ene reaction/intramolecular Diels-Alder process involving 15-membered macrocyclic triazatriynes and enediynes (eq 17).[21]



Ar = 2,4,6-triisopropylbenzene

Diels-Alder Cycloadditions of Vinylallenes

The second stage of our proposed formal [2 + 2 + 2] cycloaddition strategy includes a Diels-Alder reaction of a vinylallene.



Vinylallenes are reactive dienes in Diels-Alder reactions.[22,23] The thermal behavior of parent vinylallene **49** has been studied in the gas phase (eq 18).[24]

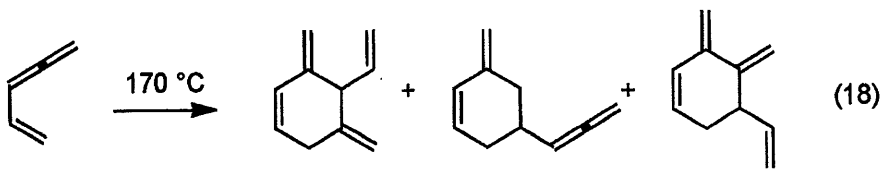
---

[21] Gonzalez, I.; Pla-Quintana, A.; Roglans, A.; Dachs, A.; Sola, M.; Parella, T.; Farjas, J.; Roura, P.; Lloveras, V.; Vidal-Gancedo, J. *Chem. Commun.* **2010**, *46*, 2944-2946.

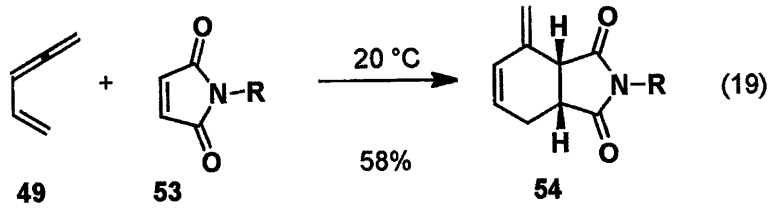
[22] For a discussion of vinylallenes in Diels-Alder reactions, see: Murakami, M.; Matsuda, T. Cycloadditions of Allenes. In *Modern Allene Chemistry*; Krause, N., Hashmi, A.S. K., Eds.; Wiley-VCH: Weinheim, 2004; Vol. 2, pp 727-815.

[23] For computational work on vinylallenes as dienes in the Diels-Alder reaction, see: (a) Ferreiro, M. L.; Rodriguez-Otero, J.; Cabaleiro-Lago, E. M. *Struct. Chem.* **2004**, *15*, 323-326. (b) Wright, J. B.; Pranata, J. *J. Mol. Struct.* **1999**, *460*, 67-78. (c) Manoharan, M.; Venuvanalingam, P. *J. Chem. Soc., Perkin Trans. 2* **1997**, 1800-1804.

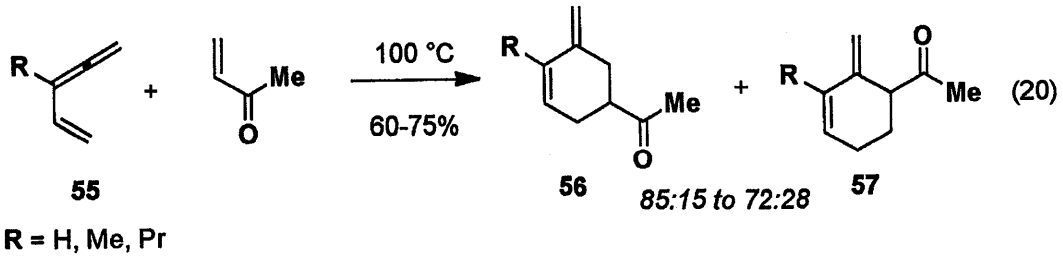
[24] Schneider, R.; Siegel, H.; Hopf, H. *Liebigs Ann. Chem.* **1981**, 1812-1825.



The reaction of vinylallene **49** with a maleimide dienophile gave a good yield of the Diels-Alder product **54** (eq 19).[25]



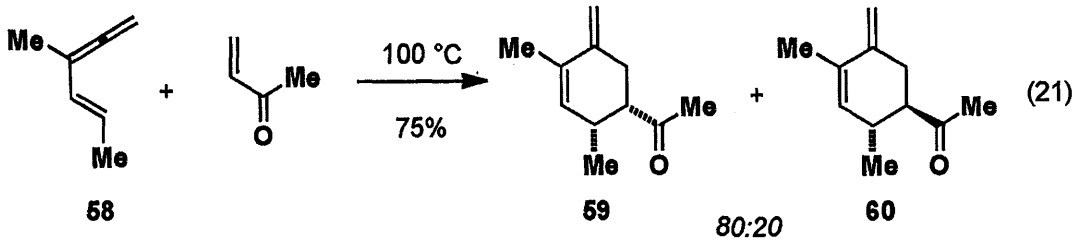
The regiochemistry and diastereoselectivity of Diels-Alder reactions of substituted vinylallenes have been studied with methyl vinyl ketone as the dienophile. As shown in eq 20, moderate regioselectivity was observed with vinylallenes that have alkyl groups at the internal allene position.[26] The lowest regioselectivity (72:28) was observed for the parent unsubstituted vinylallene.[27]



If there is a substituent at the vinyl terminus, a single regioisomer is formed in good yield, with the endo product **59** predominating (eq 21).[26]

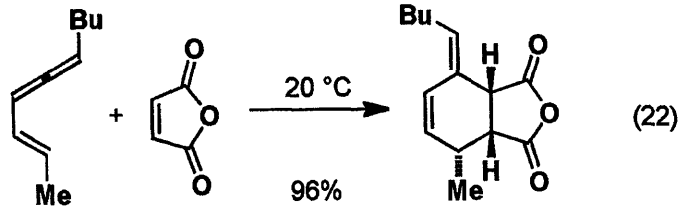
---

[25] Jones, E. R. H.; Lee, H. H.; Whiting, M. C. *J. Chem. Soc.* **1960**, 341-346.
[26] Bertrand, M.; Grimaldi, J.; Waegell, B. *Bull. Soc. Chim. Fr.* **1971**, 962-973.
[27] Bertrand, M.; Grimaldi, J.; Waegell, B. *Chem. Commun.* **1968**, 1141-1142.



58 59 80:20 60

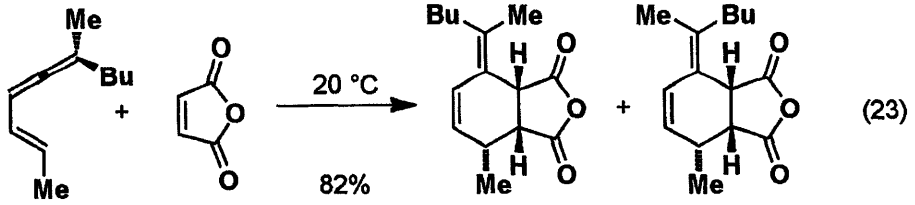
The diastereoselectivity of the cycloaddition has also been investigated using vinylallenes with substituents at the allenic terminus. In these cases, the dienophile approaches from the less-hindered face of the allene, favoring the cycloadduct with the *E*-configuration at the exocyclic olefin (eq 22).[28]



61 62

89:11 *E:Z*

When there are two substituents at the allenic terminus, the *E/Z* ratio depends on the relative size of the substituents. The small steric difference between methyl and butyl groups accounts for the modest selectivity observed in eq 23. In addition, only endo products were obtained.



63 64 (75:25) 65

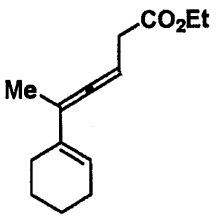
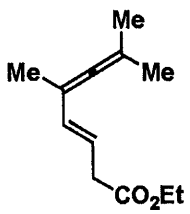
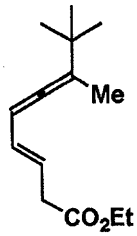
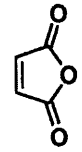
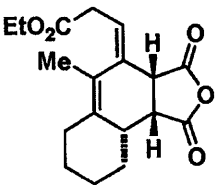
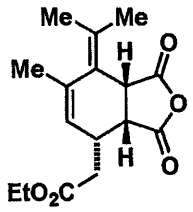
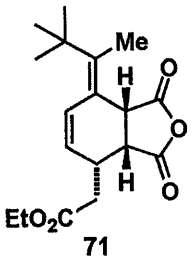
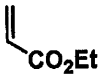
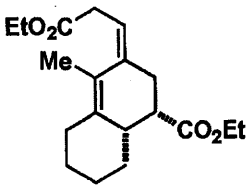
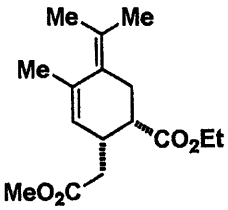
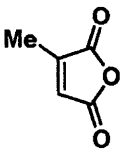
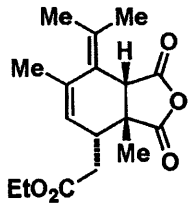
Krause and coworkers reported an important contribution to the study of vinylallene Diels-Alder reactions in 1996.[29] They developed a method for the preparation of vinylallenes using conjugate additions of organocuprates to enynyl and dienynyl esters. With access to a

---

[28] Spino, C.; Thibault, C.; Gingras, S. *J. Org. Chem.* **1998**, *63*, 5283-5287.
[29] Koop, U.; Handke, G.; Krause, N. *Liebigs Ann.* **1996**, 1487-1499.

variety of highly substituted vinylallenes, they were able to assess the regio- and diastereoselectivity of cycloadditions with several dienophiles (Table 1).

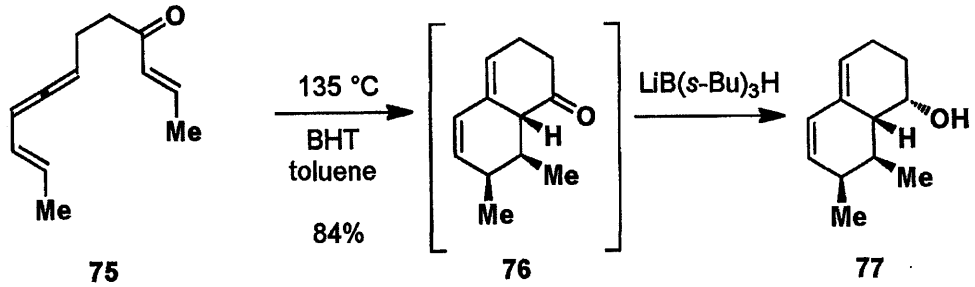
Table 1. Diels-Alder Cycloadditions of Substituted Vinylallenes with Maleic Anhydride, Methyl Acrylate, and Methylmaleic Anhydride[1,2]

	 **66**	 **67**	 **68**
	 **69** 75% single isomer	 **70** 58% single isomer	 **71** 57% single isomer
	 **72** 76% 83:17 *endo/exo*	 **73** 87% 75:25 *endo/exo*	
		 **74** 62% single isomer	

[1] Koop, U.; Handke, G.; Krause, N. *Liebigs Ann.* **1996**, 1487-1499. [2] Cycloadducts **69** and **70** were prepared in toluene at rt. Cycloadducts **71-74** were prepared in toluene at reflux.

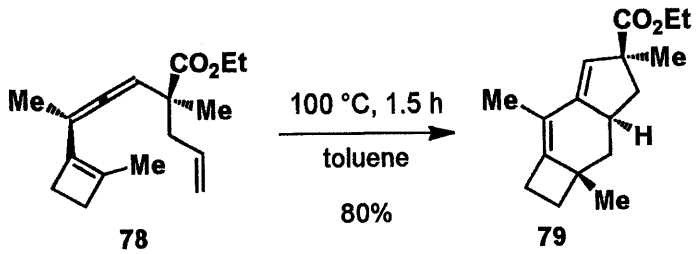
With maleic anhydride as the dienophile, exclusively endo products were observed (**69-71**). With less reactive methyl acrylate, a major endo product (**72**, **73**) was formed along with some minor exo product, and with methylmaleic anhydride, the reaction was regio- and stereoselective, giving a single endo product **74**. The product structures were assigned based on ^{1}H NMR data (coupling constant as well as nOe experiments) and X-ray structure analysis.

Diels-Alder reactions of vinylallenes as the diene component have also been carried out in an intramolecular fashion. In the total synthesis of (+)-compactin, Keck utilized a vinylallene tethered to an enone to furnish bicyclic intermediate **77** as a single diastereomer after reduction of the unstable ketone (eq 24).[30]



75 **76** **77** (24)

An interesting example of this type of reaction was reported in Krause's synthesis of racemic sterpurene derivatives using a vinylallene in which the alkene moiety is part of a cyclobutene ring (eq 25).[31] The substrate **78** was a 2:1 mixture of diastereomers at the carbon α to the ester, and the product retained the 2:1 ratio.



78 **79** (25)

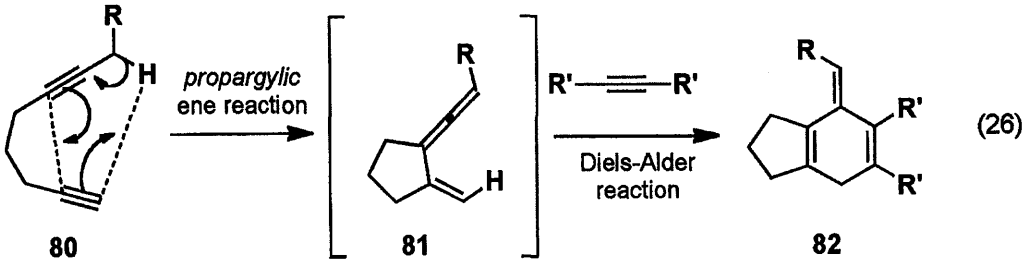
Overall, vinylallenes are highly reactive dienes in Diels-Alder reactions with standard electron-deficient dienophiles. They react with good regioselectivity, good diastereoselectivity

---

[30] Keck, G. E.; Kachensky, D. F. *J. Org. Chem.* **1986**, *51*, 2487-2493.
[31] Krause, N. *Liebigs Ann. Chem.* **1993**, 521-525.

(with the endo product favored), and good selectivity with regard to the geometry of the exocyclic olefin.

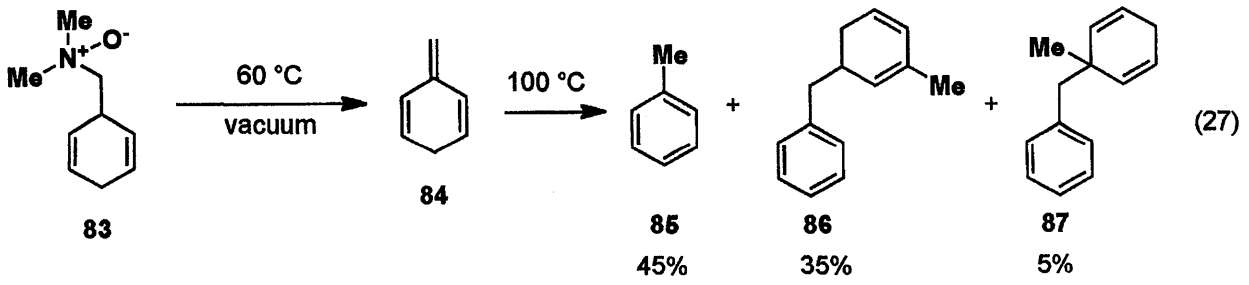
Calculations have suggested that vinylallene is less reactive than 1,3-butadiene in Diels-Alder cycloadditions, with an activation energy that is 2-3 kcal/mol higher.[23c] In our proposed formal [2 + 2 + 2] process, the vinylallene intermediates will be necessarily in the s-cis conformation due to the ring that is generated from the tether, so we expect that these vinylallenes will be highly reactive dienophiles (eq 26).



(26)

Synthesis and Stability of Isotoluenes

As shown in eq 26, the initial product of the proposed formal [2 + 2 + 2] cycloaddition would be an isotoluene derivative **82** in the case where the dienophile is an alkyne. *p*-Isotoluene has been prepared and studied by Gajewski, Bartmess, and coworkers (eq 27).[32]



(27)

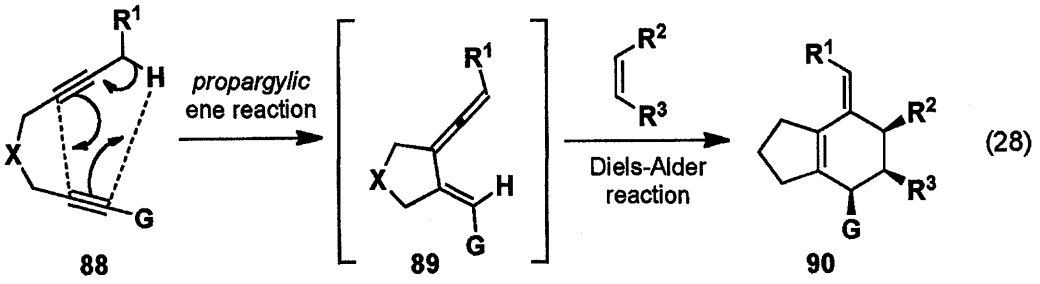
When heated at 100 °C, *p*-isotoluene **84** isomerizes to toluene **85** as the major product. In addition, two dimerization products were isolated. The ΔH for conversion of **84** to **85** was experimentally determined to be 24 ± 3 kcal/mol, and surprisingly **84** can be handled at room temperature for up to 1 h before being consumed by tautomerization![32d]

---

[32] (a) Gajewski, J. J.; Gortva, A. M. *J. Am. Chem. Soc.* **1982**, *104*, 334-335. (b) Gajewski, J. J.; Gortva, A. M. *J. Org. Chem.* **1989**, *54*, 373-378. (c) Bartmess, J. E. *J. Am. Chem. Soc.* **1982**, *104*, 335-337. (d) Bartmess, J. E.; Griffith, S. S. *J. Am. Chem. Soc.* **1990**, *112*, 2931-2936.

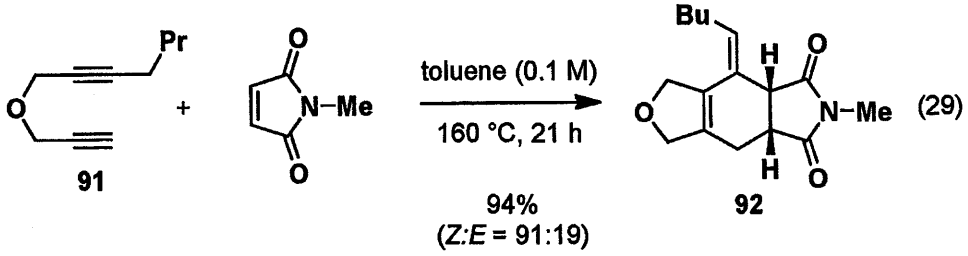
Chapter 2 – Results and Discussion

The goal of this project was to determine the scope of the bimolecular formal [2 + 2 + 2] cycloaddition shown in eq 28 with regard to the tether X, propargyl substituent R^1, alkynyl substituent G, and dienophile.



(28)

Initial work by Dr. Takeo Sakai in our laboratory on 1,6-diyne **91** with *N*-methylmaleimide as the dienophile indicated that the desired propargylic ene reaction/Diels-Alder cycloaddition cascade can proceed in excellent yield. With this encouraging result, we turned to the synthesis of a variety of substrates to investigate the effect of diyne structure on the reaction.



(29)

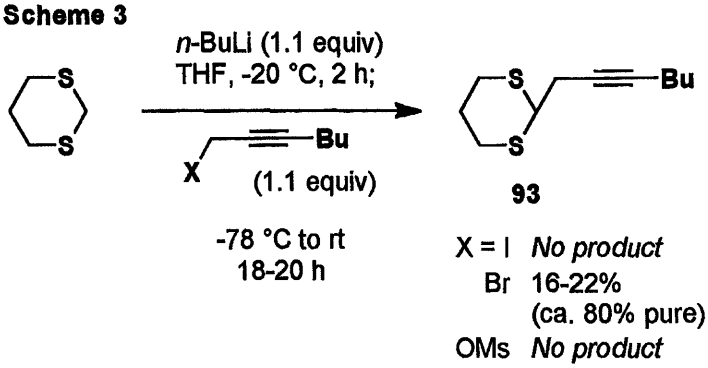
Substrate Synthesis

Variations in the nature of the tether were the first variable investigated. We were most interested in preparing 1,6-diynes with an all-carbon tether in order to maximize the synthetic utility of the tandem reaction. To this end, substrates with X = 1,3-dithiane were an attractive option. In addition to the synthetic handle provided by the dithiane for elaboration of cycloadducts, there are no examples of tethers of this type in the metal-catalyzed [2 + 2 + 2] cycloaddition literature, possibly due to the potential for sulfur to coordinate to metal centers and poison catalysts.

We envisioned an efficient synthesis of these substrates starting with sequential alkylation of the linchpin with propargyl electrophiles, followed by elaboration of a terminal alkyne into a variety of G groups using standard acetylene chemistry.

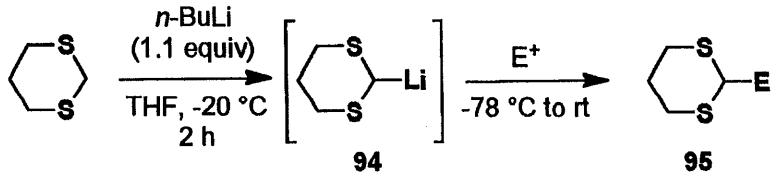
Substrate synthesis commenced with the attempted alkylation of 1,3-dithiane with 1-halo-2-heptynes (Scheme 3). The conditions for this reaction were based on a literature report by Rokach et al. of the alkylation of 1,3-dithiane with 1-bromo-2-octyne in 91% yield.[33]

Scheme 3



Unfortunately after extensive screening of conditions, including addition of HMPA, only a minor amount of product was obtained, and it could not be separated from the byproducts. In all of the reactions, the alkylating agents were consumed while the 1,3-dithiane was recovered unchanged, suggesting the possible involvement of elimination pathways. In order to investigate this puzzling result further, lithiated 1,3-dithiane was quenched with several other electrophiles (Scheme 4).

Scheme 4



E^+	Product	Yield
D_2O	95a	100%
EtI	95b	66%
$BrCH_2CCH$	95c	--
$BrCH_2CCSiMe_3$	95d	--

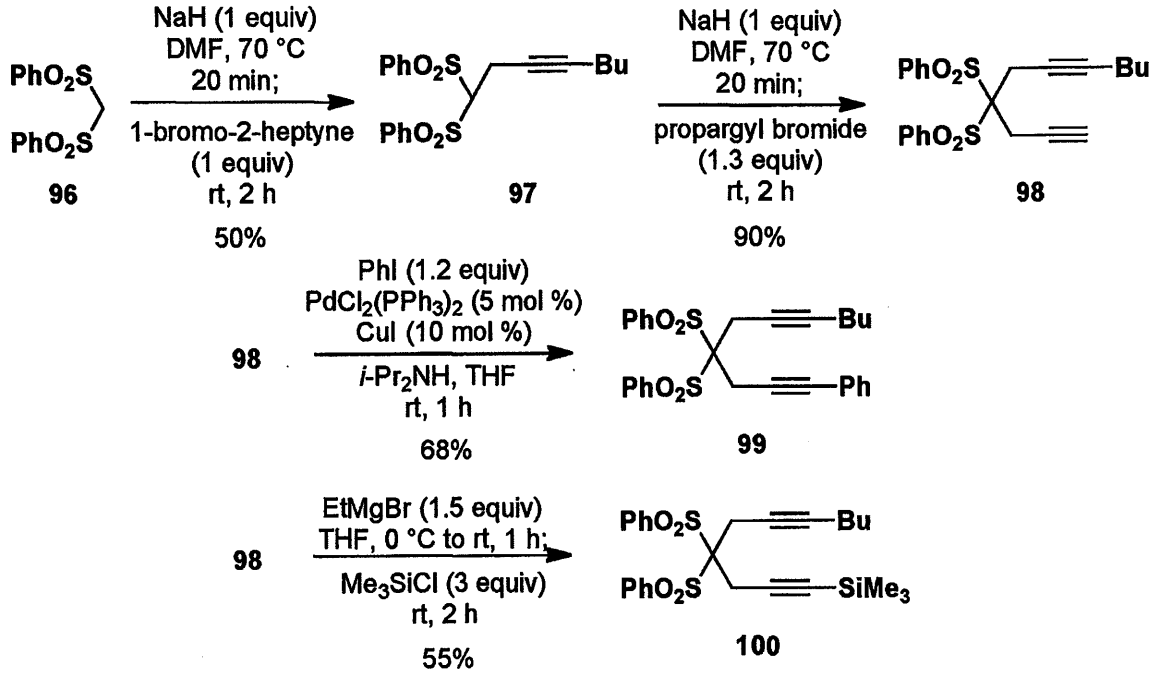
Complete deuterium incorporation was observed when **94** was quenched with D_2O. Known compound **95b** was prepared in satisfactory yield when **94** was reacted with ethyl iodide following a literature procedure.[34] However, no product was formed with propargyl bromide and TMS propargyl bromide. These results confirm that the experimental conditions are not to blame for the poor results with 1-bromo-2-heptyne, but an unexpected reaction occurs when lithiated

---

[33] Wang, S. S.; Rokach, J.; Powell, W. S.; Dekle, C.; Feinmark, S. J. *Tetrahedron Lett.* **1994**, *35*, 4051-4054.
[34] Bulman-Page et al. prepared this compound in 93% yield on 60 g scale (purification by distillation): Bulman-Page, P. C.; McKenzie, M. J.; Allin, S. M.; Klair, S. S. *Tetrahedron* **1997**, *53*, 13149-13164.

1,3-dithianes are combined with propargyl electrophiles. Our inability to repeat the result observed by Rokach is disappointing, but his publication does not offer any experimental details and it seems likely that this alkylation is particularly sensitive to the exact reaction conditions. Regardless, we next turned our attention to the system with X = $C(SO_2Ph)_2$ as an all-carbon tether that would provide a synthetic handle for elaboration of the products as well as acceleration of the intramolecular propargylic ene reaction due to a Thorpe-Ingold or gem-dialkyl-type effect.[35]

Scheme 5



Diyne **98** was prepared in two steps from commercially available bis(phenylsulfonyl)methane **96** (Scheme 5).[36,37] The first alkylation proceeds in moderate yield, with ca. 15% of doubly-alkylated product observed. The second alkylation with propargyl bromide proceeds in excellent yield. Diyne **98** was elaborated into substrates **99** and **100** in moderate yields. As will be discussed later in this chapter, the cycloadditions of **99** and **100** were problematic, so our attention turned to oxygen-tether substrates due to their synthetic accessibility and thermal stability.

---

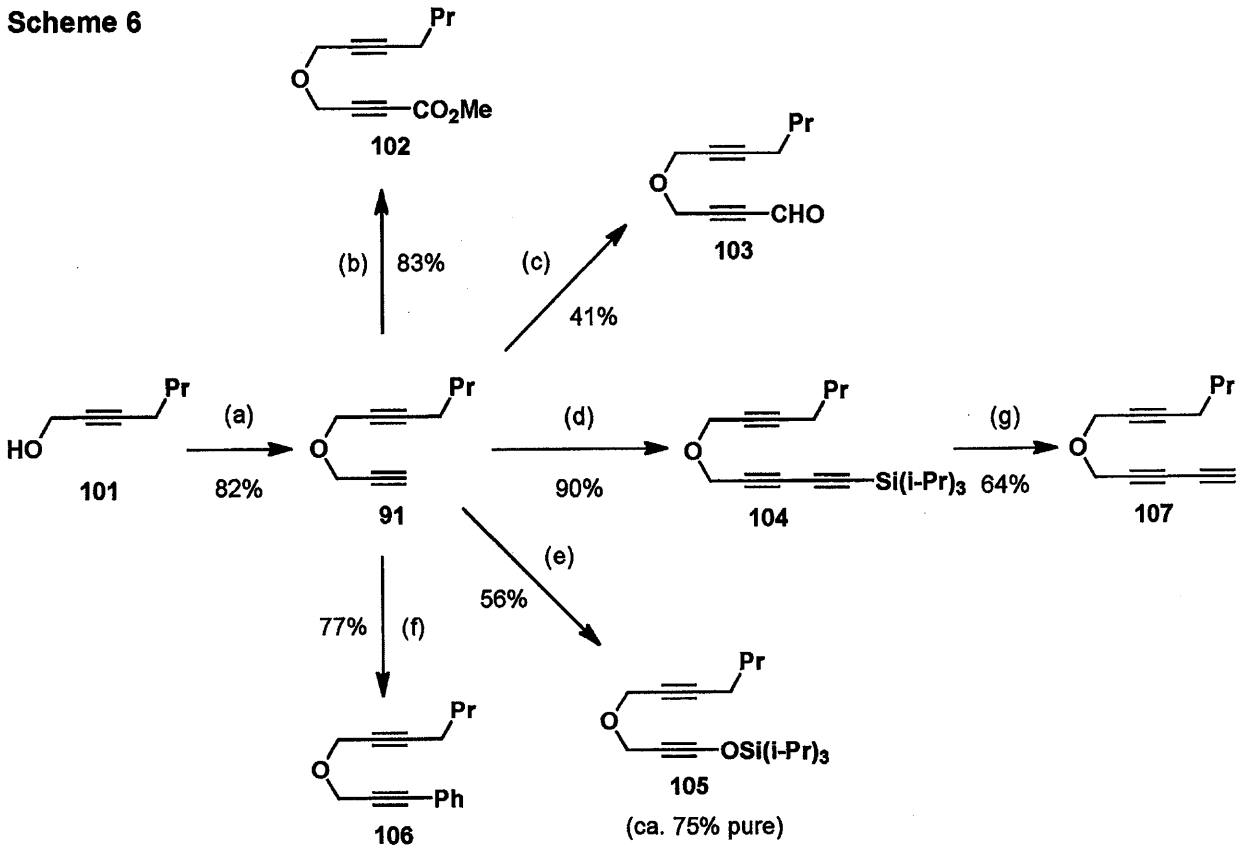
[35] For a discussion on the gem-dialkyl effect in intramolecular Diels-Alder reactions, see: Jung, M. E.; Gervay, J. *J. Am. Chem. Soc.* **1991**, *113*, 224-232.

[36] Bisphenylsulfonyl methane was prepared from benzenethiol, paraformaldehyde, and hydrogen peroxide according to a literature procedure: Cuvigny, T.; Herve du Penhoat, C.; Julia, M. *Bull. Soc. Chim. Fr.* **1982**, 43.

[37] Robinson, J. M.; Sakai, T. Okano, K.; Kitawaki, T.; Danheiser, R. L. *J. Am. Chem. Soc.* **2010**, *132*, 10039-11041.

Diyne **91** was prepared by O-alkylation of 2-heptyn-1-ol **101** (Scheme 6). In order to investigate the electronic and steric effects of substituents on the enophile alkyne, an array of 1,6-diynes with electron-withdrawing and electron-donating groups were quickly prepared from the terminal alkyne.[38] Acylation of **91** was accomplished by deprotonation, followed by addition of the lithiated acetylide intermediate to an excess of methyl chloroformate, providing alkynyl ester **102** in good yield. Cadiot-Chodkiewicz coupling with (bromoethynyl)triisopropylsilane afforded triyne **104** in excellent yield, and Sonogashira coupling with iodobenzene provided aryl alkyne **106** in good yield. Triyne **104** was also deprotected with TBAF to give terminal triyne **107**.

Scheme 6



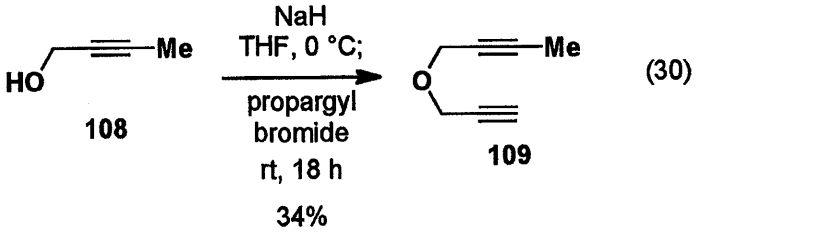
(a) NaH, THF, 0 °C; propargyl bromide, rt, 15 h. (b) *n*-BuLi, THF, -78 °C, 30 min; $ClCO_2Me$ (4 equiv), -35 °C to 10 °C, 30 min. (c) *n*-BuLi, THF, -40 °C, 30 min; DMF, rt, 30 min; 10% aq KH_2PO_4. (d) CuCl (5 mol %), $HONH_2$·HCl, 30% aq $BuNH_2$, (bromoethynyl)triisopropylsilane (1.3 equiv), THF, rt, 21 h. (e) LiHMDS, THF, -78 °C; *t*-BuOOLi, -78 °C to 0 °C; TIPSOTf, -78 °C to 0 °C. (f) $PdCl_2(PPh_3)_2$ (5 mol %), CuI (10 mol %), PhI (1.3 equiv), *i*-Pr_2NH, THF, rt, 1.5 h. (g) TBAF, THF, 0 °C, 2 h.

[38] For a discussion of the many transformations of terminal alkynes, see: Brandsma, L. Synthesis of Acetylenes, Allenes, and Cumulenes: Methods and Techniques; Elsevier: Oxford, UK; 2004.

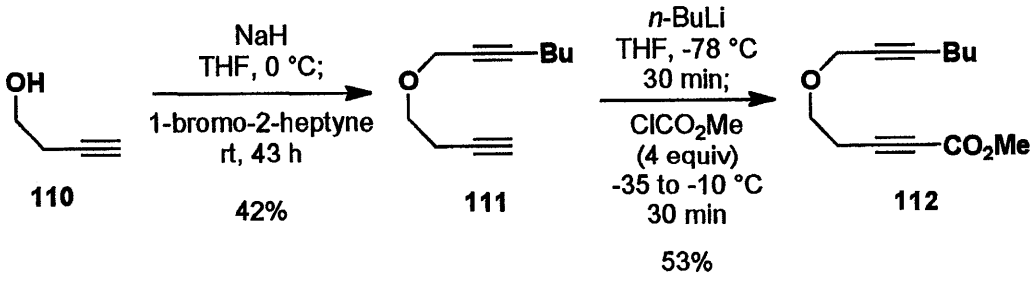
The more difficult transformations were formylation of the terminal alkyne to give α,β-unsaturated aldehyde **103** and oxidation of the terminal alkyne to the silyl ynol ether **105**. Acetylenic aldehyde **103** is especially sensitive to acid and nucleophiles. When the reaction of the lithiated alkyne with DMF was carried out using a reverse quench with phosphate buffer,[39] a moderate yield of the aldehyde was obtained. As will be discussed later in this chapter, cycloadditions with this aldehyde were problematic so the synthesis of this compound was not further optimized.

Silyl ynol ether **105** was prepared using Julia's method for oxidation of carbanions with lithium *tert*-butyl peroxide.[40] Unfortunately the product was contaminated with ca. 25% of the silylated alkyne and these two very non-polar compounds could not be separated.

In order to investigate the effect of the propargyl substituent on the propargylic ene reaction, diyne **109**[41] was prepared following a literature procedure (eq 30). Substrates **111** and **112**, with four-atom tethers, were prepared using analogous reactions (eq 31) which were not optimized.



(30)

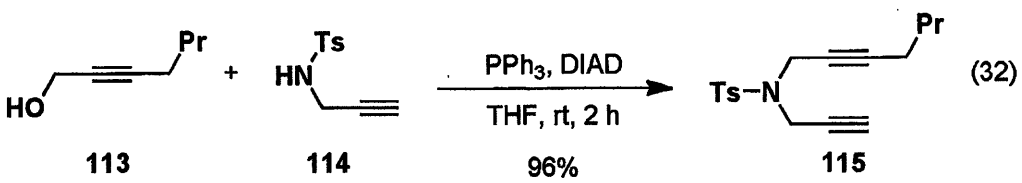


(31)

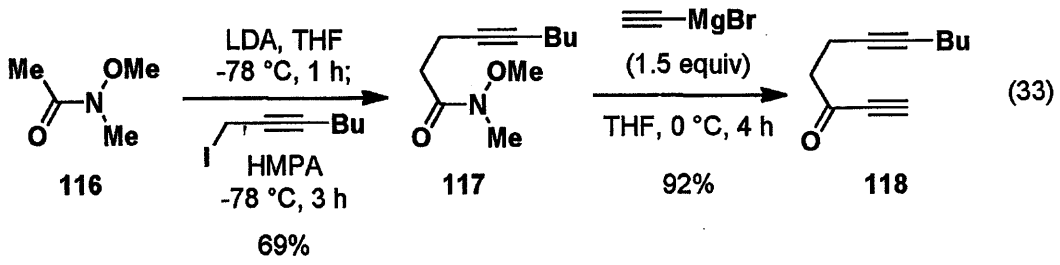
In addition to the substrates with oxygen-containing tethers, a substrate with a nitrogen atom in the tether was prepared by Mitsunobu reaction of 4-methyl-*N*-(prop-2-yn-1-yl)benzenesulfonamide **114** with 2-heptyn-1-ol **113** in excellent yield (eq 32).

---

[39] Journet, M.; Cai, Dongwei, DiMichele, L. M.; Larsen, R. D. *Tetrahedron Lett.* **1998**, *39*, 6427-6428.
[40] Julia, M.; Saint-Jalmes, V. P.; Verpeaux, J.-N. *Synlett* **1993**, 233-234.
[41] Chang, H.-T.; Jeganmohan, M.; Cheng, C.-H. *Org. Lett.* **2007**, *9*, 505-508.



In order to further investigate the electronic effects of the tether on the propargylic ene reaction, Dr. Takafumi Kitawaki prepared ketone tether substrate **118** using alkylation of commercially available *N*-methoxy-*N*-methylacetamide **116** followed by addition of ethynyl magnesium bromide (eq 33).



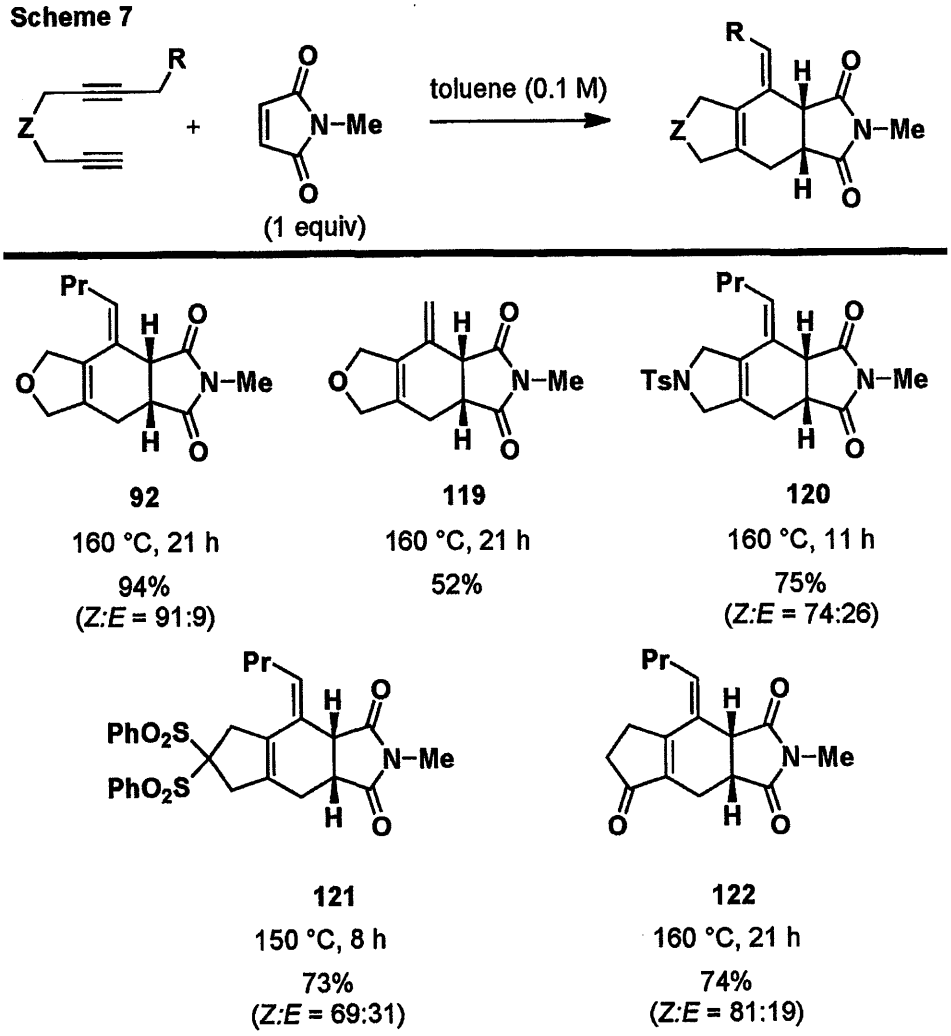
Tandem Reactions – *Alkenyl Dienophiles*

Examples of the formal [2 + 2 + 2] cycloaddition using *N*-methylmaleimide as the dienophile are shown in Scheme 7 below. These cases illustrate the effects of variations of the 1,6-diyne tether and propargylic substituent R on the facility of the propargylic ene reaction.

Good yields were obtained with only one equivalent of the dienophile, in contrast to most cases of the metal-catalyzed bimolecular [2 + 2 + 2] cycloaddition process, where a large excess of the third alkyne or alkene is needed. In these cases of propargylic ene reactions involving unactivated alkynes as enophiles, the reaction requires temperatures in the range of 150-160 °C to proceed efficiently.

Assuming that the propargylic ene reaction is the rate-determining step, which seems reasonable based on the literature example of vinylallene participating in a Diels-Alder cycloaddition with a maleimide at room temperature,[25] the fastest propargylic ene reaction in this series occurs with bissulfone **98**, affording cycloadduct **121**, followed by *N*-tosyl substrate **115**, giving cycloadduct **120**. In the case of diyne **109**, where the alkyne substituent is methyl instead of butyl, the tandem reaction rate is not affected.

Scheme 7



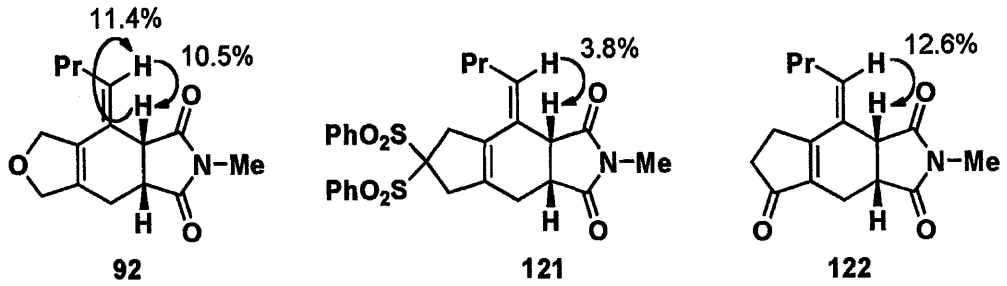
The yield of exocyclic methylene product **119** is lower than the others due to product decomposition under the reaction conditions. This was confirmed by resubjecting pure product **119** to heating in toluene. Cycloadducts **120** and **121**[42] were also found to be thermally unstable.

The products are formed as predominantly the *Z* isomers, as expected based on the approach of the dienophile to the less hindered face of the allene. This is consistent with the literature examples of Diels-Alder cycloadditions of vinylallenes with maleic anhydride as the dienophile.[28,29] The assignment of *Z*-stereochemistry was established by differential nOe experiments (Scheme 8).

---

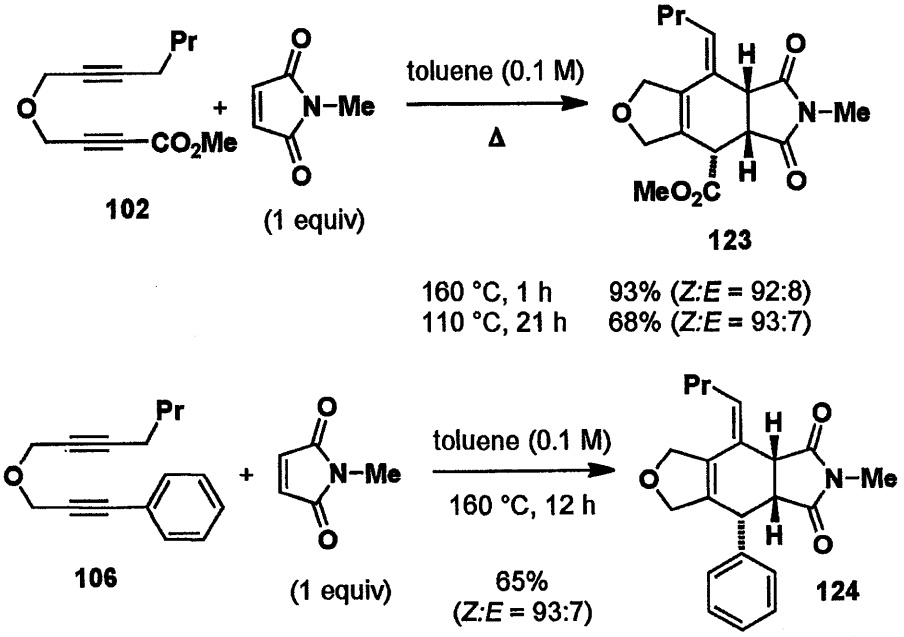
[42] Cycloaddition attempts using bissulfone substrates **99** (G = Ph) and **100** (G = $SiMe_3$) were unsuccessful due to the thermal instability of the tether, leading to a complex mixture of products.

Scheme 8. Differential nOe experiments determine olefin geometry.



Further examples demonstrating the scope of the tandem reaction are shown in Scheme 9. The reaction proceeded well with *N*-methylmaleimide and diyne substrates bearing a substituent on the enophile alkyne.

Scheme 9

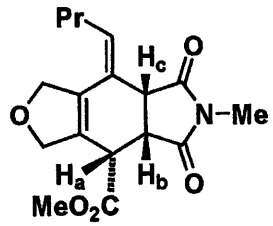


Intramolecular ene reactions of 1,6-dienes are known to proceed at an elevated rate when the enophile alkene bears an electron-withdrawing group.[15] In the propargylic ene reaction of 1,6-diyne **102**, the reaction was complete within 1 h at 160 °C compared to 21 h at 160 °C for the substrate **91** which has a terminal alkyne as the enophile. This increase in rate allowed the tandem reaction of **102** to be carried out in refluxing toluene. In the case with the phenyl

substituent (diyne **106**), the tandem reaction proceeded at a slightly elevated rate relative to the unsubstituted case (160 °C, 12 h instead of 160 °C, 21 h). Interestingly, no competition from "arenyne"[43] type reactions was observed with substrate **106**.

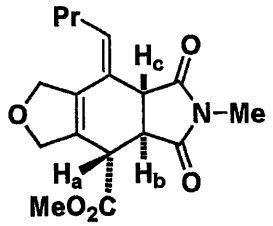
Cycloadducts **123** and **124** were formed as exclusively the endo products, with the relative stereochemistry shown in Scheme 9. This was expected based on the Alder-endo rule and it is consistent with Krause's report of reactions of substituted vinylallenes with maleic anhydride.[29] The endo stereochemistry of **123** and **124** was assigned based on comparison of the observed ^{1}H NMR coupling constants with the coupling constants predicted for the endo and exo isomers by application of the Karplus correlation to the dihedral angles calculated for each isomer using Spartan '08 (Table 2).

Table 2. Dihedral Angle Analysis[1] for Determination of Relative Stereochemistry

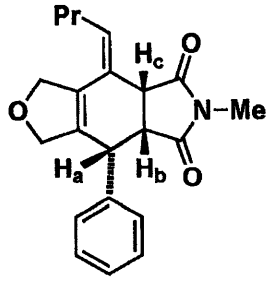


endo-**123**

		H_a, H_b	H_b, H_c
endo	dihedral angles	44	44
	calculated *J*	7 Hz	7 Hz
exo	dihedral angles	81	20
	calculated *J*	2 Hz	11 Hz
	Observed *J*	6 Hz	6 Hz

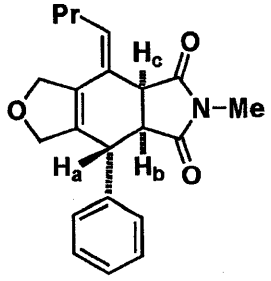


exo-**123**



endo-**124**

		H_a, H_b	H_b, H_c
endo	dihedral angles	32	46
	calculated *J*	10 Hz	7 Hz
exo	dihedral angles	86	40
	calculated *J*	1 Hz	8 Hz
	Observed *J*	5 Hz	3 Hz



exo-**124**

[1] The dihedral angles for each isomer were calculated using Spartan '08 Hartree-Fock 6-31G*

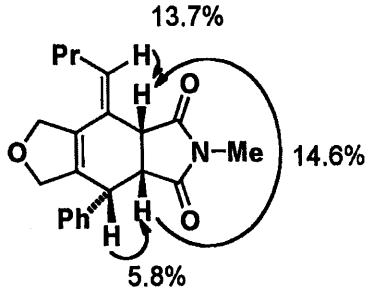
For compound **124**, the dihedral angles were calculated using MMFF, Hartree-Fock 6-31G*, and DFT B3LYP 6-31G* methods. As the results were very similar using both Hartree-

[43] Reviewed in Wessig, P.; Muller, G. *Chem. Rev.* **2008**, *108*, 2051-2063.

Fock 6-31G* and DFT B3LYP 6-31G*, the dihedral angles of compound **123** were calculated using Hartree-Fock 6-31G*. The calculated dihedral angle for H_a,H_b in the exo isomer of both compounds is 80-90°. This is inconsistent with the observed $J_{a,b}$ of 5-6 Hz.

These stereochemical assignments were confirmed with a differential nOe experiment on compound **124** (Figure 1). At this point the cis ring junction was also confirmed.

Figure 1. Differential nOe Experiments Confirm Stereochemical Assignments

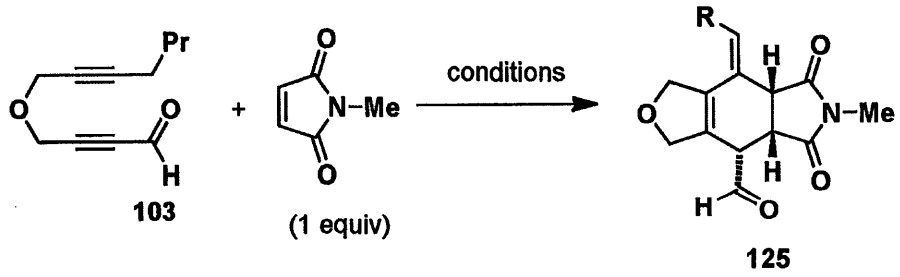


124

Z-stereochemistry: 13.7% from	5.83 (t, *J* = 7.8 Hz)	to	3.98 (d, *J* = 7.7 Hz)
Cis ring junction: 14.6% from	3.98 (d, *J* = 7.7 Hz)	to	3.46 (t, *J* = 7.9 Hz)
Endo stereochemistry: 5.8% from	3.65 (d, *J* = 8.3 Hz)	to	3.46 (t, *J* = 7.9 Hz)

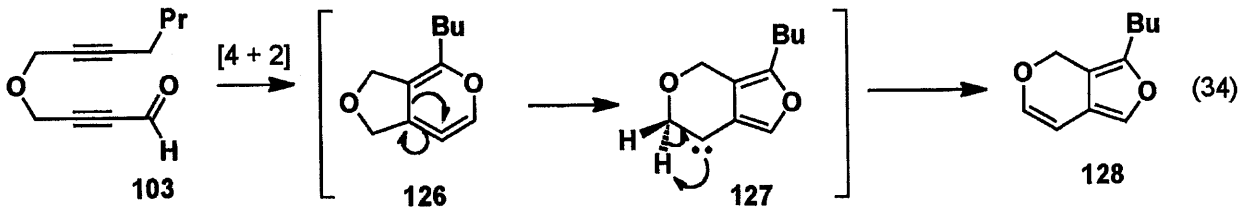
Attempts to react alkenyl aldehyde substrate **103** with *N*-methylmaleimide in the tandem reaction were unsuccessful (Scheme 10).

Scheme 10



Conditions	Temperature	Result
toluene (0.1 M)	110 °C, 17 h	Mixture of **125** and **128** in crude No pure product obtained.
Me_2AlCl (2-5 equiv) CH_2Cl_2 (0.05 M)	-78 °C	Trace **128**, mostly **103**
	-78 °C to -50 °C	No reaction
	-78 °C to rt	Decomposition

When the reaction was attempted thermally, the crude ^{1}H NMR spectrum indicated desired product **125** along with "ynone" cycloaddition[44] byproduct **128** (eq 34) and significant decomposition. Lewis-acid promotion also resulted in the formation of furan **128**.



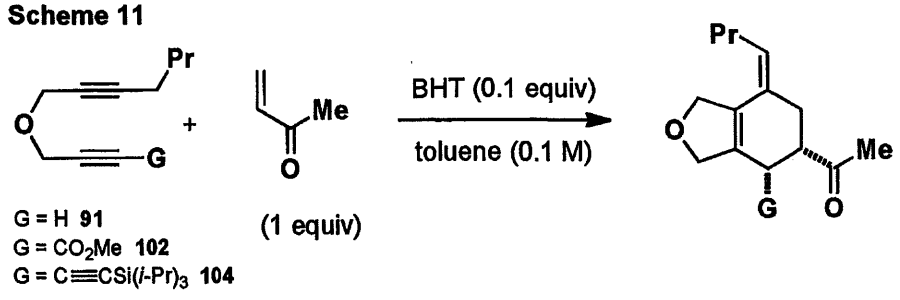
Examples of the formal [2 + 2 + 2] cycloaddition using methyl vinyl ketone as the dienophile are shown in Scheme 11 below. In reactions with dienophiles that are prone to polymerizaton such as MVK, yields were improved by addition of a small amount of BHT as a radical inhibitor. Ketone **129** was obtained in good yield along with an 11% yield of the regioisomeric Diels-Alder product.[45] This is in line with the literature report of Diels-Alder reactions of MVK with vinylallenes lacking a substituent at the vinyl terminus, where ca. 6:1 selectivity for the major regioisomer is the best reported.[26] In cases where the enophile alkyne bears an electron-withdrawing substituent, the products **130** and **131** were obtained as single regioisomers. Triyne substrate **104** underwent smooth reaction to provide ketone **131** in toluene at reflux, demonstrating that TIPS alkyne is an excellent activating group for the propargylic ene reaction.

The cycloadditions shown in Scheme 11 are completely diastereoselective, providing exclusively the endo products. The relative stereochemistry of the cycloadducts was determined by analysis of ^{1}H NMR coupling constants and calculated dihedral angles, as discussed on p. 32 for compounds **123** and **124** (Table 3). The assignment of *Z* stereochemistry for the major isomers was based on the downfield chemical shift of the alkenyl proton in the *Z* isomers compared to the *E* isomers, by analogy with the compounds for which differential nOE experiments were performed.

---

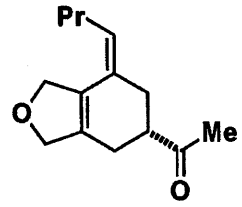
[44] Wills, M. S. B.; Danheiser, R. L. *J. Am. Chem. Soc.* **1998**, *120*, 9378-9379.
[45] The cycloaddition reaction to prepare ketone **129** was carried out by Dr. Katsu Okano.

Scheme 11



G = H **91**
G = CO_2Me **102**
G = C≡CSi(*i*-Pr)$_3$ **104**

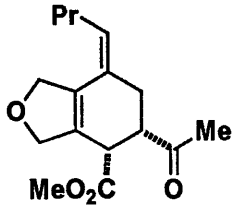
(1 equiv)



129

160 °C, 21 h

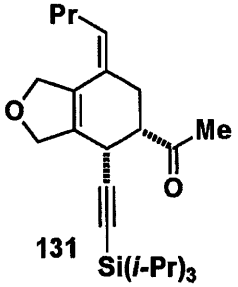
72%
(*Z*:*E* = 86:14)



130

110 °C, 19 h

57%
(*Z*:*E* = 93:7)

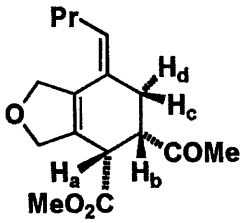


131

110 °C, 21 h

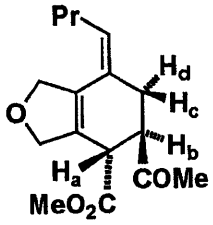
68%
(*Z*:*E* = 90:10)

Table 3. Dihedral Angle Analysis[1] for Determination of Relative Stereochemistry

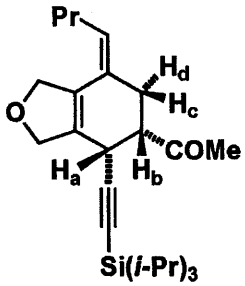


endo-**130**

		H_a, H_b	H_b, H_c	H_b, H_d
endo	dihedral angles	45	67	177
	calculated *J*	7 Hz	3.5 Hz	13 Hz
exo	dihedral angles	74	61	58
	calculated *J*	2.5 Hz	5 Hz	5 Hz
	Observed *J*	4-7 Hz[2]	3 Hz	12 Hz

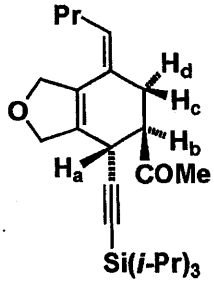


exo-**130**



endo-**131**

		H_a, H_b	H_b, H_c	H_b, H_d
endo	dihedral angles	48	67	174
	calculated *J*	7 Hz	3.5 Hz	13 Hz
exo	dihedral angles	163	64	178
	calculated *J*	13 Hz	4 Hz	13 Hz
	Observed *J*	5 Hz	3 Hz	13 Hz



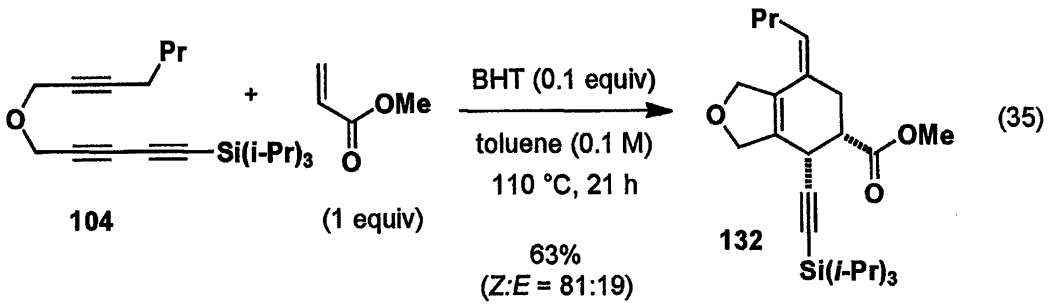
exo-**131**

[1] The dihedral angles for each isomer were calculated using Spartan '08 Hartree-Fock 6-31G*.
[2] This *J*-value is estimated based on the width of the multiplet peak.

For both **130** and **131**, the observed ^{1}H NMR coupling constants and the calculated coupling constants based on the calculated dihedral angles for the endo isomers are in good agreement. In particular, for **130**, the observed $J_{b,d}$ is 12 Hz and the calculated coupling constant for the endo isomer is 13 Hz while the value for the exo isomer is 5 Hz, so clearly the ^{1}H NMR data for **130** corresponds much more closely to the endo isomer than the exo isomer.

In the case of cycloadduct **131**, the observed $J_{a,b}$ is 5 Hz, while the calculated coupling constant for the endo isomer is 7 Hz and the exo isomer is 12 Hz.

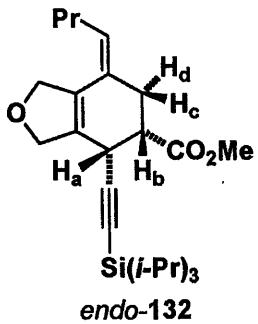
Further investigation of dienophiles in the tandem reaction revealed that methyl acrylate was an effective dienophile with triyne **104** (eq 35). The cycloadduct **132** was obtained as a single diastereomer in good yield.



(35)

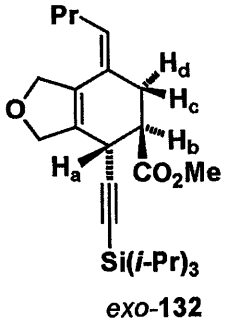
The relative stereochemistry of the cycloadduct was determined by analysis of ^{1}H NMR coupling constants and calculated dihedral angles, as discussed on p. 33 for compounds **123** and **124** (Table 4). The assignment of *Z* stereochemistry for the major isomer was based on the downfield chemical shift of the alkenyl proton in the *Z* isomer compared to the *E* isomer, by analogy with the compounds for which differential nOE experiments were completed.

Table 4. Dihedral Angle Analysis[1] for Determination of Relative Stereochemistry



endo-**132**

		H_a, H_b	H_b, H_c	H_b, H_d
endo	dihedral angles	49	59	57
	calculated *J*	4 Hz	2 Hz	3 Hz
exo	dihedral angles	168	177	67
	calculated *J*	8 Hz	10 Hz	0.5 Hz
	Observed *J*	5 Hz	2 Hz	3-5 Hz[2]



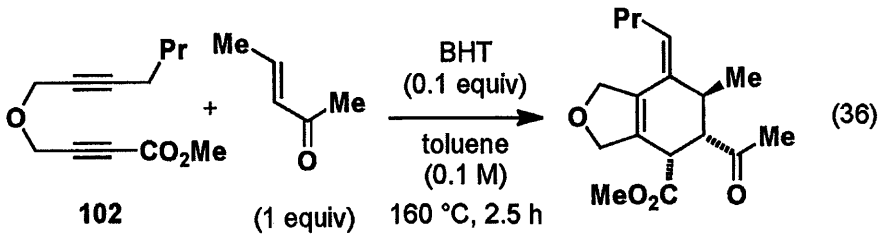
exo-**132**

[1] The dihedral angles for each isomer were calculated using Spartan '08 Hartree-Fock 6-31G*.

[2] This *J*-value is estimated based on the width of the multiplet peak.

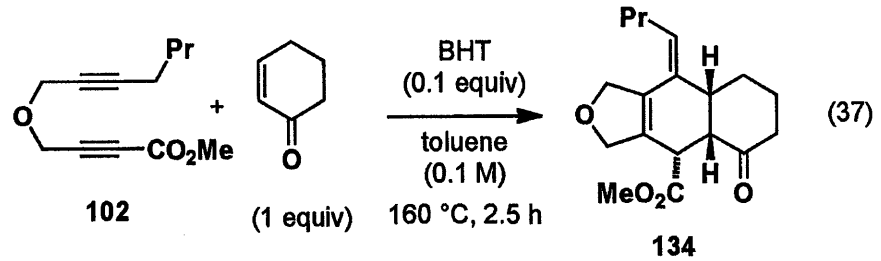
The observed *J*-values are in excellent agreement with the calculated coupling constants for the endo isomer.

Attempts to extend this method to unsymmetrical, disubstituted alkene dienophiles in order to access cyclohexene derivatives a substituent at every position in a diastereoselective fashion are shown in eq 36 and eq 37.



102 (1 equiv) 133 (36)

24%
(ca. 60% pure)



102 (1 equiv) 134 (37)

17%
(ca. 60% pure)

We hoped that the highly reactive nature of the s-cis vinylallene intermediate[46] would allow for the use of less-reactive dienophiles such as *(Z)*-3-penten-2-one and cyclohexenone. It is well established that *E,E*-exocyclic dienes undergo Diels-Alder reactions at lower temperatures than acyclic dienes which have to adopt the s-cis conformation for reaction to occur.[47] Unfortunately it appears that with less reactive disubstituted dienophiles, the vinylallene intermediate preferentially undergoes side reactions. Although in both cases complete consumption of diyne **102** was observed, only 24% of impure **133** and 17% of impure **134** were obtained. Reaction to produce **133** was also attempted in refluxing toluene, resulting in a complex mixture of products. The efficiency of these reactions may be improved by altering the

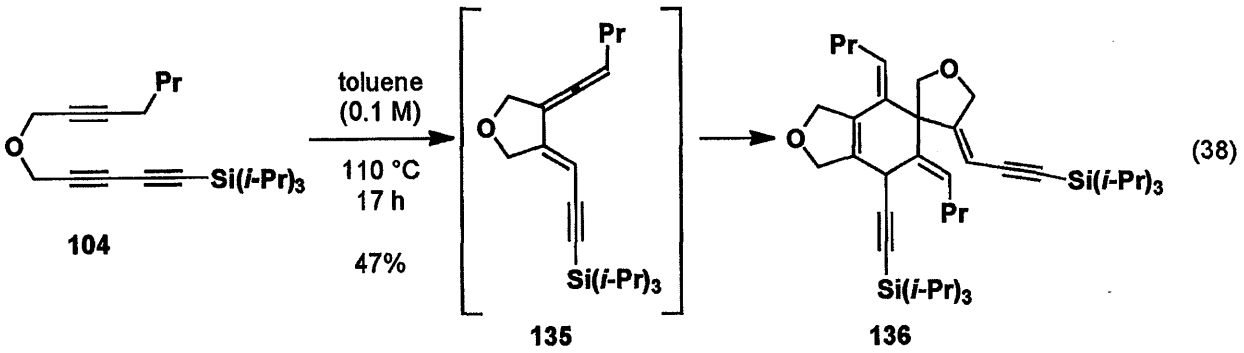
---

[46] The vinylallenes produced in this pericyclic cascade are so reactive that they can engage cyano groups as dienophiles in intramolecular Diels-Alder reactions. For application of this formal [2 + 2 + 2] strategy to the synthesis of pyridines, see: T. Sakai and R. L. Danheiser, *J. Am. Chem. Soc.* **2010**, *132*, 13203-13205.

[47] Nugent, W. A.; Calabrese, J. C. *J. Am. Chem. Soc.* **1984**, *106*, 6422-6424.

equivalents of dienophile or the concentration.

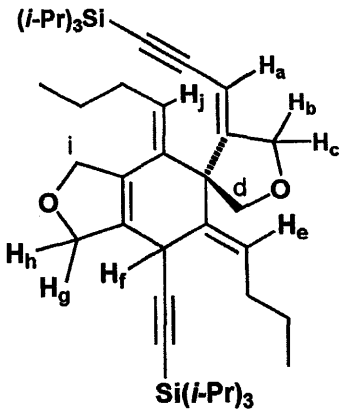
The most likely side reaction that the vinylallene undergoes is dimerization. As discussed in the previous chapter, vinylallenes are known to dimerize via Diels-Alder reactions. When diyne **104** was heated in the absence of dienophile in an attempt to isolate vinylallene intermediate **135**, a 47% yield of dimer **136** was obtained as a 84:14 mixture of two diastereomers (eq 38).



(38)

We expected that vinylallene **135** might be isolable because the steric bulk of the (triisopropyl)silyl group could slow down dimerization to the point that **133** would build up in the reaction mixture. The dimeric nature of **136** was confirmed by HRMS.[48] The structure was assigned based on ^{1}H and ^{13}C NMR chemical shifts and coupling constants (Figures 2 and 3). Only diagnostic protons and carbons are shown for clarity.

Figure 2. Diagnostic Protons for Vinylallene Dimer 136



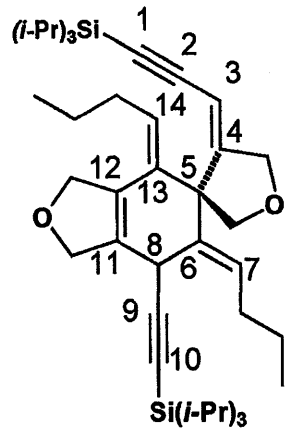
136

proton	δ (ppm)	m	J (Hz)
H_a	5.96	t	2.6
H_b	4.66	dd	7.3, 2.6
H_c	4.77-4.86	m	-
H_d	4.21	d	8.8
	3.76	d	10.0
H_e	5.63	t	7.6
H_f	3.33-3.37	m	-
H_g	5.00-5.18	m	-
H_h	4.57-4.62	m	-
H_i	4.86-4.94	m	-
H_j	5.74	t	7.4

[48] The HRMS of triyne **104** does not reveal extensive dimerization.

The three alkenyl proton resonances are triplets, as expected, with the enynyl alkenyl proton H_a exhibiting long-range coupling to the diastereotopic methylene protons H_b and H_c on the spiro-fused tetrahydrofuran ring. In the ^{13}C NMR spectrum, the enynyl alkene carbon C_4 is the furthest downfield. All of the alkene and alkyne carbons are accounted for, as well as quaternary C_5 on the spiro-fused ring and doubly-allylic, propargylic methine C_8.

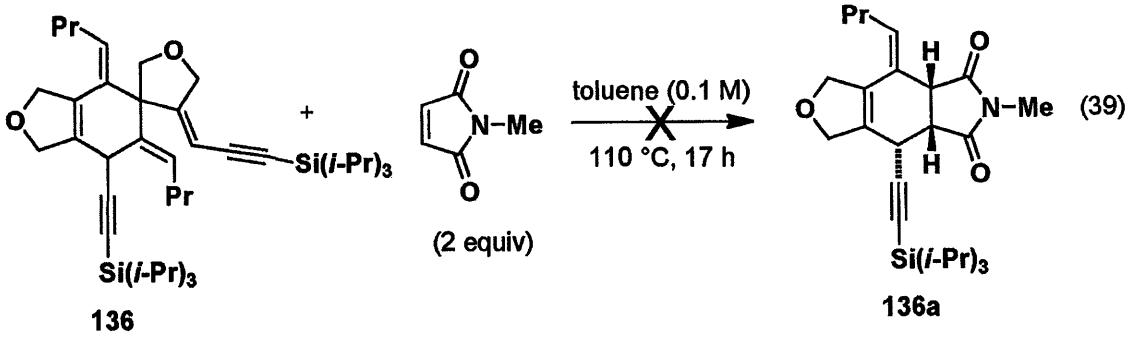
Figure 3. Diagnostic Carbons for Vinylallene Dimer 136



136

Alkyne C	δ (ppm)	Alkene C	δ (ppm)
1	96.8	3	130.1
2	104.4	4	156.5
9	85.4	6	133.6
10	103.61	7	103.65
Quat C		11	132.5
5	54.3	12	133.1
Methine C		13	137.8
8	35.8	14	130.2

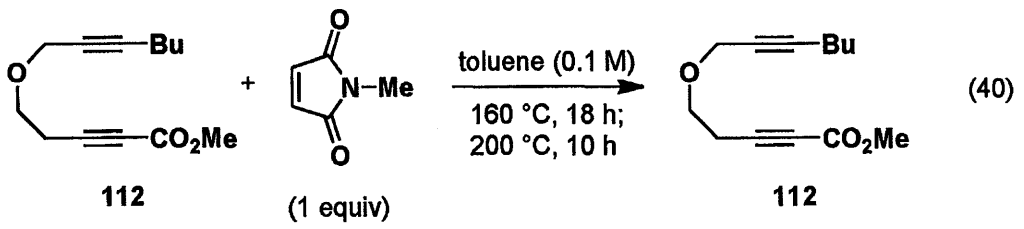
In order to determine whether vinylallene dimer **136** is a competent intermediate in the formal [2 + 2 + 2] cycloaddition process, it was heated in the presence of *N*-methylmaleimide (eq 39).



136 **136a** (39)

Vinylallene dimer **136** was fully consumed in this reaction, but none of the desired cycloadduct was formed. It seems likely that the dimerization of vinylallene **135** is not reversible, and instead decomposition reactions occur upon heating of **136**.

The pericyclic cascade process described thus far in this chapter is an efficient way to prepare fused 5-6 ring systems. We were interested in extending this method to the preparation of fused 6-6 ring systems using 1,7-diyne **112** (eq 40).



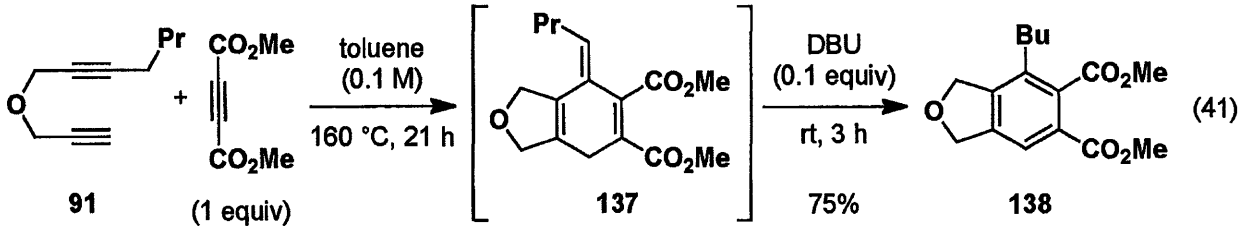
(40)

However, after prolonged heating at high temperatures diyne **112** was recovered unchanged. The dienophile decomposed under these forcing conditions. Note that in contrast to intramolecular ene reactions of 1,6-dienes, similar reactions involving 1,7-dienes require higher temperatures and proceed in lower yield.[15]

Overall, the formal [2 + 2 + 2] cycloaddition process works well with 1,6-diynes and alkene dienophiles. A variety of tethers and substituents on the enophile are tolerated. The reactions generally proceed with excellent regio- and diastereoselectivity. In many cases the reactions can be run in refluxing toluene instead of heating at 160 °C and the only additive is substoichiometric BHT in some cases. This method is atom-economical and environmentally attractive in that no reagents or metal catalysts are employed which have to be separated from the products. Only one equivalent of the dienophile is used and the 1,6-diyne substrates are readily available in 1-2 steps from commercial starting materials. This is an attractive method for rapid assembly of cyclohexene derivatives bearing multiple substituents.

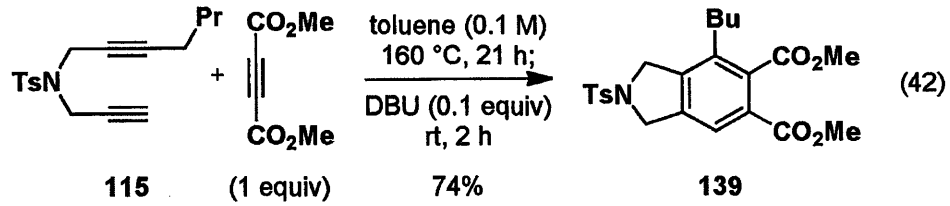
Tandem Reactions – *Alkynyl Dienophiles*

Our first attempt at using an alkynyl dienophile in the tandem process is shown in eq 41. Gratifyingly, reaction of dimethyl acetylenedicarboxylate with diyne **91** afforded pentasubstituted aryl diester **138** in 75% yield (eq 41).[49]



After the heating step, the reaction mixture contained both *p*-isotoluene **137** and final product **138** (by TLC analysis). Recall from the discussion of isotoluenes in the previous chapter that the parent isotoluene 3-methylene-1,4-cyclohexadiene is surprisingly stable and can be handled for up to 1 h at room temperature before tautomerizing and dimerizing.[32c] Isotoluene **137** bears multiple substituents, including two electron-withdrawing groups, so we expected that its stability might differ from *p*-isotoluene. Treatment of the mixture of **137** and **138** with a catalytic amount of DBU resulted in clean conversion to **138** within a few hours at room temperature.

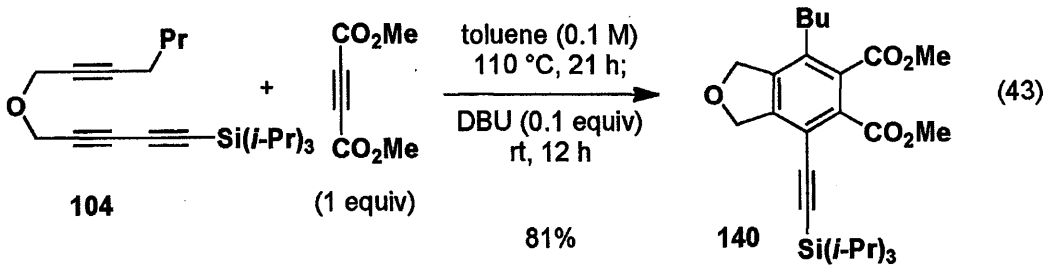
Another example of this two-step, one-pot procedure is shown in eq 42. The *N*-tosyl substrate **115** gave diester **139** in good yield.



The formal [2 + 2 + 2] cycloaddition reaction also proceeded well with triyne **104** to provide hexasubstituted aryl product **140** in excellent yield (eq 43). In this case, as with the previous examples of tandem reactions with **104**, the reaction was run in refluxing toluene.

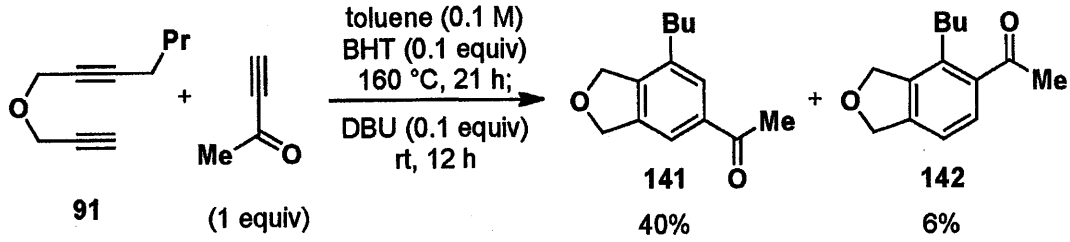
---

[49] The cycloaddition to prepare compound **138** was carried out by Dr. Takeo Sakai.



(43)

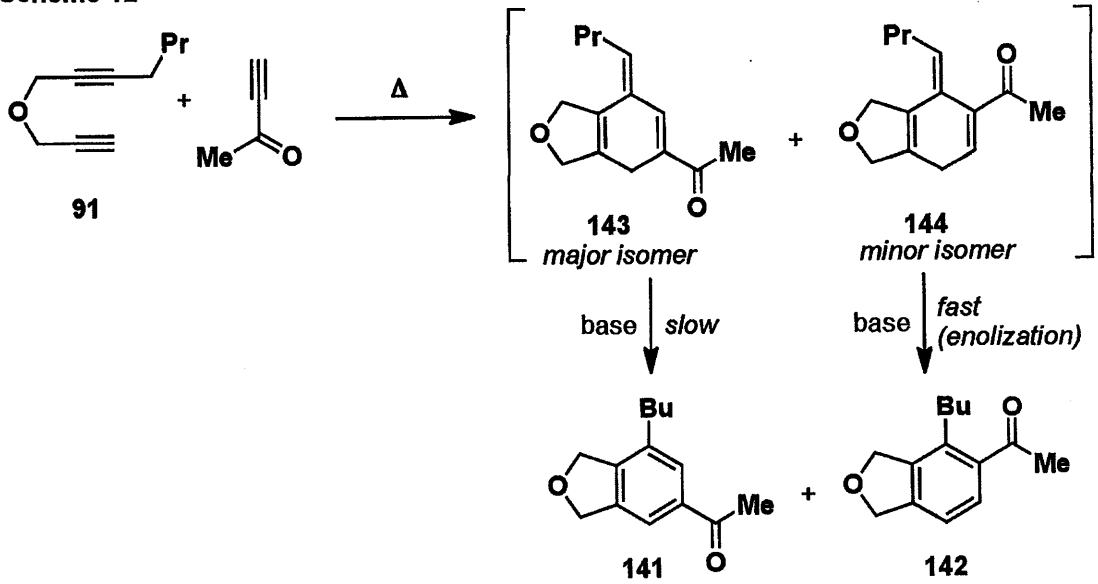
Unsymmetrical alkynyl dienophiles were examined next. Reaction of butynone with diyne **91** in the presence of 10 mol % BHT as a radical inhibitor afforded separable regioisomers **141** and **142** in moderate yield (eq 44).[50]



(44)

One concern in the reactions of unsymmetrical alkynyl dienophiles is the relative rates of isomerization of the regioisomeric isotoluene intermediates (Scheme 12).

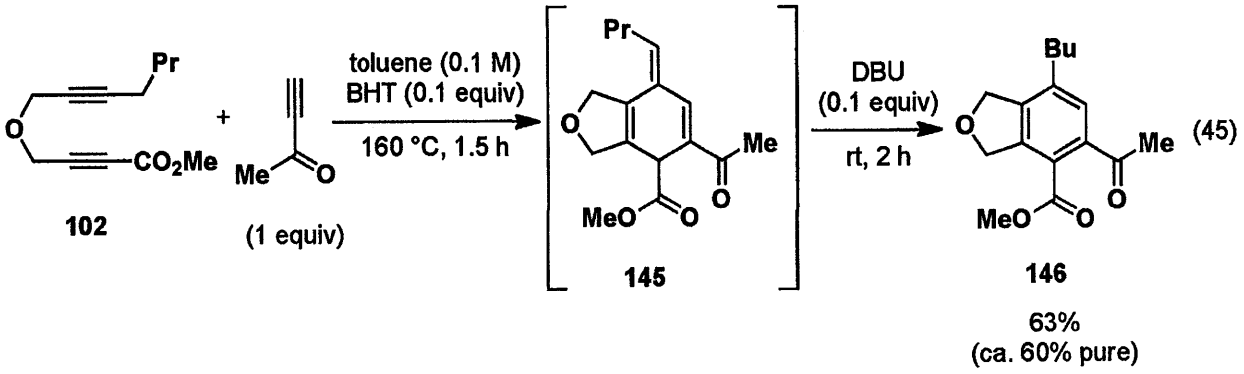
Scheme 12



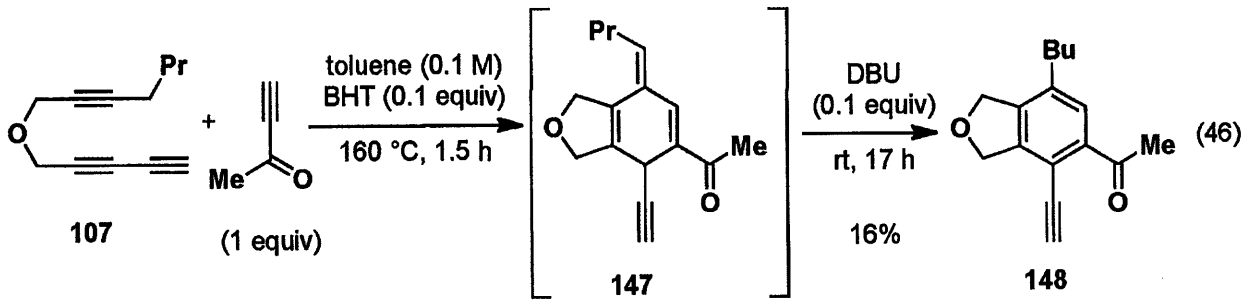
[50] The cycloaddition to produce **141** and **142** was carried out by Dr. Katsu Okano.

With unactivated diyne **91**, the isotoluene **144** produced by the minor cycloaddition pathway is expected to isomerize much more quickly than the isotoluene **143** produced by the major cycloaddition pathway due to the increased acidity of the relevant proton.

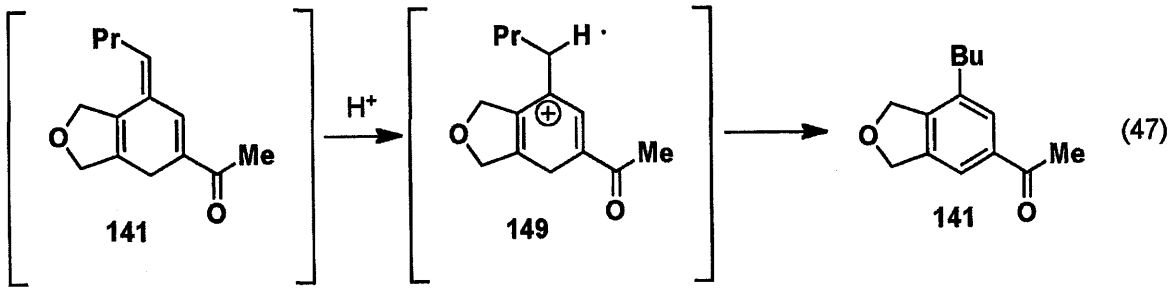
This may account for the moderate yield of **141**. If the isomerization step is slow, side reactions of the isotoluene may occur, both in the thermal step and upon treatment with base. In order to circumvent this problem, we turned our attention to diynes with electron-withdrawing groups on the enophile alkyne. Unfortunately, the reaction of alkynyl ester **102** with butynone went poorly, and while desired product **146** was obtained in moderate yield, it could not be fully separated from the unidentified byproducts (eq 45).



We expected a similar result with triyne **107**. In the previous case, the proton that needs to be removed from isotoluene **145** in the isomerization step is α to an ester. In this case, the proton is doubly allylic and α to an alkyne – less electron-withdrawing than an ester but still an activating group. Reaction of **107** with butynone afforded **148** in low yield (eq 46). The crude ^{1}H NMR spectrum did not show any evidence of the other regioisomer. The low yield is probably due to decomposition of triyne **107** under the reaction conditions. A better result might be obtained at lower temperature.



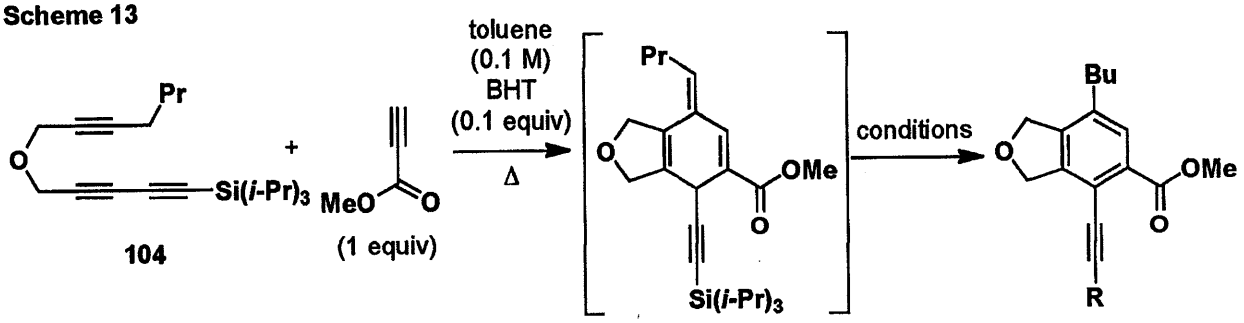
An alternative procedure for isomerization of the isotoluene intermediates that was examined involved treatment with protic acid (eq 47). This should produce a dienyl cation like **149** that is expected to quickly lose a proton to give the aromatic product.



(47)

A variety of cycloaddition and isomerization conditions were investigated for the reaction of triyne **104** with methyl propiolate (Scheme 13). In all cases the cycloaddition to produce **150** proceeded to completion, either in refluxing toluene for 11-12 h or at 160 °C for 1 h. Treatment of the reaction mixture containing isotoluene **150** and aryl product **152** with TBAF resulted in a base-promoted isomerization and concomitant deprotection of the alkyne. Compound **151** was isolated in low yield in impure form.

Scheme 13



110 °C, 11 h; TBAF, rt, 1 h	**151** 21% (ca. 80% pure)
110 °C, 12 h; DBU (0.2 equiv), rt, 19 h	Two spots on TLC, 1 aryl product
DBU (1.5 equiv), 50 °C, 41 h	Complex mixture
160 °C, 1 h; MsOH (0.6 equiv), 0 °C to rt, 1 h	Mixture of **150** and **151**
MsOH (1 equiv), 0 °C to rt, 24 h	Complex mixture

Attempts to use DBU to promote the isomerization resulted in incomplete reaction after 19 h at rt, and decomposition after prolonged heating. Treatment of the reaction mixture containing isotoluene **150** and aryl product **152** with methanesulfonic acid resulted in incomplete reaction after 1 h and decomposition after 24 h.

Overall, the use of unsymmetrical alkynyl dienophiles in the formal [2 + 2 + 2] cycloaddition is problematic due to regiochemical issues and difficulty in isomerization of the isotoluene intermediates.

Tandem Reactions – *Fully Intramolecular Cycloadditions*

In our laboratory, Dr. Takeo Sakai prepared triyne **22** and diyne **154** in order to investigate the fully intramolecular cycloadditions. Both substrates were previously prepared and cyclized by Ley and coworkers.[13] After heating **22** in toluene at 160 °C overnight, Dr. Sakai obtained unequivocal evidence that the intermediate formed in this reaction is triene **155** (eq 48), not the isomeric triene **23** reported by Ley (Figure 4).[51]

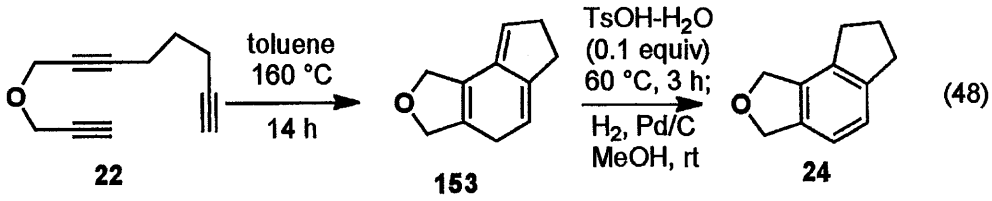
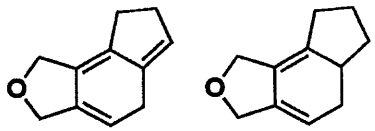


Figure 4

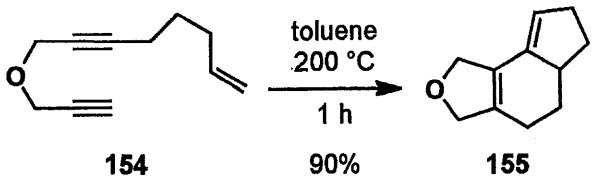
Triene **153** is the product expected if the reaction proceeds via a sequential propargylic ene/Diels-Alder cycloaddition cascade mechanism rather than the pathway proposed by Ley and coworkers (Scheme 2). Triene **153** was isomerized to **24** using protic acid. This resulted in formation of some indene byproduct that was then hydrogenated to give complete conversion to **24**.



Thermolysis of related substrate **154** provided an excellent yield of diene **155** (eq 46), the product predicted by our pericyclic cascade mechanism, rather than the isomeric diene **156** reported by Ley et al. (Figure 4).

---

[51] For a discussion of the structure assignments of **153** and **155**, see the Supporting Information for ref. 37.



154 90% 155 (49)

These results provide further support for our tandem reaction mechanism, and suggest that the intramolecular "cyclotrimerizations" reported by Johnson[12] and Parsons[14] also proceed through this pericyclic cascade rather than the suggested radical mechanisms.

Future Directions – *Synthesis of Heterocycles*

Current work in the Danheiser lab in this area is focused on extending the formal [2 + 2 + 2] cycloaddition strategy to the synthesis of nitrogen heterocycles. Dr. Takeo Sakai has already completed the study of a fully intramolecular variant, utilizing cyano groups as dienophiles.[46] Other areas of investigation include the use of imine derivatives as dienophiles (in both inter- and intramolecular reactions), as well as the use of strained cycloalkenes as dienophiles.

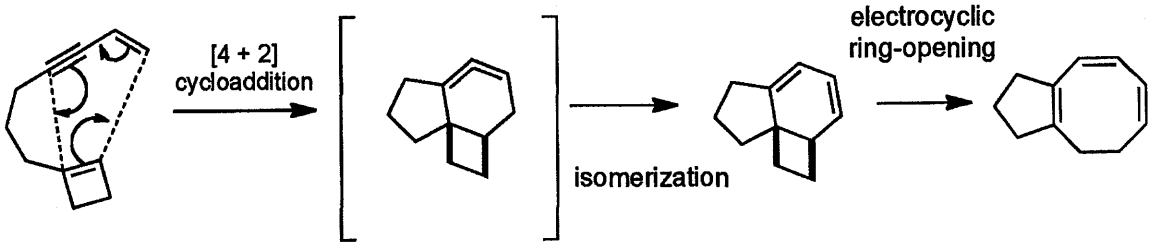
Part II

A [4 + 4] Annulation Strategy for the Synthesis of Eight-Membered Carbocycles

Chapter 1 – Introduction and Background

The convergent synthesis of highly substituted and polycyclic ring systems has been a long-standing goal in the Danheiser laboratory. While most of the work has focused on five- and six-membered rings, with a variety of interesting methods reported in the past 30 years, seven- and eight-membered rings provide a particular challenge. Many of the cyclization and annulation methods developed for common rings do not work for eight-membered rings due to ring strain and transannular interactions.[52]

The aim of the research described in Part II of this thesis was to extend the scope of the intramolecular [4 + 2] cycloaddition of conjugated enynes with alkenes previously developed in the Danheiser lab[53] to include activated cyclobutene derivatives as the enynophile. This cycloaddition was expected to provide access to cyclic allene intermediates that would then undergo a cascade of reactions to produce eight-membered ring products.



The impetus for this research was the relative lack of efficient methods for preparation of cyclooctanoid derivatives in combination with the wide variety of biologically active natural products containing this interesting carbon skeleton.

---

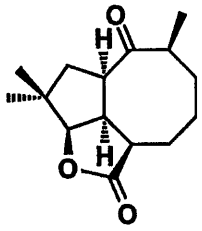
[52] For reviews on the synthesis of carbocyclic eight-membered rings, see: (a) Mehta, G.; Singh, V. *Chem. Rev.* **1999**, *99*, 881-930. (b) Petasis, N. A.; Patane, M. A. *Tetrahedron* **1992**, *48*, 5757-5821. (c) Yu, Z.-Y.; Wang, Y.; Wang, Y. *Chem. Asian J.* **2010**, *5*, 1072-1088.

[53] Danheiser, R. L.; Gould, A. E.; Fernandez de la Pradilla, R.; Helgason, A. L. *J. Org. Chem.* **1994**, *59*, 5514-5515.

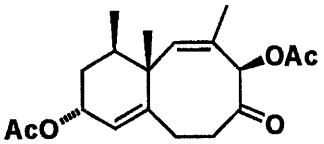
Natural Products That Contain Cyclooctane Rings

Natural products containing eight-membered carbocycles have been isolated from plants and marine organisms. While the cyclooctanoid ring is not nearly as common as smaller ring sizes, there are over 100 known terpenoid natural products containing an eight-membered carbocyclic ring.[52b] Representative examples with varying degrees of substitution and oxygenation are shown in Figure 5.

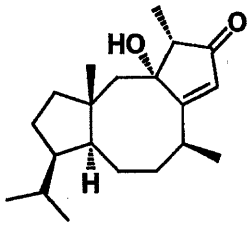
Figure 5. Cyclooctanoid Natural Products



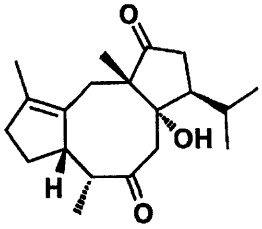
Asteriscanolide (**157**)



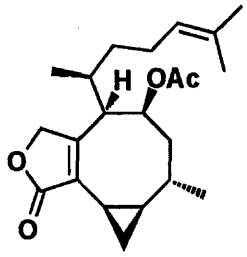
Neolemnalyl acetate (**158**)



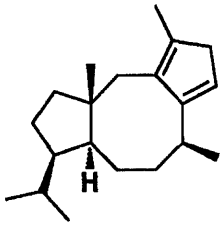
Anadensin (**159**)



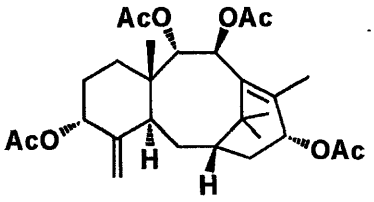
Roseadione (**160**)



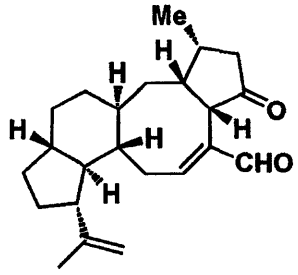
Acetoxycrenulide (**161**)



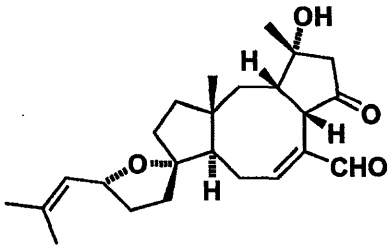
Fusicoccadiene (**162**)



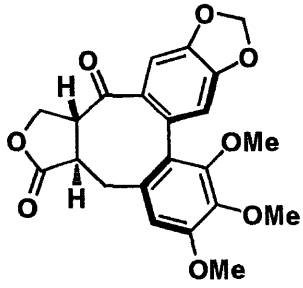
Taxusin (**163**)



Variecolin (**164**)



Ophiobolin A (**165**)



Steganone (**166**)

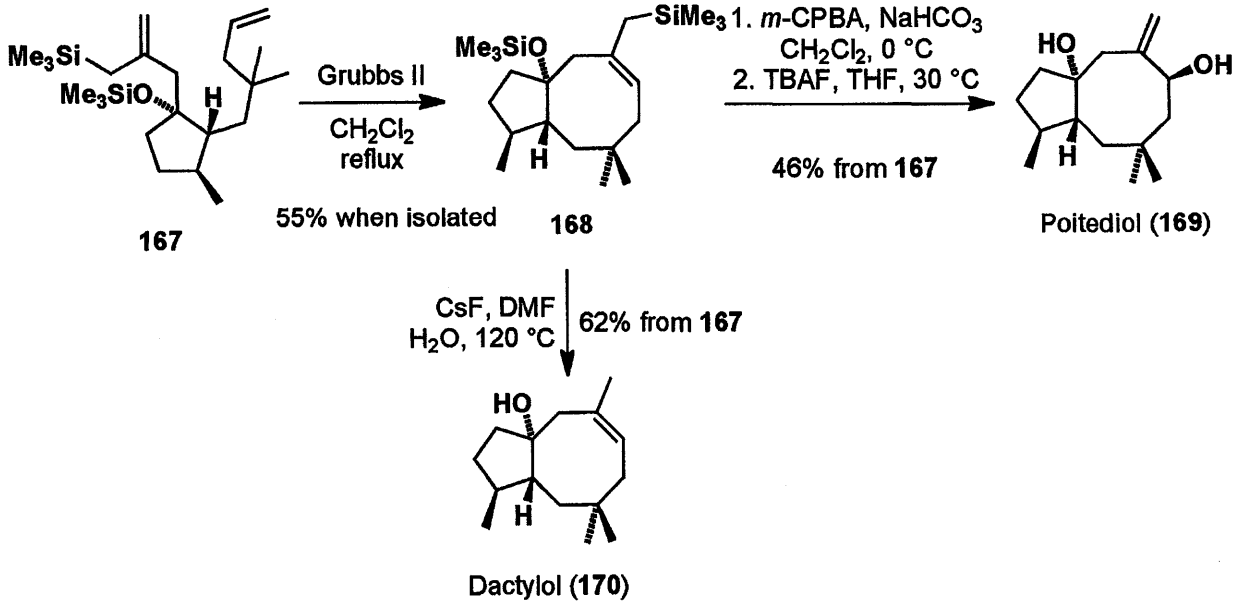
A common motif amongst these natural products is the fused 5-8 ring system, as found in the sesquiterpenoid asteriscanolide **157** as well as diterpenoids **158** – **161** and sesteterpenoids **164** – **166**. Less common is the fused 6-8 ring system, found in neolemnalyl acetate **158** as well as the taxanes, represented here by taxusin **163**.

Methods for the Preparation of Eight-Membered Carbocycles

Cyclooctanoid natural products have been the target of numerous synthetic studies due to their biological activities and interesting molecular architectures. A variety of methods have been reported for cyclooctanoid preparation, including intramolecular C-C bond formation, fragmentation reactions, ring expansions, and [3,3]-sigmatropic rearrangements. Approaches to the cycloctanoid system have been reviewed exhaustively,[52] most recently in 2010.[52c] Therefore, this section will focus on methods reported in the past five years, with examples chosen specifically to illustrate a range of tactics. The majority of the methods developed during this time have relied on intramolecular reactions that involve transition metal catalysis for ring formation.

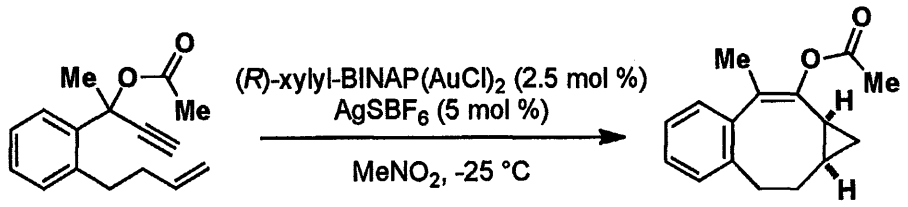
Ring-closing metathesis (RCM) is a popular approach for the preparation of medium-sized rings. In 2010, Vanderwal and coworkers reported the RCM of allysilanes in the total syntheses of poitediol **169** and dactylol **170** (Scheme 14).[54] Treatment of diene **167** with Grubbs 2nd generation catalyst afforded common intermediate **168** that was quickly elaborated to the natural products.

Scheme 14



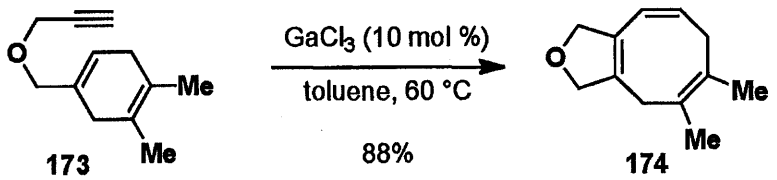
[54] Dowling, M. S.; Vanderwal, C. D. *J. Org. Chem.* **2010**, *75*, 6908-6922.

In addition to ruthenium for RCM, a variety of transition metals have been used in other C-C bond formation reactions to prepare eight-membered rings. Toste developed a method utilizing intramolecular Au(I)-catalyzed cyclization to access fused 8-3 ring systems in an enantioselective fashion from 1,8-enyne precursors (eq 50).[55]



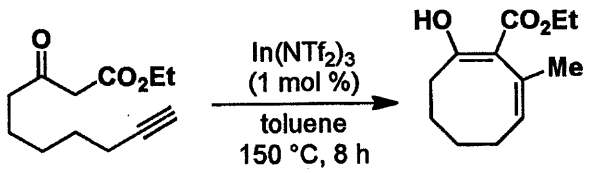
171 94% (92% ee) 172 (50)

Chung and coworkers reported a $GaCl_3$-catalyzed cycloisomerization of 1,6-enynes to afford 1,3,6-cyclooctatrienes via a ring-opening metathesis reaction (eq 51).[56]



173 88% 174 (51)

In 2008, Nakamura and coworkers reported a metal-mediated Conia ene reaction that transforms ω-alkynyl-β-ketoesters into cyclooctene products in moderate yields (eq 52).[57] This method was also applied to seven-, nine-, and in one case 15-membered carbocyclic rings.

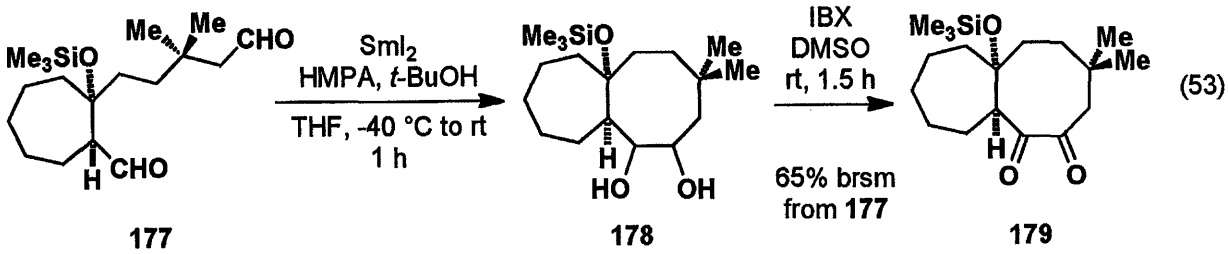


175 51% 176 (52)

---

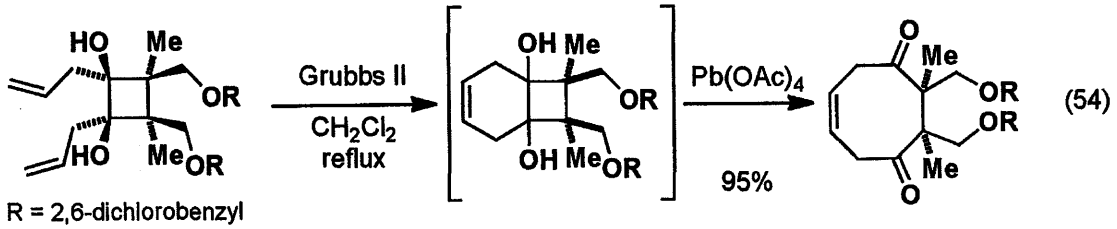
[55] Watson, I. D. G.; Ritter, S.; Toste, F. D. *J. Am. Chem. Soc.* **2009**, *131*, 2056-2057.
[56] Kim, S. M.; Lee, S. I.; Chung, Y. K. *Org. Lett.* **2006**, *8*, 5425-5427.
[57] Itoh, Y.; Tsuji, H.; Yamagata, K.-I.; Endo, K.; Tanaka, I.; Nakamura, M.; Nakamura E. *J. Am. Chem. Soc.* **2008**, *130*, 17161-17167.

Intramolecular pinacol coupling is another cyclization strategy for medium-sized ring formation. One recent example is in Paquette's synthesis of the CDE ring system of lancidodilactone G (eq 53).[58] Treatment of dialdehyde **177** with samarium iodide gave diol **178** as an inseparable mixture of diastereomers. This mixture was oxidized to diketone **179**.



177 **178** **179** (53)

Fragmentation of fused 6-4 ring systems has been used to access eight-membered carbocycles. A recent example is in the synthesis of the unnatural enantiomer of merrilactone A by Inoue and coworkers.[59] They prepared bicyclo[4.2.0]octene **181** via RCM, followed by in situ oxidative fragmentation using lead acetate to give cyclooctenedione **182** in excellent yield (eq 54).



R = 2,6-dichlorobenzyl

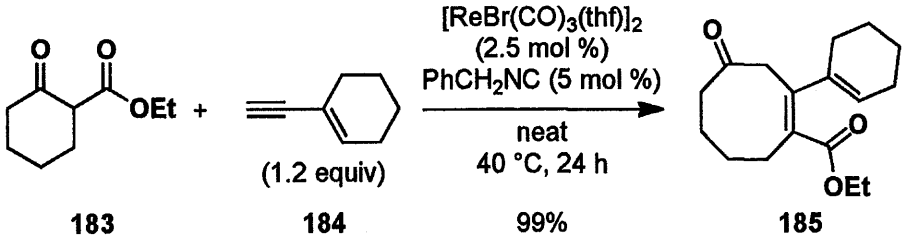
180 **181** **182** (54)

The methods discussed thus far have all relied on an intramolecular reaction of a highly functionalized substrate for ring-formation. Although the use of intermolecular reactions would be more convergent, there are only a few new examples of such reactions in the recent literature, all involving transition-metal catalysis. Three multicomponent reactions will be discussed in this section.

---

[58] Paquette, L. A.; Lai, K. W. *Org. Lett.* **2008**, *10*, 3781-3784.
[59] Inoue, M.; Lee, N.; Kasuya, S.; Sato, T.; Hirama, M.; Moriyama, M.; Fukuyama, Y. *J. Org. Chem.* **2007**, *72*, 3065-3075.

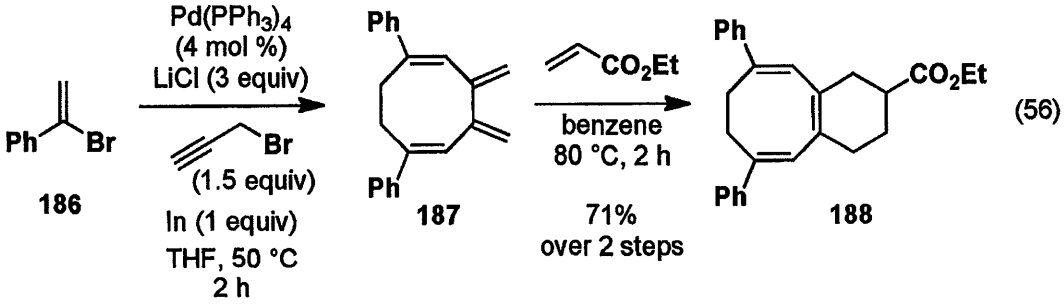
One impressive example of a two-component reaction is the rhenium-catalyzed insertion of alkynes into the C-C bond of cyclic ketoesters reported by Kuninobu and Takai in 2006 (eq 55).[60]



(55)

With only a slight excess of the terminal alkyne **184**, cyclooctene **185** was obtained in quantitative yield in a reaction with low catalyst loading and no solvent. This method was also applied to nine- and ten-membered ring synthesis with similarly good results. One limitation of this process is that it is limited to aryl- and vinyl-substituted terminal acetylenes.

Another multicomponent reaction for the preparation of cyclooctanoid derivatives is the tandem Pd-catalyzed cross-coupling/[4 + 4] cycloaddition reaction reported by Lee and coworkers (eq 56).[61] This reaction proceeds through a vinylallene intermediate.



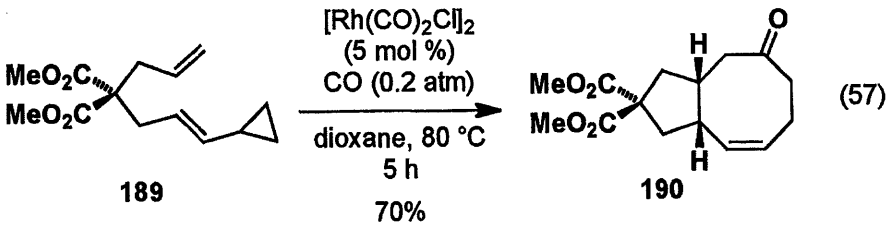
(56)

Cyclooctadiene **187** was obtained upon treatment of bromostyrene **186** and propargyl bromide with Pd(0), LiCl, and stoichiometric indium. When crude **187** was combined with ethyl acrylate at elevated temperature, **188** was produced in good yield in an overall five-component, two-pot process.

---

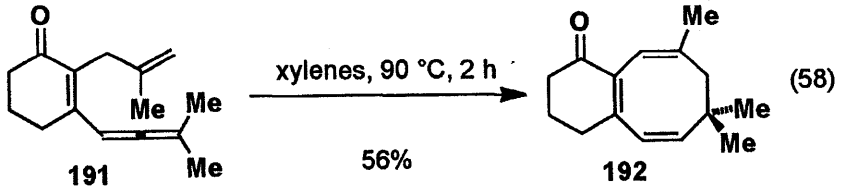
[60] Kuninobu, Y.; Kawata, A.; Takai, K. *J. Am. Chem. Soc.* **2006**, *128*, 11368-11369.
[61] Lee, P. H.; Lee, K.; Kang, Y. *J. Am. Chem. Soc.* **2006**, *128*, 1139-1146.

Yu and coworkers reported a two-component [5 + 2 + 1] cycloaddition reaction for the preparation of cyclooctenones in 2007 (eq 57).[62]



Treatment of ene-vinylcyclopropane **189** with a rhodium catalyst in the presence of carbon monoxide resulted in formation of **190** as a single diastereomer in good yield.

Our proposed [4 + 4] annulation process for the preparation of cyclooctatrienes relies on a sequence of pericyclic reactions.[63] All of the methods discussed thus far in this chapter rely on transition metal catalysts or promoters. There are some examples in the literature of the last ten years of pericyclic reaction processes for the preparation of cyclooctanoid rings, predominantly involving the 8π electrocyclic ring-closure of tetraenes.[64] In 2006, Ma and Gu reported an interesting allene cycloisomerization reaction that proceeds through a pericyclic cascade involving sigmatropic rearrangements, electrocyclic reactions, and potentially even cycloadditions (eq 58).[65] The substrate **191** was prepared via the Negishi coupling of a 2-allyl-3-halocyclohex-2-enone derivative with an allenylzinc reagent.[66]



---

[62] Wang, Y.; Wang, J.; Su, J.; Huang, F.; Jiao, L.; Liang, Y.; Yang, D.; Zhang, S.; Wender, P. A.; Yu, Z.-X. *J. Am. Chem. Soc.* **2007**, *129*, 10060-10061.

[63] For another [4 + 4] annulation reaction, see: Danheiser, R. L.; Gee, S. K.; Sard, H. *J. Am. Chem. Soc.* **1982**, *104*, 7670-7672.

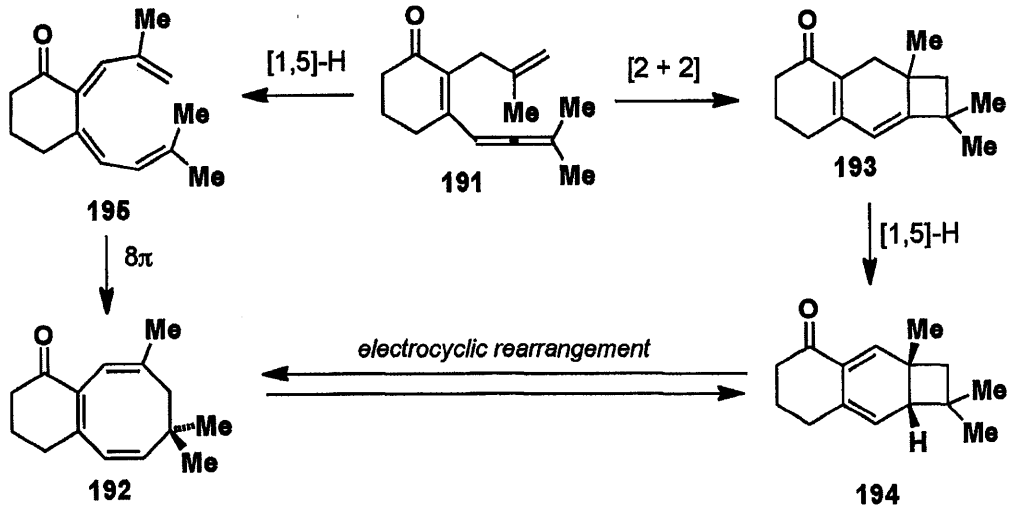
[64] (a) Bruckner, S.; Baldwin, J. E.; Adlington, R. M.; Claridge, T. D. W.; Odell, B. *Tetrahedron* **2004**, *60*, 2785-2788. (b) Magomedov, N. A.; Ruggiero, P. L.; Tang, Y. *J Am. Chem. Soc.* **2004**, *126*, 1624-1625.

[65] Ma, S.; Gu, Z. *J. Am. Chem. Soc.* **2006**, *128*, 4942-4943.

[66] Ma, S.; Gu, Z. *Chem. Eur. J.* **2008**, *14*, 2453-2464.

The authors propose two possible mechanisms for this reaction (Scheme 15).

Scheme 15

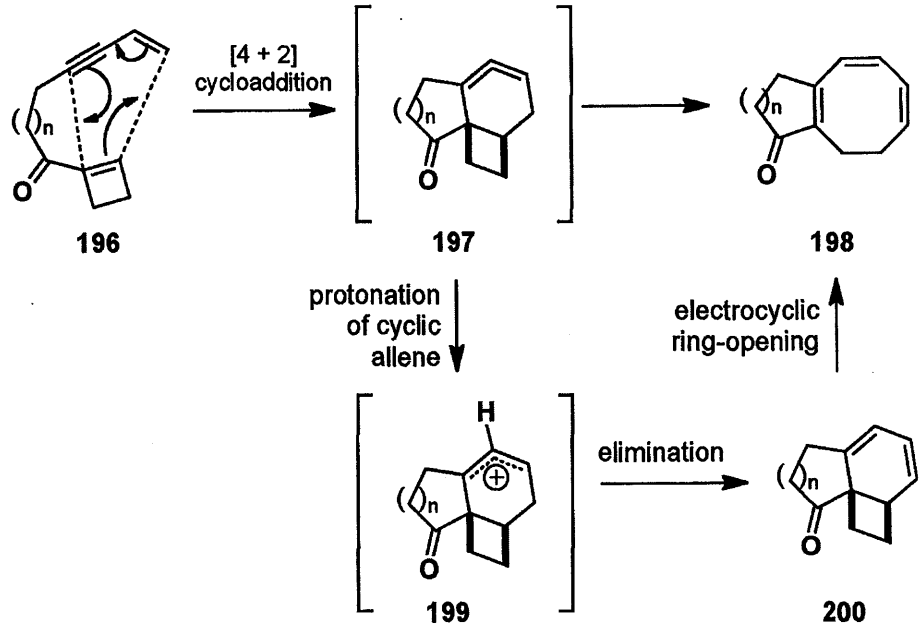


The first option is thermal [2 + 2] cycloaddition of the alkene to the distal double bond of the allene to form cyclobutane **193**. This compound could then undergo a [1,5]-hydride shift to give bicyclo[4.2.0]-2,4-octadiene **194**. Electrocyclic ring-opening would furnish the cyclooctatriene product **192**. The alternate mechanism begins with a [1,5]-hydride shift of the substrate **191** to give tetraene **195** that could then undergo an 8π electrocyclic ring-closure to give **192**. Intermediate **194** was trapped as a maleimide adduct in a Diels-Alder cycloaddition. However, due to the reversible nature of the electrocyclic rearrangement reaction converting **194** to **192**, proof of **194** in the reaction mixture does not differentiate between the two mechanisms. The bicyclo[4.2.0]-2,4-octadiene/1,3,5-cyclooctatriene equilibrium will be discussed in detail later in this chapter.

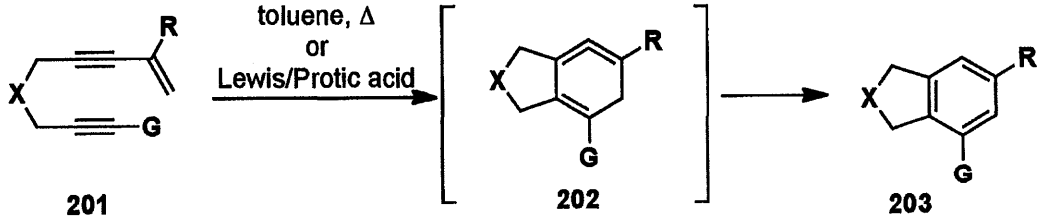
Intramolecular [4 + 2] Cycloadditions of Conjugated Enynes

The first step in our proposed [4 + 4] annulation process involves the [4 + 2] cycloaddition of a conjugated enyne with an activated cyclobutene derivative (Scheme 16). This concerted reaction would give 1,2-cyclohexadiene derivative **197**. This reactive intermediate is expected to quickly isomerize to diene **200**, most likely via allylic cation intermediate **199**. Electrocyclic ring opening of tricyclic intermediate **200** would produce the desired cyclooctatriene product **198**.

Scheme 16

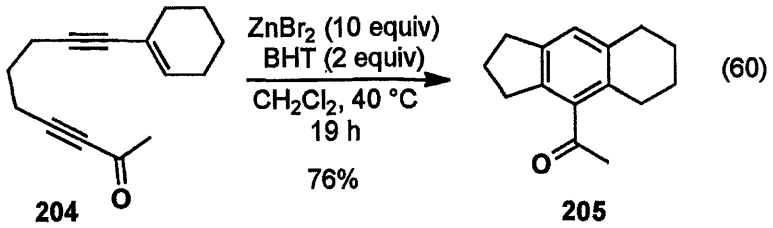


Most of the previous work on intramolecular [4 + 2] cycloadditions of conjugated enynes has focused on the use of alkynyl enynophiles to afford aromatic products (eq 59).[43] These reactions can be carried out thermally, by heating the substrate in toluene at 80-200 °C, or by using Lewis or protic acids to promote the cycloaddition.



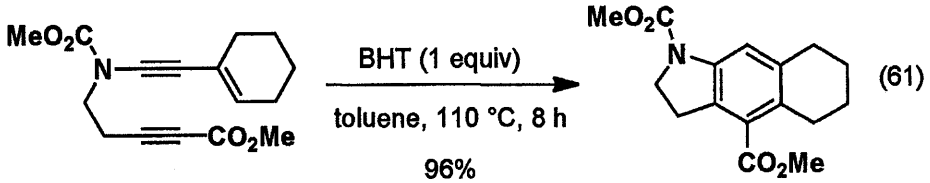
(59)

Early work in our laboratory focused on the preparation of carbocycles (e.g., eq 60).[53] Substrates with both external activating groups (electron-withdrawing groups at the terminal end of the enynophile) as well as internal activating groups (an electron-withdrawing group conjugated to the enynophile in the tether) work well under both thermal and Lewis or protic acid conditions to afford aromatic products.



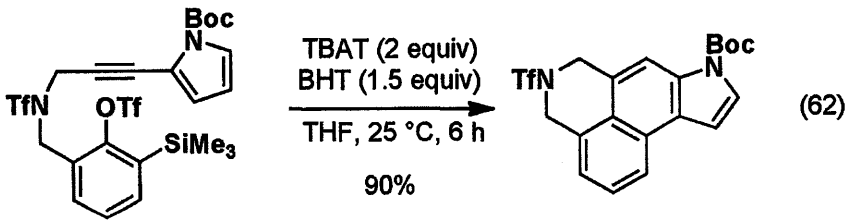
204 205 (60)

Later work investigated the preparation of heterocycles using ynamides as part of the enyne (eq 61).[67] In addition, substrates with the ynamide as the enynophile also participate in the [4 + 2] cycloaddition. The indoline products can be oxidized to indoles.



206 207 (61)

In addition, the preparation of condensed polycyclic aromatic systems was accomplished using arynes generated in situ as the enynophile (eq 62).[68]



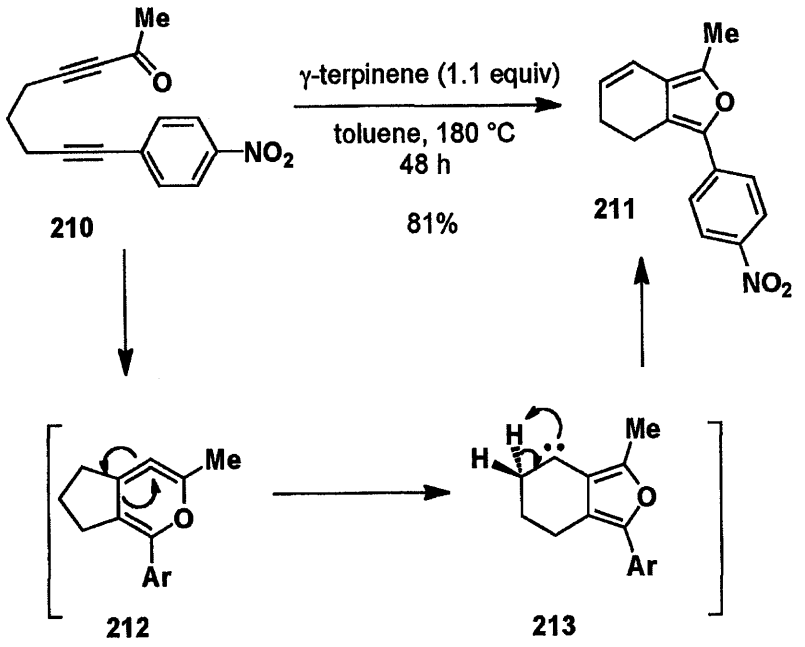
208 209 (62)

Intramolecular hetero-enyne cycloadditions have also been investigated using ynones as the conjugated enyne component (Scheme 17).[44] Furan products are produced via an interesting carbene insertion mechanism.

---

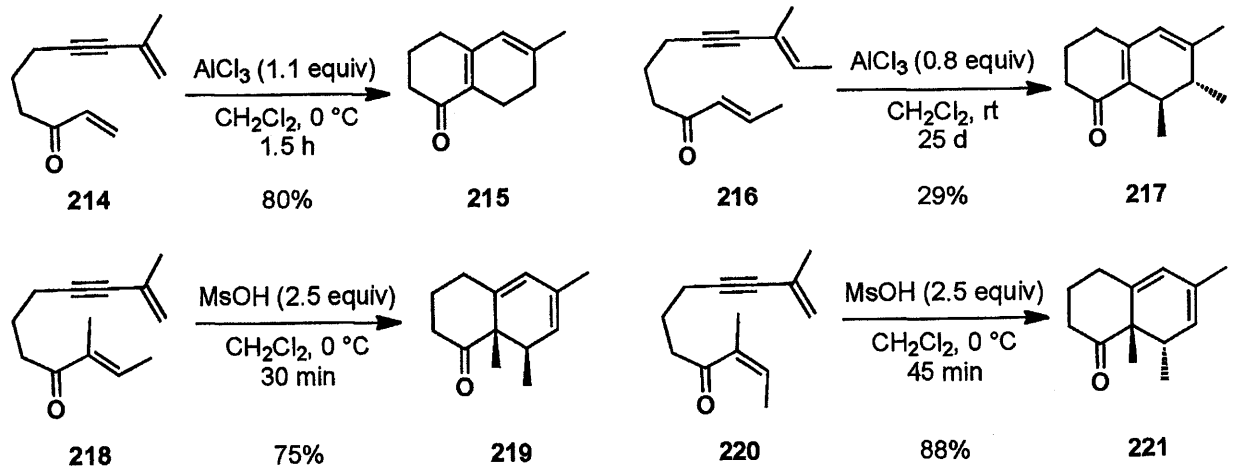
[67] Dunetz, J. R.; Danheiser, R. L. *J. Am. Chem. Soc.* **2005**, *127*, 5776-5777.
[68] Hayes, M. E.; Shinokubo, H.; Danheiser, R. L. *Org. Lett.* **2005**, *7*, 3917-3920.

Scheme 17



Four examples of intramolecular [4 + 2] cycloadditions of conjugated enynes with alkenes are shown in Scheme 18. In the simplest case, enone **214** was converted to cyclohexadiene derivative **215** in good yield upon treatment with Lewis acid.[53] The other three cases, involving multiple substituents on the enyne alkene or the enynophile alkene, were designed to probe the stereochemical aspects of the reaction.

Scheme 18. Intramolecular [4 + 2] Cycloadditions of Conjugated Enynes with Alkenyl Enynophiles



In the case of disubstituted enones **218** and **220**, reaction with protic acid afforded good yields of products **219** and **221** as single isomers.[69] ^{1}H NMR coupling constants and nOe experiments were used to determine the relative stereochemistry of the vicinal methyl groups in cycloadducts **219** and **221**. The stereoselectivity of these reactions indicates that the cycloaddition is either a concerted reaction, with suprafacial attack of the enyne on the enynophile, or it is a *very fast* stepwise reaction. Substrate **216** was prepared in an attempt to determine the endo/exo selectivity of the cycloaddition.[70] This substrate was very sluggish in reactions with Lewis acids, but treatment with $AlCl_3$ at room temperature for 25 days afforded cycloadduct **217** in low yield as a single isomer. As with the reaction to produce **215**, in this reaction the cyclic allene intermediate isomerizes to the diene product **217** that is conjugated to the ketone. Again, ^{1}H NMR coupling constants and nOe experiments were used to determine the relative stereochemistry of the vicinal methyl groups.

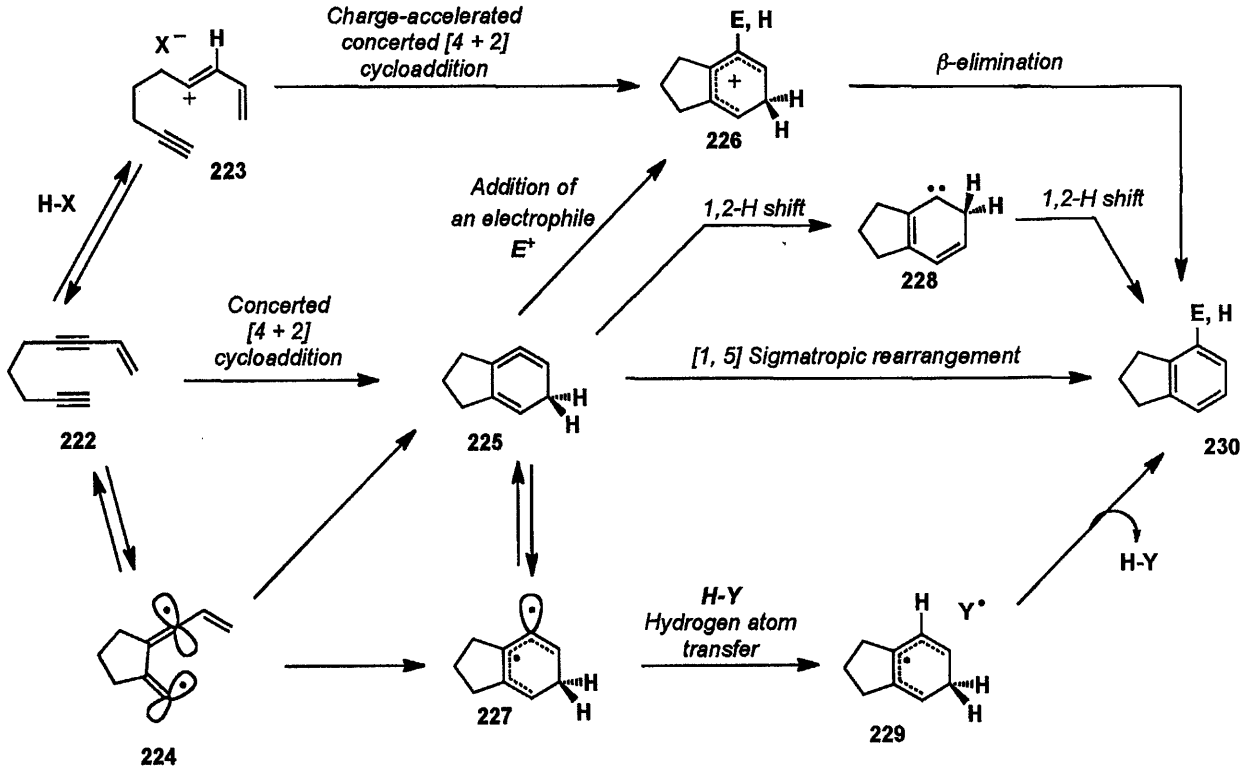
We expect these cycloadditions to proceed through a cyclic allene[71] intermediate. The mechanism for conversion of the cyclic allene to the aromatic or dihydroaromatic product depends on the specific reaction conditions, as shown in Scheme 19 below. In addition to the concerted [4 + 2] cycloaddition pathway, the reaction could proceed through a butadienyl cation intermediate **223** when run in the presence of acid, or a diradical intermediate **224** when run via thermal activation.[72] The pathways that are most relevant to the reactions that will be discussed later in this thesis are the charge-accelerated concerted [4 + 2] cycloaddition to give pentadienyl cation **226** followed by β-elimination to indan product **230**, as well as the concerted [4 + 2] cycloaddition to give 1,2,4-cyclohexatriene[73] derivative **225** followed by addition of an

---

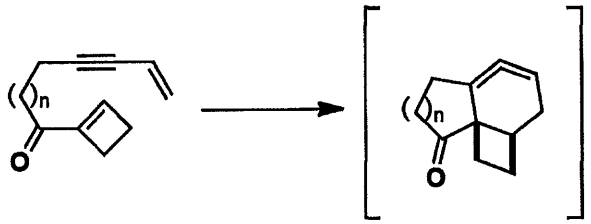
[69] Gould, A. E. Ph. D. Thesis, Massachusetts Institute of Technology, June 1996.
[70] Palucki, B. L. Ph. D. Thesis, Massachusetts Institute of Technology, June 1997.
[71] For reviews of cyclic cumulenes, see: (a) Johnson, R. P. *Chem. Rev.* **1989**, *89*, 1111-1124. (b) Christl, M. Cyclic Allenes Up to Seven-Membered Rings. In *Modern Allene Chemistry*; Krause, N.; Hashmi, S. K., Eds.; Wiley-VCH: Weinheim, 2004, pp 243-357.
[72] For a detailed discussion of these mechanistic possibilities, see: Hayes, M. E. Ph. D. Thesis, Massachusetts Institute of Technology, June 2004.
[73] For theoretical studies of 1,2,4-cyclohexatriene, see: (a) Janoschek, R. *Angew. Chem. Int Ed. Engl.* **1992**, *31*, 476-478. (b) Prall, M.; Kruger, A.; Schreiner, P. R.; Hopf, H. *Chem. Eur. J.* **2001**, *7*, 4386-4394. (c) Engels, B.; Schoneboom, J. C.; Munster, A. F.; Groetsch, S.; Christl, M. *J. Am. Chem. Soc.* **2002**, *124*, 287-297. (d) Rodriguez, D.; Navarro-Vasquez, A.; Castedo, L.; Dominguez, D.; Saa, C. *J. Org. Chem.* **2003**, *68*, 1938-1946. (e) Daoust, K. J.; Hernandez, S. M.; Konrad, K. M.; Mackie, I. D.; Winstanley Jr., J.; Johnson, R. P. *J. Org. Chem.* **2006**, *71*, 5708-5714.

electrophile to give **226** and finally β–elimination to afford **230**.

Scheme 19. Possible Mechanisms for the Intramolecular [4 + 2] Cycloaddition of Conjugated Enynes



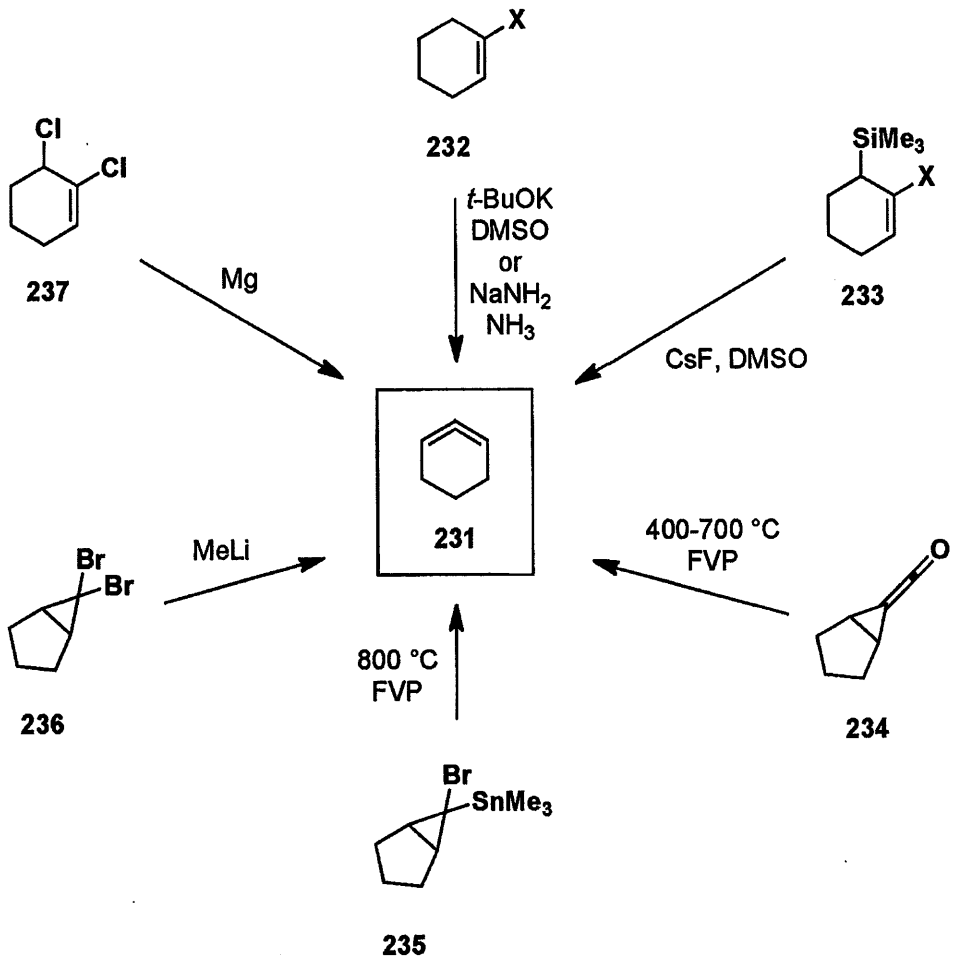
In our proposed [4 + 4] annulation process, the cyclic allene produced would be 1,2-cyclohexadiene derivative **197** instead of an isoaromatic 1,2,4-cyclohexatriene (eq 63).



196 **197** (63)

1,2-Cyclohexadiene has been prepared previously by multiple routes involving eliminations of cyclohexene derivatives and rearrangements of cyclopropane derivatives (Scheme 20).

Scheme 20. Preparative Methods for 1,2-Cyclohexadiene



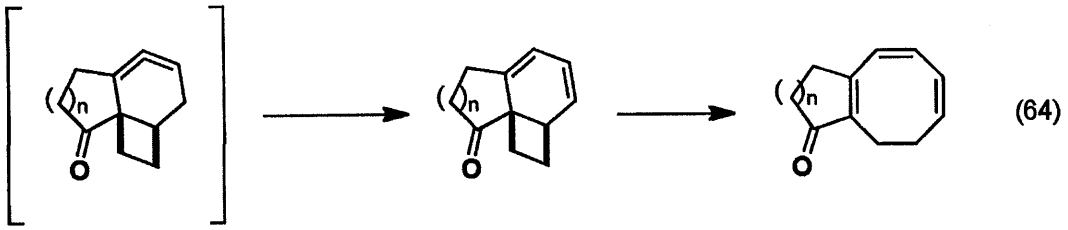
Bottini and coworkers prepared 1,2-cyclohexadiene **231** via base-induced elimination of a vinyl halide **232** in order to measure the relative reactivity of the cyclic allene with a variety of conjugated dienes and styrene.[74] In their studies on synthetic methods for 1,2,3-cyclohexatriene and cyclohexen-3-yne, Johnson et al. also prepared 1,2-cyclohexadiene **231** by fluoride-induced β-elimination of allylsilane **233** as well as treatment of dichloride **237** with magnesium.[75] Wentrup and coworkers reported direct spectroscopic observation of the formation of 1,2-cyclohexadiene **231** by flash vacuum pyrolysis (FVP) of cyclopropylketene **234**.[76] They observed that upon warming from 170 K, **231** dimerized via a [2 + 2] pathway. Sander et al.

---

[74] Bottini, A. T.; Hilton, L. L.; Plott, J. *Tetrahedron* **1975**, *31*, 1997-2001.
[75] Shakespeare, W. C.; Johnson, R. P. *J. Am. Chem. Soc.* **1990**, *112*, 8578-8579.
[76] Wentrup, C.; Gross, G.; Maquestiau, A.; Flammang, R. *Angew. Chem. Int. Ed. Engl.* **1983**, *22*, 542-543.

studied the pyrolysis of bromostannylcyclopropane **235**.[77] They observed that above 600 °C, the major hydrocarbon products are ethylene and 1-butene-3-yne, derived presumably from a retro-Diels-Alder reaction of 1,2-cyclohexadiene **231**. Moore and Moser developed an efficient route to **231** via the ring opening of dibromocyclopropane **236** with methyllithium.[78] They observed the formation of tetramers of **231** at -80 °C and dimers of **231** at 35 °C

The next stage of our proposed [4 + 4] annulation process is isomerization of the 1,2-cyclohexadiene derivative **197** to 1,3-cyclohexadiene **200**, followed by electrocyclic ring opening to give cyclooctatriene **198** (eq 64).



197 **200** **198** (64)

The electrocyclic ring opening of bicyclo[4.2.0]-2,4-octadiene derivatives will be discussed in detail in the next section of this chapter.

Bicyclo[4.2.0]-2,4-octadiene/1,3,5-Cyclooctatriene Equilibria

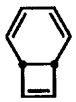
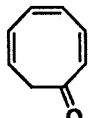
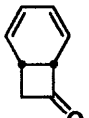
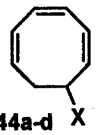
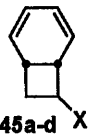
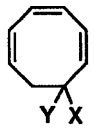
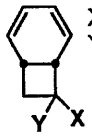
The equilibrium between cyclooctatrienes and bicylooctadienes has been extensively studied.[79] As shown in Table 5, the equilibrium ratio of the two isomers depends on the substitution pattern.[80] Cyclooctatetraene **238** does not interconvert with the bicyclic isomer **239** even at 100 °C, and 1,3,5-cyclooctatriene **240** exists as a 89:11 ratio with the bicyclic isomer **241** at 60 °C.[81] The general trend is that in less substituted cyclooctatrienes, the ring-opened form is favored, and in more substituted cyclooctatrienes, the ring-closed bicyclic form is favored. The

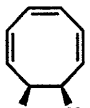
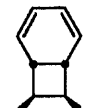
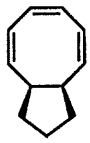
---

[77] Runge, A.; Sander, W. *Tetrahedron Lett.* **1986**, *27*, 5835-5338.
[78] Moore, W. R.; Moser, W. R. *J. Am. Chem. Soc.* **1970**, *92*, 5469-5474.
[79] Marvell, E. B. Thermal Electrocyclic Reactions. New York: Academic Press, 1980.
[80] For additional examples, see: (a) Graham, C. R.; Scholes, G.; Brookhart, M. *J. Am. Chem. Soc.* **1977**, *99*, 1180-1188. (b) Kice, J. L.; Cantrell, T. S. *J. Am. Chem. Soc.* **1963**, *85*, 2298-2302.
[81] Huisgen, R.; Boche, G.; Dahmen, A.; Hetchl, W. *Tetrahedron Lett.* **1968**, *9*, 5215-5219.

examples shown in Table 5 involve substituents at C_7 and C_8. Simple cyclooctatrienes with substituents at the olefinic carbons have not been investigated in great detail.[82,83,84] The ratio of the two isomers is also expected to be affected by ring strain and conjugation effects which can potentially shift the equilibrium in either direction.

Table 5. Experimentally Determined Equilibrium Ratios for 1,3,5-Cyclooctatrienes/Bicyclo[4.2.0]-2,4-octadienes

Cyclooctatriene	Bicyclooctadiene		Temp	Ratio
 **238**	 **239**		100 °C	>99:1[1]
 **240**	 **241**		60 °C	89:11[1]
 **242**	 **243**		60 °C	93:7[1]
 **244a-d**	 **245a-d**	X = Br OAc N_3 OH	60 °C 60 °C 35 °C 35 °C	65:35[1] 47:53[1] 25:75[1] 10:90[1]
 **246a-b**	 **247a-b**	X = OMe Y = OMe X = OH Y = Me	60 °C 35 °C	5:95[1] 5:95[1]

Cyclooctatriene	Bicyclooctadiene		Temp	Ratio
 **248a-b**	 **249a-b**	X = Cl Me	60 °C 60 °C	20:80[1] 19:81[1]
 **250a-c**	 **251a-c**	X = Cl Me OAc	-30 °C 60 °C 60 °C	1:99[1] 6:94[1] 5:95[1]
 **252**	 **253**		58 °C	3:97[2]
 **254**	 **255**		58 °C	50:50[2]

[1] Huisgen, R.; Boche, G.; Dahmen, A.; Hetchl, W. *Tetrahedron Lett.* **1968**, *50*, 5215-5219.
[2] Cotton, F. A.; Deganelo, G. *J. Am. Chem. Soc.* **1973**, *95*, 396-402.

The equilibrium between cyclooctatrienone **242** and bicyclo[4.2.0]-2,4-octadiene **243** is especially interesting to us. As will be discussed in the next chapter, the first substrates we

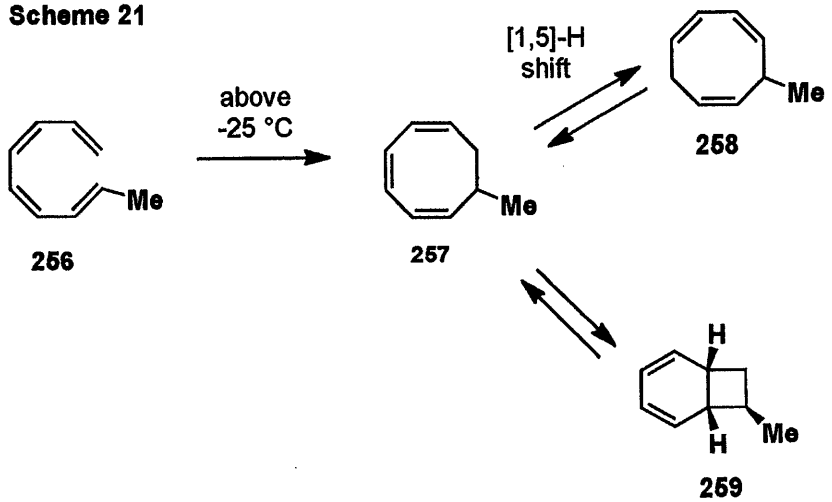
[82] For the preparation and isomerization of highly fluorinated 3,5,7-cyclooctatrienes, see: Rahman, M. M.; Secor, B. A.; Morgan, K. M.; Shafer, P. R.; Leman, D. M. *J. Am. Chem. Soc.* **1990**, *112*, 5986-5990.
[83] For a study of cyclooctatrienes with C_1 and C_7 substituents, see: Wagner, P. J.; Nahm, K. *J. Am. Chem. Soc.* **1987**, *109*, 6528-6530.
[84] 2,5-Diphenyl-1,3-5-cyclooctatriene exists exclusively as the bicyclic isomer: Oda, M.; Kanao, Y. *Bull. Chem. Soc. Japan* **1979**, *52*, 3765-3766.

investigated were cyclobutenone derivatives that would afford cyclooctatrienones in the proposed [4 + 4] annulation process.

Cyclooctatrienes with one substituent at C-7 (**244a-d**) exist as a mixture of isomers at the temperatures studied, with the ratio varying from 65:35 for X = Br to 10:90 for X = OH. Cyclooctatrienes with geminal substituents at C-7 (**246a-b**) exist as predominantly the ring-closed bicyclic isomers **247a-b** at the temperatures studied. In the case of cyclooctatrienes with two vicinal substituents at C-7 and C-8, both cis and trans substituents push the equilibrium towards the bicyclic ring-closed isomer, with trans substituents giving 6:94 to 1:99 ratios (**250a-c**). Finally, in cases where the cyclooctatriene has a fused ring at C_7-C_8, the isomer ratio is 3:97 in the case of a cyclopentane ring (**252**) and 50:50 in the case of a cyclohexane ring (**254**).[85] The enthalpy change for many of these isomerization reactions has been calculated by Fry.[86]

There are only a few examples of stable 1,3,5-cyclooctatrienes in the literature.[65] The only known cyclooctatriene natural product is 7-methylcycloocta-1,3,5-triene (**257**), isolated from a marine algae in minute amounts (Scheme 21).[87] At temperatures above 50 °C, **257** undergoes reversible electrocyclic ring-closure to form **259** and a [1,5]-hydride shift to form isomeric cyclooctatriene **258**.

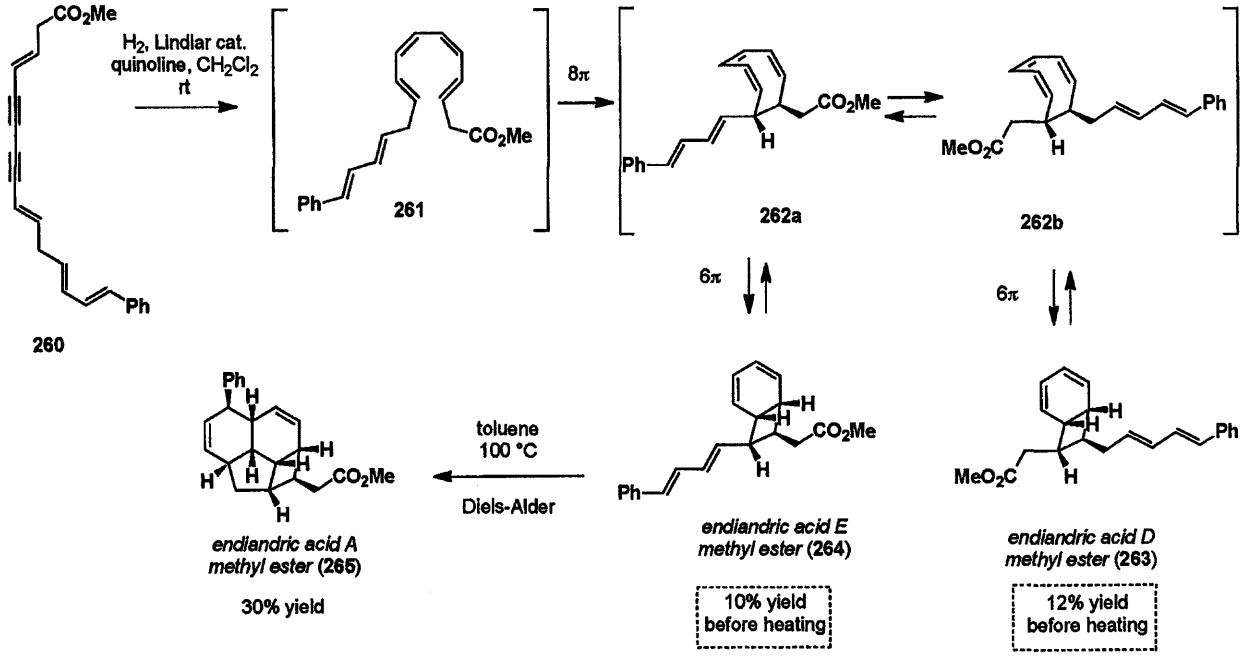
Scheme 21



[85] Cotton, F. A.; Deganelo, G. *J. Am. Chem. Soc.* **1973**, *95*, 396-402.
[86] Fry, A. *Tetrahedron* **2008**, *64*, 2101-2103.
[87] (a) Pohnert, G.; Boland, W. *Tetrahedron* **1994**, *50*, 10235-10244. (b) Pohnert, G.; Boland, W. *Nat. Prod. Reports* **2002**, *19*, 108-122.

In his biomimetic synthesis of the endiandric acid natural products, Nicolaou utilized the cyclooctatriene/bicyclooctadiene equilibrium to his advantage (Scheme 22).[88] Tetraene **261** was formed in situ by catalytic hydrogenation. This compound underwent an 8π electrocyclic ring-closure to give diastereomeric cycloctatrienes **262a** and **262b**. These diastereomers are formed by the two modes of conrotatory cyclization and they interconvert rapidly by ring inversion. Cyclooctatriene **262a** undergoes a distrotatory 6π electrocyclic ring-closure to give cyclooctadiene **264**.

Scheme 22. Biomimetic Synthesis of Endiandric Acids



Upon heating, **264** undergoes an intramolecular Diels-Alder reaction to give **265**. Nicolaou and coworkers found that heating **263** in d_8-toluene at 70 °C allowed for observation of the conversion of **263** to **264**, presumably via intermediates **262a-b** although these compounds were not observed. Compound **264** is consumed and transformed to **265**. This work provided support for Black's hypothesis[89] that the endiandric acids, which are isolated from nature in

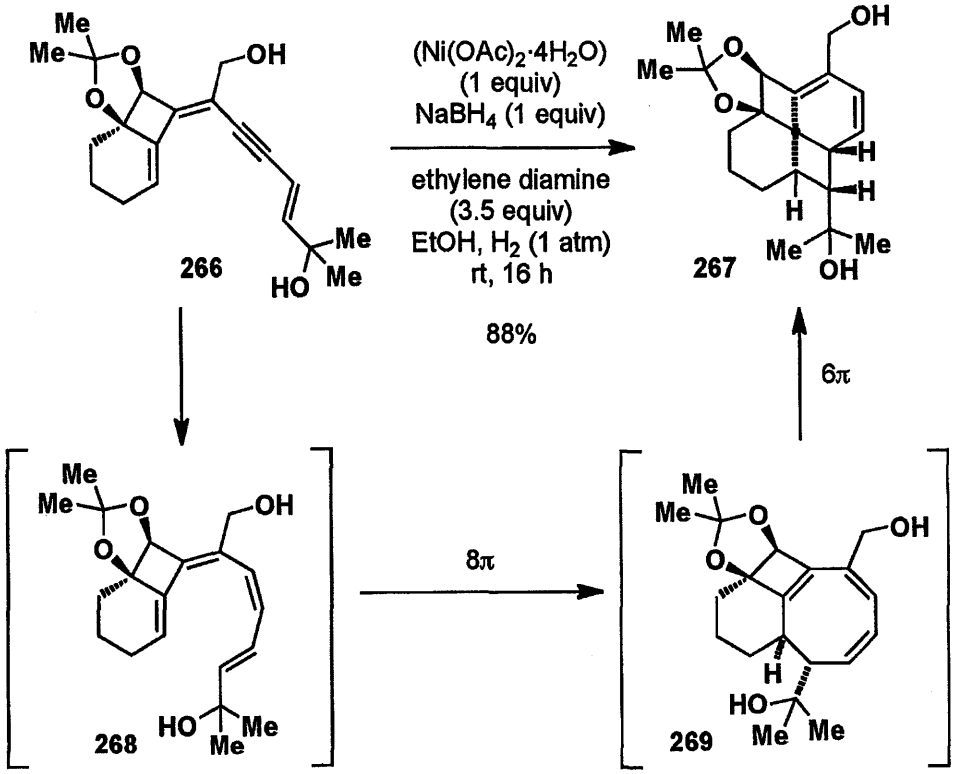
---

[88] Nicolaou, K. C.; Petasis, N. A.; Zipkin, R. E. *J. Am. Chem. Soc.* **1982,** *104,* 5560-5562.
[89] Bandaranayake, W. M.; Banfield, J. E.; Black, D. St. C. *J. Chem.* Soc., *Chem. Commun.* **1980**, 902-903.

racemic form, are biosynthesized via a non-enzymatic cascade of pericyclic reactions.[90]

Another example of the cyclooctatriene/bicyclooctadiene equilibrium in the synthesis of complex molecules is in Suffert's synthesis of fenestradienes via in situ generated cyclooctatriene intermediates (Scheme 23).[91] Nickel-catalyzed semihydrogenation of trienyne **266** gave fenestradiene **267** in good yield as a single diastereomer. This impressive transformation can be explained by a tandem 8π-6π electrocyclization process.

Scheme 23



Based on these reports, we expected that in some cases our bicyclo[4.2.0]-2,4-octadiene intermediates might be isolable and in other cases they would undergo electrocyclic ring-opening to give the desired cyclooctatriene products under the cycloaddition reaction conditions.

---

[90] For a review of biomimetic and biosynthetic electrocyclizations, see: Beaudry, C. M.; Malerich, J. P.; Trauner, D. *Chem. Rev.* **2005**, *105*, 4757-4778.

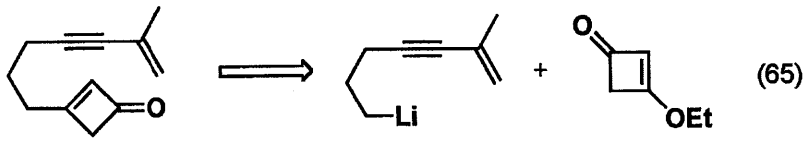
[91] (a) Hulot, C.; Blond, G.; Suffert, J. *J. Am. Chem. Soc.* **2008**, *130*, 5046-5047. (b) Hulot, C.; Amiri, S.; Blond, G.; Schreiner, P.; Suffert, J. *J. Am. Chem. Soc.* **2009**, *131*, 13387-13398.

Chapter 2 – Synthesis of Substrates for [4 + 4] Annulation Studies

Most of the substrates for the [4 + 4] annulation studies were prepared in 3-4 steps (longest linear sequence) from commercial starting materials. All of the enynes were prepared via Sonogashira coupling reactions of terminal alkynes.[92] While some of the key reactions to form the substrates proceeded in only 50-60% yield, several hundred milligrams of substrate could be obtained in each run, allowing for extensive investigation of the [4 + 4] annulation reaction.

Cyclobutenone and Cyclobutenedione Substrates

Our general strategy for the synthesis of the substrates for the [4 + 4] annulation reaction involved the combination of an enynyl alkyllithium species (generated in situ from the alkyl iodide) with the appropriate cyclobutenyl electrophile (e.g., eq 65).



(65)

270 **271** **272**

In the case of cyclobutenone substrate **270**, the electrophile required is 3-ethoxycyclobutenone **272**. This compound can be prepared by addition of ketene to ethoxyacetylene.[93] The addition of alkyllithium and Grignard reagents to **272**, followed by acid-promoted hydrolysis to the cyclobutenone, is well precedented.[94] The addition of alkyllithium reagents to squarate derivatives, followed by acid-promoted hydrolysis to cyclobutenediones, is also known.[95]

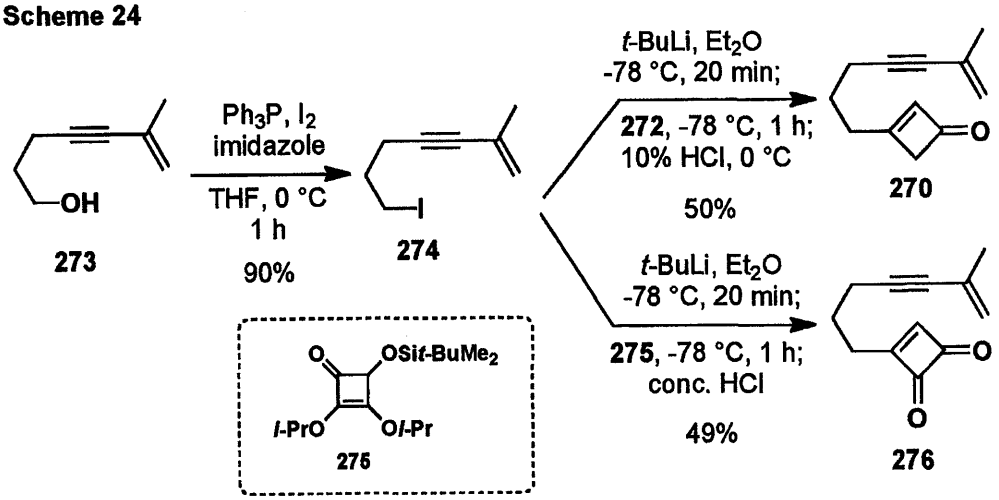
The preparation of cyclobutenone **270** and cyclobutenedione **276** is shown in Scheme 24.

---

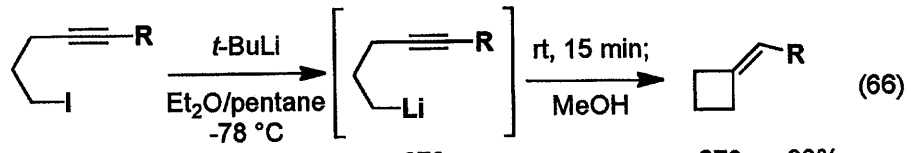
[92] Sonogashira, K. in Metal-Catalyzed Cross-Coupling Reactions; de Meijere, A.; Diederich, F.; Eds.; Weinheim: Wiley-VCH, 2004.
[93] Wasserman, H. H.; Piper, J. U.; Dehmlow, E. V. *J. Org. Chem.* **1973**, *38*, 1451-1455.
[94] (a) Ficini, J.; Claeys, M.; Depezay, J. C. *Tetrahedron Lett.* **1973**, *14*, 3357-3359. (b) Ficini, J.; Genet, J. P. *Tetrahedron Lett.* **1975**, *16*, 2633-2636.
[95] Liebeskind, L. S.; Fengl, R. W.; Wirtz K. R.; Shawe, T. T. *J. Org. Chem.* **1988**, *53*, 2482-2488.

Enynyl alcohol **273**[96] was prepared by Sonogashira coupling of 4-pentyn-1-ol with 2-bromopropene. Alcohol **273** was converted to iodide **274**[97] under standard conditions in excellent yield. Metal-halogen exchange[98] of iodide **274** with two equivalents of *t*-BuLi afforded alkylithium intermediate **271**. Addition of the cyclobutenyl electrophiles **272** and **275**, followed by treatment with acid afforded the substrates **270** and **276** in moderate yield. Squarate derivative **275**[99] was prepared from squaric acid in 3 steps following the procedure of Liebeskind.[95]

Scheme 24



The moderate yields of these reactions can be attributed to side reactions of the alkyllithium intermediate **271**. 3-Alkynyl alkyllithium species generated via lithium-iodide exchange are known to cyclize upon warming to room temperature to give alkylidene cyclobutanes (eq 66).[100]



R = Ph **277a**
R = $SiMe_3$ **277b**

278a
278b

279a 93%
279b 89%

Although our reactions were carried out at - 78 °C, TLC analysis of the reaction mixtures

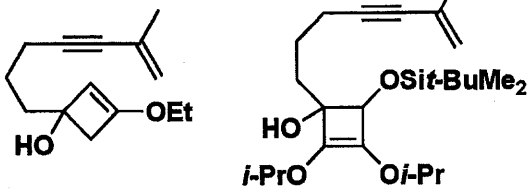
---

[96] Hashmi, A. K. S.; Sinha, P. *Adv. Synth. Catal.* **2004**, *346*, 432-438.
[97] Previously prepared in 71% yield over 2 steps by alkylation of 2-methylbut-1-en-3-yne with 1-chloro-3-bromopropane followed by Finkelstein reaction with NaI, see ref 68.
[98] Reviewed in: Bailey, W. F.; Patricia, J. J. *J. Organomet. Chem.* **1988**, *352*, 1-46.
[99] I would like to thank Tom Willumstad for the preparation of a batch of **275**.
[100] Bailey, W. F.; Ovaska, T. V. *J. Am. Chem. Soc.* **1993**, *115*, 3080-3090.

indicated several spots in addition to the intermediate tertiary alcohols (Figure 6). These byproducts were not isolated for characterization.

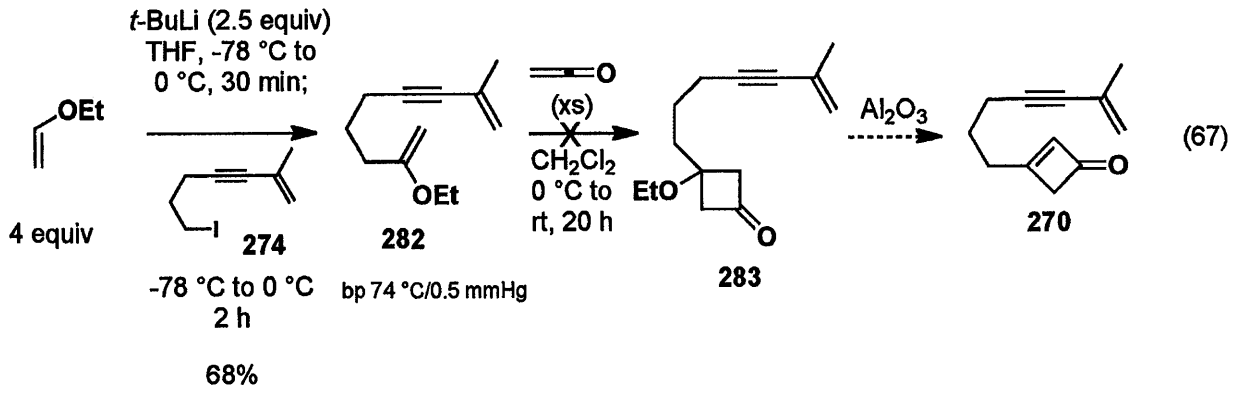
The acid-promoted hydrolysis of **280** to cyclobutanone **270** using 10% HCl suffered from poor reproducibility. Conversion of **280** to **270** could also be accomplished by treatment of the reaction mixture with trifluoroacetic anhydride to form the tertiary trifluoroacetate derivative, followed by hydrolysis with aqueous sodium bicarbonate. This procedure afforded **270** in a reproducible 42% yield. The conversion of **281** to **276** requires strong acid, so alternative conditions were not explored.

Figure 6



280 **281**

Due to the moderate yields of these reactions, an alternative route to cyclobutenone **270** was investigated utilizing a common intermediate, iodide **274** (eq 67).



(67)

Huisgen and Mayr have shown that 2-substituted cyclobutenones can be prepared by the [2 + 2] cycloaddition of ketene with vinyl ethers, followed by chromatography of the product on neutral or basic alumina.[101] Ethanol is eliminated during chromatography, affording the cyclobutenones in 30-80% yield. We attempted to extend this method to 3-substituted cyclobutenones without success.

Vinyl ether **282** was prepared by alkylation of lithiated ethyl vinyl ether. Acid-sensitive **282** was purified by distillation. Ketene (generated by pyrolysis of acetone) was bubbled through

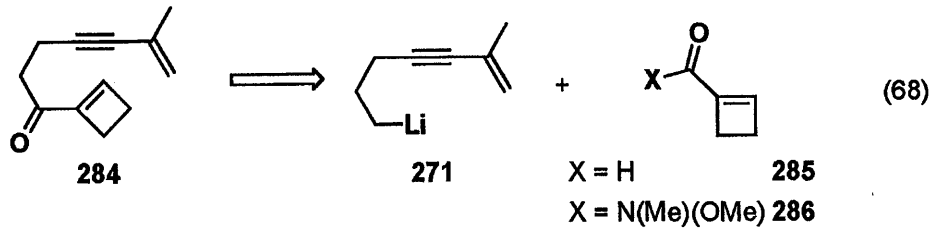
---

[101] Mayr, H.; Huisgen, R. *Angew. Chem., Int. Ed.* **1975**, *14*, 499-500.

a solution of **282** in dichloromethane in an attempt to prepare **283**. Unfortunately, the main product from this reaction was diketene, and most of the starting material remained unreacted. A small amount of desired **283** formed but it could not be separated from the diketene and vinyl ether **282**. It appears that disubstituted vinyl ethers like **282** are very sluggish in the [2 + 2] reaction with ketene. In fact, vinyl ethers of this type have been shown to react slowly with diphenylketene to give α-methylene oxetane derivatives.[102] This route was abandoned in favor of the 3-ethoxycylobutenone carbonyl addition/acidic hydrolysis strategy outlined previously.

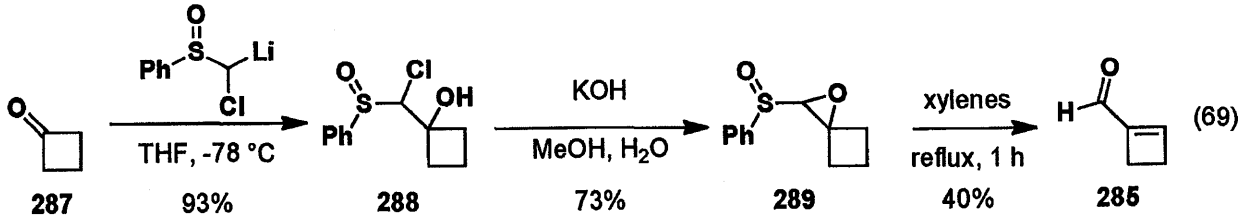
Cyclobutenyl Ketone Substrates

Preparation of substrates with the electron-withdrawing group in the tether required a cyclobutenyl electrophile with a carbonyl group external to the ring (eq 68).



(68)

Candidates for electrophile included cyclobutenyl aldehyde **285** as well as cyclobutenyl Weinreb amide[103] **286**. Aldehyde **285** is a known compound, previously prepared by one-carbon homologation of cyclobutanone **287** via α-epoxy sulfoxide **289** (eq 69).[104]



(69)

While aldehyde **285** would probably be more reactive in the alkyllithium addition step,

---

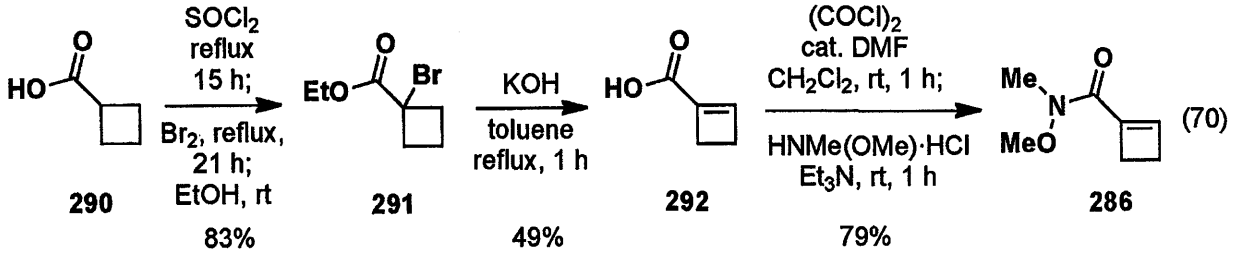
[102] Machiguchi, T.; Okamoto, J.; Takachi, J.; Hasegawa, T.; Yamabe, S.; Minato, T. *J. Am. Chem. Soc.* **2003**, *125*, 14446-14448.

[103] Weinreb amides have been used extensively in synthesis. See: (a) Sibi, M. P.; *Organic Prep. and Proc. Int.* **1993**, *25*, 15-40. (b) Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815-3818.

[104] Reutrakal, V.; Kanghae, W. *Tetrahedron Lett.* **1977**, *18*, 1377-1380.

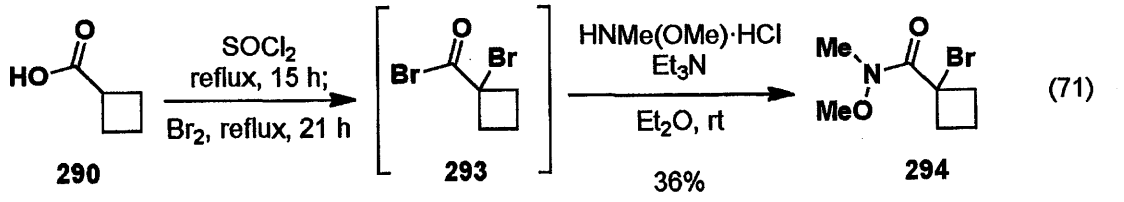
using it as the electrophile would require an additional oxidation reaction to afford the cyclobutenyl ketone substrate, whereas cyclobutenyl Weinreb amide **286** would furnish the cyclobutenyl ketone directly from addition of the enynyl alkyllithium species **271**.

Cyclobutenyl Weinreb amide **286** was prepared in three steps from commercially available cyclobutane carboxylic acid **290** (eq 70).



Hell-Vollhard-Zelinsky reaction of **290** with bromine furnished an α-bromoacyl bromide intermediate that was quenched with ethanol to give **291**. Elimination of HBr was accomplished by refluxing **291** with potassium hydroxide. Cyclobutene carboxylic acid **292**[105] was recrystallized from pentane at -78 °C to give a white powder that was stable to storage for a maximum of one week in the dark at -18 °C. The Weinreb amide was synthesized in good yield using oxalyl chloride to prepare the acyl chloride in situ, followed by treatment with *N,O*-dimethylhydroxylamine hydrochloride. Amide **286**[106] is stable to storage at -18 °C for over a month.

Due to the low yield of the elimination reaction to give cyclobutene **292**, we investigated an alternative route to Weinreb amide **286**. In order to avoid formation and isolation of unstable **292**, the α-bromoacyl bromide intermediate **293** obtained in the Hell-Vollhard-Zelinsky reaction was treated with *N,O*-dimethylhydroxylamine hydrochloride to give α-bromo Weinreb amide **294** in low yield (eq 71).



We were concerned that treatment of **294** with potassium hydroxide would result in

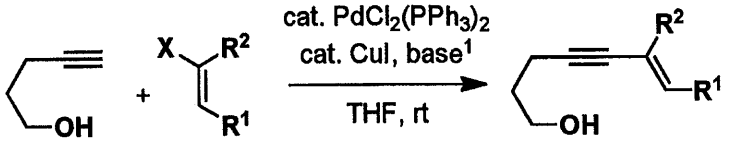
---

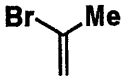
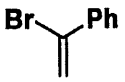
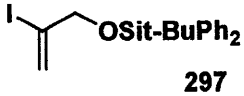
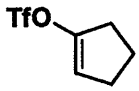
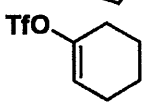
[105] Song, A.; Parker, K. A.; Sampson, N. S. *J. Am. Chem. Soc.* **2009**, *131*, 3444-3445.
[106] I would like to thank Phil Hamzik for the preparation of a batch of **286**.

hydrolysis of the amide, so potassium *tert*-butoxide was investigated first. Even when the reaction was heated at 50 °C, only trace amounts of the desired product **286** were formed. When the reaction was carried out with potassium hydroxide in refluxing toluene, again only ca. 10% conversion to cyclobutene **286** was observed. The low reactivity of α-bromo amide **294**, compared to α-bromo ester **291** was unexpected and may be due to subtle conformational, electronic, and steric effects.

A variety of enynes were prepared by Sonogashira reaction of 4-pentyn-1-ol with vinyl halides and triflates in good to excellent yields (Table 6).

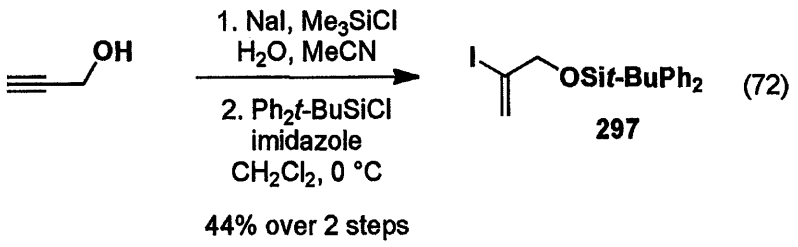
Table 6. Sonogashira Couplings to Furnish Conjugated Enynes



Vinyl halide or triflate		Base	Rxn time	Product	Yield
	**295**	Et_3N	21 h	**273**	90%
	**296**	Et_3N	1 h	**300**	81%
	**186**	Et_3N	17 h	**301**	75%
	**297**	Et_3N	21 h	**302**	85%
	**298**	i-Pr_2NH	1 h	**303**	88%
	**299**	i-Pr_2NH	1 h	**304**	92%

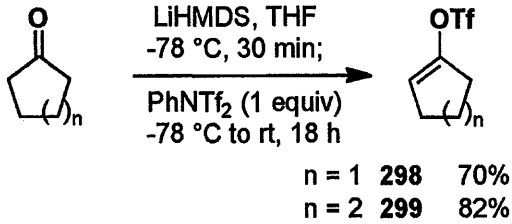
[1] These reactions were run using 2 mol % $PdCl_2(PPh_3)_2$ and 4 mol % CuI. The reactions with *i*-Pr_2NH were run neat in the amine (no THF solvent).

Vinyl iodide **297** was prepared in two steps from propargyl alcohol following the procedure developed for synthesis of the corresponding TBDMS derivative (eq 72).[107]



(72)

Vinyl triflates **298**[108] and **299**[109] were prepared from the lithium enolates of cyclopentanone and cyclohexanone using *N*-phenyltrifluoromethanesulfonimide[110] in good yields (eq 73).

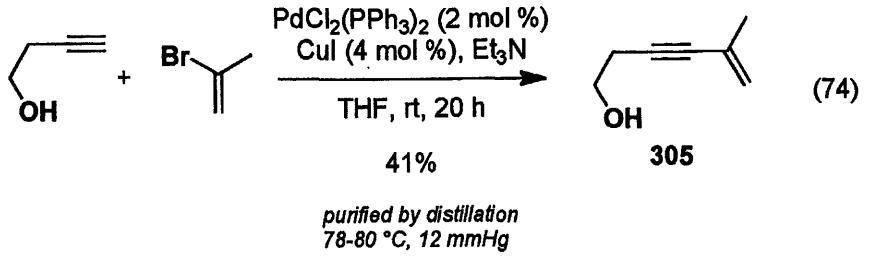


(73)

The shorter tether enynyl alcohol **305**[70] was prepared in a similar fashion to the compounds described in Table 6 (eq 74). Many of these enynyl alcohols are volatile due to their low molecular weights, so purification of **305** was attempted by distillation rather than column chromatography, giving the product in low yield on gram scale. This reaction was not optimized. As will be discussed in the next chapter, the cycloaddition substrate **284** derived from **305** did not work well in the [4 + 4] annulation so the reactions used to prepare it were not repeated.

---

[107] Amos, D. T. Ph. D. Thesis, Massachusetts Institute of Technology, September 2003.
[108] Stanislawski, P. C.; Willis, A. C.; Banwell, M. G. *Org. Lett.* **2006**, *8*, 2143-2146.
[109] Previously prepared using LDA instead of LiHMDs in 55% yield: Tessier, P. E.; Nguyen, N.; Clay, M. D.; Fallis, A. G. *Org. Lett.* **2005**, *7*, 767-770. This compound has also been prepared under a variety of conditions using Tf_2O in low yield.
[110] Mc Murry, J. E.; Scott, W. J. *Tetrahedron Lett.* **1983**, *24*, 979-982.



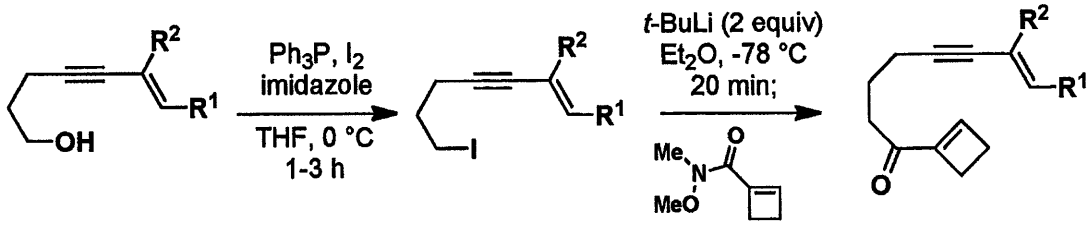
(74)

Enynyl alcohol **301** (R^1 = H, R^2 = Ph) decomposed upon storage overnight at 4-8 °C. The other enynyl alcohols **273**, **300**, **302-304** were converted to the corresponding iodides under standard conditions in good yields (Table 7). Metal-halogen exchange of the iodides **306-311** with *t*-BuLi followed by trapping of the intermediate alkyllithium species with Weinreb amide **286** afforded the cyclobutenyl ketones in moderate yields.

It is well known that in order to minimize byproduct formation in lithium-halogen exchange reactions, an ether-pentane solvent mixture should be used.[111] However, in the synthesis of cyclobutenyl ketone **312**, we found that there was no difference in yield between using ether-pentane and using just ether (with a pentane contribution from the *t*-BuLi solution). In addition, Weinreb amide **286** was found to be minimally soluble in ether-pentane mixtures at -78 °C, so THF was added as a co-solvent, improving the yield and reproducibility of the reactions.

[111] Applequist, D. E.; O'Brien, D. F. *J. Am. Chem. Soc.* **1963**, *85*, 743-748.

Table 7. Synthesis of Cyclobutenyl Ketone Substrates



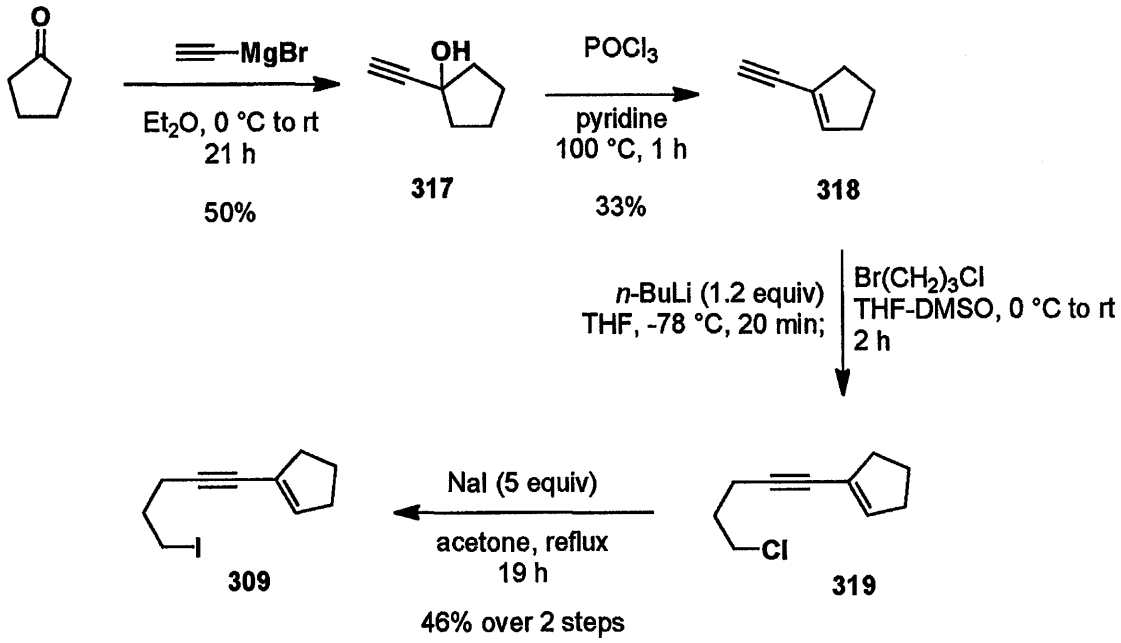
Alcohol	R^1, R^2	Iodide	Yield	Substrate	Yield
273	H, Me	**274**	90%	**312**	50%
301	H, H	**307**	94%	**313**	55%
302	H, OSi*t*-BuPh$_2$	**308**	85%	OSi*t*-BuPh$_2$ **314**	53%[2]
303	$(CH_2)_3$	**309**	82%	**315**	64%
304	$(CH_2)_4$	**310**	89%	**316**	56%
305	H, Me	**311**	81%	**284**	41%

[1] THF was used as a co-solvent to prepare **313-316**. THF was used as an additive to prepare **312** and **284**. [2] Compound **314** was isolated ca. 80% pure. The contaminant is *t*-BuPh$_2$SiOH.

An alternative route to cyclobutenyl ketone **315** was initially investigated prior to the preparation of cyclopentenyl triflate **298** for cross-coupling reactions. This route relied on the

elimination reaction of propargylic alcohol **317**[112,113] followed by alkylation of the terminal alkyne **318** with 1-bromo-3-chloropropane and finally Finkelstein reaction of chloride **319** to give iodide **309** (Scheme 25). Due to the low yields of these 4 steps, this route was abandoned in favor of the Sonogashira route outlined above.

Scheme 25

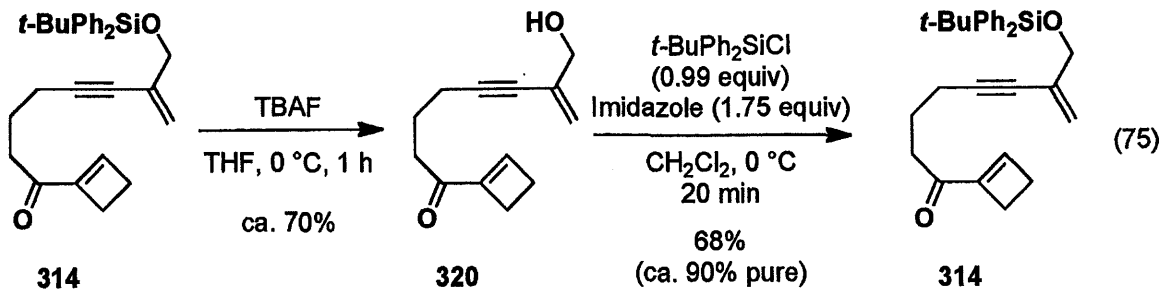


Substrate **314** was isolated in impure form, contaminated with ca. 20% by weight *t*-$BuPh_2SiOH$ (by ^1H NMR analysis). This silanol impurity co-elutes with the desired product in all of the TLC conditions examined, preventing isolation of pure compound. In an attempt to obtain enough pure substrate for cycloaddition studies, **314** was deprotected using TBAF, purified to separate out all of the silanol, and then the silyl group was reinstalled (eq 75).

---

[112] Compound **317** was prepared according to: House, H. O.; Phillips, W. V.; Sayer, T. S. B.; Yau, C.-C. *J. Org. Chem.* **1978**, *43*, 700-710.

[113] Collins, P.W.; Gasiecki, A. F.; Perkins, W. E.; Gullikson, G. W.; Bianchi, R. G.; Kramer, S. W.; Ng, E. E. Y.; Sewnton, L. *J. Med. Chem.* **1990**, *33*, 2784-2793.



Unfortunately, even when the silylating agent was used as the limiting reagent, **314** was still isolated in impure form, contaminated with ca. 10% by weight *t*-BuPh$_2$SiOH (by ^{1}H NMR analysis). In this reaction, all of the alcohol **320** was consumed and control experiments indicated that the unreacted *t*-BuPh$_2$SiCl should have survived the workup conditions. This suggests that **314** is sensitive to acid, and an elimination reaction occurrs to liberate the silanol from the compound. Substrate **314** may also be sensitive to base, explaining the presence of silanol impurity after metal-halogen exchange of iodide **308**.

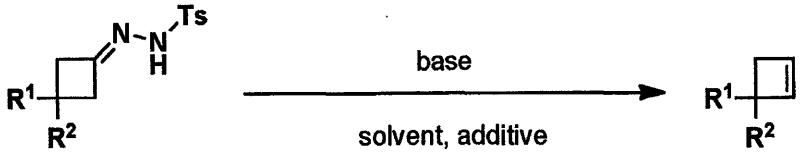
In addition to variations on the enyne moiety, we were also interested in investigating substituted cyclobutene derivatives in the [4 + 4] annulation reaction. Although there are only a few examples of Shapiro reactions of cyclobutanone derivatives in the literature, and in all of these cases the intermediate cyclobutenyllithium species are quenched with water to give unsubstituted olefin products (Table 8), we hoped that we might be able to use this powerful transformation to access a cyclobutenyl ketone with a cyclopentane ring fused to the cyclobutene ring.

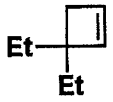
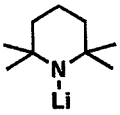
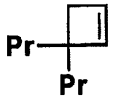
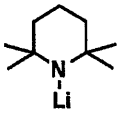
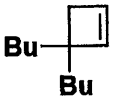
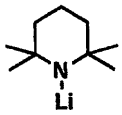
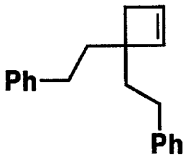
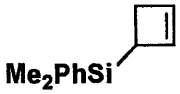
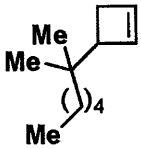
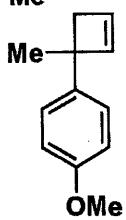
As shown in Table 8 below, a variety of bases and solvents have been used to prepare cyclobutenes **329-336** in yields ranging from 28-74% starting with mono- and disubstituted cyclobutane tosylhydrazone precursors. To the best of our knowledge, these are the only reported examples of Shapiro reactions on sulfonylhydrazones derived from cyclobutanones.[114]

---

[114] (a) Alder, R. W.; Allen, P. R.; Anderson, K. R.; Butts, C. B.; Khrosravi, E.; Martin, A.; Maunder, C. M.; Orpen, G.; St. Pourcain, C. B. *J. Chem. Soc., Perkin Trans. 2* **1998**, 2083-2108. (b) Hasegawa, M.; Usui, I.; Konno, S.; Murakami, M. *Org. Biomol. Chem.* **2010**, *8*, 4169-4175. (c) Bassindale, M. J.; Hamley, P.; Harrity, J. P. A. *Tetrahedron Lett.* **2001**, *42*, 9055-9057.

Table 8. Literature Reports of Shapiro Reactions of Cyclobutanone Derivatives



Tosyl-hydrazone	R^1	R^2	Conditions	Product		Yield
321	Et	Et	LDA, THF		**329**	28%[1]
322	$(CH_2)_5$		LDA, THF		**330**	30%[1]
323	*n*-Pr	*n*-Pr	 THF		**331**	60%[1]
324	*n*-Bu	*n*-Bu	 THF, Et_2O		**332**	36%[1]
325	$(CH_2)_2Ph$	$(CH_2)_2Ph$	 THF, Et_2O		**333**	34%[1]
326	$SiMe_2Ph$	H	*n*-BuLi, TMEDA hexanes		**334**	61%[2]
327	$C(Me)_2(CH_2)_4CH_3$	H	*n*-BuLi, TMEDA hexanes		**335**	38%[2]
328	Me	*p*-OMe-C_6H_4	*n*-BuLi, THF		**336**	74%[3]

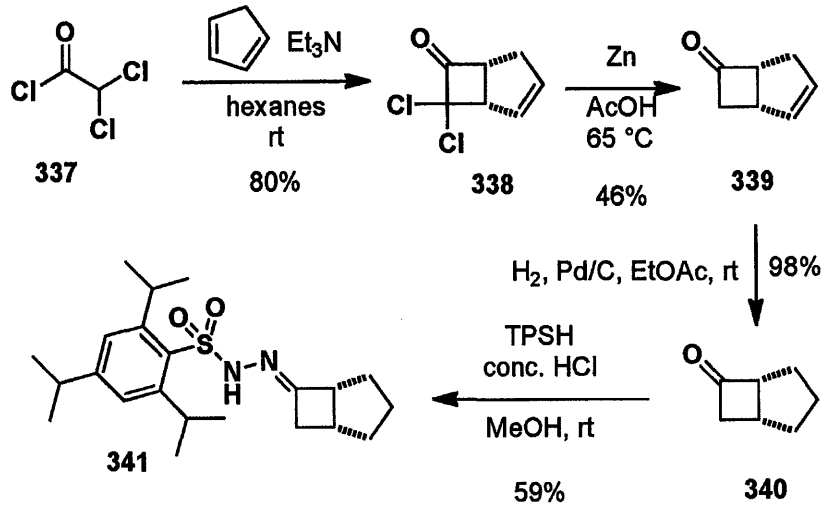
[1] Alder, R. W.; Allen, P. R.; Anderson, K. R.; Butts, C. B.; Khrosravi, E.; Martin, A.; Maunder, C. M.; Orpen, G.; St. Pourcain, C. B. *J. Chem. Soc., Perkin Trans. 2* **1998**, 2083-2108.

[2] Hasegawa, M.; Usui, I.; Konno, S.; Murakami, M. *Org. Biomol. Chem.* **2010**, *8*, 4169-4175.

[3] Bassindale, M. J.; Hamley, P.; Harrity, J. P. A. *Tetrahedron Lett.* **2001**, *42*, 9055-9057.

We used a Shapiro reaction[115] to prepare a substituted cyclobutenyl ketone. The sulfonylhydrazone substrate for the Shapiro reaction was prepared from known cyclobutanone **340** (Scheme 26). Starting with α-dichloroacetyl chloride **337**, cyclobutanone **338** was obtained by the [2 + 2] cycloaddition of dichloroketene with cyclopentadiene in good yield.[116] The dichlorocyclobutanone was dechlorinated in moderate yield using zinc in acetic acid to furnish **339**.[116] Hydrogenation by modification of a patent procedure[117] (1 atm H_2 instead of 70 psi/~5 atm H_2; at rt instead of 30 °C) afforded cyclobutanone **340** in excellent yield. Condensation with 2,4,6-(triisopropyl)benzenesulfonyl hydrazide (TPSH)[118] in methanol[119] gave sulfonylhydrazone **341** in moderate yield as a mixture of rotamers.

Scheme 26



The electrophile partner for the Shapiro reaction was prepared in three steps from carboxylic acid **342** (Scheme 27). The Sonogashira reaction with 2-bromopropene did not go to completion. The terminal alkyne **342** and enyne **344** could not be separated, so the product mixture was resubjected to the reaction conditions in order to obtain pure Weinreb amide **344**.

---

[115] (a) Shapiro, R. H. *Org. React.* **1976**, *23*, 405-507. (b) Adlington, R. M.; Barrett, A. G. M. *Acc. Chem. Res.* **1983**, *16*, 55-59. (c) Chamberlin, A. R.; Bloom, S. H. *Org. React.* **1990**, *39*, 1-83.

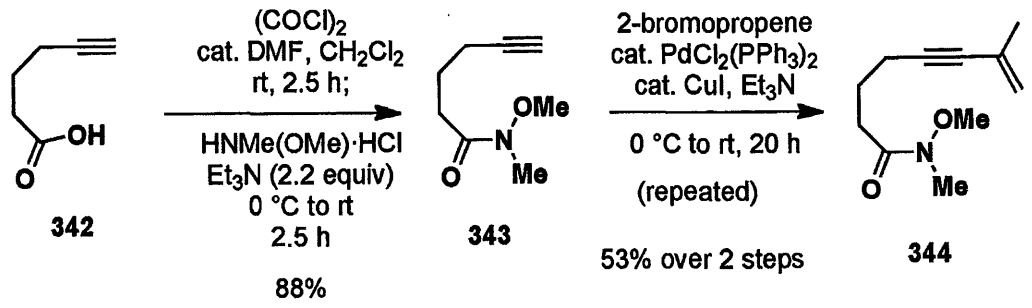
[116] Grieco, P. A. *J. Org. Chem.* **1972**, *37*, 2363-2364.

[117] Blakemore, D. C.; Bryans, J. S.; Williams, S. C. Pfizer, Inc. US2003/78300 A1, **2003**.

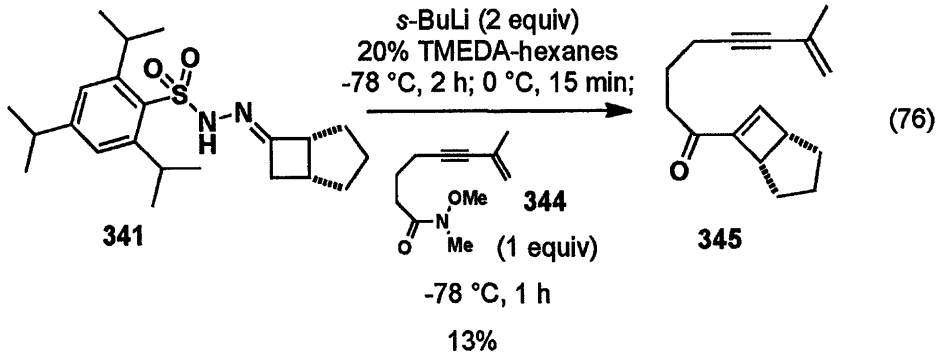
[118] Prepared by reaction of 2,4,6-(triisopropyl)benzenesulfonyl choride with hydrazine hydrate according to: Cusak, N. J.; Reese, C. B.; Risius, A. C.; Roozpeikar, B. *Tetrahedron* **1976**, *32*, 2157-2162.

[119] For condensation conditions for both hindered and unhindered ketones, see: Chamberlin, A. R.; Stemke, J. E.; Bond, F. T. *J. Org. Chem.* **1978**, *43*, 147-154.

Scheme 27



The Shapiro reaction was carried out using a TMEDA-hexanes solvent mixture in order to prevent protonation of the intermediate vinyllithium species by ethereal solvents.[120]

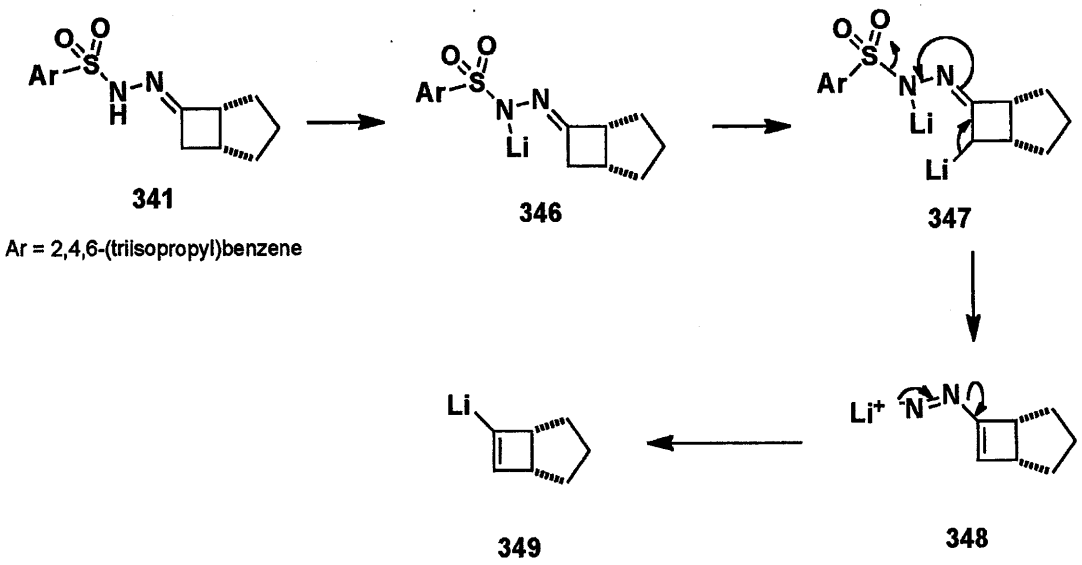


The best run of this reaction resulted in a low yield of cyclobutenyl ketone **345**. The difficult step in this reaction appears to be vinyllithium formation, as shown Scheme 28 below. The mechanism of this Shapiro reaction involves deprotonation of the sulfonylhydrazone both on the nitrogen and at the α-carbon, giving dilithio intermediate **347**. In the synthesis of substrate **345**, a 2,4,6-(triisopropyl)benezesulfonylhydrazone was used instead of the typical tosylhydrazone to avoid competing deprotonation at the ortho positions on the aryl ring. Tosylhydrazones typically require > 2 equivalents of the alkylithium base, and also an excess of electrophile. Since our electrophile, Weinreb amide **344**, was not trivial to prepare, we elected to use the more substituted hydrazone.

---

[120] Stemke, J. E.; Bond, F. T. *Tetrahedron Lett.* **1975**, *16*, 1815-1818.

Scheme 28. Mechanism of the Shapiro Reaction

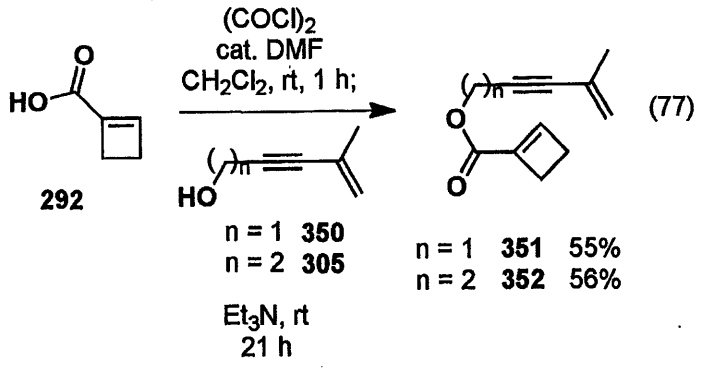


TLC analysis of the reaction mixture prior to addition of the electrophile indicated the formation of multiple products. Most of Weinreb amide **344** was recovered upon workup of the reaction. It is likely that use of the corresponding aldehyde as the electrophile would improve the efficiency of this reaction, and the vinyllithium formation step could probably be improved. However, as will be discussed in the next chapter, cyclobutenyl ketone **345** was problematic in the [4 + 4] annulation reaction, so the synthesis of this compound was not optimized.

Cyclobutenyl Ester Substrates

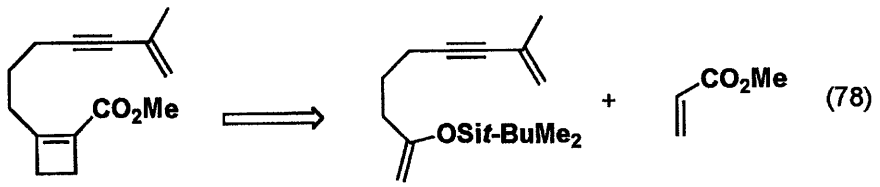
Cyclobutenyl esters **351** and **352** were prepared from the corresponding alcohols **350**[121] and **305** and cyclobutene carboxylic acid **292** (eq 77). In situ formation of the acyl chloride, followed by addition of the alcohols and triethylamine gave the desired esters in moderate yield.

[121] Park. J.; Ho, P.; Kim, S. H. *Org. Lett.* **2008**, *10*, 5067-5070.



We were also interested in cyclobutenyl esters in which the ester is external to the tether. Our strategy for preparation of this type of substrate relied on the [2 + 2] cycloaddition of silyl enol ethers with the α,β-unsaturated esters developed by Ihara and coworkers.[122] They utilized a a stepwise process involving Michael reaction of the enolate derived from the silyl enol ether with the acrylate, followed by an intramolecular aldol reaction to give cyclobutane rings with multiple substituents.

We envisioned that cyclobutenyl ester **353** could be prepared from silyl enol ether **354** and methyl acrylate (eq 78). The initial product would be a β-siloxy ester that could then undergo elimination of the silanol to give cyclobutenyl ester **353**.



353 **354**

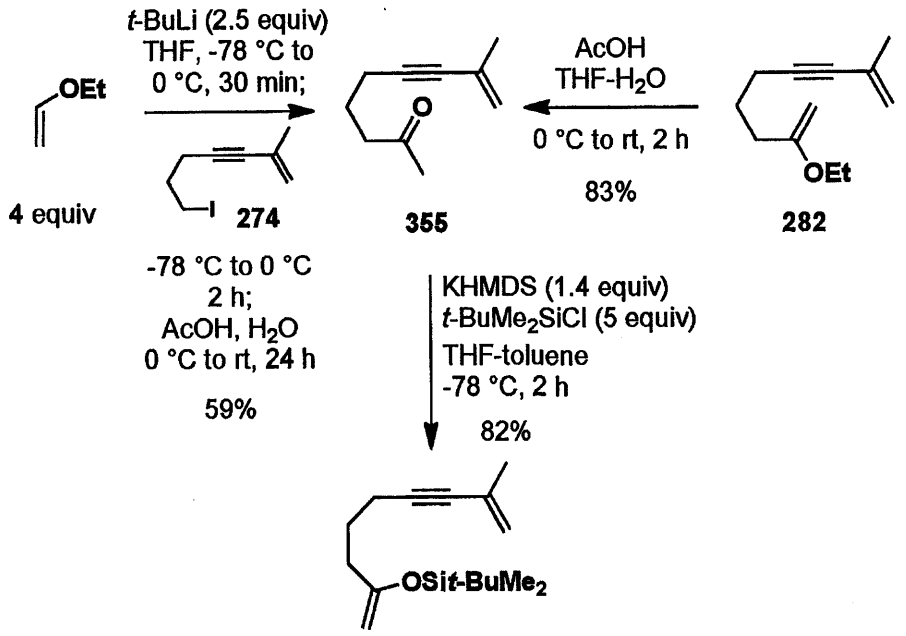
Silyl enol ether **354** was prepared from the corresponding methyl ketone **355**. This ketone was initially obtained by hydrolysis of vinyl ether **282** (previously prepared for [2 + 2] cycloadditions with ketene). A one-pot procedure from ethyl vinyl ether to ketone **355** was also developed. Regioselective formation of enol silyl ether **354** was accomplished by carrying out the enolate formation step using KHMDS in the presence of a large excess of the silylating agent.[123]

---

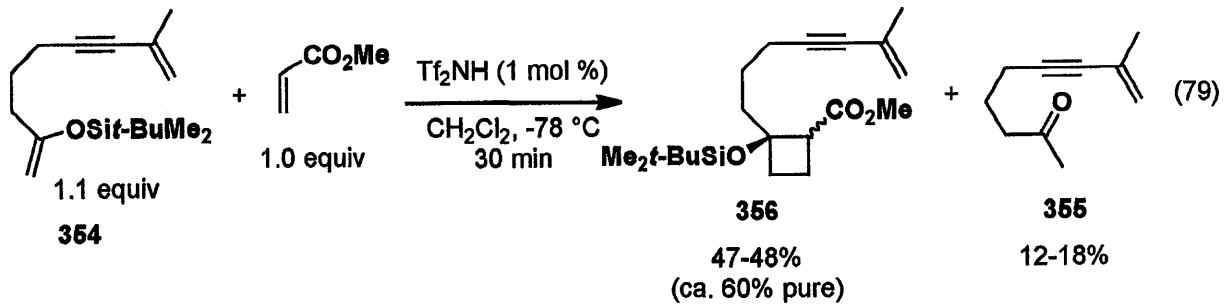
[122] (a) Takasu, K.; Ueno, M.; Inanaga, K.; Ihara, M. *J. Org. Chem.* **2004**, *69*, 517-521. (b) Takasu, K.; Miyakawa, Y.; Ihara, M.; Tokuyama, H. *Chem. Pharm. Bull.* **2008**, *56*, 1205-1206. (c) Takasu, K.; Ishii, T.; Inanaga, K.; Ihara, M. *Org. Synth.* **2006**, *83*, 193-199.

[123] Corey, E. J.; Sodeoka, M. *Tetrahedron Lett.* **1991**, *32*, 7005-7008.

Scheme 29

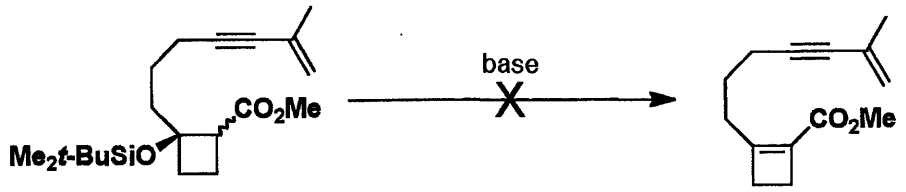


The Ihara [2 + 2] cycloaddition gave cyclobutane **356** in moderate yield as a mixture of diastereomers (eq 79). This material was contaminated with unidentified byproducts. A small amount of ketone **355**, resulting from hydrolysis of **354**, was also obtained.



Impure cyclobutane **356** was subjected to a several conditions for elimination of the β-siloxy group (Scheme 30). With LDA, the starting material was consumed and a complex mixture of products was produced. It is likely that the ca. 40% impurity in **356** contains enolizable protons, so it is possible that upon treatment with LDA, bimolecular reactions occur. Sodium hydride gave no reaction in THF, even at reflux, and treatment with NaH in DMF resulted in decomposition.

Scheme 30

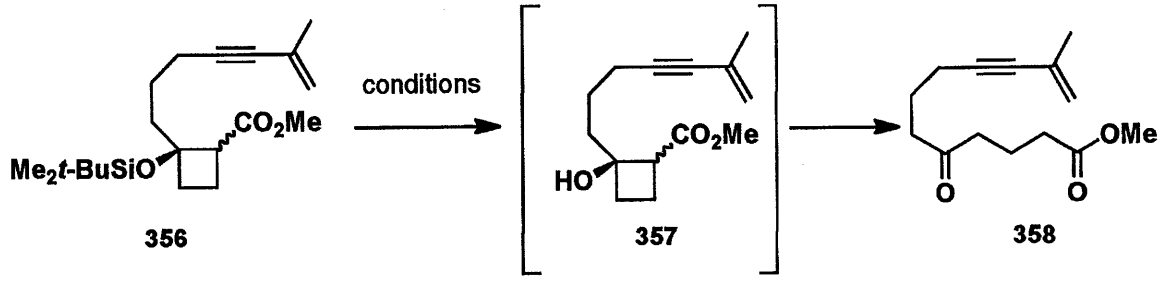


356 353

LDA (1.3 equiv), THF -78 °C to rt, 2 h	Messy reaction Multiple products	NaH, DMF rt, 6 h	Decomposition
LDA (5 equiv), THF -78 °C, 6 h; 0 °C, 30 min	Messy reacton Multiple products	NaH, THF, rt, 1.5 h; reflux, 4.5 h	No reaction

Deprotection of **356** was attempted next. We hoped to install a less bulky group that would also be a better leaving group for the elimination. Treatment of **356** with TBAF and TBAF/AcOH[124] resulted in formation of retro-aldol product **358**. None of the desired α-alkoxy ester **357** was obtained. Deprotection was attempted under acidic conditions using formic acid[125] to avoid the retro-aldol pathway, but even after stirring for 3 days with aqueous formic acid in THF, the starting material **356** was recovered unchanged.

Scheme 31

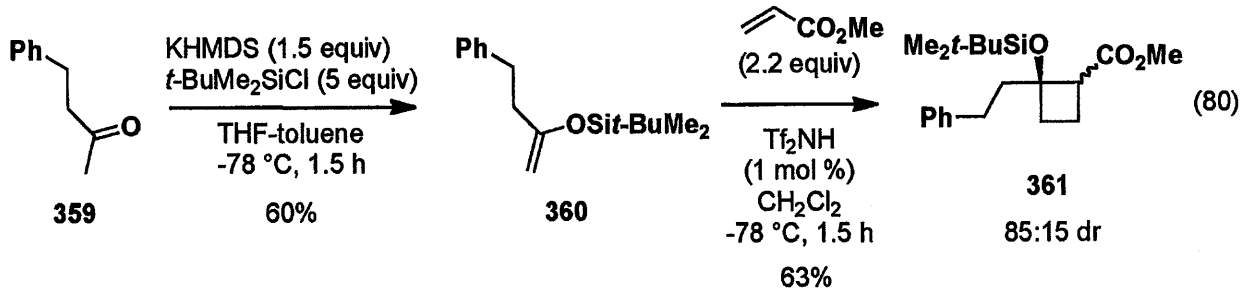


356 357 358

TBAF (2.2 equiv) THF, 0 °C, 1 h; rt, 23 h	55% of **358**
TBAF (3 equiv) AcOH (1 equiv) THF, rt, 3 days	**358** is main product (not purified)
HCO_2H (20 equiv) H_2O-THF rt, 3 days	no reaction

[124] Kende, A. S.; Lui, K.; Kaldor, I.; Dorey, G.; Koch, K. *J. Am. Chem. Soc.* **1995**, *117*, 8358-8270.
[125] Smith III, A. B.; Ott, G. R. *J. Am. Chem. Soc.* **1996**, *118*, 13095-13096.

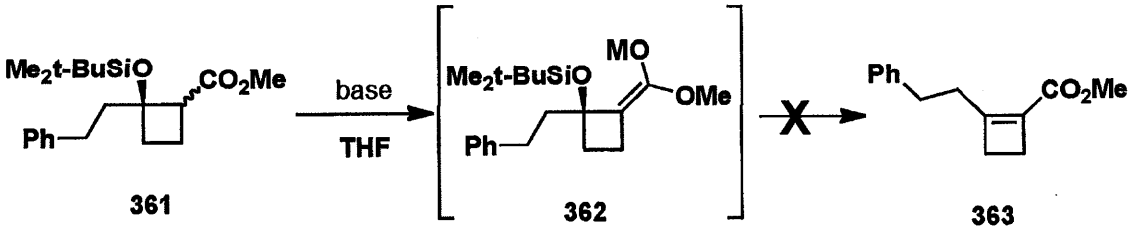
We turned next to a model compound in order to determine if the desired elimination reaction is possible on a less functionalized substrate. Cyclobutane **361** was prepared as shown in eq 80, starting from benzylacetone **359**. In this case, an excess of methyl acrylate was used in the [2 + 2] cycloaddition step to drive the reaction to completion. Cyclobutane **361** was isolated as a pure compound with 85:15 dr, in contrast to **356** which was only ca. 60% pure, suggesting that the presence of the conjugated enyne during the protic acid-catalyzed cycloaddition is problematic.



(80)

Cyclobutane **361** was subjected to a variety of elimination conditions (Table 9). The diasteromeric ratio was used to probe whether or not enolate formation occurred upon treatment of **361** with base. The literature examples of Ihara [2 + 2] cycloadditions all involve cyclic enol silyl ethers, and the products are predominantly the kinetic *trans* isomers.[122] In our examples, with the acylic enol silyl ethers, we were not able to determine which diastereomer is the major component based on the spectral data, but we expected to see a change in dr if enolate formation occurred under the reaction conditions.

Table 9. Attempted Elimination Reactions



Base	Temp	dr of recovered 361
NaH	-78 °C to rt	58:42
KHMDS	-78 °C to -50 °C	85:15
KOt-Bu	-78 °C to -50 °C	85:15
	0 °C to rt	85:15

None of the desired cyclobutenyl ester **363** was obtained in these reactions. Interestingly, the only erosion of dr observed was with sodium hydride in THF, even though sodium hydride is sparingly soluble in THF at the temperatures studied. Bulky bases like KHMDS and KO*t*-Bu appeared unreactive towards **361**.

The low reactivity of **361** toward elimination may be due to conformational and steric effects. There is a continuous spectrum of elimination pathways, ranging from the extremes of a concerted E2 reaction to a two-step E1cb reaction (through intermediate enolate **362**). E2 elimination requires that the proton be coplanar to the leaving group, with the lower energy option involving an antiperiplanar arrangement. If the major diastereomer of **361** is *trans*, then the α-proton and the siloxy group may achieve a synperiplanar relationship. If the major diastereomer of **361** is *cis*, then the α-proton and the siloxy group may achieve an antiperiplanar relationship. In the E1cb pathway, enolate formation introduces increased strain into the already strained four-membered ring. In both cases, the energy of the transition state will be elevated by the ring strain that develops as two carbons in the small ring change from sp^3 to sp^2 hybridization.

While the reactions to produce cyclobutenyl ester **353** were not successful, we were still able to obtain 11 different substrates for annulation studies, with a variety of tethers, a variety of substituents on the enyne, and two substitution patterns on the cyclobutene moiety.

Chapter 3 – [4 + 4] Annulation Studies[126]

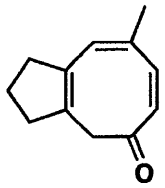
Cyclobutenone Substrate

Due to the thermal instability of cyclobutenes,[127] we expected that the [4 + 4] annulation reaction would work best when carried out with protic or Lewis acids rather than with heating. Annulation studies commenced with cyclobutenone **270** (Table 10).

Cyclobutenone **270** was treated with a variety of Lewis acids as well as methanesulfonic acid. In an initial study, Jennie Fong found that substrate **270** was generally unreactive towards Lewis and protic acids at low temperature (based on TLC analysis). After warming to room temperature and stirring for extended reaction times, decomposition was observed (Table 10, entries 3-7). When $BF_3{\cdot}OEt_2$ was used as the promoter, the desired product **366** was observed for the first time, and this compound was isolated in 35% yield (Table 10, entry 8).

Structure **366** was assigned to the product of the [4 + 4] annulation reaction of cyclobutenone **270** based on ^1H and ^{13}C NMR chemical shifts and ^1H NMR coupling constants, as outlined in Table 11 below. Comparison of these values with the values reported for the most similar known compound, 2,4,6-cyclooctatrienone (**368**) (Figure 6a), indicated close agreement in both the proton[128] and carbon[129] NMR spectra. In addition, the IR spectrum of **366** has a strong peak at 1661 cm^{-1}, consistent with a highly conjugated ketone. The IR spectrum **368** has a strong peak at 1655 cm^{-1}.[128]

Figure 6a



368

---

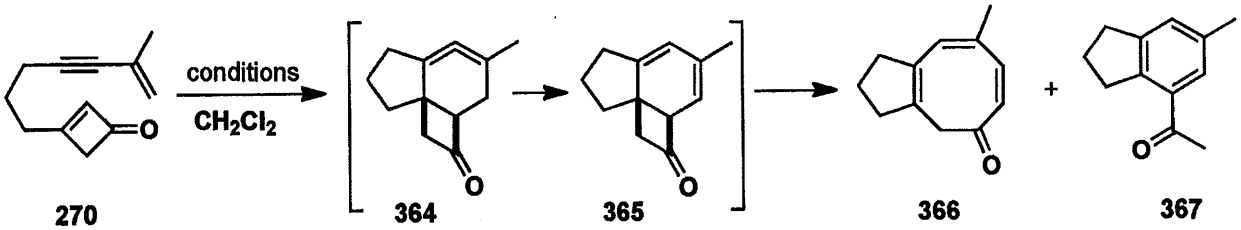
[126] Some preliminary experiments on the [4 + 4] annulation were carried out by Jennie Fong. See: Fong, J. M. S. Thesis, Massachusetts Institute of Technology, June 2008.

[127] Danheiser, R. L.; Dudley, G. B.; Austin, W. F. Product Class 13: Alkenylketenes. In *Science of Synthesis*; Danheiser, R. L., Ed.; Thieme: Stuttgart, Germany, 2006; Vol. 23, pp 493-568.

[128] Adam, W.; Cueto, O.; De Lucchi, O. *Chem. Ber.* **1982**, *115*, 1170-1177.

[129] Meier, H.; Lorch, M.; Petersen, H.; Gugel, H. *Chem. Ber.* **1982**, *115*, 1418-1424.

Table 10. [4 + 4] Annulation Reactions of Cyclobutenone 270

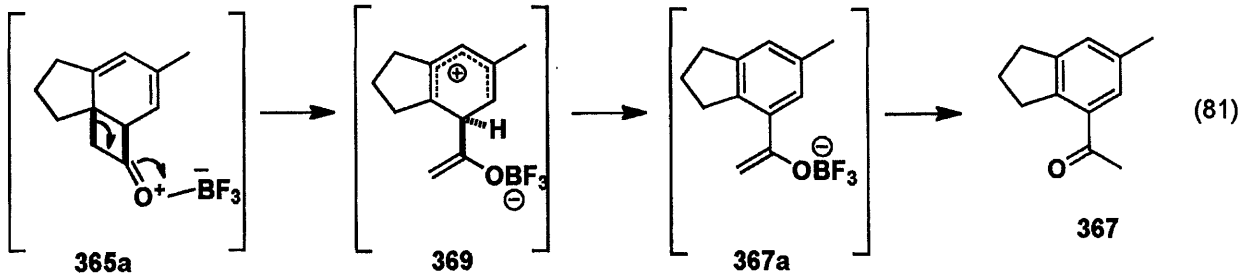


270 364 365 366 367

Entry[1]	Conditions	Result (^{1}H NMR)	Yield of 366[2]	Yield of 367[2]
1	MsOH (1 equiv) -78 °C, 1 h	Mostly **270**, trace **365**	-	-
2	MsOH (1.5 equiv) -60 °C, 30 min; -60 to -15 °C, 1 h	ca. 3% conversion to **365** (5.12, 5.36 ppm)	-	-
3	MsOH (1.5 equiv) 0 °C to rt, 20 h	Complex mixture	-	-
4	$AlCl_3$ (2 equiv) -78 °C to rt, 13 h	Complex mixture	-	-
5	Me_2AlCl (1.5 equiv) -40 °C to 0 °C, 75 h	Complex mixture	-	-
6	$Au(Ph_3P)_3Cl$ (4 mol %) $AgBF_4$ (4 mol %) 0 °C to rt, 16 days	Complex mixture	-	-
7	Et_3SiOTf (1 equiv) 0 °C, 17 h	Complex mixture	-	-
8	$BF_3{\cdot}OEt_2$ (1.1 equiv) rt, 21 h	55:45 **366:367**	35%	not determined
9	$BF_3{\cdot}OEt_2$ (1.1 equiv) 0 °C to rt, 26 h	50:50 **366:367**	27%	25%
10	$BF_3{\cdot}OEt_2$ (1.4 equiv) BHT (1 equiv) reflux, 4.5 h	Mixture of products	30%	36%

[1] Entries 3 and 4-8 were carried out by Jennie Fong. [2] Isolated yield of products determined purified by column chromatography.

In addition to the desired cyclooctatrienone **366**, a byproduct was formed in nearly equal amounts. The structure of this compound was assigned to be indan **367** by comparison of its spectral data with the ^{1}H and ^{13}C NMR data of this compound which had been previously prepared in our laboratory by an independent route.[69] Byproduct **367** is believed to arise from fragmentation of intermediate diene **365**, to form the dienyl cation species **369** (eq 81).

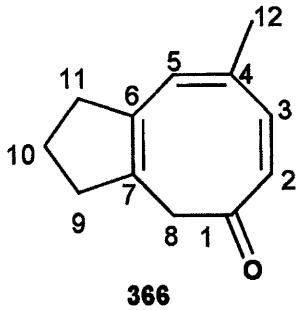


(81)

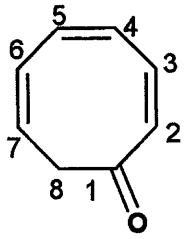
We had not predicted that this fragmentation reaction would occur, although in retrospect it is clear that the tricyclic structure with the fused cyclobutanone ring is probably quite strained.

The annulation reaction was next attempted with heating (Table 10, entry 10). When the cycloaddition was carried out in refluxing dichloromethane, the cyclobutenone was fully consumed within 4.5 h and three products were isolated: desired cyclooctatrienone **366** in 30% yield, undesired indan **367** in 36% yield, and an unidentified compound in ca. 20% yield. IR indicated that this compound was not cyclobutanone **365** (C=O stretch at 1700 cm^{-1} instead of the expected ca. 1775 cm^{-1} for a cyclobutanone), and when this compound was resubjected to the reaction conditions ($BF_3 \cdot OEt_2$, BHT, CH_2Cl_2, 40 °C), neither **366** or **367** was formed and the starting material was recovered unchanged. To date the structure of this byproduct has not been identified.

Table 11. ^{1}H and ^{13}C NMR Assignments for 366 and 2,4,6-Cyclooctatrienone (368)



366

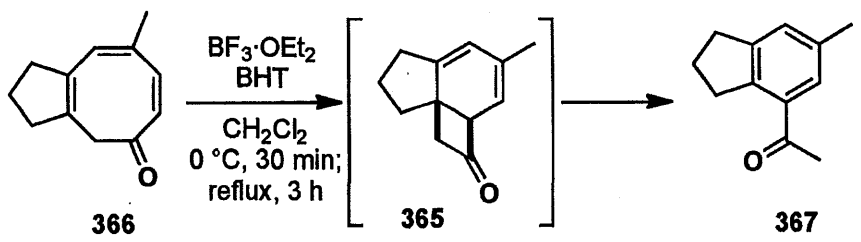


368

Atom #	^{1}H NMR[1] δ (multiplicity, *J* (Hz))	^{13}C NMR[2] δ	Atom #	^{1}H NMR[3] δ (multiplicity, *J* (Hz))	^{13}C NMR[4] δ
1	-	190.9	1	-	191.9
2	6.36-6.41 (m)	130.0	2	5.56-6.90 (m)	130.0
3	6.61 (d, 13.3)	141.4	3	5.56-6.90 (m)	138.0
4	-	132.9	4	-	137.0
5	6.36-6.41 (m)	135.4	5	5.56-6.90 (m)	126.4
6	-	139.4	6	5.60-5.90 (m)	133.4
7	-	139.7	7	5.60-5.90 (m)	129.6
8	2.91 (s)	44.4	8	3.00 (d, 8)	43.6
9	2.49 (q, 7.5)	36.7			
10	1.93 (pent, 7.6)	23.1			
11	2.49 (q, 7.5)	35.8			
12	2.11 (s)	26.7			

[1] 400 MHz, $CDCl_3$. [2] 100 MHz, $CDCl_3$.
[3] Adam, W.; Cueto, O.; De Lucchi, O. *Chem. Ber.* **1982**, *115*, 1170-1177. (CCl_4)
[4] Meier, H.; Lorch, M.; Petersen, H.; Gugel, H. *Chem. Ber.* **1982**, *115*, 1418-1424. ($CDCl_3$)

In order to investigate the potential equilibrium between diene **365** and cyclooctatrienone **366**, we resubjected the pure cyclooctatrienone product to the [4 + 4] annulation reaction conditions (eq 82).



(82)

^{1}H NMR: 90:10 **366**:**367**

If **365** and **366** were in equilibrium (via electrocyclic ring opening/closure) under our reaction conditions, we would expect some of fragmentation product **367** to form upon heating of **366**. In fact, upon treatment with $BF_3{\cdot}OEt_2$ in dichloromethane at reflux, ca. 10% conversion of **366** to **367** was observed by ^{1}H NMR analysis. No other compounds (besides BHT) were visible in the ^{1}H NMR spectrum. In addition, when this same reaction was carried out using $BF_3{\cdot}OEt_2$ at rt for 52 h, only ca. 4% conversion of **366** to **367** was observed, indicating that the warmer reaction conditions accelerate formation of the byproduct, as was previously observed in the [4 + 4] annulation (Table 10, entry 10). From these experiments, we believe that cyclooctatrienone **366** and bicyclooctadiene **365** are in equilibrium under the annulation reaction conditions, but the equilibrium favors **366** to such a great extent that the majority of the fragmentation product **367** formed in the reaction arises from fragmentation of **365** *immediately* after it forms in the initial [4 + 2] cycloaddition.

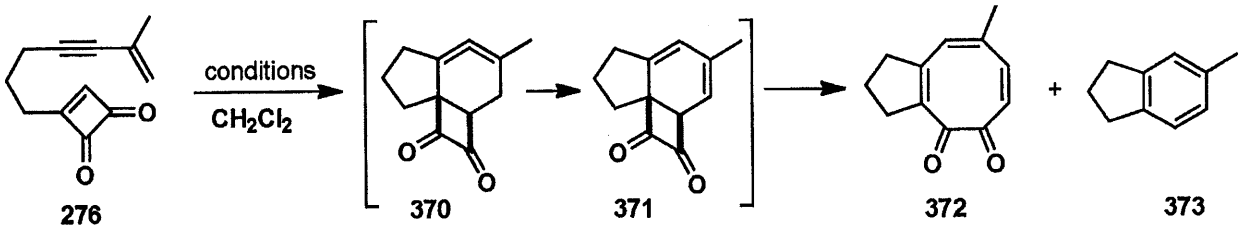
At this point we turned to the cyclobutenedione substrate. Much later, after successful results using methanesulfonic acid had been obtained with the cyclobutenyl ketone series of substrates, we returned to the [4 + 4] annulation of cyclobutenone **270** (Table 10, entries 1-2). Treatment of cyclobutenone **270** with MsOH at low temperature appeared to result in no reaction based on TLC analysis, as Jennie Fong had observed, but when the reaction was quenched without warming above -15 °C, and then worked up, diene **365** was observed in trace amounts in the ^{1}H NMR spectrum. This result suggests that protic acids can promote the desired [4 + 2] reaction at low temperature, but the reaction is so slow as to not be synthetically useful.

Cyclobutenedione Substrate

In light of the unexpected fragmentation reaction observed with the 3-substituted cyclobutenone **270**, we next turned our attention to cyclobutenedione **276** (Table 12). We

expected that this substrate might be especially reactive in the [4 + 2] cycloaddition due to the presence of two electron-withdrawing groups on the enynophile, although the aromatic character of the cyclobutenedione ring may make it less reactive than a cyclobutenone.

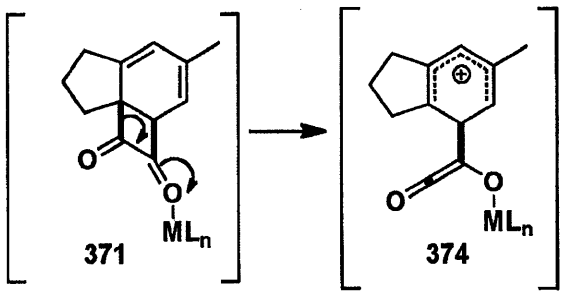
Table 12. [4 + 4] Annulation Reactions of Cyclobutenedione 276



Entry	Conditions	Result (^{1}H NMR)	Yield of 372	Yield of 373
1	$BF_3{\cdot}OEt_2$ (1 equiv) 0 °C to rt, 19 h	Polymer	-	-
2	Me_2AlCl (1 equiv) -78 °C to rt, 5 h	Polymer	-	-
3	$TiCl_4$ (2 equiv) -78 °C to rt, 1 h	Polymer	-	-
4	$ZnCl_2$ (1.4 equiv) Et_2O, -78 °C to rt, 20 h	Decomposition	-	-
5	MsOH (1 equiv) -78 °C to rt, 20 h	Complex mixture	-	-
6	$AgClO_4$ (1 equiv) -78 °C to rt, 21 h	No reaction	-	-
7	$PdCl_2(PPh_3)_2$ (15 mol %) 0 °C to rt, 21 h	No reaction	-	-
8	$MgBr_2{\cdot}OEt_2$ (1.5 equiv) benzene, rt, 6 h	43:57 **276**:**373**	-	not determined
9	$Mg(ClO_4)_2$ (1.3 equiv) THF, rt, 50 h	No reaction	-	-
10	$Mg(OTf)_2$ (1 equiv) benzene, rt, 48 h	No reaction	-	-

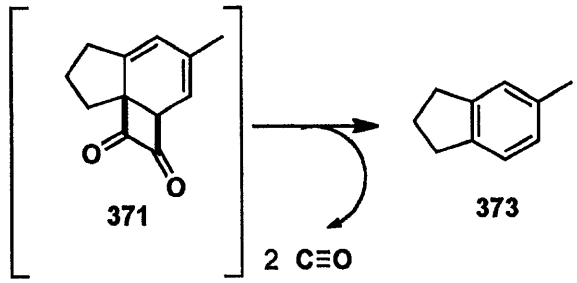
We anticipated that the electrocyclic ring opening of **371** would be very fast due to the increased strain of the cyclobutanedione ring relative to a cyclobutanone ring, and fragmentation of **371** was expected to be less likely because this process would form a high-energy ketene (eq

83). If we succeeded in preparing cyclooctatriene-1,2-dione product **372**, this would be the first example of isolation of this type of pseudo-aromatic ring system.[130]



(83)

Unfortunately, treatment of cyclobutenedione **276** with Lewis acids resulted in formation of oligomeric or polymeric material (Table 12, entries 1-4). The only case where an identifiable product was obtained was when magnesium bromide was used as the promoter. This resulted in formation of indan **373**[69] (Table 12, entry 8). None of the desired cycloctatriene-1,2-dione **372** was observed in any of the reactions. The indan is presumably formed via a fragmentation reaction of **371**, where two molecules of carbon monoxide are lost (eq 84).



(84)

Rubin and Harel have shown that thermolysis of cyclobutanediones leads to evolution of carbon monoxide and formation of alkenes in a variety of systems.[131] Most of the examples in their report required temperatures of 110-150 °C; however, when the product of thermolysis is an aromatic ring instead of an alkene, the thermolysis occurs at lower temperature. When naphthalene is the product, the thermolysis occurs at 35 °C with a half-life of 2.4 hours.

---

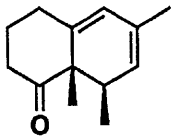
[130] Jakins, C.; Lewars, E. *J. Mol. Struct.* **2000**, *531*, 181-192.
[131] Rubin, M. B.; Harel, Y. *Tetrahedron Lett.* **1987**, *44*, 5373-5376.

This suggests that indan **373** could form from diene **371** at room temperature. The role of the Lewis acid in this fragmentation was not determined. The formation of **373** indicates that the desired [4 + 4] annulation is occurring, but based on the instability of diene **371**, it is not likely that the desired product **372** could be isolated from this reaction under any conditions.

Cyclobutenyl Ketone Substrates

The [4 + 4] annulation reactions of cyclobutenyl ketone substrates were not expected to suffer from the fragmentation problems outlined above for the cyclobutenone and cyclobutenedione substrates. The first cyclobutenyl ketone we investigated was **312** (Table 13). We chose the four-atom tether substrate for our initial investigations because the diene intermediate **378** expected to be produced in the [4 + 4] annulation would be structurally similar to known compound **219** (Figure 7).[69]

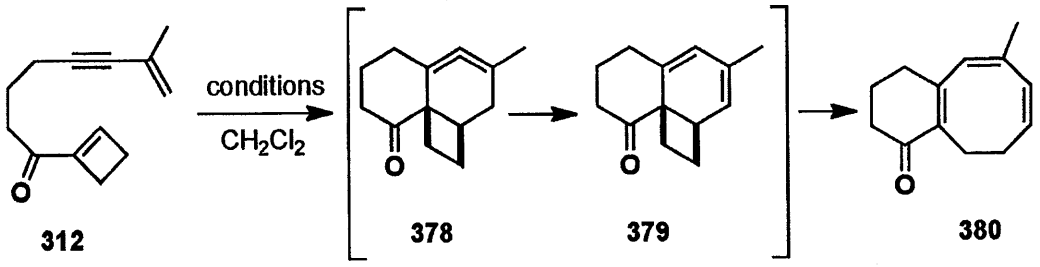
Figure 7



219

Cyclobutenyl ketone **312** is prone to polymerization. Treatment with $BF_3{\cdot}OEt_2$ at low temperature in the presence of BHT afforded a trace amount of the desired cyclooctatriene **380** (Table 13, entry 2). Refluxing a dichloromethane solution of **312** with trifluoroacetic acid for over 2 days gave ca. 7% conversion to cyclooctatriene **380** (Table 13, entry 4). The purely thermal reaction was also attempted (Table 13, entry 7). Cyclobutenyl ketone **312** was unreactive at 110 °C, and at 130 °C the starting material was consumed to give a complex mixture of diene **379**, cyclooctatriene **380**, and unidentified byproducts.

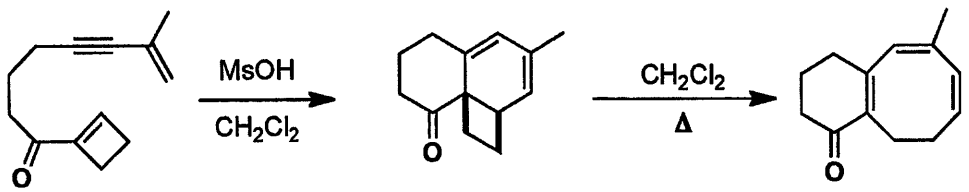
Table 13. [4 + 4] Screening Reactions of Cyclobutenyl Ketone 312



Entry	Conditions	Result (^{1}H NMR)	Yield
1	$BF_3{\cdot}OEt_2$ (1.1 equiv) -78 °C to 0 °C, 2 h	Polymer	-
2	$BF_3{\cdot}OEt_2$ (1.5 equiv) BHT (1 equiv) -55 °C, 2 h	Trace **380**, mostly polymer	-
3	$AlCl_3$ (1.4 equiv) -78 °C, 4.5 h; 0 °C, 10 min	Polymer	-
4	TFA (1.5 equiv) reflux, 50 h	93:7 **312:380**	not determined
5	MsOH (2.5 equiv) 0 °C, 15 min	Dimeric byproduct	-
6	MsOH (1 equiv) 0 °C, 20 min; rt, 3 h	Mixture of products Major product is **379**	-
7	BHT (1 equiv) toluene 110 °C, 1 h; 130 °C, 12 h	Complex mixture trace **379** and **380**	not determined

Methanesulfonic acid was expected to be a good promoter for this reaction, based on the previous work in our laboratory by Dr. Roberto Fernandez and Alexandra Gould on intramolecular [4 + 2] cycloadditions of conjugated enynes with acyclic enones.[69] An excess of MsOH was first tried at 0 °C, following the conditions used to prepare **219** (Figure 7 on the previous page). This resulted in formation of an unidentified "dimeric" byproduct (Table 13, entry 5). Next we tried stoichiometric MsOH and found that this gave a mixture of products, with diene **379** as the major component (Table 13, entry 6). With this encouraging result, we decided to screen conditions using MsOH to give clean formation of diene **379** (Table 14). We expected to be able to convert **379** to **380** in a subsequent step by heating under neutral conditions.

Table 14. [4 + 4] Annulation Reactions of Cyclobutenyl Ketone 312



312 **379** **380**

Entry	MsOH (equiv)	Time, Temp	Result (^{1}H NMR)	Δ	Isolated Yield of 380
1	1.1	0 °C, 5 min	Mostly **379** Some **312 remains**	–	-
2	1.1	0 °C, 10 min	Mostly **379** all of **312** consumed	–	-
3	1.0	-50 °C to -10 °C 3 h	Mostly **379** all of **312** consumed	reflux[1] 1 h	Not determined (clean conversion to **380**)
4	1.0	-78 °C to -40 °C 1 h	Clean formation of **379**	40 °C, 1 h; 70 °C, 2 h	62%
5	1.0	-78 °C, 1 h	Clean formation of **379**, low mass balance[2]	80 °C, 8 h	42%
6	1.0	-78 °C, 4 h	Clean formation of **379** (by TLC analysis) *Not concentrated*	70 °C, 5 h	69%

[1] This electrocyclic ring-opening was carried out in $CDCl_3$ and monitored by ^{1}H NMR. [2] Some of diene **379** was lost to evaporation upon concentration at 20 mmHg.

Treatment of **312** with a slight excess of MsOH at 0 °C resulted in complete consumption of starting material after 10 min (Table 14, entry 2). Following the progress of this reaction by TLC was challenging due to the similar polarities of the starting material and diene **379**, but after extensive experimentation we found that eluting the TLC plates twice with 5% ethyl acetate/hexanes separated the spots enough that they could be distinguished by the slightly different shades of blue that appear upon visualization with *p*-anisaldehyde stain.

Due to the rapid reaction observed at 0 °C, the reaction was next attempted at -50 °C (Table 14, entry 3). These conditions gave efficient formation of diene **379**. A solution of **379** in

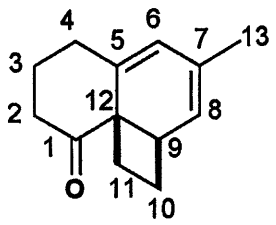
$CDCl_3$ was heated to affect the electrocyclic ring opening, giving clean conversion to the desired cyclooctatriene **380**.

In the next attempt, the cycloaddition was run at -78 to -40 °C in order to minimize byproduct formation (Table 14, entry 4). Diene **379** was isolated for full characterization, and then diluted in CH_2Cl_2 and heated. The electrocyclic ring opening does not occur at an appreciable rate at 40 °C. We found that heating at 70 °C (in a threaded Pyrex tube) was necessary to produce the cyclooctatriene product **380**, in this case in 62% overall yield from enyne **312**.

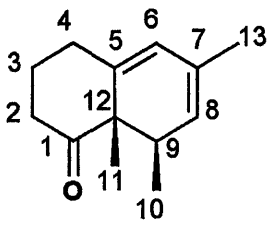
In order to maximize the yield, the cycloaddition was repeated without concentration of the intermediate diene (Table 14, entry 6). In this case, after all of **312** had been converted to **379**, the reaction was quenched with aqueous sodium bicarbonate. The organic layer was separated, dried over sodium sulfate, and filtered into a threaded Pyrex tube. After degassing the solution with argon, it was heated at 70 °C for 5 h. This run gave the desired cyclooctatriene **380** in 69% yield.

The structure assignments of diene **379** and cyclooctatriene **380** were made based on comparison of the ^1H NMR and ^{13}C NMR spectra of these compounds to the spectral data for the most similar known compounds. For diene **379**, the comparison was made to diene **219**[69] (Table 15). Diene **379** exhibits an IR stretch at 1707 cm^{-1}, consistent with a non-conjugated ketone; diene **219** exhibits an IR stretch at 1700 cm^{-1} for the analogous carbonyl. The diagnostic proton resonances are the alkenyl protons, at 6.07 and 5.68 ppm. These resonances are consistent with the corresponding resonances of diene **219**. The methine proton H-9 appears in the ^1H NMR spectrum as a quartet at 3.43 ppm. The ^{13}C resonances of diene **379** are also very close to those of diene **219**, with the only variation being between the methylenes C-10 and C-11 in **379** compared to the methyl groups C-10 and C-11 in **219**. As expected, the methylene carbons of the cyclobutane ring of **379** are further downfield than the methyl carbons of diene **219**.

Table 15. ^{1}H and ^{13}C NMR Assignments for 379 and 219



379



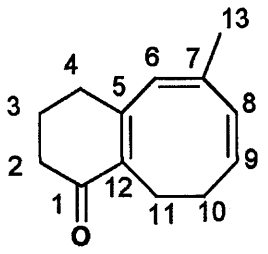
219

Atom #	^{1}H NMR[1] δ (multiplicity, *J* (Hz))	^{13}C NMR[2] δ	Atom #	^{1}H NMR[3] δ (multiplicity, *J* (Hz))	^{13}C NMR[3] δ
1	-	212.9	1	-	214.9
2	2.50-2.60 (m)	35.1	2	2.37-2.54 (m)	37.0
3	1.82-1.88 (m)	22.4	3	1.88-2.07 (m)	25.3
4	2.30-2.38 (m)	34.1	4	1.88-2.07 (m) 2.37-2.54 (m)	37.0
5	-	138.7	5	-	143.5
6	6.07 (s)	120.9	6	5.80 (s)	120.1
7	-	122.7	7	-	120.0
8	5.68 (dd, 6.9, 3.8)	134.4	8	5.50 (t, 4.3)	134.8
9	3.43 (q, 8.2)	33.1	9	2.59-2.67 (m)	33.0
10	2.14-2.28 (m)	24.5	10	0.95 (d, 6.4)	16.5
11	2.14-2.28 (m)	29.4	11	1.10 (s)	12.5
12	-	50.6	12	-	48.9
13	1.79 (s)	21.4	13	1.72 (s)	22.8

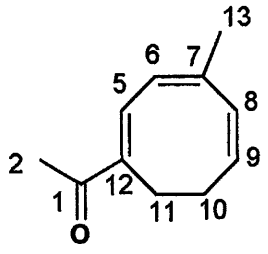
[1] 400 MHz, $CDCl_3$. [2]100 MHz, $CDCl_3$. [3]Gould, A. E. Ph. D. Thesis, Massachusetts Institute of Technology, June 1996. (300 MHz, $CDCl_3$, 75 MHz, $CDCl_3$)

For cyclooctatriene **380**, the comparison of spectral data was made to cyclooctatriene **381**[132] (Table 16). The ^{1}H NMR and ^{13}C NMR resonances line up nicely, especially those for the diagnostic alkenyl protons and carbons.

Table 16. ^{1}H and ^{13}C NMR Peak Assignments for 380 and 381



380



381

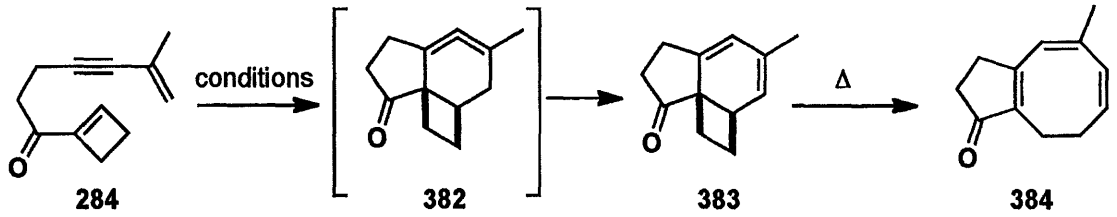
Atom #	^{1}H NMR[1] δ (multiplicity, *J* (Hz))	^{13}C NMR[2] δ	Atom #	^{1}H NMR[3] δ (multiplicity, *J* (Hz))	^{13}C NMR[3] δ
1	-	199.2	1	-	198.9
2	2.54 (t, 6.0)	36.8	2	2.57 (t, 5.0)	25.9
3	1.97 (pent, 5.5)	23.8			
4	2.30 (t, 5.9)	30.6			
5	-	155.8	5	7.05 (d, 5.0)	144.1
6	5.69 (s)	127.6	6	5.72-5.87 (m)	127.8
7	-	138.0	7	-	139.5
8	5.72 (d, 13.3)	136.9	8	5.72-5.87 (m)	138.8
9	5.60 (dt, 13.3, 2.2)	125.4	9	5.66 (br d, 13.0)	121.4
10	2.32-2.38 (m)	38.1	10	2.34 (s)	29.3
11	2.43 (t, 6.6)	26.2	11	2.31-2.43 (m)	25.2
12	-	132.7	12	-	132.9
13	1.95 (d, 1.2)	23.0	13	1.96 (br s)	24.1

[1] 400 MHz, $CDCl_3$. [2] 100 MHz, $CDCl_3$. [3] Tooru, F.; Ohsaka, T.; Inoue, T.; Takeda, T. *Tetrahedron Lett.* **1988**, *29*, 6283-6286. ($CDCl_3$)

[132] Tooru, F.; Ohsaka, T.; Inoue, T.; Takeda, T. *Tetrahedron Lett.* **1988**, *29*, 6283-6286.

This encouraging initial result with a cyclobutenyl ketone substrate inspired us to look at a variety of other cyclobutenyl ketones. We next turned our attention to three-atom tether cyclobutenyl ketone **284**. Unfortunately, this compound proved to be completely unreactive towards methanesulfonic acid, even at room temperature (Table 17).

Table 17. Attempted [4 + 4] Annulation Reactions of Cyclobutenyl Ketone 284



284 **382** **383** **384**

Entry	Conditions	Time, Temp	Result (TLC)	Δ	Result
1	MsOH (1.4 equiv) CH_2Cl_2	-78 °C, 2.5 h; -50 °C, 1 h; -30 °C, 10 min; 0 °C, 15 min	No reaction	–	-
2	MsOH (1 equiv) CH_2Cl_2	rt, 1 h; 40 °C, 18 h	No reaction at rt Decomposition at reflux	–	-
3	BHT (1 equiv) toluene	110 °C, 1 h; 150 °C, 4 h	No reaction at 110 °C 70:30[1] ratio of 2 compounds after 150 °C, 4 h	$CDCl_3$ 60 °C, 20 h; 150 °C, 1.5 h	No change upon heating

[1] Ratio determined by ^1H NMR analysis

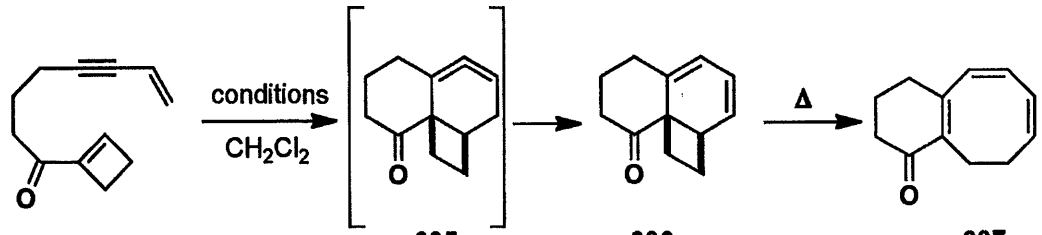
When the annulation reaction was attempted thermally, cyclobutenyl ketone **284** was consumed at 150 °C within 4 h to form two new compounds (Table 17, entry 3). The spectral data of both new compounds is inconsistent with the desired diene **383** and the desired cyclooctatriene **384**. When this mixture of unidentified compounds was heated, no new products were observed and the product ratio did not change. The two products could not be separated for full characterization.

The low reactivity of **284** towards MsOH may be attributed to the increased strain of the transition state to form cyclic allene intermediate **382** relative to the transition state for four-atom tether cyclic allene **378**. There is a high barrier to accessing the reactive conformation of **284** due to the geometric constraints introduced by the sp^2 carbon in the tether, so this annulation cannot be carried out at room temperature or below. When heating was employed, decomposition was

observed in the presence of protic acid and byproduct formation was observed in the absence of acid.

Due to the low reactivity of three-atom tether substrate **284**, we decided to investigate the effect of the enyne substituents on the annulation reaction using four-atom tether cyclobutenyl ketone substrates. We expected that the methyl group on the enyne of cyclobutenyl ketone **312** should not have a large effect on the annulation reaction. However, cyclobutenyl ketone **313**, with an unsubstituted enyne, was found to be completely unreactive in the presence of MsOH at -78 °C (Table 18).

Table 18. [4 + 4] Annulation Reactions of Cyclobutenyl Ketone 313



313 385 386 387

Entry	MsOH (equiv)	Time, Temp	Result (^{1}H NMR)	Δ	Yield 386	Yield 387
1	1.0	-78 °C, 2 h	No Reaction	–	-	-
2	1.5	-78 °C, 2.5 h	No Reaction	–	-	-
3	1.0	-78 °C, 20 min; -50 °C, 20 min; -40 °C, 50 min	40:60 **313**:**386**	–	-	-
4	1.0	-40 °C, 4 h	Clean formation of **386**	$ClCH_2CH_2Cl$ 150 °C, 18 h	30%	25%[1]

[1] This compound was obtained in ca. 90% purity after column chromatography.

This cyclobutenyl ketone was found to undergo the desired [4 + 2] cycloaddition with MsOH at -40 °C (Table 18, entry 3). The progress of the reaction was very hard to follow by TLC due to co-elution of the starting material and intermediate **386**. When diene **386** was heated at 70 °C, the expected electrocyclic ring opening reaction did not occur. The temperature had to be raised to 100 °C for any reaction to be observed by TLC analysis, and even at 150 °C (after changing the solvent to 1,2-dichloroethane), the electrocyclic ring opening was found to be very

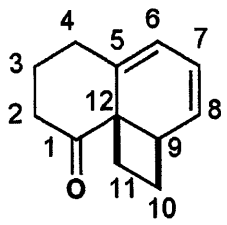
sluggish. In the best run to date, the desired cyclooctatriene **387** was obtained in 25% yield, along with 30% yield of diene **386** (ca. 90% purity) (Table 18, entry 4). The combined yield of **387** and **386** of 55% suggests that the annulation reaction could proceed to give ca. 55% yield of cyclooctatriene **387** if the electrocyclic ring opening conditions were improved. Since this step requires high temperatures and long reaction times, perhaps the efficiency of the electrocyclic reaction might be increased by using an aromatic solvent and BHT as a radical inhibitor.

The structures of **386** and **387** were assigned based on their ^{1}H NMR chemical shifts and coupling constants, in comparison to the previously prepared compounds **387** and **380** (Tables 19-20). As only a small amount of cyclooctatriene **387** was produced, we were not able to get a satisfactory ^{13}C NMR spectrum, but from the ^{1}H NMR data an unambiguous structure assignment was obtained.

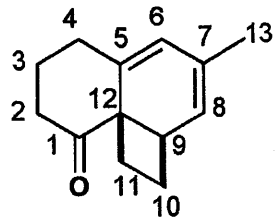
One potential explanation for the low observed rate of the electrocyclic ring opening would be the presence of an equilibrium between diene **386** and cyclooctatriene **387**. In order to investigate this possibility, pure cyclooctatriene **387** was heated in 1,2-dichloroethane at 130 °C for 21 h. TLC and ^{1}H NMR analysis revealed slight decomposition. None of diene **386** was observed. When a sample of diene **386** was heated in 1,2-dichloroethane at 130 °C for 21 h, slow conversion to cyclooctatriene **387** was observed. These experiments suggest that equilibration is not the issue; the electrocyclic ring opening is just slow.

Work on this case is continuing. We are interested in optimizing the electrocyclic ring opening step of the annulation reaction in order to obtain a moderate to good yield of the cyclooctatriene product.

Table 19. ^{1}H and ^{13}C NMR Assignments for 386 and 379



386

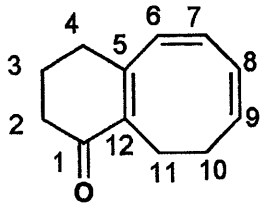


379

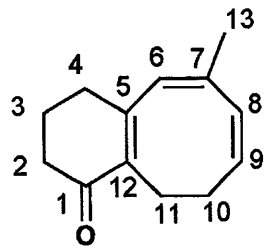
Atom #	^{1}H NMR[1] δ (multiplicity, *J* (Hz))	^{13}C NMR[2] δ	Atom #	^{1}H NMR[1] δ (multiplicity, *J* (Hz))	^{13}C NMR[2] δ
1	-	212.3	1	-	212.9
2	2.50-2.62 (m)	34.9	2	2.50-2.60 (m)	35.1
3	1.77-1.87 (m)	21.3	3	1.82-1.88 (m)	22.4
4	2.33-2.50 (m)	34.3	4	2.30-2.38 (m)	34.1
5	-	138.0	5	-	138.7
6	5.65-5.75 (m)	123.3	6	6.07 (s)	120.9
7	6.30 (dd, 10.0, 2.6)	125.8	7	-	122.7
8	5.79 (dd, 6.6, 3.7)	127.7	8	5.68 (dd, 6.9, 3.8)	134.4
9	3.44 (q, 8.2)	28.8	9	3.43 (q, 8.2)	33.1
10	1.87-2.09 (m)	22.5	10	2.14-2.28 (m)	24.5
11	2.09-2.33 (m)	28.0	11	2.14-2.28 (m)	29.4
12	-	51.4	12	-	50.6
			13	1.79 (s)	21.4

[1] 400 MHz, $CDCl_3$. [2] 100 MHz, $CDCl_3$.

Table 20. ^{1}H NMR Assignments for 387 and 380



387



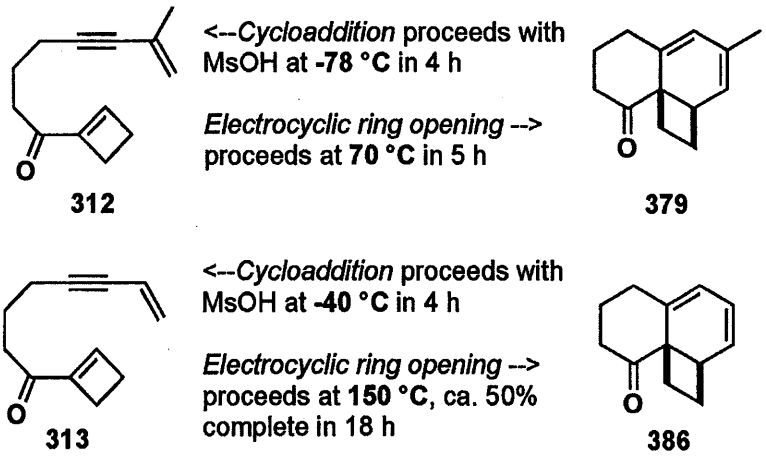
380

Atom #	^{1}H NMR[1] δ (multiplicity, *J* (Hz))	Atom #	^{1}H NMR[1] δ (multiplicity, *J* (Hz))
1	-	1	-
2	2.58 (t, 5.8)	2	2.54 (t, 6.0)
3	2.00 (pent, 6.3)	3	1.97 (pent, 5.5)
4	2.34 (t, 6.0)	4	2.30 (t, 5.9)
5	-	5	-
6	5.79-5.89 (m)	6	5.69 (s)
7	5.79-5.89 (m)	7	-
8	5.96 (dd, 12.2, 5.9)	8	5.72 (d, 13.3)
9	5.68-5.76 (m)	9	5.60 (dt, 13.2, 2.2)
10	2.35-2.46 (m)	10	2.32-2.38 (m)
11	2.45 (t, 6.7)	11	2.43 (t, 6.6)
12	-	12	-
		13	1.95 (d, 1.2)

[1] 400 MHz, $CDCl_3$.

The difference in reactivity between substrates **312** and **313** was surprising (Figure 8). The more substituted enyne **312** is more electron rich than the enyne **313**, so we expected that the [4 + 2] cycloaddition may be faster for substrate **312** than **313**. In the previous work in our lab on intramolecular [4 + 2] cycloadditions of conjugated enynes with alkynes, Alexandra Gould observed that substrates without substitution on the enyne alkene were sluggish relative to the isopropenyl-type substrates.[69] However, we did not expect the cycloaddition of **313** to require reaction at 40 °C higher temperature!

Figure 8



Also surprising was the observation that the electrocyclic ring opening reaction of diene **379** is facile while diene **386** requires forcing conditions for the desired reaction to occur. Recall from the discussion of 3,5,7-cyclooctatriene/bicyclo[4.2.0]-2,4-octadiene equilibria in Chapter 2 of this part of this thesis that substituents on the cyclobutane ring are known to have a large effect on the equilibrium ratio of the two isomers. However, substituents on the diene have not been extensively studied.[82,83,84] We did not expect diene **386** to be so stable. In fact, it is the only bicyclooctadiene intermediate produced in this study that 1s stable to silica gel chromatography.

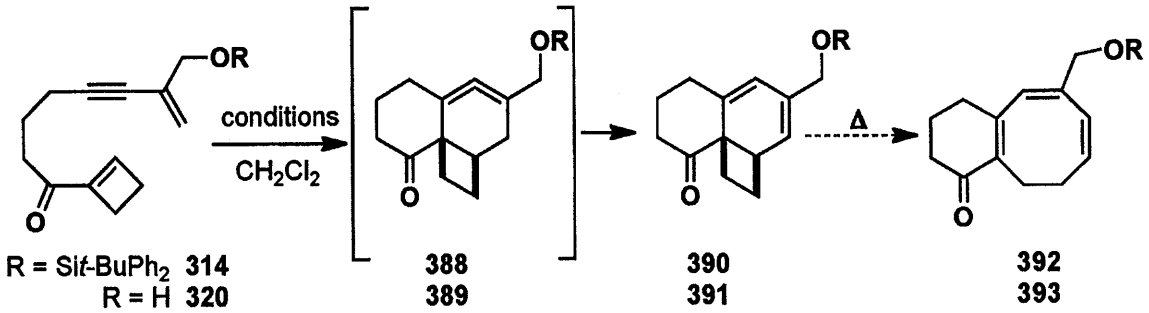
In order to investigate the effect of the enyne substituent further, we next turned to cyclobutenyl ketones **314**[133] and **320**. These substrates have a substituent on the internal alkene carbon of the enyne, so they should behave more like **312** than **313**. Our main concern with **314** and **320** was their stability to strong acid. When **320** was treated with MsOH at low temperature, no reaction was observed (by TLC analysis) and ^{1}H NMR analysis of the crude product indicated

[133] Ketone **314** was prepared in ca. 90% purity. The impurity is *t*-$BuPh_2SiOH$.

slight decomposition of the starting material (Table 21, entry 1). Considering that the starting alcohol was not stable to acid at low temperature, we presumed that at the higher temperature required for the desired [4 + 2] cycloaddition to occur, complete decomposition of the starting material would result, and so we did not attempt further annulations with this substrate.

When cyclobutenyl ketone **314** was treated with MsOH at -78 °C, no reaction was observed (by TLC analysis). Warming to -55 °C resulted in a new spot appearing on the TLC plate, and when the reaction was worked up and the crude product analyzed by ^{1}H NMR we determined that the silyl group had cleaved and the resulting free alcohol had decomposed (Table 21, entry 2).

Table 21. Attempted [4 + 4] Annulation Reactions of Cyclobutenyl Ketones 314 and 320



Entry	R	MsOH (equiv)	Temp, Time	Result (^{1}H NMR)
1	H	1.0	-78 °C, 3 h	Low conversion to unidentified products
2	Si*t*-BuPh$_2$	1.0	-78 °C, 30 min; -55 °C, 3 h	Cleavage of Si*t*-BuPh$_2$, decomposition

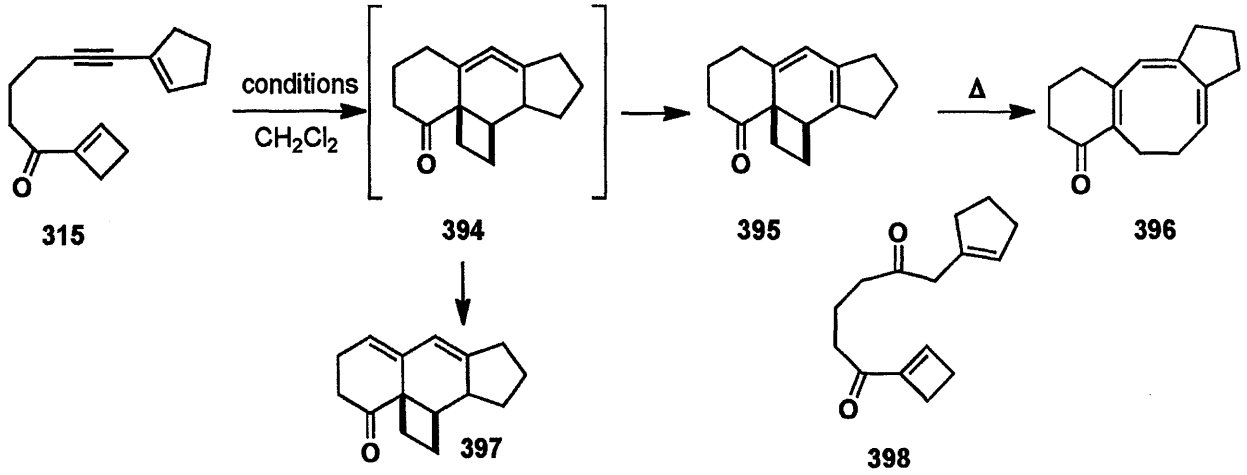
These results suggest that alkyl groups are tolerated at the internal alkene carbon of the enyne, but CH_2OH and CH_2OSiR_3 are not stable to the reaction conditions. Considering that the OH/OR group is in the allylic position, it is not surprising that it was unstable in the presence of strong protic acid. Perhaps a similar substrate with an extra methylene spacer (CH_2CH_2OR) would work better in the [4 + 4] annulation process.

We next turned our attention to [4 + 4] annulation substrates that bear a fused ring on the enyne alkene, with the goal of obtaining tricyclic cyclooctatriene products. Cyclobutenyl ketone **315** was treated with MsOH at low temperature to afford tetracyclic diene **395** (Table 22). This

diene undergoes electrocyclic ring opening to give cyclooctatriene **396** in moderate yield at 70 °C within 2.5-3 h (Table 22, entries 1 and 3).

A variety of parameters were screened in an attempt to improve the yield of this reaction. The amount of methanesulfonic acid was varied from 1-2 equiv, the reaction concentration was tried at 0.05 M and 0.01 M, and the addition of BHT additive was investigated. We found that the [4 + 2] cycloaddition of cyclobutenyl ketone **315** is slow at -78 °C when only 1 equiv of MsOH is used, and in order to have complete consumption of starting material in a reasonable amount of time, 1.5-2 equiv of MsOH are necessary. Presumably the reaction is slow due to increased steric hindrance on the enyne.

Table 22. [4 + 4] Annulation Reactions of Cyclobutenyl Ketone 315



Entry	MsOH (equiv)	Temp, Time	Result (^{1}H NMR)	Δ	Yield of 396
1	1.0 + 1.0	-78 °C, 1 h; -60 °C, 3 h	50:50 **395:397**[1]	CH_2Cl_2 70 °C, 3 h	40%
2	1.0	-78 °C, 4 h	75:20:5 **315:395:397**[1]	-	-
3	1.5	-78 °C, 25 min	50:50 **395:397**[1]	CH_2Cl_2 70 °C, 2.5 h	34%
4	1.15	-78 °C, 1.5 h	50:50 **395:397**	-	-
5[2]	1.3	-78 °C, 3 h	25:25:50 **315:395:397**	-	-
6	2.0	-78 °C, 25 min	10:70:20 **395:397:398**	-	-
7	1.5	BHT (1 equiv) -78 °C, 4 h	17:57:26 **395:397:398**	-	-

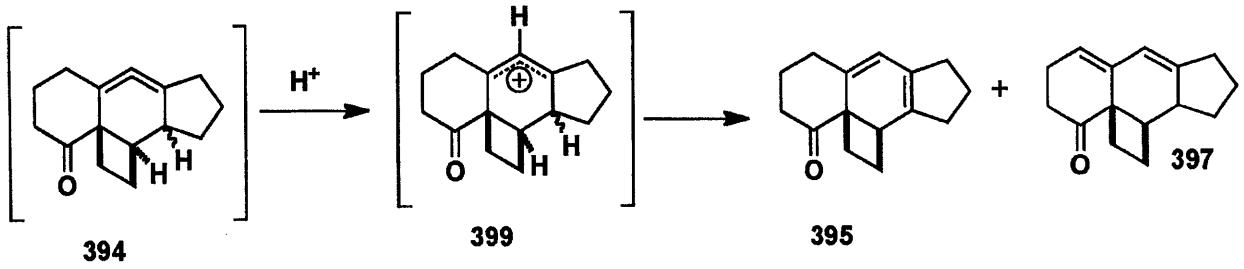
[1] This ratio estimated based on TLC analysis. [2] This reaction was run 0.05 M in CH_2Cl_2. Entries 1-4 and 6-7 were run 0.01 M in CH_2Cl_2.

As shown in Table 22, in this [4 + 2] cycloaddition the desired diene **395** was produced along with isomeric diene **397** and diketone byproduct **398**. The possibility of the cyclic allene intermediate isomerizing to dienes other than 1,3-cyclohexadienes has not been discussed previously in this thesis because this type of reaction was not observed in any of the previously

discussed cycloadditions. The mechanism for formation of diketone **398** will be discussed later in this chapter.

The isomerization of cyclic allene **394** to diene **395** is presumed to proceed through an allylic cation intermediate obtained by protonation of the allene (Scheme 32). We do not know if the [4 + 2] cycloaddition proceeds in the endo or exo fashion. There are two possible stereoisomers of vinylallene **394**, and therefore two possible isomers of allylic cation **399**.

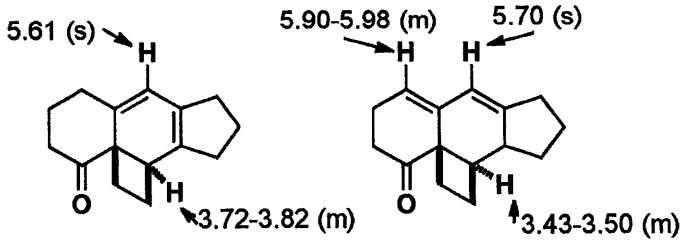
Scheme 32



394 **399** **395**

A mixture of diene isomers was observed in all runs of the cycloaddition. Since diene **395** was not isolated as a single compound, in the structure assignment only the diagnostic alkene and methine protons are shown (Figure 9). Due to the mixture of diene isomers produced, the yield of the desired cyclooctatriene **396** is only moderate and further variation of the reaction conditions is not likely to increase the yield significantly.

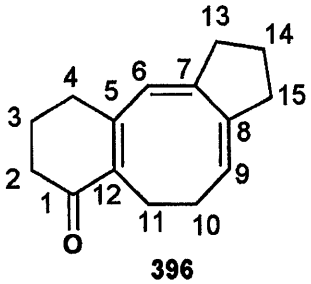
Figure 9. Diagnostic Protons for Dienes 395, 397



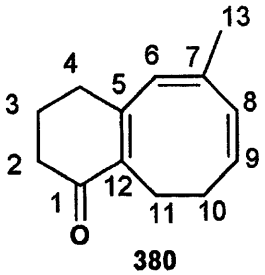
395 **397**

The structure assignment of cyclooctatriene **396** is based on ^{1}H and ^{13}C NMR analysis, with comparison to the previously isolated cyclooctatriene **380** (Table 23).

Table 23. ^{1}H and ^{13}C NMR Assignments for 396 and 380



396



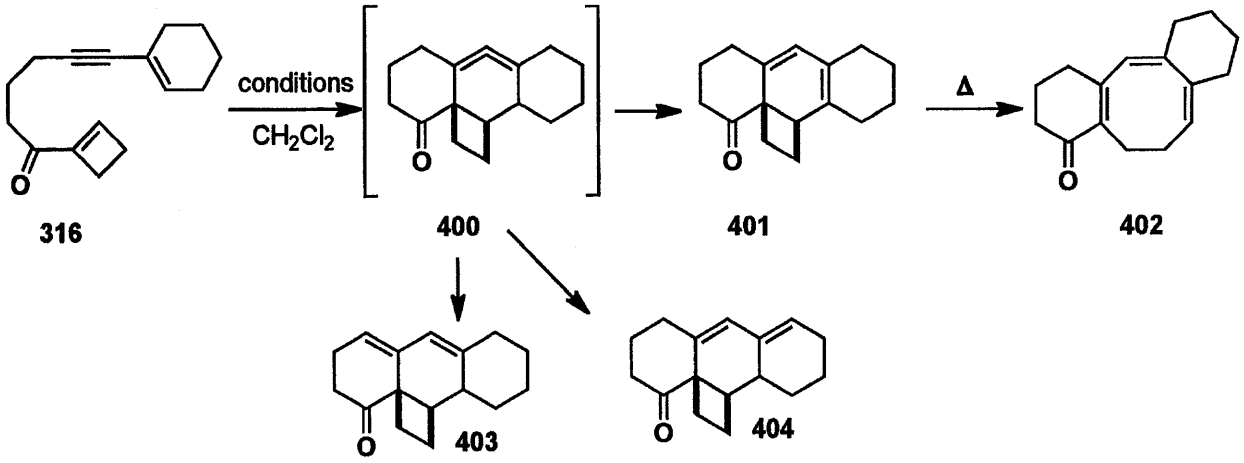
380

Atom #	^{1}H NMR[1] δ (multiplicity, *J* (Hz))	^{13}C NMR[2] δ	Atom #	^{1}H NMR[1] δ (multiplicity, *J* (Hz))	^{13}C NMR[2] δ
1	-	199.1	1	-	199.2
2	2.51-2.57 (m)	37.9	2	2.54 (t, 6.0)	36.8
3	1.98 (pent, 6.3)	23.1	3	1.97 (pent, 5.5)	23.8
4	2.34 (t, 6.0)	31.4	4	2.30 (t, 5.9)	30.6
5	-	154.9	5	-	155.8
6	5.81-5.98 (m)	122.8	6	5.69 (s)	127.6
7	-	145.2	7	-	138.0
8	-	137.2	8	5.72 (d, 13.3)	136.9
9	5.76-5.80 (m)	136.5	9	5.60 (dt, 13.3, 2.2)	125.4
10	2.61 (td, 7.5, 1.6)	32.0	10	2.32-2.38 (m)	38.1
11	2.39-2.46 (m)	23.6	11	2.43 (t, 6.6)	26.2
12	-	129.4	12	-	132.7
13	2.39-2.46 (m)	38.06	13	1.95 (d, 1.2)	23.0
14	1.65 (pent, 7.4)	21.9			
15	2.39-2.46 (m)	38.04			

[1] 400 MHz, $CDCl_3$. [2] 100 MHz, $CDCl_3$.

The [4 + 4] annulation of cylobutenyl ketone **316** was explored next (Table 24). We were interested to see if the cyclohexenyl enyne behaved differently from the cyclopentenyl enyne in the [4 + 2] cycloaddition step.

Table 24. [4 + 4] Annulation Reactions of Cyclobutenyl Ketone 316

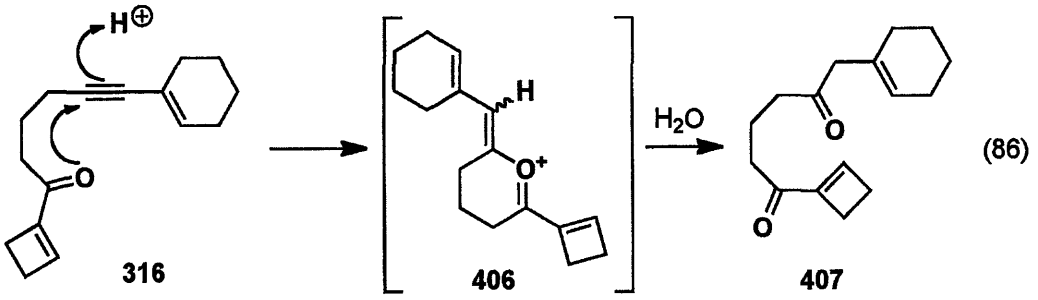


Entry	MsOH (equiv)	Temp, Time	Result (^{1}H NMR)	Δ	Yield of 402
1	1.0	-78 °C, 4 h	11:57:23:8 **316:401:403:404**	-	-
2	1.5	-78 °C, 15 min	6:60:25:8 **316:401:403:404**	-	-
3	1.0	-78 °C, 3 h	-	CH_2Cl_2 70 °C, 14 h	26%
4	1.0	-78 °C, 6 h	-	CH_2Cl_2 85 °C, 8 h	23%

When cyclobutenyl ketone **316** was treated with MsOH at low temperature, the [4 + 2] cycloaddition proceeded to give a mixture of diene products. The desired diene **401** was the main product, but isomeric dienes **403** and **404** were also formed in significant amounts. In addition, as was observed with structurally similar substrate **315**, a diketone byproduct was produced in the [4 + 2] cycloaddition step (eq 86). When the crude diene mixture was heated at 70 °C for 14 h, traces of diene **401** remained and desired cyclooctatriene **402** was isolated in 26% yield (Table 24, entry 3). In another run, the heating step was carried out at 85 °C. The electrocyclic ring opening went to completion in 8 h, but unfortunately the isolated yield of cyclooctatriene **402** was only 23%.

Diketone **407** presumably forms via intermediate **406** that is generated from the cyclization of **316** in the presence of acid as shown in eq 86. This intermediate hydrolyzes in the workup to produce **407**. This type of intramolecular reaction has been observed in the Danheiser

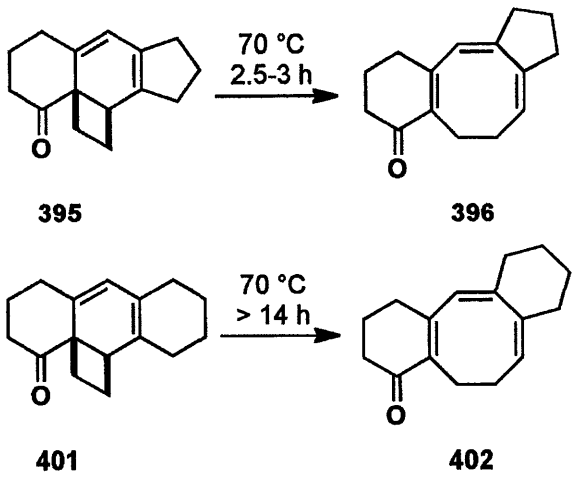
laboratory previously when especially unreactive substrates were attempted in [4 + 2] cycloadditions of conjugated enynes with alkynes.[70]



The results with substrate **316** are similar to the results with substrate **315** discussed previously. The [4 + 2] cycloaddition is slow when only 1 equiv of MsOH is used, and very rapid when the acid is increased to 1.5 equiv.

The cycloaddition reaction produces a mixture of dienes and the yield of the desired product after the heating step was disappointing (23-26%). The main observed difference between the [4 + 4] annulation of cyclobutenyl ketone **315** and cyclobutenyl ketone **316** is in the electrocyclic ring opening step. In the former case the reaction is complete within 2.5-3 h at 70 °C whereas in the latter case the reaction is incomplete after 14 h at 70 °C (Scheme 33).

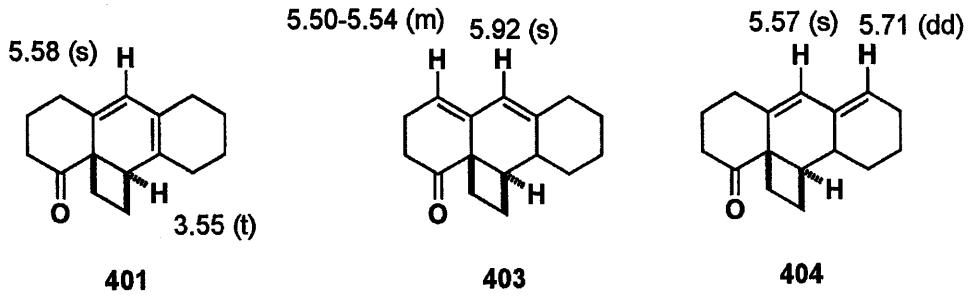
Scheme 33



This difference in reactivity can be attributed to the increase strain of diene **395** compared to diene **401**. However, we did not expect such a large difference in reaction times.

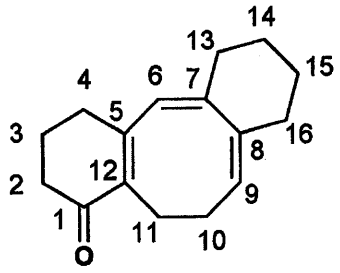
Because diene **401** was not isolated as a pure compound, in the structure assignment only the diagnostic alkene and methine protons are shown (Figure 10). The structural assignment of **402** was made based on ^{1}H and ^{13}C NMR data in comparison to the most similar previously prepared compound, cyclooctatriene **396** (Table 25).

Figure 10. Diagnostic Protons for Dienes 401, 403, and 404

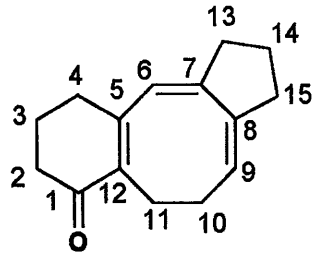


401 **403** **404**

Table 25. ^{1}H and ^{13}C NMR Assignments for 402 and 396



402



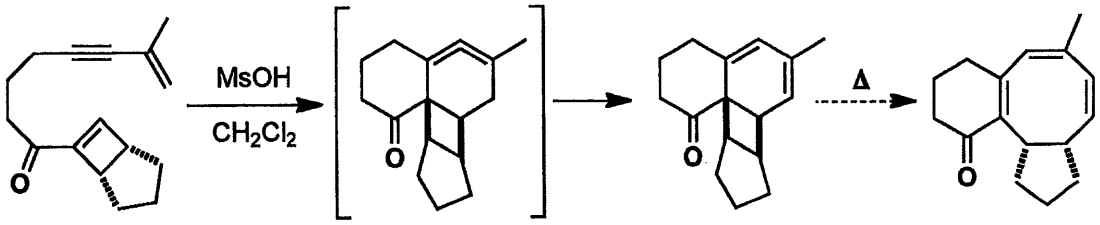
396

Atom #	^{1}H NMR[1] δ (multiplicity, *J* (Hz))	^{13}C NMR[2] δ	Atom #	^{1}H NMR[1] δ (multiplicity, *J* (Hz))	^{13}C NMR[2] δ
1	-	199.2	1	-	199.1
2	2.52 (t, 6.4)	41.6	2	2.51-2.57 (m)	37.9
3	1.95 (pent, 6.4)	28.2	3	1.98 (pent, 6.3)	23.1
4	2.34 (t, 5.9)	28.9	4	2.34 (t, 6.0)	31.4
5	-	155.6	5	-	154.9
6	5.66 (s)	122.5	6	5.81-5.98 (m)	122.8
7	-	145.0	7	-	145.2
8	-	137.0	8	-	137.2
9	5.42 (t, 4.3)	136.2	9	5.76-5.80 (m)	136.5
10	2.20-2.28 (m)	30.4	10	2.61 (td, 7.5, 1.6)	32.0
11	2.41 (t, 6.7)	28.5	11	2.39-2.46 (m)	23.6
12	-	124.0	12	-	129.4
13	2.03-2.11 (m)	38.7	13	2.39-2.46 (m)	38.06
14	1.60-1.74 (m)	23.8	14	1.65 (pent, 7.4)	21.9
15	1.60-1.74 (m)	23.0	15	2.39-2.46 (m)	38.04
16	2.29 (t, 6.0)	38.2			

[1] 400 MHz, $CDCl_3$. [2] 100 MHz, $CDCl_3$.

With our study of variations of the enyne substituents complete, we next turned to variations of the cyclobutene substituents. Cyclobutenyl ketone **345** did not react with 1 equiv of MsOH at -78 °C (Table 25, entry 1).

Table 26. [4 + 4] Annulation Reactions of Cyclobutenyl Ketone 345

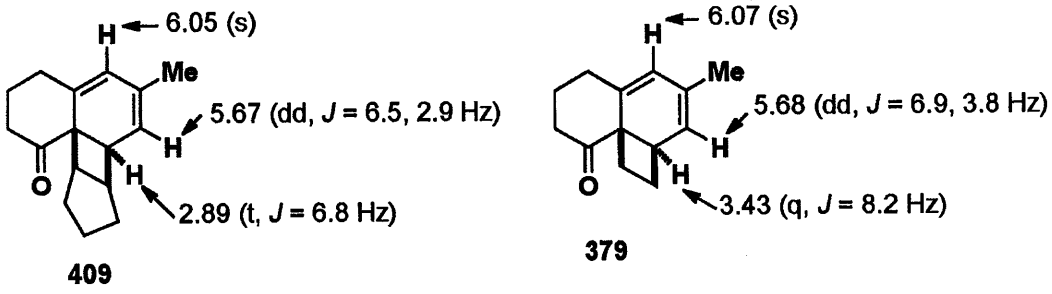


345 408 409 410

Entry	MsOH (equiv)	Temp, Time	Result (^{1}H NMR)	Δ	Result
1	1.0	-78 °C, 2 h	No reaction	-	-
2	2.0	-78 °C, 1.5 h	**409** + 3 byproducts	-	-
3	1.0	-78 °C, 10 min; 0 °C, 1 min	**409** + 3 byproducts	CH_2Cl_2 70 °C, 57 h	No change

When the amount of acid was increased to 2 equiv, the desired [4 + 2] cycloaddition occurred to give a mixture of desired diene **409** and three unidentified byproducts. When this mixture was heated at 70 °C, the product composition did not change, even after heating for 57 h. It appears that the electrocyclic ring opening of **409** to **410** has a high activation barrier. The structure assignment of **409** was made based on comparison of the diagnostic alkenyl and methine protons in the ^{1}H NMR spectrum with previously prepared diene **379** (Figure 11).

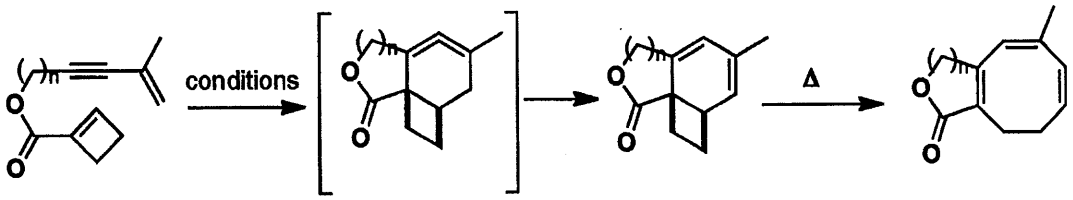
Figure 11. Diagnostic ^{1}H NMR Resonances of Dienes 409 and 378



Cyclobutenyl Esters

[4 + 4] annulation reactions of cyclobutenyl ester substrates were not successful. As shown in Table 27, ester **351** and ester **352** were both unreactive towards methanesulfonic acid, even at 0 °C (Table 27, entries 1 and 5).

Table 27. Attempted [4 + 4] Annulation Reactions of Cyclobutenyl Esters 351 and 352



n = 1 **351**
n = 2 **352**

411
412

413
414

415
416

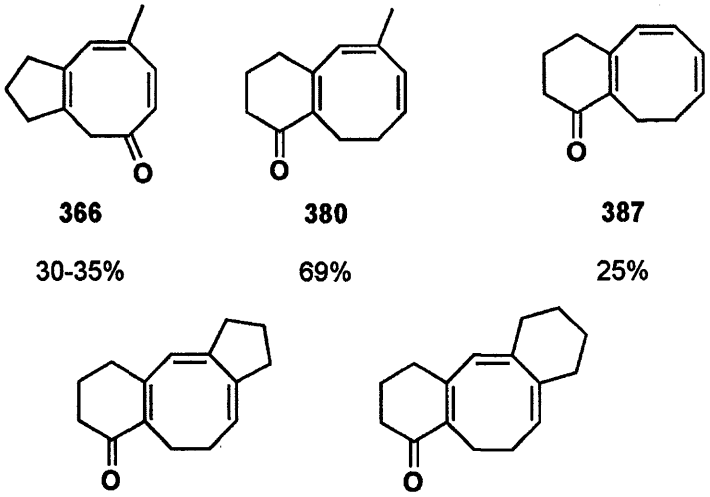
Entry	n	Conditions	Result (^{1}H NMR)	Δ	Result
1	1	MsOH (1.5 equiv) CH_2Cl_2, -78 °C, 1 h; -40 °C to 0 °C, 2 h	No reaction	–	-
2	1	TFA (1 equiv) CH_2Cl_2, 45 °C, 2 h; 70 °C, 16 h	No reaction	–	-
3	1	$BF_3{\cdot}OEt_2$ (3 equiv) CH_2Cl_2, 40 °C, 16 h	No reaction	–	-
4	1	BHT (3 equiv) toluene, 110 °C, 1 h; 150 °C, 3 h	Mixture of 2 byproducts	$CDCl_3$ 60 °C, 20 h; 130 °C, 5 h	No change upon heating
5	2	MsOH (2 equiv) CH_2Cl_2, -78 °C to 0 °C, 3 h	No reaction	-	-
6	2	MsOH (1 equiv) CH_2Cl_2, 40 °C 22 h	Mixture of 2 byproducts	-	-

When ester **351** with a three-atom tether was heated in the presence of BHT, a mixture of two unidentified byproducts was produced (Table 27, entry 4). When ester **352** with a four-atom tether was heated in the presence of MsOH, a mixture of two unidentified byproducts was

formed (Table 27, entry 6). The spectral data of these byproducts is inconsistent with the desired dienes **413** and **414** as well as the desired cyclooctatrienes **415** and **416**. None of the byproducts could be isolated as a single compound for full characterization. The low reactivity of the ester substrates can be attributed to the higher barrier to achieving the reactive conformation relative to the ketone substrates.

Overall, the [4 + 4] annulation process has been used to prepare five previously unknown cyclooctatrienes (Figure 12). The yields for the two-step annulation process range from poor to good. We found that varying the substituents on the enyne alkene has a large effect on the facility and efficiency of [4 + 2] cycloaddition step as well as the isomerization and ring opening steps.

Figure 12. Cyclooctatriene Products Produced in the [4 + 4] Annulation Reaction



366 30-35%

380 69%

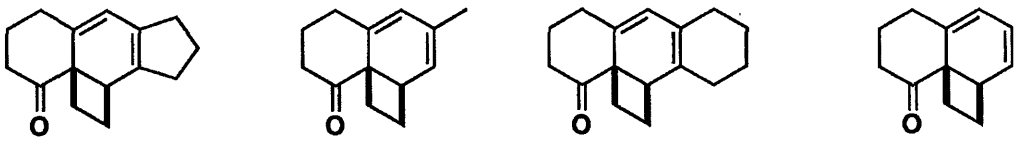
387 25%

396 34-40%

402 23-26%

During the [4 + 4] annulation study, the electrocyclic ring opening reactions of highly substituted bicyclo[4.2.0]-2,4-octadienes were investigated. We found that the substituents on the diene had a major effect on the ring opening reaction. The dienes in Figure 13 are arranged from most reactive in the electrocyclic ring opening to least reactive from left to right.

Figure 13. Bicyclo[4.2.0]-2,4-octadiene Ring Opening Reactions



395 70 °C, 2.5-3 h

379 70 °C, 5 h

401 70 °C, 14 h or 85 °C, 8 h

386 150 °C, 18 h ca. 50% conversion

Part III

Synthesis of Amides in Supercritical Carbon Dioxide

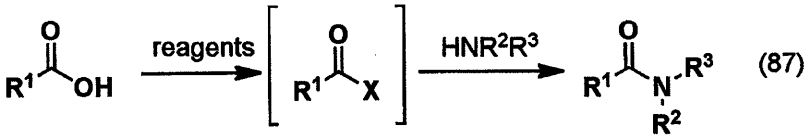
Chapter 1 – Introduction and Background

The Danheiser laboratory and the Tester laboratory in the Chemical Engineering Department at MIT have collaborated for many years, exploring various aspects of organic synthesis in supercritical carbon dioxide. The specific focus of this collaboration was on carbon-nitrogen bond-forming reactions. Part III of this thesis discusses the synthesis of amides in supercritical carbon dioxide.

Amide Bond-Forming Strategies

The amide is a ubiquitous functional group. As well as being the main chemical linkage in proteins, amides are found in many synthetic polymers, biologically active natural products, and pharmaceutically active small molecules. In 1999, it was estimated that amide bonds are present in 25% of known drug molecules.[134] More recently, a survey of 128 syntheses of drug candidate molecules at Pfizer, GSK, and AstraZeneca revealed that 8% of the reactions in the syntheses were acylations of amines.[135]

Acylation of amines is the most common method for amide bond formation.[136] Direct condensations of carboxylic acids with amines (via the ammonium carboxylate salts) requires high temperatures (>160 °C) that are usually not compatible with other functional groups in the molecule. Therefore, activated carboxylic acid derivatives, generated in a separate step or in situ, are needed (eq 87).



417 418 419 (87)

Activated carboxylic acid derivatives include acyl chlorides, mixed anhydrides, and acyl azides. In addition, a variety of coupling agents have been developed that generate activated carboxylic acids in situ. Carbodiimides, phosphonium salts, and uronium salts can be used to

---

[134] Ghose, A. K.; Viswanadhan, V. N.; Wendoloski, J. J. *J. Comb. Chem.* **1999**, *1*, 55-68.
[135] Carey, J. S.; Laffan, D.; Thomson, C.; Williams, M. T. *Org. Biomol. Chem.* **2006**, *4*, 2337-2347.
[136] For a review of amide and peptide bond-forming methods, see: Montalbetti, C. A. G. N.; Falque, V. *Tetrahedron* **2005**, *61*, 10827-10852.

prepare amides from carboxylic acids and amines under mild conditions.[137] Use of these reagents results in the creation of a stoichiometric amount of chemical waste. While much work has been done on optimizing the separation of the byproducts, resulting in many simple and reproducible procedures, the lack of atom economy in most coupling methods is striking.

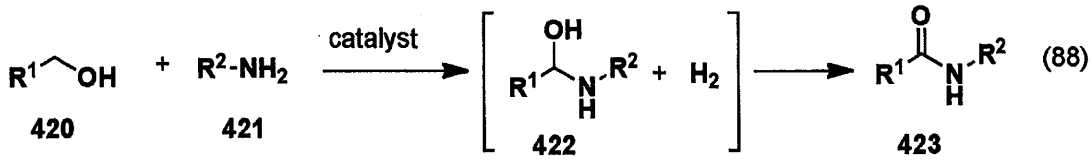
New reagents and conditions for amide bond formation are frequently described in the literature. Improvements to methods using acyl chlorides as the activated carboxylic acid derivative have been recently reported, including the use of a weak inorganic base as an acid scavenger to minimize racemization,[138] as well as the use of samarium iodide as an additive to synthesize amides under neutral conditions.[139] Borate esters have been used stoichiometrically and catalytically to form amides directly from carboxylic acids and amines.[140] Recently disclosed stoichiometric reagents for direct amide bond formation include 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride (DMT-MM),[141] benzenesulfonic anhydride,[142a] and pyridine-3-carboxylic anhydride (3-PCA).[142b] DMT-MM is notable in that this reagent allows for the facile preparation of primary amides from carboxylic acids and aqueous ammonia.

In addition to the borate esters mentioned above, other catalysts for direct amide bond formation have been developed. Clark and coworkers reported a reusable heterogenous silica catalyst that can be utilized to prepare secondary amides in good yields from carboxylic acids and amines in refluxing toluene.[143] Hall and coworkers have described the use of ortho-haloboronic acids as organocatalysts to facilitate direct amide bond formation at room temperature.[144]

An emerging area in amide bond formation is the transition metal catalyzed oxidative amide synthesis from alcohols and amines.[145] Hydrogen gas is the only byproduct in this atom-economical process (eq 88).

---

[137] For a review of coupling reagents, see: Valeur, E.; Bradley, M. *Chem. Soc. Rev.* **2009**, *38*, 606-631.
[138] Zhang, L.; Wang, X.-J.; Wang, J.; Grinberg, N.; Krishnamurthy, D. K.; Senanayake, C. H. *Tetrahedron Lett.* **2009**, *50*, 2964-2966.
[139] Shi, F.; Li, J.; Li, C.; Jia, X. *Tetrahedron Lett.* **2010**, *51*, 6049-6051.
[140] (a) Starkov, P.; Sheppard, T. D. *Org. Biomol. Chem.* **2011**, *9*, 1320-1323. (b) Charville, H.; Jackson, D.; Hodges, G.; Whiting, A. *Chem. Commun.* **2010**, *46*, 1813-1823.
[141] Mizuhara, T.; Hoiki, K.; Yamada, M.; Sasaki, H.; Morisaki, D.; Kunishima, M. *Chem. Lett.* **2008**, *37*, 1190-1191.
[142] (a) Funasaka, S.; Kato, K.; Mukaiyama, T. *Chem Lett.* **2007**, *36*, 1456-1457. (b) Funasaka, S.; Mukaiyama, T. *Chem. Lett.* **2007**, *36*, 658-659.
[143] Comerford, J. W.; Clark, J. H.; Macquarrie, D. J.; Breeden, S. W. *Chem. Commun.* **2009**, *45*, 2562-2564.
[144] Al-Zoubi, R. M.; Marion, O.; Hall, D. G. *Angew. Chem. Int. Ed.* **2008**, *47*, 2876-2879.
[145] Reviewed in: Hong, S. H.; Chen. C. *Org. Biomol. Chem.* **2011**, *9*, 20-26.



The reactions are presumed to proceed via oxidation of the alcohol to the corresponding aldehyde followed by formation of aminal **422**. Two mechanistic options for conversion of aminal **422** into amide **423** have been proposed: oxidation, or dehydration to the imine followed by hydrogenation.

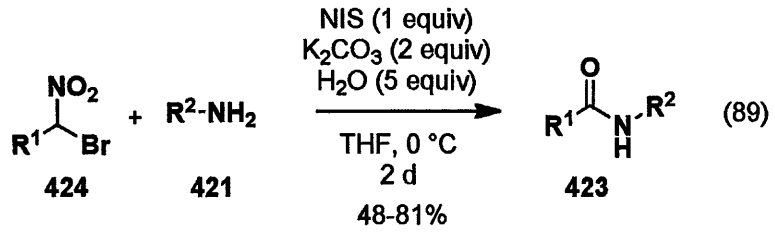
In 2007, Milstein and coworkers reported the first example of this reaction using ruthenium pincer complexes and primary amines in refluxing toluene.[146] Madsen and coworkers have shown that ruthenium *N*-heterocyclic carbene complexes can be used to prepare secondary amides from unhindered primary alcohols and amines.[147] These reactions typically require 5 mol% of the catalyst, 5 mol% of a tricycloalkyl phosphine ligand, and 10 mol% of potassium *tert*-butoxide. The reactions are carried out in refluxing toluene. Hong et al. have studied the activity of Ru(II) and Ru(0) complexes in this reaction, and they have developed phosphine-free catalyst systems.[148] In the vast majority of the examples reported, this oxidative amide synthesis is used to prepare secondary amides from primary amines. Limited catalytic activity was observed with secondary amines, less basic aryl amines, and sterically hindered alcohols and amines. In addition to ruthenium catalysts, rhenium[149] and heterogenous silver catalysts[150] have been reported.

Another method for amide synthesis is the insertion of amines into the C-H bond of aldehydes. Chan and coworkers described the use of Ru(II) porphyrin complexes to prepare *N*-tosyl amides from aliphatic and aromatic aldehydes using PhI=NTs as the nitrogen source in 2008.[151a] An improved method using Cu(I) and Cu(II) salts was reported in 2010.[151b]

---

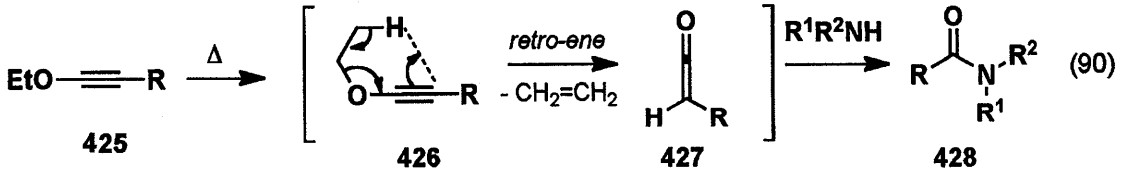
[146] Gunanathan, C.; Ben-David, Y.; Milstein, D. *Science* **2007**, *317*, 790-792.
[147] (a) Dam, J. H.; Osztrovszky, G.; Nordstrom, L. U.; Madsen, R. *Chem. Eur. J.* **2010**, *16*, 6820-6827. (b) Nordstrom, L. U.; Vogt, H.; Madsen, R. *J. Am. Chem. Soc.* **2008**, *130*, 17672-17673.
[148] (a) Muthaiah, S.; Ghosh, S. C.; Jee, J.-E.; Chen, C.; Zhang, J.; Hong, S. H. *J. Org. Chem.* **2010**, *75*, 3002-2006. (b) Ghost, S. C.; Hong, S. H. *Eur. J. Org. Chem.* **2010**, 4266-4270. (c) Ghosh, S. C.; Muthaiah, S.; Zhang, Y.; Xu, X.; Hong, S. H. *Adv. Synth. Catal.* **2009**, *351*, 2643-2649.
[149] Zweifel, T.; Naubron, J. V.; Grutzmacher, H. *Angew. Chem. Int. Ed.* **2009**, *48*, 559-563.
[150] Shimizu, K.; Oshima, K.; Satsuma, A. *Chem. Eur. J.* **2009**, *15*, 9977-9980.
[151] (a) Chang, J. W. W.; Chan, P. W. H. *Angew. Chem. Int. Ed.* **2008**, *47*, 1138-1140. (b) Chang, J. W. W.; Ton, T. M. U.; Tania, S.; Taylor, P. C.; Chan, P. W. H. *Chem. Commun.* **2010**, *46*, 922-924.

The amide bond-forming methods described thus far rely on alcohols, aldehydes, and carboxylic acids as starting materials. In 2010, Johnston and coworkers unveiled a hydrative amide synthesis using α-bromo nitroalkanes and primary amines (eq 89).[152]



NIS, potassium carbonate, and water are the only added reagents and these reactions are carried out at 0 °C instead of the elevated temperatures required for many of the catalytic methods outlined above. This reaction works well for α-branched primary amines. This interesting amide synthesis involves an electrophilic *N*-iodoamine intermediate as opposed to the usual nucleophilic amines. However, this method suffers from poor atom economy, as many of the atoms in the reagents are not present in the product.

For our study of amide synthesis in supercritical carbon dioxide, we chose an atom-economical acylation method, namely the use of ketenes that are generated in situ from the pyrolysis of alkynyl ethers (eq 90).[153]



Ficini and later Arens were the first to report that alkynyl ethers undergo a retro-ene

---

[152] Shen, B.; Makley, D. M.; Johnston, J. N. *Nature* **2010**, *465*, 1027-1030.

[153] For examples of the trapping of ketene derivatives generated from alkynyl ethers with nucleophiles, see: (a) Funk, R. L.; Abelman, M. M.; Jellison, K. M. *Synlett.* **1989**, 36-37. (b) Valenti, E.; Pericks, M. A.; Serratosa, F.; Maii, D. *J. Chem. Res. (S).* **1990**, 118. (c) Valenti, E.; Pericks, M. A.; Serratosa, F. *J. Org. Chem.* **1990**, *55*, 395-397. (d) Magriotis, P. A.; Vourloumis, D.; Scott, M. E.; Tarli, A. *Tetrahedron Lett.* **1993**, *34*, 2071-2074. (e) Liang, L.; Ramseshan, M.; Magee, D. I. *Tetrahedron. Lett.* **1993**, *49*, 2159-2168. (f) MaGee, D. I.; Ramaseshan, M. *Synlett.* **1994**, 743-744. (g) MaGee, D. I.; Ramaseshan, M.; Leach, J. D. *Can. J. Chem.* **1995**, *73*, 2111-2118.

reaction to give ketenes that can be trapped by various nucleophiles.[154] Ethoxy alkynyl ethers undergo the retro-ene reaction at ca. 120 °C and branched alkynyl ethers undergo the reaction at lower temperatures. For example, *t*-butoxy alkynyl ethers react to give ketenes in refluxing chloroform.[153c] The pyrolysis of alkynyl ethers in the presence of amines to generate amides has been applied to lactam synthesis by MaGee.[153f,g]

Overall, this method of amide bond formation is atom-economical (with ethylene as the only byproduct in the case of ethoxy alkynyl ethers) and simple to carry out, with no additional reagents or catalysts besides the alkynyl ether and amine. As part of the Danheiser laboratory's research on methods for environmentally benign organic synthesis, we were interested in preparing amides from alkynyl ethers using supercritical carbon dioxide as the solvent.

Supercritical Carbon Dioxide as a Reaction Medium

Solvents are used in most organic chemical reactions to aid in heat and mass transfer as well as to control reaction rates and selectivity by allowing for variation of concentration. Volatile organic solvents have many widely recognized drawbacks, including toxicity, flammability, and the potential for environmental damage upon accidental release or disposal.[155] Due to increased awareness regarding sustainability, synthetic chemists and chemical engineers have begun investigating the use of "alternative" solvents in earnest. In the field of "green chemistry," the development of alternative solvents has been one of the most active areas of research.[156] Water, ionic liquids, fluorous solvent systems, and supercritical carbon dioxide ($scCO_2$)[157] have been studied as replacements for conventional organic solvents.

Carbon dioxide is inexpensive, non-flammable, non-toxic, and readily available. Unlike

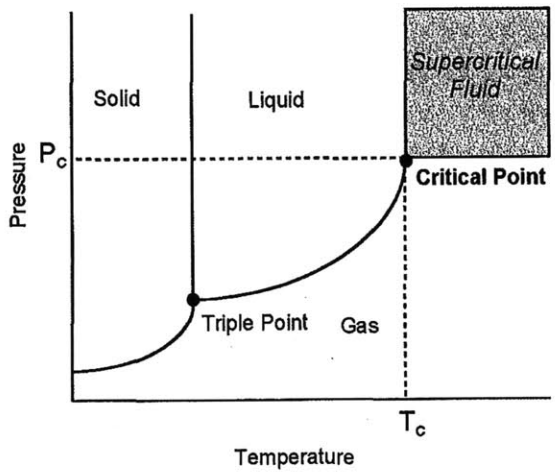
---

[154] (a) Ficini, J. *Bull. Soc. Chim. Fr.* **1954**, 1367-1369. (b) Nieuwenhuis, J.; Arens, J. F. *Rel. Trav. Chim. Pays-Bas* **1958**, *77*, 761-768 (c) van Daalen, J. J.; Kraak, A.; Arens, J. F. *Recl. Trav. Chim. Pays-Bas* **1961**, *80*, 810-818.
[155] For a review of alternative solvents, see: Clark, J. H.; Tavener, S. J. *Org. Proc. Res. Dev.* **2007**, *11*, 149-155.
[156] Anastas, P. T.; Kirchoff, M. M. *Acc. Chem. Res.* **2002**, *35*, 686-694.
[157] Reviews on organic synthesis in supercritical carbon dioxide: (a) Rayner, C. M. *Org. Proc. Res. Dev.* **2007**, *11*, 121-132. (b) Beckman, E. J. *J. Supercrit. Fluids* **2004**, *28*, 121-191. (c) Oakes, R. S.; Clifford, A. A.; Rayner, C. M. *J. Chem. Soc., Perkin Trans. 1* **2001**, 917-941. (d) Tester, J. W.; Danheiser, R. L.; Weinstein, R. D.; Renslo, A.; Taylor, J. D.; Steinfeld, J. I.; In *Green Chemistry Syntheses and Processes;* Anastas, P.T.; Heine, L. G.; Williamson, T. C., Eds.; Washington, D. C.: Oxford University Press, 2000. (e) Jessop, P. G.; Leitner, W. *Chemical Synthesis Using Supercritical Fluids;* Wiley-VCH: Weinheim, 1999. (f) Leitner, W. *Top. Curr. Chem.* **1999**, *206*, 107-132.

conventional hydrocarbon and chlorinated organic solvents, disposal of CO_2 does not require incineration or produce any pollution. Due to the high volatility of CO_2, it may be vented directly from a reaction vessel into the atmosphere and any solid or liquid contaminants will be left behind. Water is often touted as a "green" solvent; however, contaminated water from reactions run in aqueous solutions often needs to be treated before it can be released into the environment.

Supercritical fluids are attractive solvents for organic synthesis due to their "tunability." Supercritical fluids have characteristics intermediate between liquids and gases. Small changes in temperature and pressure near the critical point can result in large changes in density, viscosity, and diffusivity.[158] In comparison to other solvents such as water or hexane, the supercritical state of CO_2 can be achieved at a relatively low temperature and pressure (T_c = 31.1 °C, P_c = 73.8 bar) (Figure 14).

Figure 14



Fluid	T_c (°C)	P_c (bar)
CHF_3	26	49
CO_2	31	74
NH_3	133	112
hexane	234	30
H_2O	374	220

The tunability of $scCO_2$ could allow for selective solvation of compounds. This may permit development of environmentally friendly post-reaction purification protocols. In general, $scCO_2$ is a good solvent for relatively non-polar compounds as well as highly-fluorinated compounds. However, this does not constrain its use as a solvent because the addition of a small amount of co-solvent such as methanol or toluene can adjust the polarity enough to solubilize the reactants and products in a typical organic reaction. In the case of catalytic reactions in $scCO_2$,

[158] For a discussion on the properties of supercritical fluids, see: Clifford, A. A. *Fundamentals of Supercritical Fluids;* Oxford University Press: Oxford, 1998.

the catalyst and ligand structure can be modified to enhance the solubility of the reactants.[159]

Industrial processes[160] using $scCO_2$ include caffeine extraction and fluoropolymer synthesis. In addition, $scCO_2$ has found use in commercial dry cleaning to a limited extent. In synthetic chemistry, a wide variety of reactions have been carried out in $scCO_2$, including catalytic hydrogenation,[161] oxidation reactions,[162,163] cycloadditions,[164,165] enzyme-catalyzed reactions,[166] olefin-metathesis,[167] hydroformylation reactions,[168] and palladium-catalyzed couplings.[169]

In addition to the environmentally benign nature of synthetic chemistry in $scCO_2$, in some cases using this replacement solvent results in improvements in conversion, selectivity, and reaction rates in comparison to conventional reaction media. In particular, the gas-like nature of $scCO_2$ permits complete miscibility with H_2, O_2, and CO, whereas in conventional solvents the

---

[159] For a discussion of $scCO_2$ in organometallic chemistry, see: Leitner, W. *Acc. Chem. Res.* **2002**, *35*, 746-756.

[160] Licence, P.; Ke, J.; Sokolova, M.; Ross, S. K.; Poliakoff, M. *Green Chem.* **2003**, *5*, 99-104.

[161] For examples, see: (a) Chatterjee, M.; Sato, M.; Kawanami, H.; Yokoyama, T.; Suzuki, T.; Ishizaka, T. *Adv. Synth. Catal.* **2010**, *352*, 2394-2398. (b) Hitzler, M. G.; Smail, F. R.; Ross, S. K.; Poliakoff, M. *Org. Process. Res. Dev.* **1998**, *2*, 137-146. (c) Burk, M. J.; Feng, S.; Gross, M. F.; Tumas, W. *J. Am. Chem. Soc.* **1995**, *117*, 8277-8278. (d) Minder, B.; Mallat, T.; Pickel, K. H.; Steiner, K.; Baiker, A. *Catal. Lett.* **1995**, *34*, 1-9. (e) Jessop, P. G.; Ikariya, T.; Noyori, R. *Nature* **1994**, *368*, 231-233.

[162] For a review, see: Campestrini, S.; Tonellato, U. *Curr. Org. Chem.* **2005**, *9*, 31-47.

[163] For recent examples, see: (a) Mello, R.; Olmos, A.; Alcalde-Aragones, A.; Diaz-Rodriguez, A.; Gonzalez-Nunez, M. E.; Asensio, G. *Eur. J. Org. Chem.* **2010**, 6200-6206. (b) Herbert, M.; Montilla, F.; Galindo, A. *Dalton Trans.* **2010**, *39*, 900-907. (c) Mello, R.; Olmos, A.; Parra-Carbonell, J.; Gonzalez-Nunez, M. E.; Asensio, G. *Green Chem.* **2009**, *11*, 994-999.

[164] For examples of Diels Alder reactions in $scCO_2$, see: (a) Renslo, A. R.; Weinstein, R. D.; Tester, J. W.; Danheiser, R. L. *J. Org. Chem.* **1997**, *62*, 4530-4533. (b) Weinstein, R. D.; Renslo, A. R.; Danheiser, R. L.; Harris, J. G.; Tester, J. W. *J. Phys. Chem.* **1996**, *100*, 12337-12341. (c) Weinstein, R. D.; Renslo, A. R.; Danheiser, R. L.; Tester, J. W. *J. Phys. Chem. B*, **1999**, *103*, 2878-2887. (d) Clifford, A. A.; Pople, K.; Gaskill, W. J.; Bartle, K. D.; Rayner, C. M. *Chem. Commun.* **1997**, 595-596. (e) Clifford, A. A.; Pople, K.; Gaskill, W. J.; Bartle, K. D.; Rayner, C. M. *J. Chem. Soc., Faraday Trans.* **1998**, *94*, 1451-1456. (f) Oakes, R. S.; Heppenstall, T. J.; Shezad, N.; Clifford, A. A.; Rayner, C. M. *Chem. Commun.* **1999**, 1459-1460. (g) Chapuis, C.; Kucharska, A.; Rzepecki, P; Jurczak, J. *Helv. Chim. Acta.* **1998**, *81*, 2314-2325. (h) Matsui, J.; Tsuchiya, T.; Odashima, K.; Kobayashi, S. *Chem. Lett.* **2000**, 178-179. (i) Fukuzawa, S.; Metoki, K.; Esumi, S. *Tetrahedron.* **2003**, *59*, 10445-10452.

[165] For examples of dipolar cycloadditions, see: (a) Lee, C. K. Y.; Holmes, A. B.; Al-Duri, B.; Leeke, G. A.; Santos, R. C. D.; Seville, J. P. K. *Chem. Commun.* **2004**, 2622-2623. (b) Totoe, H.; McGowin, A. E.; Turnbull, K. *J. Supercrit. Fluid.* **2000**, *18*, 131-140. (c) McGowin, A. E.; Jackson, L.. Marshall, L. W.; Turnbull, K. *Org. Prep. Proc. Int.* **2001**, *33*, 100-102.

[166] For a review, see: Matsuda, T.; Harada, T.; Nakamura, K. *Green. Chem.* **2004**, *6*, 440-444.

[167] (a) Furstner, A.; Ackermann, L.; Beck, K.; Hori, H.; Koch, D.; Langemann, K.; Liebl, M.; Six, C.; Leitner, W. *J. Am. Chem. Soc.* **2001**, *123*, 9000-9006. (b) Furstner, A.; Koch, D.; Langemann, K.; Leitner, W.; Six, C. *Angew. Chem. Int. Ed.* **1997**, *36*, 2466-2469.

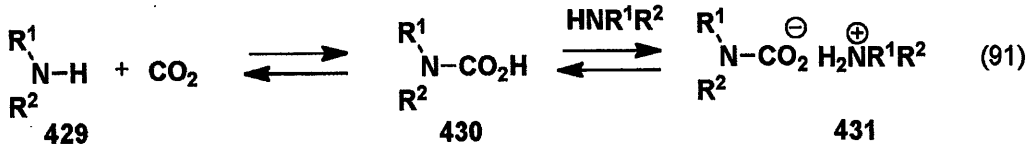
[168] (a) Koch, T. J.; Desset, S. L.; Leitner, W. *Green Chem.* **2010**, *12*, 1719-1721. (b) Estorach, C. T.; Orejon, A.; Masdeu-Bulto, A. M. *Green Chem.* **2008**, *10*, 545-552.

[169] (a) Leeke, G. A.; Santos, R. C. D.; Al-Duri, B.; Seville, J. P. K.; Smith, C. J.; Lee, C. K. Y.; Holmes, A. B.; McConvey, I. F. *Org. Proc. Res. Dev.* **2007**, *11*, 144-148. (b) Smith, C. J.; Tsang, M. W. S.; Holmes, A. B.; Danheiser, R. L.; Tester, J. W. *Org. Biomol. Chem.* **2005**, *3*, 3767-3781 and references therein.

solubility of the gas in the reaction medium is often the rate-limiting factor.

Carbon-Nitrogen Bond-Forming Reactions in Supercritical Carbon Dioxide

Although the use of $scCO_2$ in a variety of synthetic transformations is now well documented, there are only a few examples of carbon-nitrogen bond formation in $scCO_2$,[170] principally due to the facility of the reaction of amines with this electrophilic solvent.[171] CO_2 reacts reversibly with primary and secondary amines to form carbamic acids **430** and carbamic acid salts **431** (eq 91).



429 **430** **431** (91)

The reversible formation of carbamic acids and carbamic acid salts from amines in CO_2 is a serious concern when transferring carbon-nitrogen bond-forming reactions from conventional solvents to $scCO_2$. The formation of these intermediates may compromise the reactivity of the amine, leading to the formation of undesired byproducts and polymers.

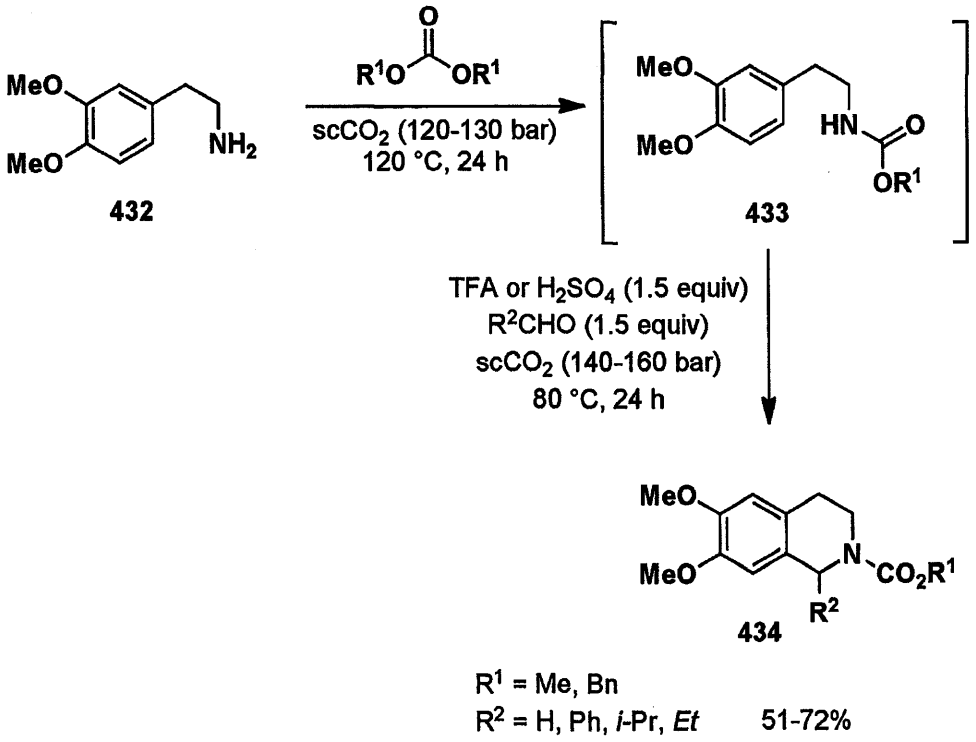
---

[170] For examples, see: (a) Jessop, P. G.; Hsiao, Y.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1996**, *118*, 344-355. (b) Wittmann, K.; Wisniewski, W.; Mynott, R.; Leitner, W.; Kranemann, C. L.; Rische, T.; Eilbracht, P.; Kluwer, S.; Ernsting, J. M.; Elsevier, C. J. *Chem. Eur. J.* **2001**, *7*, 4584-4589. (c) Shi, M.; Cui, S.-C.; Li, Q.-J. *Tetrahedron* **2004**, *60*, 6163-6167. (d) Smith, C. J.; Early, T. R.; Holmes, A. B.; Shute, R. E. *Chem. Commun.* **2004**, 1976-1977. (e) Smith, C. J.; Tsang, M. W. S.; Holmes, A. B.; Danheiser, R. L.; Tester, J. W. *Org. Biomol. Chem.* **2005**, *3*, 3767-3781. (f) Dunetz, J. R.; Ciccolini, R. P.; Froling, M.; Paap, S. M.; Allen, A. J.; Holmes, A. B.; Tester, J. W.; Danheiser, R. L. *Chem. Commun.* **2005**, 4465-4467. (g) Kayaki, Y.; Yamamoto, M.; Suzuki, T.; Ikariya, T. *Green Chem.* **2006**, *8*, 1019-1021. (h) Fuchter, M. J.; Smith, C. J.; Tsang, M. W. S.; Boyer, A.; Saubern, S.; Ryan, J. H.; Holmes, A. B. *Chem. Commun.* **2008**, 2152-2154. (i) Dou, X.-Y.; He, L.-N.; Yang, Z.-Z.; Wang, J.-L. *Synlett* **2010**, 2159-2163.

[171] (a) Dell'Amico, D. B.; Calderazzo, F.; Labella, L.; Marchetti, F.; Pampaloni, G. *Chem. Rev.* **2003**, *103*, 3857-3897. (b) Aresta, M.; Ballivet-Tkatchenko, D.; Dell'Amico, D. B.; Bonnet, M. C.; Boschi, D.; Calderazzo, F.; Faure, R.; Labella, L.; Marchetti, F. *Chem. Commun.* **2000**, 1099-1100. (c) Park, J.-Y.; Yoon, S. J.; Lee, H. *Environ. Sci. Technol.* **2003**, *37*, 1670-1675. (d) Masuda, K.; Ito, Y.; Horiguchi, M; Fujita, H. *Tetrahedron* **2005**, *61*, 213-229. (e) For a study of the effect of increased steric demand on the formation of carbamic acids and carbamates from primary amines, see: Fischer, H.; Gyllenhaal, O.; Vessman, J.; Albert, K. *Anal. Chem.* **2003**, *75*, 622-626. (f) For a discussion on the effect of temperature and solvation effects on carbamic acid and carbamate salt equilibrium, see: Dijkstra, Z. J.; Doornbos, A. R.; Weyten, H.; Ernsting, J. M.; Elsevier, C. J.; Keurentjes, J. T. F. *J. Supercrit. Fluid.* **2007**, *41*, 109-114 and references therein.

Our laboratory has developed a method for the synthesis of *N*-heterocycles using the Pictet-Spengler reaction in $scCO_2/CO_2$-expanded media. In these reactions, CO_2 serves as both the solvent and as one of the reagents (Scheme 33).[170f]

Scheme 33

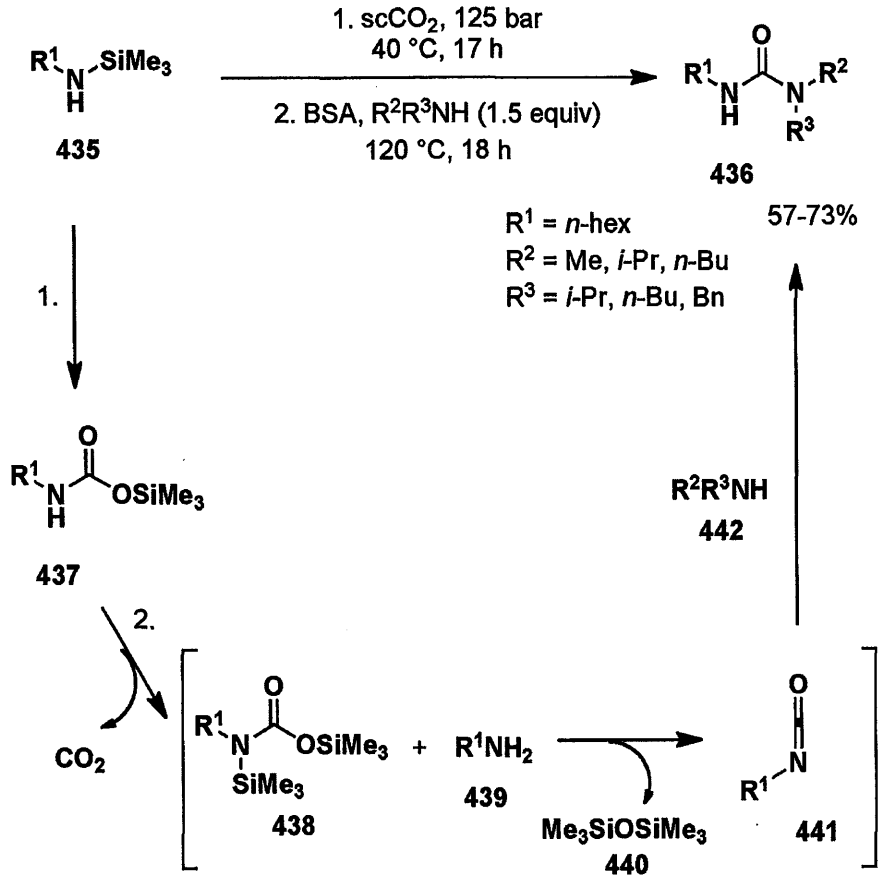


R^1 = Me, Bn
R^2 = H, Ph, *i*-Pr, *Et* 51-72%

The reaction of primary amines such as **432** with aldehydes under standard Pictet-Spengler conditions in $scCO_2$ leads to the formation of polymeric materials. An in situ protection strategy was employed in order to produce the desired heterocycles. Amine **432** is in equilibrium under the reaction conditions with the corresponding carbamic acid and carbamate salt derivatives, but it can be converted in situ to carbamate **433** by treatment with a dialkyl carbonate. Addition of an aldehyde and protic acid to intermediate **433** leads to the desired cyclization reaction, affording tetrahydroisoquinoline derivatives **434** in good yields.

A more recent example of C-N bond formation in $scCO_2$ is the synthesis of *O*-silylcarbamates and ureas from *N*-silylamines by Holmes et al.[170h] They developed an efficient, two-step, one-pot method for the preparation of unsymmetrical ureas (Scheme 34).

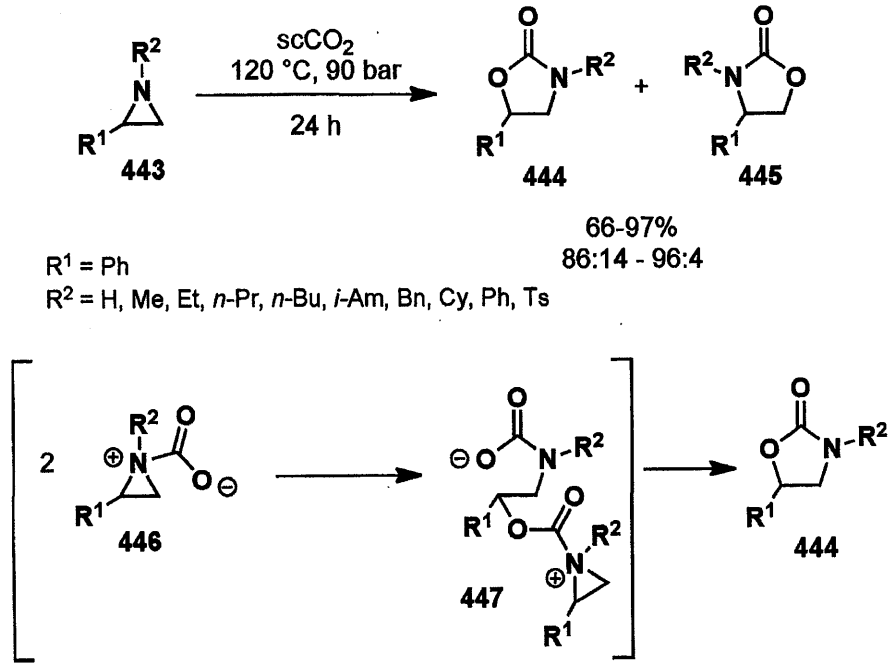
Scheme 34



In the first step of this reaction, CO_2 inserts into the N-Si bond of the *N*-silylamine to form *O*-silylcarbamate **437**. The CO_2 is vented from the reaction vessel and the crude carbamate is treated with acid and a secondary amine. When the mixture is heated to 120 °C, autosilylation occurs between two molecules of **437** to give *N,O*-bissilylated species **438** and primary amine **439** along with a molecule of CO_2. The unstable *N,O*-bissilylated species **438** is converted into isocyanate **441** upon the loss of hexamethyldisiloxane **440**. Isocyanate **441** is trapped with the secondary amine **442** to give the unsymmetrical urea **436** in good yield.

Another recent example of C-N bond formation in $scCO_2$ is the synthesis of 5-aryl-2-oxazolidinones via a catalyst-free cycloaddition reaction of aziridines with CO_2 developed by He and coworkers (Scheme 35).[170i] As was the case with the silylcarbamate synthesis discussed above, in this method CO_2 is used as a one-carbon building block in addition to being the reaction solvent.

Scheme 35



The proposed mechanism for this reaction involves reaction of the aziridine with CO_2 to form **446** followed by the combination of two molecules of **446** to give intermediate **447**. The regioselectivity of the attack of the carboxylate on the aziridinium ring determines the product ratio. Intermediate **447** then cyclizes to the oxazolidinone **444**, releasing a molecule of **446**.

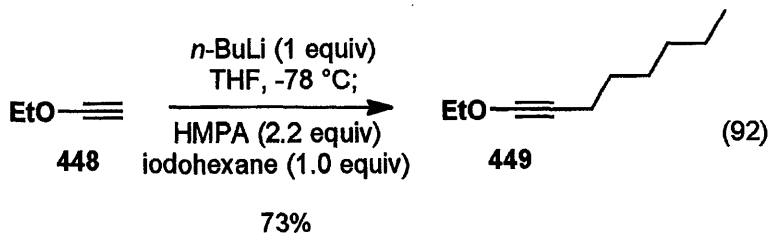
The study of C-N bond-forming reactions in $scCO_2$ continues. Work towards expanding the range of C-N bond forming reactions that can be carried out in this benign replacement solvent is especially urgent due to the prevalence of pharmaceuticals and fine chemicals containing functional groups that incorporate nitrogen. The next chapter will discuss our investigation of amide synthesis in $scCO_2$ in collaboration with the Tester laboratory.

Chapter 2 – Results and Discussion

The goal of this project was to develop a method for amide bond formation that is compatible with the use of $scCO_2$ as the reaction medium. We began by preparing alkynyl ether substrates, followed by optimization of the reaction conditions, and finally an investigation of the scope of the reaction with regard to the alkynyl ether and the amine.[172] Our main interest in the preparation of the substrates was to access significant (3-5 mmol) quantities of the compounds in a rapid fashion.

Preparation of Alkynyl Ethers

The initial feasibility and scope of amine experiments in this study were carried out using 1-ethoxy-1-octyne **449**, prepared by alkylation of commercially available ethoxyacetylene **448** following the method of Kocienski (eq 92).[173,174] Lithiated ethoxyacetylene can also be generated from chloroacetaldehyde diethyl acetal using the method of Raucher.[175]



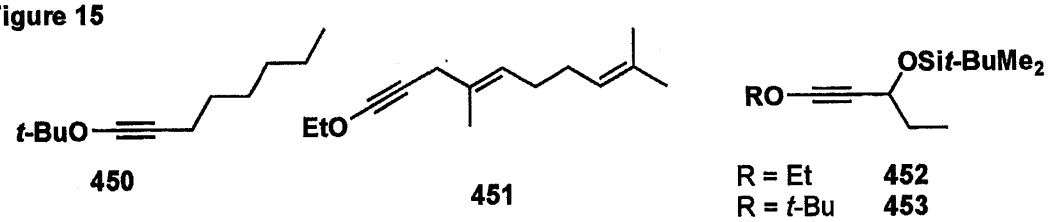
(92)

In addition to alkynyl ether **449**, Xiao Yin Mak also prepared *t*-butoxy alkynyl ether **450**,[176] alkynyl ethers **452** and **453**[177] with oxygen substituents and **451**[178] with alkenyl substituents (Figure 15).

---

[172] Most of the synthetic chemistry in this project was carried out by Xiao Yin Mak. See: Mak, X. Y. Ph. D. Thesis, Massachusetts Institute of Technology, September 2008.
[173] Pons, J.-M.; Kocienski, P. *Tetrahedron Lett.* **1989**, *30*, 1833-1836.
[174] Mak, X. Y.; Ciccolini, R. P.; Robinson, J. M.; Tester, J. W.; Danhesier, R. L. *J. Org. Chem.* **2009**, *74*, 9381-9387.
[175] Raucher, S.; Bray, B. L. *J. Org. Chem.* **1987**, *52*, 2332-2333.
[176] Prepared using a modification of Green's method of addition of potassium alkoxide to dichloroacetylenes: Moyano, A.; Charbonnier, F.; Greene, A. E. *J. Org. Chem.* **1987**, *52*, 2919-2922.
[177] Prepared in two steps by addition of an in situ generated lithium ethoxyacetylide to propionaldehyde, followed by protection with TBSCl and imidazole.

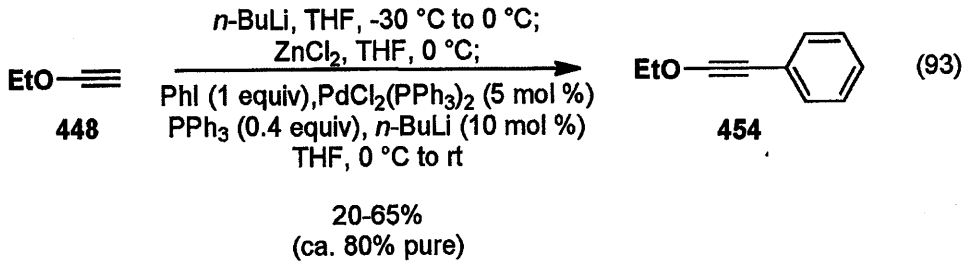
Figure 15



450 **451**

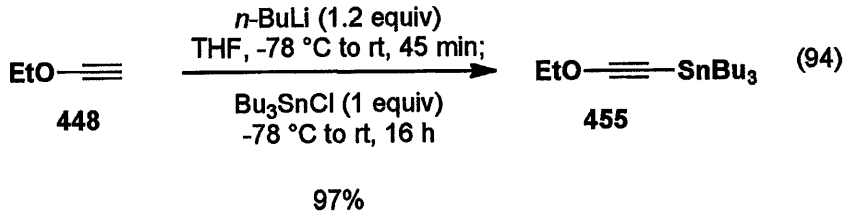
R = Et **452**
R = *t*-Bu **453**

In addition to these alkyl substituted alkynyl ethers, we were also interested in investigating aryl substituted alkynyl ethers. Preparation of alkynyl ether **454** was attempted by Negishi coupling (eq 93).[179]



This reaction failed to give a satisfactory yield of pure **454**. The product was contaminated with biphenyl and other impurities that could not be removed by column chromatography. In fact, **454** was very acid sensitive and decomposed on silica gel even when the silica gel was deactivated with triethylamine.

Stille coupling of alkynyl stannane **455** with iodobenzene was also attempted.[180] Alkynyl stannane **455** was prepared in excellent yield from ethoxyacetylene **448** (eq 94).



97%

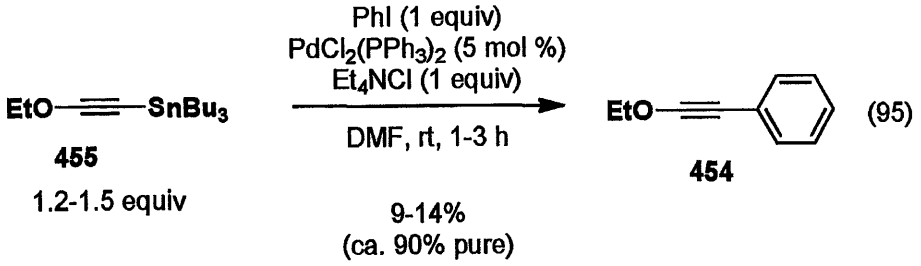
---

[178] Prepared by reaction of the Grignard derivative of ethoxyacetylene **448** with geranyl mesylate formed in situ from geraniol.

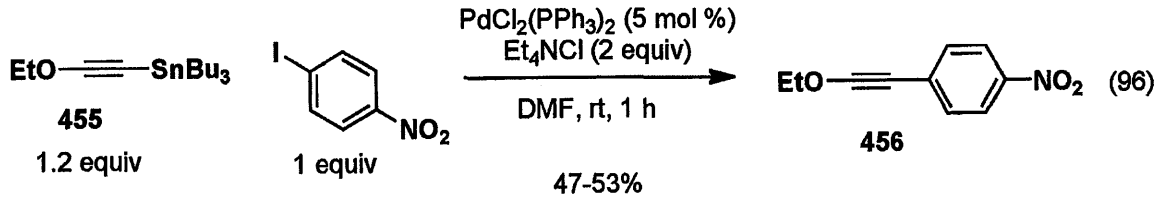
[179] Ethoxy alkyne **454** was previously prepared by Negishi coupling of lithium ethoxyalkyne generated in situ from 1,2-dichlorovinyl ethers, see: Himbert, G.; Loffler, A. *Synthesis* **1992**, 495-498.

[180] Following a literature procedure: Sakamoto, T.; Yasuhara, A.; Kondo, Y.; Yamanaka, H. *Chem. Pharm. Bull.* **1994**, *42*, 2032-2035.

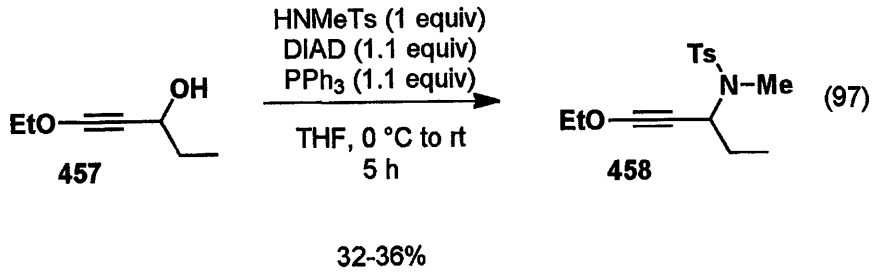
The Stille reaction was problematic. The desired product **454** was formed along with several impurities and **454** could not be purified by column chromatography without extensive decomposition (eq 95).



Due to the extreme sensitivity of **454**, we next turned our attention to *p*-nitrobenzene derivative **456**. This compound was expected to be more stable to purification. Following Sakamoto's procedure, we were able to obtain a moderate yield of **456**, in agreement with their reported 52-62% yield (eq 96).[180]

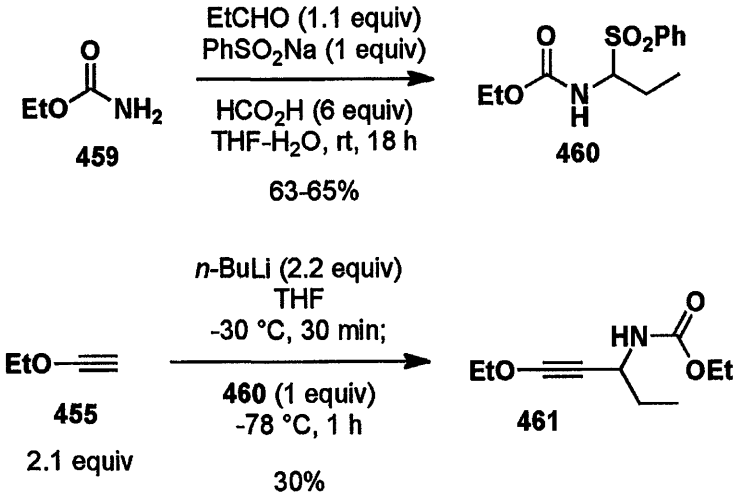


In addition to the aryl alkynyl ethers, we were also interested in investigating alkynyl ethers with amino substituents. Tosylamine **458** was prepared by Mitsunobu reaction of propargyl alcohol **457**[175] with *N*-methyltosylamine (eq 97). The moderate yield of this reaction is due the product decomposing under the reaction conditions.



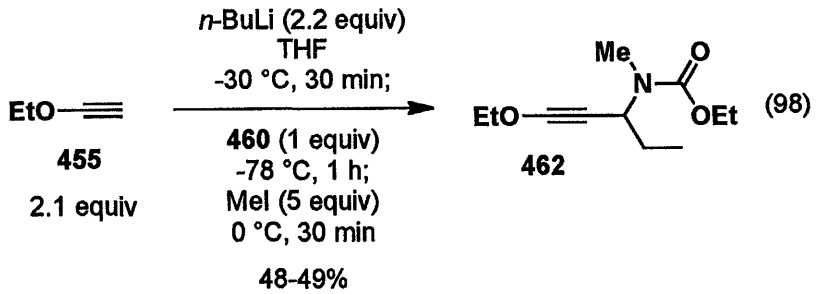
As will be discussed later in this chapter, alkynyl ether **458** did not work well in the desired amide bond formation reaction, so additional alkynyl ethers with amino substituents were considered. Carbamate **461** was prepared by the addition of lithium ethoxyacetylide to the *N*-acyl amine that was formed in situ from α-amido sulfone **460**, following the method of Petrini.[181] One unfortunate limitation of Petrini's method is the requirement that two equivalents of the lithium acetylide be used. Sulfone **460** was accessed in one step from ethyl carbamate (Scheme 36).

Scheme 36



The low yield of **461** is attributed to the instability of the product to purification. Column chromatography of **461** on neutral alumina, acetone-deactivated silica gel, and triethylamine-deactivated silica gel gave similar results.

The yield of this reaction was slightly improved when the product was methylated in situ to give tertiary carbamate **462** (eq 98).



(98)

[181] For reactions with alkyl acetylides, see: Mecozzi, T.; Petrini, M. *J. Org. Chem.* **1999**, *64*, 8970-8972.

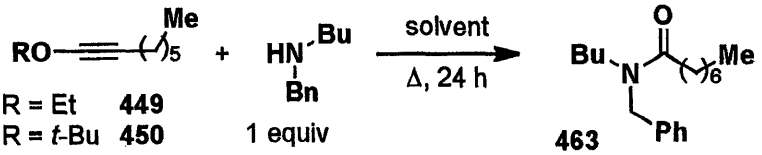
Amide Bond Forming Reactions in Supercritical Carbon Dioxide

All reactions in $scCO_2$ were performed in a Thar stainless steel view cell reactor fitted with two coaxial sapphire windows, allowing visual inspection.[174,182] The exterior of the cell was wrapped tightly with insulated heating tape which was interfaced to a temperature controller. The cell temperature and pressure were monitored with an internal thermocouple probe and a pressure gauge. The cell reactor was placed on a magnetic stirrer and the reactor contents were mixed using a magnetic stir bar. The reactants were charged into the reactor via syringe, either as a solution in dichloromethane or neat. The minimal solvent used to transfer the reactants, if any, was then removed by evacuation of the reactor cell that was purged with argon prior to introduction of CO_2. Further details on the reactor set-up are presented in the Experimental Section.

Optimization of Conditions for Amide Synthesis in $scCO_2$

Initial feasibility experiments were carried out using 1-ethoxy-1-octyne **449** and *N*-benzylbutylamine (Table 28).[183]

Table 28. Optimization of Conditions for Amide Synthesis



R = Et **449**
R = *t*-Bu **450**

1 equiv

463

entry	alkynyl ether	solvent	temp (°C)	pressure (bar)	yield (%)
1	**449**	toluene	120	1.3[a]	88
2	**449**	CO_2	120	215	85
3	**449**	CO_2	120	394	86
4	**449**	CO_2	130	228	88
5	**450**	CO_2	90	218	82

[a] Calculated value based on the vapor pressure of toluene at 120 °C

[182] The reactor was operated by Rocco Ciccolini. See: Ciccolini, R. P. Ph. D. Thesis, Massachusetts Institute of Technology, June 2008.

[183] All of the reactions in Table 28 were carried out by Xiao Yin Mak.

We found that the yield of **463** when the reaction was run in toluene could be replicated in $scCO_2$ at 130 °C (entry 4) and we were pleased to observe that there was no interference from the reversible reaction of the amine with CO_2. When *t*-butoxy alkynyl ether **450** was used, the reaction could be carried out at 90 °C instead of 130 °C (entry 5). Each reaction was run at the minimum pressure required to solubilize the reactants at the start of the reaction except for entry 3, where the pressure was maintained at 394 bar throughout the reaction in order to maintain a single phase.[184]

^{1}H NMR analysis of the crude products of these reactions revealed that efficient amide formation had occurred. No ketene dimers or products of the [2 + 2] cycloaddition of the ketene and alkynyl ether were observed. Depressurization of the reaction mixture after 24 h provided amide **463** as an oil, which was determined to be 95-98% pure by ^{1}H NMR analysis. In these experiments the product was found to be contaminated with some solid debris originating from abrasion of the o-rings. Consequently, amide **463** was transferred out of the reactor and subjected to column chromatography to remove this material, resulting in the loss of ca. 5% of the product, as estimated based on control experiments.

Scope of the Reaction with Respect to Amine

A variety of amines participate in the desired amide bond-forming reaction in supercritical carbon dioxide (Table 29). The reaction pressure was selected based on the minimum pressure sufficient to solubilize both the amine and the alkynyl ether and at least initially form a homogeneous solution at the elevated reaction temperature. In each case, however, the product amides were observed to eventually separate from the reaction mixture as a second, liquid phase.

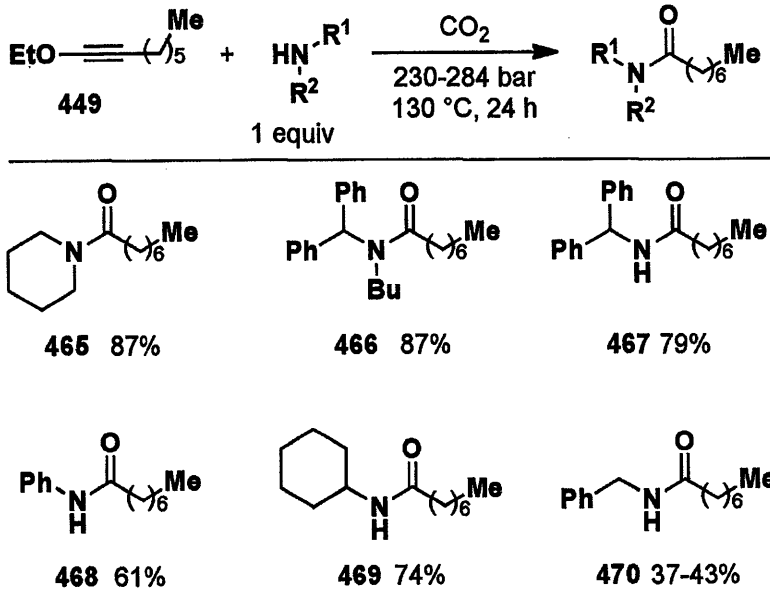
As shown in Table 29 below, secondary amines readily undergo reaction in $scCO_2$ to afford the desired amides in good yield. In addition, α-branched primary amines participated in the reaction to give amides **467** and **469** in good yields. Aniline also participated in the reaction, producing amide **468** in moderate yield. The limitation of this method was revealed by the

---

[184] For an in-depth discussion of phase behavior in these reactions, see references 174 and 182.

reaction with benzylamine. In this case, we believe that the equilibrium between amine and carbamic acid described in eq 91 shifts in favor of the carbamic acid due to the less sterically hindered nature of the amine. In this case, the amide product **470** was isolated in moderate 37-43% yield.[185]

Table 29. Reaction of Amines[1] with 1-Ethoxy-1-octyne in $scCO_2$



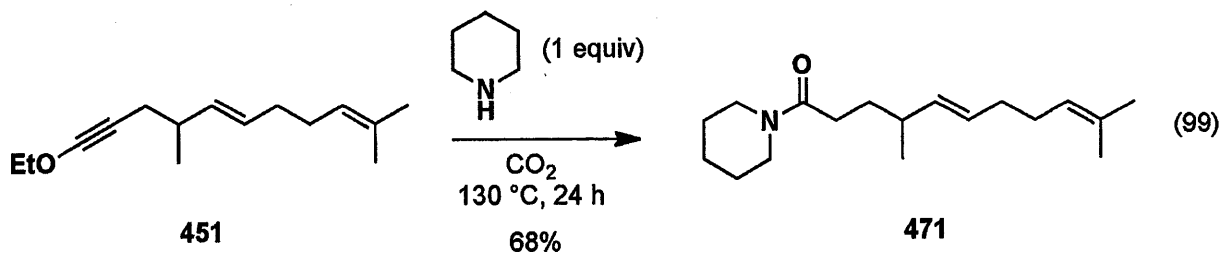
[1] Reactions to prepare **465-468** and **470** were carried out by Xiao Yin Mak.

Scope of the Reaction with Respect to Alkynyl Ether

We next turned our attention to the application of this chemistry to the preparation of amides starting from a variety of alkynyl ether derivatives. As shown in eq 99,[186] the reaction proceeded well with alkynyl ether **451** bearing alkenyl substituents.

[185] Alternative explanations for the lower yields with primary amines based on phase partitioning effects were ruled out by control experiments. See ref 174.

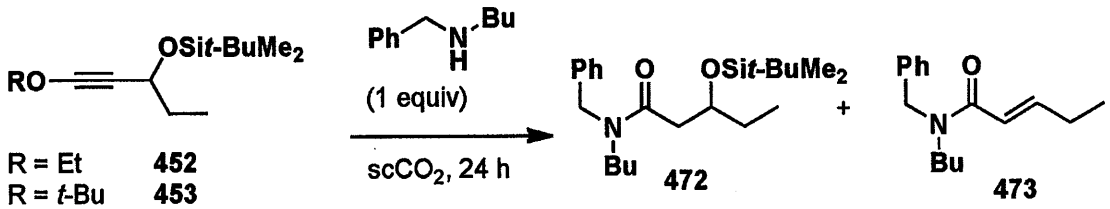
[186] Reactions to prepare amides **471** and **472** were carried out by Xiao Yin Mak.



(99)

In the case of alkynyl ether **452**, when the reaction was carried out at 130 °C, the desired product **472** was formed along with α,β-unsaturated amide **473** (Table 30).[186] When *t*-butoxy alkynyl ether **453** was used instead, the reaction was carried out at 90 °C and the desired amide **472** was formed in 80% yield, with only 3% of the α,β-unsaturated byproduct **473** obtained.

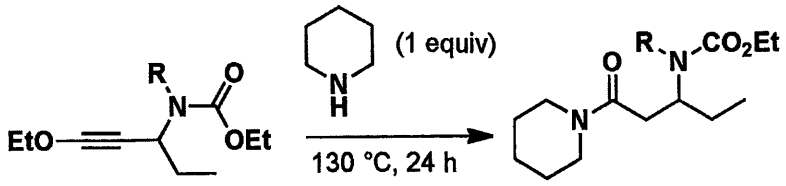
Table 30. Preparation of β-Siloxy Amide 472



entry	alkynyl ether	temp	Yield of **472**	Yield of **473**
1	**452**	130 °C	56%	31%
2	**453**	90 °C	80%	3%

Alkynyl ethers **461** and **462** bearing carbamate substituents did not suffer from β-elimination reactions (Table 31).

Table 31. Preparation of β-Amino Amides



R = H **461**
R = Me **462**

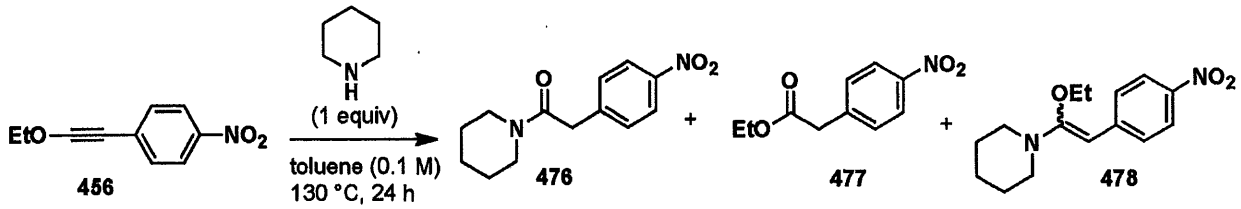
R = H **474**
R = Me **475**

entry	alkynyl ether	solvent	amide	yield
1	**461**	CO_2	**474**	66%
2	**462**	CO_2	**475**	85%
3	**462**	toluene	**475**	69%

Both alkynyl ethers gave good yields of the desired amide products in $scCO_2$ (entries 1-2). Interestingly, when the reaction with alkynyl ether **462** was carried out in toluene for comparison, the yield of amide **475** dropped to 69% from 85% (entry 3).

Aryl alkynyl ether **456** and alkynyl ether **458** bearing a *N*-tosyl group were not investigated in $scCO_2$ because they did not work well in control experiments in toluene. All of the reactor experiments were done on 3.5 mmol scale, and we were not interested in preparing gram quantities of sensitive substrates when it was likely that the amide bond-forming reactions would be problematic. As shown in Table 32, heating alkynyl ether **456** with piperidine in toluene afforded a mixture of products.

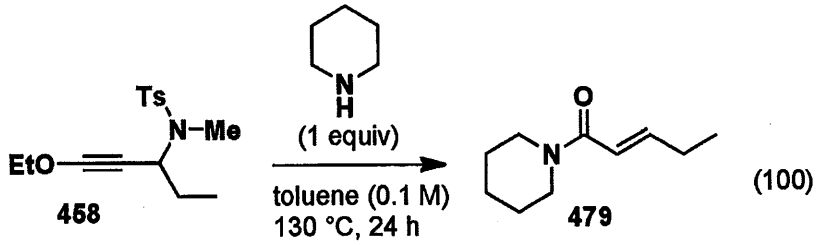
Table 32. Attempts to Prepare α-Aryl Amide 476



entry	Info on Conditions	product ratio (by ^{1}H NMR analysis) amide **476**: ester **477**: *O,N*-ketene acetal **478**		
1	-	15	11	74
2	**456** was dried over $MgSO_4$ before use	1	7	71
3	Reaction was run over 3A molecular sieves	70	30	0
4	**456** was dried by azeotropic removal of benzene under vacuum	23	9	68
5	**456** was washed with satd aq $NaHCO_3$ before use	25	0	75
6	**456** was dried over 4A MS for 1 h prior to reaction	34	11	55

Alkynyl ether **456** is sensitive to the conjugate addition of nucleophiles, and when the amide bond forming reaction was run with piperidine, the *O,N*-ketene acetal **478** was formed as the main product. In the first run, the desired amide **476** was formed as a minor product, along with a nearly equal amount of ester **477**. A variety of treatments were attempted to remove traces of water and acid from alkynyl ether **456** prior to the reaction (Table 32, entries 2 and 4-6). In these runs the product ratio changed, but *O,N*-ketene acetal **478** was always the major product. When the reaction was run over 3Å molecular sieves (entry 3), finally the desired amide **476** was formed as the major product, but it was contaminated with a significant amount of the ester **477**. Considering that we were trying to develop a simple method for amide bond formation without tedious purification of products, we decided not to investigate alkynyl ether **456** in $scCO_2$. It is possible that the product ratio would be improved in CO_2, but we did not want to introduce variations such as molecular sieves into our general procedure.

In a test run in toluene, alkynyl ether **458** gave the α,β-unsaturated amide product **479** as the only product (eq 100). The formation of this byproduct via a β-elimination reaction may be suppressed in $scCO_2$, however this reaction was not attempted in that solvent.



(100)

Summary

Carbon dioxide has been employed as an environmentally benign alternative to conventional solvents for the synthesis of amides via ketenes that are generated by the retro-ene reaction of alkynyl ethers. Although the alkynyl ethers were not prepared via "green" methods, this study was meant to be a proof-of-concept exercise with regard to the feasibility and scope of amide bond formation using amines in CO_2. Although the alkynyl ethers were prepared by reactions of lithiated ethoxyacetylene, the carboxylic acid starting materials required to prepare the desired amide products using standard acylation chemistry would involve multistep syntheses as well, at least for the more functionalized cases.

Overall, this method of amide synthesis works well with a variety of alkynyl ethers and primary and secondary amines to give amide products bearing functional groups, including β-siloxy and β-amino substituents as well as alkenyl substituents. Xiao Yin Mak also explored the application of this method to macrocyclic lactam synthesis.[187]

[187] See references 172 and 174 for a discussion of the lactam synthesis experiments.

Part IV

Experimental Section

Experimental Section for Part I and Part II

General Procedures. All reactions were performed in flame-dried or oven-dried glassware under a positive pressure of argon. Reactions were magnetically stirred unless otherwise indicated. Air- and moisture-sensitive liquids and solutions were transferred by syringe or cannula and introduced into reaction vessels through rubber septa. Reaction product solutions and chromatography fractions were concentrated by rotary evaporation at ca. 20 mmHg and then at 0.1 mmHg (vacuum pump) unless otherwise indicated. Thin layer chromatography was performed on EMD precoated glass-backed silica gel 60 F-254 0.25 mm plates. Column chromatography was performed on Sorbet Technologies Standard Grade silica gel 60 (230-400 mesh) or on EMD Chromatographic Grade basic alumina (80-325 mesh).

Materials. Commercial grade reagents and solvents were used without further purification except as indicated below. Dichloromethane, diethyl ether, and tetrahydrofuran were purified by pressure filtration through activated alumina. Toluene was purified by pressure filtration through activated alumina and Cu(II) oxide. Methyl chloroformate, methyl acrylate, ethyl vinyl ether, and oxalyl chloride were distilled at atmospheric pressure under argon. Diisopropylamine, triethylamine, pentane, and hexanes were distilled under argon from calcium hydride. Methyl vinyl ketone, dimethylacetylene dicarboxylate, and 3-butyn-1-ol were distilled under vacuum immediately prior to use. CuI was purified by soxhlet extraction with THF for 48 h, followed by drying under vacuum (0.1 mmHg) over P_2O_5 for 24 h. Iodobenzene and 2-bromopropene were filtered through activated basic alumina before use. *n*-Butyllithium was titrated according to the Watson-Eastham method using BHT in THF with 1,10-phenanthroline as an indicator.[188] *t*-Butyllithium and *s*-butyllithium were titrated in pentane with menthol at 0 °C using 1,10-phenanthroline as the indicator. (Bromoethynyl)triisopropylsilane,[189] 1-bromo-2-heptyne,[190] 4-methyl-*N*-(prop-2-yn-1-yl)benzenesulfonamide (**114**),[191] 4-oxaocta-1,6-diyne,[41] 3-

---

[188] (a) Watson, S. C.; Eastham, J. F. *J. Organomet. Chem.* **1967**, *9*, 165-167. (b) Ellison, R. A.; Griffin, R.; Kotsonis, F. N. *J. Organomet. Chem.* **1972**, *36*, 209-213.

[189] Rubin, Y.; Lin, S. S.; Knobler, C. B.; Anthony, J.; Boldi, A. M.; Diederich, F. *J. Am. Chem. Soc.* **1991**, *113*, 6943-6949.

[190] Kalgutkar, A. S.; Kozak, K. R.; Crews, B. C.; Hochgesang, G. P.; Marnett, L. J. *J. Med. Chem.* **1998**, *41*, 4800-4818.

[191] Dieltiens, N.; Moonen, K.; Stevens, C. V. *Chem. Eur. J.* **2007**, *13*, 203-214.

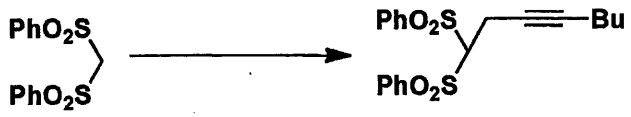
ethoxycyclobutanone (**272**),[93] cyclobutene carboxylic acid (**292**),[105] 5-methylhex-5-en-3-yn-1-ol (**305**),[70] 4-methylpent-4-en-2-ynol (**350**),[121] cyclopentenyl trifluoromethanesulfonate **298**,[108] cis-bicyclo[3.2.0]heptan-6-one (**340**),[116,117] and 2,4,6-triisopropylbenzenesulfonylhydrazide[192] and 4-(*tert*-butyldimethylsilyloxy)-2,3-diisopropoxycyclobut-2-enone (**275**)[95] were prepared according to previously reported procedures. Cyclohexenyl trifluoromethanesulfonate **299** was prepared according to a minor modification of a literature procedure.[109]

Acetone-deactivated silica gel was prepared by mixing acetone with silica gel (ca. 10 mL/g) for 5 min, and then using this slurry to build the column, followed by flushing the column with two column volumes of hexanes.

Instrumentation. Infrared spectra were obtained using a Perkin Elmer 2000 FT-IR spectrophotometer. ^{1}H NMR spectra were recorded on Bruker Avance-400 (400 MHz) spectrometers. ^{1}H NMR chemical shifts are expressed in parts per million (δ) downfield from tetramethylsilane (with the $CHCl_3$ peak at 7.27 ppm used as a standard). ^{13}C NMR spectra were recorded on Bruker Avance-400 (100 MHz) spectrometers. ^{13}C NMR chemical shifts are expressed in parts per million (δ) downfield from tetramethylsilane (with the central peak of $CHCl_3$ at 77.23 ppm used as a standard). High-resolution mass spectra (HRMS) were measured on a Bruker Daltonics APEXII 3 tesla Fourier transform mass spectrometer.

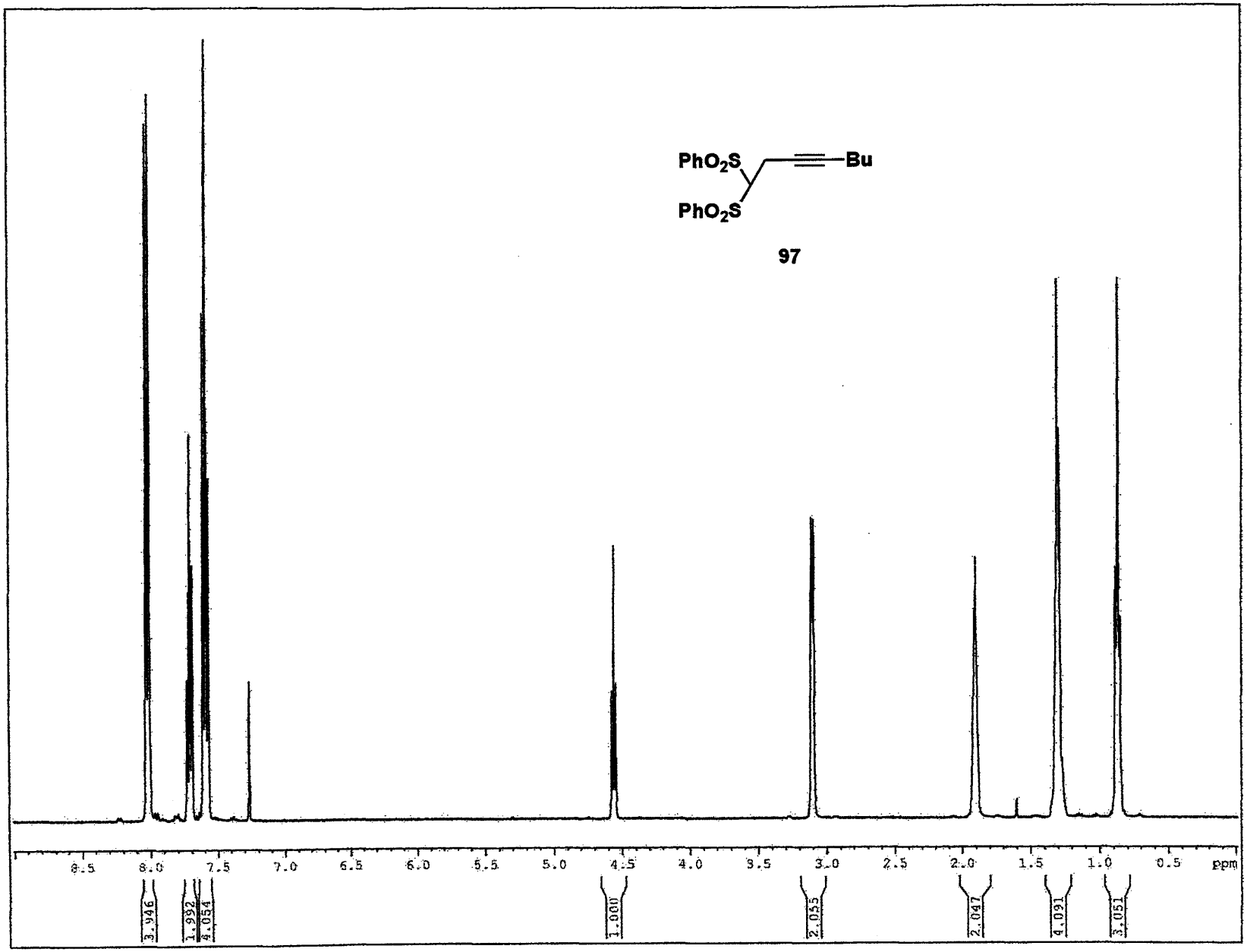
---

[192] Cusak, N. J.; Reese, C. B.; Risius, A. C.; Roozpeikar, B. *Tetrahedron* **1976**, *32*, 2157-2162.



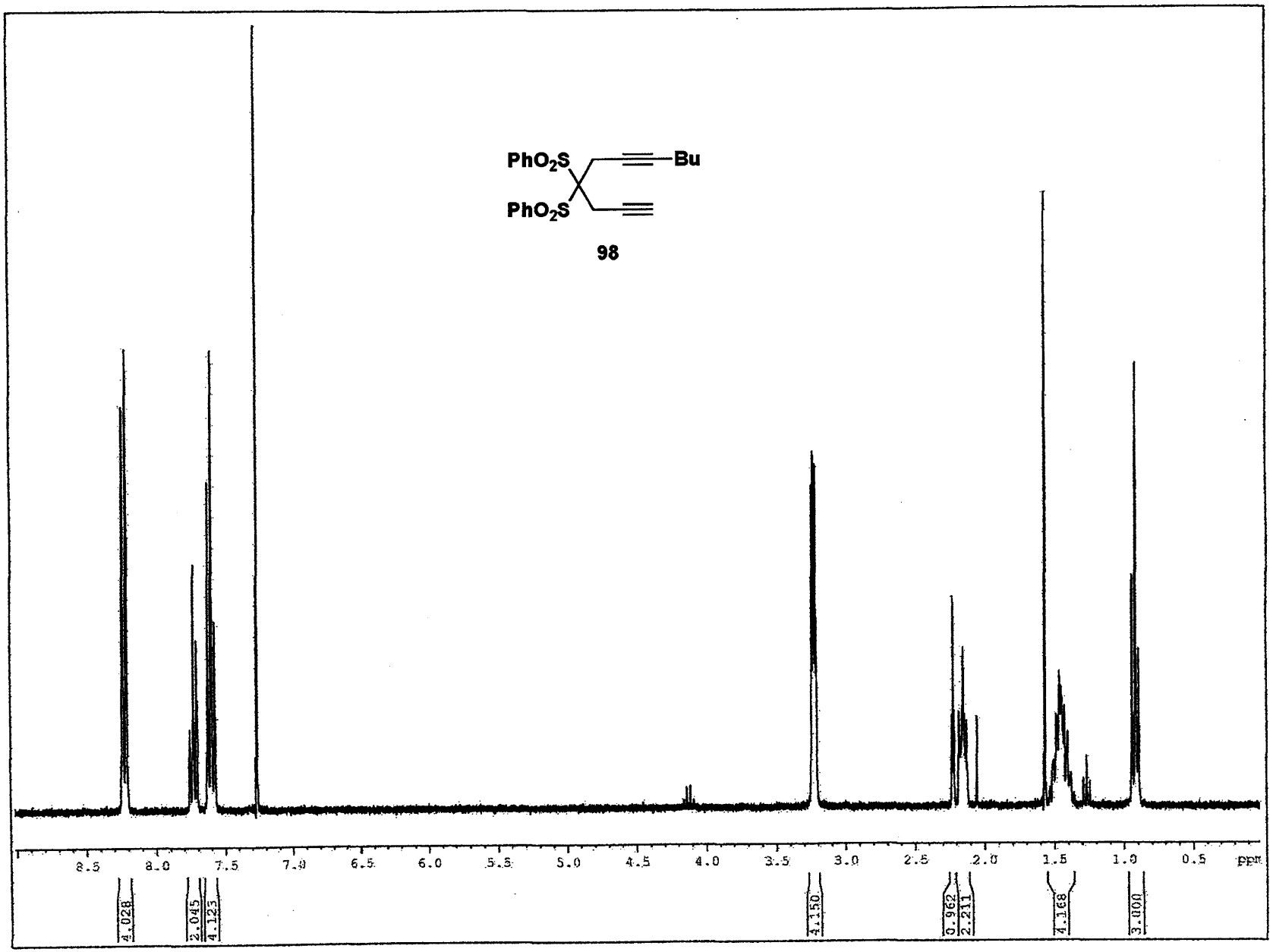
96 97

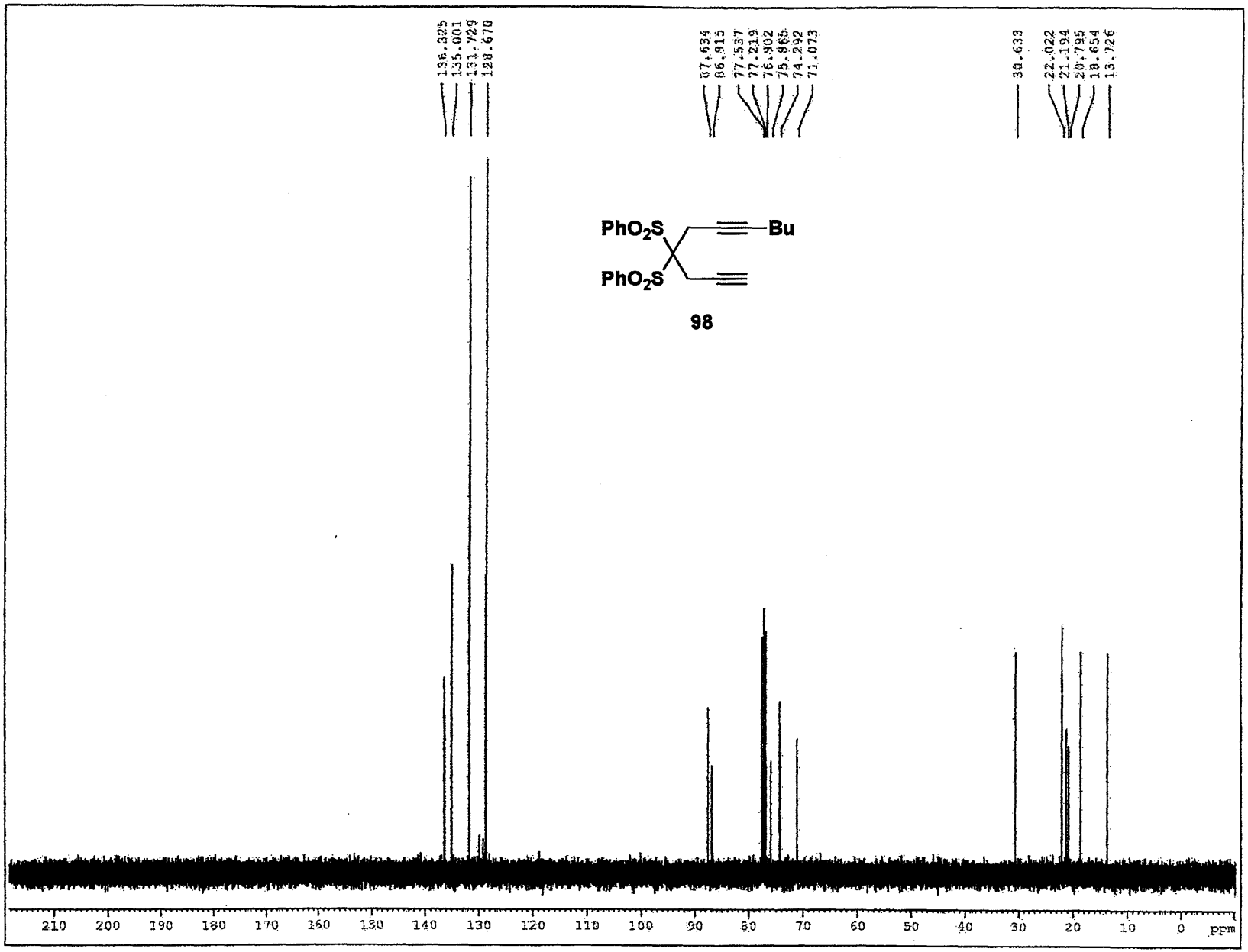
1,1-Bis(phenylsulfonyl)oct-3-yne (97). A 50-mL, three-necked, round-bottomed flask equipped with a rubber septum, glass stopper, and an argon inlet adapter was charged with sodium hydride (60% dispersion in mineral oil, 0.405 g, 10.1 mmol, 1.0 equiv) and 5 mL of DMF. A solution of bis(phenylsulfonyl)methane **96** (3.000 g, 10.1 mmol, 1.0 equiv) in 4 mL of DMF was added dropwise via cannula over 5 min (1 mL DMF rinse). After 10 min, the reaction mixture was heated at 70 °C for 20 min, and then cooled to rt. A solution of 1-bromo-2-heptyne (1.772 g, 10.1 mmol, 1.0 equiv) in 5 mL of DMF was added dropwise via cannula over 40 min (2 mL DMF rinse). The reaction mixture was stirred at rt for 2 h and then diluted with 75 mL of satd aq NH_4Cl solution. The resulting mixture was extracted with two 50-mL portions of Et_2O and 250 mL of EtOAc, and the combined organic phases were dried over $MgSO_4$, filtered, and concentrated to give 7.652 g of orange oil. Purification by column chromatography on 153 g of silica gel (elution with 15-20% EtOAc-hexanes) provided 1.979 g (50%) of **97** as a white solid: mp 84-85 °C; IR (thin film) 2956, 2934, 1584, 1448, 1328, 1198, 1151, 1079, 729, and 686 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, J = 8.2 Hz, 4 H), 7.72 (t, J = 7.4 Hz, 2 H), 7.60 (t, J = 7.7 Hz, 4 H), 4.56 (t, J = 6.1 Hz, 1 H), 3.06-3.14 (m, 2 H), 1.87-1.95 (m, 2 H), 1.28-1.36 (m, 4 H), 0.88 (t, J = 6.8 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.2,134.9, 130.0, 129.2, 84.8, 82.7, 72.7, 30.6, 22.0, 18.5, 17.2, 13.7; HRMS-ESI *(m/z)*: $[M + H]^+$ calcd for $C_{20}H_{22}O_4S_2$: 391.1032, found: 391.1045.

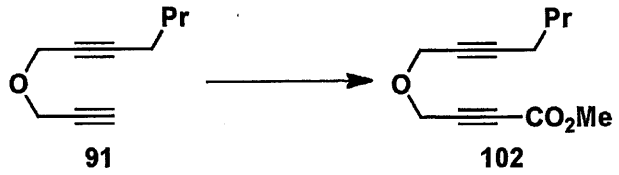

PhO2S
PhO2S
Bu
97
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
3.946
1.992
4.054
1.000
2.055
2.047
4.091
3.051

97 98

4,4-Bis(phenylsulfonyl)undec-1,6-diyne (98) A 50-mL, three-necked, round-bottomed flask equipped with a glass stopper, rubber septum, and an argon inlet adapter was charged with sodium hydride (60% dispersion in mineral oil, 0.144 g, 2.9 mmol, 1.1 equiv) and 3 mL of DMF. A solution of alkyne **97** (1.016 g, 2.6 mmol, 1.0 equiv) in 8 mL of DMF was added dropwise via cannula over 15 min (2 mL DMF rinse). The orange reaction mixture was heated at 70 °C for 20 min and then cooled to rt. Propargyl bromide solution (0.41 mL of a 8.19 M solution in toluene, 3.4 mmol, 1.3 equiv) was added dropwise via syringe over 30 sec. After 2 h, the reaction mixture was diluted with 25 mL of satd aq $NaHCO_3$ solution and extracted with three 50-mL portions of EtOAc. The combined organic phases were washed with 50 mL of brine, dried over Na_2SO_4, filtered, and concentrated to give 2.194 g of a brown oil. Purification by column chromatography on 132 g of acetone-deactivated silica gel (elution with 10% EtOAc-hexanes) afforded 1.005 g (90%) of diyne **98** as a very pale yellow oil: IR (neat) 3278, 2957, 2872, 1584, 2478, 1448, 1428, 1336, 1150, 1078, 999, and 845 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.23 (d, J = 8.4 Hz, 4 H), 7.73 (t, J = 7.4 Hz, 2 H), 7.60 (t, J = 7.8 Hz, 4 H), 3.24 (d, J = 2.5 Hz, 2 H), 3.20-3.23 (m, 2 H), 2.23 (t, J = 2.5 Hz, 1 H), 2.15 (m, 2 H), 1.35-1.53 (m, 4 H), 0.90 (t, J = 7.0 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.3, 135.0, 131.8, 128.7, 87.6, 86.9, 75.9, 74.3, 71.0, 30.6, 22.0, 21.2, 20.8, 18.7, 13.7; HRMS-ESI *(m/z)*: $[M + H]^+$ calcd for $C_{23}H_{24}O_4S_2$: 429.1189, found: 429.1204.

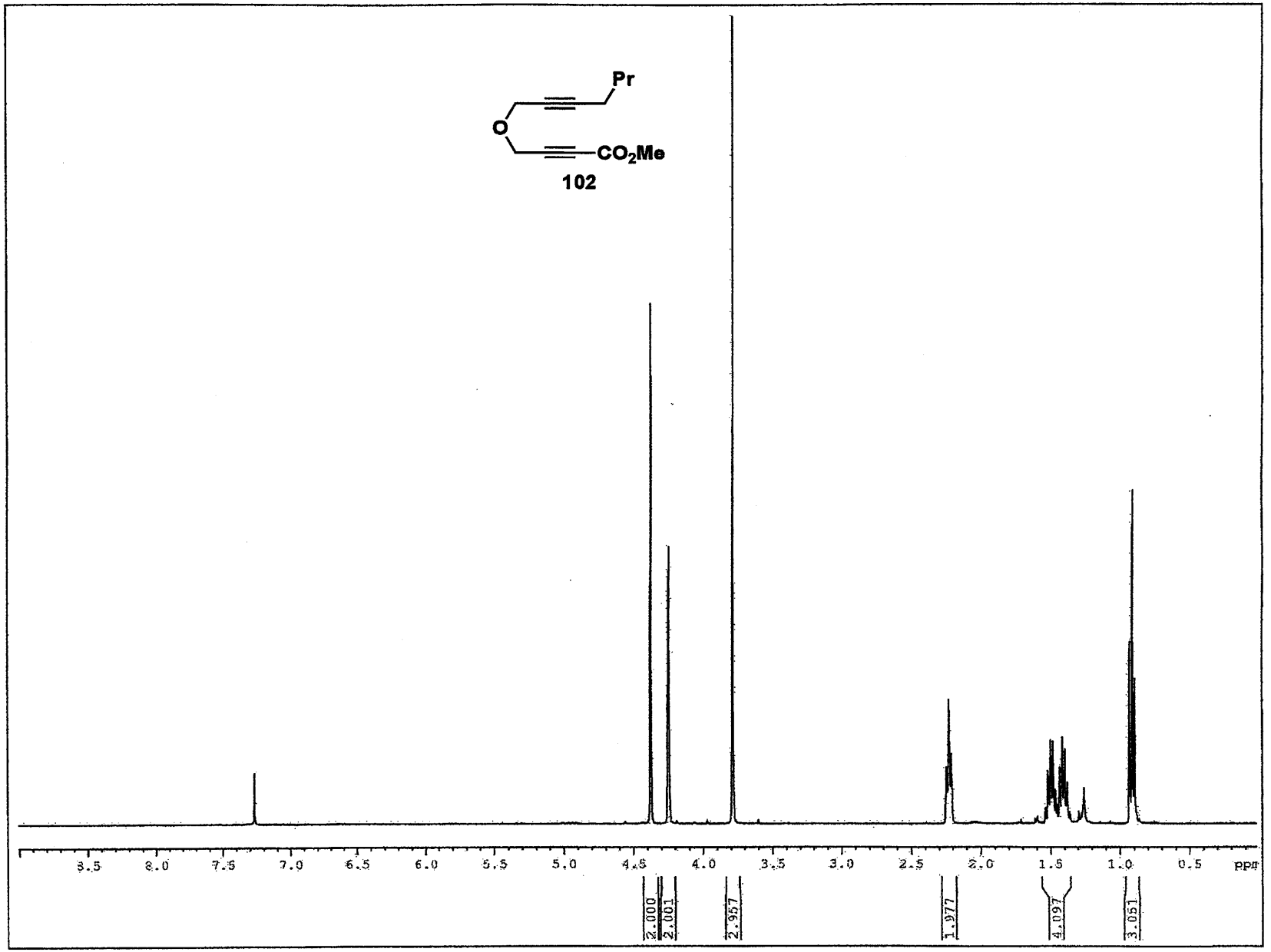

PhO2S
Bu
PhO2S
98
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
4.028
2.045
4.123
4.150
0.962
2.211
4.168
3.000

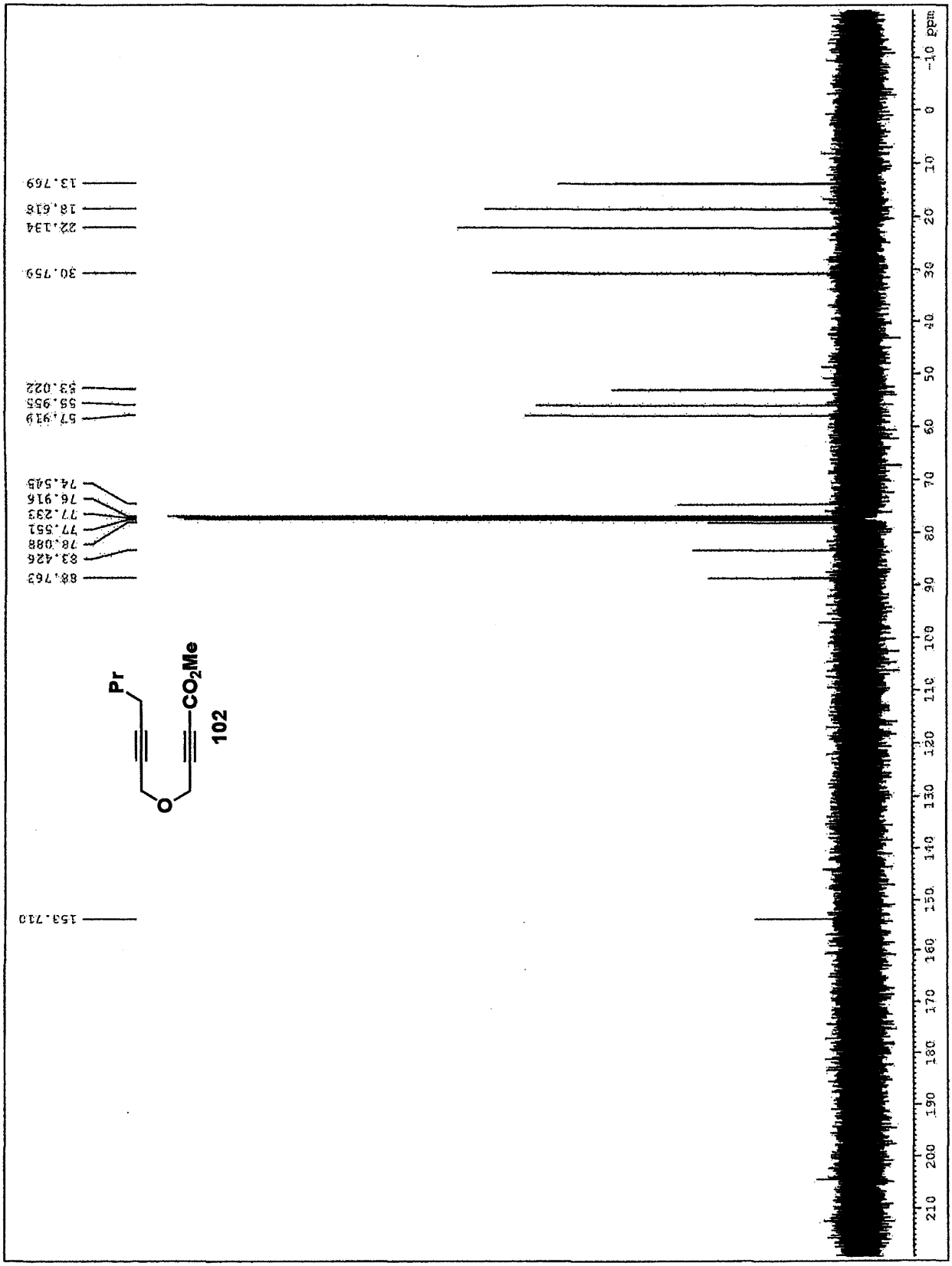

136.325
135.001
131.729
128.670
87.634
86.915
77.537
77.219
76.902
75.865
74.292
71.073
30.633
22.022
21.194
20.795
18.654
13.726
PhO2S
PhO2S
Bu
98
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

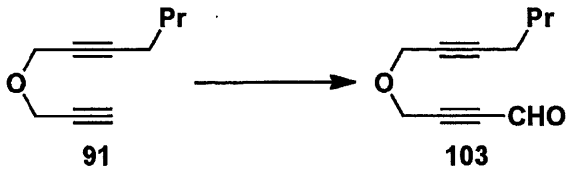


91 102

Methyl 5-oxadodeca-2,7-diynoate (102). A 25-mL, three-necked, round-bottomed flask equipped with an argon inlet adapter, two rubber septa, and a thermocouple probe was charged with diyne **91** (0.432 g, 2.87 mmol, 1.0 equiv) and 6 mL of Et_2O. The reaction mixture was cooled to -78 °C and *n*-BuLi solution (2.70 M in hexanes, 1.20 mL, 3.24 mmol, 1.1 equiv) was added dropwise over 4 min. The pale yellow reaction mixture was stirred at -78 °C for 30 min. A flame-dried, 50-mL, three-necked, round-bottomed flask equipped with an argon inlet adapter, two rubber septa, and a thermocouple probe was charged with methyl chloroformate (0.90 mL, 1.10 g, 11.6 mmol, 4.0 equiv) and 7 mL of Et_2O. This solution was cooled to -35 °C and the lithium acetylide solution was added dropwise via cannula over 12 min (2-mL Et_2O rinse). The reaction mixture was allowed to warm to -25 °C, stirred for 30 min, and then warmed to -10 °C and quenched by addition of 10 mL of satd aq NH_4Cl solution. The resulting mixture was extracted with 150 mL of Et_2O, and the organic layer was washed with 50 mL of brine, dried over Na_2SO_4, filtered, and concentrated to give 0.616 g of yellow oil. Purification by column chromatography on 123 g of silica gel (elution with 4-5% EtOAc-hexanes) gave 0.494 g (83%) of ester **102** as a pale yellow oil: IR (neat) 2932, 2361, 2238, 1718, 1495, 1436, 1347, 1258, 1136, 1052, 896, and 751 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.39 (s, 2 H), 4.26 (t, J = 1.9 Hz, 2 H), 3.80 (s, 3 H), 2.23 (tt, J = 7.0, 2.0 Hz, 2 H), 1.36-1.55 (m, 4 H), 0.92 (t, J = 7.2 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.7, 88.8, 83.4, 78.1, 74.5, 57.9, 56.0, 53.0, 30.8, 22.1, 18.6, 13.8; HRMS-DART *(m/z)* calcd for $C_{12}H_{16}O_3$ $[M + H]^+$: 209.1172, found: 209.1172.

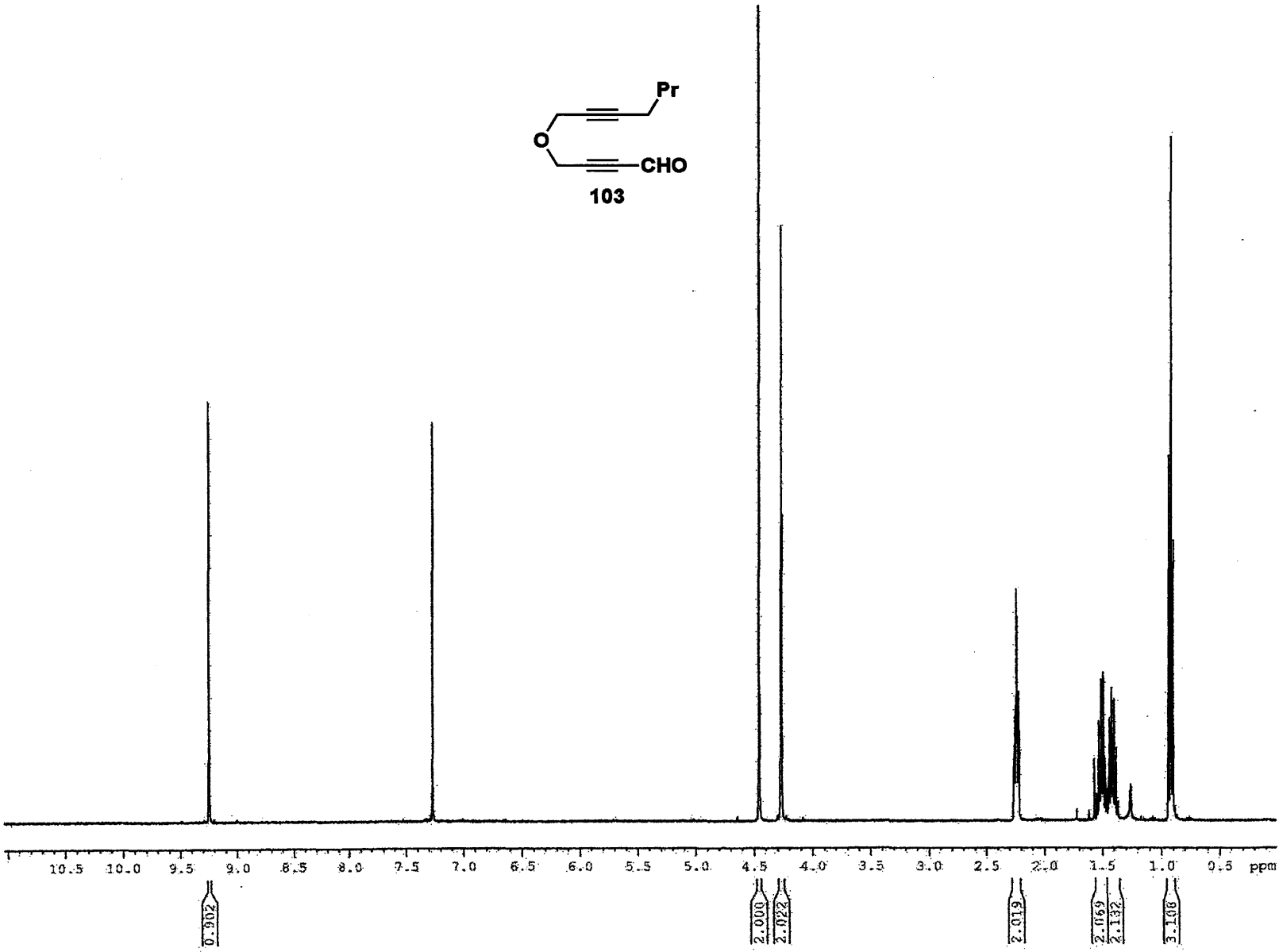

Pr
O
CO2Me
102
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
2.000
2.001
2.957
1.977
4.097
3.051

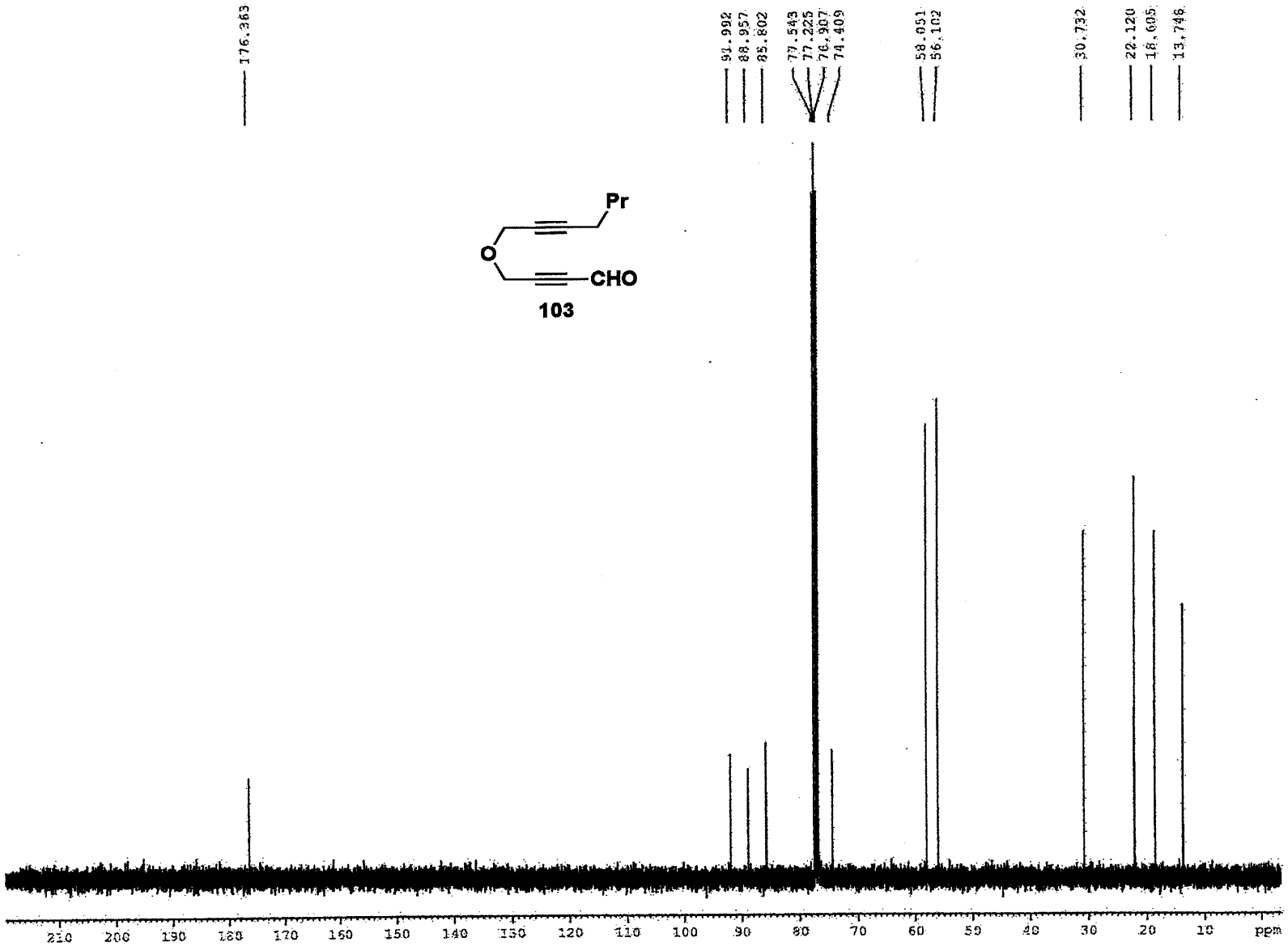

13.769
18.618
22.134
30.759
53.022
55.955
57.919
74.545
76.916
77.233
77.551
78.088
83.426
88.763
153.710
Pr
CO2Me
O
102
ppm

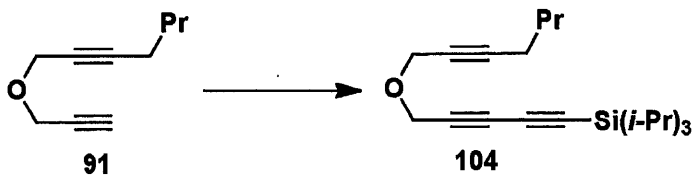


91 103

5-Oxadodeca-2,7-diynal (103). A 25-mL, three-necked, round-bottomed flask equipped with an argon inlet adapter, two rubber septa, and a thermocouple probe was charged with diyne **91** (0.311 g, 2.07 mmol, 1 equiv) and 5.2 mL of THF. The reaction mixture was cooled to -40 °C and *n*-BuLi solution (2.48 M solution in hexanes, 0.84 mL, 2.1 mmol, 1 equiv) was added dropwise over 5 min. The reaction mixture was stirred at -40 °C for 3 min, and then DMF (0.32 mL, 0.30 g, 4.1 mmol, 2 equiv) was added in one portion. The reaction mixture was warmed to rt, stirred 30 min, and then poured into a vigorously stirred biphasic mixture of 10% aq KH_2PO_4 (10 mL, 8.2 mmol, 4 equiv) in 10 mL of Et_2O that was cooled at 0 °C. The organic layer was separated and washed with two 8-mL portions of H_2O. The combined aqueous layers were extracted with 6 mL of Et_2O. The organic layers were combined and dried over $MgSO_4$, filtered, and concentrated to give 0.246 g of pale yellow oil. Purification by column chromatography on 16 g of silica gel (elution with 2-4% EtOAc-hexanes) afforded 0.152 g (41%) of aldehyde **103** as a pale yellow oil: IR (neat) 2862, 2250, 2206, 1674, 1466, 1432, 1382, 1346, 1245, 1113, 1076, 928, 898, 817, and 728 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.25 (s, 1 H), 4.46 (d, J = 0.5 Hz, 2 H), 4.27 (t, J = 2.2 Hz, 2 H), 2.26 (tt, J = 7.0, 2.2 Hz, 2 H), 1.47-1.58 (m, 2 H), 1.35-1.46 (m, 2 H), 0.92 (t, J = 7.2 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.4, 92.0, 89.0, 85.8, 74.4, 58.0, 56.1, 30.7, 22.1, 13.7; HRMS-DART *(m/z)* calcd for $C_{11}H_{14}O_2$ $[M + H]^+$: 179.1072, found: 179.1075.

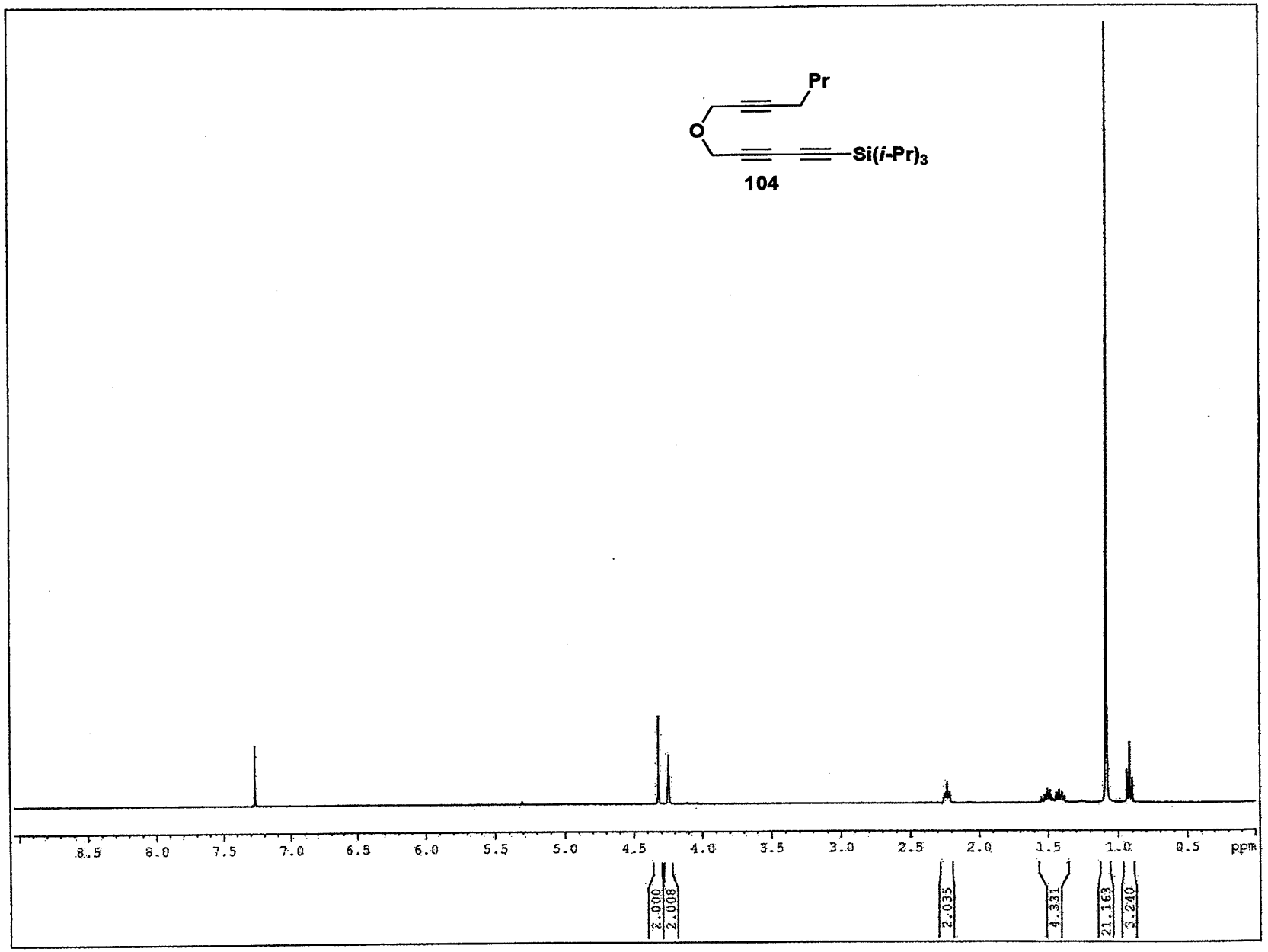

Pr
O
CHO
103
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
0.902
2.000
2.022
2.019
2.069
2.132
3.166

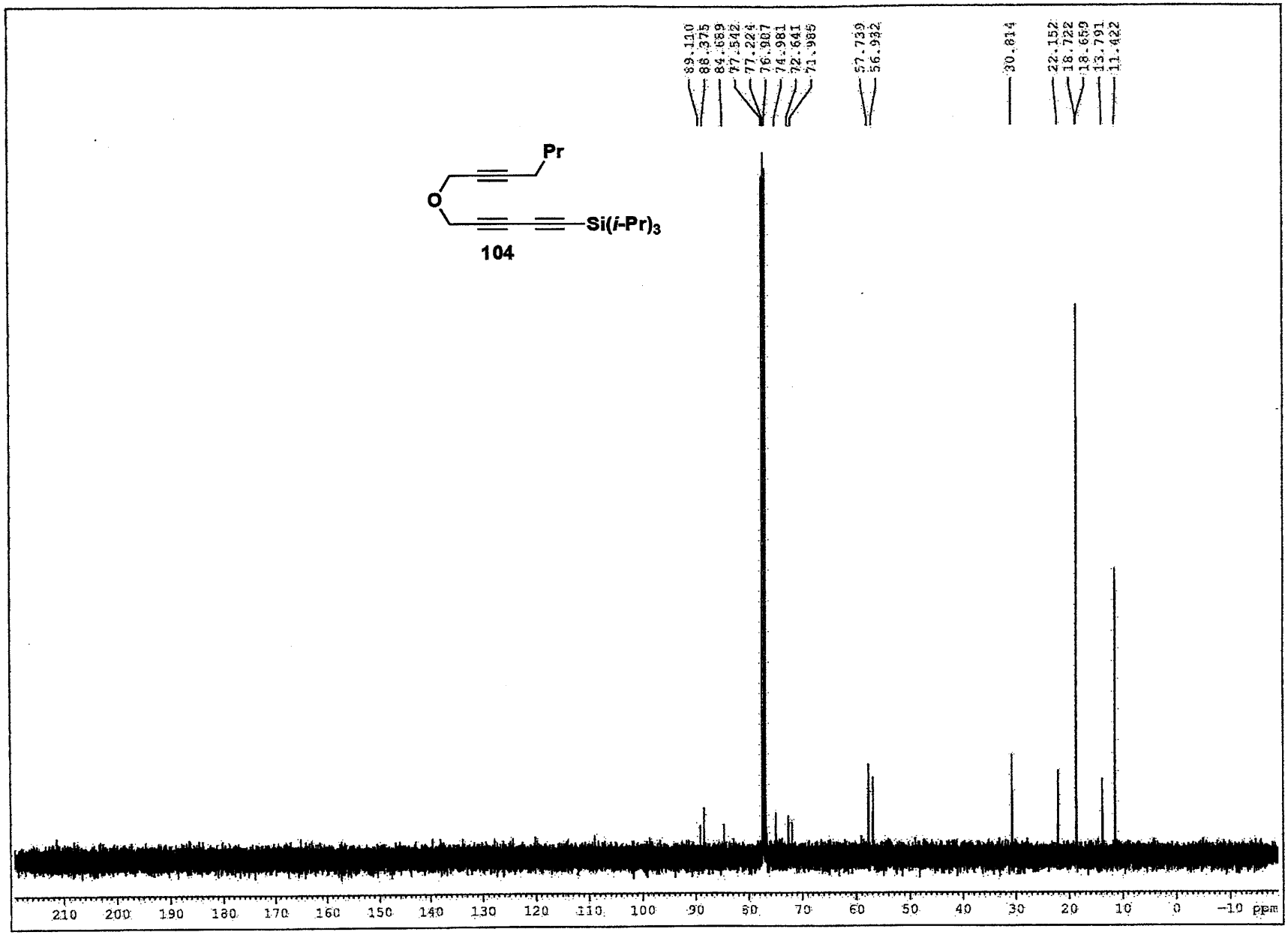

176.363
91.992
88.957
85.802
77.543
77.225
76.907
74.409
58.051
56.102
30.732
22.120
18.605
13.746
Pr
O
CHO
103
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

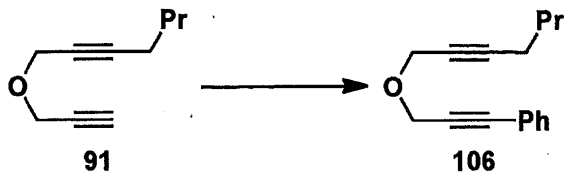


91 104

1-(Triisopropylsilyl)-6-oxatridec-1,3,8-triyne (104). A 100-mL, three-necked, round-bottomed flask equipped with an argon inlet adapter, glass stopper, and rubber septum was charged with diyne **91** (0.216 g, 1.44 mmol, 1.0 equiv), 4 mL of THF, 13 mL of $BuNH_2$ solution (30% w/w in H_2O) and hydroxylamine hydrochloride (0.203 g, 2.92 mmol, 2.0 equiv). CuCl (0.007 g, 0.07 mmol, 0.05 equiv) was added and then a solution of (bromoethynyl)triisopropylsilane (0.480 g, 1.84 mmol, 1.3 equiv) in 9 mL of THF was added dropwise via cannula over 15 min (1-mL THF rinse). The reaction mixture was stirred in the dark at rt for 21 h and then 2.5 mL of 20% aq NaCN solution was added. The resulting mixture was extracted with three 50-mL portions of Et_2O and the combined organic layers were washed with 20 mL of brine, dried over $MgSO_4$, filtered, and concentrated to give 0.573 g of a golden yellow oil. Purification by column chromatography on 17 g of acetone-deactivated silica gel (elution with hexanes) afforded 0.427 g (90%) of triyne **104** as a pale yellow oil: IR (neat) 2106, 1463, 1344, 1136, 1075, 883, and 798 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.32 (s, 2 H), 4.25 (t, J = 2.1 Hz, 2 H), 2.24 (tt, J = 7.0, 2.1 Hz, 2 H), 1.36-1.56 (m, 4 H), 1.09 (s, 21 H), 0.97 (t, J = 7.3 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 89.1, 88.4, 84.7, 75.0, 72.6, 72.0, 57.7, 56.9, 30.8, 22.2, 18.72, 18.66, 13.8, 11.4; HRMS-DART *(m/z)* calcd for $[M + H]^+$ $C_{21}H_{34}OSi$: 331.2457, found: 331.2461.


Pr
O
Si(i-Pr)3
104
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
2.000
2.008
2.035
4.331
21.163
3.240

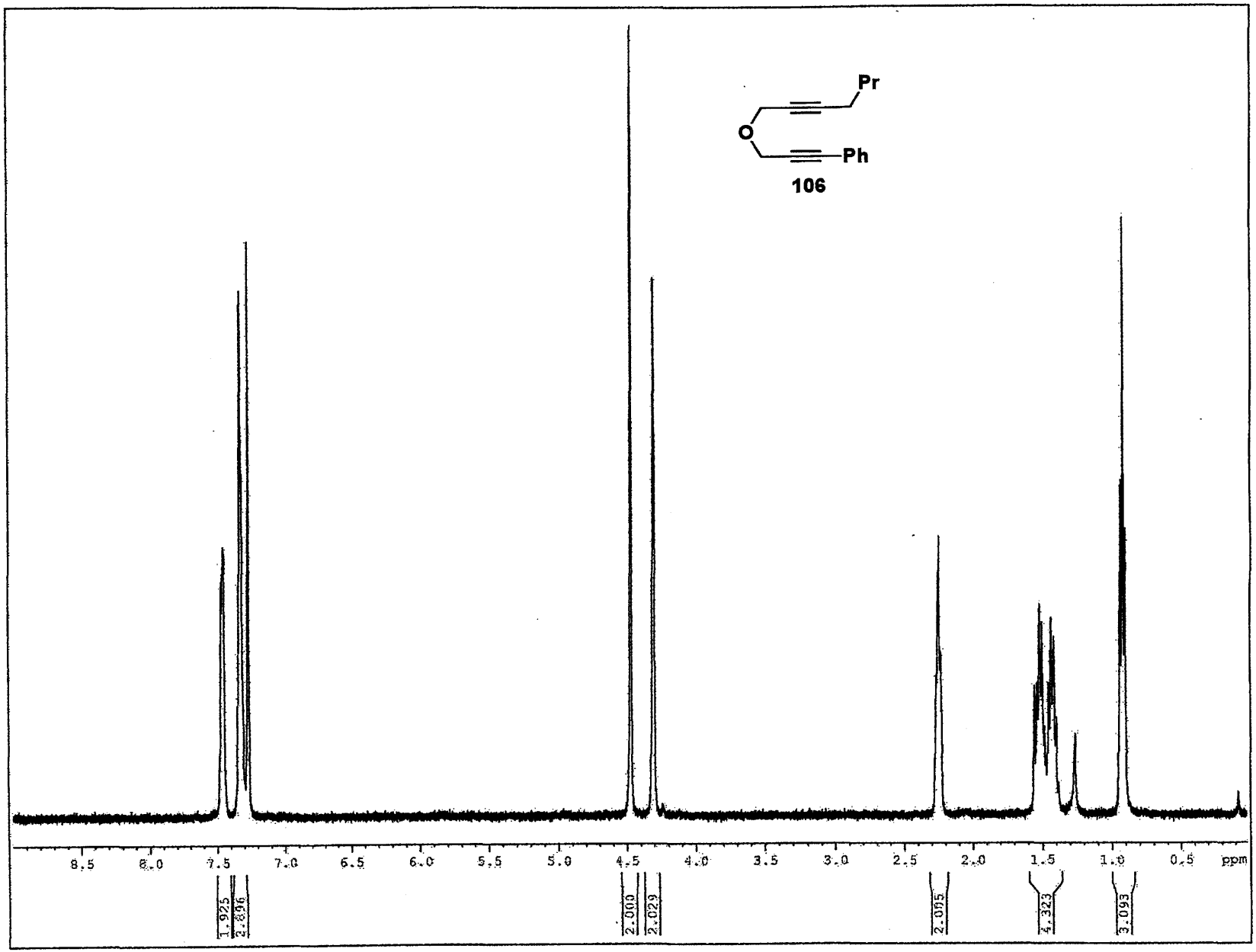

89.110
88.375
84.689
77.542
77.224
76.987
74.981
72.641
71.985
57.739
56.932
30.814
22.152
18.722
18.659
13.791
11.422
Pr
O
Si(i-Pr)3
104
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 ppm



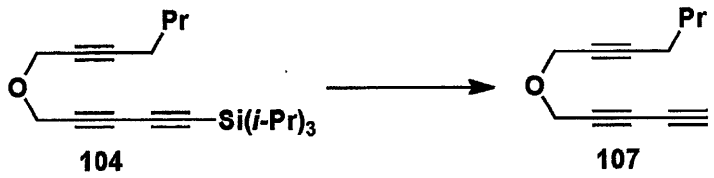
[3-(2-Heptyn-1-yloxy)-1-propyn-1-yl]benzene (106). A 50-mL, three-necked, round-bottomed flask equipped with an argon inlet adapter and two rubber septa was charged with $PdCl_2(PPh_3)_2$ (0.032 g, 0.046 mmol, 0.05 equiv), CuI (0.018 g, 0.093 mmol, 0.10 equiv), and 2 mL of THF. Diisopropylamine (0.26 mL, 0.19 g, 1.8 mmol, 2.0 equiv) and iodobenzene (0.13 mL, 0.24 g, 1.2 mmol, 1.3 equiv) were added. A solution of diyne **91** (0.138 g, 0.921 mmol, 1.0 equiv) in 6 mL of THF was added dropwise via cannula over 30 min (1.2-mL THF rinse). The brown reaction mixture was stirred at rt in the dark for 1.5 h and then filtered through a plug of 1 g of Silica gel with the aid of 100 mL of Et_2O. The filtrate was washed with two 20-mL portions of satd aq $NaHCO_3$ solution and 20 mL of brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated to give 0.301 g of red oil. Purification by column chromatography on 30 g of silica gel (elution with 0.5-1% EtOAc-hexanes) afforded 0.162 g (77%) of arylalkyne **106**[193] as a yellow oil: ^1H NMR (400 MHz, $CDCl_3$) δ 7.43-7.49 (m, 2 H), 7.29-7.35 (m, 3 H), 4.47 (s, 2 H), 4.31 (t, J = 2.1 Hz, 2 H), 2.21-2.29 (m, 2 H), 1.47-1.57 (m, 2 H), 1.38-1.47 (m, 2H), 0.92 (t, J = 7.2 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 132.0, 128.6, 128.4, 122.7, 87.9, 86.7, 84.7, 75.3, 57.5, 57.3, 30.8, 22.1, 18.6, 13.8.

---

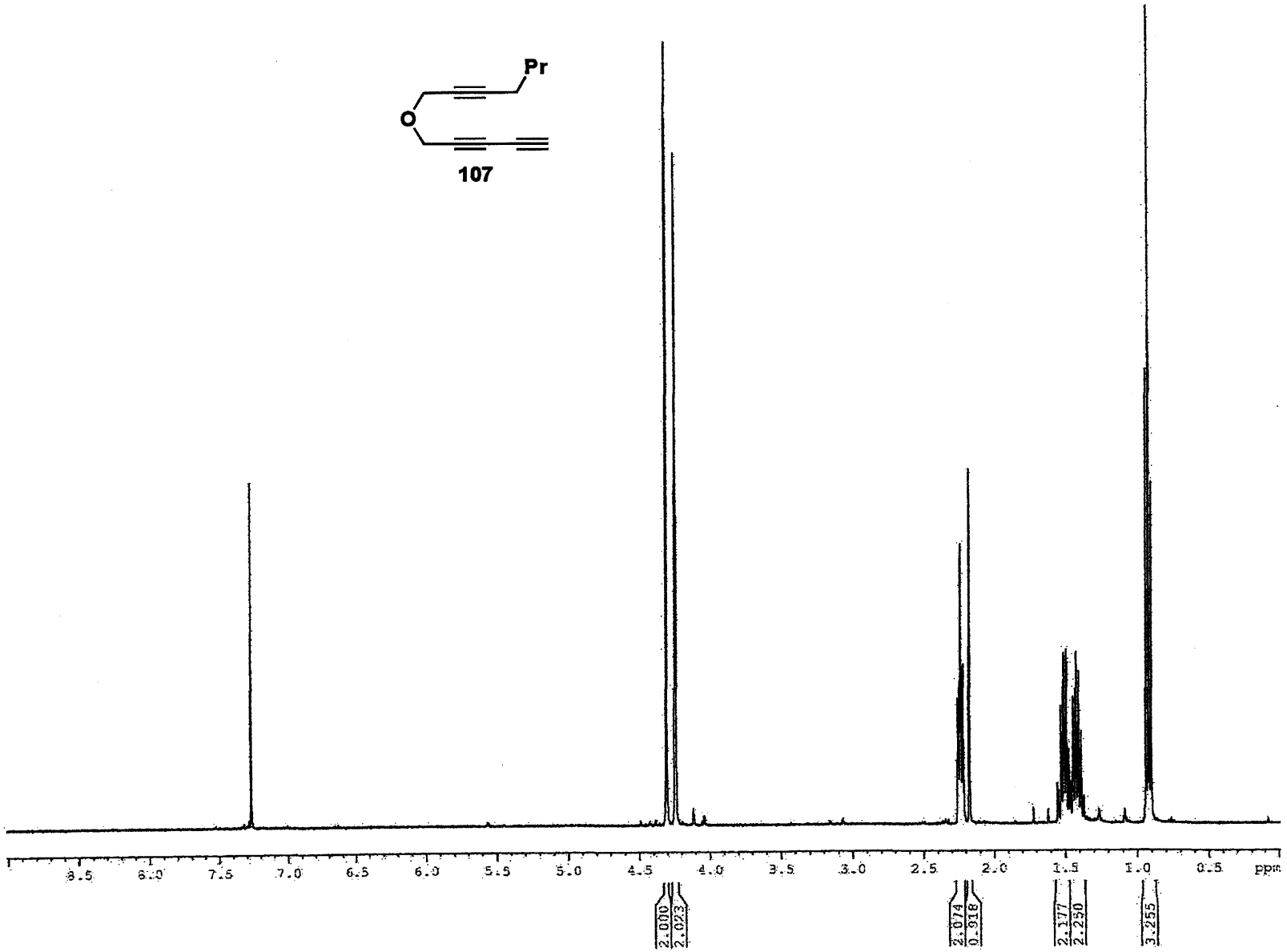
[193] Spectroscopic data were identical with that previously reported: Jung, I. G.; Seo, J.; Lee, S. I.; Choi, S. Y.; Chung, Y. K. *Organometallics* **2006**, *25*, 4240-4242.

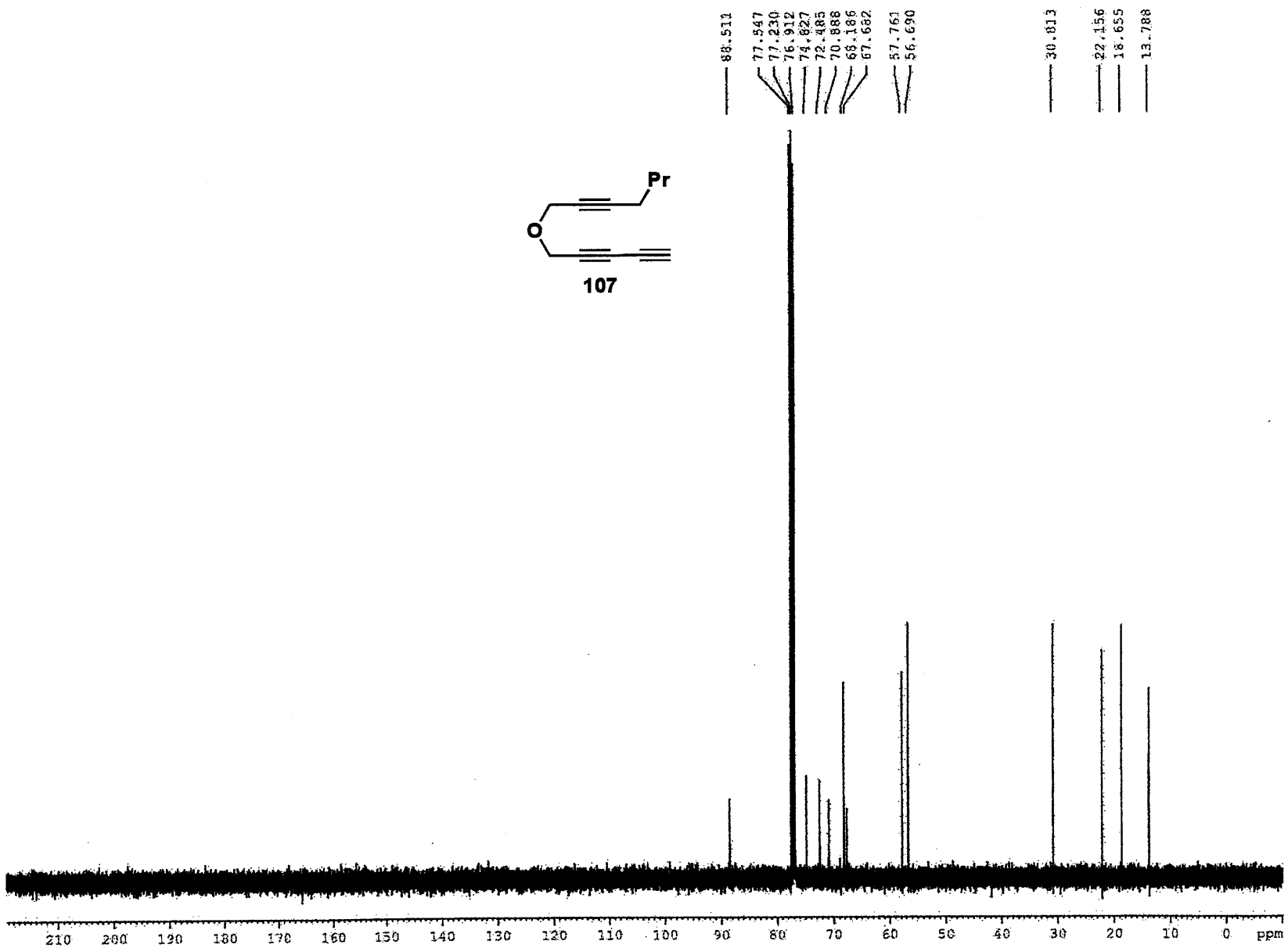

Pr
O
Ph
106
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
1.925
2.896
2.000
2.029
2.065
4.323
3.093

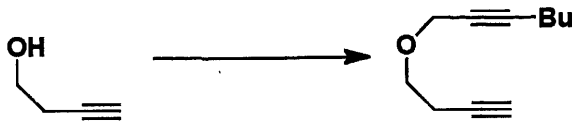
131.930
128.639
128.444
122.748
87.927
86.650
84.791
77.544
77.226
76.909
75.301
57.459
57.256
30.818
22.121
18.648
13.764
Pr
Ph
106
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm



6-Oxatridec-1,3,8-triyne (107). A 25-mL, two-necked, round-bottomed flask equipped with an argon inlet adapter and a rubber septum was charged with triyne **104** (0.287 g, 0.869 mmol, 1 equiv) and 8.6 mL of THF. The reaction mixture was cooled to 0 °C and TBAF solution (1.0 M in THF, 1.04 mL, 1.04 mmol, 1.2 equiv) was added dropwise over 2 min. The dark brown reaction mixture was stirred at 0 °C for 2 h, and then 1 mL of satd aq $NaHCO_3$ solution and 5 mL of H_2O were added. The resulting mixture was extracted with 100 mL of Et_2O and the organic layer was dried over Na_2SO_4, filtered, and concentrated to give 0.297 g of brown oil. Purification by column chromatography on 15 g of acetone-deactivated silica gel (elution with hexanes) afforded 0.096 g (64%) of triyne **107** as a golden yellow oil: IR (neat) 2224, 1466, 1433, 1352, 1135, 1074, and 895 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.31 (d, J = 1.0 Hz, 2 H), 4.24 (t, J = 2.1 Hz, 2 H), 2.24 (tt, J = 7.0, 2.1 Hz, 2 H), 2.16-2.19 (m, 1 H), 1.46-1.56 (m, 2 H), 1.36-1.45 (m, 2 H), 0.92 (t, J = 7.2 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 88.5, 74.8, 72.5, 70.9, 68.2, 67.7, 57.8, 56.7, 30.8, 22.1, 18.7, 13.8; HRMS-ESI *(m/z)* calcd for $C_{12}H_{14}O$ $[M + Na]^+$: 197.0937, found: 197.0943.

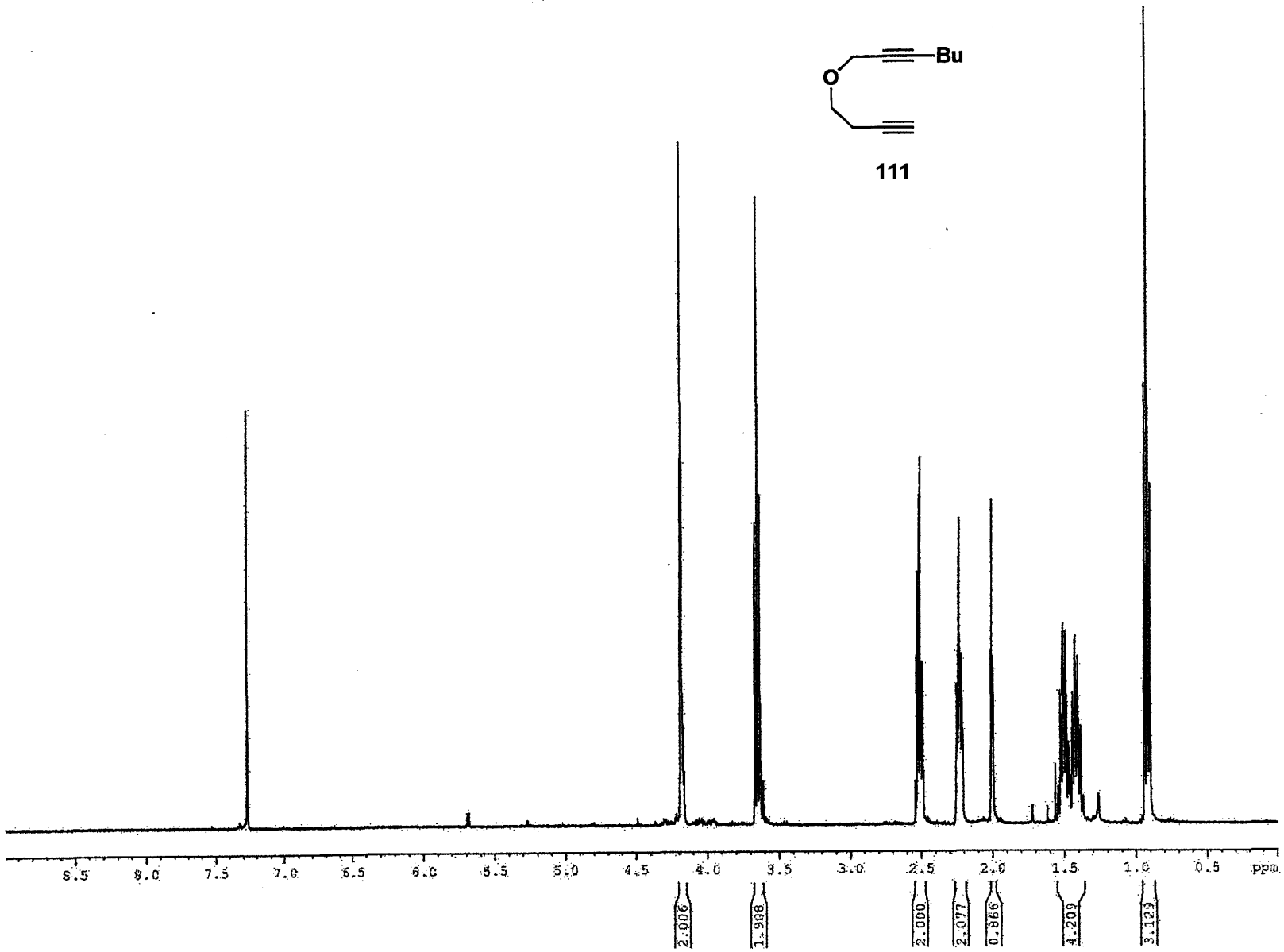

Pr
O
107
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
2.000
2.023
2.074
0.918
2.177
2.250
3.255

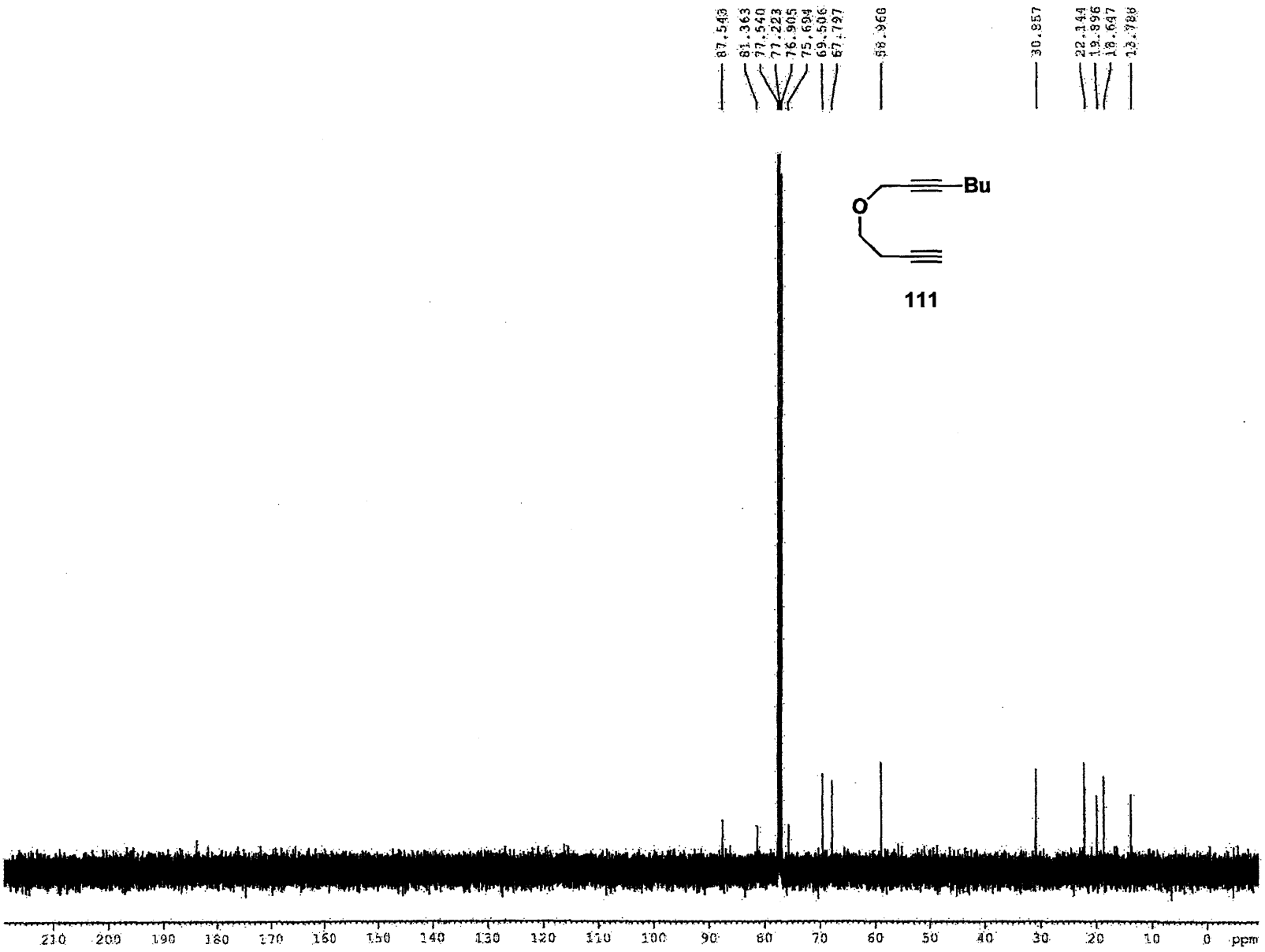

88.511
77.547
77.230
76.912
74.827
72.485
70.888
68.186
67.662
57.761
56.690
30.813
22.156
18.655
13.788
Pr
O
107
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

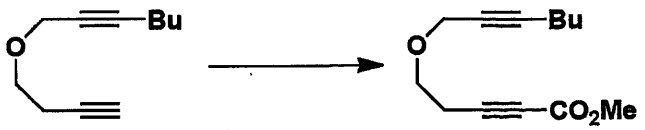


110 111

5-Oxadodeca-1,7-diyne (111). A 50-mL, three-necked, round-bottomed flask equipped with an argon inlet adapter and two rubber septa was charged with sodium hydride (60% dispersion in mineral oil, 0.263 g, 6.56 mmol, 1.1 equiv) and 10 mL of THF. The reaction mixture was cooled to 0 °C and 3-butyn-1-ol **110** (0.45 mL, 0.42 g, 5.9 mmol, 1 equiv) was added dropwise over 1 min. The reaction mixture was stirred at 0 °C for 1 h (gas evolution). A solution of 1-bromo-2-heptyne (1.062 g, 6.06 mmol, 1.02 equiv) in 5 mL of THF was added dropwise via cannula over 1 min. The yellow reaction mixture was warmed to rt and stirred in the dark for 43 h. The resulting pale orange slurry was diluted with 10 mL of satd aq NH_4Cl solution and extracted with three 50-mL portions of Et_2O. The combined organic layers were washed with 50 mL of brine, dried over $MgSO_4$, filtered, and concentrated to give 1.019 g of red oil. Purification by column chromatography on 87 g of silica gel (elution with 0-10% EtOAc-hexanes) afforded 0.407 g (42%) of diyne **111** as a yellow oil: IR (neat) 2236, 1466, 1357, 1136, 1095, and 1013 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.18 (t, J = 2.2 Hz, 2 H), 3.64 (t, J = 7.0 Hz, 2 H), 2.51 (td, J = 7.0, 2.7 Hz, 2 H), 2.23 (tt, J = 7.0, 2.1 Hz, 2 H), 2.00 (t, J = 2.7 Hz, 1 H), 1.45-1.56 (m, 2 H), 1.37-1.45 (m, 2 H), 0.92 (t, J = 7.2 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 87.5, 81.4, 75.7, 69.5, 67.8, 59.0, 30.9, 22.1, 19.9, 18.6, 13.8; HRMS-ESI *(m/z)* calcd for $C_{11}H_{16}O$ [M + H]$^+$: 165.1274, found: 165.1277.

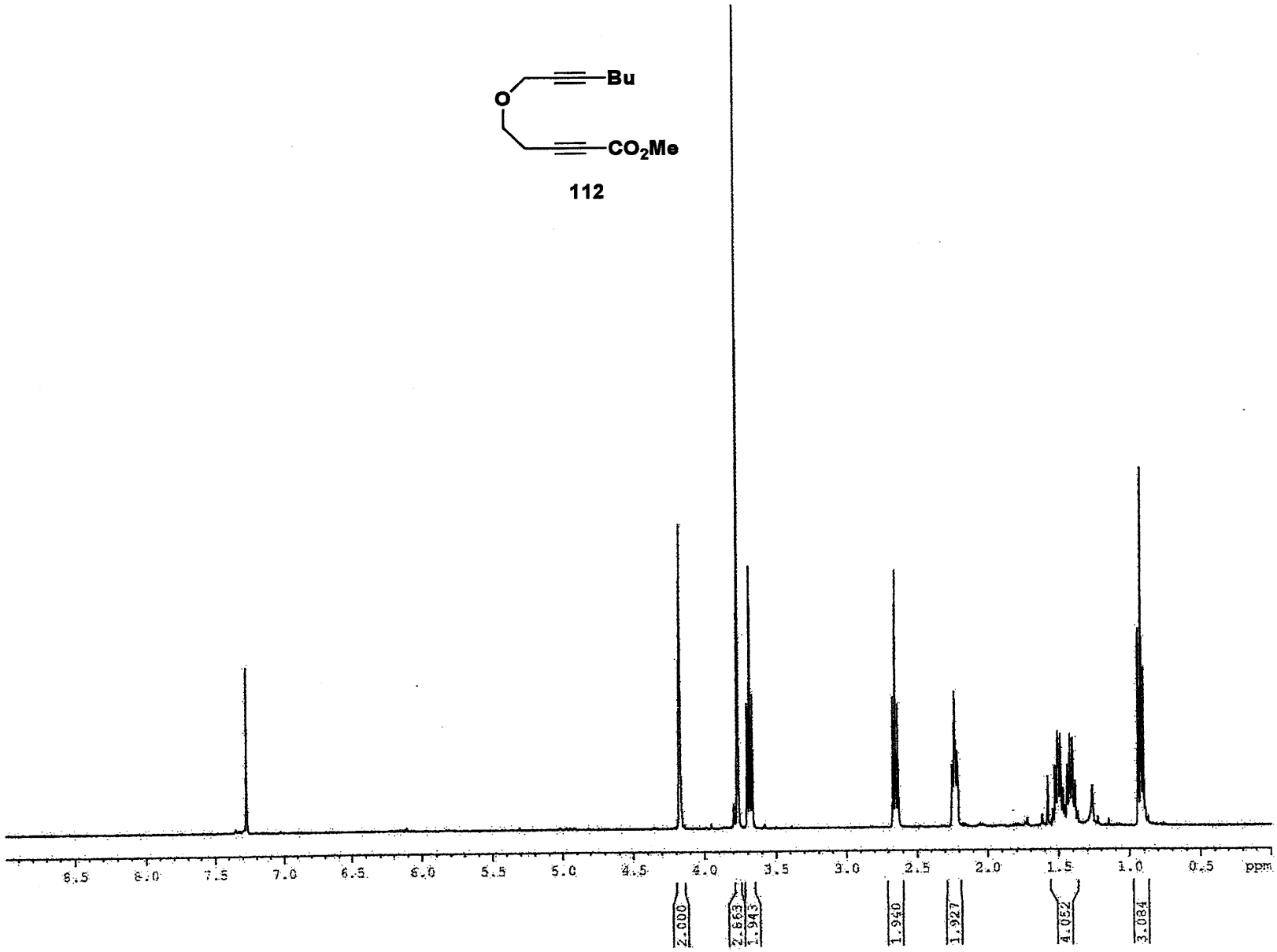

Bu
O
111
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
2.006
1.908
2.000
2.077
0.866
4.209
3.129


87.545
81.363
77.540
77.223
76.905
75.694
69.506
67.797
58.968
30.857
22.144
19.896
18.647
13.786
Bu
O
111
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

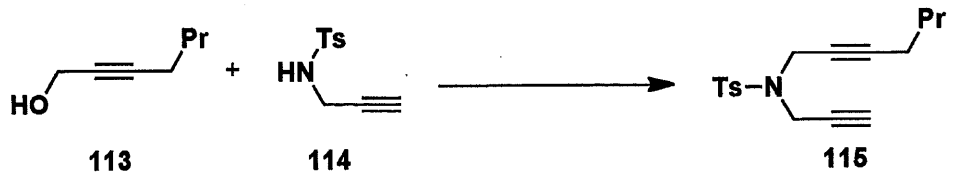


111 112

Methyl 6-oxatrideca-2,8-diynoate (112). A 25-mL, three-necked, round-bottomed flask equipped with an argon inlet adapter, two rubber septa, and a thermocouple probe was charged with diyne **111** (0.300 g, 1.83 mmol, 1 equiv) and 3 mL of Et_2O. The reaction mixture was cooled to -78 °C and *n*-BuLi solution (2.48 M in hexanes, 0.85 mL, 2.1 mmol, 1.1 equiv), was added dropwise over 4 min. The pale orange reaction mixture was stirred at -78 °C for 20 min. A 50-mL, three-necked, round-bottomed flask equipped with an argon inlet adapter, two rubber septa, and a thermocouple probe was charged with methyl chloroformate (0.60 mL, 0.73 g, 7.7 mmol, 4.2 equiv) and 4 mL of Et_2O. This solution was cooled to -35 °C and the lithium acetylide solution was added dropwise via cannula over 5 min (1-mL Et_2O rinse). The reaction mixture was warmed to -25 °C and stirred for 25 min, and then warmed to -10 °C and quenched by addition of 5 mL of satd aq NH_4Cl solution. The reaction mixture was diluted with 10 mL of H_2O and extracted with 100 mL of Et_2O. The organic layer was washed with 25 mL of brine, dried over $MgSO_4$, filtered, and concentrated to give 0.371 g of yellow oil. Purification by column chromatography on 74 g of silica gel (elution with 3-4% EtOAc-hexanes) afforded 0.215 g (53%) of diyne **112** as a yellow oil: IR (neat) 2873, 2242, 1716, 1435, 1357, 1256, 1136, 1078, and 753 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.17 (t, J = 2.1 Hz, 2 H), 3.78 (s, 3 H), 3.68 (t, J = 6.9 Hz, 2 H), 2.65 (t, J = 6.9 Hz, 2 H), 2.23 (tt, J = 7.0, 2.0 Hz, 2 H), 1.36-1.55 (m, 4 H), 0.92 (t, J = 7.2 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.2, 87.8, 86.4, 75.4, 73.7, 66.6, 59.0, 52.8, 30.8, 22.1, 20.1, 18.6, 13.7; HRMS-DART *(m/z)* calcd for $C_{13}H_{18}O_3$ $[M + H]^+$: 223.1334, found: 223.1338.

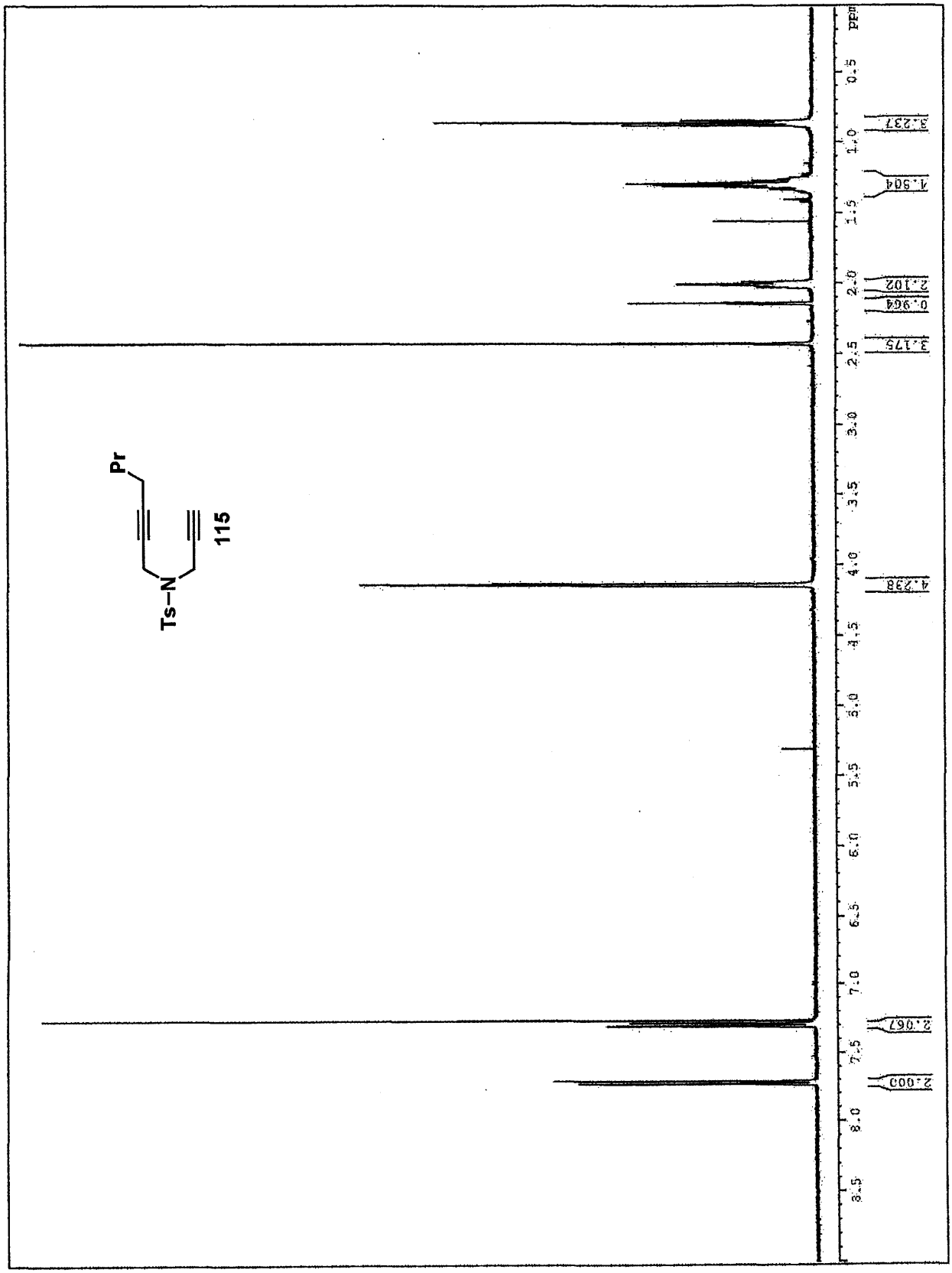

Bu
O
CO2Me
112
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
2.000
2.663
1.943
1.940
1.927
4.052
3.084

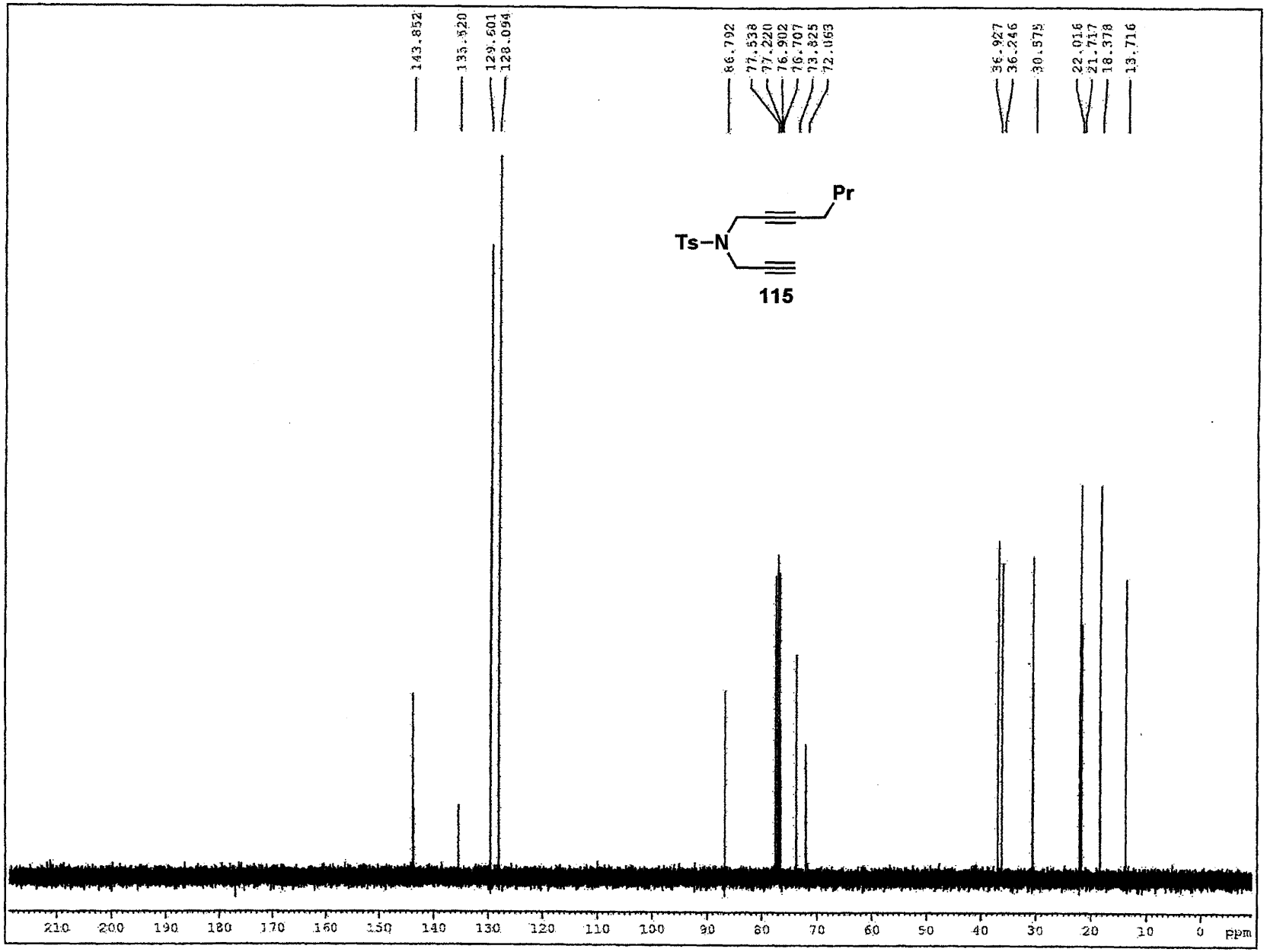
154.191
87.797
86.381
77.544
77.227
76.909
75.415
73.750
66.586
59.008
52.816
30.805
22.127
20.155
18.603
13.757
Bu
O
CO2Me
112
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

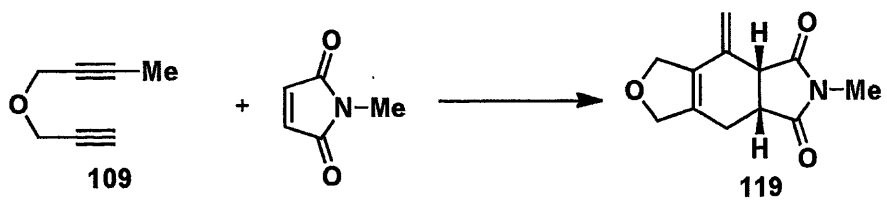


113 114 115

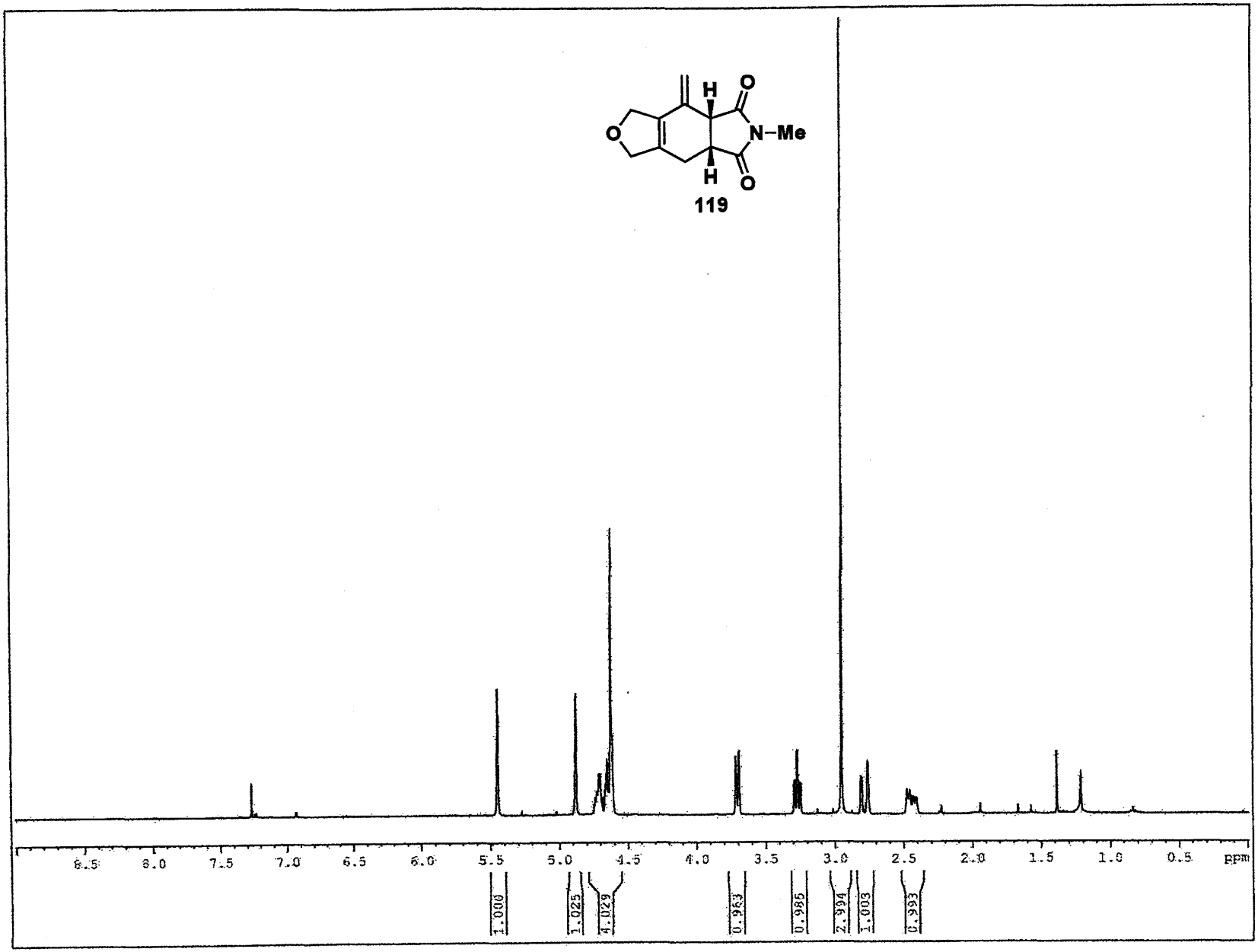
4-(*p*-Toluenesulfonyl)-4-azaundec-1,6-diyne (115). A 25-mL, three-necked, round-bottomed flask equipped with an argon inlet adapter and two rubber septa was charged with sulfonamide **114** (0.193 g, 0.92 mmol, 1.07 equiv), triphenylphosphine (0.272 g, 1.0 mmol, 1.2 equiv), and 4.3 mL of THF. 2-Heptyn-1-ol **113** (0.11 mL, 0.10 g, 0.86 mmol, 1.0 equiv) was added in one portion and then DIAD (0.20 mL, 0.21 g, 1.0 mmol, 1.2 equiv) was added dropwise over 2 min. The reaction mixture was stirred at rt for 2 h and then concentrated to give 0.918 g of a pale yellow oil. Purification by column chromatography on 18 g of silica gel (elution with 20% EtOAc-hexanes) provided 0.254 g (96%) of diyne **115** as a pale yellow oil: IR (neat) 3285, 2959, 2933, 2873, 2233, 1598, 1495, 1433, 1352, 1252, 1164, 1094, 898, 815, 752, and 660 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.69-7.74 (m, 2 H), 7.27-7.32 (m, 2 H), 4.15-4.56 (m, 4 H), 2.42 (s, 3 H), 2.14 (t, J = 2.4 Hz, 1 H), 2.00 (tt, J = 6.8, 2.4 Hz, 2 H), 1.22-1.35 (m, 4 H), 0.86 (t, J = 7.2 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.9, 135.5, 129.6, 128.1, 86.8, 76.7, 73.8, 72.0, 36.9, 36.2, 30.6, 22.0, 21.7, 18.4, 13.7; HRMS-ESI *(m/z)*: $[M + Na]^+$ calcd for $C_{17}H_{21}NO_2S$: 326.1185, found: 326.1193.

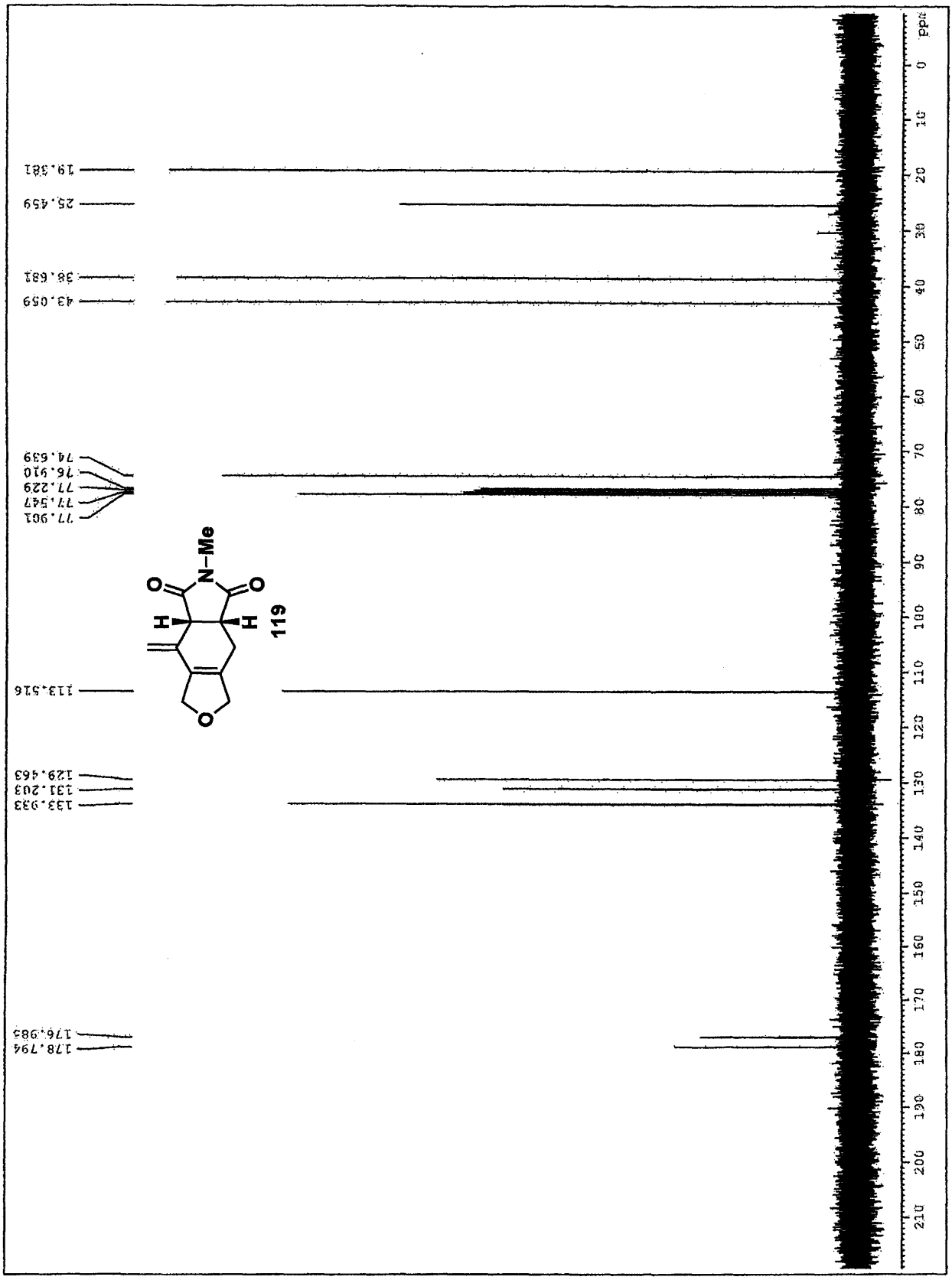

Pr
Ts–N
115
2.000
2.067
4.238
3.175
0.964
2.102
1.504
3.237
ppm

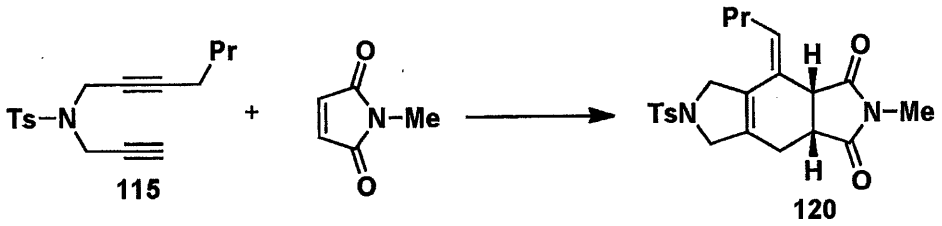

143.852
135.620
129.601
128.094
86.792
77.538
77.220
76.902
76.707
73.825
72.063
36.927
36.246
30.575
22.016
21.717
18.378
13.716
Pr
Ts–N
115
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm



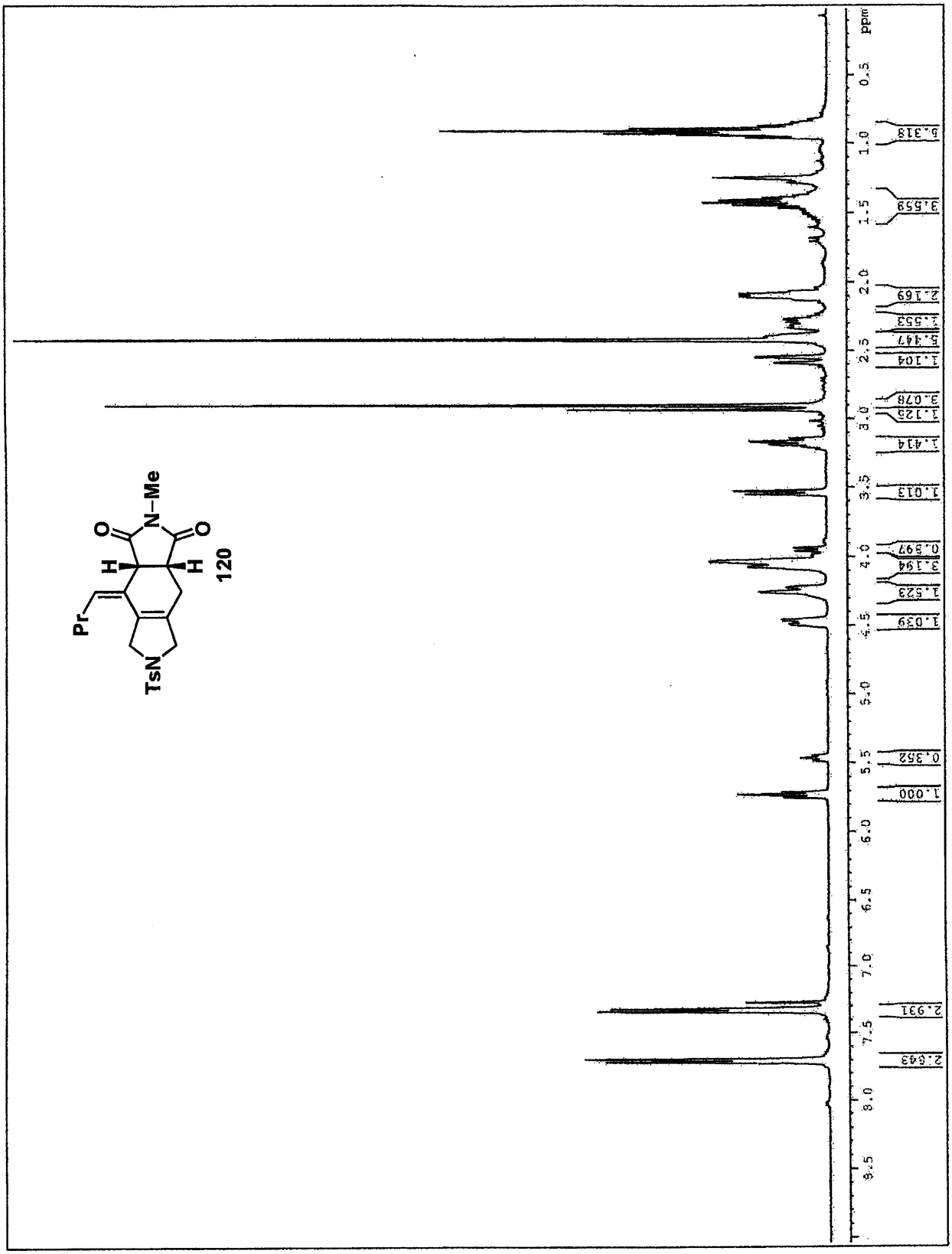
***cis*-4-Methylene-6-methyl-4,4a,7a,8-tetrahydro-1*H*-furo[3,4-*f*]isoindole-5,7(3*H*,6*H*)-dione (119).** A 10-cm threaded Pyrex tube (25 mm O.D.; 17 mm I.D.) equipped with a rubber septum fitted with an argon inlet needle was charged with *N*-methylmaleimide (0.112 g, 1.00 mmol, 1.0 equiv) and a solution of diyne **109** (0.109 g, 1.00 mmol, 1.0 equiv) in 10 mL of toluene. The reaction mixture was degassed via three freeze-pump-thaw cycles (-196 °C, <0.5 mmHg) and then the tube was sealed with a threaded Teflon cap. The reaction mixture was heated at 160 °C for 18 h and then cooled to rt and concentrated to give 0.348 g of yellow oil. Purification by column chromatography on 16 g of silica gel (elution with 40-70% Et_2O-hexanes) provided 0.113 g (52%) of diene **119** as a white solid: mp 117-119 °C; IR (thin film) 2918, 2886, 2857, 1703, 1436, 1383, 1364, 1309, 1217, 1051, 896, and 791 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.45 (s, 1 H), 4.88 (s, 1 H), 4.60-4.75 (m, 4 H), 3.70 (d, J = 8.5 Hz, 1 H), 3.27 (td, J = 8.5, 2.4 Hz, 1 H), 2.95 (s, 3 H), 2.79 (d, J = 17.5 Hz, 1 H), 2.44 (dd, J = 17.5, 8.5 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.8, 177.0, 133.9, 131.2, 129.5, 113.5, 77.9, 74.6, 43.0, 38.7, 25.4, 19.4; HRMS-ESI *(m/z)*: $[M + Na]^+$ calcd for $C_{12}H_{13}NO_3$: 242.0788, found: 242.0796.

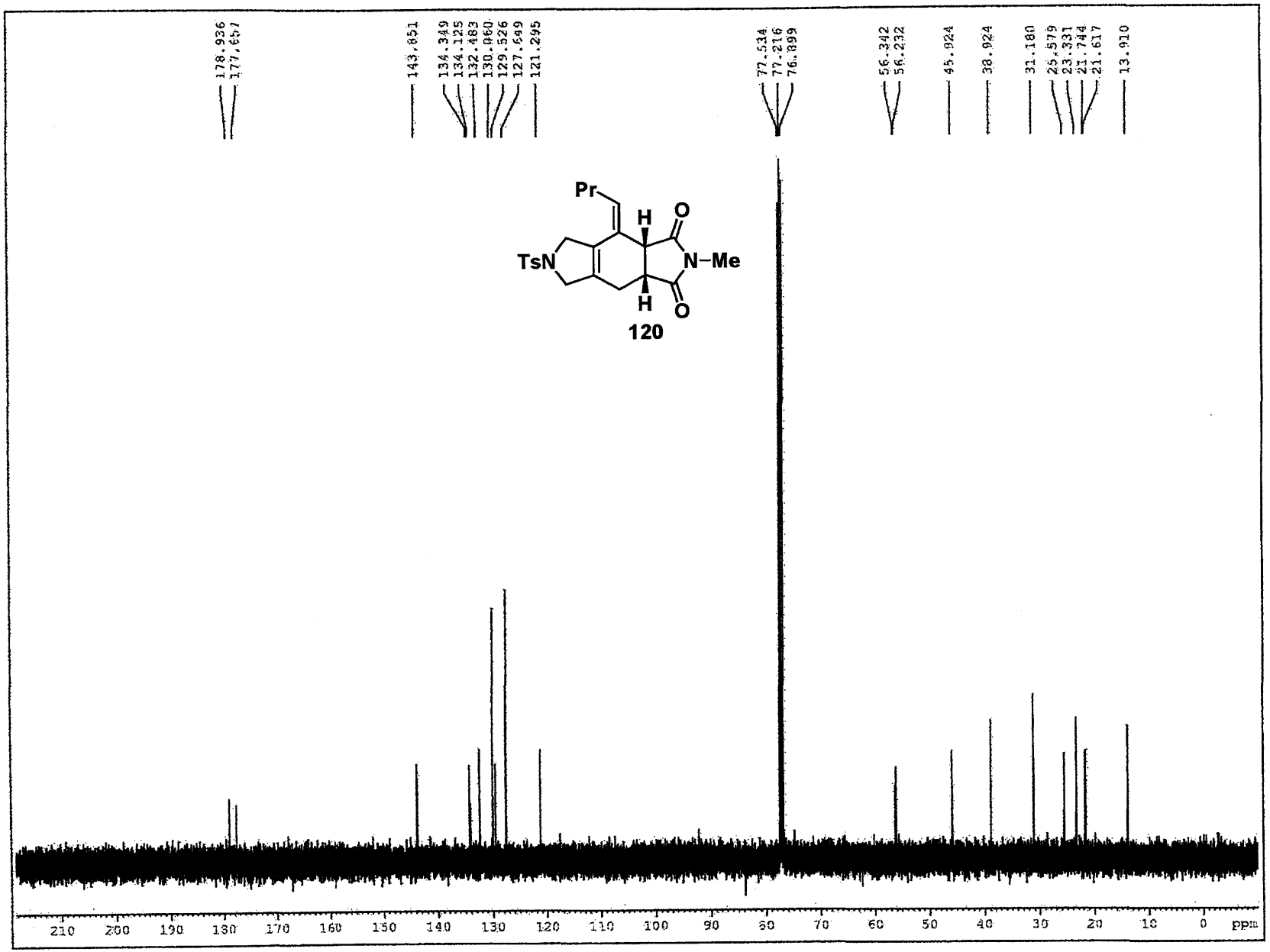

H
O
N–Me
O
H
O
119
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
1.000
1.025
4.029
0.963
0.985
2.994
1.003
0.993

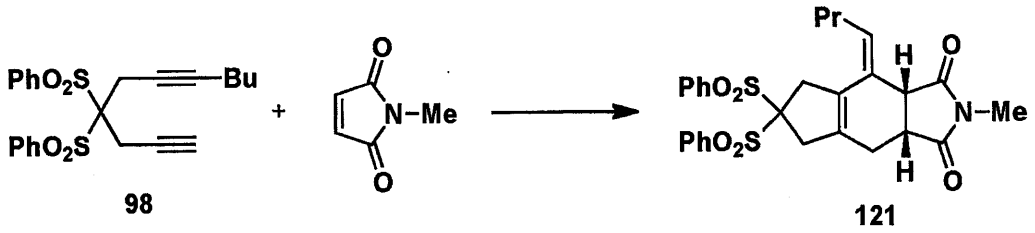

19.581
25.459
38.681
43.059
74.639
76.910
77.229
77.547
77.901
113.516
129.463
131.203
133.933
176.985
178.794
N–Me
O
O
H
H
119
ppm



(*Z*)-*cis*-2-(*p*-Toluenesulfonyl)-4-butylidene-6-methyl-4,4a,7a,8-tetrahydro-1*H*-pyrollo[3,4-*f*]isoindole-5,7(3*H*,6*H*)-dione (120). A 10-cm threaded Pyrex tube (20 mm O.D.; 13 mm I.D.) equippedwith a rubber septum fitted with an argon inlet needle was charged with *N*-methylmaleimide (0.041 g, 0.37 mmol, 1.0 equiv) and a solution of diyne **115** (0.113 g, 0.37 mmol, 1.0 equiv) in 3.7 mL of toluene. The reaction mixture was degassed via three freeze-pump-thaw cycles (-196 °C, <0.5 mmHg) and then the tube was sealed with a threaded Teflon cap. The reaction mixture was heated at 160 °C for 11 h and then cooled to rt and concentrated to give 0.161 g of a tan solid. Purification by column chromatography on 16 g of silica gel (elution with 30-40% EtOAc-hexanes) gave 0.115 g (75%) of a mixture of diene **120** and the corresponding *E* isomer (74:26 by ^{1}H NMR analysis) as a pale orange solid: mp 87-88 °C; IR (thin film) 2871, 2255, 1778, 1703, 1599, 1435, 1383, 1345, 1288, 1164, 1103, 915, 816, 732, and 671 cm^{-1}; HRMS-ESI *(m/z)*: $[M + Na]^+$ calcd for $C_{22}H_{26}N_2O_4S$: 437.1505, found: 437.1515. For the major *Z* isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, J = 8.0 Hz, 2 H), 7.33 (d, J = 7.9 Hz, 2 H), 5.73 (t, J = 7.5 Hz, 1 H), 4.43-4.57 (m, 1 H), 4.01-4.12 (m, 3 H), 3.54 (d, J = 8.6 Hz, 1 H), 3.13-3.24 (m, 1 H), 2.91 (s, 3 H), 2.57 (d, J = 17.5 Hz, 1 H), 2.43 (s, 3 H), 2.24-2.35 (m, 1 H), 2.05-2.14 (m, 2 H), 1.37-1.49 (m, 2 H), 0.93 (t, J = 7.4 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.9, 177.6, 143.8, 134.3, 134.1, 132.5, 130.0, 129.5, 127.6, 121.3, 56.3, 56.2, 45.9, 38.9, 31.2, 25.6, 23.3, 21.7, 21.6, 13.9. Assignment of *Z* stereochemistry for the major isomer is based on the downfield chemical shift of the alkenyl proton in the *Z* isomer (5.73 ppm) compared to the E isomer (5.47 ppm) by analogy with compound **92**. For the minor *E* isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, J = 8.0 Hz, 2 H), 7.33 (d, J = 7.9 Hz, 2 H), 5.47 (t, J = 7.2 Hz, 1 H), 4.20-4.32 (m, 4 H), 3.95 (d, J = 8.9 Hz, 1 H), 3.13-3.24 (m, 1 H), 2.94 (s, 3 H), 2.43 (s, 3 H), 2.37-2.44 (m, 3 H), 2.24-2.35 (m, 1 H), 1.37-1.49 (m, 2 H), 0.94 (t, J = 7.5 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.1, 176.3, 143.8, 134.2, 133.0, 131.1, 130.1, 128.5, 127.7, 122.0, 57.4, 54.3, 40.9, 38.5, 31.3, 25.5, 22.8, 22.3, 21.7, 14.1.

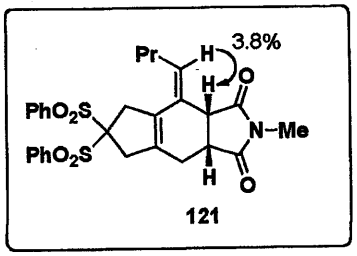

N–Me
O
O
H
H
Pr
TsN
120
ppm
9.318
3.559
2.169
1.553
5.447
1.104
3.078
1.125
1.414
1.013
0.597
3.194
1.523
1.039
0.352
1.000
2.931
2.643

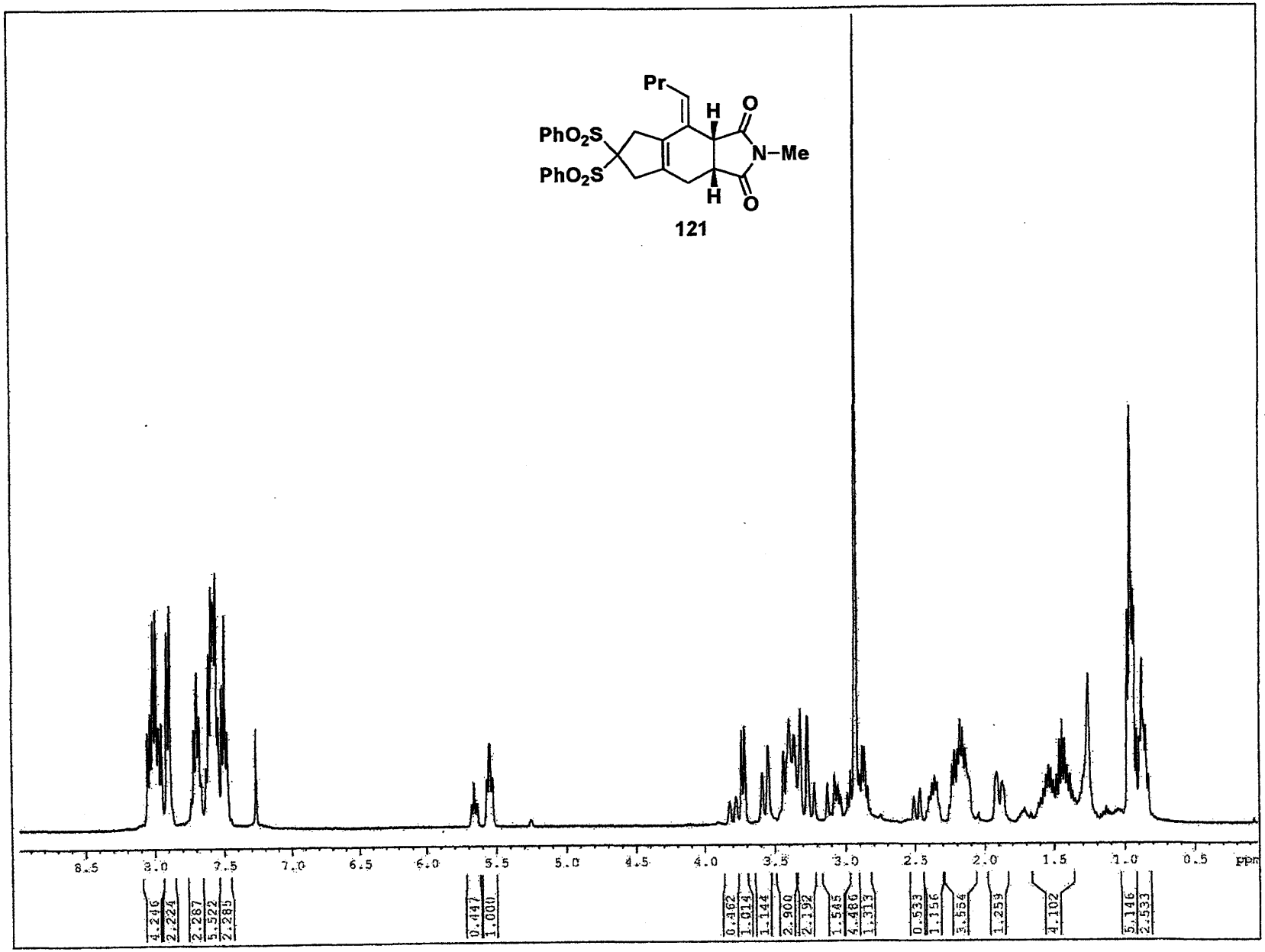

178.936
177.657
143.651
134.349
134.125
132.483
130.060
129.526
127.649
121.295
77.534
77.216
76.899
56.342
56.232
45.924
38.924
31.180
25.579
23.331
21.744
21.617
13.910
Pr
H
O
TsN
N–Me
H
O
120
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

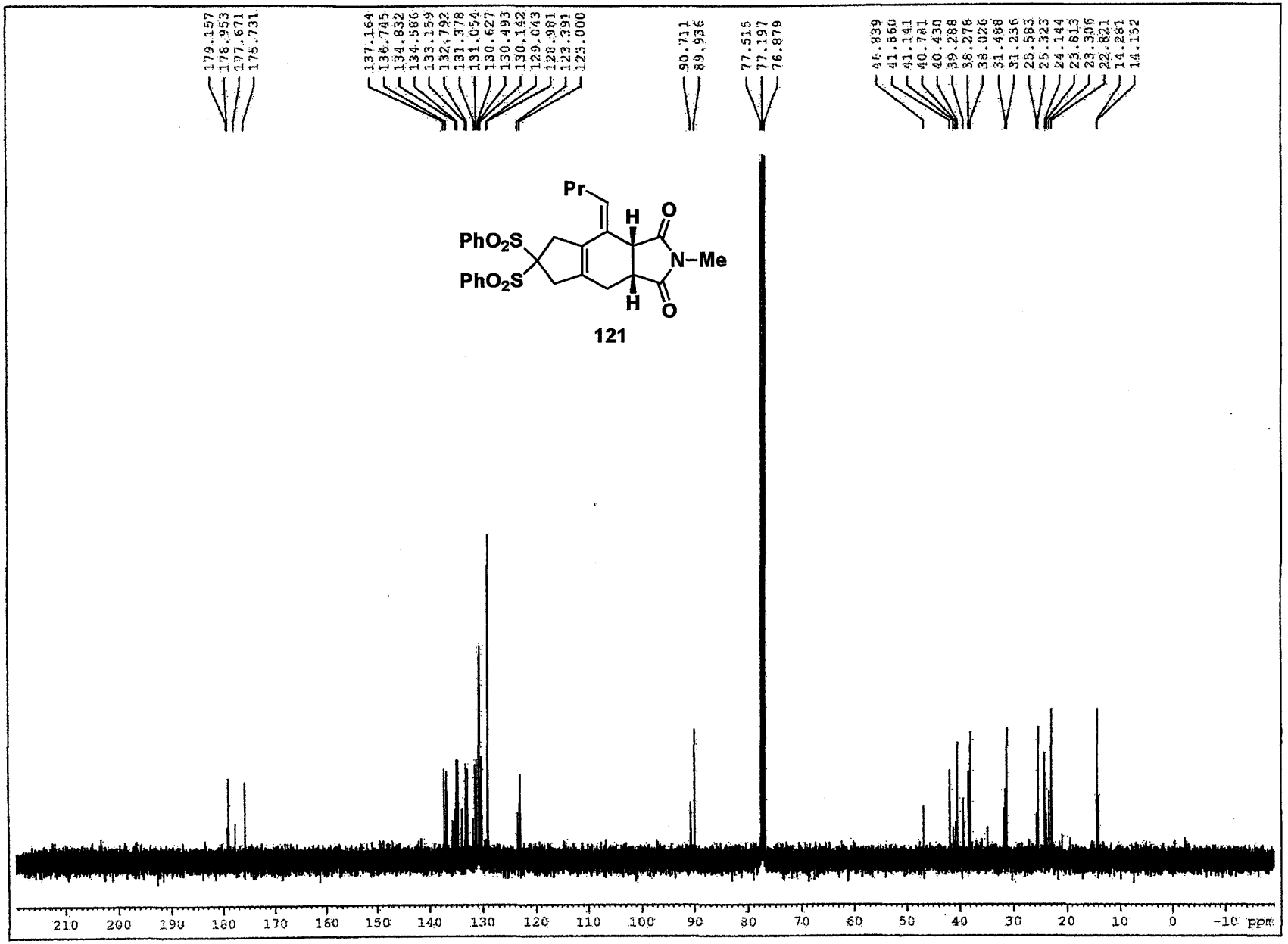


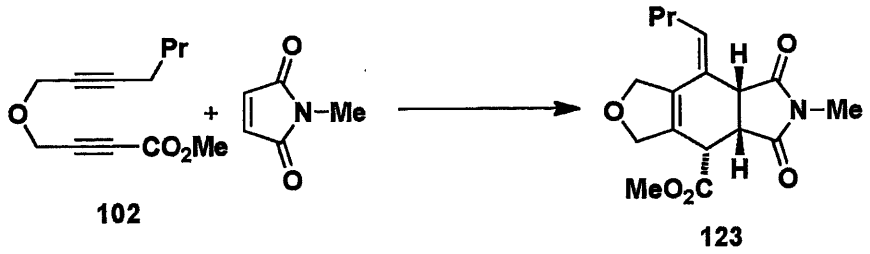
(*Z*)-*cis*-4-Butylidene-2-methyl-6,6-bis(phenylsulfonyl)-3a,4,6,7,8,8a-hexahydrocyclopenta-[*f*]isoindole-1,3(2*H*,5*H*)-dione (121). A-10 cm threaded Pyrex tube (18 mm O.D.; 13 mm I.D.) equipped with a rubber septum fitted with an argon inlet needle was charged with *N*-methylmaleimide (0.030 g, 0.27 mmol, 1.0 equiv) and a solution of diyne **98** (0.114 g, 0.27 mmol, 1.0 equiv) in 2.7 mL of toluene. The reaction mixture was degassed via three freeze-pump-thaw cycles (-196 °C, <0.5 mmHg) and then the tube was sealed with a threaded Teflon cap. The reaction mixture was heated at 150 °C for 8 h and then cooled to rt and concentrated to give 0.159 g of a brown oil. Purification by column chromatography on 12 g of silica gel (elution with 20-50% EtOAc-hexanes) gave 0.105 g (73%) of a mixture of diene **121** and the corresponding *E* isomer (69:31 by ^{1}H NMR analysis) as a tan solid: mp 94-96 °C; IR (thin film) 2872, 2256, 1777, 1704, 1584, 1447, 1382, 1330, 1312, 1147, 1079, 913, 728, and 688 cm^{-1}; HRMS-ESI *(m/z)*: $[M + Na]^+$ calcd for $C_{28}H_{29}NO_6S_2$: 562.1329, found: 562.1323; For the major *Z* isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94-8.06 (m, 4 H), 7.66-7.74 (m, 2H), 7.53-7.65 (m, 4 H), 5.54 (t, *J* = 7.2 Hz, 1 H), 3.73 (d, *J* = 17.7 Hz, 1 H), 3.20-3.47 (m, 4 H), 2.93 (s, 3 H), 2.83-2.91 (m, 1 H), 2.30-2.42 (m, 1 H), 2.10-2.27 (m, 2 H), 1.84-1.94 (m, 1 H), 1.37-1.61 (m, 2 H), 0.90-1.00 (m, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.0, 175.7, 136.7, 134.6, 132.8, 131.0, 130.5, 129.0, 128.9, 123.0, 89.9, 46.8, 40.8, 40.4, 38.0, 31.2, 25.3, 23.8, 22.8, 14.2. The assignment of *Z* stereochemistry for the major isomer is based on a differential nOe experiment (500 MHz, $CDCl_3$): 3.8% from 5.54 ppm to 3.73 ppm.

For the minor *E* isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, *J* = 8.0 Hz, 4 H), 7.53-7.65 (m, 2 H), 7.49 (t, *J* = 7.7 Hz, 4 H), 5.66 (t, *J* = 7.4 Hz, 1 H), 3.80 (d, *J* = 8.4 Hz, 1 H), 3.53-3.62 (m, 2 H), 3.02-3.14 (m, 2 H), 2.94-3.00 (m, 1 H), 2.93 (s, 3 H), 2.49 (d, *J* = 16.7 Hz, 1 H), 2.10-2.27 (m, 3 H), 1.37-1.61 (m, 2 H), 0.90-1.00 (m, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.3, 177.7, 137.2, 134.9, 133.2, 131.4, 130.6, 130.1, 129.0, 123.4, 90.7, 41.9, 41.1, 39.3, 38.3, 31.5, 25.6, 24.1, 23.3, 14.1.




Pr
H
O
PhO2S
N–Me
PhO2S
H
O
121
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
4.246
2.224
2.287
5.522
2.285
0.447
1.000
0.462
1.014
1.144
2.900
2.192
1.545
4.486
1.313
0.533
1.156
3.564
1.259
4.102
5.146
2.533


179.157
176.953
177.671
175.731
137.164
136.745
134.832
134.566
133.159
132.792
131.378
131.054
130.627
130.493
130.142
129.043
128.981
123.391
123.000
90.711
89.936
77.515
77.197
76.879
46.839
41.860
41.141
40.781
40.430
39.288
38.276
38.026
31.488
31.236
25.563
25.323
24.144
23.813
23.306
22.821
14.281
14.152
Pr
H
O
PhO2S
N–Me
PhO2S
H
O
121
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
ppm



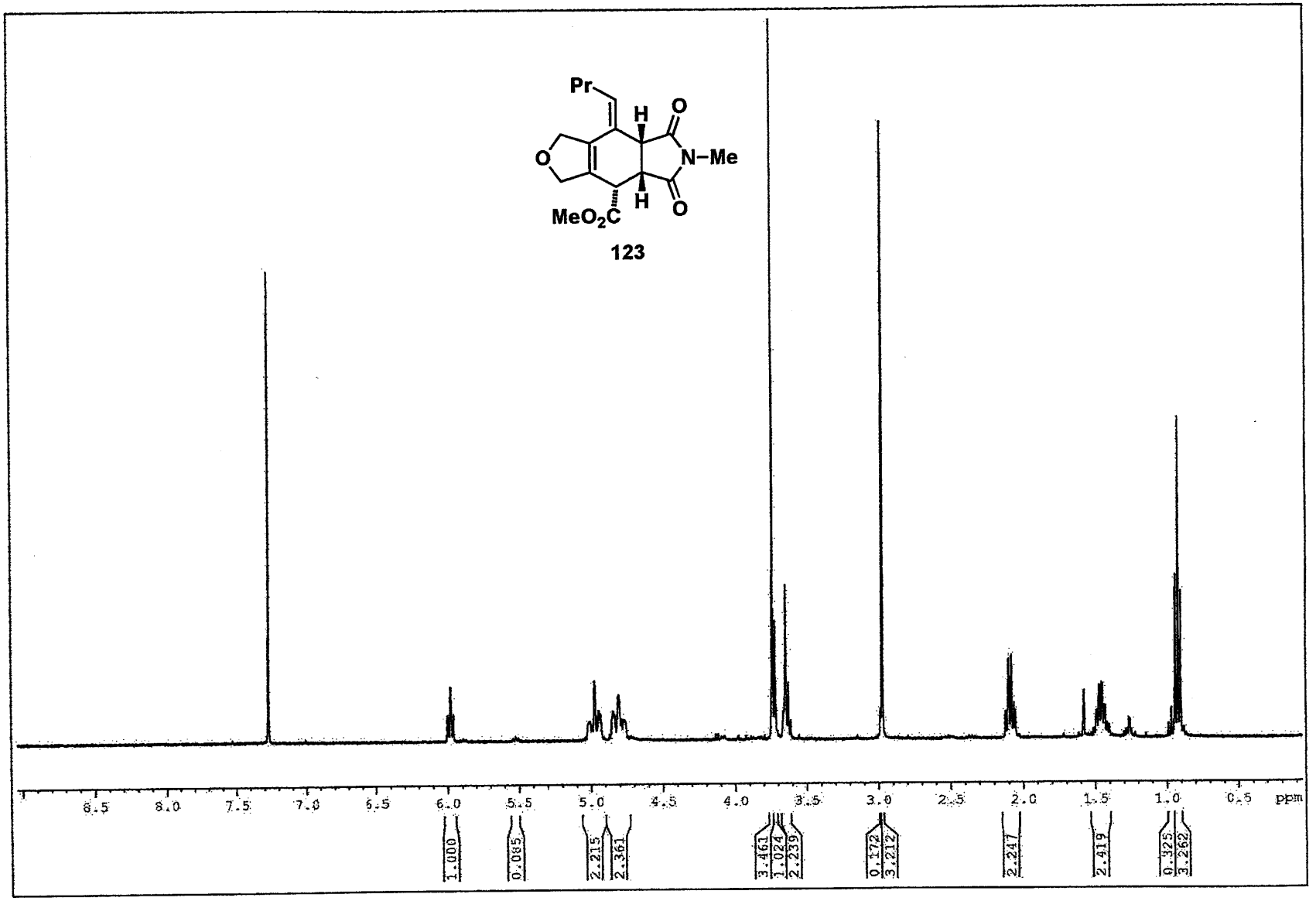
***(Z)-cis*-Methyl 8-butylidene-6-methyl-5,7-dioxo-3,4,4a,5,6,7,7a,8-octahydro-1*H*-furo[3,4-*f*]isoindole-4-carboxylate (123): Method A (160 °C).** A 10-cm threaded Pyrex tube (25 mm O.D.; 17 mm I.D.) equipped with a rubber septum fitted with an argon inlet needle was charged with *N*-methylmaleimide (0.054 g, 0.49 mmol, 1.0 equiv) and a solution of diyne **102** (0.101 g, 0.49 mmol, 1.0 equiv) in 4.9 mL of toluene. The reaction mixture was degassed via three freeze-pump-thaw cycles (-196 °C, <0.5 mmHg) and then the tube was sealed with a threaded Teflon cap. The reaction mixture was heated at 160 °C for 1 h and then cooled to rt and concentrated to give 0.207 g of a yellow oil. Purification by column chromatography on 16 g of silica gel (elution with 15-30% EtOAc-hexanes) afforded 0.145 g (93%) of a mixture of diene **123**[194] and the corresponding *E* isomer (92:8 by ^{1}H NMR analysis) as a white solid: mp 29 °C; IR (thin film) 2958, 2873, 2255, 1738, 1703, 1438, 1384, 1288, 1203, 1055, 916, and 732 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.98 (t, J = 7.8 Hz, 1 H), 4.89-5.04 (m, 2 H), 4.74-4.89 (m, 2 H), 3.75 (s, 3 H), 3.71-3.75 (m, 1 H), 3.64-3.68 (m, 1 H), 3.63 (t, J = 6.2 Hz, 1 H), 2.97 (s, 3 H), 2.01 (q, J = 7.2 Hz, 2 H), 1.42-1.51 (m, 2 H), 0.92 (t, J = 7.3 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.2, 177.1, 170.2, 134.7, 133.7, 131.4, 120.8, 76.1, 76.0, 52.6, 45.6, 42.5, 39.3, 31.5, 25.4, 23.2, 13.9; HRMS-ESI *(m/z)* [M + Na]$^+$ calcd for $C_{17}H_{21}NO_5$: 342.1317, found: 342.1322. Assignment of *Z* stereochemistry for the major isomer is based on the downfield chemical shift of the alkenyl proton in the *Z* isomer (5.98 ppm) relative to the *E* isomer (5.51 ppm) by analogy with compound 92.

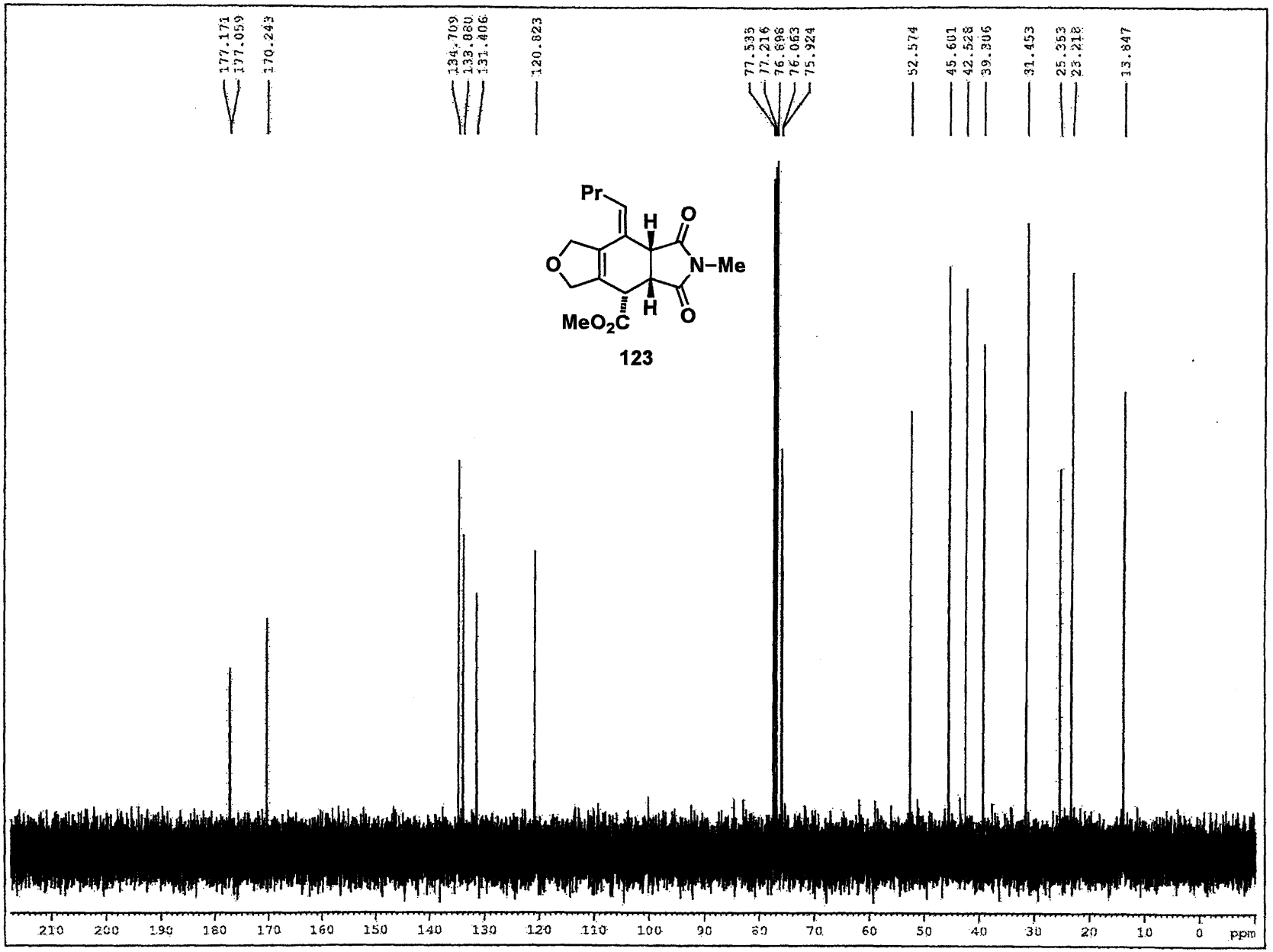
***(Z)-cis*-Methyl 8-butylidene-6-methyl-5,7-dioxo-3,4,4a,5,6,7,7a,8-octahydro-1*H*-furo[3,4-*f*]isoindole-4-carboxylate (123): Method B (110 °C).** A 25-mL, round-bottomed flask equipped with a coldfinger condenser was charged with diyne **102** (0.110 g, 0.53 mmol, 1.0

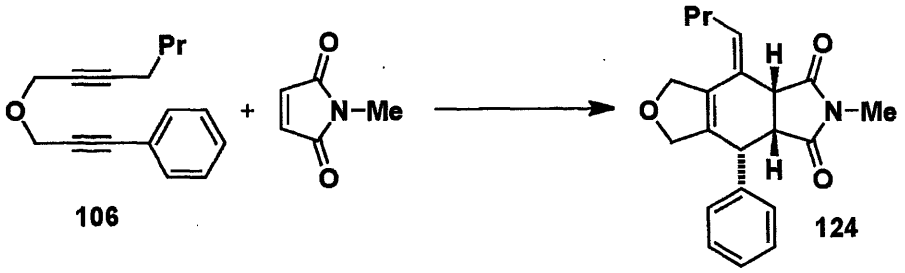
---

[194] The endo stereochemistry was assigned based on comparison of the observed ^{1}H NMR coupling constants with the coupling constants predicted for the endo and exo isomers by application of the Karplus correlation to the dihedral angles calculated for each isomer using Spartan '08 Hartree-Fock 6-31G*.

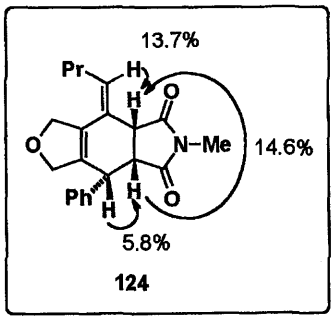
equiv), *N*-methylmaleimide (0.059 g, 0.53 mmol, 1.0 equiv), and 5.3 mL of toluene. The reaction mixture was heated at reflux for 21 h and then cooled to rt and concentrated to give 0.213 g of yellow oil. Purification by column chromatography on 16 g of silica gel (elution with 30% EtOAc-hexanes) provided 0.115 g (68%) of a mixture of **123** and the corresponding *E* isomer (93:7 by ^{1}H NMR analysis) as a white solid.

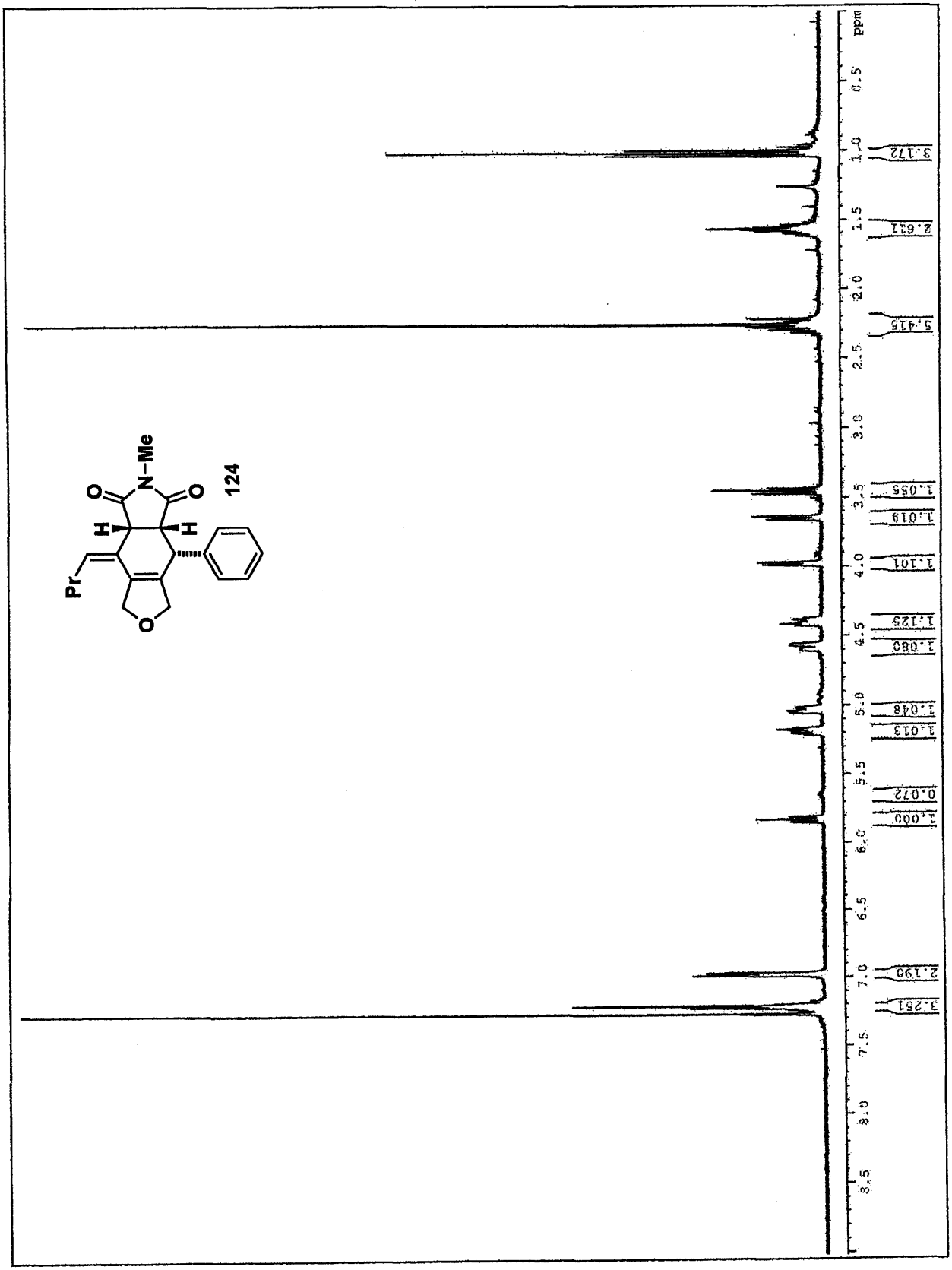

Pr
H
O
O
N–Me
H
MeO2C
123
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
1.000
0.085
2.215
2.361
3.461
1.024
2.239
0.172
3.212
2.247
2.419
0.325
3.262


177.171
177.059
170.243
134.709
133.880
131.406
120.823
77.535
77.216
76.898
76.063
75.924
52.574
45.601
42.528
39.306
31.453
25.353
23.218
13.847
Pr
H
O
O
N–Me
H
MeO2C
123
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

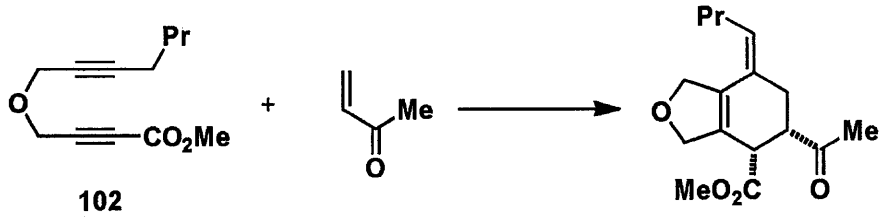


(*Z*)-*cis,trans*-4-Butylidene-6-methyl-8-phenyl-4,4a,7a,8-tetrahydro-1*H*-furo[3,4-*f*]isoindole-5,7(3*H*,6*H*)-dione (124). An 8-cm threaded Pyrex tube (24 mm O.D.; 18 mm I.D.) equipped with a rubber septum fitted with an argon inlet needle was charged with *N*-methylmaleimide (0.050 g, 0.45 mmol, 1.0 equiv) and a solution of diyne **106** (0.101 g, 0.45 mmol, 1.0 equiv) in 4.5 mL of toluene. The reaction mixture was degassed via three freeze-pump-thaw cycles (-196 °C, <0.5 mmHg) and then the tube was sealed with a threaded Teflon cap. The reaction mixture was heated at 160 °C for 12 h and then cooled to rt and concentrated to give 0.214 g of an orange oil. Purification by column chromatography on 21 g of acetone-deactivated silica gel (elution with 25% EtOAc-hexanes) gave 0.099 g (65%) of a mixture of diene **124** and the corresponding *E* isomer (93:7 by ^{1}H NMR analysis) as a pale yellow solid: mp 51-53 °C; IR (thin film) 2959, 2871, 1706, 1494, 1434, 1381, 1292, 1272, 1073, 1013, 756, and 705 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16-7.26 (m, 3 H), 6.98 (dd, J = 7.8, 2.1 Hz, 2 H), 5.83 (t, J = 7.8 Hz, 1 H), 5.15-5.23 (m, 1 H), 5.00-5.07 (m, 1 H), 4.54-4.63 (m, 1 H), 4.40 (dt, J = 13.2, 4.7 Hz, 1 H), 3.98 (d, J = 7.7 Hz, 1 H), 3.65 (d, J = 8.3 Hz, 1 H), 3.46 (t, J = 7.9 Hz, 1 H), 2.21-2.33 (m, 2 H), 2.26 (s, 3 H), 1.51-1.62 (m, 2 H), 1.02 (t, J = 7.3 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.1, 176.8, 136.4, 135.6, 135.5, 132.4, 128.8, 128.6, 128.1, 119.2, 76.6, 75.7, 45.7, 45.1, 39.4, 31.5, 23.8, 23.6, 13.9; HRMS-ESI *(m/z)* $[M + H]^+$ calcd for $C_{21}H_{23}NO_3$: 338.1751, found: 338.1763. The assignment of *Z* stereochemistry for the major isomer is based on a differential nOe experiment (500 MHz, $CDCl_3$): 13.7% from 5.83 ppm to 3.98 ppm. The assignment of endo stereochemistry is based on analysis of ^{1}H NMR coupling constants[16] and was confirmed by a differential nOe experiment (500 MHz, $CDCl_3$): 5.8% from 3.65 ppm to 3.46 ppm.

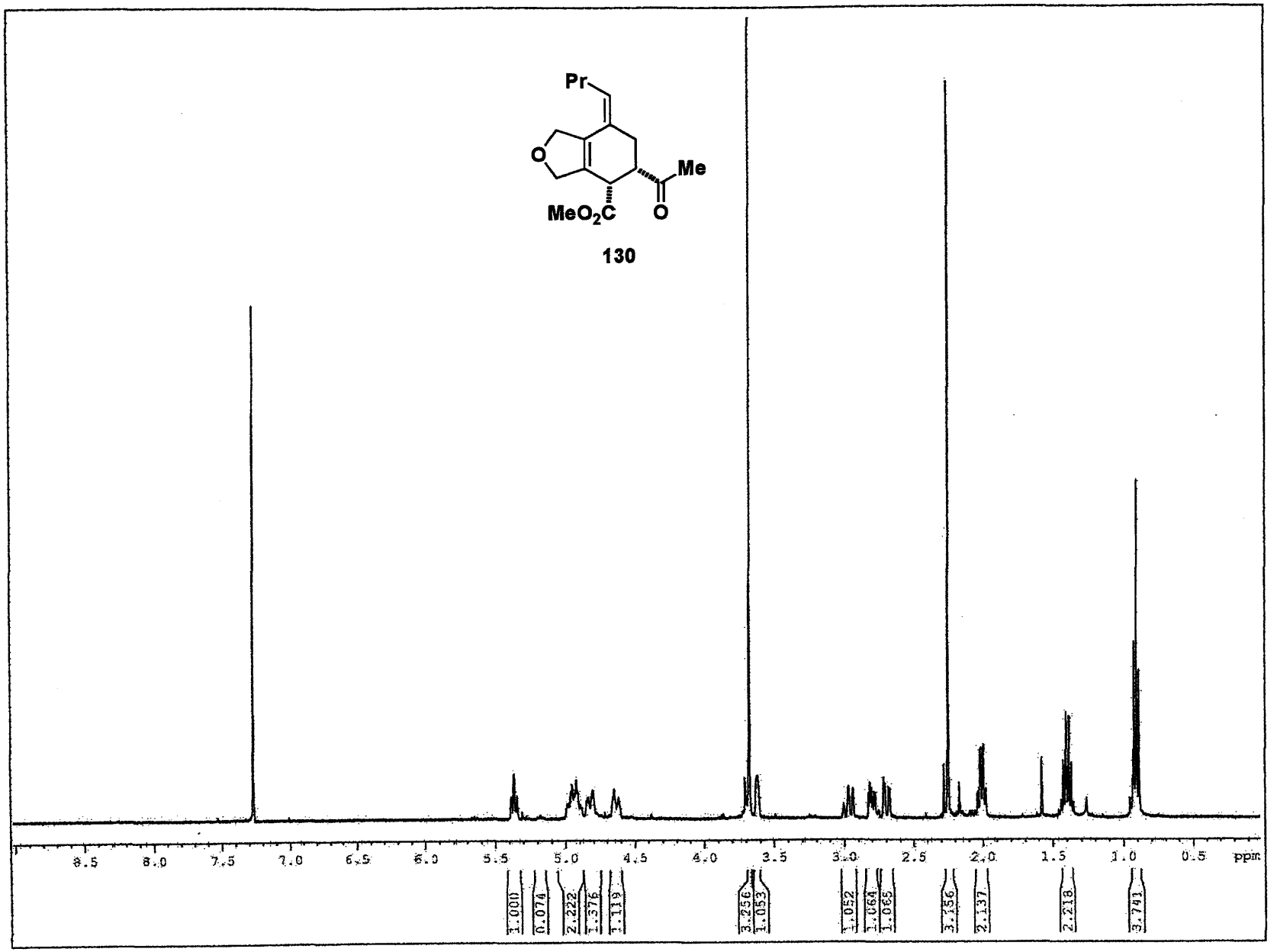


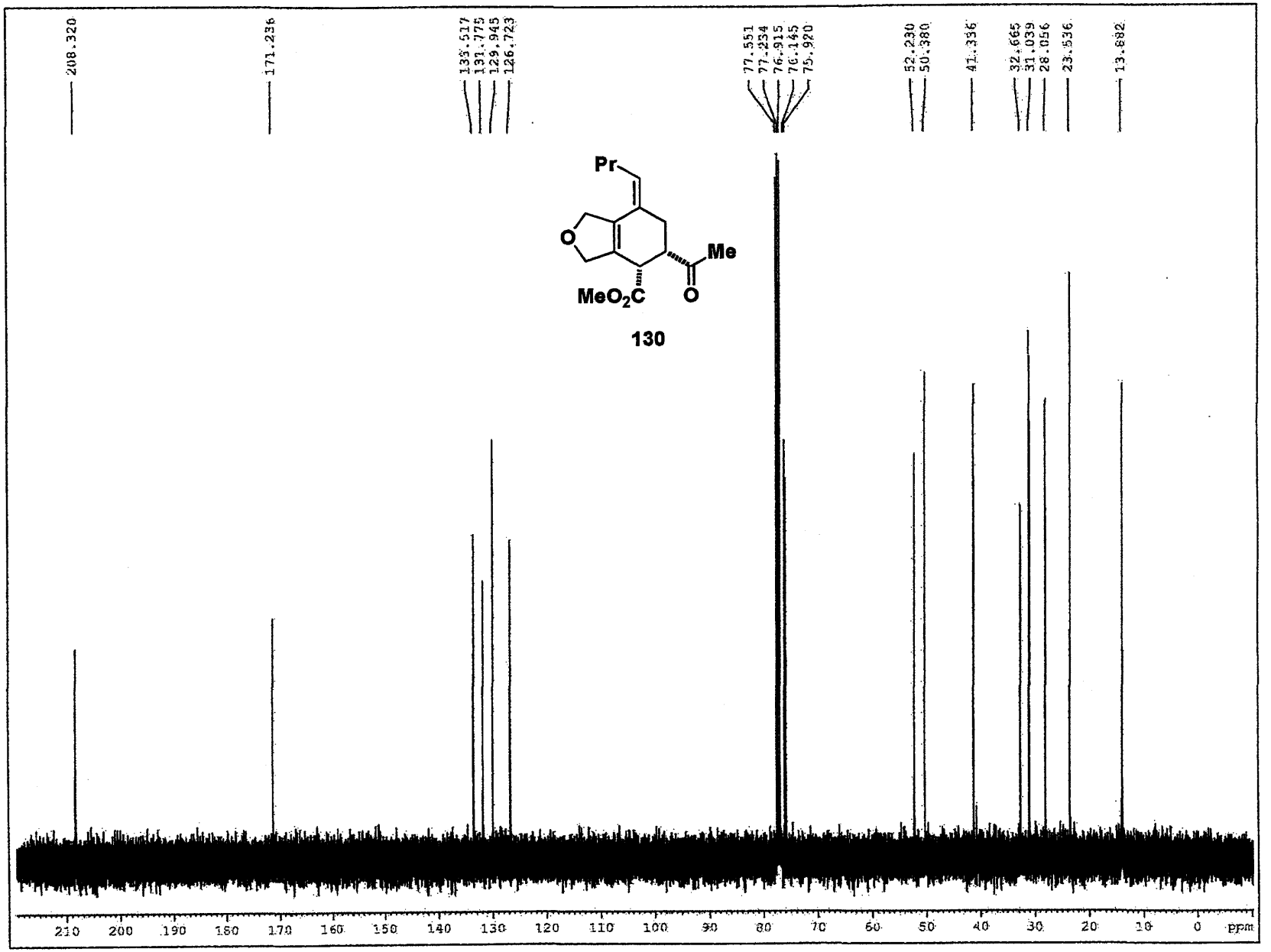

N-Me
O
O
H
H
Pr
O
124
ppm
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
3.172
2.611
5.415
1.055
1.019
1.101
1.125
1.080
1.048
1.013
0.072
1.000
2.190
3.251

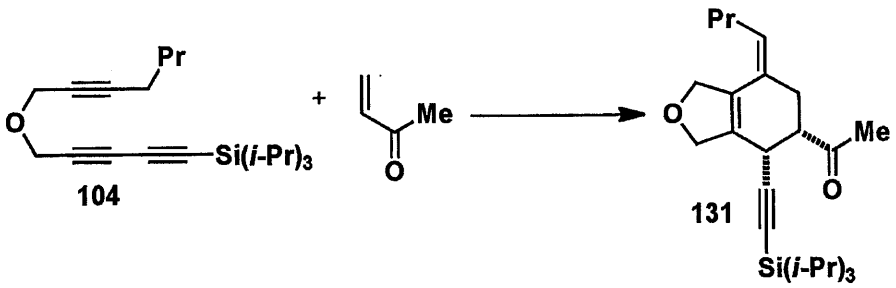
177.103
176.774
136.440
135.620
135.536
132.644
128.774
128.564
128.060
119.197
77.535
77.217
76.898
76.551
75.737
45.731
45.094
39.493
31.462
23.844
23.567
13.897
Pr
H
O
N–Me
O
H
O
124
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm



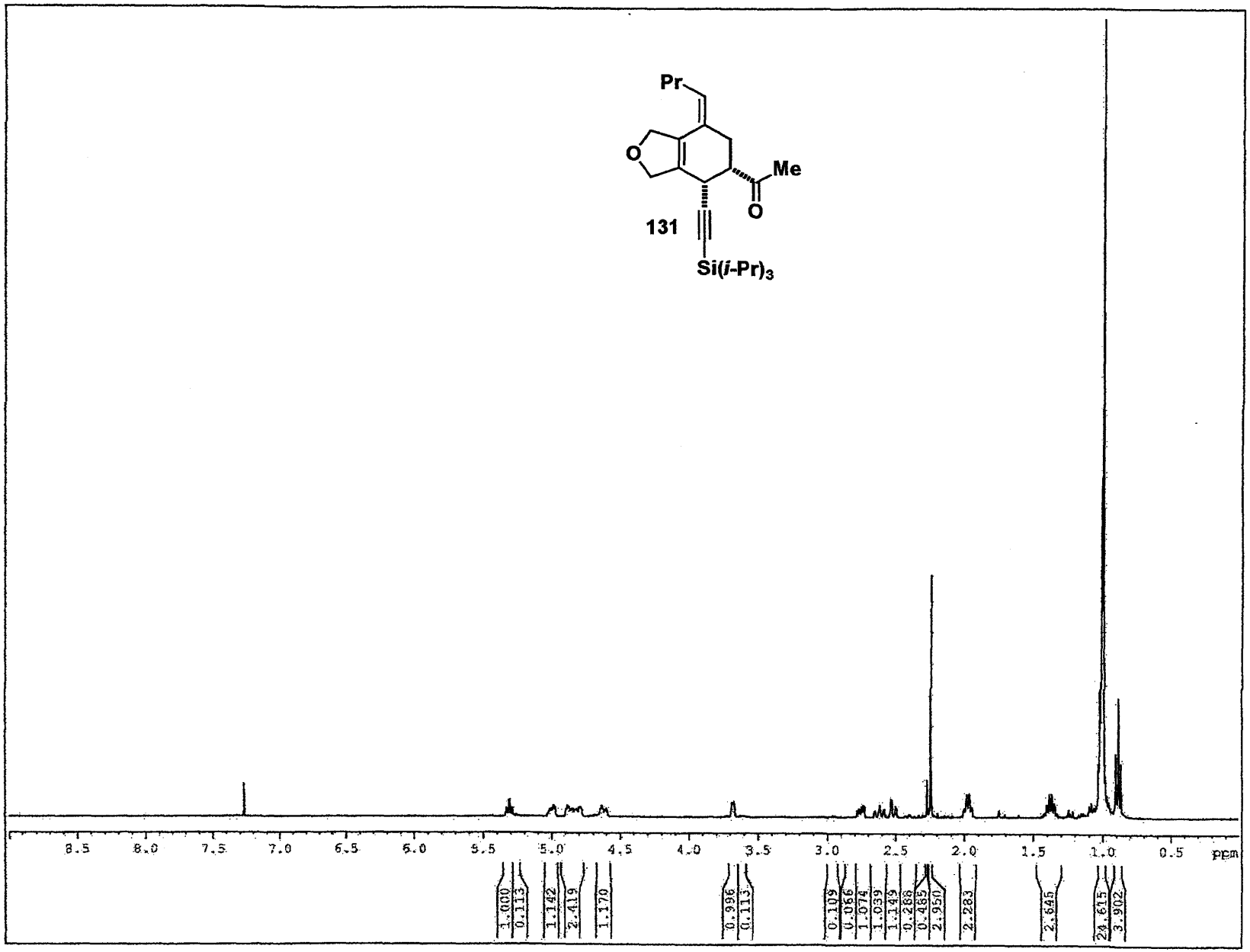
(*Z*)-*cis*-Methyl 5-acetyl-7-butylidene-1,3,4,5,6,7-hexahydroisobenzofuran-4-carboxylate (130). A 25-mL, round-bottomed flask equipped with a coldfinger condenser was charged with diyne **102** (0.101 g, 0.486 mmol, 1.0 equiv), BHT (0.011 g, 0.050 mmol, 0.1 equiv), methyl vinyl ketone (0.0395 mL, 0.034 g, 0.486 mmol, 1.0 equiv), and 5 mL of toluene. The reaction mixture was heated at reflux for 19 h and then cooled to rt and concentrated to give 0.165 g of yellow oil. Purification by column chromatography on 16 g of silica gel (elution with 20% EtOAc-hexanes) provided 0.088 g (57%) of a mixture of keto ester **130** and the corresponding *E* isomer (93:7 by ^{1}H NMR analysis) as a pale yellow oil: IR (neat) 2957, 2856, 1737, 1713, 1434, 1357, 1174, 1078, 921, and 732 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.37 (t, *J* = 7.7 Hz, 1 H), 4.87-5.01 (m, 2 H), 4.78-4.86 (m, 1 H), 4.59-4.67 (m, 1 H), 3.68 (s, 3 H), 3.60-3.64 (m, 1 H), 2.97 (t, *J* = 13.2 Hz, 1 H), 2.77-2.84 (m, 1 H), 2.69 (dd, *J* = 14.4, 3.4 Hz, 1 H), 2.26 (s, 3 H), 2.01 (q, *J* = 7.5 Hz, 2 H), 1.35-1.47 (m, 2 H), 0.91 (t, *J* = 7.4 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.3, 171.2, 133.5, 131.8, 129.9, 126.7, 76.1, 75.9, 52.2, 50.4, 41.3, 32.7, 31.0, 28.1, 23.5, 13.9; HRMS-ESI *(m/z)* $[M + Na]^+$ calcd for $C_{16}H_{22}O_4$: 301.1416, found: 301.1420. Assignment of *Z* stereochemistry for the major isomer is based on the downfield chemical shift of the alkenyl proton in the *Z* isomer (5.37 ppm) compared to the *E* isomer (5.18 ppm) by analogy with compounds **92** and **124**. The assignment of endo stereochemistry is based on analysis of ^{1}H NMR coupling constants.[194]


Pr
O
Me
MeO2C
O
130
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
1.000
0.074
2.222
1.376
1.119
3.256
1.053
1.052
1.064
1.065
3.156
2.137
2.218
3.741

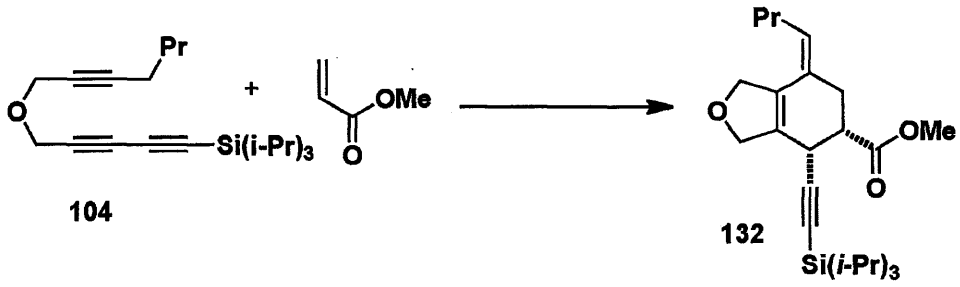

208.320
171.236
135.517
131.775
129.945
126.723
77.551
77.234
76.915
76.145
75.920
52.230
50.380
41.336
32.665
31.039
28.056
23.536
13.682
Pr
O
Me
MeO2C
O
130
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm



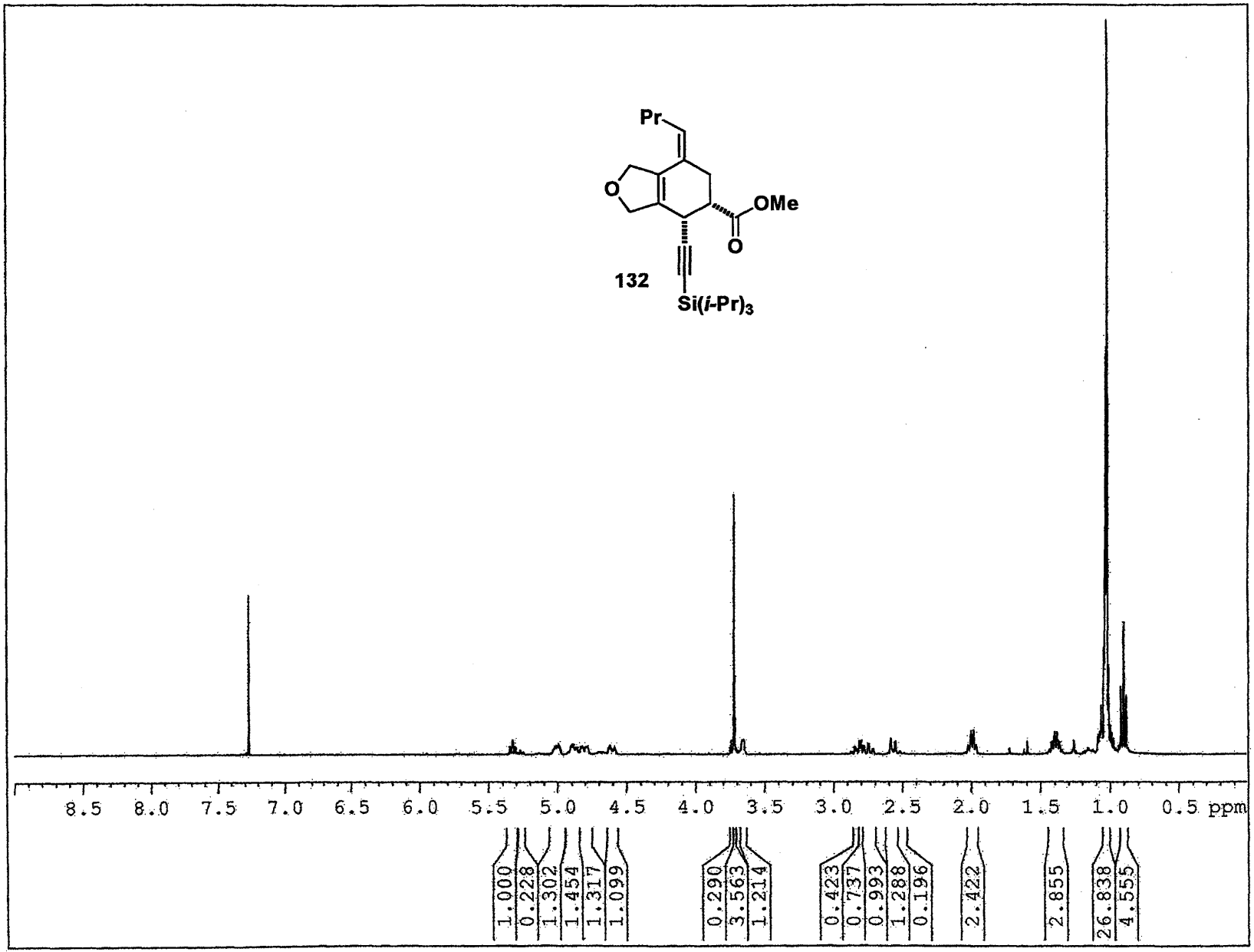
1-((*Z*)-*cis*-7-Butylidene-4-((triisopropylsilyl)ethyn-1-yl)-1,3,4,5,6,7-hexahydroisobenzofuran-5-yl)ethanone (131). A 25-mL, round-bottomed flask equipped with a coldfinger condenser was charged with triyne **104** (0.099 g, 0.30 mmol, 1.0 equiv), BHT (0.007 g, 0.03 mmol, 0.1 equiv), and 3 mL of toluene. Methyl vinyl ketone (0.024 mL, 0.021 g, 0.30 mmol, 1.0 equiv) was added and the reaction mixture was heated at reflux for 21 h. The reaction mixture was cooled to rt and concentrated to give 0.143 g of brown oil. Purification by column chromatography on 14 g of silica gel (elution with 10% EtOAc-hexanes) afforded 0.081 g (68%) of a mixture of ketone **131** and the corresponding *E* isomer (90:10 by ^{1}H NMR analysis) as a pale yellow oil: IR (neat) 2170, 1715, 1463, 1361, 1167, 1077, 1050, 996, 919, and 883 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.31 (t, J = 7.6 Hz, 1 H), 4.96-5.04 (m, 1 H), 4.87-4.91 (m, 2 H), 4.58-4.65 (m, 1 H), 3.68 (d, J = 4.9 Hz, 1 H), 2.75 (ddd, J = 12.0, 5.3, 3.1 Hz, 1 H), 2.62 (t, J = 13.0 Hz, 1 H), 2.52 (dd, J = 14.4, 2.9 Hz, 1 H), 2.25 (s, 3 H), 1.98 (q, J = 7.4 Hz, 2 H), 1.33-1.42 (m, 2 H), 0.98-1.04 (m, 21 H), 0.89 (t, J = 7.3 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.0, 133.8, 132.1, 129.3, 127.3, 103.3, 85.0, 76.4, 75.4, 52.1, 31.3, 31.1, 29.1, 28.1, 23.6, 18.7, 13.9, 11.3; HRMS-ESI *(m/z)* $[M + H]^+$ calcd for $C_{25}H_{40}O_2Si$: 401.2870, found: 401.2874. Assignment of *Z* stereochemistry for the major isomer is based on the downfield chemical shift of the alkenyl proton in the *Z* isomer (5.31 ppm) compared to the *E* isomer (5.26 ppm) by analogy with compounds **92** and **124**. The assignment of endo stereochemistry is based on analysis of ^{1}H NMR coupling constants.[194]


Pr
O
Me
O
131
Si(i-Pr)3
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
3.000
0.113
1.142
2.419
1.170
0.996
0.113
0.109
0.066
1.074
1.039
1.149
0.288
0.485
2.950
2.283
2.645
24.615
3.902

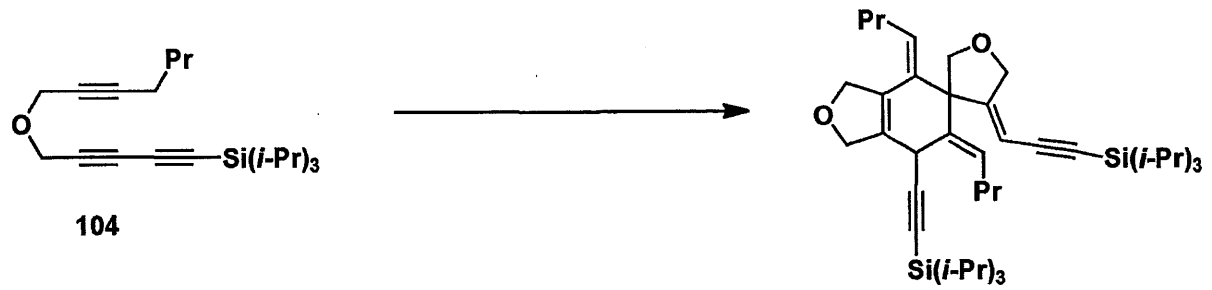
206.967
133.845
132.112
129.345
127.318
103.304
85.031
77.549
77.231
76.913
76.375
75.397
52.135
31.314
31.121
29.152
28.124
23.575
18.726
13.908
11.269
Pr
O
Me
O
131
Si(i-Pr)3
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm



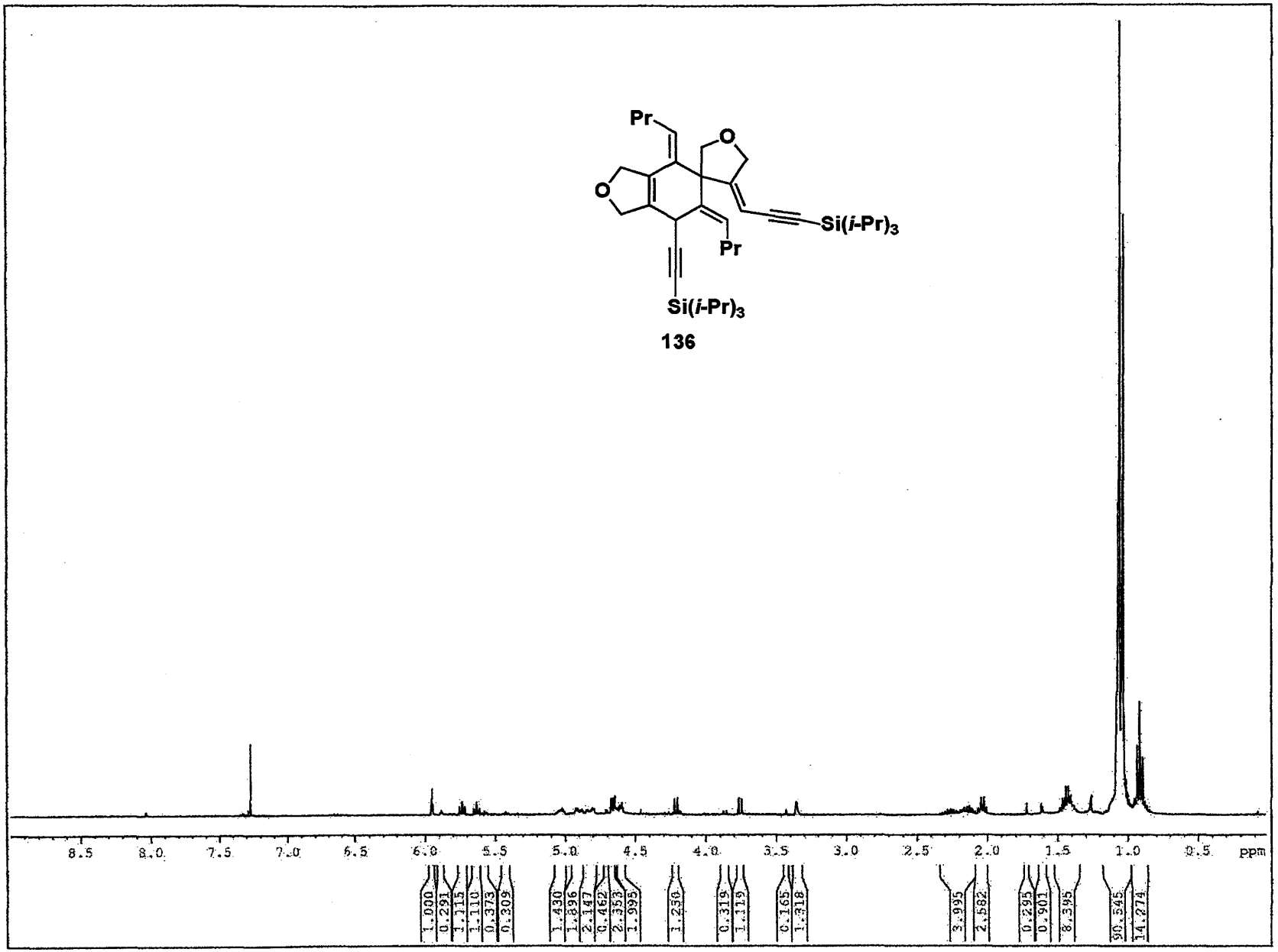
7-Butylidene-5-carbomethoxy-*(Z)-cis*-4-((triisopropylsilyl)ethyn-1-yl)-1,3,4,5,6,7-hexahydroisobenzofuran (132). A 25-mL, round-bottomed flask equipped with a coldfinger condenser was charged with triyne **104** (0.101 g, 0.31 mmol, 1.0 equiv), BHT (0.007 g, 0.03 mmol, 0.1 equiv), and 3.1 mL of toluene. Methyl acrylate (0.028 mL, 0.026 g, 0.31 mmol, 1.0 equiv) was added and the reaction mixture was heated at reflux for 21 h. The reaction mixture was cooled to rt and concentrated to give 0.142 g of orange oil. Purification by column chromatography on 14 g of silica gel (elution with 10% EtOAc-hexanes) afforded 0.080 g (63%) of a mixture of **132** and the corresponding *E* isomer (81:19 by ^{1}H NMR analysis) as a yellow oil: IR (neat) 2957, 2865, 2172, 1746, 1463, 1436, 1177, 1078, 1018, 997, 919, and 883 cm^{-1}. For the major *Z* isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.32 (t, *J* = 7.5 Hz, 1 H), 4.97-5.05 (m, 1 H), 4.85-4.91 (m, 1 H), 4.77-4.84 (m, 1 H), 4.57-4.64 (m, 1 H), 3.72 (s, 3 H), 3.64-3.67 (m, 1 H), 2.80 (dd, *J* = 5.1, 2.3 Hz, 1 H), 2.70-2.79 (m, 1 H), 2.54-2.59 (m, 1 H), 1.99 (q, *J* = 7.2 Hz, 2 H), 1.34-1.45 (m, 2 H), 1.01-1.05 (m, 21 H), 0.90 (t, *J* = 7.3 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.7, 134.3, 131.8, 129.3, 127.3, 103.9, 84.1, 76.4, 75.5, 52.0, 44.8, 31.8, 31.1, 29.5, 18.79, 18.78, 14.0, 11.3. Assignment of *Z* stereochemistry for the major isomer is based on the downfield chemical shift of the alkenyl proton in the *Z* isomer (5.32 ppm) compared to the *E* isomer (5.27 ppm) by analogy with compounds **92** and **195**. The assignment of endo stereochemistry is based on analysis of ^{1}H NMR coupling constants.[194] For the minor *E* isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.27 (t, *J* = 8.0 Hz, 1 H), 4.50-4.94 (m, 2 H), 4.64-4.72 (m, 2 H), 3.71 (s, 3 H), 3.64-3.67 (m, 1 H), 2.82-2.85 (m, 2 H), 2.47-2.53 (m, 1 H), 1.99 (q, *J* = 7.2 Hz, 2 H), 1.34-1.45 (m, 2 H), 1.01-1.05 (m, 21 H), 0.90 (t, *J* = 7.3 Hz, 3 H); HRMS-ESI *(m/z)* [M + Na]$^+$ calcd for $C_{25}H_{40}O_3Si$: 439.2644, found: 439.2650.

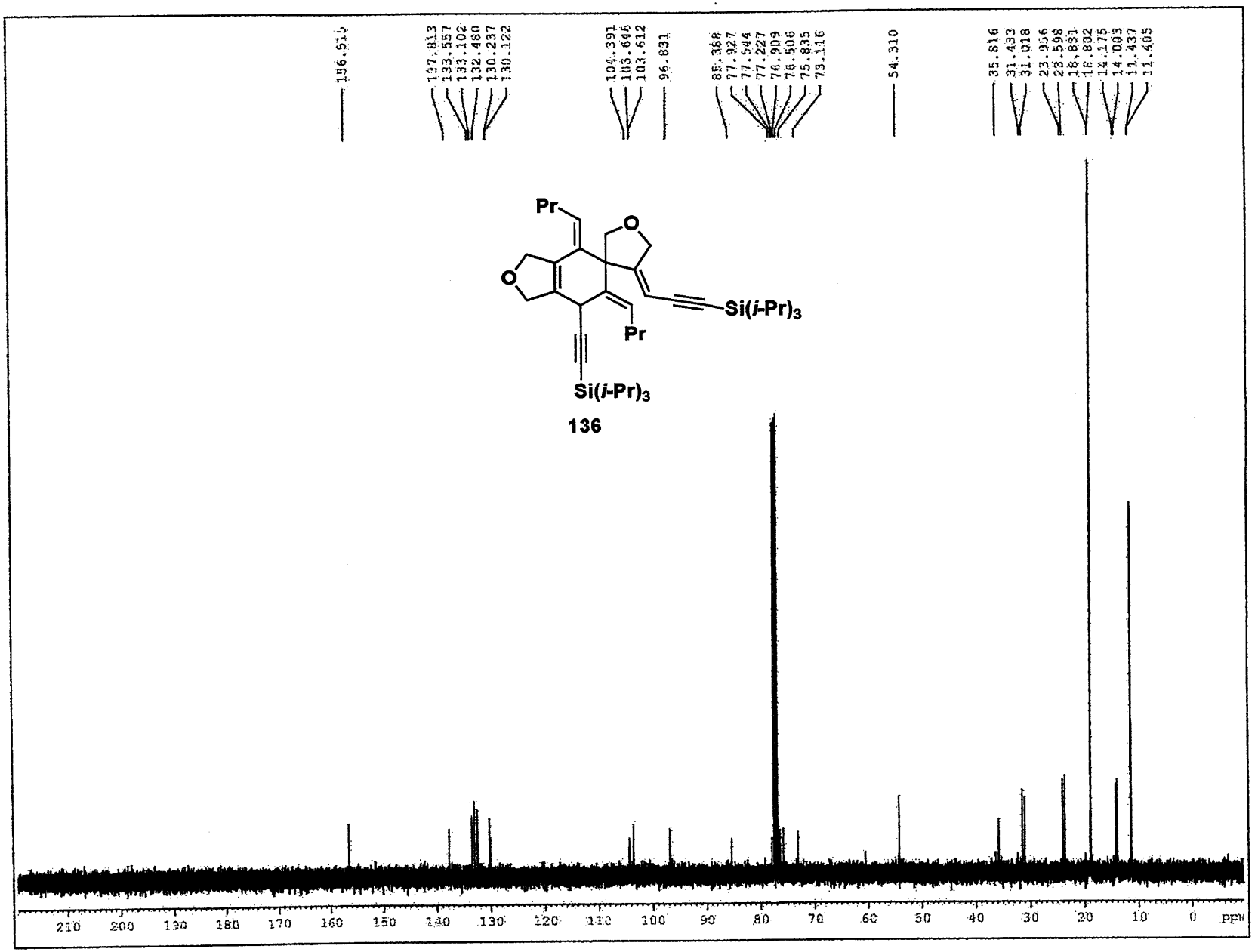

Pr
O
OMe
O
132
Si(i-Pr)3
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
1.000
0.228
1.302
1.454
1.317
1.099
0.290
3.563
1.214
0.423
0.737
0.993
1.288
0.196
2.422
2.855
26.838
4.555

172.663
134.257
131.766
129.338
127.252
103.869
84.076
77.672
77.254
76.937
76.430
75.460
52.050
44.820
31.755
31.141
29.509
18.792
18.785
13.959
11.333
Pr
O
OMe
O
132
Si(i-Pr)3
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm



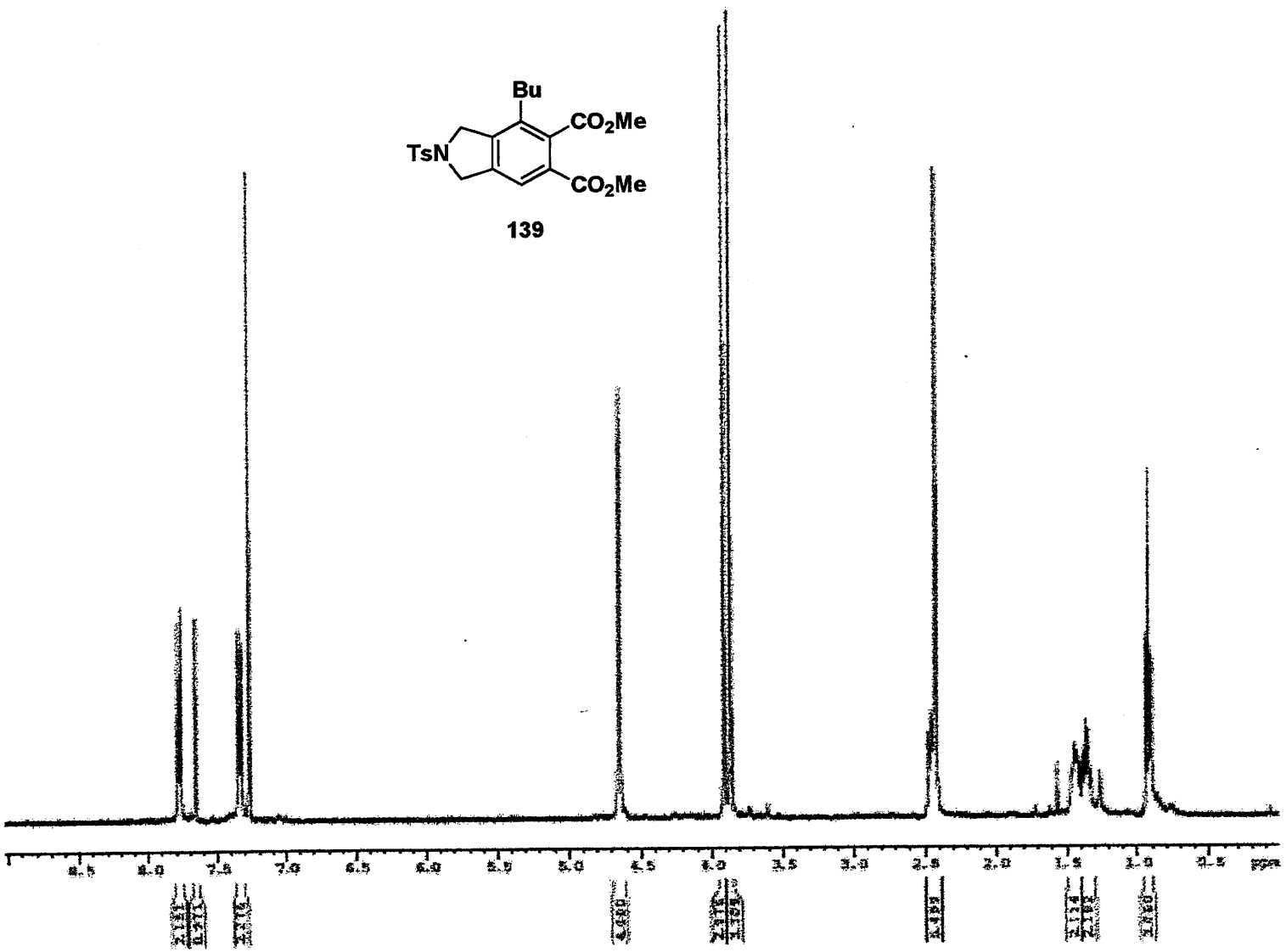
Vinylallene dimer (136). A 100-mL, round-bottomed flask equipped with a reflux condenser fitted with an argon inlet adapter was charged with triyne **104** (0.097 g, 0.29 mmol, 1.0 equiv) and 29 mL of toluene. The reaction mixture was heated at reflux for 17 h and then cooled to rt and concentrated to give 0.101 g of orange oil. Purification by column chromatography on 19 g of silica gel (elution with 1-2% EtOAc-hexanes) provided 0.046 g (47%) of dimer **136** (82:18 mixture of isomers by 1H NMR analysis) as a yellow oil: IR (thin film): 2866, 2137, 1731, 1464, 1382, 1071, 997, 883, and 678 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.96 (t, J = 2.6 Hz, 1 H); 5.74 (t, J = 7.4 Hz, 1 H), 5.63 (t, J = 7.6 Hz, 1 H), 5.00-5.08 (m, 1 H), 4.86-4.94 (m, 2 H), 4.77-4.86 (m, 1 H), 4.66 (dd, J = 7.3, 2.6 Hz, 1 H), 4.57-4.62 (m, 1 H), 4.21 (d, J = 8.8 Hz, 1 H), 3.76 (d, J = 10.0 Hz, 1 H), 3.33-3.37 (m, 1 H), 2.08-2.33 (m, 2 H), 2.04 (q, J = 7.4 Hz, 2 H), 1.39-1.49 (m, 4 H), 1.03-1.08 (m, 42 H), 0.92 (t, J = 7.8 Hz, 6 H); peaks corresponding to minor isomer: 5.87-5.89 (m, 1 H), 5.58 (t, J = 7.4 Hz, 1 H), 5.41 (t, J = 7.5 Hz, 1 H), 3.86 (d, J = 10.0 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.5, 137.8, 133.6, 133.1, 132.5, 130.2, 130.1, 104.4, 103.65, 103.61, 96.8, 85.4, 77.9, 76.5, 75.8, 73.1, 54.3, 35.8, 31.4, 31.0, 24.0, 23.6, 18.83, 18.81, 14.2, 14.0, 11.43, 11.40; HRMS-ESI *(m/z)* $[M + H]^+$ calcd for $C_{42}H_{68}O_2Si_2$: 661.4831, found: 661.4830.


Pr
O
O
Si(i-Pr)3
Pr
Si(i-Pr)3
136
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
1.000
0.291
1.115
1.110
0.373
0.309
1.430
1.896
2.147
0.462
2.353
1.995
1.230
0.319
1.119
0.165
1.318
3.995
2.582
0.295
0.901
8.395
30.545
14.274

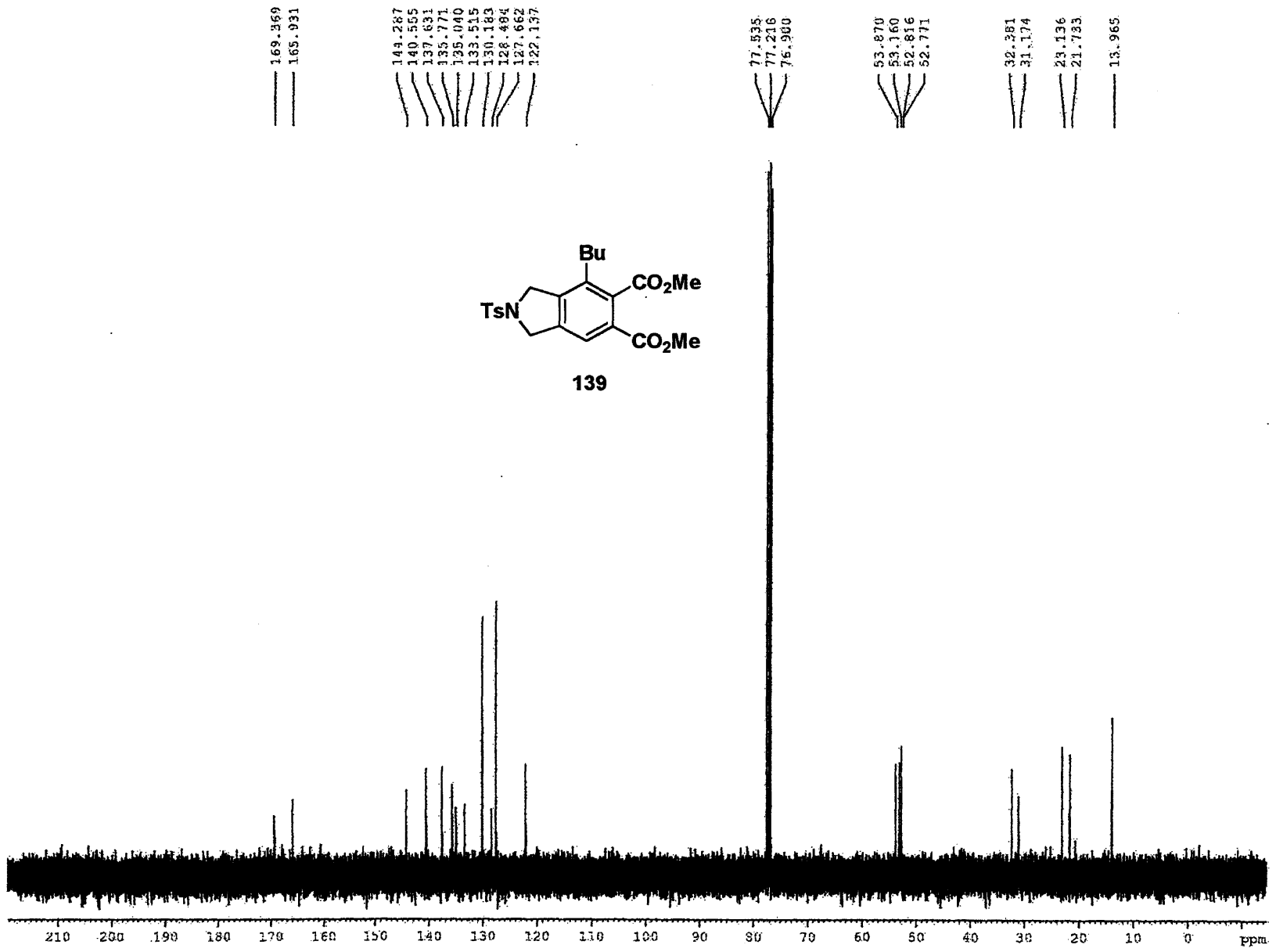

156.514
137.813
133.557
133.102
132.480
130.237
130.122
104.391
103.646
103.612
96.831
85.368
77.927
77.544
77.227
76.909
76.506
75.835
73.116
54.310
35.816
31.433
31.018
23.956
23.598
18.831
18.802
14.175
14.003
11.437
11.405
Pr
O
O
Si(i-Pr)3
Pr
Si(i-Pr)3
136
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

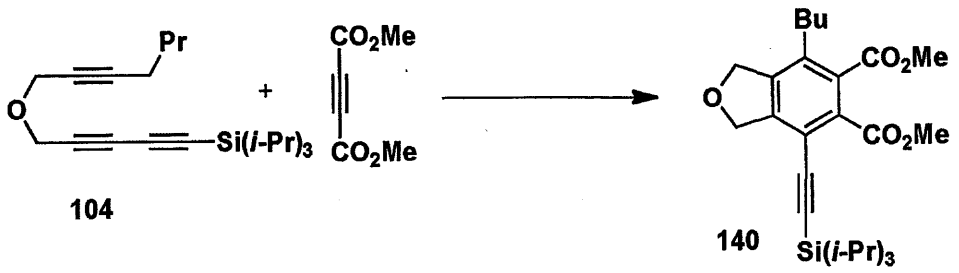
115 139

Dimethyl 4-butyl-2-tosylisoindoline-5,6-dicarboxylate (139). A threaded Pyrex tube (35 mm O.D., 25 mm I.D.) equipped with a rubber septum and argon inlet needle was charged with a solution of diyne **115** (0.109 g, 0.36 mmol, 1.0 equiv) in 36 mL of toluene. DMAD (0.044 mL, 0.050 g, 0.36 mmol, 1.0 equiv) was added. The reaction mixture was degassed via three freeze-pump-thaw cycles (-196 °C, <0.5 mmHg). The rubber septum was replaced with a Teflon cap and the reaction mixture was heated at 160 °C for 21 h and allowed to cool to rt. The Teflon cap was replaced with a septum and an argon inlet needle. DBU (0.005 mL, 0.005 g, 0.03 mmol, 0.1 equiv) was added and the reaction mixture was stirred for at rt for 2 h and then concentrated to give 0.220 g of a brown oil. Purification by column chromatography on 15 g of silica gel (elution with 20% EtOAc-hexanes) afforded 0.117 g (74%) of diester **139** as a pale white solid: mp 87-88 °C; IR (neat) 2258, 1729, 1598, 1435, 1349, 1300, 1230, 1164, 1098, 913, 732, and 668 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, J = 8.2 Hz, 2 H), 7.66 (s, 1 H), 7.34 (d, J = 8.0 Hz, 2 H), 4.65 (s, 4 H), 3.91 (s, 3 H), 3.87 (s, 3 H), 2.42-2.49 (m, 2 H), 2.42 (s, 3 H), 1.39-1.49 (m, 2 H), 1.32-1.39 (m, 2 H), 0.92 (t, J = 7.2 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.4, 165.9, 144.3, 140.6, 137.6, 135.8, 135.0, 133.5, 130.2, 128.5, 127.7, 122.1, 53.9, 53.2, 52.8, 52.8, 32.4, 31.2, 23.1, 21.7, 14.0; HRMS-ESI *(m/z)*: $[M + Na]^+$ calcd for $C_{23}H_{27}NO_6S$: 437.1505, found: 437.1515.

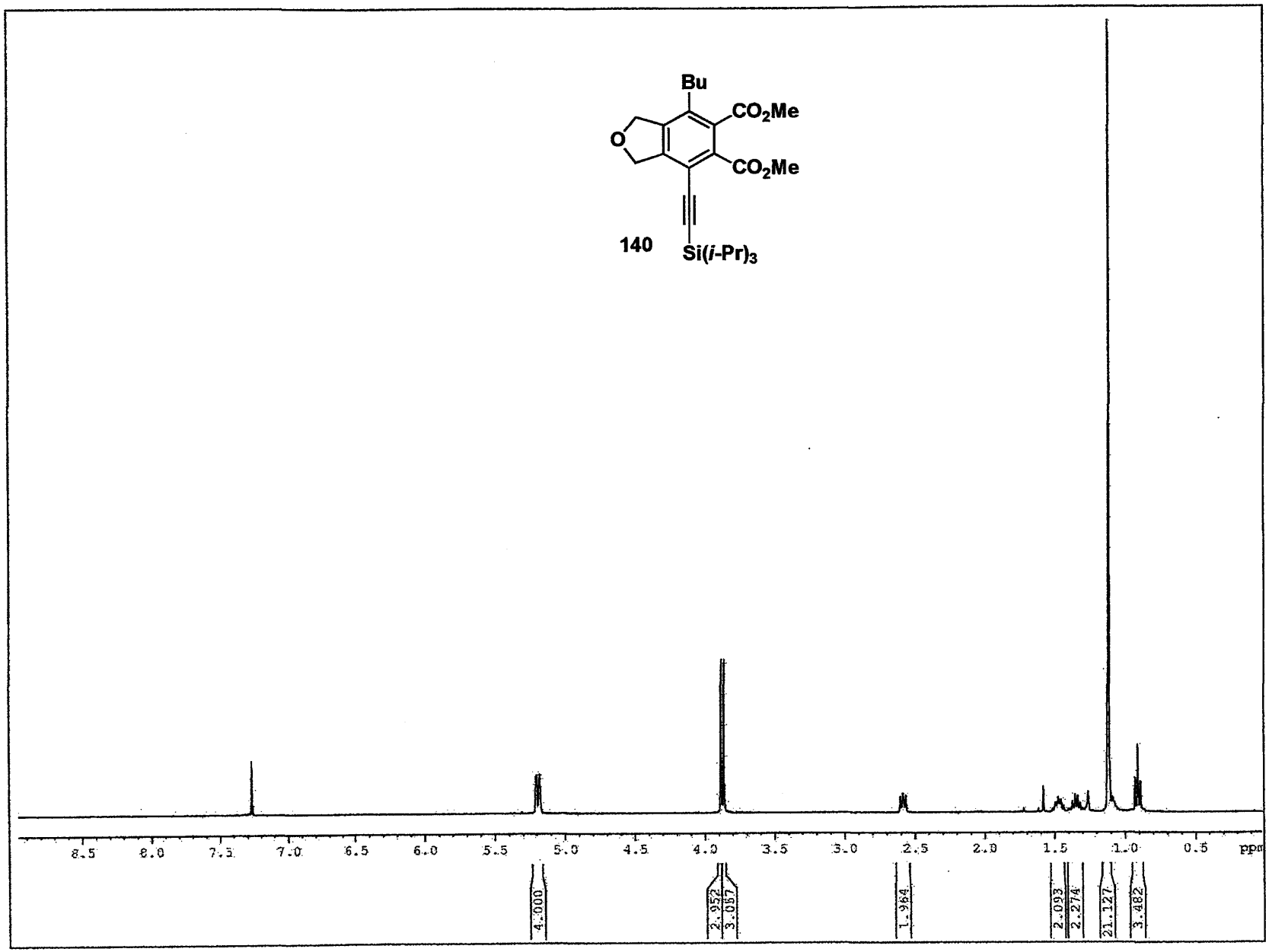


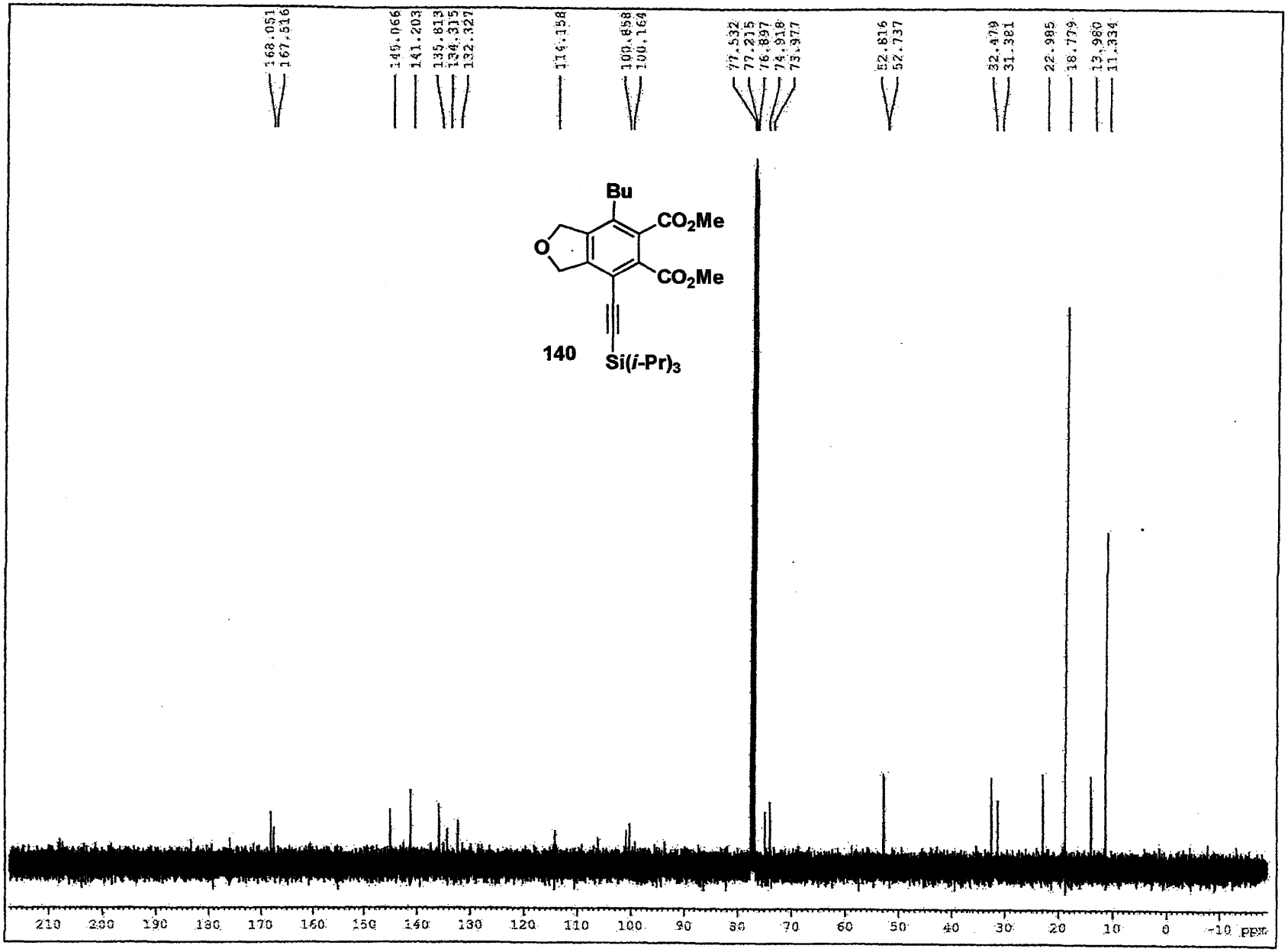
139

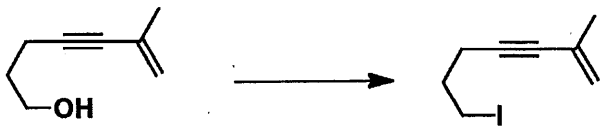

169.369
165.931
144.287
140.555
137.631
135.771
135.040
133.515
130.183
128.484
127.662
122.137
77.535
77.216
76.900
53.870
53.160
52.816
52.771
32.381
31.174
23.136
21.783
13.965
Bu
CO2Me
TsN
CO2Me
139
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm



Dimethyl 4-butyl-7-((triisopropylsilyl)ethyn-1-yl)-1,3-dihydroisobenzofuran-5,6-dicarboxylate (140). A 100-mL, round-bottomed flask equipped with a condenser fitted with an argon inlet needle was charged with triyne **104** (0.101 g, 0.306 mmol, 1.0 equiv), dimethyl acetylenedicarboxylate (0.0376 mL, 0.043 g, 0.306 mmol, 1.0 equiv), and 30 mL of toluene. The reaction mixture was heated at reflux for 21 h and then cooled to rt. DBU (0.005 mL, 0.005 g, 0.03 mmol, 0.1 equiv) was added and the reaction mixture was stirred at rt for 12 h and then concentrated to give 0.158 g of brown oil. Purification by column chromatography on 16 g of silica gel (elution with 5% EtOAc-hexanes) afforded 0.117 g (81%) of **140** as a pale yellow oil; IR (neat) 2157, 1739, 1607, 1585, 1463, 1439, 1320, 1201, 1072, and 883 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.20 (s, 2 H), 5.18 (s, 2 H), 3.89 (s, 3 H), 3.87 (s, 3 H), 2.56-2.61 (m, 2 H), 1.43-1.52 (m, 2 H), 1.31-1.38 (m, 2 H), 1.12 (s, 21 H), 0.91 (t, J = 7.3 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.0, 167.5, 145.1, 141.2, 135.8, 134.3, 132.3, 114.1, 100.9, 100.2, 74.9, 74.0, 52.8, 52.7, 32.5, 31.4, 23.0, 18.8, 14.0, 11.3; HRMS-DART *(m/z)* $[M + H]^+$ calcd for $C_{27}H_{40}O_5Si$: 473.2718, found: 473.2722.

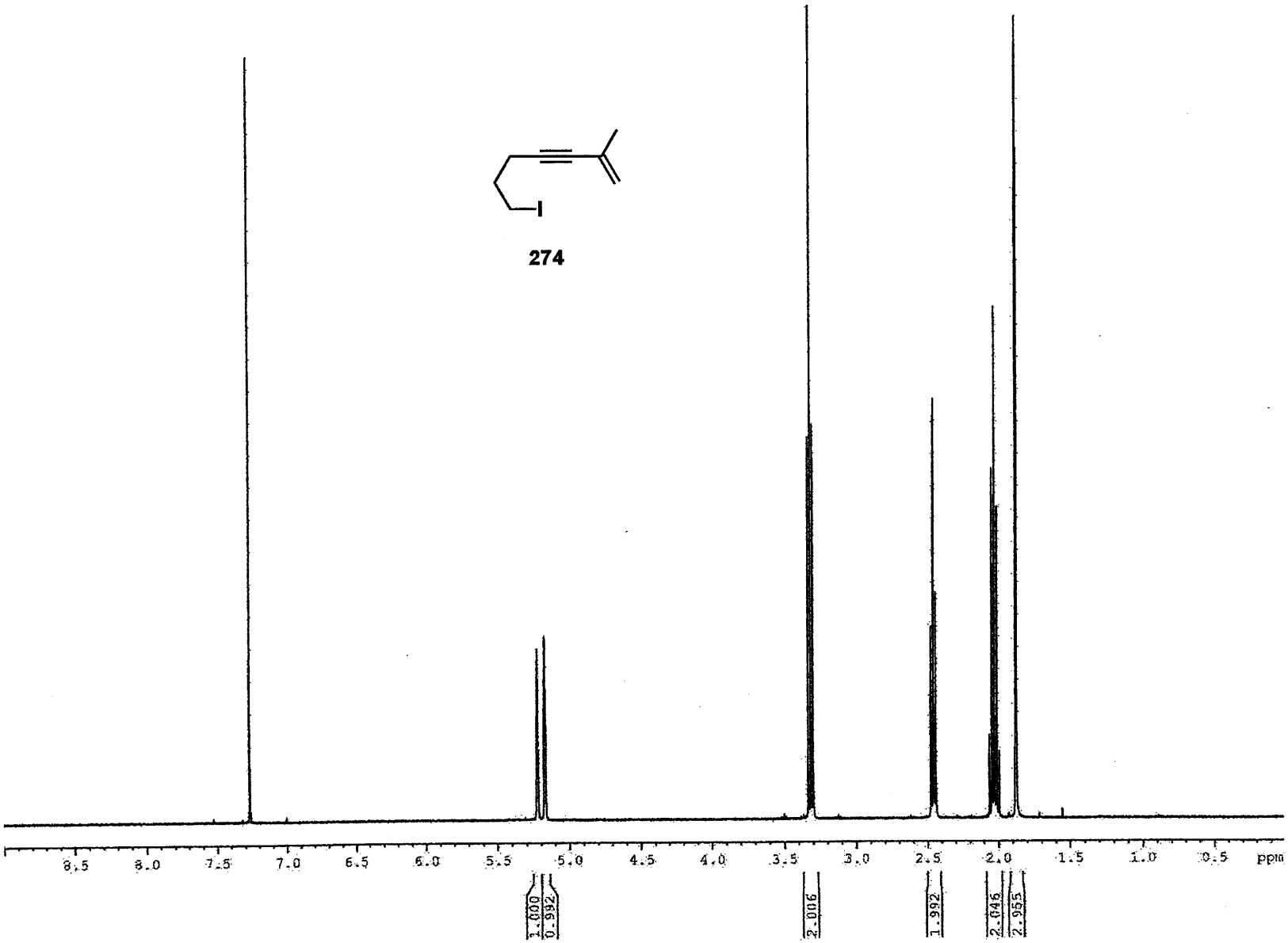

Bu
CO2Me
O
CO2Me
140
Si(i-Pr)3
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
4.000
2.952
3.087
1.964
2.093
2.274
21.127
3.482


168.051
167.516
145.066
141.203
135.813
134.315
132.327
116.158
100.858
100.164
77.532
77.215
76.897
74.918
73.977
52.816
52.737
32.479
31.381
22.985
18.779
13.980
11.334
Bu
CO2Me
CO2Me
O
140
Si(i-Pr)3
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10 ppm

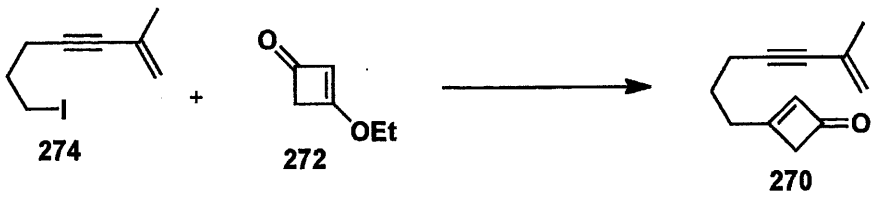


273 274

7-Iodo-2-methylhept-1-en-3-yne (274). A 50-mL, three-necked, round-bottomed flask equipped with a stir bar, rubber septum, glass stopper, and argon inlet adapter was charged with the alcohol **273** (0.759 g, 6.12 mmol, 1.0 equiv) and 10 mL of THF. The solution was cooled to 0 °C, and triphenylphosphine (1.604 g, 6.115 mmol, 1.0 equiv), imidazole (0.624 g, 9.16 mmol, 1.5 equiv), and iodine (2.310 g, 9.102 mmol, 1.5 equiv) were each added in one portion. The reaction mixture became dark brown in color. The solution was stirred at 0 °C in the dark for 2.5 h, and then diluted with 100 mL of satd aq $Na_2S_2O_3$ solution and extracted with five 50-mL portions of pentane. The combined organic layers were washed with 50 mL of brine, dried over $MgSO_4$, filtered, and concentrated at 0 °C (20 mmHg). The residue was filtered through a short plug of activated basic alumina using 80 mL of pentane and the filtrate was concentrated at 0 °C (20 mmHg) to give 1.369 g (96%) of iodide **274** as a colorless oil: IR (neat) 3094, 2950, 2919, 2229, 1796, 1614, 1427, 1221, and 895 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.21-5.24 (m, 1 H), 5.17 (app pent, J = 1.6 Hz, 1 H), 3.32 (t, J = 6.8 Hz, 2 H), 2.46 (t, J = 6.7 Hz, 2 H), 2.03 (pent, J = 6.8 Hz, 2 H), 1.88 (dd, J = 1.5, 1.1 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 127.2, 121.1, 87.0, 83.1, 32.4, 24.0, 20.5, 5.6; HRMS-ESI *(m/z)* $[M]^+$ calcd for $C_8H_{1a}I$: 233.9900, found: 233.9904.

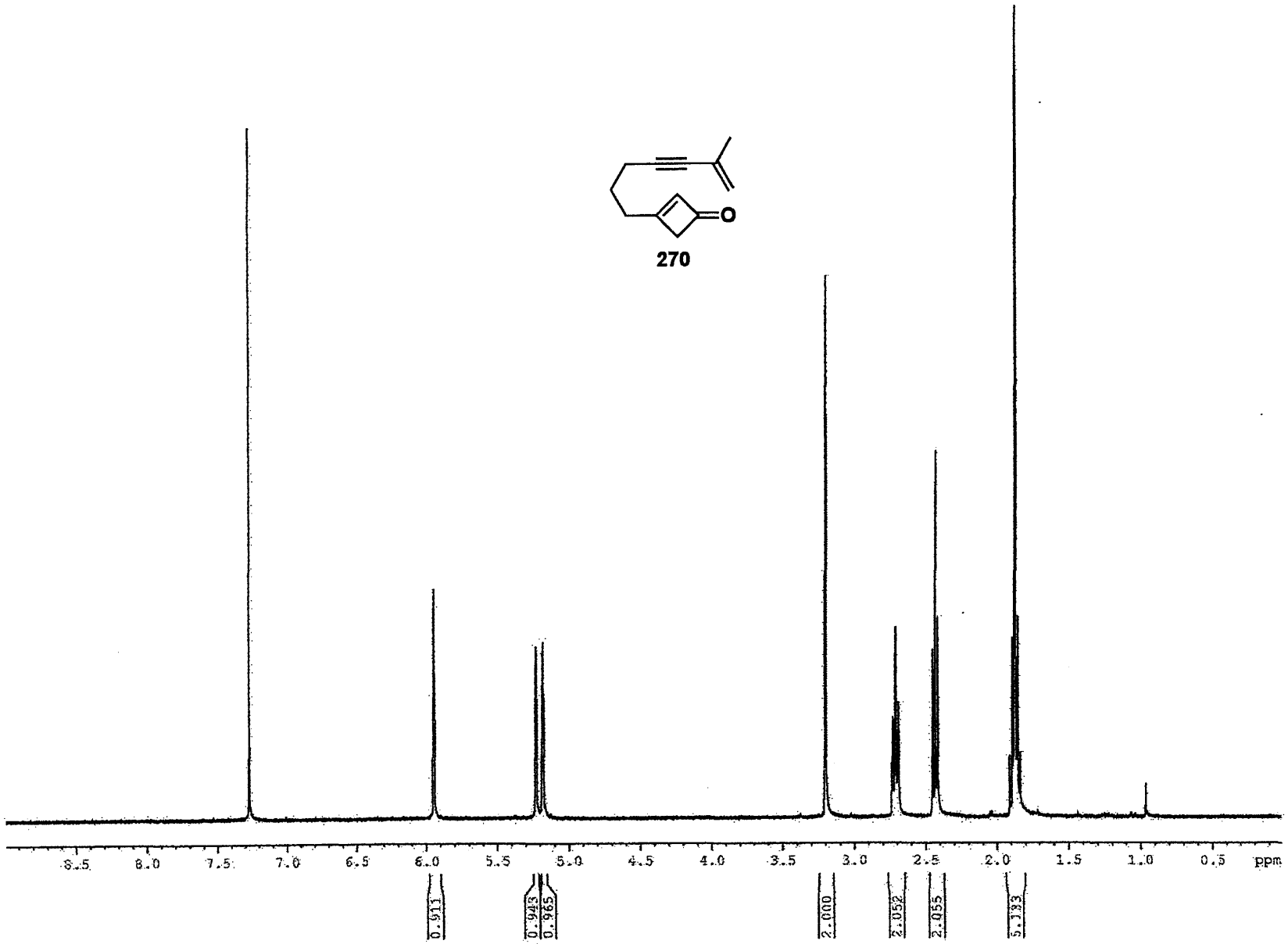

274
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
1.000
0.992
2.006
1.992
2.046
2.955

127.186
121.159
87.017
83.130
77.545
77.227
76.910
32.365
23.972
20.517
5.631
274
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

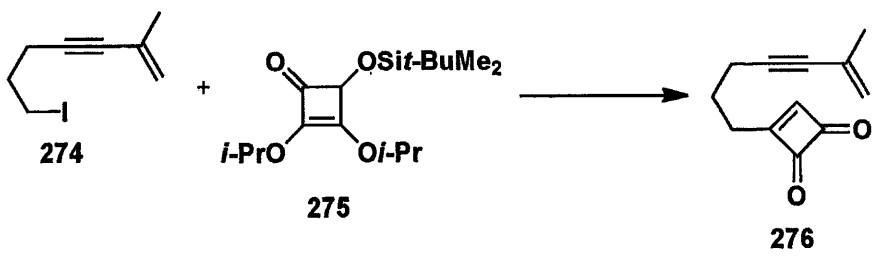


274 272 270

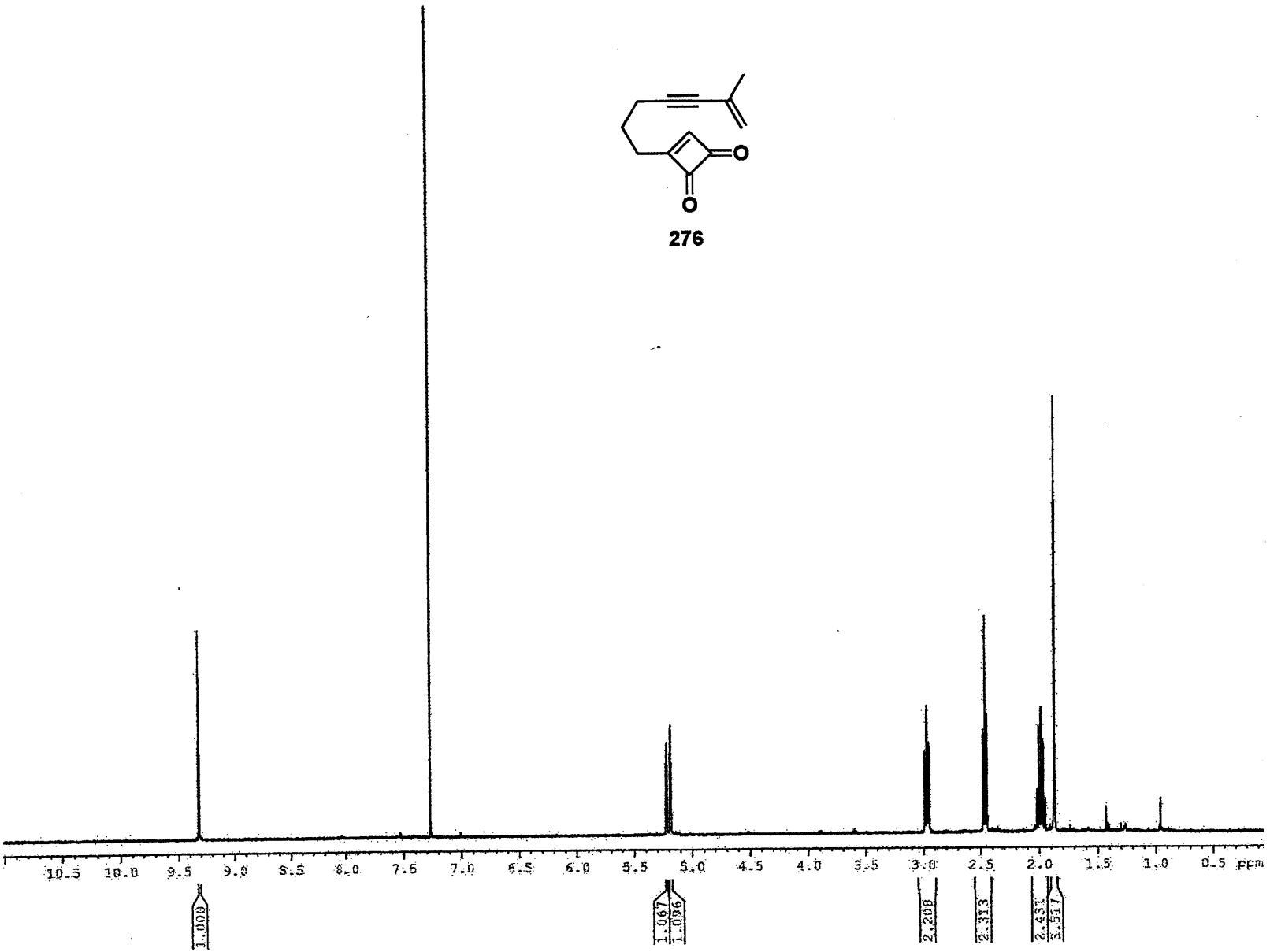
3-(6-Methylhept-6-en-4-ynyl)cyclobut-2-enone. A 100-mL, three-necked, round-bottomed flask equipped with a stir bar, rubber septum, thermocouple probe, argon inlet adapter, and 25-mL addition funnel fitted with a rubber septum was charged with the iodide **274** (1.203 g, 5.140 mmol, 1.35 equiv), 4.5 mL of pentane, and 11.4 mL of Et_2O. The solution was cooled at -78 °C while *t*-BuLi solution (1.63 M solution in pentane, 6.34 mL, 10.3 mmol, 2.7 equiv) was added dropwise via the addition funnel over 15 min. The resulting mixture was stirred at -78 °C for 5 min, and then a solution of 3-ethoxycyclobutenone (0.428 g, 3.81 mmol, 1.0 equiv) in 3 mL of Et_2O was added dropwise via cannula over 3 min (2-mL Et_2O rinse). The reaction mixture became dark orange. After 1 h, TFAA (0.92 mL, 1.4 g, 6.6 mmol, 1.7 equiv) was added dropwise via syringe over 30 sec. The reaction mixture was stirred at -78 °C for 6 h, and then 11 mL of satd aq $NaHCO_3$ solution was added dropwise via syringe over 5 min. The resulting mixture was allowed to warm to rt over 20 min and then diluted with 40 mL of Et_2O. The aqueous layer was separated and extracted with three 20-mL portions of Et_2O, and the combined organic layers were washed with 30 mL of brine, dried over $MgSO_4$, filtered, and concentrated at 5 °C (20 mmHg) to give 1.314 g of a red brown oil. Column chromatography on 255 g of silica gel (elution with 15-30% Et_2O-pentane) afforded 0.259 g (39%) of cyclobutenone **270** as a yellow-orange oil: IR (neat) 2223, 1767, 1614, 1585, 1452, 1434, 1415, 1051, 1021, 897, 860, and 840 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.95 (s, 1 H), 5.21-5.24 (m, 1 H), 5.18 (t, J = 1.7 Hz, 1 H), 3.20 (s, 2 H), 2.71 (td, J = 7.6, 1.2 Hz, 2 H), 2.43 (t, J = 6.9 Hz, 2 H), 1.83-1.92 (m 5 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.0, 180.3, 134.7, 127.1, 121.1, 87.6, 83.1, 51.0, 31.3, 25.3, 23.9, 19.1; HRMS-ESI *(m/z)* $[M + Na]^+$ calcd for $C_{12}H_{14}O$: 197.0937, found: 197.0938.


O
270
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
0.911
0.943
0.965
2.000
2.052
2.055
5.193

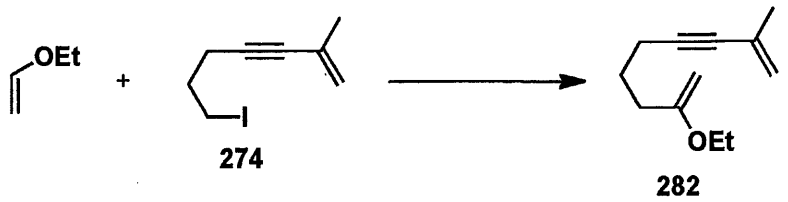
187.947
180.321
134.667
127.073
121.091
87.645
83.099
77.549
77.231
76.913
50.968
32.296
25.287
23.984
19.085
O
270
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm



3-(6-Methylhept-6-en-4-ynyl)cyclobut-3-ene-1,2-dione (276). A 100-mL, three-necked, round-bottomed flask equipped with an argon inlet adapter, two rubber septa, and a thermocouple probe was charged with iodide **274** (0.965 g, 4.1 mmol, 1.3 equiv) and 14 mL of Et_2O. The reaction mixture was cooled at -78 °C and *t*-BuLi solution (1.51 M solution in pentane, 5.5 mL, 8.2 mmol, 2.6 equiv) was added dropwise over 15 min. After 2 min, a solution of ketone **275** (1.024 g, 3.26 mmol, 1.0 equiv) in 3 mL of Et_2O was added dropwise via cannula over 3 min (1-mL Et_2O rinse). The reaction mixture was stirred at -78 °C for 1 h, then 1 mL of concd HCl (36.5-38%) was added dropwise over 1 min. The reaction mixture was allowed to warm to rt over 20 min, diluted with 50 mL of Et_2O, and washed with 10 mL of satd aq $NaHCO_3$ solution and 20 mL of brine, dried over $MgSO_4$, filtered, and concentrated to give 1.439 g of a red oil. Purification by column chromatography on 43 g of silica gel (elution with 20% EtOAc-hexanes) afforded 0.300 g (49%) of cyclobutenedione **276** as an orange oil: IR (neat) 3550, 3091, 2950, 2224, 1784, 1614, 1559, 1435, 1072, and 897 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.32 (t, J = 1.4 Hz, 1 H), 5.21-5.24 (m, 1 H), 5.18-5.20 (m, 1 H), 2.97 (td, J = 7.6, 1.2 Hz, 2 H), 2.46 (t, J = 6.7 Hz, 2 H), 1.99 (app pent, J = 7.2 Hz, 2 H), 1.87 (t, J = 1.3 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.5, 199.9, 185.2, 126.9, 121.4, 87.0, 83.8, 26.8, 24.8, 23.8, 19.1; HRMS-DART-ESI *(m/z)*: $[M]^+$ calcd for $C_{12}H_{12}O_2$: 188.0837, found 188.0835.

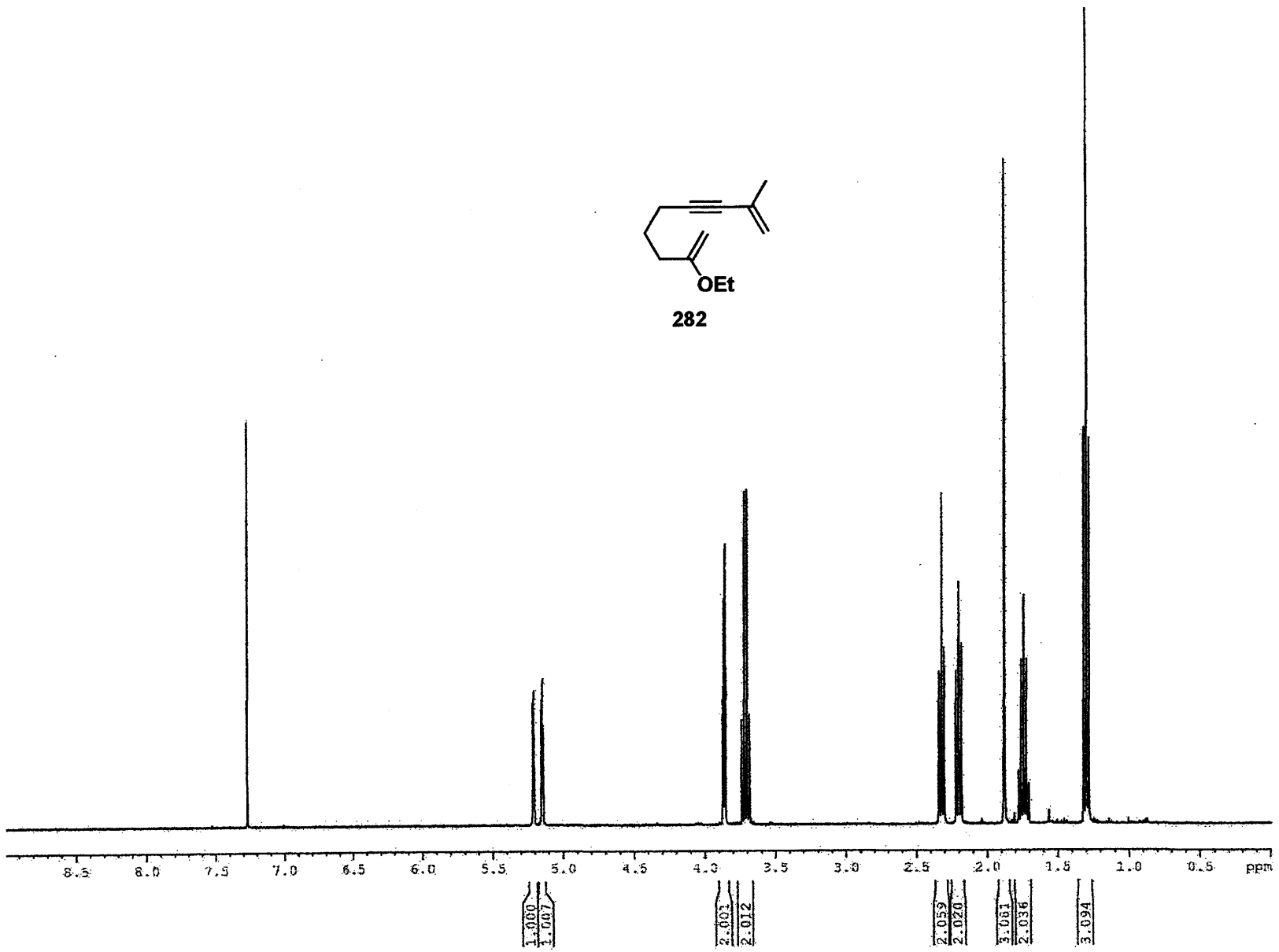

O
O
276
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
1.000
1.067
1.096
2.208
2.373
2.431
3.511

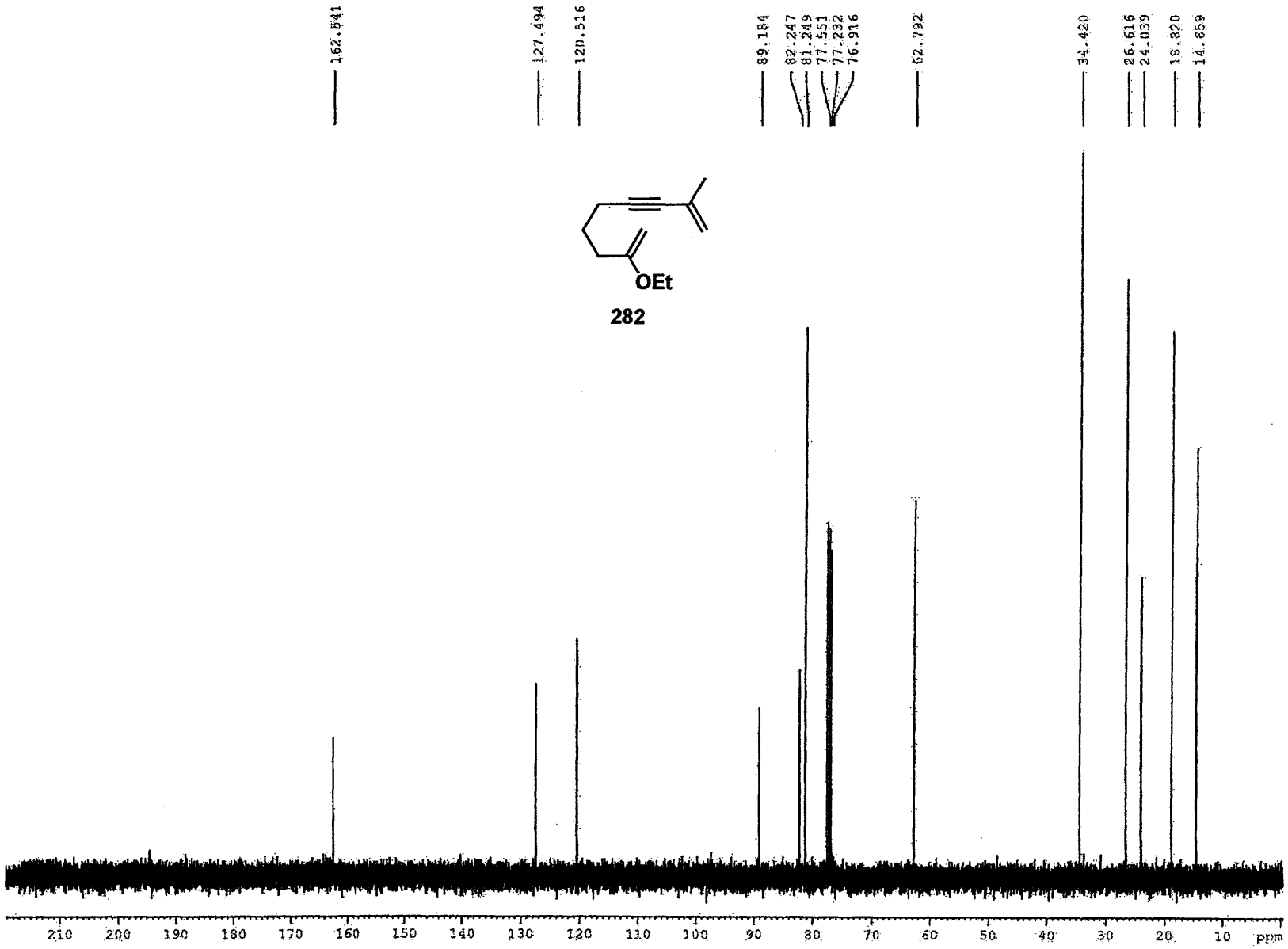
207.535
199.903
196.627
185.166
126.891
121.430
86.961
83.771
77.534
77.217
76.898
26.849
24.853
23.821
19.151
O
O
276
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

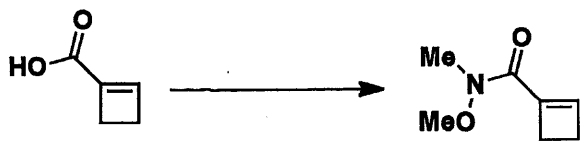


274 282

8-Ethoxy-2-methylnona-1,8-dien-3-yne (282). A 50-mL, three-necked, round-bottomed flask equipped with a stir bar, argon inlet adapter, two rubber septa, and thermocouple probe was charged with ethyl vinyl ether (1.43 mL, 1.08 g, 19.8 mmol, 3.9 equiv) and 12 mL of THF. The solution was cooled at -78 °C while *t*-BuLi (1.63 M solution in pentane, 7.7 mL, 13 mmol, 2.5 equiv) was added dropwise via syringe over 10 min. The bright yellow reaction mixture became colorless upon warming to 0 °C over 30 min. The reaction mixture was cooled back to -78 °C and a solution of iodide **274** (1.185 g, 5.063 mmol, 1.0 equiv) in 1.5 mL of THF was added dropwise via cannula over 5 min (0.5 mL THF rinse). The reaction mixture was allowed to warm to 0 °C over 30 min. After 2 h, 10 mL of satd aq NH_4Cl solution was added in one portion. The aqueous layer was separated and extracted with three 20-mL portions of Et_2O, and the combined organic layers were washed with 20 mL of brine, dried over Na_2SO_4, filtered, and concentrated to give 0.876 g of a pale yellow oil that was purified by distillation using a Perkin triangle to afford 0.610 g (68%) of vinyl ether **282** as a colorless oil: bp 74 °C (0.5 mmHg); IR (neat) 3118, 3096, 2979, 2224, 1654, 1615, 1481, 1436, 1371, 1287, 1265, 1158, 1081, 976, and 799 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.21 (br s, 1 H), 5.12-5.16 (m, 1 H), 3.87 (d, J = 1.7 Hz, 1 H), 3.86 (d, J = 1.7 Hz, 1 H), 3.71 (q, J = 7.0 Hz, 2 H), 2.32 (t, J = 7.2 Hz, 2 H), 2.20 (t, J = 7.4 Hz, 2 H), 1.86-1.89 (m, 3 H), 1.74 (pent, J = 7.3 Hz, 2 H), 1.30 (t, J = 7.0 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.5, 127.5, 120.5, 89.2, 82.2, 81.2, 62.8, 34.4, 26.6, 24.0, 18.8, 14.7; HRMS-ESI *(m/z)* $[M + H]^+$ calcd for $C_{12}H_{18}O$: 179.1436, found: 179.1433.

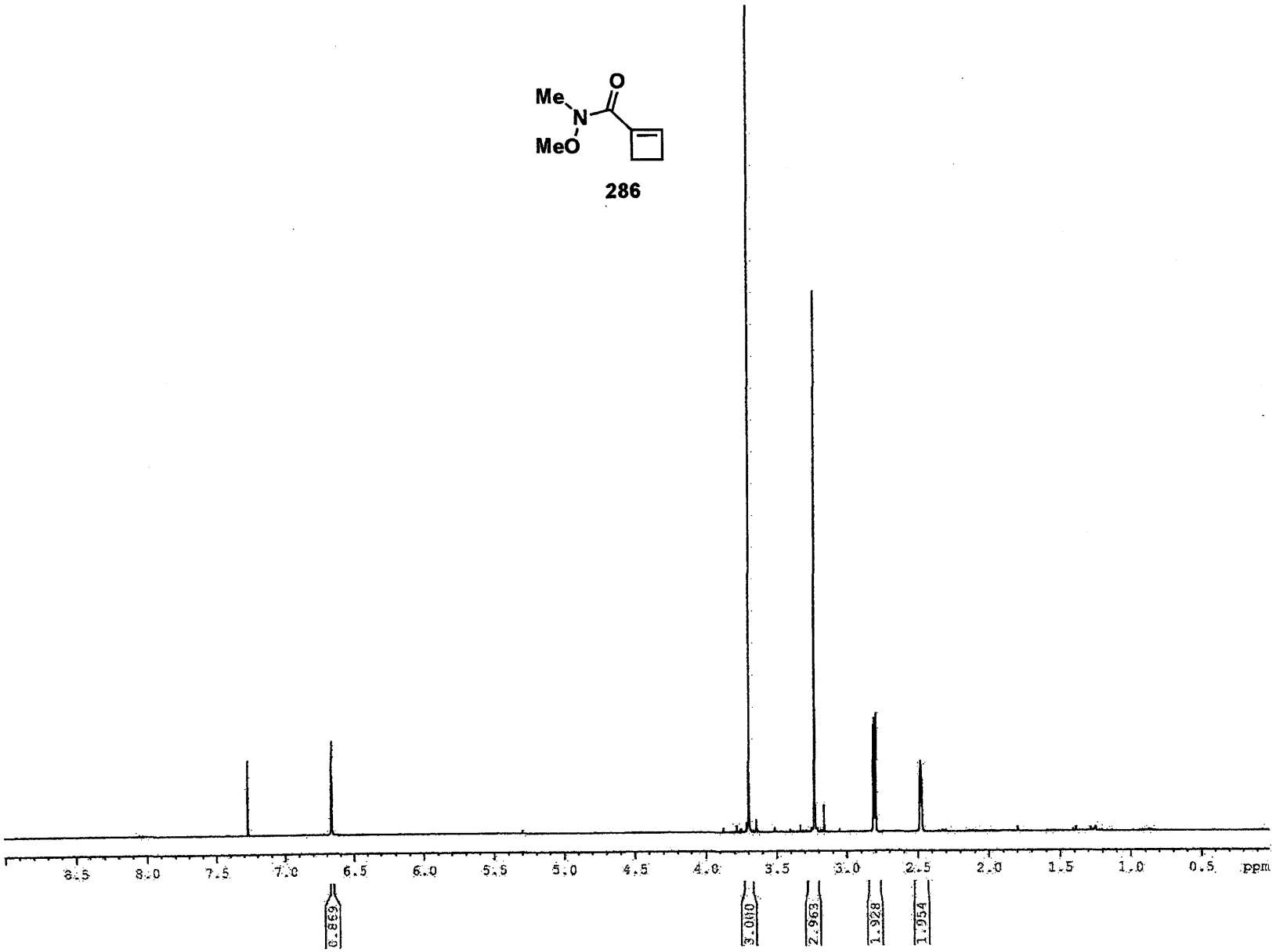

OEt
282
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
1.000
1.007
2.001
2.012
2.059
2.020
3.081
2.036
3.094

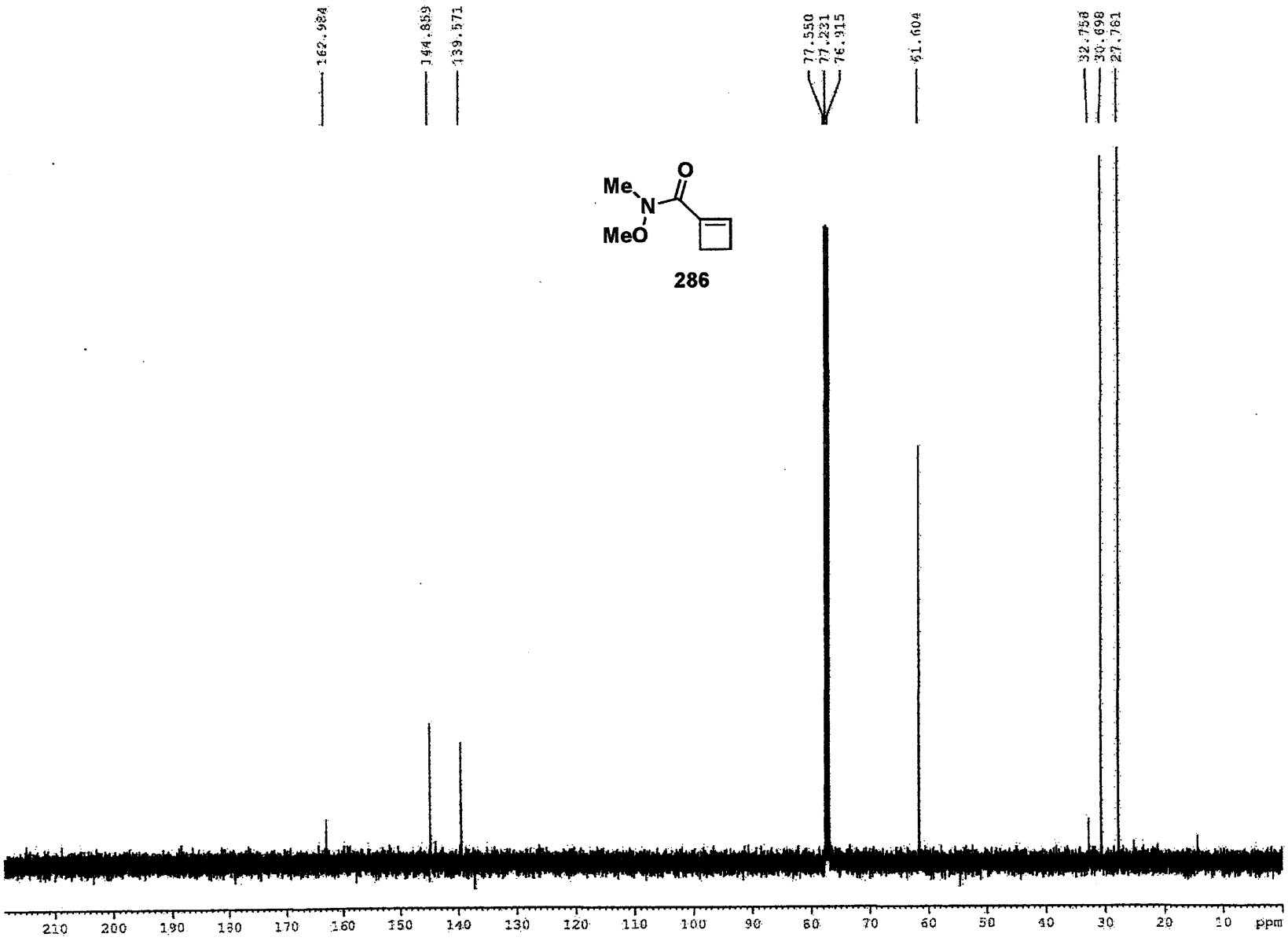

162.841
127.494
120.516
89.184
82.247
81.249
77.551
77.232
76.916
62.792
34.420
26.616
24.039
18.820
14.659
OEt
282
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

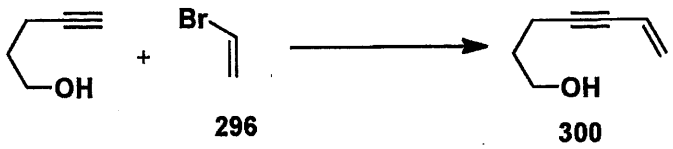


292 **286**

***N*-Methoxy-*N*-methylcyclobut-1-enecarboxamide (286).** A 250-mL, three-necked, round-bottomed flask equipped with an argon inlet adapter and two rubber septa was charged with cyclobutene carboxylic acid **292** (1.126 g, 11.48 mmol, 1.0 equiv) and 70 mL of CH_2Cl_2. Oxalyl chloride (1.02 mL, 1.53 g, 12.0 mmol, 1.05 equiv) and DMF (4 drops) were added. The reaction mixture was stirred at rt for 1 h (gas evolution), and then cooled to 0 °C. A solution of *N,O*-dimethylamine hydrochloride (1.233 g, 12.64 mmol, 1.1 equiv) and triethylamine (3.52 mL, 2.56 g, 25.3 mmol, 2.2 equiv) in 40 mL of CH_2Cl_2 was added dropwise via cannula over 5 min (5-mL CH_2Cl_2 rinse). The pale yellow reaction mixture was allowed to warm to rt and stirred for 1 h in the dark. Water (50 mL) was added and the aqueous layer was separated, neutralized with satd aq $NaHCO_3$ solution, and then extracted with two 125-mL portions of Et_2O. The combined organic layers were washed with 100 mL of brine, dried over $MgSO_4$, filtered, and concentrated to give 1.748 g of yellow oil. Purification by column chromatography on 52 g of silica gel (elution with 25-35% EtOAc-hexanes) afforded 1.282 g (79%) of Weinreb amide **286** as a very pale yellow oil: IR (neat) 2968, 2936, 1643, 1589, 1416, 1382, and 992 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.66 (t, J = 1.2 Hz, 1 H), 3.70 (s, 3 H), 3.23 (s, 3 H), 2.79-2.83 (m, 2 H), 2.48 (td, J = 3.3, 1.2 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.0, 144.9, 139.6, 61.6, 32.7, 30.7, 27.8; HRMS-ESI *(m/z)* $[M + H]^+$ calcd for $C_7H_{12}NO_2$: 142.0863, found: 142.0869.

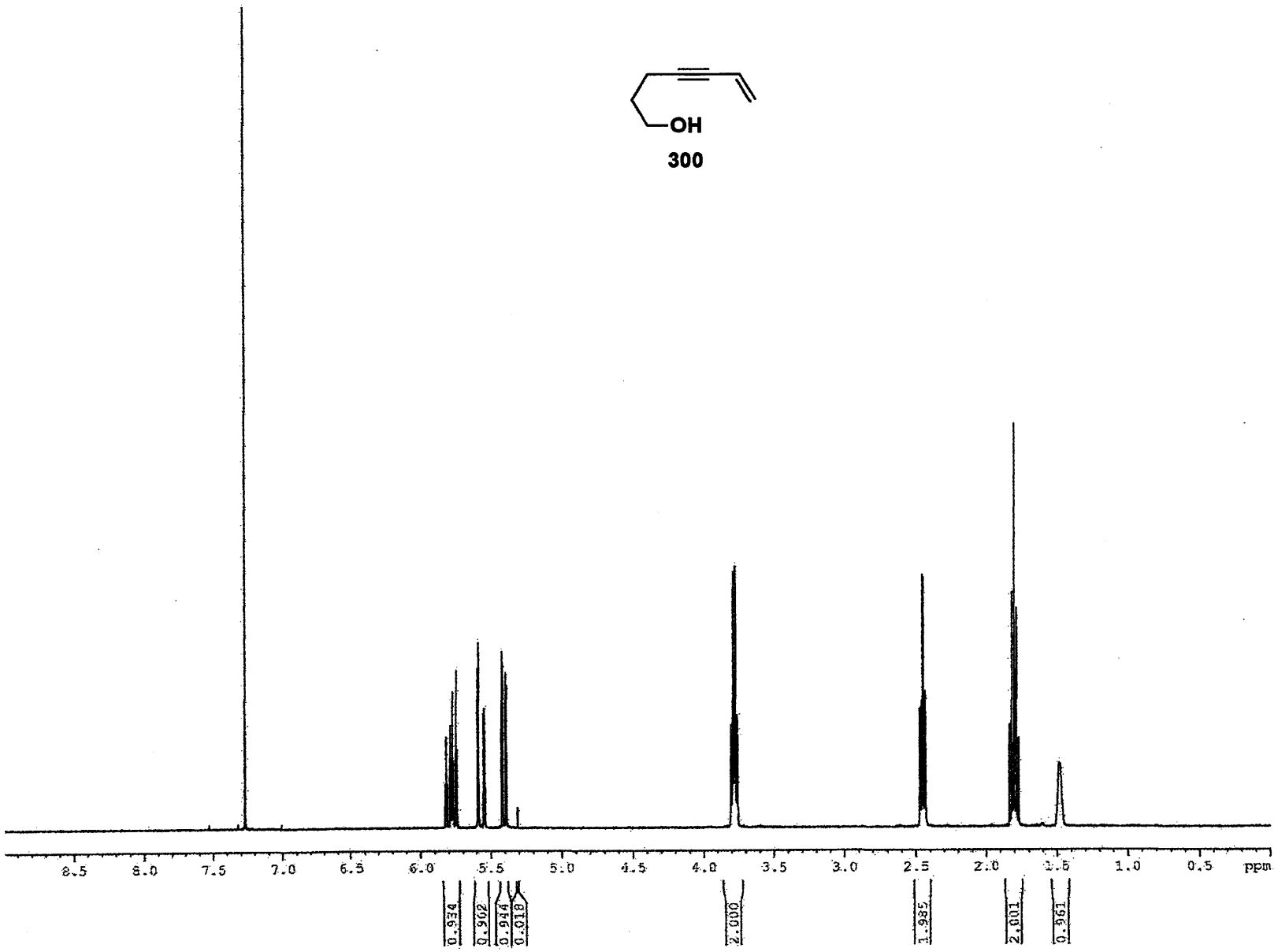

Me
N
MeO
O
286
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
0.859
3.000
2.963
1.928
1.954

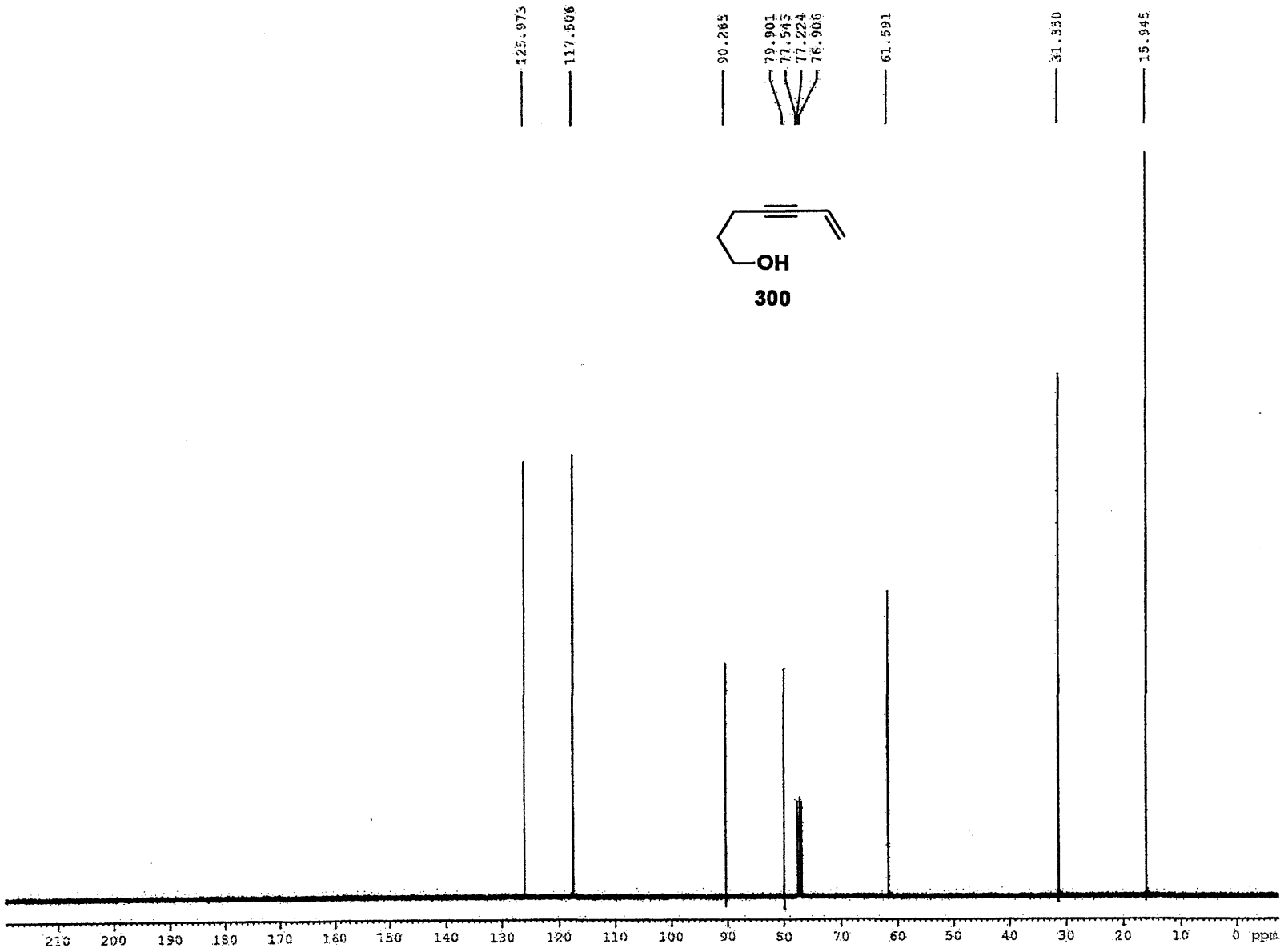

162.984
144.859
139.671
77.550
77.231
76.915
61.604
32.758
30.698
27.761
Me
N
MeO
O
286
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

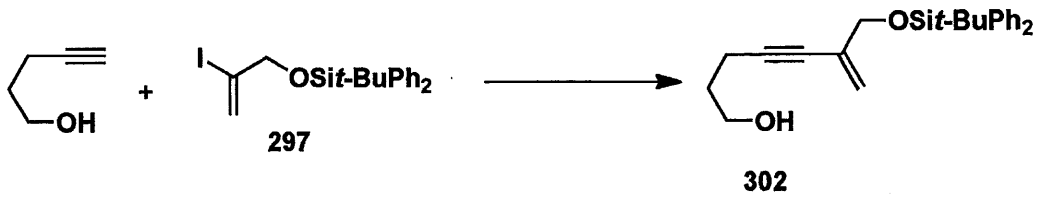


296 300

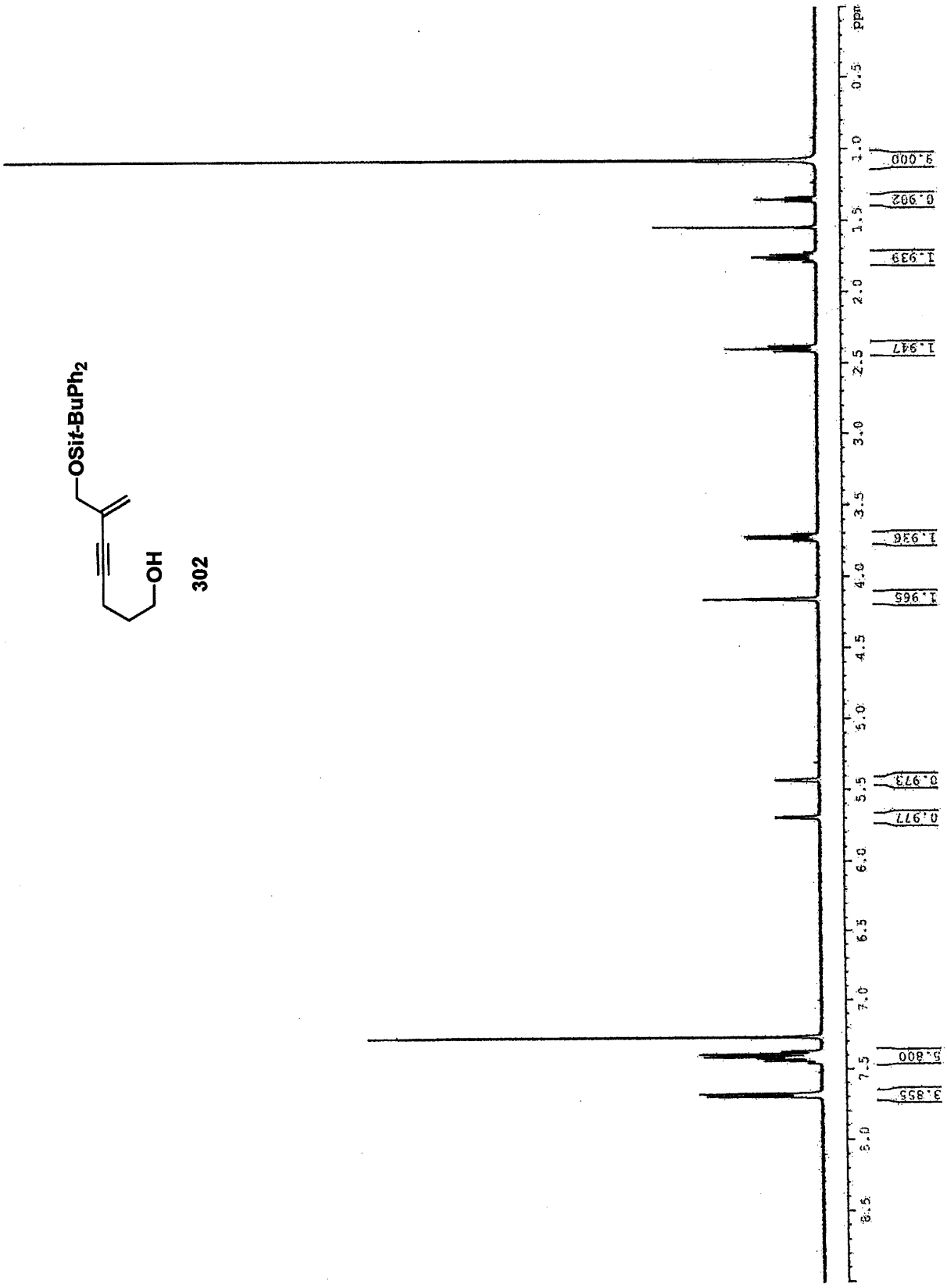
Hept-6-en-4-yn-1-ol (300). A 100-mL, three-necked, round-bottomed flask equipped with a stir bar, argon inlet adapter, two rubber septa, and thermocouple probe was charged with $PdCl_2(PPh_3)_2$ (0.281 g, 0.401 mmol, 0.02 equiv), CuI (0.152 g, 0.797 mmol, 0.04 equiv), and Et_3N (4.2 mL, 3.0 g, 30 mmol, 1.5 equiv). The orange reaction mixture was cooled to 0 °C and vinyl bromide **296** (40 mL of a 1.0 M solution in THF, 40 mmol, 2 equiv) was added in one portion. A solution of 4-pentyn-1-ol (1.86 mL, 1.68 g, 20.0 mmol, 1.0 equiv) in 2.8 mL of THF was added dropwise via cannula over 20 min (1.4-mL of THF rinse), and the dark brown reaction mixture was allowed to warm to rt over 30 min. After 1.5 h, the reaction mixture was filtered through a plug of 2 g of silica gel with the aid of 300 mL of Et_2O. The filtrate was washed with two 100-mL portions of satd aq $NaHCO_3$ solution and 100 mL of brine, dried over $MgSO_4$, filtered, and concentrated at 0 °C (20 mmHg) to provide 2.377 g of a brown oil. Column chromatography on 54 g of silica gel (elution with 15-40% Et_2O-pentane) gave 1.773 g (81%) of alcohol **300** as a golden yellow oil: IR (neat) 3334, 2949, 2227, 1841, 1609, 1433, 1061, 975, and 920 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.78 (ddt, J = 17.5, 11.0, 2.1 Hz, 1 H), 5.57 (ddd, J = 17.5, 2.2, 0.5 Hz, 1 H), 5.41 (ddd, J = 11.0, 2.2, 0.4 Hz, 1 H), 3.78 (q, J = 5.9 Hz, 2 H), 2.45 (td, J = 6.9, 2.1 Hz, 2 H), 1.80 (pent, J = 6.5 Hz, 2 H), 1.43-1.51 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 126.0, 117.5, 90.3, 79.9, 61.6, 31.4, 15.9; HRMS-ESI *(m/z)* $[M + H]^+$ calcd for $C_7H_{10}O$: 111.0810, found: 111.0805.


OH
300
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
0.954
0.968
0.944
0.918
2.000
1.985
2.001
0.961

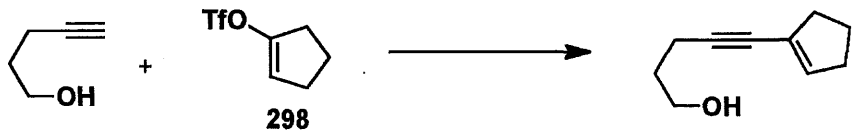

125.973
117.506
90.265
79.901
77.545
77.224
76.906
61.591
31.330
15.945
OH
300
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0 ppm



6-(*tert*-Butyldiphenylsilyloxy)methylhept-6-en-4-yn-1-ol (302). A 50-mL, three-necked, round-bottomed flask equipped with an argon inlet adapter and two rubber septa was charged with $PdCl_2(PPh_3)_2$ (0.064 g, 0.09 mmol, 0.02 equiv), CuI (0.034 g, 0.18 mmol, 0.04 equiv), and triethylamine (1.0 mL, 7.2 mmol, 1.5 equiv). The reaction mixture was cooled at 0 °C and a solution of iodide **297** (2.387 g, 5.60 mmol, 1.25 equiv) in 1 mL of THF was added dropwise over 4 min (1-mL THF rinse). A solution of 4-pentyn-1-ol (0.42 mL, 0.38 g, 4.5 mmol, 1.0 equiv) in 5.5 mL of THF was added dropwise over 10 min. The orange reaction mixture was allowed to warm to rt, stirred for 21 h, and then filtered through a plug of 2 g of silica gel with the aid of 250 mL of Et_2O. The filtrate was washed with two 75-mL portions of satd aq $NaHCO_3$ solution, followed by 75 mL of brine. The organic phase was dried over $MgSO_4$, filtered, and concentrated to give 2.53 g of orange oil. Purification by column chromatography on 51 g of silica gel (elution with 0-10% EtOAc-hexanes) afforded 1.459 g (85%) of alcohol **302** as a yellow oil: IR (neat) 3346, 2391, 2857, 2223, 1619, 1672, 1428, 1260, 1113, 902, 822, 740, and 701 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.66-7.71 (m, 4 H), 7.36-7.46 (m, 6 H), 5.67-5.72 (m, 1 H), 5.40-5.44 (m, 1 H), 4.16 (s, 2 H), 3.73 (q, J = 5.9 Hz, 2 H), 2.40 (t, J = 6.8 Hz, 2 H), 1.76 (pent, J = 6.7 Hz, 2 H), 1.35 (t, J = 5.4 Hz), 1.07 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.7, 133.5, 130.8, 129.9, 127.9, 118.6, 90.5, 79.3, 65.9, 61.9, 31.4, 27.0, 19.5, 16.0; HRMS-ESI *(m/z)* $[M + H]^+$ calcd for $C_{24}H_{30}O_2Si$: 401.1907, found: 401.1901.

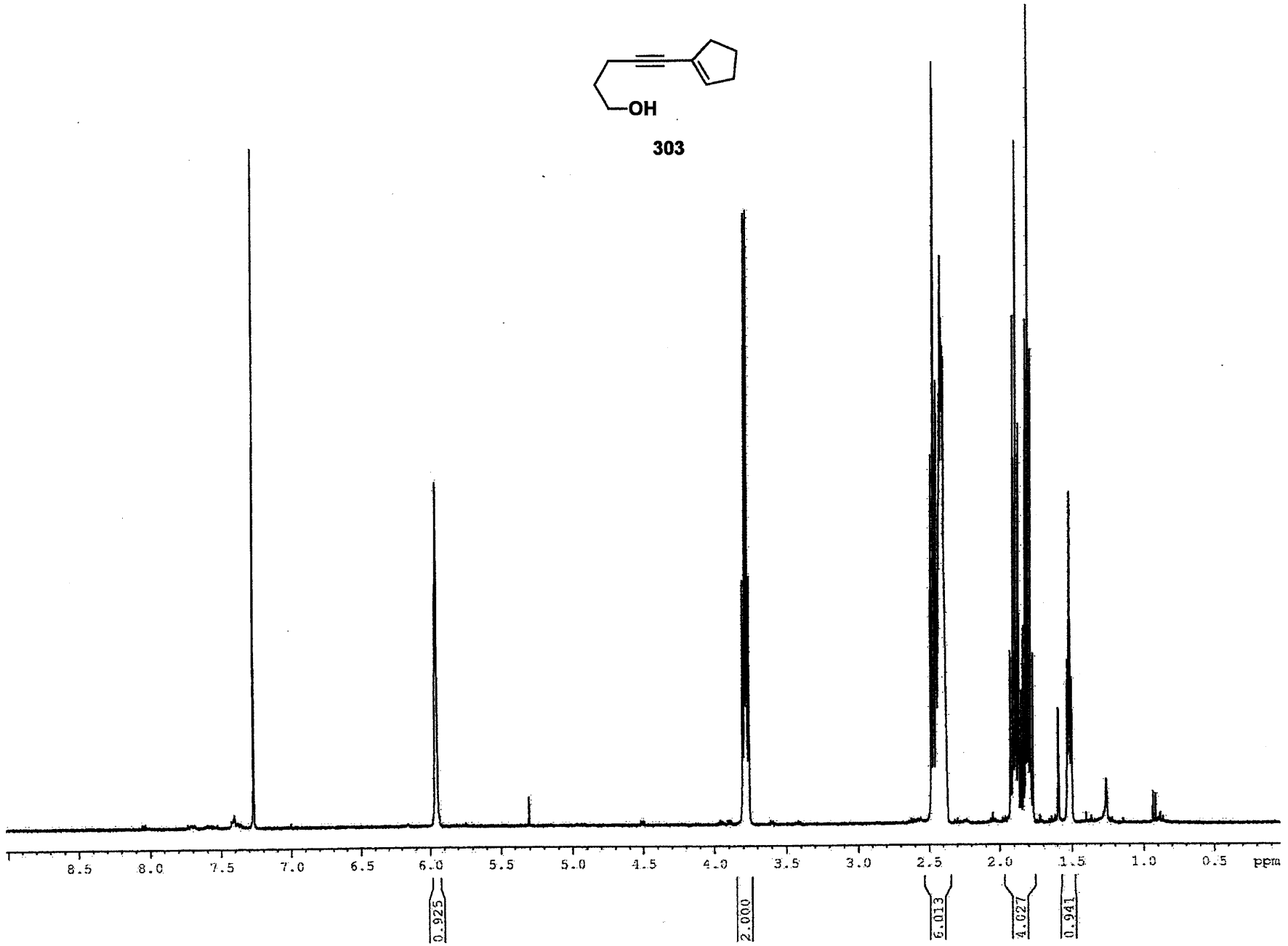

OSit-BuPh2
OH
302
9.000
0.902
1.939
1.947
1.936
1.965
0.973
0.977
5.800
3.855
ppm

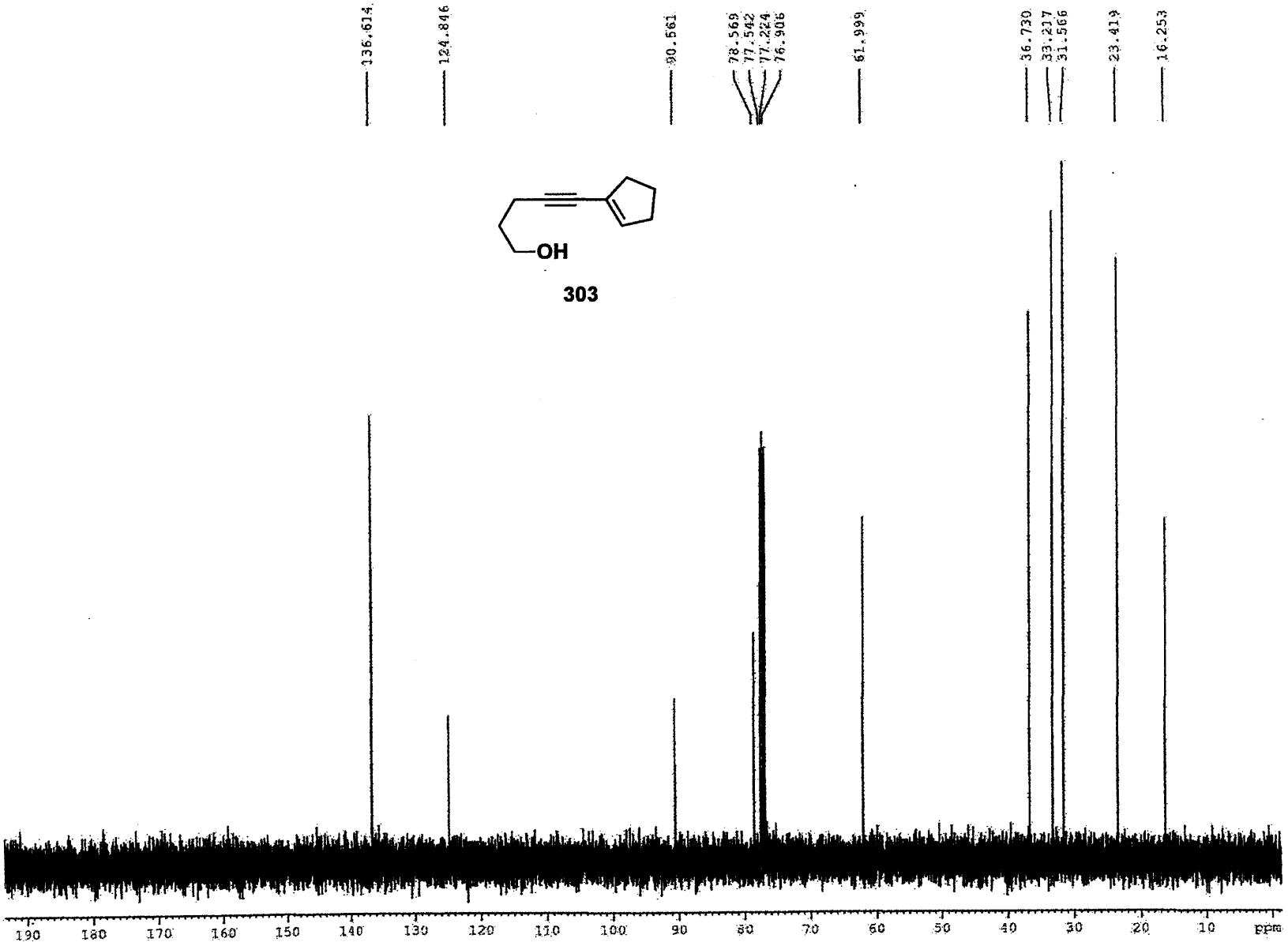
135.680
133.559
130.847
129.911
127.914
118.566
90.519
79.292
77.531
77.214
76.896
65.949
61.912
31.412
26.967
19.506
16.032
OSit-BuPh2
OH
302
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm



298 303

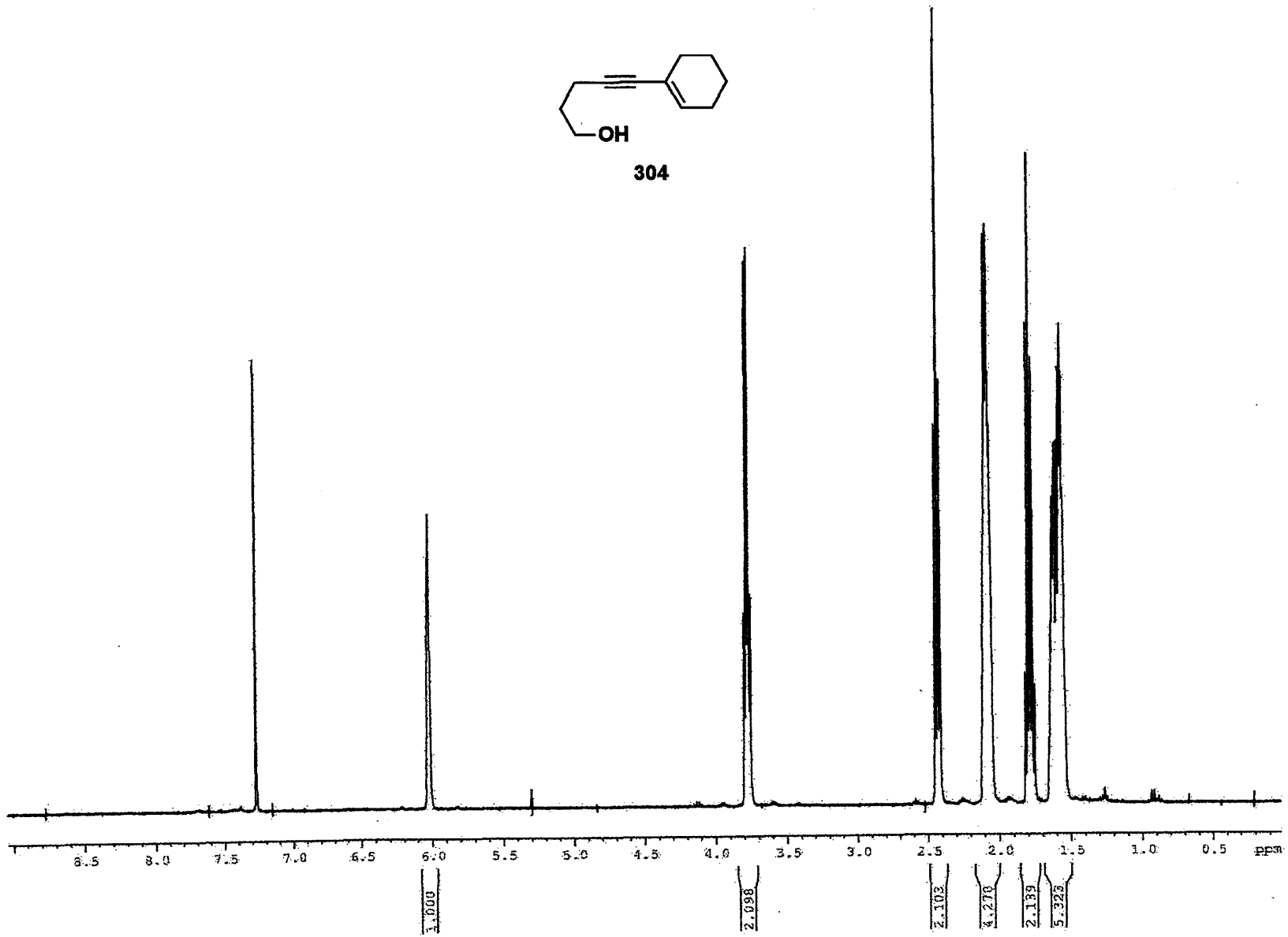
5-(Cyclopent-1-en-1-yl)pent-4-yn-1-ol (303). A 100-mL, three-necked, round-bottomed flask equipped with an argon inlet adapter and two rubber septa was charged with $PdCl_2(PPh_3)_2$ (0.069 g, 0.10 mmol, 0.02 equiv), CuI (0.038 g, 0.20 mmol, 0.04 equiv) and 10.5 mL of diisopropylamine. The orange reaction mixture was stirred at rt while a solution of vinyl triflate **298** (1.408 g, 6.51 mmol, 1.3 equiv) in 10 mL of THF was added dropwise via cannula over 2 min (1.8-mL THF rinse). The reaction mixture was stirred for 5 min, and then a solution of 4-pentyn-1-ol (0.46 mL, 0.42 g, 5.0 mmol, 1.0 equiv) in 20 mL of THF was added dropwise via cannula over 27 min. The reaction mixture was stirred at rt for 1 h, 10 mL of H_2O was added, and the resulting mixture was extracted with two 75-mL portions of Et_2O. The combined organic phases were washed with 25 mL of brine, dried over $MgSO_4$, filtered, and concentrated to give 1.517 g of orange oil. Purification by column chromatography on 91 g of silica gel (elution with 5-35% EtOAc-hexanes) afforded 0.654 g (88%) of alcohol **303** as a red oil: IR (neat) 3332, 2950, 2223, 1611, 1440, 1326, 1057, 950, and 809 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ d 5.93-5.98 (m, 1 H), 3.78 (q, J = 5.9 Hz, 2 H), 2.47 (t, J = 7.0 Hz, 2 H), 2.36-2.45 (m, 4 H), 1.89 (pent, J = 7.6 Hz, 2 H), 1.80 (pent, J = 6.2 Hz, 2 H), 1.52 (t, J = 5.4 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.6, 124.8, 90.6, 78.6, 62.0, 36.7, 33.2, 31.6, 23.4, 16.2; HRMS-ESI *(m/z)* calcd for $C_{10}H_{14}O$ $[M + H]^+$: 151.1117, found: 151.1113.

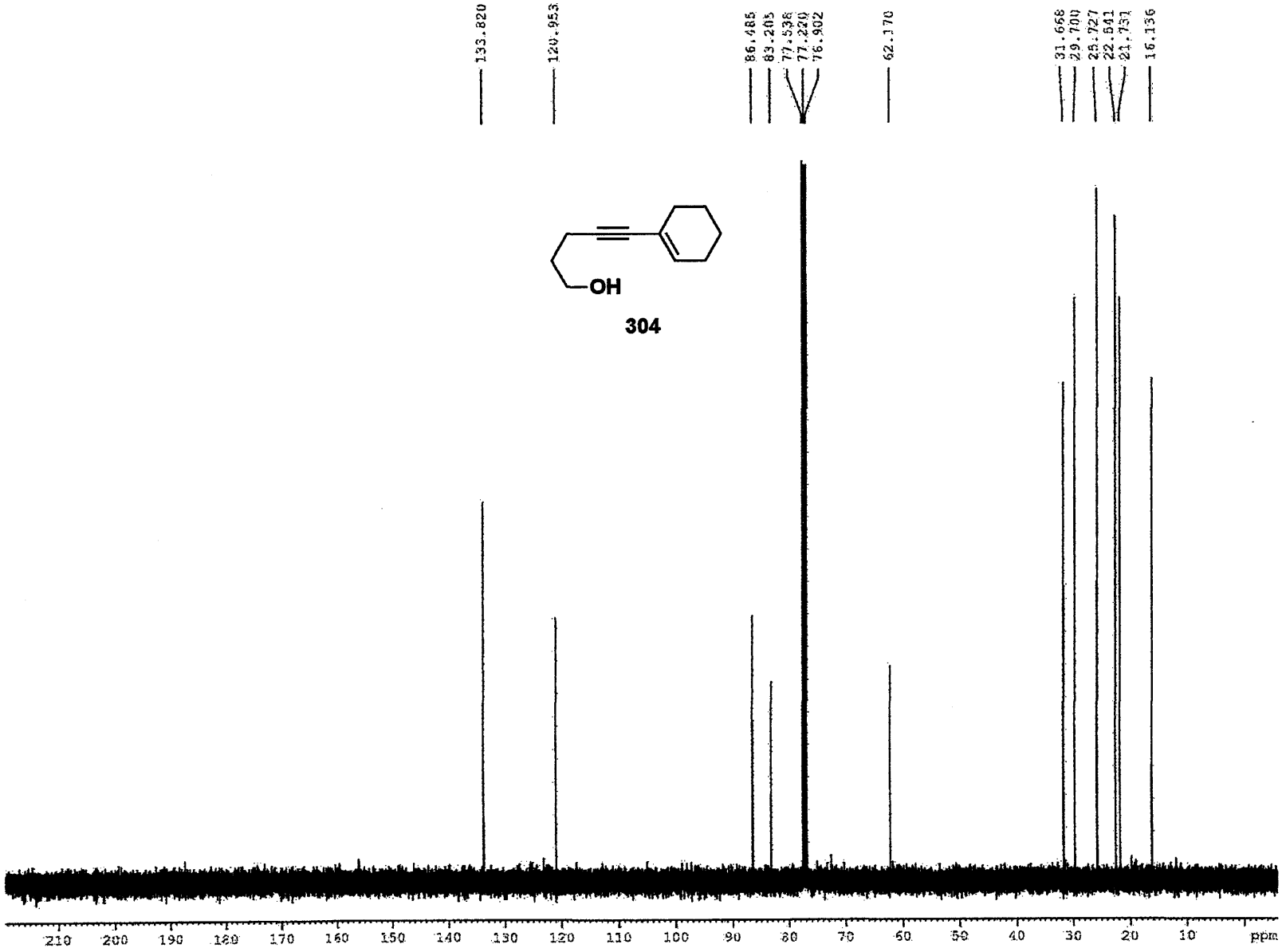

OH
303
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
0.925
2.000
6.013
4.027
0.941


136.614
124.846
90.561
78.569
77.542
77.224
76.906
61.999
36.730
33.217
31.566
23.419
16.253
OH
303
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

299 304

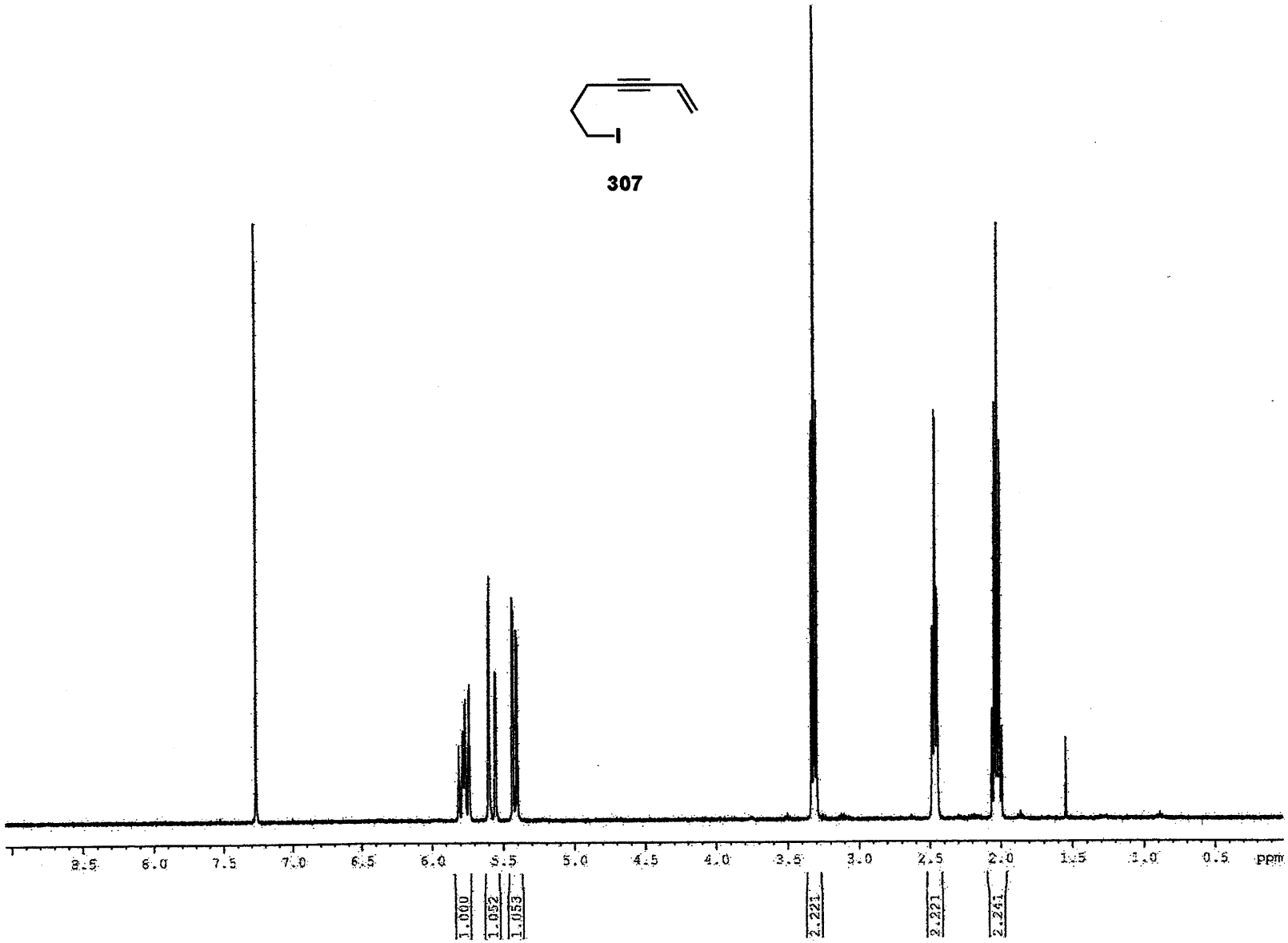
5-(Cyclohex-1-en-1-yl)pent-4-yn-1-ol (304). A 100-mL, three-necked, round-bottomed flask equipped with an argon inlet adapter and two rubber septa was charged with $PdCl_2(PPh_3)_2$ (0.077 g, 0.11 mmol, 0.01 equiv), CuI (0.041 g, 0.22 mmol, 0.04 equiv), and *i*-Pr_2NH (11.5 mL, 8.30 g, 82 mmol, 15 equiv). A solution of cyclohexenyl triflate **299** (1.639 g, 7.12 mmol, 1.3 equiv) in 11 mL of THF was added dropwise over 2 min (2-mL THF rinse), followed by a solution of 4-pentyn-1-ol (0.51 mL, 0.46 g, 5.5 mmol, 1.0 equiv), in 20 mL of THF, added dropwise over 22 min. The reaction mixture was stirred at rt for 1 h, and then 75 mL of Et_2O and 10 mL of H_2O were added. The organic phase was separated and washed with 10 mL of H_2O and 25 mL of brine, and then dried over $MgSO_4$, filtered, and concentrated to give 2.540 g of red oil. Purification by column chromatography on 152 g of silica gel (elution with 5-30% EtOAc-hexanes) afforded 0.830 g (92%) of alcohol **304** as a dark red oil: IR (neat) 3334, 2930, 2220, 1631, 1435, 1347, 1136, 1052, 918, 842, 801, and 730 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.99-6.05 (m, 1 H), 3.78 (q, J = 5.8 Hz, 2 H), 2.43 (t, J = 6.9 Hz, 2 H), 2.02-2.16 (m, 4 H), 1.79 (pent, J = 6.3 Hz, 2 H), 1,52-1.66 (m, 5 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 133.8, 121.0, 86.5, 83.2, 62.2, 31.7, 29.7, 25.7, 22.5, 21.7, 16.1; HRMS-DART *(m/z)* calcd for $C_{11}H_{16}O$ $[M + H]^+$: 165.1274, found: 165.1279.

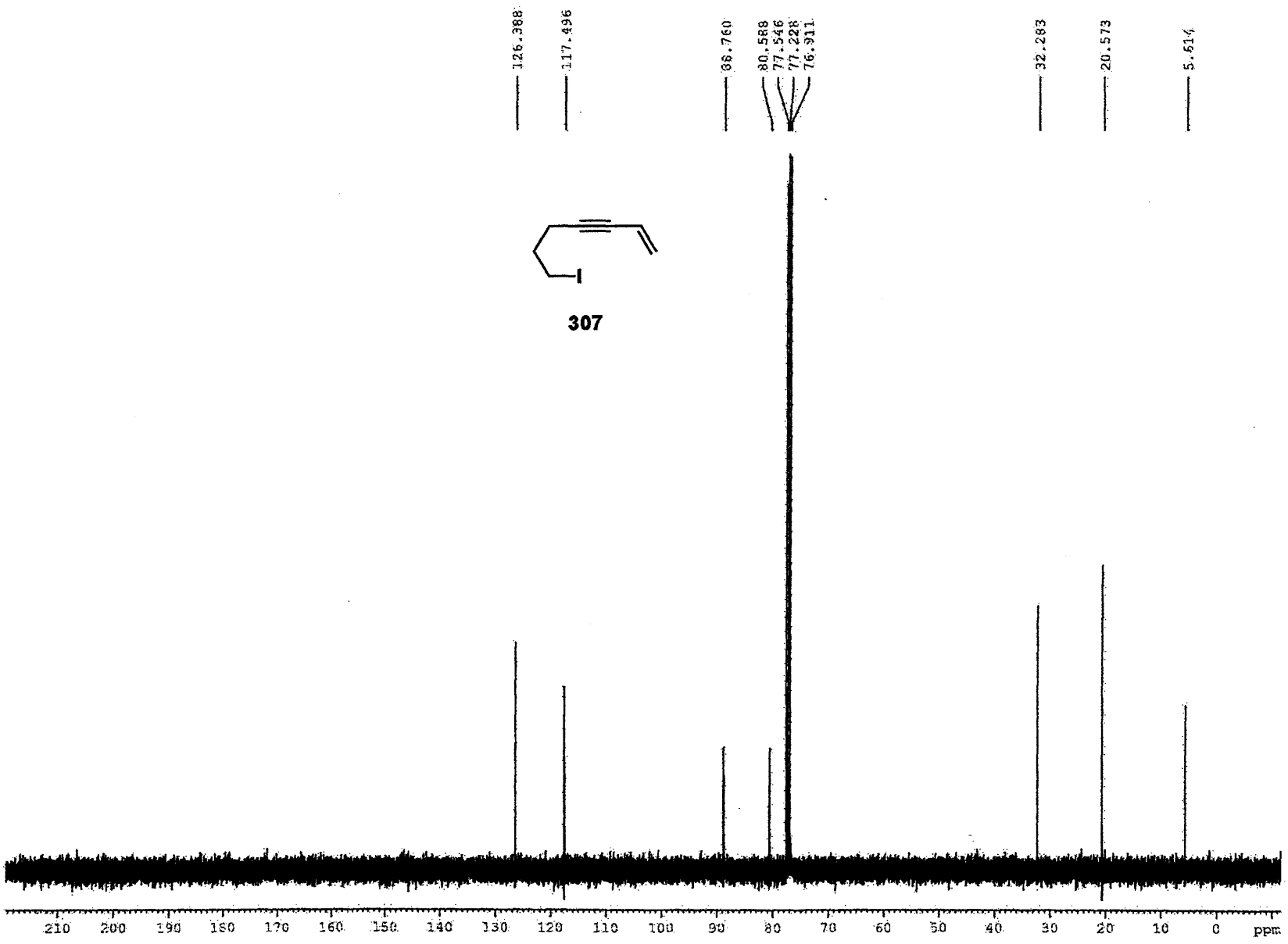

OH
304
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
1.000
2.098
2.102
4.270
2.139
5.325

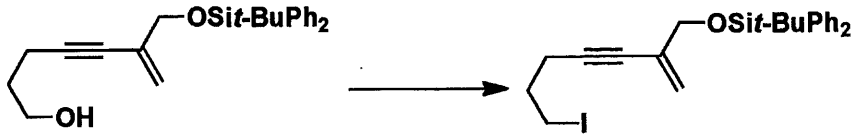

133.820
120.953
86.485
83.205
77.538
77.220
76.902
62.170
31.668
29.700
25.727
22.641
21.737
16.136
OH
304
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

301 **307**

7-Iodohept-1-en-3-yne (307). A 50-mL, three-necked, round-bottomed flask equipped with a stir bar, argon inlet adapter, glass stopper, rubber septum, and thermocouple probe was charged with alcohol **301** (0.865 g, 7.85 mmol, 1.0 equiv) and 13 mL of THF. The solution was cooled to 0 °C and imidazole (0.801 g, 11.8 mmol, 1.5 equiv), triphenylphosphine (2.059 g, 7.85 mmol, 1.0 equiv), and iodine (3.010 g, 11.86 mmol, 1.5 equiv) were each added in one portion. The reaction mixture became dark brown in color. The solution was stirred at 0 °C in the dark for 1 h, and then diluted with 75 mL of satd aq $Na_2S_2O_3$ solution and extracted with five 25-mL portions of pentane. The combined organic layers were washed with 75 mL of brine, dried over $MgSO_4$, filtered, and concentrated at 0 °C (20 mmHg). The residue was filtered through a short plug of basic alumina using 50 mL of pentane and the filtrate was concentrated at 0 °C (20 mmHg) to afford 1.625 g (94%) of iodide **307** as a colorless oil: IR (neat) 3097, 3007, 2938, 2905, 2837, 2227, 1841, 1608, 1427, 1220, 1169, 973, and 919 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.78 (ddt, J = 17.5, 11.0, 2.1 Hz, 1 H), 5.58 (ddt, J = 17.5, 2.2, 0.6 Hz, 1 H), 5.42 (dd, J = 11.0, 1.1 Hz, 1 H), 3.32 (t, J = 6.8 Hz, 2 H), 2.47 (td, J = 6.7, 2.1 Hz, 2 H), 2.03 (pent, J = 6.7 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 126.4, 117.5, 88.8, 80.6, 32.3, 20.6, 5.6; HRMS-ESI *(m/z)* calcd for C_7H_9I $[M + H]^+$: 220.9827, found: 220.9825.

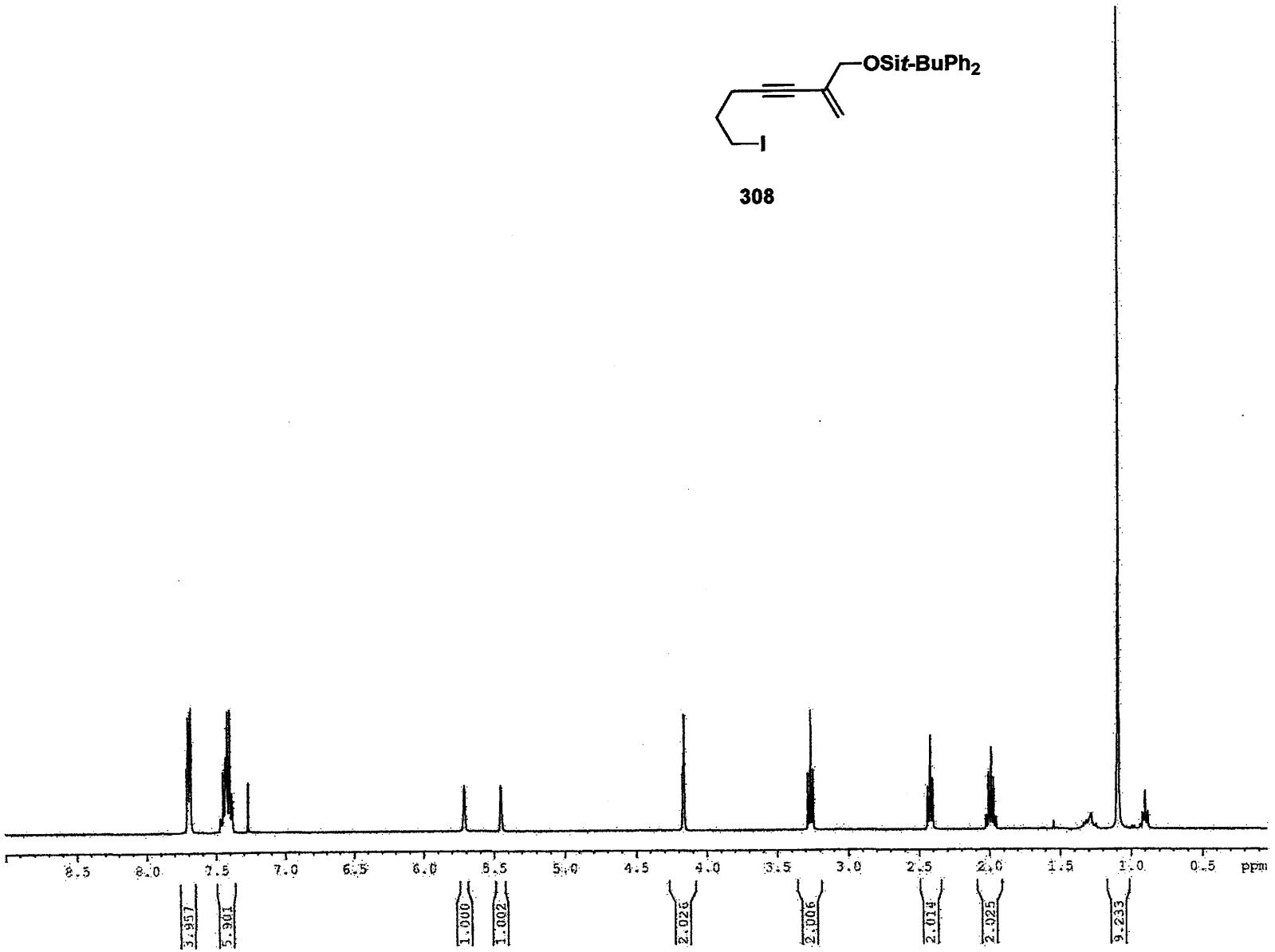

307
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
1.060
1.052
1.053
2.221
2.221
2.241

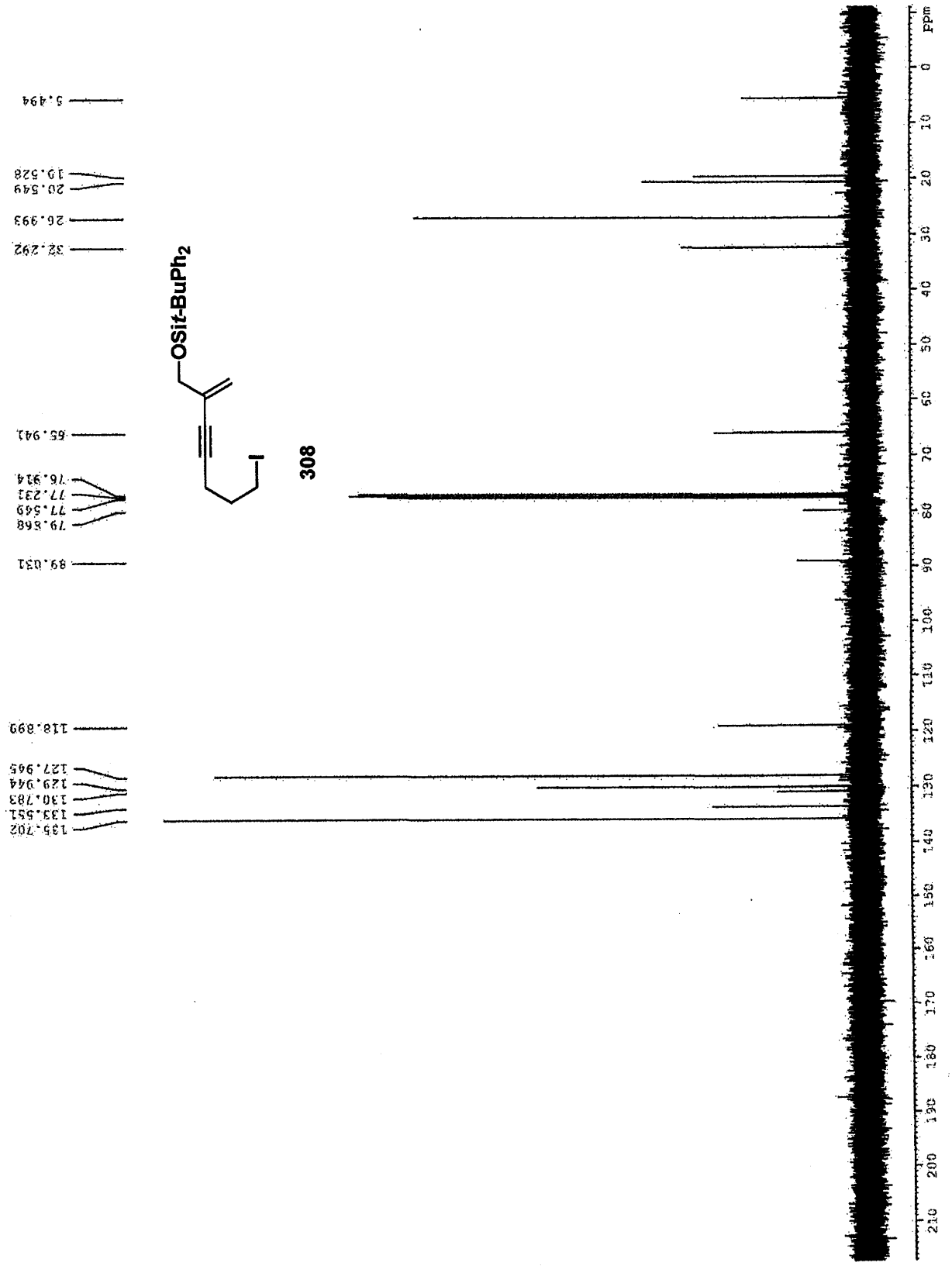

126.388
117.496
88.760
80.588
77.546
77.228
76.911
32.283
20.573
5.614
307
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

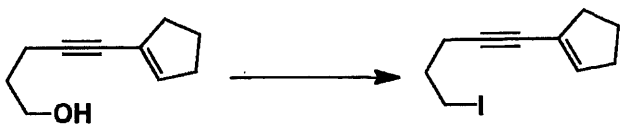


302 **308**

7-Iodo-2-(tert-butyldiphenylsilyloxy)methylhept-1-ene-3-yne (308). A 50-mL, three-necked, round-bottomed flask equipped with an argon inlet adapter, a glass stopper, and a rubber septum was charged with alcohol **302** (1.413 g, 3.73 mmol, 1.0 equiv) and 6.2 mL of THF. The reaction mixture was cooled at 0 °C while imidazole (0.381 g, 5.59 mmol, 1.5 equiv), triphenylphosphine (0.979 g, 3.73 mmol, 1.0 equiv), and iodine (1.221 g, 4.81 mmol, 1.3 equiv) were added, each in one portion. The dark brown reaction mixture was stirred at 0 °C in the dark for 2 h, and then diluted with 50 mL of satd aq $Na_2S_2O_3$ solution. The aqueous phase was separated and extracted with six 25-mL portions of hexanes. The combined organic phases were washed with 50 mL of brine, dried over $MgSO_4$, filtered, and concentrated to give a yellow oil. This material was purified by filtration through a plug of 5 g of basic alumina with the aid of 70 mL of hexanes. The filtrate was concentrated to give 1.550 g (85%) of iodide **308** as a pale yellow oil: IR (neat) 3071, 2856, 1618, 1589, 1471, 1427, 1221, 1113, 903, 822, 740, and 701 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.67-7.72 (m, 4 H), 7.37-7.48 (m, 6 H), 5.68-5.73 (m, 1 H), 5.43-5.47 (m, 1 H), 4.16 (s, 2 H), 3.27 (t, J = 6.8 Hz, 2 H), 2.42 (t, J = 6.8 Hz, 2 H), 1.99 (pent, J = 6.8 Hz, 2 H), 1.09 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.7, 133.6, 130.8, 129.9, 127.9, 118.9, 89.0, 79.9, 65.9, 32.3, 27.0, 20.5, 19.5, 5.5; HRMS-ESI *(m/z)* calcd for $C_{24}H_{29}IOSi$ $[M + H]^+$: 489.1105, found: 489.1118.

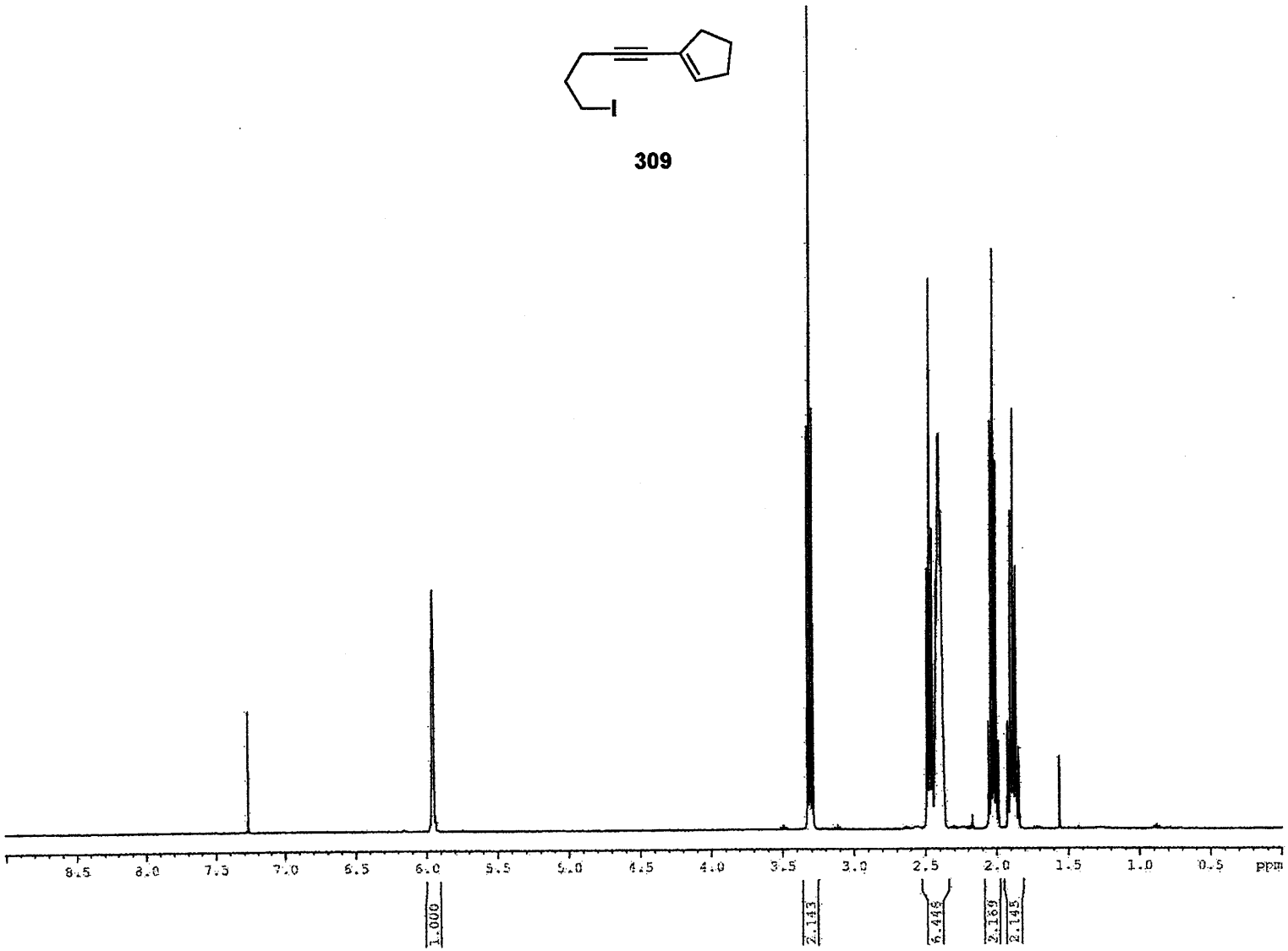

OSit-BuPh2
I
308
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
3.957
5.901
1.000
1.002
2.026
2.006
2.014
2.025
9.233

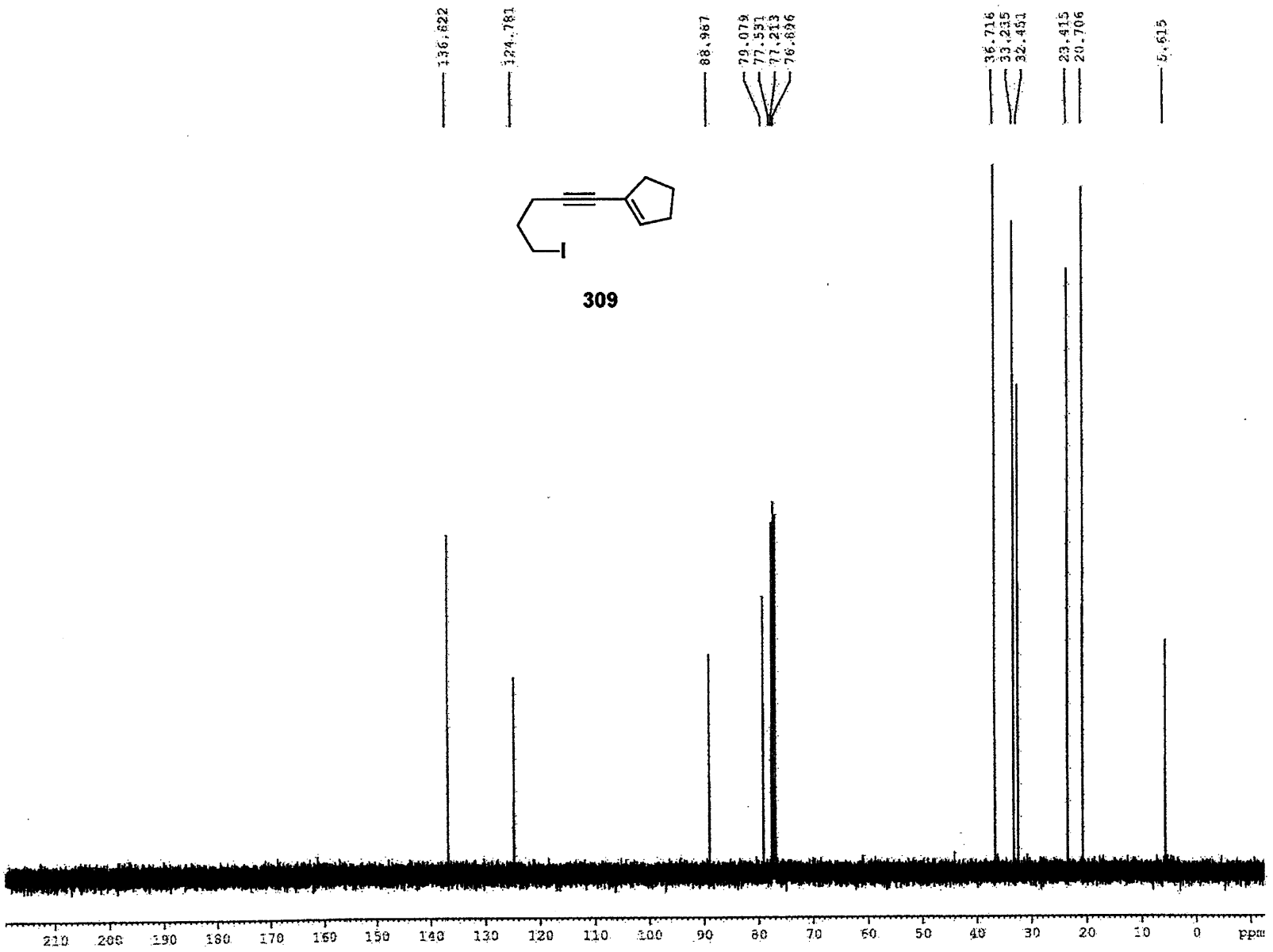

OSit-BuPh2
308
5.494
19.528
20.549
26.993
32.292
65.941
76.914
77.231
77.569
79.868
89.031
118.899
127.965
129.944
130.783
133.651
135.702
ppm

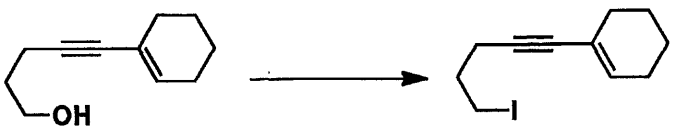


303 309

1-(5-Iodopent-1-ynyl)cyclopent-1-ene (309). A 50-mL, three-necked, round-bottomed flask equipped with an argon inlet adapter, rubber septum, and a glass stopper was charged with alcohol **303** (0.654 g, 4.35 mmol, 1.0 equiv) and 8.6 mL of THF. The reaction mixture was cooled to 0 °C and triphenylphosphine (1.142 g, 4.35 mmol, 1.0 equiv), imidazole (0.452 g, 6.64 mmol, 1.5 equiv), and iodine (1.401 g, 5.52 mmol, 1.3 equiv) were added, each in one portion. The dark brown reaction mixture was stirred at 0 °C in the dark for 1.5 h, and then 30 mL of satd aq $Na_2S_2O_3$ solution was added. The resulting mixture was extracted with six 25-mL portions of pentane. The combined organic phases were washed with 10 mL of brine, dried over $MgSO_4$, filtered, and concentrated to give a yellow oil containing some white solid. Purification by column chromatography on 16 g of silica gel (elution with pentane) afforded 0.927 g (82%) of iodide **309** as a very pale yellow oil: IR (neat) 2954, 2844, 2221, 1611, 1441, 1427, 1347, 1220, 1167, 949, and 809 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.95-5.99 (m, 1 H), 3.32 (t, J = 6.8 Hz, 2 H), 2.48 (t, J = 6.7 Hz, 2 H), 2.37-2.45 (m, 4 H), 2.13 (pent, J = 6.8 Hz, 2 H), 1.89 (pent, J = 7.5 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.8, 124.8, 89.0, 79.1, 36.7, 33.2, 32.4, 23.4, 20.7, 5.6; HRMS-ESI *(m/z)* calcd for $C_{10}H_{13}I$ $[M + H]^+$: 261.0135, found: 261.0144.

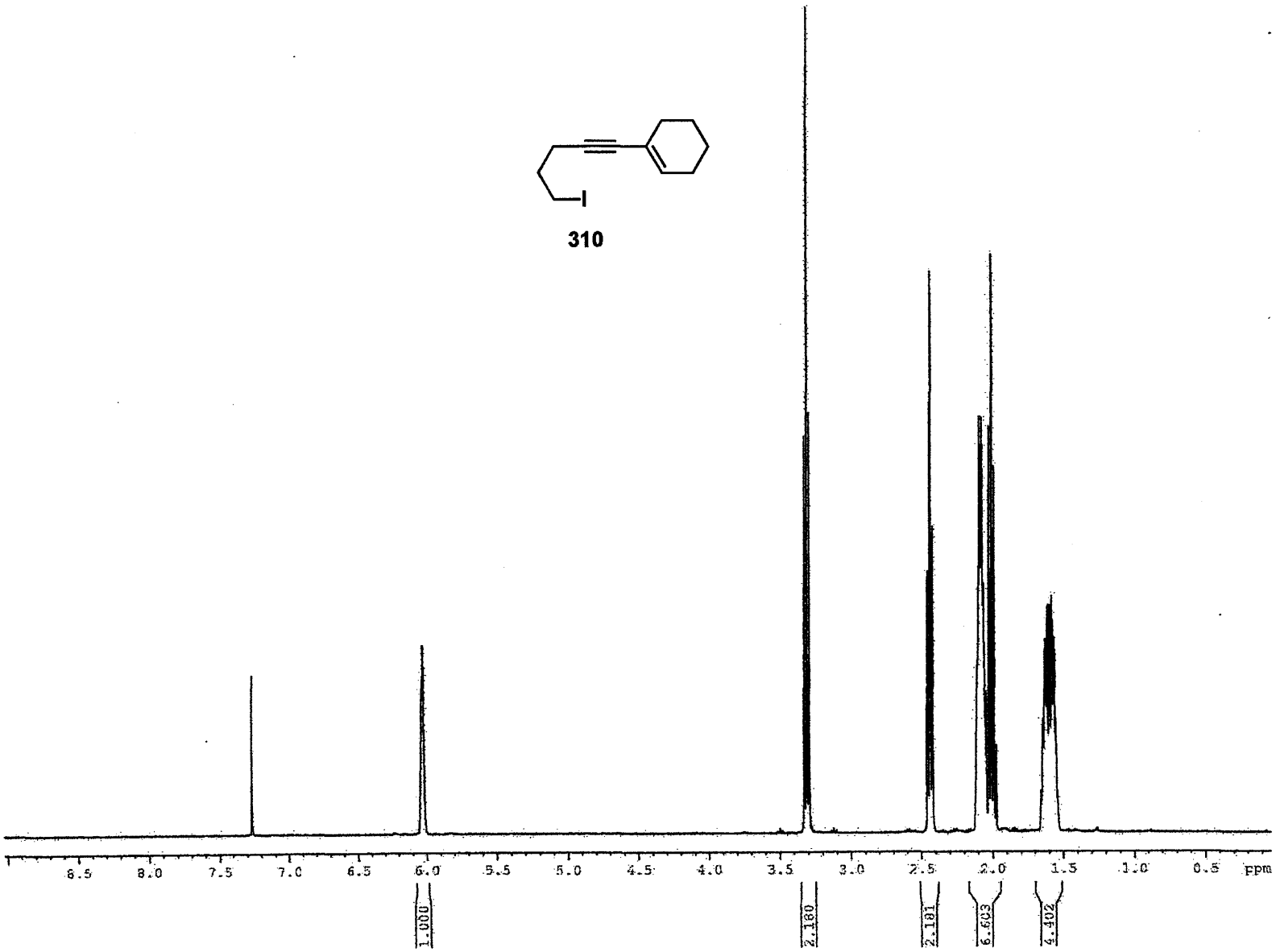

309
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
1.000
2.143
6.448
2.169
2.145


136.622
124.781
88.967
79.079
77.531
77.213
76.896
36.716
33.235
32.451
23.415
20.706
5.615
309
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

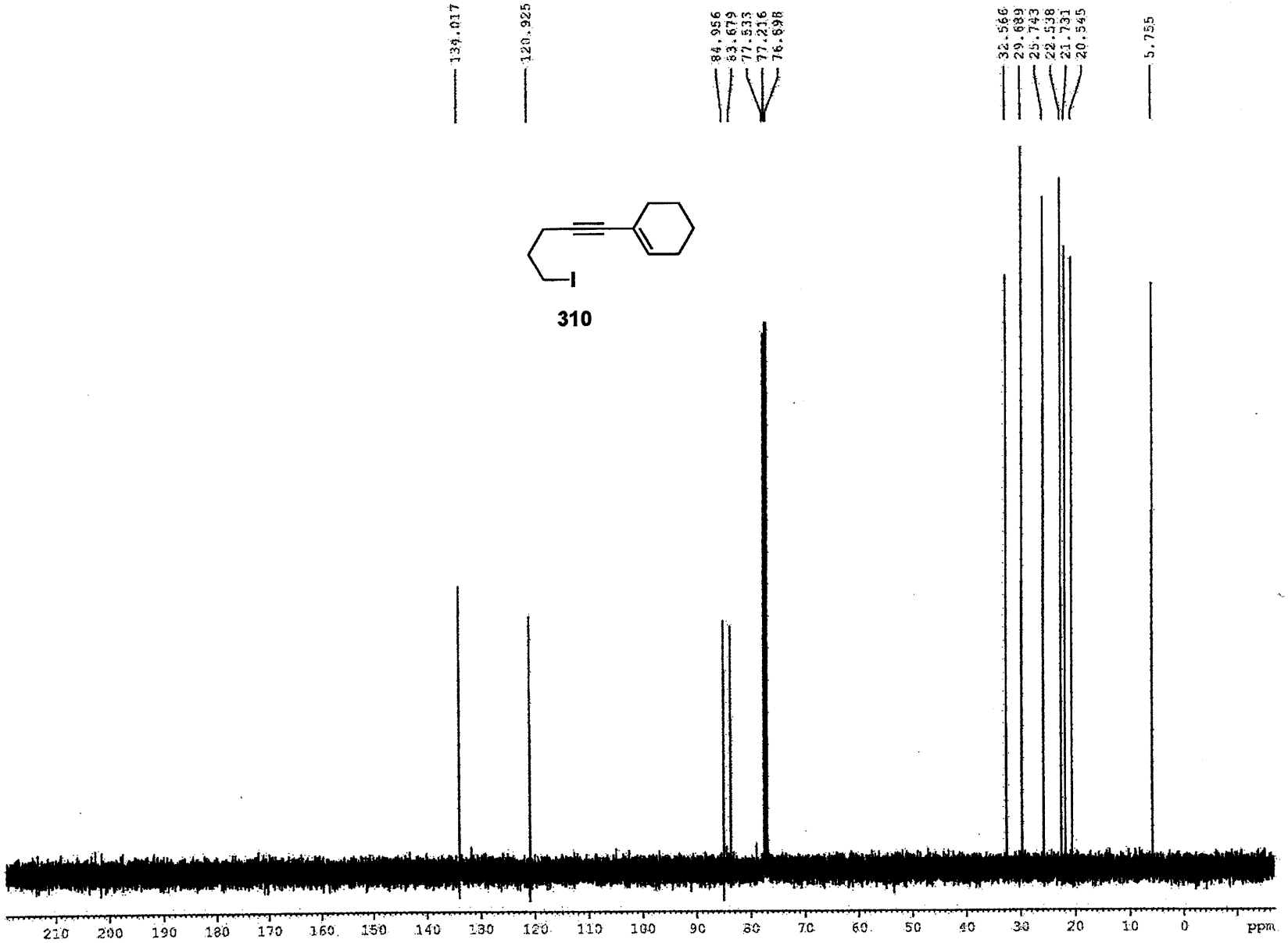


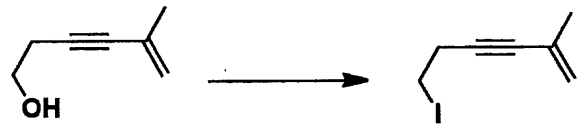
304 310

1-(5-Iodopent-1-ynyl)cyclohex-1-ene (310). A 50-mL, three-necked, round-bottomed flask equipped with an argon inlet adapter, a glass stopper, and a rubber septum was charged with alcohol **304** (0.825 g, 5.02 mmol, 1.0 equiv) and 8.4 mL of THF. The reaction mixture was cooled at 0 °C while imidazole (0.513 g, 7.53 mmol, 1.5 equiv), triphenylphosphine (1.318 g, 5.02 mmol, 1.0 equiv), and iodine (1.912 g, 7.53 mmol, 1.5 equiv) were added, each in one portion. The dark brown reaction mixture was stirred at 0 °C in the dark for 1 h, and then diluted with 80 mL of satd aq $Na_2S_2O_3$ solution. The aqueous phase was separated and extracted with six 25-mL portions of pentane. The combined organic phases were washed with 80 mL of brine, dried over $MgSO_4$, filtered, and concentrated to give a pale yellow oil. This material was filtered through a plug of 7 g of basic alumina with the aid of 75 mL of pentane. The filtrate was concentrated to afford 1.221 g (89%) of iodide **310** as a pale yellow oil: IR (neat) 3024, 2857, 2221, 1631, 1434, 1346, 1267, 1220, 1166, 1150, 1076, 1048, 916, 842, 800, and 725 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.00-6.06 (s, 1 H), 3.31 (t, J = 6.8 Hz, 2 H), 2.44 (t, J = 6.7 Hz, 2 H), 2.04-2.13 (m, 4 H), 2.01 (pent, J = 6.8 Hz), 1.53-1.67 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.0, 121.0, 85.0, 83.7, 32.6, 29.7, 25.7, 22.5, 21.7, 20.5, 5.7; HRMS-DART *(m/z)* calcd for $C_{11}H_{15}I$ $[M + H]^+$: 275.0291, found: 275.0295.


8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
1.000
2.180
2.191
6.603
4.402

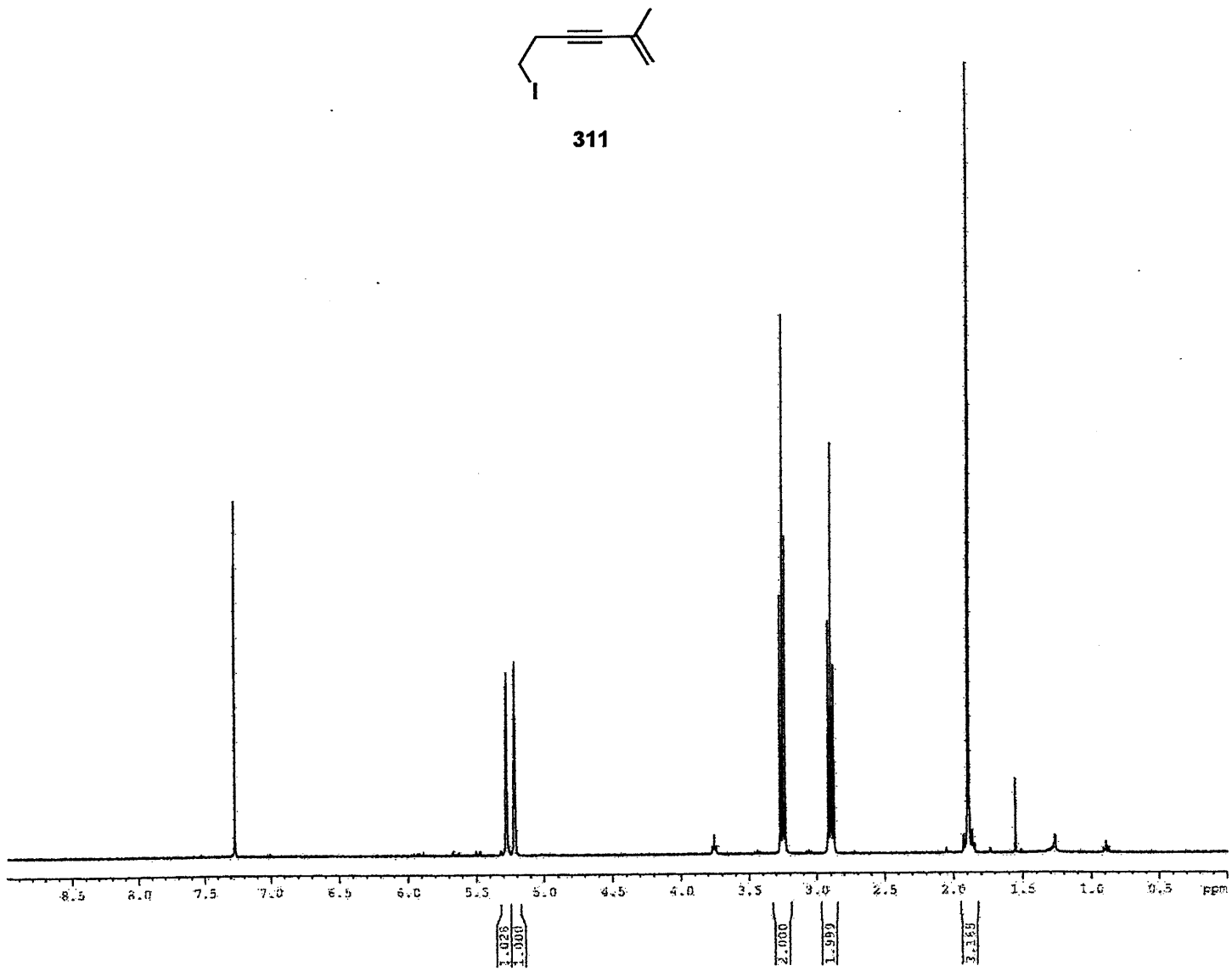
310

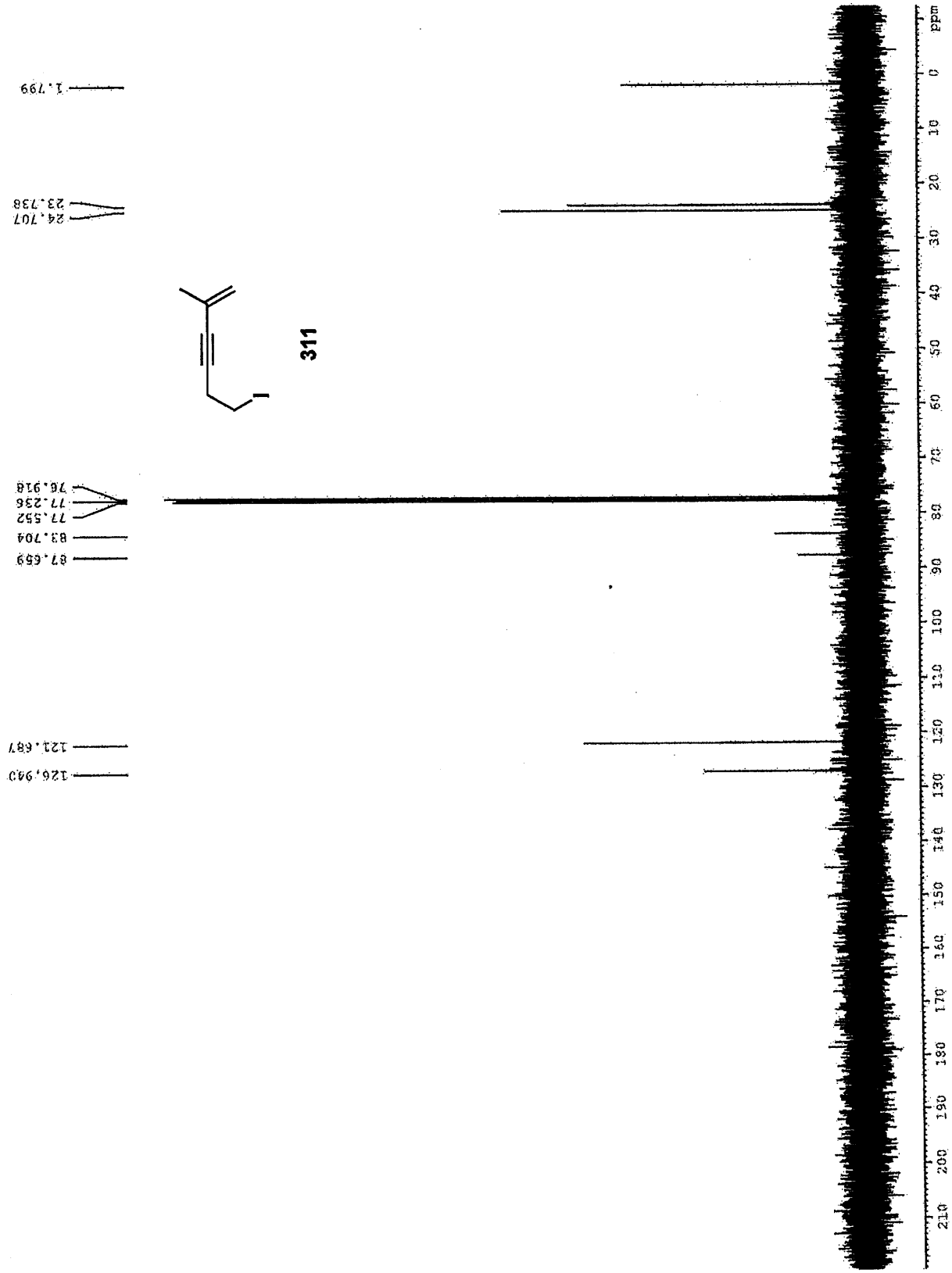

134.017
120.925
84.956
83.679
77.533
77.216
76.898
32.566
29.689
25.743
22.538
21.731
20.545
5.755
I
310
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

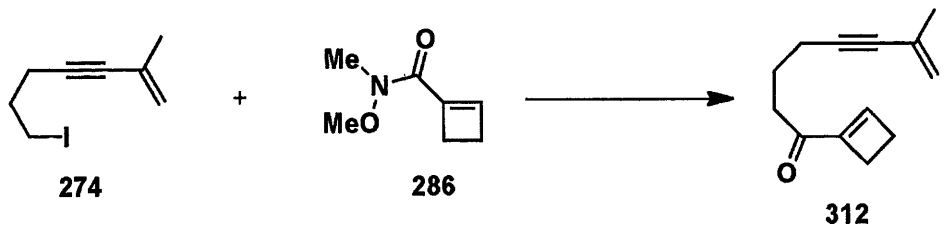


305 **311**

6-Iodo-2-methylhex-1-en-3-yne (311). A 25-mL, three-necked, round-bottomed flask equipped with an argon inlet adapter, rubber septum, and a glass stopper was charged with 5-methylhex-5-en-3-yn-1-ol **305** (0.347 g, 3.15 mmol, 1.0 equiv) and 5.4 mL of THF. The reaction mixture was cooled to 0 °C and triphenylphosphine (0.826 g, 3.15 mmol, 1.0 equiv), imidazole (0.321 g, 4.71 mmol, 1.5 equiv), and iodine (1.199 g, 4.72 mmol, 1.5 equiv) were added, each in one portion. The dark brown reaction mixture was stirred at 0 °C in the dark for 30 min, and then allowed to warm to rt and stirred for 30 min. The reaction mixture was diluted with 2 mL of H_2O and extracted one 10-mL portion of pentane and three 25-mL portions of pentane. The combined organic phases were washed with 50 mL of satd aq $Na_2S_2O_3$ solution and 25 mL of brine, then dried over $MgSO_4$, filtered, and concentrated to give a yellow oil. This material was filtered through a plug of 5 g of neutral alumina with the aid of 30 mL of pentane. The filtrate was concentrated to afford 0.560 g (81%) of iodide **311** as a colorless oil: 2970, 2920, 2222, 1680, 1613, 1433, 1372, 1331, 1287, 1247, 1172, 1039, and 897 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.26-5.29 (m, 1 H), 5.20-5.23 (m, 1 H), 3.25 (t, J = 7.4 Hz, 2 H), 2.90 (t, J = 7.4 Hz, 2 H), 1.87-1.91 (m, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 126.9, 121.7, 87.7, 83.7, 24.7, 23.7, 1.8; HRMS-ESI *(m/z)* calcd for C_7H_9I $[M + H]^+$: 220.9827, found: 220.9826.


311
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
1.026
1.000
2.000
1.999
3.169

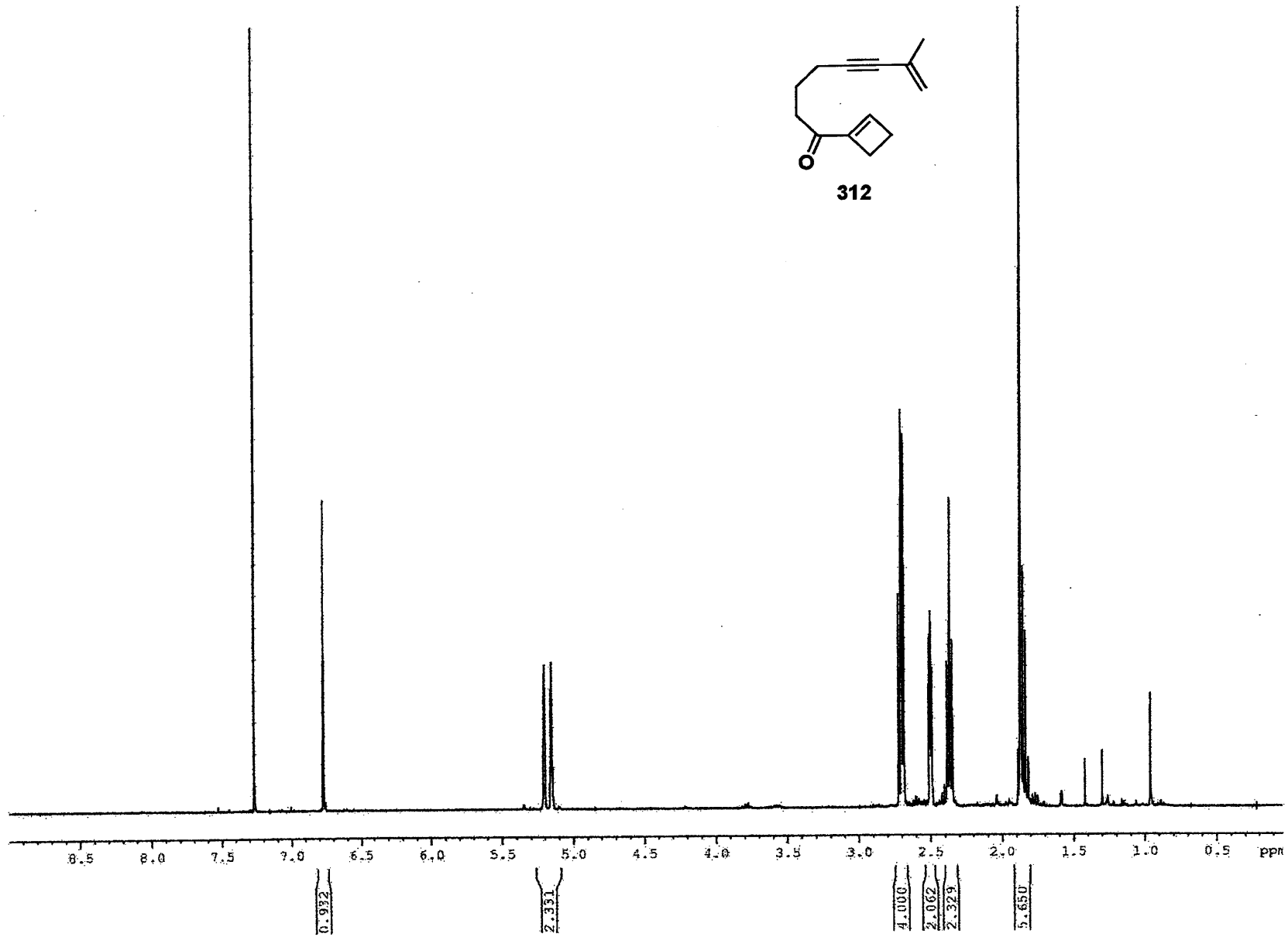

311
1.799
23.738
24.707
76.918
77.236
77.552
83.704
87.659
121.687
126.940
ppm

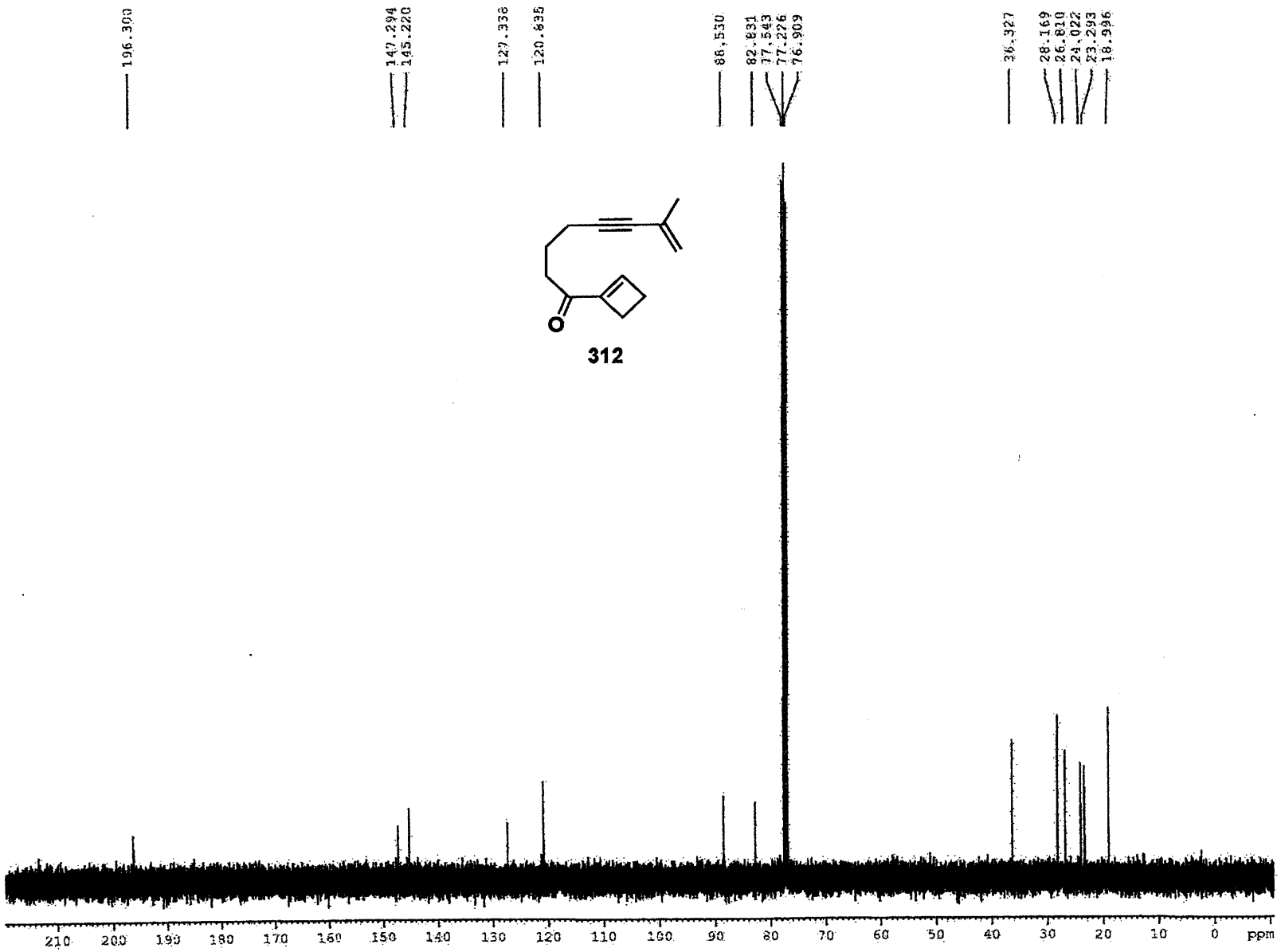


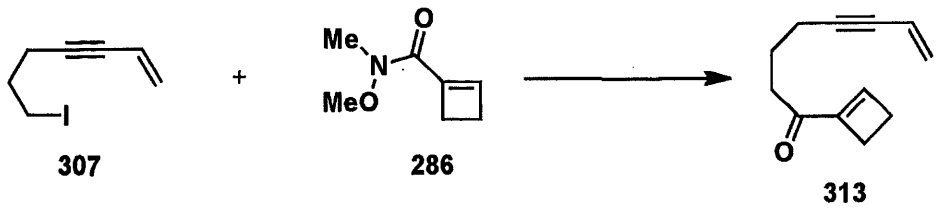
274 286 312

1-Cyclobutenyl-7-methyloct-7-en-5-yn-1-one (312). A 50-mL, three-necked, round-bottomed flask equipped with an argon inlet adapter, two rubber septa, and a thermocouple probe was charged with iodide **274** (0.443 g, 1.89 mmol, 1.2 equiv) and 4 mL of Et_2O. The reaction mixture was cooled to -78 °C and *t*-BuLi solution (1.47 M in pentane, 2.57 mL, 3.78 mmol, 2.4 equiv) was added dropwise over 15 min. The reaction mixture was stirred at -78 °C for 20 min. A solution of Weinreb amide **286** (0.224 g, 1.59 mmol, 1.0 equiv) in 3 mL of Et_2O was added dropwise via cannula over 3 min (1 mL Et_2O rinse). The reaction mixture was stirred at -78 °C for 1 h, and then 1 mL of THF[195] was added. The reaction mixture was stirred at -78 °C for 30 min, then 10 mL of satd aq NH_4Cl solution was added. The reaction mixture was warmed to 0 °C over 15 min, and then extracted with two 50-mL portions of Et_2O. The combined organic phases were washed with 20 mL of satd aq $NaHCO_3$ solution and 20 mL of brine, then dried over $MgSO_4$, filtered, and concentrated to give 0.456 g of pale yellow oil. Purification by column chromatography on 46 g of acetone-deactivated silica gel (elution with 0-7% EtOAc-hexanes) afforded 0.150 g (50%) of enone **512** as a yellow oil: IR (neat) 2224, 1709, 1672, 1614, 1598, 1434, 1372, and 895 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.78 (t, J = 1.3 Hz, 1 H), 5.19-5.22 (m, 2 H), 5.14-5.17 (m, 1 H), 2.69-2.71 (m, 2 H), 2.70 (t, J = 7.3 Hz, 2 H), 2.48-2.51 (m, 2 H), 2.37 (t, J = 6.9 Hz, 2 H), 1.87 (dd, J = 1.5, 1.0 Hz, 3 H), 1.85 (pent, J = 7.0 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.3, 147.3, 145.2, 127.3, 120.8, 88.5, 82.8, 36.3, 28.2, 26.8, 24.0, 23.3, 19.0; HRMS-ESI *(m/z)* $[M + H]^+$ calcd for $C_{13}H_{16}O$: 211.1093, found: 211.1088.

[195] Weinreb amide **286** is sparingly soluble in Et_2O-pentane mixtures at -78 °C. THF was added to dissolve the amide and form a homogeneous reaction mixture.


O
312
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
0.932
2.331
4.000
2.062
2.329
5.650

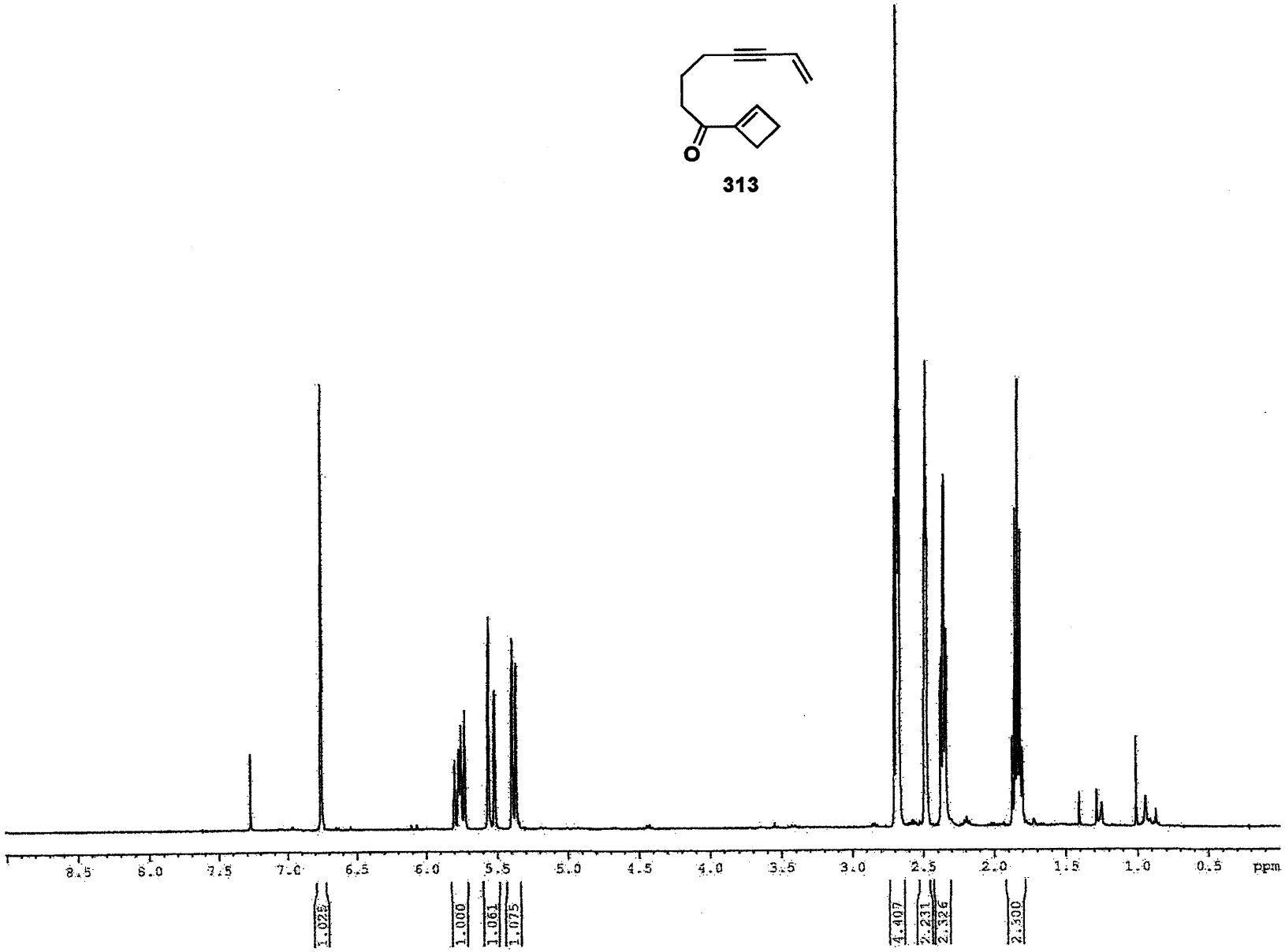

196.300
147.294
145.220
127.338
120.635
88.530
82.831
77.543
77.226
76.909
36.327
28.169
26.810
24.022
23.293
18.996
O
312
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm



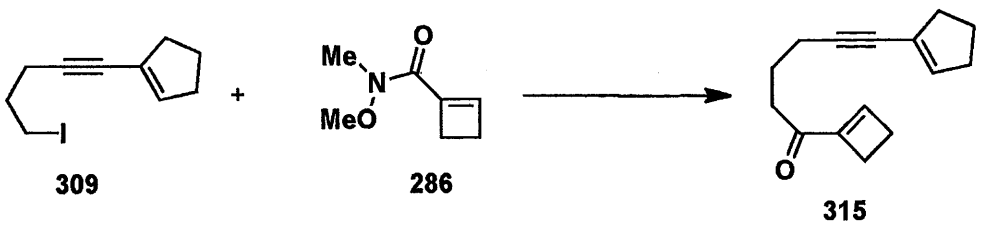
307 286 313

1-Cyclobutenylyloct-7-en-5-yn-1-one (313). A 50-mL, three-necked, round-bottomed flask equipped with an argon inlet adapter, two rubber septa, and a thermocouple probe was charged with iodide **307** (1.163 g, 3.58 mmol, 1.15 equiv) and 10.4 mL of Et_2O. The reaction mixture was cooled to -78 °C and *t*-BuLi solution (1.70 M in pentane, 4.25 mL, 7.22 mmol, 2.32 equiv) was added dropwise over 9 min. The bright yellow reaction mixture was stirred at -78 °C for 20 min, and then a solution of Weinreb amide **286** (0.440 g, 3.12 mmol, 1.00 equiv) in THF[196] (5.2 mL) was added dropwise over 8 min. The reaction mixture was stirred at -78 °C for 1 h, and then 20 mL of satd aq NH_4Cl solution was added dropwise over 5 min. The reaction mixture was warmed to 0 °C over 10 min and then diluted with 100 mL of Et_2O and 25 mL of satd aq NH_4Cl solution. The aqueous phase was separated and extracted with two 50-mL portions of Et_2O. The combined organic phases were washed with 50 mL of brine, dried over $MgSO_4$, filtered, and concentrated (5-10 °C, 20 mmHg) to give 1.041 g of yellow oil. Purification by column chromatography on 115 g of acetone-deactivated silica gel (elution with 0-5% EtOAc-hexanes) provided 0.300 g (55%) of enone **313** as a pale yellow oil: IR (neat) 2226, 1671, 1589, 1435, 1372, 1334, 1231, 1190, 1073, 1000, 975, 917, 855, and 730 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.76 (s, 1 H), 5.76 (dt, J = 17.5, 11.0, 2.1 Hz, 1 H), 5.54 (dd, J = 17.5, 2.1 Hz, 1 H), 5.38 (dd, J = 11.0, 2.1 Hz, 1 H), 2.64-2.73 (m, 4 H), 2.46-2.51 (m, 2 H), 2.36 (td, J = 6.8, 1.7 Hz, 2 H), 1.84 (pent, J = 7.0 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.1, 147.2, 117.6, 90.2, 80.2, 36.2, 28.1, 26.7, 23.1, 19.0; HRMS-ESI *(m/z)* $[M + H]^+$ cald for $C_{12}H_{14}O$: 175.1117, found: 175.1126.

[196] Weinreb amide **286** is sparingly soluble in Et_2O-pentane mixtures at -78 °C so THF added to form a homogeneous reaction mixture.


O
313
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
1.028
1.000
1.061
1.075
4.407
2.231
2.326
2.300

196.070
147.166
145.072
125.884
117.567
90.167
80.205
77.484
77.166
76.848
36.236
28.083
26.710
23.114
18.962
313
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

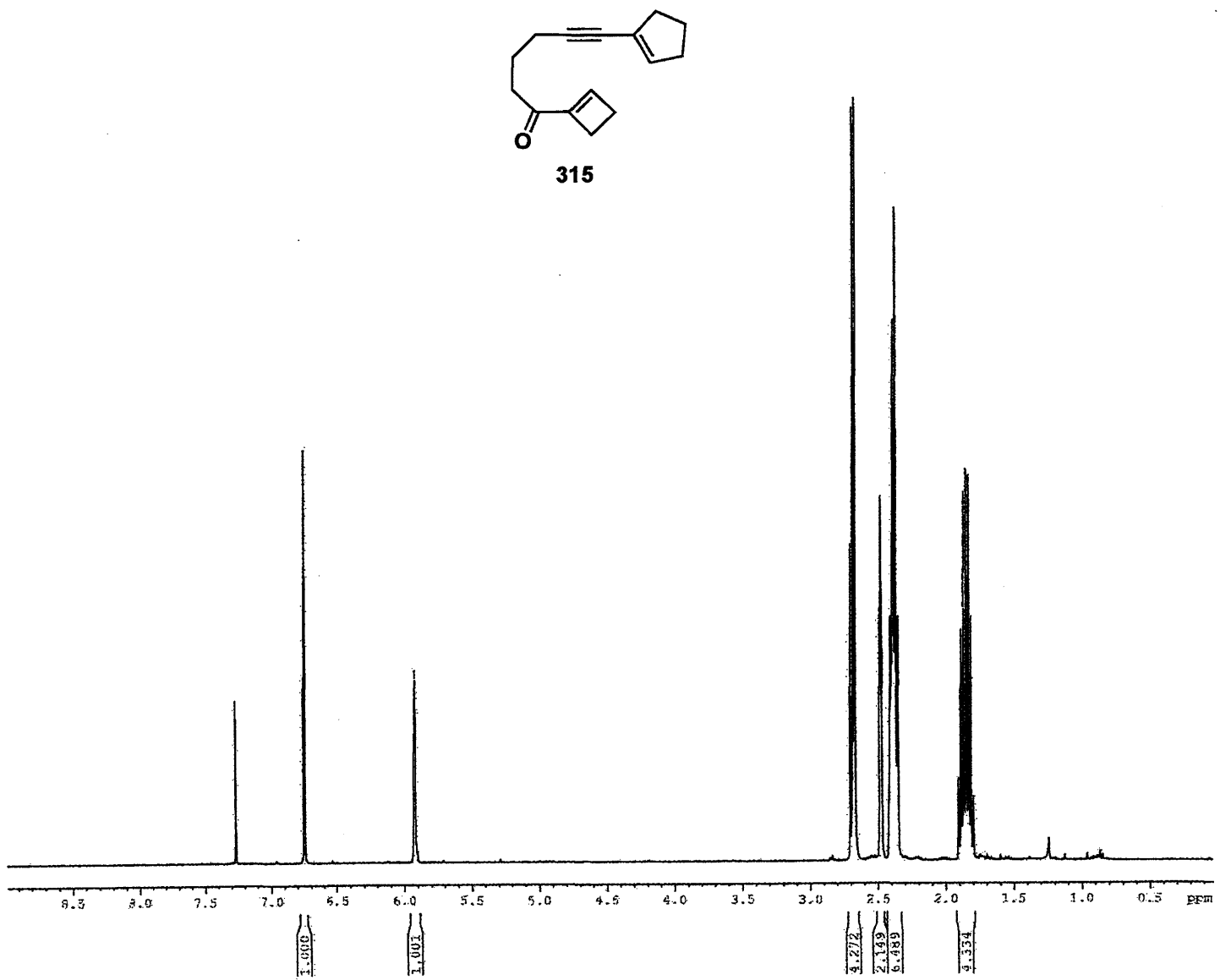


309 286 315

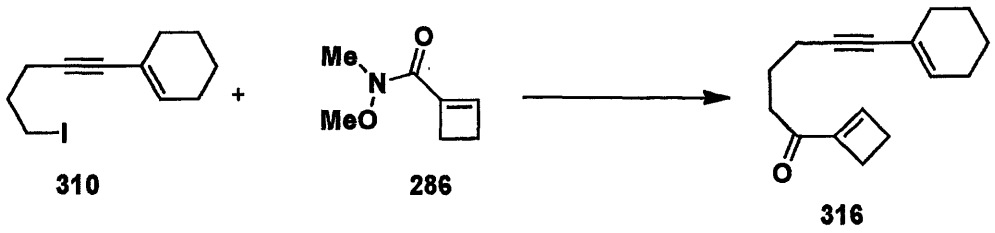
1-Cyclobutenyl-6-(cyclopent-1-en-1-yl)-hex-5-yn-1-one (315). A 100-mL, three-necked, round-bottomed flask equipped with an argon inlet adapter, two rubber septa, and a thermocouple probe was charged with iodide **309** (0.898 g, 3.45 mmol, 1.15 equiv) and 10 mL of Et_2O. The reaction mixture was cooled to -78 °C and *t*-BuLi solution (1.39 M in pentane, 5.00 mL, 6.95 mmol, 2.32 equiv) was added dropwise over 4 min. The reaction mixture was stirred at -78 °C for 20 min and then a solution of Weinreb amide **286** (0.423 g, 3.00 mmol, 1.0 equiv) in 5 mL of THF[197] was added dropwise via cannula over 7 min. The reaction mixture was stirred at -78 °C for 1 h, and then 20 mL of satd aq NH_4Cl solution was added. The resulting mixture was allowed to warm to 0 °C over 15 min, and diluted with 5 mL of H_2O and 100 mL of Et_2O. The organic layer was separated and washed with 10 mL of satd aq NH_4Cl solution. The aqueous layers were combined and extracted with 100 mL of Et_2O, and the combined organic phases were washed with 50 mL of brine, dried over $MgSO_4$, filtered, and concentrated to give 0.766 g of yellow oil. Purification by column chromatography on 115 g of acetone-deactivated silica gel (elution with 0-5% EtOAc-hexanes) afforded 0.410 g (64%) of enone **315** as a white solid, mp 30-32 °C: IR (thin film) 2932, 1671, 1589, 1441, 1373, 1231, 1071, and 949 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.74-6.79 (m, 1 H), 5.91-5.98 (m, 1 H), 2.67-2.74 (m, 4 H), 2.48-2.52 (m, 2 H), 2.36-2.46 (m, 6 H), 1.82-1.93 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.2, 147.2, 145.1, 136.4, 124.9, 90.5, 78.8, 36.7, 36.3, 33.2, 28.1, 26.7, 23.4, 23.3, 19.2; HRMS-ESI *(m/z)* calcd for $C_{15}H_{18}O$ $[M + H]^+$: 215.1430, found: 215.1427.

---

[197] Weinreb amide **286** is sparingly soluble in Et_2O-pentane mixtures at -78 °C to THF was added to form a homogeneous reaction mixture.


O
315
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
1.000
1.001
3.272
2.149
6.489
4.334

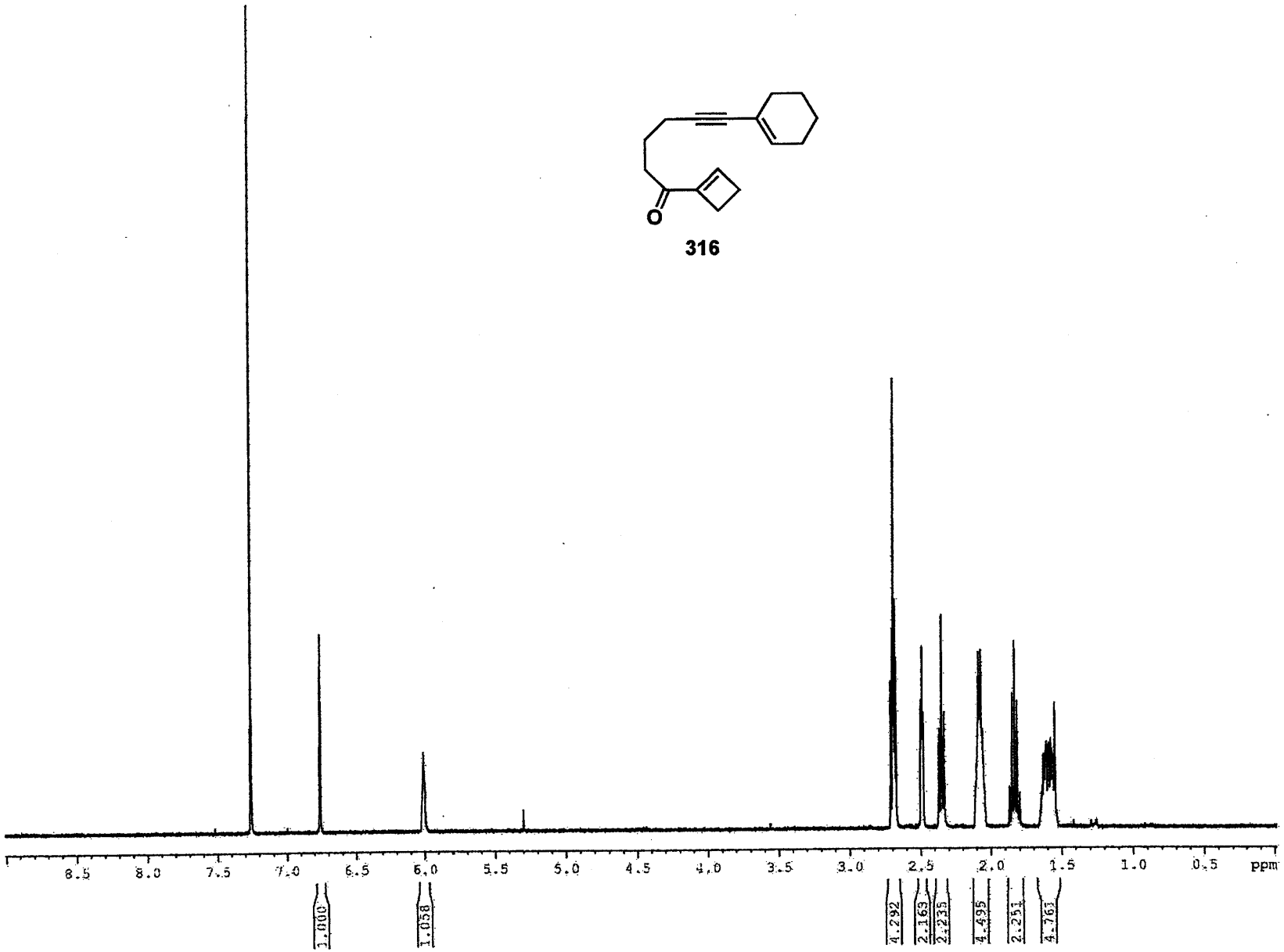
196.240
147.246
145.108
136.437
124.944
90.495
78.756
77.541
77.223
76.906
36.744
36.326
33.201
28.122
26.751
23.406
23.351
19.166
O
315
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm



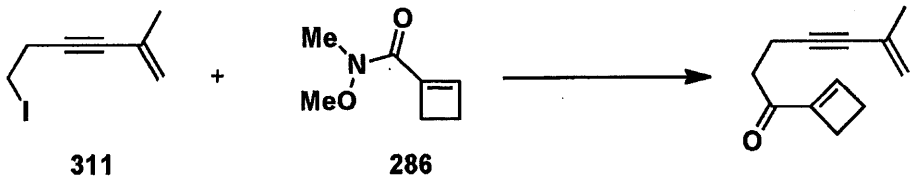
310 286 316

1-Cyclobutenyl-6-(cyclohex-1-en-1-yl)-hex-5-yn-1-one (316). A 100-mL, three-necked, round-bottomed flask equipped with an argon inlet adapter, two rubber septa, and a thermocouple probe was charged with iodide **310** (1.161 g, 4.23 mmol, 1.14 equiv) and 12.2 mL of Et_2O. The reaction mixture was cooled to -78 °C and *t*-BuLi solution (1.32 M in pentane, 6.45 mL, 8.51 mmol, 2.30 equiv) was added dropwise over 6 min. The bright yellow reaction mixture was stirred at -78 °C for 10 min, and then a solution of Weinreb amide **286** (0.522 g, 3.70 mmol, 1.00 equiv) in 6.2 mL of THF[198] was added dropwise over 7 min. The reaction mixture was stirred at -78 °C for 1 h, and then 40 mL of satd aq NH_4Cl solution was added dropwise over 5 min. The reaction mixture was warmed to 0 °C over 10 min, and then diluted with 10 mL of 10% aq HCl solution and 200 mL of Et_2O. The aqueous phase was separated and extracted with 50 mL of Et_2O. The combined organic phases were washed with 50 mL of brine, dried over $MgSO_4$, filtered, and concentrated to give 1.281 g of yellow oil. Purification by column chromatography on 152 g of acetone-deactivated silica gel (elution with 0-4% EtOAc-hexanes) afforded 0.469 g (56%) of enone **316** as a colorless oil: IR (neat) 2222, 1672, 1589, 1436, 1371, 1346, 1231, 1190, 1075, 996, 918, 843, 800, and 734 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.76 (s, 1 H), 5.89-6.03 (m, 1 H), 2.66-2.72 (m, 4 H), 2.47-2.51 (m, 2 H), 2.35 (t, J = 6.9 Hz, 2 H), 2.12-2.22 (m, 4 H), 1.83 (pent, J = 7.0 Hz, 2 H), 1.53-1.66 (m, 4 H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 196.4, 147.3, 145.0, 133.6, 121.1, 86.5, 83.4, 36.4, 29.8, 28.1, 26.7, 25.7, 23.5, 22.6, 21.8, 19.0; HRMS-ESI *(m/z)* $[M + H]^+$ calcd for $C_{16}H_{20}O$: 229.1587, found: 229.1577.

[198] Weinreb amide **286** is sparingly soluble in Et_2O-pentane mixtures at -78 °C so THF was added to form a homogeneous reaction mixture.


O
316
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
1.000
1.058
4.292
2.163
2.235
4.495
2.251
4.761

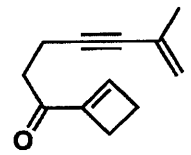
196.361
147.327
145.081
133.654
121.083
86.462
83.369
77.557
77.239
76.922
36.809
29.761
28.175
26.787
25.746
23.528
22.576
21.767
19.047
O
316
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm



311 286 284

1-Cyclobutenyl-6-methylhept-6-en-4-yn-1-one (284). A 50-mL, three-necked, round-bottomed flask equipped with an argon inlet adapter, two rubber septa, and a thermocouple probe was charged with iodide **311** (0.446 g, 2.03 mmol, 1.2 equiv) and 4.7 mL of Et_2O. The reaction mixture was cooled to -78 °C and *t*-BuLi solution (1.47 M in pentane, 2.76 mL, 4.06 mmol, 2.3 equiv) was added dropwise over 10 min. The reaction mixture was stirred at -78 °C for 20 min, and then a solution of Weinreb amide **286** (0.246 g, 1.74 mmol, 1.0 equiv) in 3 mL of Et_2O was added dropwise via cannula over 3 min (1-mL Et_2O rinse). The reaction mixture was stirred at -78 °C for 1 h, and then 1 mL of THF[199] was added. The resulting mixture was stirred at -78 °C for an additional 30 min and then quenched by addition of 10 mL of satd aq NH_4Cl solution. The cooling bath was removed and the resulting mixture was allowed to warm to 0 °C over 15 min, and then extracted with two 50-mL portions of Et_2O. The combined organic layers were washed with 20 mL of satd aq $NaHCO_3$ and 20 mL of brine, dried over $MgSO_4$, filtered, and concentrated to give 0.511 g of yellow oil. Purification by column chromatography on 46 g of acetone-deactivated silica gel (elution with 6% EtOAc-hexanes) afforded 0.123 g (41%) of enone **284** as a pale yellow oil: IR (neat) 2924, 2227, 1674, 1613, 1589, 1435, 1370, 1290, 1219, 1191, 1055, 982, and 895 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.79 (t, J = 1.2 Hz, 1 H), 5.18-5.22 (m, 1 H), 5.12-5.17 (m, 1 H), 2.78-2.84 (m, 2 H), 2.68-2.72 (m, 2 H), 2.58-2.63 (m, 2 H), 2.48-2.53 (m, 2 H), 1.84-1.87 (m, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.3, 146.8, 145.6, 127.2, 120.9, 87.9, 82.4, 36.7, 28.1, 26.9, 23.8, 14.1; HRMS-DART *(m/z)* calcd for $C_{12}H_{14}O$ [M + H]$^+$: 175.1117, found: 175.1125.

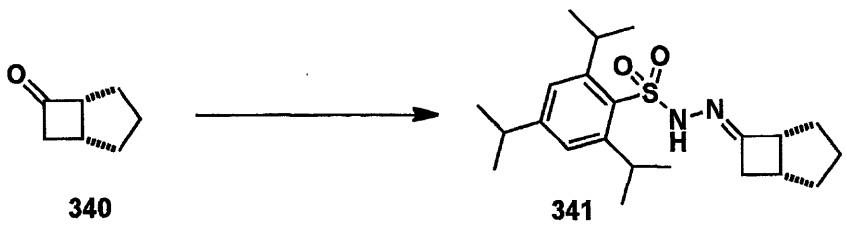
[199] Weinreb amide **286** is sparingly soluble in Et_2O-pentane mixtures at -78 °C. THF was added to dissolve the amide and form a homogeneous reaction mixture.



284

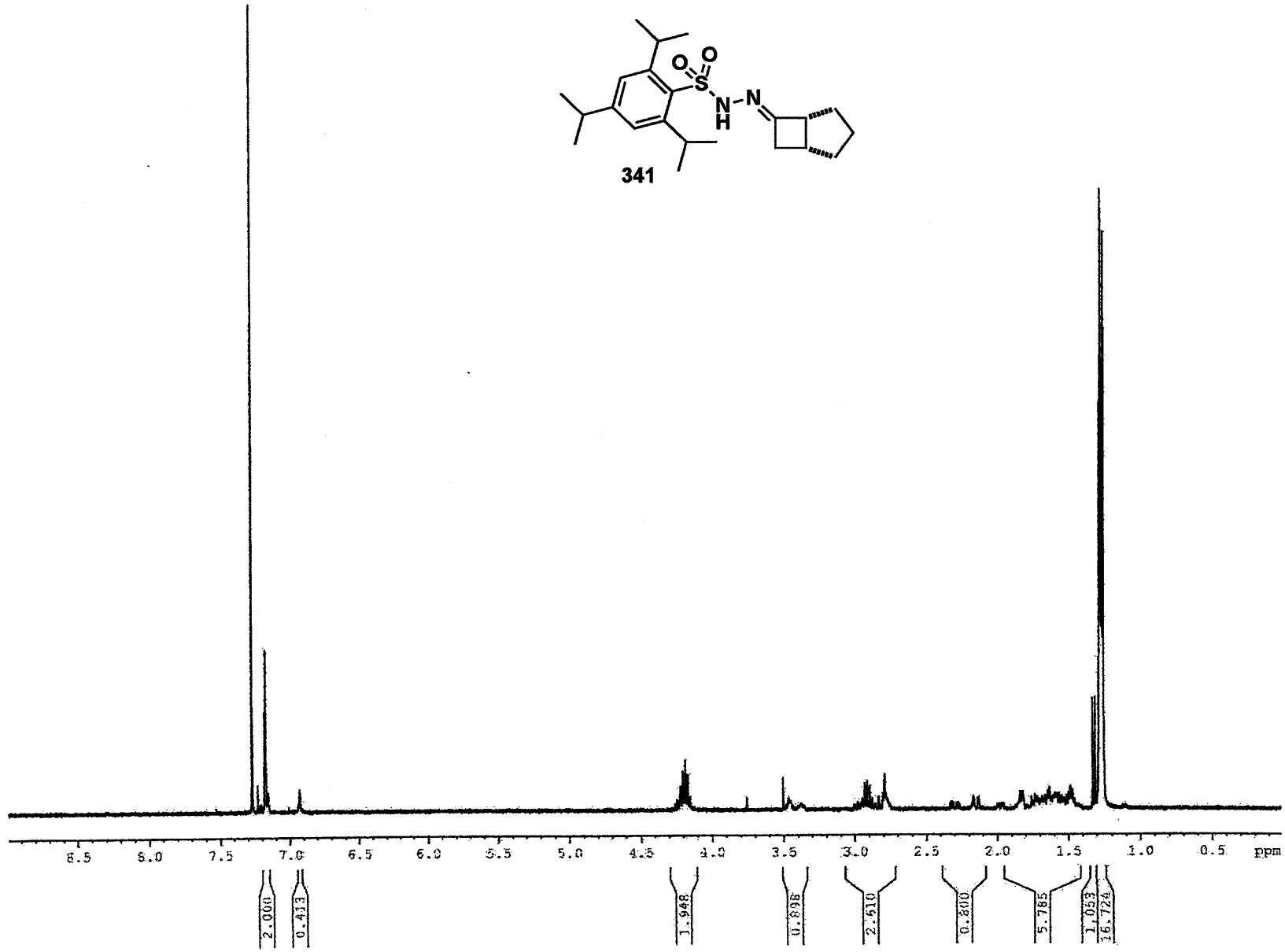
9.5
9.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
1.000
1.063
1.072
2.105
2.235
2.184
2.170
3.222

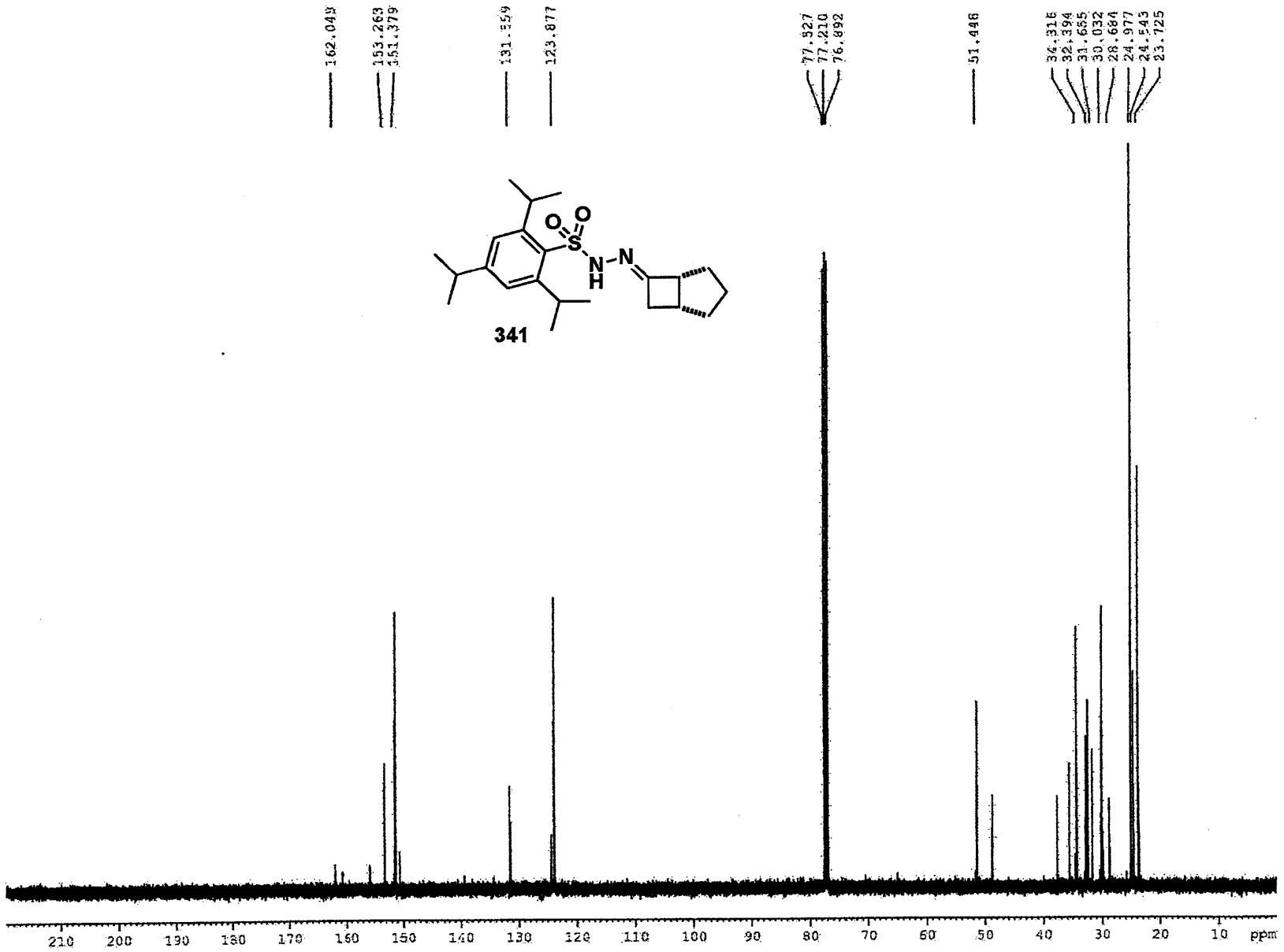
194.300
146.643
145.640
127.166
120.921
87.917
82.371
77.548
77.231
76.913
36.727
28.115
26.922
23.831
14.134
O
284
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm



340 341

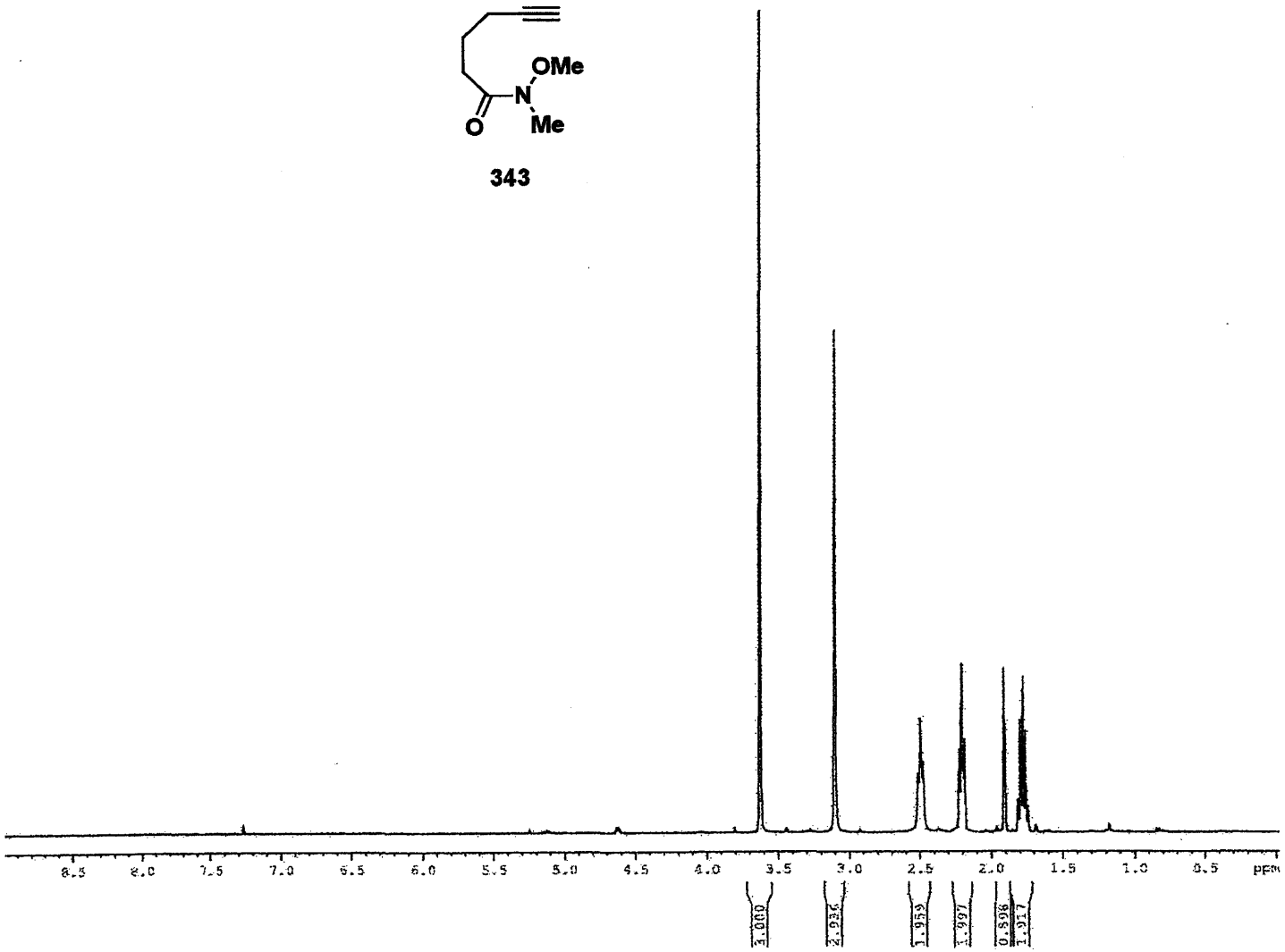
***(E)-cis*-(Bicyclo[3.2.0]heptan-6-ylidene)-2,4,6-triisopropylbenzenesulfonohydrazide (341)**. A 50-mL, round-bottomed flask equipped with a rubber septum and an argon inlet needle was charged with 2,4,6-triisopropylbenzenesulfonylhydrazide (1.226 g, 4.11 mmol, 1.0 equiv) and 1 mL of MeOH. A solution of cyclobutenone **340** (0.453 g, 4.11 mmol, 1.0 equiv) in 3 mL of MeOH was added via cannula (1.1-mL MeOH rinse). Concentrated HCl (0.05 mL) was added in one portion to the resulting white slurry. The solids dissolved and the reaction mixture became pale yellow. The solution was allowed to stand at -18 °C for 18 h and then the pale yellow solution was decanted from the resulting white precipitate. The solids were washed with 2 mL of MeOH and then dried on high vacuum (ca. 0.15 mmHg) to give 0.942 g (59%) of **341** as white crystals, mp 53-55 °C: IR (thin film) 3213, 2959, 2869, 1599, 1463, 1426, 1383, 1319, 1165, 1154, 1035, and 910 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.13-7.19 (m, 2 H), 4.10-4.28 (m, 2 H), 3.35-3.50 (m, 1 H), 2.70-3.00 (m, 3 H), 1.94-2.35 (m, 1 H), 1.75-1.87 (m, 1 H), 1.40-1.75 (m, 5 H), 1.29-1.33 (m, 1 H), 1.23-1.29 (m, 18 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.0, 153.3, 151.4, 131.6, 123.9, 51.4, 35.5, 34.3, 32.4, 31.7, 30.0, 28.7, 25.0, 24.5, 23.7; HRMS-DART *(m/z)* calcd for $C_{22}H_{34}N_2O_2S$ $[M + H]^+$: 391.2414, found: 391.2404.

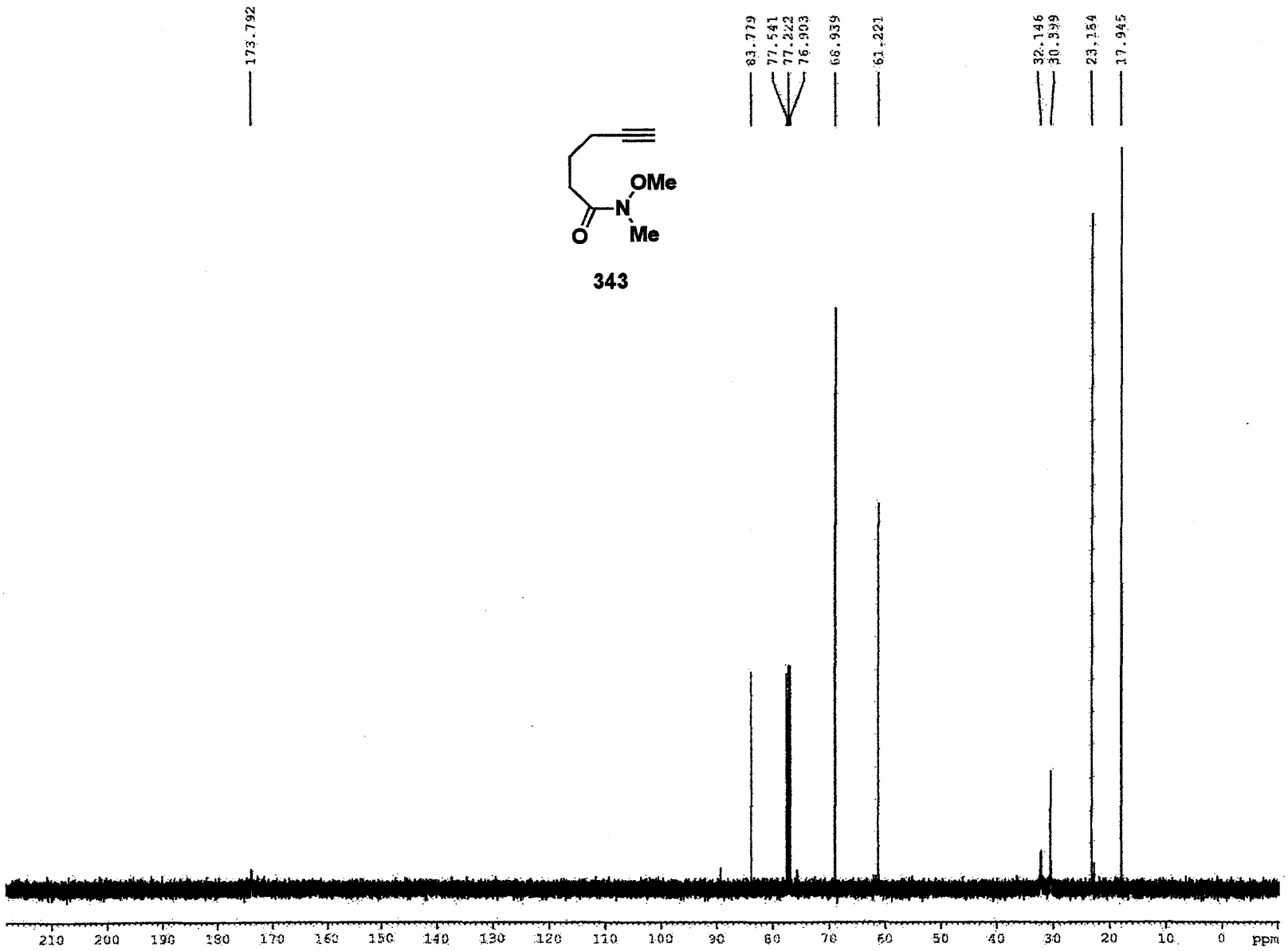

341
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
2.000
0.413
1.948
0.898
2.610
0.800
5.785
1.053
16.724

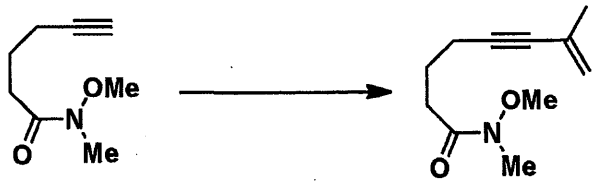

162.049
153.263
151.379
131.559
123.877
77.327
77.210
76.892
51.446
34.316
32.394
31.655
30.032
28.684
24.977
24.543
23.725
341
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

342 343

***N*-Methoxy-*N*-methyl-5-hexynamide (343).** A 100-mL, three-necked, round-bottomed flask equipped with an argon inlet adapter and two rubber septa was charged with 5-hexynoic acid **342** (1.65 mL, 1.68 g, 15.0 mmol, 1.0 equiv) and 40 mL of CH_2Cl_2. Oxalyl chloride (1.33 mL, 2.00 g, 15.7 mmol, 1.05 equiv) and DMF (2 drops) were added and the reaction mixture was stirred at rt for 2.5 h (gas evolution). A 250-mL, three-necked, round-bottomed flask equipped with an argon inlet adapter and two rubber septa was charged with *N,O*-dimethylamine hydrochloride (1.605 g, 16.4 mmol, 1.1 equiv), triethylamine (4.60 mL, 3.34 g, 33.0 mmol, 2.2 equiv), and 55 mL of CH_2Cl_2. This mixture was cooled to 0 °C and the acyl chloride solution was added dropwise via cannula over 20 min (5-mL CH_2Cl_2 rinse). The reaction mixture was allowed to warm to rt, stirred for 2.5 h, and then 35 mL of H_2O was added. The aqueous phase was separated and extracted with 100 mL of Et_2O. The combined organic phases were washed with 50 mL of brine, dried over $MgSO_4$, filtered, and concentrated to give 2.126 g of yellow oil. Purification by column chromatography on 64 g of silica gel (elution with 30-40% EtOAc-hexanes) afforded 2.038 g (88%) of Weinreb amide **343** as a colorless oil: IR (neat) 3294, 2940, 2116, 1664, 1418, 1387, 1180, 1108, and 995 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.63 (s, 3 H). 3.11 (s, 3 H), 2.50 (t, J = 7.2 Hz Hz, 2 H), 2.21 (td, J = 6.9, 2.7 Hz, 2 H), 1.91 (t, J = 2.5 Hz, 1 H), 1.73-1.83 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.8, 83.8, 68.9, 61.2, 32.1, 30.4, 23.2, 17.9; HRMS-DART *(m/z)* calcd for $C_8H_{13}NO_2$ $[M + H]^+$: 156.1019, found: 156.1025.


OMe
N
Me
O
343
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
3.000
2.936
1.959
1.997
0.896
1.917

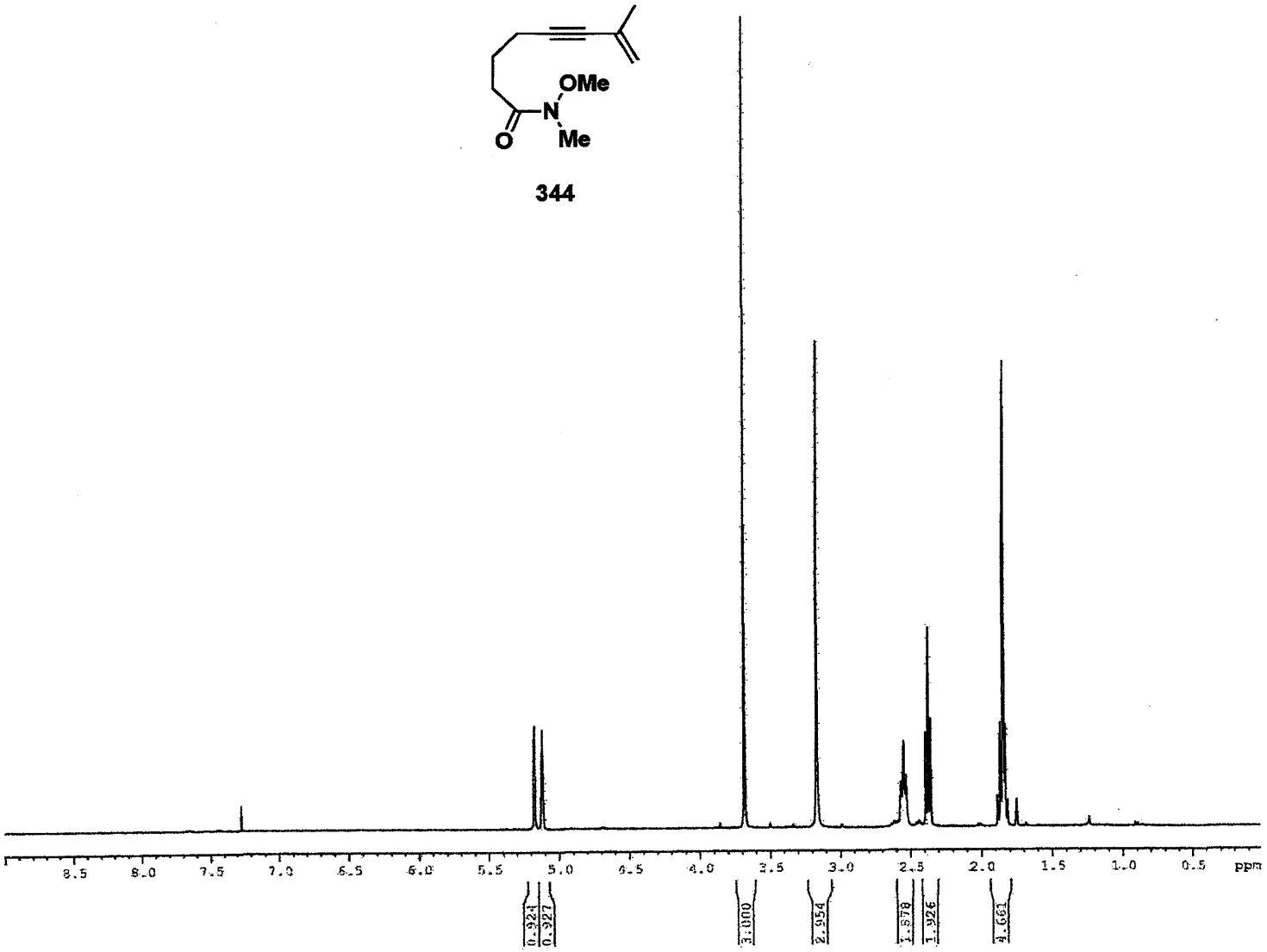

173.792
83.779
77.541
77.222
76.903
66.939
61.221
32.146
30.999
23.154
17.945
OMe
N
Me
O
343
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

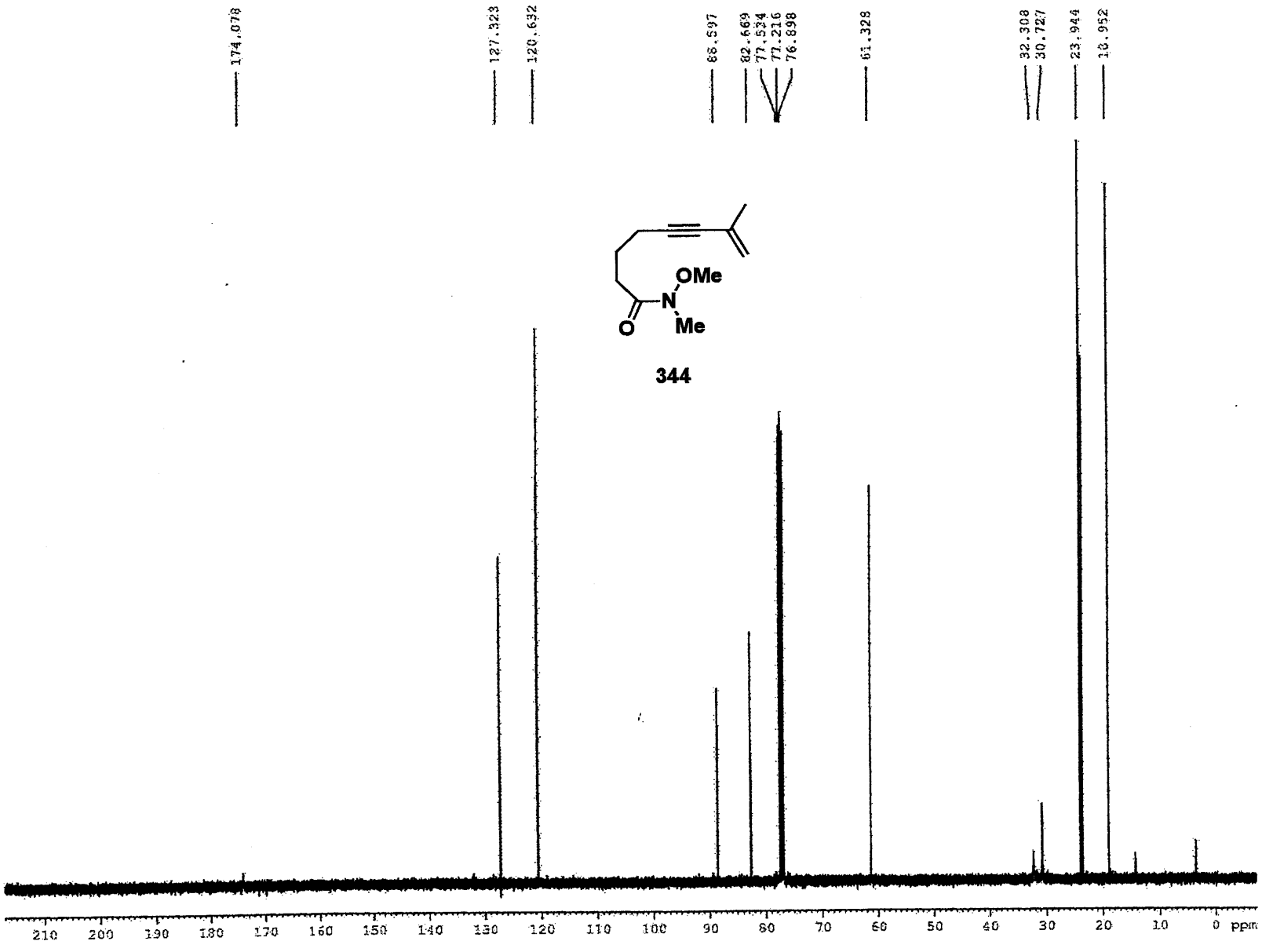


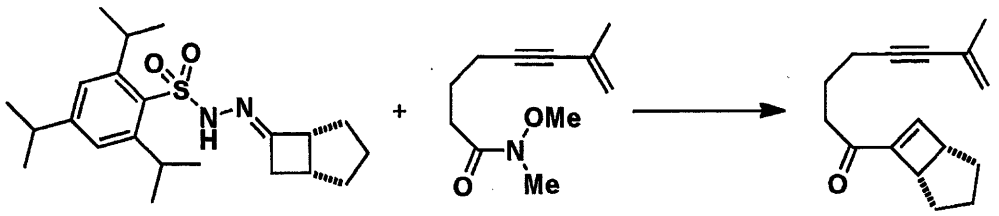
343 344

***N*-Methoxy-*N*-methyl-7-methyloct-7-en-5-ynamide (344).** A 25-mL, three-necked, round-bottomed flask equipped with an argon inlet adapter and two rubber septa was charged with $PdCl_2(PPh_3)_2$ (0.091 g, 0.13 mmol, 0.02 equiv), CuI (0.050 g, 0.26 mmol, 0.04 equiv), and triethylamine (1.36 mL, 0.99 g, 9.8 mmol, 1.5 equiv). The reaction mixture was cooled at 0 °C while 2-bromopropene (0.75 mL, 1.02 g, 8.44 mmol, 1.3 equiv) was added. A solution of alkyne **343** (1.009 g, 6.50 mmol, 1.00 equiv) in 2.6 mL of THF was added dropwise over 20 min. The reaction mixture was allowed to warm to rt and stirred for 20 h in the dark. The reaction mixture was filtered through a plug of 2 g of silica gel with the aid of 150 mL of Et_2O. The filtrate washed with 50 mL of satd aq $NaHCO_3$ solution and 50 mL of brine, and then dried over $MgSO_4$, filtered, and concentrated to give 1.484 g of orange oil. ^1H NMR analysis revealed that this was a ca. 50:50 mixture of **343** and **344**. This material was resubjected to the reaction conditions[200] outlined above to give 0.853 g of red oil. This material was purified by column chromatography on 16 g of silica gel (elution with 25% EtOAc-hexanes) to give 0.678 g (53%) of Weinreb amide **344** as a yellow oil: IR (neat) 2223, 1666, 1614, 1417, 1386, 1179, 1107, 999, and 895 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.17-5.23 (m, 1 H), 5.12-5.16 (m, 1 H), 3.69 (s, 3 H), 3.17 (s, 3 H), 2.55 (t, J = 7.3 Hz, 2 H), 2.38 (t, J = 6.9 Hz, 2 H), 1.88 (s, 3 H), 1.87 (pent, J = 7.0 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.1, 127.3, 120.6, 88.6, 82.7, 61.3, 32.3, 30.7, 23.9, 19.0; HRMS-ESI *(m/z)* calcd for $C_{11}H_{17}NO_2$ $[M + H]^+$: 196.1332, found: 196.1340.

[200] This procedure is not optimized. It was only included in this thesis because the product, Weinreb amide **344**, was used in a later reaction.


OMe
N
Me
O
344
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
0.924
0.927
3.000
2.954
1.878
1.926
4.661


174.078
127.323
120.632
88.597
82.669
77.534
77.216
76.898
61.328
32.308
30.727
23.944
18.952
OMe
N
Me
O
344
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0 ppm



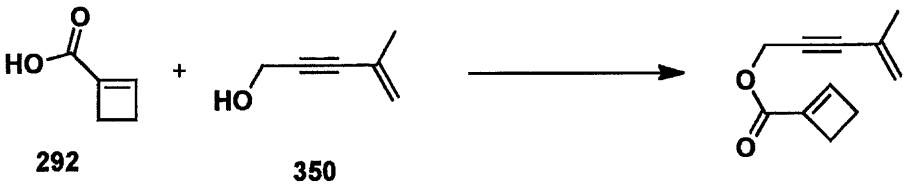
341 344 345

1-*cis*-(Bicyclo[3.2.0]hept-6-en-6-yl)-7-methyloct-7-en-5-yn-1-one (345). A 50-mL, three-necked, round-bottomed flask equipped with an argon inlet adapter, two rubber septa, and a thermocouple probe was charged with sulfonylhydrazone **341** (0.488 g, 1.25 mmol, 1.00 equiv), TMEDA (1.20 mL, 0.94 g, 8.0 mmol, 6.4 equiv), and 6 mL of hexanes. The reaction mixture was cooled to -78 °C and *s*-BuLi solution (1.37 M in cyclohexane, 1.82 mL, 2.50 mmol, 2.00 equiv) was added dropwise over 2 min. The orange reaction mixture was stirred at -78 °C for 2 h, and then warmed to 0 °C and stirred for 15 min. The reaction mixture was cooled back to -78 °C and a solution of Weinreb amide **344** (0.244 g, 1.25 mmol, 1.00 equiv) in 1 mL of hexanes was added dropwise over 3 min. The reaction mixture was stirred at -78 °C for 1 h and then 10 mL of satd aq NH_4Cl was added. The reaction mixture was warmed to 0 °C over 15 min, and then diluted with 100 mL of Et_2O. The organic phase was separated and washed with 25 mL of brine, dried over $MgSO_4$, filtered, and concentrated to give 0.798 g of yellow oil. Purification by column chromatography on 80 g of acetone-deactivated silica gel (elution with 1-35% EtOAc-hexanes) provided 0.036 g (13%)[201] of enone **345** as a pale yellow oil: IR (neat) 2223, 1670, 1613, 1589, 1444, 1371, 1398, 1217, 1190, 1076, 1022, 892, and 803 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.63 (s, 1 H), 5.18-5.23 (m, 1 H), 5.12-5.18 (m, 1 H), 3.53-3.41 (m, 1 H), 3.08-3.13 (m, 1 H), 2.67 (td, J = 6.5, 1.9 Hz, 2 H), 2.35 (t, J = 6.8 Hz 2 H), 1.88 (s, 3 H), 1.81-1.86 (m, 2 H), 1.75-1.81 (m, 1 H), 1.50-1.75 (m, 2 H), 1.22-1.36 (m, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.5, 146.6, 146.0, 127.3, 120.8, 88.5, 82.8, 46.0, 44.2, 36.8, 25.80, 25.79, 24.0, 23.4, 23.3, 19.0; HRMS-DART *(m/z)* calcd for $C_{16}H_{20}O$ $[M + H]^+$: 229.1587, found: 229.1577.

[201] This procedure is not optimized. It was only included in this thesis because the product, enone **345**, was used in [4 + 4] annulation studies.

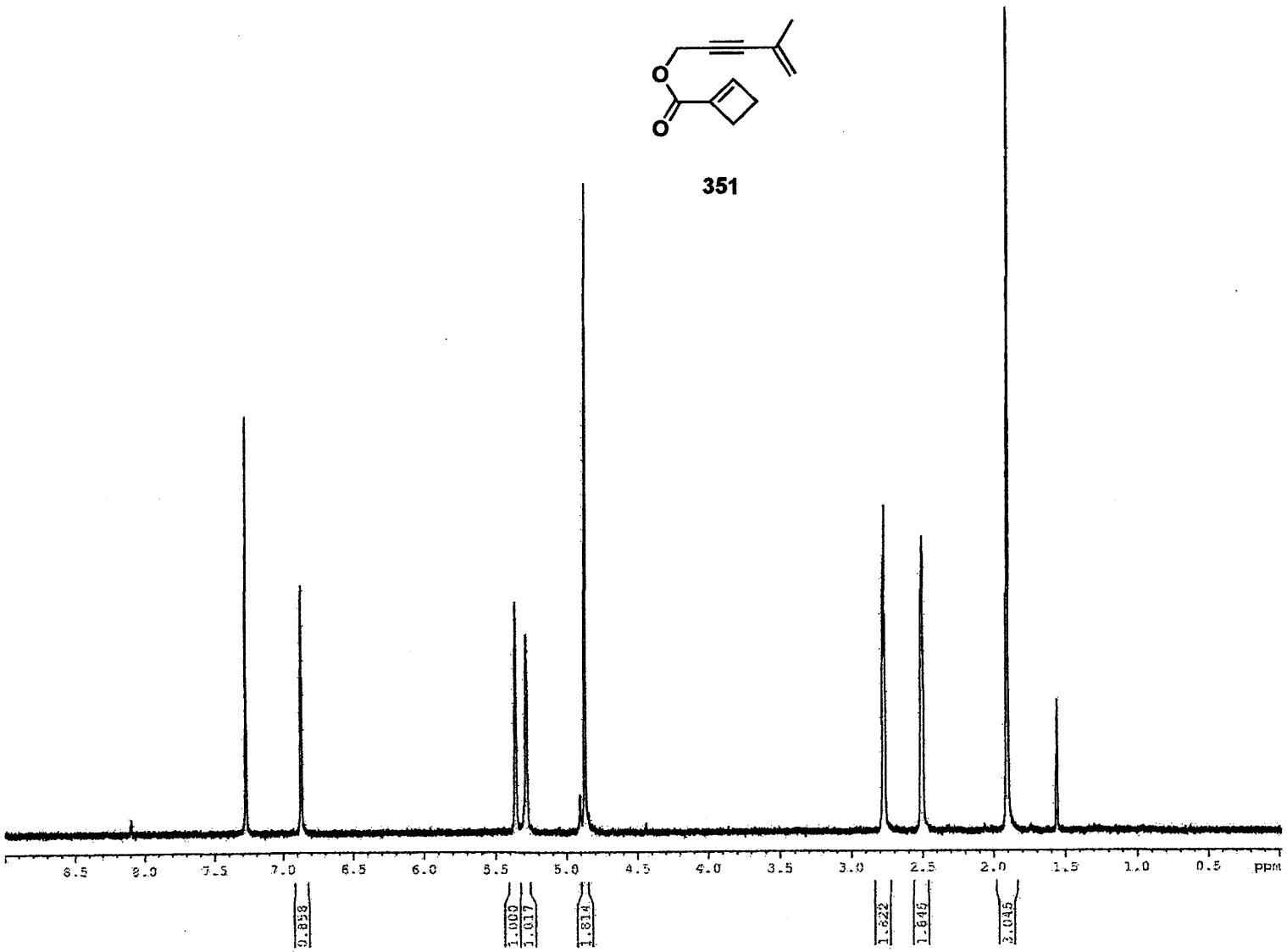
O
345
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
1.000
1.059
1.058
1.002
1.033
2.117
2.193
3.338
1.950
2.647
3.076
3.038

196.487
146.641
146.042
127.349
120.787
88.522
82.819
77.547
77.230
76.912
45.962
44.258
36.779
25.792
24.003
23.373
23.266
O
345
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm



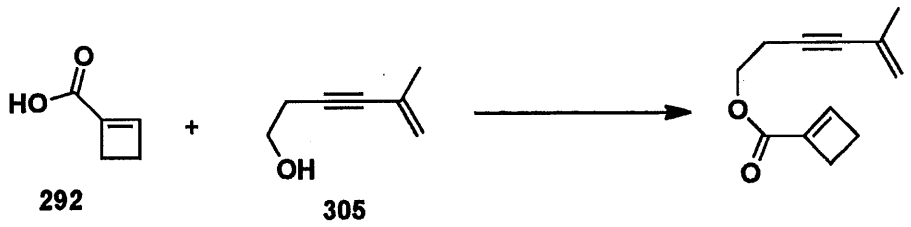
292 350 351

4-Methylpent-4-en-2-yn-1-yl cyclobut-1-enecarboxylate (351). A 50-mL, three-necked, round-bottomed flask equipped with an argon inlet adapter and two rubber septa was charged with cyclobutene carboxylic acid **292** (0.201 g, 2.05 mmol, 1.0 equiv) and 5 mL of CH_2Cl_2. Oxalyl chloride (0.18 mL, 0.27 g, 2.1 mmol, 1.0 equiv) and DMF (1 drop) were added and the resulting mixture was stirred at rt in the dark for 1 h (gas evolution). The reaction mixture was cooled to 0 °C and a solution of 4-methylpent-4-en-2-yn-1-ol **350** (0.212 g, 2.2 mmol, 1.1 equiv) and triethylamine (0.61 mL, 0.44 g, 4.3 mmol, 2.1 equiv) in 4 mL of CH_2Cl_2 was added dropwise via cannula over 2 min (1.2-mL CH_2Cl_2 rinse). The reaction mixture was warmed to rt, stirred for 21 h, and then diluted with 5 mL of satd aq $NaHCO_3$ solution. The resulting mixture was extracted with 100 mL of CH_2Cl_2. The organic layer was dried over $MgSO_4$, filtered, and concentrated to give 0.446 g of brown oil. Purification by column chromatography on 27 g of silica gel (elution with 3% EtOAc-hexanes) afforded 0.200 g (55%) of ester **351** as a colorless oil: IR (neat) 2234, 1726, 1610, 1440, 1375, 1313, 1247, 1187, 1113, 965, and 907 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.85-6.89 (m, 1 H), 5.34-5.38 (m, 1 H), 5.26-5.31 (m, 1 H), 4.86-4.87 (m, 2 H), 2.75-2.79 (m, 2 H), 2.48-2.53 (m, 2 H), 1.89-1.93 (m, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.5, 147.9, 138.0, 126.2, 123.2, 87.7, 82.2, 52.5, 29.3, 17.5, 23.3; HRMS-ESI *(m/z)* calcd for $C_{11}H_{12}O_2$ $[M + H]^+$: 177.0910, found: 177.0917.


O
O
351
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
0.858
1.000
1.017
1.814
1.622
1.646
2.045

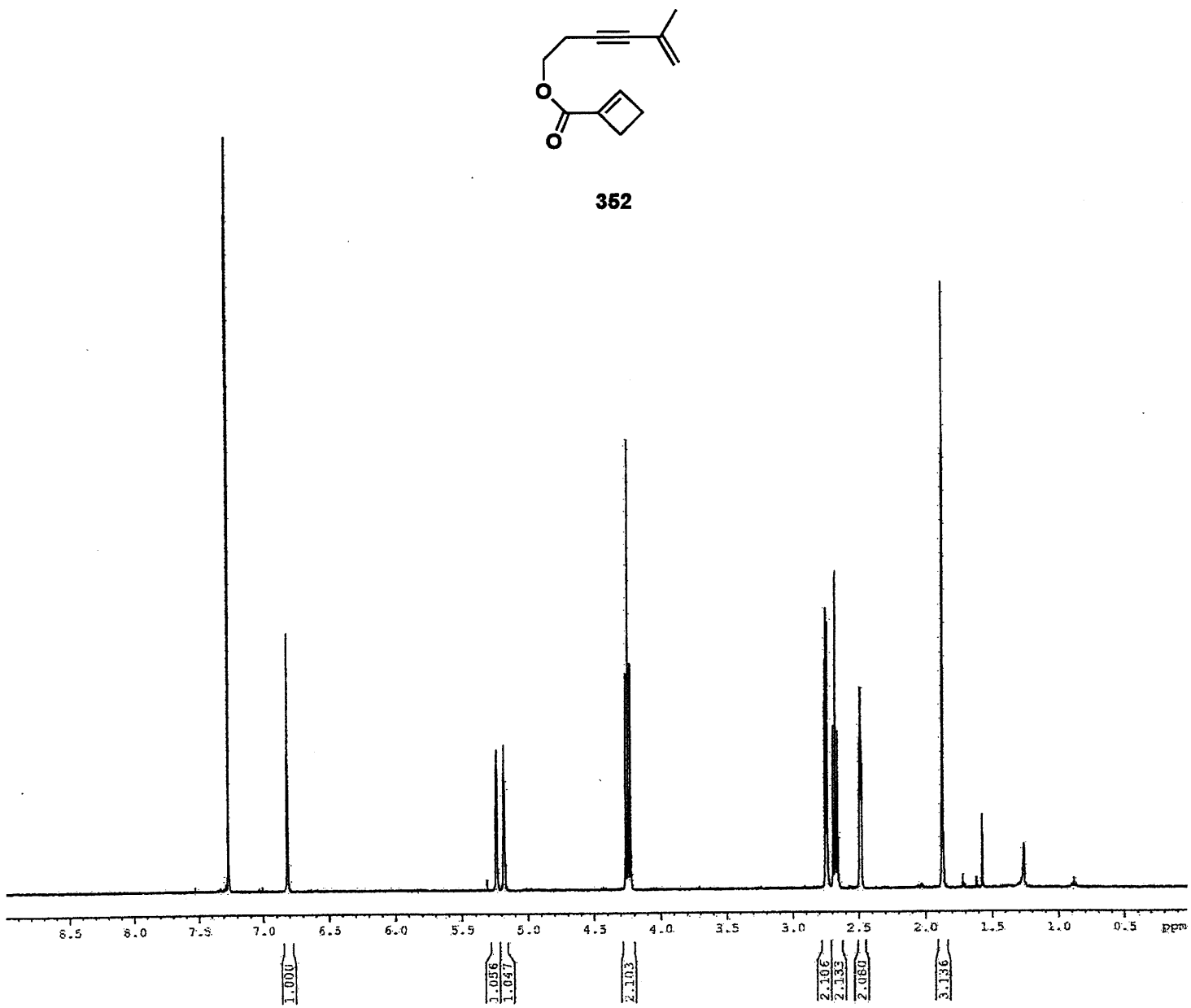
161.483
147.912
138.084
126.201
123.170
87.741
82.199
77.548
77.231
76.914
52.504
29.349
27.493
23.328
O
O
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

351

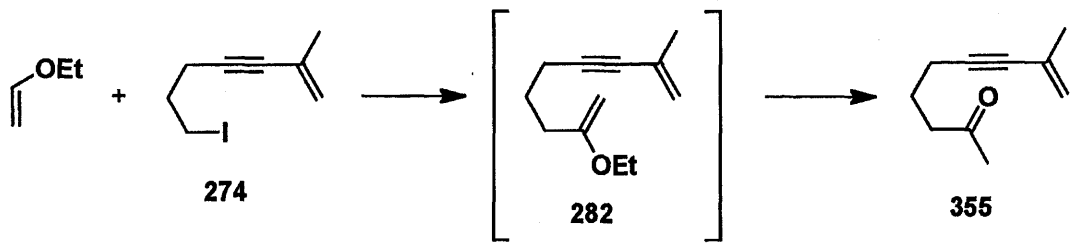


292 305 352

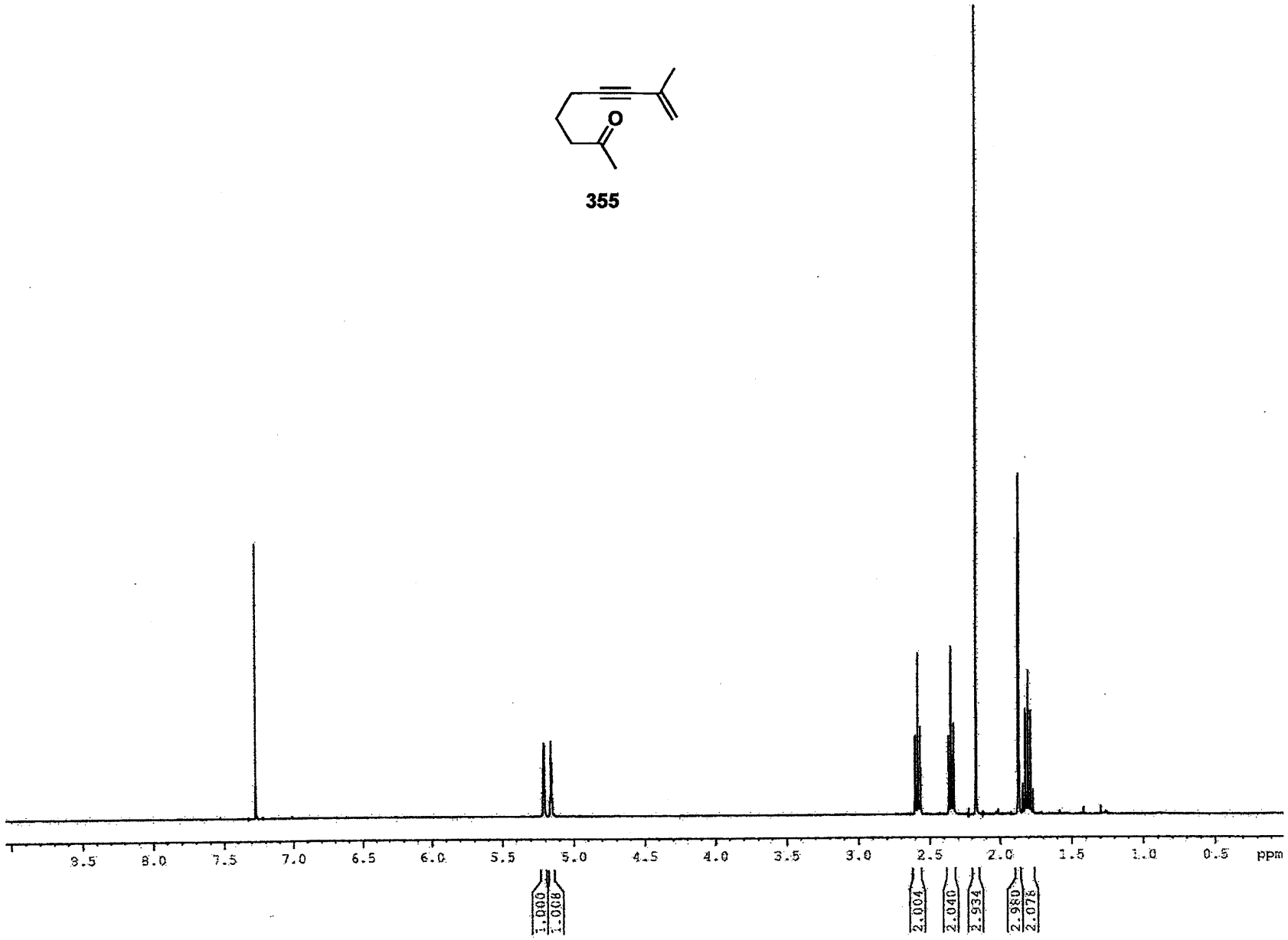
5-Methylhex-5-en-3-yn-1-yl cyclobut-1-enecarboxylate (352). A 50-mL, three-necked, round-bottomed flask equipped with an argon inlet adapter and two rubber septa was charged with cyclobutene carboxylic acid **292** (0.157 g, 1.60 mmol, 1.0 equiv) and 6 mL of CH_2Cl_2. Oxalyl chloride (0.14 mL, 0.21 g, 1.6 mmol, 1.0 equiv) and DMF (1 drop) were added and the reaction mixture was stirred in the dark for 2 h (gas evolution). The resulting mixture was cooled to 0 °C and a solution of 5-methylhex-5-en-3-yn-1-ol **305** (0.177 g, 1.60 mmol, 1.0 equiv) and triethylamine (0.45 mL, 0.33 g, 3.2 mmol, 2.0 equiv) in 2.4 mL of CH_2Cl_2 was added dropwise via cannula over 3 min (1-mL CH_2Cl_2 rinse). The reaction mixture was warmed to rt and stirred for 20 h, and then 5 mL of satd aq $NaHCO_3$ solution was added. The resulting mixture was extracted with 150 mL of CH_2Cl_2. The organic layer was dried over Na_2SO_4, filtered, and concentrated to give 0.351 g of brown oil. Purification by column chromatography on 35 g of silica gel (elution with 3-5% EtOAc-hexanes) afforded 0.169 g (56%) of ester **352** as a colorless oil: IR (neat) 2230, 1723, 1611, 1441, 1386, 1319, 1282, 1250, 1188, 1120, 997, and 899 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.82 (t, J = 1.2 Hz, 1 H), 5.22-5.26 (m, 1 H), 5.16-5.20 (m, 1 H), 4.25 (t, J = 7.1 Hz, 2 H), 2.72-2.76 (m, 2 H), 2.68 (t, J = 7.1 Hz, 2 H), 2.44-2.51 (m, 2 H), 1.87 (dd, J = 1.4, 1.1 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.1, 147.2, 138.6, 127.0, 121.4, 84.6, 83.5, 62.1, 29.3, 27.4, 23.8, 20.0; HRMS-ESI *(m/z)* calcd for $C_{12}H_{14}O_2$ $[M + H]^+$: 191.1067, found: 191.1072.


O
O
352
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
1.000
1.056
1.047
2.103
2.106
2.133
2.060
3.136

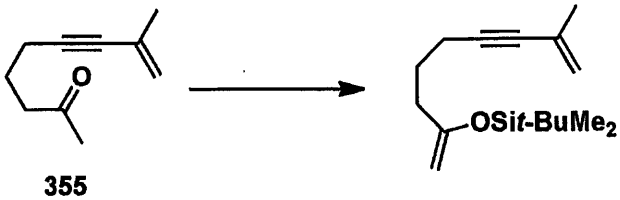
352



8-Methylnon-8-en-6-yn-2-one (355). A 250-mL, three-necked, round-bottomed flask equipped with an argon inlet adapter, a 50-mL addition funnel fitted with a rubber septum, a rubber septum, and a thermocouple probe was charged with ethyl vinyl ether (5.74 mL, 4.33 g, 60 mmol, 4 equiv) and 35 mL of THF. The reaction mixture was cooled at -78 °C and *t*-BuLi solution (1.45 M solution in pentane, 26 mL, 38 mmol, 2.5 equiv) was added via addition funnel over 15 min. The bright yellow reaction mixture became colorless upon warming to 5 °C over 40 min. The reaction mixture was recooled to -78 °C and a solution of the iodide **274** (3.503 g, 15.0 mmol, 1.0 equiv) in 4 mL of THF was added dropwise via cannula over 5 min (2-mL THF rinse). The reaction mixture was allowed to warm to 0 °C. After 2 h, acetic acid (21 mL) and H_2O (10 mL) were each added in one portion. The reaction mixture was allowed to warm to rt and stirred for 24 h. The resulting mixture was diluted with 100 mL of Et_2O, washed with three 50-mL portions of satd aq $NaHCO_3$ solution and 50 mL of brine, dried over $MgSO_4$, filtered, and concentrated to give 2.56 g of an orange oil. Purification by column chromatography on 77 g of silica gel (elution with 5% EtOAc-hexanes) provided 1.330 g (59%) of ketone **355** as a yellow oil: IR (neat) 3415, 3096, 2954, 2226, 1716, 1614, 1435, 1371, 1159, and 895 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.20-5.22 (m, 1 H), 5.15-5.17 (m, 1 H), 2.59 (t, J = 7.2 Hz, 2 H), 2.35 (t, J = 6.9 Hz, 2 H), 2.17 (s, 3 H), 1.89 (dd, J = 1.5, 1.0 Hz, 3 H), 1.81 (app pent, J = 7.1 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.6, 127.3, 120.9, 88.4, 82.8, 42.5, 30.3, 24.0, 22.8, 18.9; HRMS-ESI *(m/z)*: $[M + Na]^+$ calcd for $C_{10}H_{14}O$: 173.0937, found: 173.0940.

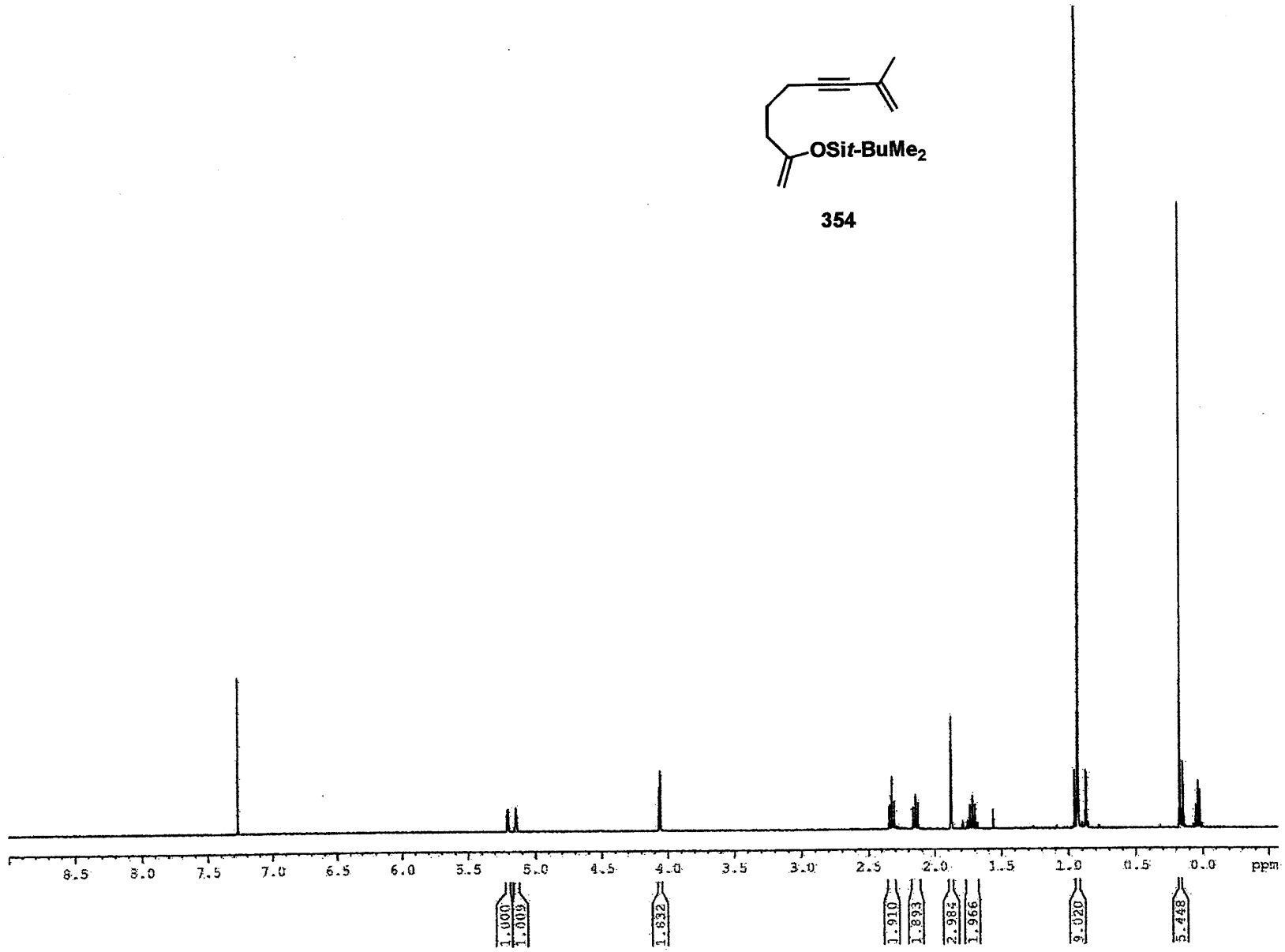

O
355
9.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
1.000
1.008
2.004
2.040
2.934
2.980
2.078

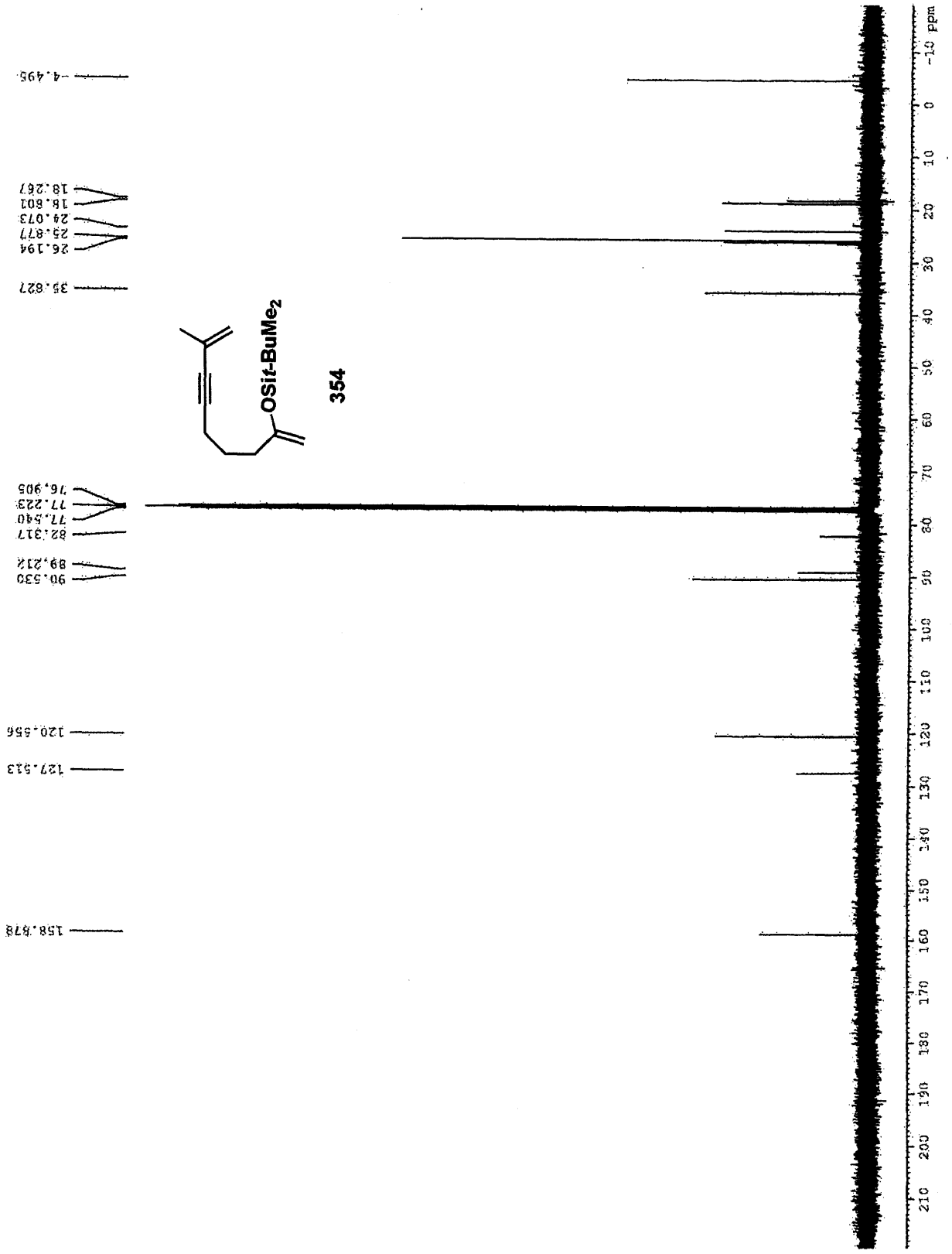
208.611
127.279
120.870
88.345
82.808
77.537
77.220
76.902
42.458
30.269
23.986
22.741
18.780
O
355
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

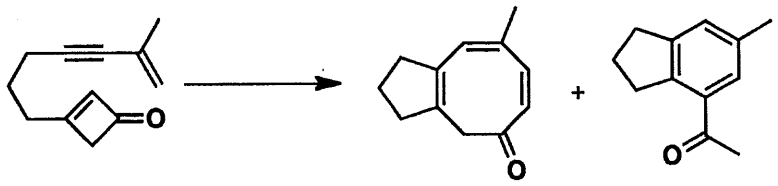


355 354

***tert*-Butyldimethyl(8-methylnona-1,8-dien-6-yn-2-yloxy)silane (354).** A 25-mL, three-necked, round-bottomed flask equipped with an argon inlet adapter, two rubber septa, and a thermocouple probe was charged with *t*-butyldimethylsilyl chloride (0.756 g, 5.0 mmol, 5.0 equiv) and 5 mL of THF. The reaction mixture was cooled at -78 °C while KHMDS solution (0.5 M solution in toluene, 3.0 mL, 1.5 mmol, 1.5 equiv) was added in one portion. A solution of ketone **355** (0.157 g, 1.0 mmol, 1.0 equiv) in 4 mL of toluene was cooled at -78 °C and added dropwise via cannula over 1 h (1 mL toluene rinse). The reaction mixture was stirred for 2 h at -78 °C, 1.5 mL of Et_3N was added, and the resulting mixture was poured into 3 mL of satd aq $NaHCO_3$ solution. The aqueous phase was separated and extracted with two 25-mL portions of hexanes. The combined organic phases were washed with 10 mL of H_2O, dried over Na_2SO_4, filtered, and concentrated to give 0.692 g of a yellow oil. Purification by column chromatography on 14 g of silica gel (elution with 1% Et_3N-hexanes and 2% Et_3N-3% EtOAc-hexanes) afforded 0.225 g (82%) of silyl enol ether **354** as a colorless oil: IR (neat) 3112, 3097, 2957, 2931, 2899, 2859, 2225, 1787, 1617, 1473, 1257, 1059, 1004, and 839 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.19-5.22 (m, 1 H), 5.13-5.16 (m, 1 H), 4.07 (d, J = 0.7 Hz, 1 H), 4.06 (d, J = 0.7 Hz, 1 H), 2.33 (t, J = 7.1 Hz, 2 H), 2.15 (t, J = 7.4 Hz, 2 H), 1.88 (m, 3 H), 1.72 (app pent, J = 7.2 Hz, 2 H), 0.93 (s, 9 H), 0.17 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.9, 127.5, 120.6, 90.5, 82.3, 35.8, 26.2, 25.9, 24.1, 18.8, 18.3; HRMS-ESI *(m/z)*: $[M + H]^+$ calcd for $C_{16}H_{29}OSi$: 265.1982, found: 265.1991.

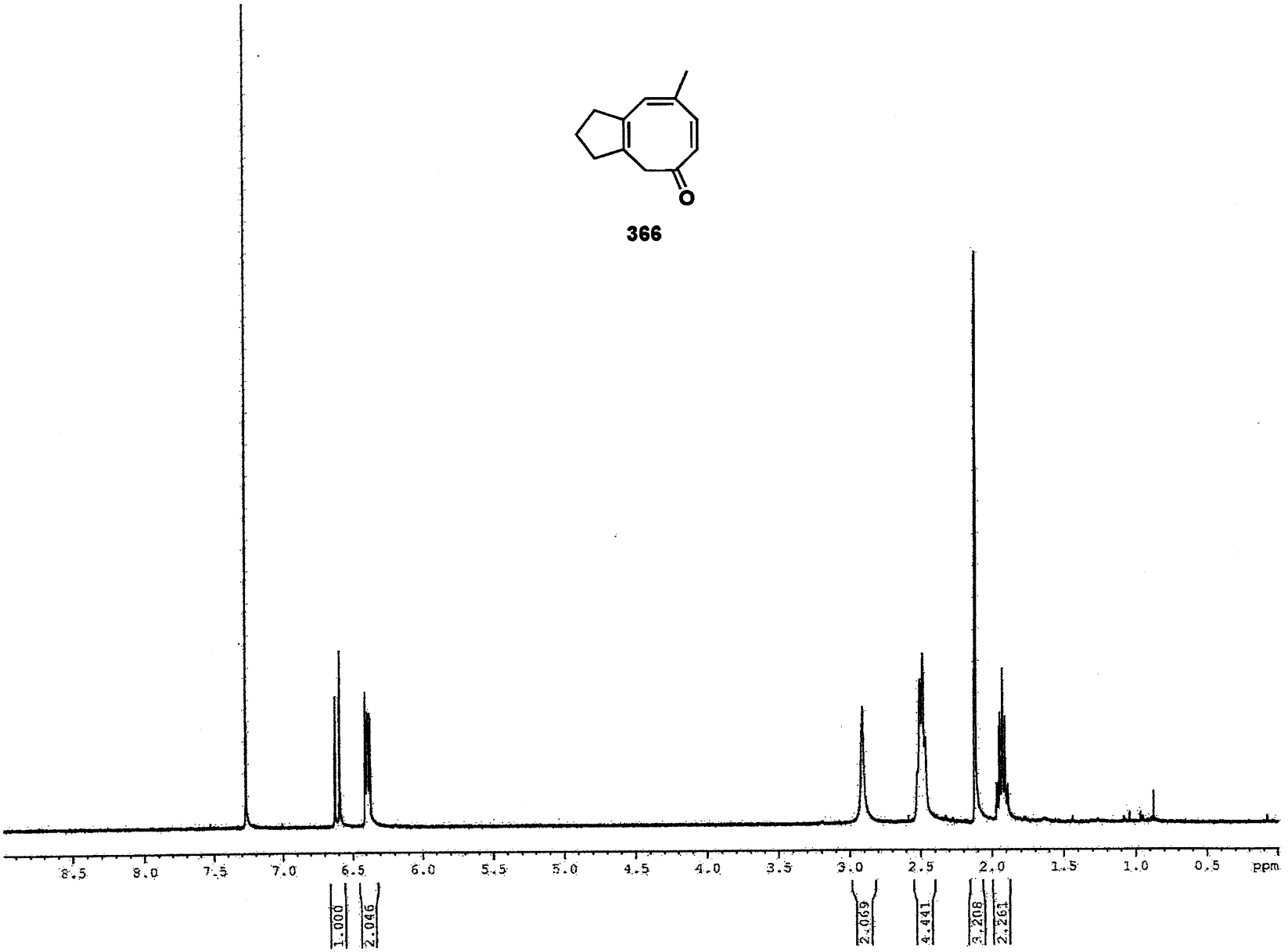

OSit-BuMe2
354
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm
1.000
1.009
1.832
1.910
1.893
2.984
1.966
9.020
5.448

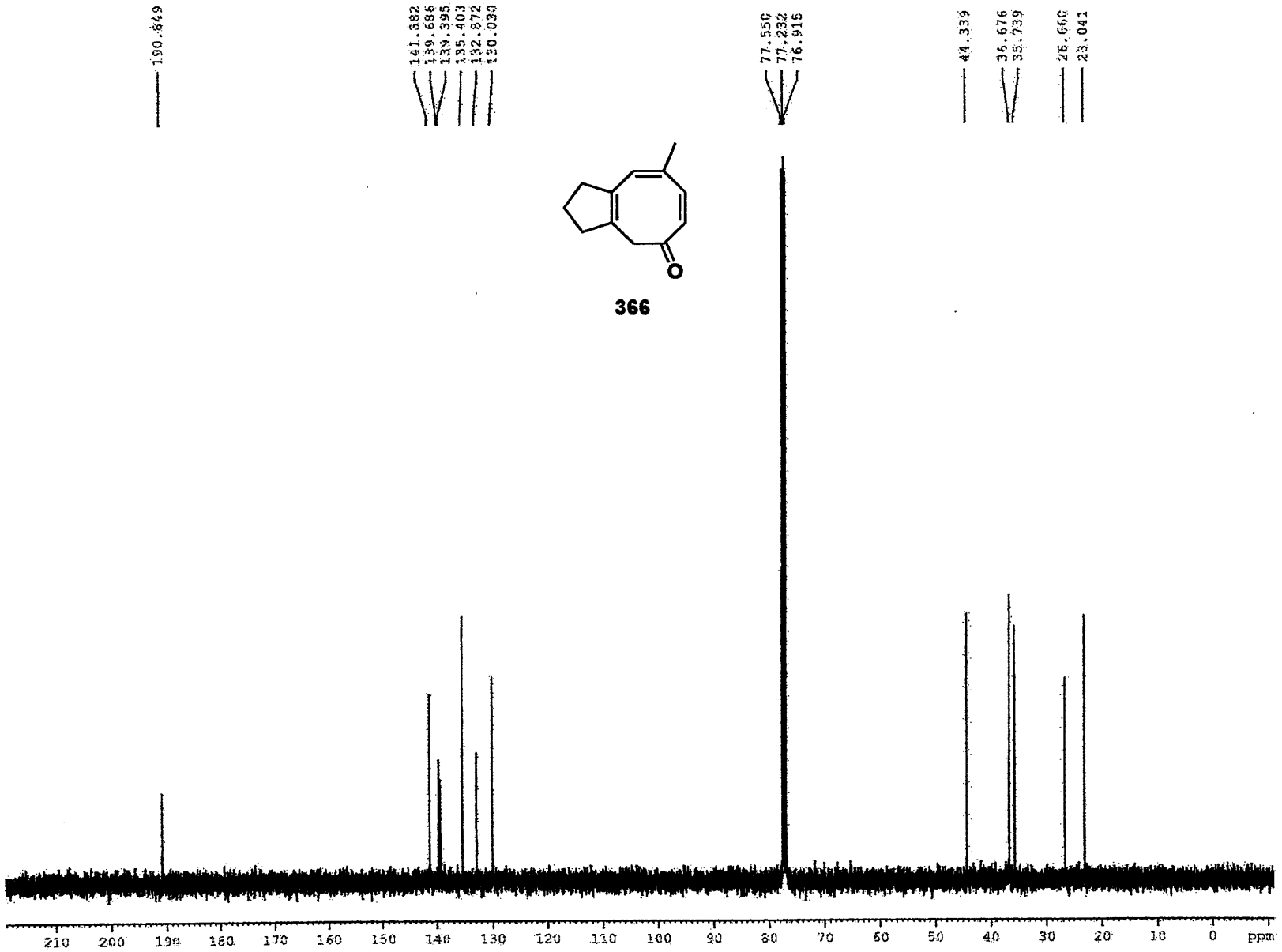

OSit-BuMe2
354
-4.495
18.267
18.601
24.073
25.877
26.194
35.827
76.905
77.223
77.540
82.317
89.212
90.530
120.556
127.513
158.878
-10 ppm
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210

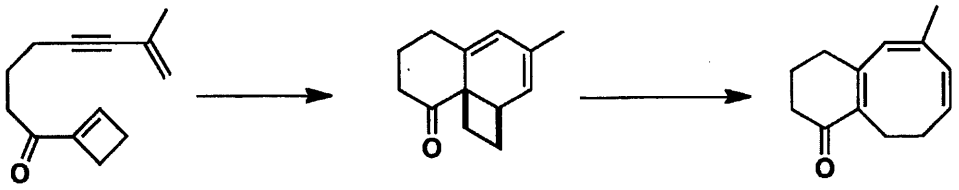


270 366 367

(2Z, 4Z, 6Z)-4-Methyl-6,7-cyclopentacycloocta-2,4,6-trienone (366). A threaded Pyrex tube (35 mm O.D., 30 mm I.D) equipped with a stir bar, rubber septum, and argon inlet needle was charged with cyclobutenone **270** (0.206 g, 1.18 mmol, 1.0 equiv), BHT (0.261 g, 1.18 mmol, 1.0 equiv), and 24 mL of CH_2Cl_2. The pale yellow solution was cooled to 0 °C and $BF_3{\cdot}OEt_2$ (0.20 mL, 0.23 g, 1.6 mmol, 1.4 equiv) was added dropwise via syringe over 30 sec. The reaction mixture was stirred at 0 °C for 20 min while the color changed to orange and then tan. The rubber septum was replaced with a Teflon cap, and the reaction mixture was heated at 50 °C. After 4 h, the solution was cooled to rt and the Teflon cap was replaced with a rubber septum and argon inlet needle. The reaction mixture was cooled to 0 °C and 3 mL of satd aq $NaHCO_3$ solution was added dropwise via syringe over 1 min. The resulting mixture was extracted with two 20-mL portions of CH_2Cl_2 and the combined organic layers were washed with 20 ml of brine, dried over $MgSO_4$, filtered, and concentrated at 10 °C (20 mmHg) to give 0.478 g of a brown oil. Column chromatography on 48 g of silica gel (elution with 5-20% Et_2O-pentane) afforded 0.061 g (30%) of cyclooctatrienone **366** as a yellow oil and 0.075 g (36%) of indan **367** as a yellow oil. For cyclooctatrienone **366**: IR (neat) 3301, 2955, 2916, 2844, 1661, 1615, 1564, 1434, 1286, 1234, 1200, 1029, and 820 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.61 (d, J = 13.3 Hz, 1 H), 6.36-6.41 (m, 2 H), 2.91 (br s, 2 H), 2.49 (app q, J = 7.5 Hz, 4 H), 2.11 (s, 3 H), 1.93 (pent, J = 7.6 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.9, 141.4, 139.7, 139. 4, 135.4, 132.9, 130.0, 44.4, 36.7, 35.8, 26.7, 23.1; HRMS-ESI *(m/z)* $[M + Na]^+$ calcd for $C_{12}H_{14}O$: 197.0937, found: 197.0935. For indan **367**[69] ^1H NMR (400 MHz, $CDCl_3$) δ 7.47 (s, 1 H), 7.24 (s, 1 H), 3.21 (t, J = 7.4 Hz, 2 H), 2.88 (t, J = 7.6 Hz, 2 H), 2.58 (s, 3H), 2.37 (s, 3 H), 2.07 (pent, J = 7.5 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.3, 146.6, 142.6, 136.0, 133.9, 129.6, 128.3, 33.9, 32.4, 29.8, 28.6, 25.5, 21.3.


O
366
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
1.000
2.046
2.069
4.441
3.208
2.261


190.849
141.382
139.686
139.395
135.403
132.872
130.030
77.550
77.232
76.916
44.339
36.676
35.739
26.660
23.041
O
366
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

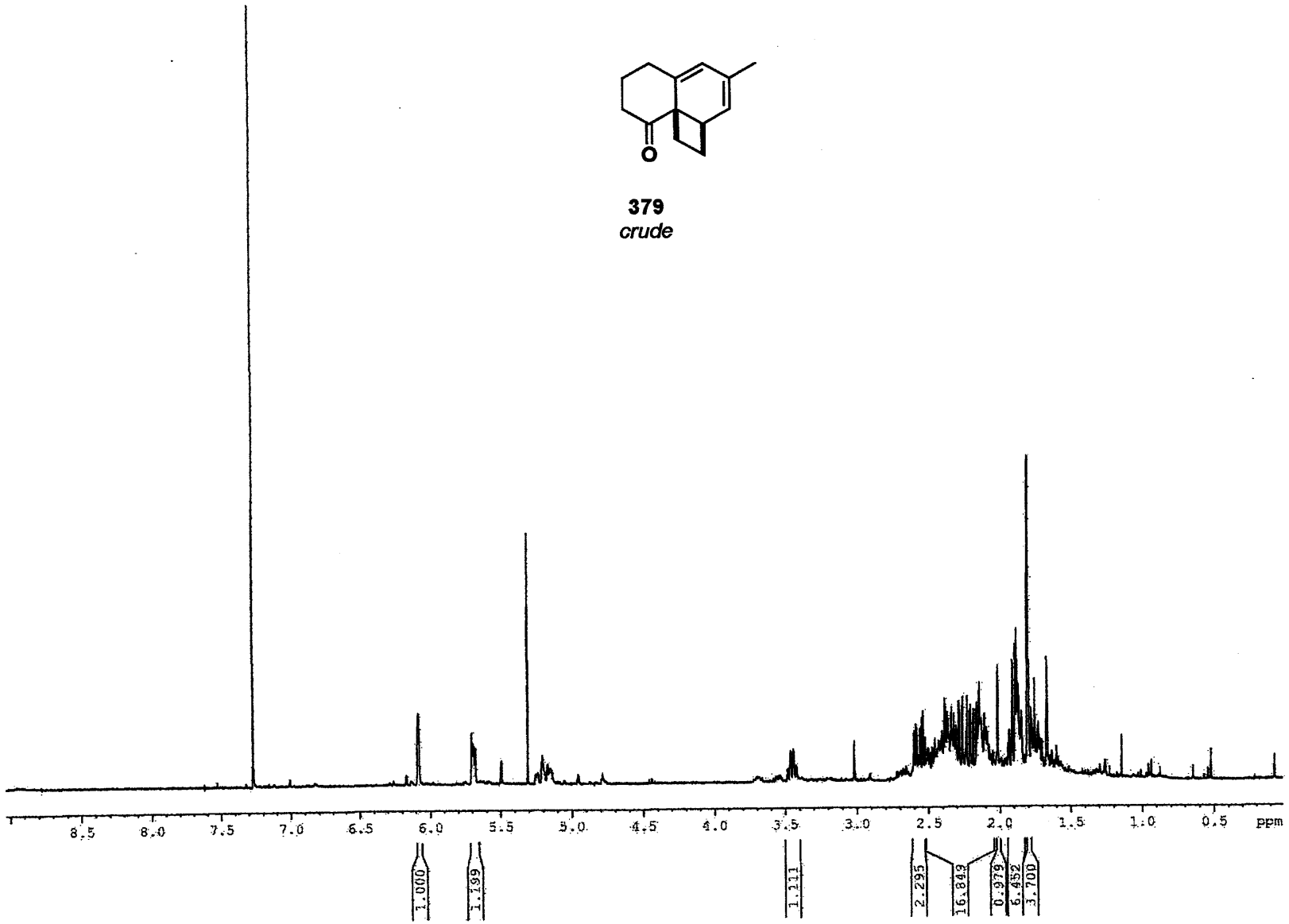


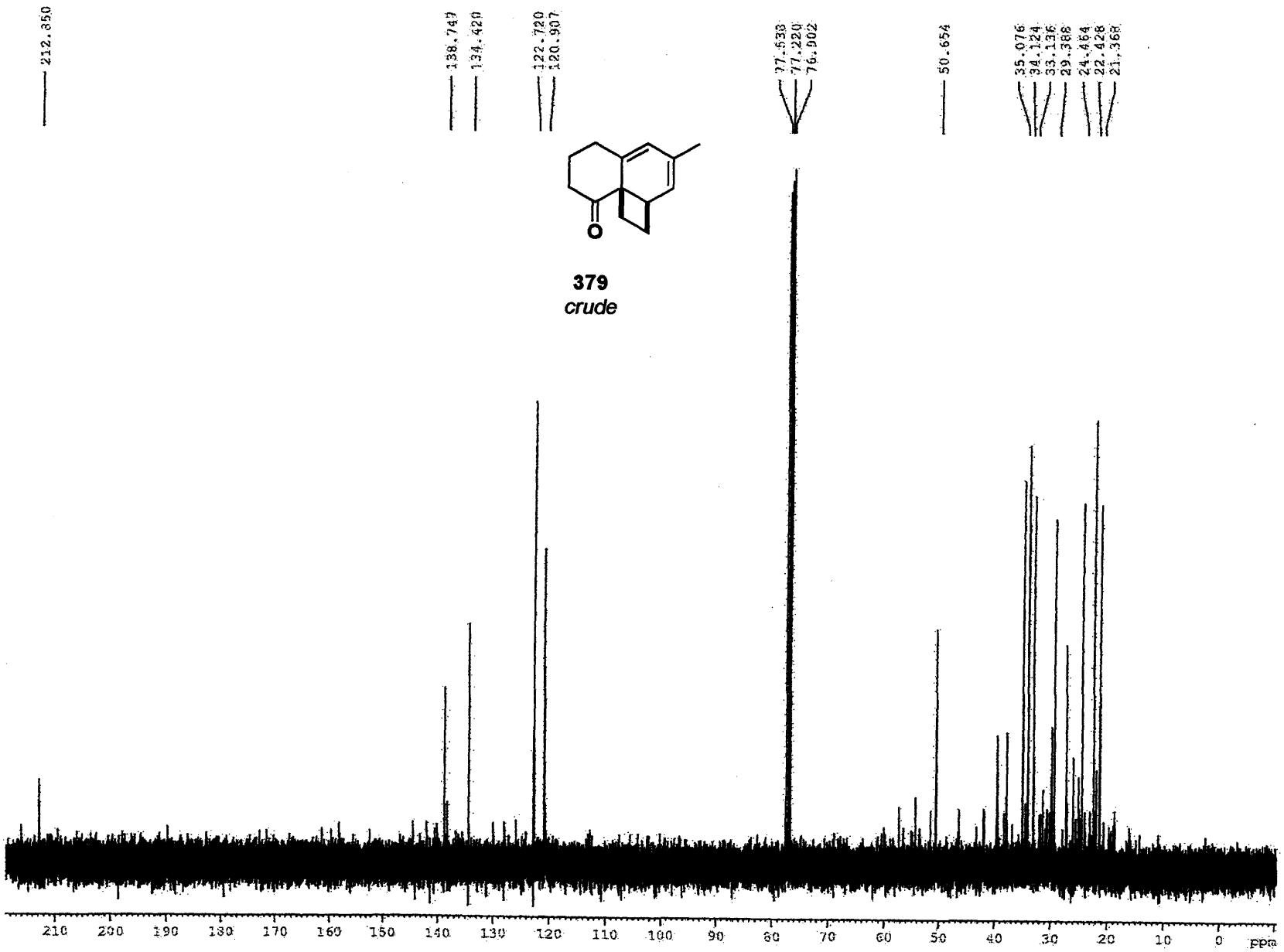
312 379 380

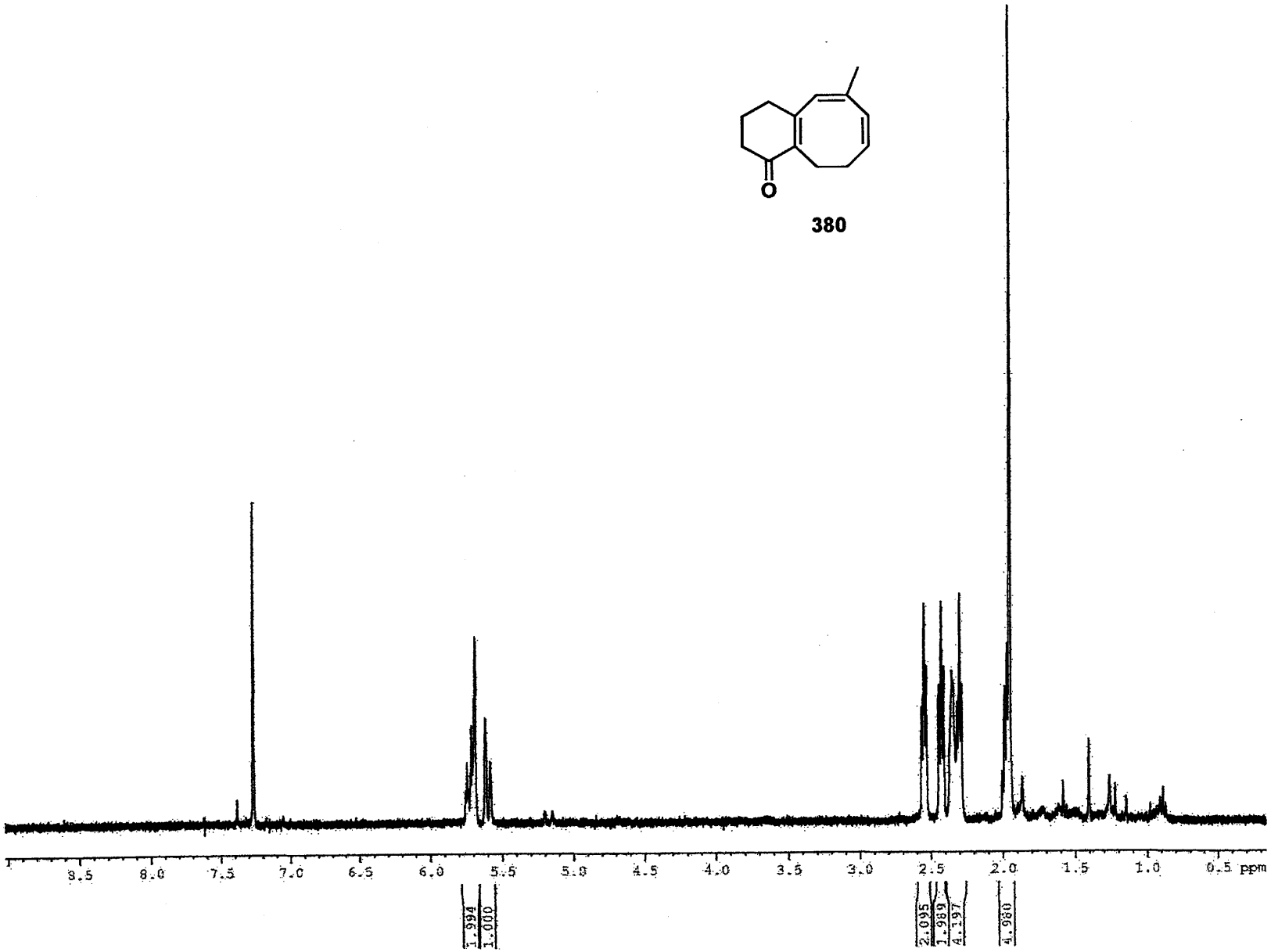
(5*Z*,7*Z*)-6-Methyl-3,4,9,10-tetrahydrobenzo[8]annulen-1(2*H*)-one (380). A 250-mL, three-necked, round-bottomed flask equipped with an argon inlet adapter, two rubber septa, and a thermocouple probe was charged with enone **312** (0.107 g, 0.569 mmol, 1.0 equiv) and 57 mL of CH_2Cl_2. The reaction mixture was cooled to -78 °C and methanesulfonic acid solution (0.24 M in CH_2Cl_2, 2.35 mL, 0.57 mmol, 1.0 equiv) was added dropwise over 5 min. The yellow reaction mixture was stirred at -78 °C for 4 h, and then 10 mL of satd aq $NaHCO_3$ solution was added dropwise over 5 min. The resulting mixture was warmed to 0 °C and then diluted with 10 mL of brine. The organic phase[202] was dried over Na_2SO_4 and filtered into a threaded Pyrex tube (28 mm I.D., 35 mm O.D., 20-cm long). The pale blue reaction mixture was degassed with argon for 5 min, and then the tube was sealed with a threaded Teflon cap. The reaction mixture was heated at 70 °C for 5 h, and then cooled to rt and concentrated to give 0.125 g of brown oil. Purification by column chromatography on 16 g of silica gel (elution with 8% EtOAc-hexanes) afforded 0.074 g (69%) of cyclooctatriene **380** as a yellow oil: IR (neat) 3307, 2932, 1663, 1609, 1433, 1374, 1299, 1176, 1128, 819, 756, and 718 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.72 (d, J = 13.3 Hz, 1 H), 5.69 (s, 1 H), 5.60 (dt, J = 13.3, 2.2 Hz, 1 H), 2.54 (t, J = 6.0 Hz, 2 H), 2.43 (t, J = 6.6 Hz, 2 H), 2.32-2.38 (m, 2 H), 2.30 (t, J = 5.9 Hz, 2 H), 1.97 (pent, J = 5.5 Hz, 2 H), 1.95 (d, J = 1.2 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.2, 155.8, 138.0, 136.9, 132.7, 127.6, 125.4, 38.1, 30.6, 26.2, 23.8, 23.0; HRMS-ESI *(m/z)* calcd for $C_{13}H_{16}O$ $[M + H]^+$: 189.1279, found: 189.1277.

---

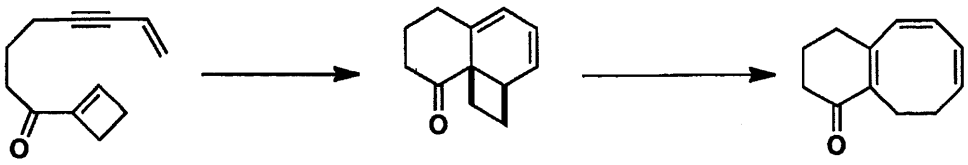
[202] In a separate run, the organic phase was concentrated to give 0.055 g of brown oil that was determined to be diene **379**: IR (neat) 2936, 1707, 1442, 1365, 1333, 1195, 1020, 885, and 734 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.07 (s, 1 H), 5.68 (dd, J = 6.9, 3.8 Hz, 1 H), 3.43 (q, J = 8.2 Hz, 1 H), 2.50-2.60 (m, 2 H), 2.30-2.38 (m, 2 H), 2.14-2.28 (m, 4 H), 1.82-1.88 (m, 2 H), 1.79 (s, 3 H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 212.9, 138.7, 134.4, 122.7, 120.9, 50.6, 35.1, 34.1, 33.1, 29.4, 24.5, 22.4, 21.4.


O
379
crude
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
1.000
1.199
1.111
2.295
16.849
0.979
6.452
3.700


212.850
138.747
134.420
122.720
120.907
77.538
77.220
76.902
50.654
35.076
34.124
33.136
29.388
24.464
22.428
21.368
O
379
crude
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm


O
380
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5 ppm
1.994
1.000
2.095
1.989
4.197
4.980

199.653
155.791
137.982
136.946
132.755
127.574
125.411
77.543
77.226
76.908
38.135
36.806
30.593
30.024
26.244
24.863
23.783
23.022
O
380
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm



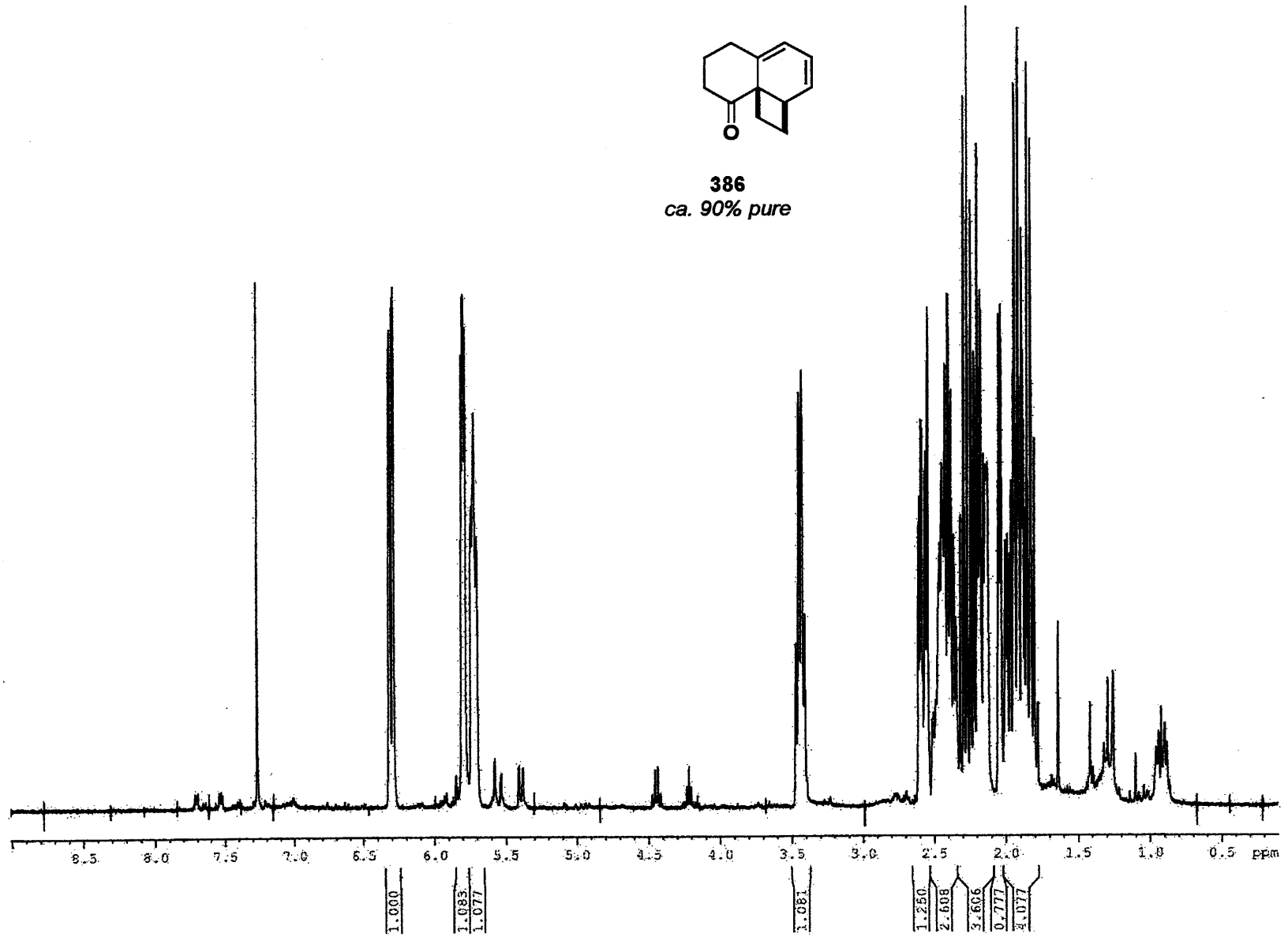
313 386 387

(5*Z*,7*Z*)-3,4,9,10-Tetrahydrobenzo[8]annulen-1(2*H*)-one (387). A 250-mL, three-necked, round-bottomed flask equipped with an argon inlet adapter, two rubber septa, and a thermocouple probe was charged with enone **313** (0.102 g, 0.585 mmol, 1.00 equiv) and 58 mL of CH_2Cl_2. The reaction mixture was cooled to -40 °C and methanesulfonic acid solution (0.24 M in CH_2Cl_2, 2.45 mL, 0.588 mmol, 1.00 equiv) was added dropwise over 1 min. The reaction mixture was stirred at -40 °C for 4 h and then 10 mL of satd aq $NaHCO_3$ solution was added dropwise over 5 min. The reaction mixture was warmed to 0 °C over 10 min and then washed with 10 mL of brine. The organic phase[203] was dried over $MgSO_4$, filtered, and concentrated (5-10 °C, 20 mmHg) to give a yellow oil. This material was dissolved in 58 mL of 1,2-dichloroethane and transferred to a threaded Pyrex tube (28 mm I.D., 35 mm O.D., 20-cm long). The pale yellow reaction mixture was degassed with argon for 5 min, and then the tube was sealed with a threaded Teflon cap. The reaction mixture was heated at 150 °C for 18 h, and then cooled to rt and concentrated to give 0.286 g of brown oil. Purification by column chromatography on 150 g of silica gel (elution with 4% EtOAc-hexanes) afforded 0.025 g (25%) of cyclooctatriene **387**[204] as a yellow oil and 0.030 g (30%) of diene **386** as an orange oil (ca. 90% purity by ^{1}H NMR analysis). For cyclooctatriene **387**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.96 (dd, J = 12.2, 5.9 Hz, 1 H), 5.79-5.89 (m, 2 H), 5.68-5.76 (m, 1 H), 2.58 (t, J = 5.8 Hz, 2 H), 2.45 (t, J = 6.7 Hz, 2 H), 2.35-2.46 (m, 2 H), 2.34 (t, J = 6.0 Hz, 2 H), 2.00 (pent, J = 6.3 Hz, 2 H); for diene **386**: IR (neat) 2226, 1707, 1432, 1330, 1193, 1072, 899, 821, and 736 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.30 (td, J = 10.0, 2.6 Hz, 1 H), 5.79 (dd, J = 6.6, 3.7 Hz), 5.65-5.75 (m, 1 H), 3.44 (q, J = 8.2 Hz, 1 H), 2.50-2.62 (m, 2 H), 2.33-2.50 (m, 2 H), 2.09-2.33 (m, 2 H), 1.97-2.09 (m, 2 H) 1.77-1.87 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.3, 138.0, 127.7, 125.8, 123.3, 51.4, 34.9, 34.3, 28.8, 28.0, 22.5, 21.3.

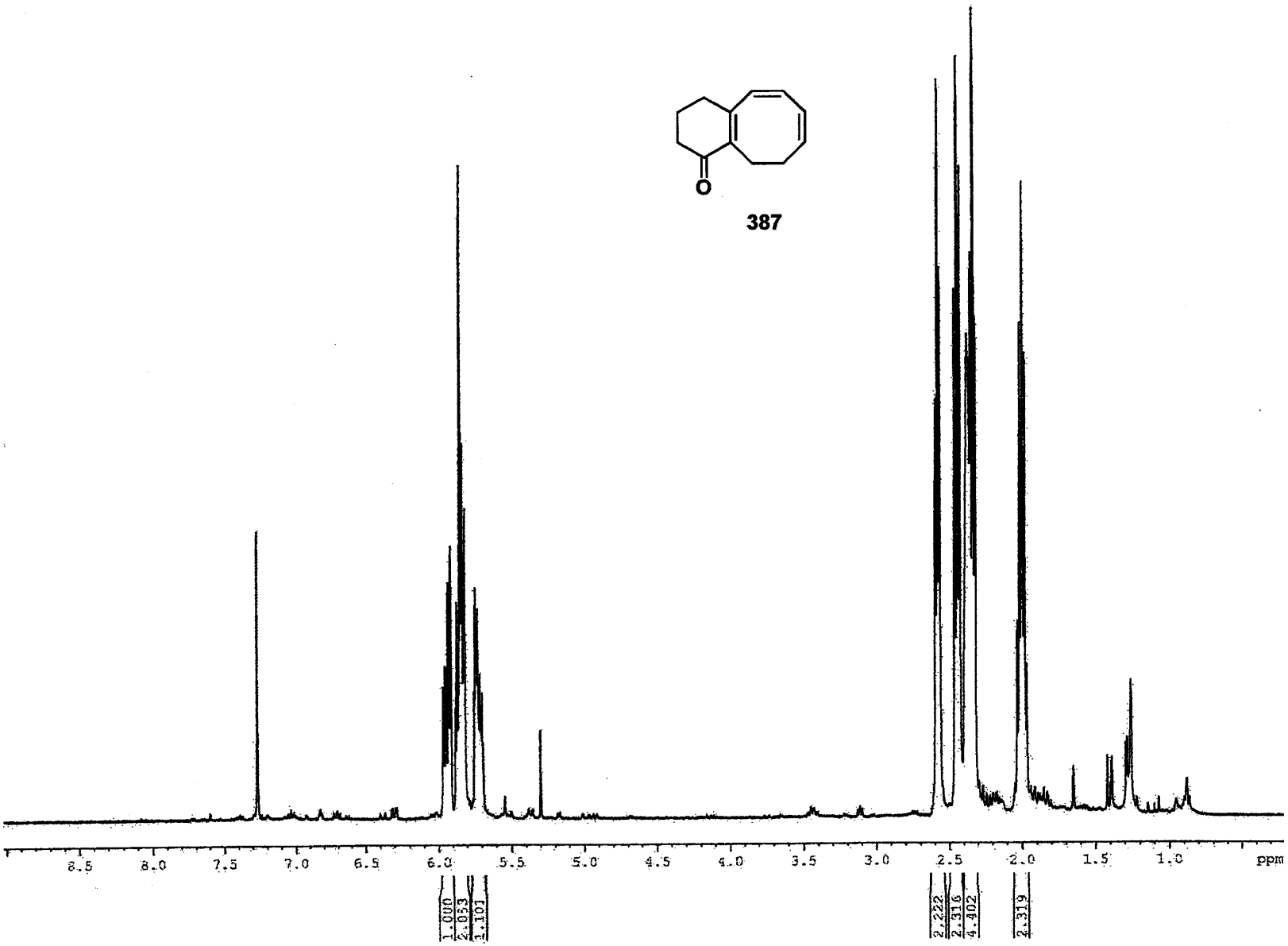
---

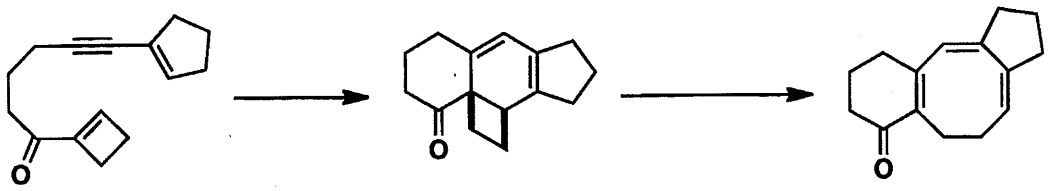
[203] In a previous run, the organic phase was concentrated and analyzed by ^{1}H NMR to reveal that it contains diene **386** as the main component.

[204] Due to the small quantity of cyclooctatriene **387** produced in this reaction, satisfactory ^{13}C NMR and IR spectra, could not be obtained.


O
386
ca. 90% pure
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
1.000
1.083
1.077
1.081
1.250
2.608
3.606
0.777
4.077

212.331
137.966
127.556
125.839
123.927
77.521
77.203
76.885
51.443
34.932
34.284
28.778
27.989
22.523
21.285
386
ca. 90% pure
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm


O
387
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm
1.000
2.053
1.101
2.222
2.316
4.402
2.319

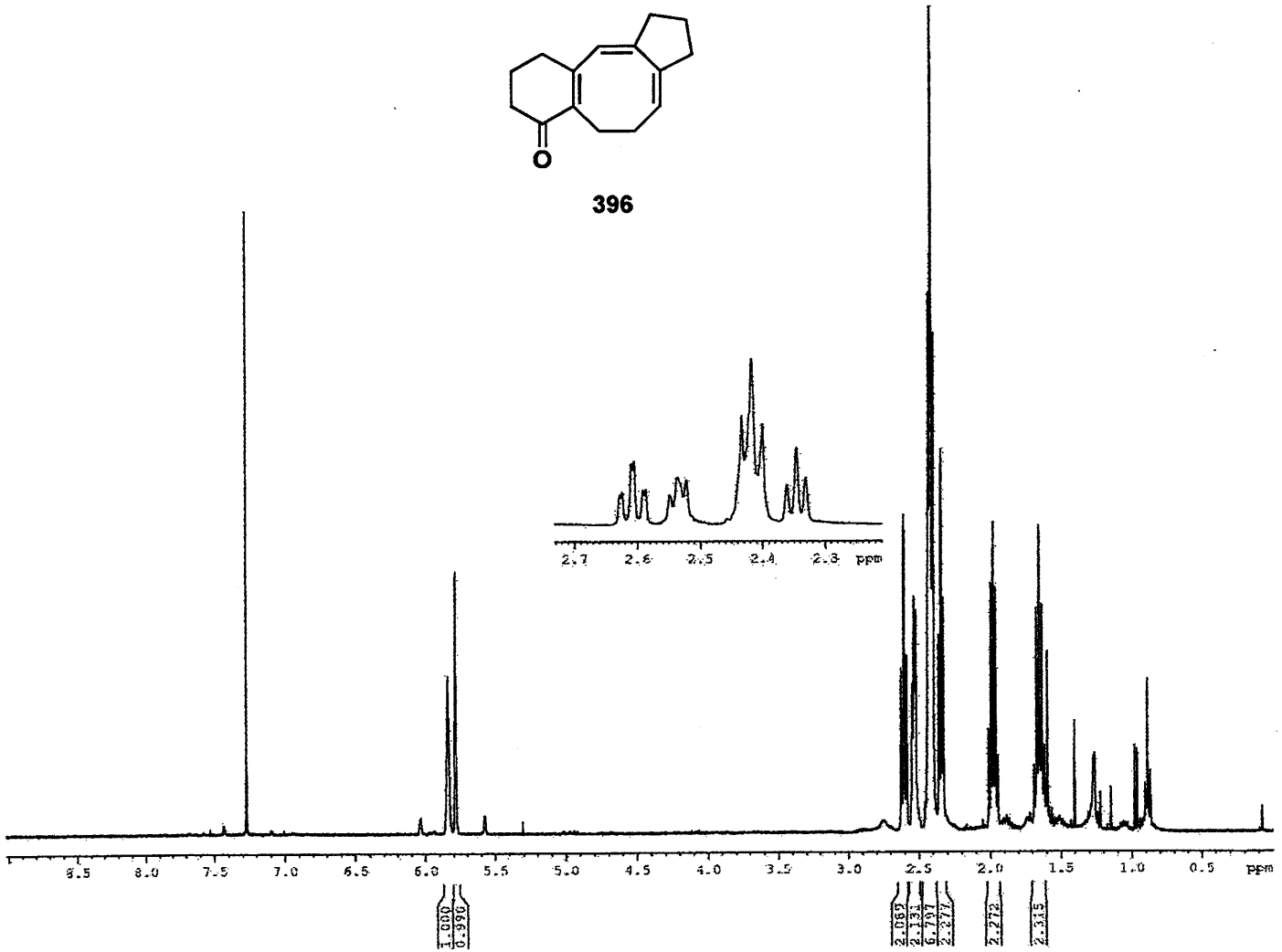


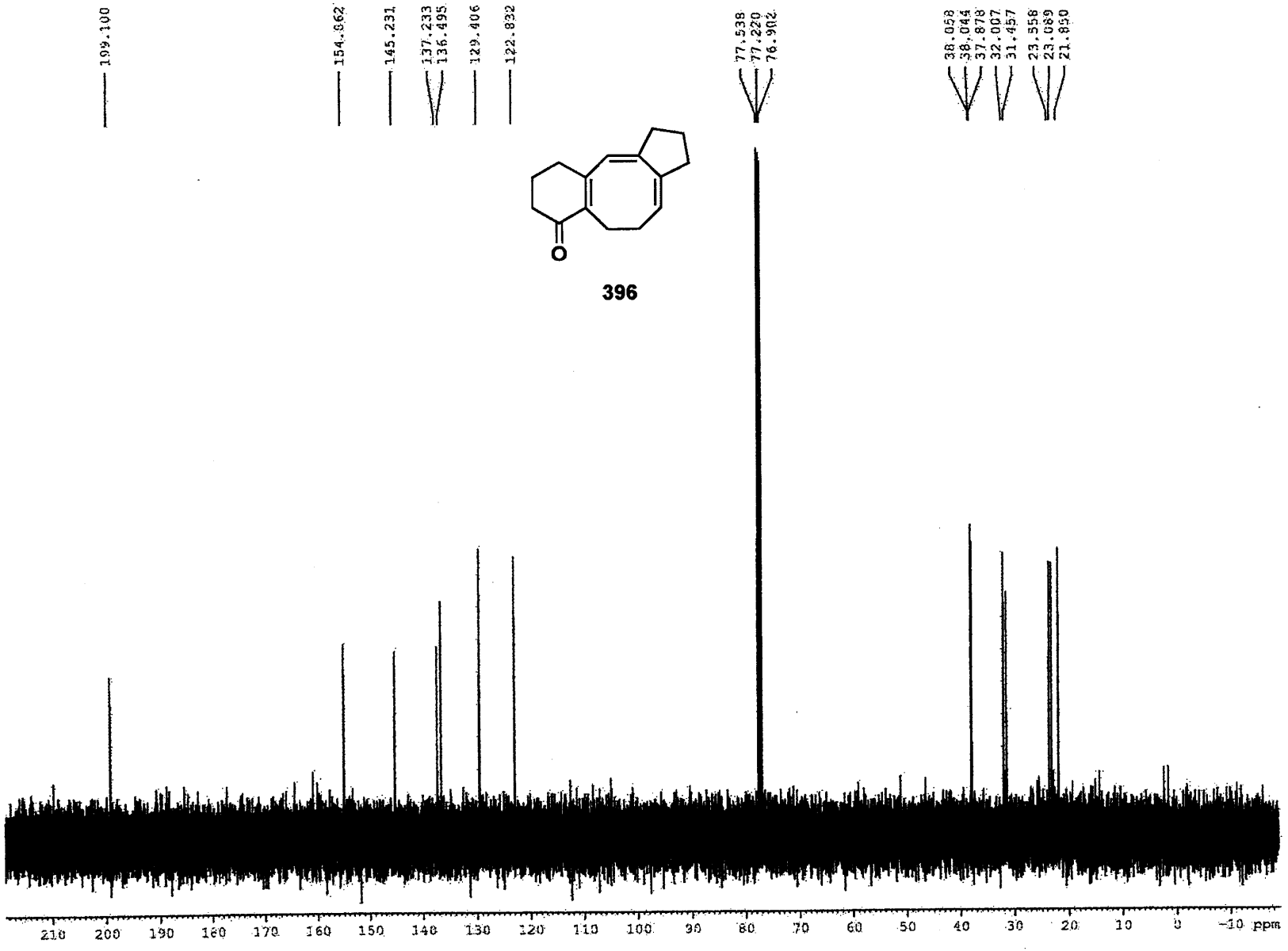
315 395 396

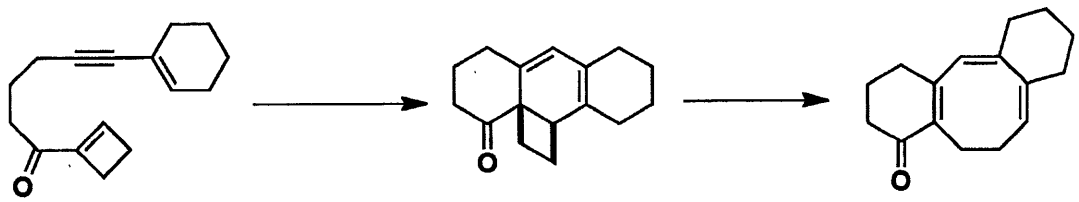
(3a*Z*,11*Z*)-2,3,5,6,9,10-Hexahydro-1*H*-benzo[*a*]cyclopenta[*d*][8]annulen-7(8*H*)-one (396). A 250-mL, three-necked, round-bottomed flask equipped with an argon inlet adapter, two rubber septa, and a thermocouple probe was charged with enone **315** (0.095 g, 0.44 mmol, 1.0 equiv) and 44 mL of CH_2Cl_2. The reaction mixture was cooled to -78 °C and methanesulfonic acid solution (0.24 M in CH_2Cl_2, 1.82 mL, 0.44 mmol, 1.0 equiv) was added dropwise over 1 min. The pale yellow reaction mixture was stirred at -78 °C for 1 h, and then additional methanesulfonic acid solution (0.24 M in CH_2Cl_2, 0.90 mL, 0.22 mmol, 0.5 equiv) was added. After 30 min at -78 °C, the reaction mixture was warmed to -60 °C, stirred for 1 h, and then additional methanesulfonic acid solution (0.24 M in CH_2Cl_2, 0.90 mL, 0.22 mmol, 0.5 equiv) was added. The green reaction mixture was stirred at -60 °C for 3 h, and then 10 mL of satd aq $NaHCO_3$ solution was added. The reaction mixture was warmed to 0 °C over 10 min. The blue organic phase[205] was separated, dried over Na_2SO_4, and then filtered into a threaded Pyrex tube (35 mm O.D.; 28 mm I.D.; 15-cm long) equipped with a stir bar, rubber septum, and an argon inlet needle. The reaction mixture was degassed with argon for 5 min and then the tube was sealed with a threaded Teflon cap. The reaction mixture was heated at 70 °C for 3 h, and then cooled to rt and concentrated to give 0.124 g of green oil. Purification by column chromatography on 16 g of silica gel (elution with 3-8% EtOAc-hexanes) afforded 0.038 g (40%) of cyclooctatriene **396** as an orange oil: IR (neat) 2929, 1659, 1601, 1433, 1370, 1327, 1299, 1175, 1127, 920, 815, and 732 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.81-5.89 (m, 1 H), 5.76-5.80 (m, 1 H), 2.61 (td, J = 7.5, 1.6 Hz, 2 H), 2.51-2.57 (m, 2 H), 2.39-2.46 (m, 6 H), 2.34 (t, J = 6.0 Hz, 2 H), 1.90 (pent, J = 6.3 Hz, 2 H), 1.65 (pent, J = 7.4 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.1, 154.9, 145.2, 137.2, 136.5, 129.4, 122.8, 38.05, 38.04, 37.9, 32.0, 31.4, 23.6, 23.1, 21.9; HRMS-DART *(m/z)* calcd for $C_{15}H_{18}O$ $[M + H]^+$: 215.1430, found: 215.1423.

---

[205] This organic phase is presumed to contain diene **395**. In a separate run, the organic phase was concentrated to afford 0.009 g of yellow oil that was shown to be a mixture of enyne **315** and diene **395**. The diene is characterized by the ^1H NMR resonances at 5.62 ppm (s, 1 H) corresponding to the alkenyl proton and 3.75-3.83 (m, 1 H) corresponding to the allylic methine proton.


O
396
2.7
2.6
2.5
2.4
2.3
ppm
9.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
1.000
0.996
2.065
2.133
6.797
2.377
2.272
2.315


199.100
154.862
145.231
137.233
136.495
129.406
122.832
77.538
77.220
76.902
38.058
38.044
37.878
32.007
31.457
23.556
23.089
21.850
O
396
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 ppm

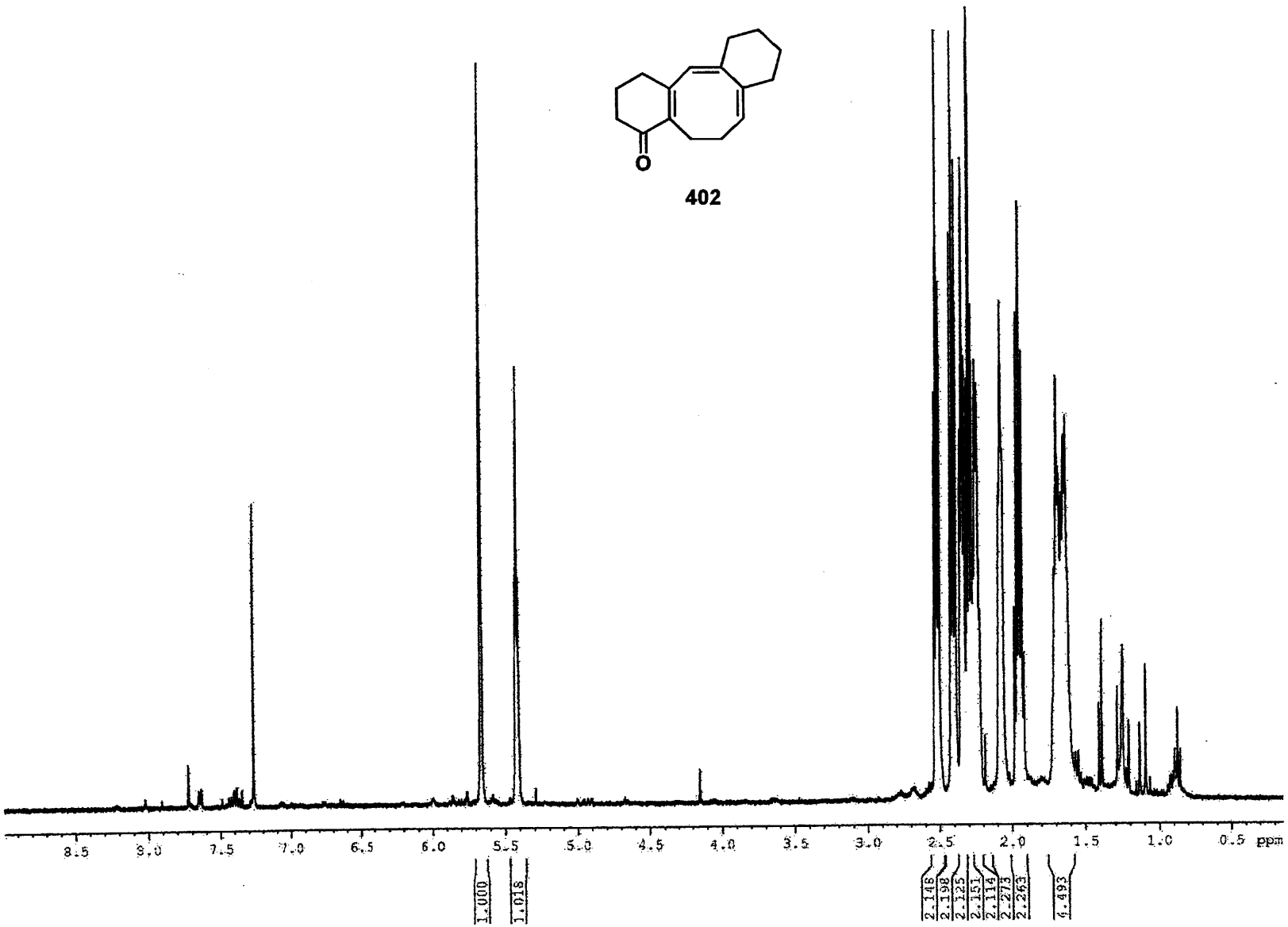


316 401 402

(7*Z*,11a*Z*)-2,3,5,6,8,9,10,11-Octahydrodibenzo[*a*,*d*][8]annulen-4(1*H*)-one (402). A 250-mL, three-necked, round-bottomed flask equipped with an argon inlet adapter, two rubber septa, and a thermocouple probe was charged with enone **316** (0.017 g, 0.469 mmol, 1.00 equiv) and 47 mL of CH_2Cl_2. The reaction mixture was cooled to -78 °C and methanesulfonic acid solution (0.24 M in CH_2Cl_2, 2.02 mL, 0.489 mmol, 1.04 equiv) was added dropwise over 2 min. The reaction mixture was stirred at -78 °C for 3 h, and then 10 mL of satd aq $NaHCO_3$ solution was added dropwise over 5 min. The reaction mixture was warmed to 0°C over 10 min, and then diluted with 10 mL of brine. The organic phase[206] was separated and dried over Na_2SO_4 and then filtered into a threaded Pyrex tube (35 mm O.D.; 28 mm I.D.; 15-cm long) equipped with a stir bar, rubber septum, and an argon inlet needle. The reaction mixture was degassed with argon for 5 min and then the tube was sealed with a threaded Teflon cap. The reaction mixture was heated at 70 °C for 14 h, and then cooled to rt and concentrated to give 0.112 g of brown oil. Purification by column chromatography on 17 g of silica gel (elution with 5% EtOAc-hexanes) provided 0.028 g (26%) of cyclooctatriene **402** as an orange oil: IR (neat) 2248, 1663, 1436, 1372, 1300, 1240, 1177, 1127, 1100, 1025, 956, 917, 854, 821, and 733 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.66 (s, 1 H), 5.42 (t, J = 4.3 Hz, 1 H), 2.41 (t, J = 6.7 Hz, 2 H), 2.52 (t, J = 6.4 Hz, 2 H), 2.34 (t, J = 5.9 Hz, 2 H), 2.29 (t, J = 6.0 Hz, 2 H), 2.03-2.11 (m, 2 H), 1.95 (pent, J = 6.4 Hz, 2 H), 1.60-1.74 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.2, 155.6, 145.0, 137.0, 136.2, 124.0, 122.5, 41.6, 38.7, 38.2, 30.4, 28.9, 28.5, 28.2, 23.8, 23.0; HRMS-DART *(m/z)* calcd for $C_{16}H_{20}O$ $[M + H]^+$: 229.1592, found: 229.1590.

---

[206] The organic phase is presumed to contain diene **401**. In a separate run, the organic phase was concentrated to afford 0.012 g of brown oil that was shown to be a mixture of diene **401** and other compounds. This diene is characterized by the ^1H NMR resonances at 5.58 ppm corresponding to the alkenyl proton and 3.55 ppm corresponding to the allylic methine proton.


O
402
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
1.000
1.016
2.148
2.198
2.125
2.151
2.114
2.273
2.263
4.493

199.246
155.629
144.991
136.989
136.200
123.969
122.511
77.524
77.211
76.894
41.642
38.745
38.161
30.370
28.911
28.460
28.254
23.781
23.002
O
402
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

Experimental Section for Part III

Equipment. All amide synthesis reactions using carbon dioxide (CO_2) were performed in the 25-mL (nominal) Thar stainless steel view cell reactor (model 05422-2) shown in Figure 1. A schematic flow diagram of the experimental apparatus is shown in Figure 2. With fittings, the actual vessel volume was 31.8 ± 0.3 mL. The reactor allowed visual access via two 1-in. coaxial sapphire window assemblies. Cell pressure was monitored by a Swagelok pressure gauge (model PGI-63C-PG6000-LAQX, 1 to 415 bar span, accurate to ± 6 bar) and a Newark pressure transducer (model MSP-300-05K-P-4-N-1, 1 to 346 bar range, accurate to ± 3.5 bar) interfaced with a Measurement Computing data acquisition (DAQ) module and a local computer. Cell temperature was measured by an Omega J-type dual-element thermocouple (model SIC316SS-125U-6-DUAL, accurate to ± 0.1 OC) connected to both a local Omega controller (model CN9121A) and the DAQ system. Temperature set-points were achieved within ± 0.5 °C by interfacing the controller with a Powerstat variable autotransformer (model 3PN116B) and Omega insulated heating tape (model STHO51-080) wrapped tightly around the exterior cell wall. Inlet and outlet valves were needle-type and obtained from High Pressure Equipment (model 15-21AMINMA). Agitation was provided by a Teflon-coated magnetic stir bar driven externally by a Corning stir plate (model PC-410).

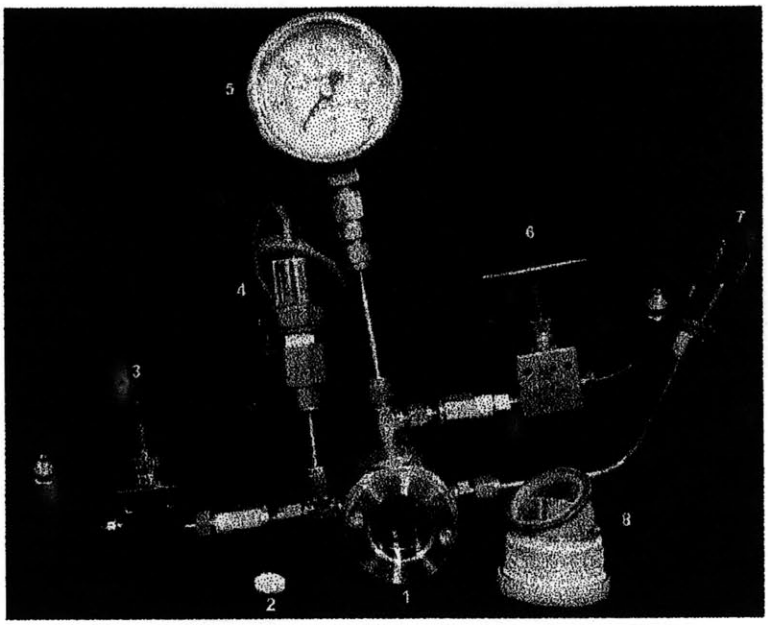


Figure 1. Photograph of the stainless steel view cell reactor: (1) view cell with the front window assembly installed; (2) magnetic stir bar; (3) inlet valve; (4) pressure transducer; (5) pressure gauge; (6) outlet valve; (7) thermocouple; (8) back window assembly (from top to bottom: fluoropolymer-encapsulated viton o-ring, sapphire window, cap).

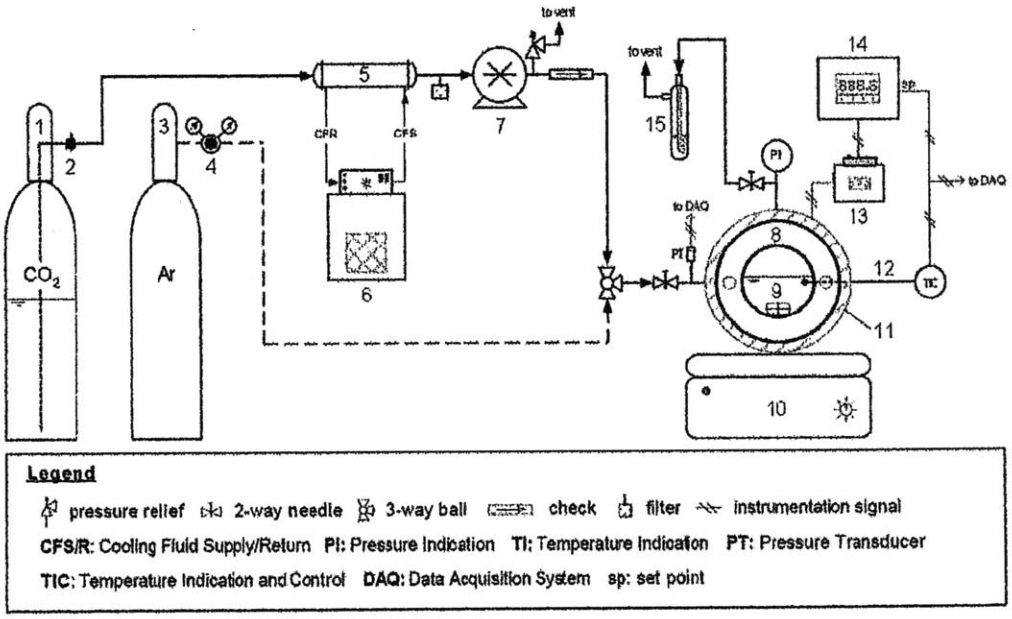
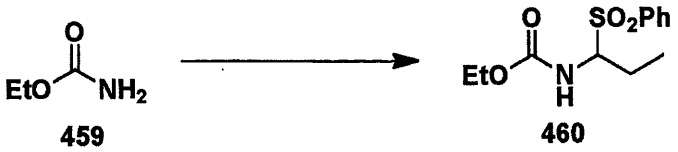


Figure 2. Simplified schematic flow diagram of the experimental apparatus (not to scale): (1) liquid carbon dioxide supply cylinder; (2) liquid regulator; (3) gaseous argon supply cylinder; (4) gas regulator; (5) shell-and-tube heat exchanger; (6) refrigerated circulating bath; (7) metering pump; (8) view cell (9) magnetic stir bar; (10) stir plate; (11) insulated heating tape; (12) thermocouple; (13) variable autotransformer; (14) temperature controller; (15) sparge chamber.

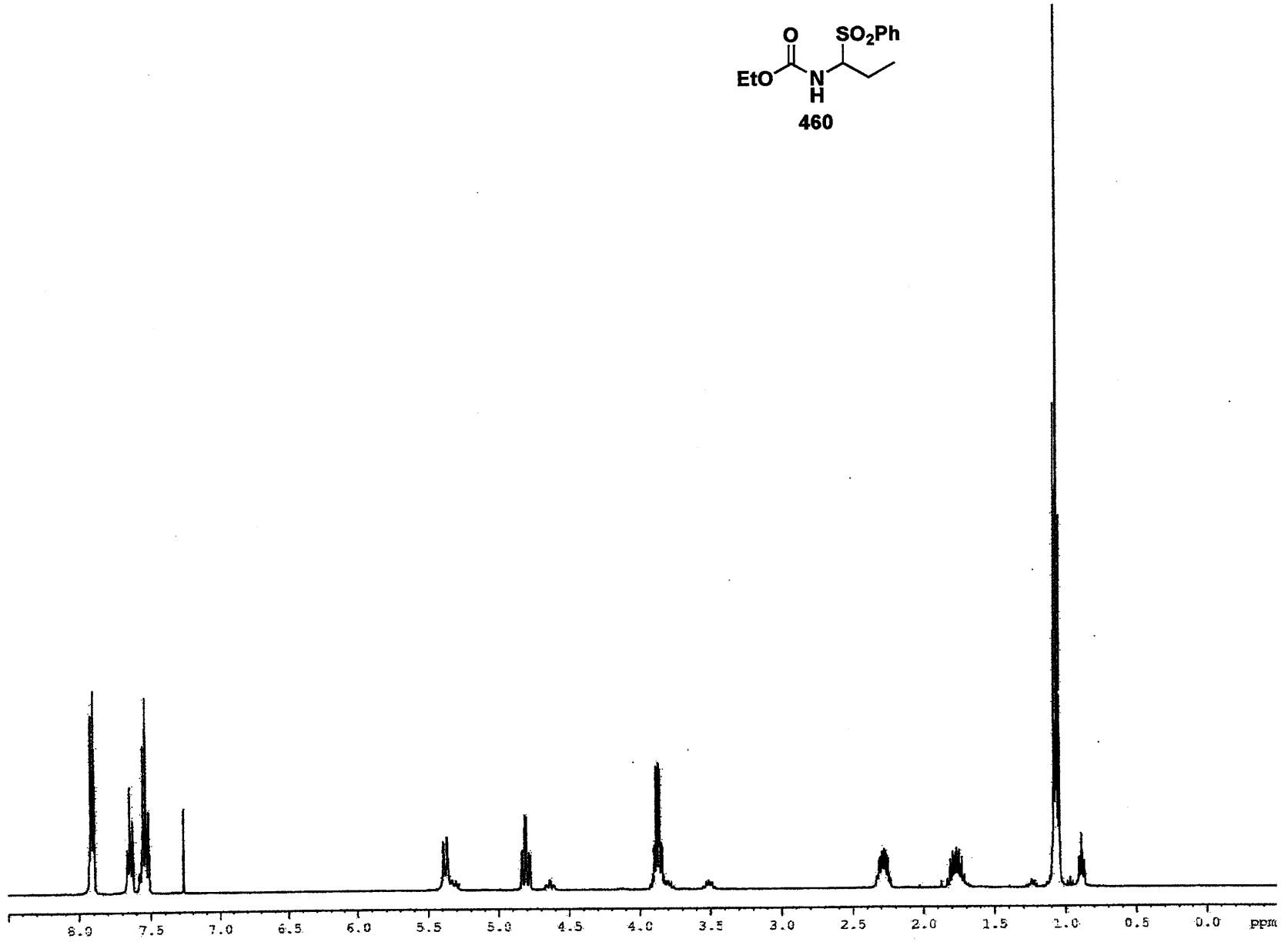
General Procedures. All reactions other than those conducted in $scCO_2$ were performed in flame-dried or oven-dried glassware under a positive pressure of argon. Reaction mixtures were stirred magnetically unless otherwise indicated. Air- and moisture-sensitive liquids and solutions were transferred by syringe or cannula and introduced into reaction vessels through rubber septa. Reaction product solutions and chromatography fractions were concentrated by rotary evaporation at ca. 20 mmHg. Column chromatography was performed on EM Science silica gel 60 or Silicycle silica gel 60 (230-400 mesh).

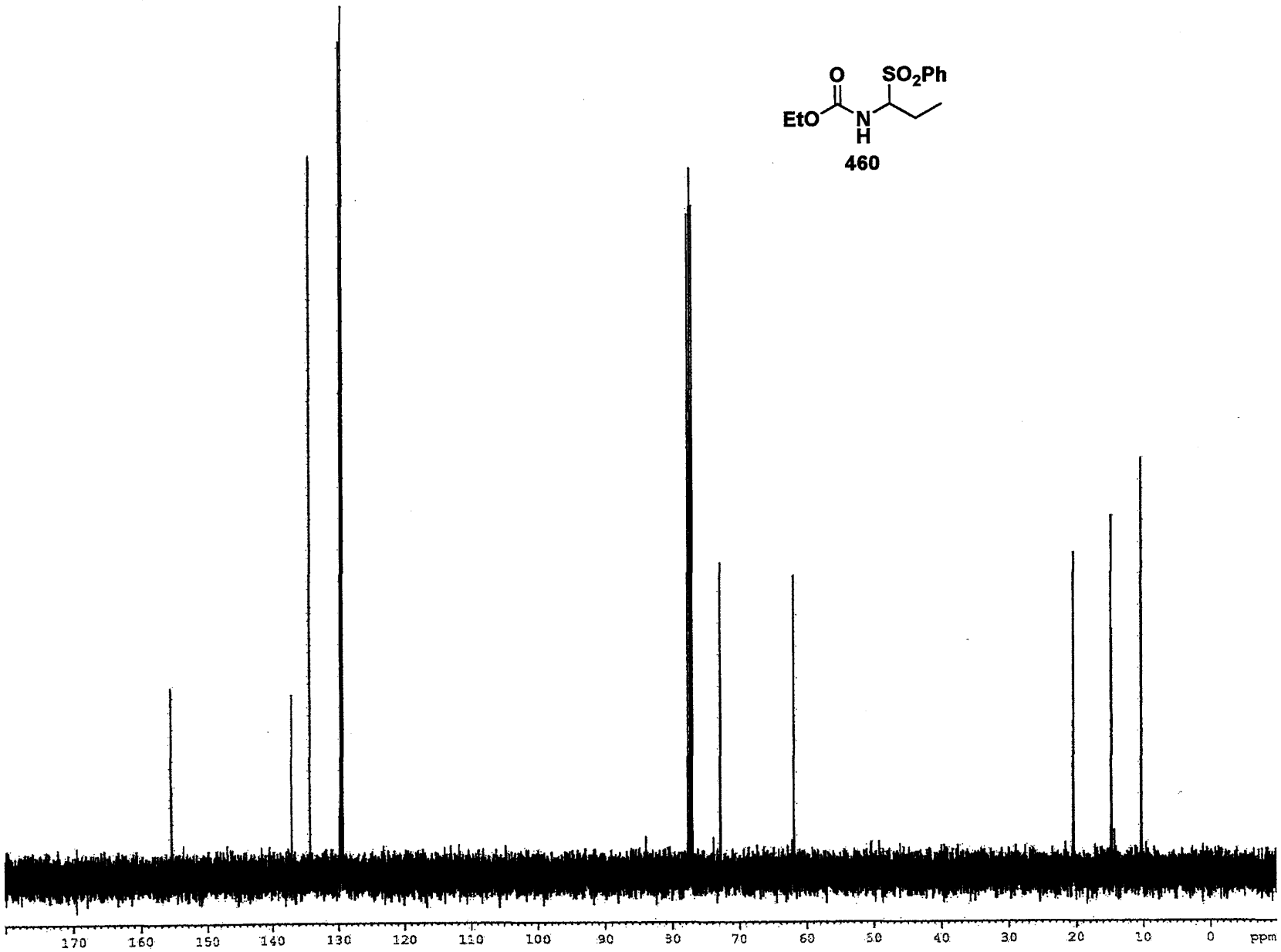
Materials. Commercial grade reagents and solvents were used without further purification except as indicated below. Dichloromethane, diethyl ether, and tetrahydrofuran were purified by pressure filtration through activated alumnia. Toluene was purified by pressure filtration through activated alumina and Cu(II) oxide. Ethoxyacetylene (-50% w/wt in hexanes, Alfa Aesar) and propionaldehyde were distilled at atmospheric pressure under argon. Piperidine and cyclohexylamine were distilled under argon from calcium hydride prior to use.

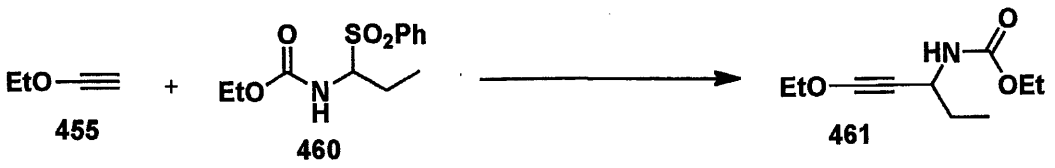
Instrumentation. Melting points were determined with a Fisher-Johns melting point apparatus and are uncorrected. Infrared spectra were obtained using a Perkin Elmer 2000 FT-IR spectrophotometer. ^1H NMR spectra were recorded on Bruker Avance-400 (400 MHz) spectrometers. ^1H NMR chemical shifts are expressed in parts per million (δ) downfield from tetramethylsilane (with the $CHCl_3$ peak at 7.27 ppm used as a standard). ^{13}C NMR spectra were recorded on Bruker Avance-400 (400 MHz) spectrometers. ^{13}C NMR chemical shifts are expressed in parts per million (δ) downfield from tetramethylsilane (with the central peak of $CHCl_3$ at 77.23 ppm used as a standard). High resolution mass spectra (HRMS) were measured on a Bruker Daltonics APEXII 3 tesla Fourier transform mass spectrometer.



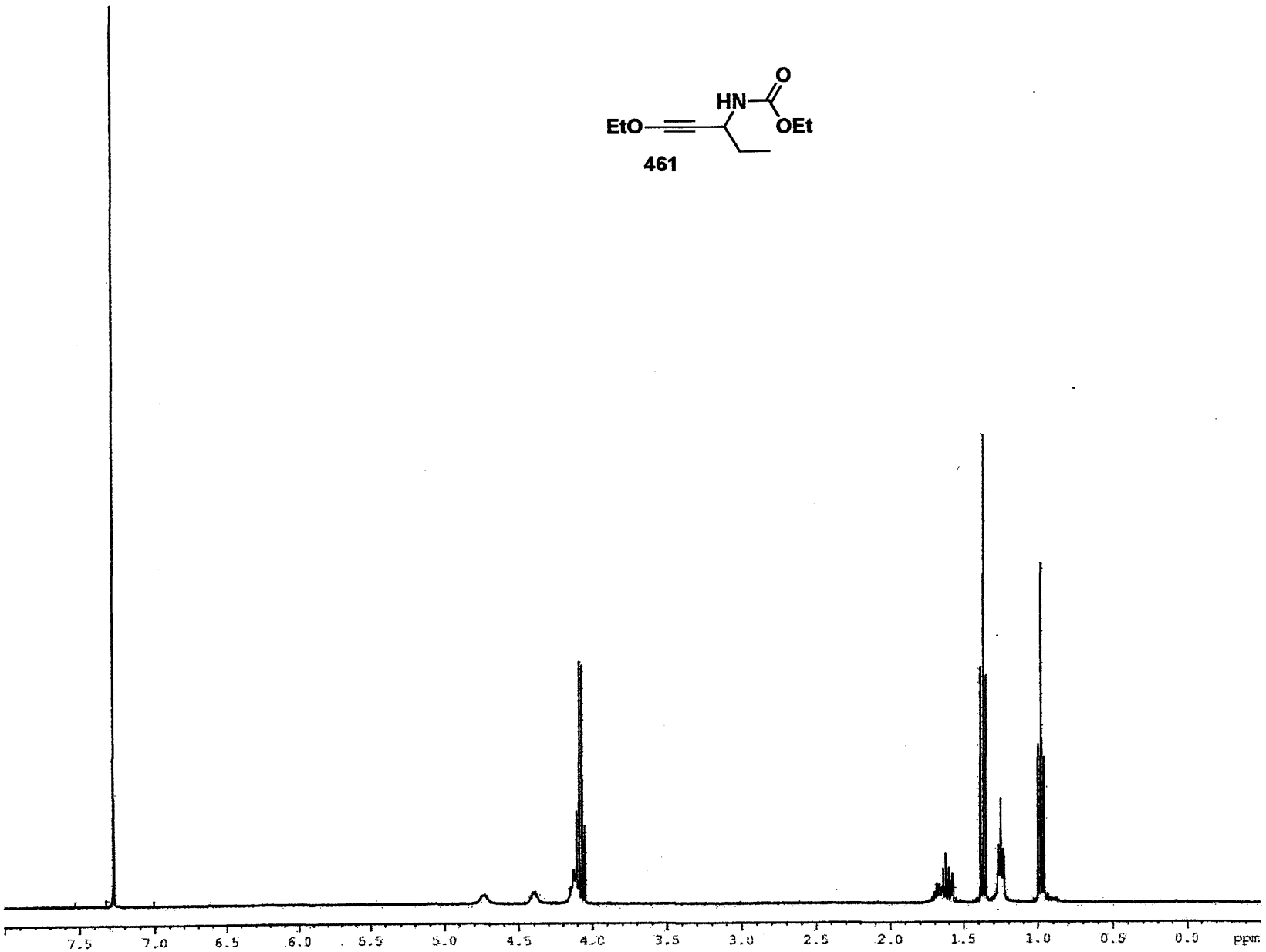
Ethyl 1-(phenylsulfonyl)propylcarbamate (460). A 100-mL, three-necked, round-bottomed flask equipped with a rubber septum, argon inlet adapter, and glass stopper was charged with ethyl carbamate **459** (1.777 g, 19.95 mmol, 1.0 equiv), THF (8 mL), H_2O (20 mL), and sodium benzenesulfonate (3.276 g, 19.95 mmol, 1.0 equiv). Propionaldehyde (1.58 mL, 1.27 g, 21.9 mmol, 1.1 equiv) was added, followed by formic acid (4.8 mL, 5.9 g, 130 mmol, 6.4 equiv), each in one portion via syringe. After 1 h the solution became cloudy and remained cloudy for the remainder of the reaction. After 18 h the reaction mixture was extracted with two 150-mL portions of CH_2Cl_2 and the combined organic layers were washed with 100 mL of brine, dried over $MgSO_4$, filtered, and concentrated onto 2.5 g of silica gel. The free-flowing powder was placed at the top of a column of 150 g of silica gel and eluted with 0-50% EtOAc-hexanes to provide 3.492 g (65%) of the sulfone **460** as a white solid: mp 77-78 °C; IR (neat) 3324, 1728, 1307, and 1144 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, J = 7.2 Hz, 2 H), 7.64 (t, J = 7.4 Hz, 2 H), 7.54 (t, J = 7.7 Hz, 2 H), 5.38 (d, J = 10.8 Hz, 1 H), 5.31 (d, J = 10.2 Hz, minor rotamer), 4.81 (td, J = 10.8, 3.5 Hz, 1 H), 4.64 (td, J = 18.8, 3.1 Hz, minor rotamer), 3.86 (qd, J = 7.1, 2.2 Hz, 2 H), 3.85 (m, minor rotamer), 3.51 (m, minor rotamer), 2.29 (qdd, J = 14.5, 10.9, 7.2 Hz, 1 H), 1.77 (qdd, J = 14.2, 7.5, 3.5 Hz, 1 H), 1.07 (t, J = 7.2 Hz, 6 H), 0.89 (t, J = 1.0 Hz, minor rotamer); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.5, 137.1, 134.3, 129.6, 129.4, 72.8, 62.0, 20.4, 14.7, 10.2; HRMS-ESI *(m/z)* $[M + Na]^+$ calcd for $C_{12}H_{17}NO_4S$: 294.0776, found: 294.0767.

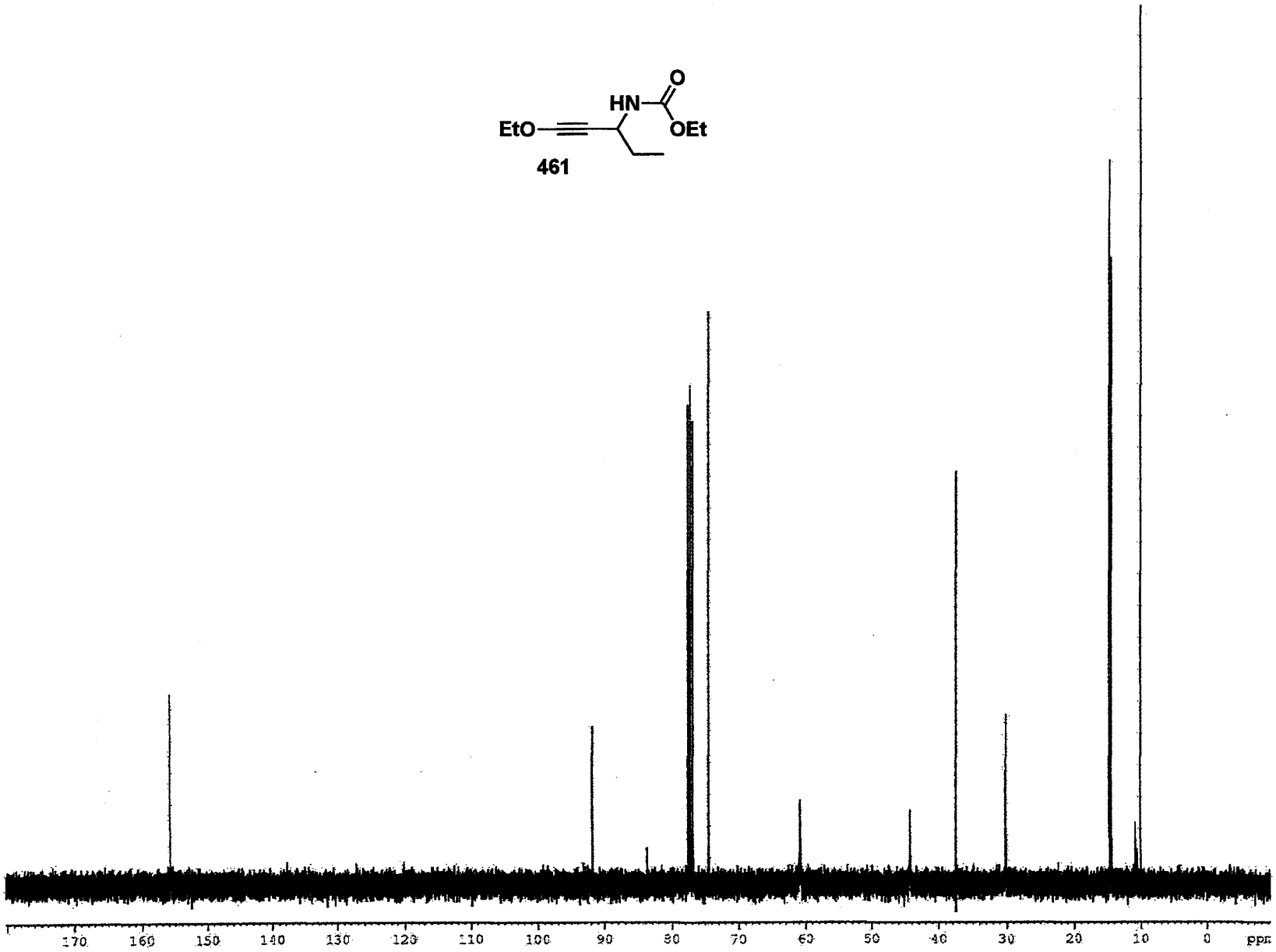

O
SO2Ph
EtO
N
H
460
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm

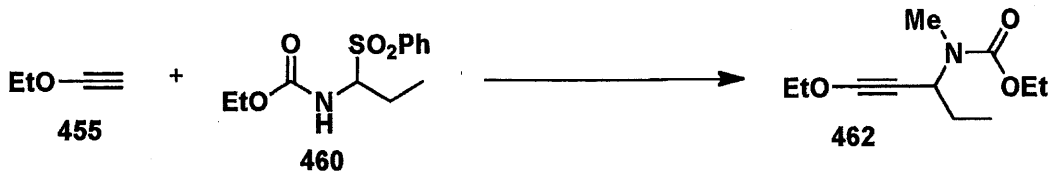

O
SO2Ph
EtO
N
H
460
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm



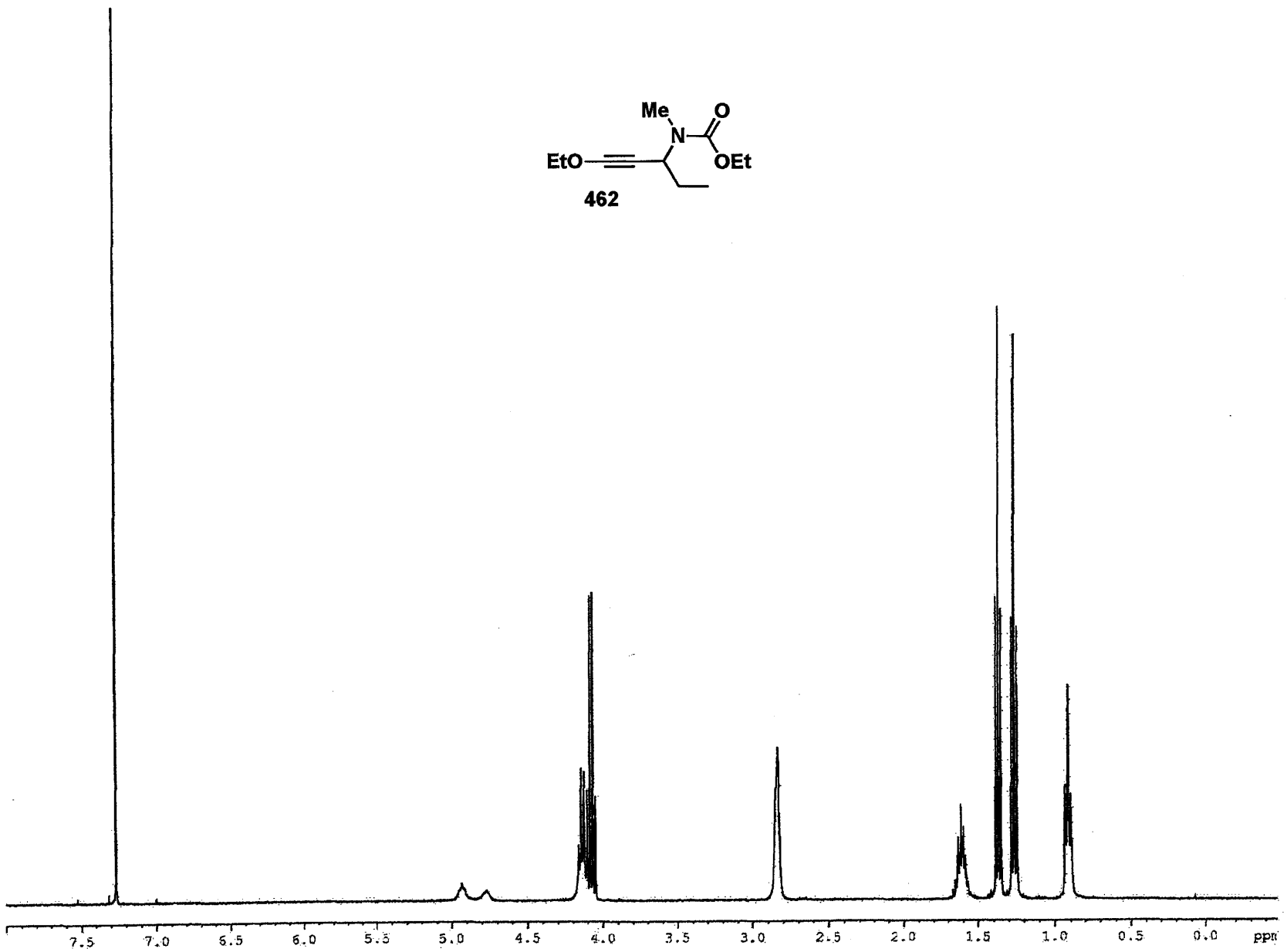
1-Ethoxypent-1-yn-3-ylethyl carbamate (461). A 250-mL, one-necked, round-bottomed flask equipped with a rubber septum and argon inlet needle was charged with ethoxyacetylene **455** solution (6.09 M in hexanes, 3.90 mL, 1.67 g, 23.6 mmol, 2.1 equiv) and 88 mL of THF and then cooled to -30 °C. *n*-BuLi solution (2.57 M in hexanes, 9.70 mL, 1.60 g, 24.9 mmol, 2.2 equiv) was added dropwise via syringe over 7 min to give a yellow solution. After 30 min, the reaction mixture was cooled to -78 °C and a solution of ethyl 1-(phenylsulfonyl)propylcarbamate **460** (3.063 g, 11.29 mmol, 1.0 equiv) in 18 mL of THF was added dropwise via cannula over 10 min (10-mL THF rinse). The resulting mixture was stirred at -78 °C for 1 h and then 22 mL of satd aq NH_4Cl solution was rapidly added. The resulting mixture was allowed to warm to rt, diluted with 120 mL of H_2O, and extracted with 250 mL of CH_2Cl_2. The organic layer was washed with 200 mL of brine, dried over Na_2SO_4, filtered, and concentrated to give 2.133 g of a yellow oil. Column chromatography on 128 g of basic alumina (gradient elution with 0-15% EtOAc-hexanes) provided 1.064 g of a pale yellow oil, which was further purified on a second column of 42 g of basic alumina (gradient elution with 5-8% EtOAc-hexanes) to provide 0.677 g (30%) of **461** as a pale yellow oil: IR (neat) 3327, 2269, 1696, 1524, 1296, and 1235 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.73 (br s, 1 H), 4.35-4.45 (m, 1 H), 4.11 (q, J = 7.0 Hz, 2 H), 4.08 (q, J = 7.1 Hz, 2 H), 1.57-1.71 (m, 2 H), 1.36 (t, J = 7.1 Hz, 3 H), 1.25 (t, J = 7.1 Hz, 3 H), 0.98 (t, J = 7.4 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.8, 91.8, 74.5, 60.9, 44.3, 37.5, 30.2, 14.7, 14.4, 10.1; HRMS-ESI *(m/z)* $[M + H]^+$ calcd for $C_{10}H_{18}NO_3$: 200.1287, found: 200.1277.

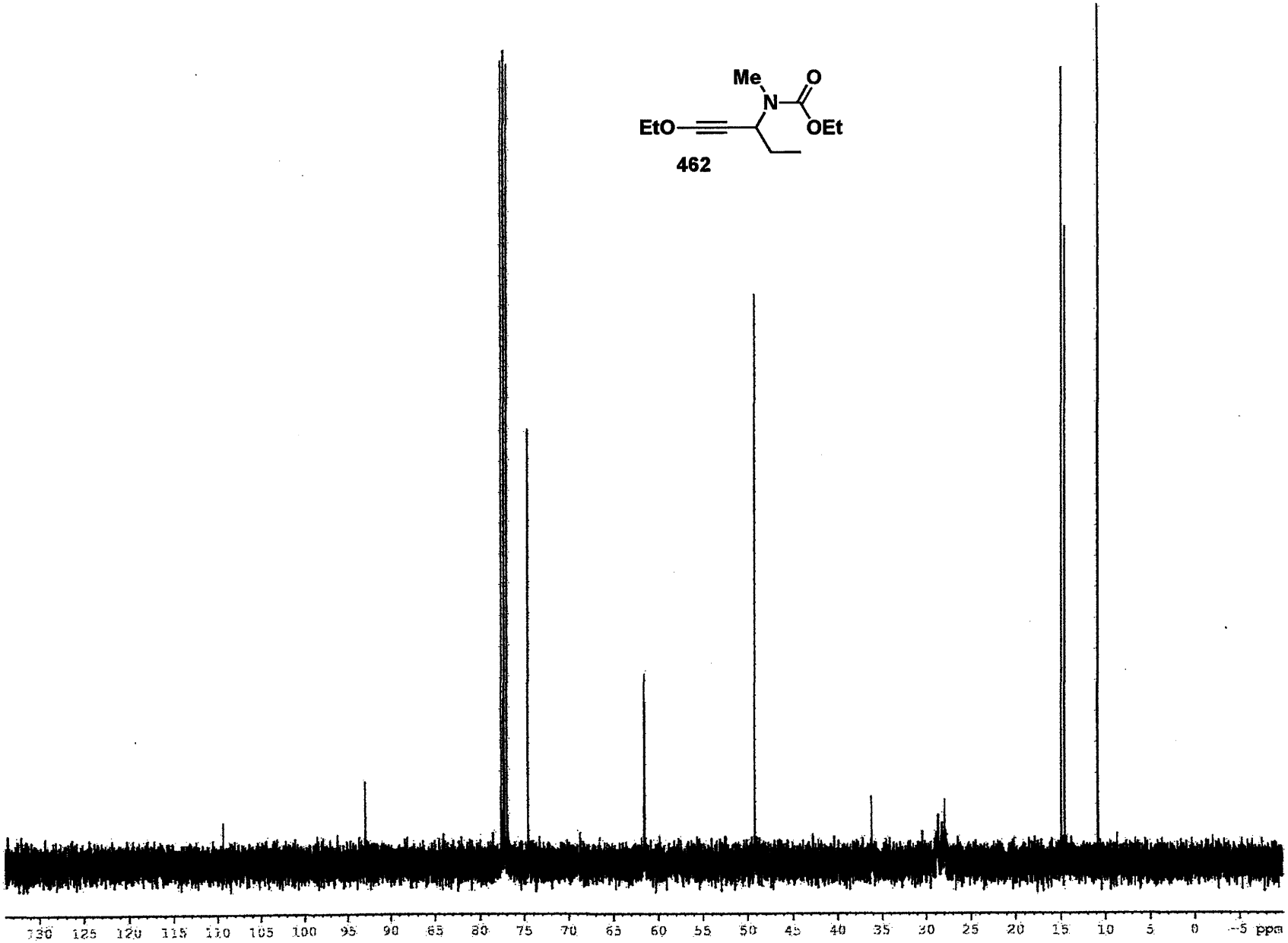

EtO
HN
O
OEt
461
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm

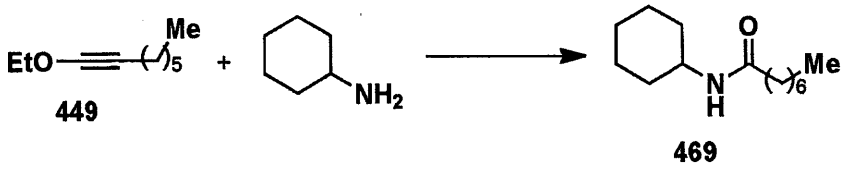

HN
O
EtO
OEt
461
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm



1-Ethoxypent-1-yn-3-yl-*N*-methylethyl carbamate (462). A 250-mL, one-necked, round-bottomed flask equipped with a rubber septum and argon inlet needle was charged with ethoxyacetylene **455** solution (6.77 M in hexanes, 2.81 mL, 1.33 g, 19.0 mmol, 2.1 equiv) and 70 mL of THF, and then cooled at -30 °C while *n*-BuLi solution (2.57 M in hexanes, 7.74 mL, 1.27 g, 19.9 mmol, 2.2 equiv) was added dropwise via syringe over 5 min to give a yellow solution. After 30 min, the reaction mixture was cooled to -78 °C and a solution of ethyl 1-(phenylsulfonyl)propylcarbamate **460** (2.455 g, 9.05 mmol, 1.0 equiv) in 17 mL of THF was added dropwise via cannula over 5 min (5.6-mL THF rinse). After 1 h, MeI (2.82 mL, 6.43 g, 45.3 mmol, 5 equiv) was added in one portion via syringe. The reaction mixture was allowed to warm to 0 °C, stirred for 30 min, and then treated with 18 mL of satd aq NH_4Cl solution. The resulting mixture was allowed to warm to rt, diluted with 100 mL of H_2O, and then extracted with two 150-mL portions of CH_2Cl_2. The combined organic layers were washed with 100 mL of brine, dried over Na_2SO_4, filtered, and concentrated to give 1.917 g of a yellow oil. Column chromatography on 48 g of acetone-deactivated silica gel (elution with 0.5% Et_3N-hexanes) provided 0.802 g (42%) of **462** as a pale yellow oil and 0.458 g of impure material. The impure material was loaded onto a column of 15 g of basic alumina and eluted with 0-5% EtOAc-hexanes to provide 0.120 g (6%) of **462**; total yield 0.922 g (48%): IR (neat) 2267, 1698, 1302 and 1239 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.94 (m, 1 H), 4.87 (m, minor rotamer), 4.14 (q, J = 7.1 Hz, 2 H), 4.08 (q, J = 7.1 Hz, 2 H), 2.84 (br s, 3 H), 1.56-1.67 (m, 2 H), 1.37 (t, J = 7.1 Hz, 3 H), 1.26 (t, J = 7.1 Hz, 3 H), 0.91 (t, J = 7.3 Hz , 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 109.5, 93.1, 74.7, 61.6, 49.4, 36.3, 28.8, 28.0, 15.0, 14.6, 10.9; HRMS-ESI *(m/z)* $[M + Na]^+$ calcd for $C_{11}H_{19}NO_3$: 236.1263, found: 236.1255.


Me
N
O
EtO
OEt
462
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm

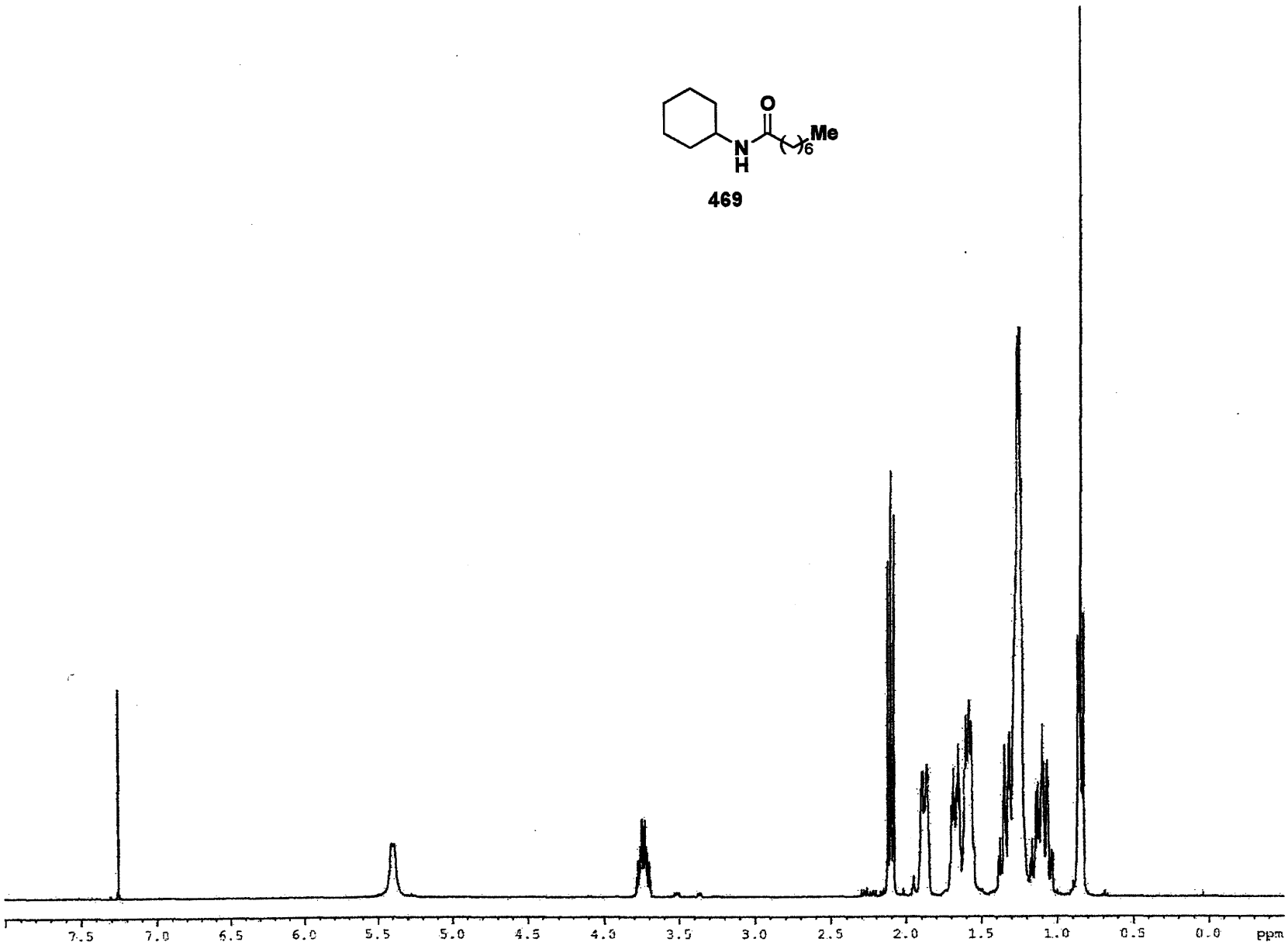

Me
O
N
EtO
OEt
462
130 125 120 115 110 105 100 95 90 85 80 75 70 65 60 55 50 45 40 35 30 25 20 15 10 5 0 -5 ppm



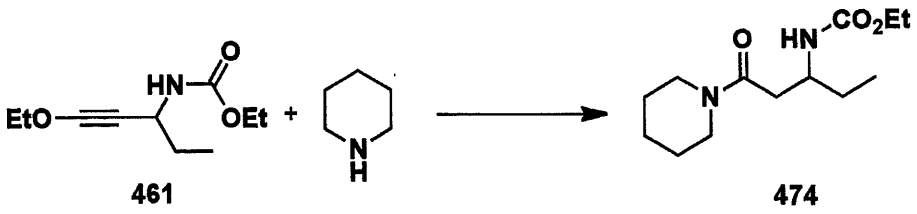
449 469

***N*-Cyclohexyloctanamide (469).** A 25-mL, stainless steel view cell reactor was charged with cyclohexylamine (0.39 mL, 0.34 g, 3.4 mmol) and ethoxy-1-octyne **449** (0.235 g, 3.40 mmol). The reactor was pressurized to 50 bar with CO_2, heated to 130 °C, and then pressurized with additional CO_2 to 230 bar. The reaction mixture was stirred at 130 °C (230 bar) for 24 h and then allowed to cool to rt. The reactor outlet valve was opened, and the CO_2 phase was vented through a bubbler containing 15 mL of CH_2Cl_2. The residual oil in the reactor was purified by column chromatography on 10 g of silica gel (elution with 10-20% EtOAc/hexanes) to provide 0.564 g (74%) of amide 15 as a white solid with spectral data consistent with that previously reported.[207]

[207] Lucking, U.; Tucci, F. C.; Rudkevich, D. M.; Rebek, J. *J. Am. Chem. Soc.* **2000**, *122*, 8880-8889.

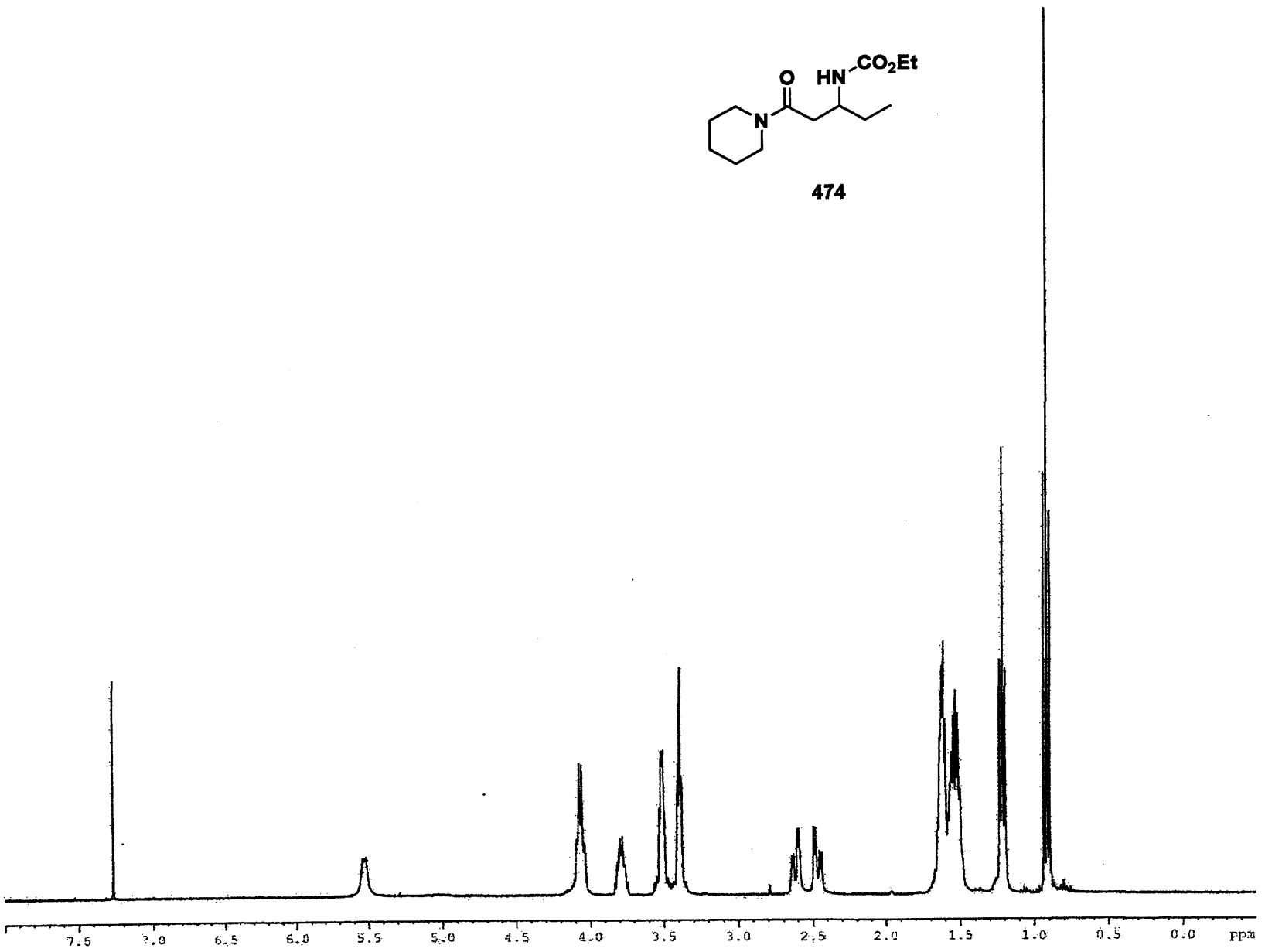


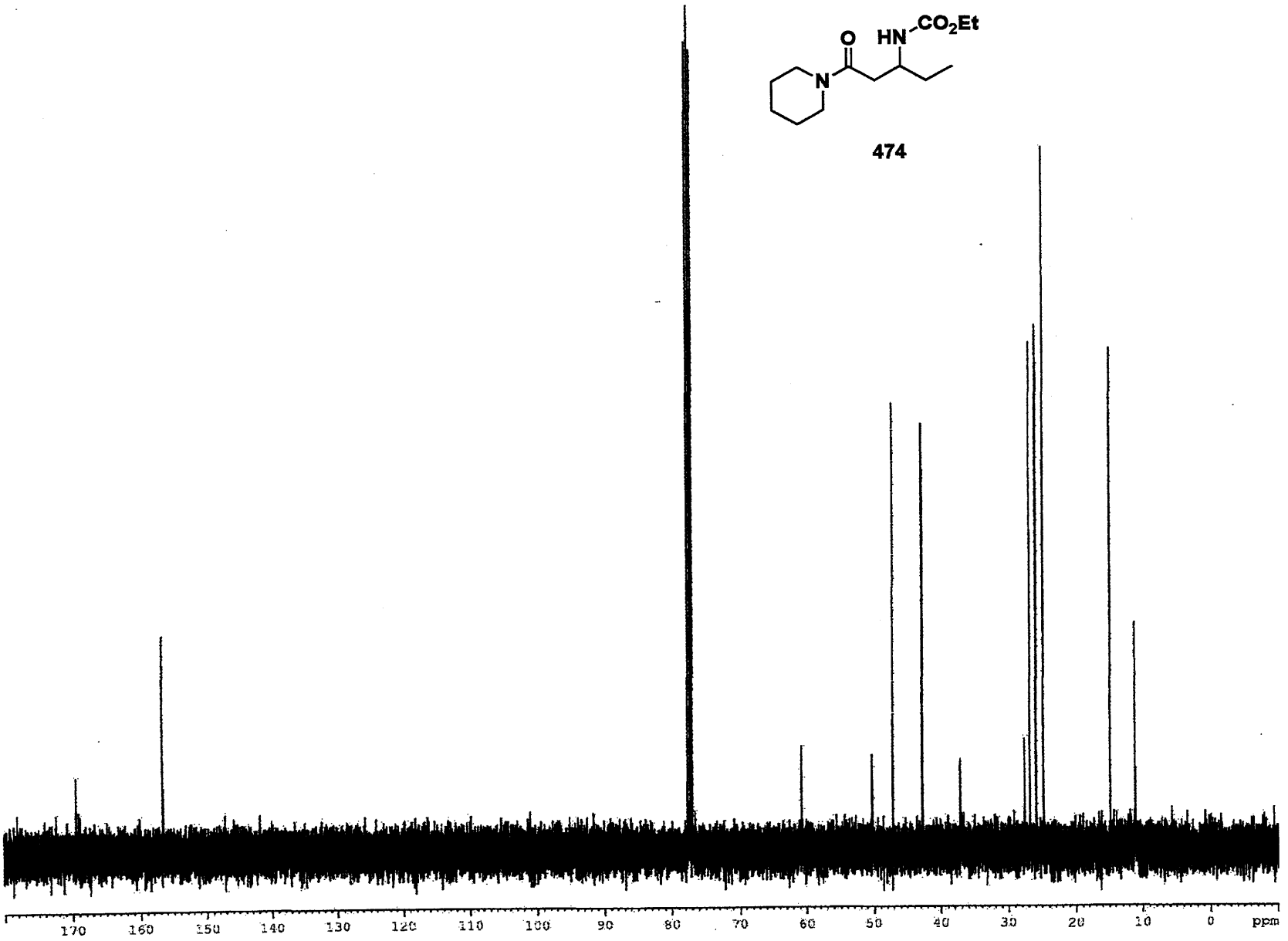
469

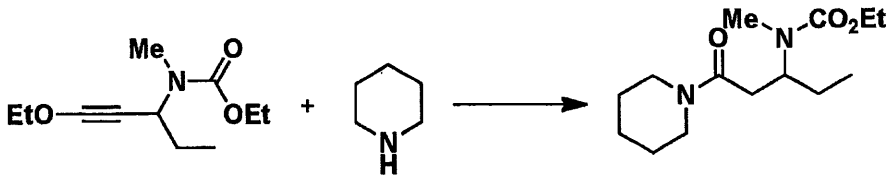


461 474

5-Oxo-5-(piperidin-1-yl)pentan-3-ylcarbamic Acid Ethyl Ester (474). A 25-mL, stainless steel view cell reactor was charged with piperidine (0.34 mL, 0.29 g, 3.4 mmol) and alkynyl ether **461** (0.677 g, 3.40 mmol, 1.0 equiv). The reactor was pressurized to 50 bar with CO_2, heated to 130 °C, and then pressurized with additional CO_2 to 242 bar. The reaction mixture was stirred at 130 °C (242 bar) for 24 h and then allowed to cool to rt. The reactor outlet valve was opened, and the CO_2 phase was vented through a bubbler containing 15 mL of CH_2Cl_2. The residual oil in the reactor was purified by column chromatography on 40 g of acetone-deactivated silica gel (gradient elution with 20-75% EtOAc/hexanes) provided 0.576 g (66%) of amide **474** as a yellow-orange oil: IR (neat) 3314, 1718, 1628, 1533, and 1240 cm^{-1}; ^{1}HNMR (400 MHz, $CDCl_3$) δ 5.53 (d, J = 7.9 Hz, 1 H), 4.06 (q, J = 6.9 Hz, 2 H), 3.74-3.83 (m, 1 H), 3.46-3.57 (m, 2 H), 3.39 (t, J = 4.7 Hz, 2 H), 2.62 (dd, J = 15.3, 4.9 Hz, 1 H), 2.47 (dd, J = 15.3, 5.7 Hz, 1 H), 1.48-1.69 (m, 8 H), 1.21 (t, J = 7.1 Hz, 3 H), 0.92 (t, J = 7.4 Hz, 3 H). ^{13}C NMR(100 MHz, $CDCl_3$) δ 168.9, 156.5, 60.6, 50.1, 42.6, 37.0, 26.6, 25.7, 24.6, 14.7, 11.0. HRMS-ESI (m/z): $[M + H]^+$ calcd for $C_{13}H_{25}N_2O3$: 257.1860, found: 257.1850.

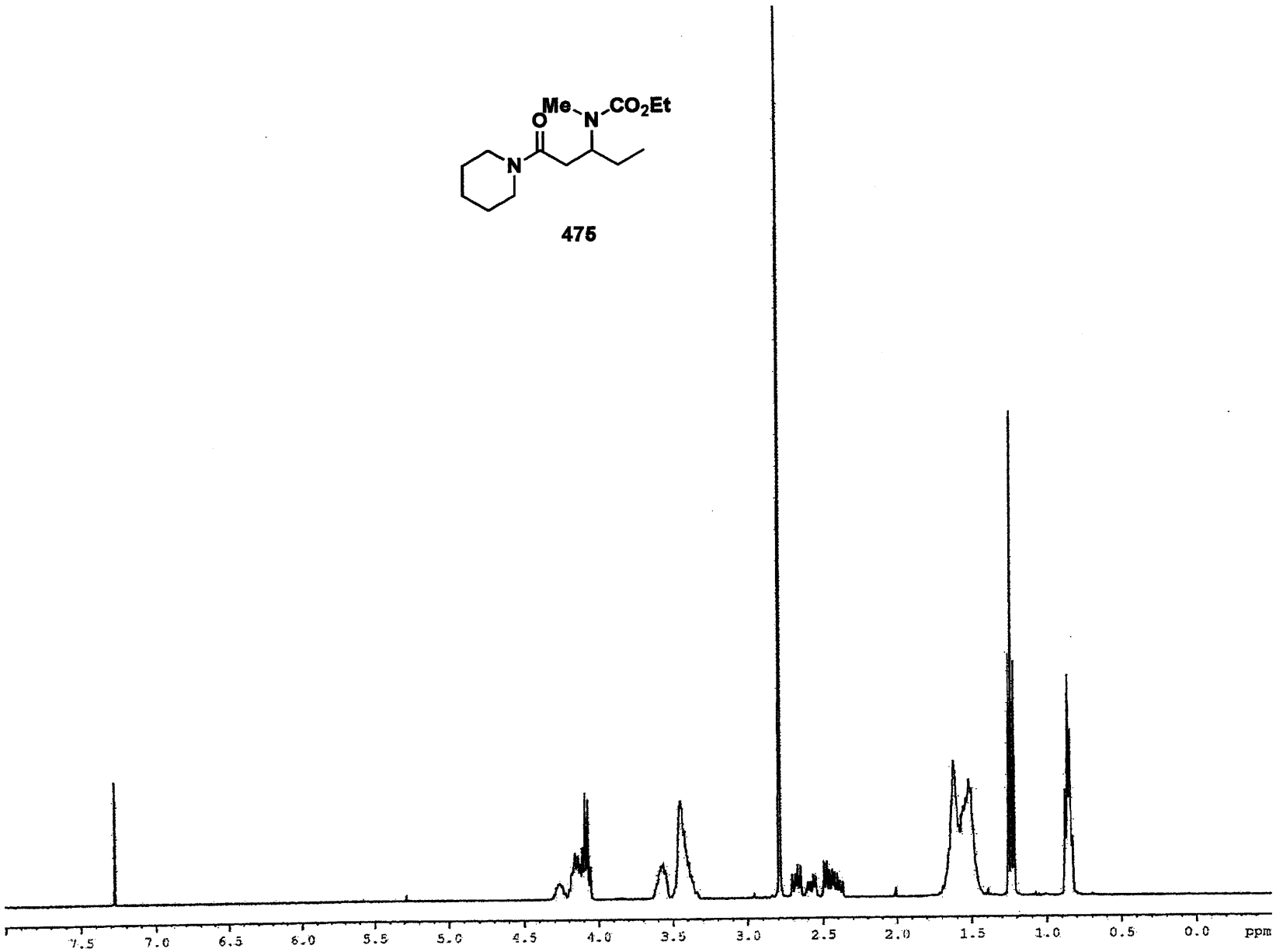

O
HN
CO2Et
N
474
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm


O
HN
CO2Et
N
474
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

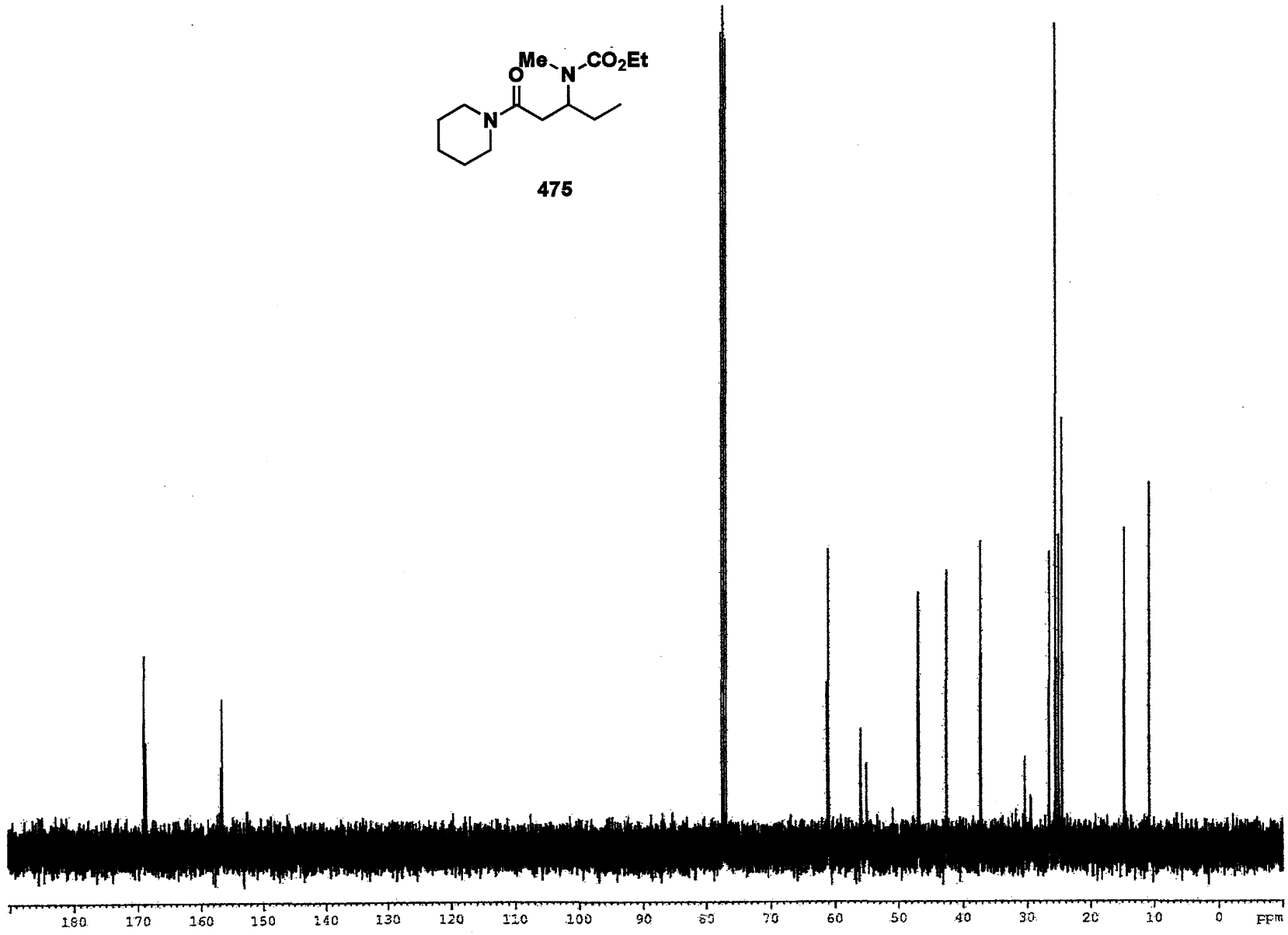


462 475

5-Oxo-5-(piperidin-1-yl)pentan-3-yl-N-methylcarbamic Acid Ethyl Ester (475). A 25-mL, stainless steel view cell reactor was charged with piperidine (0.34 mL, 0.29 g, 3.4 mmol) and alkynyl ether **462** (0.725 g, 3.40 mmol). The reactor was pressurized to 50 bar with CO_2, heated to 130 °C, and then pressurized with additional CO_2 to 222 bar. The reaction mixture was stirred at 130 °C (222 bar) for 24 h and then allowed to cool to rt. The reactor outlet valve was opened, and the CO_2 phase was vented through a bubbler containing 15 mL of CH_2Cl_2. The residual oil in the reactor was purified by column chromatography on 40 g of acetone-deactivated silica gel (gradient elution with 25-60% EtOAc/hexanes) provided 0.778 g (85%) of amide **475** as a yellow oil: IR (neat) 1695, 1640, and 1254 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.21-4.32 (m, 1 H), 4.16-4.20 (m, minor rotamer), 4.15 (q, J = 7.0 Hz, minor rotamer), 4.09 (q, J = 7.2 Hz, 2H), 3.35-3.62 (m, 4 H), 2.79 (s, 3H), 2.66 (dd, J = 14.1, 7.9 Hz, 1H), 2.57 (dd, J = 14.5, 6.5 Hz, minor rotamer), 2.46 (dd, J = 14.2, 7.0 Hz, 1H), 2.41 (dd, J = 14.5, 7.7 Hz, minor rotamer), 1.42-1.71 (m, 8 H), 1.23 (t, J = 7.1 Hz, 3 H), 0.87 (t, J = 7.3 Hz, 3 H), 0.85 (t, J = 7.2 Hz, minor rotamer); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.9, 156.6, 61.0, 56.0, 47.0, 42.6, 37.2, 26.6, 25.4, 24.5,14.6, 10.9; minor rotamer δ 168.7, 156.7, 61.2, 55.1, 46.9, 42.7, 37.3, 26.5, 25.0, 14.7, 10.8. HRMS-ESI (m/z): $[M + Na]^+$ calcd for $C_{14}H_{26}N_2O_3$: 293.1841, found: 293.1843.



475


Me
N
CO2Et
O
N
475
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm