INTRAMOLECULAR [4 + 2] CYCLOADDITIONS OF CONJUGATED ENYNES WITH HIGHLY STRAINED CYCLIC ALKENES

by

Jennie Fong
B.A., Chemistry with Biochemistry Emphasis
University of San Diego, 2005

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

MASTER OF SCIENCE

at the

MASSACHUSETTS INSTITUTE OF TECHNOLOGY

June 2008

Signature of Author.... .....
Department of Chemistry
5 February 2008

Certified by.....
Rick L. Danheiser
Arthur C. Cope Professor of Chemistry, Thesis Supervisor

Accepted by..... .....
Robert W. Field
Departmental Committee on Graduate Studies

Debts of Gratitude

I'd like to begin by thanking Prof. Rick L. Danheiser for providing me the opportunity to work in his laboratory and for allowing me to write up the challenging chemistry with which I undertook for this thesis. I am grateful for his contributions and support during my graduate studies.

My fellow Danheiser group members cannot go without recognition as these were the people who added life to the daily routine. First off, I owe special thanks to Eva-Maria Tanzer, a.k.a. German (Chocolate Cake with Coconut on Top), for helping me survive Summer '07 in the lab (as I literally strangled my cyclopropenes) with her remarkable humor, support, understanding, and company in our "jinxed corner," a.k.a. "the corner of destruction." She was also brave (and thus crazy) enough to willingly risk her safety as I maneuvered us throughout New England in Prius Zipcars for our outreach outings. Best of luck to her as she finishes up her studies in Würzburg! I find it gratifying to have had the opportunity to work with all the other talented members of the group (in order of disappearance, i.e. departure from MIT): Charnsak (Touch) Thongsornkleeb for providing grad school survival tips, Javier Horta for sharing his insights on teaching, Denali Lopez, Mandeep Virdi, and Kevin Maloney for bearing with me during my starter project period and the time thereafter, Yukinari Kobayashi, and Wes Austin for constantly replenishing my glassware drawers, and in no particular order, Xiao Yin Mak for offering her knowledge concerning my chemistry, Tammy Lam for her sincere efforts to cheer me up, Shaun Fontaine (three letters: PVA), Julia Robinson (gotta love them enynes and enynophiles!), Lucy Kohnen, Cindy Crosswhite, Olesya Haze, and Dr. J.C. Choi. And best of luck to the rising undergrad talents of the group, Paul Boudreau and Dennis Huang.

I owe special thanks to Prof. Greg Fu for his guidance and support during my time in the chemistry program.

Many thanks to my editorial board for helping me piece together this thesis: Rick, Xiao Yin, Julia and Shaun.

My survival in grad school would not have been possible in the absence of the many awesome people I was able to befriend and the handful of activities in which I had the opportunity to participate while at MIT. I'd like to give a shout-out to my fellow classmates of the second floor: Omar Ahmad, Ivan Vilotijevic and Brian Underwood. Despite their badgering me from the other side of the glass (as if I'm a zoo animal), they will be remembered for providing motivation, laughter and company during my time in 18. I'd also like to thank Meiliana Tjandra and Dr. Jun Qi for being wonderful neighbors in 18. Investment of my time in the MIT Women's Club Ice Hockey team was definitely an invaluable experience and made immense contributions towards my well-being as a grad student and as a person. I am truly thankful to have had the experience of learning and playing an awesome sport with a fabulous group of ladies and coaches (puck, I'm going to miss y'all!). Appreciation also goes to the Dry-Icers D+ IM hockey team, the MIT Rowing Club, ReachOut, Chemistry Outreach Program, and the Z-Center's aquatics for providing outlets from the daily grind, making the days as a grad student much more endurable.

Reflection of my time at MIT is not complete without acknowledging my former academic advisor, Dr. Debbie Tahmassebi who supplied me with words of wisdom and

encouragement from the other side of the country, and my former research advisor, Dr. Tom Shields at the University of San Diego. I am also thankful for the efforts of Dr. Pete Iovine (USD), Paul Frail (University of Pennsylvania), Prof. Mike Therien (UPenn), and the entire chemistry (and now also biochemistry) department at USD. Without these figures and their dedication to my undergraduate education and confidence in me, I would not have had the opportunity to attend MIT.

For the sentimental kid in me, I owe appreciation to Atom (my atomic crimson-colored betta fish) and his company for two years. I missed having therapeutic conversations with him my last four months of grad studies after he swam on to a better place.

Last but never least, I also owe a tremendous amount of appreciation to my family and friends for their relentless support during my graduate studies and for my decisions and journeys in life. I value the phone conversations (usually in the form of ranting from my end of the line) we shared as they helped me put things back into perspective and clarify my passions and goals in life. I may have been MIA for the majority of the past several years, but everyone held and continues to hold a special place in my heart and thoughts. Most notably, I am forever indebted to my parents for their guidance and patience, and for their confidence in me. Words cannot express how much I am thankful to have their unyielding love and support.

To Mom and Dad

INTRAMOLECULAR [4 + 2] CYCLOADDITIONS OF CONJUGATED ENYNES WITH HIGHLY STRAINED CYCLIC ALKENES

by

Jennie Fong

Submitted to the Department of Chemistry
on 5 February 2008 in Partial Fulfillment of the
Requirements for the Degree of Master of Science

ABSTRACT

Seven- and eight-membered carbocycles are key features in numerous naturally occurring organic substances, many of which are biologically important natural products. This thesis describes studies directed towards the development of a [4 + 3] annulation strategy for the synthesis of seven-membered carbocycles involving the intramolecular [4 + 2] cycloadditions of conjugated enynes with cyclopropenes. A new [4 + 4] annulation method has been developed for the synthesis of eight-membered carbocycles involving cycloadditions of cyclobutenones with conjugated enynes.

Thesis Supervisor: Rick L. Danheiser
Title: Professor of Chemistry

Table of Contents

Part I

Introduction and Background

Seven- and Eight-Membered Carbocyclic Compounds

Seven- and eight-membered carbocycles are key features in numerous naturally occurring organic substances, many of which are biologically important natural products. Examples of natural products that incorporate a seven-membered carbocycle in their structures are colchicine (**1**),[1] which is used to treat gout, and the antibiotic guanacastepene (**2**).[2] The anticancer agent taxol (**3**)[3] and the veterinary antibiotic pleuromutilin (**4**)[4] are just two examples of compounds that each contain an eight-membered carbocycle in their structure.

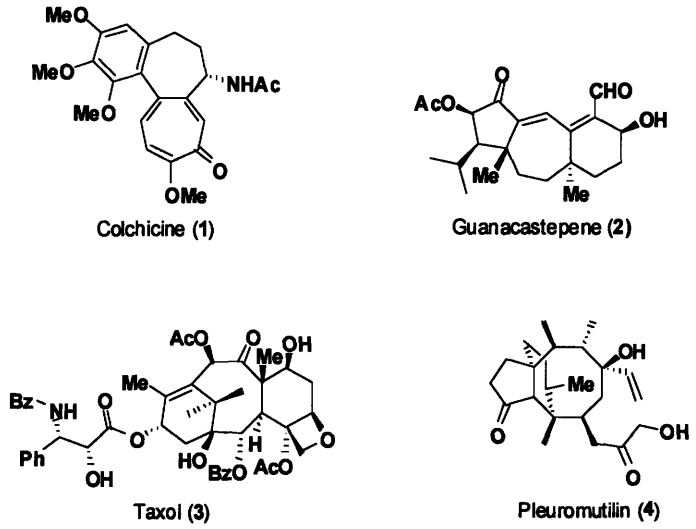


Figure 1

General approaches to access seven- and eight-membered carbocycles include annulations, cycloadditions, cyclizations, and ring-expansions. Of these, annulations and cycloadditions usually lead to the most convergent synthetic routes and are therefore often the most efficient. Attractive annulations to construct seven-[5,6] and eight-membered

---

[1] For a review of colchicine, see: Dustin, P. *Pharmocol. Rev.* **1963**, *15*, 449 and references therein.

[2] Reviewed in: Singh M. P.; Janso J. E.; Luckman S. W.; Brady S. F.; Clardy J.; Greenstein M.; Maiese W. M. *J. Antibiot.* **2000**, *53*, 256.

[3] Reviewed in: Miller, R. W. *J. Nat. Prod.* **1980**, *43*, 425.

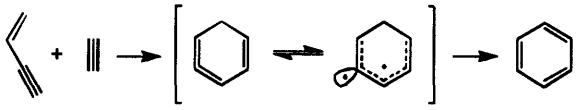
[4] Reviewed in: (a) Gregor, H. *Antibiot.* **1979**, *5*, 344; (b) Butler, M. S.; Buss, A. D. *Biochem. Pharmacol.* **2006**, *71*, 919.

[5] Reviews of [4 + 3] annulations: Rigby, J. H.; Pigge, F. C. *Org. React.* **1997**, *51*, 351. (b) Harmata, M. *Acc. Chem. Res.* **2001**, *34*, 595.

[6] For reviews and examples of other annulation routes to seven-membered rings, see: (a) Katritzky, A. R. *Chem. Rev.* **1989**, *89*, 827. (b) Wender. P. A.; Jesudason, C. D.; Nakahira, H.; Tamura, N.; Tebbe, A. L.; Ueno, Y. *J. Am. Chem. Soc.* **1997**, *119*, 12976. (c) López, F.; Castedo, L.; Mascareñas, J. L. *Org. Lett.* **2002**, *4*, 3683. (d) Yu, Z-X.; Wender, P. A.; Houk, K. N. *J. Am. Chem. Soc.* **2004**, *126*, 9154. (e) Wender, P. A.; Gamber, G. G.; Williams, T. J. "Rhodium(I)-Catalyzed [5 + 2], [6 + 2], and [5 + 2 + 1] Cycloadditions: New Reactions for Organic Synthesis", In *Modern Rhodium-Catalyzed Organic Reactions*;

carbocycles[7] include the rhodium-catalyzed cycloadditions developed by Wender[6e] as well as the [4 + 4] annulation for eight-membered carbocycles developed in our laboratory.[8] In this thesis I will discuss a new strategy for the synthesis of seven- and eight- membered carbocycles based on the intramolecular enyne cycloaddition reaction (Scheme 1) that has been comprehensively investigated in our laboratory.

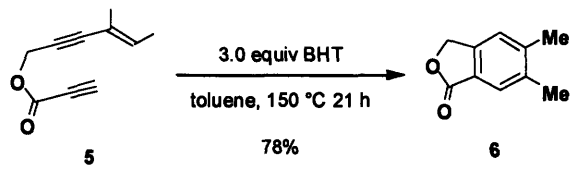
Scheme 1



[4 + 2] Cycloaddition of Conjugated Enynes

Studies of intramolecular [4 + 2] cycloadditions of conjugated enynes in the Danheiser laboratory began with studies of the scope and mechanism of the reaction with alkynes as the 2π partner, yielding benzenoid products (Scheme 2), while cycloadditions with alkenyl enynophiles were shown to produce dihydroaromatic compounds[9] (Scheme 3). Elaborations of the enynophile include the use of ynamides[10] and arynes,[11] which provide access to nitrogen heterocycles and highly condensed polycyclic aromatic compounds, respectively.

Scheme 2



Evan, A. P., Ed.; Wiley-VCH: Weinheim, 2005; pp 263-299 and references therein. (f) Trost, B. M.; Shen, H. C.; Horne, D. B.; Toste, F. D.; Steinmetz, B. G.; Koradin, C. *Chem. Eur. J.* **2005**, *11*, 2577. (g) Battiste, M. A.; Pelphrey, P. M.; Wright, D. L. *Chem. Eur. J.* **2006**, *12*, 3438.

[7] For a review on annulation routes to eight-membered carbocyles, see: Mehta, G.; Singh, V. *Chem. Rev.* **1999**, *99*, 991.

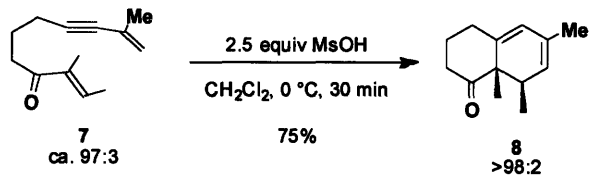
[8] Danheiser, R. L.; Gee, S. K.; Sard, H. *J. Am. Chem. Soc.* **1982**, *104*, 7670.

[9] Danheiser, R. L.; Gould, A. E.; Fernández de la Pradilla, R.; Helgason, A. L. *J. Org. Chem.* **1994**, *59*, 5514.

[10] Dunetz, J. R.; Danheiser, R. L. *J. Am. Chem. Soc.* **2005**, *127*, 5776.

[11] Hayes, M. E.; Shinokubo, H.; Danheiser, R. L. *Org Lett.* **2005**, *7*, 3917.

Scheme 3



Substitution on the enyne and enynophile can be varied to a great extent, allowing access to an assortment of cyclic products. Cycloaddition substrates can be defined as either unactivated or activated depending on the nature of the substituent on the enynophile component. Substrates with enynophiles that bear electron-withdrawing substituents (EWG) are considered activated and these substrates can be further divided into two categories, type I and type II (Figure 2).

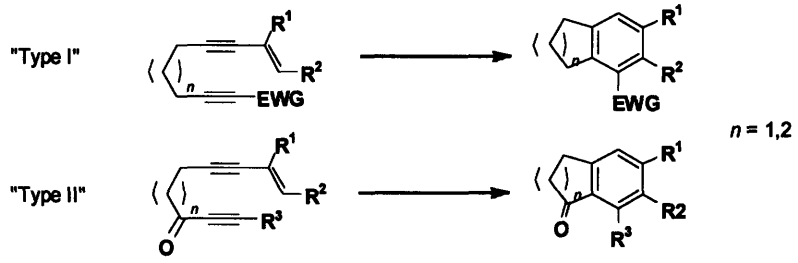


Figure 2. Two Classes of Cycloaddition Substrates

Research was also aimed at the elucidation of the mechanism of the [4 + 2] enyne cycloaddition. Scheme 4 summarizes the several pathways that could account for the mechanism of the enyne cycloaddition. Under thermal conditions, a typical substrate **9** undergoes a concerted cycloaddition to form the high energy cyclic allene intermediate **12**.[12,13,14] This step is supported by Ananikov's *ab initio* calculations[15] for this transformation. For "arenyne" substrates where the enyne double bond is embedded within an aromatic ring, however, a stepwise pathway involving a biradical intermediate of type **13** has been proposed by Domínguez and Saá.[14d] Isomerization from the cyclic

[12] For the first reference to a cyclic allene intermediate in the cycloaddition of a conjugated enyne, see: Dykstra, H. R. *J. Am. Chem. Soc.* **1934**, *56*, 1625.

[13] For reviews on cyclic cumulenes, see (a) Johnson, R. P. *Chem. Rev.* **1989**, *89*, 1111. (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.

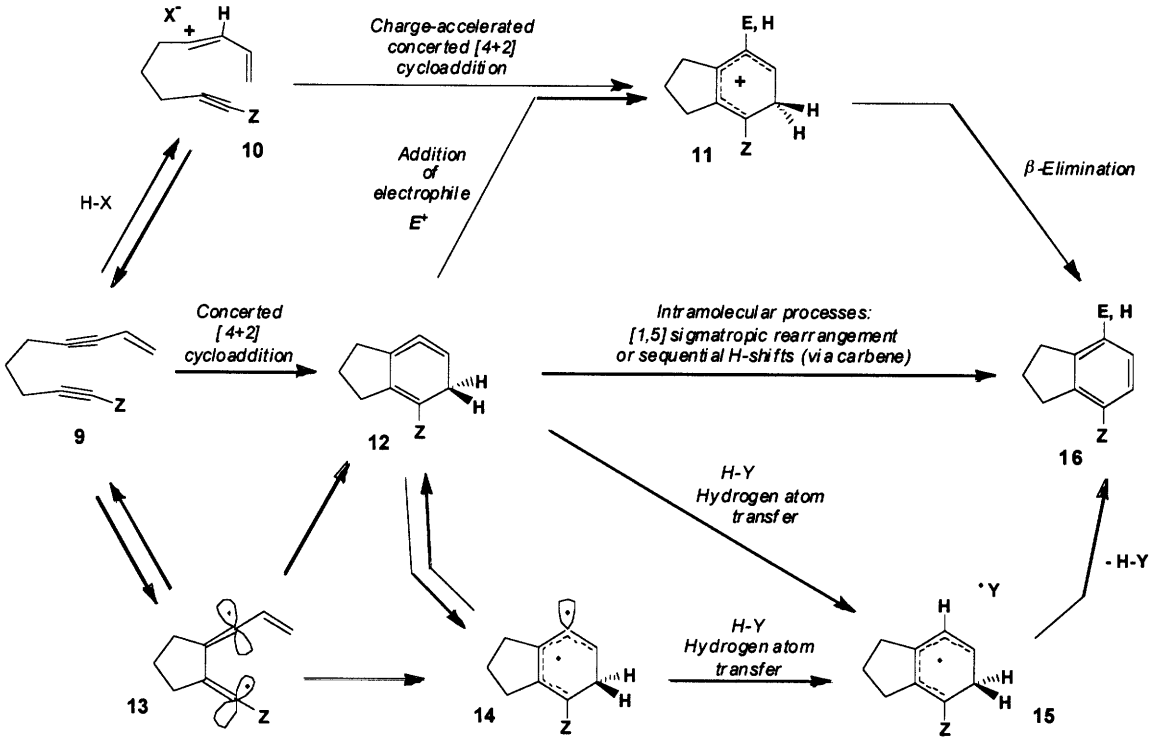
[14] For theoretical studies on 1,2,4-cyclohexatriene, see (a) Janoschek, R. *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 476. (b) Prall, M.; Kruger, A.; Schreiner, P. R.; Hopf, H. *Chem. Eur. J.* **2001**, *7*, 4386. (c) Engels, B.; Schöneboom, J. C.; Munster, A. F.; Groetsch, S.; Christl, M. *J. Am. Chem. Soc.* **2002**, *124*, 287. (d) Rodriguez, D.; Navarro-Vazquez, A.; Castedo, L.; Dominguez, D.; Saa, C. *J. Org. Chem.* **2003**, *68*, 1938.

[15] Ananikov, V. P. *J. Phys. Org. Chem.* **2001**, *14*, 109.

allene intermediate to **16** can proceed as shown by several different pathways depending on the reaction conditions.[14d,16]

Ongoing research on enyne cycloadditions in our laboratory includes the extension of the transformation to provide an assortment of different types of cyclic compounds. Herein, the extension of the enyne cycloaddition to generate seven- and eight-membered carbocycles will be discussed

Scheme 4



New Annulation Strategies for Seven- and Eight-Membered Carbocycles

Our proposed [4 + 3] annulation strategy for the synthesis of seven-membered carbocycles is focused on intramolecular [4 + 2] cycloadditions of conjugated enynes with cyclopropenes (Scheme 5). [4 + 2] Cycloaddition of **17** is expected to form cyclic allene intermediate **18**, which should isomerize to the diene **19**. This diene is expected undergo facile [3,3]-sigmatropic (Cope) rearrangement[17,18] to provide cycloheptatriene

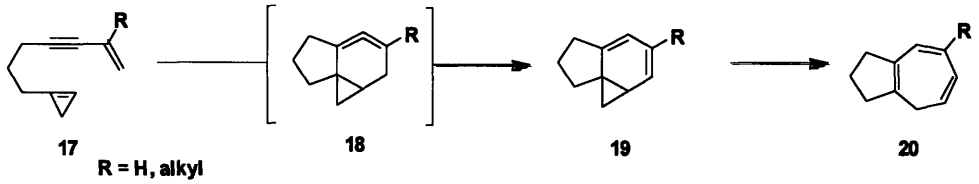
[16] For the relationship of isomerization pathways to reaction conditions, refer to Chapter 2 of: Hayes, M. E. Ph.D. Thesis, Massachusetts Institute of Technology, Cambridge, MA, 2004 and references therein.

[17] Reviewed in (a) Maier, G. *Angew. Chem. Int. Ed.* **1967**, *6*, 402. (b) Davies, H. M. L. *Tetrahedron* **1993**, *49*, 5203. (c) Kantorowski, E. J.; Kurth, M. J. *Tetrahedron* **2000**, *56*, 4317.

[18] Reviewed in: Hill, R. K. Cope, Oxy-Cope and Anionic Oxy-Cope Rearrangements. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I, Paquette, L. A., Eds.; Pergamon Press: Oxford, 1991; pp 785-826.

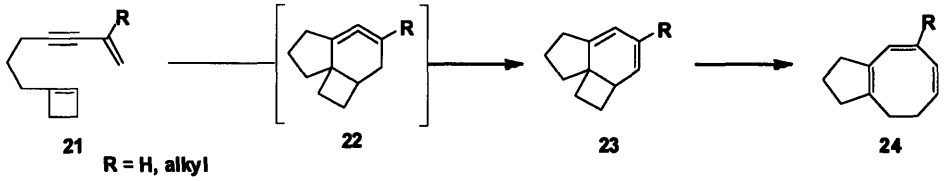
20. Studies of unactivated as well as both type I- and type II-activated substrates are described in detail in Part II of this thesis.

Scheme 5



Similarly, we also envisioned a [4 + 4] annulation method that involves enyne cycloaddition with the π-bond of a cyclobutene (Scheme 6). [4 + 2] Cycloaddition of **21** should provide the bicyclic diene **23**, which is expected to undergo Cope rearrangement[18] to give cyclooctatriene **24**. Due to the more expeditious preparation of cyclobutenone substrates versus cyclobutenyl substrates, our initial studies of the proposed [4 + 4] annulation utilized cyclobutenones as the enynophile. In these reactions the carbonyl group was expected to serve as an enynophile activating group, rendering these compounds as type II-activated substrates (Figure 2). Note that the ketone can be positioned at either C-2 or C-3 of the cyclobutenyl skeleton. The details of our [4 + 4] annulation investigation are described in Part III of this dissertation.

Scheme 6



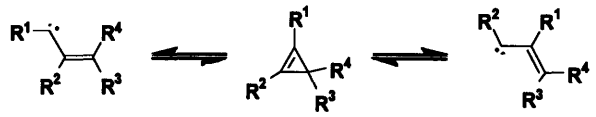
Part II

Enyne Cycloadditions with Cyclopropenes

Introduction

The outcome of our proposed [4 + 3] annulation (Scheme 5) hinges on the competition between the desired [4 + 2] enyne cycloaddition and the ring opening of the cyclopropene to produce a vinylcarbene (Scheme 7).[19] The vinylcarbene could be in equilibrium with the cyclopropene and could undergo further rearrangement depending on reaction conditions and substituent effects. Temperatures of 185 °C and above are generally required for ring-opening of simple cyclopropenes, though the amount of thermal energy required to trigger ring opening is dependent on the electronic effects of the substituents at all three positions of the ring. Electron-withdrawing groups at C-1 or C-2 and electron-donating groups at C-3 lead to ring opening at lower temperatures.

Scheme 7



Synthesis of Cyclopropenyl Cycloaddition Substrates

Cyclopropenes can be accessed via several different routes.[20,21] We anticipated that our requisite cycloaddition substrates could be readily prepared in several steps using recent methods developed by Fox and co-workers in conjunction with the classic rhodium-catalyzed cyclopropenation of alkynes with diazo esters.[21a] Fox has reported that lithiation of cyclopropenyl acids such as **25** provides fully substituted cyclopropenes in excellent yields[21b] (e.g. Scheme 8). We considered this "dianion approach" to be attractive for the installation of the enynyl tether and/or activating groups on the enynophile of our proposed cycloaddition substrates.

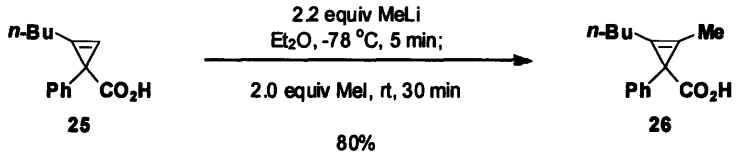
---

[19] Reviewed in: Baird, M. S. *Chem. Rev.* **2003**, *103*, 1271.

[20] Reviewed in (a) Baird, M. S. *Top. Curr. Chem.* **1988**, *144*, 137 and references therein. (b) Rubin, M.; Rubina, M.; and Gevorgyan, V. *Synthesis* **2006**, *8*, 1221 and references therein.

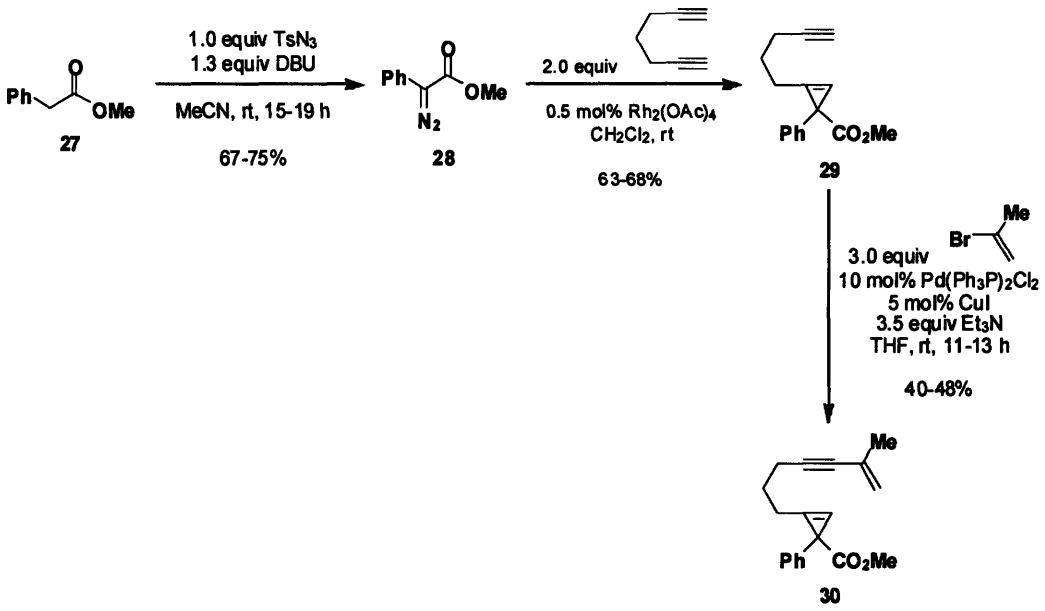
[21] (a) Liao, L.; Zhang, F.; Yan, N.; Golen, J. A.; Fox, J. M. *Tetrahedron* **2004**, *60*, 1803. (b) Liao, L.; Yan, N.; Fox, J. M. *Org. Lett.* **2004**, *6*, 4937. (c) Fox, J. M.; Yan, N. *Curr. Org. Chem.* **2005**, *9*, 719.

Scheme 8



Preparation of our "unactivated" substrate **30** began with the rhodium-catalyzed mono-cyclopropenation of 1,6-heptadiyne with diazo ester **28** to afford cyclopropene **29** in good yield (Scheme 9). The known requisite diazo ester **28** was prepared via diazo transfer of tosyl azide[22] and the commercially available ester **27**. Substrate **30** was subsequently obtained in moderate yield from Sonogashira coupling of terminal alkyne **29** with 2-bromopropene.

Scheme 9

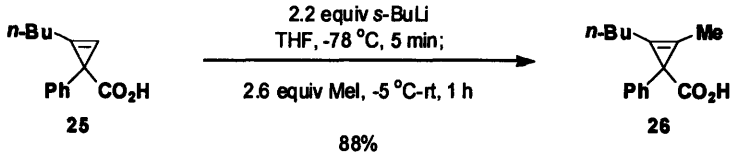


Our approach for the construction of type I-activated substrates utilized Fox's dianion chemistry.[21b] Initially, we performed model studies on acid **25** to confirm that we could reproduce the reaction illustrated in Scheme 8 due to the challenging nature of Fox's chemistry. Following the reported procedure using both freshly prepared[23] (as reported in Fox's procedure) and commercial MeLi failed to deliver the fully substituted cyclopropene **26**. At this point we consulted with Professor Fox and he informed us that

[22] Prepared from the reaction of tosyl chloride and sodium azide according to: Ghosh, A. K.; Bischoff, A.; Cappiello, J. *Eur. J. Org. Chem.* **2003**, 821.
[23] Schöllkopf, U., Paust, J.; Patsch, M. R. *Org. Synth.* **1969**, *49*, 86.

his laboratory had also sometimes encountered problems in reproducing their original published results. Prompted by our inquiry, Professor Fox carried out further experiments that led to the following recommendations. First, the reaction proceeds best when THF is used rather than diethyl ether as solvent. This does not affect the deprotonation step, but does affect the success of the alkylation of the cyclopropenyllithium species. Second, the dilithium intermediate has limited stability at room temperature and the reaction mixture should not be allowed to stir for more than a few minutes at 0 °C or higher temperatures. Finally, although Fox did find the reaction in THF to be reproducible using MeLi, because of the variable quality of MeLi from different sources, he recommended that it may be advisable to use *s*-BuLi in its place. When both modifications were applied in our hands, the model reaction proceeded smoothly in good yield (Scheme 10). We later found that substituting *n*-BuLi for *s*-BuLi provides comparable results, and for all further reactions, *n*-BuLi was used for the generation of the dilithio species.

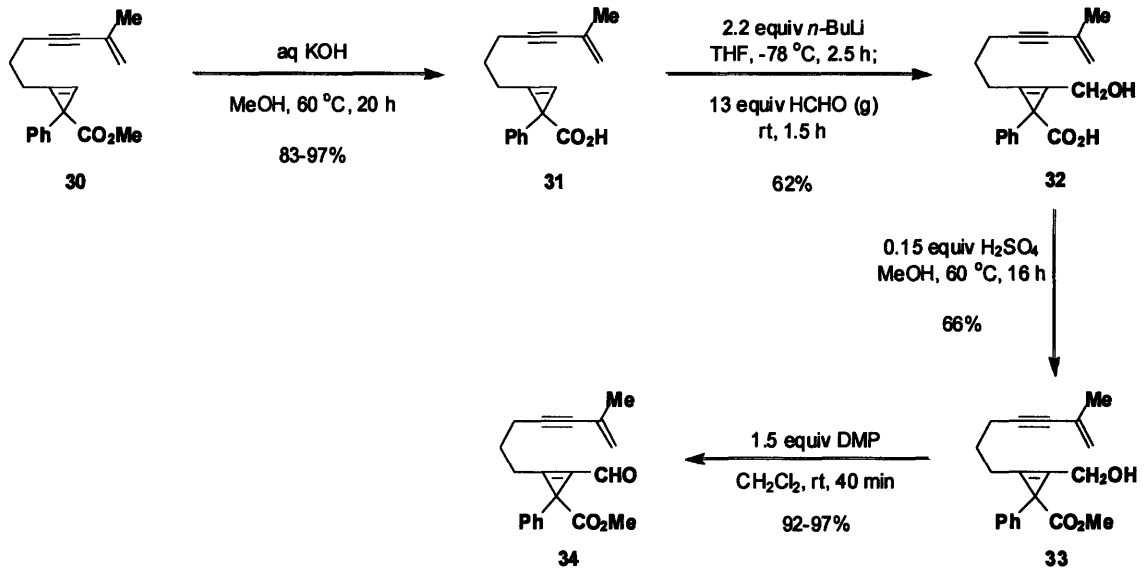
Scheme 10



For the preparation of the aldehyde-activated type I substrate **34**, ester **30** was hydrolyzed to give acid **31** as shown in Scheme 11. The dilithium derivative of **31** was successfully trapped with monomeric formaldehyde, generated via the pyrolysis of paraformaldehyde,[24] to provide the primary alcohol **32** in good yield. Ester **33** obtained via Fischer esterification was successfully oxidized to the aldehyde-activated substrate under mild Dess-Martin conditions. It was desirable to convert acid **32** to an ester prior to cycloaddition in order to facilitate analysis by TLC as well as purification.

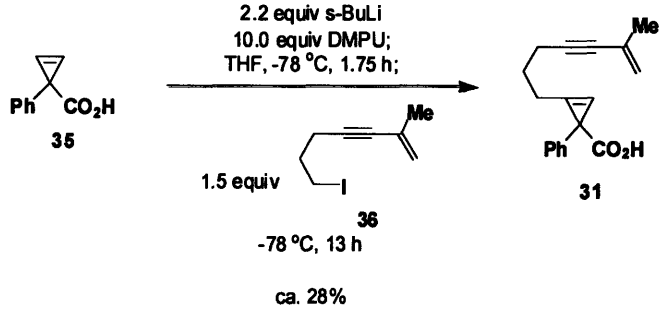
[24] For the use of additives and trapping of a cyclopropenyllithium compound with monomeric formaldehyde, see: Nakamura, E. *J. Org. Chem.* **1989**, *54*, 4727.

Scheme 11



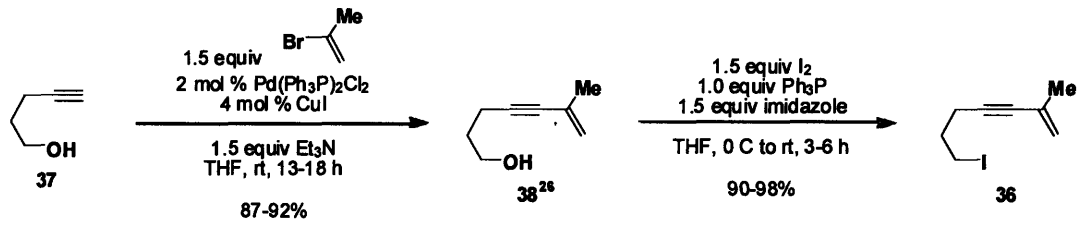
An alternative route to key intermediate **31** was investigated based on the alkylation of a cyclopropenyllithium species with iodide **36**. This approach was attractive as it could potentially provide access to a variety of different cycloaddition substrates beginning with a common cyclopropene intermediate **35**.[25] Although alkylation of the dilithium derivative of **35** with MeI using the method of Fox was successful, we were unable to achieve alkylation using the less reactive alkyl iodide **36** (Scheme 12). In the presence of DMPU,[24] some of the desired product (**31**) was formed, but difficulties were encountered in separating this compound from DMPU and this approach was abandoned.

Scheme 12



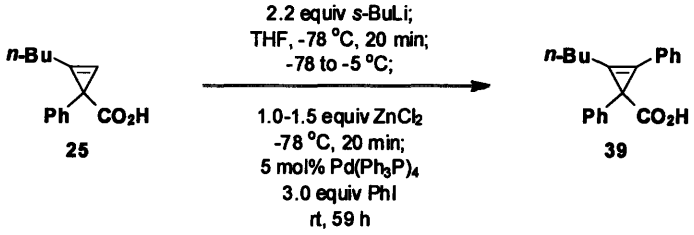
[25] Prepared in two steps from TMS-acetylene and diazo ester **28**[21b]

Scheme 13



Alkynyl substituents can also be activating groups[27] in enyne-type cycloadditions and we were thus interested in constructing type I substrates in which the cyclopropene π-bond bears a silyl-protected acetylene group. We began with model studies that again relied on cyclopropenyl metal chemistry developed by Fox and co-workers.[21b] In our hands, the Negishi coupling of the cyclopropenylzinc intermediate derived from **25** with iodobenzene to give **39** was unsuccessful (Scheme 14). Fox previously reported Negishi couplings of very similar cyclopropenylzinc intermediates with various iodoarenes to provide products in 63-69% yield. Unfortunately, we were unable to achieve the desired reaction in more than ca. 20% yield and recovered mostly unreacted starting material in these experiments.

Scheme 14



de Meijere has reported the preparation of the alkynylcyclopropene **42** in 49% yield from the Negishi coupling outlined in Scheme 15.[28] However, our attempt to apply similar conditions to the coupling of the model cyclopropene **25** with the TMS-protected iodoacetylene[29] **43** surprisingly provided only recovered starting material and a few minor side-products (Scheme 16).

---

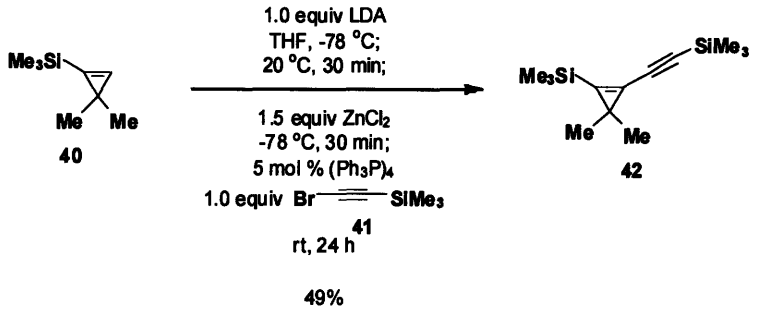
[26] The procedure follows that previously reported for the preparation of this compound; see Hashmi, A. K. S. and Sinha, P. *Adv. Synth. Catal.* **2004**, *346*, 432.

[27] Wills, M. S. B.; Danheiser, R. L. *J. Am. Chem. Soc.* **1998**, *120*, 9378.

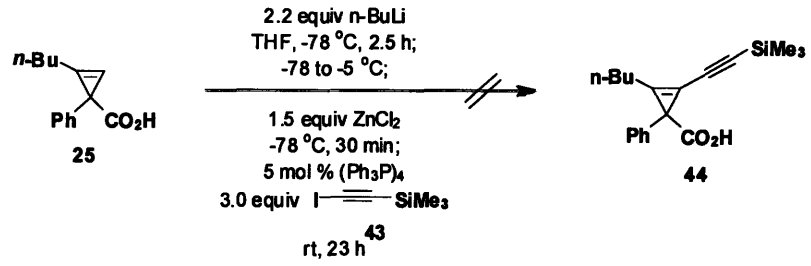
[28] Untiedt, S. and de Meijere, A. *Chem. Ber.* **1994**, *127*, 1511.

[29] Iodoacetylene **43** was prepared according to Amatore,C.; Blart, E.; Genet, J.P.; Jutand, A.; Lemaire-Audoire, S.; Savignac, M. *J. Org. Chem.* **1995**, *60*, 6829.

Scheme 15

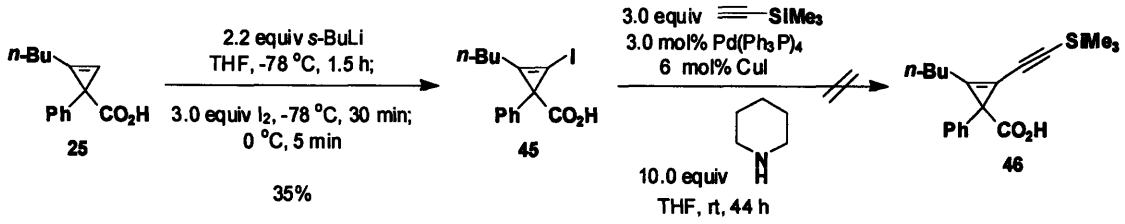


Scheme 16



An alternative attempt to prepare the alkynyl cyclopropene **44** involved the Sonogashira coupling of iodocyclopropene **45** and trimethylsilylacetylene (Scheme 17). Iodocyclopropene **45** was accessed via iodination[30] of the model cyclopropene **25**. Unfortunately, the Sonogashira reaction failed, and we abandoned attempts to prepare this class of cycloaddition substrates.

Scheme 17

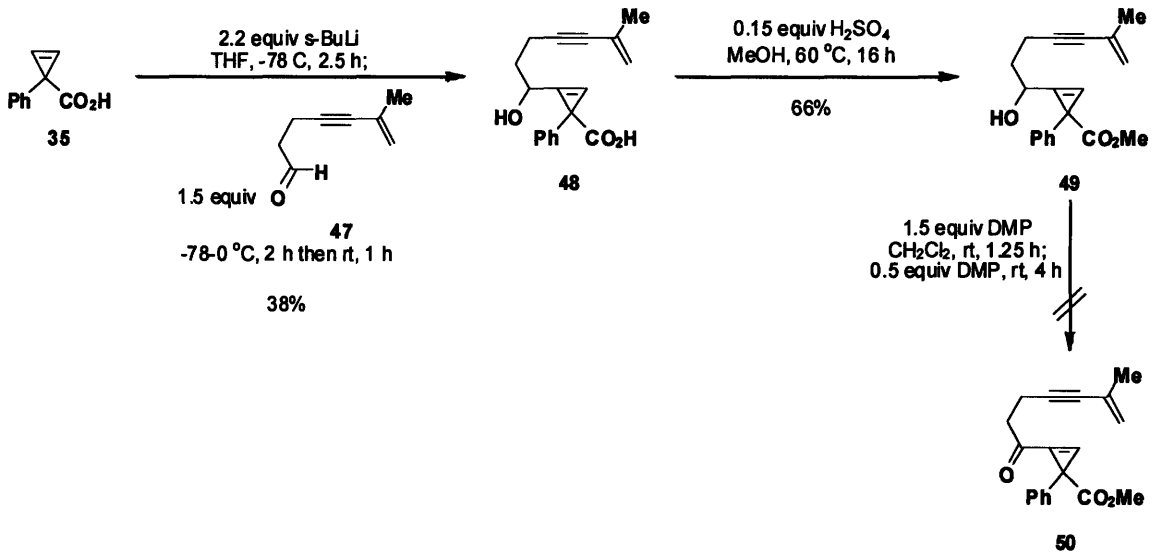


Scheme 18 outlines the synthesis of a type II cycloaddition substrate in which the activating group is incorporated in the tether connecting the cyclopropene to the enyne moiety. Alcohol **48** was successfully prepared from cyclopropene **35** and aldehyde **47** (Scheme 19), albeit in poor yield, but the oxidation of the ester derivative (**49**) with the

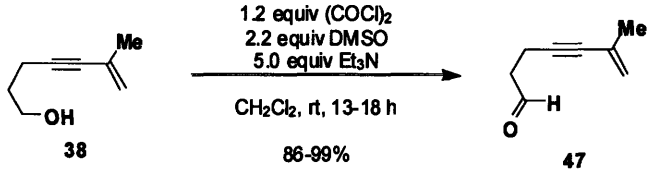
[30] The procedure follows a modification of the previously reported preparation of a similar cyclopropenyl iodide: Weatherhead-Kloster, R. A.; Corey, E. J. *Org. Lett.* **2006**, *8*, 171.

Dess-Martin reagent resulted in a complex mixture of uncharacterizable products. An alternative approach to ketone **50** based on the addition of a cyclopropenyllithium species to a carboxylate salt was briefly examined but was also unsuccessful

Scheme 18

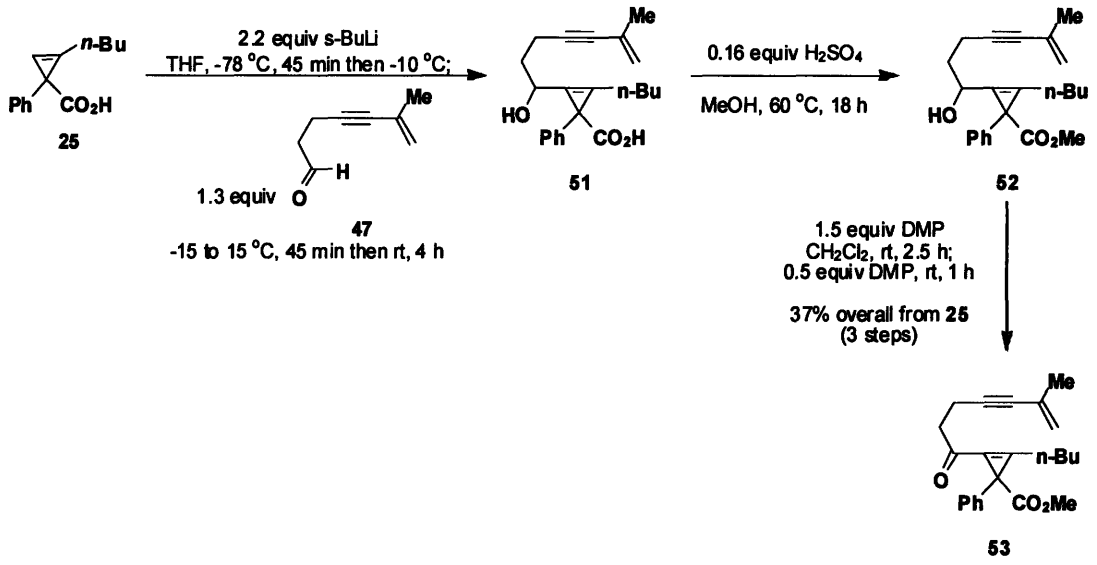


Scheme 19



We next turned our attention to the synthesis of an analogous cycloaddition substrate with a more highly substituted cyclopropene double bond, in the hope that this compound would prove more stable. As shown in Scheme 20, the tetrasubstituted cyclopropenyl substrate **51** was successfully prepared via the Fox method and was converted to the ketone **53** in 37% overall yield for three steps from cyclopropene **25**. Acid **51** was isolated as a mixture with 7% unreacted **25** after column chromatography and the cyclopropene **25** was separated out after esterification to give pure **52**.

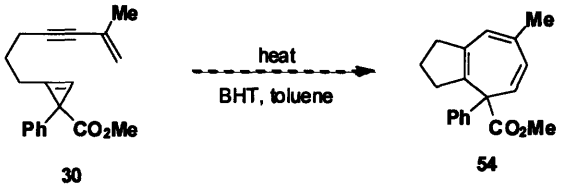
Scheme 20



Cycloaddition Studies

A preliminary study of the cycloaddition of substrate **30** under thermal conditions was conducted in order to screen for the temperature at which substantial changes occurred. A 0.05 M solution of **30** in toluene containing 3 equiv of BHT was heated from 80 to 150 °C over 67 h (Scheme 21). No change was observed by TLC analysis from 80 to 110 °C, but after 12 h of heating at 150 °C, two fairly intense spots less polar than the starting material were detected and the reaction was allowed to run for another 32 h.[31] A complex mixture of products was obtained and an attempt to isolate the products corresponding to the two most intense spots observed by TLC using column chromatography on silica gel was unsuccessful.

Scheme 21



After heating another toluene solution of **30** in the presence of 3 equiv BHT for 52 h, we attempted to isolate the product corresponding to the most intense spot observed by TLC using column chromatography on silica gel with 10% EtOAc-hexanes as the

[31] Note that the reaction tube was not fully immersed in the oil bath during the course of reaction and thus the exact temperature of the reaction mixture was not known.

eluent. ^{1}H NMR analysis of the apparently pure product (single spot by TLC analysis) isolated from this column indicated that the sample was in fact a mixture of compounds. Eluting the mixture on a TLC plate with 75% benzene-hexane resolved the product into several equally intense spots. The mixture was then further purified by column chromatography on silica gel, first eluting with 75-100% benzene-hexanes, and then twice more eluting with 100% benzene. A trace amount of the "major" product (ca. 1 mg) was obtained pure (by TLC analysis) in this fashion, but ^{1}H NMR indicated that it was not the desired seven-membered ring product **54**.

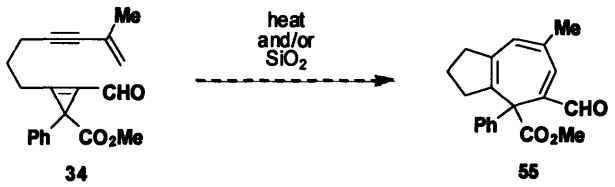
We next attempted the reaction on a larger scale at 150 °C in toluene in the absence of BHT and interrupted the reaction after only 17 h (before consumption of starting material was complete). Screening experiments had indicated that the reaction was cleaner in the absence of BHT, and we speculated that the major product was possibly undergoing some decomposition upon prolonged heating. The same intense spot observed in the previous experiment was isolated by column chromatography. This mixture of products was then subjected to preparative TLC, eluting with 70% benzene-hexanes. However, all of the bands isolated were found to consist of complex mixtures of several compounds. Due to the fruitless results from the thermal studies on cycloaddition substrate **30**, we shifted our focus to studies of the enynophile-activated substrates, **34** and **53**.

Cyclopropenyl aldehyde **34** was examined first. As mentioned previously (Scheme 11), Dess-Martin oxidation of alcohol **33** was employed to generate aldehyde **34**. Initially, we heated the crude Dess-Martin reaction mixture at 40 °C in the hope of promoting the desired cycloaddition based on previous observations by former group member Javier Horta.[32] Horta was able to initiate the cycloaddition of a few of his heteroarenyne substrates by using this approach and in a few cases, cycloaddition was promoted by the addition of SiO_2 immediately after completion of the oxidation step. After heating the crude mixture containing **34** and DMP for 19.5 h at 40 °C, TLC analysis indicated no change in the aldehyde. Up to a total of 30 equiv of SiO_2 was then added and again, no reaction was observed after 7 h in reluxing CH_2Cl_2. Heating a toluene solution of **34** in both the absence and presence of BHT at 80 to 110 °C resulted

[32] Horta, J. E. Ph.D. Thesis, Massachusetts Institute of Technology, Cambridge, MA, 2006.

in complex mixtures that were similar to those produced in the previous studies on the cycloaddition of the unactivated substrate **30**.

Scheme 22



The cycloaddition of substrate **34** was also investigated in the presence of Brønsted and Lewis acids. Interestingly, these experiments (Table 1) led to a product identified as the tetrahydrofluorene **58** (Scheme 23) in ca. 30% yield. The formation of indene **57** can be envisioned to occur via ring opening of the cyclopropene to form vinylcarbene **56**, followed by insertion of the carbene into an aryl C-H bond.[33] Indene **57** could then be converted to **58** via an acid-catalyzed ene reaction.[34]

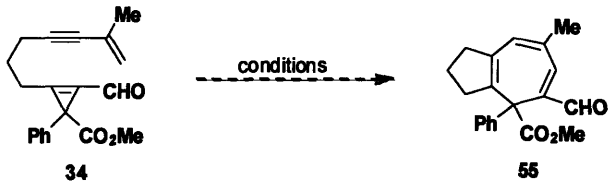


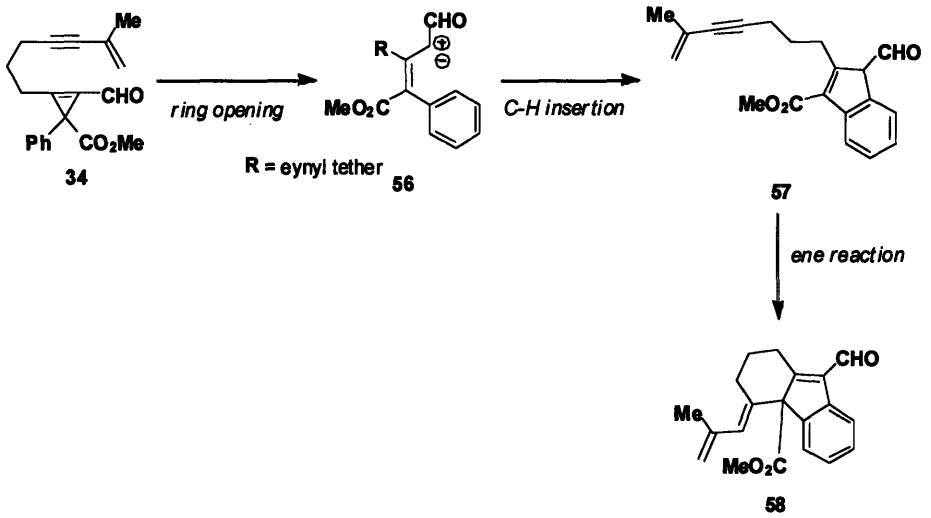
Table 1. Examination of Acids for Cycloaddition of Substrate 34

Entry	Conditions	Temperature and Time	Results
1	2.5 equiv MsOH, 0.5 M in CH_2Cl_2	0 °C for 2 h	39% yield of **58**
2	2.0 equiv $AlCl_3$ 0.5 M in CH_2Cl_2	0 °C for 1.5 h	32% yield of **58**

[33] For studies on rearrangements involving phenyl substituted cyclopropenes: (a) Battiste, M. A.; Halton, B.; Grubbs, R. H. *J. Chem. Soc., Chem. Commun.* **1967**, 907. (b) Komendantov, M. I.; Bekmukhametov, R. R.; Domnin, I. N. *Zh. Org. Khim.* **1978**, *14*, 759. (c) Komendantov, M. I.; Bekmukhametov, R. R.; Domnin, I. N. *Tetrahedron* **1978**, *34*, 2743.

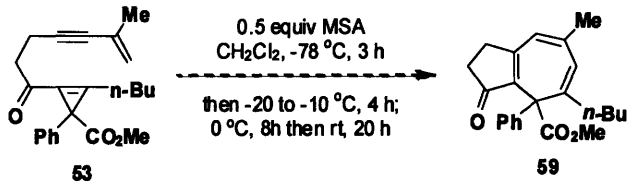
[34] For the ene rearrangement of an intermediate similar to **57**: Padwa, A.; Rieker, W. F.; Rosenthal, R. J. *J. Org. Chem.* **1984**, *49*, 1353.

Scheme 23



Investigation of the type II substrate **53** was brief and was also discouraging (Scheme 24). In the presence of catalytic MsOH, substrate **53** decomposed into a complex mixture of products and studies of the cyclopropenyl cycloaddition substrates were discontinued.

Scheme 24



Summary

Due to the array of undesirable outcomes with our proposed [4 + 3] annulation, our focus shifted to intramolecular enyne cycloadditions that exploit cyclobutenones as the 2π enynophile. Cyclobutenones in general are more stable than cyclopropenes and thus less prone to ring-opening than the more strained three-membered rings. Successful annulations of this type would furnish eight-membered rings as briefly described in Part I.

Part III

Enyne Cycloadditions with Cyclobutenones

Introduction

Cyclobutenones are useful synthetic building blocks and a variety of methods have been developed for the preparation of these strained carbocyclic rings.[35] Wasserman and co-workers observed that the [2 + 2] cycloaddition of alkynyl ethers and ketene proceeds smoothly to give 3-ethoxycyclobutenones,[36,37] which can be further elaborated by the 1,2-addition of organolithium and organomagnesium reagents.[37] Due to its attractiveness, we applied this approach for the preparation of the enyne cycloaddition substrates required for the development of our proposed [4 + 4] annulation method. The outcome of the desired transformation was expected to depend on the competition between the desired [4 + 2] cycloaddition and ring-opening of the strained four-membered ring. The latter process occurs upon heating various cyclobutenones at temperatures as low as 80 °C.[38] As a consequence of the thermal instability of cyclobutenones, cycloadditions under acid-catalyzed or acid-promoted conditions were regarded as most likely to be successful.

Synthesis of Cyclobutenone Cycloaddition Substrates

We decided to focus our initial studies on type II substrates **61** and **64** in which the enynophile activating group is the carbonyl group of the cyclobutenone. Systems in which the enynyl substituent is attached at both the C-2 and C-3 position of the cyclobutenone (Figure 3) were examined. We began with the synthesis and studies of the 3-enynyl substrate **61** as we believed it could be accessed more expeditiously than the 2-enynyl substrate **64**. 3-Enynyl cyclobutenone **61** was obtained in moderate yield via the 1,2-addition of the organolithium compound generated from iodide **36** to cyclobutenone **60** followed by acid hydrolysis (Scheme 25).

---

[35] For an overview cyclobutenone preparation, see Moore, H. W. and Yerxa, B. R. Synthetic Utility of Cyclobutenones. In *Advances in Strain in Organic Chemistry*; Holton, B., Ed.; Jai Press Ltd: London, England, 1995; Vol. 4, pp 81-162. (b) For a comprehensive review of the preparation of four-membered carbocycles, see: *Methods of Organic Chemistry (Houben-Weyl)*; de Meijere, *A.*; Ed.; Thieme: Stuttgart, Germany, 1997, Vol. E17e and f.

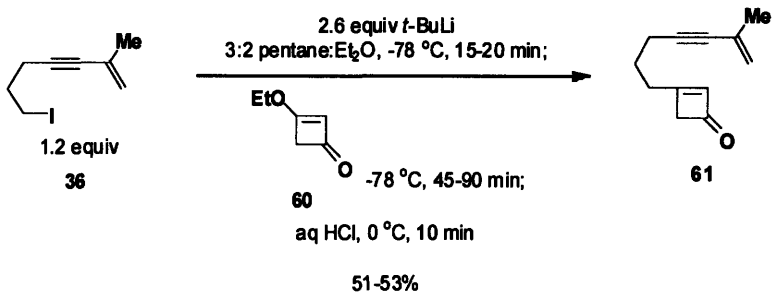
[36] Wasserman, H. H.; Piper, J. U.; Dehmlow, E. V. *J. Org. Chem.* **1973**, *38*, 1451.

[37] (a) Ficini, J.; Claeys, M.; Depezay, J. C. *Tetrahedron Lett.* **1973**, 3357. (b) Ficini, J.; Genet, J. P. *Ibid* **1975**, 2633.

[38] 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.

Figure 3

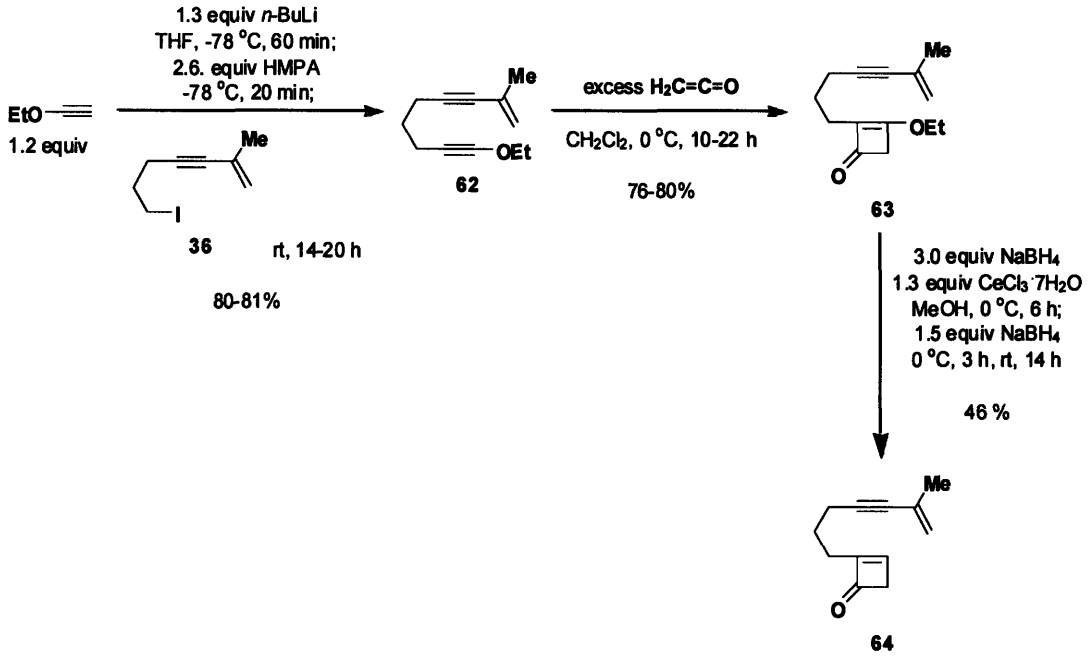
Scheme 25



2-Enynyl cyclobutenone **64** was prepared from the [2 + 2] cycloaddition of ketene with the alkynyl ether **62** (Scheme 26). Alkyne **62** was generated from the substitution reaction of lithium ethoxyacetylide with iodide **36**, providing ethoxyacetylene **62** in excellent yield. Literature reports of a similar reaction using iodohexane as the electrophile (86% yield) called for 2.6 equiv of HMPA,[39] but we found this could be reduced to 2.2 equiv, and we later demonstrated for a homolog of **62** that 1.6 equiv of HMPA works comparably well (75% yield). Luche reduction of ethoxycyclobutenone **63** provided cycloaddition substrate **64** in moderate yield.

[39] (a) Kocienski, P. J.; Pelotier, B.; Pons, J.-M.; Prideaux, H. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1382. (b) Pons, J.-M. and Kocienski, P. *Tet. Lett.* **1989**, *30*, 1833

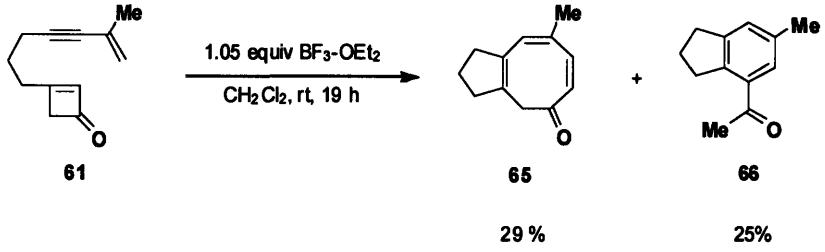
Scheme 26



Cycloaddition Studies

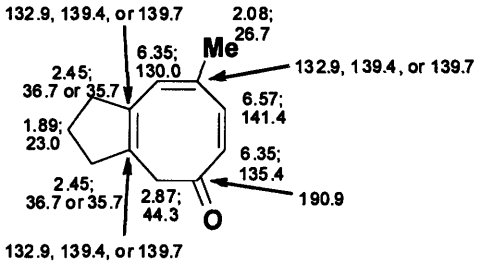
A variety of conditions were examined for the enyne cycloaddition of the 3-substituted substrate cyclobutenone **61**, including both Brønsted and Lewis acids as well as transition metals. In the presence of boron trifluoride etherate, the desired [4 + 4] annulation product, cyclooctatrienone **65,** was generated in 29% yield accompanied by a byproduct identified as the indan **66** (Scheme 27).

Scheme 27



NMR analysis supports the assignment of the major product as the cyclooctatrienone **65**. The assignment of both the ^{1}H and ^{13}C NMR spectra for **65** is shown in Figure 4 and tabulated in Table 2. The assignments of the alkenyl protons on the eight-membered ring are based on the *cis* coupling between H-6 and H-7, with H-7 being more deshielded as usual for the β-position of an α,β-enone. The DEPT spectrum of **65** distinguished carbons 3a and 9a from the alkenyl carbons that bear protons (carbons

6, 7, and 9), and with the aid of heteronuclear correlation data (HSQC), carbons 6, 7 and 9 were assigned their respective chemical shifts (Figure 5). These assignments are reasonable as the shift for carbon 7 is expected to appear most downfield due to the deshielding effect described above. The heteronuclear correlation data permitted the assignment of the methylene carbons on the five-membered ring of **65**. A strong IR (neat) absorption at 1659 cm^{-1} is consistent with the highly conjugated ketone on the eight-membered ring of **65**.



^{1}H NMR ($CDCl_3$, 400 MHz), ppm (top)
^{13}C NMR ($CDCl_3$, 100 MHz), ppm (bottom)

Figure 4. NMR Data for Cyclooctatrienone 65

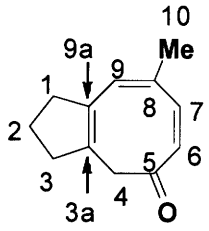


Table 2: NMR Data for Cyclooctatrienone 65

Atom #	^{1}H NMR:[a] δ [multiplicity, J (Hz)]	^{13}C NMR:[b] δ
1	2.45 (t, 7.6)	36.7 or 35.7
2	1.89 (q, 7.6)	23.0
3	2.45 (t, 7.6)	36.7 or 35.7
3a	--	132.9, 139.4, or 139.7
4	2.87 (s)	44.3
5	--	190.9
6	6.35 (d, 12.8)	135.4
7	6.57 (d, 13.3)	141.4
8	--	132.9, 139.4, or 139.7
9	6.35 (s)	130.0
9a	--	132.9, 139.4, or 139.7
10	2.08 (s)	26.7

[a] $CDCl_3$, 400 MHz
[b] $CDCl_3$, 100 MHz

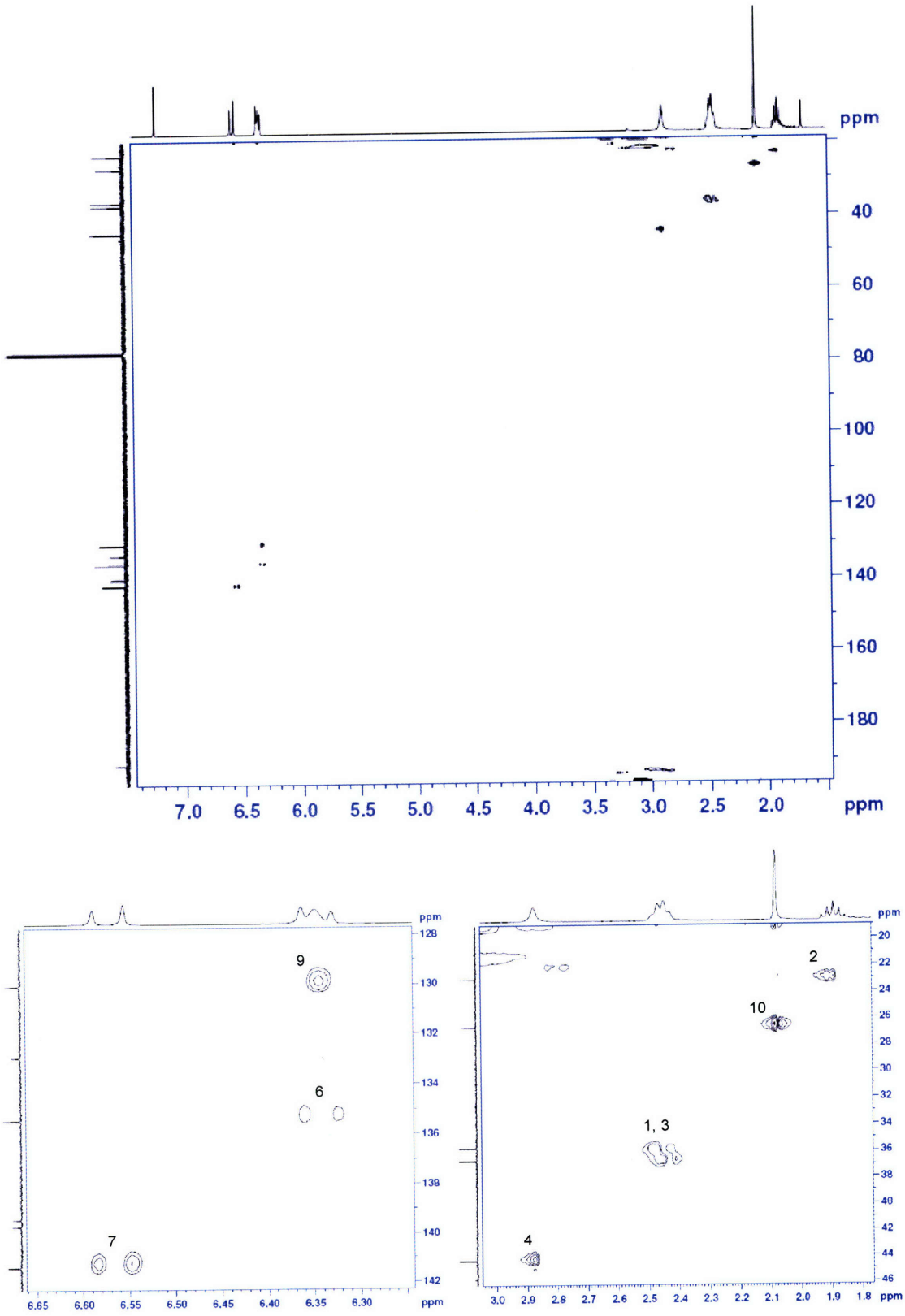
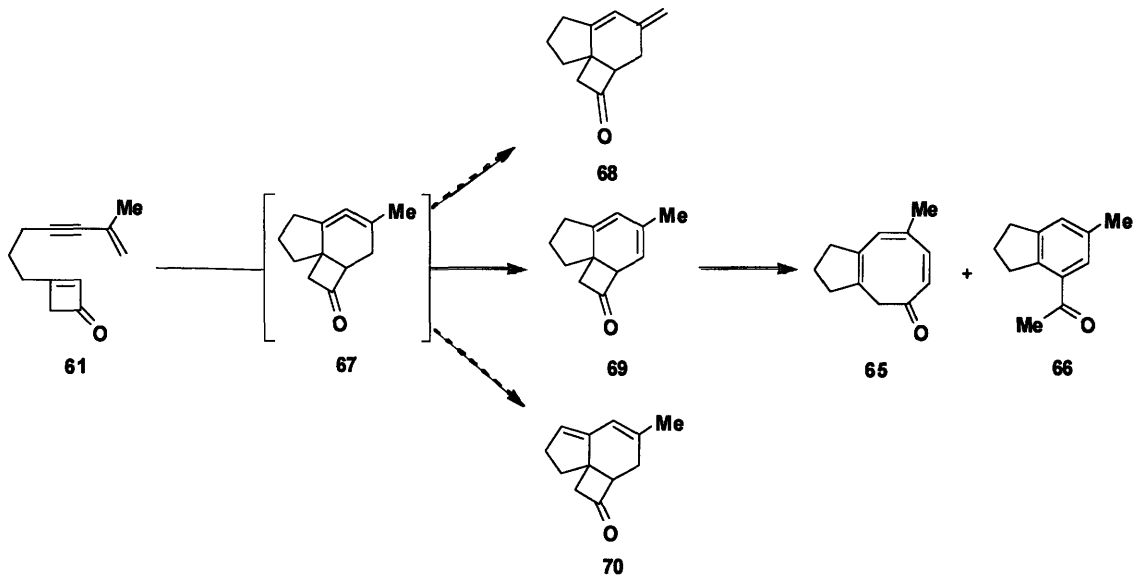


Figure 5. HSQC Spectrum for Cyclooctatrienone 65

The mechanism for the enyne cycloaddition discussed at the beginning of this thesis (Scheme 4) can account for the formation of cyclooctatrienone **65**. Specifically, **65** can form via the [3,3]-sigmatropic (Cope) rearrangement of tricyclic intermediate **69** which originates from isomerization of cyclic allene **67** (Scheme 28). Note that two other dienes, **68** and **70**, can also arise from the common cyclic allene intermediate **67**, but neither of these was observed by ^{1}H NMR analysis of the products of any of the cycloadditions we have run to date.

Scheme 28



Interestingly, however, a significant amount of an aromatic byproduct was also isolated from the cycloadditions conditions we have examined (Scheme 27). This major side-product was identified as indan **66**, which was previously synthesized by former group member Sandy Gould via the cycloaddition of a methyl ketone-activated alkynyl substrate.[9] The formation of the indan in our enyne cycloaddition is believed to proceed via the mechanism depicted in Scheme 29. In the presence of trace amounts of acid (wet BF_3-OEt_2 is the likely source), **69** is protonated to form the carbocation intermediate **71** which fragments[40] to generate the highly delocalized pentadienyl carbocation **72**.

[40] Lee-Ruff, E. New Synthetic Pathways from Cyclobutenones. In *Advances in Strain in Organic Chemistry*; Holton, B., Ed.; Jai Press Ltd: London, England; Greenwich, Connecticut, 1991; Vol. 1, pp 167-174.

Aromatization and tautomerization then provides the indan **66**. Alternatively, fragmentation may proceed directly via a ketone-BF_3 complex. Note that it is possible that an alternative mode of fragmentation via carbocation **73** could conceivably lead to the formation of the desired cyclooctatrienone as shown.

Scheme 29

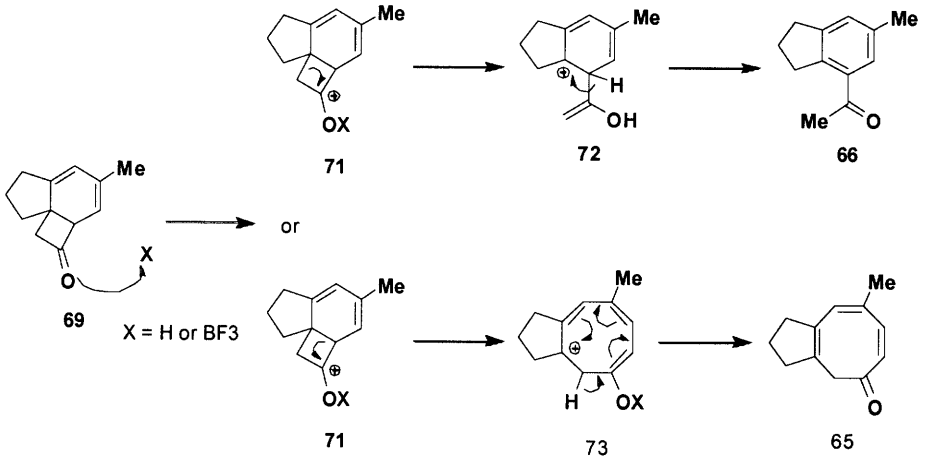


Table 3 summarizes the results of our study to date on the use of boron trifluoride etherate to promote cycloadditions of **61**. With 0.6 equiv of BF_3-OEt_2, no significant changes were observed by TLC from -40 to 0 °C over a total of 52 h (entry 1). The spot by TLC that corresponds to the cyclooctatrienone was visible after 3 h at rt, and after complete consumption of the starting material, cyclooctatrienone **65** was isolated in 34% yield. Entries 2 and 3 in Table 3 describe additional cycloaddition runs with cyclobutenone **61** at room temperature.

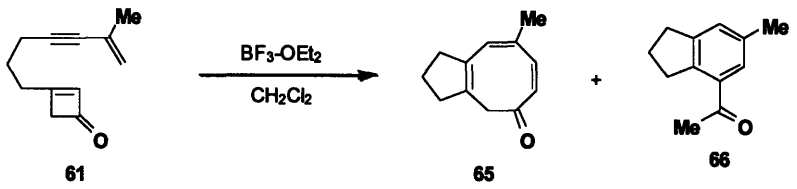
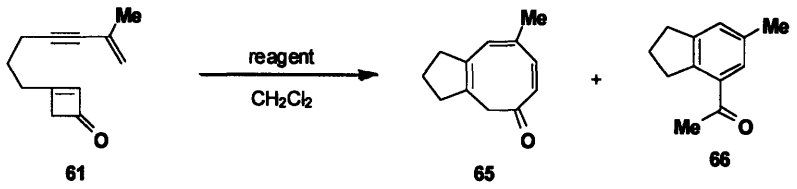


Table 3. BF_3-OEt_2 conditions examined for Cycloaddition Substrate 61

Entry	Conditions	Ratio of 65:66 (by ^{1}H NMR)	Yield of 65[a]
1	0.6 equiv BF_3-OEt_2 -40 °C for 17 h, -15 °C for 17 h, 0 °C for 18 h, and rt for 29 h; then added additional 0.4 equiv BF_3-OEt_2 rt for 16 h	51:49	34
2	1.1 equiv BF_3-OEt_2 rt for 19 h	Not determined	17
3	1.1 equiv BF_3-OEt_2 rt for 21 h	55:45	35

[a] The yields for **66** were not determined.

Table 4 summarizes the results of our further attempts to optimize the [4 + 4] annulation of substrate **61** to give **65**. Cyclooctatrienone **65** was generated under the majority of the conditions listed in Table 4, albeit with starting material also remaining in the majority of the runs. Further studies are planned to improve on the results obtained to date.



61 65 66

Table 4. Examination of various conditions for Cycloaddition Substrate 61

Entry	Reagent	Temperature and time	Results[a]
1	1.5 equiv MsOH	0 °C for 1.5 h, rt for 18 h	26:23:51 mixture of **65**:**66**:**61**
2	2.0 equiv $AlCl_3$	0 °C for 45 min, -78 °C to rt for 13 h	Complex mixture with ca. 1% **65**
3	1.5 equiv Me_2AlCl	-40 °C for 20 h, -15 °C for 5 h, 0 °C for 48 h	Complex mixture with 7:93 ratio of **65**:**61**
4	4.0 mol% $Au(Ph_3P)_3Cl$ and 4.0 mol% $AgBF_4$	0 °C for 18 h, rt for 16 days	Complex mixture with no **65** and 13:87 ratio of **66**:**61**
5	1.0 equiv Et_3SiOTf	0 °C 16.5 h	Complex mixture with 25:47:28 of **65**:**66**:**61**
6	1.0 equiv $TiCl_4$	-50 °C for 5 h, -20 °C for 16 h	Complex mixture

[a] Ratios determined from ^1H NMR spectra

It should be noted that the proposed intermediate 1,3-cyclohexadiene **69** has not been detected by ^1H NMR spectroscopy in the crude mixture of these reactions. In future work, it is planned to carefully monitor the reaction progress by TLC and spectroscopy to track for the formation and consumption of this intermediate during the course of the reaction. We hypothesize that 1,3-cyclohexadiene **69** should exhibit a half-life long enough for its presence to be observed in the reaction mixture and we hope to develop experimental conditions that will allow us to isolate the diene intermediate, and thus verify that the cycloaddition does indeed follow the mechanistic course proposed in Scheme 28.

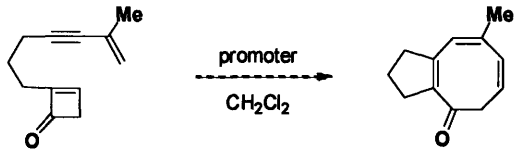
Although analyses of spectral data support the assignment of the structure of the desired cyclooctatrienone, it is still necessary to compare our data with that of known similar compounds. Unfortunately, little data exists in the literature for

cyclooctatrienones with substitution patterns similar to **65**. Investigation of the cycloaddition of the 3-enynyl cyclobutenone substrate **74** (figure 6) is of interest as the resulting cyclooctatrienone should be converted via hydrogenation and/or deoxygenation of the ketone to a known compound.

74

Figure 6

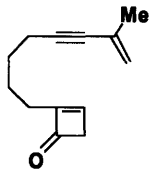
With the success of the enyne cycloaddition for the 3-sustituted cyclobutenone **61**, we turned our attention to the 2-substituted substrate, **64**. Unfortunately, we were not able to detect the formation of cyclooctatrienone **75** under the conditions examined to date (Table 5). Future directions for this system include studies of the cycloaddition under other Lewis and Brønsted acidic conditions. Additionally, investigations on the homolog **76** (Figure 7) may be worthwhile as well because a preliminary study of molecular models of 3-substituted substrate **61** and 2-substituted substrate **64** seem to suggest that the conformation of the latter may prevent the reactive enyne moiety to reach the enynophile for cycloaddition to occur.



64 **75**

Table 5. Conditions Examined for Cycloaddition Substrate 64

Entry	Reagent	Temperature and time	Results
1	1.1 equiv $BF_3{\cdot}OEt_2$	rt for 14 h	Complex mixture
2	1.1 equiv $BF_3{\cdot}OEt_2$	-78 °C for 8 h, -50 °C for 37 h, -20 °C for 24 h	Complex mixture with about 50% remaining **64** (by TLC)
3	1.5 equiv MsOH	rt for 4 days	Complex mixture with about 60% remaining **64** (by TLC)
4	1.5 equiv Me_2AlCl	-78 °C for 8 h, -50 °C for 39 h, rt for 30 h	Complex mixture



76

Figure 7

Summary

A new [4 + 4] annulation method has been developed for the synthesis of eight-membered carbocycles that involves intramolecular [4 + 2] cycloaddition of conjugated enynes with cyclobutenones.

Part IV

Experimental Section

General Procedures. All reactions were performed in flame-dried glassware under a positive pressure of argon and stirred magnetically unless otherwise indicated. Air- and moisture-sensitive liquids and solutions were transferred via syringe or cannula and were introduced into reaction vessels through rubber septa. Reaction product solutions and chromatography fractions were concentrated by using a Büchi rotary evaporator at 15-20 mmHg and then at 0.05 mmHg (vacuum pump) unless otherwise indicated. Column chromatography was performed on EM Science silica gel 60 (35-75 μm) or Silicycle silica gel 60 (230-400 mesh).

Materials. Commercial grade reagents and solvents were used without further purification except as indicated below.

(a) Purified by pressure filtration through activated alumina:
Dichloromethane, diethyl ether, and tetrahydrofuran

(b) Purified by pressure filtration through activated alumina and Cu(II) oxide:
Toluene

(c) Distilled under argon or vacuum:
Hexamethyl phosphoramide, oxalyl chloride

(d) Distilled under argon from calcium hydride:
Acetonitrile, boron trifluoride etherate, pentane, and triethylamine

(e) Dried under vacuum:
Cerium (III) chloride heptahydrate, paraformaldehyde

(f) Other:
Copper (I) was extracted in a Soxhlet extractor and then dried under vacuum;
Ethoxyacetylene was predried over $CaCl_2$ and then distilled neat;
n-Butyllithium was titrated according to the Watson-Eastham method using menthol or BHT in THF at 0 °C with 1,10-phenanthroline as an indicator[41];
tert-Butyllithium was titrated according to the double deprotonation method in THF at rt using diphenyacetic acid as an indicator[42]

---

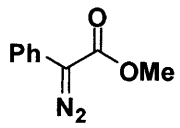
[41] (a) Watson, S. C.; Eastham, J. F. *J. Organomet. Chem.* **1967**, *9*, 165. (b) Ellison, R. A.; Griffin, R.; Kotsonis, F. N. *Organomet. Chem.* **1972**,*369*, 209.
[42] Kofron, W. G.; Baclawski, L. M. *J. Org. Chem.* **1976**, *41*, 1879

Instrumentation. Infrared spectra werea obtained using a Perkin Elmer 2000 FT-IR spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were measured with Inova 300, and Bruker 400 spectrometers. ^{1}H NMR chemical shifts are expressed in parts per million (δ) downfield from tetramethylsilane (with the $CHCl_3$ peak at 7.24 ppm used as a standard on the Bruker spectrometers and 7.27 ppm on the Inova). ^{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 telsa Fourier transform mass spectrometer. Elemental analyses were performed by E&R Microanalytical Laboratory, Inc. of Parsippany, NJ.

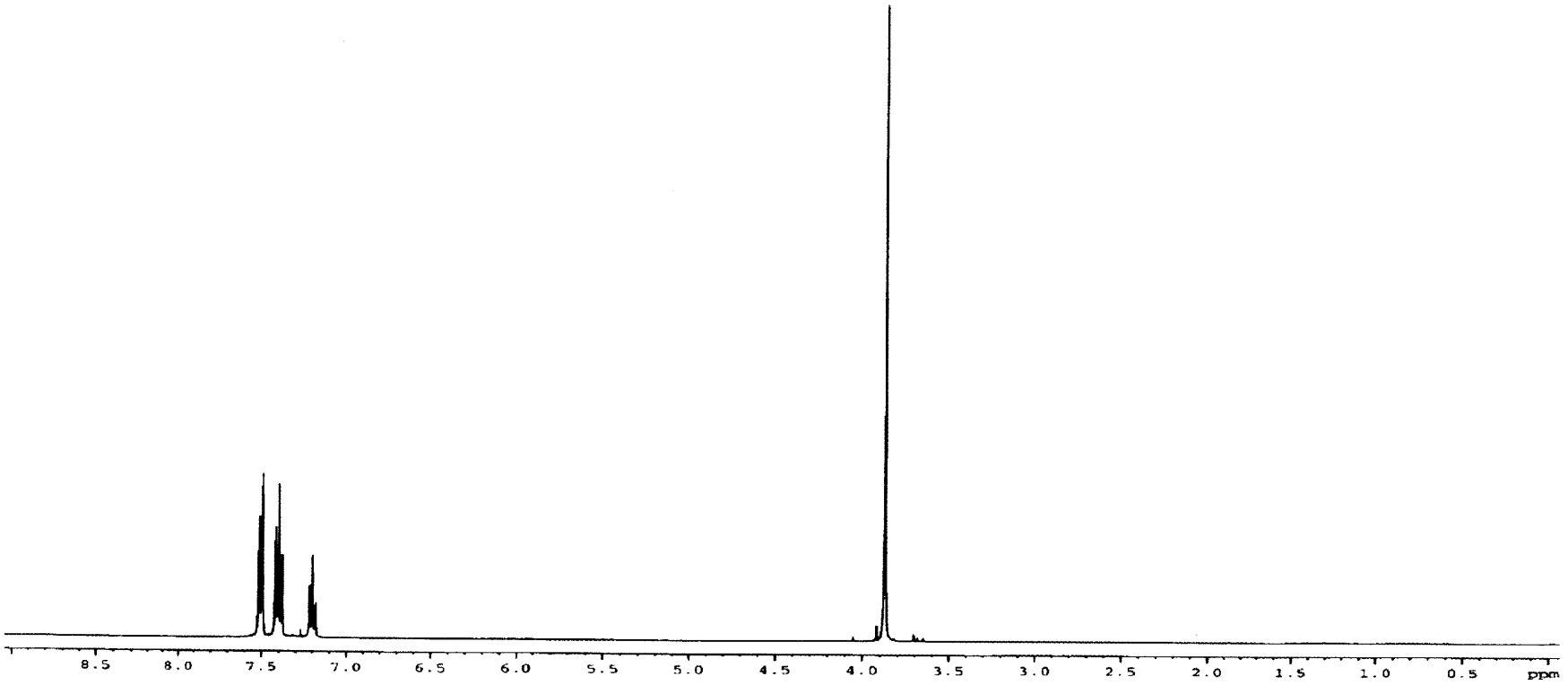
Methyl 2-diazo-2-phenylacetate[43] **(28).** A flame-dried, 500-mL, round-bottomed flask equipped with a rubber septum and argon inlet adapter was charged with TsN_3 (16.800 g, 81.9 mmol), 115 mL of acetonitrile, and the ester **27** (11.54 mL, 12.30 g, 81.9 mmol) and then cooled to 0 °C. DBU (16.0 mL, 16.3 g, 107 mmol) was added dropwise over 20 min via syringe, and after 5 min the cooling bath was removed and the reaction mixture was allowed to stir at rt for 21 h. Concentration of the reaction mixture provided a red-orange residue, which was dissolved in 150 mL of CH_2Cl_2, washed with three 200-mL portions of saturated NH_4Cl solution, 200 mL of water, and 100 mL of brine, dried over $MgSO_4$, filtered, and concentrated to give a red-orange oil containing a sticky brownish-orange solid. Hexane (50 mL) was added at which point a white precipitate appeared. The orange solution was carefully decanted from the insoluble solids which were washed with 150 mL of hexane. The combined hexane washes were concentrated to provide 12.915 g of an orange oil. Column chromatography on 260 g of silica gel (elution with 10% EtOAc- hexanes) gave 3.645 g of **28** as an orange oil. Mixed fractions (7.607 g) were further purified on 300 g of silica gel (elution with 10% EtOAc-hexanes) to provide 3.762 g of additional **28** and 2.717 g of mixed fractions which were combined with 3.841 g of the sticky solid that had been washed with hexane earlier. This material was dissolved in 150 mL of CH_2Cl_2 and concentrated onto 20 g of silica gel. The free-flowing powder was placed at the top of a column of 165 g of silica gel and eluted with 10% EtOAc-hexanes to give 2.851 g of additional **28**; total yield 10.258 g (71%): IR (neat): 2954, 2400, 2086, 1704, 1287, 1249 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.49-7.52 (m, 2 H), 7.38-7.42 (m, 2 H), 7.18-7.22 (m, 1 H), 3.87 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.6, 129.0, 125.8, 125.5, 123.9, 52.0, 63.3.

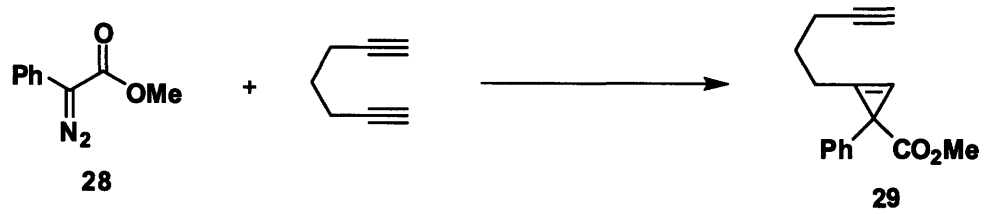
---

[43] This procedure is based on the preparation of this compound by Chuprakov, S.; Rubin, M.; Gevorgyan, V. *J. Am. Chem. Soc.* **2005**, *127*, 3714.

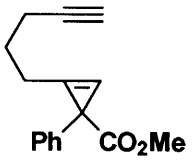


28

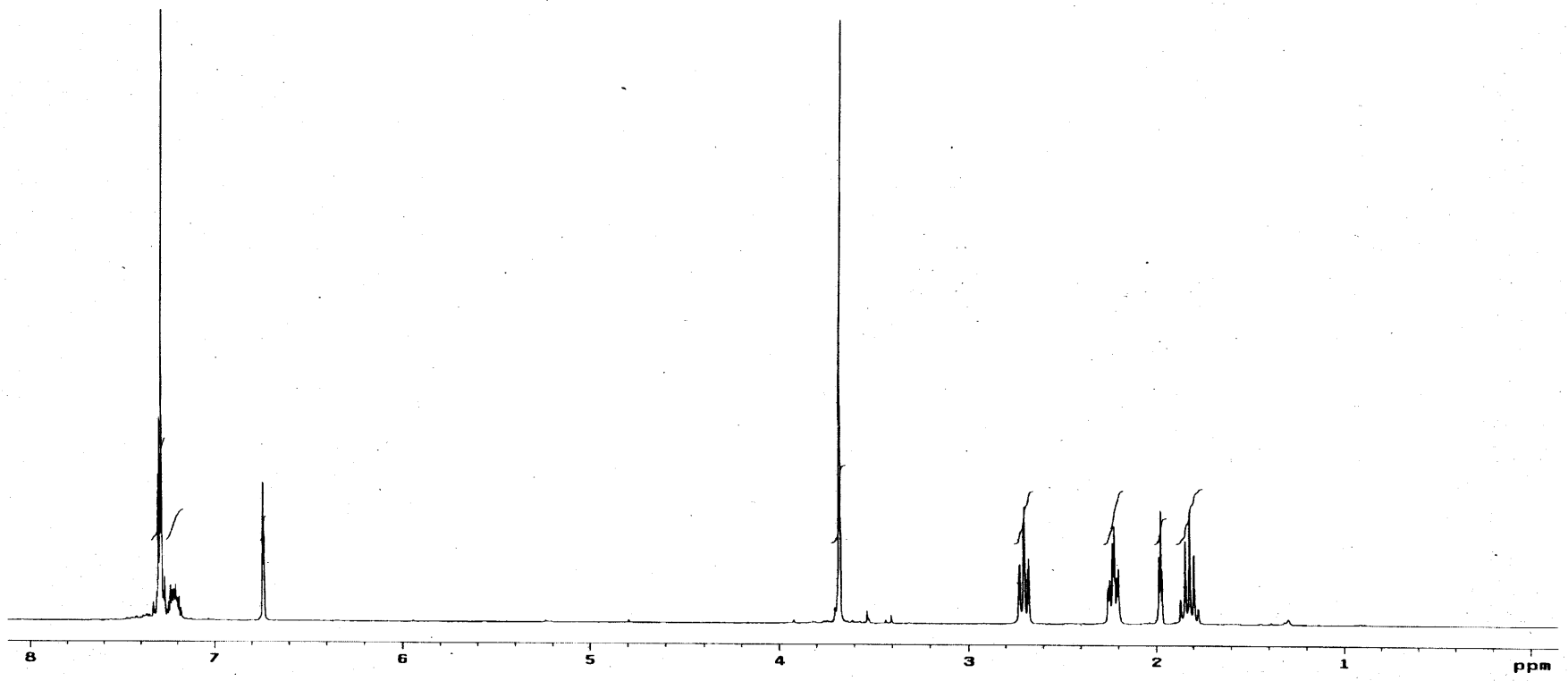


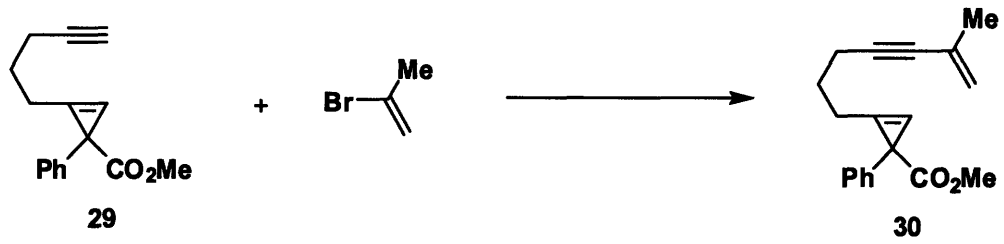


Methyl 2-(pent-4-ynyl)-1-phenylcycloprop-2-enecarboxylate (29). A flame-dried, 100-mL, two-necked, pear-shaped flask equipped with a rubber septum and argon inlet adapter was charged with $Rh_2(OAc)_4$ (0.042 g, 0.094 mmol), 36 mL of CH_2Cl_2, and 1,6-heptadiyne (4.3 mL, 3.2 g, 37.6 mmol). Diazo ester **28** (0.992 M in CH_2Cl_2, 19.0 mL, 18.8 mmol) was added via syringe pump over 18 h. After the addition was complete, the brownish-orange mixture was stirred at rt for 30 min. The reaction mixture was filtered through a pad of Celite in a sintered glass funnel with the aid of 40 mL of CH_2Cl_2 and concentrated to afford 4.593 g of a brownish-orange oil. Column chromatography on 225 g of silica gel (elution with 10-20% EtOAc-hexanes) afforded 3.057 g (68%) of **29** an orange oil: IR (neat): 3290, 2950, 2117, 1717, 1601, 1287, 1224 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.28-7.34 (m, 4 H), 7.20-7.26 (m, 1 H), 6.74 (t, J = 1.4 Hz, 1 H), 3.68 (s, 3 H), 2.70 (td, J = 1.3, 7.3 Hz, 2 H), 2.24 (td, J = 2.6, 7.0 Hz, 2 H), 1.98 (t, J = 2.6 Hz, 1 H), 1.82 (quintet, J = 7.1, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.8, 141.5, 128.3, 128.1, 126.4, 120.1, 97.9, 83.3, 69.2, 52.1, 33.0, 25.6, 23.5, 17.9.

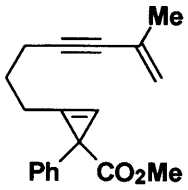


29

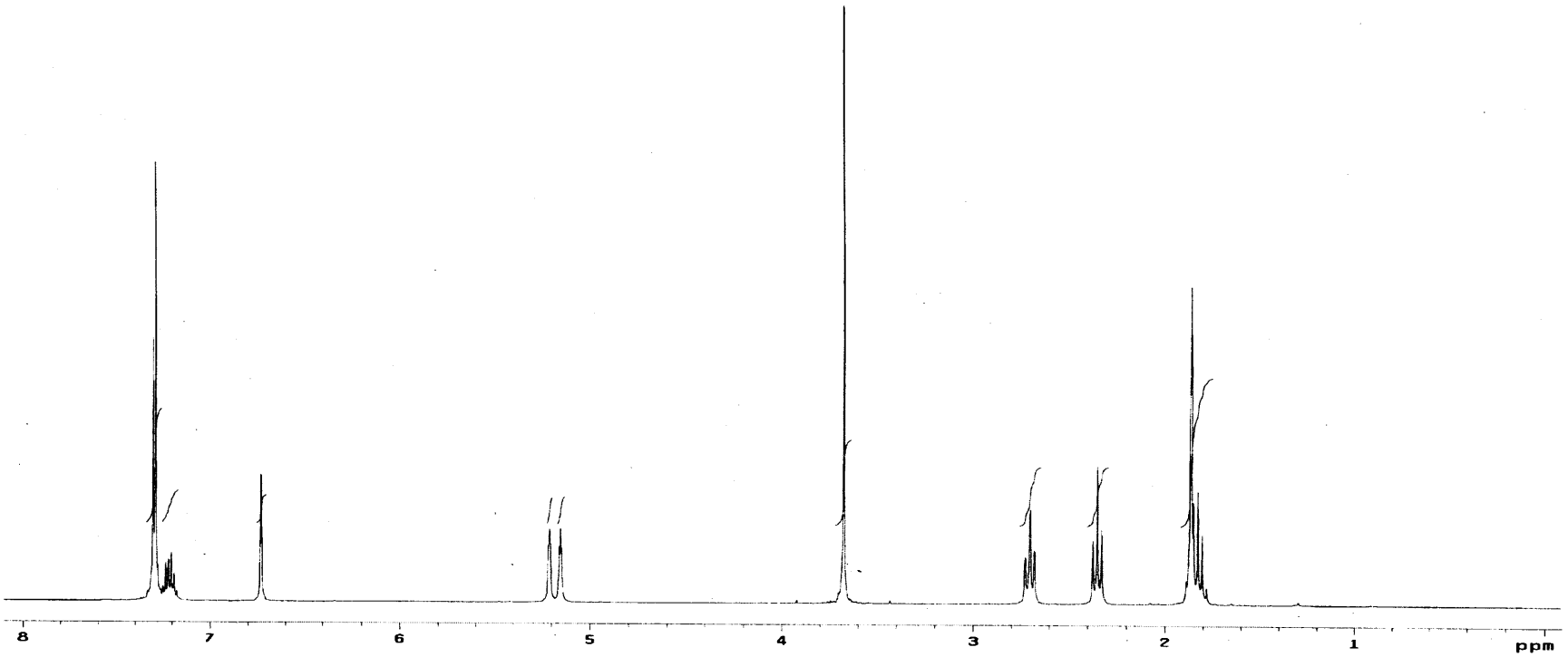


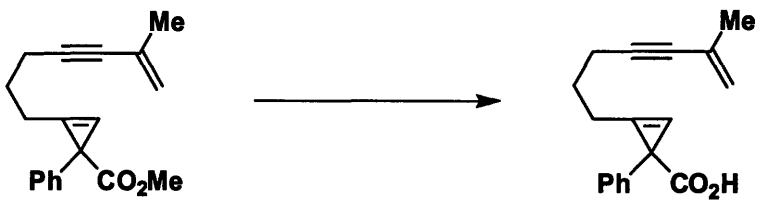


Methyl 2-(6-methylhept-6-en-4-ynyl)-1-phenylcycloprop-2-enecarboxylate (30). A flame-dried, 100-mL, two-necked, pear-shaped flask equipped with a rubber septum and 60-mL pressure-equalizing addition funnel fitted with an argon-inlet adapter was charged with $Pd(Ph_3P)_2Cl_2$ (0.645 g, 0.920 mmol), CuI (0.089 g, 0.460 mmol), 17 mL of THF, and triethylamine (4.5 mL, 3.3 g, 33 mmol). The mixture was cooled at 0 °C in an ice bath while 2-bromopropene (2.5 mL, 3.4 g, 28 mmol) was added in one portion via syringe. A solution of alkyne **29** (2.211 g, 9.20 mmol) in 20 mL of THF was added dropwise over 40 min (3 mL of THF rinse). The cooling bath was removed, and the reaction mixture was allowed to stir for 12 h at rt. The red-orange mixture with suspended orange solids was then filtered through a 3-cm plug of silica gel in a sintered glass funnel with the aid of 80 mL of Et_2O. The filtrate was washed with three 50-mL portions of saturated $NaHCO_3$ solution, 50 mL of water, 50 mL of brine, dried over $MgSO_4$, filtered, and concentrated to give 3.020 g of a brownish-red oil with red precipitate. This material was dissolved in 60 mL of CH_2Cl_2 and concentrated onto 10 g of silica gel. The free-flowing powder was placed at the top of a column of 240 g of silica gel and eluted with 10% EtOAc-hexanes to afford 1.200 g (47%) of **30** as a yellow-orange oil: IR (neat): 2950, 2224, 1717, 1614, 1288,1224, 894 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.26-7.33 (m, 4 H), 7.18-7.25 (m, 1 H), 6.73 (t, J = 1.2 Hz, 1 H), 5.22 (s, 1 H), 5.16 (app t, J = 1.8 Hz, 1 H), 3.68 (s, 3 H), 2.70 (td, J = 7.3, 1,2 Hz, 2 H), 2.35 (t J = 7.0 Hz, 2 H), 1.87 (s, 3 H), 1.83 (quintet, J = 7.2 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.7, 141.5, 128.2, 128.0, 127.0, 126.2, 120.6, 120.0, 97.7, 87.9, 82.6, 51.9, 32.9, 25.8, 23.7, 23.5, 18.6.



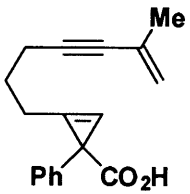
30



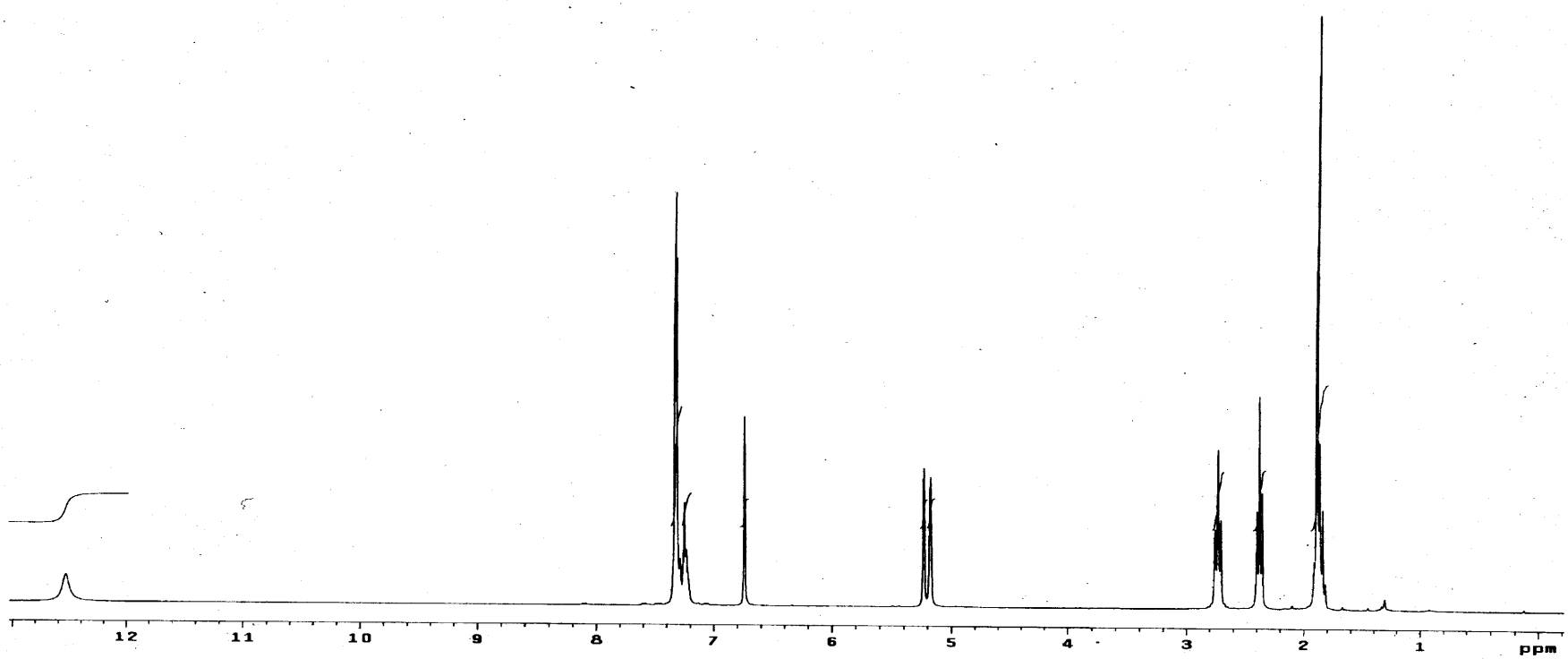


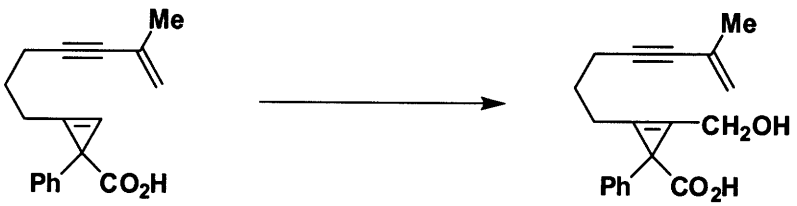
30 31

2-(6-Methylhept-6-en-4-ynyl)-1-phenylcycloprop-2-enecarboxylic acid (31). A 100-mL, two-necked, pear-shaped flask equipped with a rubber septum with argon inlet needle and a 20-mL pressure-equalizing addition funnel fitted with a rubber septum was charged with a solution of ester **30** (2.004 g, 7.15 mmol) in 16 mL of MeOH and cooled to 0 °C. KOH (8.5 % w/v aqueous solution, 12.0 mL, 11.9 g, 17.9 mmol) was added dropwise over 15 min via the addition funnel, and the resulting orange biphasic mixture was stirred at 0 °C for 15 min. The addition funnel was replaced by a coldfinger reflux condenser with argon-inlet side-arm and the argon-inlet needle was removed from the septum. The reaction mixture was then stirred in an oil bath pre-heated to 60 °C for 20 h. Concentration of the resulting mixture provided a biphasic residue which was cooled to 0 °C and acidified to pH 1.5 with 7 mL of 6 M aqueous HCl solution. The resulting mixture was diluted with 10 mL of CH_2Cl_2, and the aqueous layer was separated and extracted with three 20-mL portions of CH_2Cl_2. The combined organic phases were washed with 40 mL of saturated $NaHCO_3$, 40 mL of water, and 40 mL brine, dried over $MgSO_4$, filtered, and concentrated to give 1.947 g of an orange oil. Column chromatography on 80 g of silica gel (elution with 15-50 % EtOAc-hexanes) afforded 1.720 g (99%) of **31** as a yellow-orange oil. IR (neat): 3584, 2951, 2224, 1685, 1613, 1255, 896 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 12.53 (br s, 1 H), 7.25-7.33 (m, 4 H), 7.21-7.25 (m, 1 H), 6.74 (app s, 1 H), 5.23 (s, 1H), 5.18 (s, 1 H), 2.73 (t, J = 7.1 Hz, 2 H), 2.38 (t, J = 6.9 Hz, 2 H), 1.89 (s, 3 H), 1.86 (quintet, J = 7.1 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 182.5, 140.8, 128.5 128.2, 127.2, 126.6, 120.9, 120.0, 97.3, 88.0, 82.9, 82.8, 26.0, 23.9, 23.7, 18.9.



31



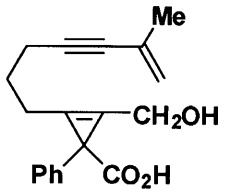


31 32

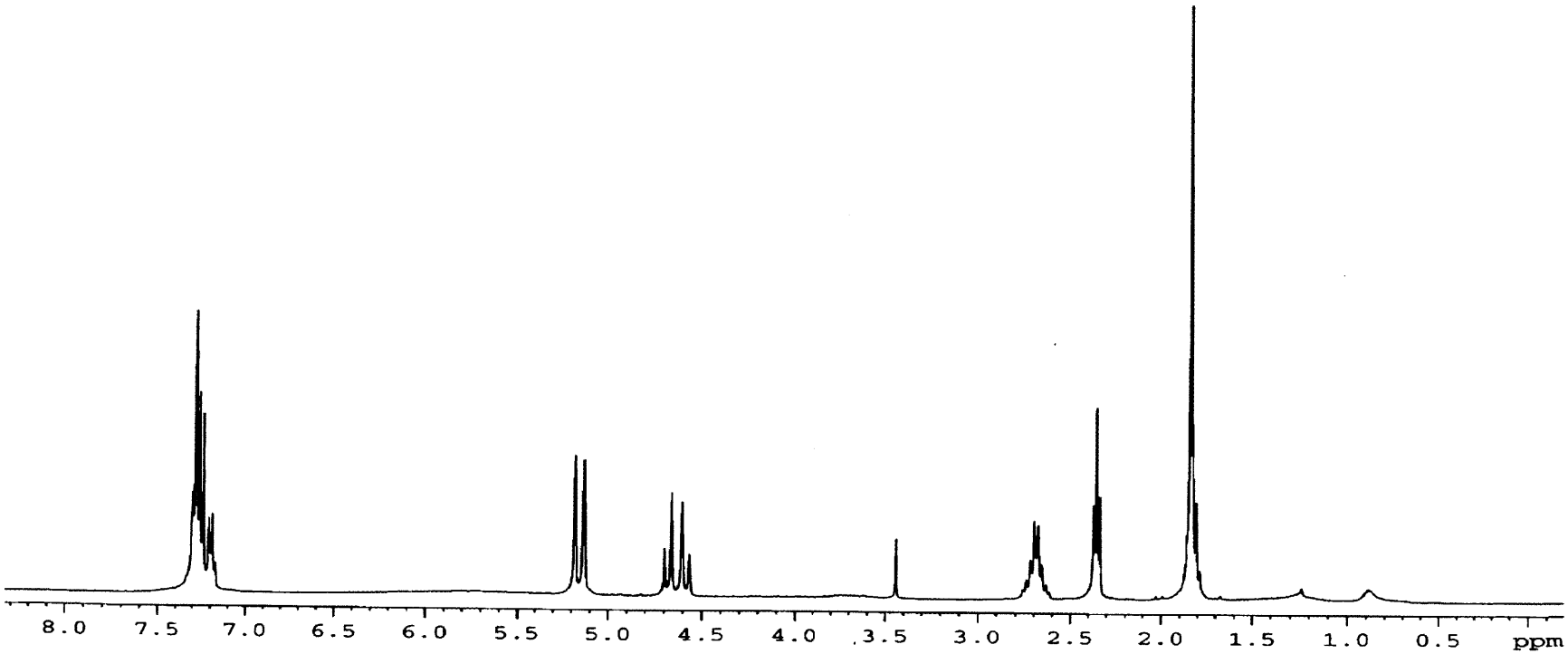
2-(Hydroxymethyl)-3-(6-methylhept-6-en-4-ynyl)-1-phenylcycloprop-2-enecarboxylic acid (32). A flame-dried, 100-mL, recovery flask equipped with a rubber septum, argon inlet needle, and thermocouple was charged with a solution of cyclopropene **31** (1.777g, 6.67 mmol) in 40 mL of THF and cooled to -78 °C. *n*-Butyllithium (2.49 M in hexane, 5.9 mL, 14.7 mmol) was added dropwise over 5 min via syringe, and the resulting dark red mixture was stirred at -78 °C for 2.5 h. The cooling bath was removed, and the red-brown reaction mixture was allowed to warm to -40 °C and then maintained at this temperature in a dry-ice/acetone bath.

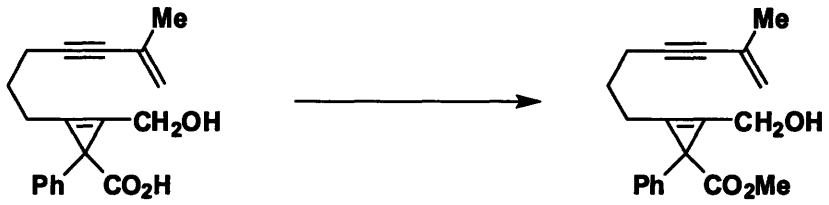
A flamed-dried, 10-mL, two-necked, round-bottomed flask equipped with a glass stopper and argon inlet adapter was charged with paraformaldehyde (2.005 g, 66.7 mmol). The glass stopper was replaced with an outlet adapter fitted with tygon tubing attached to a drying tube (Ca_2SO_4). The exit of the drying tube was attached to tygon tubing equipped at its other end with a needle adapter and a 20-G, 4-in needle. The needle was immersed into the reaction mixture. The flask was immersed in an oil bath preheated at 170-190 °C and the monomeric formaldehyde thus generated was bubbled into the reaction mixture over 25 min. Some monomeric formaldehyde polymerized in the tygon tubing. The inlet needle in the reaction mixture became clogged three times during the course of bubbling and was replaced by new needles (20-G, 4-in and then two 15-G, 12-in needles). The internal temperature of the reaction mixture fluctuated between -40 and -20 °C during the addition of formaldehyde. After the addition of formaldehyde, the yellow reaction mixture was allowed to stir at -20 to 0 °C for 30 min. The temperature of the reaction mixture was maintained at 0 °C, and additional formaldehyde gas generated from paraformaldehyde (0.602 g, 20.0 mmol) was bubbled into the reaction mixture over 10 min. The cooling bath was removed, and the mixture was allowed to stir at rt for 1.5 h. The reaction mixture was diluted with 50 mL of water and acidified to pH 1 with 10 mL of 1 M aqueous HCl and 2 mL of 6 M aqueous HCl.

The aqueous layer was separated and extracted with three 60-mL portions of CH_2Cl_2. The combined organic phases were washed with 150 mL of saturated $NaHCO_3$ solution and 150 mL of brine, dried over $MgSO_4$, filtered, and concentrated to give 1.976 g of a brownish-yellow oil. This material was dissolved in 50 mL of CH_2Cl_2 and concentrated onto 6.5 g of silica gel. The free-flowing powder was placed at the top of a column of 198 g of silica gel and eluted with 10% MeOH-CH_2Cl_2 to furnish 1.216 g (62%) of **32** as a golden-yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26-7.31 (m, 4 H), 7.17-7.21 (m, 1 H), 5.18 (s, 1 H), 5.13 (s, 1H), 4.68, 4.58 (AB, J = 15.2 Hz, each 1 H), 2.62-2.76 (m, 2 H), 2.35 (t, J = 6.86 Hz, 2 H), 1.83 (s, 3 H), 1.82 (quintet, J = 7.2 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.3, 140.8, 128.7, 128.3, 127.1, 126.6, 120.9, 112.9, 109.2, 88.1, 82.9, 55.9, 35.8, 26.1, 23.9, 23.3, 18.8.



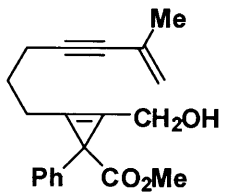
32



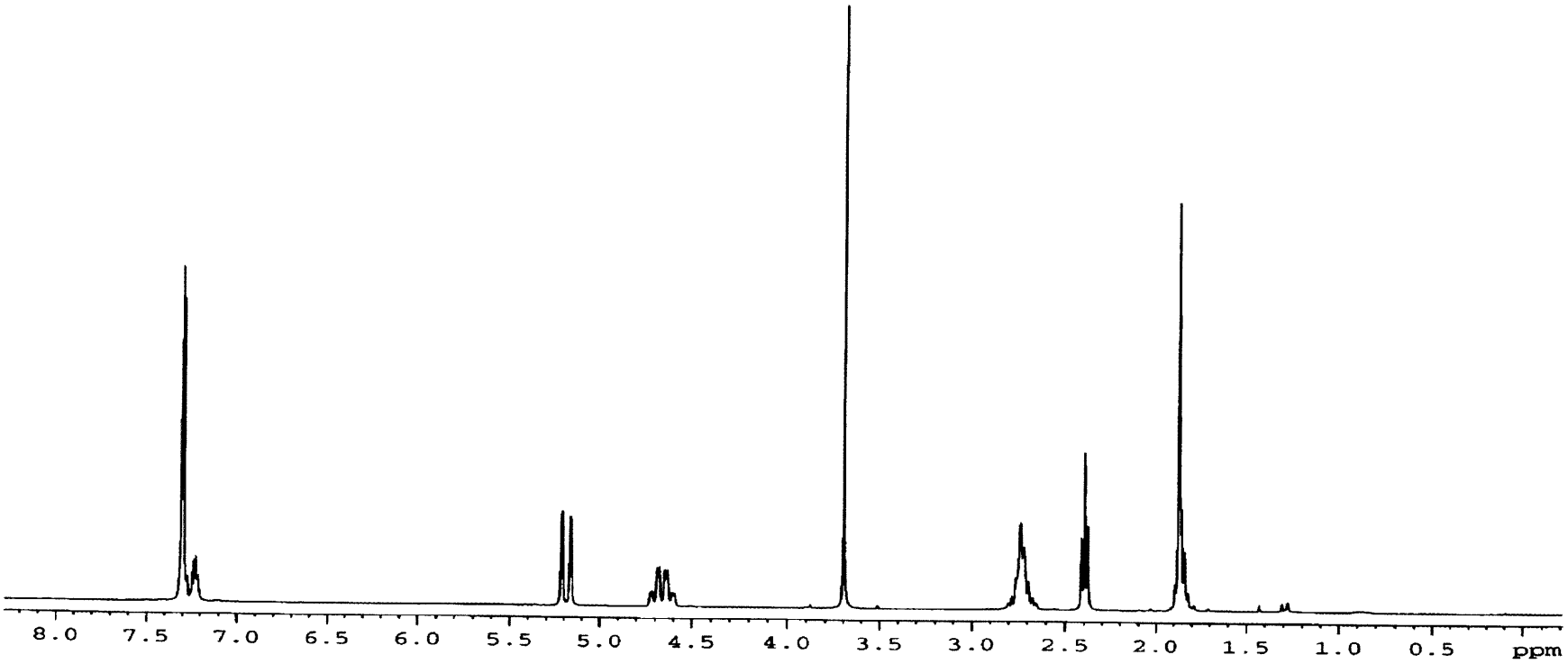


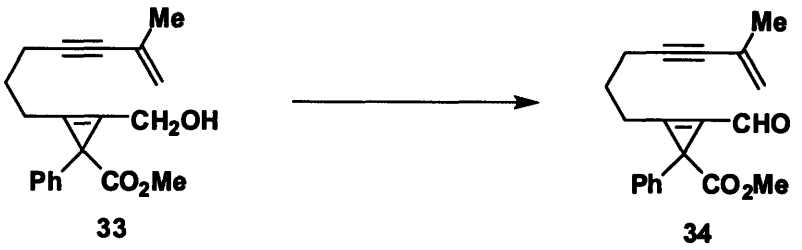
32 33

Methyl 2-(hydroxymethyl)-3-(6-methylhept-6-en-4-ynyl)-1-phenylcycloprop-2-enecarboxylate (33). A flame-dried, 100-mL, two-necked, pear-shaped flask equipped with a rubber septum and coldfinger reflux condenser with argon inlet side-arm was charged with a solution of acid **32** (0.894 g, 3.02 mmol) in 30 mL of MeOH. Concd H_2SO_4 (0.38 mL, 0.453 mmol) was added dropwise over 10 s and the resulting mixture was stirred in an oil bath preheated at 60 °C for 16 h. The resulting brownish-yellow and cloudy mixture was diluted with 10 mL of water and then concentrated. The residue was diluted with 10 mL of EtOAc, and the aqueous layer was separated and extracted with two 10-mL portions of EtOAc. The combined organic layers were washed with 20 mL of saturated $NaHCO_3$ solution, 10 mL of water and 10 mL of brine, dried over $MgSO_4$, filtered, and concentrated to give 0.935 g of a brownish-yellow oil. Column chromatrography on 94 g of silica gel (elution with 30% EtOAc-hexanes) afforded 0.622 g (66%) of **33** as a pale yellow oil: IR (neat): 3436, 3093, 3085, 2950, 2223, 1718, 1699, 1613, 1288, 1220 cm^{-2}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.27-7.31 (m, 4 H), 7.20-7.25 (m, 1H), 5.21 (s, 1 H), 5.15 (s, 1H), 4.70, 4.62 (ABX, J_{AB} = 15.2 Hz, J_{AX} = 5.4 Hz, each 1 H), 3.70 (s, 3 H), 2.65-2.80 (m, 3 H), 2.40 (t, J = 6.9 Hz, 2 H), 1.87 (s, 3 H), 1.86 (quintet, J = 6.9 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 176.2, 141.4, 128.5, 128.3, 127.2, 126.6, 120.9, 113.0, 110.2, 88.1, 82.9, 56.3, 52.3, 36.2, 26.2, 23.9, 23.4, 18.9.

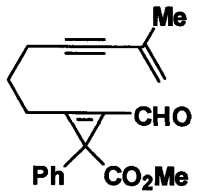


33

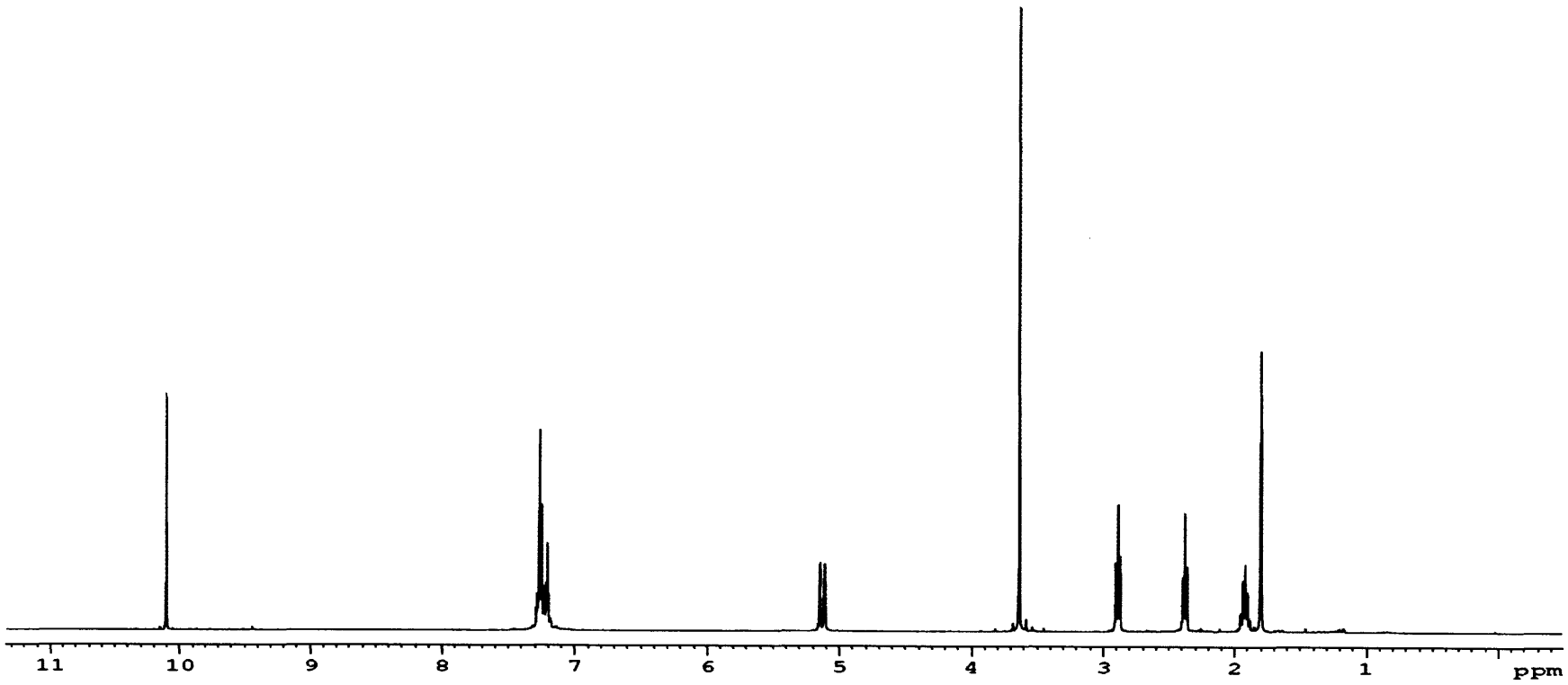




Methyl 2-formyl-3-(6-methylhept-6-en-4-ynyl)-1-phenylcycloprop-2-enecarboxylate (34). A flame-dried, 25-mL, two-necked, pear-shaped flask equipped with a rubber septum and argon inlet adapter was charged with alcohol **33** (0.325 g, 1.05 mmol), 7 mL of CH_2Cl_2, and Dess-Martin periodinane (0.670 g, 1.58 mmol). The reaction mixture was stirred at rt for 40 min and then filtered through a silica gel plug in a sintered glass funnel with the aid of 40 mL of 30% EtOAc-hexanes. Concentration furnished 0.321 g of **34** as a pale yellow oil that was used in the next step without further purification: IR (neat): 3432, 3087, 3059, 2952, 2222, 1725, 1673, 1613, 1235 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 10.10 (s, 1 H), 7.25-7.29 (m, 1H), 7.18-7.24 (m, 1 H), 5.15 (s, 1 H), 5.11 (app t, J = 1.7 Hz, 1 H), 3.64 (s, 3 H), 2.89 (t, J = 7.4 Hz, 2 H), 2.38 (t, J = 6.8 Hz, 2 H), 1.92 (quintet, J = 7.1 Hz, 2 H), 1.80 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.8, 173.1, 139.0, 134.6, 128.9, 128.6, 127.5, 127.0, 121.2, 109.1, 87.2, 83.4, 52.7, 37.9, 26.0, 25.5, 23.9, 18.9.

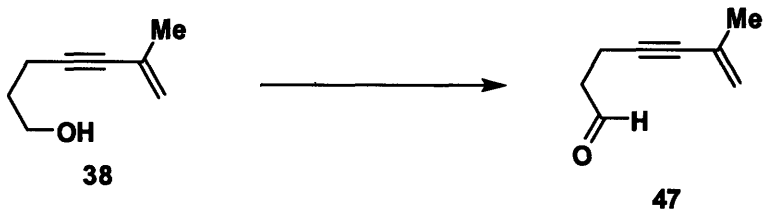


34

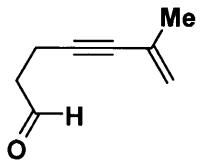


38

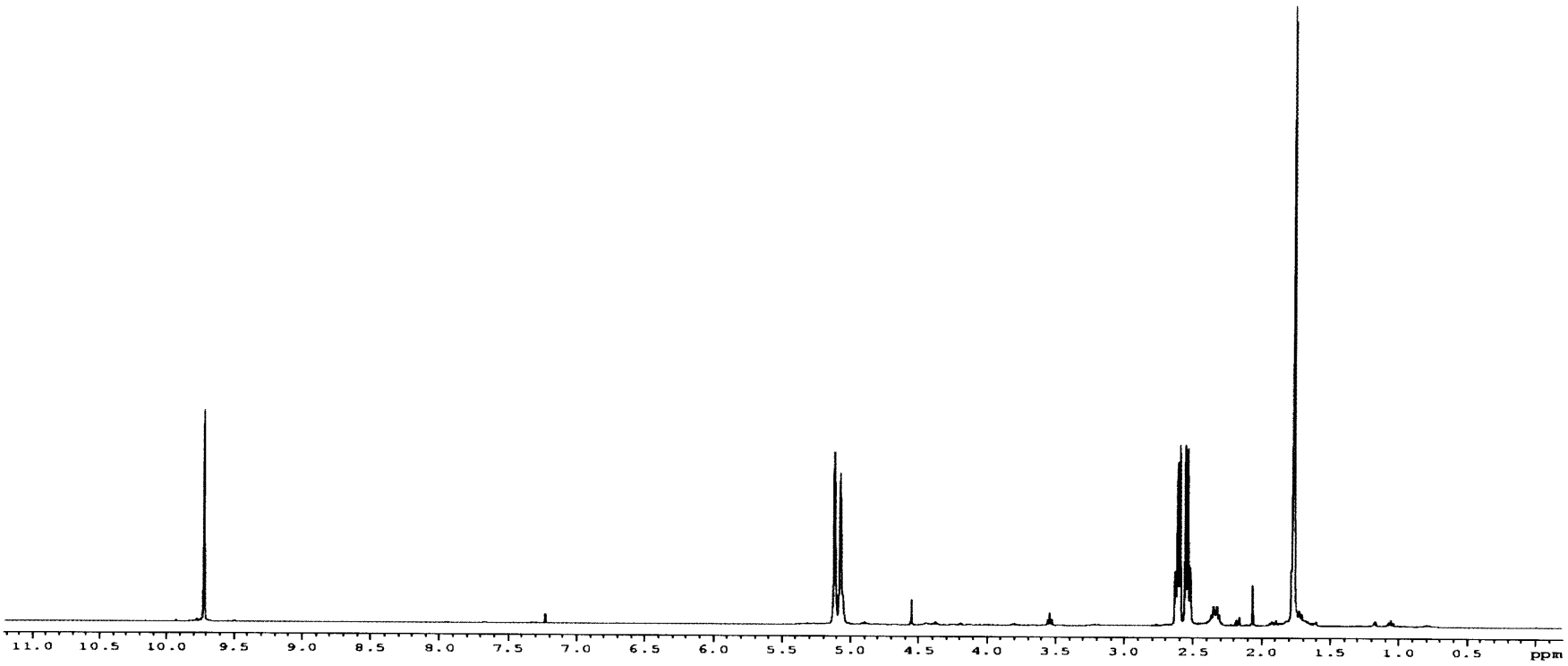
6-Methylhept-6-en-4-yn-1-ol[26] (38). A flame-dried, 100-mL, three-necked, round-bottomed flask equipped with a rubber septum, 10-mL pressure-equalizing addition funnel fitted with a rubber septum, and argon inlet adapter was charged with $Pd(Ph_3P)_2Cl_2$ (1.187 g, 1.69 mmol), CuI (0.644 g, 3.37 mmol), 45 mL of THF, and Et_3N (17.5 mL, 12.5 g, 126 mmol). The mixture was cooled to 0 °C, and 2-bromopropene (11.2 mL, 15.3 g, 126 mmol) was added in one portion via syringe. 4-Pentynol (8.0 mL, 7.1 g, 84 mmol) was added dropwise via addition funnel over 15 min (3 mL of THF rinse). The cooling bath was removed, and the black reaction mixture was allowed to stir at rt for 17 h. The reaction mixture was then filtered through a 3-cm plug of silica gel in a sintered glass funnel with the aid of 200 mL of Et_2O and then concentrated. The dark green residue was dissolved in 50 mL of Et_2O, washed with three 60–mL portions of saturated $NaHCO_3$ solution and 40 mL of brine, dried over $MgSO_4$, filtered, and concentrated to give 10.211 g of a greenish-black oil. Column chromatography on 300 g of silica gel (elution with 20% EtOAc-hexanes) afforded 9.168 g (88%) of **38** as a tan-colored oil with spectroscopic data identical to that previously reported for this compound.[26]

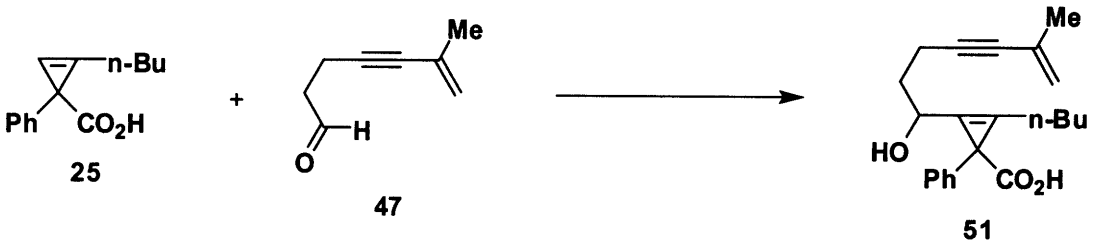


6-Methylhept-6-en-4-ynal (47). A flame-dried, 100-mL recovery flask equipped with a rubber septum and argon inlet needle was charged with a solution of oxalyl chloride (0.78 mL, 1.2 g, 9.1 mmol) in 15 mL of CH_2Cl_2 and cooled at -78 °C while DMSO (1.2 mL, 1.3 g, 16.7 mmol) was added in one portion. The resulting mixture was stirred at -78 °C for 10 min and then a solution of alcohol **38** (0.940 g, 7.57 mmol) in 12 mL of CH_2Cl_2 was added dropwise via cannula over 10 min (3 ml of CH_2Cl_2 rinse). After 15 min, triethylamine (5.0 mL 3.6 g, 36 mmol) was added dropwise over 15 min via syringe, and the resulting mixture was stirred at -78 °C for 20 min. The cooling bath was then removed and the reaction mixture was allowed to stir at rt for 37 h. The resulting mixture was diluted with 30 mL of saturated NH_4Cl solution, and the aqueous layer was separated and extracted with three 20-mL portions of CH_2Cl_2. The combined organic layers were washed with 40 mL of water and 40 mL of brine, dried over $MgSO_4$, filtered, and concentrated to give 0.915 g of **38**as a tan-colored oil that was used in the next step without further purification: IR (neat): 3096, 2832, 2728, 2227, 1728, 1614, 897 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.72 (s, 1 H), 5.12 (s, 1H), 5.08 (s, 1 H), 2.52-2.63 (m, 4 H), 1.77 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.6, 126.9, 121.2, 86.9, 82.7, 42.7, 23.7, 12.6.

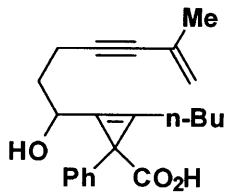

Me
H
O

47

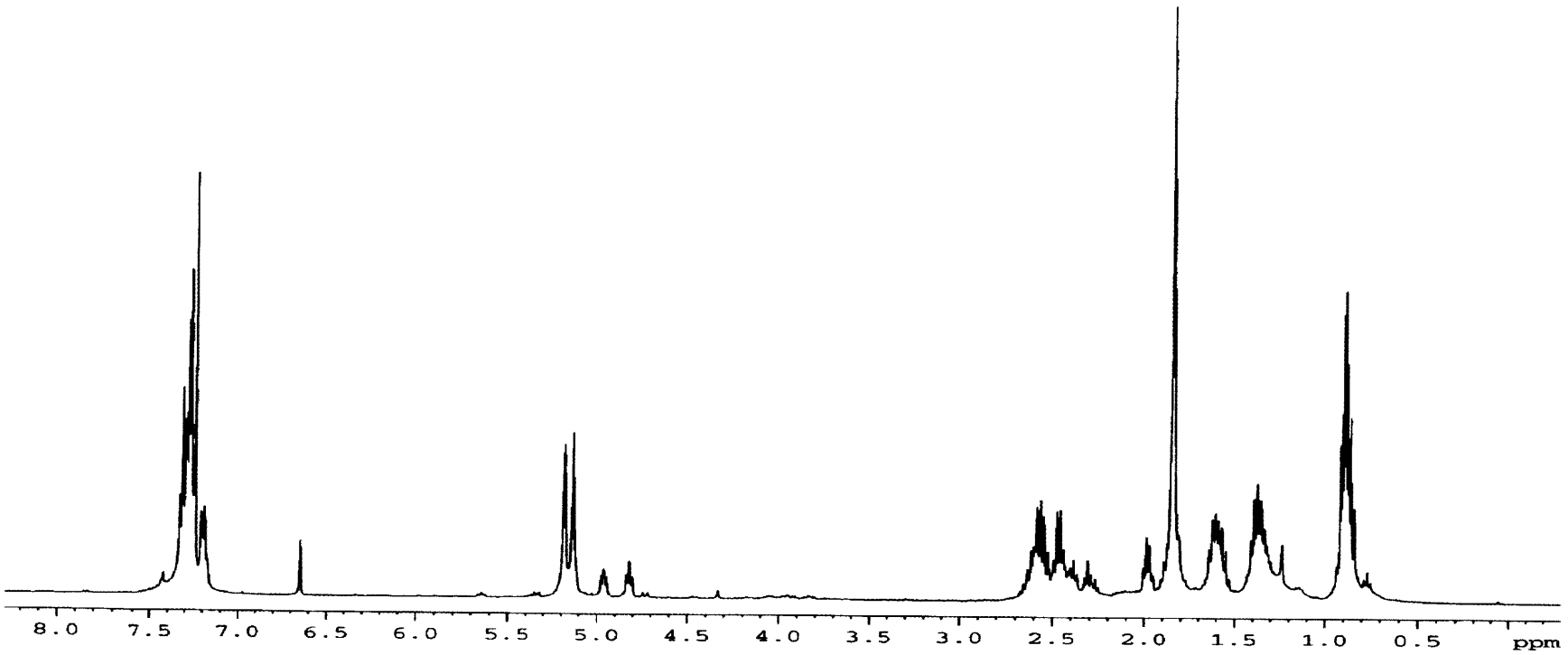

11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

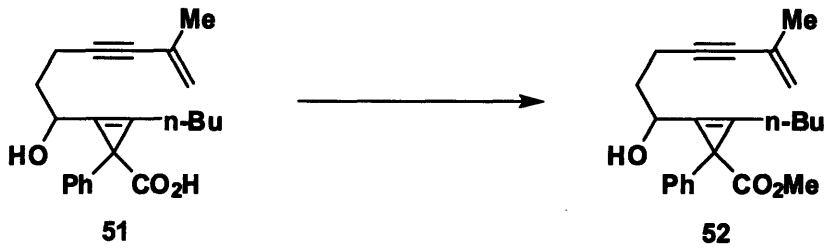


2-Butyl-3-(1-hydroxy-6-methylhept-6-en-4-ynyl)-1-phenylcycloprop-2-enecarboxylic acid (51). A flame-dried, 50-mL, recovery flask equipped with a rubber septum and argon-inlet needle was charged with a solution of cyclopropene **25**[21a] (0.780 g, 3.61 mmol) in 16 mL of THF and cooled at -78 °C while *n*-butyllithium (2.49 M in hexane, 3.2 mL, 7.9 mmol) was added dropwise over 4 min. The resulting yellow-orange mixture was stirred at -78 °C for 45 min, the cooling bath was removed, and the mixture was allowed to warm to -10 °C and maintained at -10 °C in a dry-ice/acetone bath. Aldehyde **47** (0.571 g, 4.69 mmol) was added dropwise over 2 min via cannula (1 mL of THF rinse), and the resulting brownish-red mixture was stirred at -15 to -5 °C for 45 min. The cooling bath was then removed and the reaction mixture was stirred at rt for 4 h. The resulting mixture was diluted with 20 mL of water, and acidified to pH 1 with 5 mL of 10% aqueous HCl solution. The aqueous layer was separated and extracted with two 15-mL portions of EtOAc. The combined organic layers were washed with 25 mL of saturated $NaHCO_3$, 25 mL of water and 25 mL of brine, dried over $MgSO_4$, filtered, and concentrated to give 1.532 g of a yellow-orange oil. This material was dissolved in 30 mL of CH_2Cl_2 and concentrated onto 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 0-7% MeOH-CH_2Cl_2 to furnish 0.963 g of a 93:7 mixture of **51** (1:1 mixture of diastereomers) and unreacted cyclopropene **25** as a yellow oil. Spectral data is reported for both diastereomers: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.25-7.34 (m, 8 H), 7.18-7.21 (m, 2 H), 5.18 (s, 2H), 5.13 (app t, J = 1.6 Hz, 2 H), 4.96 (t, J = 6.5, 1 H), 4.82 (t, J = 6.5, 1 H), 2.35-2.67 (m, 8 H), 1.90-2.01 (m, 4 H), 1.84 (s, 6 H)1.53-1.67 (m, 4 H), 1.30-1.41 (m, 4 H), 0.84-0.91 (app m, 6 H), ^{13}C NMR (100 MHz, $CDCl_3$): δ 182.1, 182.0, 141.0, 140.8, 128.7, 128.7, 128.6, 128.4, 127.2, 127.2, 126.7, 126.7, 121.0, 121.0, 113.7, 113.4, 111.5, 111.1, 88.0, 88.0, 82.9, 82.8, 66.0, 65.8, 36.2, 35.8, 35.4, 34.3, 29.4, 29.3, 24.4, 23.9, 23.5, 22.9, 22.7, 22.6, 15.6, 15.6, 13.9, 13.9.

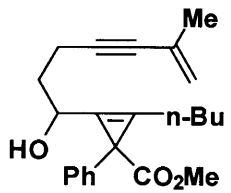


51

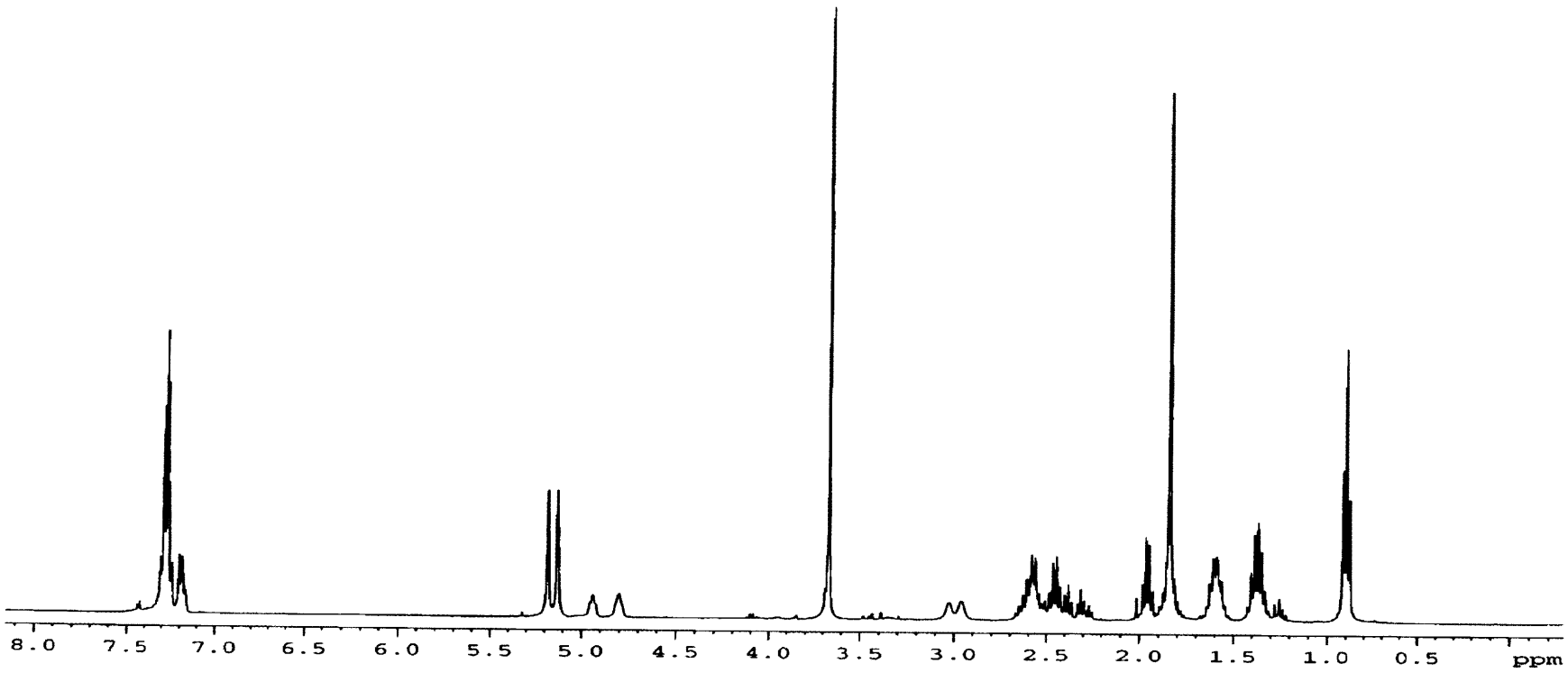


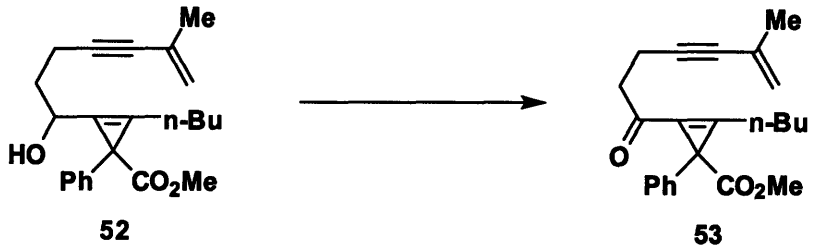


Methyl 2-butyl-3-(1-hydroxy-6-methylhept-6-en-4-ynyl)-1-phenylcycloprop-2-enecarboxylate (52). A flame-dried, 50-mL, three-necked, round bottomed flask equipped with a glass stopper, rubber septum, and coldfinger reflux condenser with argon inlet side-arm was charged with acid **51** (0.930 g of 93:7 mixture of **51** and **25**, ca. 0.89 g, ca. 2.6 mmol of **51**), 25 mL of MeOH, and concd H_2SO_4 (0.023 mL, 0.412 mmol). The mixture was stirred in an oil bath preheated at 60 °C for 18 h. The reaction mixture was then allowed to cool to rt, diluted with 20 mL of water, and concentrated. The residue was diluted with 15 mL of EtOAc, and the aqueous layer was separated and extracted with two 15-mL portions of EtOAc. The combined organic layers were washed with 20 mL of saturated $NaHCO_3$ solution, 20 mL of water and 30 mL of brine, dried over $MgSO_4$, filtered, and concentrated to give 0.912 g of a brown oil. Column chromatrography on 91 g of silica gel (elution with 30% EtOAc-hexanes) afforded 0.496 g of **52** (1:1 mixture of diastereomers) as a golden yellow oil. Spectral data is reported for both diastereomers: IR (neat): 3439, 3058, 3025, 2956, 2933, 2226, 1718, 1699, 1614, 1288, 1270, 1222 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.24-7.31 (m, 8 H), 7.16-7.21 (m, 2 H), 5.18 (s, 2 H), 5.13 (app t, J = 1.6, 2 H), 4.94 (t, J = 6.1 Hz, 1 H), 4.80 (app s, 1 H), 3.66 (s, 6 H), 3.03 (br s, 1 H), 2.96 (br s, H), 2.63 (s, 6 H), 2.25-2.67 (m, 8 H), 1.96 (q, J = 6.9 Hz, 2 H), 1.82-1.88 (m, 2 H), 1.84 (s, 6 H), 1.54-1.64 (m, 4 H), (app septet, J = 7.3 Hz, 4 H), 0.89 (td, J = 1.9, 7.4 Hz, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.5, 176.4, 141.7, 141.5, 128.4, 128.4, 128.2, 128.2, 127.2, 127.1, 126.4, 126.4, 120.8, 120.8, 113.6, 113.5, 112.0, 111.7, 88.1, 88.0, 82.6, 82.6, 65.8, 65.6, 52.3, 52.2, 36.5, 36.2, 35.3, 34.4, 29.3, 29.3, 24.2, 24.2, 23.9, 23.9, 22.6, 22.5, 15.5, 15.4, 13.8, 13.8.

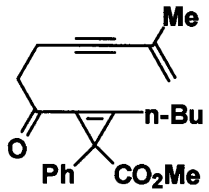


52

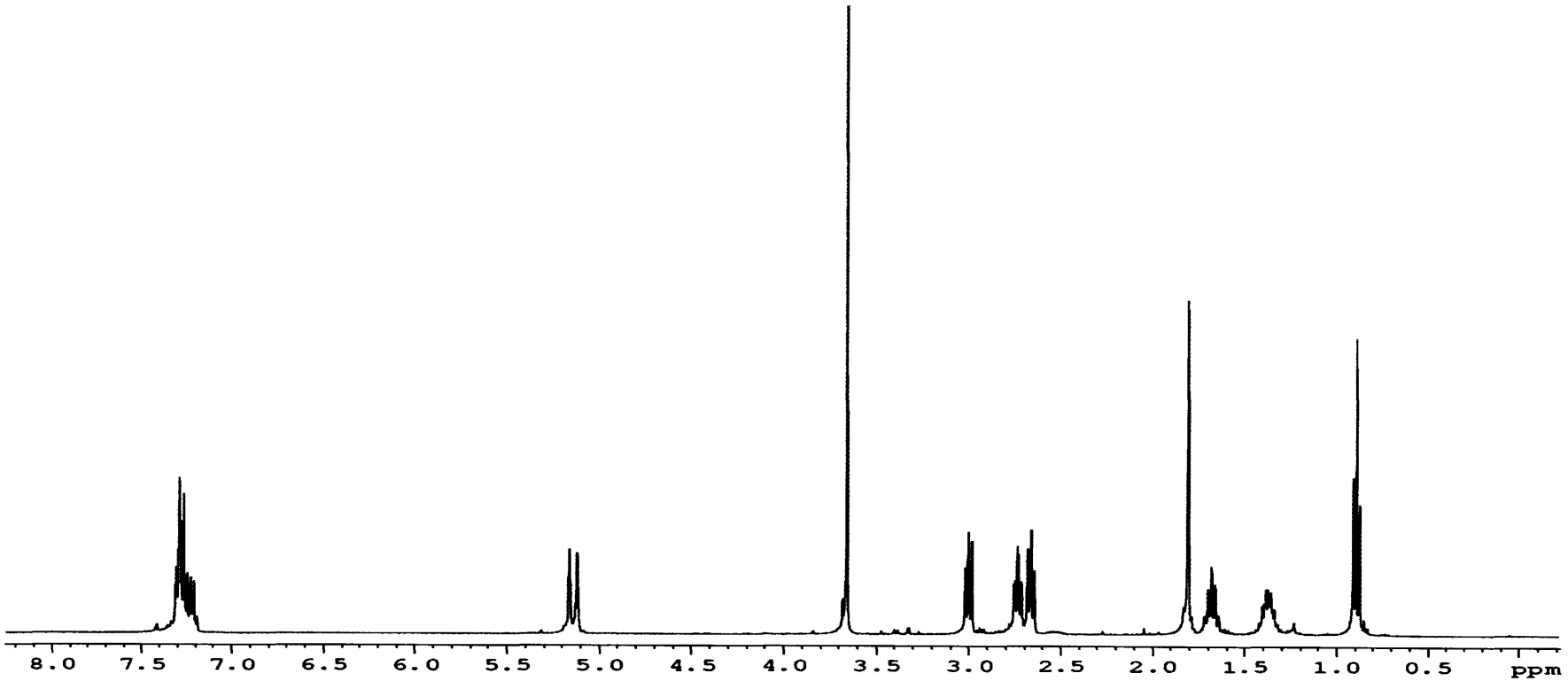


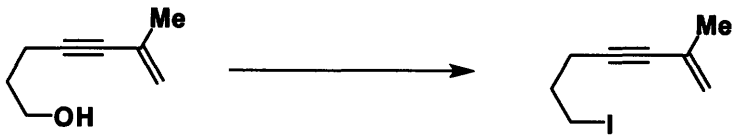


Methyl 2-butyl-3-(6-methylhept-6-en-4-ynoyl)-1-phenylcycloprop-2-enecarboxylate (53). A flame-dried, 25-mL, two-necked, pear-shaped flask equipped with a rubber septum and argon-inlet adapter was charged with alcohol **52** (0.212 g, 0.601 mmol), 4 mL of CH_2Cl_2, and Dess-Martin periodinane (0.382 g, 0.902 mmol). The reaction mixture was stirred at rt for 2.5 h. Additional Dess-Martin periodinane (0.127 g, 0.300 mmol) was added, and the resulting mixture was stirred at rt for 1 h. The reaction mixture was then filtered through a 2-cm plug of silica gel in a sintered funnel with the aid of 30 mL of 30% EtOAc-hexane and concentrated to provide 0.224 g of a yellow-orange oil. Column chromatography on 22 g of acetone-deactivated silica gel (gradient elution with 15-30% EtOAc-hexanes) furnished 0.203 g (37% overall for three steps from **25**) of **53** as a yellow oil: IR (neat): 3094, 2956, 2229, 1726, 1681, 1614, 1229 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.26-7.31 (m, 4 H), 7.19-7.24 (m, 1H), 5.16 (s, 1 H), 5.12 (s, 1 H), 3.65 (s, 3 H), 3.00 (t, J = 7.3 Hz, 2 H), 2.71-2.75 (td, J = 7.5, 2.4 Hz, 2 H), 2.66 (t, J = 7.4 Hz, 2 H), 1.80 (s, 3 H), 1.64-1.72 (m, 2 H), 1.32-1.43 (m, 2H), 0.89 (t, J = 7.4 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 189.0, 173.5, 139.5, 131.3, 128.7, 128.5, 127.2, 127.0, 121.2, 108.1, 87.4, 82.6, 52.5, 42.5, 37.8, 28.9, 25.9, 23.8, 22.6, 14.0, 13.8; HRMS (ESI) *m/z*: $[M+Na]^+$ calcd for $C_{23}H_{26}O_3$ 373.1774, found 373.1778.



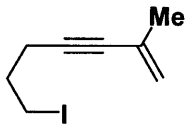
53



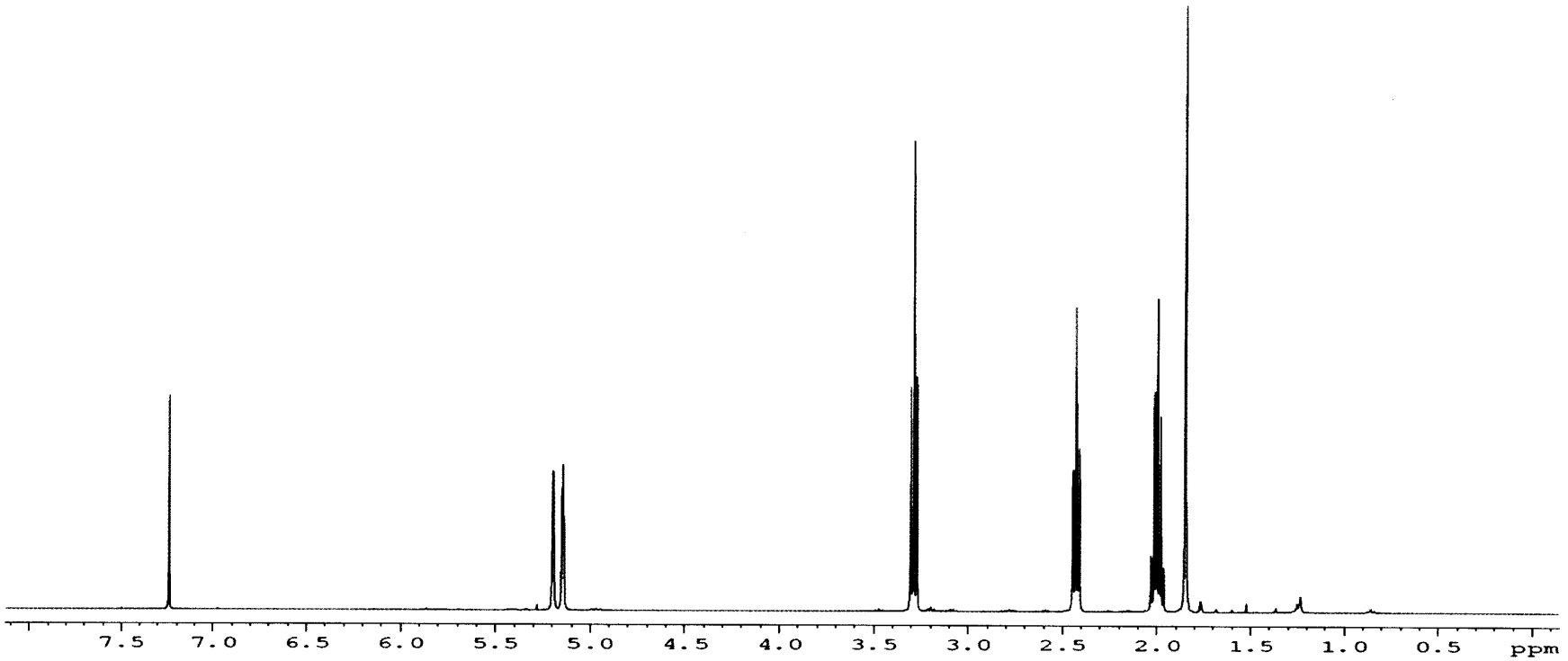


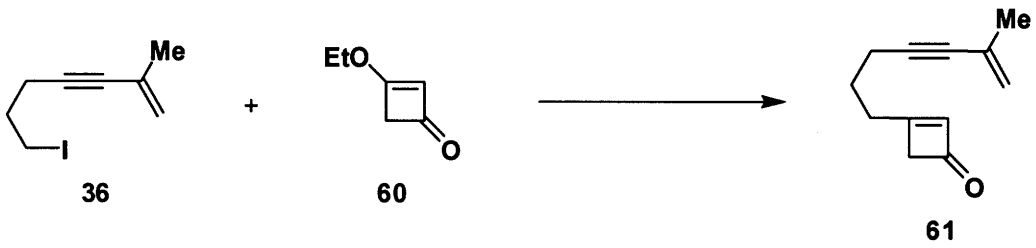
38 36

7-Iodo-2-methylhept-1-en-3-yne (36). A flame-dried, 100-mL, three-necked, round-bottomed flask equipped with a glass stopper, rubber septum, and argon inlet adapter was charged with a solution of alcohol **38** (4.025 g, 32.4 mmol) in 55 mL of THF and cooled to 0 °C. Imidazole (3.306 g, 48.6 mmol), triphenylphosphine (8.499 g, 32.4 mmol), and iodine (12.337 g, 48.6 mmol) were added and the resulting brown mixture was stirred at 0 °C for 10 min. The cooling bath was removed, the flask was wrapped in aluminum foil, and the reaction mixture was stirred in the dark for 20 h. The resulting mixture was diluted with 55 mL of water and the aqueous layer was separated and extracted with four 60-mL portions of pentane. The combined organic phases were washed with 150 mL of saturated $Na_2S_2O_3$ solution and 150 mL of brine, dried over $MgSO_4$, filtered, and concentrated to provide a golden-yellow oil. This material was filtered through a 4-cm plug of alumina in a sintered glass funnel with the aid of 80 mL of Et_2O to afford 6.953 g of **36** as of a pale yellow oil: IR (neat): 3094, 2950, 2919, 2229, 1614 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.20 (s, 1 H), 5.14 (app t, J = 1.7 Hz, 1 H), 3.29 (t, J = 6.8 Hz, 2 H), 2.43 (t, J = 6.7 Hz), 2.00 (quintet, J = 6.8 Hz, 2 H), 1.85 (app t, J = 1.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 127.1, 121.1, 87.0, 83.1, 32.3, 23.9, 20.5, 5.6.

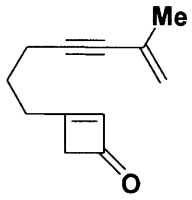


36

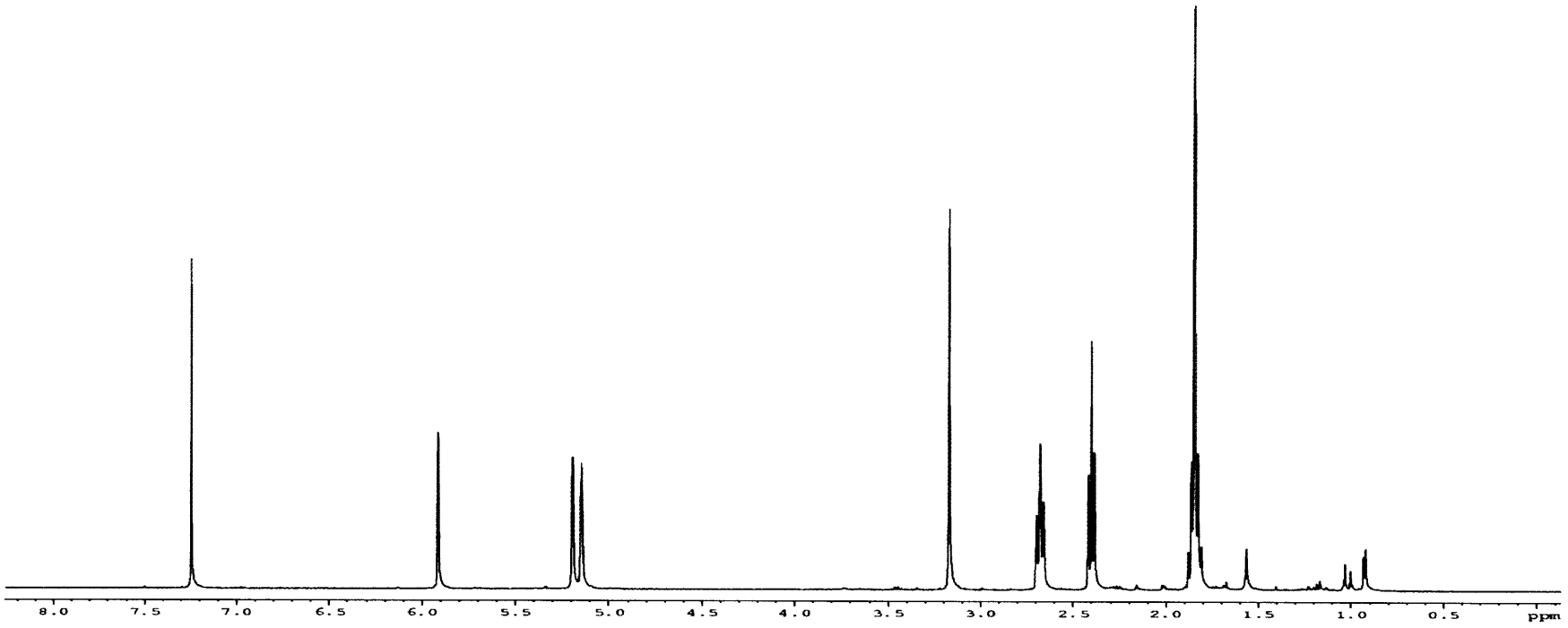


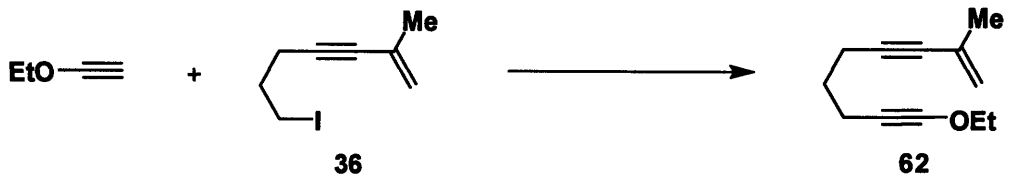


3-(6-Methylhept-6-en-4-ynyl)cyclobut-2-enone (61). A flame-dried, 100-mL, three-necked, round-bottomed flask equipped with a rubber septum, 20-mL pressure-equalizing addition funnel fitted with a rubber septum, and argon inlet adapter was charged with the iodide **36** (1.919 g, 8.2 mmol), 22 mL of pentane, and 16 mL of Et_2O and then cooled to -78 °C. *t*-BuLi (1.60 M in pentane, 10.2 mL, 16.4 mmol) was added dropwise over 10 min via addition funnel (2 mL of pentane rinse) and the resulting mixture was stirred at -78 °C for 20 min. A solution of ketone **60**[34] (0.707 g, 6.31 mmol) in 10 mL of Et_2O was added dropwise over 10 min via the addition funnel (2 mL of Et_2O rinse) and the golden-yellow reaction mixture was stirred at -78 °C for 75 min. The cooling bath was removed, and the reaction mixture was allowed to warm to 0 °C. The resulting mixture was cooled at 0 °C in an ice bath while 20 mL of 10% aq HCl solution was added over 5 min and the resulting yellow biphasic mixture was stirred at 0 °C for 10 min. The organic layer was separated and washed with 20 mL of 10% aq HCl solution and 20 mL of saturated $NaHCO_3$ solution. The combined aqueous phases were neutralized to pH 7 by the addition of ca. 27 mL with 4.0 M aqueous NaOH solution and then extracted with two 25-mL portions of Et_2O. The combined organic phases were washed with 40 mL of brine, dried over $MgSO_4$, filtered, and concentrated to provide 1.559 g of a brownish-yellow oil. Column chromatography on 250 g of silica gel (elution with 20-50% Et_2O-pentane) afforded 0.558 g (51%) of **61** as a pale-yellow oil: IR (neat): 3507, 3096, 2950, 2224, 1761, 1614, 1585 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.91 (s, 1H), 5.20 (s, 1 H), 5.15 (s, 1 H), 3.17 (s, 2 H), 2.68 (t, J = 7.5 Hz, 2 H), 2.40 (t, J = 6.9 Hz, 2 H), 1.85 (quintet, J = 7.2 Hz, 2 H), 1.85 (s, 3 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.

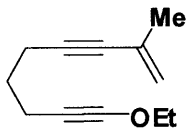


61

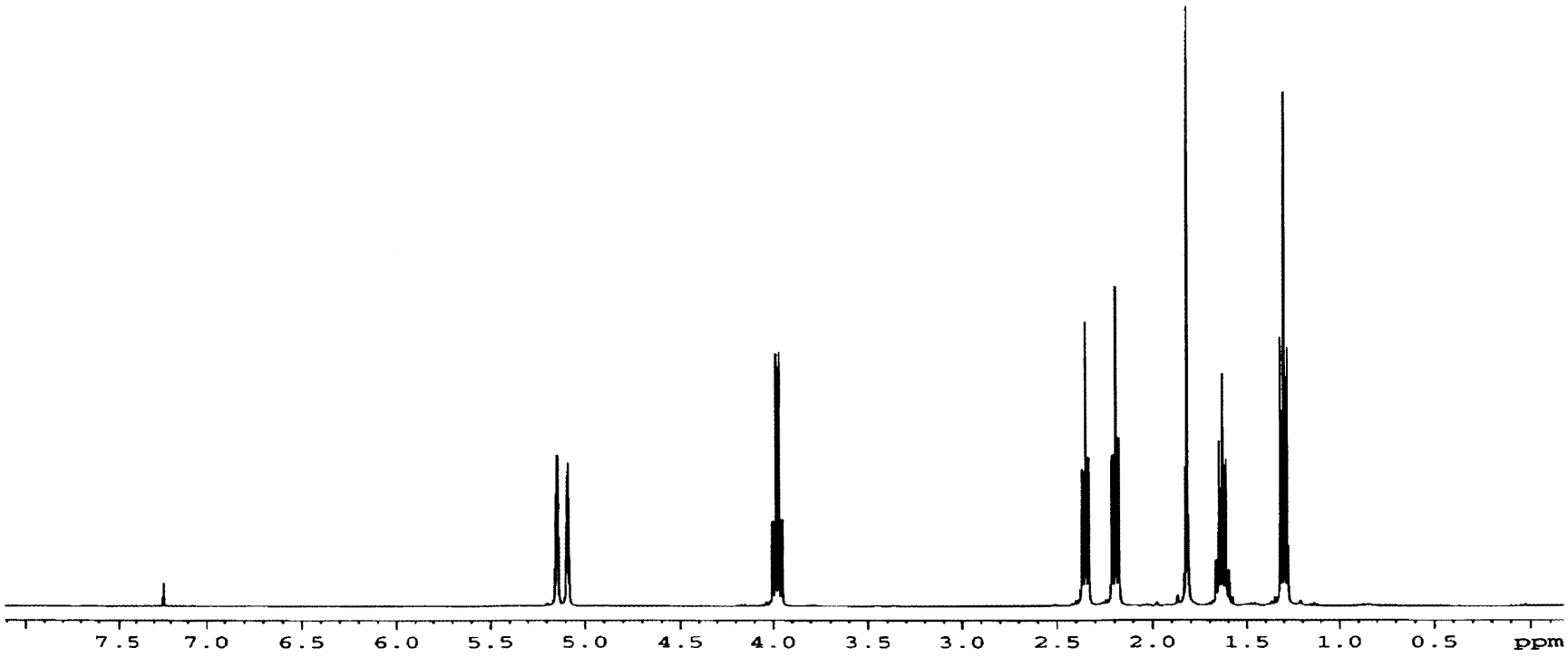


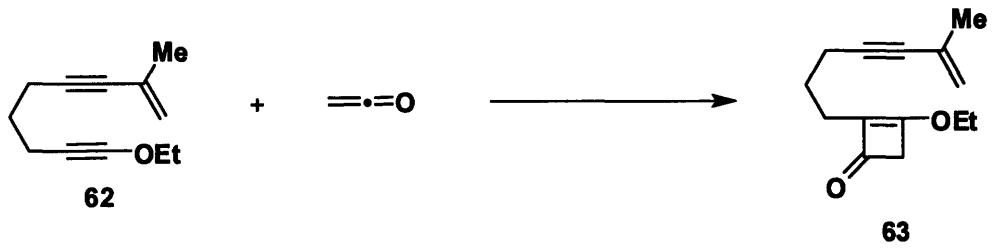


9-Ethoxy-2-methylnona-1-en-3,8-diyne (62). A flame-dried, 100-mL, three-necked, round-bottomed flask equipped with a rubber septum, 10-mL pressure-equalizing addition funnel fitted with a rubber septum, and argon inlet adapter was charged with a solution of ethoxyacetylene (1.543 g, 22.0 mmol) in 20 mL of THF and cooled at -78 °C while *n*-butyllithium (2.57 M in hexane, 9.3 mL, 23.8 mmol) was added dropwise over 10 min via the addition funnel (3 mL of THF rinse). The resulting yellow mixture was stirred at -78 °C for 60 min. HMPA (7.0 mL, 7.2 g, 40 mmol) was then added in one portion via syringe, and the resulting mixture was stirred at -78 °C for 20 min. A solution of iodide **36** (4.284 g, 18.3 mmol) in 4 mL of THF was added dropwise over 7 min via cannula (3 mL of THF rinse). The cooling bath was removed and the yellow-orange mixture was stirred for 42 h at rt. The resulting mixture was diluted with 120 mL of Et_2O and 40 mL of water. The organic layer was separated and washed with four 40 mL-portions of water and 40 mL of brine, dried over $MgSO_4$, filtered, and concentrated to provide 3.083 g of a brown oil. Column chromatography on 150 g of silica gel (elution with 2% Et_2O-pentane) afforded 2.569 g (81%) of **62** as a pale yellow oil: IR (neat): 3484, 3096, 2951, 2273, 2227, 1615, 1224 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.15 (s, 1H), 5.09 (s, 1 H), 3.98 (q, J = 7.1 Hz, 2 H), 2.35 (t, J = 7.1 Hz, 2 H), 2.19 (t, J = 6.9 Hz, 2 H), 1.82, (s, 3 H), 1.63 (quintet, J = 7.0 Hz), 1.30 (t, J = 7.1 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 127.4, 120.6, 89.9, 88.8, 82.3, 74.0, 36.5, 29.0, 24.0, 18.5, 16.7, 14.5; HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{12}H_{16}O$ 177.1274, found 177.1281.



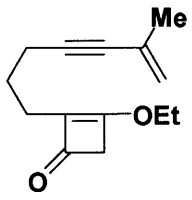
62



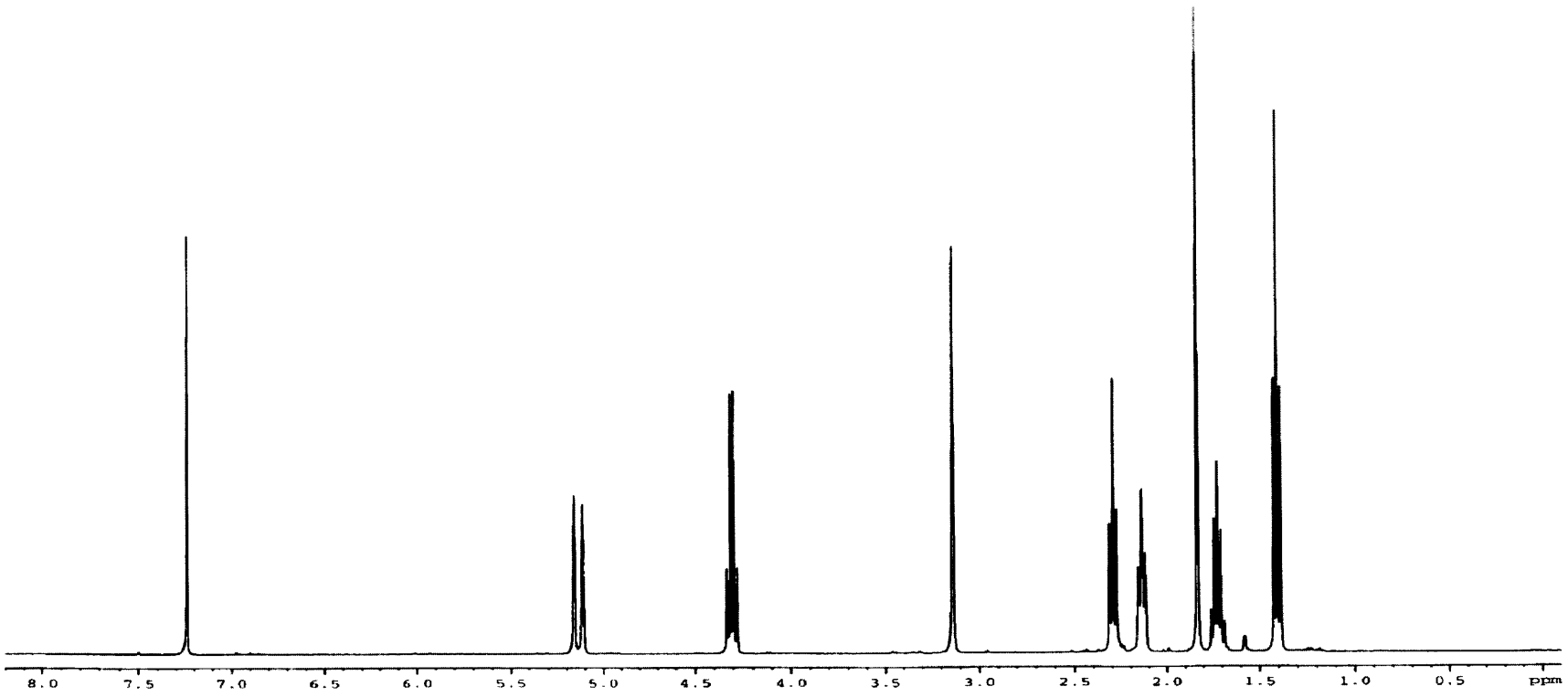


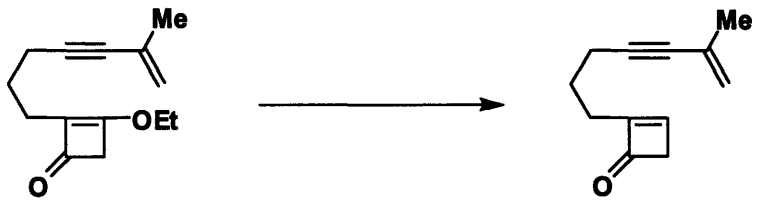
3-Ethoxy-2-(6-methylhept-6-en-4-ynyl)cyclobut-2-enone (63). A flame-dried, 25-mL, two-necked, pear-shaped flask equipped with a rubber septum and thermometer adapter fitted with a Pasteur pipet connected to a ketene generator was charged with a solution of alkyne **62** (2.563 g, 14.5 mmol) in 10 mL of CH_2Cl_2 and cooled to 0 °C. Ketene (generated via the pyrolysis of acetone over a hot filament by the method of Williams and Hurd[44]) was bubbled through the solution at 0 °C for 14 h, and then for 8 h at rt. The brown reaction mixture was concentrated to provide 7.077 g of a brown oil. Column chromatography on 180 g of silica gel (60% Et_2O-pentane) afforded 2.563 g (76%) of **63** as a yellow-orange oil: IR (neat): 3500, 3095, 2922, 2223, 1756, 1622, 1288 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.12 (s, 1H), 5.07 (app t, J = 7.1 Hz, 1 H), 4.27 (q, J = 7.1 Hz, 2 H), 3.10 (t, J = 1.9 Hz, 2 H), 2.25 (t, J = 7.0 Hz, 2 H), 2.10 (tt, J = 7.5, 1.9 Hz, 2 H), 1.79 (s, 3 H), 1.79 (quintet, J = 7.2 Hz), 1.37 (t, J = 7.5 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 185.2, 176.3, 127.3, 120.9, 120.6, 88.6, 82.5, 69.2, 46.9, 26.6, 23.9, 21.6, 19.1, 15.5; HRMS (ESI) *m/z*: $[M+Na]^+$ calcd for $C_{14}H_{18}O_2$ 241.1199, found 241.1191.

[44] Williams, J. W.; Hurd, C. D. *J. Org. Chem.* **1940**, *5*, 122.



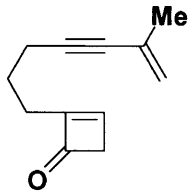
63



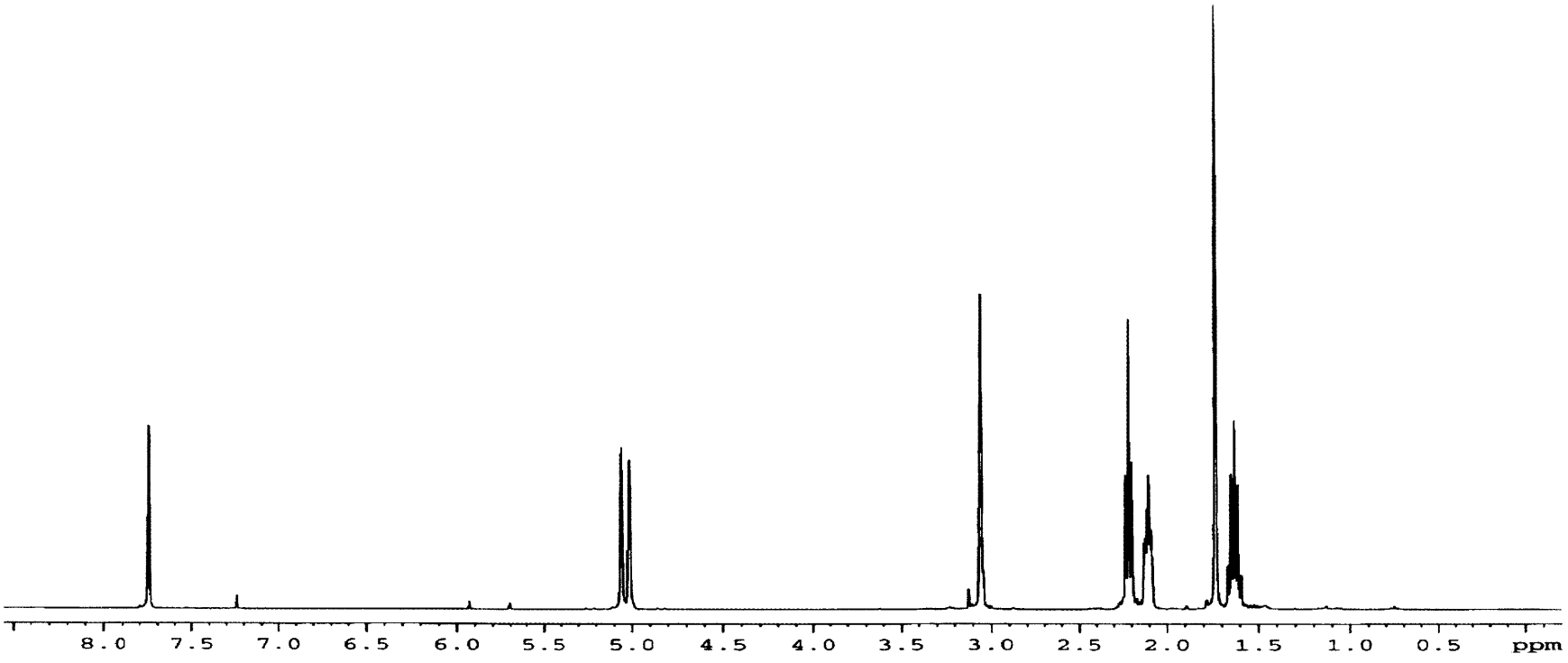


63 64

2-(6-Methylhept-6-en-4-ynyl)cyclobut-2-enone (64). A flame-dried, 100-mL, three-necked, round-bottomed flask equipped with a rubber septum, pressure-equalized solid addition funnel fitted with a glass stopper, and argon inlet adapter was charged with a solution of enone **63** (2.410 g, 11.0 mmol) in 55 mL of MeOH and cooled to 0 °C. $CeCl_3$ (5.328 g, 14.3 mmol) was added in one-portion, and after all the solid had dissolved, $NaBH_4$ (1.250 g, 33.0 mmol) was added over 20 min via the solid addition funnel. The evolution of H_2 gas was observed. The resulting mixture was allowed to stir at 0 °C for 6 h. Additional $NaBH_4$ (0.626 g, 16.5 mmol) was added in one portion (H_2 evolution). The resulting mixture was allowed to stir at 0 °C for 3 h, and then at rt for 14 h. The reaction mixture was recooled to 0 °C, diluted with 35 mL of 10% aq HCl solution, and stirred at 0 °C for 10 min. The aqueous layer was then separated and extracted with three 40-mL portions of CH_2Cl_2, and the combined organic phases were washed with 150 mL of saturated $NaHCO_3$ and 150 mL of brine, dried over $MgSO_4$, filtered, and concentrated to give 1.977 g of a golden-yellow oil. Column chromatography on 190 g of silica gel (elution with 15% Et_2O-pentane) furnished 0.883 g (46%) of **64** as a pale-yellow oil: IR (neat): 3500, 3095, 2924, 2252, 2221, 1758, 1676, 1613 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.75 (s, 1 H), 5.06 (s, 1H), 5.02 (s, 1 H), 3.06 (s, 2 H), 2.21 (t, J = 7.0 Hz, 2 H), 2.11 (td, J = 7.5, 1.3 Hz, 2 H), 1.73 (s, 1 H), 1.62 (quintet, J = 7.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.4, 154.8, 154.7, 127.0, 120.5, 88.0, 82.5, 48.1, 25.4, 23.9, 23.7, 18.8.



64



Jennie Fong

Education

- **Massachusetts Institute of Technology** Sept. 2005 to Feb. 2008
  S.M., Organic Chemistry, expected June 2008
  Thesis: "Intramolecular [4 + 2] Cycloadditions of Conjugated Enynes with Highly Strained Cyclic Alkenes"
  Advisor: Prof. Rick L. Danheiser
- **University of San Diego** Sept. 2001 to May 2005
  B.A., Chemistry with Biochemistry Emphasis, *magna cum laude*, received May 2005
  Honors Thesis: "A Fluorescent Biosensor for ATP Based on 2-Aminopurine-Modified RNA Aptamers"
  Advisor: Dr. Thomas P. Shields

Research Experience

- **Graduate research assistant** Jan. 2006 to Feb. 2008
  Massachusetts Institute of Technology
  Advisor: Prof. Rick L. Danheiser
- **Research assistant** Jan. 2005 to June 2005
  University of San Diego
  Advisor: Dr. Peter M. Iovine
  Undergraduate research assistant Jan. 2003 to May 2005
  University of San Diego
  Advisor: Dr. Thomas P. Shields
  Undergraduate research assistant June 2004 to Aug. 2004
  University of Pennsylvania
  Advisor: Dr. Michael J. Therien

Teaching Experience

- **Chemistry Outreach Program** Jan. 2007 to Jan. 2008
  Massachusetts Institute of Technology
- **Teaching Assistant** Sept. 2005 to Dec. 2005, Mar. 2006 to May 2006
  Massachusetts Institute of Technology
- **Tutor** Jan. 2003 to May 2005
  University of San Diego
- **Laboratory Teaching Assistant** Sept. 2002 to May 2005
  University of San Diego

Honors and Awards

National Science Foundation Graduate Research Fellowship, 2005 to 2008
Barry M. Goldwater Scholarship, 2004 to 2005
2003 Class Legacy Scholarship, 2003 to 2004
University of San Diego Trustees Scholarship, 2001 to 2005

Affiliations

Phi Beta Kappa, member since 2005
American Chemical Society, member since 2003
National Society of Collegiate Scholars, member since 2002

Publications

Frail, P.R., Susumu, K., Huynh, M., Fong, J., Kikkawa, J.M.; Therien, M.J. Modulation of Dark Conductivity over a 1×10^{-12} to 1×10^{-5} S/cm Range Through Ancillary Group Modificaiton in Amorphous Solids of Ethyne-Bridged (Porphinato)zinc(II) Oligomers. *Chem. Mater.* **2007**, *19*, 6062.