Synthesis of Polycyclic Furans via the Generation and Rearrangement of Strained Heterocyclic Allenes

by

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B. A. Chemistry
Wesleyan University, 1993

Submitted to the Department of Chemistry
in Partial Fulfillment of the Requirements for the
Degree of

Doctor of Philosophy
at the
Massachusetts Institute of Technology
June 1998

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Acknowledgments

I first would like to thank my research advisor, Professor Rick Danheiser, for providing the opportunity and funding to work in his group for the past five years. I would also like to thank Rick for enhancing both my technical and intellectual knowledge of organic chemistry. I believe the lessons I learned while working in his group will be invaluable to me in my future career as a chemist and teacher.

I would also like to thank another member of the MIT faculty, Professor Scott Virgil, for helpful discussions about my research. I would especially like to thank him for his assistance in generating a mechanistic proposal to account for my results as well as for his advice in how to grow a crystal of one of my products for X-ray analysis.

My undergraduate research advisor, Professor Albert Fry, also deserves thanks for inspiring me to be an organic chemist. Without his encouragement and support, I would never have pursued a career in chemistry. I wrote in the acknowledgments of my undergraduate thesis that I hoped to one day be half the person and chemist he is. That sentiment is as true today as it was five years ago.

I wish to thank several former members of the Danheiser group. Kathy Lee was my first bay mate and taught me the ropes of life in the Danheiser lab. I admire Kathy for her intelligence, sense of humor and her taste in music (especially Ween)! I wish her all the best in her new job. Scott Sattovia was my second bay mate and I thank him for numerous loans of distilled chemicals and for enhancing my appreciation of country music. Scott was a great bay mate and I wish him all the best in medical school. I would also like to thank other former members of the satellite lab, Sandy Gould, Mike Lawlor and Alex Huboux for all of their advice and assistance over the years. I would especially like to thank Mike for always being there to help me decipher the cancer training grant payroll snafus! Finally, I would like to thank my "other advisor", Brenda Palucki. Brenda is an excellent chemist and great friend. I thank her for always being there for me to give advice and support (and for being willing to join me for coffee and bagels each Saturday morning). I wish Brenda the best of luck with her career as well as with her new house!!

I also wish to thank the current members of the Danheiser group who have provided much support and helpful ideas during my graduate career. Kevin Shea is a good friend and I thank him for his support the past few years. I especially thank him for patiently listening to me vent without ever complaining. Kevin is an excellent chemist and will one day be an excellent professor. I wish him the best of luck in his future pursuits. Greg Dudley has been a great next-door neighbor and co-worker (although I could have done without his choice of morning radio stations). I admire his intelligence and sense of humor. Matt Martin I need to especially thank for all of his assistance over the years whether it involved solving problems with the computer or delivering parts of my thesis to Rick. I truly appreciate all of his help. I hope for his sake that the Red Sox can end the curse before too long!! I wish my fellow fifth-year, Adam Renslo all the best with finishing up at MIT and with his post-doc at Scripps. It's hard to believe that it's finally our turn to graduate! I would also like to thank Rob Niger for all of his illuminating revelations about women that he shared with me whether I wanted to hear them or not. Although he denies it, Rob is a nice guy underneath and I wish him the best

of luck. I also would like to remind him not to forget our little wager. How many years left now???? Finally, I would like to thank Dawn Bennett for obtaining many PO numbers for me. I also wish her luck with the rest of her graduate career and with the outreach program.

I would also like to thank Dana Buske for her support. I admire Dana for her intelligence, perseverance and sense of humor. Dana is a good friend and I am really glad we got to know each other through our work in Women in Chemistry. I wish her all the best in her remaining time at MIT and with her future pursuits.

I am grateful to Kevin, Greg, Dawn, and Dana for proofreading this thesis. Their comments definitely improved the quality of the document. I would also like to thank Matt and Kevin for delivering parts of my thesis to Rick during the past few months. I definitely owe all of you a trip to Toscanini's!

In addition to people at MIT, I would like to thank my friends and family for their support over the years. I would like to thank Agnes Lee, Angela Noll, Telory Williamson, and Natasha Herron for believing in me and for supporting me through good times and bad. I also want to thank them for keeping me in touch with life outside of the lab and not letting me lose perspective on what is really important. I am especially grateful to my family for all of their confidence in me and encouragement during my entire life. I would never have been able to accomplish what I have without the support and love of my parents, sisters and grandparents. I only wish I could explain to them what I have been doing for the past five years!! Finally, I would like to thank my husband and my best friend, Ted. I thank him for his unconditional love and understanding over the past five years. Words could never express how grateful I am for his love and support and how I lucky I feel to have him in my life.

To my family

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Submitted to the Department of Chemistry
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ABSTRACT

An examination of the intramolecular reactions of conjugated ynones and related heteroenynes with alkynes has revealed that the ultimate products of these reactions are polycyclic furans. During the course of our investigation, we examined a variety of factors that affect the transformation including the nature of the heteroenyne, substitution on the alkyne, and the length and nature of the tether between the two components. From these studies a number of generalizations can be made concerning the types of substrates that undergo the transformation.

We have also investigated the mechanism of the process. To account for furan formation we propose the following reaction sequence: First a [4+2] cycloaddition occurs between the heteroenyne and the alkyne to generate a strained heterocyclic allene. This allene then rearranges to a furfuryl carbene which undergoes a subsequent intramolecular C-H insertion reaction to generate the observed furan product. Our mechanistic proposal is supported by precedent from the literature as well as experimental evidence that indicates both a heterocyclic allene and furfuryl carbene are involved in the reaction pathway.

Thesis Supervisor: Rick L. Danheiser

Title: Professor of Chemistry

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PART I

Introduction and Background: Cycloaddition Reactions of Enynes and 1-Oxabutadienes

Chapter 1

Introduction

A New Cycloaddition Strategy

In the field of organic synthesis, cycloadditions such as the Diels-Alder reaction perform a vital role due to their convergent, regio- and stereoselective features.[1] Both inter- and intramolecular variants have been utilized extensively in the preparation of natural products and commercially important organic compounds. Intramolecular cycloadditions demonstrate particular efficiency as several different bonds and rings can be created simultaneously.

Research in our laboratory has focused on developing new cycloadditions of highly unsaturated, conjugated substrates for the construction of polycyclic molecules. These cycloadditions are mechanistically related to cycloaromatization reactions, electrocyclic processes that have recently garnered much attention in the literature.[2] As illustrated in Scheme 1, cycloaromatizations involve the thermal cyclization of highly unsaturated, conjugated substrates to form high-energy, biradical aromatic species. The Bergman and neocarzinostatin cyclizations have been the subject of considerable interest recently due to their implication in the mechanism of action in a number of interesting

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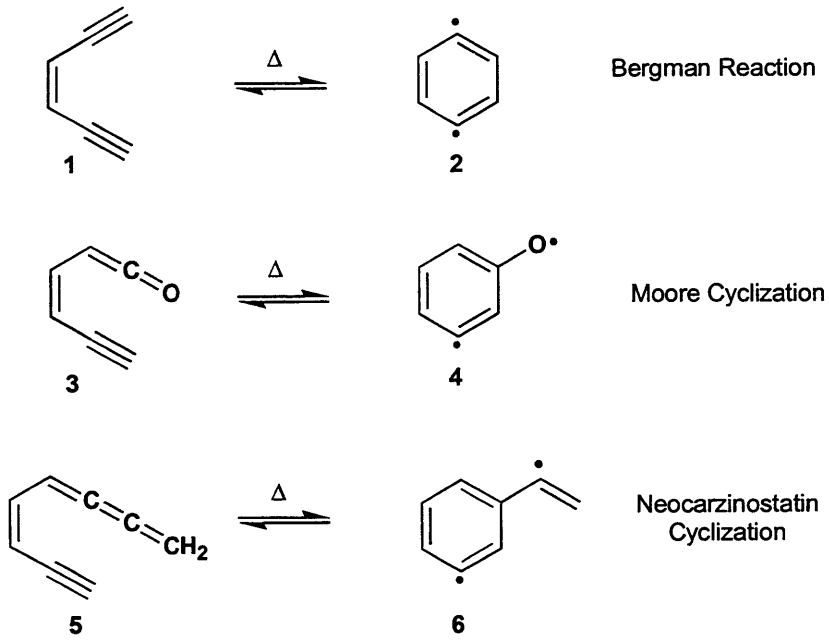
[1]For reviews of the Diels-Alder reaction, see: (a) Oppolzer, W. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds.; Pergamon Press: Oxford, 1991, Vol. 5, pp 315-399. (b) Roush, W. R., In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds.; Pergamon Press: Oxford, 1991, Vol. 5, pp 513-550. (c) Ciganek, E. In *Organic Reactions*; Dauben, W. G., Ed.; John Wiley & Sons: New York, 1984, Vol. 32, pp 1-374.

[2]For a recent review, see: Gleiter, R.; Kratz, D. *Angew. Chem. Int. Ed. Eng.* **1993**, *32*, 842.

antitumor agents. It is believed that both the endiyne antitumor antibiotics[3] and neocarzinostatin[4] function via the formation of 1,4-biradicals, **2** and **6**, which subsequently cleave DNA, thereby promoting cell death. In addition to work on the biological importance of these reactions, several groups have also investigated the synthetic utility of these reactions in the construction of polycyclic aromatic compounds via tandem cycloaromatization-radical cyclization sequences.[5]

Scheme 1



While these reactions involve novel and interesting chemistry, they also possess limitations as general methods for ring construction. First, using these methods to create highly substituted aromatic products often requires the synthesis of cyclization substrates

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[3]For a review on the chemistry and biology of enydiyne anticancer antibiotics, see: Nicolaou, K. C.; Dai, W. –M. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1387 and references cited therein

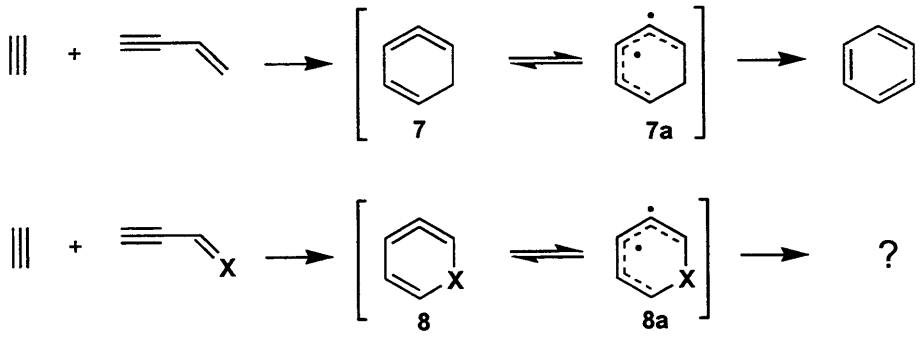
[4] For a review of the mechanism of action of the neocarzinostatin chromophore, see: (a) Goldberg, I. H. *Acc. Chem. Res.* **1991**, *24*, 191. Also see: (b) Myers, A. G.; Arvedson, S. P.; Lee, R. W. *J. Am. Chem. Soc.* **1996**, *118*, 4725.

[5] For recent reviews, see: (a) Wang, K. K. *Chem. Rev.* **1996**, *96*, 207. (b) Grissom, J. W.; Gunawardena, G. U.; Klingberg, D.: Huang, D. *Tetrahedron*, **1996**, *52*, 6453.

of comparable complexity to the aromatic products. More importantly, cycloaromatizations are *cyclization* processes in which only a single bond is formed, and therefore are much less convergent in character than *annulation*[6] strategies.

As stated above, a number of years ago our laboratory began to explore the development of new cycloadditions of highly unsaturated, conjugated compounds with mechanistic similarities to cycloaromatizations. The advantages of these reactions include the synthetic accessibility of the reactants and the convergency of the transformation since it is an *annulation* not a *cyclization*. The first systems investigated involved the [4+2] cycloadditions of conjugated enynes. This thesis will outline the extension of that work to the [4+2] cycloadditions of heteroenynes, specifically ynones and related species. As shown below, the cycloaddition of an enyne or heteroenyne with an alkyne is expected to provide high energy cyclic allene (**7** or **8**) or biradical (**7a** or **8a**) intermediates (Scheme 2). In the all-carbon case, these intermediates can then isomerize to furnish an aromatic product. With the heteroenynes, however, simple isomerization to produce an aromatic product cannot occur. Discussion of additional mechanistic pathways for the heteroenyne case will be postponed until Part II of this thesis.

Scheme 2

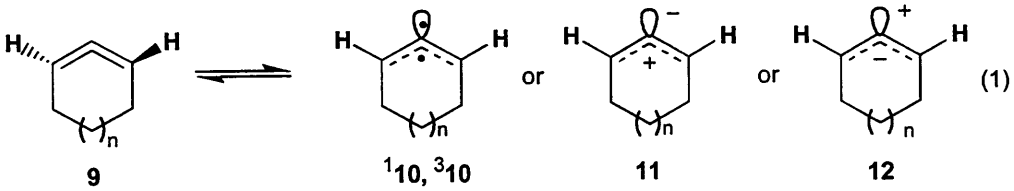


[6] An annulation is defined as a ring-forming reaction in which two molecular fragments are united with the formation of two new bonds. See: Danheiser, R. L.; Gee, S. K.; Sard, H. *J. Am. Chem. Soc.* **1982**, *104*, 7670.

Cyclic Allenes: Background

One unusual feature of the enyne and related cycloadditions is the possible involvement of a strained cyclic allene in these processes. While carbocyclic allenes have been the subject of numerous investigations,[7] much less is known about derivatives containing a heteroatom within the ring system. By definition, an allene consists of three carbon atoms bound to each other with two orthogonal double bonds and two σ bonds. Studies have shown that ten-membered rings are the smallest carbocyclic system that can accommodate this linear array without distortion. If distortion occurs, it weakens the π bonds of the system since it involves the coupled motions of bending and twisting the allene bonds. Consequently, small cyclic allene ring systems are very high in energy.

Cyclic allenes **9** are chiral, but as the size of the ring decreases, ring strain increases thereby decreasing the energy barrier to π-bond rotation and resulting in the interconversion of enantiomers. Eventually, the energy required for maintaining π overlap is overcome by ring strain, and a planar geometry results. The planar achiral molecule contains an allyl system, orthogonal to an sp^2-hybrid orbital at the central carbon of the system. This system has four possible electronic configurations: a singlet and triplet diradical, ^{1}**10** and ^{3}**10**, and two zwitterions, **11** and **12** (eq 1).



9 ^{1}**10**, ^{3}**10** **11** **12**

[7] For reviews on cyclic allenes, see: (a) Johnson, R. P. *Chem. Rev.* **1989**, *89*, 1111. (b) Johnson, R. P. In *Molecular Structure and Energetics;* Liebman, J. F.; Greenberg, A., Eds.; VCH: Deerfield Beach, Florida, 1986; Vol. 3, Chapter 3.

To date, the smallest isolable, unsubstituted carbocyclic allene that has been prepared is 1,2-cyclononadiene.[8] Simple substituted seven and eight membered carbocyclic allenes have also been synthesized or generated and then trapped as dimerization products.[9] Due to high ring strain, the six membered cyclic allene, 1,2-cyclohexadiene, has not been isolated, but it has been synthesized and trapped in various ways. The methods used to synthesize 1,2-cyclohexadiene include base-induced elimination of a vinyl halide,[10] flash vacuum pyrolysis of a cyclopropyl ketene[11] or a bromostannylcyclopropane,[12] fluoride-induced β-elimination of a α-silyl vinyl halide,[13] and the ring opening of a dibromocyclopropane precursor.[7a,7b] The chemistry of 1,2-cyclohexadiene involves [2+2] cycloadditions, [4+2] cycloadditions with both cyclic and acyclic dienes, tetramer formation, and reactions with nucleophiles at the central carbon.[14,15,16,17,18]

Unlike studies on the parent 1,2-cyclohexadiene, reports on derivatives containing a heteroatom within the ring are much scarcer in the literature. It has only been in the last decade that any reports have surfaced on the generation and interception of oxo

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[8](a) Blomquist, A.; Burger, R. E., Jr.; Liu, L. H.; Bohrer, J. C.; Sucsy, A. C.; Kleis, J. *J. Am. Chem. Soc.* **1951**, *73*, 5510. (b) Skatteböl, L. *Tetrahedron Lett.* **1961**, 167. (c) Skatteböl, L.; Solomon, S. *Org. Synth.* **1960**, *49*, 35.

[9] For substituted 1,2-cyclooctadienes, see: Price J. P.; Johnson, R. P. *Tetrahedron Lett.* **1986**, *27*, 4679. For isolation of trapped products of 1,2-cycloheptadiene, see: Balci, M.; Jones, W. M. *J. Am. Chem. Soc.* **1980**, *102*, 7607.

[10] (a) Wittig, G.; Fritze, P. *Angew. Chem., Int. Ed. Engl.* **1966**, *5*, 684. (b) Wittig, G.; Fritze, P. *Justus Liebigs Ann. Chem.* **1968**, *711*, 82.

[11] Wentrup, C.; Gross, G.; Maquestiau, A.; Flammang, R. *Angew. Chem., Int. Ed. Engl.* **1983**, *27*, 542.

[12] Runge, A.; Sander, W. *Tetrahedron Lett.* **1986**, *27*, 5835.

[13] (a) Shakespeare, W. C.; Johnson, R. P. *J. Am. Chem. Soc.* **1990**, *112*, 8578. (b) Sütbeyaz, Y.; Ceylan, M.; Secen, H. *J. Chem. Research (S)* **1993**, 293.

[14] Moore, W. R.; Moser, W. R. *J. Am. Chem. Soc.* **1970**, *92*, 5469.

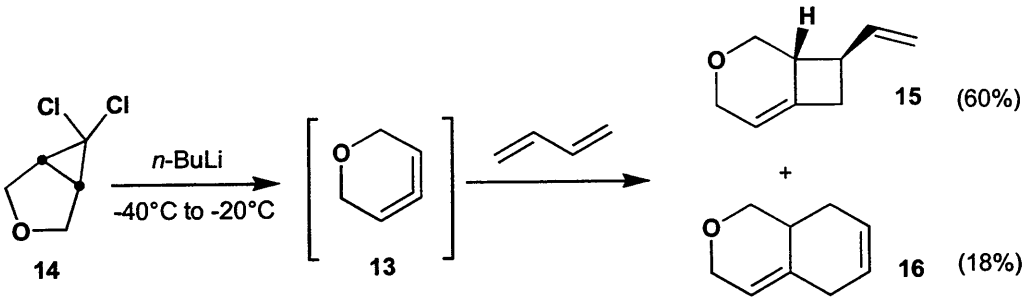
[15]Bottini, A. T.; Hilton, L. L.; Plott, J. *Tetrahedron* **1975**, *31*, 1997.

[16] (a) Christl, M.; Schreck, M. *Chem. Ber.* **1987**, *120*, 915. (b) Christl, M.; Schreck, M. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 449.

[17] Harnos, S.; Tivakornpannarai, S.; Waali, E. E. *Tetrahedron* **1986**, *27*, 3701.

[18] Moore, W. R.; Mosser, W. R. *J. Org. Chem.* **1970**, *35*, 908.

derivatives of this reactive intermediate. In 1987, Schreck and Christl reported the synthesis of 1-oxa-3,4-cyclohexadiene **13** via the treatment of dichloropropane **14** with *n*-butyllithium at low temperatures.[19] The resulting heterocyclic allene was trapped in both [2+2] and [4+2] processes with a variety of activated acyclic alkenes and dienes, among them 1,3-butadiene (eq 2). The authors speculated that the oxo derivative should have a more bent allene moiety in comparison to the parent compound, 1,2-cyclohexadiene, due to the smaller covalent radius of an oxygen atom compared to a carbon atom, and should therefore exhibit a higher strain energy. No evidence was presented to support this suggestion.



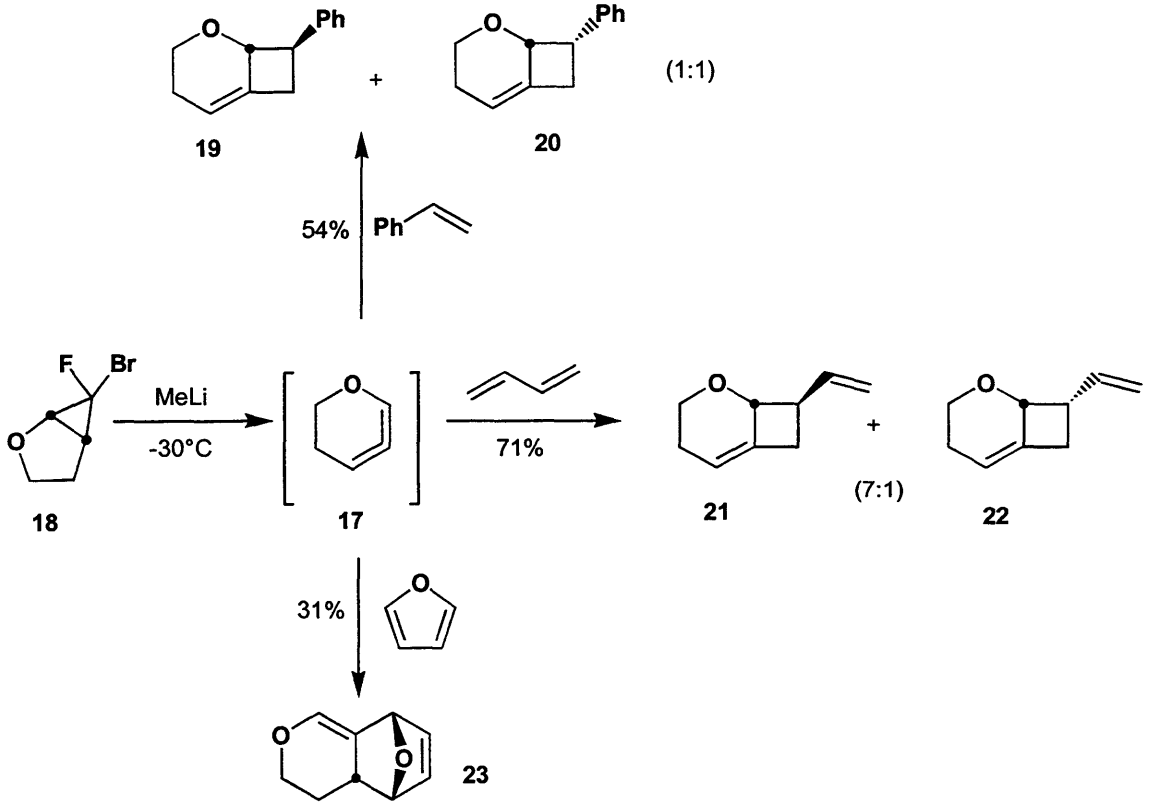
14 13 (2)

A few years later in 1989, Christl and Braun reported the successful generation and interception of the isomeric system, 1-oxa-2,3-cyclohexadiene **17**.[20] In contrast to their earlier work with the 3,4-cyclohexadiene precursor **14**, the analogous dichloride failed to produce the trapping products of the desired 2,3-cyclohexadiene **17** in high yields. As illustrated in Scheme 3, the researchers ultimately found that bromofluorocyclopropane **18** could serve as a source of the desired allene. Presumably, halogen-metal exchange proceeded faster with this dihalide and the presence of a fluorine

[19] Schreck, M.; Christl, M. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 690.
[20] Christl, M.; Braun, M. *Chem. Ber.* **1989**, *122*, 1939.

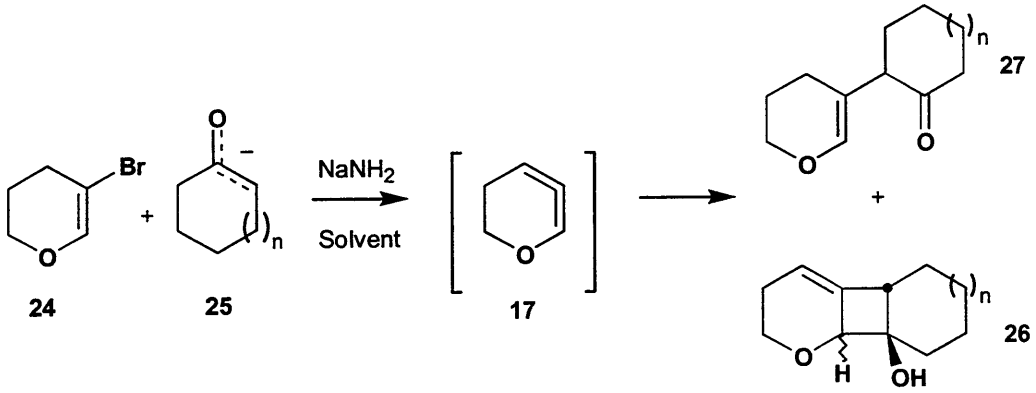
substituent rather than a chlorine substituent imparted additional stability to the cyclopropyllithium intermediate. Treatment of the dihalide **18** with methyllithium and a variety of cycloaddition partners furnished trapping products in 31-71% yields. While [2+2] cycloadducts were formed exclusively when the allene was generated in styrene solvents and as major products when the solvent was a diene, [4+2] cycloadducts were formed exclusively in furan solvents and only as minor products in diene solvents. The [2+2] and [4+2] cycloadditions also displayed different chemoselectivities. While the former occurs on the electron-rich enol ether double bond, the latter takes place at the double bond more remote from the oxygen.

Scheme 3

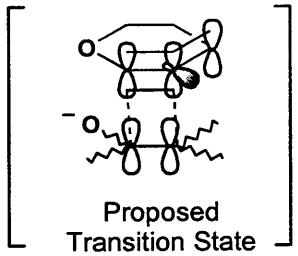


In addition to the report that utilized the ring opening of a dihalocyclopropyl precursor to generate cyclic allene **17**, studies have appeared in the literature outlining the

synthesis of this cyclic allene via elimination of a vinyl halide precursor. In 1991, Caubére and co-workers reported that dehydro-dihydropyrans can be easily generated and condensed with ketone enolates by nucleophilic "aggregative activation" of $NaNH_2$.[21] Exposure of 5-bromo-3,4-dihydropyran **24** to a cycloalkanone enolate in the presence of $NaNH_2$ produces products consistent with condensation of the enolate with the heterocyclic allene intermediate **17** in 48-71% yield. (eq 3).



(3)



The authors proposed that the methylenecyclobutanol products arise from an initial concerted or quasi-concerted cycloaddition of the cyclic allene with the enolate. The ketone product then arises from a slow opening of the resulting alkoxy intermediate. Due to the cis ring junction between the four membered ring and the carbocycle, the authors claimed that a syn addition of the ketone enolate must take place with a highly

[21] For the first report, see: (a) Jamart-Grégorie, B.; Grand, V.; Ianelli, S.; Nardelli, M.; Caubére, P. *Tetrahedron Lett.* **1991**, *31*, 7603. See also: (b) Jamart-Grégoire, B.; Mercier-Girardot, S.; Ianelli, S.; Nardelli, M.; Caubére, P. *Tetrahedron.* **1995**, *51*, 1973. (c) Ianelli, S., Nardelli, M.; Belletti, D.; Jamart-Grégoire, B.; Mercier-Girardot, S.; Caubére, P. *Acta Cryst.* **1996**, *C52*, 237.

polarized transition state. Under their proposal, in the transition state the heterocyclic allene would contain an electron rich sp^2 or pseudo sp^2 orbital on the central atom and an electron deficient π system.

In 1991, Ruzziconi and co-workers reported another synthesis of cyclic allene **17** from the vinyl bromide **24** by treatment with potassium *tert*-butoxide in the presence of 18-crown-6 and subsequent trapping of the heterocyclic allene with dienes or olefins in moderate yields.[22] The authors observe regio- and steroselectivities in complete agreement with those reported by Christl and Braun.

Ruzziconi and co-workers also commented on the structure of cyclic allene **17**. They proposed that the two extreme situations, the planar (0° twist angle) and the orthogonal (90° twist angle) geometries are both unlikely, although the latter could receive stabilization from a through-space interaction with charge transfer from the oxygen to the C-3 carbon. Citing recent work reporting a twist angle of 58° for a seven membered cyclic ketene imine,[23] the authors concluded the intermediate is probably moderately distorted.

In our proposed cycloaddition of a conjugated heteroenyne with an alkyne (see Scheme 2 above), a heterocyclic allene related to those described above, but containing an additional double bond in the ring, would be formed. The oxygen variant of this system is not known and only in the last three years have any reports surfaced on the corresponding aza and thio compounds. The analogous carbocyclic system, however, has been studied more extensively.

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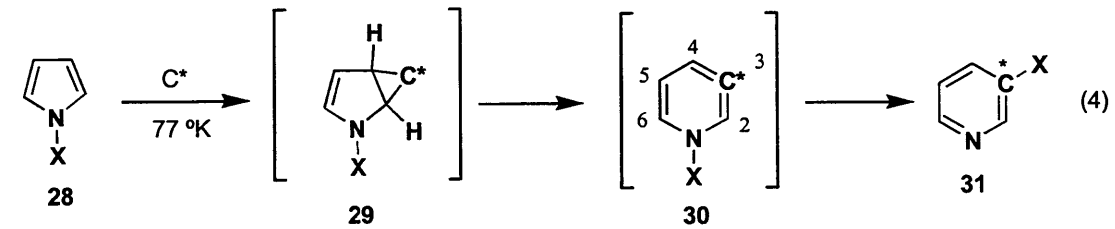
[22] Ruzziconi, R.; Naruse, Y.; Schlosser, M. *Tetrahedron* **1991**, *47*, 4603.
[23] Huisgen, R.; Langhals, H.; Nöth, H. *J. Org. Chem.* **1990**, 55, 1412.

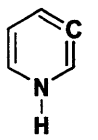
In 1994, Shevlin and Emanuel reported that the reaction of pyrroles **28** with atomic carbon generates pyridines **31** via the intermediacy of azacyclohexatrienes **30** (eq 4).[24] Reaction of pyrroles with atomic carbon was achieved by co-condensing the two species at 77 °K in a conventional carbon arc reaction. In an attempt to elucidate the mechanistic course of the reaction, the experiment was repeated using graphite rods that had been packed with ^{13}C carbon powder. An examination of the ^{13}C NMR spectrum of the pyridine generated in this reaction indicated an enrichment of carbon at the 3-position. In addition, when atomic carbon was condensed with pyrrole-1-d_1, the pyridine product only showed deuterium incorporation at C-3. Based on these experiments, the researchers concluded that the pathway for the reaction involves attack of carbon on the double bond of the pyrroles to generate bicyclic carbenes **29**, which then undergo an electrocyclic ring opening reaction to generate trienes of type **30**. Protonation or deuteration of these strained species then generates pyridines **31**. The authors further proposed that the final protonation/deuteration occurs via an intermolecular process rather than a [1,5] sigmatropic migration since an examination of the geometry of triene **30** indicates that the H on N is in the plane of the ring 3.3 Å from C-3. This proposal was supported by the generation of pyridine-3-d_1 when pyrrole was condensed with CH_3OD.



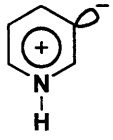
(4)

[24] Emanuel, C. J.; Shevlin, P. B. *J. Am. Chem. Soc.* **1994**, *116*, 5991.

Shelvin and Emanuel also commented on the nature of triene **30**. Optimization of the geometry of triene **30** with no symmetry constraints at the MP2/631-G* level indicates the hydrogen atoms on C-2 and C-4 lie in the plane of the ring (H-C_2-C_4-H dihedral angle = 0.79°) and C-3 has a calculated charge of –1.08. In addition, the AM1-calculated C4-C5 and C5-C6 bond distances are both 1.40 Å. Based on these calculations, the authors proposed that the triene intermediate is better represented as pyridinium ylide **32** rather that as cyclic allene **30**.

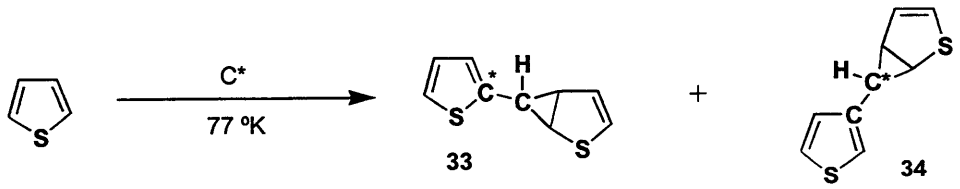


30



32

In contrast to the ylide **32**, the corresponding sulfur heterocycle is believed to possess a cyclic allene structure as the ground state. In 1997, Shelvin and co-workers reported that co-condensing thiophene with carbon atoms enriched in ^{13}C and extracting the residue with hexane yields carbene condensation products **33** and **34** (eq 5).[25]



C* = ^{13}C (5)

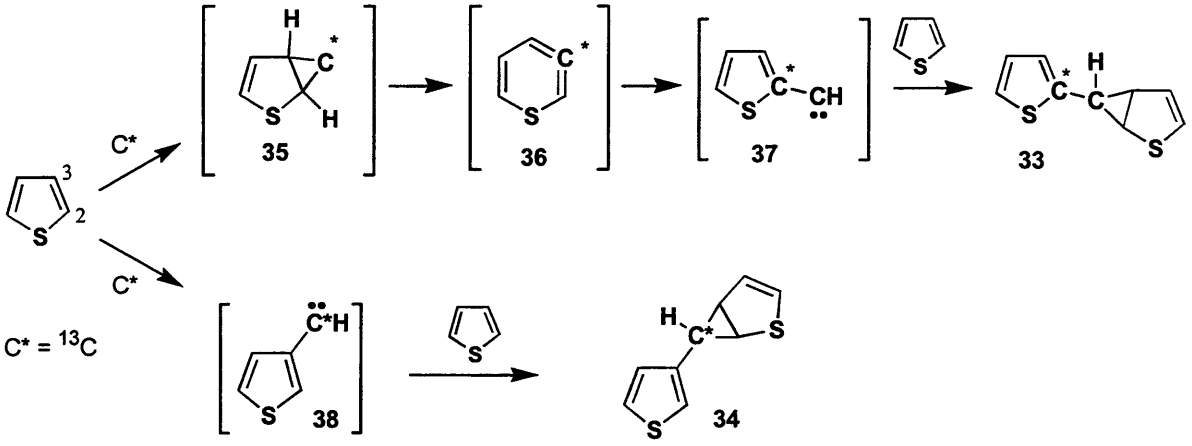
33 **34**

To account for the formation of product **33**, the authors proposed that the cyclic allene intermediate **36** rearranges to carbene **37** which condenses with another molecule of thiophene (Scheme 4). In contrast, due to the location of the labeled carbon, product **34** cannot arise from rearrangement of allene **36**. Instead, the authors proposed that

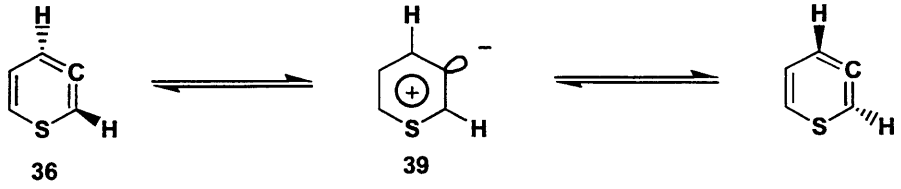
[25] Pan, W.; Balci, M.; Shevlin, P. B. *J. Am. Chem. Soc.* **1997**, *119*, 5035.

product **34** arises from an initial C-H insertion of the atomic carbon at C-3 followed by condensation with a second molecule of thiophene.

Scheme 4



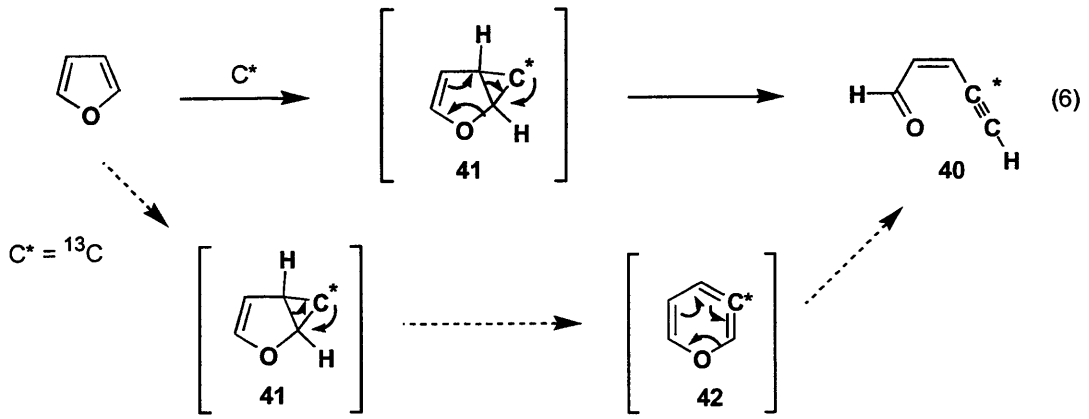
Shelvin and co-workers also performed preliminary calculations to support the assignment of the cyclic allene as the ground state of the system. Their preliminary calculations (MP2/6-31G*) indicate that allene **36** lies 8.5 kcal below thiopyrylium ylide **39** and that ylide **39** is actually an intermediate connecting the two enantiomeric forms of **36**. Thus it appears that the nature of the heteroatom influences the nature of the heterocyclic triene.



It should be noted that when atomic carbon was generated by the pyrolysis of 5-diazotetrazole in the presence of gaseous furan, major product was aldehyde **40** (eq 6).[26] The authors contend that with oxygen system, the initial condensation product **41**

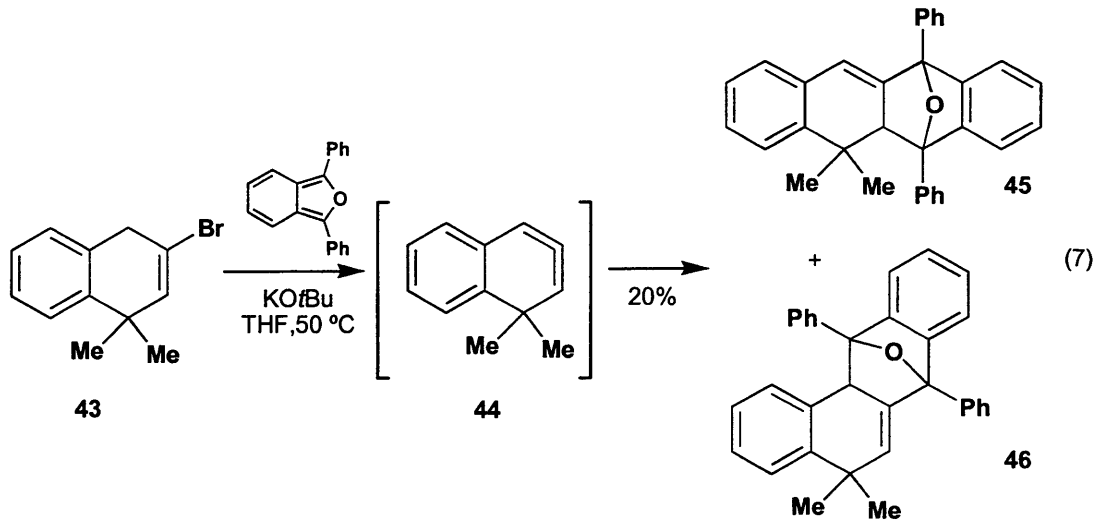
[26] Shevlin, P. B.; Dyer, S. F.; *J. Am. Chem. Soc.* **1979**, *101*, 1303.

undergoes a ring opening to furnish aldehyde **40** rather than the corresponding cyclic triene **42**. No evidence was provided to support this proposal nor do the authors note that the identical product would be generated if triene **42** did form and then underwent an electrocyclic ring opening.



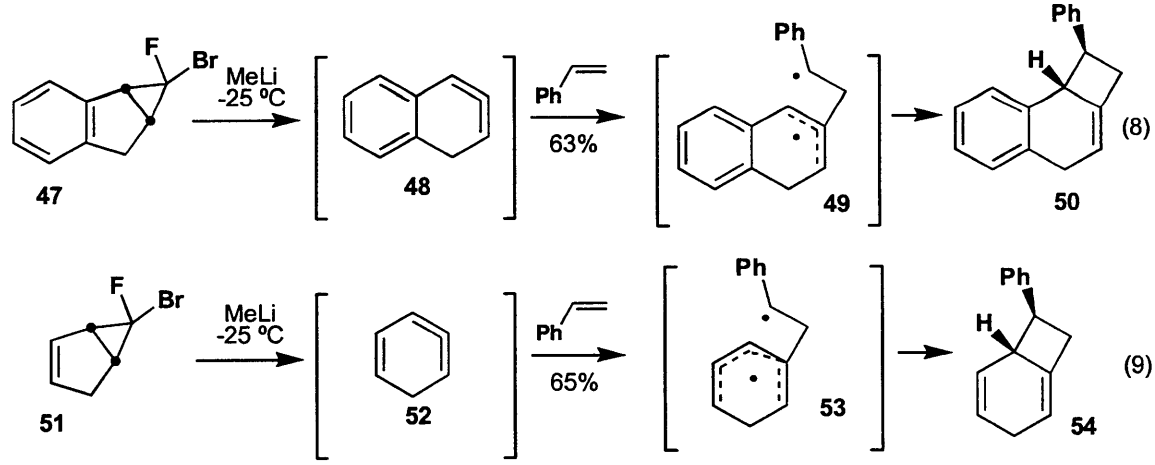
In contrast to the limited reports on heterocyclic triene systems, the analogous carbocyclic system has been studied more extensively, both experimentally and theoretically. In 1987, Miller and Shi reported the generation and interception of the isonapthalene **44** (eq 7).[27] Treatment of a solution of vinyl bromide **43** and 1,3-diphenylisobenzo[c]furan in THF with potassium *tert*-butoxide at 50 °C gave a 3:2 mixture of cycloadducts **45** and **46** in 20% yield. Further evidence for the intermediacy of the cyclic allene **44** was obtained from the reaction of vinyl bromide **43** with potassium *tert*-butoxide in the absence of 1,3-diphenylisobenzo[c]furan at 50 °C which yielded an enol ether from addition of *tert*-butoxide to the strained double bond of **44**.

[27] Miller, B.; Shi, X. *J. Am. Chem. Soc.* **1987**, *109*, 578.



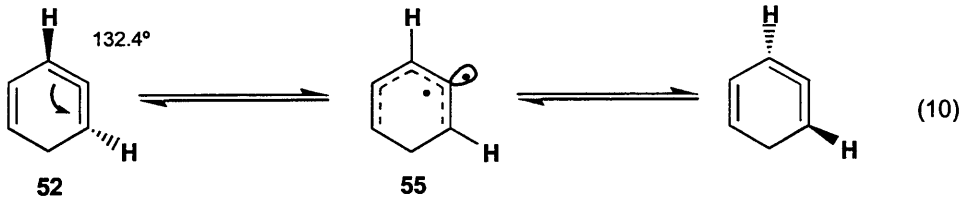
(7)

In 1992, Christl and co-workers reported the generation and trapping of two isoaromatic compounds, isonaphthalene **48** and isobenzene **52**.[28] Solutions of 1-bromo-1-fluorocyclopropanes **47** or **51** were treated with methyllithium at –25 °C to give cycloadducts **50** and **54** in 63% and 65% yield respectively (eq 8 and 9). Christl and co-workers proposed that the cyclic allenes **48** and **52** first react with the styrene to furnish diradicals **49** and **53** which then close under kinetic control to furnish the non-conjugated products **50** and **54**.



[28] Christl, M.; Braun, M.; Müller, G. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 473.

Janoschek has performed several calculations on isobenzene **52**.[29] For example, using the semiempirical AM1 method he predicted the heat of formation of **52** to be 93.7 kcal/mol and the allene to be bent almost 48° from linearity (eq 10). The energy barrier for racemization for this molecule was found to be very low, only 2 kcal/mol, and racemization was predicted to occur through singlet diradical **55**; therefore, the allene was predicted to be configurationally stable only at low temperatures.



52 55 (10)

Feasibility of the Cycloaddition

In considering the [4+2] cycloaddition of conjugated enynes and heteroenynes with acetylenes to generate 1,2,4-cyclohexatriene intermediates (Scheme 2) one must consider the energetic feasibility of the process. Although a cycloaddition of this type might appear to be an energetically unfavorable process, two weak acetylenic π bonds are being broken (ca. 51 kcal/mol each), while two strong carbon-carbon σ bonds are formed (ca. 84 kcal/mole each).[30] This examination of bond energies, however, fails to take into account the ring strain of the cyclic allene. While no data is available for the oxo derivative, a calculation for the carbocyclic substrate can be performed utilizing the heat of formation calculated for 1,2,4-cyclohexatriene by Janoschek[25] and Benson group

[29] Janoschek, R. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 476.
[30] Mean bond energy values at 25 °C. March, J. *Advanced Organic Chemistry*, 3rd ed.; Wiley: New York, 1985, p 23.

additivities.[31] Based on this data we estimate the enthalpy of the reaction (ΔH_R) for the intermolecular cycloaddition to be exothermic by –29.7 kcal/mole.[32]

Recently, Johnson reported ab initio calculations for this cycloaddition at the MP4SDTQ/6-31G*//MP2/6-31G* level and predicted ΔH_R = -25.4 kcal/mole and ΔG_R = -13.4 kcal/mol.[33] Johnson also performed the same calculations on the intermolecular cycloaddition of a conjugated enyne with an alkene and found ΔH_R = -12.7 kcal/mole and ΔG_R = 0.9 kcal/mol.

Another concern with regard to the feasibility of the cycloaddition reaction is whether a concerted process would be possible. In the Diels-Alder reaction, the diene components contain sp^2-hybridized carbons with 120° bond angles, which allow for effective overlap between the termini of the diene (in the s-cis conformation) and the termini of the dienophile. Due to the linear nature of the acetylene moiety of enynes, concerted overlap with "enynophiles" would appear to be quite difficult. However, it is the geometry of the transition state not the ground state of the reactants that must be considered. In fact, acetylenic bonds are readily deformed from their linear ground state geometry and often undergo pericyclic reactions with ease.[34] For example, Huntsmann and Wristers[35] demonstrated that diyne **56** undergoes the Cope rearrangement under

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[31] For Benson group additivity values see: (a) Benson, S. W. *Thermodynamic Kinetics*; Wiley: New York, 1976. For a recent review on Benson additivities, see: (b) Cohen, N.; Benson, S. W. *Chem. Rev.* **1993**, *93*, 2419.

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

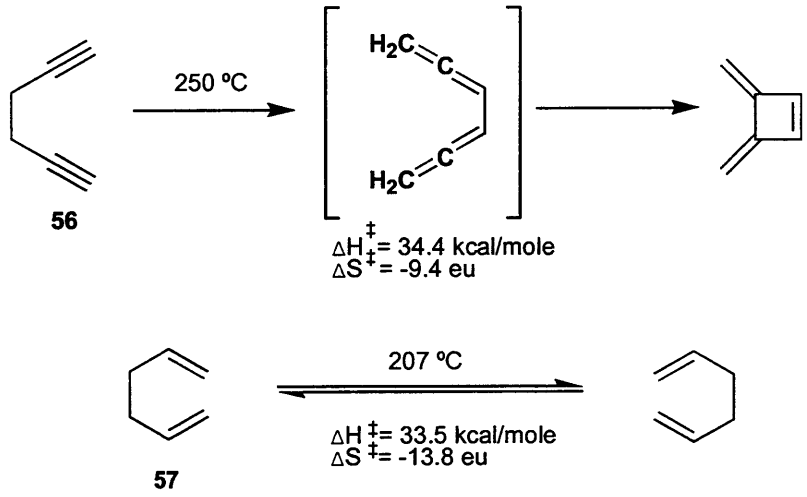
[33] Burrell, R. C.; Daoust, K. J.; Bradley, A. Z.; DiRico, K. J.; Johnson, R. P. *J. Am. Chem. Soc.* **1996**, *118*, 4218.

[34] For a review of acetylenes in pericyclic reactions, see: Viola, A.; Collins, J. J.; Filipp, N. *Tetrahedron* **1981**, *37*, 3765.

[35] Huntsmann, W. D.; Wristers, H. J. *J. Am. Chem. Soc.* **1967**, *89*, 342.

similar conditions used for the rearrangement of diene **57**,[36] and found that the enthalpy and entropy of activation are similar for the two processes (Scheme 5).

Scheme 5



Summary

We are interested in developing cycloaddition reactions mechanistically related to cycloaromatization reactions. As described in this chapter, calculations on the feasibility of the cycloaddition of a conjugated enyne with an alkyne have predicted that the reaction should be exothermic. The next three chapters will outline the scattered examples of enyne cycloadditions existing in the literature, our initial progress in this field, and an overview of the Diels-Alder reaction of oxabutadienes. The remainder of this thesis will then outline the development of a novel variant of the enyne cycloaddition, specifically utilizing ynones and related species as heteroenyne substrates.

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[36] Doering, W. v. E.; Toscano, V. G.; Beasley, G. H. *Tetrahedron* **1971**, *27*, 5299.

Chapter 2

[4+2] Cycloaddition Reactions of Conjugated Enynes Prior to 1990

Introduction

Several examples of the cycloaddition of conjugated enynes with alkenes and alkynes can be found scattered throughout the literature.[37] The earliest examples of reactions of this general type involve not enynes, but arenynes, in which the double bond of the conjugated enyne system is embedded within an aromatic ring. This chapter reviews the synthetic and mechanistic studies of the enyne cycloaddition that were reported prior to 1990. Chapter 3 will then detail previous work on the enyne cycloaddition from 1990 to the present.

[4+2] Cycloaddition Reactions of Conjugated Arenynes

In 1898, Michael and Bucher attempted to condense phenylpropiolic acid (**58**) with acetic anhydride in order to generate β-hydroxycinnamic acid **59**, but instead produced 1-phenyl-2,3-napthalene dicarboxylic anhydride **60** presumably via an arenyne cycloaddition of the anhydride of phenylpropiolic acid (Scheme 6).[38] To the best of our knowledge, this is the first example of an arenyne reacting with an alkyne to form an aromatic product in which two carbon-carbon bonds are formed along with an isomerization. Bucher later reported that ester and acid chloride derivatives of

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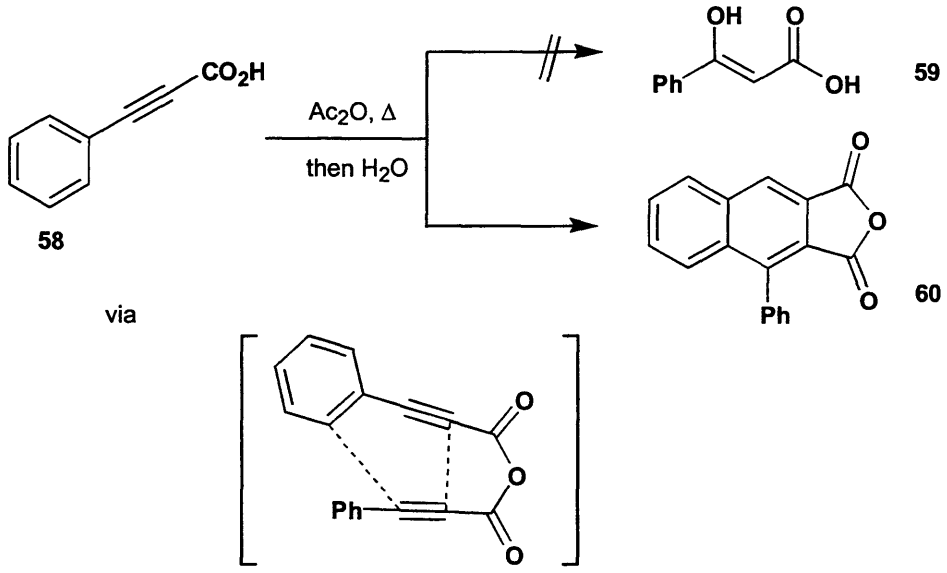
[37] Early examples are collected in: (a) Onishchenko, S. *Diene Synthesis* Israel Program for Scientific Translations: Jerusalem, 1964; pp 249-254, 635-637. (b) Vartanyan, S. A. *Russ. Chem. Rev.* **1962**, *31*, 529. (c) Viehe, H. G. *Chemistry of Acetylenes*; Marcel Dekker: New York, 1969; pp 494-496. (d) Johnson, A. W. *The Chemistry of Acetylenic Compounds*; Edward Arnold Press: London, 1950; Vol. II, pp 76-79.

[38] Michael, A.; Bucher, J. E. *Am. Chem. J.* **1898**, *20*, 89.

phenylpropiolic acid and substituted phenylpropiolic acids also participate in similar reactions.[39]

Scheme 6



Several decades later,[40] Baddar and co-workers expanded the scope of the Michael-Bucher reaction and investigated the regiochemical course of the reaction using unsymmetrical anhydrides of substituted phenylpropiolic acids. Although these studies failed to reveal any clear trends about the regioselectivity of the cycloaddition, this work did indicate the generality of the transformation.

Further studies on the dimerization of substituted phenylpropiolic acids were conducted by the groups of Stevenson[41] and Ward.[42] These researchers reported that

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[39] Bucher, J. E. *J. Am. Chem. Soc.* **1910**, *32*, 212.

[40] (a) Baddar, F. G. *J. Chem. Soc.* **1947**, 224. (b) Baddar, F. G.; El-Assal, L. S. *J. Chem. Soc.* **1948**, 1267. (c) Baddar, F. G.; El-Assal, L. S. *J. Chem. Soc.* **1951**, 1844. (d) Baddar, F. B.; El-Assal, L. S.; Doss, N. A. *J. Chem. Soc.* **1955**, 461. (e) Baddar, F. G.; Fahim, H. A.; Galaby, M. A. *J. Chem. Soc.* **1955**, 465. (f) Baddar, F. G.; El-Assal, L. S.; Doss, N. A. *J. Chem. Soc.* **1959**, 1027. (g) Baddar, F. G.; Moussa, G. E. M.; Omar, M. T. *J. Chem. Soc. (C)* **1968**, 110.

[41] (a) Brown, D.; Stevenson, R. *Tetrahedron Lett.* **1964**, 3213. (b) Brown, D.; Stevenson, R. *J. Org. Chem.* **1965**, *30*, 1759. (c) Maclean, I.; Stevenson, R. *Chem. Ind.* **1965**, 1379. (d) Maclean, I.; Stevenson, R. *J. Chem. Soc. (C)* **1966**, 1717. (e) Stevenson, R.; Weber, J. V. *J. Nat. Prod.* **1989**, *52*, 367.

[42] Cadby, P. A.; Hearn, M. T. W.; Ward, A. D. *Aust. J. Chem.* **1973**, *26*, 557.

milder procedures could effect the transformation, thus expanding the general utility of the cycloaddition in organic synthesis. Specifically, their results indicated the arenyne cycloaddition could be accomplished by treatment of arylpropiolic acids with N, N-dicyclohexylcarbodiimide (DCC)[37,38] or a combination of P4-VP, a solid phase co-polymer of 4-vinylpyridine, and thionyl chloride.[37e]

As illustrated above, early studies of the arenyne cycloaddition all involved the examination of substrates with substituted alkynyl arenynophiles. The reaction, however, has been extended to substrates with terminal acetylenes as arenynophiles. In 1963, Campbell and Grimmett reported the reaction of propiolic acid with a variety of substituted aryl-propiolic acids by subjecting a mixture of acetylenic acids to acetic anhydride and heat.[43] Later, Klemm and co-workers also expanded the scope of the Michael-Bucher reaction to include a variety of substituted and unsubstituted arenynophiles with ester and amide tethers between the two reaction partners.[44]

The mechanism for the cycloaddition of arenynes remains unresolved. Bucher offered proposals to account for the generation of naphthalene **60**, but this was before the nature of bonding was well understood.[39] In 1969, Whitlock and co-workers investigated the mechanism of the Michael-Bucher reaction,[45] reporting the isolation of a mixture of naphthalene **60** and deuterium incorporated naphthalene **60a** when phenylpropiolic acid was heated in acid anhydride and deuterated acetic acid (Scheme 7). Based on these

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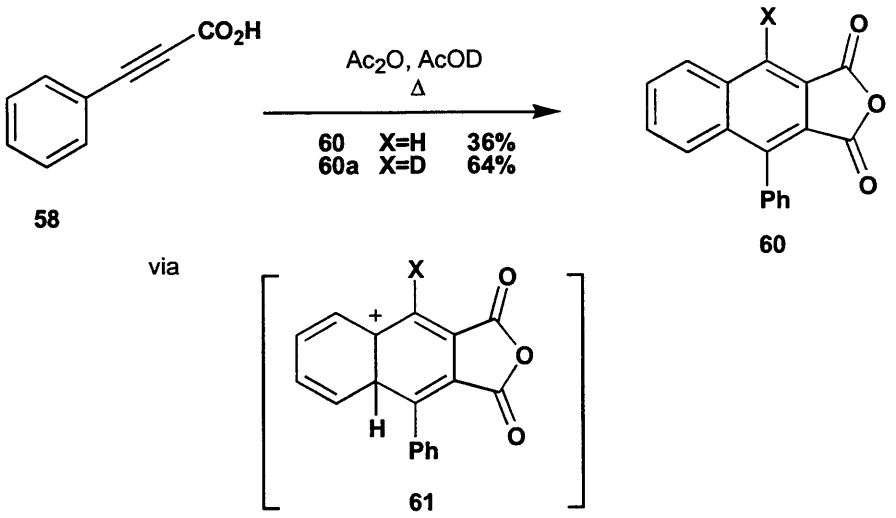
[43] Campbell, A. D.; Grimmett, M. R. *Aust. J. Chem.* **1963**, *16*, 854.
[44] (a) Klemm, L. H.; Hsu Lee, D.; Gopinath, K. W.; Klopfenstein, C. E. *J. Org. Chem.* **1966**, *31*, 2376. (b) Klemm, L. H.; Gopinath, K. W.; Hsu Lee, D.; Kelly, F. W.; Trod, E.; McGuire, T. M. *Tetrahedron* **1966**, *22*, 1797. (c) Klemm, L. H.; Klemm, R. A.; Santhanam, P. A.; White, D. V. *J. Org. Chem.* **1971**, *36*, 2169. (d) Klemm, L. H.; McGuire, T. M. *J. Heterocycl. Chem.* **1972**, *9*, 1215. (e) Klemm, L. H.; McGuire, T. M.; Gopinath, K. W. *J. Org. Chem.* **1976**, *41*, 2571. (f) Klemm, L. H.; Tran, V. T.; Olson, D. R. *J. Heterocycl. Chem.* **1976**, *13*, 741.
[45] Whitlock, H. W. Jr.; Wu, E.-M.; Whitlock, B. J. *J. Org. Chem.* **1969**, *34*, 1857.

deuterium labeling experiments, Whitlock proposed that the anhydride intermediate undergoes simultaneous protonation and ring formation to give a cyclohexadienyl cation intermediate **61** which loses a proton to furnish the observed naphthalene **60**.

Scheme 7

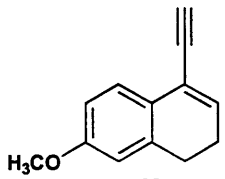


Upon examining Whitlock's mechanistic proposal, some questions arise. First, he proposes protonation of the alkyne at the benzyllic position to develop positive charge adjacent to a carbonyl group; however, this is not the thermodynamically favored site of protonation. In addition, deuterium would appear in the same position in the product if protonation of the allene occurred after the cycloaddition; hence other mechanisms may be operative. Furthermore, since the reaction can be promoted with DCC and in the presence of an acid scavenger (P4-VP), acid does not seem obligatory to promote the transformation. It must be concluded that the mechanism of the Michael-Bucher reaction remains unresolved.

Intermolecular [4+2] Cycloaddition Reactions of Conjugated Enynes

Soon after the report of the Michael-Bucher reaction, several scattered examples appeared of the intermolecular cycloadditions of conjugated enynes. These reports involved a limited number of substrates and in each case, the corresponding cycloaddition product was only produced in low yield. Despite the synthetic limitations of these findings, the studies did provide precedent for utilizing enynes in intramolecular cycloaddition reactions.

The first two reports of intermolecular cycloadditions of enynes involved the reactions of vinylacetylenes. In 1934, Dykstra reported that when vinylacetylene was heated in the presence of catalytic amounts of various acids and carboxylic anhydrides, dimerization occurred to generate styrene in small amounts.[46] To account for styrene formation, Dykstra proposed the intermediacy of a cyclic allene resulting from a "Diels-Alder diene reaction". Although Dykstra discounted this intermediate as "impossible stereochemically" and proposed an alternate mechanism to account for the styrene formation, he is the first person to connect the enyne cycloaddition with the Diels-Alder reaction. A few years later, Dane and co-workers also reported the cycloadditions of an electron rich enyne **62**, with several alkenes and alkynes in diethyl ether at room temperature.[47] Recently this cycloaddition has been reexamined and doubts were raised as to whether the reaction can proceed without acid promotion (see Part I, Chapter 3).

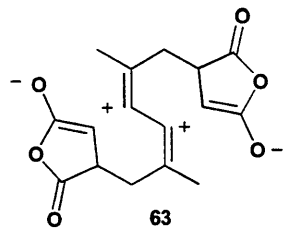


62

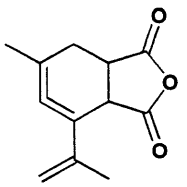
[46] Dykstra, H. B. *J. Am. Chem. Soc.* **1934**, *56*, 1625.
[47] (a) Dane, E.; Höss, O.; Bindseil, A. W.; Schmitt, J. *Ann. Chem.* **1937**, *523*, 39. (b) Dane, E.; Höss, O.; Schmitt, J.; Schön, O. *Ann. Chem.* **1938**, *536*, 183.

The other examples of intermolecular cycloadditions of enynes prior to 1990 involve the use of dienynes as substrates. In the 1940's, Butz and co-workers reported the thermal condensation of a variety of dienynes with a variety of enynophiles in double cycloaddition reactions to produce tetracyclic products.[48] A few isolated examples of double cycloaddition reactions followed a few years later.[49] In all cases, however, the yields for the reactions were poor; suggesting that the intermolecular cycloaddition of dienynes has limited synthetic utility.

Butz and co-workers proposed two mechanistic possibilities for the reactions of the dienynes with maleic anhydride.[45a] One pathway involves a stepwise mechanism in which two molecules of maleic anhydride react with a dienyne, such as 2,5-dimethyl-hexa-1,5-dien-3-yne, to afford a zwitterionic intermediate **63**, which then cyclizes to afford the observed product. The other proposal involves a concerted pathway via the intermediacy of a cyclic allene **64**. Citing Favorski's successful generation of 1,2-cycloheptadiene,[50] these researchers suggested that the lifetime of allene **64** may be long enough such that another molecule of maleic anhydride could add to furnish the observed tetracyclic product.



63



64

[48] (a) Butz, L. W.; Gaddis, A. M.; Butz, E. W. J.; Davis, R. E. *J. Org. Chem.* **1940**, *5*, 379. (b) Butz, L. W.; Gaddis, A. M.; Butz, E. W. J. *J. Am. Chem. Soc.* **1940**, *62*, 995. (c) Butz, L. W.; Joshel, L. M. *J. Am. Chem. Soc.* **1941**, *63*, 3344. (d) Joshel, L. M.; Butz, L. W.; Feldman, J. *J. Am. Chem. Soc.* **1941**, *63*, 3348. (e) Butz, L. W.; Joshel, L. M. *J. Am. Chem. Soc.* **1942**, *64*, 1311. (f) Nudenberg, W.; Butz, L. W. *J. Am. Chem. Soc.* **1943**, *65*, 2059. (g) Butz, L. W.; Gaddis, A. M.; Butz, E. W. J. *J. Am. Chem. Soc.* **1947**, *69*, 924.

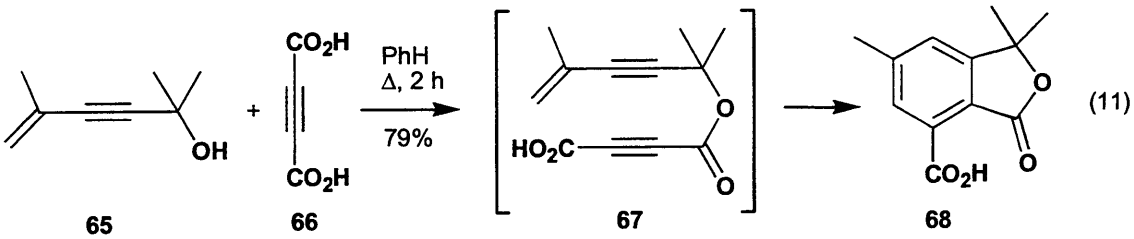
[49] Ray, F. E.; Sawicki, E.; Borum, O. H. *J. Am. Chem. Soc.* **1952**, *74*, 1247. (b) Israelashvili, S.; Edlitz-Pfeffermann, J. *J. Am. Chem. Soc.* **1952**, *74*, 5780.

[50] Favorskii, A. E. *Bull. Soc. Chim.* **1936**, *3*, 1727.

Intramolecular [4+2] Cycloaddition Reactions of Conjugated Enynes

In contrast to the intermolecular cycloadditions of conjugated enynes, a review of the literature reveals several examples of highly efficient intramolecular cycloadditions of conjugated enynes. In general, intramolecular cycloaddition reactions are entropically more favorable than intermolecular processes. In addition, intramolecular reactions can create multiple rings in one step and are therefore more efficient as methods for constructing polycyclic systems.

The first example of an intramolecular enyne cycloaddition appeared in 1945 when Johnson reported the reaction of propargylic alcohol **65** with acetylenedicarboxylic acid to give phthalide **68** in good yield (eq 11).[51] As illustrated below, Johnson proposed that this thermal reaction proceeds via a doubly-activated enynophile intermediate **67** resulting from condensation of the alcohol with the carboxylic acid.



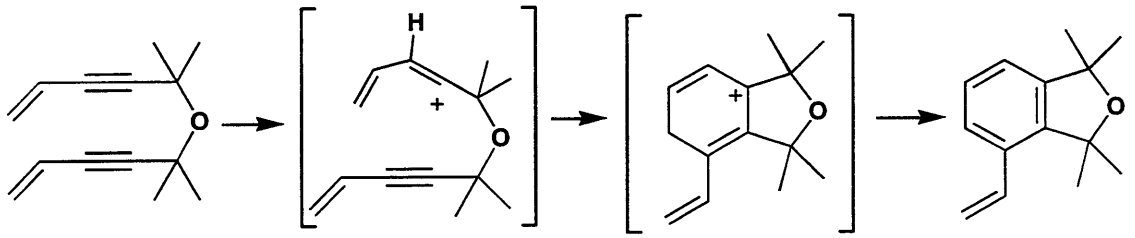
65 66 67 68 (11)

In 1959, Nazarov and co-workers extended the intramolecular enyne cycloaddition to ether substrates with the report of the dimerization and subsequent cycloaddition of various tertiary and secondary propargylic enyne alcohols upon heating under acidic conditions.[52] Nazarov et al. proposed a mechanism for the transformation that included protonation of one alkyne moiety in the symmetrical ether to yield a dienyl

[51] Johnson, A. W. *J. Chem. Soc.* **1945**, 715.
[52] Nazarov, I. N.; Verkholetova, G. P.; Torgov, I. V. *J. Gen. Chem. USSR (Engl. Transl.)* **1959**, *29*, 3277.

cation intermediate **70**, which next undergoes a [4+2] cycloaddition followed by loss of a proton to furnish the observed isocoumaran products (Scheme 8).

Scheme 8



69 **70** **71** **72**

To the best of our knowledge, Nazarov and co-workers were the first to propose a dienyl cation intermediate in the cycloaddition of a conjugated enyne. The alkyne protonation they propose, however, is not the thermodynamically favored protonation. Perhaps protonation of the acetylene is reversible, and therefore a Curtin-Hammett situation arises in which the cycloaddition of the less thermodynamically stable dienyl cation occurs with more facility.

In a study related to the work of Nazarov et al., Hakopian and co-workers examined the intramolecular cycloadditions of several unsaturated ethers.[53] These researchers determined that the thermal cycloaddition of the substrates proceeded much more efficiently and at lower temperatures when the alkynyl enynophile contained an electron acceptor group compared to when it contained an electron donator group. We believe these results suggest that the cycloaddition of conjugated enynes may be LUMO-controlled with respect to the enynophile.

[53] (a) Hakopian, L. A.; Gezalian, G. I.; Grigorian, S. G.; Matsoyan, S. G. *Arm. Khim. Zh.* **1974**, *27*, 764. (b) Hakopian, L. A.; Gezalian, G. I.; Matsoyan, S. G. *Arm. Khim. Zh.* **1974**, *27*, 768. (c) Hakopian, L. A.; Gezalian, G. I.; Matsoyan, S. G. *Arm. Khim. Zh.* **1975**, *28*, 72.

Summary

In summary, research carried out prior to 1990 revealed several examples of thermal, and protic acid-promoted cycloadditions of arenynes and conjugated enynes; however the scope and potential utility of these reactions in organic synthesis had not been demonstrated. In fact, most of the intramolecular examples contained oxygen in the connecting chain, and no examples of substrates containing only carbon atoms in the tether had been reported. Several mechanisms had been proposed for these reactions, but little experimental evidence supporting these proposals had been produced.

Chapter 3

[4+2] Cycloaddition Reactions of Conjugated Enynes Since 1990

Introduction

Recent work on the cycloaddition reactions of conjugated enynes has focused on establishing the scope and mechanism for the intramolecular variant. In addition to developments in these areas, some of the early studies of intermolecular enyne cycloadditions have been revisited and further elaborated. This chapter will outline the investigations on the cycloaddition reactions of conjugated enynes that have occurred from 1990 to the present.

Intermolecular [4+2] Cycloaddition Reactions of Conjugated Enynes

Recently, Miller and Ionescu[54] reexamined the intermolecular cycloaddition reaction of enyne **62** with maleic anhydride originally reported by Dane in 1937 (See Part I, Chapter 2). In contrast to Dane, Miller and Ionescu found that this reaction fails to proceed unless a sub-stoichiometric amount of either HCl (g) or HBr (g) was added to the reaction mixture. Due to the requirement for HX in these reactions, Miller and Ionescu proposed a hydrogen halide-catalyzed mechanism that involves the formation of a halodiene (Scheme 9). As shown below, they suggested that the electron-rich enyne **62** is first protonated to give benzylic-allenyl cation **73a/b**. Cation **73b** is subsequently trapped by the halide ion to afford allenyl halide **74**. Protonation at the central carbon of allene **74** followed by elimination provides halodiene **75**, which then undergoes a Diels-Alder cycloaddition to give cycloadduct **76**. Elimination of HX regenerates the catalyst and produces the observed product **77**.

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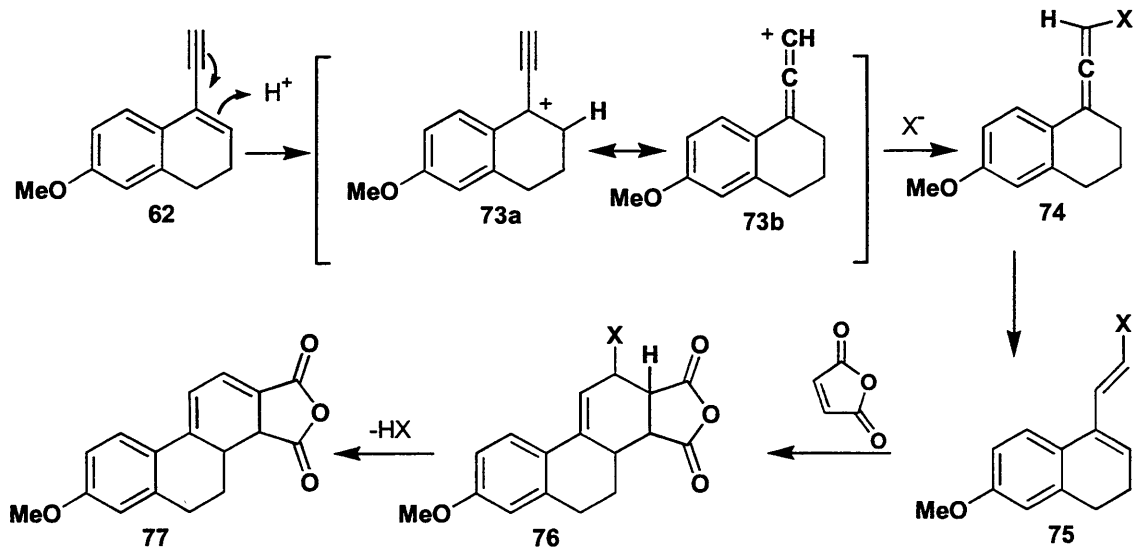
[54] Miller, B.; Ionescu, D. *Tetrahedron Lett.* **1994**, *35*, 6615.

Scheme 9



Miller et al. independently synthesized halodiene **75** (X = Br and Cl) and found that both dienes react with maleic anhydride to provide product mixtures "essentially identical" with the products obtained by the hydrogen halide-catalyzed reaction of enyne **62** with maleic anhydride, although no yields were reported. These results suggest that the [4+2] cycloaddition of halodiene **75** (X = Br or Cl) with maleic anhydride can occur and halodiene **75** may be an intermediate in the hydrogen halide-catalyzed reaction of enyne **62** with maleic anhydride.

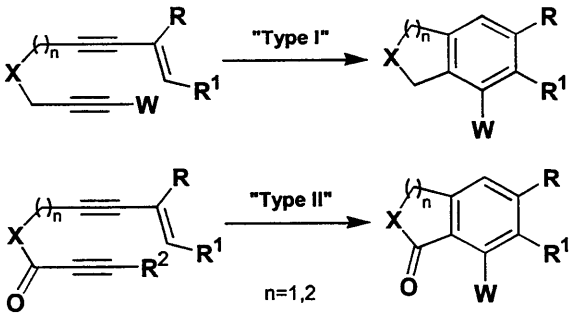
Miller and co-workers[55] have also recently reexamined the double cycloaddition reactions of dienynes pioneered by Butz (see Part I, Chapter 2). Based on a crystal structure of one of the tetracyclic products and extensive NMR experiments on a second product, the researchers concluded that the reaction proceeds with suprafacial addition of the alkene. These results support a concerted or very fast stepwise mechanism for these double cycloaddition reactions.

[55] Ionescu, D.; Silverton, J. V.; Dickinson, L. C.; Miller, B. *Tetrahedron Lett.* **1996**, *37*, 1559.

Intramolecular [4+2] Cycloaddition Reactions of Conjugated Enynes

In 1994, our laboratory reported the first systematic investigation of the scope and mechanism of the intramolecular [4+2] cycloaddition of conjugated enynes.[32] In particular, this report focused on the synthesis of aromatic and dihydroaromatic carbocycles from the cycloadditions of substrates containing a carbon tether between the two reaction partners.[56] The initial goals of this work included establishing the feasibility of the transformation with only carbon atoms in the tether, optimizing the conditions for the practical applications of this methodology in organic synthesis, and investigating the mechanism and stereochemistry of the reaction. Later, this work was extended to include the synthesis of heterocycles by employing substrates containing a heteroatom in the tether.[57]

The general types of substrates examined in this cycloaddition are summarized below. "Type I" cycloaddition substrates are defined as those substrates in which the alkynyl enynophile contains an activating group (i.e., electron-withdrawing group, W) external to the connecting chain. "Type II" cycloaddition substrates are those in which the alkynyl enynophile contains an activating group within the connecting chain.



[56] For a detailed account of the scope and mechanistic studies of these systems, see: Gould, A. E. Ph. D. Thesis, Massachusetts Institute of Technology, June 1996.

[57] For a detailed account of the extension of this chemistry to substrates containing heteroatoms in the connecting chain, see: Palucki, B. L. Ph. D. Thesis, Massachusetts Institute of Technology, June 1997.

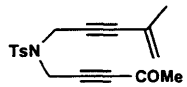
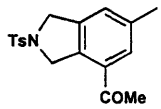
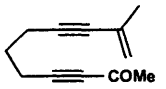
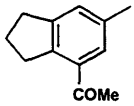
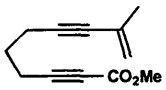
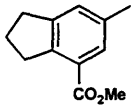
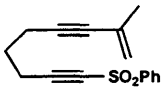
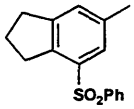
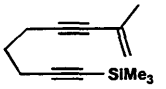
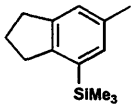
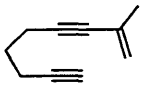
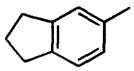
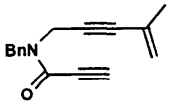
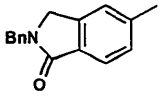
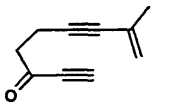
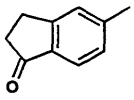
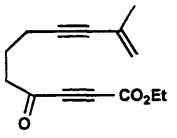
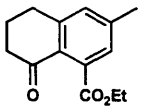
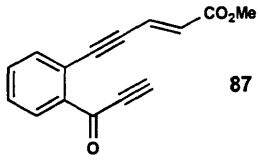
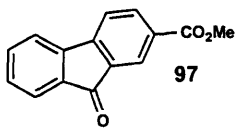
A sample of the scope of the thermal cycloaddition is presented in Table 1. The optimal conditions for the thermal cycloaddition were determined to involve heating a degassed 0.1-0.25 M solution of the substrate in toluene or cyclohexane in the presence of one or more equivalents of a radical scavenger such as phenol, 2,6-di-*tert*-butyl-4-methylphenol (BHT), or *p*-methoxyphenol (PMP). The incorporation of phenolic additives in the reaction mixture improved the yield of the cycloaddition for ketone **79** by about 15%. Other radical inhibitors failed to improve the efficiency of the reaction. For example, with ester substrate **80**, the use of γ-terpinene as the additive led to the formation of the cycloadduct in lower yield (31%).

As illustrated in the table, "type I" cycloaddition substrates with a variety of substituents on the enynophile undergo the thermal cycloaddition (entries 1-6). Substrates containing electron-withdrawing groups on the alkynyl enynophile undergo the cycloaddition with the greatest facility, while those with less activated enynophiles require more elevated temperatures. In fact, substrates containing a thiophenyl or methyl group on the enynophile failed to form any cycloaddition products, even at high temperatures. The thiophenyl substrate decomposed at both 180 °C and 250 °C, and no reaction was observed from the thermolysis of the methyl substrate at 180 °C. With respect to the nature of the connecting chain, "type I" substrates containing an all-carbon tether react in higher yields than those containing nitrogen in the connecting chain (entry 1 vs. entry 2).

It was also found that "type II" cycloaddition substrates undergo the thermal cycloaddition to give good yields of aromatic products (entries 7-10). An examination of the effect of substitution on the enynophile revealed that a second electron-withdrawing

group on the alkyne can facilitate the reaction (entry 9). Of additional note is the effect of the incorporation of an aromatic ring within the tether.[58] These substrates undergo the cycloaddition at much lower reaction temperatures (entry 10). Due to the additional constraints imposed by the aromatic ring, the entropy of activation for the reaction should be lowered, thereby reducing the temperature needed to promote the transformation.

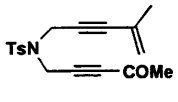
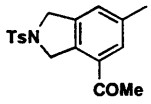
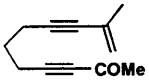
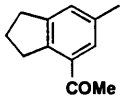
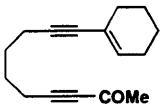
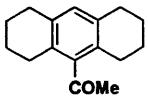
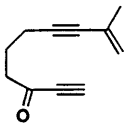
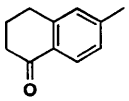
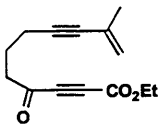
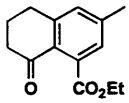
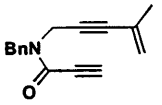
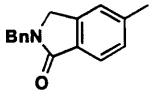
Table 1. Thermal Enyne Cycloadditions

Entry	Substrate		Cycloadduct		Conditions	Yield (%)
1		78		88	1 equiv BHT tol, 122 °C, 3 h	36
2		79		89	1 equiv PhOH tol, 180 °C, 7 h	52
3		80		90	1 equiv PhOH tol, 180 °C, 7 h	50
4		81		91	1 equiv BHT tol, 180 °C, 7 h	77
5		82		92	1 equiv PMP cyclohexane 250 °C, 36 h	48
6		83		93	1 equiv PMP cyclohexane 250 °C, 36 h	26
7		84		94	3 equiv BHT tol, 120 °C, 6 h	94
8		85		95	3 equiv BHT tol, 180 °C, 16 h	68
9		86		96	3 equiv BHT tol, 130 °C, 16 h	69
10		87		97	5 equiv BHT tol, 111 °C, 1 h	55

[58] Helgason, A. L. Ph. D. Thesis, Massachusetts Institute of Technology, June 1994.

Once the feasibility of the transformation had been established by the thermal studies, promotion by Lewis and protic acids was investigated. It is well documented in the literature that other [4+2] cycloaddition processes such as the Diels-Alder and ene reactions can be promoted by both Lewis and protic acids,[59,60] thereby allowing the reactions to occur at lower temperatures. Studies revealed that the enyne cycloadditions can also be promoted and even catalyzed by both Lewis and protic acids. Table 2 provides a sample of the scope of the Lewis and protic acid-promoted cycloaddition reactions.

Table 2. Lewis and Protic Acid-Promoted Cycloaddition Reactions of Enynes

Entry	Substrate		Cycloadduct		Conditions	Yield (%)
1		78		88	10 equiv $ZnBr_2$ 2 equiv BHT, CH_2Cl_2 reflux, 3 days	64
2		79		89	10 equiv $ZnBr_2$ 2 equiv BHT, CH_2Cl_2 reflux, 72 h	55
3		98		100	10 equiv$ZnBr_2$ 2 equiv BHT , $ClCH_2CH_2Cl$ reflux, 18 h	60
4		99		101	10 equiv $ZnBr_2$ 2 equiv BHT, CH_2Cl_2 reflux, 18 h	68
					1 1 equiv $AlCl_3$ CH_2Cl_2, 0 °C, 30 min	90
					3 equiv Me_2AlCl CH_2Cl_2, -78 °C→ rt, 8 h	48
5		86		96	2.5 equiv MsOH CH_2Cl_2, 0 °C, 30 min	87
					3 equiv $AlCl_3$ CH_2Cl_2, rt, 90 min	74
6		84		94	2.4 equiv MsOH $ClCH_2CH_2Cl$, 74-80 °C, 24 h	56

[59] For a general review of the acceleration of Diels-Alder reactions, see: Pindur, U.; Lutz, G.; Otto, C. *Chem. Rev.* **1993**, *93*, 741.

[60] For additional reviews, see (a) Roush, W. R. In *Cycloadditions*; Curran, D. P., Ed.; Jai: Greenwich, CT, 1990; Vol. 2, pp 91-146. (b) Craig, D. *Chem. Soc. Rev.* **1987**, *16*, 187.

A variety of Lewis and protic acids were found to promote the enyne cycloaddition. Among the most successful Lewis acids were aluminum chloride, dimethylaluminum chloride, and zinc bromide.[61] The ability of dimethylaluminum chloride to promote the reaction is significant since Me_2AlCl is also an acid scavenger, indicating that HX is not necessary to promote the reaction. The reactions with the zinc bromide were complicated by the fact that adventitious HBr may also be acting as a catalytic species. Initially, the reactions were run with commercial, unpurified chloroform as the solvent. Commercial chloroform contains traces of ethanol and water, and these contaminants can react with zinc bromide to form HBr. In fact, when two equivalents of water were added to the reaction mixture, cycloadduct formation proceeded at a slightly faster rate compared to the reaction in the absence of water. Consequently, the active species in the former system may be HBr, not zinc bromide. Furthermore, when the reaction was repeated using completely anhydrous conditions, the cycloaddition was found to proceed much more slowly. These results indicate adventitious acid may be promoting the reactions.

A variety of protic acids were also examined as promoters of the enyne cycloaddition, including trifluoroacetic, *p*-toluenesulfonic, methanesulfonic, camphorsulfonic, and trifluoromethanesulfonic acids.[61] Based on optimization studies performed on enyne substrate **99**, methanesulfonic and trifluoromethanesulfonic acids proved to be the best protic acid-promoters of the reaction. While the cycloaddition of enyne **99** with one equivalent of methanesulfonic acid proceeded at 25 °C to afford tetralone **101** in 85% in 19 hours, with two equivalents of trifluoroacetic or one

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[61] Fernández de la Pradilla, R.; Massachusetts Institute of Technology, unpublished results

equivalent of *p*-toluenesulfonic acid the reactions were not complete after two days at 25 °C. In addition, with two equivalents of camphorsulfonic acid there was no evidence of cycloaddition product after 26 h at 25 °C.

Although a variety of "type I" substrates were examined, only ketone substrates were found to benefit from Lewis or protic acid promotion. Other derivatives with either electron-withdrawing or electron-donating groups on the enynophiles either did not react or decomposed when treated with a variety of Lewis and protic acids.

A variety of substituted "type II" cycloaddition substrates were also examined. In general two trends emerged. First, increasing the substitution on the enynophile of these substrates can decrease the efficiency of the reaction. For example, in contrast to the thermal results, substitution of a second electron-withdrawing group on the alkyne enynophile slows the reaction; ester **86** required both higher temperatures and additional equivalents of aluminum trichloride to undergo the cycloaddition compared to enyne **99** (entry 5 vs. entry 4). Secondly, both Lewis and protic acid-promoted cycloadditions of "type II" amide substrates require higher temperatures and proceed in lower yields compared to the cycloadditions of the all-carbon substrates.

The effect of the length and nature of the connection chain was found to be similar to the effects observed in the Lewis acid-catalyzed intramolecular Diels-Alder reaction. For the "type I" substrates, increasing the tether length from three to four carbons slowed the reaction dramatically. These results agree with the increased entropy component required to bring the longer tether into a reactive conformation. With the "type II" all-carbon substrates, however, those with a four-carbon tether are the most reactive substrates under Lewis or protic acid conditions while those with a three carbon

tether fail to react. The shorter chain length of these compounds may prevent effective overlap between the carbonyl and the alkyne of the enynophile in the transition state. In contrast, the opposite effect was observed for amide substrates. While "type II" amide substrates with a three-atom tether undergo the Lewis and protic acid-promoted cycloadditions in moderate yields, the substrates with a four-atom tether only produce decomposition products and byproducts. Presumably the amide substrates with four-atom tethers can undergo side reactions with greater facility that the desired cycloaddition reactions.

The effect of incorporation of an aromatic ring in the connecting chain of "type II" substrates was also examined. While these substrates provided moderate to high yields of cycloadducts under thermal conditions, under acid-promotion only low to moderate yields were obtained. This fact might result from an increased sensitivity of aryl-substituted enynes to the acidic reaction conditions.

In the previous chapter, literature studies on the cycloadditions of enynes were presented which included various mechanistic proposals to account for the products observed in these reactions. Scheme 10 outlines those pathways our laboratory considers the most important based on both previous work and our own mechanistic studies.[62] We believe that depending on the reaction conditions, different intermediates may be involved in the reaction. Under thermal conditions, the key intermediates may be cyclic allene **103** and/or biradical **104**. Under acid-promotion conditions, the key intermediate may be dienyl cation **105** or a corresponding ion pair or dienyl halide derivative.

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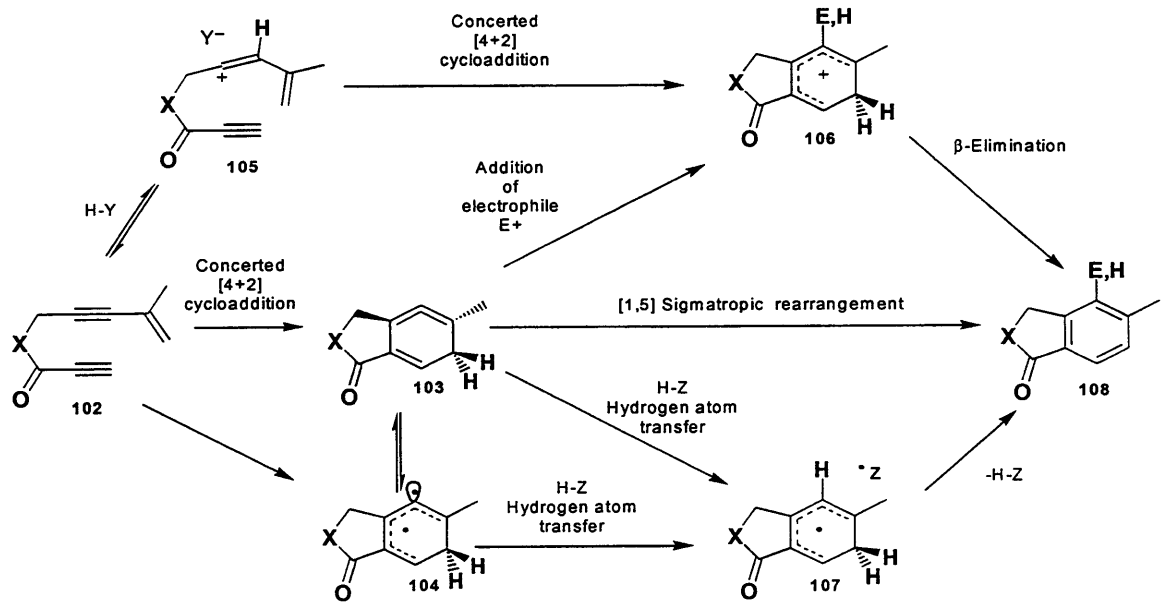
[62]For a detailed explanation of these proposed pathways and the mechanistic experiments performed, see: (a) Gould, A. E. Ph.D. Thesis, Massachusetts Institute of Technology, June 1996. (b) Palucki, B. L. Ph.D. Thesis, Massachusetts Institute of Technology, June 1997.

Scheme 10



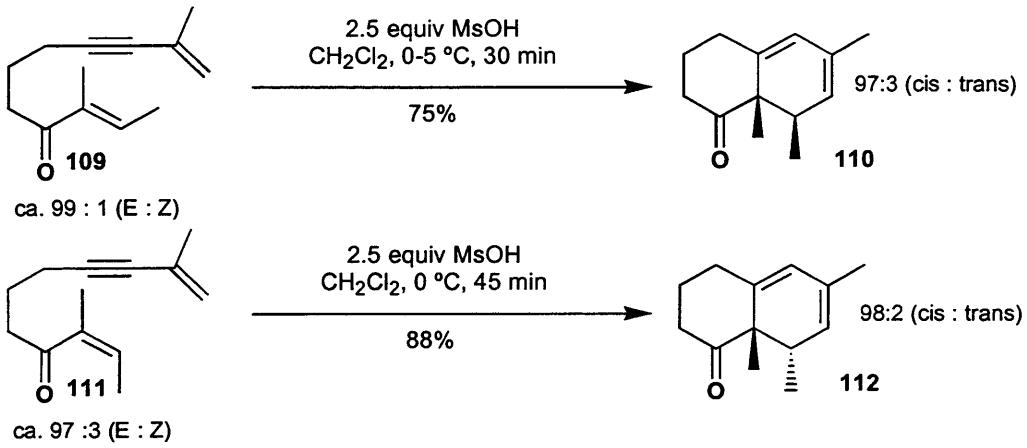
In addition to the mechanistic studies, experiments were also conducted to determine the stereochemical course of the reaction. These reactions focused on establishing whether the intramolecular enyne cycloaddition proceeds in a stereospecific fashion with respect to the geometry of an olefinic enynophile, and whether the reaction proceeds with high endo or exo selectivity.[63] To address the first question, Dr. Roberto Fernández and Dr. Alexandra Gould examined the cycloadditions of enynes **109** and **111**. As illustrated in Scheme 11, these enynes undergo the methanesulfonic acid-promoted cycloadditions in a suprafacial manner with respect to the enone moiety.[64] It can be concluded, therefore, that the intramolecular enyne cycloaddition reaction must proceed

[63] During these studies, Miller et al. reexamined the double thermal cycloaddition of dienynes with olefinic dienophiles, first reported by Butz in the 1940's, and established that the reactions proceed stereospecifically with retention of configuration with respect to the dienophile.

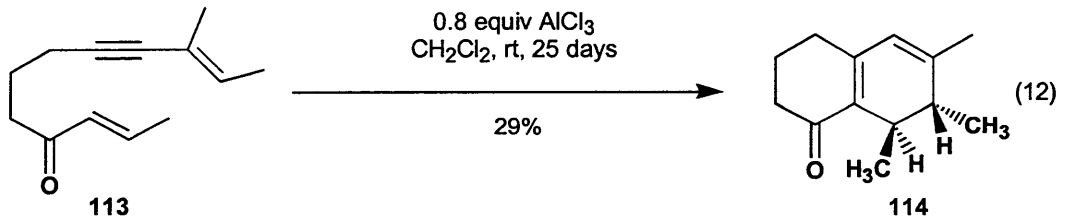
[64] The assignments of the products were based on ^{1}H NMR decoupling experiments and by nOe measurements. For a more detailed discussion, see: Palucki, B. L. Ph. D. Thesis, Massachusetts Institute of Technology, June 1997.

via a concerted or stepwise mechanism in which the ring closure of any intermediate is extremely rapid.

Scheme 11



To address the endo-exo selectivity in the intramolecular enyne cycloaddition, Dr Gould examined the aluminum chloride-promoted cycloaddition of enyne **113**. As illustrated below, she found that the endo product was produced exclusively, albeit in low yield (eq 12).[65] Hence, the intramolecular enyne cycloaddition proceeds with high endo selectivity.

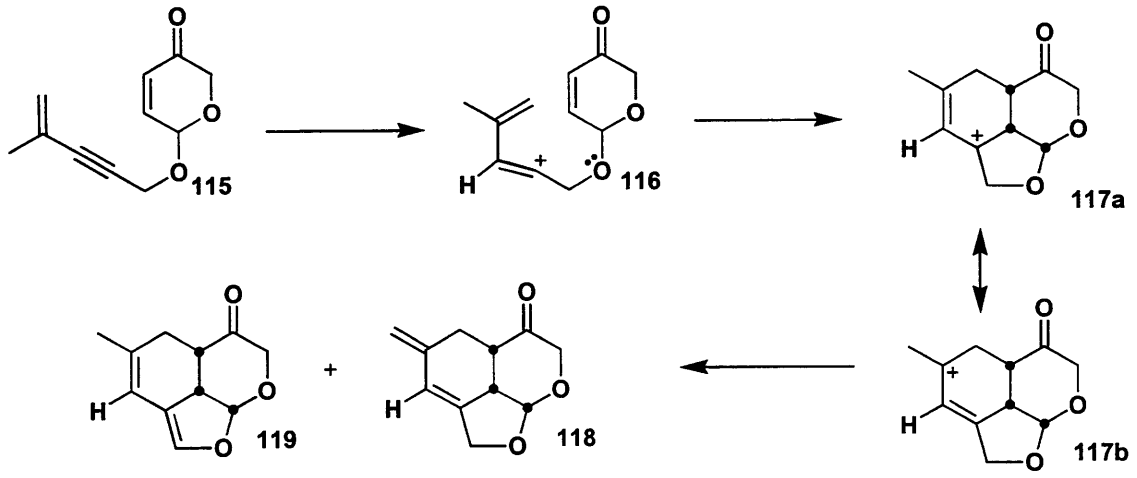


During the course of our studies, reports of enyne cycloadditions emerged from other laboratories. In particular, Hoffmann and co-workers reported a detailed investigation of various intramolecular enyne cycloadditions utilizing acetal substrates

[65] The assignment of the product was based on ^1H NMR decoupling experiments and by nOe measurements. For a more detailed discussion, see: Palucki, B. L. Ph.D. Thesis, Massachusetts Institute of Technology, June 1997

that possess olefinic enynophiles.[66] As shown in Scheme 12, Hoffmann and co-workers proposed a mechanism to account for their results involving the intermediacy of a dienyl cation **116**, although they failed to cite the fact that Nazarov et al. had previously suggested this mechanism to account for a closely related reaction (Scheme 8).

Scheme 12



Similar to Nazarov's proposal, this mechanism requires that protonation of the enyne produces the less thermodynamically stable dienyl cation; Hoffmann et al. suggest that the allylic oxygen stabilizes this dienyl cation in **116** by a "1,3-through space interaction". Once the dienyl cation **116** is formed, a cycloaddition followed by elimination of a proton can generate both the observed products **118** and **119.**

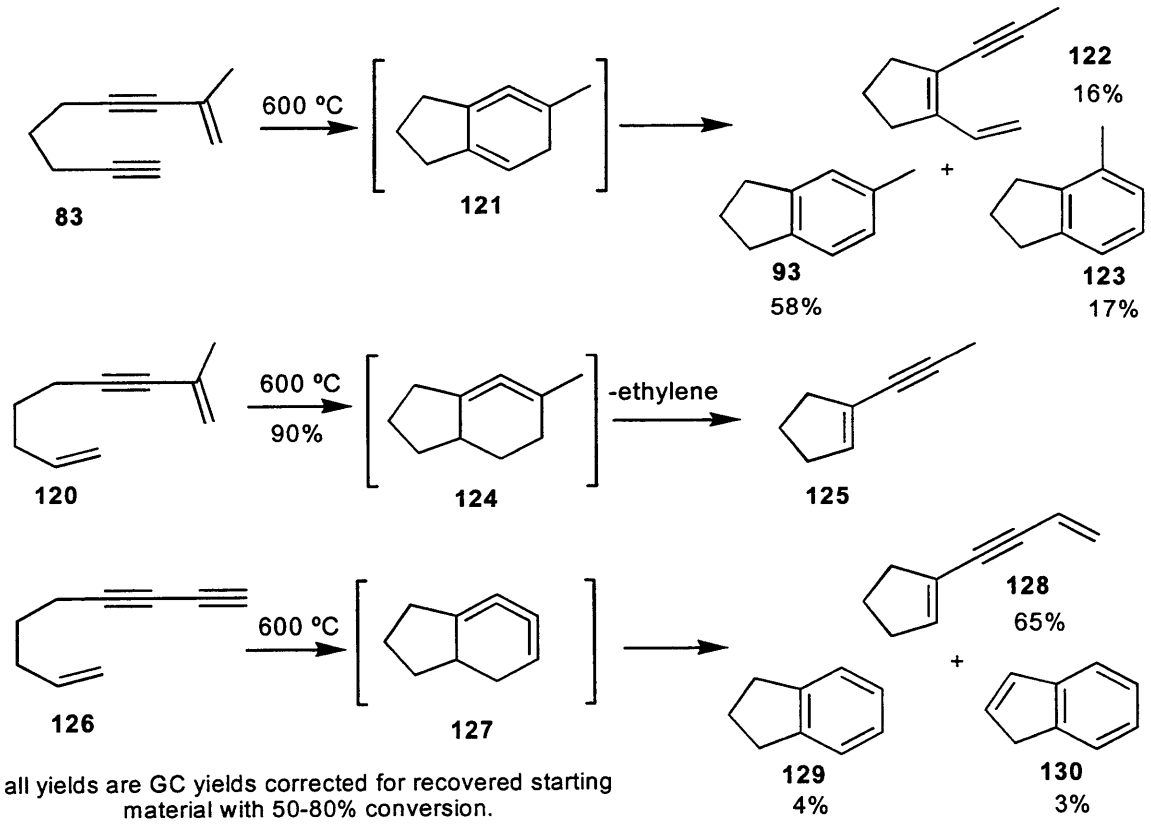
Hoffmann et al. performed numerous experiments to support their mechanistic proposal. As evidence for their theory that the allylic oxygen stabilizes the dienyl cation in **116**, the authors cite the fact that when the tether length is increased by one carbon atom, the acetal substrate fails to react. They argue that the longer separation decreases the ability of the oxygen to stabilize the dienyl cation. In addition, they rule out

[66] Hoffman, H. M. R.; Krumwiede, D.; Mucha, B.; Oehlerking, H. H.; Prahst, G. W. *Tetrahedron*, **1993**, *49*, 8999.

protonation at the terminus of the enyne with subsequent generation of a propargylic cation intermediate since the cycloaddition of a substrate with deuterium substitution on the terminus of the enyne produces a tricyclic product with no evidence of deuterium loss or deuterium scrambling.

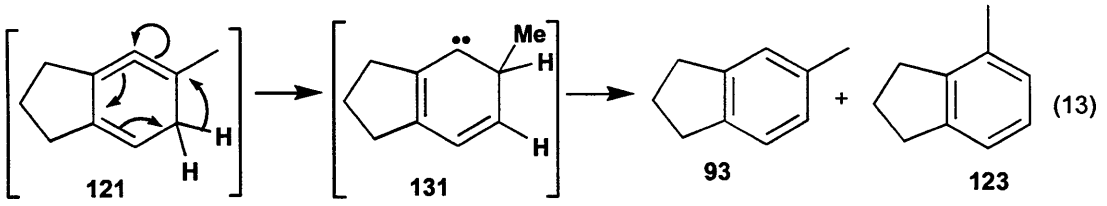
In two reports published after our initial study, Johnson and co-workers have disclosed several enyne cycloadditions conducted under vapor (flash) vacuum pyrolysis (FVP) conditions. As illustrated in Scheme 13, Johnson and co-workers[33] discovered that the FVP cycloadditions of our enyne substrate **83,** enyne **120**, and diyne **126**, produce products consistent with the intermediacy of cyclic allenes **121** and **124**, and cyclic 1,2,3-cummulene **127**, respectively. Specifically, the observed ring-opened products arise from either a six-electron electrocyclic ring opening or a cycloreversion of the cyclic allenes or cyclic cummulenes.

Scheme 13

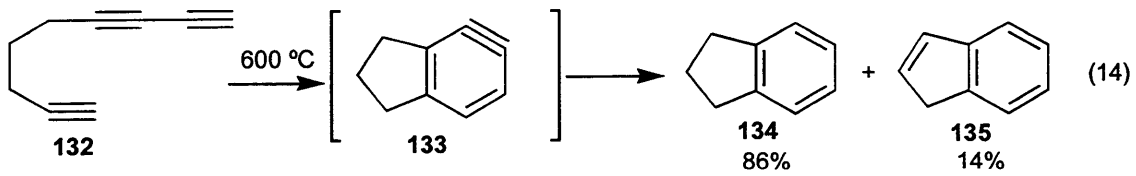


all yields are GC yields corrected for recovered starting material with 50-80% conversion.

Johnson also argued that isolation of the rearranged cycloaddition product **123** from enyne **83** is consistent with the intermediacy of a cyclic allene. He suggested that cyclic allene **121** could undergo a 1,2-hydrogen shift to give a carbene intermediate **131** which could then undergo a methyl or hydrogen insertion to furnish the observed products (eq 13)



More recently Johnson and Bradley[67] also reported a similar FVP cycloaddition of diyne **132** where the diynophile is an alkyne and the intermediate is benzyne derivative **133** (eq 14). Johnson and Bradley suggested that benzyne derivative **133** first adds two hydrogens to form indan (**134**) which then further dehydrogenates under the pyrolysis conditions to form indene (**135**).



all yields GC yields corrected for recovered starting material with 50-80% conversion.

Summary

Overall, synthetic studies on the [4+2] cycloaddition of conjugated enynes have revealed the potential utility of the intramolecular variant for the construction of polycyclic aromatic compounds. The first stage of our systematic investigation of the

[67] Bradley, A. Z.; Johnson, R. P *J. Am. Chem. Soc.* **1997**, *119*, 9917.

scope and mechanism of the cycloaddition of substrates containing only carbon atoms revealed the generality of the process. Later the methodology was expanded to include the synthesis of heterocycles via the incorporation of heteroatoms within the tether between the two reactive components. Various mechanisms were proposed to account for the transformation, including the intermediacy of a cyclic allene, a dienyl cation and a biradical. The goal of my research has been to expand the intramolecular enyne cycloaddition to heteroenynes, specifically ynones and related species. Chapter 4 briefly outlines the related hetero Diels-Alder reactions of 1-oxabutadienes and then Part II describes the results of the extension of the enyne cycloaddition to heteroenynes.

Chapter 4

Diels-Alder Reactions of 1-Oxabutadienes

Introduction

Since the heteroenynes we have examined in our intramolecular cycloaddition studies include ynones and related species, this chapter will outline the related behavior of oxabutadienes in hetero Diels-Alder cycloaddition reactions. The first example of a Diels-Alder reaction utilizing an oxabutadiene appeared in 1938 when Sherlin and co-workers reported that under thermal conditions acrolein dimerizes to yield a dihydropyran derivative.[68] Since that initial report, an extensive number of studies on the Diels-Alder reactions of oxabutadienes have appeared in the literature. In addition, the subject has been the focus of numerous reviews providing a thorough understanding of the mechanism, scope, and synthetic applications of these reactions.[69]

Intermolecular [4+2] Cycloadditions of 1-Oxabutadienes

Although the initial reports of 1-oxabutadiene cycloadditions involved dimerization reactions in which the "oxadienophile" is an electron-deficient π bond, 1-

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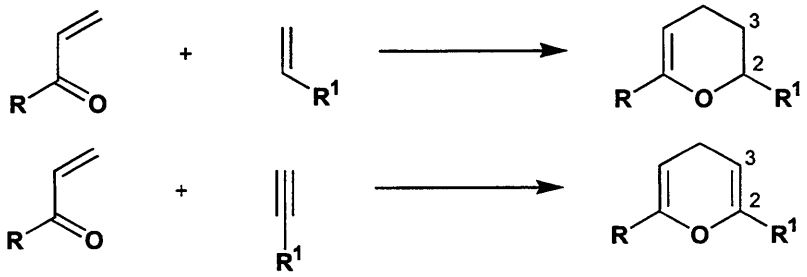
[68] Sherlin, S. M.; Berlin, A. Y.; Serebrennikova, T. A.; Rabinovitch, R. F. *J. Gen. Chem. USSR* **1938**, *8*, 22.
[69] For recent reviews, see: (a) Tietze, L. F.; Kettschau, G. *Topics in Curr. Chem.* **1997**, *189*, 1. (b) Boger, D. L.; Weinreb, S. M. *Hetero Diels-Alder Methodology in Organic Synthesis; Academic Press*: New York, 1987. (c) Desimoni, G.; Tacconi, G. *Chem. Rev.* **1975**, *75*, 651. For selected additional reviews, see: (d) Needleman, S. B.; Chang Kuo, M. C. *Chem. Rev.* **1962**, *62*, 405. (e) Colonge, J.; Descotes, G. In *1,4-Cycloaddition Reactions, The Diels-Alder Reaction in Heterocyclic Syntheses*, Hamer, J., Ed.; Academic Press: New York, 1967, Chapter 9. (f) Sauer, J. *Angew. Chem. Int. Ed. Engl.* **1967**, *6*, 16. (g) Mundy, B. P.; Lipkowitz, K. B.; Dirks, G. W. *Heterocycles* **1977**, *6*, 51. (h) Sauer, J.; Sustmann, R. *Angew. Chem. Int. Ed. Engl.* **1980**, *19*, 779. (i) Kato, T.; Katagiri, N.; Yamamoto, Y. *Heterocycles* **1980**, *14*, 1333. (j) Seoane, C.; Soto, J. L.; Quinteiro, M. *Heterocycles* **1980**, *14*, 337. (k) Onho, M.; Sasaki, T. *J. Syn. Org. Chem. Jpn.* **1984**, *42*, 126. (l) Clemens, R. J. *Chem. Rev.* **1986**, *86*, 241.

oxabutadienes generally undergo LUMO-controlled, inverse electron demand Diels-Alder reactions with electron-rich or unactivated olefins or acetylenes.[69b] As shown below, these intermolecular [4+2] cycloadditions usually proceed with excellent regioselectivity to form 2-substituted pyran derivatives almost exclusively (eq 15).[69]



(15)

Theoretical calculations indicate that the formation of the 2-substituted pyran isomer occurs through an endo approach of the reactants in which the new carbon-carbon bond is more fully formed than the new carbon-oxygen bond; in other words, the mechanism involves a concerted but nonsynchronous [4+2] cycloaddition. Exceptions to the predicted regioselectivity all involve reactions of poorly matched electron-deficient 1-oxabutadienes with electron-deficient dienophiles.[69b]

Scheme 14 summarizes the range of typical intermolecular Diels-Alder reactions of unactivated 1-oxabutadienes with electron-rich or unactivated alkenes and acetylenes.[69] Reaction temperatures in the range of 150-200 °C are usually required to promote these reactions, often leading to competing dimerization of the oxabutadiene or the electron-rich dienophile.[70] Classic techniques that have been employed to address this problem include the addition of a radical inhibitor to the reaction mixture and the use of an excess of the oxabutadiene substrate.

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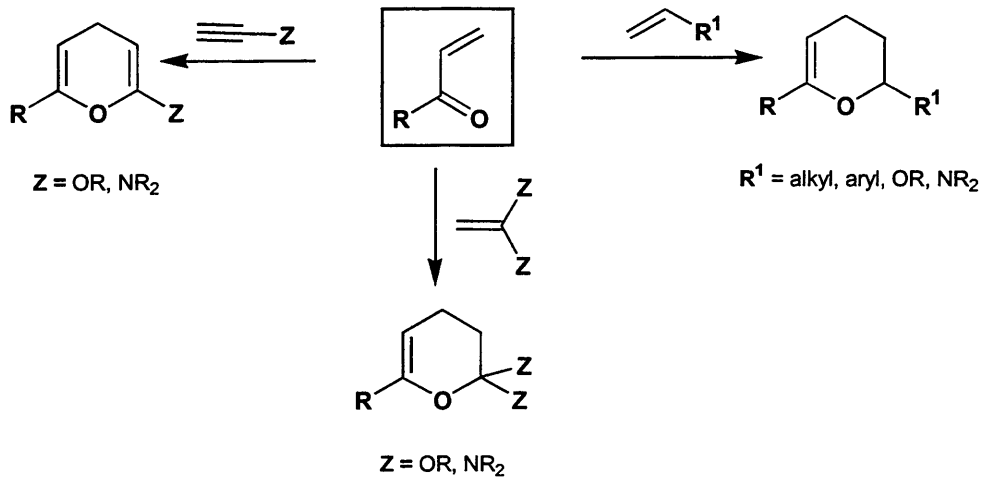
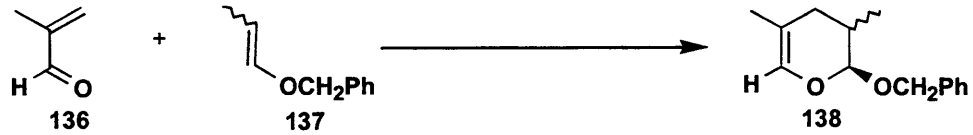
[70] For an example, see: Ireland, R. E.; Habich, D. *Tetrahedron Lett.***1980**, *21*, 1389.

Scheme 14



Three additional strategies have recently appeared to facilitate the Diels-Alder reactions of unactivated 1-oxabutadienes: Lewis acid promotion, use of high-pressure conditions, and microwave-activation. The cycloaddition of α,β-unsaturated aldehyde **136** with vinyl ether **137** illustrates the use of Lewis acid promoters (eq 16).[71] While the unpromoted reaction proceeds only in 13% yield and requires a reaction temperature of 250 °C, in the presence of one equivalent of $AlCl_3$ the reaction proceeds at room temperature to afford desired pyran **138** in 63% yield. Use of Lewis acids to promote these reactions, however, is limited due to the instability of the pyran cycloadducts to acidic reaction conditions.[71]

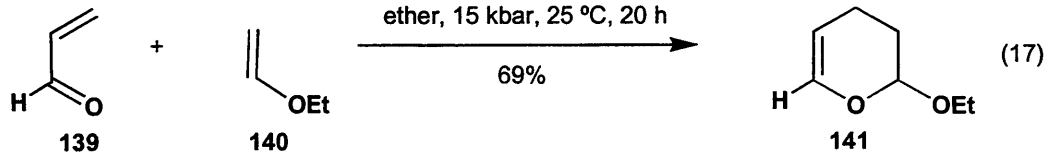


(16)

Promoter	Temp (°C)	Time (h)	Yield (%)
none	250	10	13
1.0 equiv $AlCl_3$	25	3	63

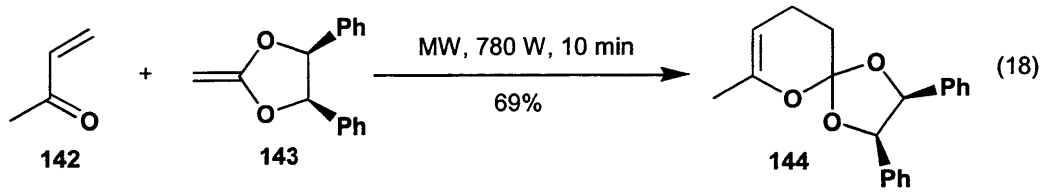
[71] (a) Snider, B. B.; Phillips, G. B. *J. Org Chem.* **1983**, *48*, 2789. For additional examples of the Lewis acid promotion of this reaction, see: (b) Yamamoto, Y., Suzuki, H.; Mora-Oka, Y. *Chem. Lett.* **1986**, 73. (c) Danishefsky, S.; Bednarski, M. *Tetrahedron Lett.* **1984**, *25*, 721. (d) Menicagli, R.; Malanga, C.; Lardicci, L. *J. Org Chem.* **1982**, *47*, 2288. (e) Takahashi, M.; Suzuki, H.; Mora-Oka, Y.; Ikawa, T. *Tetrahedron Lett.* **1982**, *23*, 1097. (d) Takahashi, M.; Suzuki, H.; Mora-Oka, Y.; Ikawa, T. *Chem. Lett.* **1981**, 1435.

A second method to promote the Diels-Alder reactions of unactivated 1-oxabutadienes with electron-rich or unactivated alkenes utilizes high-pressure techniques. An illustration of this approach is shown below in the cycloaddition of α,β-unsaturated aldehyde **139** with vinyl ether **140** (eq 17).[72]



139 **140** **141** (17)

A third technique that has been employed to accelerate the hetero Diels-Alder reactions of unactivated oxabutadienes involves the application of microwave radiation. As shown below, under microwave radiation, the normally unreactive methyl vinyl ketone (**142**) participates in a cycloaddition with the highly sensitive ketene acetal **143** to furnish dihydropyran **144** in 69% yield within 10 min at 20 °C (eq 18).[73]



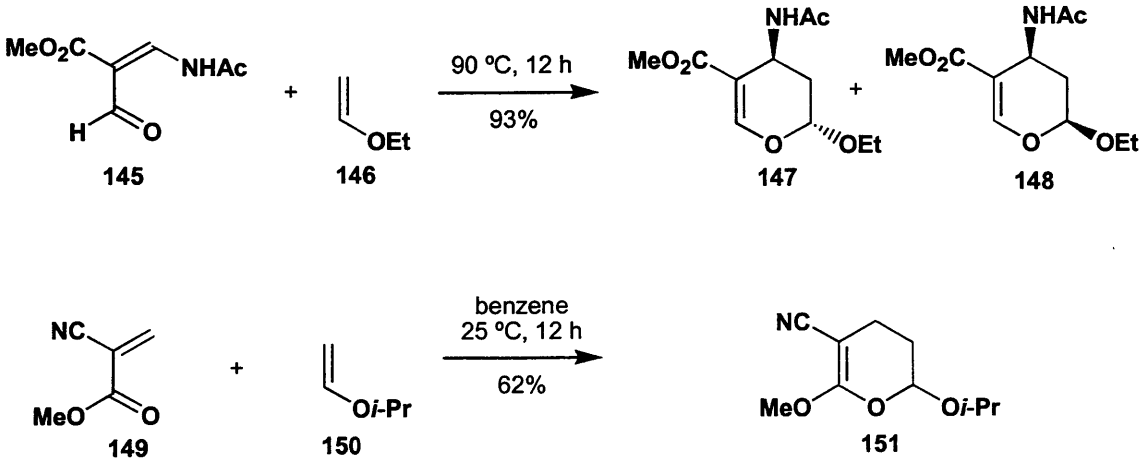
142 **143** **144** (18)

The introduction of an electron-withdrawing group at the C-2, C-3, or C-4 position of 1-oxabutadiene also enhances the rate of intermolecular cycloaddition with electron-rich dienophiles. Scheme 15 illustrates two recent reports of thermal

[72] Dauben, W. G.; Krabbenhoft, H. D. *J. Org. Chem.* **1977**, *42*, 282.
[73] Diaz-Ortiz, A.; Diez-Barra, E.; de la Hoz, A.; Prieto, P.; Moreno, A. *J. Chem. Soc. Perkin Trans. 1* **1994**, 3595.

intermolecular Diels-Alder reactions utilizing activated oxabutadiene substrates with additional electron-withdrawing substituents.[74]

Scheme 15



Intramolecular Reactions of 1-Oxabutadienes

Intramolecular Diels-Alder reactions of oxabutadienes occur much more easily than their intermolecular counterparts due to the entropic advantage gained by tethering the two reactants. In fact, intramolecular Diels-Alder reactions of activated 1-oxabutadienes with electron-rich, unactivated, and electron-poor dienophiles are all known.[75] In contrast, reports of *unactivated* 1-oxabutadienes participating in intramolecular Diels-Alder reactions are quite limited due to competition between the desired reaction and the intramolecular ene reaction.[76]

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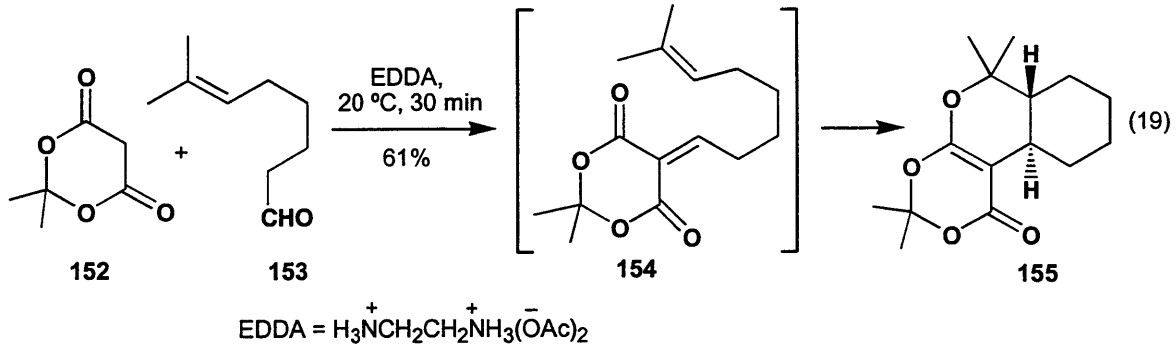
[74] (a) For the Diels-Alder reaction of the N-acyl-2-methoxycarbonyl enaminecarboxaldehyde, see: Tietze, L. –F.; Harms, K.; Sheldrick, G. M. *Tetrahedron Lett.* **1985**, *26*, 5273. (b) For the Diels-Alder reaction of the α-cyano α,β-unsaturated ester, see: Hall, H. K. Jr.; Rasoul, H. A. A.; Gillard, M.; Abdelkader, M.; Nogues, P.; Sentman, R. C. *Tetrahedron Lett.* **1982**, *23*, 603.

[75] (a) Oppolzer, W. *Angew. Chem. Int. Ed. Engl.* **1977**, *16*, 10. (b) Brieger, G.; Bennett, J. N. *Chem. Rev.* **1980**, *80*, 63. (c) Ciganek, E. *Org. React.* **1984**, *32*, 1. (d) Fallis, A. G. *Can. J. Chem.* **1984**, *62*, 183.

[76] (a) For an example under thermal reaction conditions, see: Snider, B. B.; Duncia, J. B. *J. Org. Chem.* **1980**, *45*, 3461. (b) For an example under Lewis acid-promoted conditions, see: Tietze, L. -F. *J. Heterocyclic. Chem.* **1990**, *27*, 47.

If the intramolecular oxabutadiene substrate contains an additional electron-withdrawing group at the C-3 position, exceptionally effective regio- and stereoselective [4+2] cycloadditions can occur. An example is found in the *in situ* formation and cycloaddition of substrate **154** (eq 19).[77] Condensation of Meldrum's acid (**152**) with aldehyde **153** generates substrate **154**, which undergoes an intramolecular Diels-Alder reaction to furnish tricyclic dihydropyran **155**. In general, the stereochemistry of the reacting oxabutadiene system, nature of the tether, and substitution pattern of the alkene dienophile all affect the rate, and stereo- and regioselectivity of the [4+2] cycloaddition.[77]



(19)

EDDA = $H_3\overset{+}{N}CH_2CH_2\overset{+}{N}H_3(\bar{O}Ac)_2$

Asymmetric Diels-Alder Reactions of 1-Oxabutadienes

In recent years, asymmetric variants of both the inter- and intramolecular Diels-Alder reactions of oxabutadienes have also been reported (Scheme 16). For example, exposure of oxabutadiene **156**, which contains an oxazolidinone moiety, to enol ether **157** in the presence of a bidentate Lewis acid induces an intermolecular cycloaddition that exhibits high endo selectivity and excellent asymmetric induction.[78] High asymmetric

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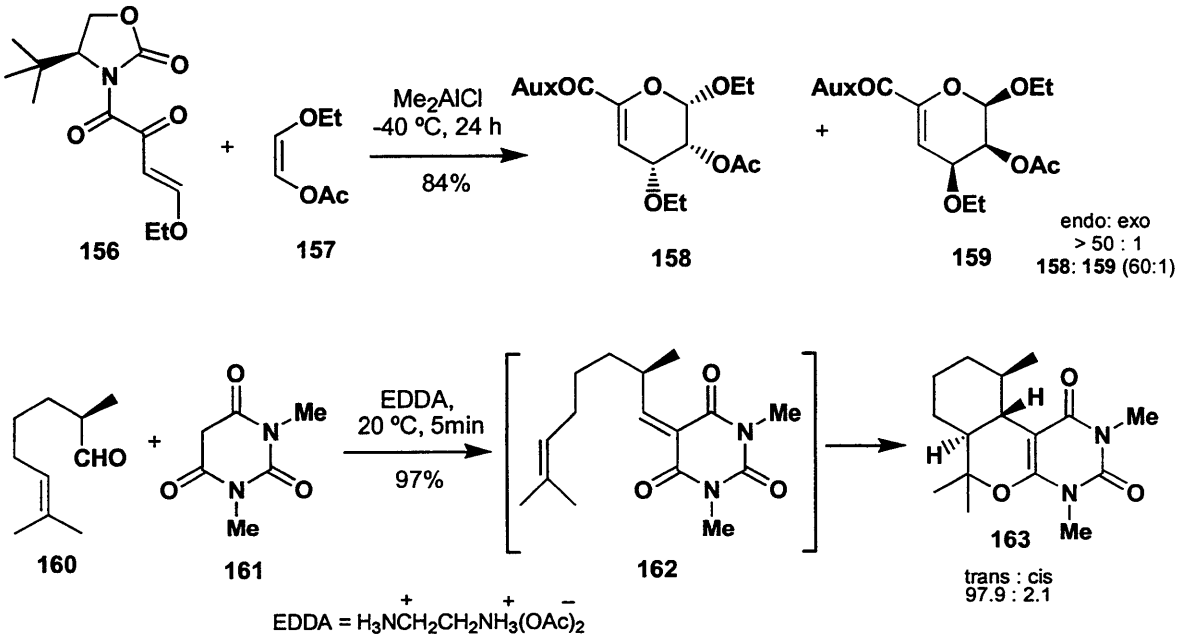
[77] For a review of work in this area, see: Tietze, L. –F.; In *Selectivity - A Goal for Synthetic Efficiency*; Trost, B. M.; Bartmann, W., Eds.; Verlag Chemie: Weinheim, 1984, pp 299-316.

[78] (a) Tietze, L. -F.; Schneider, C.; Grote, A. *Chem. Eur J.* **1996**, *2*, 139. (b) Tietze, L. -F.; Schneider, C.; Montenbruck, A. *Angew Chem. Int. Ed. Engl.* **1994**, *33*, 980.

induction was also found in the intramolecular Diels-Alder reactions of substrates containing a stereogenic center within the tether.[79] As illustrated below, such a system can be easily constructed by the *in situ* condensation of chiral aldehyde **160** with 1,3-dicarbonyl compound **161**. It was further found that when the stereogenic center is in a position adjacent to either the oxadiene or the dienophile, the reaction exhibits excellent diastereoselectivity. This high selectivity can be explained by the requirement that the tether substituent have an pseudo-equatorial orientation in the chair-like transition state to avoid severe 1,3-allylic strain with the oxadiene or dienophile.

Scheme 16



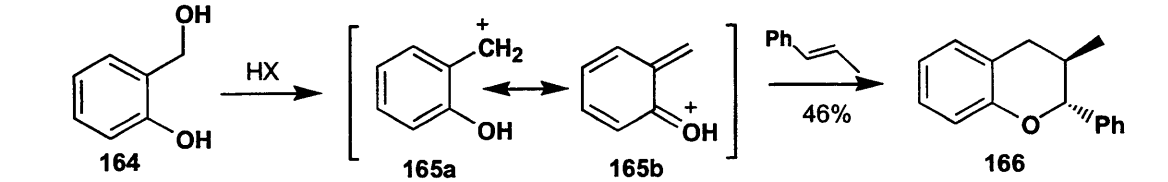
Cationic [4⁺+2] Cycloadditions of 1-Oxabutadienes

A limited number of 1-oxabutadiene systems bearing a formal positive charge have been reported to undergo "[4⁺+2] polar cycloadditions". The classification of these transformations as "polar" cycloadditions was developed to distinguish those

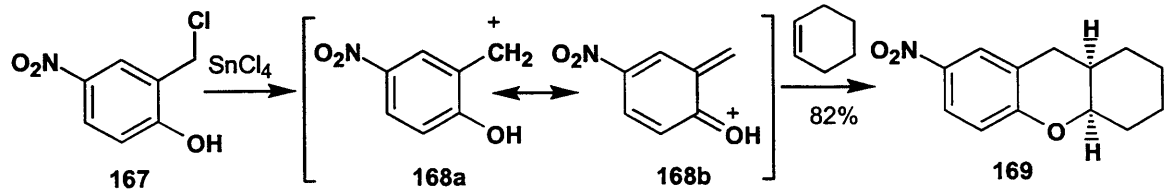
[79] Tietze, L. -F.; Geissler, H.; Fennen, J.; Brumby, T.; Brand, S.; Schulz, G. *J. Org. Chem.* **1994**, *59*, 182.

cycloadditions employing cationic or anionic components from those employing dipolar or uncharged substrates and was not intended to imply that these transformations proceed through stepwise addition-cyclization reaction pathways.[80]

One type of cationic oxabutadiene that has been shown to participate in a range of regio- and stereospecific [4$^+$+2] cycloadditions is the *o*-hydroxybenzyl cation. As demonstrated by Schmidt, *o*-hydroxybenzyl cations **165** and **168** can be generated *in situ* by either the treatment of *o*-hydroxybenzyl alcohol (**164**) with protic acid or by the treatment of the *o*-hydroxybenzyl chloride **167** with tin (IV) chloride (eq 20).[81] Once the cations are formed, they each undergo a [4$^+$+2] cycloaddition with an alkene to furnish pyran products **166** and **169** respectively. A noteworthy feature of these reactions is that the geometry of the alkene dienophile determines the orientation of the substituents on the pyran product.

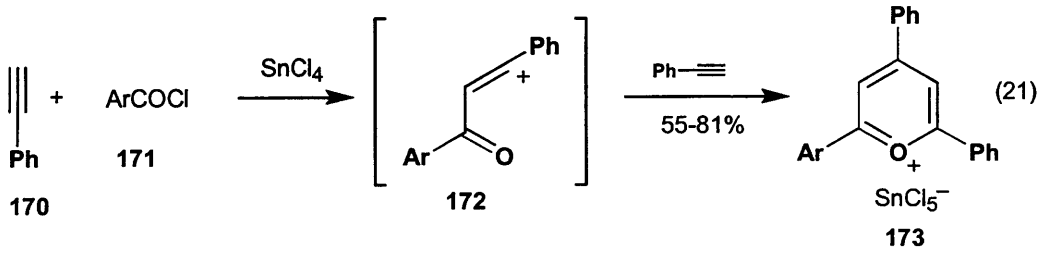


(20)



[80] For a review of polar cycloadditions, see: (a) Schmidt, R. R. *Angew. Chem. Int. Ed. Engl.* **1973**, *12*, 212. (b) Bradsher, C. K. *Adv. Heterocycl. Chem.* **1974**, *16*, 289.
[81] Schmidt, R. R. *Tetrahedron Lett.* **1969**, 5279.

Schmidt has also demonstrated that β-acylvinyl carbocations can participate in [4$^+$ +2] cycloadditions.[82] Treatment of phenylacetylene with aryl acid chloride **170** in the presence of tin (IV) chloride results in the formation of pyrylium salt **173** in 55-81% yield (eq 21). This reaction involves acylation of phenylacetylene to generate carbocation intermediate **172**, followed by a [4$^+$+2] cycloaddition with a second molecule of phenylacetylene to furnish pyrylium salt **173**.



Summary

The current literature contains examples of both inter-and intramolecular variants of the Diels-Alder reactions of 1-oxabutadienes. Due to their electron-deficient nature, 1-oxabutadienes generally participate in LUMO-controlled, inverse electron demand Diels-Alder reactions with electron-rich or unactivated dienophiles. The entropic advantage gained in the intramolecular variant, however, has been shown to be sufficient to also promote oxabutadiene participation in [4+2] cycloadditions with electron-deficient dienophiles. In addition, Lewis acids, high-pressure conditions, and microwave-activation have all been successfully employed to accelerate slow Diels-Alder reactions of oxabutadienes. Finally, cationic 1-oxabutadiene systems have also been shown to participate in [4$^+$+2] cycloadditions with a range of reaction partners.

[82] Schmidt, R. R. *Angew. Chem. Int. Ed. Engl.* **1964**, *3*, 387.

PART II

Intramolecular [4+2] Cycloaddition Reactions of Conjugated Ynones and Related Heteroenynes: Synthesis of Polycyclic Furans via the Generation and Rearrangement of Strained Heterocyclic Allenes

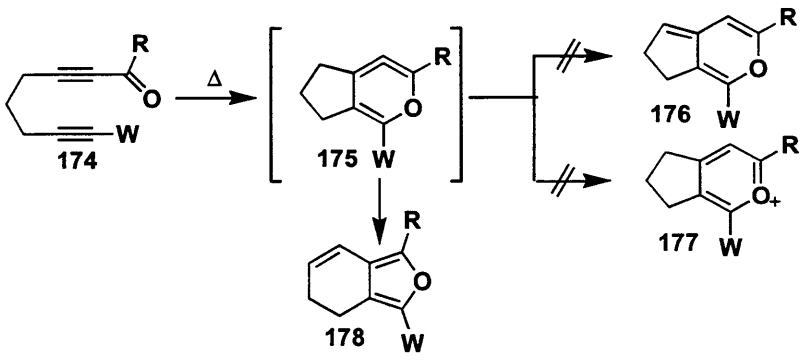
Chapter 1

Introduction

An Unexpected Result

As stated previously, a number of years ago our laboratory began investigating the intramolecular [4+2] cycloadditions of conjugated enynes. The remainder of this thesis will outline the extension of that work to the intramolecular [4+2] cycloadditions of heteroenynes, specifically ynones and related species. In the enyne cycloadditions studied previously (see Scheme 2), the initial cyclic allene intermediate can isomerize to furnish an aromatic product. In the heteroenyne series, however, a similar isomerization of the corresponding heterocyclic intermediate cannot occur. As shown in Scheme 17, two conceivable pathways for the cyclic allene result in the formation of either pyran **176** or pyrylium cation **177**, but neither of these products was isolated from the thermal reactions of ynone substrates **174**; the products of these reactions were instead bicyclic furans **178**![83] Although furan formation was not expected, it provided exciting possibilities for the application of this reaction in organic synthesis.

Scheme 17



[83] This structure assignment was based on NMR and IR data for the cycloaddition products as well as an X-ray crystal structure of one derivative. For a more detailed discussion of assignments, see Part II, Chapter 3. For a detailed proposal of the mechanism for furan formation, see Part II, Chapter 4.

Significance of Furans

Furans are probably the most prominent class of five-membered heteroaromatic compounds due to their great abundance in nature as well as their importance as intermediates in organic synthesis. Most naturally occurring furans are of botanical origin, although a few have been isolated from both fungi and mammals.[84] Furans are also utilized in the food industry as natural and artificial flavors, fragrances, and preservatives.[85] In addition, many furans have pharmaceutical uses as antiulcer, sedative, and antibacterial agents.[86] Recently, two polycyclic furans, halenaquinone and xestoquinone, have attracted attention due to their biological activity as inotropic agents and protein kinase inhibitors.[87] These compounds are particularly intriguing to us since their skeletons contain the 3,4-fused furan that is generated by the intramolecular ynone cycloaddition we have discovered. In addition to their biological importance, furans also have importance as intermediates in organic synthesis.[88] For example, various furans have been utilized as dienes in the Diels-Alder [4+2] cycloaddition,[89] as masked carboxylic acids,[90] and as 1,4-diketone equivalents.[91]

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[84] (a) Dean, F. M. In *Naturally Occurring Oxygen Ring Compounds*; Butterworths: London, 1963. (b) Spiteller, M.; Spiteller, G.; Hoyer, G. -A. *Chem. Ber.* **1980**, *113*, 699. (c) Puchta, V.; Spiteller, G.; Weidinger, H. *Liebigs Ann. Chem.* **1988**, 25. (d) Sand, D. M.; Glass, R. L.; Olson, D. L.; Pike, H. M.; Schlenk, H. *Biochimica et Biophysica Acta* **1984**, *793*, 429.

[85] *The Chemistry of Heterocyclic Flavouring and Aroma Compounds;* Vernin, G., Ed.; Ellis Horwood: Chichester, 1982.

[86] For a review of the medicinal uses of nitrofurans, see: *Nitrofurans: Chemistry, Metabolism, Mutagenesis, and Carcinogenesis*; Bryan, G. T., Ed.; Carcinogenesis - A Comprehensive Survey, Vol. 4; Raven Press: New York, 1978.

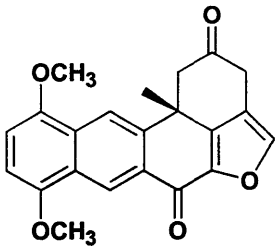
[87] For isolation/activity of the quinone derivatives, see: (a) Roll, D. M.; Scheuer, P. J.; Matsumoto, G. K.; Clardy, J. *J. Am. Chem. Soc.* **1983**, *105*, 6177. (b) Nakamura, H.; Kobayashi, J.; Kobayashi, M.; Ohizumi, Y.; Hirata, Y. *Chem. Lett.* **1985**, 713. (c) Lee, R. H.; Slate, D. L.; Moretti, R.; Alvi, K. A.; Crews, P. *Biochem. Biophys. Res. Commun.* **1992**, *184*, 765.

[88] For an overview, see: Lipshutz, B. H. *Chem. Rev.* **1986**, 795.

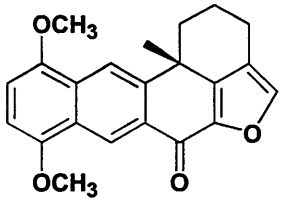
[89] For a recent review, see: (a) Kappee, C. O.; Murphree, S. S.; Padwa, A. *Tetrahedron* **1997**, *53*, 14179.

[90] For examples, see: (a) Wiesner, K.; Tsai, T. Y. R. *Pure Appl. Chem.* **1986**, *58*, 799. (b) Lociuro, S.; Tsai, T. Y. R.; Wiesner, K. *Tetrahedron* **1988**, *44*, 35.

[91] For an example, see: Büchi, G.; Wüest, H. *J. Org. Chem.* **1966**, *31*, 977.



(+) Halenoquinone
Protein Kinase Inhibitor



(+) Xestoquinone
Inotropic Agent

Synthetic Approaches to Furans

The widespread importance of furans has led to the development of an extensive array of synthetic approaches to the furan skeleton.[92] Despite the numerous methods developed to synthesize furans, relatively few general methods are available for the construction of 3,4-substituted or 3,4-fused derivatives. Our intramolecular ynone cycloaddition, however, can be used to generate both systems. The cycloaddition produces a 3,4-fused furan directly, and if the cycloaddition substrate contains a heteroatom in the tether, then the resulting six-membered ring should often be cleavable to generate a monocyclic 3,4-substituted furan. This brief overview will highlight the known approaches to 3,4-substituted and 3,4-fused furans with a focus on recent developments.

Most traditional approaches to the furan skeleton create the carbon-oxygen bond by utilizing the nucleophilic nature of the oxygen atom. A recent report employs this

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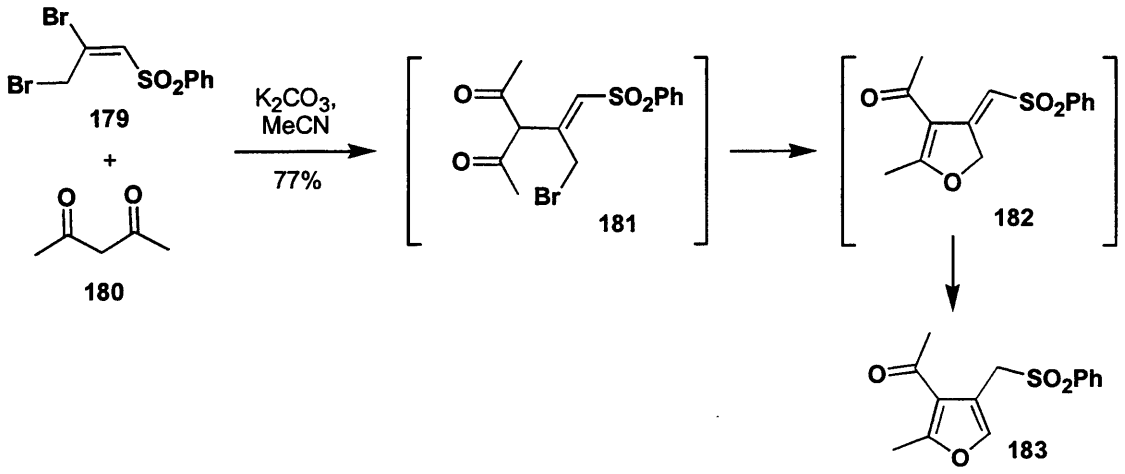
[92] For two reviews of the recent literature, see: (a) Gilchrist, T. L. *Contemporary Organic Synthesis* **1994**, *1*, 205. (b) Gilchrist, T. L. *Contemporary Organic Synthesis* **1995**, *2*, 337. For general reviews on the synthesis and chemistry of furans, see: (c) Dean, F. M.; Sargent, M. V.; In *Comprehensive Heterocyclic Chemistry*; Bird, C. W.; Cheeseman, G. W. H., Eds.; Pergamon Press: New York, 1984, Vol. 4, part 3, pp 531-656. (d) Donnelly, D. M. X.; Meegan, M. J. In *Comprehensive Heterocyclic Chemistry*; Bird, C. W.; Cheeseman, G. W. H., Eds.; Pergamon Press: New York, 1984, Vol. 4, part 3, pp 657-712. (e) Williams, A. *Furans: Synthesis and Applications;* Noyes Data: Park Ridge, 1973.

classic strategy to synthesize trisubstituted furan **183** (Scheme 18).[93] After the condensation of vinyl sulfone **179** with the enolate of diketone **180** via an addition-elimination pathway, an intramolecular O-alkylation occurs to afford dihydrofuran **182** which subsequently isomerizes to furan **183**.

Scheme 18



Studies have also been reported describing the generation of 3,4-substituted or 3,4-fused furans from acetylenic ethers. As shown below, these routes include the base-promoted rearrangement and cyclization of dipropargylic ether **184**[94] and the base-promoted rearrangement and subsequent cycloaddition of enyne ether **187**[95] (Scheme 19). In the first case, the authors suggest that deprotonation of diallenyl ether intermediate **185** induces a cyclization which affords furan **186**. In the second case, the authors propose that diallene intermediate **188** undergoes a [4+2] cycloaddition to furnish 3,4-fused furan **189**.

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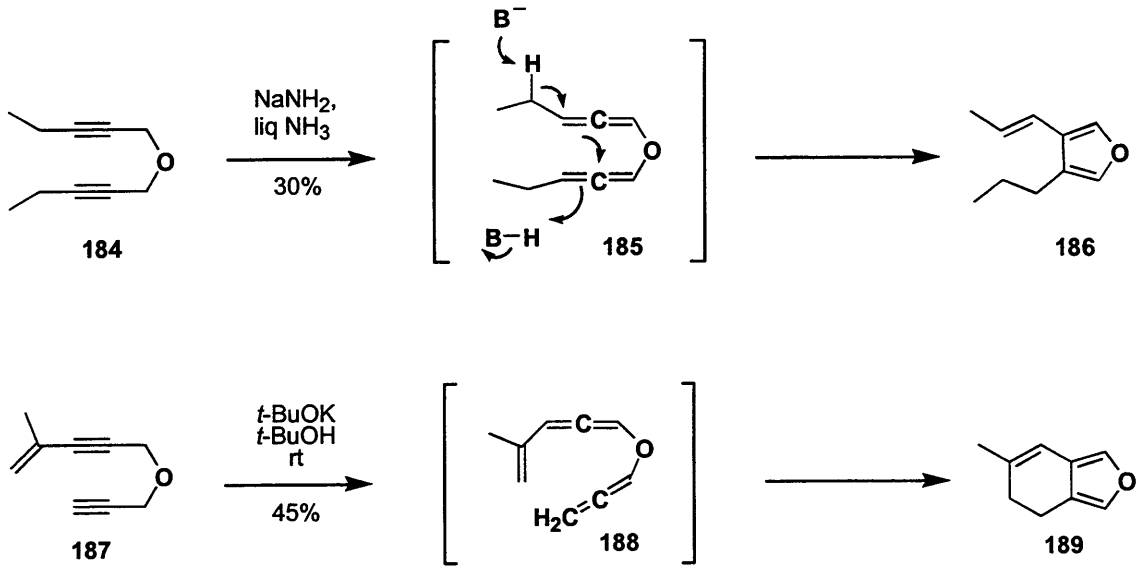
[93] (a) Padwa, A.; Austin, D. J.; Ishida, M.; Muller, C. L.; Murphree, S. S.; Yeske, P. E. *J. Org. Chem.* **1992**, *57*, 1161. For a related example, see: (b)Padwa, A.; Ishida, M. *Tetrahedron Lett.* **1991**, *32*, 5673.
[94] Montjin, P. P.; Kupecz, A.; Brandsma, L.; Arens, J. F. *Recl. Trav. Chim. Pays-Bas* **1969**, *88*, 958.
[95] Bartlett, A. J.; Laird, T.; Ollis, W. D. *J. Chem. Soc., Chem. Commun.* **1974**, 496.

Scheme 19



Along with the methods described above, reports have also appeared on the transformation of 2-substituted furans to 3,4-fused furans via the "furan ring transfer" (FRT) reaction of allenyl furfuryl ethers.[96,97] Kanematsu and co-workers[97] have reported that treatment of the alkynyl furfuryl ether **190** with base followed by exposure of the resulting product to hydrogenation conditions affords the bicyclic furan **194** in 90% overall yield from ether **190** (Scheme 20). The authors propose that the exposure of the propargylic ether to base isomerizes the alkyne to an allene. The resulting allenyl furfuryl ether **191** then undergoes an intramolecular Diels-Alder reaction followed by base-catalyzed cleavage of the resulting adduct **192** to provide the unstable 3,4-fused furan **193**. It is this furan that is then hydrogenated to produce the final isolated product.

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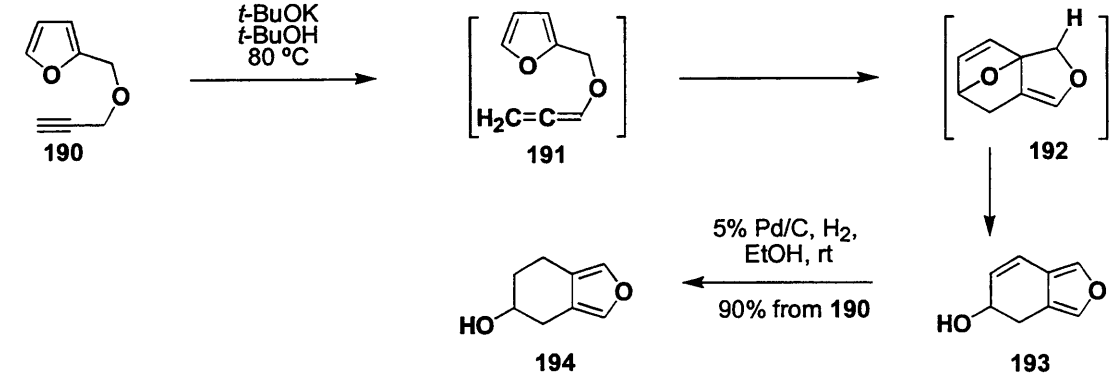
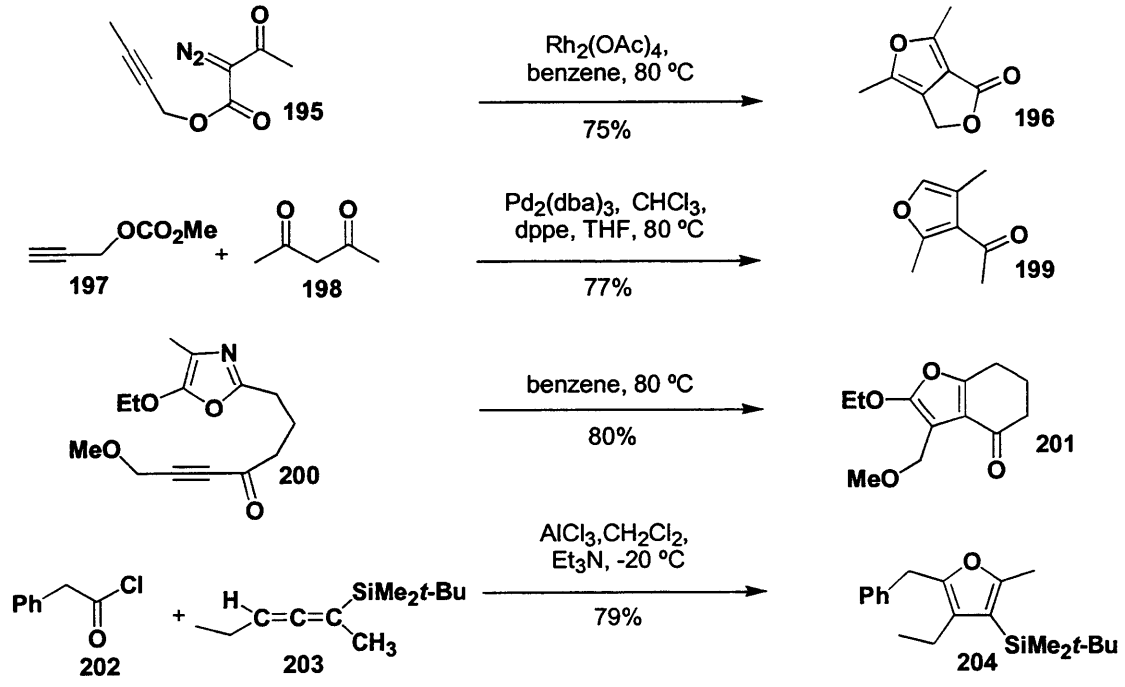
[96] Yamaguchi, Y.; Tatsuta, N.; Soejima, S.; Hayakawa, K.; Kanematsu, K. *Heterocycles* **1990**, *30*, 223.
[97] Baba, Y.; Sakamoto, T.; Soejima, S.; Kanematsu, K. *Tetrahedron* **1994**, *50*, 5645.

Scheme 20



A third approach to the synthesis of 3,4-substituted or 3,4-fused furans involves the use of [3+2] annulations to construct the furan skeleton. As illustrated below, a wide variety of substrates have been utilized in these transformations including stabilized carbenoids,[98] allenyl metal species,[99] isoxazoles,[100] and allenylsilanes[101] (Scheme 21).

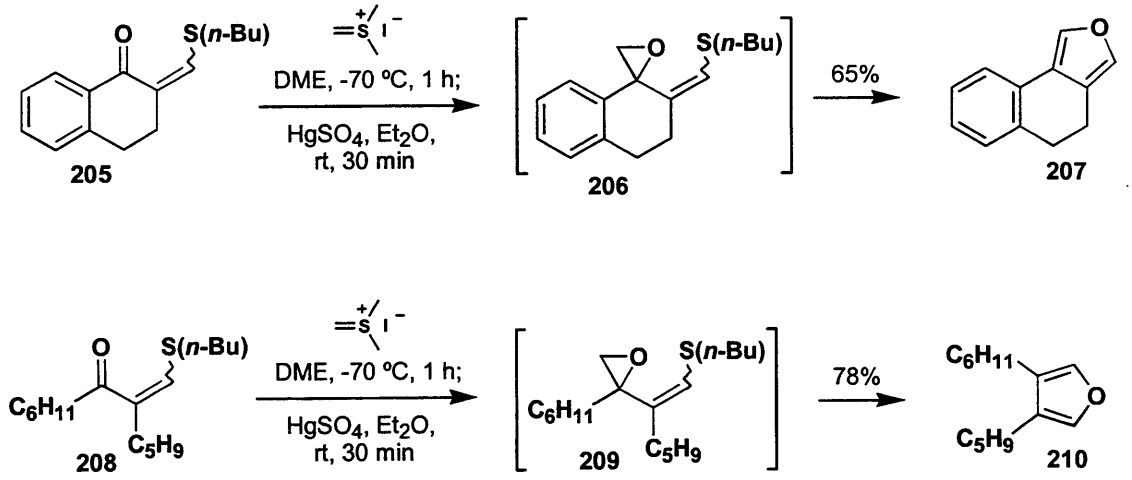
Scheme 21



[98] Padwa, A.; Kinder, F. R. *J. Org. Chem.* **1993**, *58*, 21.
[99] Minami, I.; Yuhara, M.; Watanabe, H.; Tsuji, J. *J. Organomet. Chem.* **1987**, *334*, 225.
[100] Jacobi, P. A.; Craig, T. A.; Walker, D. G.; Arrick, B. A. Frechette, R. F. *J. Am. Chem. Soc.* **1984**, *106*, 5585. For a related example, see: (b) Jacobi, P.; Selnick, H. G. *J. Am. Chem. Soc.* **1984**, *106*, 3041.
[101] Danheiser, R. L.; Stoner, E. J.; Koyama, H.; Yamashita, D. S.; Klade, C. A. *J. Am. Chem. Soc.* **1989**, *111*, 4407.

In addition to [3+2] annulation methods, strategies involving [4+1] annulations have also been reported that use α-keto-dithioketene acetals and α-keto thioenol ethers as 1,3-dicarbonyl equivalents.[102] As illustrated below, this strategy works well for both the synthesis of 3,4-fused furan **207** and 3,4-substituted furan **210** (Scheme 22).[103] Exposure of α-ketothioenol ethers **205** or **208** to dimethylsulfonium ylide generates epoxides **206** and **209** that rearrange with subsequent elimination of thiolate to generate furans **207** and **210**.

Scheme 22



The final type of annulation methodology used to generate highly substituted furans involves multiple component annulations. As shown below, work in this area includes an unusual tantalum-mediated [2+2+1] annulation to furnish the 2,3,4-trisubstituted furan **215** (Scheme 23).[104]

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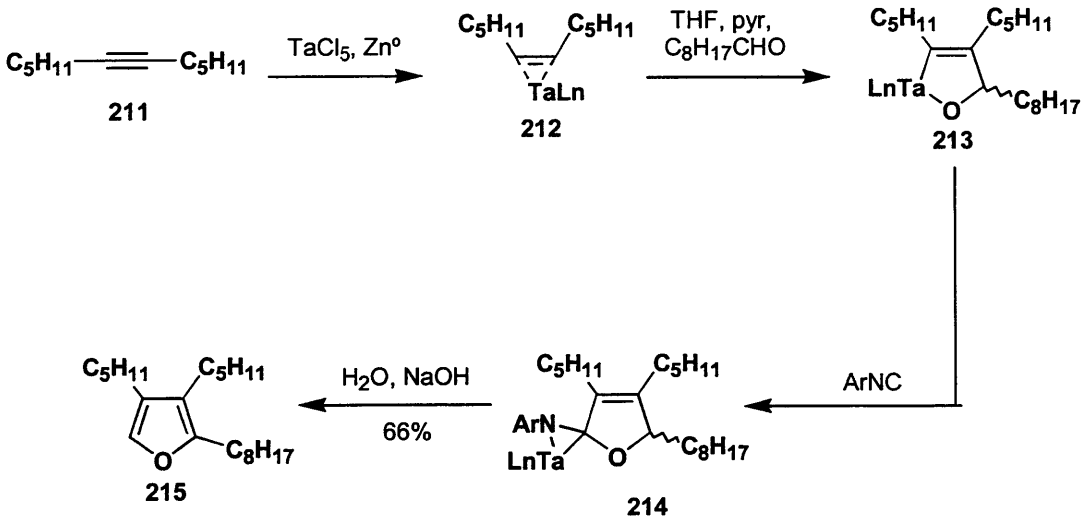
[102] (a) Okazaki, R.; Negishi, Y.; Inamoto, N. *J. Org. Chem.* **1984**, *49*, 3819. (b) Harris, C. M.; Cleary, J. J.; Harris, T. M. *J. Org. Chem.* **1974**, *39*, 72. (c) Price, M. E.; Schore, N. E. *J. Org. Chem.* **1989**, *54*, 2777.
[103] Garst, M. E.; Spencer, T. A. *J. Am. Chem. Soc.* **1973**, *95*, 250.
[104] Takai, K.; Tezuka, M.; Kataoka, Y.; Utimoto, K. *J. Org. Chem.* **1990**, *55*, 5310.

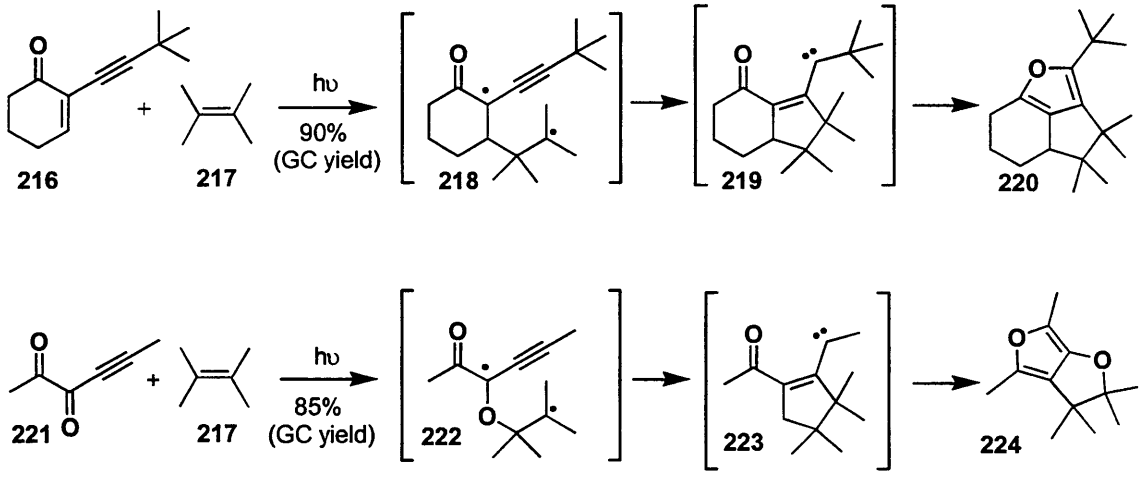
Scheme 23



In addition to the annulation methods described above, tandem photocycloadditions have also been utilized in the construction of 3,4-fused furans. As illustrated in Scheme 24, the photocycloaddition of 2-alkynyl cycloalkenone **216** to alkene **217** furnishes the tricyclic furan **220**.[105] The authors propose a cascade pathway to account for furan formation that includes the generation of biradical **218**, intramolecular radical cyclization to form carbene **219**, and then electrocyclic closure of the carbene on the carbonyl group to furnish the observed tricyclic product. This work has also been extended to generate bicyclic furan **224** by using conjugated acetylenic α-diketone **221** as the photocycloaddition substrate instead of cycloalkenone **216**.[106]

[105] (a) Margaretha, P.; Reichow, S.; Agosta, W. C. *J. Chem. Soc., Chem. Commun.* **1992**, 797. (b) Margaretha, P.; Reichow, S.; Agosta, W. C. *J. Org. Chem.* **1994**, *59*, 5393.
[106] Mukherjee, A. K.; Margaretha, P.; Agosta, W. C. *J. Org. Chem.* **1996**, *61*, 3388.

Scheme 24



Summary

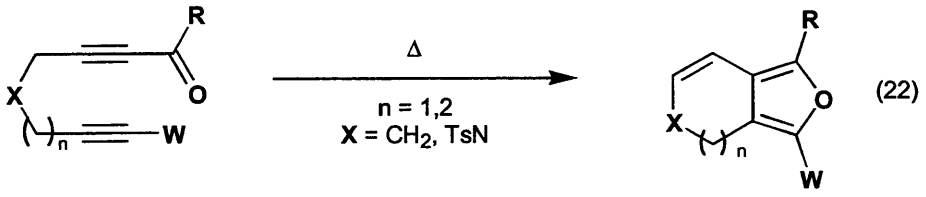
Although the literature contains a wide range of approaches to the synthesis of furans, few general methods exist for the preparation of 3,4 substituted or 3,4-fused derivatives. In addition, many of the existing routes require the construction of synthetically complex precursors. Thus, we believe that the intramolecular heteroenyne [4+2] cycloaddition route to highly substituted furans would be a useful addition to the field of furan synthesis. The next three chapters will outline the synthesis of the intramolecular ynone substrates and related species, the scope of the reaction, and our mechanistic proposal to account for furan formation.

Chapter 2

Synthesis of Heteroenyne Cycloaddition Substrates

Introduction

Intramolecular cycloaddition reactions are a convergent and efficient method for the synthesis of substituted polycyclic compounds.[107] As stated earlier, the goal of my research was to extend the intramolecular cycloaddition of conjugated enynes to heteroenyne substrates, specifically ynones and related systems. Based on our previous work with enyne substrates, we envisioned studying heteroenyne substrates of the general type shown below (eq 22). This chapter will detail the synthesis of a variety of these compounds. Chapter 3 will then discuss our work on the cycloaddition reactions of these substrates, and Chapter 4 will outline our studies on the mechanism of the transformation.



(22)

Ynone Cycloaddition Substrates

Most of the cycloaddition substrates synthesized in our investigation contain an α,β-acetylenic ketone or *ynone* as the heteroenyne component. This class of substrates includes compounds bearing both electron-withdrawing and electron-donating substituents on the alkyne ynonophile, as well as some compounds with unactivated

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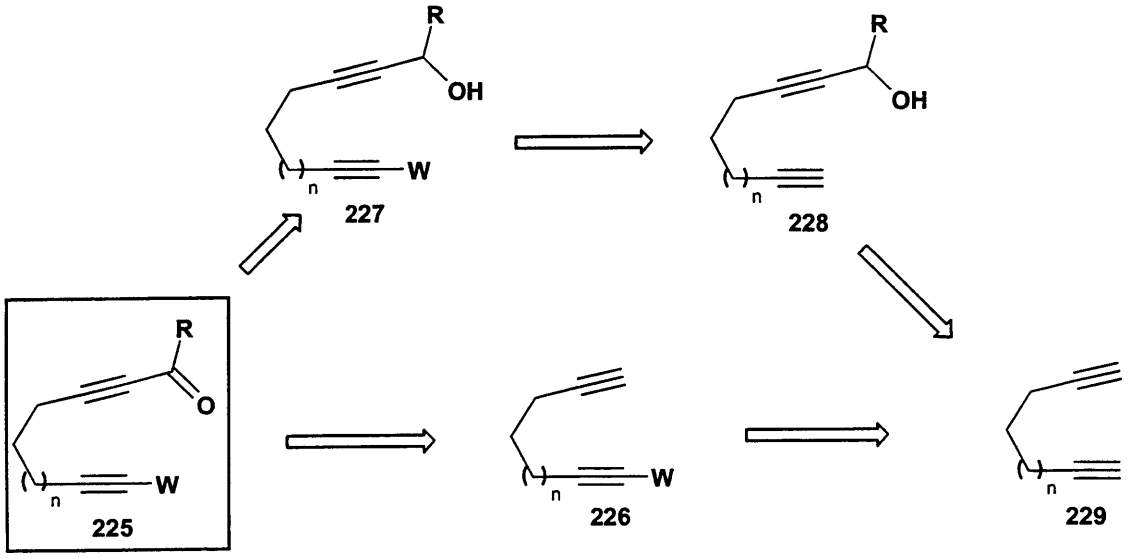
[107] For a review on cycloadditions, see: *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I. Paquette, L. A., Eds.; Pergamon: Oxford, 1991; Vol. 5.

alkyne units. A retrosynthetic analysis of the ynone substrates reveals that they can be easily constructed via synthetic elaboration of the appropriate core diyne unit **229**.[108] As shown below, the carbonyl portion of the ynone could either be installed directly from the mono-functionalized diynes **226**, or alternatively, generated from oxidation of the appropriate propargylic alcohols **227** (Scheme 25).

Scheme 25



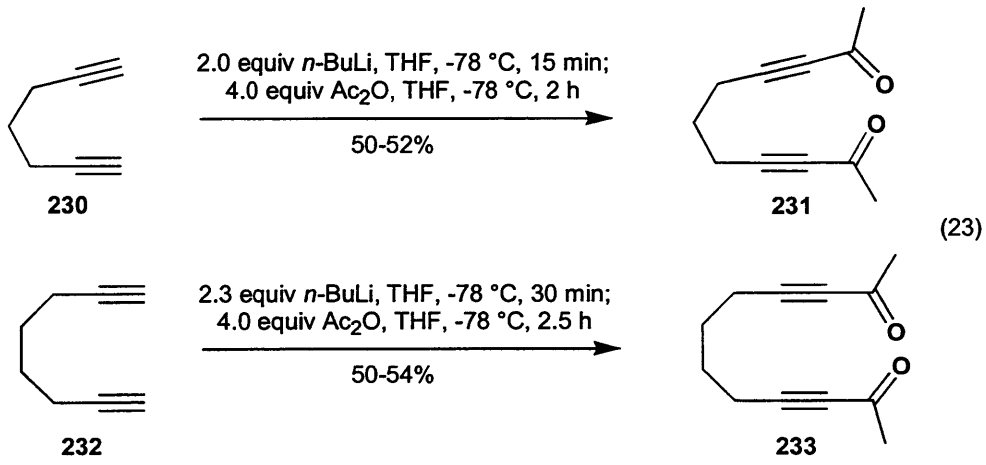
(a) Synthesis of Ynone Cycloaddition Substrates by Acylation

As discussed above, one route to the desired ynone substrates involves direct installation of the carbonyl portion of the ynone from an acetylene precursor. Using this approach, a series of methyl alkynyl ketones were generated via acylation of the corresponding lithium acetylide derivatives with acetic anhydride. A potential side reaction under these conditions involves proton transfer from the ketone product to the acetylide resulting in incomplete acylation. In addition, the product ketone could be attacked by the acetylide resulting in generation of the bispropargylic alcohol. In order to

[108] Both 1,6-heptadiyne and 1,7-octadiyne are commercially available.

minimize such side reactions, inverse addition conditions were employed in which the lithium acetylide derivative was added to an excess of acetic anhydride. [109]

The first two substrates that were synthesized using this strategy were the simple, symmetrical diones **231** and **233** (eq 23). Since the carbonyl portion of the ynone and the activating group on the alkyne ynonophile are identical, these substrates could be generated in one step from commercially available 1,6-heptadiyne and 1,7-octadiyne respectively by the double acylation of the corresponding lithium diacetylide derivative. Despite employing inverse addition conditions, incomplete acylation was observed in both cases; the desired diones were only generated in moderate yield and the monoacylated diynes was produced in ca. 20% yield (due to the volatile nature of the diynes themselves, the amount of starting material remaining after the reaction could not be determined). This incomplete acylation is consistent with the reported behavior of the corresponding enyne substrates.[56,57]

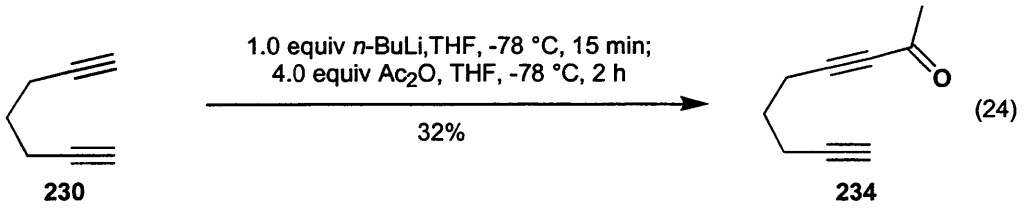


(23)

This reaction sequence was also utilized to generate the corresponding monoacylated substrate **234** (eq 24). In this case, the lithium monoacetylide derivative

[109] For a general procedure on the acylation of acetylenes, see: Brandsma, L. *Preparative Acetylenic Chemistry*, 2nd ed.; Elsevier: Amsterdam, 1988; p 104.

was prepared by the addition of only one equivalent of *n*-BuLi to the diyne, and then the resulting solution was added to an excess of acetic anhydride.



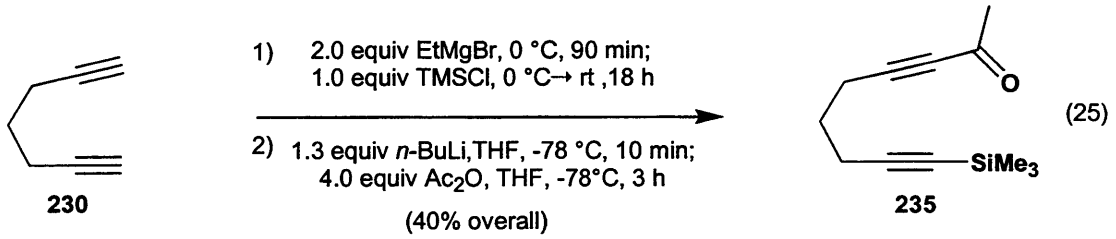
(24)

Unfortunately, these conditions only furnished the desired ketone **234** in 32% yield. Successful monoacylation was supported by the existence of a carbonyl carbon resonance at 184.5 ppm and a terminal acetylenic carbon resonance at 69.3 ppm in the ^{13}C NMR spectrum. In addition, the IR spectrum contains both a carbonyl stretching band at 1670 cm^{-1} and an acetylenic carbon-hydrogen stretching band at 3300 cm^{-1}. The major byproduct of this reaction was the doubly acetylated derivative **231** (ca. 15%). In an attempt to increase the yield of monoketone **234**, the reaction was repeated using EtMgBr as the base. Use of the Grignard reagent, however, failed to produce a higher yield of the desired product as ketone **234** was only generated in 22% yield and the corresponding dione **231** was isolated in 20% yield. One can assume that the low yield of product in these reactions results from protonation of the lithium acetylide regenerating the diyne starting material.[110] Since the diyne is volatile, it is probably lost during the workup of the reaction

Two other ynone substrates that were generated by direct acylation of acetylenes were alkynylsilyl substrates **235** and **241**. The former substrate, with a carbon tether

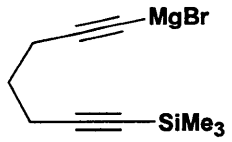
[110] It is possible that the use of a less polar solvent such as diethyl ether or use of a cerium acetylide would improve the yield of the transformation, but these modifications were not investigated. For an example of the reaction of a cerium acetylide with an enolizable ketone to generate alcohol products, see: Imamoto, T.; Sugiura, Y.; Takiyama, N. *Tetrahedron Lett.* **1984**, *25*, 4233.

between the two reactive components, was generated by silylation of diyne **230** followed by acylation of the resulting monosilylated derivative (eq 25).

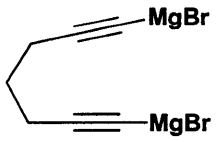


230 **235** (25)

Problems arose in monosilylating diyne **230** and in separating the desired monosilylated compound from the disilylated derivative. The largest amount of monosilylated derivative was produced when diyne **230** was treated with two equivalents of EtMgBr followed by the addition of one equivalent of trimethylsilyl chloride (TMSCl).[111] Although not anticipated, presumably the silylation of the monoGrignard intermediate **236** occurs less readily than the initial silylation of diGrignard **237**.[112] Unfortunately, the monosilylated adduct could not be separated from the disilylated adduct, so the mixture (ca. 75% monosilylated diyne by ^{1}H NMR) was subjected to the acylation conditions and then the desired ketone was isolated by column chromatography in 40% overall yield from diyne **230**.



236



237

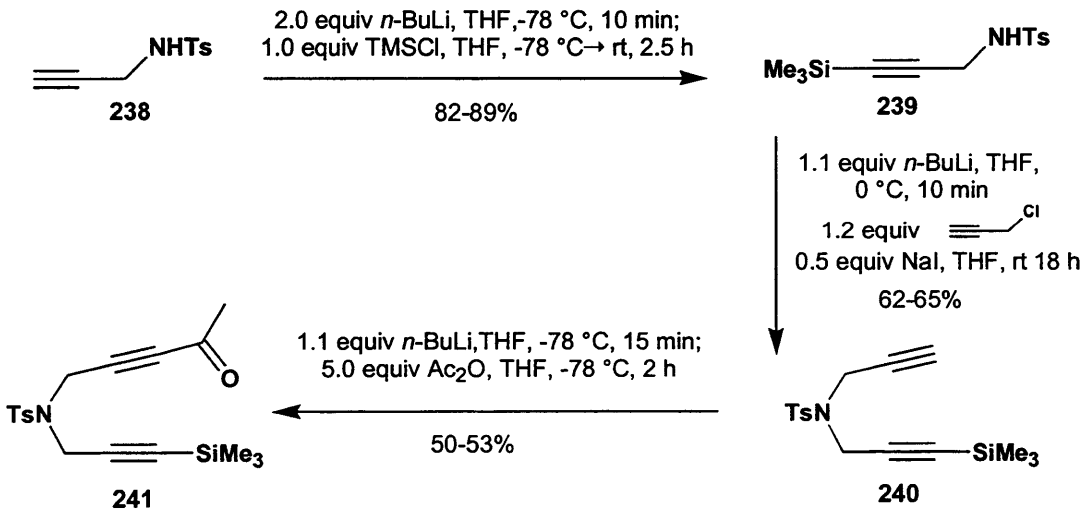
A related alkynylsilane cycloaddition substrate was also synthesized that contains a heteroatom within the tether between the ynone and alkyne ynonophile. In the enyne

[111] For a general procedure for the silylation of acetylenes, see: Brandsma, L. *Preparative Acetylenic Chemistry*, 2nd ed.; Elsevier: Amsterdam, 1988; p 107.

[112] Perhaps the greater reactivity of the diGrignard relates to the exact nature of the species (i.e. if it is an aggregate, if it is solvated, etc.)

cycloaddition, substrates with both all-carbon chains and those containing a nitrogen in the tether were found to participate in the intramolecular cycloaddition. We synthesized sulfonamide **241** to determine whether the heteroenyne cycloaddition could also tolerate a heteroatom tether between the two reactive components. Once again, the carbonyl portion of the ynone was installed by acylation of the corresponding silyl precursor **240** (Scheme 26). As shown below, alkynylsilane intermediate **240** was synthesized in two steps from the known sulfonamide **238**.[113] Selective silylation of the acetylene in **238** was achieved in excellent yield by treatment with two equivalents of *n*-BuLi in THF at –78 °C, followed by addition of one equivalent of TMSCl, and then warming to room temperature. Selective silylation of the alkyne was confirmed by the presence of the amine proton at 4.53 ppm in the ^{1}H NMR spectrum and the presence of the amine nitrogen-hydrogen stretching band at 3380 cm^{-1} in the IR spectrum.

Scheme 26



[113] The sulfonamide was synthesized from propargylamine following the method of Oppolzer, W.; Ruiz-Montes, J. *Helv. Chem. Acta* **1993**, *76*, 1266.

Alkylation of propargylic sulfonamide **239** was then accomplished in 62-65% yield by treatment with *n*-BuLi at 0 °C in THF followed by the addition of propargyl chloride and sodium iodide.[114] The presence of four acetylenic carbon resonances in the ^{13}C NMR spectrum at 97.3, 91.2, 76.3, and 73.7 ppm and the presence of a terminal acetylenic carbon-hydrogen stretch at 3300 cm^{-1} in the IR spectrum confirmed that the alkylation had been successful.

To complete the synthesis of sulfonamide substrate **241,** the standard conditions were utilized to acylate the terminal acetylene. Exposure of the diyne **240** to *n*-BuLi in THF at –78 °C followed by the addition of the resulting lithium acetylide to excess acetic anhydride furnished the desired alkynyl ketone **241** in 50-53% after purification by column chromatography. Once again, incomplete acylation was observed, and the corrected yield of ketone **241** was 71-74% when based on recovered starting material.

As described above, a series of methyl alkynyl ketones were conveniently prepared by acylating a functionalized diyne precursor. The main problem encountered in this approach involved incomplete acylation due to the quenching of the lithium acetylide derivatives by proton transfer from the ketone products. The next section outlines the generation of additional ynone substrates via an alternative synthetic route: oxidation of an appropriate propargylic alcohol precursor.

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[114] For examples of alkylations of N-alkyl sulfonamides, see: (a) Lansbury, P. T.; Scharf, D. J. *J. Am. Chem. Soc.* **1968**, *90*, 536. (b) Oppolzer, W.; Gaudin, J.-M.; Bedoya-Zurita, M.; Hueso-Rodriguez, J.; Raynham, T. M.; Robyr, C. *Tetrahedron Lett.* **1988**, *29*, 4709. (c) Oppolzer, W.; Bedoya-Zurita, M.; Switzer, C. Y. *Tetrahedron Lett.* **1988**, *29*, 6433. (d) Oppolzer, W.; Bienayme, H.; Genevois-Borella, A. *J. Am. Chem. Soc.* **1991**, *113*, 9660. (e) Oppolzer, W.; Ruiz-Montes, J. *Helv. Chem. Acta* **1993**, *76*, 1266.

b) Synthesis of Ynone Cycloaddition Substrates by Oxidation of Propargylic Alcohols

As discussed above, a second approach to the synthesis of α,β-acetylenic ketones involves the oxidation of the corresponding propargylic alcohol. We prepared a number of ynone substrates with a variety of different ynonophiles using this strategy. In all cases, the reagent used to effect the desired oxidation was the Dess-Martin periodinane reagent, which we and others have found gives excellent results in the oxidation of propargylic alcohols.[115] In addition, the mildness of this reagent made it a good choice since it could be employed in the presence of a variety of functional groups.

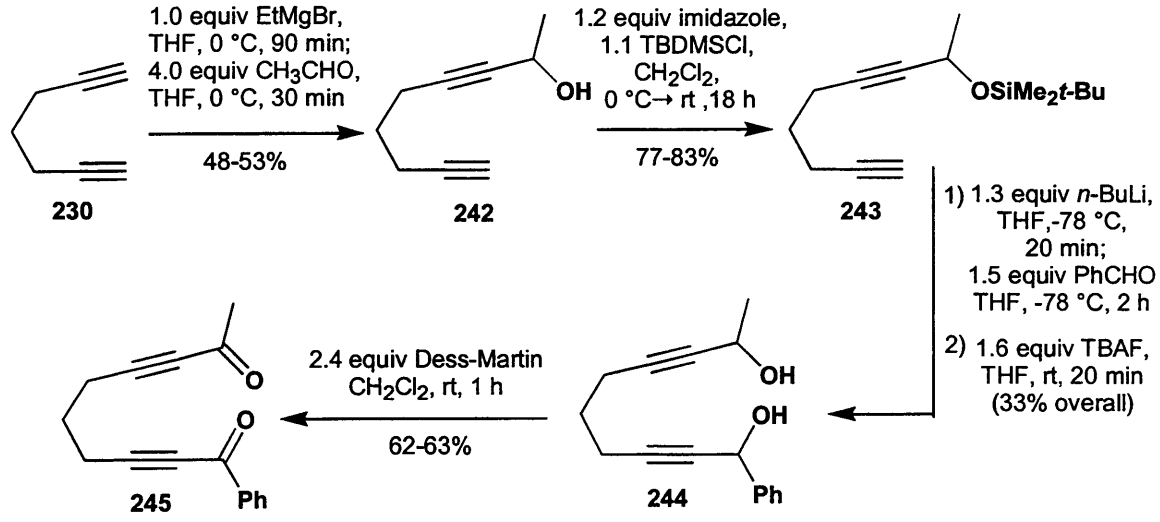
In order to probe how the type of ynone affects its reactivity as the 4π component of the cycloaddition, the unsymmetrical dione **245** was synthesized in five steps from diyne **230** (Scheme 27). Since this substrate contains two ketones, the synthetic route involved construction of diol **244** and then a double oxidation to generate the desired diketone **245**. First, the acetylide derivative of 1,6-heptadiene was added to acetaldehyde following the procedure of Trost[116] to afford the desired alcohol in 48-53% yield. Formation of propargylic alcohol **242** was supported by the presence of a terminal acetylenic carbon resonance in the ^{13}C NMR spectrum at 68.9 ppm and a broad oxygen-hydrogen stretching band in the IR spectrum at 3350 cm^{-1}. The low yield of this reaction can be attributed to the formation of the diol product from addition to both acetylenes; this product was formed in about 40% yield. In an attempt to increase the yield of the desired alcohol, the reaction was repeated using *n*-BuLi instead of EtMgBr. Use of the

[115] (a) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1984**, *48*, 4156. (b) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277. For an improved preparative procedure that was used to prepare this reagent, see: (c) Ireland, R. E.; Liu, L. *J. Org. Chem.* **1993**, *58*, 2899. (d) The author wishes to thank Dr. Alexandra Gould for preparing this reagent.

[116] Trost, B. M.; Romero, D. L.; Rise, F. *J. Am. Chem. Soc.* **1994**, *116*, 4268.

Grignard reagent proved to be critical, however, as the corresponding lithium acetylide gave the monoadduct in only 25% yield while the bisadduct was generated in 65% yield.

Scheme 27



The next stage of the synthesis involved conversion of alcohol **242** to the dione precursor **244**. Alcohol **242** was first protected in good yield by treatment with imidazole and *tert*-butyldimethylsilyl chloride (TBDMSCl),[117] and then the benzylic alcohol was installed by the addition of the acetylide derivative of **243** to benzaldehyde. The product was shown by ^{1}H NMR to be a 91:9 inseparable mixture of the desired propargyl alcohol and 1-phenyl-pentanol. Due to the large polarity difference between a diol and an alcohol, it was thought that once the silyl group was removed the desired diol **244** would be separable from the 1-phenyl-pentanol. Indeed, treatment of the impure alcohol with tetrabutylammonium fluoride (TBAF) in THF[118] for 20 min at room temperature

[117] For a representative procedure to protect alcohols as TBDMS ethers, see: Suzuki, T.; Sato, E.; Unno, K.; Kametani, T. *J. Chem. Soc., Perkin Trans. 1* **1986**, 2263.
[118] Kocieński, P. *Protecting Groups;* Georg Thieme Verlag Stuttgart: New York, 1994, pp 35.

followed by purification by column chromatography afforded the desired diol **244** in 33% overall yield from silyl ether **243**.

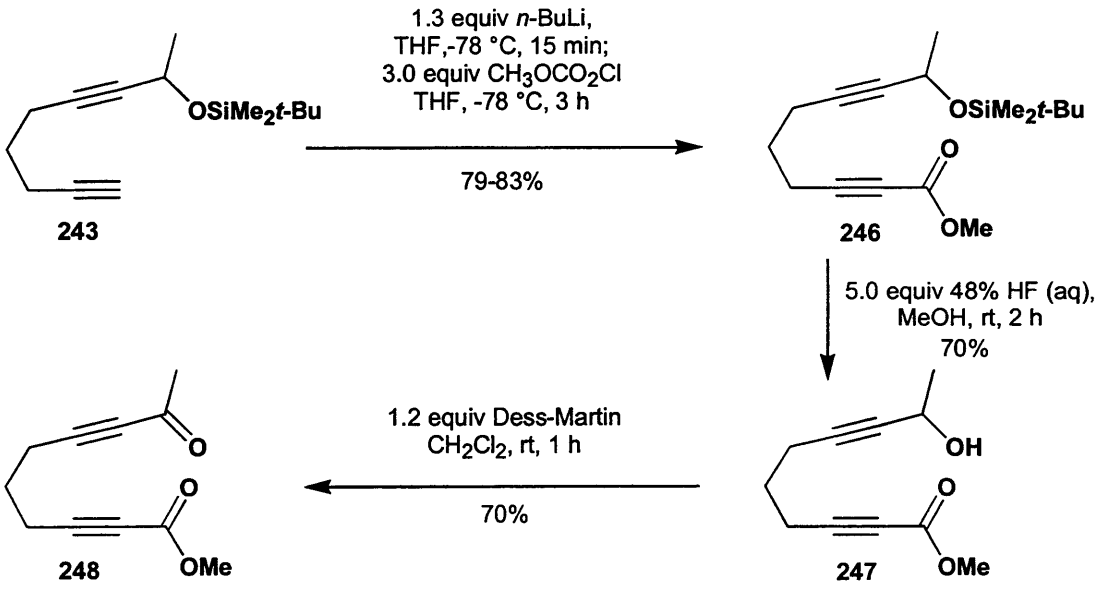
With diol **244** in hand, the remaining step involved oxidation of the two alcohol groups to ketones. As discussed above, the Dess-Martin reagent was employed and the desired dione **245** was generated in 62-63% yield after column chromatography. It should be noted that an alternative route to diol **244** involves the reaction of the doubly deprotonated derivative of alcohol **242** with benzaldehyde. Due to concerns about competing reaction at oxygen, this route was not explored.

An additional substrate that was generated from protected alcohol **243** is methyl ester substrate **248** (Scheme 28). This system was investigated in order to determine whether an ester could act as an activating group for the ynonophile, and to examine the competition between an acetylenic ketone and an acetylenic ester as the 4π component of the cycloaddition. As illustrated below, the desired ester substrate **248** was synthesized in three steps from silyl ether **243**. First the methyl ester was installed via treatment of the lithium acetylide of **243** with methyl chloroformate.[119] It should be noted that direct installation of the methyl ester from exposure of the doubly deprotonated derivative of **242** to methyl chloroformate was also investigated, but the reaction produced a substantial amount of the carbonate (34% yield) so this route was abandoned. To complete the synthesis of substrate **248** from methyl ester **246**, the silyl group was removed and the resulting alcohol group was oxidized to a ketone. Due to the sensitivity of the acetylenic ester to basic conditions,[120] TBAF was not a suitable reagent to remove

[119] For a general procedure for the synthesis of acetylenic esters, see: Brandsma, L. *Preparative Acetylenic Chemistry*, 2nd ed.; Elsevier: Amsterdam, 1988; p 101.
[120] Treatment of acetylenic ester **246** with TBAF resulted in multiple products by TLC analysis of the crude reaction mixture.

the silyl group. Instead, alcohol **247** was prepared in 70% yield after column chromatography by the treatment of silyl ether **246** with excess aqueous HF in methanol at 25 °C.[121] Subsequent oxidation of alcohol **247** using the Dess-Martin reagent then furnished the desired substrate **248** in 70% yield after column chromatography.

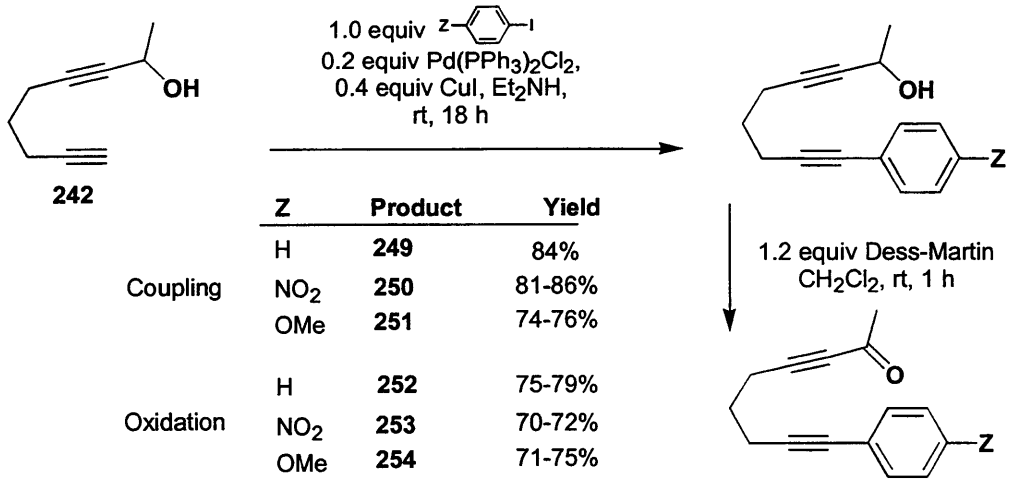
Scheme 28



In contrast to the two substrates discussed above, a number of other ynones could be generated from propargylic alcohol **242** without protection of the alcohol functionality. One such class of substrates involves aryl acetylenes as the ynonophilic component. Within this group of substrates, compounds with a range of substituents on the aryl group were synthesized in order to examine the effect that the electronic nature of the ynonophile exerts upon the cycloaddition. As shown below, substrates containing a phenyl group, an electron-withdrawing *p*-nitrophenyl group, and an electron-donating *p*-methoxyphenyl group were all generated in two steps from alcohol **242** (Scheme 29).

[121] For a representative procedure for the deprotection of TBDMS protected alcohols, see: Burke, S. D.; Cobb, J. E.; Takeuchi, K. *J. Org. Chem.* **1985**, *50*, 3421.

Scheme 29



	Z	Product	Yield
	H	**249**	84%
Coupling	NO_2	**250**	81-86%
	OMe	**251**	74-76%
	H	**252**	75-79%
Oxidation	NO_2	**253**	70-72%
	OMe	**254**	71-75%

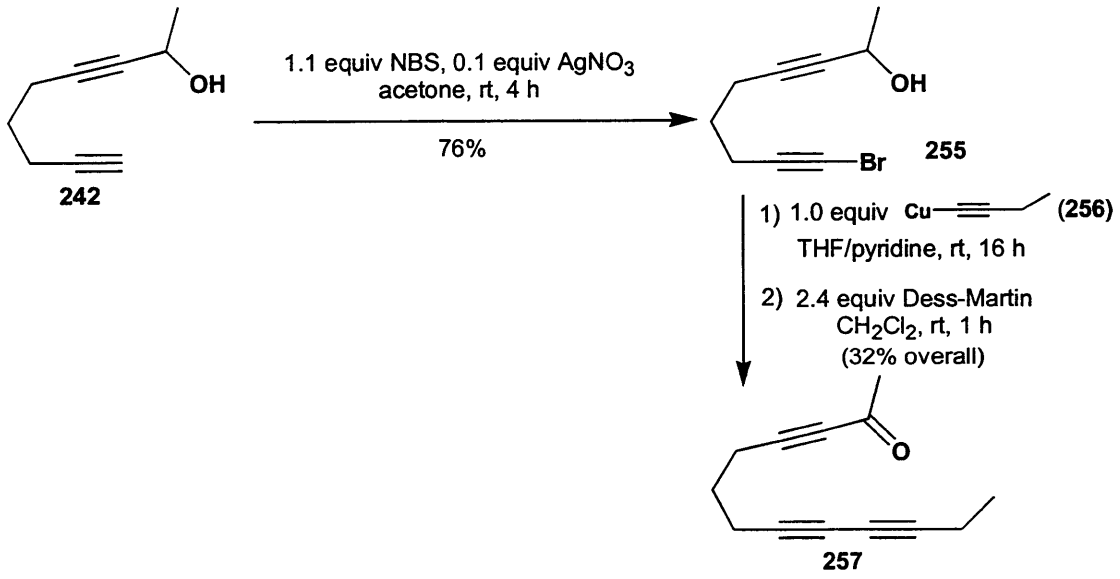
The first step in the synthesis of these substrates involved the installation of the aryl group by a palladium-catalyzed Castro-Stephens coupling[122] between alcohol **242** and the appropriate aryl iodide. In each case, the desired aryl derivative **249**, **250**, or **251** was isolated in good yield after column chromatography. Subsequent oxidation of the alcohols using the Dess-Martin periodinane then furnished the corresponding ketones, **252**, **253** and **254** in good yields after column chromatography.

Conjugated diyne **257** is another substrate we investigated that contains an unsaturated substituent on the alkyne ynonophile. This substrate was synthesized in three steps from propargyl alcohol **242** as shown in Scheme 30. Generation of the diyne moiety required formation of bromoacetylene **255** and then coupling with 1-butyne. To generate the bromoacetylene, alcohol **242** was treated with *N*-bromosuccinimide (NBS) and a catalytic amount of silver nitrate.[123] Support for the successful formation of bromoacetylene **255** is found in the absence of both the acetylenic proton resonance in

[122] (a) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, 4467. (b) Takahashi, S.; Kuroyama, Y.; Sonogashira, K.; Hagihara, N. *Synthesis* **1980**, 627. (c) Alami, M.; Ferri, F.; Linstrumelle, G. *Tetrahedron Lett.* **1993**, *34*, 6403. (d) Chemin, D.; Linstrumelle, G. *Tetrahedron* **1994**, *50*, 5335.
[123] Hofmeister, H.; Annen, K.; Laurent, H.; Wiechert, R. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 727.

the ^{1}H NMR spectrum and the acetylenic carbon-hydrogen stretch in the IR spectrum. Installation of the alkyne was then accomplished by the treatment of *in situ* prepared copper (I) acetylide **256** with bromoacetylene **255** in THF/pyridine at 25 °C.[124] The resulting product was found by ^{1}H NMR to be a 88:12 inseparable mixture of the desired diyne and debrominated alcohol **242**. Since the copper (I) acetylide was generated from 1-butyne, *n*-BuLi, and CuI, the formation of alcohol **242** might arise from halogen metal exchange on the bromoacetylene **255** by residual *n*-BuLi. The resulting lithium acetylide derivative would then be quenched in the workup to afford alcohol **242**. To generate the desired substrate, the mixture of alcohols was then oxidized using the Dess-Martin reagent, and the desired diyne substrate **257** was isolated by column chromatography in 32% overall yield from bromoacetylene **255**.

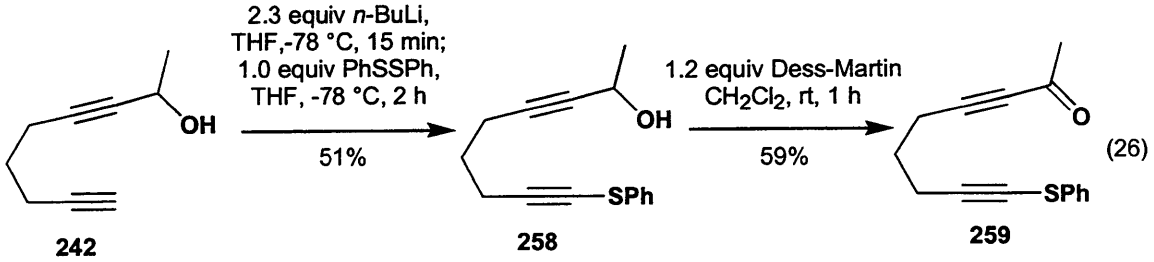
Scheme 30



An additional substrate that was synthesized from alcohol **242** contains a phenyl sulfide substituent on the alkyne. As outlined below, thioacetylene **259** was synthesized

[124] Miller, J. A.; Zweifel, G. *Synthesis* **1983**, 128.

in two steps from propargyl alcohol **242** (eq 26). Treatment of the doubly deprotonated derivative of alcohol **242** with phenyl disulfide furnished sulfide **258** in 51% after column chromatography.[125] In contrast to the reaction of this species with methyl chloroformate, no evidence of reaction at oxygen was observed. Presumably this result can be explained by invoking hard/soft acid base theory since the soft disulfide should prefer to react with the soft lithium acetylide over the hard alkoxide. Evidence for the selective attack on carbon exists in the IR spectrum, which exhibits a broad oxygen-hydrogen stretching band at 3350 cm^{-1} and an alcohol proton resonance at 1.84 ppm in the ^1H NMR spectrum. To complete the synthesis of sulfide substrate **259**, the Dess-Martin reagent was employed to oxidize the alcohol functionality to a ketone. Exposure of phenyl sulfide **258** to 1.2 equivalents of the periodinane in methylene chloride at 25 °C furnished the desired ynone substrate **259** in 59% yield after column chromatography.

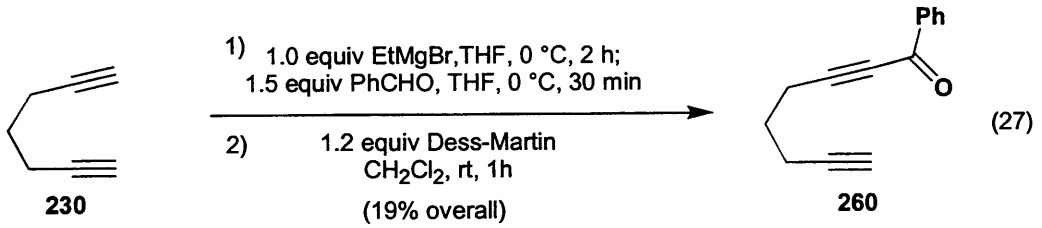


(26)

The final ynone substrate that was generated from a propargylic alcohol precursor was phenyl ynone **260** (eq 27). Installation of the alcohol moiety was accomplished by the method of Trost,[114] but the desired propargylic alcohol could only be isolated in ca. 85% purity by ^1H NMR. The impurity appeared to be the product of the condensation of the Grignard reagent with benzaldehyde, 1-phenyl-1-propanol, and could not be separated

[125] For a general procedure on the synthesis of acetylenic sulfides, see: Brandsma, L. *Preparative Acetylenic Chemistry*, 2nd ed.; Elsevier: Amsterdam, 1988; p 238.

from the desired alcohol. Again, the major byproduct of the reaction was the diol, which was produced in 30% yield. The impure alcohol mixture was then oxidized by exposure to the Dess-Martin reagent and the desired ketone **260** was isolated by column chromatography in 19% overall yield from diyne **230**. Ketone **260** exhibits both a carbonyl carbon resonance at 177.9 ppm and a terminal acetylenic carbon resonance at 69.5 ppm in the ^{13}C NMR spectrum. In addition, the IR spectrum contains both a ketone carbonyl stretching band at 1630 cm^{-1} and an acetylenic carbon-hydrogen stretching band at 3280 cm^{-1}.



(27)

Other Heteroenyne Cycloaddition Substrates

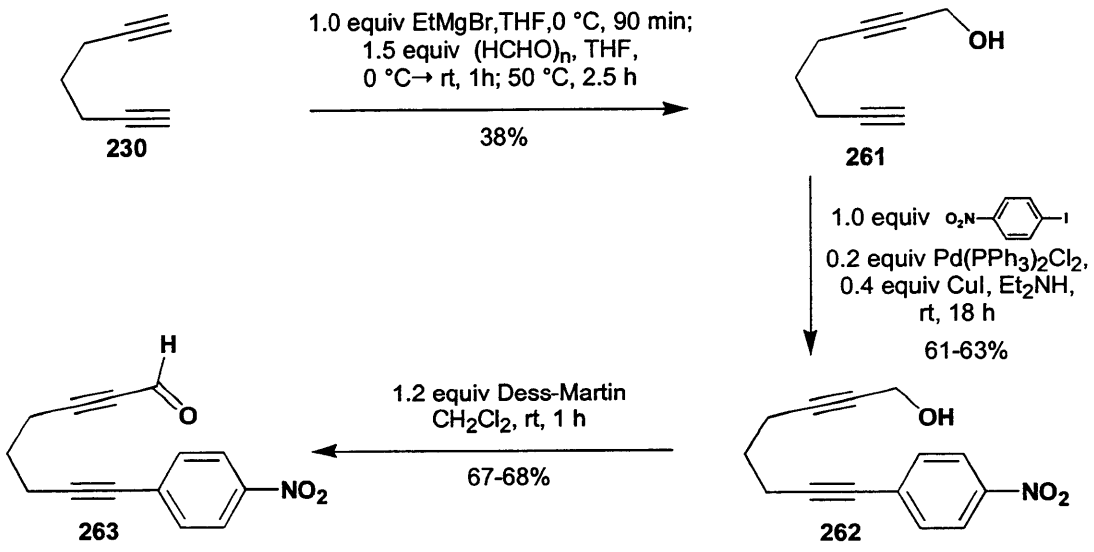
The reactivity of a variety of other acetylenic carbonyl compounds as the 4π component of the cycloaddition was also investigated. This section describes the syntheses of cycloaddition substrates containing an α,β-acetylenic aldehyde, an α,β-acetylenic acylsilane, and an α,β-acetylenic thioester as the heteroenyne.

(a) Synthesis of an α,β-Acetylenic Aldehyde Cycloaddition Substrate

To compare the ability of acetylenic ketones and acetylenic aldehydes to act as the 4π component in the intramolecular heteroenyne cycloaddition, an α,β-acetylenic

aldehyde **263** was synthesized with a *p*-nitrophenyl substituent on the alkyne 2π component. As shown in Scheme 31, the strategy used to construct this substrate was identical to that used to prepare ynone substrate **253** (Scheme 29) except that the initial step utilized paraformaldehyde instead of acetaldehyde. Treatment of diyne **230** with EtMgBr followed by the addition of paraformaldehyde furnished the desired primary propargyl alcohol **261** in 38% yield after column chromatography.[126] Again, the low yield results from problems with competing formation of the diol (30%). Formation of the desired propargylic alcohol **261** was supported by the presence of a terminal acetylenic carbon resonance in the ^{13}C NMR spectrum at 68.9 ppm and a broad oxygen-hydrogen stretching band in the IR spectrum at 3340 cm^{-1}.

Scheme 31



A palladium-mediated Castro-Stevens coupling[120] between alcohol **261** and 1-iodo-4-nitrobenzene then furnished alcohol **262** in moderate yield. To complete the

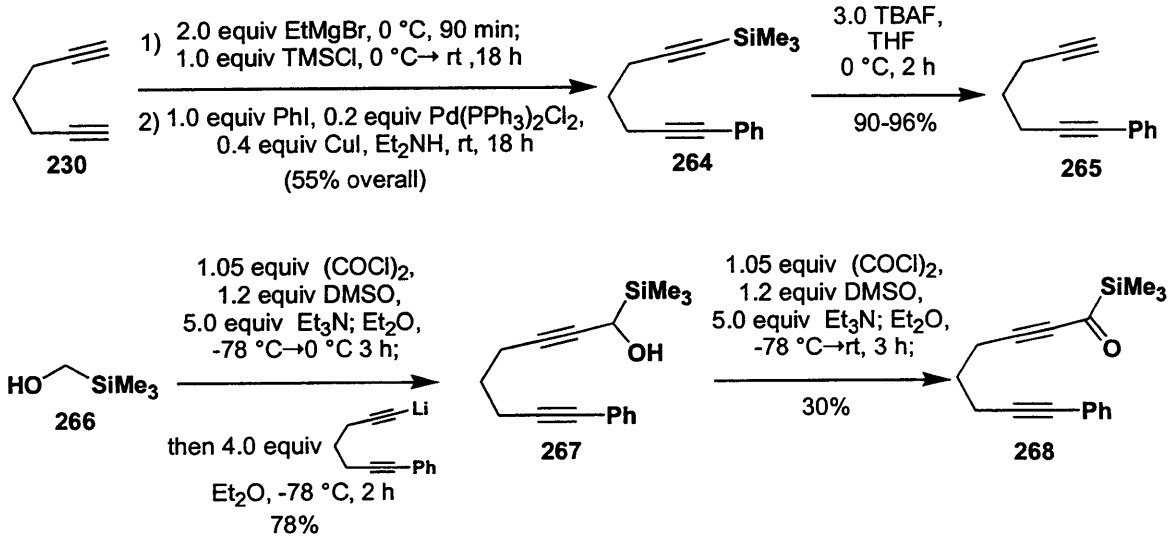
[126] For a related general procedure to generate primary propargylic alcohols that utilizes *n*-BuLi instead of a Grignard reagent, see, : Brandsma, L. *Preparative Acetylenic Chemistry*, 2nd ed.; Elsevier: Amsterdam, 1988; p 81.

synthesis of aldehyde **263**, alcohol **262** was oxidized using the Dess-Martin reagent to furnish the desired substrate in 67-68% yield after column chromatography. Formation of the aldehyde was supported by a presence of an aldehyde proton at 9.12 ppm in the ^1H NMR spectrum.

(b) Synthesis of an α,β-Acetylenic Acylsilane Cycloaddition Substrate

A third type of heteroenyne that was synthesized contained an α,β-acetylenic acylsilane as the heteroenyne component. As shown below, the acylsilane was generated by the oxidation of propargylic α-hydroxysilylane **267**, which in turn was synthesized from the addition of the lithium derivative of phenyl acetylene **265** to (trimethylsilyl)formaldehyde (Scheme 32).

Scheme 32



The initial phase of the synthetic route involved the generation of phenyl acetylene **265** from commercially available diyne **230**. First, diyne **230** was monosilylated by treatment with two equivalents of EtMgBr followed by one equivalent

of TMSCl. As discussed above, it was impossible to completely separate the monosilylated product from the disilylated product, so the mixture was carried on to the next step in the sequence, a palladium-catalyzed Castro-Stevens coupling reaction[120] with iodobenzene. After the coupling, the desired silyl phenyl acetylene **264** could be isolated by column chromatography in 55% overall yield from diyne **230**. Removal of the silyl protecting group was then accomplished by exposure of **264** to TBAF, which furnished phenyl acetylene **265** in excellent yield.

The next phase of the synthesis involved the installation of the α-hydroxysilyl moiety.[127] After (trimethylsilyl)formaldehyde was generated *in situ* via a Swern oxidation of commercially available (trimethylsilyl)methanol (**266**), four equivalents of the lithium acetylide of alkyne **265** were added to the reaction solution at –78 °C. The mixture was then warmed to 25 °C and quenched to furnish the desired propargylic α-hydroxysilane **267** in 78% yield after column chromatography. The number of equivalents of lithium acetylide employed in this reaction exert a large effect on the efficiency of the transformation. When only three equivalents of the acetylide were used, the yield fell to 15%. In addition, when a five-fold excess of (trimethylsilyl)methanol (**266**) was used, the desired compound was only produced in 54% yield. The propargylic α-hydroxysilane **267** exhibits a broad oxygen-hydrogen stretching band at 3400 cm^{-1} in the IR spectrum.

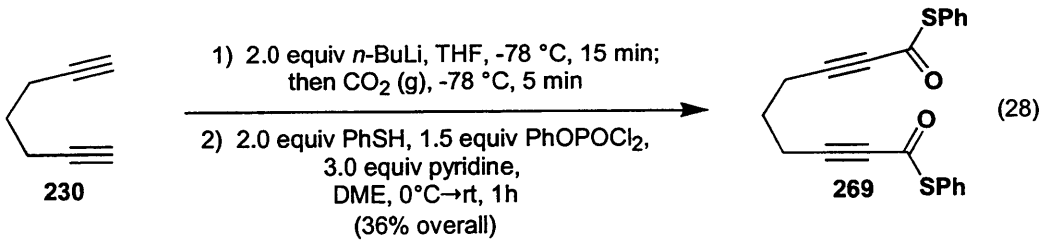
The α-hydroxysilane **267** was then oxidized to the desired acylsilane **268** in 30% yield via a Swern oxidation. The low yield was both disappointing and surprising based on the fact that acetylenic acylsilanes had been synthesized previously using this

[127] Linderman, R. J.; Suhr, Y. *J. Org. Chem.* **1988**, *53*, 1569.

strategy.[127] In an attempt to bolster the yield, use of the Dess-Martin periodinane as the oxidant was also investigated, but unfortunately treatment with this reagent resulted in loss of the silicon group and formation of the corresponding aldehyde. The acylsilane substrate **268** exhibits an acylsilane carbonyl stretching band at 1600 cm^{-1} in the IR spectrum and an acylsilane carbon resonance at 226.6 ppm in the ^{13}C NMR spectrum.

(c) Synthesis of an Alkynyl Thioester Cycloaddition Substrate

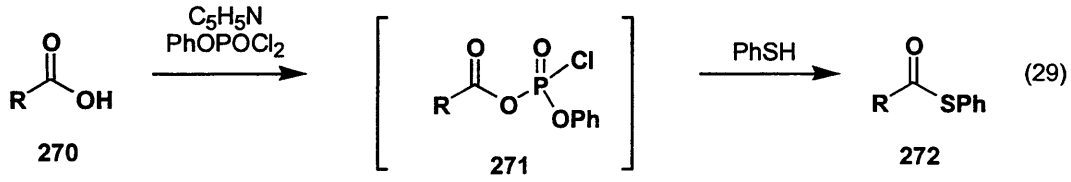
The fourth type of heteroenyne substrate that was synthesized contains a thiol ester as both the carbonyl portion of the heteroenyne and the activating group on the alkyne. As shown below, bisthiol ester **269** was constructed in two steps from commercially available diyne **230** (eq 28). First, the diacid was generated by exposure of the diyne to two equivalents of *n*-BuLi and then bubbling CO_2 gas into the solution for five minutes.[128] After an acidic workup, the resulting crude diacid was dissolved in dimethoxyethane (DME). Subsequent treatment at 0 °C with thiophenol, phenyl dichlorophosphate, and pyridine[129] then furnished the desired bisthiol ester **269** in 36% overall yield from diyne **230** after column chromatography. The bisthiol ester exhibits a thioester carbon resonance at 175.6 ppm in the ^{13}C NMR spectrum and a thioester carbonyl stretching band at 1640 cm^{-1} in the IR spectrum.



(28)

[128] For a general procedure to synthesize acetylenic carboxylic acids, see: Brandsma, L. *Preparative Acetylenic Chemistry*, 2nd ed.; Elsevier: Amsterdam, 1988; p 100.
[129] For a general procedure to convert carboxylic acids to thioesters, see: Liu, H.-J.; Sabesan, S. I. *Can. J. Chem.* **1980**, *58*, 2645.

As shown below, the role of the phenyl dichlorophosphate in the above transformation is to activate the carboxylic acid to attack by thiophenol (eq 29). Addition of pyridine and phenyl dichlorophosphate generates intermediate **271**, which is subsequently attacked by the thiolphenol to generate thiol ester **272**.



270 271 272 (29)

Summary

This chapter has outlined the syntheses of a variety of ynone cycloaddition substrates and related species. These substrates enabled us to examine the both the scope and mechanism of the [4+2] heteroenyne cycloaddition. The next chapter will disclose our findings on the scope of the transformation and the following chapter will outline our proposed mechanism to account for furan formation.

Chapter 3

Scope of the Intramolecular Ynone Cycloaddition

Introduction

The goal of my research has been to extend the intramolecular [4+2] cycloaddition of conjugated enynes to *heteroenyne* substrates, specifically ynones and related species. The previous chapter outlined the synthesis of the substrates employed in this study and this chapter will detail their behavior in intramolecular cycloaddition reactions. Specifically, this chapter discusses the evidence that a bicyclic furan is the ultimate product of the reaction, describes the scope of the transformation, and discusses the significance of the reaction as a method for the synthesis of highly substituted furans.

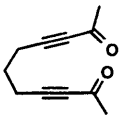
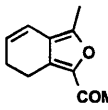
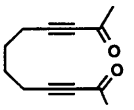
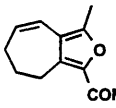
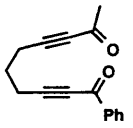
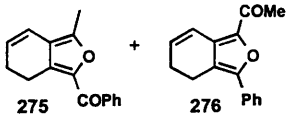
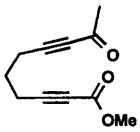
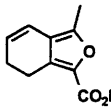
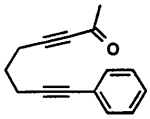
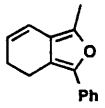
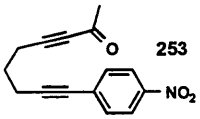
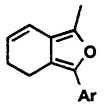
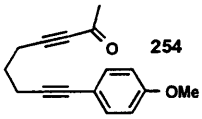
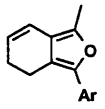
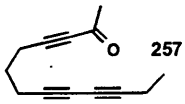
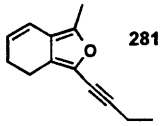
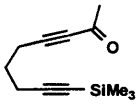
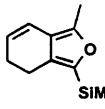
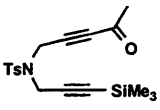
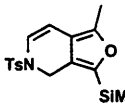
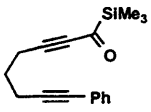
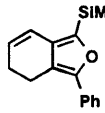
General Features of the Transformation

The results from our investigation of the scope of the thermal reaction of conjugated ynones and related species are presented in Table 3. The conditions for effecting the reaction involve heating a degassed 0.1M solution of the substrate in toluene in the presence of 1.1 equivalents of γ-terpinene in a resealable tube.[130] The choice of solvent and the concentration of the reaction solution were selected based on previous work performed on the related enyne cycloaddition.[56,57,131] The addition of γ-terpinene

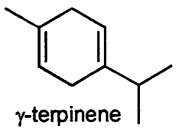
[130] The tubes are threaded Pyrex tubes with a side arm equipped with an argon inlet adapter and they were sealed with a threaded Teflon cap.

[131] Since the use of a 0.1M solution of the substrate in toluene provided the furan products in good yields, the effect of using different solvents or other reaction concentrations was not examined.

Table 3. Thermal Heteroenyne Cycloadditions

Entry	Substrate	Cycloadduct	Conditions	Yield (%)
1	 231	 273	1.1 equiv γ-terpinene tol, 180 °C, 48 h	80
2	 233	 274	1.1 equiv γ-terpinene tol, 220 °C, 72 h	20
3	 245	 275 + 276	1.1 equiv γ-terpinene tol, 180 °C, 48 h	68 (275:276 87:13)
4	 248	 277	1.1 equiv γ-terpinene tol, 180 °C, 54 h	50
5	 252	 278	1.1 equiv γ-terpinene tol, 180 °C, 48 h	70
6	 253	 279	1.1 equiv γ-terpinene tol, 180 °C, 48 h	81
7	 254	 280	1.1 equiv γ-terpinene tol, 180 °C, 77 h	58 (~90% punty by ^{1}H NMR)
8	 257	 281	1.1 equiv γ-terpinene tol, 180 °C, 6 h	56
9	 235	 282	1.1 equiv γ-terpinene tol, 220 °C, 72 h	50
10	 241	 283	1.1 equiv γ-terpinene tol, 120 °C, 16 h	64
11	 268	 284	1.1 equiv γ-terpinene tol, 180 °C, 20 h	36

exerts a strong effect on the efficiency of the desired transformation. When dione **231** was heated without γ-terpinene or in the presence of only a substoichiometric amount of the additive (0.2 equivalents), the yield of furan **273** fell from 80% to 65%. We believe the γ-terpinine,[132] a cyclohexadiene derivative, acts as a radical inhibitor and prevents polymerization of the heteroenyne substrates at the elevated reaction temperatures.


γ-terpinene

Other additives that might function as radical inhibitors were not as effective and resulted in lower yields of furan **273**. When 1.1 equivalents of saccharin were added instead of γ-terpinene, furan **273** was only produced in 60% yield. In addition, when the γ-terpinene was replaced by 3.5 equivalents of 2,6-di-*tert*-butyl-4-methylphenol (BHT), furan **273** was only formed in 26% yield. This last result was interesting since the addition of BHT improved the yields of the thermal reaction of the corresponding enyne substrates while the addition of γ-terpinene did not.[56] Phenolic additives may improve the efficiency of the enyne cycloadditions in that they might facilitate the isomerization of the resulting cyclic allene intermediate to an aromatic product by donating or accepting a proton or hydrogen atom.[133] In the heteroenyne case, such an isomerization cannot occur.

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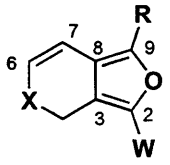
[132] γ-Terpinene was used instead of cyclohexadiene because it is relatively inexpensive.
[133] For a discussion of the mechanistic pathway for the enyne cycloaddition see Part I, Chapter 3.

Evidence for Furan Formation

As stated previously, the generation of a bicyclic furan from the intramolecular cycloaddition of conjugated ynones was not anticipated. In fact, we initially thought that the product of the reaction would be the corresponding pyran derivative. Upon closer examination of spectral data, however, we determined that the products were actually 3,4-fused furans. As shown in Table 4, the furan products all exhibit common features in the ^{1}H NMR and ^{13}C NMR spectra.

Table 4. Spectral Data of Furan Products ($CDCl_3$)

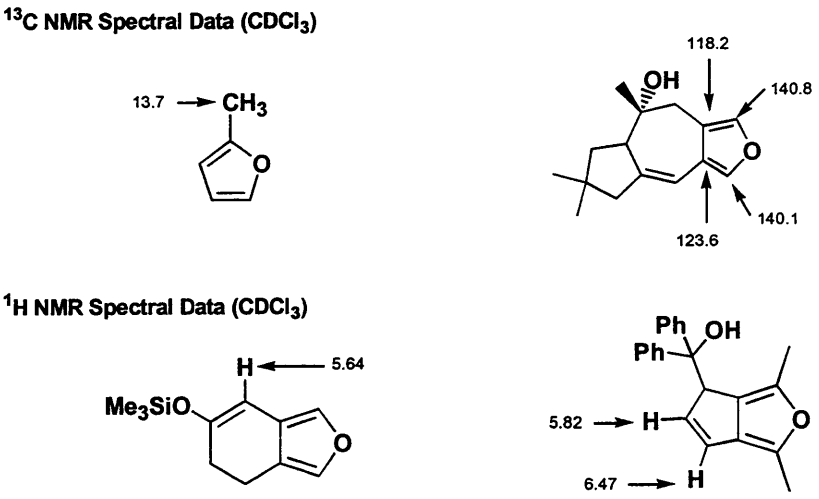


Furan	R	W	X	C-2	C-3	C-8	C-9	C- R	H-6	H-7
273	Me	COMe	CH_2	145.4	119.8	130.5	148.9	12.0	5.83	6.29
275	Me	COPh	CH_2	145.2	120.0	133.6	149.7	12.2	5.90	6.36
277	Me	CO_2Me	CH_2	136.2	119.2	131.6	149.1	11.9	5.81	6.28
278	Me	Ph	CH_2	144.7	118.8	131.8	144.5	11.7	5.86	6.45
279	Me	*p*-NO_2Ph	CH_2	145.2	119.6	137.6	147.1	11.8	5.83	6.36
280	Me	*p*-OMePh	CH_2	144.0	118.4	124.8	144.5	11.6	5.84	6.41
281	Me	≡—	CH_2	129.8	117.4	124.6	145.4	11.8	5.75	6.29
282	Me	$SiMe_3$	CH_2	150.0	116.9	131.3	149.1	11.8	5.77	6.39
283	Me	$SiMe_3$	NTs	150.5	122.5	134.8	148.7	11.8	6.61	5.67
284	$SiMe_3$	Ph	CH_2	152.2	120.0	133.0	149.8	—	5.88	6.58

In the ^{13}C NMR spectrum, each compound possesses two carbon-carbon double bond resonances between 130-150 ppm corresponding to C-2 and C-9 on the furan ring, and two carbon-carbon double bond resonances between 117-133 ppm corresponding to C-3 and C-8 on the furan ring. In addition, the products all exhibit two carbon-carbon

double bond resonances between 117-125 ppm corresponding the olefinic carbons in the six-membered ring. The furan products generated from methyl alkynyl ketones also exhibit a peak ~12 ppm corresponding to the methyl substituent at C-9 of the furan skeleton. In the ^{1}H NMR spectrum, each bicyclic furan product exhibits two vinyl protons between 5.6-6.6 ppm with a coupling constant of ~10 Hz corresponding to the cis vinyl protons on the six-membered ring. These spectral characteristics are consistent with those previously reported for furan derivatives (Scheme 33).[97, 134]

Scheme 33



The strongest evidence to support furan formation is the X-ray crystal structure of product **279**.[135,136] As shown in the ORTEP drawing, the X-ray analysis supports the 3,4-fused furan skeleton with an R1 value of 0.0546. Based on this crystal structure and the spectral evidence, we are confident that the product of the thermal reaction of ynones and related substrates is a 3,4-fused furan.

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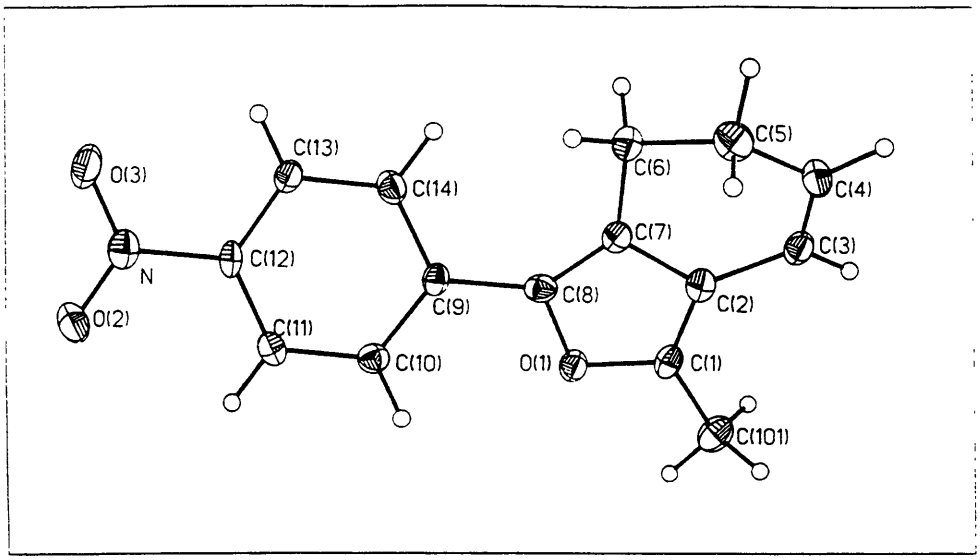
[134] (a) For data on the tricyclic furan see, Battaglia, R.; De Bernardi, M.; Fronza, G.; Mellerio, G.; Bidari, G.; Vita-Finsi, P. *J. Nat. Products* **1980**, *43*, 319. For data on the [3.3.0] bicyclic furan, see (b) Cantrell, T. S.; Harrison, B. L. *Tetrahedron Lett.* **1969**, 1299.

[135] The author wishes to thank Dr. William Davis for obtaining the X-ray crystal structure of furan **279**.

[136] A crystal suitable for X-ray analysis was obtained by recrystallization of furan **279** from hexane.



R1 = 0.0546

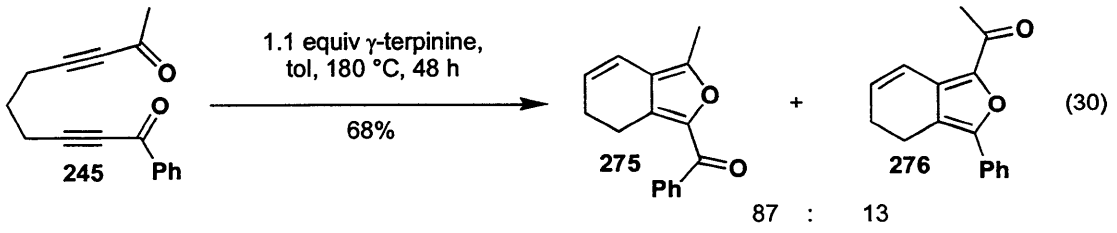
Scope of the Transformation

Our exploration of the scope of the intramolecular cycloaddition of conjugated heteroenynes has revealed that the reaction is quite general when the heteroenyne is an ynone. As illustrated in Table 3, the intramolecular cycloaddition methodology provides access to polycyclic furans containing a variety of substitution patterns. It should be noted, however, that the Table only illustrates the successful cases that were examined. In the course of our investigation, we examined a variety of features of the reaction including the nature of the heteroenyne, substituent effects on the heteroenynophile, and the nature and length of the connecting chain. From these studies, a number of generalizations can be made concerning the types of substrates that will undergo the transformation.

(a) Nature of the Heteroenyne

During the course of the investigation, one area of interest was what types of heteroenynes would undergo the transformation. As illustrated in Table 3, ynone

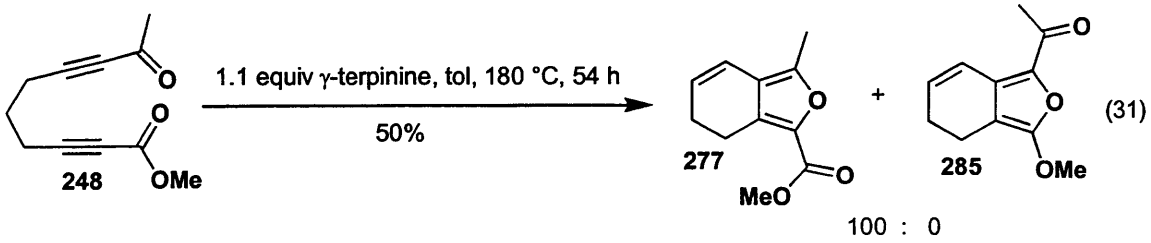
substrates provide the corresponding furan products in good yield. Within this class of substrates, unsymmetrical dione **245** provided the opportunity to compare the tendency of methyl and phenyl substituted alkynyl ketones to participate as the 4π component of the cycloaddition. Thermolysis of dione **245** provided an 87:13 mixture of furan products **275** and **276** in 68% yield (eq 27). A sample of the major isomer was isolated by additional column chromatography and characterized. Support for the identification of furan **275** as the major product of the reaction comes from the ^{13}C NMR spectrum that exhibits an alkyl resonance at 12.2 ppm characteristic of a methyl substituent on a furan. If furan **276** had been the major product, one would have expected the ^{13}C spectrum to contain an alkyl resonance at ~24 ppm corresponding to the methyl group of the ketone; no such signal appears in the spectrum of the major product. In addition, furan **275** exhibits aromatic protons at 7.98 ppm (d, 2H), 7.54 ppm (t, 1H), 7.47 ppm (app t, 2H) characteristic of a phenyl ketone. The formation of furan **275** as the major product of the reaction seems to indicate that the methyl alkynyl ketone participates in the cycloaddition more readily than the phenyl alkynyl ketone, which enjoys more resonance stabilization.



(30)

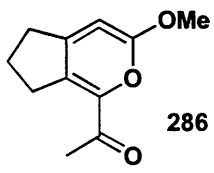
Additional evidence that delocalization of the heteroenyne carbonyl inhibits the cycloaddition was found in the behavior of substrate **248**. With this substrate, the competition is between the acetylenic ketone and the acetylenic ester to act as the 4π component of the reaction. As shown below, thermolysis of substrate **248** provided only

furan **277** in 50% yield (eq 31). Furan **277** exhibits an alkyl resonance at 11.9 ppm and an ester carbonyl resonance at 159.8 ppm in the ^{13}C NMR spectrum. None of furan product **285**, which would have been formed if the acetylenic ester had acted as the heteroenyne, was observed in this reaction. Again it appears that resonance delocalization in the carbonyl group inhibits the ability of the heteroenyne to participate in the transformation.



(31)

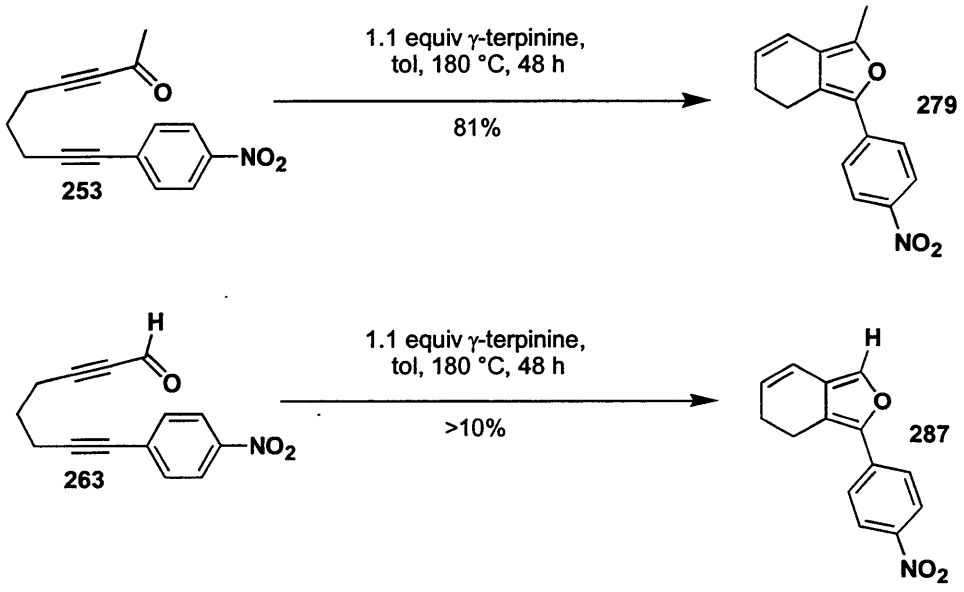
It should be noted, however, that other scenarios could explain our failure to isolate furan product **285** in this reaction. For example, it is possible that the cycloaddition occurs, but the resulting heterocyclic allene **286** then undergoes alternate reactions rather than rearrangement to the furan. One such alternative reaction is a retro [4+2] cycloaddition that would regenerate substrate **248**. Hetero Diels-Alder reactions of α,β unsaturated esters have been reported to be reversible,[137] and it is possible that allene **286** undergoes cycloreversion before it can rearrange to a furan product. In addition, it is possible that methoxy-substituted furan product **285** is formed but decomposes under the reaction conditions.



[137] (a) Snider, B. B.; Roush, D. M.; Killinger, T. A. *J. Am. Chem. Soc.* **1979**, *101*, 6023. (b) Snider B. B.; Roush, D. M. *J. Org. Chem.* **1979**, *44*, 4229. (c) Tietze, L. –F.; Beifuss, U. *Tetrahedron Lett.* **1986**, *27*, 1767.

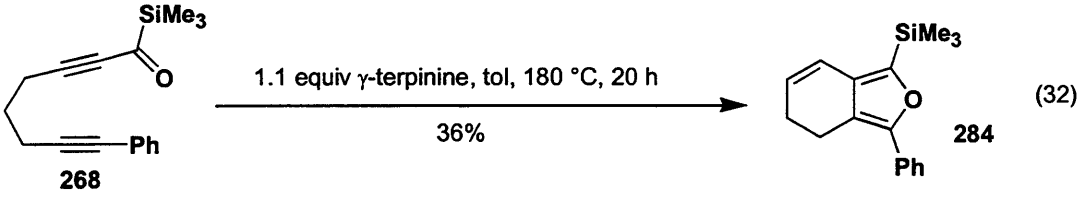
Another type of heteroenyne that was examined was the α,β-acetylenic aldehyde **263**. While thermolysis of ynone substrate **253** produced the expected furan in excellent yield, thermolysis of **263** produced only traces (2-10%) of furan **287** (Scheme 34). TLC analysis of the crude reaction mixture showed the presence of numerous byproducts. One possible explanation for the difference in behavior between ketone **253** and aldehyde **263** could be the stability of the less substituted furan **287** at the elevated temperature of the reaction. Perhaps, the lack of a substituent on the C-9 site of the furan skeleton facilitates decomposition of the product under the reaction conditions. Also likely is the possibility that the α,β-acetylenic aldehyde starting material is simply less stable than the corresponding ketone at elevated temperatures and is subject to destructive side reactions.

Scheme 34



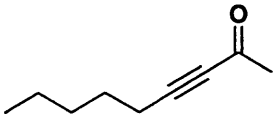
In an attempt to apply this methodology to the synthesis of furans without a substituent at C-9, a substrate with an α,β-acetylenic acylsilane as the heteroenyne was

investigated. Hetero Diels-Alder reactions of vinyl acylsilanes are known,[138] and it was envisioned that this substrate could provide access to the desired furan by removal of the silicon group after furan formation. As shown below, thermolysis of acylsilane **268** provided furan **284** in 36% yield (eq 32). The ^{1}H NMR spectrum for furan **284** exhibits vinyl proton resonances at 6.59 and 5.88 ppm, and the ^{13}C NMR spectrum shows ten carbon-carbon double bond resonances.

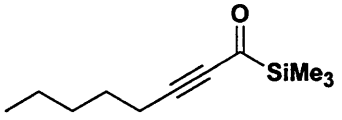


(32)

Although the yield of the transformation was disappointing, it did establish the feasibility of using an acetylenic acylsilane as the heteroenyne. One explanation for the low yield of silyl furan **284** could be the thermal instability of the acylsilane substrate. In an attempt to determine if acylsilane **268** was stable at the elevated reaction temperatures, stability studies were run on model compounds **288** and **289**. After heating ketone **288** in toluene in the presence of 1.1 equivalents of γ-terpinene at 180 °C for 20 h, the compound was recovered in 91% yield after column chromatography. In contrast, after exposure of acylsilane **289** to the same conditions, only 48% yield of the compound could be recovered. TLC analysis of the crude reaction mixture showed the presence of numerous byproducts. These stability problems may relate to the lability of the silyl group; thus, use of a substrate with a larger silyl group may increase the efficiency of the reaction.



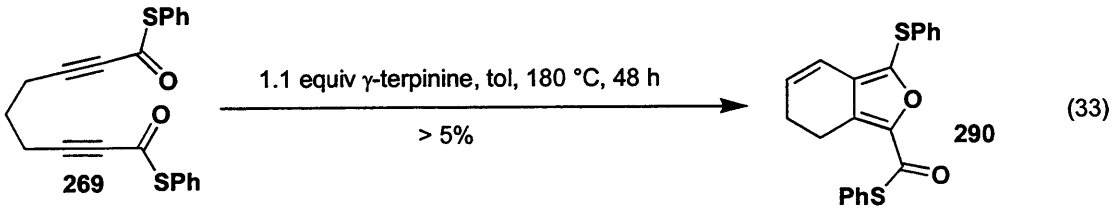
288



289

[138] Reich, H. J.; Kelly, M. J.; Olson, R. E.; Holtan, R. C. *Tetrahedron* **1983**, *39*, 949.

The final type of heteroenyne substrate that was examined was an α,β-acetylenic thiol ester. Again it was hoped that this substrate could provide access to furan products without a substituent at C-9 since removal of the sulfur group from the cylcoadducts by reduction should be straightforward. Unfortunately, thermolysis of bisthiol ester **269** produced only a trace of the desired furan **290** (eq 33). TLC analysis of the crude reaction mixture showed the presence of numerous (>12) products. It is unclear if the lack of success with this substrate relates to the instability of the substrate or product under the reaction conditions, or inherent difficulties with the acetylenic thiol ester acting as a heteroenyne.



(33)

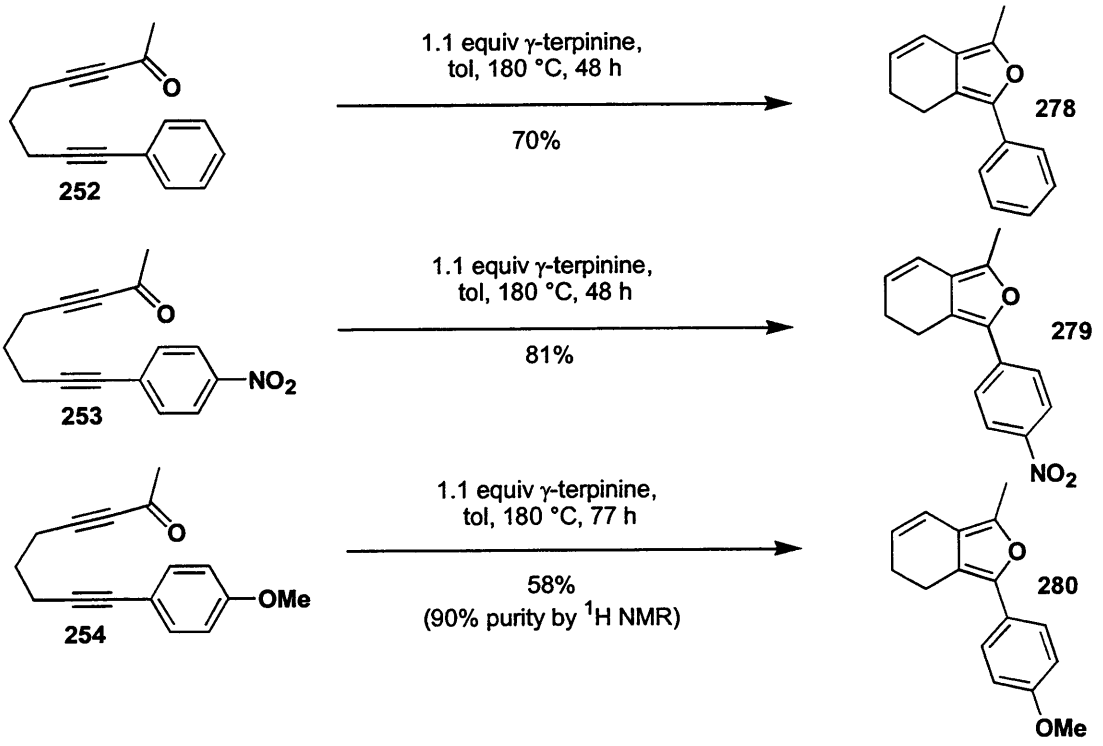
In conclusion, among the heteroenynes examined, to date, the α,β-acetylenic ketones undergo the desired transformation with the greatest efficiency. In addition, it appears that the more delocalized the carbonyl portion of the heteroenyne, the less its tendency to participate as the 4π component of the reaction.

(b) Nature of the Ynonophile

An examination of ynone substrates with a variety of substituents on the alkyne ynonophile provided the opportunity to examine how the nature of the ynonophile affects the transformation. In general, the reaction proceeds the best when an electron-withdrawing group activates the alkyne. This fact indicates that the reaction may be LUMO-controlled with respect to the alkyne ynonophile.

The behavior of three aryl derivatives **252**, **253**, and **254** illustrates the influence the electronic nature of the ynonophile exerts on the reaction (Scheme 35). The desired transformation proceeds in the highest yield (81%) when the alkyne contains an electron-deficient phenyl group and in the lowest yield (~58%) when the alkyne contains an electron-rich phenyl group. The aryl substrates were also used to perform a preliminary analysis of the kinetics of the transformation. Monitoring the disappearance of starting material and appearance of product during the thermolysis of substrates **252** and **254** in sealed NMR tubes in deuterated toluene revealed that the reaction is first order with respect to the ynone substrate. In addition, the half-life for the process is 4.1 h for substrate **252** and 5.2 h for substrate **254**. This corresponds to a relative rate of 1.3 to 1.0. Therefore, if one assumes that the cycloaddition is the rate-limiting step of the reaction, the cycloaddition proceeds slightly faster when the substrate has an electron-poor ynonophile than when it has an electron-rich ynonophile. Combined with the relative efficiency of the three reactions, these kinetic results suggest that the transformation may be LUMO-controlled with respect to the alkyne ynonophile.

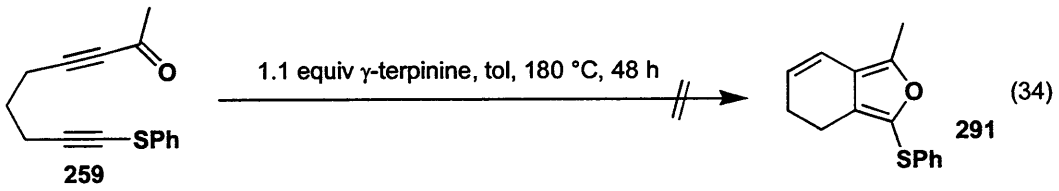
Scheme 35



Further evidence that the reaction may be LUMO-controlled with respect to the alkyne ynonophile was obtained from the behavior of substrates containing either electron-rich or unactivated alkyne units. An acetylenic sulfide may be such an alkyne. Sulfides can donate electron density via a resonance contribution of the lone pairs on sulfur, but sulfides can also withdraw electron density due to the inductive effect. In the case of the uncatalyzed Diels-Alder reaction, it appears the sulfide acts as an electron-donating group, since vinyl sulfides are known to participate in inverse electron demand Diels-Alder reactions with electron-poor dienes.[139] When substrate **259**, which contains a thiophenyl substituent on the alkyne, was subjected to the reaction conditions, none of the desired furan product could be isolated (eq 34). Analysis of the crude reaction mixture

[139] For a review on sulfur functionalities in cycloadditions, see: (a) De Lucchi, O.; Pasquato, L. *Tetrahedron* **1988**, *44*, 6755. For an example of an intramolecular inverse electron demand Diels-Alder reaction of a vinyl sulfide, see: (b) Williams, D. R.; Gaston, R. D. *Tetrahedron Lett.* **1986**, *27*, 1485.

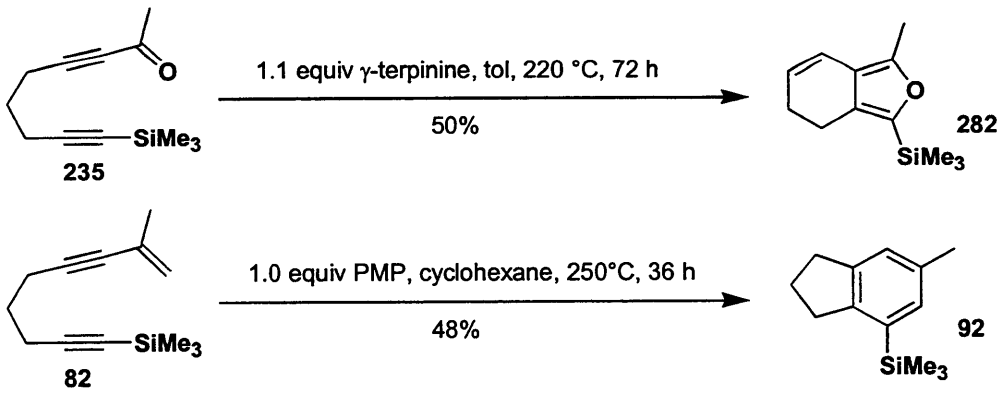
by TLC and ^{1}H NMR revealed the presence of numerous (>10) products. If the sulfide is acting as an electron-donating group as it appears to do in the Diels-Alder reaction, the lack of success of this transformation could indicate that the reaction is LUMO-controlled with respect to the alkyne ynonophile.



(34)

Substrates containing unactivated ynonophiles require higher reaction temperatures for longer amounts of time to produce the desired furan products. This trend mirrors the behavior of the enyne substrates. As shown in Scheme 36, thermolysis of silyl substrate **235** at 220 °C for 72 h produced furan **282** in 50% yield after column chromatography. The analogous enyne substrate also requires an elevated reaction temperature[140] to effect the desired thermal cycloaddition.

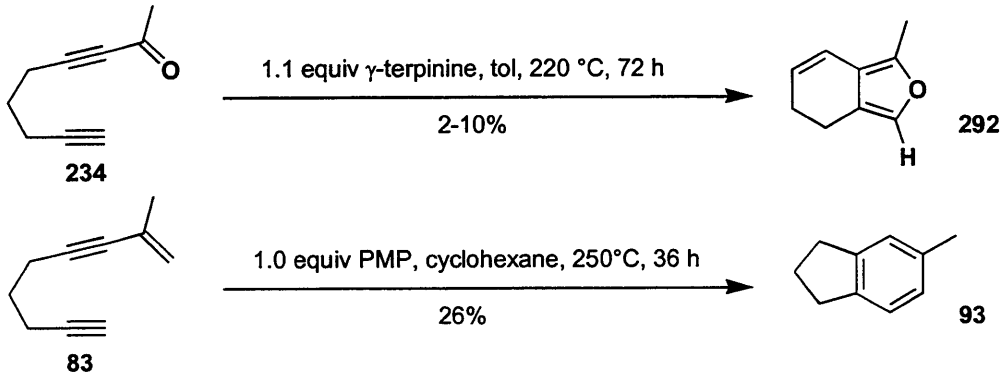
Scheme 36



[140] Thermolysis of the corresponding enyne substrate with a ketone substituent on the alkyne enynophile at 180 °C for 7 h produced the desired aromatic product in 50% yield (See Table 1, Part I, Chapter 3).

Ynone substrates that contain a terminal alkyne as the ynonophile also require higher reaction temperatures to undergo the desired reaction. Again this behavior parallels the behavior of the corresponding enyne substrates. When methyl and phenyl acetylenic ketones **234** and **260** were subjected to the standard thermolysis conditions at 180 °C, no reaction was observed for either substrate. When substrate **234** was heated at 220 °C for 72 h, however, the corresponding furan **292** was isolated in small amounts (Scheme 37). Like aldehyde substrate **263** discussed above, the yield of the reaction fluctuated on various runs. Again it seems that the lack of a substituent on the furan skeleton, in this case on C-2, leads to decomposition of the furan product under the reaction conditions.

Scheme 37

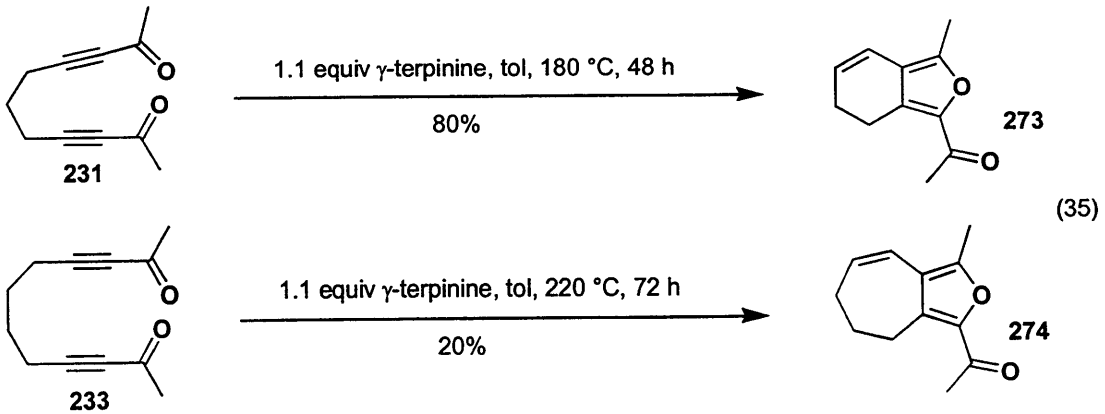


In conclusion, the nature of the substituent on the alkyne ynonophile exerts a strong effect on the efficiency of the transformation. The reaction proceeds best when the alkyne contains an electron-withdrawing activating group and not at all when the alkyne contains an electron-donating activating group. When the ynone cycloaddition substrate contains an unactivated alkyne, higher reaction temperatures must be employed to effect the desired transformation. These results indicate that the reaction may be

LUMO-controlled with respect to the ynonophile. While this behavior mirrors that of the enyne substrates, it is surprising considering the behavior of oxabutadienes in the hetero Diels-Alder reaction. While examples are known of intramolecular Diels-Alder reactions between oxabutadienes and electron-poor dienophiles, the reaction seems to proceed best with electron-rich dienophiles.[69] In general, oxabutadienes tend to participate preferentially in inverse electron demand Diels-Alder reactions that are LUMO-controlled with respect to the oxabutadiene.

(c) Nature of the Tether

The last feature of the transformation that was examined was how the nature of the tether between the ynone and ynonophile affects the reaction. One variable that was examined was the length of the tether. While thermolysis of dione substrate **231** generates furan **273** in high yield, the homologous dione substrate **233** with a four-carbon tether only produces furan **274** in low yield even at more elevated temperatures (eq 35). The ^{13}C NMR spectrum of furan **274** exhibits an alkyl resonance at 12.0 ppm and a carbonyl resonance at 188.8 ppm. In addition, the ^{1}H NMR spectrum shows vinyl proton resonances at 6.08 and 5.72 ppm.

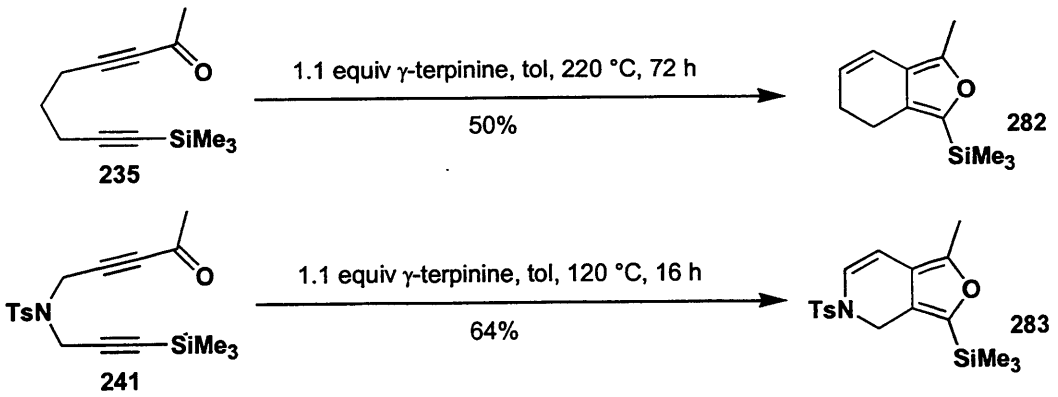


(35)

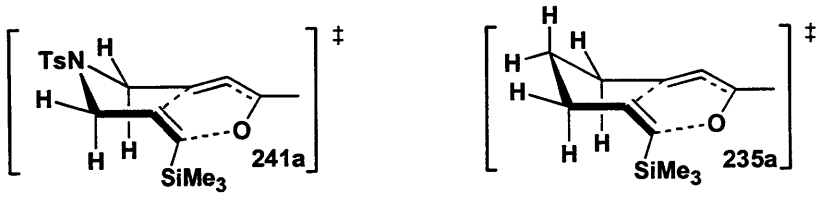
Presumably the low yield of product produced by the reaction of substrate **233** can be attributed to entropic considerations. A longer tether between the two reaction partners introduces more degrees of freedom into the system, and therefore creates more conformations where the ynone and ynonophile cannot attain the proper orientation needed to react.

A second tether variable that was evaluated was the influence of a heteroatom within the chain. As discussed earlier, if the tether contains a heteroatom, then the resulting six-membered ring should often be cleavable to generate a monocyclic 3,4-substituted furan. Based on previous work on the enyne cycloaddition,[57] we believed intramolecular cycloadditions of ynones with a heteroatom in the tether should be feasible. As shown in Scheme 38, not only does substrate **241** that contains a sulfonamide within the tether undergo the desired transformation, but also the reaction occurs at a substantially lower temperature. While conversion of the silyl substrate **235** with an all-carbon tether requires a reaction temperature of 220 °C, the cycloaddition of the corresponding sulfonamide substrate **241** only requires 120 °C. Thermolysis of substrate **241** at 120 °C for 16 h produced furan **283** in 64 % yield.

Scheme 38



One possible explanation for the difference in reactivity between ynones **235** and **241** is an inductive effect of the nitrogen atom in the tether of the latter substrate that could activate the alkyne ynonophile. In addition, the substitution of a nitrogen atom for a carbon atom in the tether may decrease the nonbonding or eclipsing interactions that develop in the five-membered ring of the transition state for the cycloaddition.



Other intramolecular reactions exhibit similar behavior when a carbon atom in the tether is replaced with a heteroatom. The corresponding enyne substrates require lower reaction temperatures when a nitrogen is incorporated in the tether.[57] In addition, similar behavior has been reported in the zirconium-promoted bicyclization of enynes.[141] Negishi and co-workers observed differences in reactivity between a substituted hept-1-en-6-yne substrate containing an amine in the tether and the analogous substrate with an all-carbon tether, but they did not offer an explanation for their findings.

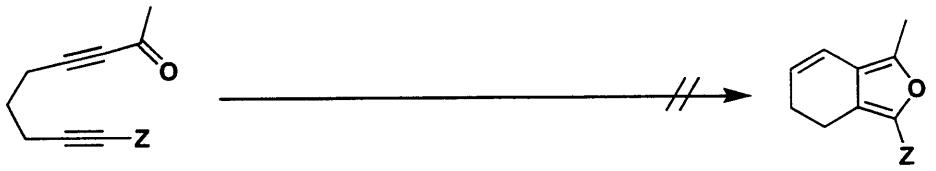
Lewis and Protic Acid Promotion

Since both the intramolecular cycloaddition of conjugated enynes[56,57] and the Diels-Alder reaction of oxabutadienes[69] could be promoted by the addition of Lewis and protic acids, we decided to investigate if these reagents could also promote the ynone cycloaddition. Unfortunately, neither the addition of zinc bromide or methanesulfonic

[141] (a) Negishi, E.; Swanson, D. R.; Cederbaum, F. E.; Takahashi, T. *Tetrahedron Lett.* **1987**, *28*, 917. (b) Negishi, E.; Holmes, S. J.; Tour, J. M.; Miller, J. A.; Cederbaum, F. E.; Swanson, D. R.; Takahashi, T. *J. Am. Chem. Soc.* **1989**, *111*, 3336.

acid promoted the desired transformations (Scheme 39). When dione **231** was stirred at 25 °C in CH_2Cl_2 in the presence of 10.0 equivalents of zinc bromide and 4.0 equivalents of BHT, there was no reaction by either TLC or ^1H NMR analysis of the crude reaction mixture. The same result occurred with phenyl substrate **260**. In addition, when dione **231** was treated with 2.5 equivalents of methanesulfonic acid in CH_2Cl_2 at 0 °C and then warmed to 25 °C, TLC and ^1H NMR analysis of the crude reaction mixture showed no evidence of furan formation, only decomposition of the starting material. Similar results were again observed with phenyl substrate **260**.

Scheme 39



	Z	Conditions	Result
Lewis Acid	COMe	10.0 equiv $ZnBr_2$, 4.0 equiv BHT, CH_2Cl_2, rt, 4 days	No reaction by TLC or ^1H NMR analysis
	Ph	10.0 equiv $ZnBr_2$, 4.0 equiv BHT, CH_2Cl_2, rt 4h then 40°C 20 h	No reaction by TLC or ^1H NMR analysis
Protic Acid	COMe	2.5 MSA, CH_2Cl_2, 0°C→rt, 36h	Uncharacterizable byproducts
	Ph	2.5 MSA, CH_2Cl_2, 0°C→rt, 20 h	Uncharacterizable byproducts

The lack of success in promoting the ynone cycloaddition with Lewis or protic acids may again indicate that the reaction is LUMO-controlled with respect to the alkyne ynonophile. In the enyne cycloaddition, which is believed to be LUMO-controlled with respect to the enynophile, Lewis and protic acid promotion is only successful when the substrate contains a carbonyl group activating the enynophile.[56,57] Presumably, complexation of the Lewis or protic acid with the carbonyl moiety lowers the LUMO of the enynophile thereby promoting the reaction. In the case of the Diels-Alder reactions

of oxabutadienes, the reaction is generally LUMO-controlled with respect to the oxabutadiene.[69] Lewis acid complexation with the carbonyl moiety of the oxabutadiene lowers its LUMO and therefore promotes the reaction.[69c] With the ynone substrates, complexation with the ketone moiety would again lower the frontier molecular orbitals of the ynone. If the reaction is LUMO-controlled with respect to the alkyne ynonophile, however, the complexation would inhibit rather than promote the desired cycloaddition since it would increase the gap between the HOMO of the ynone and the LUMO of the alkyne.

Synthetic Value of the Transformation

Comparison of known methods to synthesize highly substituted 3,4-fused furans and our ynone cycloaddition methodology reveals advantages in the latter process. In general, the ynone substrates are more synthetically accessible than other 3,4-fused furan precursors (see Part II, Chapter 1). The acidity of the acetylenic proton as well as the wide range of carbon-carbon bond forming reactions based on alkynes, including coupling reactions catalyzed by transition-metals, together offer many different methods for constructing conjugated ynones. All of the ynone substrates that were examined in this study could be synthesized in five or fewer steps from commercially available compounds. In addition, our transformation results in a 3,4-fused furan with substitution on both C-2 and C-5. Many of the alternative methods have only been used to produce 3,4-fused furans with either no substituents on C-2 or C-5 or a substituent on only one of those sites. Altering the furan precursors in these alternative methods to generate highly substituted furans could cause synthetic complications (see Part II, Chapter 1). Finally,

the ynone cycloaddition methodology could also be applied to the synthesis of 3,4-substituted furans. As described earlier, if the ynone substrate contains a heteroatom in the tether, the six-membered ring of the corresponding furan could be opened to generate a 3,4-substituted furan. Based on these considerations, we believe our transformation will significantly impact the field of furan synthesis.

Summary

This chapter has outlined the scope of the intramolecular cycloaddition of conjugated ynones and related species. The reaction proceeds with the most efficiency when the heteroenyne is an α,β-acetylenic ketone and the alkyne ynonophile contains an electron-withdrawing substituent. Presumably this indicates the reaction is LUMO-controlled with respect to the alkyne ynonophile. In addition, the transformation proceeds at lower temperatures with a sulfonamide tether between the two reactive components rather than an all-carbon chain. The next chapter will discuss our studies on the mechanism of furan formation.

Chapter 4

Mechanistic Studies on the Generation of Polycyclic Furans from the Cycloaddition Reactions of Conjugated Ynones

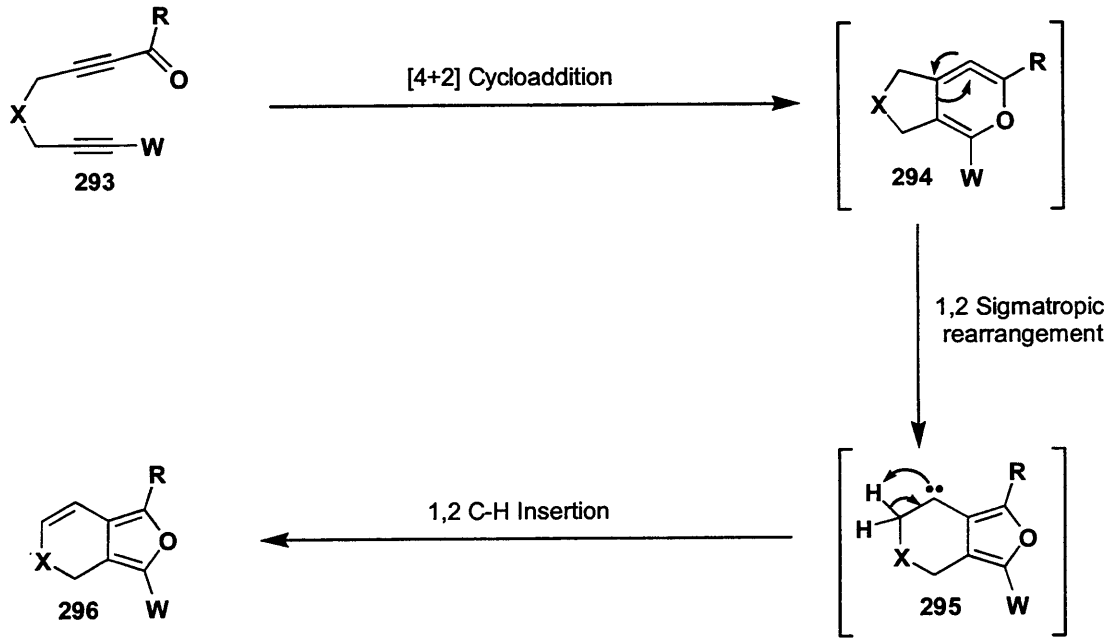
Introduction

The preceding chapter discussed the scope of the cycloaddition reactions of conjugated ynones and related heteroenynes. This chapter will detail our examination of the mechanism of those transformations. The first section outlines our mechanistic proposal to account for furan formation, and then the second section will describe precedent for the steps in our proposed mechanism from the literature and previous studies on the mechanism of the related enyne cycloaddition. In addition, this section describes the experimental evidence we have obtained to support our mechanistic proposal.

Mechanistic Proposal

Our mechanistic proposal to account for furan formation from the thermolysis of conjugated ynones and related heteroenynes is outlined in Scheme 40. First, we suggest an intramolecular [4+2] cycloaddition occurs to furnish strained heterocyclic allene **294**. A subsequent 1,2-sigmatropic rearrangement of allene **294** then generates carbene intermediate **295**, which undergoes a 1,2-C-H insertion reaction to furnish the observed furan product **296**.

Scheme 40



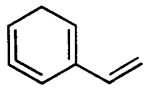
Support for the Proposed Mechanism

The following sections describe in detail the literature precedent for proposing the intermediacy of heterocyclic allene **294** and furfurylcarbene **295** in the generation of furan **296**. In addition, these sections include a presentation of the experimental evidence we have obtained to support the involvement of these intermediates in the reaction pathway.

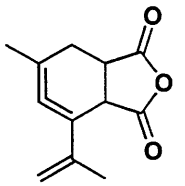
(a) Evidence in Support of the [4+2] Cycloaddition Step

The cycloaddition step proposed in Scheme 40 finds precedent in the related reactions of conjugated enynes. As discussed in Part I, to the best of our knowledge Dykstra was the first person to propose a cyclic allene intermediate in an enyne cycloaddition. To account for styrene formation from the thermolysis of vinylacetylene in the presence of acids, Dykstra proposed the intermediacy of cyclic allene **297** resulting

from a "Diels-Alder diene reaction" (Part I, Chapter 2).[46] No mechanistic evidence, however, was offered to support this proposal. Butz and co-workers also proposed the intermediacy of a cyclic allene in the intermolecular double cycloaddition of dienynes (Part I, Chapter 2).[48] For example, they suggested that cyclic allene **64** could be an intermediate in the double cycloaddition of maleic anhydride with 2,5-dimethyl-hexa-1,5-dien-3-yne.[48a] Again, no mechanistic experiments were performed to support this proposal.



297



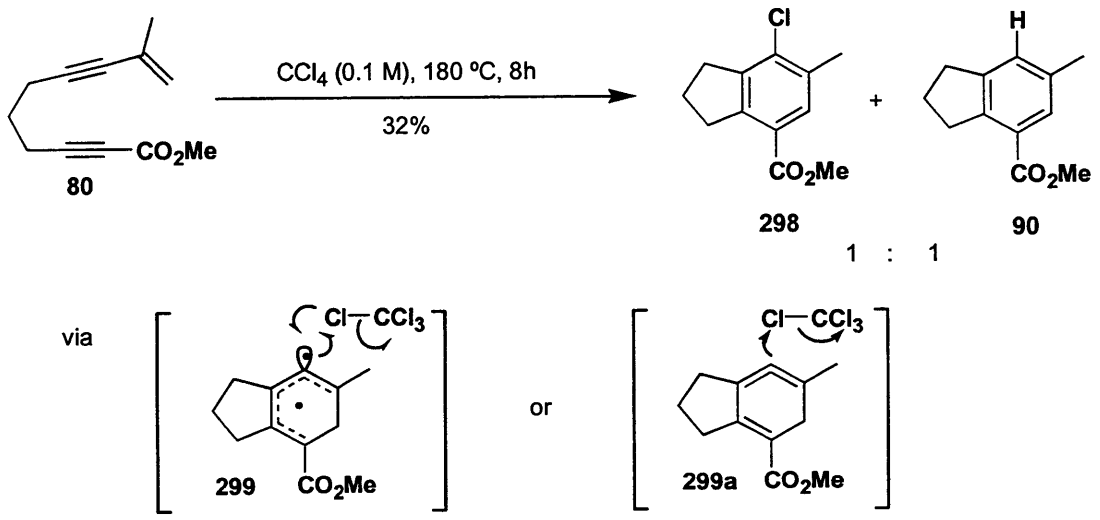
64

Before our laboratory began its exploration of the scope and mechanism of the intramolecular enyne cycloaddition, no experimental evidence existed in the literature to support the intermediacy of a cyclic allene in the transformation. As discussed earlier, if a cyclic allene was formed in the cycloaddition of an enyne with an alkyne, it is possible it would be in equilibrium with the corresponding biradical species (Part I, Chapter 1). Janoscheck has calculated that the energy barrier between the allene and biradical forms of the parent system, 1,2,4 cyclohexatriene, is only 2 kcal/mol.[29] To support the intermediacy of a cyclic allene and/or a biradical in the thermal enyne cycloaddition reaction, our laboratory conducted experiments designed to trap these species.

As shown below, Dr. Alexandra Gould found that heating enyne **80** at 180 °C for 8 h in carbon tetrachloride provided a 1:1 mixture of chloroindan **298** and indan **90** (Scheme 41).[56] Presumably chlorine incorporation occurs from a radical substitution

reaction between biradical intermediate **299** and carbon tetrachloride. It is possible, however, that due the high reaction temperature and the fact that cyclic allene intermediate **299a** is very strained, that chlorine incorporation arises from a nucleophilic substitution reaction between the allene intermediate and carbon tetrachloride. No chlorine incorporation was observed when indan **90** was heated at 180 °C for 8 h in the presence of carbon tetrachloride, confirming that chlorine incorporation occurs before the formation of the aromatic product. It can be concluded, therefore, that the isolation of the chlorinated product **298** supports the existence of a biradical and/or a cyclic allene intermediate in the thermal enyne cycloaddition reaction.

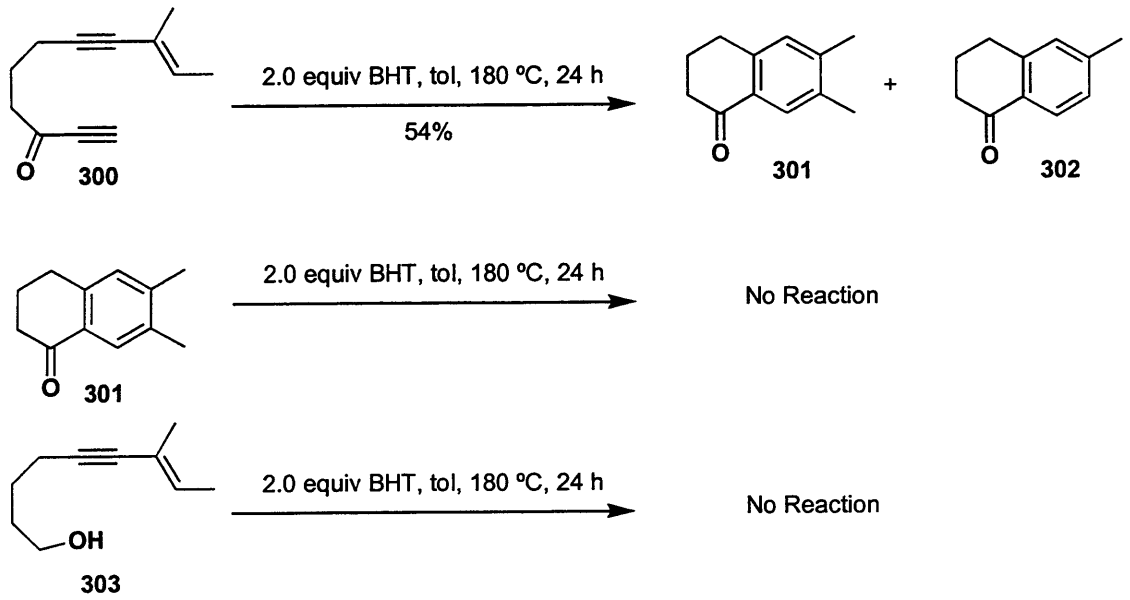
Scheme 41



While exploring the effect of substitution on the enyne, Dr. Gould also observed the formation of a byproduct that supports the intermediacy of a biradical. Heating enyne **300** at 180 °C for 24 h resulted in the formation of a 1:1 mixture of tetralone **301** and demethylated tetralone **302** in 54% combined yield (Scheme 42).[56] Control experiments indicate that the demethylation occurs through an intermediate involved in the

cycloaddition since no demethylation was observed when either tetralone **301** or alcohol **303** were subjected to the reaction conditions. All attempts to determine the fate of the methyl group in the reaction were unsuccessful,[56] but it was determined that the amount of demethylated product decreases at lower reaction temperatures.[57]

Scheme 42



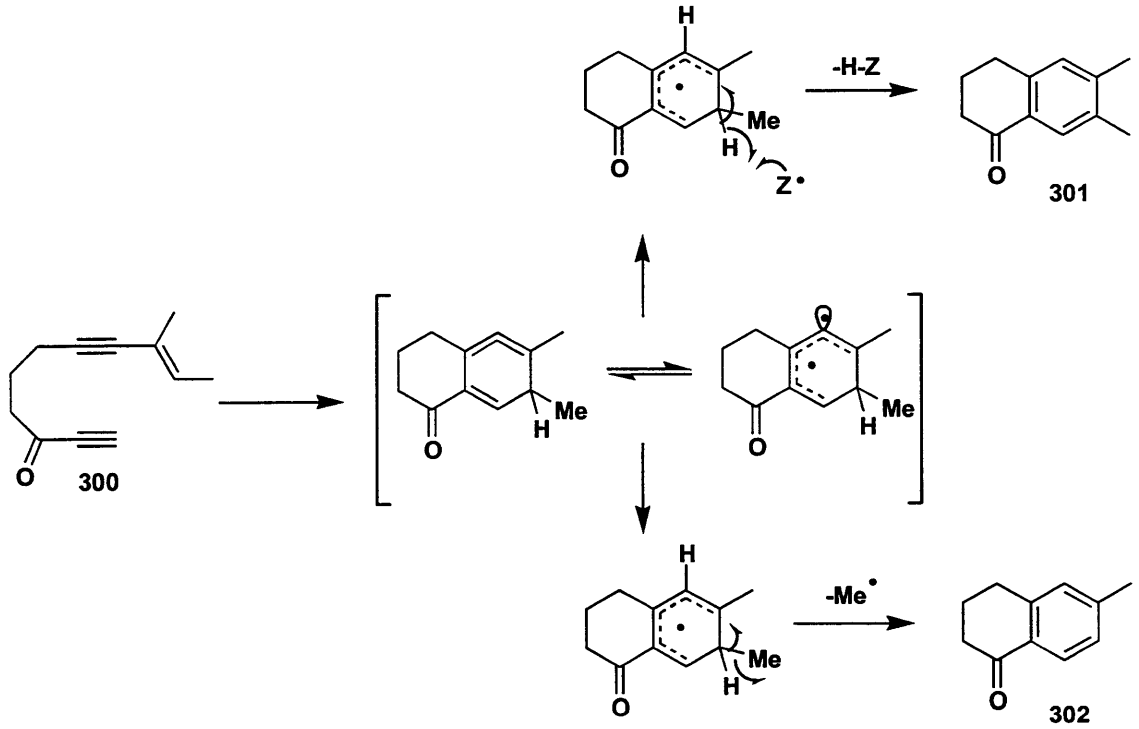
A mechanism to account for the demethylation phenomenon is outlined below (Scheme 43). The "normal" reaction pathway we have proposed for the enyne cycloaddition involves bimolecular H-atom abstraction to provide the dimethyl-substituted product **301**. An alternative pathway involves a unimolecular fragmentation with loss of the methyl group to produce the monomethyl-substituted product **302**.[142,143] The temperature dependence of the extent of demethylation could be due to the entropic

[142] For examples of related radical fragmentation processes, see: (a) Hart, H.; DeVrieze, J. D. *Tetrahedron Lett.* **1968**, 4257. (b) Franz, J. A.; Camaioni, D. M. *J. Org. Chem.* **1980**, *45*, 5247. For the reaction of methyl radicals with phenols, see: (c) Mulcahy, M. F. R.; Tucker, B. G.; Williams, D. J.; Wilmshurst, J. R. *Aust. J. Chem.* **1967**, *20*, 1155.

[143] For examples of unimolecular methyl and alkyl fragmentations, see: (a) Ingold, K. U. In *Free Radicals*; Kochi, J. K., Ed.; John Wiley & Sons: New York, 1973; Vol. I, pp 99-102. (b) Kochi, J. K.; Krusic, P. J. *J. Am. Chem. Soc.* **1969**, *91*, 3944. (c) Gray, P.; Williams, A. *Chem. Rev.* **1959**, *59*, 239.

contribution to the free energy of activation ($\Delta G^{\ddagger} = \Delta H^{\ddagger} - T\Delta S^{\ddagger}$). The entropy of activation ($\Delta S^{\ddagger}$) is expected to be positive (favorable) for the fragmentation pathway, but negative (unfavorable) for the H-atom abstraction pathway. Higher reaction temperatures should thus favor the fragmentation pathway, since higher temperatures amplify the contribution of the entropy term to the overall activation energy ($\Delta G^{\ddagger}$) for the transformation.

Scheme 43

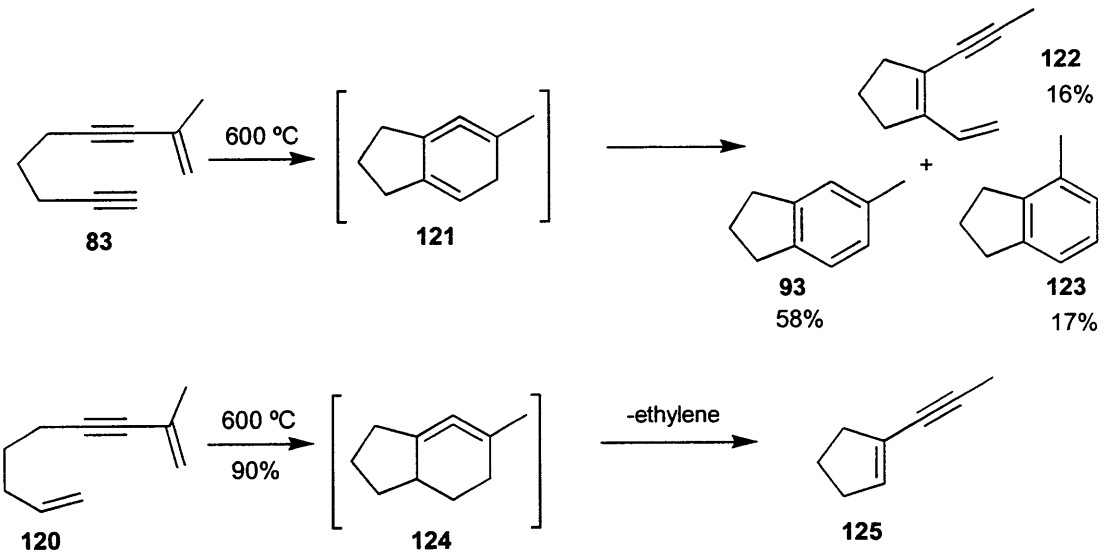


During the course of our studies, R. P. Johnson and co-workers reported experimental evidence that supports the intermediacy of cyclic allenes in enyne cycloadditions (Part I, Chapter 3). Exposure of enynes **83**[144] and **120** to flash vacuum pyrolysis (FVP) conditions produces ring-opened products **122** and **125** (Scheme 44).[33] Johnson and co-workers proposed that these products form via a six-electron

[144] Cycloaddition of this enyne to afford indan **93** had previously been reported by our group.[32]

electrocyclic ring opening and a cycloreversion of cyclic allene intermediates **121** and **124**. As discussed earlier (see Part I, Chapter 3), formation of the rearranged cycloaddition product **123** from the FVP reaction of enyne **83** is also consistent with the intermediacy of a cyclic allene. To the best of our knowledge, Johnson's work represents the first experimental evidence that specifically supports the intermediacy of a cyclic allene in the enyne cycloaddition reaction.

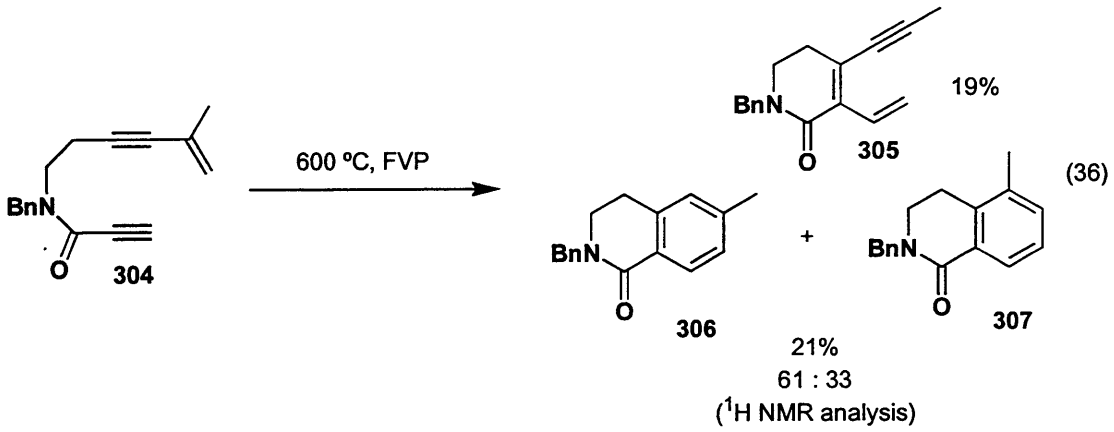
Scheme 44



all yields are GC yields corrected for recovered starting material with 50-80% conversion.

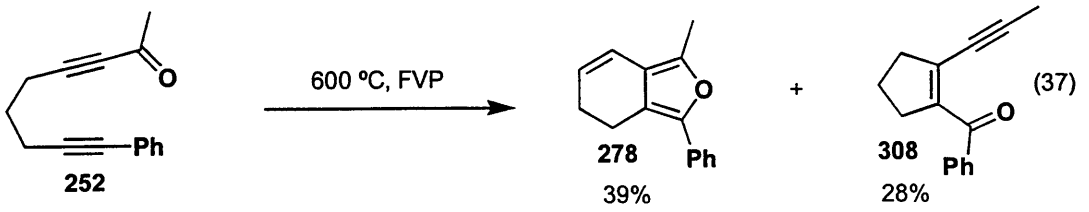
In contrast to Johnson's results, researchers in our laboratory have never observed ring-opened products in our *solution* thermolyses of conjugated enynes. We believe the high temperatures employed under the FVP conditions enable the cyclic allene intermediate to access this alternative pathway. To test this hypothesis and to determine if synthetically important "activated" enyne substrates would also yield byproducts consistent with a cyclic allene, one of our enyne substrates was subjected to FVP conditions. Dr. Brenda Palucki found that pyrolysis of enyne **304** at 600 °C produced

three major products: the ring opened lactam **305**, and aromatic lactams **306** and **307** (eq 36).[57] These results mirror those obtained by Johnson and further support the intermediacy of a cyclic allene in the intramolecular cycloaddition reactions of conjugated enynes.



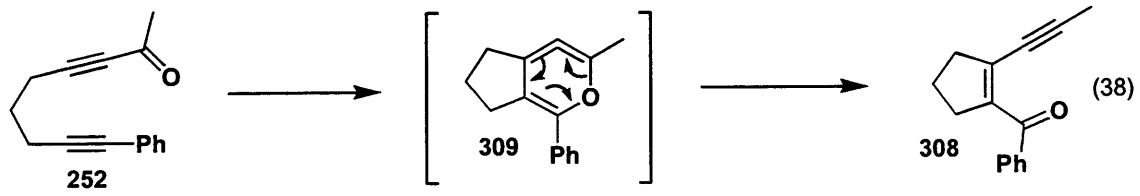
(36)

To determine whether our heteroenyne system would yield products consistent with a heterocyclic allene intermediate, we decided to expose an ynone substrate to the FVP conditions. Isolation of the corresponding ring-opened product would support our proposal that a heterocyclic allene intermediate is involved in furan formation. Consequently, ynone **252** was subjected to FVP conditions and two major products were formed: furan **278** and the unsaturated ketone **308** (eq 37). The ^{13}C NMR spectrum of ketone **308** exhibits two acetylenic carbon resonances at 97.3 and 76.0 ppm, a carbonyl carbon resonance at 195.4 ppm, and an alkyl carbon resonance at 4.4 ppm. In addition, the IR spectrum of ketone **308** shows an acetylenic carbon-carbon bond stretching band at 2220 cm^{-1} and a carbonyl stretching band at 1630 cm^{-1}.



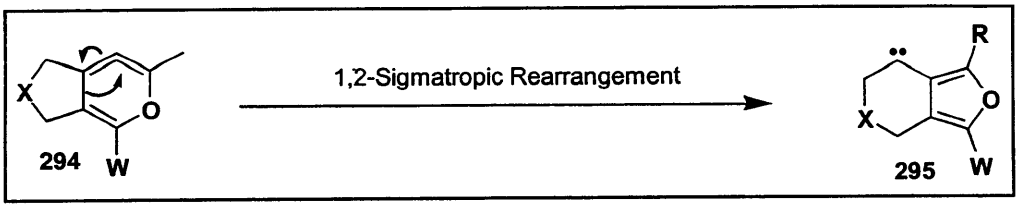
(37)

The isolation of ketone **308** is consistent with the intermediacy of a heterocyclic allene. As shown below, the ring-opened product can be formed via a six-electron electrocyclic ring opening of the proposed heterocyclic allene intermediate **309** (eq 38). We are unable to account for the formation of this byproduct by any other pathway. Thus, this experiment supports the first step in the proposed mechanism of furan formation, an intramolecular [4+2] cycloaddition to generate a strained heterocyclic allene intermediate (Scheme 40). It should be noted that byproduct **308** was not observed in the solution thermolysis of **252** at 180 °C; as discussed earlier, we believe that only at high temperatures can the heterocyclic allene intermediate access the electrocyclic ring opening pathway.



(38)

(b) Evidence in Support of the 1,2-Sigmatropic Rearrangement Step

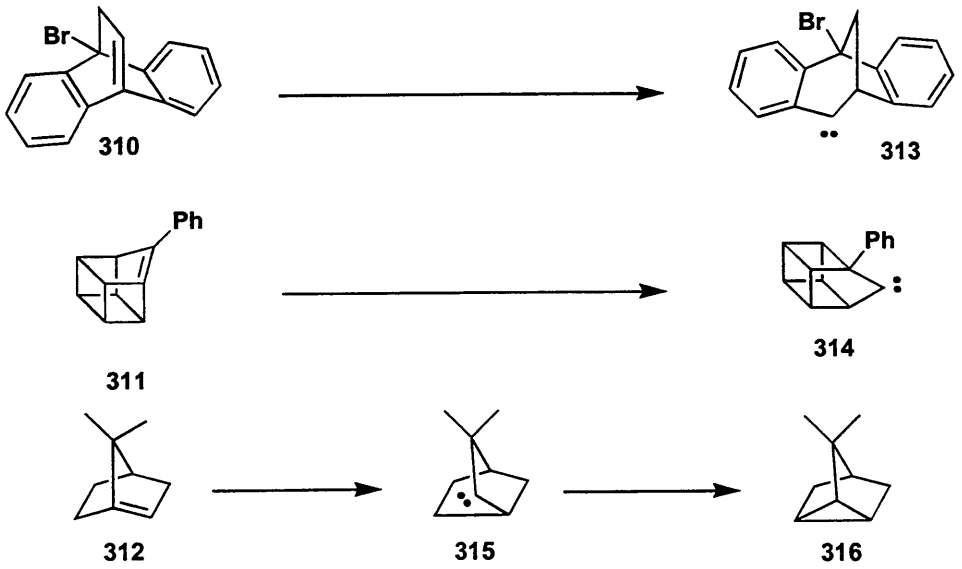


The next step in our proposed mechanism involves a 1,2-sigmatropic rearrangement of strained heterocyclic allene **294** to form furfurylcarbene **295**. Precedent for this rearrangement can be found in the literature in the thermal rearrangements of certain strained π systems to carbenes, the gas phase rearrangements of 1,2,4,6-

cycloheptatetraenes to benzylic carbenes, and the recently reported gas phase rearrangement of thiacyclohexa-2,3,5-triene to thiophenenyl carbene. The following sections will review the literature in these areas as well as detail our mechanistic experiments to support the intermediacy of a carbene in the reaction pathway.

As noted above, precedent for the proposed rearrangement can be found in the rearrangement of certain highly strained π systems to carbenes. As shown in Scheme 45, examples of such a transformation include the rearrangements of bridgehead olefins **310**,[145] **311**,[146] and **312**.[147] In all three cases the strained alkenes were generated *in situ*, and in two of the cases the researchers were able to provide evidence for a carbene intermediate by trapping experiments.[137,138] Carbene **313** was successfully trapped with DMSO, THF, and cyclohexene, while carbene **314** was trapped with various olefins and ethanol. In the third case, the researchers speculated that carbene **315** had been produced due to the isolation of the corresponding nortricyclene **316** from the reaction solution.[139]

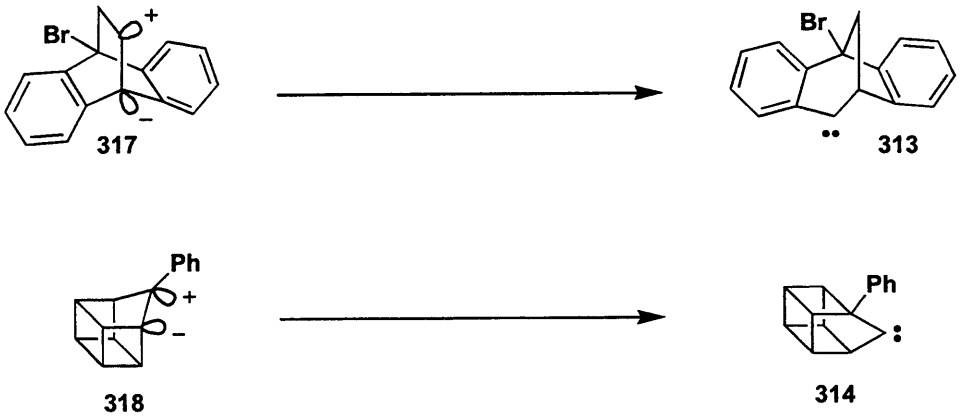
Scheme 45



[145] Chan, T. H.; Massuda, D. *J. Am. Chem. Soc.* **1977**, *99*, 936.
[146] Eaton, P. E.; Hoffmann, K-L. *J. Am. Chem. Soc.* **1987**, *109*, 5285.
[147] Barton, T. J.; Yeh, M-H. *Tetrahedron Lett.* **1987**, *28*, 6421.

In an attempt to explain this unusual rearrangement, two of the research groups commented on the nature of the bridgehead olefins.[137,138] Citing the theory[148] that the zwitterionic state of a 90°-twisted ethylene would become stabilized relative to the diradical state if the alkene is substituted by polar substituents or if one of the CH_2 groups is pyramidal, the researchers proposed that the rearrangements of olefins **310** and **311** occur from the zwitteronic species **317** and **318**, respectively (Scheme 46). A Wagner-Meerwein shift could then generate carbene intermediates **313** and **314**.

Scheme 46



Precedent for our proposed rearrangement also can be found in the gas phase interconversion between 2,4,6-cycloheptatetraenes and phenyl carbenes.[149] An example of this transformation is shown below in the formation of tropone (**323**) and *o*-cresol (**324**) from the pyrolysis of either meta or para tetrazoles **319** and **320** (eq 39).[149b]

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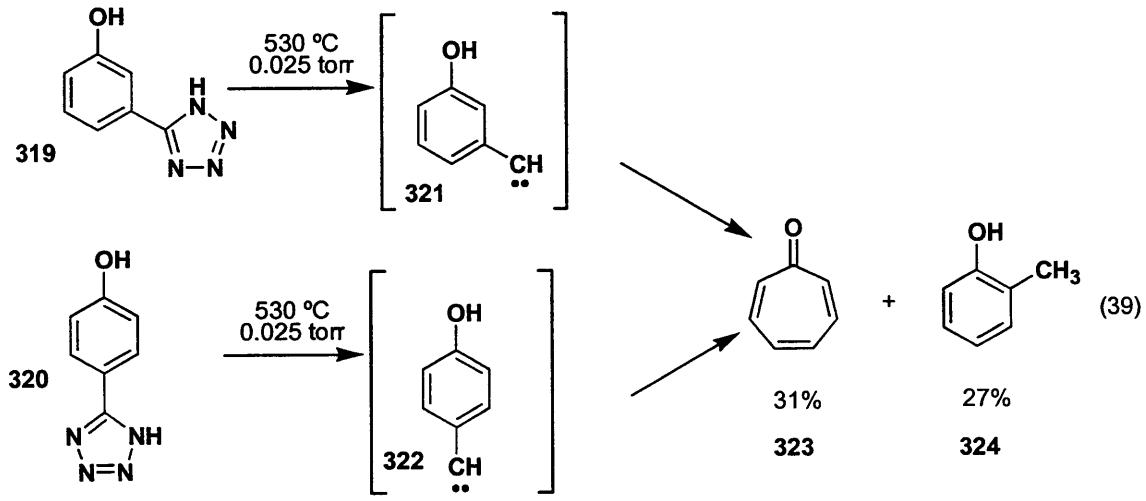
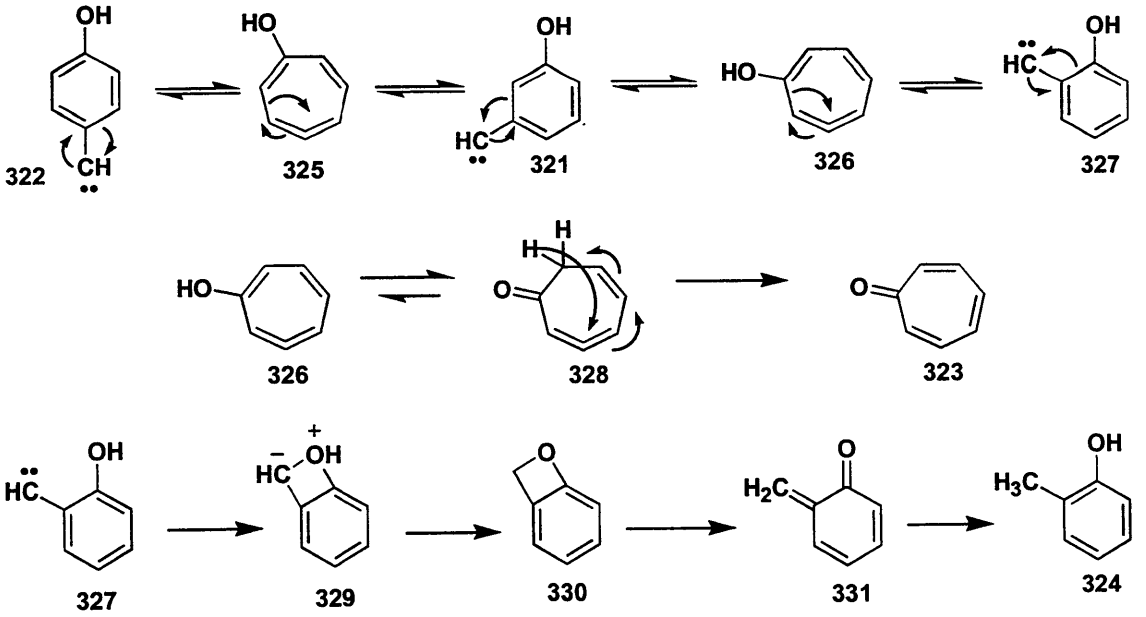
[148] (a) Salem, L. *Science* **1976**, *191*, 822. (b) Brooks, B. R.; Schaefer, H. F. III *J. Am. Chem. Soc.* **1979**, *101*, 307.

[149] For recent reports on the rearrangement, see (a) Patterson, E. V.; McMahon, R. J. *J. Org. Chem.* **1997**, *62*, 4398. (b) Golden, A. H.; Jones, M. Jr. *J. Org. Chem.* **1996**, *61*, 4460. (c) Schreiner, P. R.; Karney, W. L.; von Ragué Schleyer, P.; Thatcher-Borden, W.; Hamilton, T. P.; Schaefer, H. F. III *J. Org. Chem.* **1996**, *61*, 7030. (d) Kumar, A.; Narayanan, R.; Shechter, H. *J. Org. Chem.* **1996**, *61*, 4462. (e) Wong, M. W.; Wentrup, C. *J. Org. Chem.* **1996**, *61*, 7022. For a recent review, see (f) Gaspar, P. P.; Hsu, J-P.; Chari, S.; Jones, M. Jr. *Tetrahedron* **1985**, *41*, 1479.



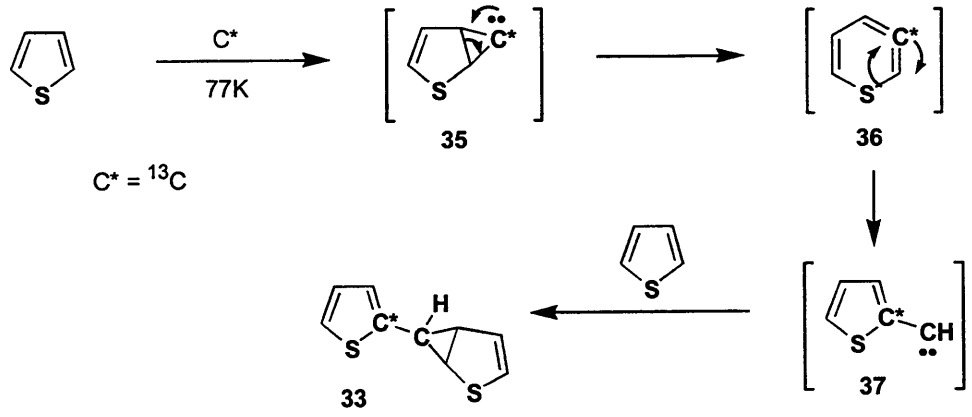
To explain the formation of these products, Jones and co-workers proposed a ring-expansion/ring-contraction mechanism that involves the interconversion of the para, meta, and ortho carbenes with the corresponding cycloheptatetraenes (Scheme 47). In this mechanism, the formation of tropone (**323**) arises from ketonization of one of the seven-membered rings followed by a [1,5] hydrogen shift. The *o*-cresol (**324**) is produced from para carbene **327** by a cascade sequence that involves the intermediacy of ylide **329**, benzooxetene **330**, and *o*-benzoquinone methide (**331**).

Scheme 47



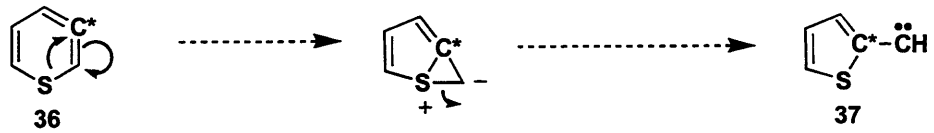
Perhaps the strongest literature precedent for the generation of furfurylcarbene **295** from a 1,2 sigmatropic rearrangement of heterocyclic allene **294** is the recently reported thiacyclohexatriene-thiophenyl carbene rearrangement.[25] As shown below, one of the products of the condensation of thiophene with carbon atoms enriched in ^{13}C, is the tricyclic compound **33** (Scheme 48). To account for the formation this product, Shelvin and co-workers proposed that the heterocyclic allene intermediate **36**[150] rearranges to carbene **37**, which subsequently reacts with another thiophene to generate tricycle **33**.

Scheme 48

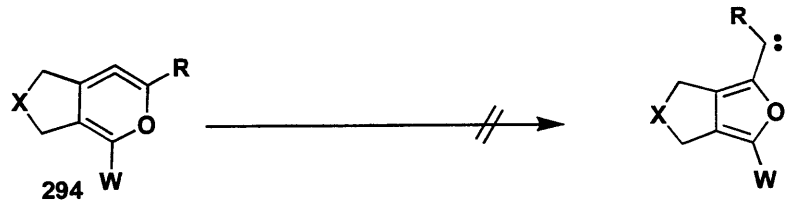


It is interesting to note that Shelvin and co-workers do not observe products resulting from the formation of 3-thienylmethylene (**332**), the carbene that would result if a rearrangement analogous to the one we propose for our heterocyclic allene had occurred. While no rationale was suggested as to why heterocyclic allene **36** rearranges exclusively to 2-thienylmethylene (**37**), perhaps the rearrangement proceeds through an ylide intermediate due to the polarizability of the lone pairs on the sulfur.

[150] For a discussion on the nature of this heterocyclic allene, see: Part I, Chapter 1.

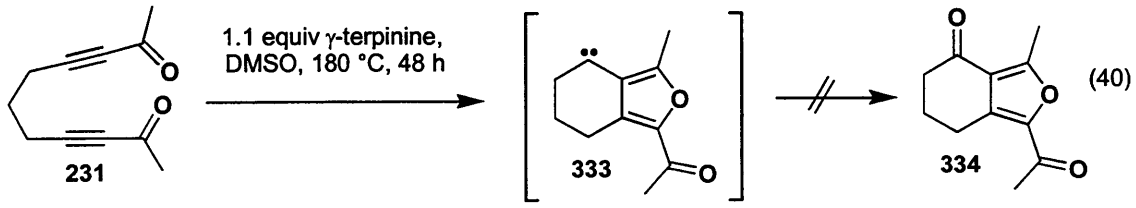


The lack of formation of the 2-furfurylcarbene in our system also deserves discussion. Our substrate incorporates an oxygen as the heteroatom, and perhaps the formation of an ylide intermediate is not as facile with this less polarizable heteroatom. In addition, if rearrangement to the 2-furfurylcarbene were to occur, it would generate a very strained ring system.



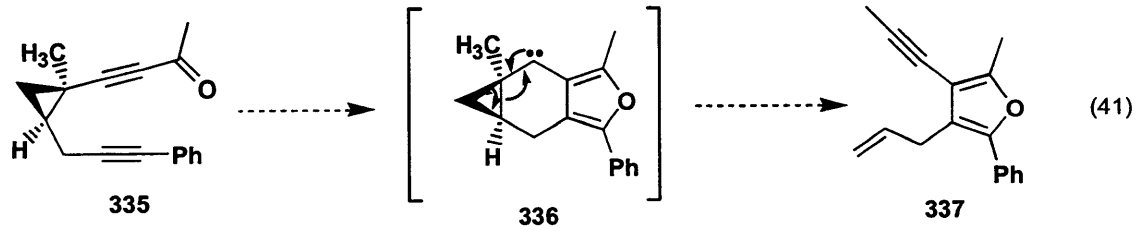
A key goal of our mechanistic investigation was to gather experimental evidence that furfurylcarbene **295** was an intermediate in furan formation. Initially, we attempted to trap this carbene intermediate by using DMSO as the reaction solvent (eq 40). Unfortunately, thermolysis of ynone **231** under the indicated conditions led to none of the desired trapping product **334** and afforded only uncharacterizable black tar. Although other compounds could conceivably be employed as trapping agents, we abandoned this approach due to our concern that the extremely facile intramolecular C-H insertion would occur before intermolecular trapping by the solvent. Note that in the successful trapping

experiments described above with carbenes **313** and **314**, C-H insertion is not expected to occur since it would result in the formation of a very strained bridgehead olefin.



(40)

As an alternative plan to provide evidence in support the intermediacy of a carbene, we considered designing an ynone cycloaddition substrate that would generate a carbene which would then undergo a characteristic fragmentation reaction. Isolation of the fragmentation product would then constitute evidence that a carbene intermediate is involved in the reaction pathway. The ynone substrate chosen for study was cyclopropane **335**, which contains a cyclopropyl group fused to the tether between the ynone and alkyne ynonophile. Once formed, we expected that the carbene intermediate **336** would fragment to generate the 3,4-subsituted furan **337** (eq 41). We believe that no other intermediate or pathway could give rise to this specific tetrasubstituted furan.



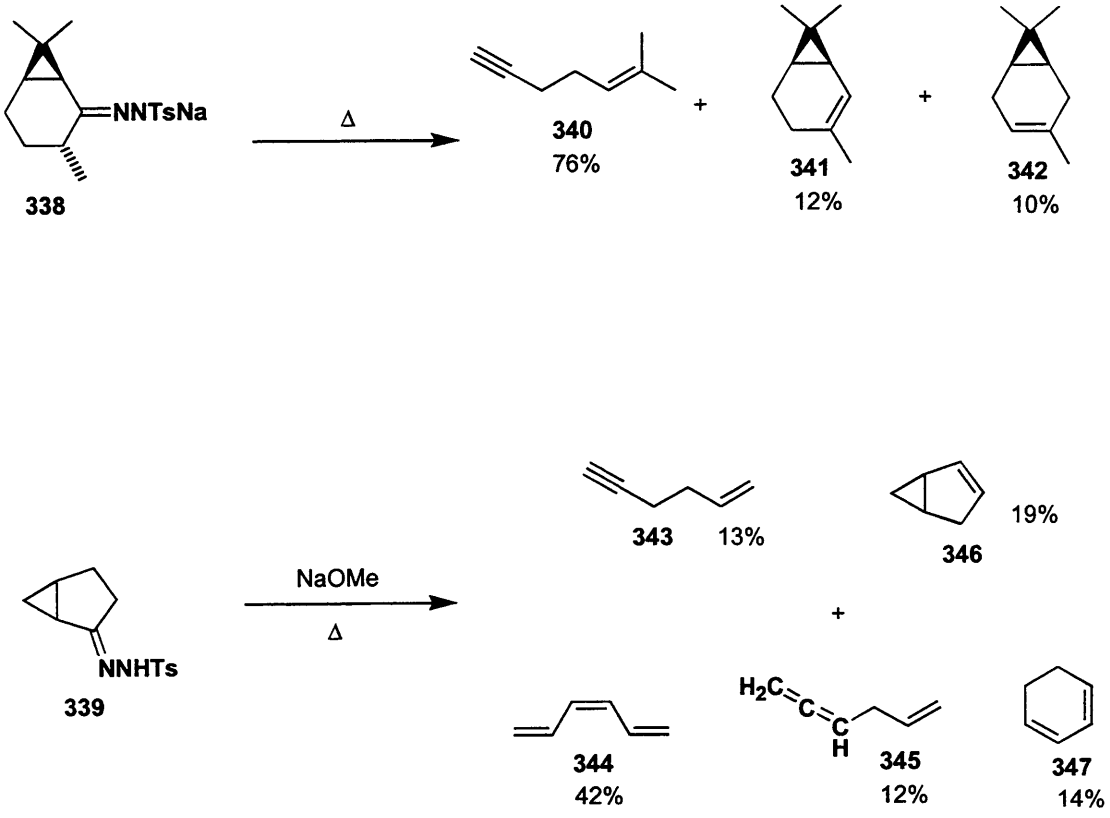
(41)

A few examples of the fragmentation of α-cyclopropyl carbenes have been reported in the literature.[151] As illustrated in Scheme 49, when α-cyclopropyl carbenes

[151] For two examples, see: (a) Wheeler, J. W.; Chung, R. H.; Vaishnav, Y. N.; Shroff, C. C. *J. Org. Chem.* **1969**, *34*, 545. (b) Freeman, P. K.; Kuper, D. G. *J. Org. Chem.* **1965**, *30*, 1047. For a theoretical discussion of the energetics of the fragmentation reaction of cyclopropylmethylene, see: (c) Shevlin, P. B.; McKee, M. L. *J. Am.. Chem. Soc.* **1989**, *111*, 519.

were generated from the corresponding tosylhydrazone salts by either application of heat to the preformed salt[144a] or treatment of the tosylhydrazone with sodium methoxide,[144b] fragmentations of the type we propose occurred to produce enynes **340** and **343**.[152]

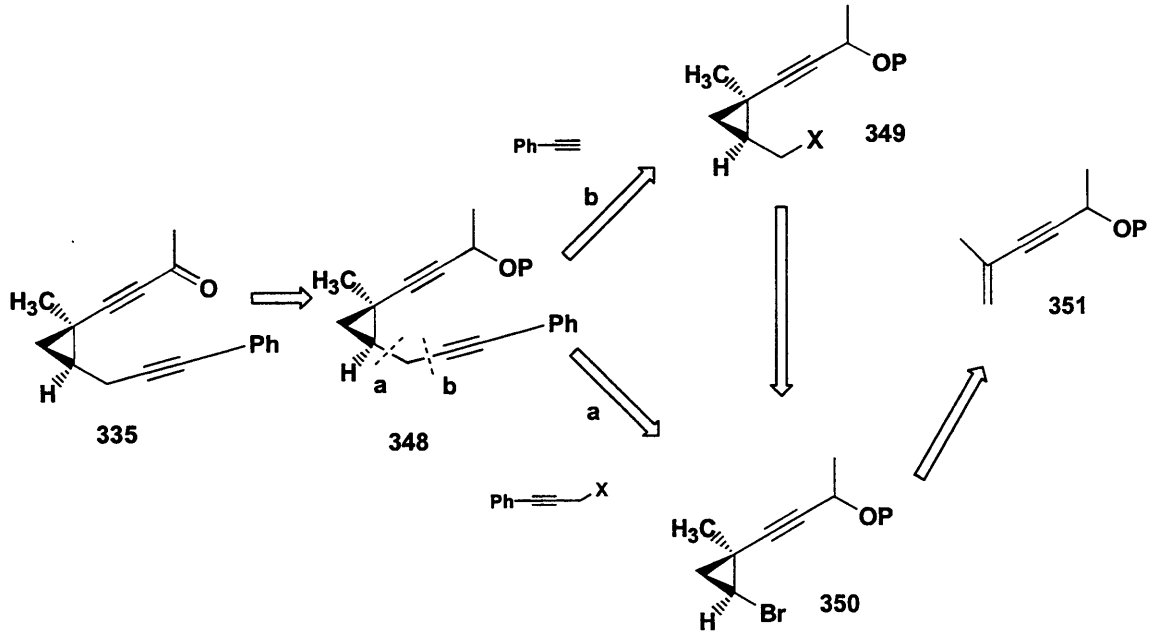
Scheme 49



As shown in Scheme 50, a retrosynthetic analysis of the proposed ynone cycloaddition substrate **335** reveals two reasonable disconnections, a and b. Both routes require the synthesis of bromocyclopropane intermediate **350**, and these approaches were investigated simultaneously.

[152] The allene and diene products **344** and **345** are also believed to arise from fragmentations via isomerization of alkyne **343** under the basic conditions.

Scheme 50

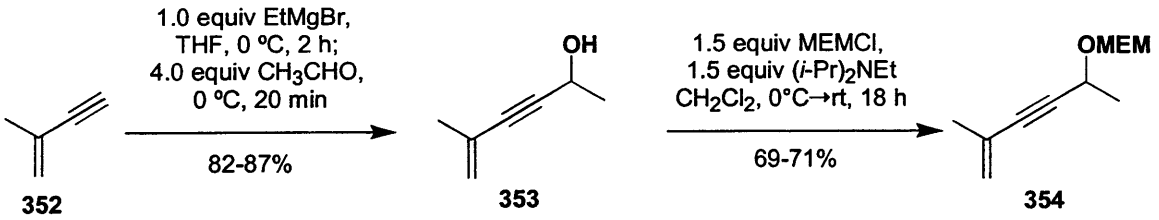


It should be noted that the cis orientation between the bromine atom and alkyne moiety in the key bromocyclopropane **350** is absolutely necessary, since in order for the cycloaddition to occur, the ynone and alkyne ynonophile in **335** must possess a cis orientation. It was envisioned that the desired bromocyclopropane **350** could be created from a dibromocyclopropane precursor through selective removal of the bromine atom cis to the methyl group (vide infra). The dibromocyclopropane substrate, in turn, could be derived from protected enyne alcohol **351**.

As shown in Scheme 51, the MEM-protected enyne alcohol **354** was synthesized in two steps from commercially available isopropenylacetylene (**352**). First, construction of the alcohol **353** was accomplished in excellent yield using the method of Trost,[114] and then the hydroxyl group was protected using the classic conditions pioneered by Corey.[153]

[153] Corey, E.; J.; Gras, J. –L.; Ulrich, P. *Tetrahedron Lett.* **1976**, 809.

Scheme 51



The next stage of the synthesis involved the conversion of protected enyne alcohol **354** to bromocyclopropane **356** (Scheme 52). A survey of the literature revealed that various methods are available for the first step of this sequence, the generation of a dibromocyclopropane via addition of dibromocarbene to an alkene.[154] Conditions that have been used specifically to generate propargylic dibromocyclopropanes include the classic Doering conditions[155] as well as phase transfer conditions.[156] In general, enynes undergo cyclopropanations less readily than simple alkenes; presumably the electron-withdrawing nature of the alkyne group deactivates the alkene toward reaction with dibromocarbene.

In our hands, use of the Doering conditions provided the desired dibromocyclopropane in only 33-38% yield. Support for successful cyclopropanation was found in the ^{13}C NMR spectrum that exhibits cyclopropyl carbon resonances at 38.5, 34.5, and 23.8 ppm. No evidence of dibromocarbene addition to the alkyne was observed; the other isolable compound was unreacted starting material. Dibromocyclopropane **355** is assumed to be a 1:1 mixture of diastereomers although the

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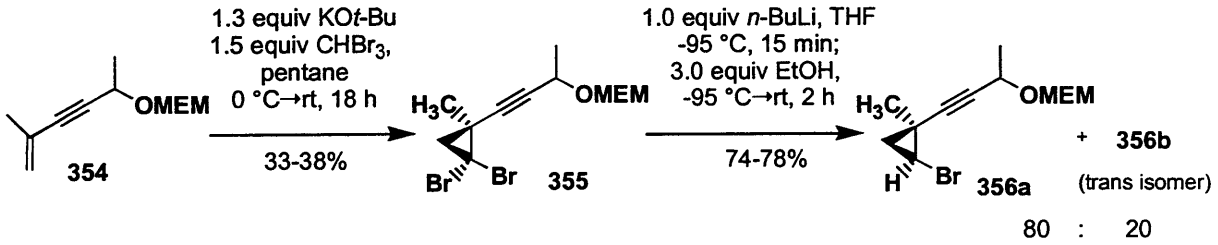
[154] Dibromocyclopropanes are conveniently prepared by the reaction of alkenes with (a) $CHBr_3$-KO-*t*-Bu (Doering, W. von E.; Hoffmann, A. K *J. Am. Chem. Soc.* **1954**, *76*, 5162.) (b) $CHBr_3$-NaOH-*n*-Bu_3N (Markosa, M.; Fedorynski, M. *Rocz. Chem.* **1976**, *50*, 2223.) (c) $PhHgCBr_3$ (Seyferth, D. *Acc. Chem. Res.* **1972**, *5*, 65.)

[155] For examples of the successful generation of dihalocyclopropanes from enynes using these conditions, see: (a) D'yakonov, A.; Danilkina, L. P. *Zh. Obshch. Khim* **1964**, *34*, 738. (b) Vo-Quang, L.; Cadiot, P. *Bull. Soc. Chim. Fr.* **1965**, 1518.

[156] (a) Ivanov, A. L.; Domnin, I. N. *Zh. Obshch. Khim* **1988**, *24*, 2547. (b) Denisov, V. R.; Lupaeva, M. L.; Alekseeva, E. M; Schaumann, E. *Zh. Obshch. Khim* **1990**, *26*, 299.

diastereomers could not be resolved by ^{1}H NMR, ^{13}C NMR or TLC analysis. The isomer ratio is of no consequence since in the final step of the synthesis this site will be oxidized to generate the carbonyl portion of the ynone. Due to the low yield of product, the use of phase transfer conditions was also investigated. Unfortunately, these conditions failed to produce any appreciable amount of the desired dibromocyclopropane; the only other isolable compound was again unreacted starting material.

Scheme 52



Several reagents can be employed to reduce dibromocyclopropanes to monocyclopropanes including zinc dust,[157] tri-*n*-butyltin hydride[158] and alkyllithium reagents.[159] In our case, the stereoselectivity of the reduction was crucial so we opted to reduce dibromocyclopropane **355** by halogen-metal exchange followed by quenching the resulting cyclopropyllithium intermediates with ethanol. As expected, the desired cis isomer was formed preferentially. Support for the assignment of the major isomer was obtained by a nOe experiment. Irradiation of the methyl group on the cyclopropane resulted in 10% enhancement of the cyclopropyl ring hydrogen thereby indicating that the two have a cis orientation.

The selectivity of the bromide removal arises from steric factors.[159] Initially, halogen-metal exchange occurs mainly at the least hindered site, in this case on the

[157] Piers, E.; Morton, H. E.; Nagakura, I.; Thies, R. W. *Can. J. Chem.* **1983**, *61*, 1226.
[158] Landgrebe, J. A.; Becker, L. W. *J. Org. Chem.* **1968**, *33*, 1173.
[159] Kitatani, K.; Hiyama, T.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 3288.

bromine atom cis to the alkyne. The resulting cyclopropyllithium species then enters into an equilibrium with the minor isomer in which the "lithium" group is trans to the alkyne. Because the alkyne moiety is smaller than the methyl group, the isomer with the smaller "lithium" group trans to the alkyne and the larger bromine atom trans to the more sterically demanding methyl group is favored. This preference leads to the predominant formation of bromocyclopropane **356a** when the lithium intermediates are quenched.

An alternative route to bromocyclopropane **356** might involve direct addition of bromocarbene to the protected enyne alcohol.[160] Based on the literature examples of the addition of halocarbenes to alkenes, however, it appears that the cis/trans selectivity of these reactions is poor unless the alkene is in a medium-large sized ring. Because of concerns that selectivity would also be poor with our system, this route was not investigated.

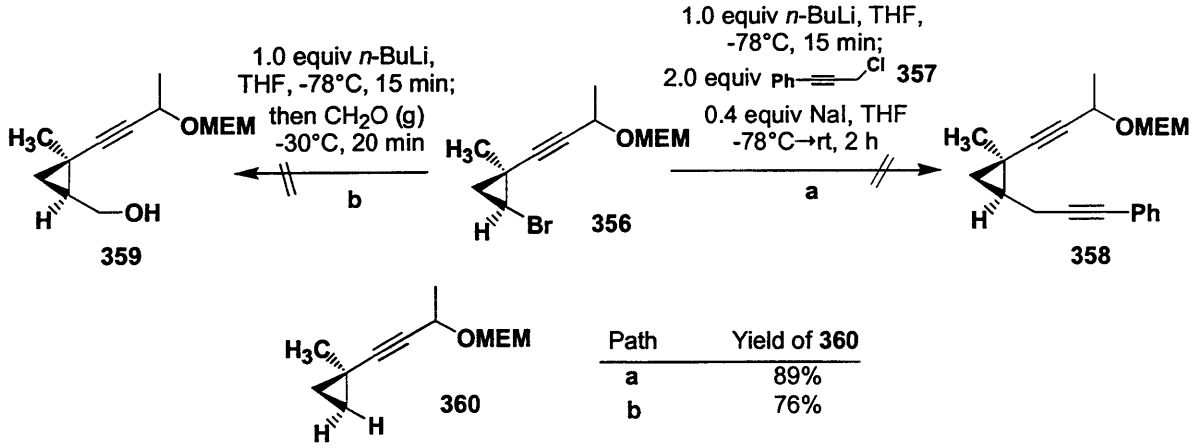
With the key monobromocyclopropane[161] in hand, the next task was to install the alkyne ynonophile on the cyclopropyl ring. As outlined in the retrosynthetic analysis shown above (Scheme 50), two options were considered with regard to how to attach the alkyne. In one route, the cyclopropyllithium species derived from bromocyclopropane **350** could be alkylated with the appropriate propargylic halide to afford **348** (path a), or alternatively, an additional CH_2X moiety could be added to the cyclopropane ring and then the resulting intermediate **349** could be reacted with lithium phenylacetylide (path b). As shown below in Scheme 53, the cyclopropyllithium compound derived from **356**

[160] For examples of the addition of monohalocarbenes to alkenes, see (a) Dehmlow, E. V.; Stütten, J. *Tetrahedron Lett.* **1991**, *32*, 6105. (b) Miyano, S.; Hashimoto, H. *Bull. Chem. Soc. Jpn.* **1975**, *48*, 3665. (c) Martel, B.; Hiriart, J. M. *Synthesis*, **1972**, 201.

[161] In all subsequent reactions, only the major cis isomer will be shown. During all additional reactions the isomer ratio remained constant (approximately 6:1 in favor of the cis isomer).

could neither be alkylated[159] with propargyl chloride **357**[162] or added to formaldehyde.[163] In both cases, the only isolated product was the debrominated cyclopropane **360**. These results were surprising, especially the failure of the cyclopropyllithium species to react with the very reactive gaseous formaldehyde. Although it was not anticipated, perhaps the low reactivity of the lithium derivative of **356** is due to some type of complexation between the oxygen atoms of the MEM group and the lithium.

Scheme 53



With the lack of success with the MEM protected substrate **356**, our attention turned to the TBDMS protected substrate **363**, which does not contain additional oxygen functionality in the protective group. As shown in Scheme 54, substrate **363** was synthesized by a route analogous to that outlined above for the MEM-protected substrate **356**. Support for the assignment of the cis isomer as the major dibromide reduction product was again obtained by a nOe experiment. Irradiation of the methyl group on the cyclopropane **363a** resulted in a 6% enhancement of the corresponding cyclopropyl ring hydrogen, indicating that the two have a cis orientation.

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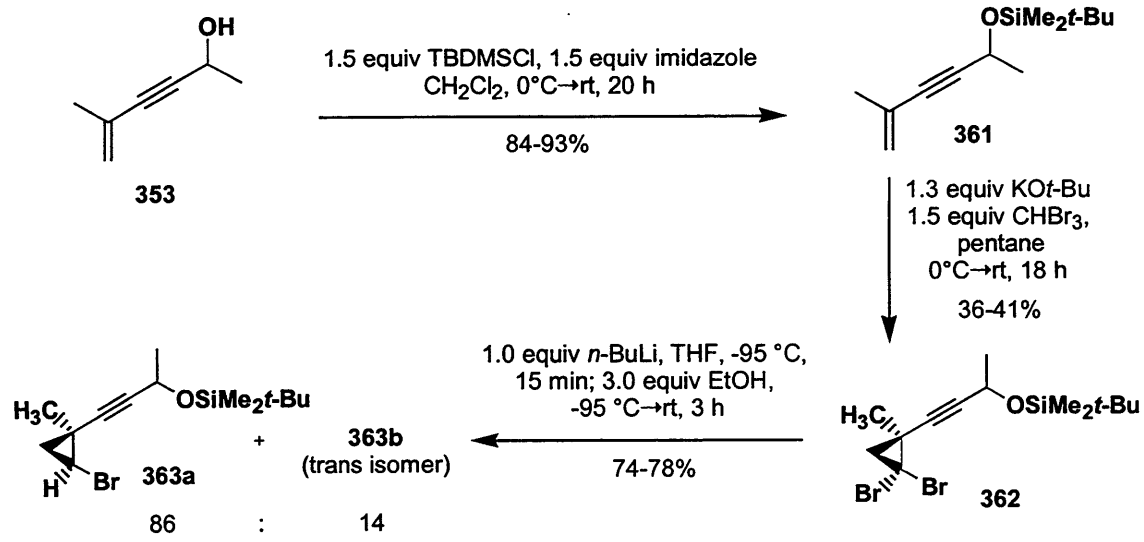
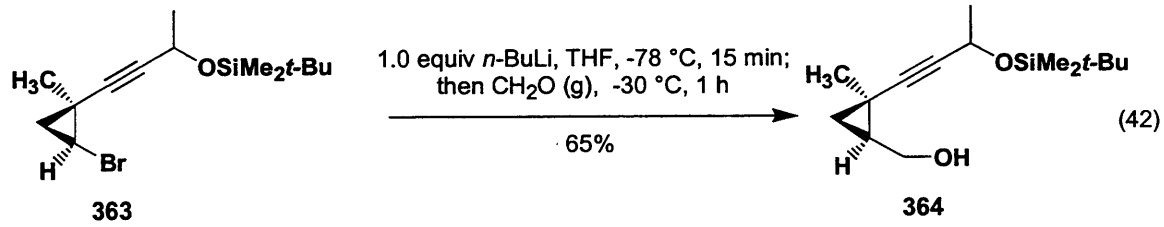
[162] Propargyl halide **257** was generated in two steps from phenylacetylene in 50% yield.

[163] For an experimental procedure for the preparation of alcohols using gaseous formaldehyde and a detailed apparatus setup, see: Smith, III, A. B.; Branca, S. J.; Guaciaro, M. A.; Wovkulich, P. M.; Korn, A. *Organic Synthesis* **1990**, *Collected Vol. 7*, 271.

Scheme 54



The first reaction examined with the TBDMS protected substrate[161] was the condensation of the lithium derivative with gaseous formaldehyde. In contrast to the MEM protected substrate, halogen metal exchange followed by treatment with gaseous formaldehyde furnished the desired alcohol **364** in 65% after column chromatography (eq 42). At this point, in the interest of time and since the importance of the cyclopropyl substrate was its behavior under the thermolysis conditions, work on the direct alkylation pathway was postponed and alcohol **364** was carried forward in the synthesis of the desired ynone substrate **335**.

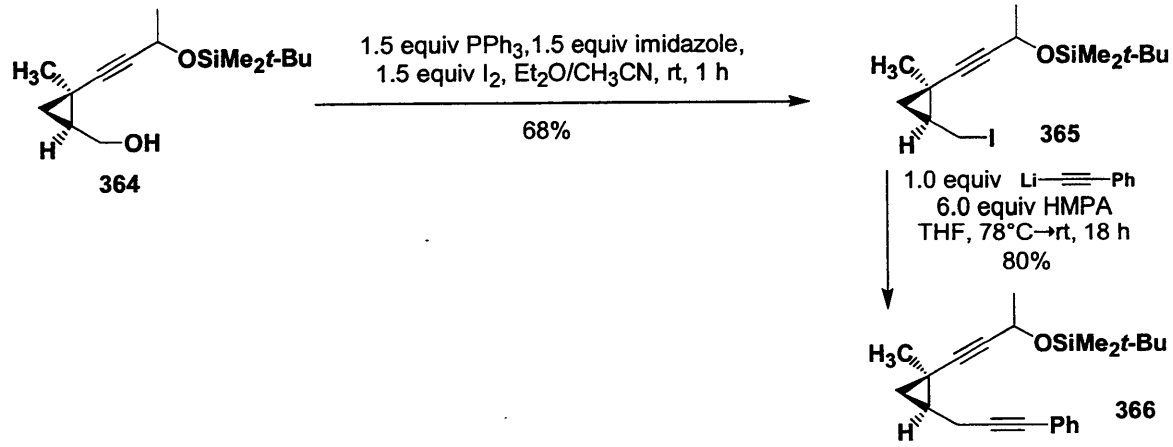


(42)

The next stage of the synthesis involved the conversion of alcohol **364** to the corresponding iodide and then alkynylation with lithium phenylacetylene. As shown in

Scheme 55, use of Corey's iodination conditions[164] furnished the desired iodide **365** in good yield. Subsequent alkynylation of the iodide with lithium phenylacetylide in THF in the presence of excess hexamethylphosphoramide (HMPA)[165] then provided the desired cyclopropane **366** in excellent yield after column chromatography. One interesting feature of the alkynylation is the importance of careful purification of the iodide. Initially, there were some concerns as to the stability of the iodide, so it was used in the alkynylation without purification. When the crude iodide was used, however, only a 15-20% yield was obtained for the two steps. In contrast, when the iodide was purified by column chromatography prior to the alkynylation, the overall yield for the two steps jumped to 55%. Perhaps the lower yield in the first reaction is due to the presence of HI or I_2 in the crude iodide. Support for successful alkylation is found in the ^{13}C NMR spectrum of cyclopropane **366**, which exhibits four acetylenic carbon resonances at 89.2, 86.1, 81.5, and 80.7 ppm.

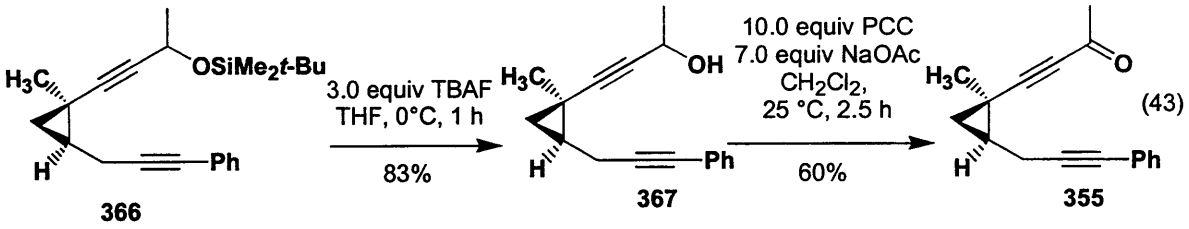
Scheme 55



[164] For a general reference, see: (a) Garegg, P. J.; Samuelsson, B. *J. Chem. Soc. Perkin Trans. 1* **1980**, 2866. For use of the Et_2O/CH_3CN solvent system, see: (b) Corey, E. J.; Pyne, S. G.; Su, W-g. *Tetrahedron Lett.* **1983**, *24*, 4883.

[165] For the use of polar aprotic additives in the alkylation of acetylenes, see: (a) Schill, G.; Merkel, C. *Chem. Ber.* **1978**, *111*, 1446. (b) Beckmann, W.; Doerjer, G.; Logemann, E.; Merkel, C.; Schill, G.; Zürcher, C. *Synthesis.* **1975**, 423. (c) Brattesani, D. N.; Heathcock, C. H. *Syn. Commun.* **1973**, *3*, 245. (d) Schwartz, M.; Waters, R. M. *Synthesis.* **1972**, 567. (e) Chong, J. M.; Wong, S. *Tetrahedron Lett.* **1986**, *27*, 5445. For a review on the use of HMPA, see: (f) Normant, H. *Angew. Chem.; Int. Ed. Engl.* **1967**, *6*, 1046.

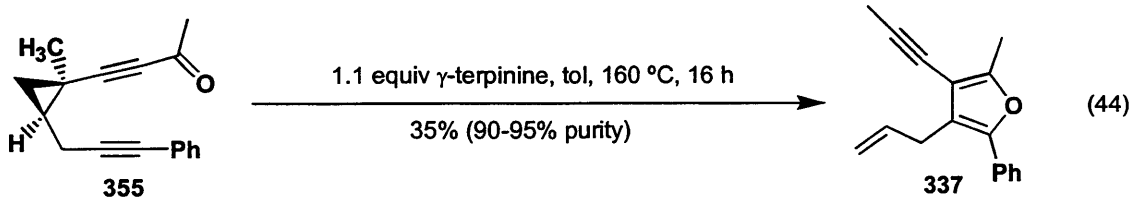
With diyne **366** in hand, the synthesis of the desired ynone substrate **355** was completed in two additional steps (eq 43). First the silyl group was removed by treatment of cyclopropane **366** with TBAF, and then the resulting alcohol **367** was oxidized to ynone **355** by treatment with a buffered solution of pyridinium chlorochromate (PCC).[166]



With the successful development of a route to ynone **355**, we subjected the substrate to the cycloaddition reaction conditions. Thermolysis of ynone **355** at 150 °C for 16 h produced a number of products by TLC analysis. To our delight, the major product that was isolated after column chromatography appeared to be the anticipated fragmentation product **357** (eq 44)! Unfortunately, purification by column chromatography could only afford the fragmentation product in 90-95% purity by ^{1}H NMR analysis. Additional purification by column chromatography failed to improve the purity of the compound. Based on the ^{13}C NMR spectrum of the impure product, it appeared that the contaminant did not contain an alkyne. Since transition-metals are known to complex alkynes and the polarity of the complex should be quite different from that of the alkyne, we decided to use a complexation/decomplexation strategy to obtain a pure sample of **357**.

---

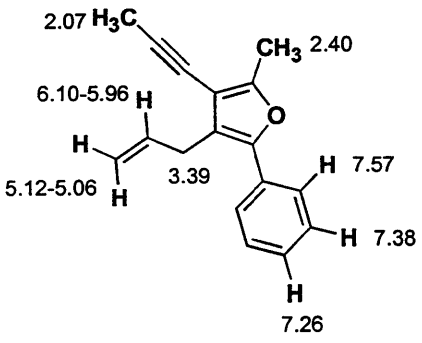
[166] For a review on PCC, see; Piancatelli, G.; Scettri, A.; D'Auria, M. *Synthesis* **1982**, 245. For another example, see: (b) Corey, E. J.; Schmidt, G. *Tetrahedron Lett.* **1979**, 399.



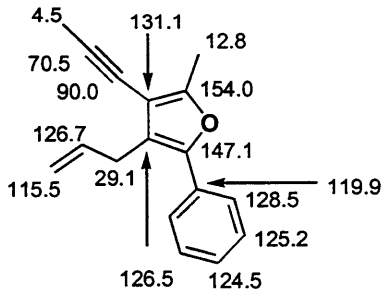
(44)

As we had hoped, complexation of the alkyne on furan **357** with dicobaltoctacarbonyl,[167] purification of the resulting complex by column chromatography, and demetalation of the alkyne by exposure to 4-methylmorpholine *N*-oxide (NMO)[168] resulted in a pure sample of the fragmentation product. As shown below, furan **357** exhibits an alkyl carbon resonance at 4.5 ppm characteristic of a methyl substituent on an acetylene and two acetylenic carbon resonances at 90.0 and 70.5 ppm in the ^{13}C NMR spectrum. In addition, the ^{1}H NMR spectrum contains vinyl protons at 6.10-5.96 ppm (m, J = 12.8 Hz, J = 15.5 Hz, J = 4.7 Hz, 1H) and 5.12-5.06 ppm (m, J = 12.8 Hz, J = 15.5 Hz, J = 2.2 Hz, 2H). The isolation of this fragmentation product lends support to our proposal that furfurylcarbene **295** is an intermediate in the reaction pathway (Scheme 40).

^{1}H NMR data ($CDCl_3$)



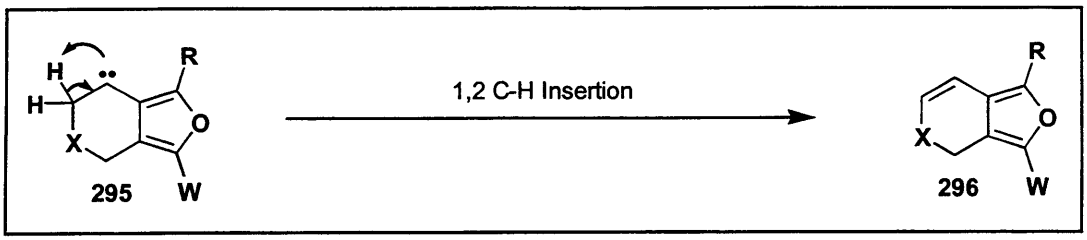
^{13}C NMR data ($CDCl_3$)



[167] For the experimental conditions used to complex the alkyne, see: Saha, M.; Muchmore, S.; van der Helm, D.; Nicholas, K. M. *J. Org. Chem.* **1986**, *51*, 1960.

[168] For an example of decomplexation using NMO, see: Magnus, P.; Annoura, H.; Harling, J. *J. Org. Chem.* **1990**, *55*, 1709.

(c) Evidence in Support of the C-H Insertion Step



The final step in our proposed mechanism involves furfurylcarbene intermediate **295** undergoing an intramolecular C-H insertion reaction. Carbenes undergo C-H insertion reactions with great ease, [169] and support for our proposed C-H insertion can be found in the literature on furfurylcarbene species.

A survey of the limited literature on furfurylcarbenes reveals that both 2-and 3-furfurylcarbenes have been generated via pyrolysis of the corresponding tosylhydrazone sodium salts (Scheme 56). Once generated, 2-furfurylcarbene (**369**) undergoes a fragmentation reaction to generate unsaturated aldehyde **370**.[170] Presumably the fragmentation is driven by the formation of the strong carbonyl bond. If a 2-furfurylcarbene is generated that can also undergo a C-H insertion like carbene **372**, the fragmentation pathway still dominates although the corresponding C-H insertion product is observed in low yield.[170] In contrast to the behavior of 2-furfurylcarbene (**369**), once 3-furfurylcarbene (**376**) is generated, it dimerizes to a mixture of cis and trans ethylenes **377**.[171] Carbene dimerizations are not common and the isolation of such a large amount of the dimer indicates that 3-furfurylcarbene is a relatively stable carbene species.

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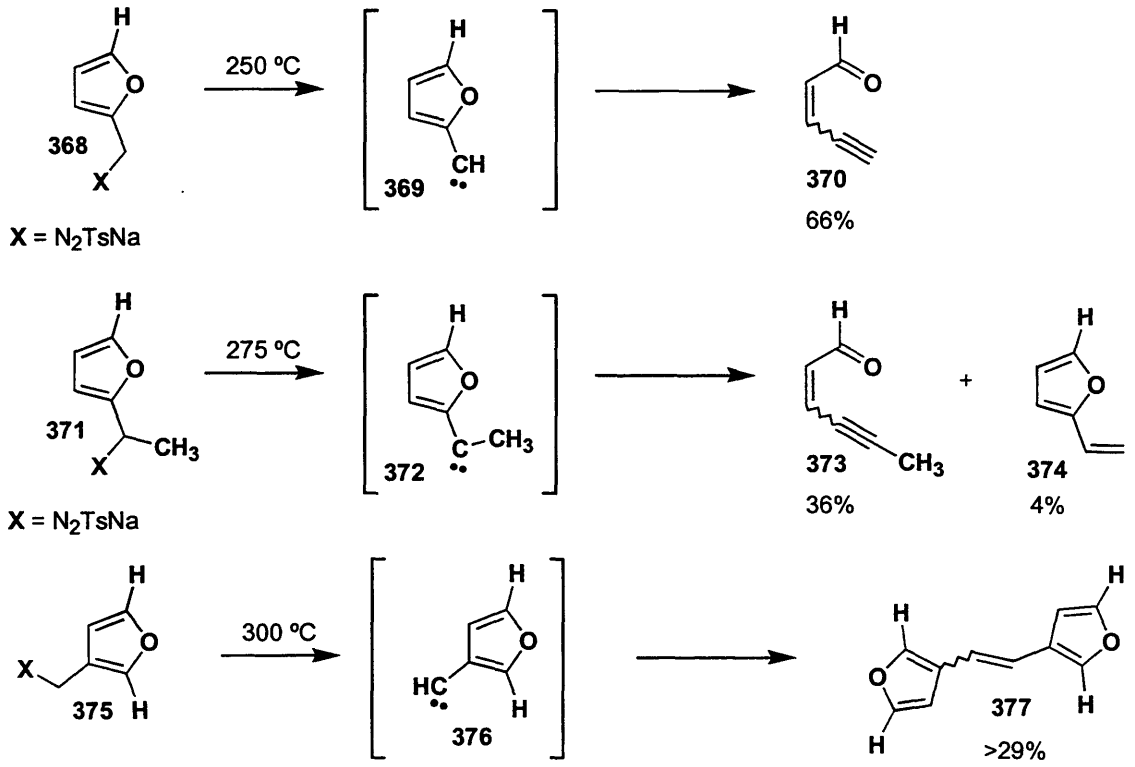
[169] For a review of the rearrangements of carbenes and nitrenes, see: Jones, W. M. Jr. In *Rearrangements in Ground and Excited States*; DeMayo, P. Ed.; Academic Press: New York, 1980, Vol. 1, pp 95-160.
[170] Hoffman, R. V.; Shechter, H. *J. Am. Chem. Soc.* **1971**, *93*, 5940. For other examples of the fragmentation reactions of 2-furfurylcarbenes see : (b) Hoffman, R. V.; Shechter, H. *J. Am. Chem. Soc.* **1978**, *100*, 7934. (c) Khasanova, T.; Sheridan, R. S. *J. Am. Chem. Soc.* **1998**, *120*, 233.
[171] Hoffman, R. V.; Orphanides, G. G.; Shechter, H. *J. Am. Chem. Soc.* **1978**, *100*, 7927.

Additional factors leading to dimerization in this system could be that no C-H insertion or fragmentation pathways are available. To the best of our knowledge, the behavior of a 3-furfurylcarbene species that can undergo a C-H insertion pathway has not been examined.

Scheme 56



In our proposed mechanism, a 3-furfurylcarbene species would be generated, but unlike the parent 3-furfurylcarbene (**376**), a C-H insertion pathway is available. We believe that once generated, our 3-furfurylcarbene intermediate **295** undergoes a rapid C-H insertion to generate the observed furan product **296**.

Summary

This chapter has outlined our mechanistic proposal to account for furan formation. We believe the heteroenyne substrates first undergo a [4+2] cycloaddition to furnish strained heterocyclic allenes. A subsequent 1,2-sigmatropic rearrangement then generates furfurylcarbene species that undergo a C-H insertion reaction to produce the observed furan products. Support for the involvement of both the allene and carbene intermediates can be found in the literature, and in the case of the allene, in the previous studies on the mechanism of the enyne cycloaddition. In addition, we have obtained experimental evidence in the form of ring-opened byproducts that are consistent with the intermediacy of both a heterocyclic allene and a furfurylcarbene. We believe the literature and experimental evidence strongly support our proposed pathway for furan formation.

PART III

Experimental Section

General Procedures

All reactions were performed in flame-dried glassware under a positive pressure of nitrogen or argon. Reaction mixtures were stirred magnetically unless otherwise indicated except for sealed tube reactions, which were not stirred. Air- and moisture-sensitive liquids and solutions were transferred via syringe or cannula into reaction vessels through rubber septa. Reaction product solutions and chromatography fractions were concentrated by using a Büchi evaporator at ca. 20 mmHg unless otherwise indicated.

Materials

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

(a) Distilled under argon or vacuum from calcium hydride:

dichloromethane, dimethylsulfoxide, toluene, triethylamine, diethylamine, hexamethylphosphoramide, pentane and pyridine.

(b) Distilled under argon or vacuum from sodium benzophenone ketyl or dianion:

tetrahydrofuran, diethyl ether, benzene, and dimethoxyethane.

(c) Distilled under argon from quinoline:

acetic anhydride.

(d) Distilled under argon:

methyl chloroformate, benzaldehyde, γ-terpinene, trimethylsilyl chloride, oxalyl chloride, propargyl chloride (also passed through Al_2O_3), and thiophenol.

(e) Other

N-Bromosuccinimide was recrystallized from water,[172] and paraformaldehyde was dried under vacuum (0.1 mmHg) over phosphorus pentoxide.

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[172] Virgil, S. C. In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; Wiley: Chichester, 1995, Vol. 1; pp 768-773.

under vacuum (0.1 mmHg) over phosphorus pentoxide, potassium *tert*-butoxide was sublimed, bromoform was passed through a short column of Al_2O_3 immediately before use, and copper (I) iodide was recrystallized from aqueous potassium iodide.[173]

Alkyllithium reagents were titrated in tetrahydrofuran or hexane at 0 °C using 1-10-phenanthroline as an indicator.[174]

Chromatography

(a) Analytical thin-layer chromatography (TLC)

Analytical thin-layer chromatography (TLC) was performed on Merck pre-coated glass-backed 0.25 mm silica gel 60-F-254 plates. Visualization of spots was effected by one or more of the following techniques: (a) ultraviolet irradiation, (b) exposure to iodine vapor, (c) immersion of the plate in an ethanolic solution of 3% *p*-anisaldehyde containing 0.5% concentrated sulfuric acid followed by heating to ca. 200 °C, and (d) immersion of the plate in an ethanolic solution of 3% *p*-vanillin containing 0.5% concentrated sulfuric acid followed by heating to ca. 200 °C.

(b) Column chromatography

Column chromatography was performed on ICN silica gel (32-60 μm).

Instrumentation

(a) Melting/boiling points

Melting points (mp) were determined with a Fischer-Johns melting point apparatus and are uncorrected. Boiling points are also uncorrected.

(b) Spectrometry

^{1}H NMR spectra were measured with Varian XL-300 (300 MHz), Unity-300 (300 MHz), and Unity-500 (500 MHz) instruments. Chemical shifts are expressed in parts per

[173] *Inorganic Synthesis* **1963**, *7*, 10.
[174] Watson, S. C.; Eastham, J. F. *J. Organomet. Chem.* **1967**, *9*, 165.

million (δ) downfield from tetramethylsilane (with the $CHCl_3$ peak at 7.26 ppm used as a standard). ^{13}C NMR spectra were measured with Varian XL-300 (75 MHz) and Unity-300 (75 MHz) spectrometers. Chemical shifts are expressed in parts per million (δ) downfield from tetramethylsilane (with the central peak of $CHCl_3$ at 77.0 ppm used as a standard). Infrared spectra (IR) were obtained using a Perkin Elmer 1320 grating spectrophotometer.

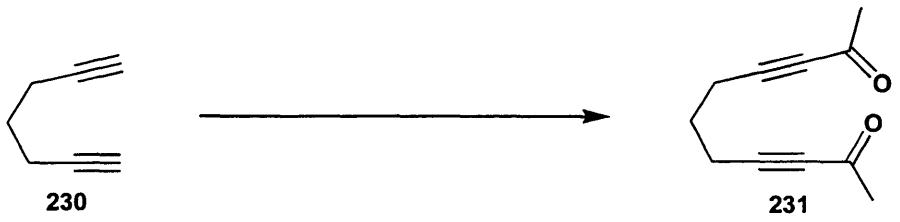
(c) Elemental analyses

Robertson Laboratory, Inc. of Madison, New Jersey performed elemental analyses.

(d) Flash vacuum pyrolyses

Flash vacuum pyrolyses (FVP) were performed using FVP glassware from Aldrich,[175] Lindgerg Mini-Mite Tube Furnace model #55035 (maximum oven temperature is 1100 °C), and a Büchi Kugelrohr oven model GKR-50 (maximum oven temperature is 250 °C).

[175] For a list of the glassware from Aldrich, see: *Aldrichimica Acta* **1983**, *16*, 1.



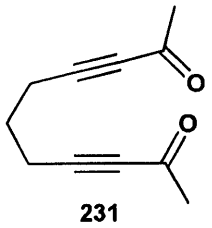
230 231

Undeca-3,8-diyn-2,10-dione (231)

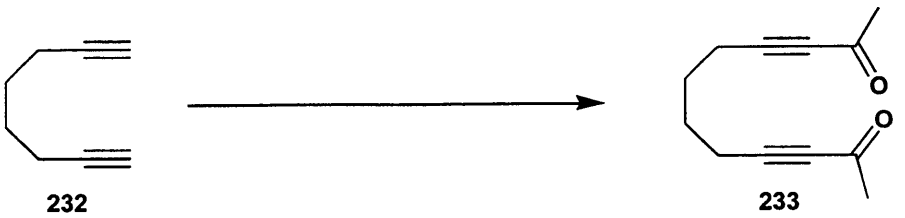
A 50-mL, two-necked, round-bottomed flask equipped with an argon inlet adapter and rubber septum was charged with 1,6-heptadiyne (**230**) (0.32 mL, 0.261 g, 2.84 mmol) and 36 mL of tetrahydrofuran, and cooled at -78 °C with a dry ice-acetone bath. A *n*-butyllithium solution (2.39 M in hexanes, 2.38 mL, 5.68 mmol) was added dropwise via syringe over 5 min and the resulting mixture was stirred at -78 °C for 15 min.

A 100-mL, three-necked, round-bottomed flask equipped with an argon inlet adapter, rubber septum, and glass stopper was charged with acetic anhydride (1.05 mL, 1.16 g, 11.36 mmol) and 8 mL of tetrahydrofuran, and the resulting solution was cooled at –78 °C with a dry ice-acetone bath. The lithium acetylide solution was transferred into this solution dropwise via cannula over 10 min, and the resulting mixture was then stirred at -78 °C for 2 h. The reaction mixture was diluted with 20 mL of a 10:1 mixture of saturated NH_4Cl solution and concentrated NH_4OH, and then allowed to warm to 25 °C. The aqueous layer was separated and extracted with two 30-mL portions of diethyl ether. The combined organic phases were washed with 20 mL of saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford 0.460 g of a yellow oil. Column chromatography on 15 g of silica gel (elution with 35% diethyl ether-pentane) provided 0.262 g (52%) of dione **231** as a light yellow oil.

IR (film)	2990, 2960, 2210, 1680, 1420, 1465, 1420, 1380, 1230, 1010, and 970 cm^{-1}.
^1H NMR (300 MHz, $CDCl_3$)	2.40 (t, J = 7.0 Hz, 4H), 2.21 (s, 6H), and 1.76 (quintet, J = 7.0 Hz, 2H).
^{13}C NMR (75MHz, $CDCl_3$)	184.3, 91.4, 81.7, 32.5, 25.5, and 17.7.



231



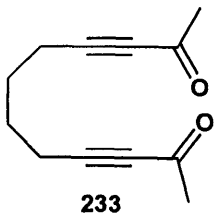
232 233

Dodeca-3,9-diyn-2,11-one (233)

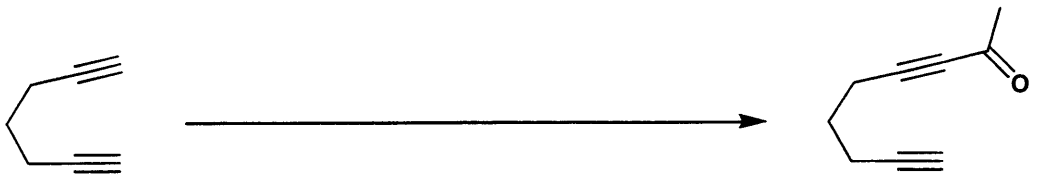
A 250-mL, round-bottomed flask equipped an argon inlet adapter and rubber septum was charged with 1,7 octadiyne (**232**) (0.546 mL, 0.446 g, 4.20 mmol) and 70 mL of tetrahydrofuran, and cooled at -78 °C with a dry ice-acetone bath. A *n*-butyllithium solution (2.41 M in hexanes, 4.0 mL, 9.66 mmol) was added dropwise via syringe over 7 min and the resulting mixture was stirred at -78 °C for 30 min.

A 250-mL, three-necked, round-bottomed flask equipped with an argon inlet adapter, rubber septum, and glass stopper was charged with acetic anhydride (1.55 mL, 1.72 g, 16.8 mmol) and 14 mL of tetrahydrofuran, and the resulting solution was cooled at -78 °C with a dry ice-acetone bath. The lithium acetylide solution was transferred into this solution dropwise via cannula over 15 min, and the resulting mixture was then stirred at -78 °C for 2.5 h. The reaction mixture was diluted with 40 mL of a 10:1 mixture of saturated NH_4Cl solution and concentrated NH_4OH, and then allowed to warm to 25 °C. The aqueous layer was separated and extracted with two 40-mL portions of diethyl ether. The combined organic phases were washed with 40 mL of saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford 0.968 g of a yellow oil. Column chromatography on 25 g of silica gel (elution with 30% diethyl ether-pentane) provided 0.403 g (50%) of dione **233** as a colorless oil.

IR (film)	3000, 2960, 2880, 2220, 1660, 1420, 1360, 1320, 1220, 1010 and 950 cm^{-1}.
^1H NMR (300 MHz, $CDCl_3$)	2.35 (t, J = 7.0 Hz, 4H), 2.25 (s, 6H), and 1.64 (quintet, J = 7.0 Hz, 4H).
^{13}C NMR (75 MHz, $CDCl_3$)	184.6, 92.6, 81.6, 32.6, 26.5, and 18.3.



233



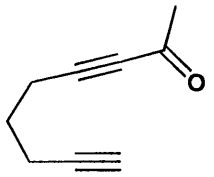
230 234

Nona-3,8-diyn-2-one (234)

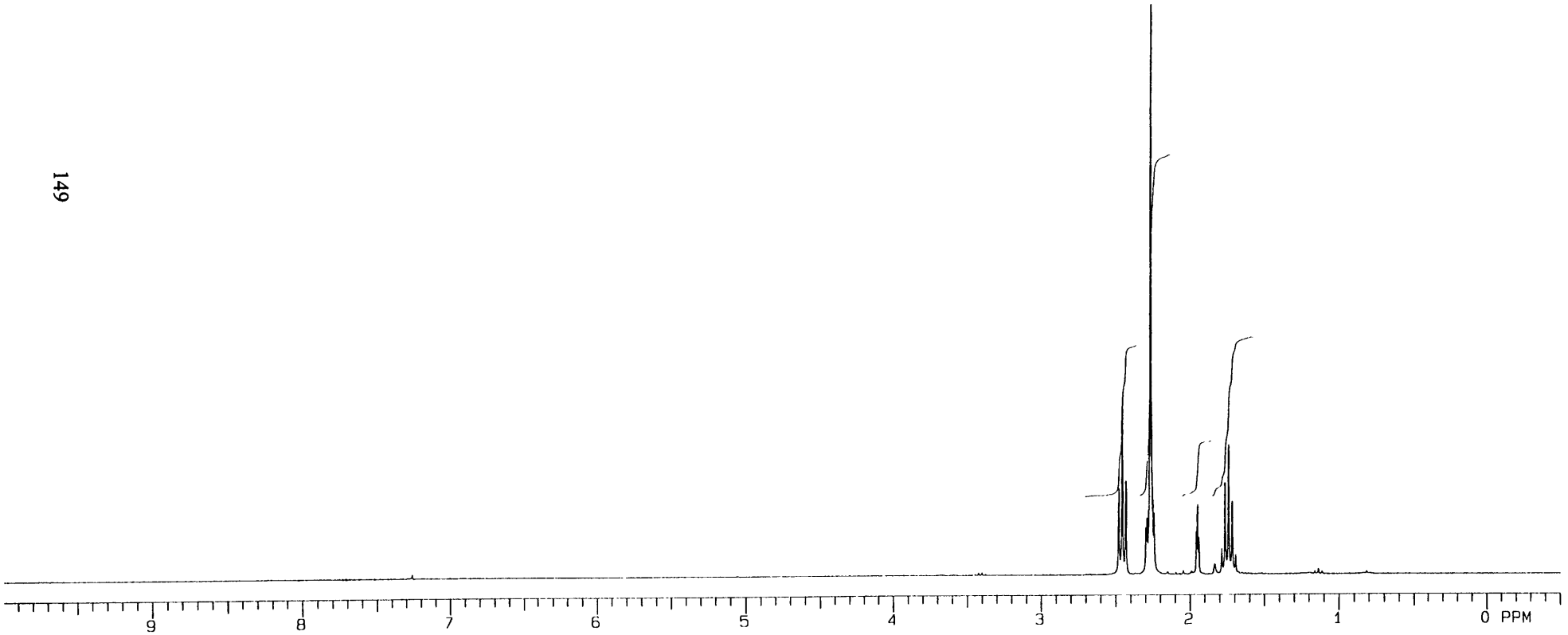
A 100-mL, two-necked, round-bottomed flask equipped with a rubber septum and argon inlet adapter was charged with 1,6-heptadiyne (**230**) (0.415 mL, 0.338 g, 3.67 mmol) and 62 mL of tetrahydrofuran, and cooled at -78 °C with a dry ice-acetone bath. A *n*-butyllithium solution (2.41 M in hexanes, 1.52 mL, 3.67 mmol) was added dropwise via syringe over 5 min and the resulting mixture was stirred at -78 °C for 15 min.

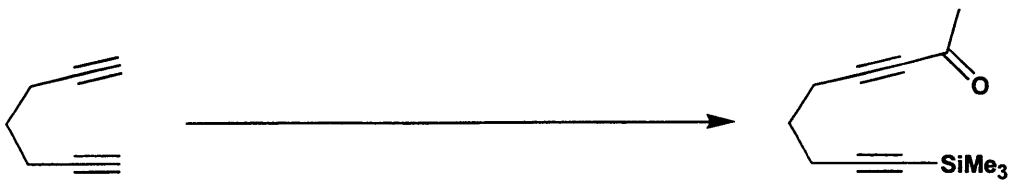
A 100-mL, two-necked, round-bottomed flask equipped with an argon inlet adapter and rubber septum was charged with acetic anhydride (1.02 mL, 1.12 g, 11.0 mmol) and 13 mL of tetrahydrofuran, and the resulting solution was cooled at -78 °C with a dry ice-acetone bath. The lithium acetylide solution was transferred into this solution dropwise via cannula over 10 min, and the resulting mixture was then stirred at -78 °C for 2 h. The reaction mixture was diluted with 20 mL of a 10:1 mixture of saturated NH_4Cl solution and concentrated NH_4OH, and then allowed to warm to 25 °C. The aqueous layer was separated and extracted with two 30-mL portions of diethyl ether. The combined organic phases were washed with 20 mL of saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford 0.303 g of a yellow oil. Column chromatography on 15 g of silica gel (elution with 20% diethyl ether-pentane) provided 0.160 g (32%) of methyl ketone **234** as a colorless oil.

IR (film)	3300, 3000, 2940, 2920, 2900, 2260, 2210, 1670, 1420, 1360, 1330, 1310, 1290, 1230, 1050, 1010, and 960 cm^{-1}.
^1H NMR (300 MHz, $CDCl_3$)	2.45 (t, J = 7.1 Hz, 2H), 2.27 (t of d, J = 7.0 Hz, J = 2.6 Hz, 2H), 2.26 (s, 3H), 1.95 (t, J = 2.6 Hz, 1H) and 1.76 (app quintet, J = 7.0 Hz, 2H).
^{13}C NMR (75 MHz, $CDCl_3$)	184.5, 92.3, 82.6, 81.6, 69.3, 32.6, 26.4, 17.7, and 17.4.



234





230 235

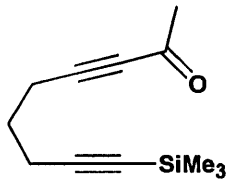
9-(Trimethylsilyl)-nona-3,8-diyn-2-one (235)

A 100-mL, three-necked, round-bottomed flask equipped with rubber septum, glass stopper, and argon inlet adapter was charged with 1,6-heptadiyne (**230**) (0.480 mL, 0.392 g, 4.26 mmol) and 54 mL of tetrahydrofuran and the resulting solution was cooled at 0 °C using an ice-water bath. An ethylmagnesium bromide solution (3.0 M in diethyl ether, 4.26 mL, 12.78 mmol) was added dropwise via syringe over 8 min. The resulting mixture was stirred at 0 °C for 90 min then trimethylsilyl chloride (0.541 mL, 0.462 g, 4.26 mmol) was added via syringe dropwise over 2 min. The reaction was stirred at 0 °C for 2 h and then allowed to warm slowly to 25 °C over 16 h. The resulting solution was diluted with 30 mL of saturated NH_4Cl solution and the aqueous layer was separated and extracted with three 30-mL portions of diethyl ether. The combined organic phases were washed with 40 mL of saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford 0.816 g of a colorless oil. Column chromatography on 10 g of silica gel (elution with 5% diethyl ether-pentane) provided 0.556 g of a colorless oil. The oil was shown by ^1H NMR to be a roughly 3:1 mixture of the desired 1-(trimethylsilyl)-hepta-1,6-diyne and 1,9-(trimethylsilyl)-hepta-1,6-diyne and was carried on without further purification to the next step in the sequence.

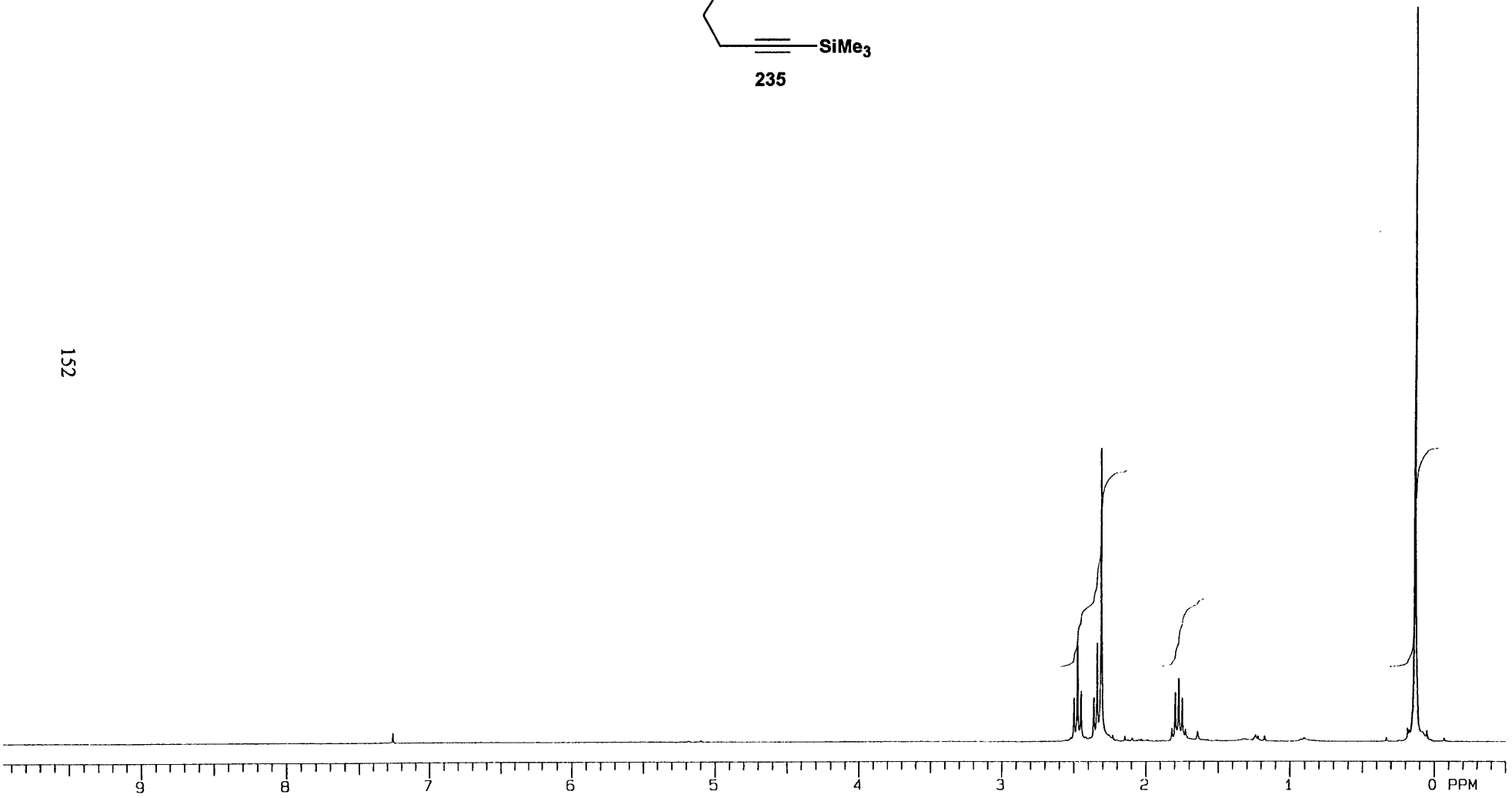
A 100-mL, round-bottomed flask equipped with rubber septum with argon inlet needle was charged via cannula with a solution of the above oil in 35 mL of tetrahydrofuran, and the resulting solution was cooled at -78 °C with a dry ice-acetone bath. A *n*-butyllithium solution (2.41 M in hexanes, 1.15 mL, 2.77 mmol) was added dropwise via syringe over 3 min and the resulting mixture was stirred at -78 °C for 10 min.

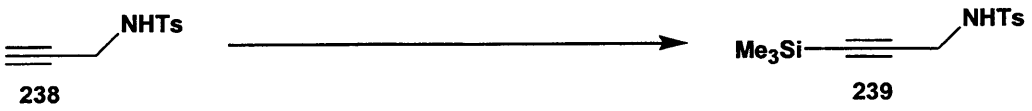
A 100-mL, three-necked, round-bottomed flask equipped with an argon inlet adapter, rubber septum, and glass stopper was charged with acetic anhydride (0.295 mL, 0.326 g, 3.20 mmol) and 8 mL of tetrahydrofuran, and the resulting solution was cooled at -78 °C with a dry ice-acetone bath. The lithium acetylide solution was transferred into this solution dropwise via cannula over 10 min, and the resulting mixture was then stirred at -78 °C for 3 h. The reaction mixture was diluted with 40 mL of a 10:1 mixture of saturated NH_4Cl solution and concentrated NH_4OH, and then allowed to warm to 25 °C. The aqueous layer was separated and extracted with two 30-mL portions of diethyl ether. The combined organic phases were washed with 40 mL of saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford 0.600 g of a yellow oil. Column chromatography on 20 g of silica gel (elution with 10% diethyl ether-pentane) provided 0.353 g (40% for the two steps) of methyl ketone **235** as a colorless oil.

IR (film)	2940, 2890, 2200, 2160, 1650, 1420, 1350, 1240, 1220, 1030, 1010, 940, 910, 830, and 750 cm^{-1}.
^1H NMR (300 MHz, $CDCl_3$)	2.47 (t, J = 7.1 Hz, 2H), 2.33 (t, J = 6.9 Hz, 2H), 2.31 (s, 3H), 1.77 (app quintet, J = 7.0 Hz, 2H) and 0.13 (s, 9H).
^{13}C NMR (75 MHz, $CDCl_3$)	184.7, 105.3, 92.7, 85.3, 81.7, 32.7, 26.7, 19.0, 17.9, and 0.0.



235

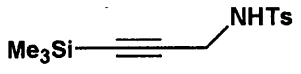




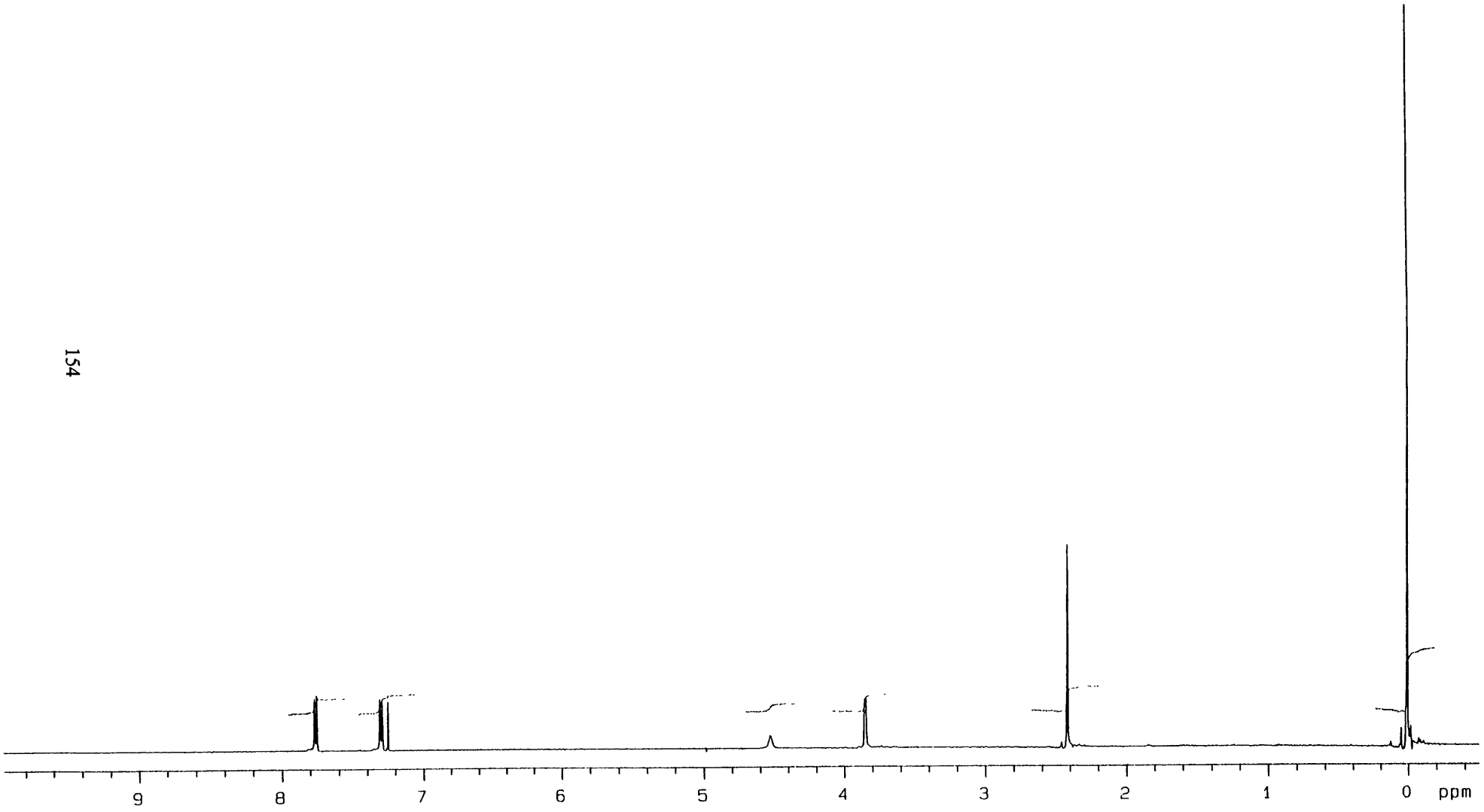
_N_-(3-Trimethylsilyl-prop-2-ynyl)-_p_-toluenesulfonamide (239)

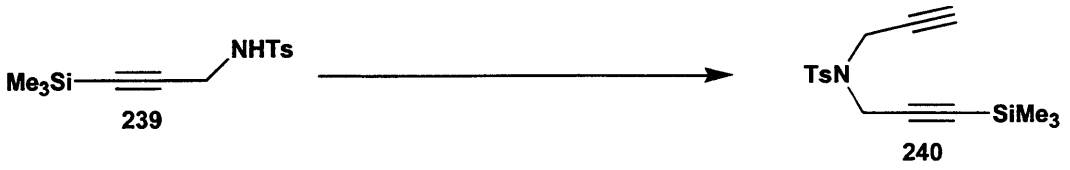
A 50-mL, three-necked, round-bottomed flask equipped with rubber septum, glass stopper, and argon inlet adapter was charged with the sulfonamide **238**[113] (1.19 g, 5.69 mmol) and 29 mL of tetrahydrofuran. The resulting solution was cooled at -78 °C using a dry ice-acetone bath then a solution of *n*-butyllithium (2.49 M in hexanes, 4.57 mL, 11.38 mmol) was added dropwise via syringe over 3 min. The resulting mixture was stirred at –78 °C for 10 min and then trimethylsilyl chloride (0.72 mL, 0.618 g, 5.69 mmol) was added dropwise over 4 min. The reaction mixture was stirred at -78 °C for an additional 10 min, and then the cooling bath was removed and the solution was stirred at room temperature for 2.5 h. The dark yellow solution was quenched by the addition of 10 mL of saturated NH_4Cl solution and then transferred to seperatory funnel containing 20 mL of diethyl ether and 20 mL of saturated NH_4Cl solution. The aqueous layer was separated and extracted with two 20-mL portions of diethyl ether. The combined organic extracts were washed with 30 mL of saturated NaCl solution, dried over Na_2SO_4, filtered, and concentrated to afford 1.43 g (89%) of sulfonamide **239** as a tan solid, mp 101-103 °C.

IR (CCl_4)	3380, 3010, 2960, 2180, 1600, 1400, 1350, 1240, 1360, 1050, 1000, and 840 cm^{-1}.
^1H NMR (300 MHz, $CDCl_3$)	7.77 (d, J = 8.3 Hz 2H), 7.31 (d, J = 8.3 Hz, 2H), 4.53 (br s, 1H), 3.86 (d, J = 4.3 Hz, 2H), 2.43 (s, 3H), and 0.02 (s, 9H).
^{13}C NMR (75 MHz, $CDCl_3$)	143.6, 136.8, 129.6, 127.4, 99.4, 89.7, 33.7, 21.5, and -0.5.



239

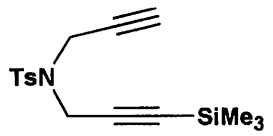




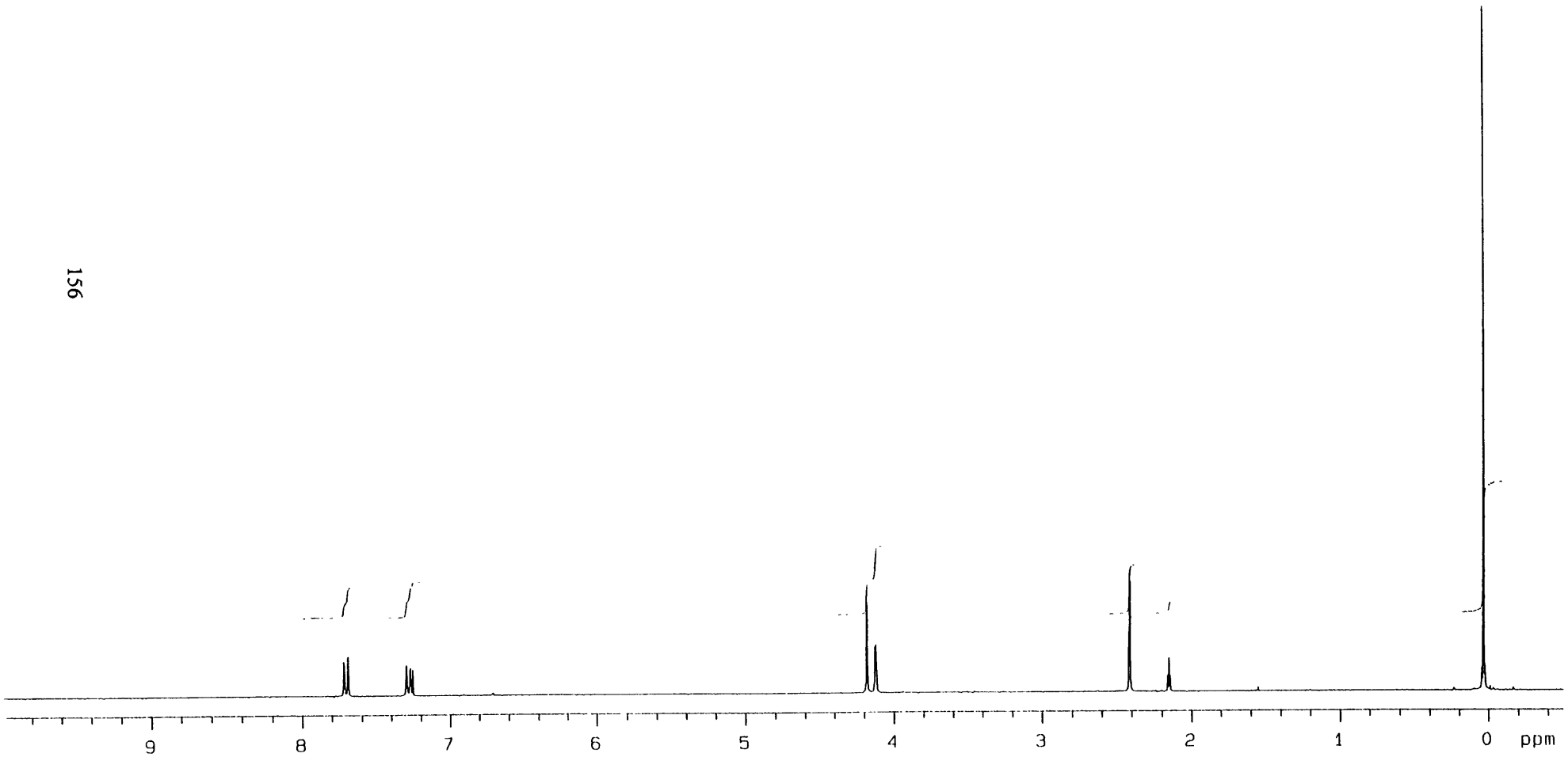
_N_-(Prop-2-ynyl)-_N_-(3-trimethylsilyl-prop-2-ynyl)-_p_-toluenesulfonamide (240)

A 100-mL, three-necked, round-bottomed flask equipped with rubber septum, glass stopper, and argon inlet adapter was charged with the sulfonamide **239** (1.43 g, 5.06 mmol) and 51 mL of tetrahydrofuran. The resulting solution was cooled at 0 °C using an ice-water bath then a solution of *n*-butyllithium (2.49 M in hexanes, 2.24 mL, 5.57 mmol) was added dropwise via syringe over 5 min. The resulting mixture was stirred at 0°C for 10 min then propargyl chloride (0.45 mL, 0.453 g, 6.07 mmol) was added dropwise over 3 min. Sodium iodide (0.125 g, 2.53 mmol) was added, the cooling bath was removed, and the solution stirred at room temperature for 18 h. The reaction was quenched by the addition of 10 mL of saturated NH_4Cl solution and then transferred to a separatory funnel containing 20 mL of diethyl ether and 30 mL of NH_4Cl solution. The aqueous layer was separated and extracted with two 20-mL portions of diethyl ether. The combined organic extracts were washed with 40 mL of saturated NaCl solution, dried over Na_2SO_4, filtered, and concentrated to afford 1.41 g of an orange solid. Column chromatography on 45 g of silica gel (elution with 10% ethyl acetate-hexane) provided 1.06 g (65%) of sulfonamide **240** as an off-white solid, mp 91-92 °C.

IR (CCl_4)	3300, 2940, 2130,1460, 1350, 1240, 1160, 1080, 1000, and 900 cm^{-1}.
^1H NMR (300 MHz, $CDCl_3$)	7.71 (d, J = 8.3 Hz 2H), 7.29 (d, J = 8.3 Hz, 2H), 4.19 (s, 2H), 4.13 (d, J = 2.4 Hz, 2H), 2.42 (s, 3H), 2.15 (t, J = 2.4, 1H), and 0.04 (s, 9H).
^{13}C NMR (75 MHz, $CDCl_3$)	143.7, 135.2, 129.5, 127.8, 97.3, 91.2, 76.3, 73.7, 37.1, 36.1, 21.5 and -0.5.



240



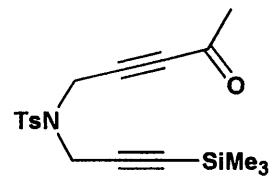
240 241

***N*-(pent-2-yn-4-one)-*N*-(3-trimethylsilyl-prop-2-ynyl)-*p*-toluenesulfonamide (241)**

A 25-mL, two-necked, round-bottomed flask equipped with an argon inlet adapter and rubber septum was charged with sulfonamide **240** (0.199 g, 0.62 mmol) and 10 mL of tetrahydrofuran, and cooled at -78 °C with a dry ice-acetone bath. A *n*-butyllithium solution (2.49 M in hexanes, 0.32 mL, 0.81 mmol) was added dropwise via syringe over 5 min and the resulting mixture was stirred at -78 °C for 15 min.

A 50-mL, two-necked, round-bottomed flask equipped with an argon inlet adapter and rubber septum was charged with acetic anhydride (0.29 mL, 0.317 g, 3.11 mmol) and 3 mL of tetrahydrofuran, and the resulting solution was cooled at -78 °C with a dry ice-acetone bath. The lithium acetylide solution was transferred into this solution dropwise via cannula over 10 min, and the resulting mixture was then stirred at -78 °C for 2 h. The reaction mixture was diluted with 20 mL of a 10:1 mixture of saturated NH_4Cl solution and concentrated NH_4OH, and then allowed to warm to 25 °C. The aqueous layer was separated and extracted with three 10-mL portions of diethyl ether. The combined organic phases were washed with 20 mL of saturated NaCl solution, dried over Na_2SO_4, filtered, and concentrated to afford 0.301 g of a yellow oil. Column chromatography on 30 g of silica gel (elution with 15% ethyl acetate-hexane) provided 0.113 g (50%) of methyl ketone **240** as a light yellow solid, mp 104-107 °C.

IR (CCl_4)	3020, 2960, 2930, 2200, 2180, 1680, 1600, 1410, 1360, 1250, 1220, 1160, 1100, 1000, 900, 840, and 740 cm^{-1}.
^1H NMR (300 MHz, $CDCl_3$)	7.71 (d, J = 8.1 Hz 2H), 7.31 (d, J = 8.1 Hz, 2H), 4.30 (s, 2H), 4.16 (s, 2H), 2.41 (s, 3H), 2.20 (s, 3H), and 0.05 (s, 9H).
^{13}C NMR (75 MHz, $CDCl_3$)	183.3, 144.1, 134.9, 129.7, 127.8, 96.8, 91.9, 84.5, 84.0, 37.7, 36.3, 32.4, 21.5, and -0.5.



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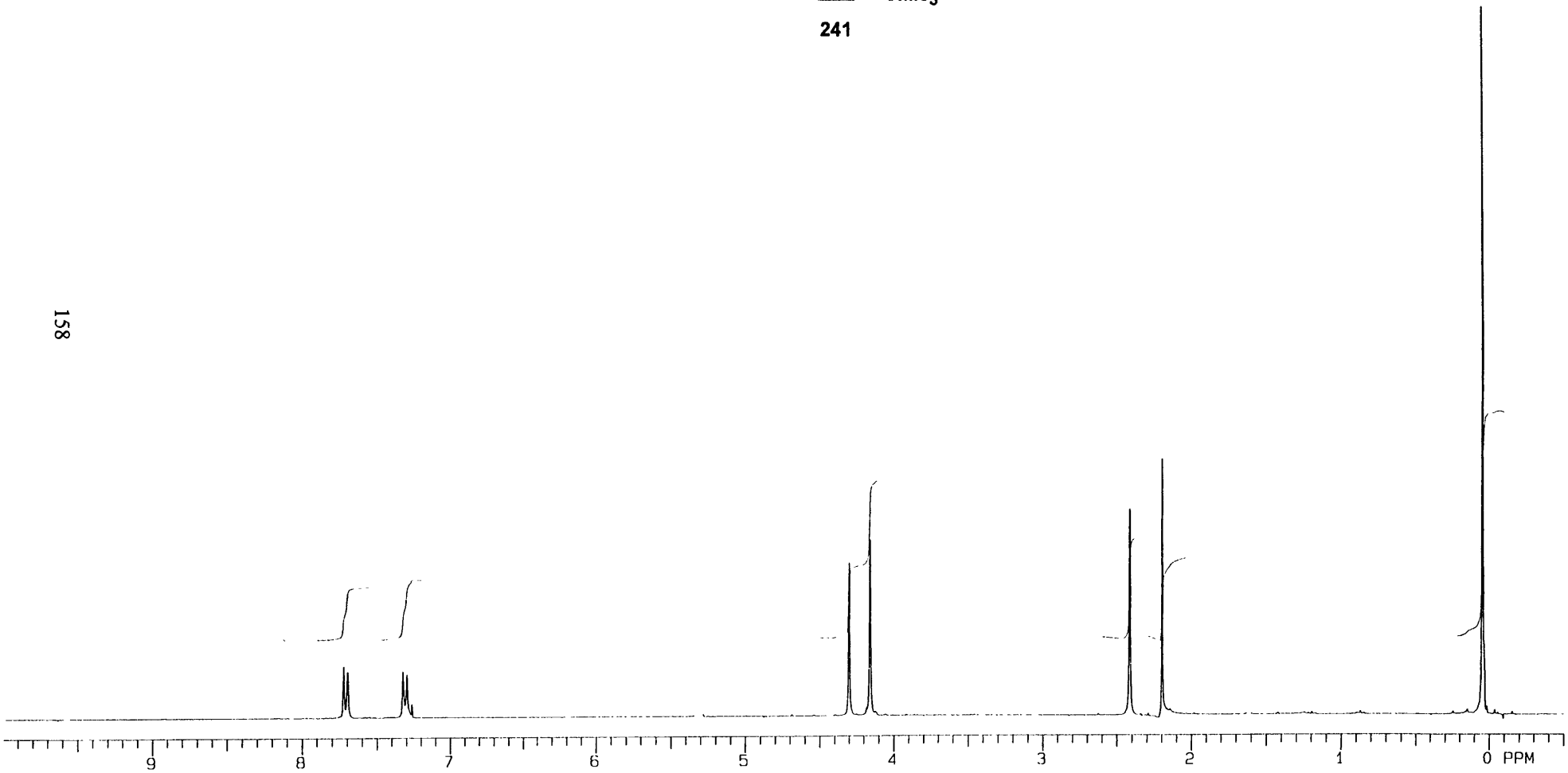
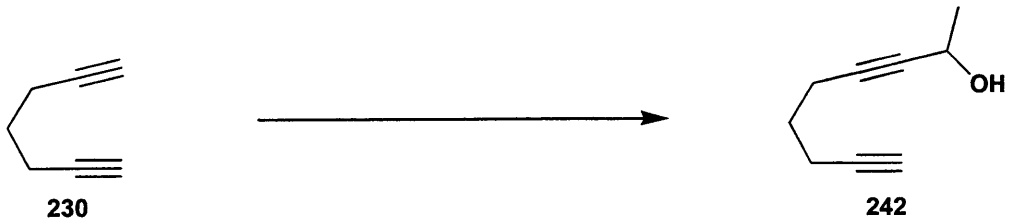


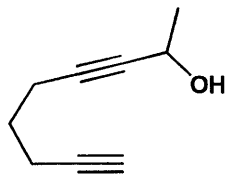


230 242

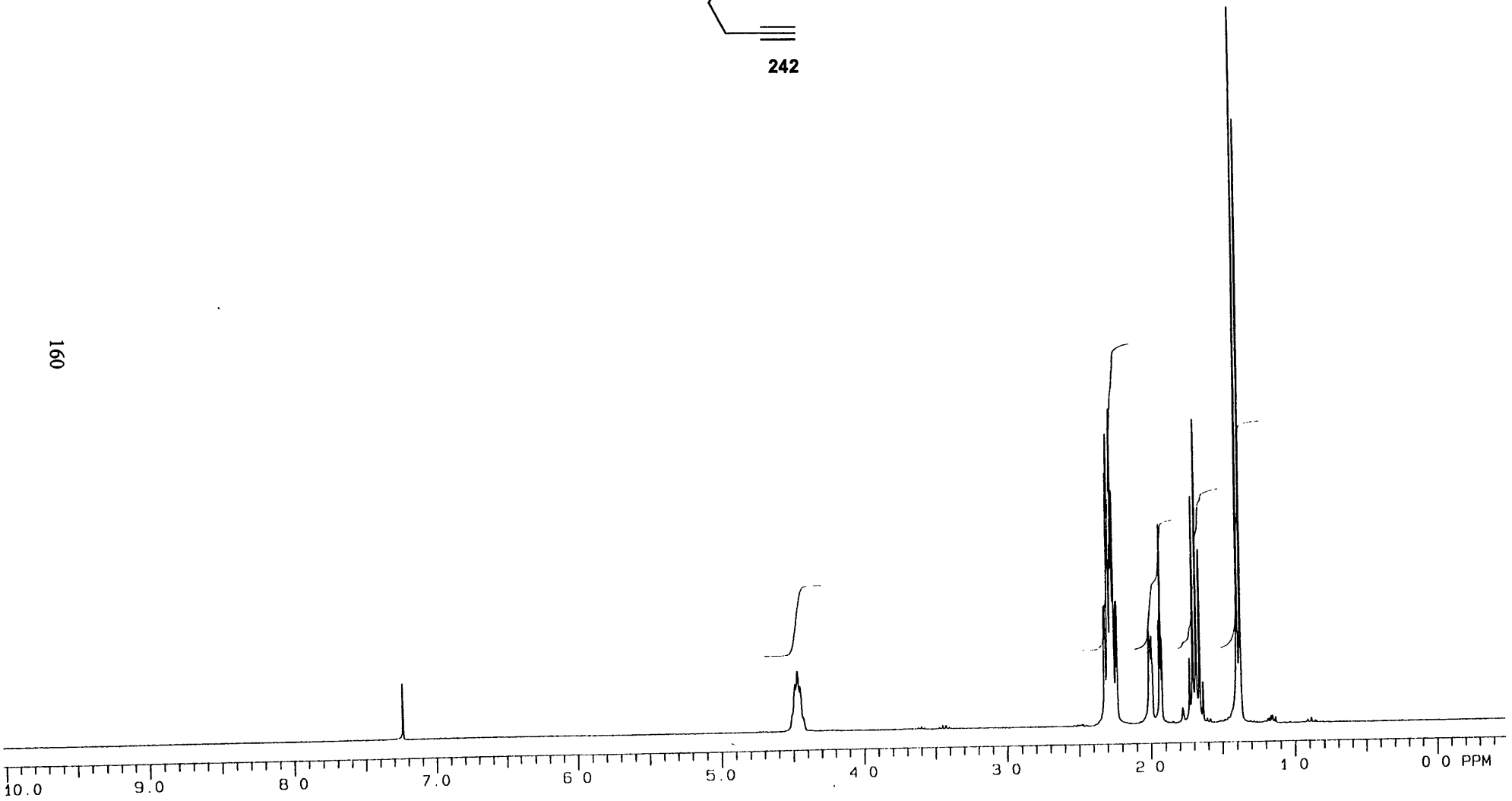
Nona-3,8-diyn-2-ol (242)

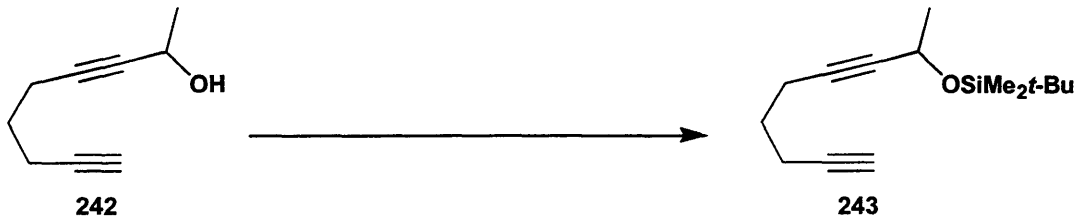
A 250-mL, three-necked, round-bottomed flask equipped with rubber septum, glass stopper, and argon inlet adapter was charged with 1,6-heptadiyne (**230**) (2.45 mL, 2.0 g, 21.7 mmol) and 150 mL of tetrahydrofuran and the resulting solution was cooled at 0 °C using an ice-water bath. An ethylmagnesium bromide solution (3.0 M in diethyl ether, 7.24 mL, 21.7 mmol) was added dropwise via syringe over 8 min. The resulting mixture was stirred at 0 °C for 90 min and then acetaldehyde (4.52 mL, 3.56 g, 86.8 mmol) was added via syringe in one portion. The reaction mixture was stirred at 0 °C for 30 min, diluted with 30 mL of saturated NH_4Cl solution, and allowed to warm to room temperature. The aqueous layer was separated and extracted with three 40-mL portions of diethyl ether. The combined organic phases were washed with 30 mL of saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford 3.15 g of a colorless oil. Column chromatography on 60 g of silica gel (elution with 30% diethyl ether-pentane) provided 1.47 g (50%) of propargylic alcohol **242** as a colorless oil.

IR (film)	3350, 3300, 3000, 2960, 2900, 2860, 2840, 2220, 2110, 1450, 1430, 1370, 1330, 1290, 1150, 1070, 1000, and 880 cm^{-1}.
^1H NMR (300 MHz, $CDCl_3$)	4.45-4.49 (m, 1H), 2.28 (t of d, J = 6.9 Hz, J =1.6 Hz, 2H), 2.28 (t of d, J = 6.8 Hz, J=1.9 Hz, 2H), 2.01 (d, J = 2.7 Hz, 1H), 1.96 (t, J = 1.9 Hz, 1H), 1.68 (app quintet, J = 6.8 Hz, 2H), and 1.39 (d, J = 6.5 Hz, 3H).
^{13}C NMR (75 MHz, $CDCl_3$)	83.5, 83.2, 83.0, 68.9, 58.5, 27.4, 24.6, 17.6, and 17.5.



242



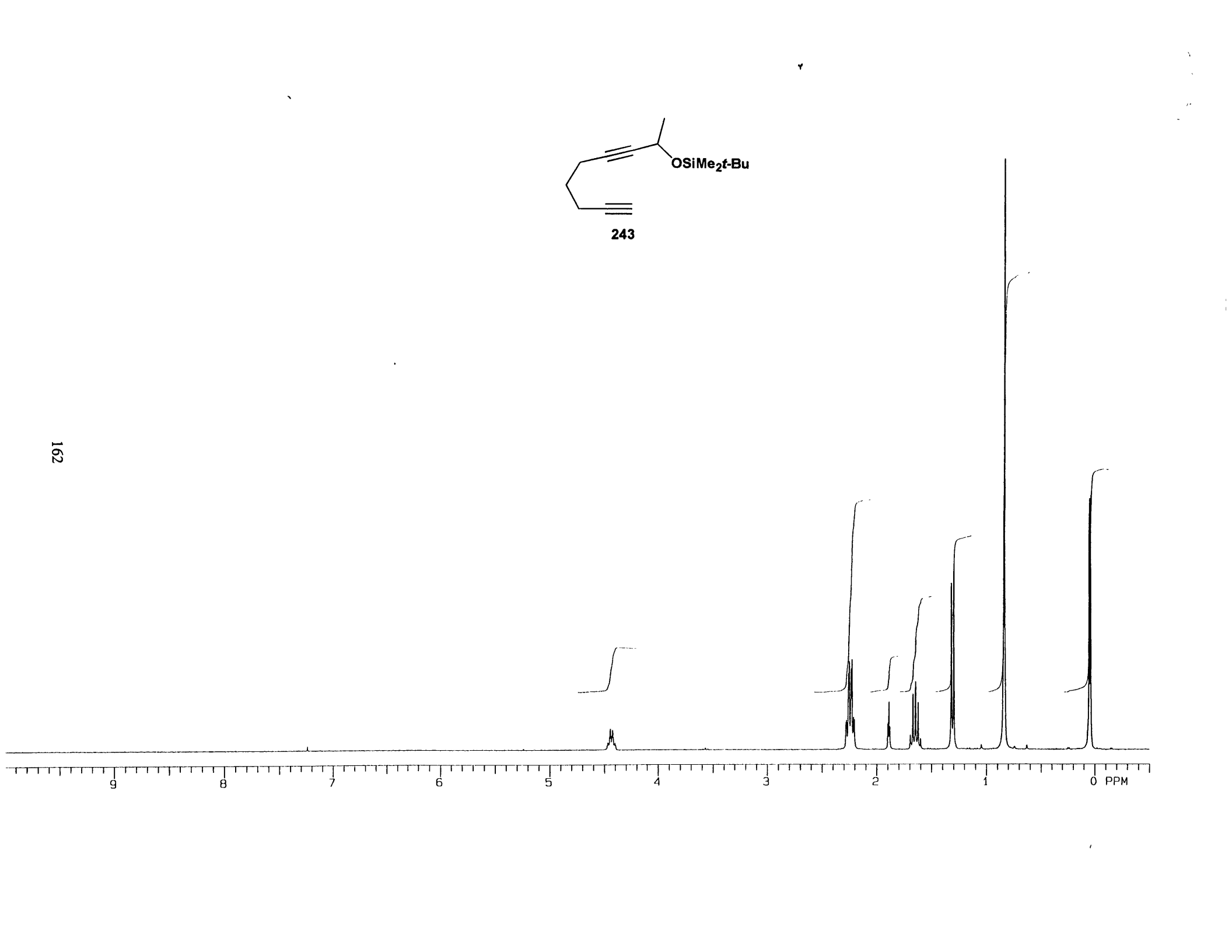


242 243

2-(*tert*-Butyldimethylsilyloxy)nona-3,8-diyne (243)

A 10-mL, round-bottomed flask equipped with rubber septum and argon needle inlet was charged with propargylic alcohol **242** (0.500 g, 3.67 mmol), 4 mL of dichloromethane, and imidazole (0.300 g, 4.40 mmol). Once the imidazole had dissolved, the solution was cooled at 0 °C using an ice-water bath and *tert*-butyldimethylsilyl chloride (0.608 g, 4.04 mmol) was added in one portion. The solution was stirred at 0 °C for 4 h and then allowed to warm to room temperature over 16 h. The reaction solution was diluted with 30 mL of saturated NH_4Cl solution and then the aqueous layer was separated and extracted with three 30-mL portions of dichloromethane. The combined organic phases were washed with 20 mL of saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford 3.15 g of a colorless oil. Column chromatography on 10 g of silica gel (elution with 10% diethyl ether-pentane) provided 0.703 g (77%) of silyl ether **243** as a colorless oil.

IR (film)	3300, 2980, 2960, 2940, 2880, 2220, 2100, 1460, 1430, 1390, 1360, 1340, 1310, 1250, 1140, 1100, 1020, 980, 940, 830, and 770 cm^{-1}.
^1H NMR (300 MHz, $CDCl_3$)	4.43-4.45 (m, 1H), 2.24 (d of t, J = 7.1 Hz, J = 1.9 Hz, 2H), 2.24 (d of t, J = 7.0 Hz, J = 2.6 Hz, 2H), 1.89 (t, J = 2.6 Hz, 1 H), 1.66 (app quintet J = 7.0 Hz, 2H), 1.31 (s, 3H), 0.84 (s, 9H), 0.06 (s, 3H) and 0.04 (s, 3H).
^{13}C NMR (75 MHz, $CDCl_3$)	83.5, 82.3, 68.7, 59.1, 27.5, 25.9, 25.8, 25.7, 18.3, 17.7, 17.5, -4.6, and -4.9.


OSiMe2t-Bu
243
9
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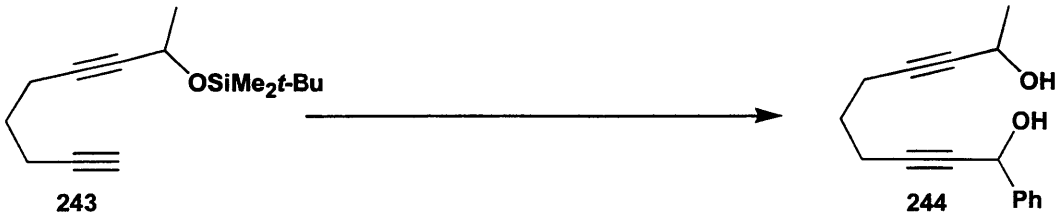


243 244

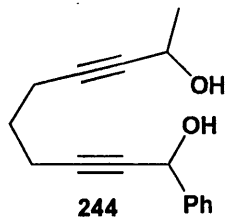
1-Phenyl-deca-2,7-diyn-1,9-diol (244)

A 25-mL, two-necked, round-bottomed flask equipped with rubber septum and argon inlet adapter was charged with silyl ether **243** (0.416 g, 1.66 mmol) and 17 mL of tetrahydrofuran and the resulting solution was cooled at -78 °C using a dry ice-acetone bath. A *n*-butyllithium solution (2.32 M in hexanes, 0.931 mL, 2.16 mmol) was added dropwise via syringe over 3 min and the resulting mixture was stirred at -78 °C for 20 min. Benzaldeyde (0.253 mL, 0.265 g, 2.49 mmol) was added and then the reaction solution was stirred at -78 °C for 2h, diluted with 20 mL of saturated NH_4Cl solution, and allowed to warm to room temperature. The aqueous layer was separated and extracted with three 30-mL portions of diethyl ether. The combined organic phases were washed with 30 mL of saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford 0.586 g of a yellow oil. Column chromatography on 15 g of silica gel (elution with 10% diethyl ether-pentane) provided 0.353 g of a colorless oil. This material was shown by ^1H NMR to be a 91:9 mixture of the desired alcohol with 1-phenyl-pentanol, and was carried on without further purification to the next step in the sequence.

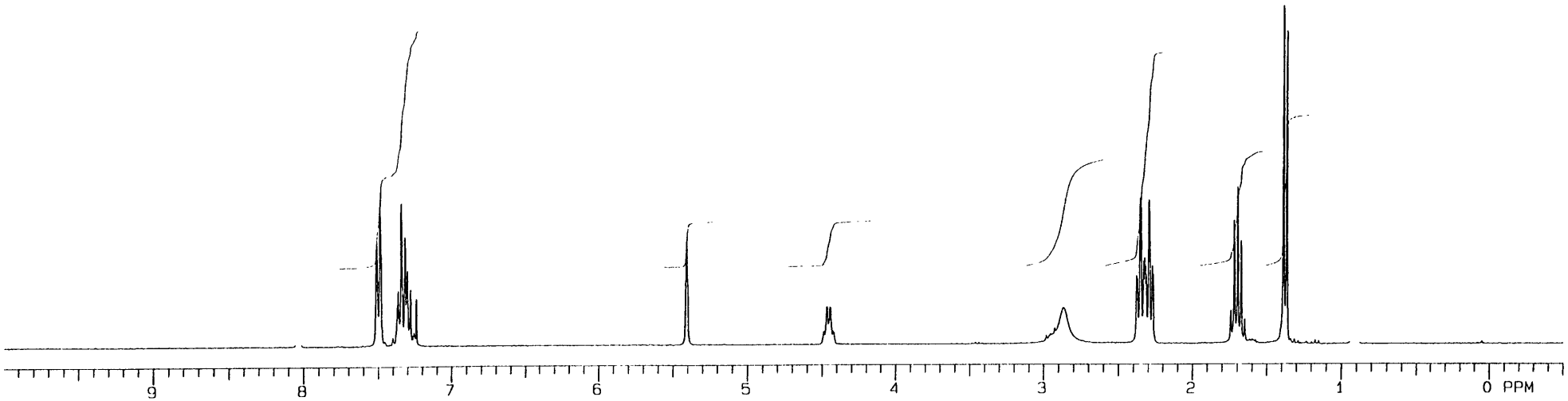
A 50-mL, round-bottomed flask equipped with rubber septum and argon inlet needle was charged via cannula with the above impure oil and 18 mL of tetrahydrofuran. A tetrabutylammonium fluoride solution (1.0 M, 2.69 mL, 2.69 mmol) was added and the resulting solution was stirred at 25 °C for 20 min. The solution was diluted with 10 mL of saturated NH_4Cl solution and then the aqueous layer was separated and extracted with three 30-mL portions of diethyl ether. The combined organic phases were washed with 30 mL of saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford

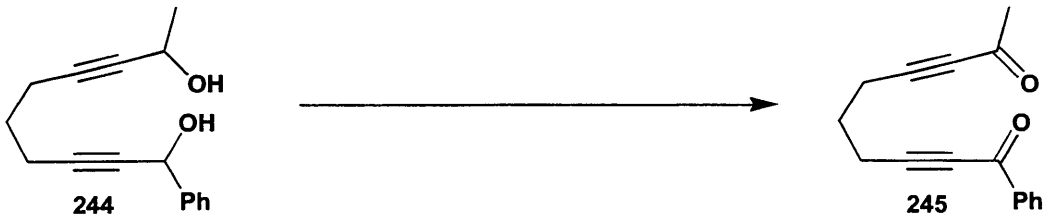
0.308 g of a yellow oil. Column chromatography on 10 g of silica gel (elution with 50% diethyl ether-pentane) provided 0.129 g (33% for the two steps) of diol **244** as a colorless oil.

IR (film)	3350, 3060, 3020, 2960, 2920, 2880, 2860, 2200, 600, 1490, 1445, 1420, 1370, 1320, 1280, 1190, 1140, 1120, 1080, 1000, 920, and 890 cm^{-1}.
^{1}H NMR (300 MHz, $CDCl_3$)	7.55-7.53 (m, 2H), 7.41-7.32 (m, 3H), 5.41 (br s, 1H), 4.52-4.49 (m, 1H) 2.92 (br s, 1H), 2.87 (br s, 1H), 2.35 (d of t, J = 7.1 Hz, J = 1.9 Hz, 2H), 2.29 (d of t, J = 7.2, J = 1.8 Hz, 2H), 1.70 (app quintet, J = 7.0 Hz, 2H), and 1.38 (d, J = 6.4 Hz, 2H)
^{13}C NMR (75 MHz, $CDCl_3$)	141.1, 128.6, 128.2, 126.6, 86.4, 83.4, 83.0, 80.7, 64.7, 58.5, 27.4, 24.6, 18.0, and 17.9.



244

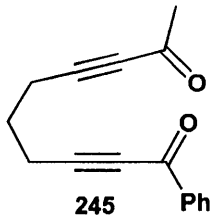




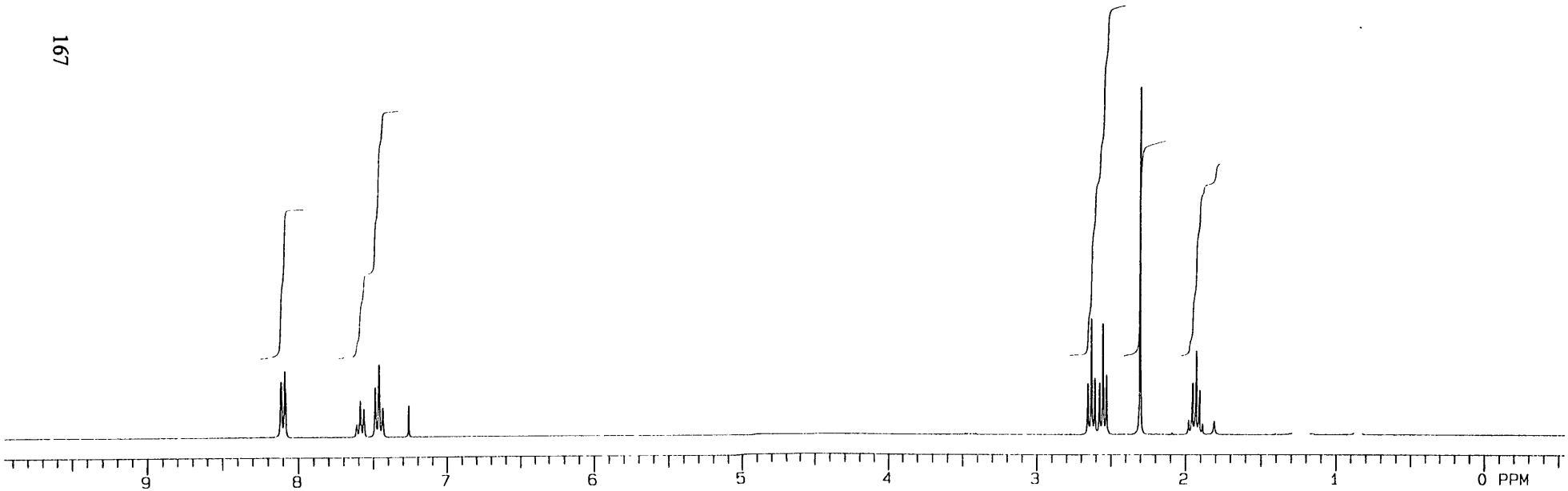
9-Benzoyl-nona-3,8-diyn-2-one (245)

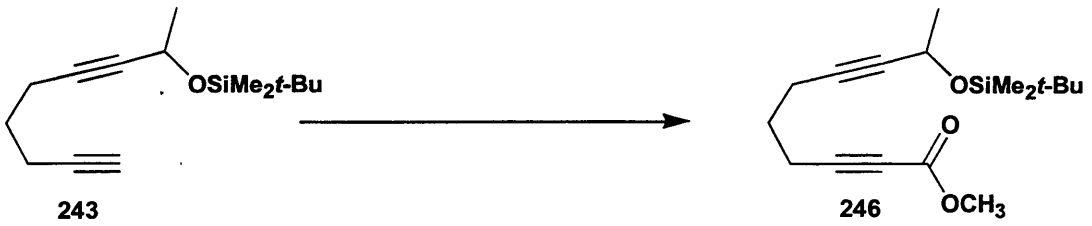
A 50-mL, round-bottomed flask equipped with rubber septum with argon inlet needle was charged with diol **244** (0.241 g, 0.987 mmol), 20 mL of dichloromethane, and the Dess-Martin reagent (1.0 g, 2.37 mmol) . The solution was stirred at 25 °C for 1 h and then concentrated and diluted with 15 mL diethyl ether and 15 mL of saturated $NaHCO_3$ solution. The aqueous layer was separated and extracted with two 30-mL portions of diethyl ether. The combined organic phases were washed with two 30-mL portions of a 1:1 mixture of saturated $NaHCO_3$ and saturated $Na_2S_2O_3$ solution, 30 mL of saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford 0.171 g of a colorless oil. Column chromatography on 10 g of silica gel (gradient elution with 20% diethyl ether-pentane) provided 0.147 g (63%) of dione **245** as a colorless oil.

IR (film)	3050, 2940, 2220, 2200, 1670, 1630, 1590, 1570, 1440, 1410, 1330, 1305, 1250, 1220, 1170, 1100, 1050, 1020, 970, 900 and 890 cm^{-1}.
^1H NMR (300 MHz, $CDCl_3$)	8.10 (d, J = 8.5 Hz, 2H), 7.57 (t, J = 7.9 Hz, 1H), 7.46 (app t, J = 8.0 Hz, 2H) 2.56 (t, J = 7.1, 2H), 2.56 (t, J = 6.9 Hz, 2H), 2.31 (s, 3H), and 1.94 (app quintet, J = 7.0 Hz, 2H).
^{13}C NMR (75 MHz, $CDCl_3$)	184.5, 177.9, 136.6, 134.0, 129.4, 128.5, 94.2, 91.5, 82.0, 80.2, 32.7, 25.8, 18.2, and 18.0.



245

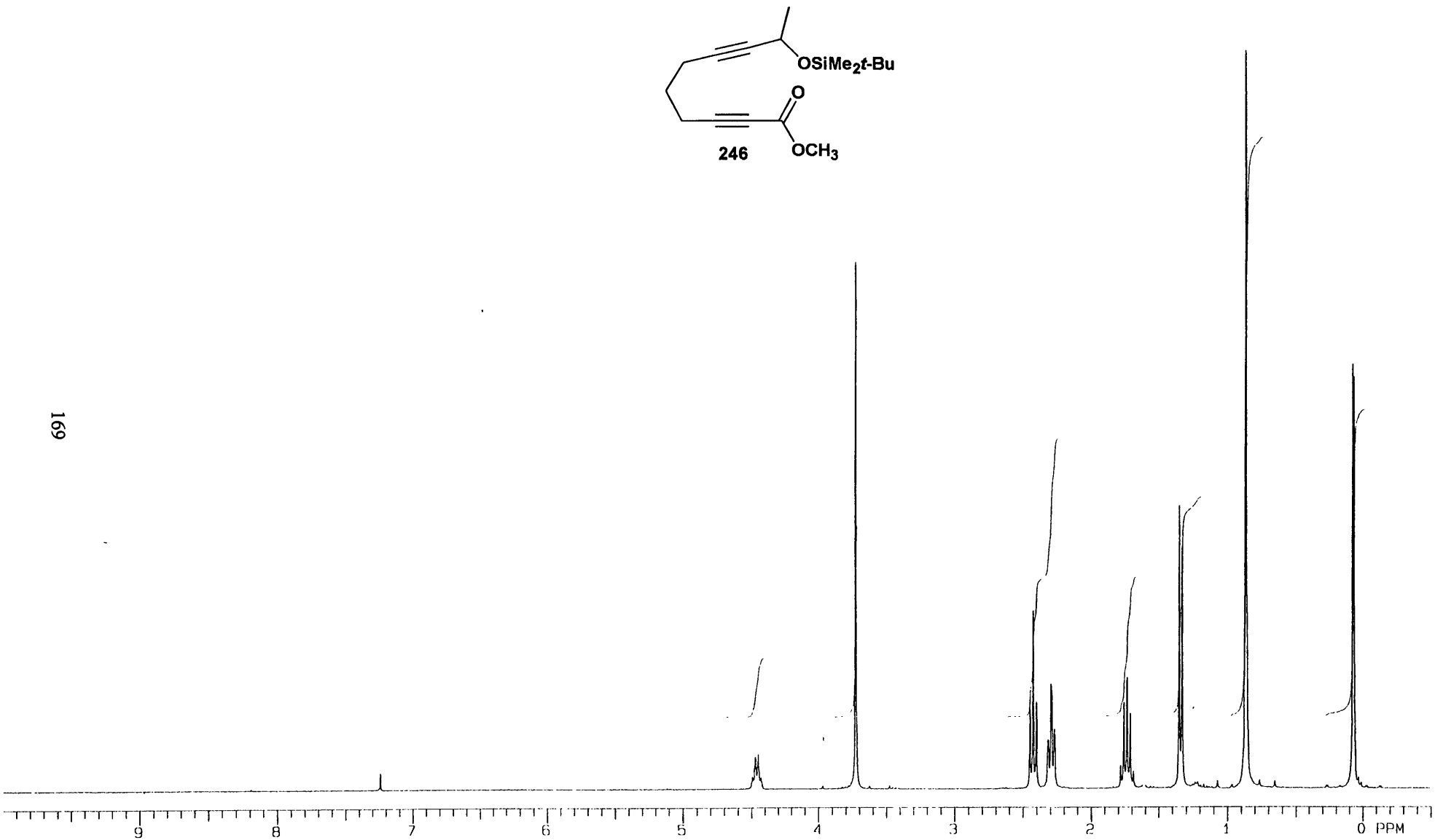


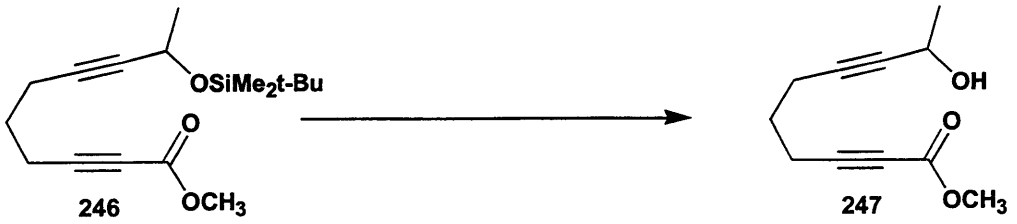


Methyl-9-(*tert*-butyldimethylsilyloxy)deca-2,7-diynoate (246)

A 100-mL, three-necked, round-bottomed flask equipped with rubber septum, glass stopper, and argon inlet adapter was charged with silyl ether **243** (0.500 g, 2.0 mmol), and 33 mL of tetrahydrofuran and cooled at -78 °C using a dry ice-acetone bath. A *n*-butyllithium solution (2.39 M in hexanes, 1.08 mL, 2.60 mmol) was added dropwise via syringe over 5 min and the resulting mixture was stirred at -78 °C for 15 min. A precooled -78 °C solution of methyl chloroformate (0.409 mL, 0.567 g, 6.0 mmol) in 7 mL of tetrahydrofuran was added dropwise via cannula over 4 min. The resulting solution was stirred at -78 °C for 3 h, and then diluted with 20 mL of saturated NH_4Cl solution and allowed to warm to room temperature. The aqueous layer was separated and extracted with three 30-mL portions of diethyl ether. The combined organic phases were washed with 30 mL of saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford 0.614 g of a colorless oil. Column chromatography on 20 g of silica gel (elution with 20% diethyl ether-pentane) provided 0.513 g (83%) of the desired ester **246** as a colorless oil.

IR (film)	3020, 2840, 2200, 1700, 1430, 1250, 1150, 1070, 1020, 930, 800, and 770 cm^{-1}.
^1H NMR (300 MHz, $CDCl_3$)	4.47-4.44 (m, 1H), 3.73 (s, 3H), 2.42 (t, J = 7.1 Hz, 2H), 2.29 (t of d, J = 6.9 Hz, J = 1.8 Hz, 2H), 1.73 (app quintet, J = 7.0 Hz, 2H), 1.34 (d, J = 6.4 Hz, 3H), 0.87 (s, 9H), 0.08 (s, 3H), and 0.07 (s, 3H).
^{13}C NMR (75 MHz, $CDCl_3$)	154.1, 88.6, 84.0, 81.6, 73.2, 59.1, 52.5, 26.5, 25.8, 25.6, 18.2, 17.8, 17.6, -4.66 and -4.96.

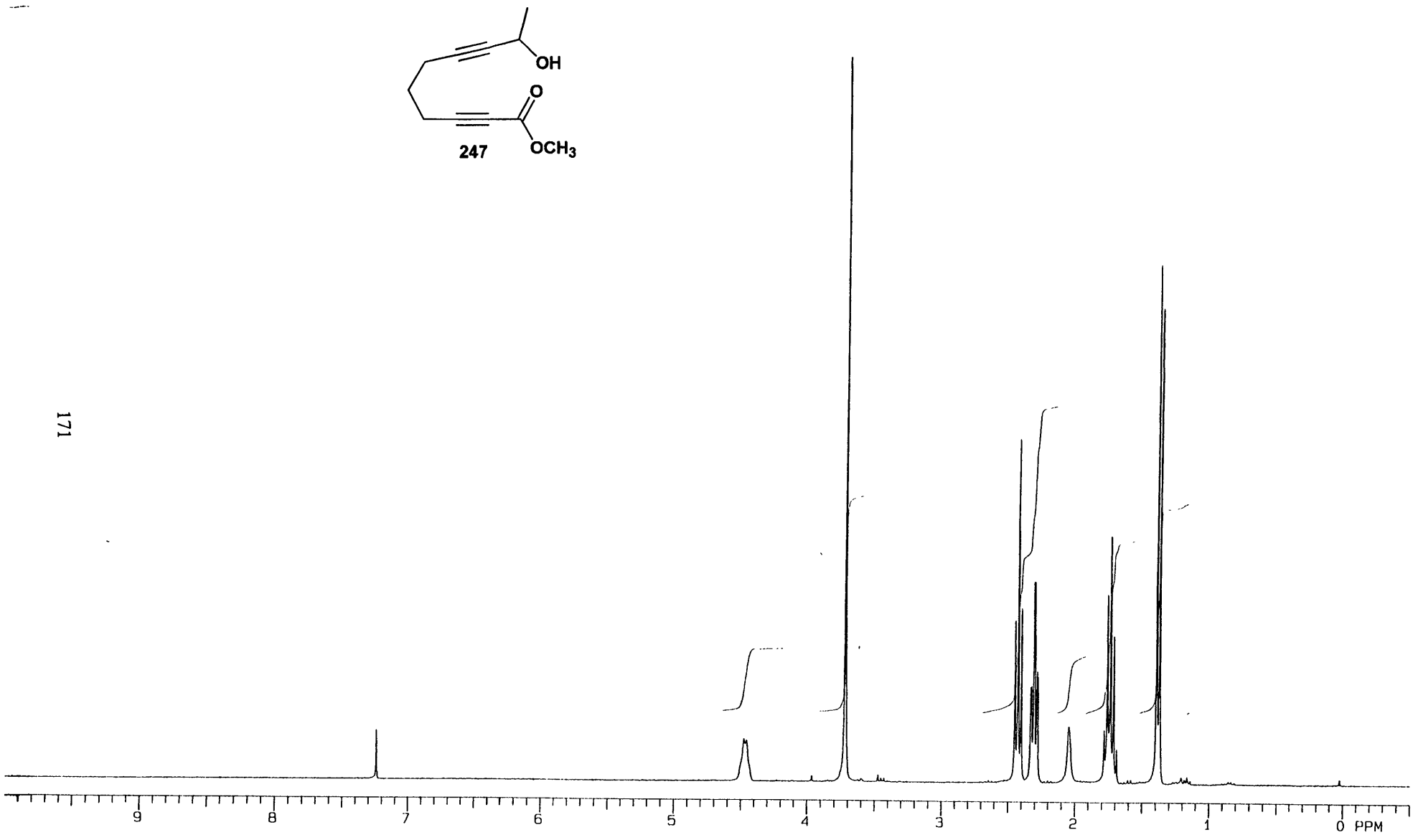

OSiMe2t-Bu
O
OCH3
246
9
8
7
6
5
4
3
2
1
0 PPM

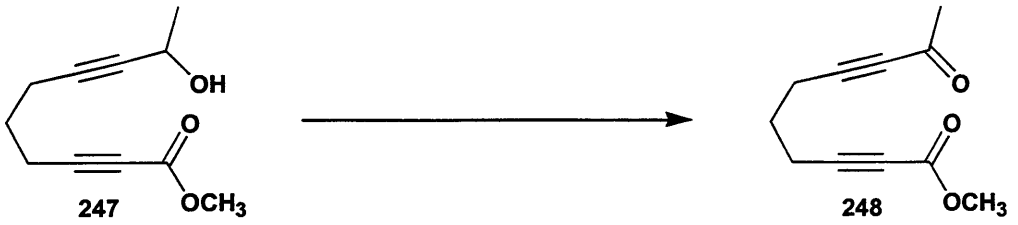


Methyl-9-hydroxy-deca-2,7-diynoate (247)

A 250-mL, round-bottomed flask equipped with rubber septum and argon inlet needle was charged with ester **246** (0.513 g, 1.66 mmol), 80 mL methanol, and 48% aqueous hydrogen fluoride (0.345 mL, 8.3 mmol) and the resulting mixture was stirred at 25 °C for 2 h. The reaction solution was neutralized by the addition of ca. 1 mL of triethylamine and diluted with 10 mL of saturated $NaHCO_3$ solution. The aqueous layer was separated and extracted with three 30-mL portions of diethyl ether. The combined organic phases were washed with 40 mL H_2O, 30 mL of saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford 0.386 g of a yellow oil. Column chromatography on 15 g of silica gel (elution with 50% diethyl ether-pentane) provided 0.224g (70%) of the desired alcohol **247** as a colorless oil.

IR (film)	3350, 2940, 2220, 1690, 1420, 1250, 1150, 1060, 1000, and 880 cm^{-1}.
^1H NMR (300 MHz, $CDCl_3$)	4.48-4.45 (m, 1H), 3.72 (s, 3H), 2.43 (t, J = 7.1 Hz, 2H), 2.31 (d of t, J = 6.9 Hz, J = 1.8 Hz, 2H), 2.05 (br s, 1H), 1.74 (app quintet, J = 7.0 Hz, 2H), and 1.66 (d, J = 6.5 Hz, 3H).
^{13}C NMR (75 MHz, $CDCl_3$)	154.2, 88.7, 83.5, 82.6, 73.3, 58.4, 52.6, 26.4, 24.6, 17.8, and 17.7.

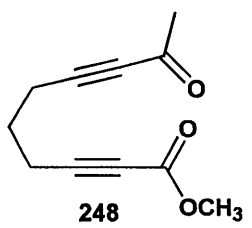

OH
O
OCH3
247
9
8
7
6
5
4
3
2
1
0 PPM



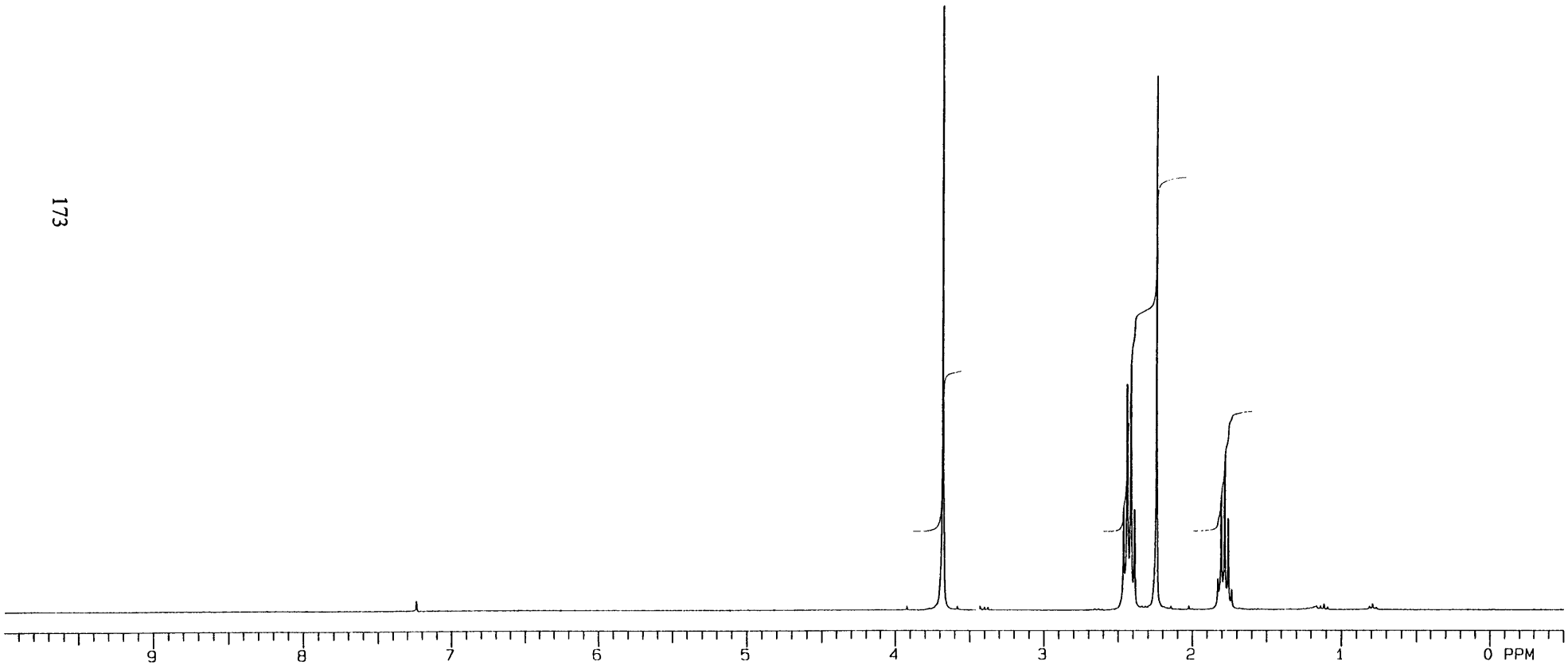
Methyl-9-oxo-deca-2,7-diynoate (248)

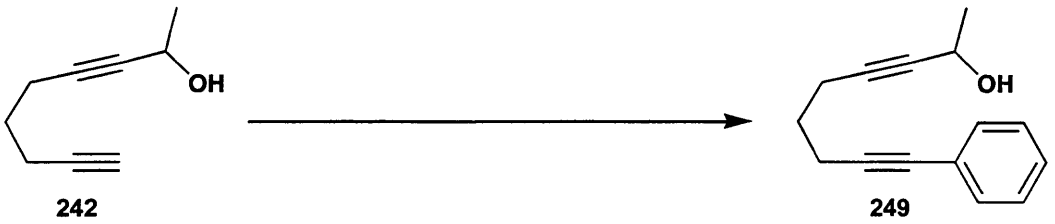
A 100-mL, round-bottomed flask equipped with rubber septum with argon inlet needle was charged with alcohol **247** (0.203 g, 1.04 mmol), 20 mL of dichloromethane, and the Dess-Martin reagent (0.531 g, 1.25 mmol). The solution stirred at 25 °C for 1 h and then concentrated and diluted with 15 mL of diethyl ether and 15 mL of saturated $NaHCO_3$ solution. The aqueous layer was separated and extracted with two 30-mL portions of diethyl ether. The combined organic phases were washed with two 30-mL portions of a 1:1 mixture of saturated $NaHCO_3$ and saturated $Na_2S_2O_3$ solution, 30 mL of saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford 0.209 g of a yellow oil. Column chromatography on 15 g of silica gel (elution with 10% diethyl ether-pentane) provided 0.139 g (70%) of ketone **248** as a colorless oil.

IR (film)	3000, 2980, 2840, 2240, 2200, 1710, 1670, 1460, 1360, 1250, 1070, 1010, 980, 810, and 740 cm^{-1}.
^1H NMR (300 MHz, $CDCl_3$)	3.68 (s, 3H), 2.43 (t, J = 7.1 Hz, 2H), 2.43 (t, J = 6.5, 2H), 2.24 (s, 3H), and 1.78 (app quintet, J = 6.8 Hz, 2H).
^{13}C NMR (75 MHz, $CDCl_3$)	184.4, 153.8, 91.4, 87.4, 81.8, 73.6, 52.5, 32.6, 25.5, 17.8, and 17.6.



248



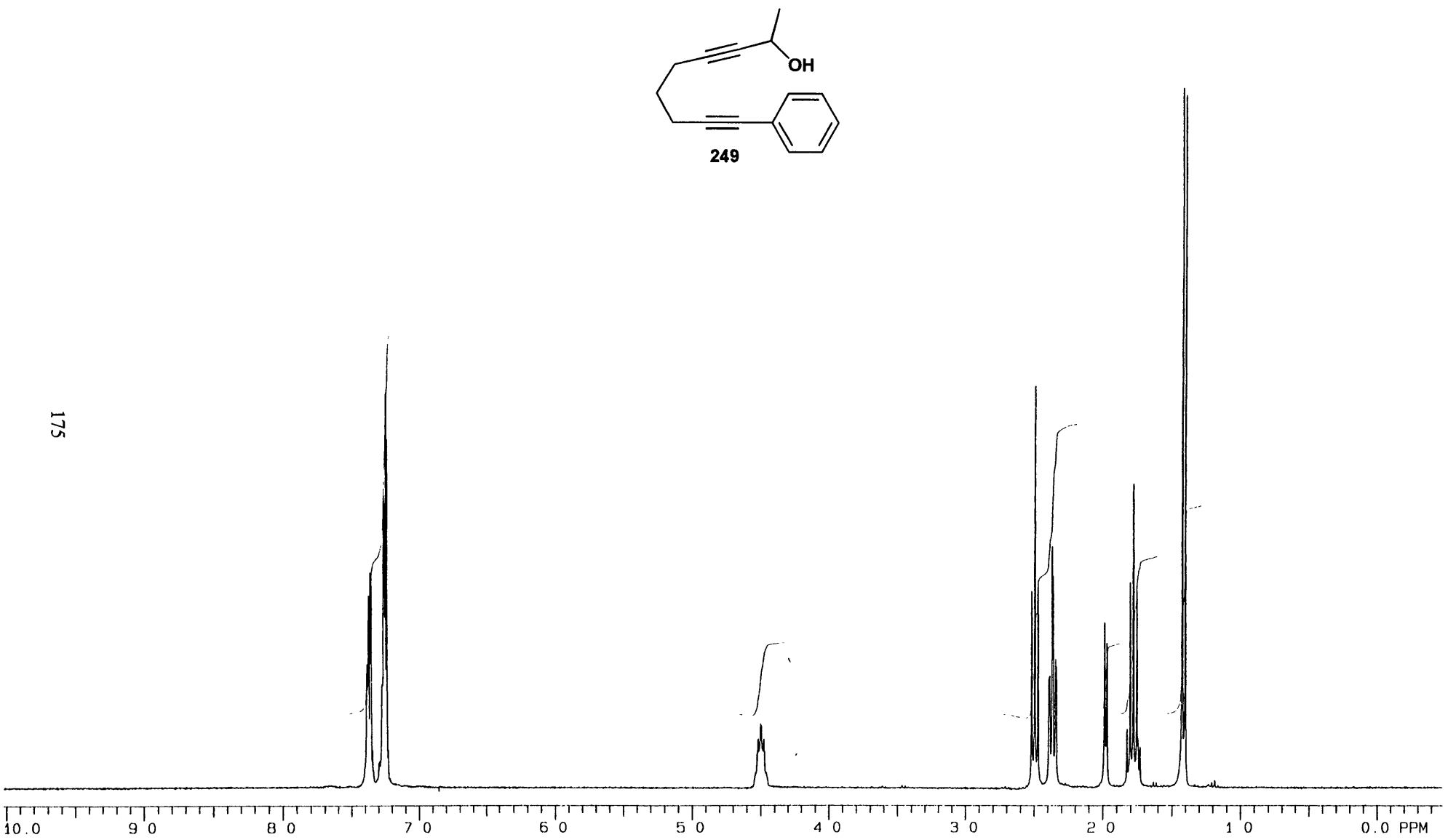


242 249

9-Phenyl-nona-3,8-diyn-2-ol (249)

A 10-mL, two-necked, round-bottomed flask equipped with rubber septum and argon inlet adapter and wrapped in aluminum foil was charged with alcohol **242** (0.251 g, 1.84 mmol) and 5 mL of diethylamine. After degassing the solution under a stream of argon for 15 minutes in the dark, iodobenzene (0.206 mL, 0.376 g, 1.84 mmol) was added dropwise via syringe over 2 min. Dichlorobis(triphenylphosphine)palladium (0.026 g, 0.037 mmol) and copper (I) iodide (0.014 g, 0.074 mmol) were added, and the resulting solution was stirred at 25 °C in the dark for 18 h. The reaction solution was concentrated and then diluted with 20 mL of H_2O and 20 mL of diethyl ether. The aqueous layer was separated and extracted with two 20-mL portions of diethyl ether. The combined organic phases were washed with 30 mL of saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford 0.536 g of an orange oil. Column chromatography on 12 g of silica gel (elution with 30% diethyl ether-pentane) provided 0.329 g (84%) of propargylic alcohol **249** as an orange oil.

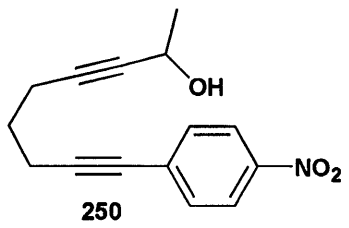
IR (film)	3360, 3100 1080, 2980, 2940, 2920, 2900, 2880, 2260, 1600, 1490, 1440, 1430, 1370, 1340, 1300, 1150, 1070, 1000, 910, 880, 750, and 690 cm^{-1}.
^1H NMR (300 MHz, $CDCl_3$)	7.39-7.35 (m, 2H), 7.27-7.23 (m, 3H), 4.47-4.53 (m, 1H), 2.49 (t, J = 6.6 Hz, 2H), 2.37 (t of d, J = 7.7 Hz, J = 2.0 Hz, 2H), 1.98 (d, J = 5.6 Hz, 1H), 1.76 (app quintet, J = 7.1 Hz, 2H), and 1.41 (d, J = 7.2 Hz, 3H).
^{13}C NMR (75 MHz, $CDCl_3$)	131.5, 128.2, 127.6, 123.7, 89.0, 83.5, 82.9, 81.2, 58.5, 27.8, 24.7, 18.5, and 17.9.


OH
249
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0 PPM

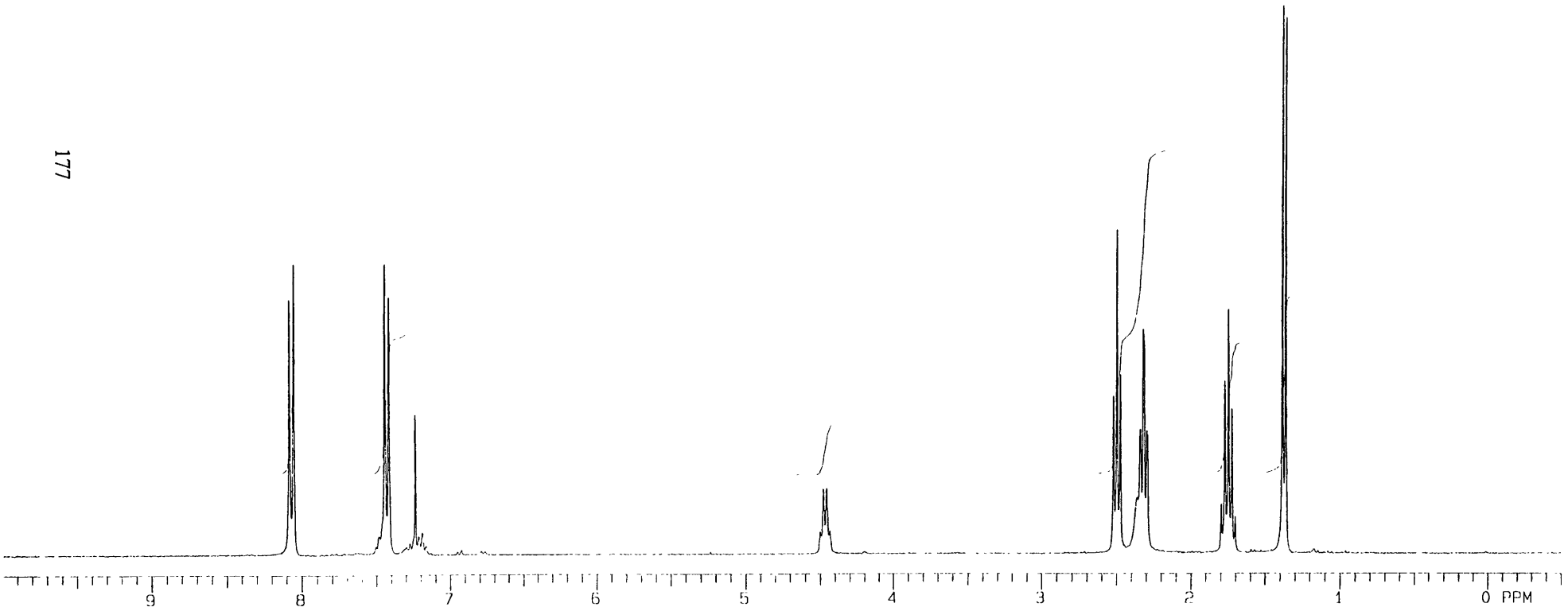
9-*p*-Nitrophenyl-nona-3,8-diyn-2-ol (250)

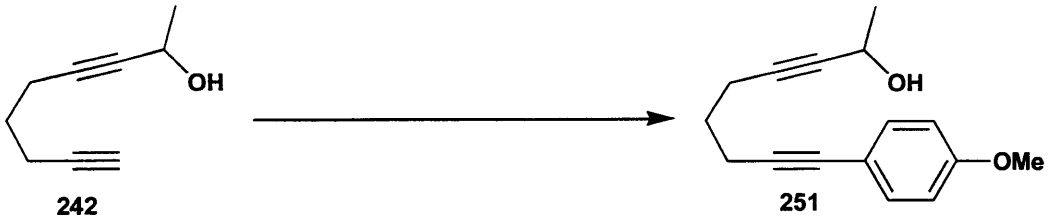
A 10-mL, two-necked, round-bottomed flask equipped with rubber septum and argon inlet adapter and wrapped in aluminum foil was charged with alcohol **242** (0.150 g, 1.10 mmol) and 3 mL of diethylamine. After degassing the solution with a stream of argon for 15 minutes in the dark, 1-iodo-4 nitrobenzene (0.274 g, 1.10 mmol), dichlorobis-(triphenylphosphine)palladium (0.015g, 0.022 mmol), and copper (I) iodide (0.004 g, 0.044 mmol) were added and the resulting solution stirred at 25 °C in the dark for 18 h. The reaction solution was concentrated and then diluted with 20 mL of H_2O and 20 mL of diethyl ether. The aqueous layer was separated and extracted with two 20-mL portions of diethyl ether. The combined organic phases were washed with 30 mL of saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford 0.447 g of an orange oil. Column chromatography on 12 g of silica gel (elution with 50% diethyl ether-pentane) provided 0.243 g (86%) of propargylic alcohol **250** as an orange oil.

IR (film)	3600, 3100, 3060, 2980, 2940, 2920, 2900, 2880, 2220, 1590, 1510, 1490, 1430, 1340, 1280, 1260, 1170, 1150, 1100, 1070, 1000, 880, 850, and 730 cm^{-1}.
^1H NMR (300 MHz, $CDCl_3$)	8.07 (d, J = 8.8 Hz, 2H), 7.46 (d, J = 8.8 Hz, 2H), 4.50-4.44 (m, 1H), 2.50 (t, J = 7.0 Hz, 2H), 2.36 (br s, 1H), 2.32 (t of d, J = 7.2 Hz, J = 1.8 Hz, 2H), 1.75 (app quintet, J = 7.1 Hz, 2H), and 1.37 (d, J = 6.6 Hz, 3H).
^{13}C NMR (75 MHz, $CDCl_3$)	146.5, 132.1, 130.7, 123.3, 95.3, 83.2, 82.6, 79.7, 58.3, 27.3, 24.5, 18.5, and 17.8.



250



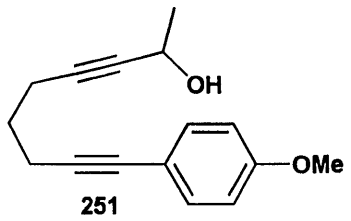


242 251

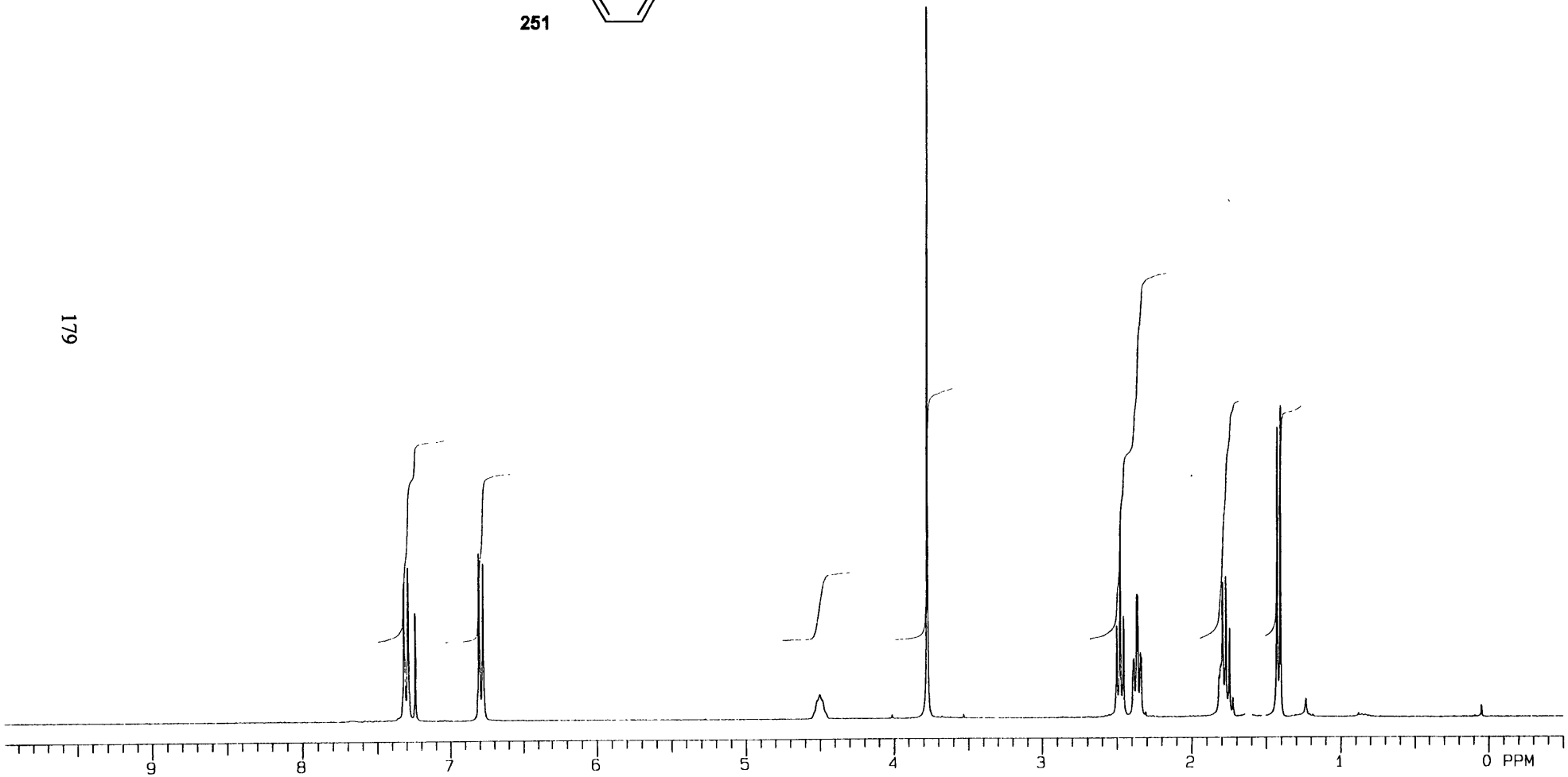
9-*p*-Methoxyphenyl-nona-3,8-diyn-2-ol (251)

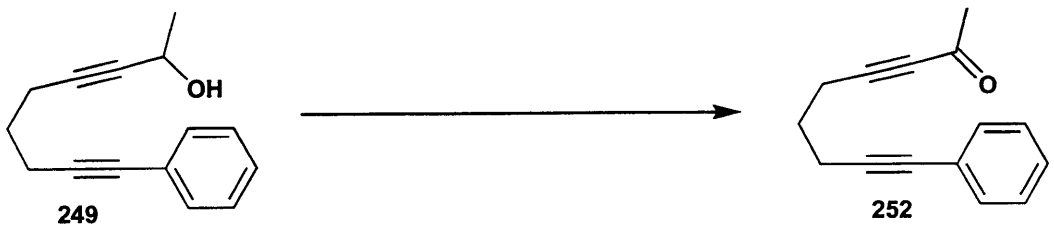
A 10-mL, two-necked, round-bottomed flask equipped with rubber septum and argon inlet adapter and wrapped in aluminum foil was charged with alcohol **242** (0.300 g, 2.20 mmol) and 6 mL of diethylamine. After degassing the solution with a stream of argon for 15 minutes in the dark, 4-iodoanisole (0.518 g, 2.20 mmol), dichlorobis-(triphenylphosphine)palladium (0.031 g, 0.044 mmol), and copper (I) iodide (0.008 g, 0.088 mmol) were added and the resulting solution stirred at 25 °C in the dark for 18 h. The reaction solution was concentrated and then diluted with 20 mL of H_2O and 20 mL of diethyl ether. The aqueous layer was separated and extracted with two 20-mL portions of diethyl ether. The combined organic phases were washed with 30 mL of saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford 0.568 g of a yellow oil. Column chromatography on 15 g of silica gel (elution with 50% diethyl ether-pentane) provided 0.400 g (75%) of propargylic alcohol **251** as a yellow oil.

IR (film)	3350, 2920, 2900, 2820, 2220, 1600, 1500, 1440, 1360, 1320, 1290, 1240, 1170, 1150, 1070, 1020, 900, 890, 830, and 730 cm^{-1}.
^1H NMR (300 MHz, $CDCl_3$)	7.31 (d, J = 8.8 Hz, 2H), 6.79 (d, J = 8.8 Hz, 2H), 4.50-4.48 (m, 1H), 3.78 (s, 3H), 2.48 (t, J = 7.0 Hz, 2H) 2.36 (t of d, J = 6.9 Hz, J = 1.8 Hz, 2H), 1.80 (br s, 1H), 1.76 (app quintet, J = 7.0 Hz, 2H), and 1.42 (d, J = 6.5 Hz, 3H).
^{13}C NMR (75 MHz, $CDCl_3$)	159.1, 132.8, 115.9, 113.8, 87.4, 83.6, 82.9, 80.9, 58.5, 55.2, 27.9, 24.7, 18.5, and 17.9.



251

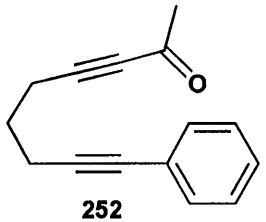




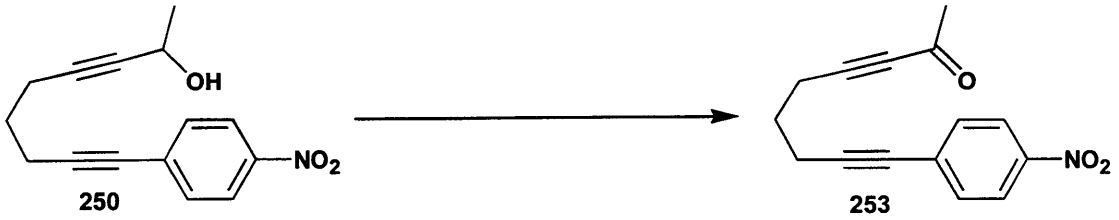
9-Phenyl-nona-3,8-diyn-2-one (252)

A 50-mL, round-bottomed flask equipped with rubber septum with argon inlet needle was charged with alcohol **249** (0.277 g, 1.31 mmol), 30 mL of dichloromethane, and the Dess-Martin reagent (0.609 g, 1.44 mmol). The solution was stirred at 25 °C for 1 h and then it was concentrated and diluted with 20 mL of diethyl ether and 20 mL of saturated $NaHCO_3$ solution. The aqueous layer was separated and extracted with two 30-mL portions of diethyl ether. The combined organic phases were washed with two 30-mL portions of a 1:1 mixture of saturated $NaHCO_3$ and saturated $Na_2S_2O_3$ solution, 30 mL of saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford 0.280 g of a yellow oil. Column chromatography on 10 g of silica gel (elution with 10% diethyl ether-pentane) provided 0.207 g (75%) of ketone **252** as a yellow oil.

IR (film)	3060, 2940, 2900, 2220, 1670, 1600, 1490, 1420, 1360, 1220, 1070, 1010, 960, 910, and 760 cm^{-1}.
^1H NMR (300 MHz, $CDCl_3$)	7.38-7.34 (m, 2H), 7.27-7.23 (m, 3H), 2.52 (t, J = 7.1 Hz, 2H), 2.52 (t, J = 6.9 Hz, 2H), 2.28 (s, 3H), and 1.84 (app quintet, J = 7.0 Hz, 2H).
^{13}C NMR (75 MHz, $CDCl_3$)	184.7, 131.5, 128.2, 127.8, 123.5, 92.7, 88.2, 81.7, 81.7, 32.7, 26.8, 18.6, and 18.0.



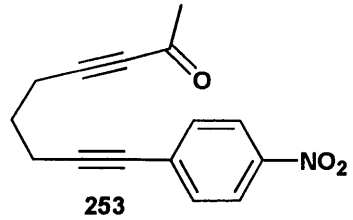
252



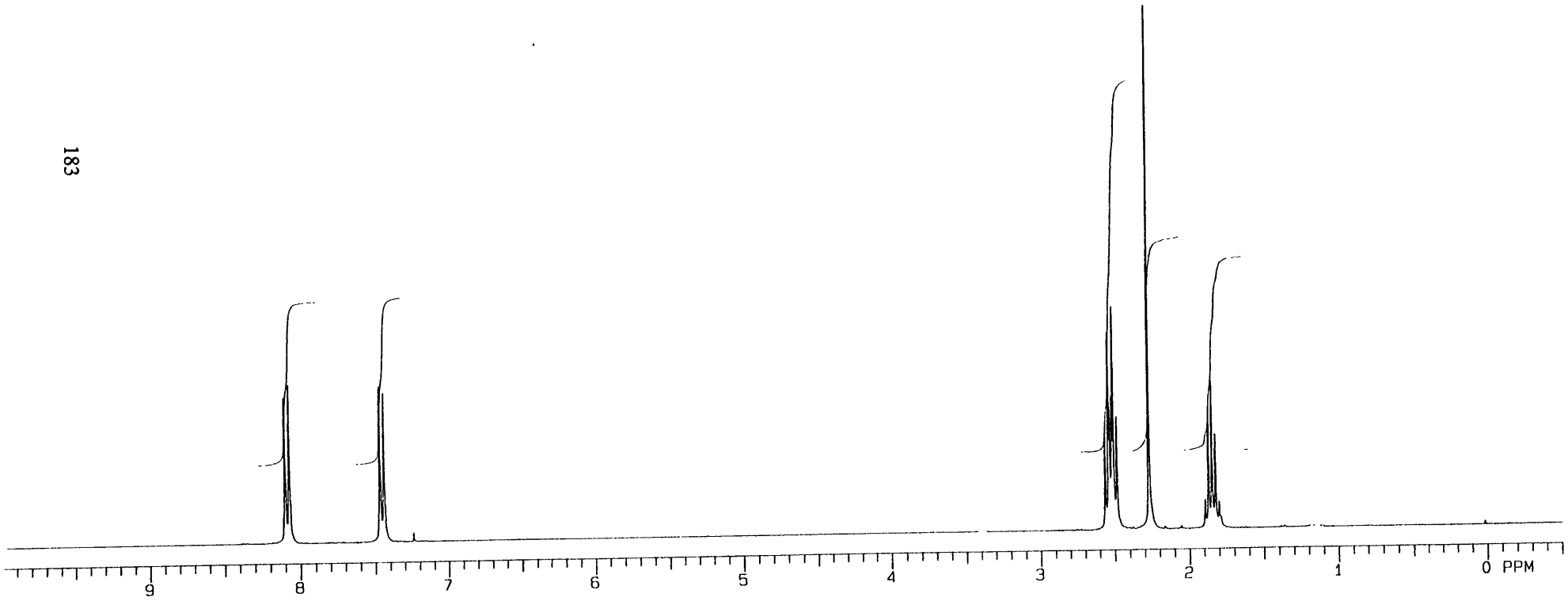
9-*p*-Nitrophenyl-nona-3,8-diyn-2-one (253)

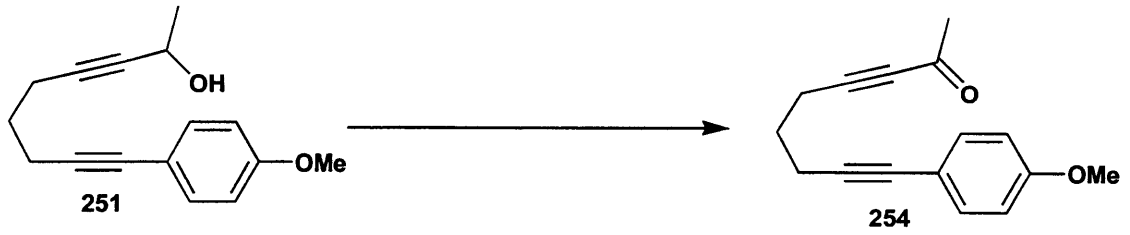
A 50-mL, round-bottomed flask equipped with rubber septum with argon inlet needle was charged with alcohol **250** (0.308 g, 1.20 mmol), 24 mL of dichloromethane, and the Dess-Martin reagent (0.611 g, 1.44 mmol). The solution was stirred at 25 °C for 1 h and then it was concentrated and diluted with 15 mL of diethyl ether and 15 mL of saturated $NaHCO_3$ solution. The aqueous layer was separated and extracted with two 30-mL portions of diethyl ether. The combined organic phases were washed with two 30-mL portions of a 1:1 mixture of saturated $NaHCO_3$ and saturated $Na_2S_2O_3$ solution, 30 mL of saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford 0.316 g of a yellow oil. Column chromatography on 10 g of silica gel (elution with 10% diethyl ether-pentane) provided 0.217 g (70%) of ketone **253** as a yellow oil.

IR (film)	3100, 3080, 2940, 2200, 1670, 1600, 1510, 1420, 1340, 1320, 1280, 1220, 1180, 1100, 1000, 960, 840, and 740 cm^{-1}.
^1H NMR (300 MHz, $CDCl_3$)	8.09 (d, J = 8.8 Hz, 2H), 7.45 (d, J = 8.8 Hz, 2H), 2.42 (t, J = 7.0 Hz, 2H), 2.42 (t, J = 7.1 Hz, 2H), 2.27 (s, 3H), and 1.85 (app quintet, J = 7.0 Hz, 2H).
^{13}C NMR (75 MHz, $CDCl_3$)	184.6, 146.7, 132.2, 130.5, 123.4, 94.4, 92.0, 81.8, 80.1, 32.6, 26.4, 18.6, and 18.0.



253

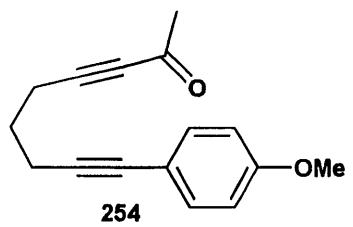




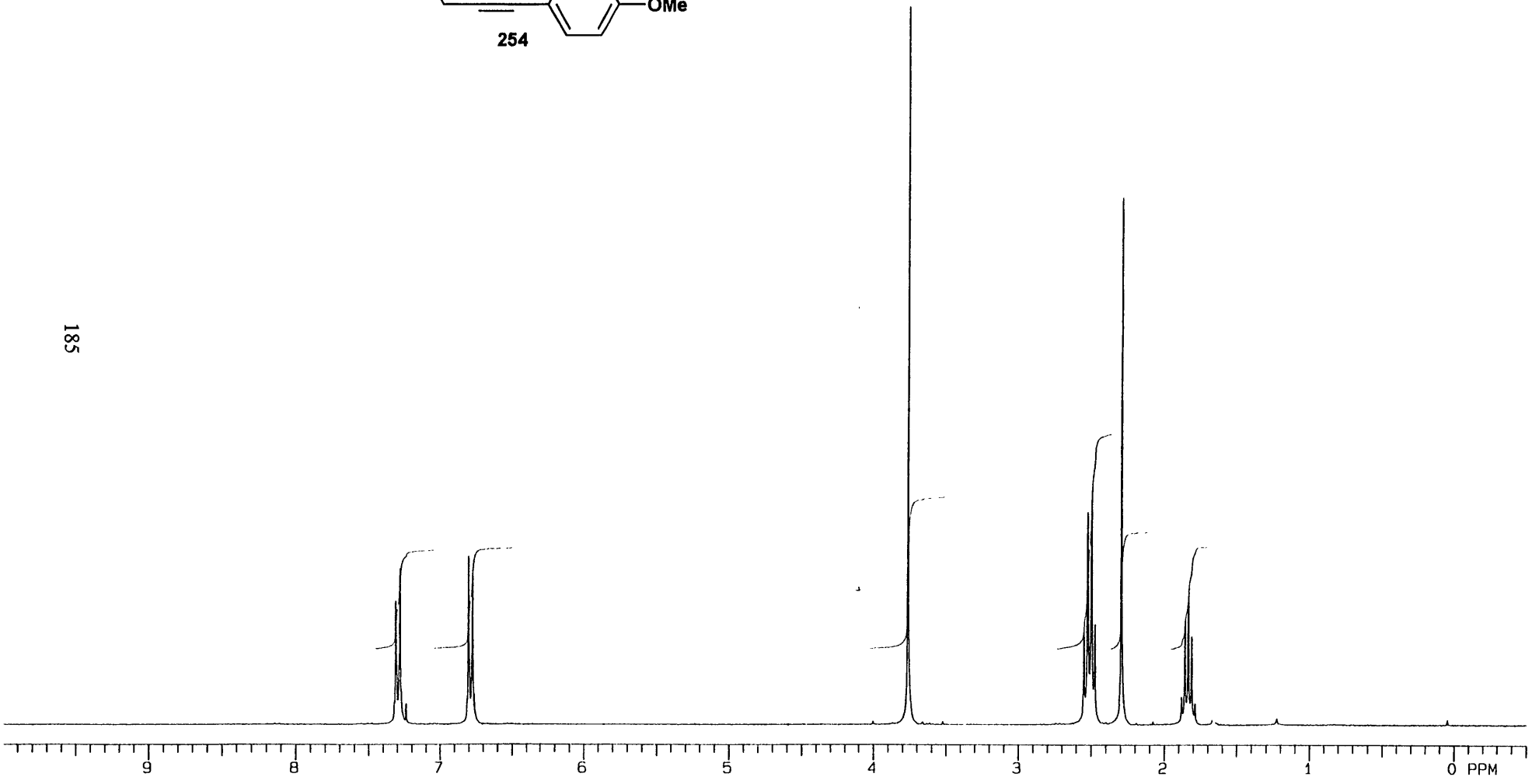
9-*p*-Methoxyphenyl-nona-3,8-diyn-2-one (254)

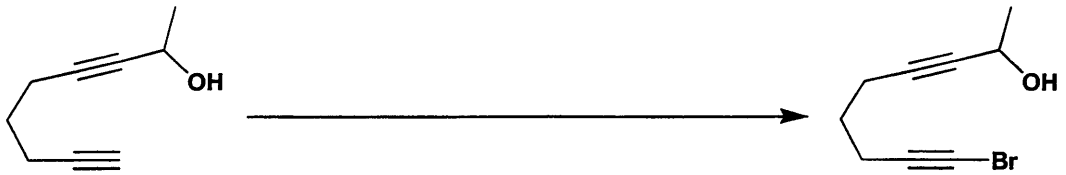
A 50-mL, round-bottomed flask equipped with a rubber septum with argon inlet needle was charged with alcohol **251** (0.394 g, 1.63 mmol), 33 mL of dichloromethane, and the Dess-Martin reagent (0.828 g, 1.95 mmol). The solution was stirred at 25 °C for 1 h and then concentrated and diluted with 15 mL diethyl ether and 15 mL of saturated $NaHCO_3$ solution. The aqueous layer was separated and extracted with two 30-mL portions of diethyl ether. The combined organic phases were washed with two 30-mL portions of a 1:1 mixture of saturated $NaHCO_3$ and saturated $Na_2S_2O_3$ solution, 30 mL of saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford 0.362 g of a yellow oil. Column chromatography on 15 g of silica gel (elution with 10% diethyl ether-pentane) provided 0.287 g (73%) of ketone **254** as a yellow oil.

IR (film)	3000, 2940, 2900, 2840, 2110, 1660, 1600, 1560, 1500, 1460, 1440, 1420, 1360, 1280, 1230, 1170, 1100, 1040, 960, 830 cm^{-1}.
^1H NMR (300 MHz, $CDCl_3$)	7.30 (d, J = 9.7 Hz, 2H), 6.78 (d, J = 9.7 Hz, 2H), 3.77 (s, 3H), 2.51 (t, J = 6.9 Hz, 2Hz), 2.51 (t, J = 7.2 Hz, 2H) 2.30 (s, 3H), 1.43 (m, 2 H); and 1.84 (app quintet, J = 7.0 Hz, 2H).
^{13}C NMR (75 MHz, $CDCl_3$)	184.6, 159.0, 132.7, 115.5, 113.7, 92.7, 86.5, 81.6, 81.3, 55.1, 32.6, 26.8, 18.5, and 17.9.



254



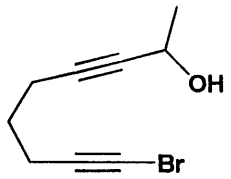


242 255

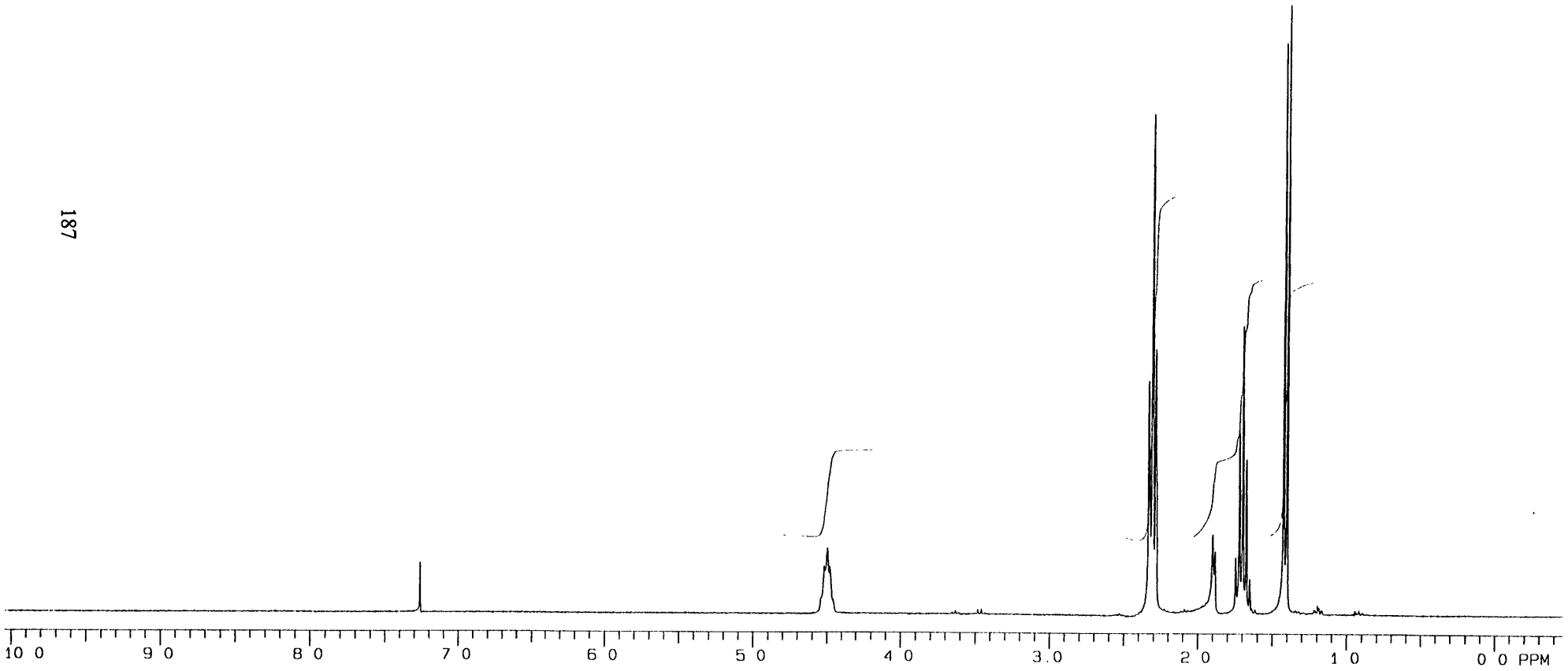
9-Bromo-nona-3,8-diyn-2-ol (255)

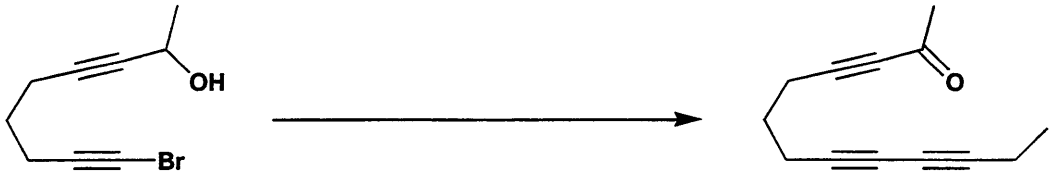
A 25-mL, three-necked, round-bottomed flask equipped with a rubber septum, argon inlet, and glass stopper and wrapped in aluminum foil was charged in the dark with alcohol **242** (0.200 g, 1.47 mmol), 10 mL acetone, *N*-bromosuccinimide (0.288 g, 1.62 mmol), and silver nitrate (0.026 g, 0.147 mmol). The solution was stirred in the dark at 25 °C for 4 h. The resulting cloudy mixture was diluted with 40 mL of H_2O and then extracted with three 40-mL portions of diethyl ether. The combined organic phases were washed with 40 mL of saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford 0.386 g of a yellow oil. Column chromatography on 12 g of silica gel (elution with 50% diethyl ether-pentane) provided 0.238 g (76%) of bromoacetylene **255** as a colorless oil.

IR (film)	3350, 2980, 2940, 2880, 2840, 2820, 2220, 2200, 1440, 1430, 1360, 1320, 1280, 1150, 1070, 1000, 940, 880, and 830 cm^{-1}
^1H NMR (300 MHz, $CDCl_3$)	4.52-4.48 (m, 1H), 2.31 (t, J = 6.7 Hz, 2H), 2.31 (t of d, J = 7.0 Hz, J = 2.6 Hz, 2H), 1.90 (d, J = 2.8 Hz, 1H), 1.70 (app quintet, J = 6.9 Hz, 2H) and 1.42 (d, J = 6.2 Hz, 3H).
^{13}C NMR (75 MHz, $CDCl_3$)	83.0, 79.2, 58.4, 38.4, 27.2, 24.6, 18.7, and 17.7.



255





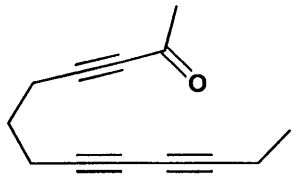
255 257

Trideca-3,8,10-triyn-2-one (257)

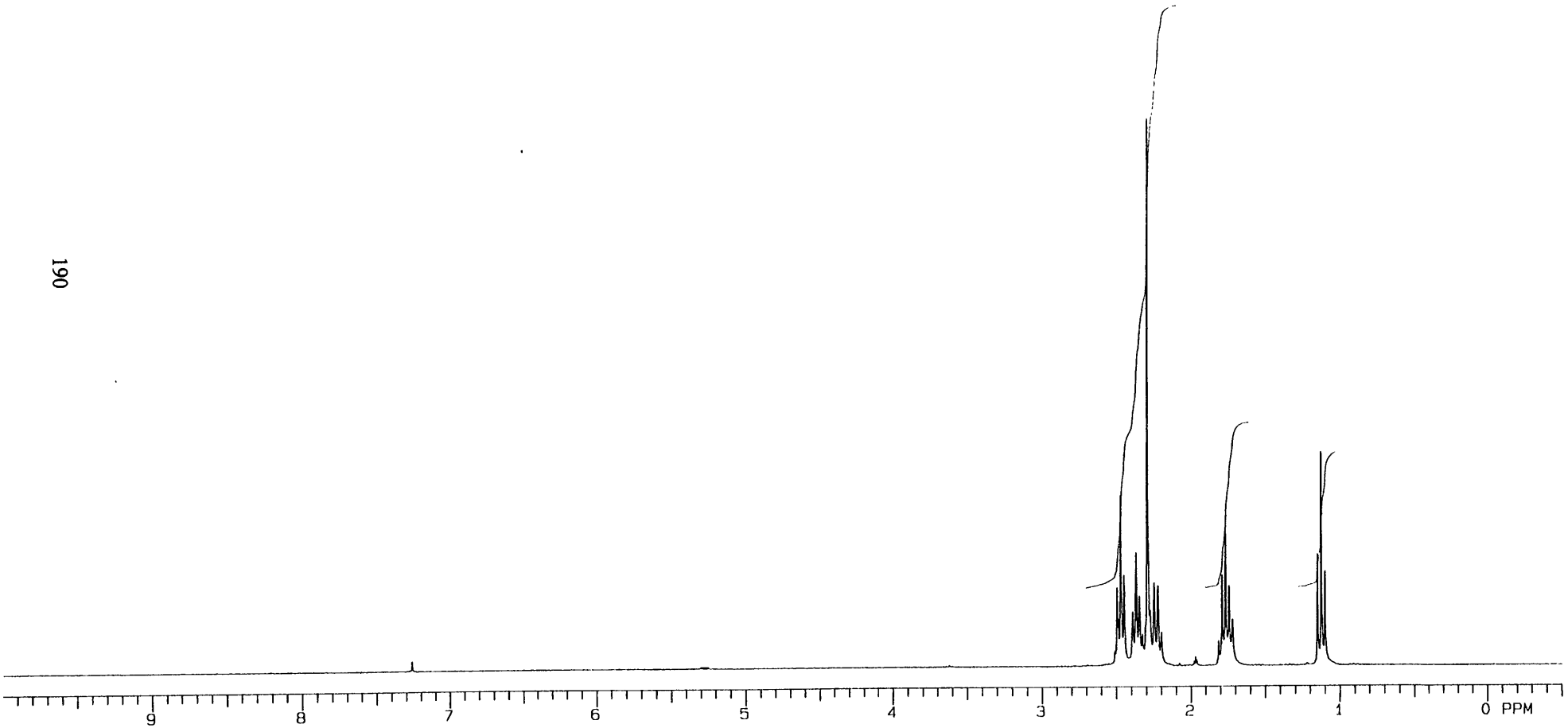
A 50-mL, three-necked, round-bottomed flask equipped with an argon inlet adapter, rubber septum, and glass stopper was charged with 8 mL of tetrahydrofuran and cooled at -78 °C using a dry ice-acetone bath. The glass stopper was replaced with a gas inlet and butyne was bubbled through the solution for 10 min. The gas inlet was removed and a *n*-butyllithium solution (2.41 M, 0.301 mL, 0.725 mmol) was added via syringe dropwise over 3 min. The solution was stirred in the dark at -78 °C for 20 min and then copper (I) bromide (0.104 g, 0.725 mmol) was added and the resulting solution was stirred at -78 °C for 15 min. The cooling bath was removed, the reaction mixture was stirred an additional 30 min, and then 15 mL of pyridine was added via syringe. A solution of bromoacetylene **255** (0.156 g, 0.725 mmol) in 2 mL of tetrahydrofuran was then added dropwise via cannula over 2 min and the resulting solution was stirred for 16 h in the dark at 25 °C. The reaction mixture was acidified with a 5N aqueous solution of hydrogen chloride and diluted with 40 mL of saturated NH_4Cl solution. The aqueous layer was separated and extracted with three 40-mL portions of diethyl ether. The combined organic phases were washed with 30 mL of saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford 0.216 g of a yellow oil. Column chromatography on 10 g of silica gel (elution with 30% diethyl ether-pentane) provided 0.104 g of a colorless oil. The oil was shown by ^1H NMR to be a 88:12 mixture of the desired trideca-3,8,10-triyn-2-ol with nona-3,8-diyn-2-ol, and was carried on without further purification to the next step in the sequence.

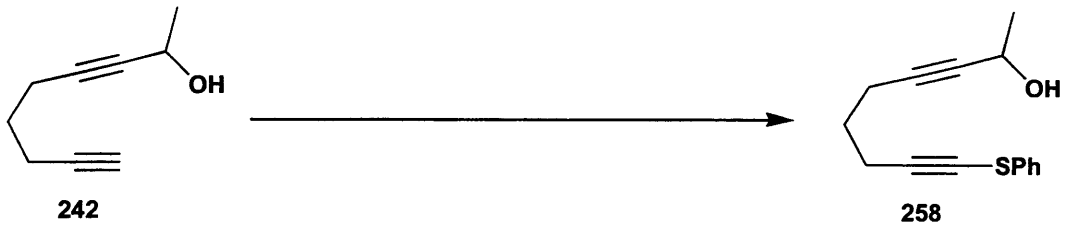
A 50-mL, round-bottomed flask equipped with rubber septum with argon inlet needle was charged via cannula with a solution of the above oil in 10 mL of dichloromethane. The Dess-Martin reagent (0.246 g, 0.580 mmol) was added and the resulting solution was stirred at 25 °C for 1h. The reaction mixture was concentrated and then diluted with 15 mL of diethyl ether and 15 mL of saturated $NaHCO_3$ solution. The aqueous layer was separated and extracted with two 30-mL portions of diethyl ether. The combined organic phases were washed with two 30-mL portions of a 1:1 mixture of saturated $NaHCO_3$ and saturated $Na_2S_2O_3$ solution, 30 mL of saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford 0.136 g of a yellow oil. Column chromatography on 15 g of silica gel (gradient elution with 20% diethyl ether-pentane) provided 0.049 g (32% for the two steps) of ketone **257** as a colorless oil.

IR (film)	2990, 2960, 2920, 2900, 2880, 2220, 2200, 2180, 1670, 1465, 1420, 1360, 1320, 1280, 1230, 1070, 1020, and 970 cm^{-1}.
^1H NMR (300 MHz, $CDCl_3$)	2.48 (t, J = 7.1 Hz, 2H), 2.36 (t, J = 7.1 Hz, 2H), 2.29 (s, 3H), 2.24 (quartet, J = 7.5 Hz, 2H), 1.75 (app quintet, J = 7.0 Hz, 2H) and 1.13 (t, J = 7.5 Hz, 3H).
^{13}C NMR (75 MHz, $CDCl_3$)	184.6, 92.2, 81.8, 79.3, 75.4, 66.4, 64.4, 32.7, 26.4, 18.3, 17.9, 13.3, and 12.8.



257



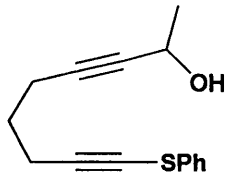


242 258

9-Thiophenyl-nona-3,8-diyn-2-ol (258)

A 50-mL, three-necked, round-bottomed flask equipped with a rubber septum, glass stopper, and addition funnel with argon inlet adapter was charged with alcohol **242** (0.205 g, 1.50 mmol) and 25 mL of tetrahydrofuran and the resulting solution was cooled at -78 °C with a dry ice-acetone bath. A *n*-butyllithium solution (2.32 M in hexanes, 1.49 mL, 3.46 mmol) was added dropwise via syringe over 4 min. The resulting mixture was stirred at -78 °C for 15 min and then the addition funnel was charged with a solution of diphenyl disulfide (0.326 g, 1.50 mmol) in 5 mL of tetrahydrofuran. The disulfide solution was added dropwise over 10 min then the reaction solution was stirred for 2 h at -78 °C. The reaction mixture was poured into 20 mL of saturated NH_4Cl solution that had been cooled to 0 °C, and allowed to warm to room temperature. The aqueous layer was separated and extracted with three 30-mL portions of diethyl ether. The combined organic phases were washed with three 40-mL portions of saturated K_2CO_3 solution, 30 mL of saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford 0.416 g of a yellow oil. Column chromatography on 20 g of silica gel (elution with 50% diethyl ether-pentane) provided 0.188 g (51%) of sulfide **258** as a colorless oil.

IR (film)	3350, 3040, 2980, 2980, 2960, 2920, 2240, 1570, 1480, 1430, 1370, 1320, 1280, 1140, 1080, 910, 880, 730 cm^{-1}.
^1H NMR (300 MHz, $CDCl_3$)	7.42 (d, J = 8.6 Hz, 2H), 7.32 (t, J = 7.8 Hz, 2H), 7.21 (t, J = 7.4 Hz, 1H), 4.47-4.53 (m, 1H), 2.57 (t, J = 7.0 Hz, 2H), 2.38 (t of d, J = 7.1 Hz, J = 2.4 Hz, 2H), 1.84 (br s, 1H), 1.82 (app quintet, J = 7.1 Hz, 2H), and 1.44 (d, J = 6.5 Hz, 3H).
^{13}C NMR (75 MHz, $CDCl_3$)	133.4, 129.0, 126.1, 125.8, 98.6, 83.1, 65.6, 58.4, 27.5, 24.6, 19.3, and 17.8.



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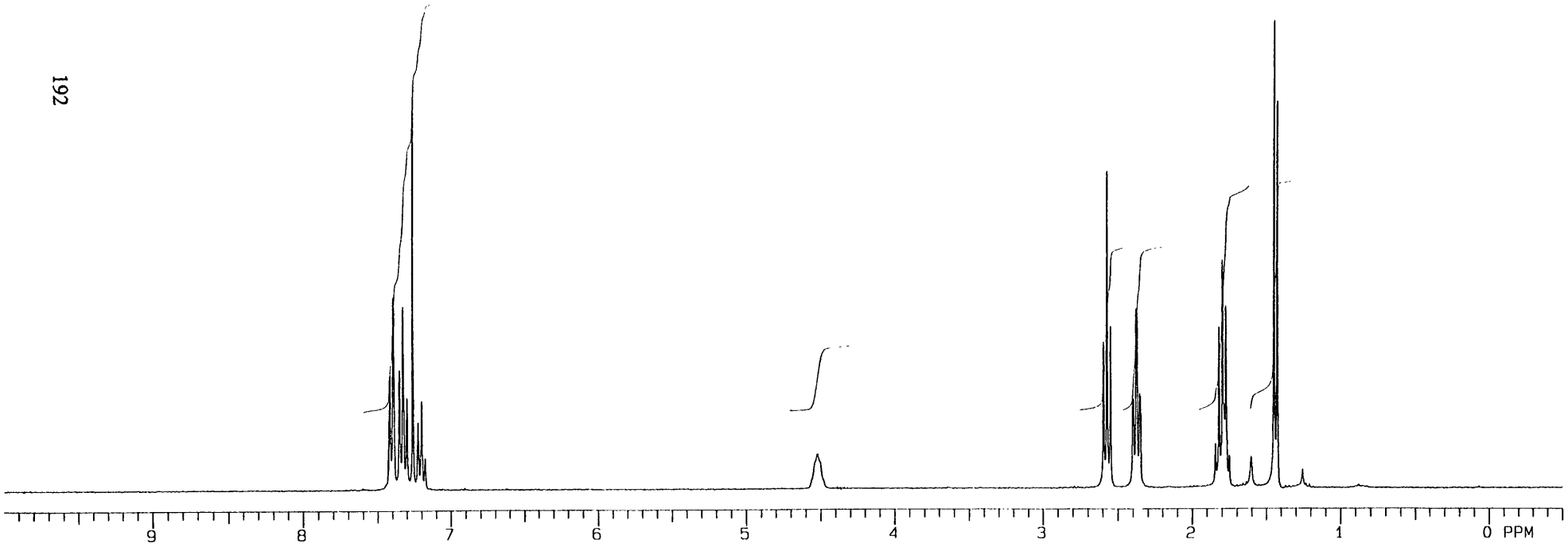
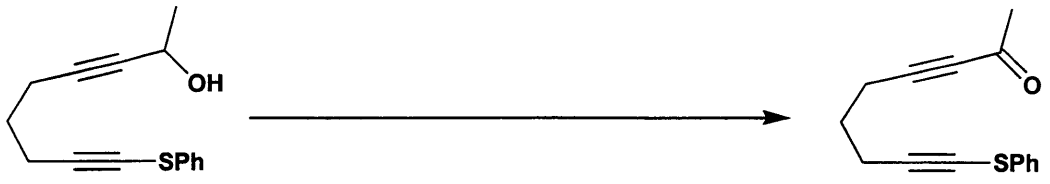


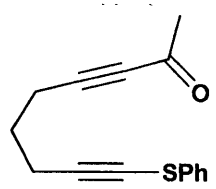


258 259

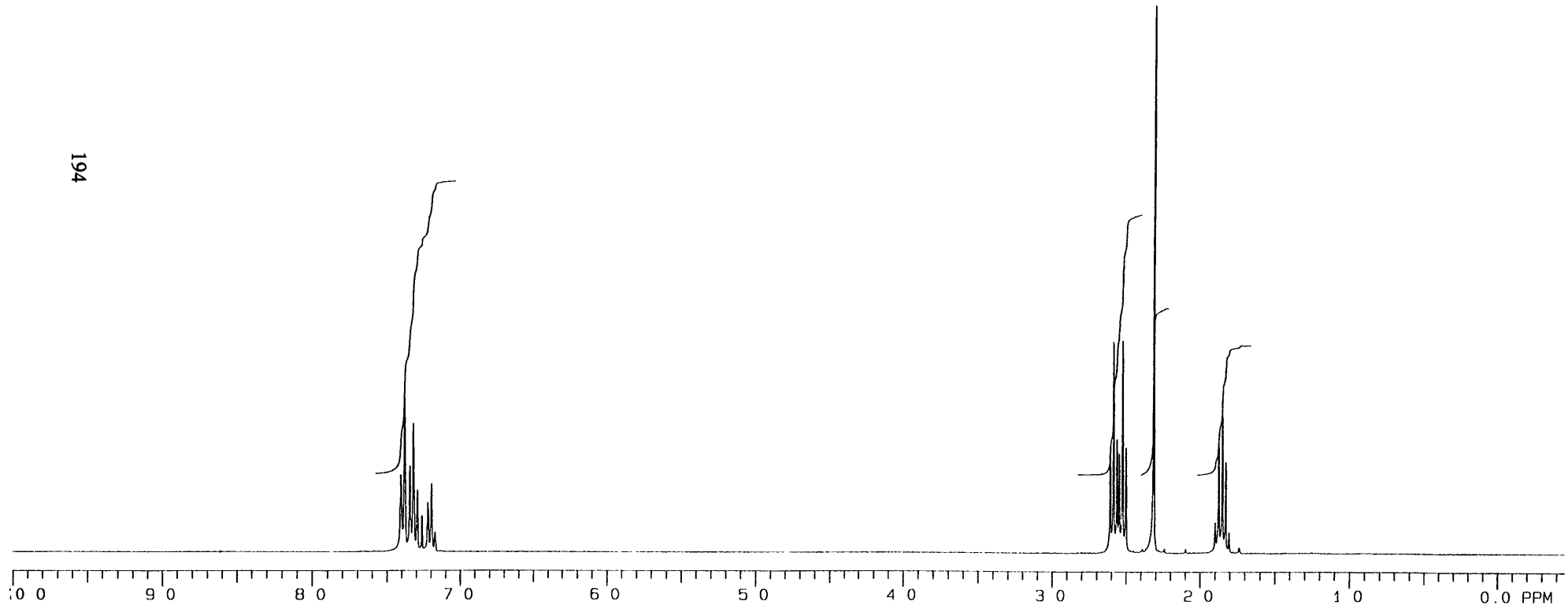
9-Thiophenyl-nona-3,8-diyn-2-one (259)

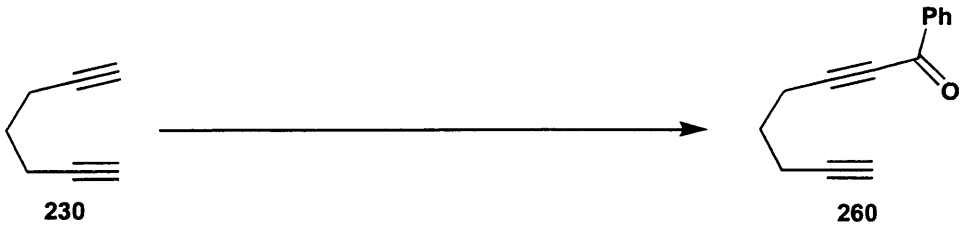
A 25-mL, round-bottomed flask equipped with rubber septum with argon inlet needle was charged with alcohol **258** (0.119 g, 0.487 mmol), 10 mL of dichloromethane, and the Dess-Martin reagent (0.248 g, 0.584 mmol). The solution was stirred at 25 °C for 1 h and then it was concentrated and diluted with 20 mL of diethyl ether and 20 mL of saturated $NaHCO_3$ solution. The aqueous layer was separated and extracted with two 30-mL portions of diethyl ether. The combined organic phases were washed with two 30-mL portions of a 1:1 mixture of saturated $NaHCO_3$ and saturated $Na_2S_2O_3$ solution, 30 mL of saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford 0.106 g of a yellow oil. Column chromatography on 5 g of silica gel (gradient elution with 20% diethyl ether-pentane) provided 0.070 g (59%) of propargyl ketone **259** as a colorless oil.

IR (film)	3040, 3000, 2940, 2920, 2200, 1670, 1580, 1480, 1430, 1410, 1360, 1220, 1080, 920, 860, and 730 cm^{-1}.
^1H NMR (300 MHz, $CDCl_3$)	7.39 (d, J = 8.5 Hz, 2H), 7.33 (t, J = 7.9 Hz, 2H), 7.21 (d, J = 7.5 Hz, 2H), 2.59 (t, J = 6.9 Hz, 2H), 2.52 (t, J = 6.7 Hz, 2H), 2.31 (s, 3H), and 1.85 (app quintet, J = 6.8 Hz, 2H).
^{13}C NMR (75 MHz, $CDCl_3$)	184.5, 133.1, 129.1, 126.2, 125.8, 97.7, 92.2, 81.8, 66.3, 32.6, 26.6, 19.4, and 17.9.



259





230 260

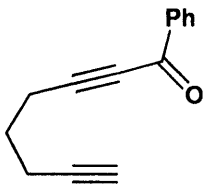
1-Benzoyl-hepta-1,6-diyne (260)

A 50-mL, three-necked, round-bottomed flask equipped with rubber septum, glass stopper, and argon inlet adapter was charged with 1,6-heptadiyne (**230**) (0.282 mL, 0.230 g, 2.50 mmol) and 25 mL of tetrahydrofuran and the resulting solution was cooled at 0 °C using an ice-water bath. An ethylmagnesium bromide solution (3.0 M in diethyl ether, 0.833 mL, 2.50 mmol) was added dropwise via syringe over 3 min. The resulting mixture was stirred at 0 °C for 2 h and then benzaldehyde (0.382 mL, 0.399 g, 3.75 mmol) was added via syringe over 3 min. The reaction mixture was stirred at 0 °C for 30 min, diluted with 15 mL of saturated NH_4Cl solution, and allowed to warm to room temperature. The aqueous layer was separated and extracted with three 30-mL portions of diethyl ether. The combined organic phases were washed with 30 mL of saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford 0.703 g of a yellow oil. Column chromatography on 30 g of silica gel (gradient elution with 15-20% diethyl ether-pentane) provided 0.180 g of impure propargylic alcohol as a colorless oil. The purity was estimated to be ca 85% by ^1H NMR analysis.

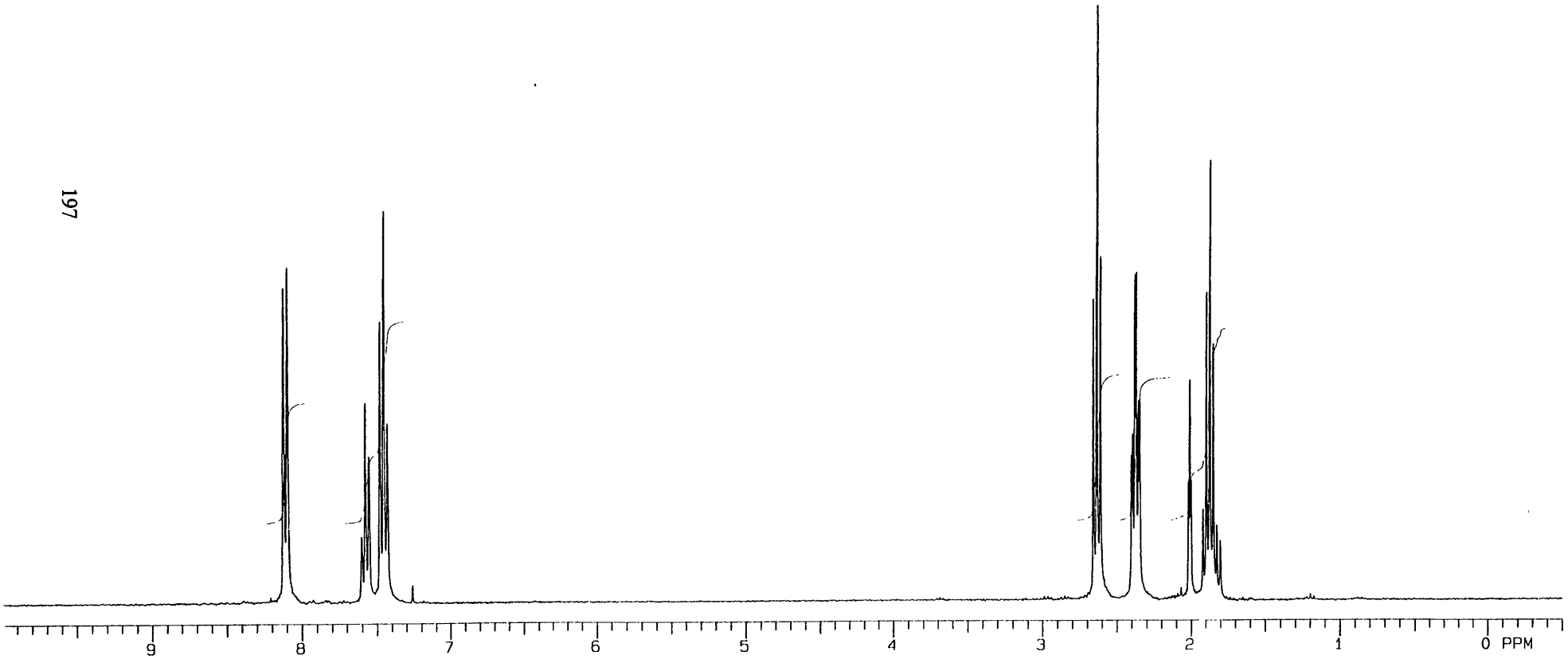
A 50-mL, round-bottomed flask equipped with rubber septum with argon inlet needle was charged with the impure alcohol, 18 mL of dichloromethane, and the Dess-Martin reagent (0.454 g, 1.07 mmol). The solution was stirred at 25 °C for 1 h and then it was concentrated and diluted with 20 mL of diethyl ether and 20 mL of saturated $NaHCO_3$ solution. The aqueous layer was separated and extracted with two 30-mL portions of diethyl ether. The combined organic phases were washed with two 30-mL portions of a 1:1 mixture of saturated $NaHCO_3$ and saturated $Na_2S_2O_3$ solution, 30 mL of saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford 0.145 g

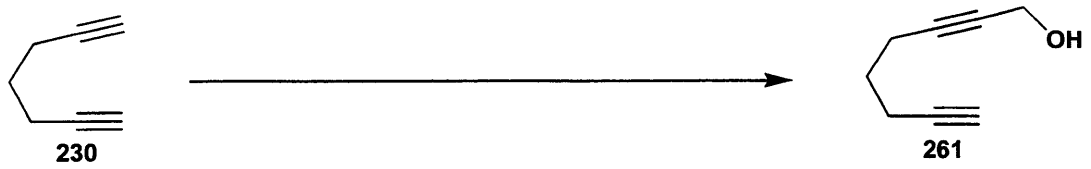
of a colorless oil. Column chromatography on 10 g of silica gel (gradient elution with 15% diethyl ether-pentane) provided 0.092 g (19% for two steps) of ketone **260** as a colorless oil.

IR (film)	3280, 3040, 3020, 2940, 2920, 2900, 2880, 2220, 2190, 1630, 1600, 1580, 1440, 1420, 1300, 1260, 1170, 1100, 1060, 1020, 980, 920, 900, 840, and 690 cm^{-1}.
^1H NMR (300 MHz, $CDCl_3$)	8.11 (d, J = 7.7 Hz, 2H), 7.58 (t, J = 7.8 Hz, 2H), 7.45 (t, J = 7.8 Hz, 2H), 2.62 (t, J = 7.1 Hz, 2H), 2.37 (t of d, J = 6.9 Hz, J = 2.6 Hz, 2H), 2.01 (t, J = 2.6 Hz, 2H), and 1.86 (app quintet, J = 7.0 Hz, 2H).
^{13}C NMR (75 MHz, $CDCl_3$)	177.9, 136.7, 133.9, 129.4, 128.4, 95.1, 82.6, 80.0, 69.5, 26.5, 18.0, and 17.6.



260





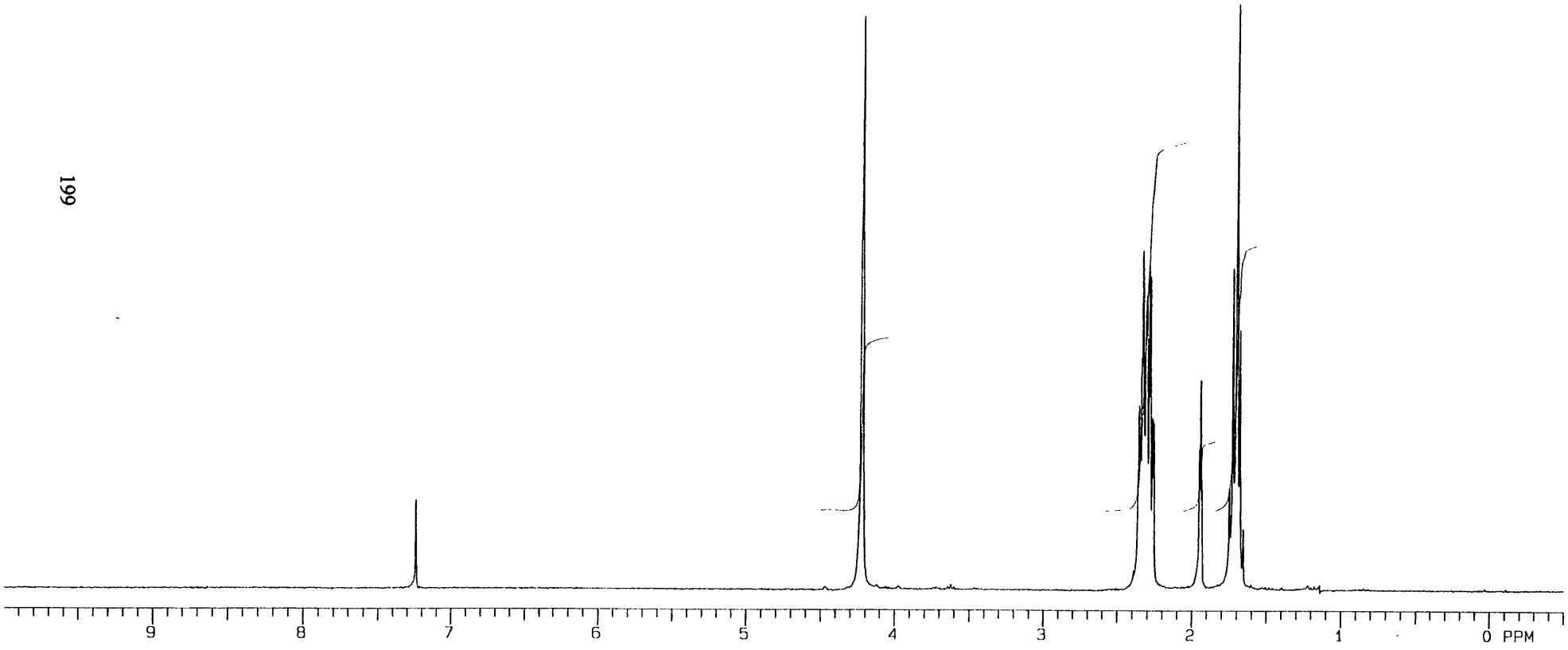
230 261

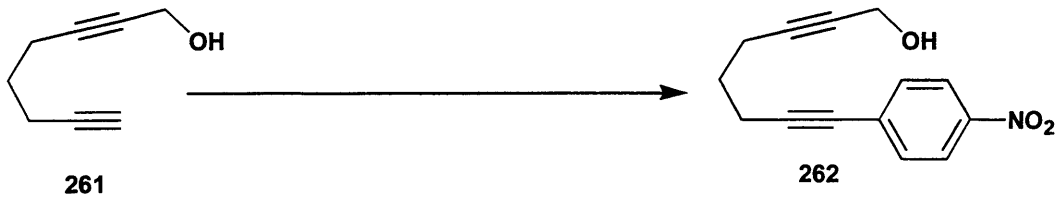
Octa-2,7-diyn-1-ol (261)

A 100-mL, three-necked, round-bottomed flask equipped with a rubber septum, glass stopper, and argon inlet adapter was charged with 1,6-heptadiyne (**230**) (0.917 mL, 0.748 g, 8.12 mmol) and 54 mL of tetrahydrofuran and the resulting solution was cooled at 0 °C using an ice-water bath. An ethylmagnesium bromide solution (3.0 M in diethyl ether, 2.71 mL, 8.12 mmol) was added dropwise via syringe over 10 min. The resulting mixture was stirred at 0 °C for 90 min and then paraformaldehyde (0.406 g, 12.2 mmol) was added in one portion. The cooling bath was removed and the reaction mixture was stirred at room temperature for 1 h and then at 50 °C for 2.5 h. The reaction mixture was quenched by the addition of 40 mL of saturated NH_4Cl solution then the aqueous layer was separated and extracted with three 30-mL portions of diethyl ether. The combined organic phases were washed with 30 mL of saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford 1.60 g of a yellow oil. Column chromatography on 20 g of silica gel (elution with 30% diethyl ether-pentane) provided 0.380 g (38%) of propargylic alcohol **261** as a colorless oil.

IR (film)	3340, 3300, 2920, 2860, 2280, 2220, 1440, 1350, 1300, 1280, 1240, 1230, and 1000 cm^{-1}.
^1H NMR (300 MHz, $CDCl_3$)	4.22 (br s, 2H), 2.31 (t of d, J = 6.8 Hz, J = 2.1 Hz, 2H), 2.29 (t of d, J = 7.1 Hz, J = 2.6 Hz, 2H), 1.94(t, J = 2.6 Hz, 1H), and 1.70 (app quintet, J = 7.0 Hz, 2H).
^{13}C NMR (75 MHz, $CDCl_3$)	85.1, 83.4, 79.1, 68.9, 51.2, 27.3, 17.7, and 17.5.

261



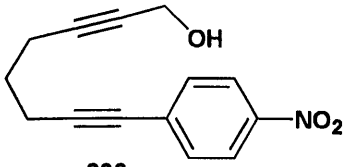


261 262

8-*p*-Nitrophenyl-octa-2,7-diyn-1-ol (262)

A 25-mL, two-necked, round-bottomed flask equipped with rubber septum and argon inlet adapter and wrapped in aluminum foil was charged with alcohol **261** (0.343 g, 2.78 mmol) and 9 mL of diethylamine. After degassing the solution with a stream of argon for 15 minutes in the dark, 1-iodo-4-nitrobenzene (0.692 g, 2.78 mmol), dichlorobis-(triphenylphosphine)palladium (0.04g, 0.06 mmol), and copper (I) iodide (0.01 g, 0.11 mmol) were added and the resulting solution was stirred at 25 °C in the dark for 18 h. The reaction solution was concentrated and then diluted with 20 mL of H_2O and 20 mL of diethyl ether. The aqueous layer was separated and extracted with two 20-mL portions of diethyl ether. The combined organic phases were washed with 30 mL of saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford 0.706 g of a reddish oil. Column chromatography on 15 g of silica gel (elution with 50% diethyl ether-pentane) provided 0.431 g (63%) of alcohol **262** as a yellow oil.

IR (film)	3350, 3100, 3060, 2930, 2900, 2860, 2260, 2220, 1590, 1510, 1490, 1430, 1380, 1340, 1310, 1290, 1170, 1120, 1100, 1010, 850, and 750 cm^{-1}.
^1H NMR (300 MHz, $CDCl_3$)	8.09 (d, J = 8.8 Hz, 2H), 7.47 (d, J = 8.8 Hz, 2H), 4.21 (d, J = 2.0 Hz, 1H), 2.52 (t, J = 7.0 Hz, 2H), 2.35 (t of t, J = 7.0 Hz, J = 2.0 Hz, 2H), 2.15 (br s, 1H), and 1.77 (app quintet, J = 7.0 Hz, 2H).
^{13}C NMR (75 MHz, $CDCl_3$)	146.5, 132.2, 130.7, 123.4, 95.2, 84.8, 79.7, 79.3, 51.1, 27.3, 18.5, and 17.9.



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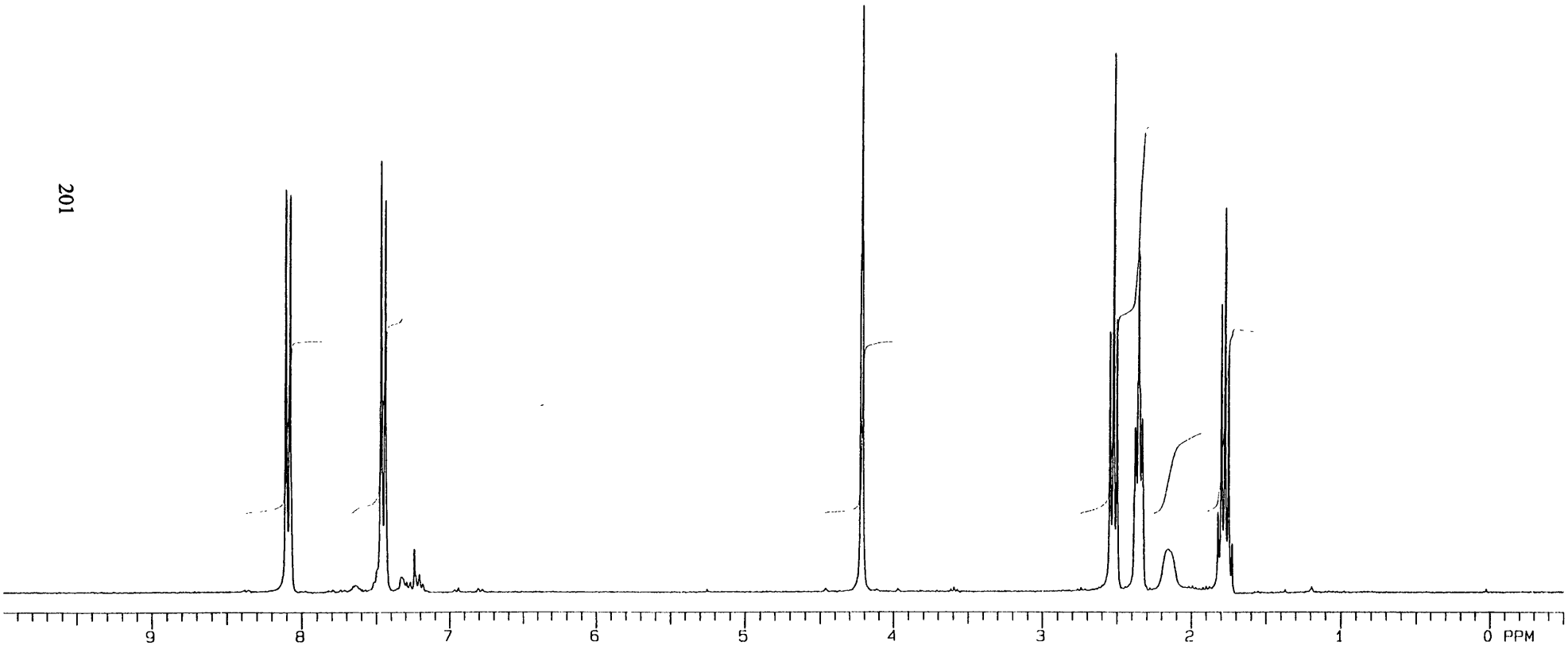
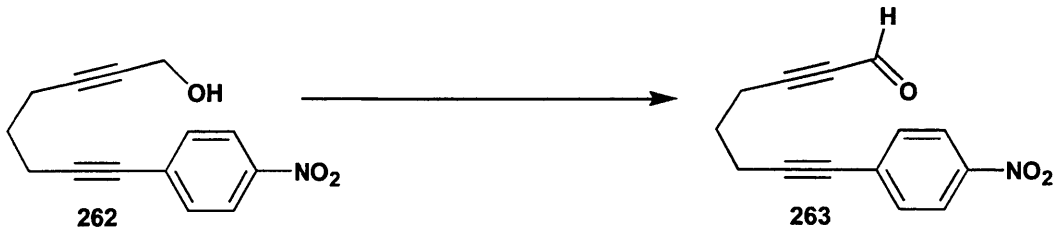


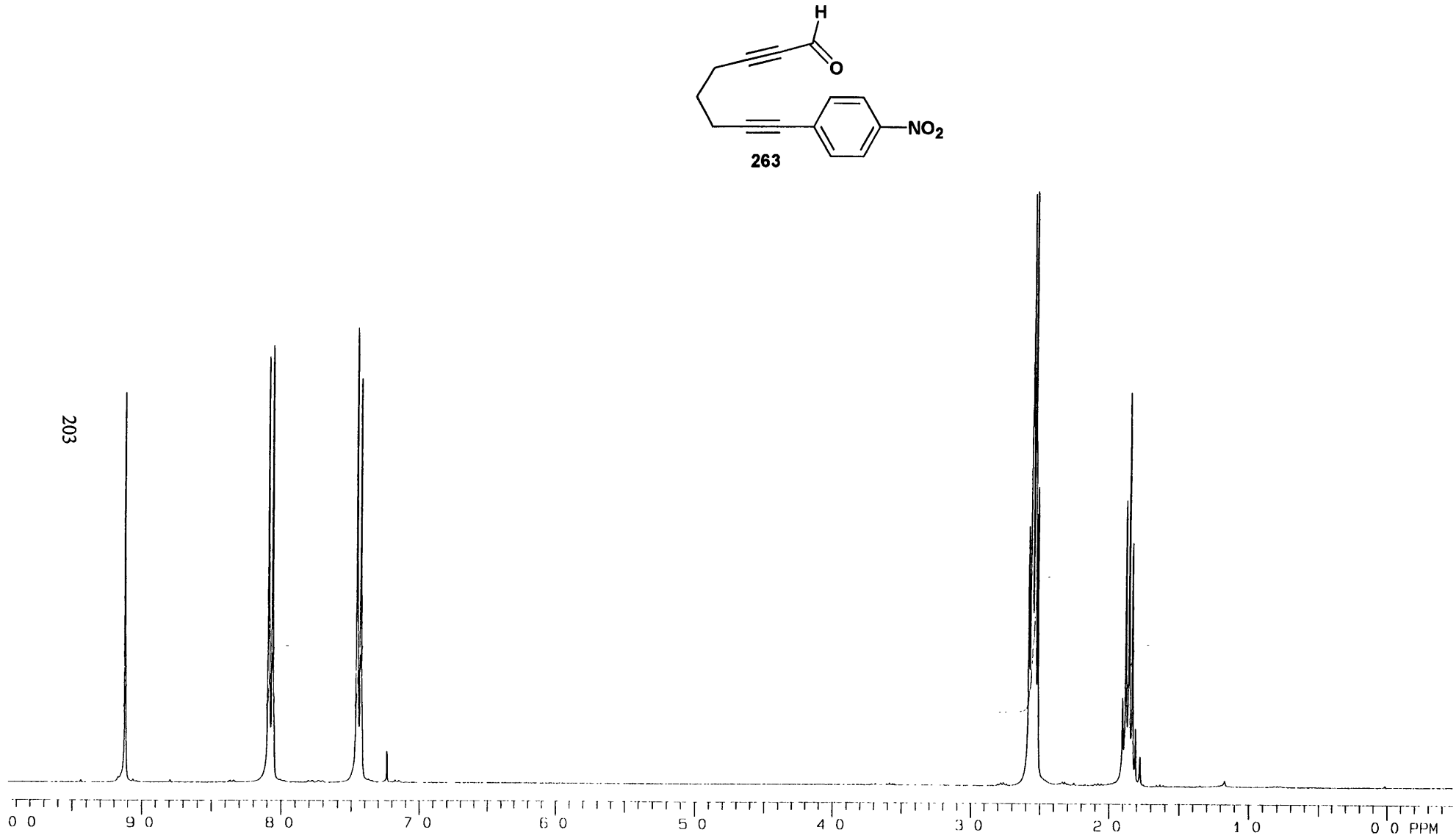


262 263

8-*p*-Nitrophenyl-octa-2,7-diyn-1-al (263)

A 50-mL, round-bottomed flask equipped with rubber septum with argon inlet needle was charged with alcohol **262** (0.220 g, 0.899 mmol), 18 mL of dichloromethane, and the Dess-Martin reagent (0.457 g, 1.08 mmol). The solution was stirred at 25 °C for 1 h and then it was concentrated and diluted with 15 mL of diethyl ether and 15 mL of saturated $NaHCO_3$ solution. The aqueous layer was separated and extracted with two 30-mL portions of diethyl ether. The combined organic phases were washed with two 30-mL portions of a 1:1 mixture of saturated $NaHCO_3$ and saturated $Na_2S_2O_3$ solution, 30 mL of saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford 0.206 g of a yellow oil. Column chromatography on 10 g of silica gel (elution with 30% diethyl ether-pentane) provided 0.150 g (67%) of aldehyde **263** as a yellow oil.

IR (film)	3100, 3080, 2940, 2900, 2880, 2620, 2260, 2200, 1650, 1600, 1510, 1480, 1450, 1430, 1380, 1340, 1310, 1280, 1270, 1130, 1100, 1050, 1010, 980, 960, 850, 800, and 740 cm^{-1}.
^1H NMR (300 MHz, $CDCl_3$)	9.12 (d, J = 2.1 Hz, 1H), 8.07 (d, J = 8.4 Hz, 2H), 7.44 (d, J = 8.4 Hz, 2H), 2.56 (t, J = 6.8 Hz, 2H), 2.56 (t, J = 7.6 Hz, 2H), and 1.86 (app quintet, J = 7.0 Hz, 2H).
^{13}C NMR (75 MHz, $CDCl_3$)	176.9, 146.6, 132.2, 130.4, 123.3, 97.2, 94.2, 81.9, 80.2, 26.2, 18.5, and 18.1.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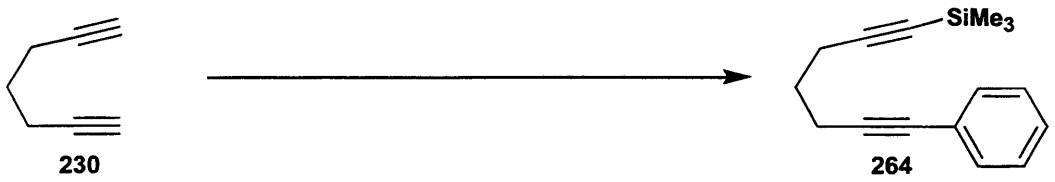


230 264

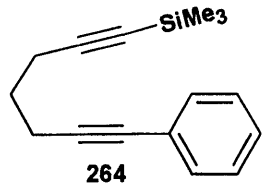
7-Phenyl-1-(trimethylsilyl)-1,6-heptadiyne (264)

A 250-mL, three-necked, round-bottomed flask equipped with rubber septum, argon inlet adapter, and glass stopper was charged with 1,6-heptadiyne (**230**) (2.06 mL, 1.68 g, 18.26 mmol,) and 91 mL of tetrahydrofuran and the resulting solution was cooled at 0 °C using a water-ice bath. An ethylmagnesium bromide solution (2.9 M in hexanes, 12.59 mL, 36.52 mmol) was added dropwise via syringe over 5 min and the resulting mixture was stirred at 0 °C for 90 min. Trimethylsilyl chloride (2.32 mL, 1.984 g, 18.26 mmol) was added and then the cooling bath was removed and the reaction solution stirred an additional 18 h at 25 °C. The reaction solution was diluted with 20 mL of saturated NH_4Cl solution and then the aqueous layer was separated and extracted with two 30-mL portions of diethyl ether. The combined organic phases were washed with 30 mL of saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford 3.61 g of a colorless oil. Column chromatography on 60g of silica gel (elution with 1% ethyl acetate-hexane) provided 2.38 g of a colorless oil. The oil was shown by ^1H NMR to be a 71:29 mixture of the desired 1-(trimethylsilyl)-1,6-heptadiyne with 1,7-di(trimethylsilyl)-1,6-heptadiyne. The amount of desired product obtained was 1.69 g (56%) by ^1H NMR. The mixture was carried on without further purification to the next step in the sequence.

A 100-mL, three-necked, round-bottomed flask equipped with rubber septum, argon inlet adapter, glass stopper and wrapped in aluminum foil was charged with the impure silylacetylene and 31 mL of diethylamine. After degassing the solution with a stream of argon for 15 minutes in the dark, iodobenzene (1.15 mL, 2.10 g, 10.28 mmol), dichlorobis-(triphenylphosphine)palladium (0.289g, 0.41 mmol), and copper (I) iodide (0.078 g, 0.41 mmol) were added. The resulting solution stirred at 25 °C in the dark for 18 h. The reaction solution was concentrated and then diluted with 10 mL of H_2O and 10

mL of diethyl ether. The aqueous layer was separated and extracted with three 10-mL portions of diethyl ether. The combined organic phases were washed with 30 mL of saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford 3.91 g of a colorless oil. Column chromatography on 60 g of silica gel (elution with 1% ethyl acetate-hexane) provided 3.47 g (55% for the two steps) of diyne **264** as a colorless oil.

IR (film)	3060, 3040, 3020, 2940, 2890, 2130, 1600, 1490, 1430, 1420, 1340, 1330, 1310, 1240, 1040, 1020, 970, 920, 820, and 740 cm^{-1}.
^1H NMR (500 MHz, $CDCl_3$)	7.38-7.36 (m, 2H), 7.26-7.24 (m, 3H), 2.51 (t, J = 6.8 Hz, 2H), 2.39 (t, J = 6.8 Hz, 2H), 1.80 (app quintet, J = 6.8 Hz, 2H), and 0.14 (s, 9H).
^{13}C NMR (75 MHz, $CDCl_3$)	131.5, 128.2, 127.6, 123.9, 103.3, 89.2., 85.2, 81.2, 27.9, 19.2, 18.6, and 0.15.



264

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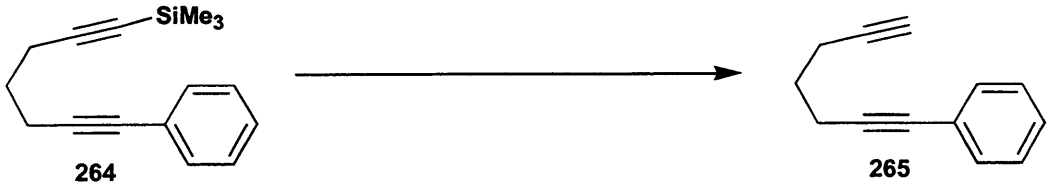
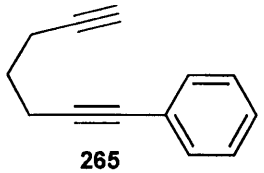


1-Phenyl-1,6-heptadiyne (265)

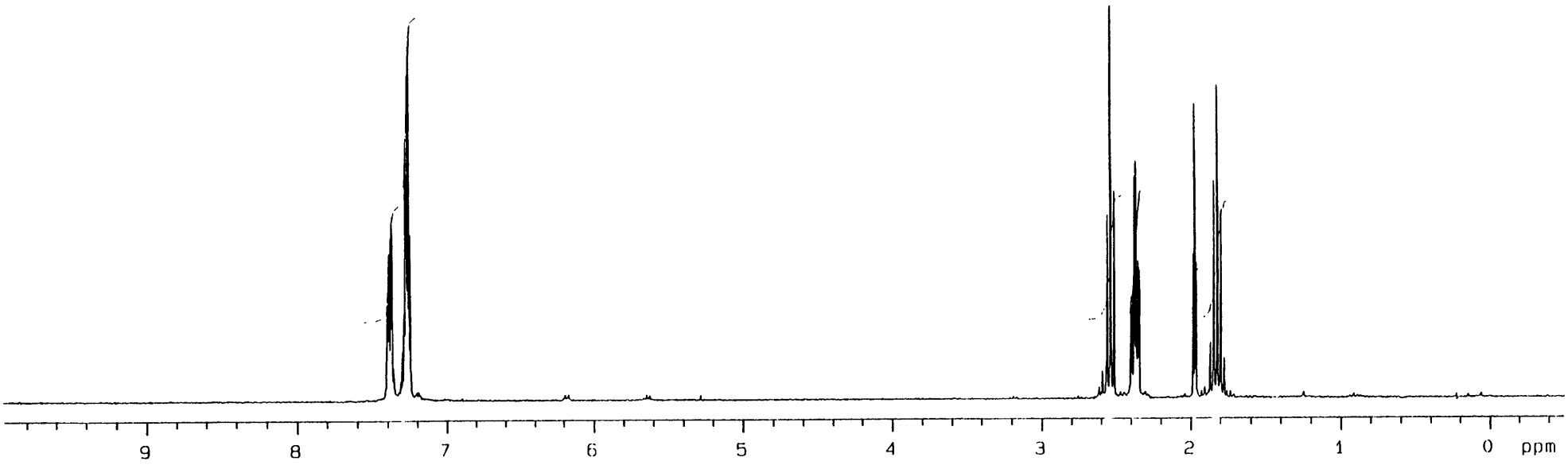
A 250-mL, three necked round-bottomed flask equipped with rubber septum, argon inlet needle, and glass stopper was charged with silyl acetylene **264** (1.344 g, 5.59 mmol) and 112 mL of tetrahydrofuran. The solution was cooled at 0 °C using a water-ice bath then a tetrabutylammonium fluoride solution (1.0 M, 16.77 mL, 16.77 mmol) was added dropwise over 6 min. The resulting solution was stirred at 0 °C for 2 h then the solution was diluted with 10 mL of saturated NH_4Cl solution. The aqueous layer was separated and extracted with three 15-mL portions of diethyl ether. The combined organic phases were washed with 30 mL of saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford 2.45 g of a brown oil. Column chromatography on 65 g of silica gel (elution with 1% ethyl acetate-hexane) afforded 0.882 g (96%) of diyne **265** as a colorless oil

IR (film)	3300, 3060, 3040, 3020, 2940, 2920, 2900, 2880, 2860, 2210, 2110, 1600, 1490, 1430, 1340, 1320, 1310, 1290, 1060, 1020, and 910 cm^{-1}.
^1H NMR (500 MHz, $CDCl_3$)	7.41-7.38 (m, 2H), 7.29-7.25 (m, 3H), 2.54 (t, J = 7.0 Hz, 2H), 2.37 (t of d, J = 7.1 Hz, J = 2.6 Hz, 2H), 1.98 (t, J = 2.6 Hz, 1H), and 1.83 (app quintet, J = 7.0 Hz, 2H).
^{13}C NMR (75 MHz, $CDCl_3$)	131.7, 128.0, 127.5, 123.6, 88.7, 83.4,81.1, 68.7, 27.5, 18.3, and 17.4.



265

208



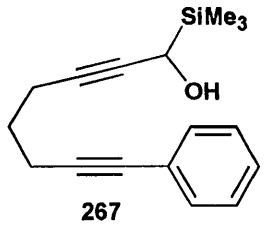
7-Phenyl-1-(trimethylsilyl)-hepta-1,6-diyn-1-ol (267)

A 50-mL, three-necked, round-bottomed flask equipped with an argon inlet adapter, rubber septum, and glass stopper was charged with 11 mL of diethyl ether and cooled at -78 °C with a dry ice-acetone bath. Oxalyl chloride (0.077 mL, 0.112 g, 0.879 mmol) was added followed by the dropwise addition of dimethylsulfoxide (0.072 mL, 0.078g, 1.000 mmol) via syringe over 2 min. The resulting mixture was warmed at -35 °C and stirred at that temperature for 1 h. The solution was recooled to -78 °C and then trimethylsilylmethanol (**266**) (0.106 mL, 0.087 g, 0.837 mmol) was added dropwise over 3 min. The solution was again warmed to -35 °C and stirred at that temperature for 1 h. After recooling the solution to -78 °C, triethylamine (0.377 mL, 0.247 g, 4.190 mmol) was added dropwise over 2 min. The solution was stirred at -78 °C for 1 h and then placed in a water/ice bath and stirred at 0 °C for an additional 2 h. The solution was then recooled to -78 °C.

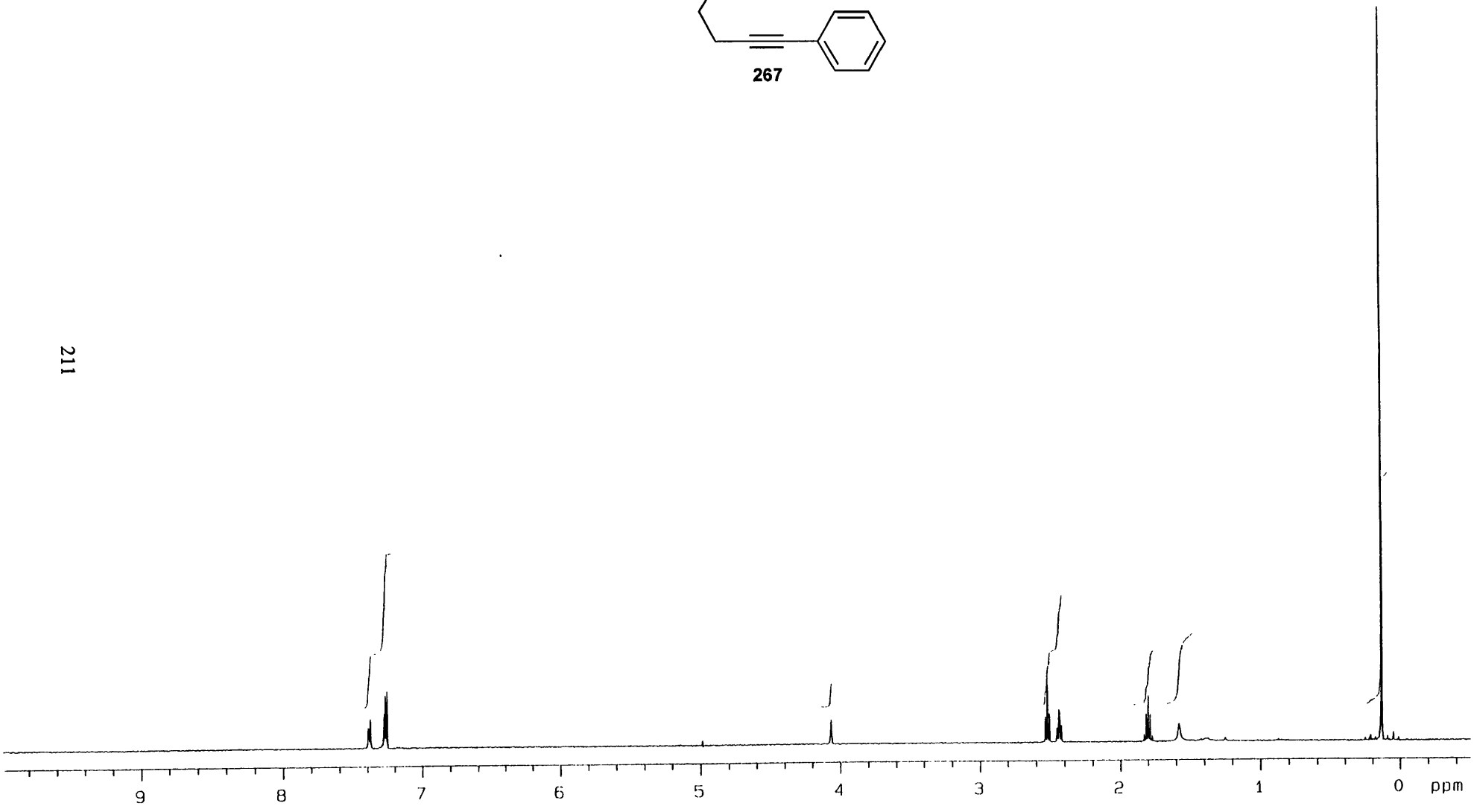
A 25-mL, round-bottomed flask equipped with a rubber septum with argon inlet needle, was charged with diyne **230** (0.55 g, 3.35 mmol) and 12 mL of diethyl ether, and the resulting solution was cooled at -78 °C with a dry ice-acetone bath. A *n*-butyllithium solution (2.38M in hexanes, 1.41 mL, 3.35 mmol) was added dropwise over 6 min then the solution stirred at -78 °C for 15 min. The lithium acetylide solution was then transferred into the 50 mL round-bottomed flask dropwise via cannula over 6 min, and the resulting mixture was then stirred at -78 °C for 2 h. The reaction mixture was diluted with 20 mL H_20 and then warmed at 25 °C. The aqueous layer was separated and extracted with two 20-mL portions of diethyl ether. The combined organic phases were washed with 30 mL of saturated NaCl solution, dried over $MgSO_4$, filtered, and

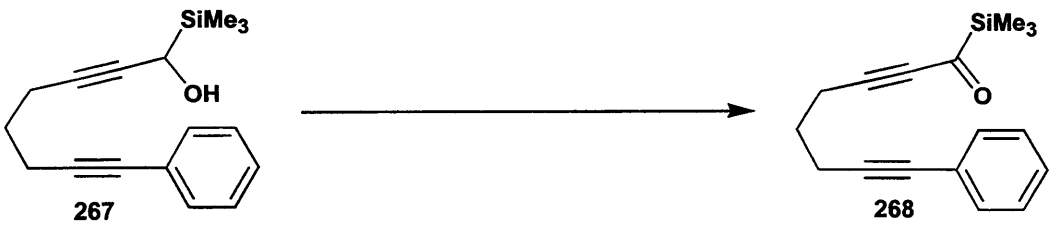
concentrated to afford 0.580 g of a brown oil. Column chromatography on 60 g of silica gel (elution with 10% diethyl ether-hexane) provided 0.176 g (78%) of α-hydroxysilane **267** as a colorless oil.

IR (film)	3400, 3060, 3040, 3020, 2960, 2900, 2820, 2210, 1600, 1490, 1420, 1340, 1240, 980, 830, 760, and 690 cm^{-1}.
^1H NMR (500 MHz, $CDCl_3$)	7.39-7.37 (m, 2H), 7.30-7.25 (m, 3H), 4.07 (t, J = 2.4 Hz, 1H), 2.52 (t, J = 7.3 Hz, 2H), 2.45 (t of d, J = 7.1 Hz, J = 2.4 Hz, 2H), 1.80 (app quintet, J = 7.0 Hz, 2H) and 0.14 (s, 9H).
^{13}C NMR (75 MHz, $CDCl_3$)	131.5, 128.1, 127.6, 123.8, 89.0, 87.2,.81.1, 81.0, 56.7, 28.0, 18.5, 18.2, and -4.3.



267



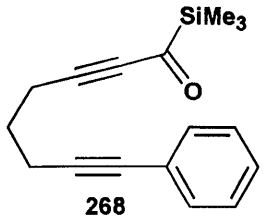


7-Phenyl-1-(trimethylsilyl)-hepta-1,6-diyn-1-one (268)

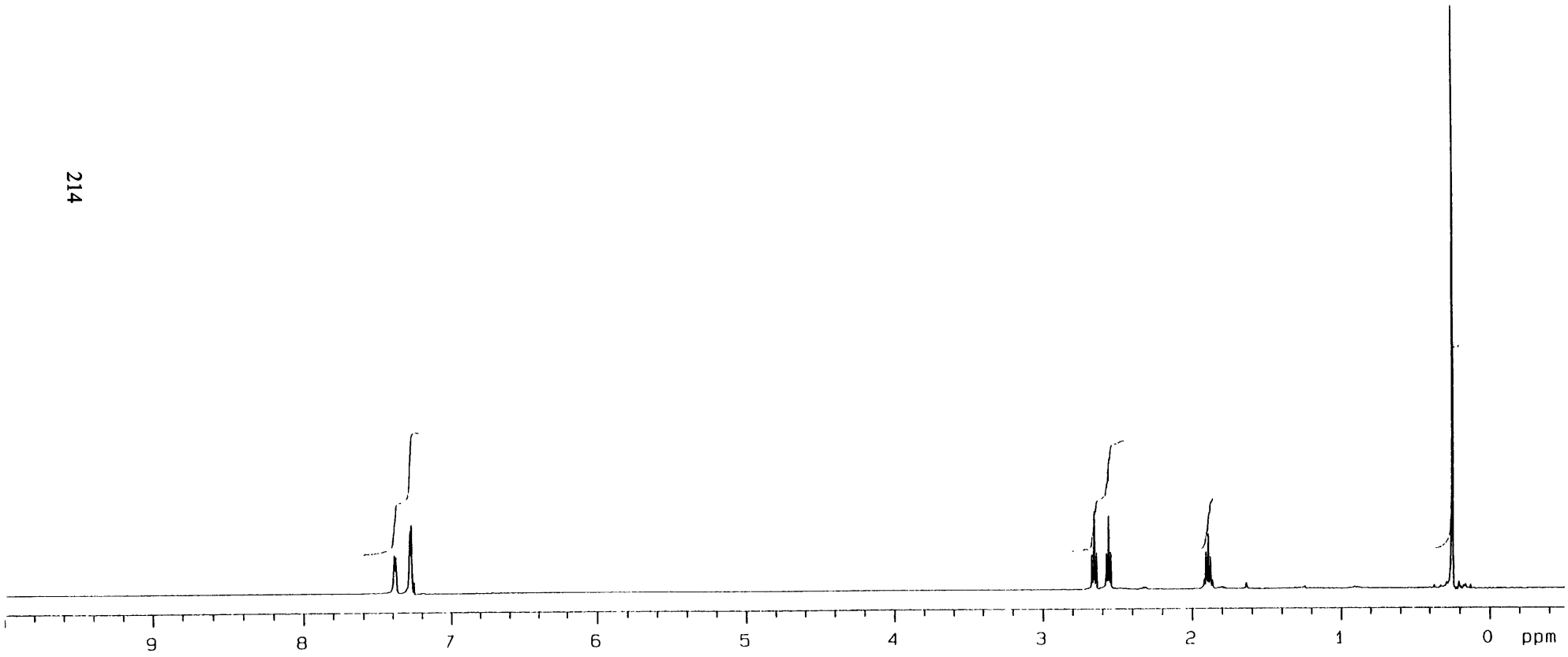
A 25-mL, two-necked, round-bottomed flask equipped with an argon inlet adapter, and rubber septum was charged with 8 mL of diethyl ether and cooled at -78 °C with a dry ice-acetone bath. Oxalyl chloride (0.060 mL, 0.087 g, 0.683 mmol) was added followed by the dropwise addition of dimethylsulfoxide (0.055 mL, 0.061g, 0.781 mmol) via syringe over 2 min. The resulting mixture was warmed to -35 °C and stirred at that temperature for 1h. The solution was recooled to -78 °C then a solution of alcohol **267** (0.176 g, 0.651 mmol) in 1 mL of tetrahydrofuran was added dropwise via cannula over 3 min. The solution was again warmed to -35 °C and stirred at that temperature for 1h. After recooling the solution to -78 °C, triethylamine (0.293 mL, 0.192 g, 3.25 mmol) was added dropwise over 2 min. The solution stirred at -78 °C for 1 h and then placed in a water/ice bath and stirred at 0 °C for an additional 2 h. The cooling bath was removed and the solution was allowed to warm to 25 °C. The reaction mixture was diluted with 10 mL water and then the aqueous layer was separated and extracted with three 30-mL portions of diethyl ether. The combined organic phases were washed with 30 mL of saturated NaCl solution, dried over Na_2SO_4, filtered, and concentrated to afford 0.103 g of a yellow oil. Column chromatography on 10 g of silica gel (elution with 10% diethyl ether-hexane) provided 0.053 g (30%) of acylsilane **268** as a yellow oil.

IR (film)	3060, 3040, 3010, 2960, 2900, 2190, 1600, 1490, 1440, 1420, 1360, 1340, 1310, 1250, 1130, 940 and 760 cm^{-1}.
^1H NMR (500 MHz, $CDCl_3$)	7.40-7.38 (m, 2H), 7.29-7.27 (m, 3H), 2.66 (t, J = 6.8 Hz, 2H), 2.56 (t, J = 6.8 Hz, 2H), 1.88 (app quintet, J = 6.8 Hz, 2H) and 0.26 (s, 9H).

^{13}C NMR (75 MHz, $CDCl_3$)	226.6, 131.5, 128.2, 127.7, 123.5, 102.2, 88.2, 84.7, 81.7, 27.0, 18.6, 18.5, and -3.6.



268



230 269

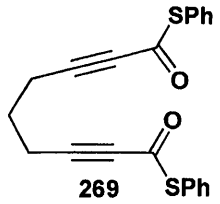
Phenyl-nona-2,7-diyn-1,9-dithioate (269)

A 50-mL, two-necked, round-bottomed flask equipped with an argon inlet adapter and rubber septum was charged with 1,6-heptadiyne (**230**) (0.313 mL, 0.255 g, 2.77 mmol) and 35 mL of tetrahydrofuran, and cooled at -78 °C with a dry ice-acetone bath. A *n*-butyllithium solution (2.59 M in hexanes, 1.78 mL, 4.62 mmol) was added dropwise via syringe over 5 min and the resulting mixture was stirred at -78 °C for 15 min. Carbon dioxide gas was then bubbled into the solution for 5 min and then the cooling bath was removed. After stirring an additional 15 min at room temperature, the reaction solution was cooled at 0 °C with an ice-water bath, quenched by the addition of 10 mL of 1.0 M HCl solution, and allowed to warm to room temperature. The aqueous layer was separated and extracted with two 30-mL portions of diethyl ether. The combined organic phases were washed with 20 mL of saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford 0.442 g of a yellow oil.

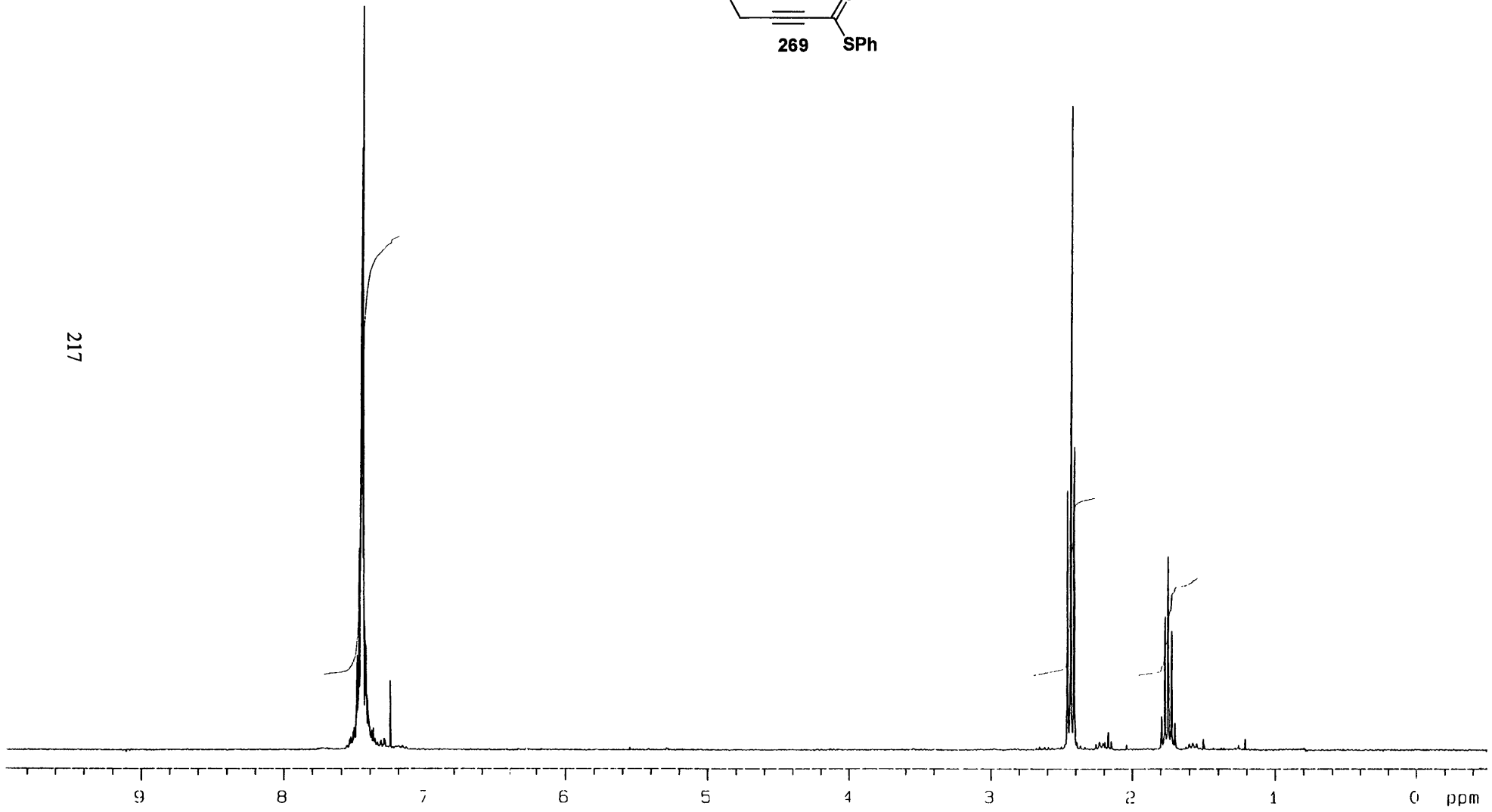
A 25-mL, two-necked, round-bottomed flask equipped with an argon inlet adapter and rubber septum was charged with the crude diacid (0.442g, 2.06 mmol) and 12 mL of dimethoxyethane, and cooled at 0 °C with an ice-water bath. Pyridine (0.856 mL, 10.58 mmol) was added dropwise via syringe followed by the addition of thiophenol (0.724 mL, 0.777 g, 7.05 mmol) and phenyl dichlorophosphate (0.791 mL, 1.17 g, 5.29 mmol). The cooling bath was removed and the reaction solution was stirred at room temperature for 1 h. The reaction mixture was poured into 30 mL of water then the aqueous layer was separated and extracted with three 30-mL portions of diethyl ether. The combined organic phases were washed with 20 mL of saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford 0.506 g of a yellow oil. Column chromatography on

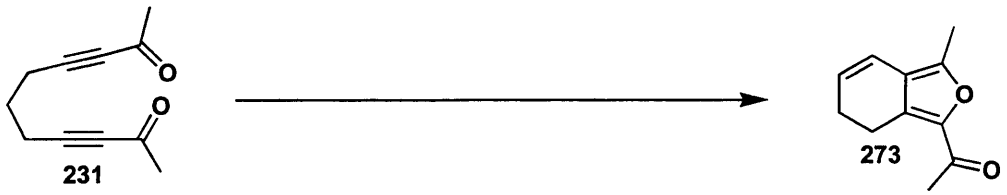
35 g of silica gel (gradient elution with 2-40% diethyl ether-pentane) provided 0.364 g (36% for the two steps) of dithioester **269** as a yellow oil.

IR (film)	3060, 2940, 2280, 2200, 1640, 1570, 1470, 1430, 1320, 1300, 1280, 1140, 1060, 1010, 960, 870, 840, and 740 and cm^{-1}.
^{1}H NMR (300 MHz, $CDCl_3$)	7.49-7.42 (m, 5H), 2.44 (t, J = 7.0 Hz, 4H), 1.75 (quart, J = 7.0 Hz 2H)
^{13}C NMR (75 MHz, $CDCl_3$)	175.6, 134.7, 130.0, 129.4, 127.0, 95.2, 78.8, 25.3, and 18.1.



269

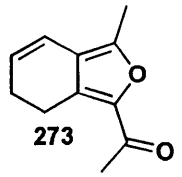




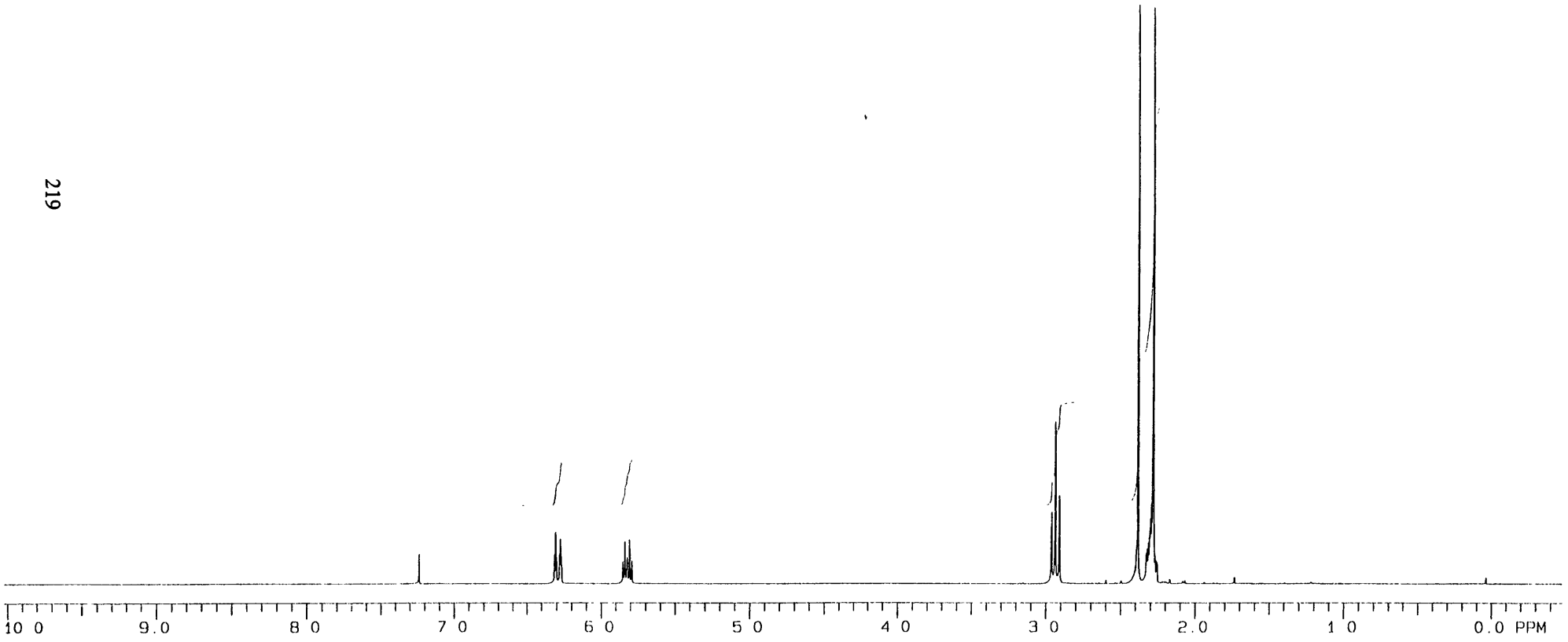
2-Acetyl-4,5-dihydro-9-methyl-isobenzofuran (273)

A threaded Pyrex tube (ca. 25-mL capacity) with a side arm equipped with a nitrogen inlet adapter was charged with ynone **231** (0.153 g, 0.869 mmol), 10 mL of toluene, and γ-terpinene (0.165 mL, 0.170 g, 0.956 mmol). The solution was degassed with a stream of argon for 1 h and then the tube was sealed with a threaded Teflon cap. The reaction mixture was heated in a 180 °C oil bath for 48 h and then allowed to cool to room temperature. Concentration gave 0.173 g of an orange oil. Column chromatography on 5 g of silica gel (gradient elution with 30% diethyl ether-pentane) provided 0.122 g (80%) of furan **273** as a yellow oil.

IR (film)	3020, 2925, 2820, 1660, 1590, 1555, 1425, 1380, 1360, 1310, 1250, 1230, 1160, 1115, 1080, 1010, 960, 930, 865, 790, 755, and 725 cm^{-1}.
^{1}H NMR (300 MHz, $CDCl_3$)	6.29 (d of t, J = 9.6 Hz, J = 2.1 Hz, 1H), 5.83 (d of t, J = 9.6 Hz, J = 4.3 Hz, 1H), 2.94 (t, J = 7.8 Hz, 2H), 2.39 (s, 3H), 2.33-2.26 (m, 2H), and 2.28 (s, 3H).
^{13}C NMR (75 MHz, $CDCl_3$)	187.9, 148.9, 145.4, 130.5, 126.9, 119.8, 117.5, 26.8, 22.7, 19.7, and 12.0



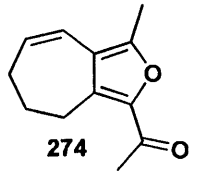
273



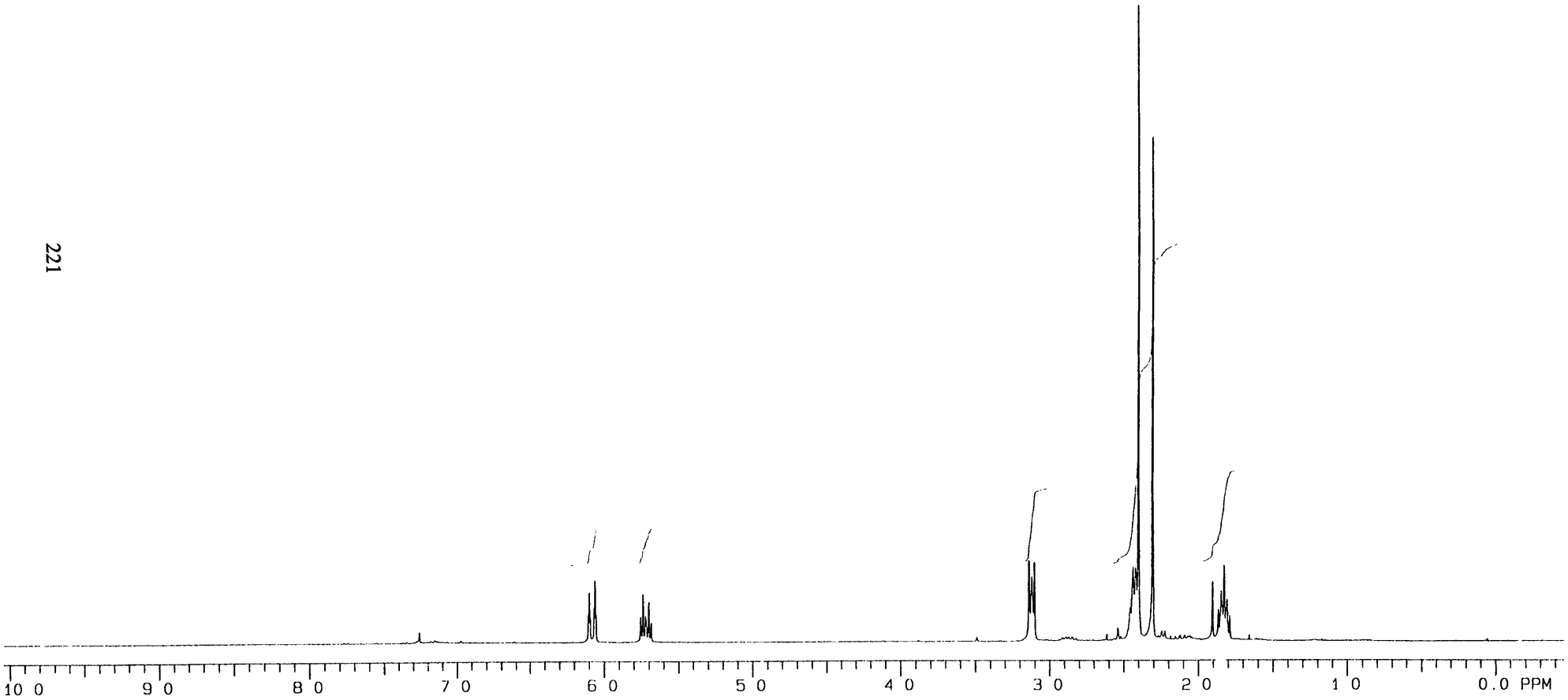
Furan 274

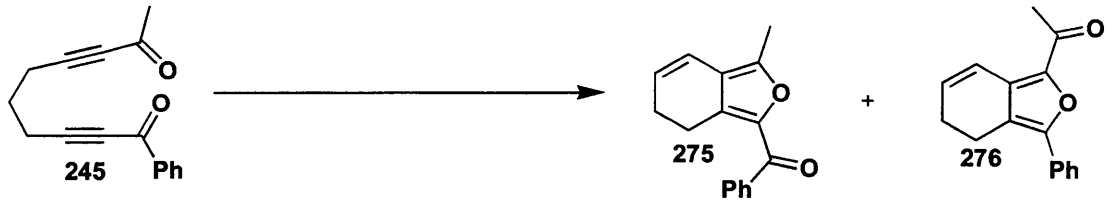
A threaded Pyrex tube (ca. 50-mL capacity) with a side arm equipped with a nitrogen inlet adapter was charged with dione **233** (0.400 g, 2.10 mmol), 21 mL of toluene, and γ-terpinene (0.406 mL, 0.345g, 2.31 mmol). The solution was degassed with a stream of argon for 1 h and then the tube was sealed with a threaded Teflon cap. The reaction mixture was heated in a 220 °C oil bath for 72 h and then allowed to cool to room temperature. Concentration gave 0.499 g of an orange oil. Column chromatography on 20 g of silica gel (gradient elution with 20% diethyl ether-pentane) provided 0.082 g (20%) of furan **274** as a yellow oil.

IR (film)	3010, 2920, 2840, 1650, 1580, 1520, 1430, 1340, 1300, 1270, 1240, 1220, 1140, 1040, 1010, 950, 880, 810 and 740 cm^{-1}.
^1H NMR (300 MHz, $CDCl_3$)	6.08 (d of t, J = 11.7 Hz, J = 1.2 Hz, 1H), 5.72 (d of t, J = 11.7 Hz, J = 4.5 Hz, 1H), 3.12 (t, J = 6.3 Hz, 2H), 2.46-2.43 (m, 2H), 2.40 (s, 3H), 2.31 (s, 3H), and 1.87-1.79 (m, 2H).
^{13}C NMR (75 MHz, $CDCl_3$)	188.8, 152.5, 145.7, 135.1, 130.2, 122.4, 118.0, 32.4, 26.9, 26.8, 24.4, and 12.0.



274





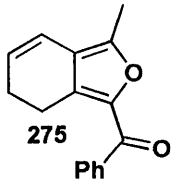
2-Benzoyl-4,5-dihydro-9-methyl-isobenzofuran (275)

9-Acetyl-4,5-dihydro-2-phenyl-isobenzofuran (276)

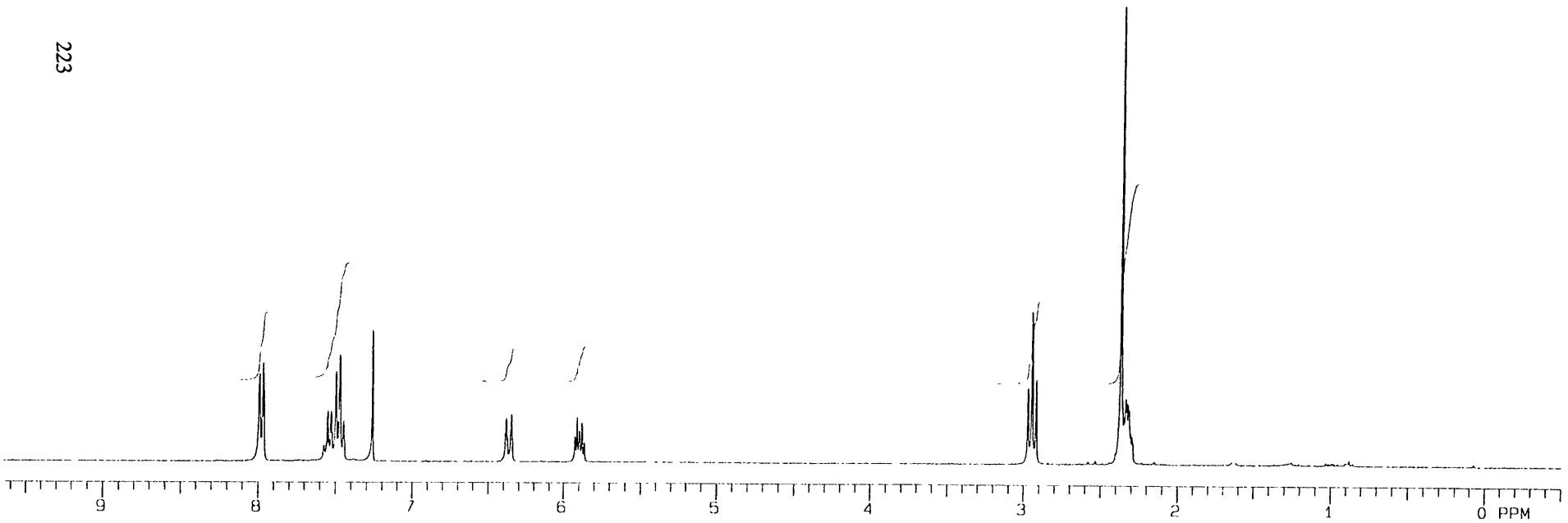
A threaded Pyrex tube (ca. 25-mL capacity) with a side arm equipped with a nitrogen inlet adapter was charged with dione **245** (0.102 g, 0.416 mmol), 4.5 mL of toluene, and γ-terpinene (0.080 mL, 0.068 g, 0.458 mmol). The solution was degassed with a stream of argon for 1 h and then the tube was sealed with a threaded Teflon cap. The reaction mixture was heated in a 180 °C oil bath for 48 h and then allowed to cool to room temperature. Concentration gave 0.163 g of an orange oil. Column chromatography on 10 g of silica gel (gradient elution with 10% diethyl ether-pentane) provided 0.105 g (68%) of a mixture of furan **275** and furan **276** as a greenish yellow oil in a ratio of 87:13 by ^{1}H NMR analysis. A pure sample of furan **275** was isolated through column chromatography and characterized.

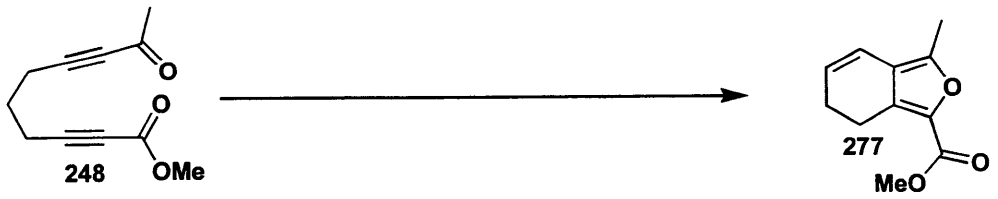
Spectral data for furan **275**:

IR (film)	3020, 2960, 2940, 2910, 1620, 1590, 1550, 1430, 1370, 1340, 1320, 1300, 1280, 1240, 1220, 1190, 1170, 1150, 1080, 1020, 950, 880, and 780 cm^{-1}.
^{1}H NMR (300 MHz, $CDCl_3$)	7.98 (d, J = 7.8 Hz, 2H), 7.54 (t, J = 7.5 Hz, 1H), 7.47 (app t, J = 7.6 Hz, 2H), 6.36 (d of t, J = 9.9 Hz, J = 1.8 Hz, 1H), 5.90 (d of t, J = 9.9 Hz, J = 4.5 Hz, 1H), 2.94 (t, J = 7.8 Hz, 2H), 2.37 (s, 3H), and 2.35-2.29 (m, 2H).
^{13}C NMR (75 MHz, $CDCl_3$)	183.1, 149.7, 145.2, 138.1, 133.7, 131.9, 129.3, 128.2, 127.3, 120.0, 117.5, 22.9, 20.3, and 12.2.



275

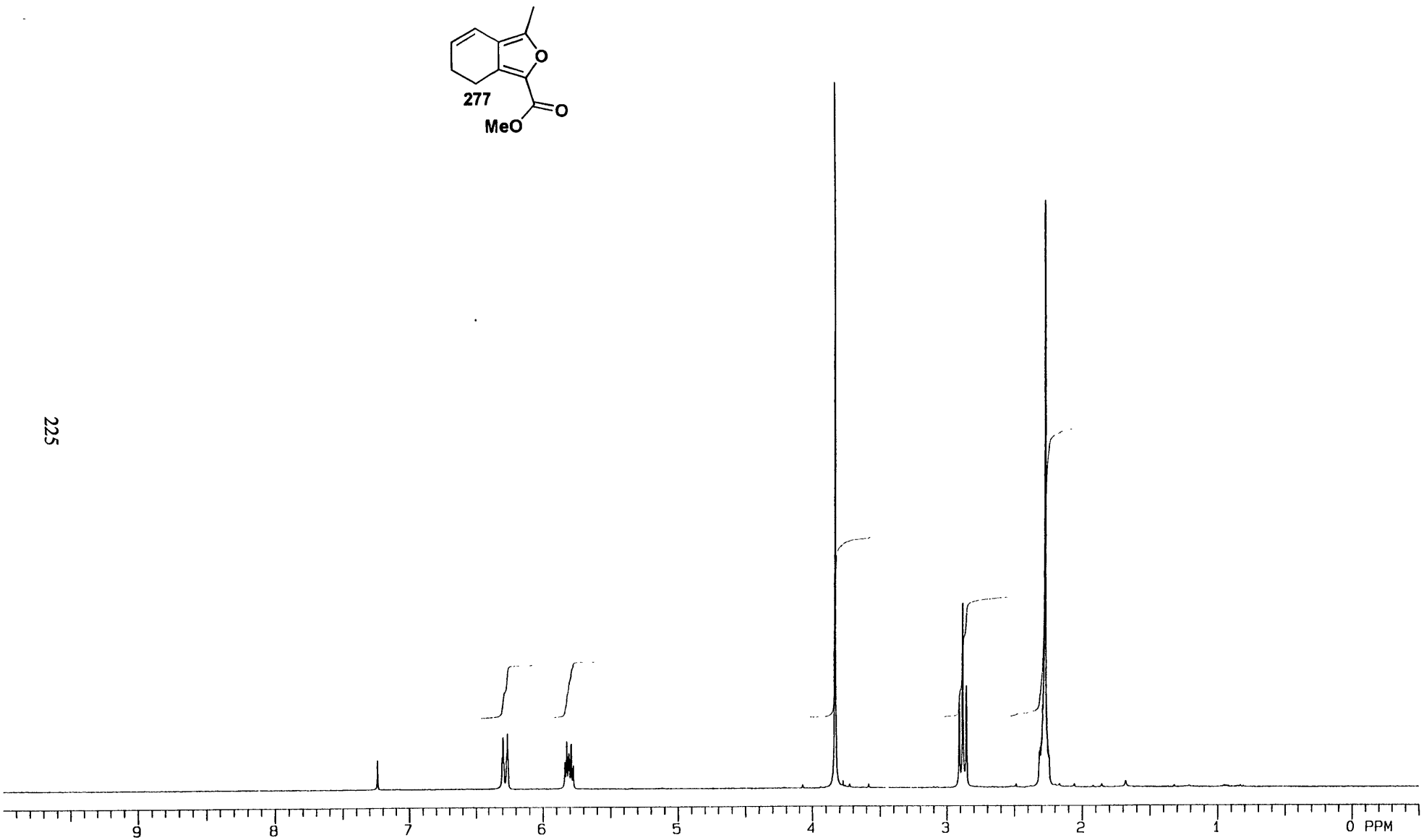


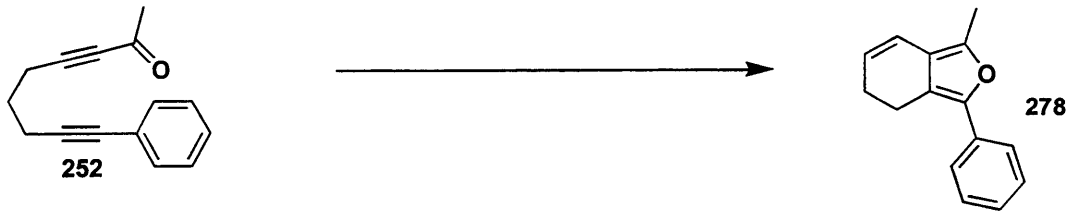


4,5-Dihydro-2-methoxycarbonyl-9-methyl-isobenzofuran (277)

A threaded Pyrex tube (ca. 25-mL capacity) with a side arm equipped with a nitrogen inlet adapter was charged with ynone **248** (0.212 g, 1.10 mmol), 11 mL of toluene, and γ-terpinene (0.210 mL, 0.178 g, 1.21 mmol). The solution was degassed with a stream of argon for 1 h and then the tube was sealed with a threaded Teflon cap. The reaction mixture was heated in a 180 °C oil bath for 54 h and then allowed to cool to room temperature. Concentration gave 0.432 g of an orange oil. Column chromatography on 10 g of silica gel (gradient elution with 20% diethyl ether-pentane) provided 0.105 g (50%) of furan **277** as a white solid. An analytical sample was obtained by recrystallization from hexane as a white solid, mp 51.0-52.0 °C.

IR (CCl_4)	3020, 2990, 2975, 2945, 2920, 1725, 1660, 1600, 1570, 1440, 1380, 1340, 1310, 1245, 1230, 1200, 1150, 1080, 1020, 970, 940, 870, and 720 cm^{-1}.	
^1H NMR (300 MHz, $CDCl_3$)	6.28 (d of t, J = 9.9 Hz, J = 1.8 Hz, 1H), 5.81 (d of t, J = 9.9 Hz, J = 4.5 Hz, 1H), 3.83 (s, 3H), 2.88 (t, J = 7.7 Hz, 2H), 2.32-2.25 (m, 2 H), and 2.27 (s, 3H).	
^{13}C NMR (75 MHz, $CDCl_3$)	159.8, 149.1, 136.2, 131.6, 126.7, 119.2, 117.6, 51.4, 22.8, 19.4, and 11.9.	
Elemental Analysis	Calcd for $C_{11}H_{12}O_3$:	C, 68.74; H, 6.29.
	Found:	C, 68.69; H, 6.03.

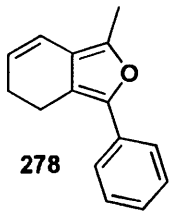

277
MeO
O
O
9
8
7
6
5
4
3
2
1
0 PPM



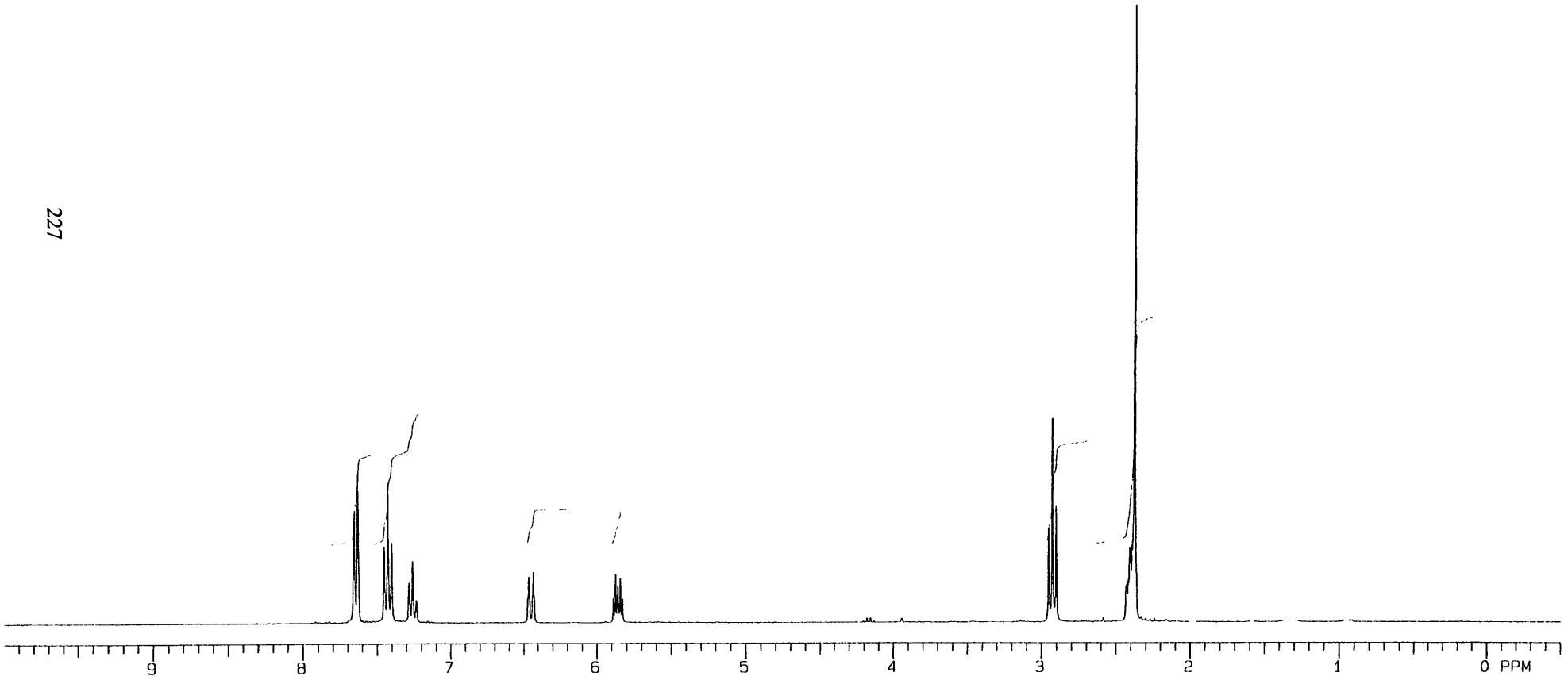
4,5-Dihydro-9-methyl-2-phenyl-isobenzofuran (278)

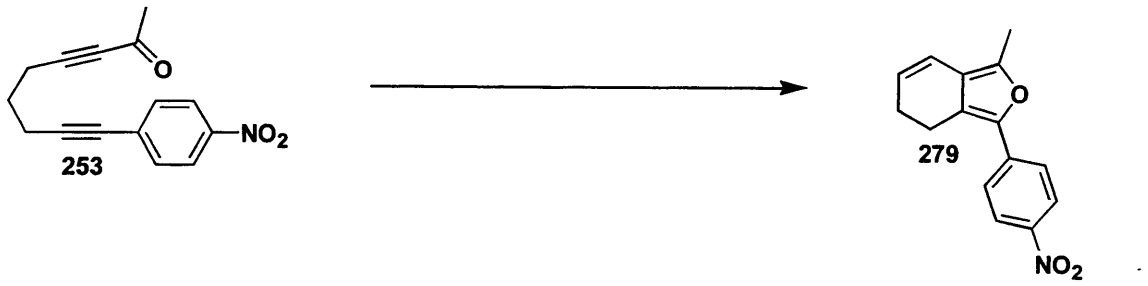
A threaded Pyrex tube (ca. 25-mL capacity) with a side arm equipped with a nitrogen inlet adapter was charged with ynone **252** (0.202 g, 0.961 mmol), 10 mL of toluene, and γ-terpinene (0.182 mL, 0.154 g, 1.06 mmol). The solution was degassed with a stream of argon for 1 h and then the tube was sealed with a threaded Teflon cap. The reaction mixture was heated in a 180 °C oil bath for 48 h and then allowed to cool to room temperature. Concentration gave 0.399 g of an orange oil. Column chromatography on 10 g of silica gel (elution with pentane) provided 0.142 g (70%) of furan **278** as a yellow oil.

IR (film)	3020, 2910, 2830, 1640, 1590, 1495, 1425, 1380, 1315, 1250, 1230, 1165, 1100, 1060, 1030, 970, 910, 870, 750, 720, and 690 cm^{-1}.
^1H NMR (300 MHz, $CDCl_3$)	7.64 (d, J = 7.8 Hz, 2H), 7.43 (app t, J = 7.4 Hz, 2H), 7.26 (t, J = 7.4 Hz, 1H), 6.45 (d of t, J = 9.9 Hz, J = 1.8 Hz, 1H), 5.86 (d of t, J = 9.9 Hz, J = 4.6 Hz, 1H), 2.93 (t, J = 7.5 Hz, 2H), 2.37 (s, 3H), and 2.43-2.37 (m, 2H).
^{13}C NMR (75 MHz, $CDCl_3$)	144.7, 144.5, 131.8, 128.5, 126.2, 125.2, 124.5, 118.8, 118.7, 116.9, 23.6, 19.7, and 11.7.



278



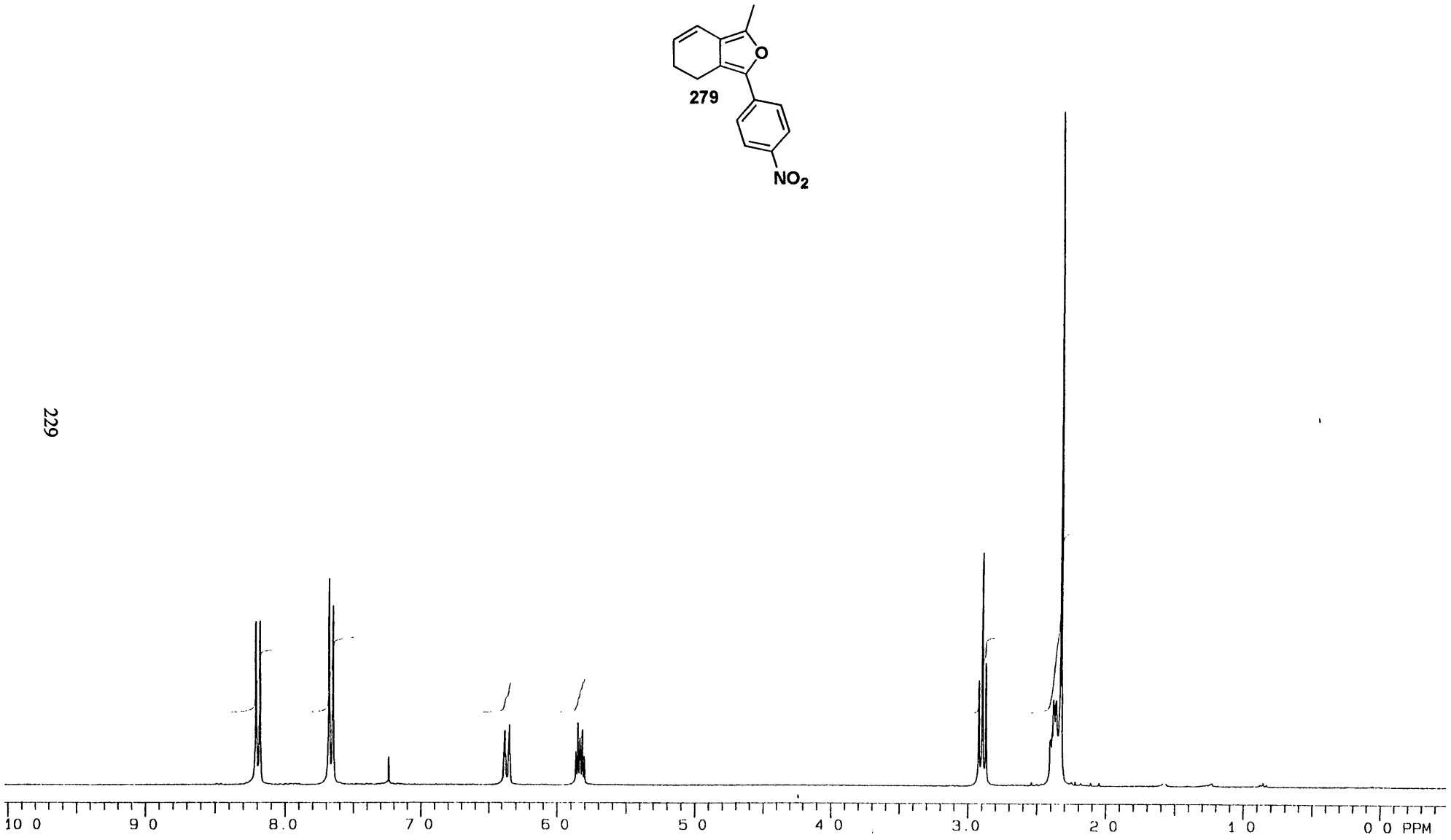


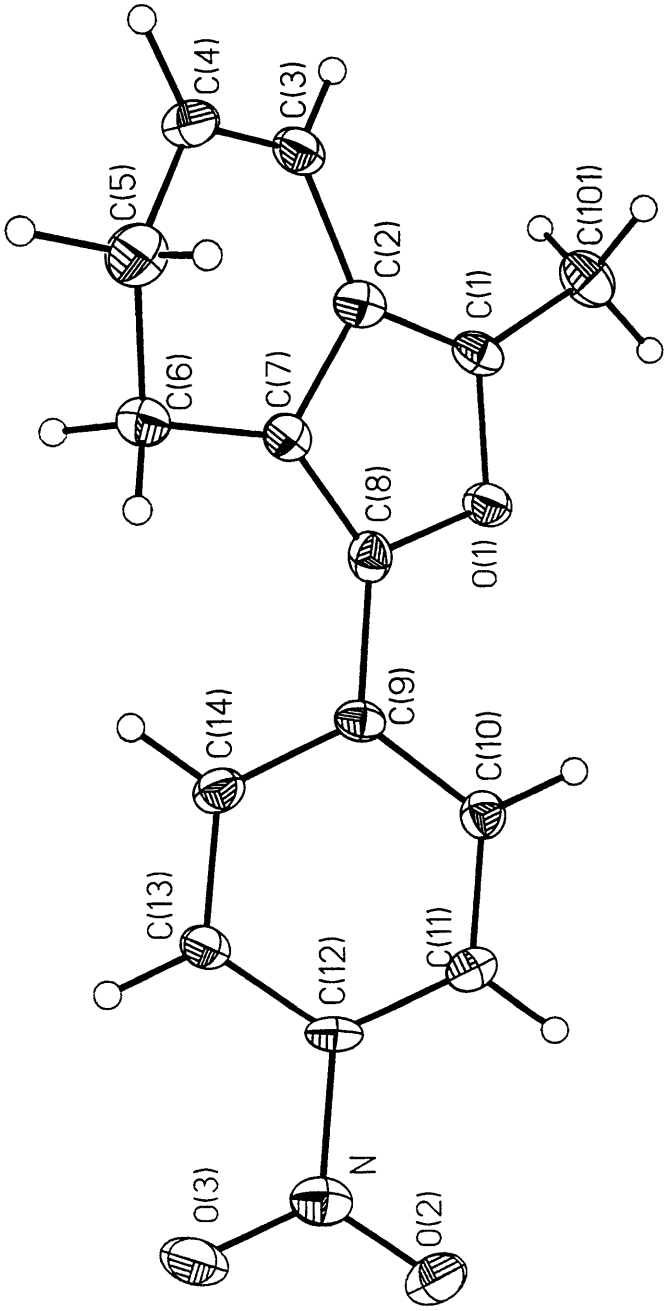
4,5-Dihydro-9-methyl-2-*p*-nitrophenyl-isobenzofuran (279)

A threaded Pyrex tube (ca. 25-mL capacity) with a side arm equipped with a nitrogen inlet adapter was charged with ynone **253** (0.200 g, 0.783 mmol), 10 mL of toluene, and γ-terpinene (0.148 mL, 0.126 g, 0.862 mmol). The solution was degassed with a stream of argon for 1 h and then the tube was sealed with a threaded Teflon cap. The reaction mixture was heated in a 180 °C oil bath for 48 h and then allowed to cool to room temperature. Concentration gave 0.674 g of an orange oil. Column chromatography on 15 g of silica gel (elution with 20% diethyl ether-pentane) provided 0.162 g (81%) of furan **279** as a yellow solid. An analytical sample was obtained by recrystallization from hexane as a yellow solid, mp 107.0-109.5 °C.

IR (CCl_4)	3020, 2980, 2960, 2920, 1645, 1590, 1510, 1425, 1370, 1340, 1310, 1250, 1220, 1175, 1105, 1050, 970, and 850 cm^{-1}.
^1H NMR (300 MHz, $CDCl_3$)	8.20 (d, J = 9.0 Hz, 2H), 7.64 (d, J = 9.0 Hz, 2H), 6.36 (d of t, J = 10.1 Hz, J = 1.9 Hz, 1H), 5.83 (d of t, J = 10.1 Hz, J = 4.4 Hz, 1H), 2.89 (t, J = 7.5 Hz, 2H), 2.41-2.35 (m, 2H), and 2.33 (s, 3H).
^{13}C NMR (75 MHz, $CDCl_3$)	147.1, 145.2, 142.8, 137.6, 125.8, 124.2, 124.1, 121.7, 119.6, 118.2, 23.3, 20.0, and 11.8.
Elemental Analysis	Calcd for $C_{15}H_{13}NO_3$: C, 70.58; H, 5.13, N, 5.49. Found: C, 70.42; H, 4.80, N, 5.09.

X-ray obtained (see following pages)


279
O
NO2
10 0
9 0
8.0
7 0
6 0
5 0
4 0
3.0
2 0
1 0
0 0 PPM


C(4)
C(3)
C(5)
C(101)
C(2)
C(1)
C(6)
C(7)
C(8)
O(1)
C(14)
C(9)
C(10)
C(13)
C(12)
C(11)
N
O(3)
O(2)

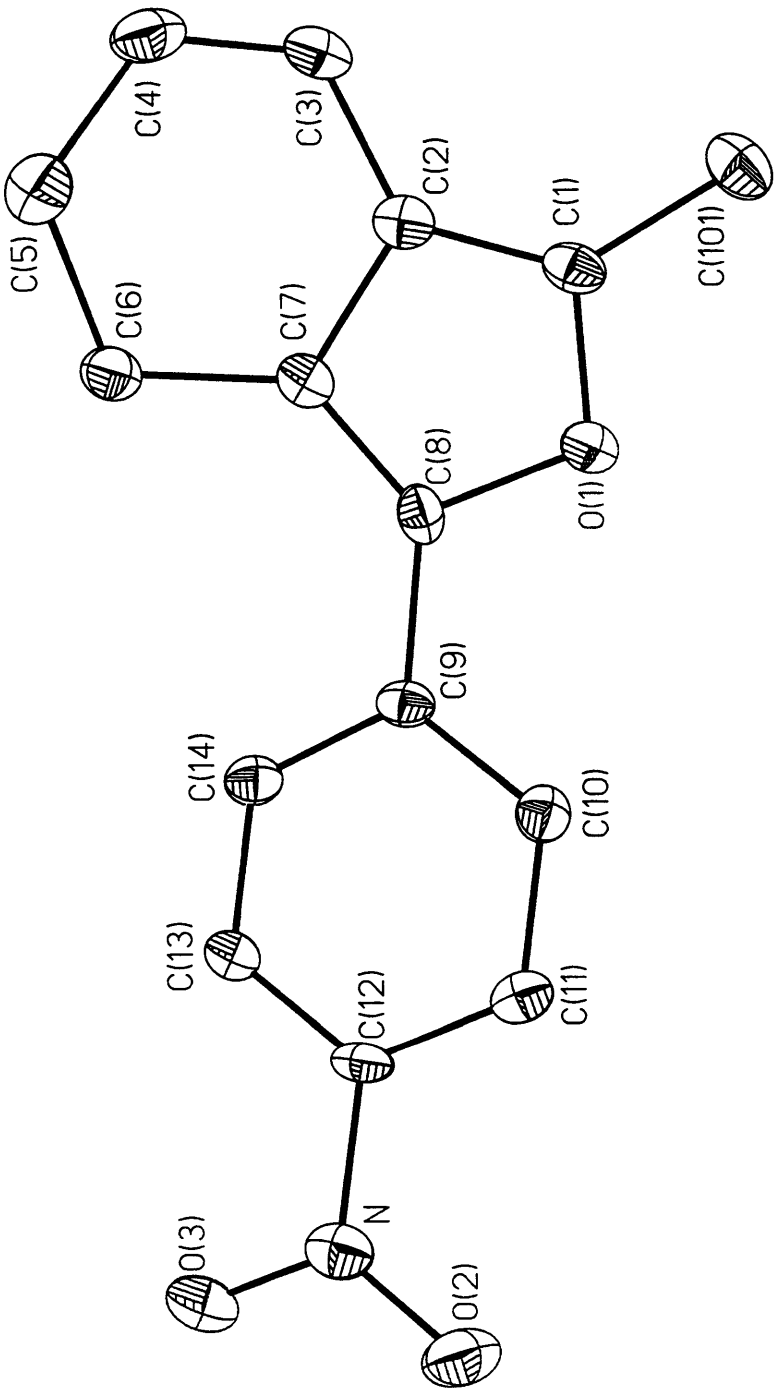

C(4)
C(3)
C(2)
C(1)
C(101)
C(5)
C(6)
C(7)
C(8)
O(1)
C(9)
C(14)
C(10)
C(13)
C(11)
C(12)
N
O(3)
O(2)

Table 1. Crystal data and structure refinement for 1.

A. Crystal Data

Identification code	96087
Empirical formula	$C_{15}H_{13}NO_3$
Formula weight	255.26
Temperature	153(2) K
Wavelength	0.71073 Å
Crystal morphology	?
Crystal size	0.18 x 0.18 x 0.18 mm
Crystal system	Triclinic
Space group	$P\bar{1}$
Unit cell dimensions	*a* = 8.7611(13) Å alpha = 90.252(3)°
	b = 8.9913(14) Å beta = 107.870(2)°
	c = 9.4145(14) Å gamma = 117.327(2)°
Volume, Z	617.7(2) $Å^3$, 2
Density (calculated)	1.372 Mg/m^3
Absorption coefficient	0.096 mm^{-1}
F(000)	268

B. Data Collection and Reduction

Diffractometer	Siemens SMART/CCD
Scan Type	ω Scans
Scan angle	0.30°
θ range for data collection	2.31 to 21.00°
Limiting indices	$-9 \le h \le 9$, $-9 \le k \le 7$, $-9 \le l \le 10$

Reflections collected	2066
Independent reflections	1326 (R_{int} = 0.0908)
Absorption correction	None

C. Solution and Refinement

Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	1239 / 0 / 173
Goodness-of-fit on F^2	1.057
Final R indices [I>2σ(I)]	R1 = 0.0546, wR2 = 0.1347
R indices (all data)	R1 = 0.0802, wR2 = 0.1550
Extinction coefficient	0.016(7)
Largest diff. peak and hole	0.409 and -0.348 eÅ^{-3}

Table 2. Atomic coordinates [x 10^4] and equivalent isotropic displacement parameters [$Å^2$ x 10^3] for 1. U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x	y	z	U(eq)
O(1)	5223(3)	3727(3)	1515(3)	29(1)
O(2)	4931(4)	9186(4)	6547(3)	44(1)
O(3)	2013(4)	7547(4)	5928(3)	46(1)
N	3497(5)	7918(4)	5795(4)	34(1)
C(1)	4891(5)	2646(5)	281(4)	27(1)
C(2)	3100(5)	1919(5)	-606(4)	27(1)
C(3)	2059(6)	727(5)	-2019(5)	32(1)
C(4)	423(6)	527(5)	-2827(5)	40(1)
C(5)	-318(6)	1605(6)	-2377(5)	44(1)
C(6)	266(5)	2090(5)	-660(4)	31(1)
C(7)	2248(5)	2592(5)	92(4)	25(1)
C(8)	3556(5)	3652(5)	1378(4)	26(1)
C(9)	3593(5)	4728(5)	2553(4)	23(1)
C(10)	5206(5)	6156(5)	3451(4)	26(1)
C(11)	5176(5)	7191(5)	4513(4)	28(1)
C(12)	3529(5)	6806(5)	4683(4)	26(1)
C(13)	1913(5)	5375(5)	3847(4)	28(1)
C(14)	1945(5)	4348(5)	2789(4)	29(1)
C(101)	6480(6)	2506(5)	172(5)	38(1)

Table 3. Bond lengths [Å] and angles [°] for 1.

O(1)-C(1)	1.379(5)	O(1)-C(8)	1.395(4)
O(2)-N	1.229(4)	O(3)-N	1.232(4)
N-C(12)	1.460(5)	C(1)-C(2)	1.355(5)
C(1)-C(101)	1.487(5)	C(2)-C(7)	1.437(6)
C(2)-C(3)	1.447(6)	C(3)-C(4)	1.326(6)
C(4)-C(5)	1.511(6)	C(5)-C(6)	1.532(6)
C(6)-C(7)	1.498(6)	C(7)-C(8)	1.350(5)
C(8)-C(9)	1.449(5)	C(9)-C(10)	1.397(5)
C(9)-C(14)	1.413(5)	C(10)-C(11)	1.378(5)
C(11)-C(12)	1.382(5)	C(12)-C(13)	1.383(5)
C(13)-C(14)	1.371(5)		

C(1)-O(1)-C(8)	106.7(3)	O(2)-N-O(3)	122.7(3)
O(2)-N-C(12)	119.3(4)	O(3)-N-C(12)	118.1(3)
C(2)-C(1)-O(1)	109.8(3)	C(2)-C(1)-C(101)	133.3(4)
O(1)-C(1)-C(101)	116.9(3)	C(1)-C(2)-C(7)	107.0(3)
C(1)-C(2)-C(3)	132.1(4)	C(7)-C(2)-C(3)	120.9(4)
C(4)-C(3)-C(2)	118.9(4)	C(3)-C(4)-C(5)	121.8(4)
C(4)-C(5)-C(6)	113.6(4)	C(7)-C(6)-C(5)	110.4(3)
C(8)-C(7)-C(2)	106.9(3)	C(8)-C(7)-C(6)	133.0(4)
C(2)-C(7)-C(6)	120.0(3)	C(7)-C(8)-O(1)	109.6(3)
C(7)-C(8)-C(9)	134.2(3)	O(1)-C(8)-C(9)	116.2(3)
C(10)-C(9)-C(14)	118.5(3)	C(10)-C(9)-C(8)	122.2(3)
C(14)-C(9)-C(8)	119.4(3)	C(11)-C(10)-C(9)	120.6(3)
C(10)-C(11)-C(12)	119.3(4)	C(11)-C(12)-C(13)	121.8(4)
C(11)-C(12)-N	119.2(4)	C(13)-C(12)-N	119.0(4)
C(14)-C(13)-C(12)	118.8(4)	C(13)-C(14)-C(9)	121.0(4)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters [$Å^2$ x 10^3] for 1.

The anisotropic displacement factor exponent takes the form:

$-2\pi^2 [(ha^*)^2 U_{11} + ... + 2hka^* b^* U_{12}]$

	U11	U22	U33	U23	U13	U12
O(1)	30(2)	31(2)	28(2)	3(1)	12(1)	17(1)
O(2)	48(2)	31(2)	43(2)	-5(2)	15(2)	12(2)
O(3)	50(2)	54(2)	45(2)	-5(2)	19(2)	31(2)
N	44(3)	33(2)	31(2)	7(2)	15(2)	23(2)
C(1)	37(3)	30(2)	25(2)	10(2)	16(2)	21(2)
C(2)	34(3)	25(2)	25(2)	8(2)	13(2)	17(2)
C(3)	40(3)	25(2)	36(3)	5(2)	23(2)	15(2)
C(4)	41(3)	34(3)	30(3)	-5(2)	14(2)	7(2)
C(5)	36(3)	51(3)	39(3)	0(2)	8(2)	19(2)
C(6)	33(2)	31(2)	32(3)	2(2)	14(2)	16(2)
C(7)	30(2)	22(2)	28(3)	8(2)	14(2)	14(2)
C(8)	20(2)	26(2)	33(3)	6(2)	9(2)	13(2)
C(9)	31(2)	24(2)	18(2)	6(2)	10(2)	16(2)
C(10)	25(2)	28(2)	25(2)	5(2)	9(2)	12(2)
C(11)	32(2)	23(2)	24(2)	1(2)	7(2)	12(2)
C(12)	37(3)	25(2)	22(2)	1(2)	11(2)	20(2)
C(13)	30(2)	30(2)	27(2)	3(2)	13(2)	16(2)
C(14)	32(2)	22(2)	31(2)	-1(2)	9(2)	13(2)
C(101)	41(3)	44(3)	43(3)	14(2)	21(2)	29(2)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$ x 10^3) for 1.

	x	y	z	U(eq)
H(3A)	2540(6)	98(5)	-2361(5)	38
H(4A)	-303(6)	-317(5)	-3713(5)	48
H(5A)	-1673(6)	977(6)	-2814(5)	53
H(5B)	108(6)	2657(6)	-2818(5)	53
H(6A)	63(5)	3048(5)	-435(4)	37
H(6B)	-490(5)	1113(5)	-254(4)	37
H(10A)	6334(5)	6415(5)	3328(4)	32
H(11A)	6276(5)	8160(5)	5123(4)	33
H(13A)	801(5)	5110(5)	4004(4)	33
H(14A)	842(5)	3366(5)	2205(4)	35
H(10C)	7577(6)	3239(5)	1043(5)	57
H(10D)	6683(6)	2864(5)	-766(5)	57
H(10B)	6227(6)	1325(5)	166(5)	57

h	k	l	10Fo	10Fc	10s	h	k	l	10Fo	10Fc	10s	h	k	l	10Fo	10Fc	10s	h	k	l	10Fo	10Fc	10s	h	k	l	10Fo	10Fc	10s
1	0	0	444	456	8	-4	7	0	69	65	2	0	-2	1	512	509	4	-1	4	1	60	66	2	-2	-4	2	83	68	2
2	0	0	181	189	2	-3	7	0	62	54	2	1	-2	1	475	481	4	0	4	1	27	23	4	-1	-4	2	42	28	1
3	0	0	53	62	5	-2	7	0	41	49	11	2	-2	1	34	33	2	1	4	1	76	77	1	0	-4	2	355	355	3
4	0	0	187	231	58	-1	7	0	61	60	2	3	-2	1	114	101	1	2	4	1	35	33	2	1	-4	2	120	130	2
5	0	0	32	38	4	0	7	0	110	109	4	4	-2	1	106	99	1	3	4	1	20	22	4	2	-4	2	20	12	3
6	0	0	272	264	2	1	7	0	37	31	6	5	-2	1	101	105	1	4	4	1	64	60	2	3	-4	2	89	83	1
7	0	0	234	235	3	-7	8	0	28	29	8	6	-2	1	147	143	2	-8	5	1	18	4	7	4	-4	2	16	26	6
-7	1	0	68	69	3	-6	8	0	48	39	4	7	-2	1	39	49	3	-7	5	1	23	26	4	5	-4	2	106	103	2
-6	1	0	99	100	1	-5	8	0	8	17	7	-7	-1	1	49	68	4	-6	5	1	83	87	1	6	-4	2	89	85	1
-5	1	0	95	99	4	-4	8	0	29	40	6	-6	-1	1	151	177	2	-5	5	1	50	60	2	7	-4	2	102	104	1
-4	1	0	118	118	1	-3	8	0	91	90	2	-5	-1	1	117	121	2	-4	5	1	169	158	2	-6	-3	2	78	85	2
-3	1	0	82	79	2	-2	8	0	54	52	2	-4	-1	1	87	84	1	-3	5	1	124	130	2	-5	-3	2	117	112	2
-2	1	0	247	247	2	-1	8	0	55	55	6	-3	-1	1	53	42	1	-2	5	1	303	316	4	-4	-3	2	78	77	2
-1	1	0	261	267	2	-4	9	0	55	50	4	-2	-1	1	261	259	2	-1	5	1	20	19	3	-3	-3	2	25	28	3
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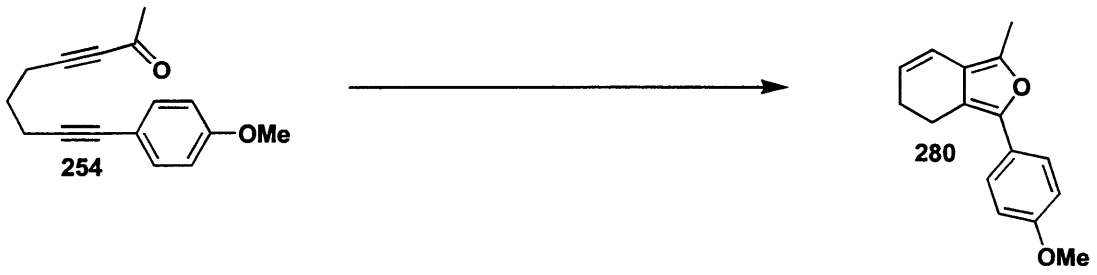
-5	1	5	38	41	2	0	-4	6	43	41	3	-1	4	6	96	124	43	-7	3	7	59	55	2	0	-1	9	52	53	3
-4	1	5	5	14	4	1	-4	6	48	48	4	0	4	6	245	242	3	-6	3	7	177	172	2	-4	0	9	54	45	4
-3	1	5	11	3	10	2	-4	6	0	1	-1	1	4	6	44	35	4	-5	3	7	139	142	2	-3	0	9	49	37	4
-2	1	5	188	187	1	3	-4	6	21	13	9	-7	5	6	19	2	11	-4	3	7	144	152	1	-2	0	9	0	6	-1
-1	1	5	223	228	2	4	-4	6	42	44	4	-6	5	6	63	59	16	-3	3	7	93	89	3	-1	0	9	35	38	4
0	1	5	162	165	1	-5	-3	6	37	38	4	-5	5	6	71	75	27	-2	3	7	22	17	4	-5	1	9	168	167	3
1	1	5	83	90	34	-4	-3	6	67	61	2	-4	5	6	148	178	63	-1	3	7	90	110	33	-4	1	9	145	152	2
2	1	5	0	13	-1	-3	-3	6	143	138	2	-3	5	6	121	130	53	0	3	7	26	36	14	-3	1	9	76	74	2

Table 6. Observed and calculated structure factors for 1

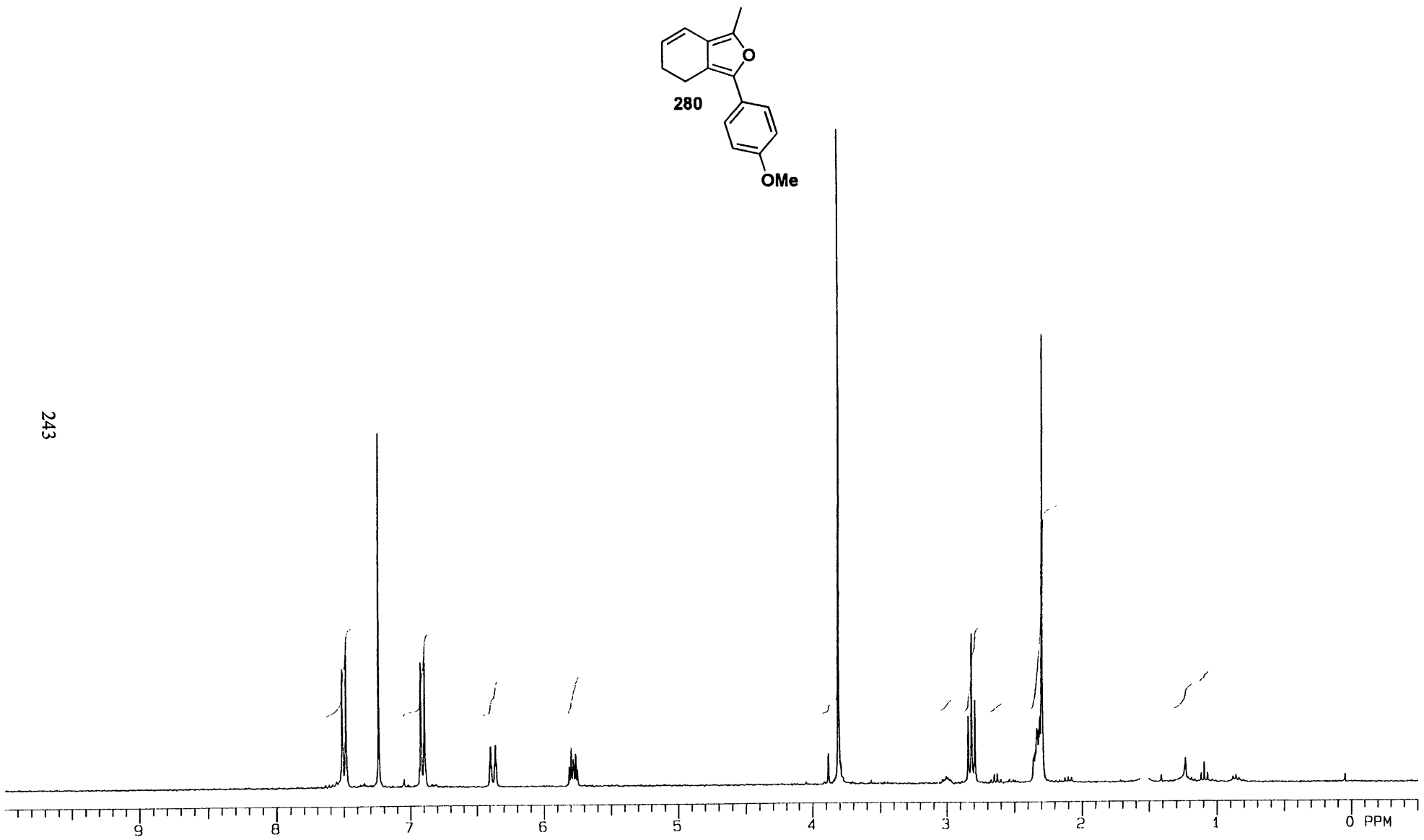
h	k	l	10Fo	10Fc	10s	h	k	l	10Fo	10Fc	10s	h	k	l	10Fo	10Fc	10s	h	k	l	10Fo	10Fc	10s	h	k	l	10Fo	10Fc	10s
-2	1	9	0	6	-1	-5	2	9	113	109	2	-3	2	9	35	21	4												
-1	1	9	20	4	7	-4	2	9	28	35	4	-2	2	9	33	30	5												



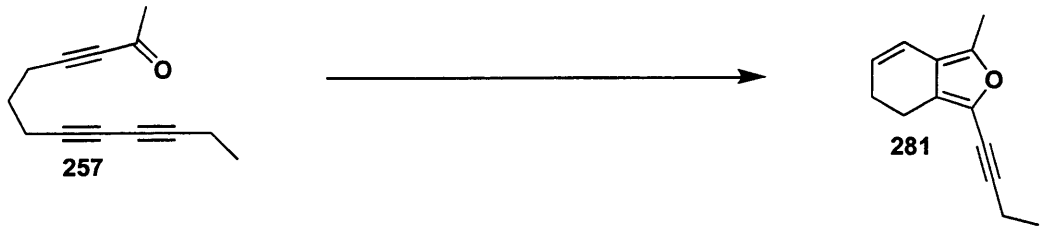
4,5-Dihydro-2-*p*-methoxyphenyl-9-methyl-isobenzofuran (280)

A threaded Pyrex tube (ca. 25-mL capacity) with a side arm equipped with a nitrogen inlet adapter was charged with ynone **254** (0.250 g, 1.04 mmol), 12 mL of toluene, and γ-terpinene (0.196 mL, 0.167 g, 1.14 mmol). The solution was degassed with a stream of argon for 1 h and then the tube was sealed with a threaded Teflon cap. The reaction mixture was heated in a 180 °C oil bath for 77 h and then allowed to cool to room temperature. Concentration gave 0.326 g of an orange oil. Column chromatography on 8 g of silica gel (elution with pentane) provided 0.145 g (58%, ~90% pure by ^{1}H NMR analysis) of furan **280** as a yellow oil.

IR (film)	3010, 2995, 2950, 2810, 1580, 1490, 1430, 1370, 1340, 1280, 1235, 1170, 1070, 1020, 780, and 720 cm^{-1}.
^{1}H NMR (300 MHz, $CDCl_3$)	7.54 (d, J = 7.8 Hz, 2H), 6.94 (d, J = 7.8 Hz, 2H), 6.41 (d of t, J = 9.9 Hz, J = 1.5 Hz, 1H), 5.84 (d of t, J = 9.9 Hz, J = 4.5 Hz, 1H), 3.82 (s, 3H), 2.85 (t, J = 7.5 Hz, 2H), 2.36-2.25 (m, 2H), and 2.33 (s, 3H).
^{13}C NMR (75 MHz, $CDCl_3$)	144.7, 144.5, 131.8, 128.5, 126.2, 125.2, 124.5, 118.8, 118.7, 116.9, 23.6, 18.7, and 11.7.



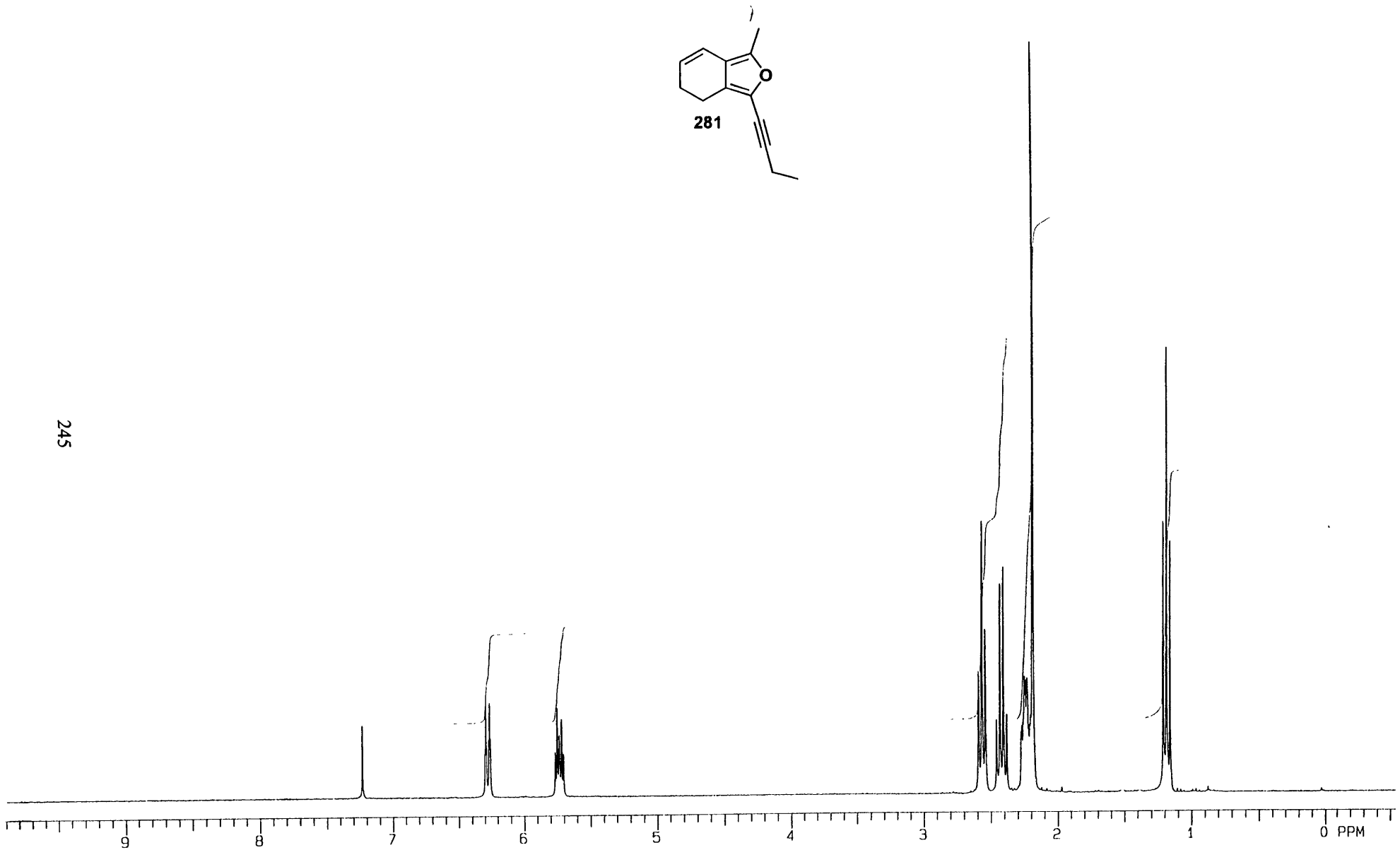
280



2-(1-Butynl)-4,5-dihydro-9-methyl-isobenzofuran (281)

A threaded Pyrex tube (ca. 25-mL capacity) with a side arm equipped with a nitrogen inlet adapter was charged with ynone **257** (0.146 g, 0.784 mmol), 8 mL of toluene, and γ–terpinene (0.149 mL, 0.126 g, 0.862 mmol). The solution was degassed with a stream of argon for 1 h and then the tube was sealed with a threaded Teflon cap. The reaction mixture was heated in a 180 °C oil bath for 6 h and then allowed to cool to room temperature. Concentration gave 0.132 g of a brown oil. Column chromatography on 10 g of silica gel (gradient elution with 5% diethyl ether-pentane) provided 0.082 g (56%) of furan **281** as a colorless oil.

IR (film)	3040, 3000, 2970, 2950, 2840, 2220, 1650, 1610, 1590, 1430, 1390, 1350, 1330, 1320, 1280, 1250, 1230, 1180, 1170, 1160, 1100, 1040, 1020, 970, 870, 790, 760, 740, and 670 cm^{-1}.
^1H NMR (300 MHz, $CDCl_3$)	6.29 (d of t, J = 9.6 Hz, J = 1.9 Hz, 1H), 5.75 (d of t, J = 9.6 Hz, J = 4.2 Hz, 1H), 2.59 (t, J = 7.5 Hz, 2H), 2.44 (quartet, J = 7.5 Hz, 2H), 2.30-2.22 (m, 2H), 2.21 (s, 3H), and 1.21 (t, J = 7.5 Hz, 3H).
^{13}C NMR (75 MHz, $CDCl_3$)	145.4, 129.8, 125.8, 124.6, 118.2, 117.4, 97.6, 69.8, 23.3, 18.4, 13.7, 13.3, and 11.8.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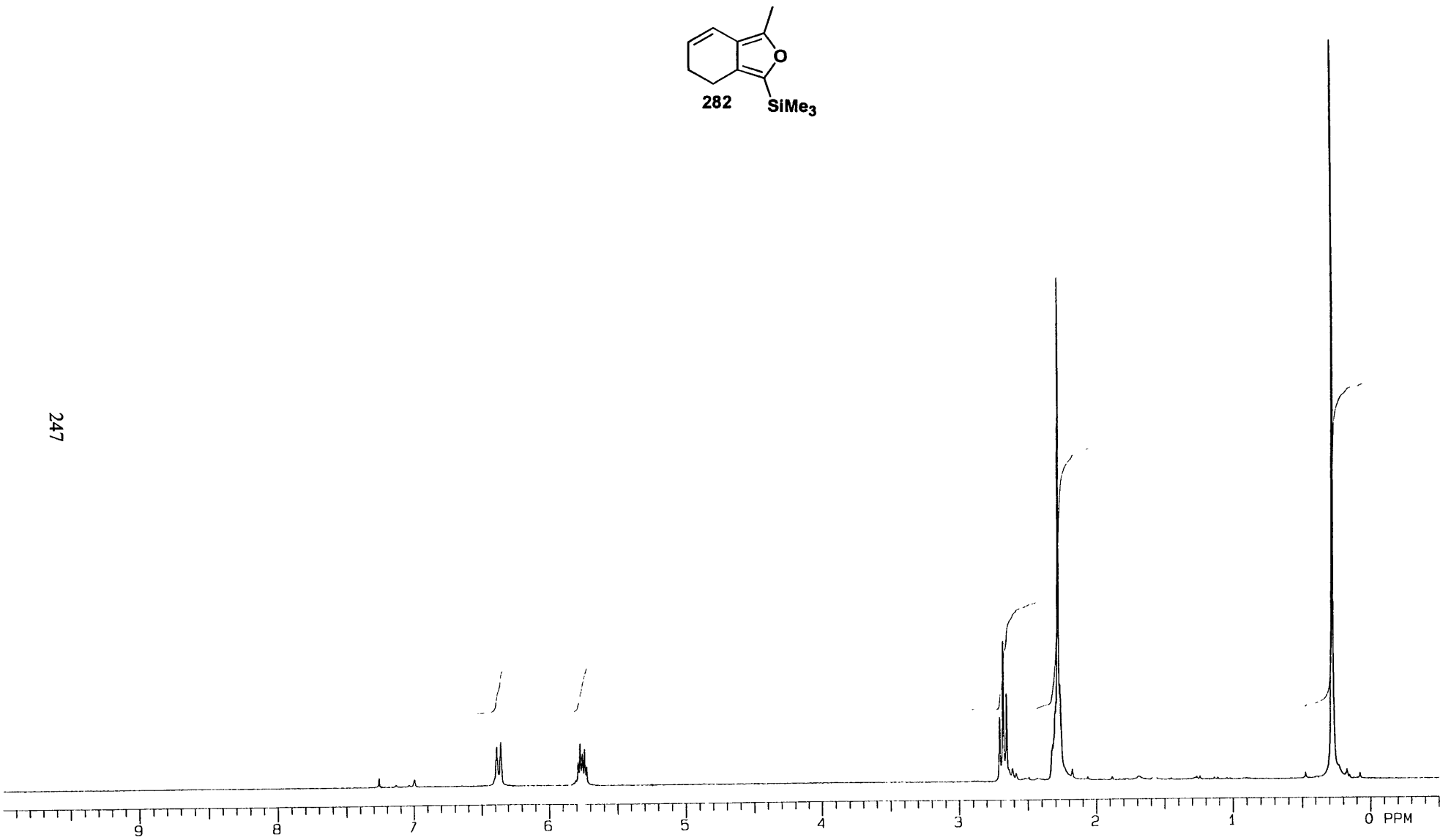
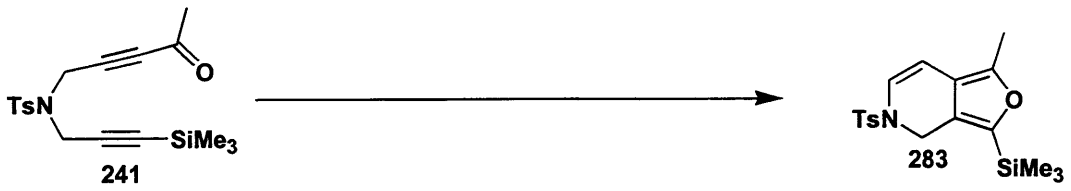
4,5-Dihydro-9-methyl-2-(trimethylsilyl)-isobenzofuran (282)

A threaded Pyrex tube (ca. 50-mL capacity) with a side arm equipped with a nitrogen inlet adapter was charged with ynone **235** (0.353 g, 1.71 mmol), 18 mL of toluene, and γ-terpinene (0.331 mL, 0.281g, 1.88 mmol). The solution was degassed with a stream of argon for 1 h and then the tube was sealed with a threaded Teflon cap. The reaction mixture was heated in a 220 °C oil bath for 72 h and then allowed to cool to room temperature. Concentration gave 0.363 g of an orange oil. Column chromatography on 20 g of silica gel (elution with pentane) provided 0.178 g (50%) of furan **282** as a colorless oil.

IR (film)	3030, 2950,2880, 2820, 1640, 1580, 1540, 1415, 1370, 1300, 1240, 1230, 1190, 1150, 1100, 1070, 1010, 960, 950, 830, 780, and 750 cm^{-1}.
^1H NMR (300 MHz, $CDCl_3$)	6.39 (d of t, J = 9.6 Hz, J = 1.3 Hz, 1H), 5.77 (d of t, J = 9.6 Hz, J = 4.5 Hz, 1H), 2.69 (t, J = 7.5 Hz, 2H), 2.38-2.28 (m, 2H), 2.29 (s, 3H), and 0.29 (s, 9H).
^{13}C NMR (75 MHz, $CDCl_3$)	150.0, 149.1, 131.3, 124.7, 118.9, 116.9, 23.8, 19.4, 11.8, and –1.2.



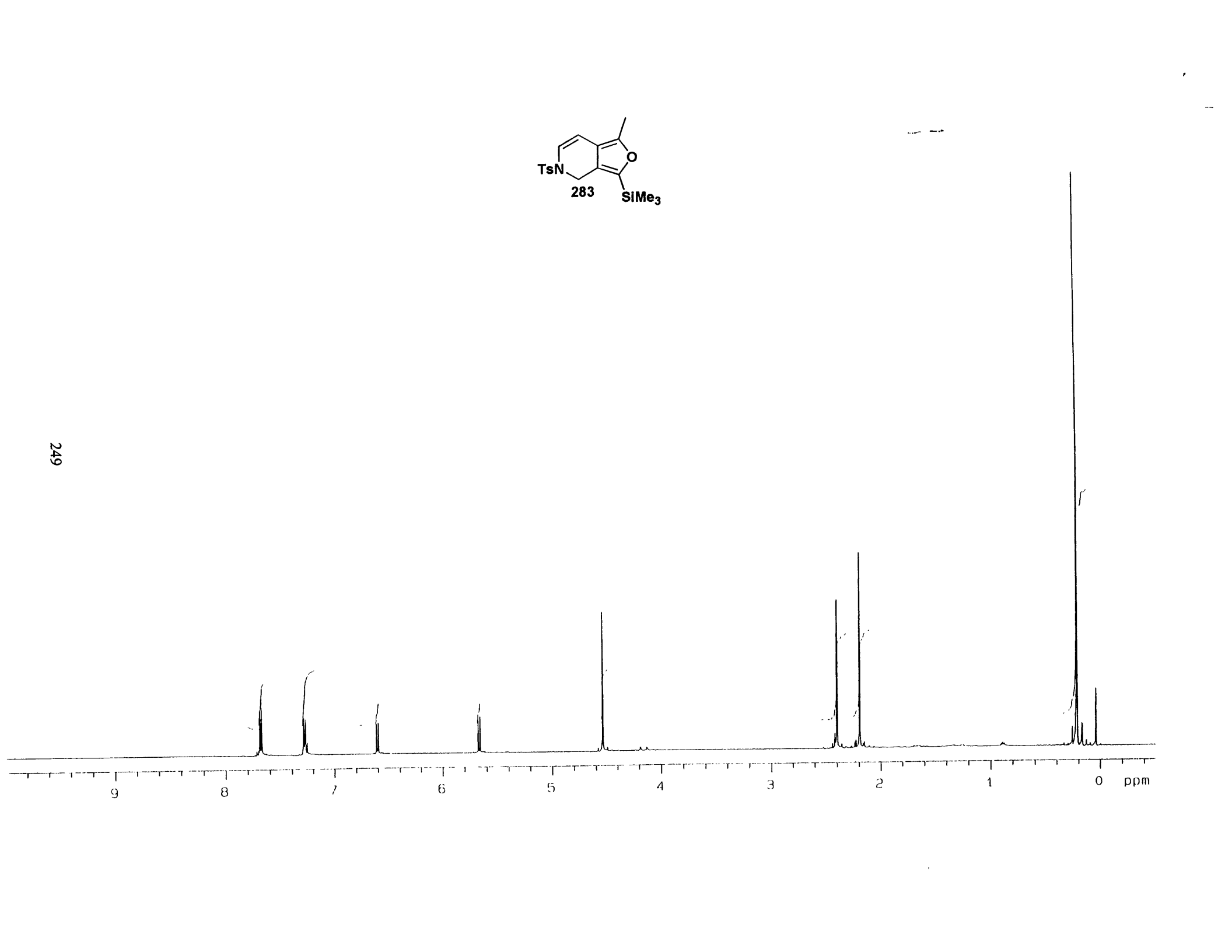
282



Furan 283

A 10-mL, round-bottomed flask equipped with a nitrogen inlet adapter was charged with sulfonamide **241** (0.097 g, 0.27 mmol), 3 mL of toluene, and γ-terpinene (0.051 mL, 0.044 g, 0.29 mmol). The solution was degassed with a stream of argon for 1 h and then the inlet adapter was replaced by a water cooled condenser. The reaction mixture was heated in a 120 °C oil bath for 16 h and then allowed to cool to room temperature. Concentration gave 0.112 g of a brown oil. Column chromatography on 10 g of silica gel (gradient elution with 2.5% ethyl acetate -hexane with 1% triethylamine) provided 0.065 g (64%) of furan **283** as a yellow oil

IR (film)	3080, 2960, 2940, 2900, 1640, 1600, 1560, 1500, 1440, 1410, 1360, 1300, 1240, 1170, 1120, 1100, 1040, 970, 940, 830, 730 cm^{-1}.
^1H NMR (500 MHz, $CDCl_3$)	7.68 (d, J = 8.3 Hz, 2H), 7.29 (d, J = 8.3 Hz, 2H), 6.61 (d, J = 7.8 Hz, 1H), 5.67 (d, J = 7.8 Hz, 1H), 4.54 (s, 2H), 2.40 (s, 3H), 2.20 (s, 3H), and 0.22 (s, 9H).
^{13}C NMR (75 MHz, $CDCl_3$)	150.5, 148.7, 143.8, 134.8, 129.7, 127.0, 125.3, 122.5, 112.5, 100.9, 41.8, 21.5, 11.8, and -1.5.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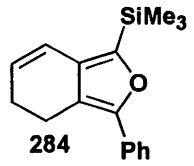
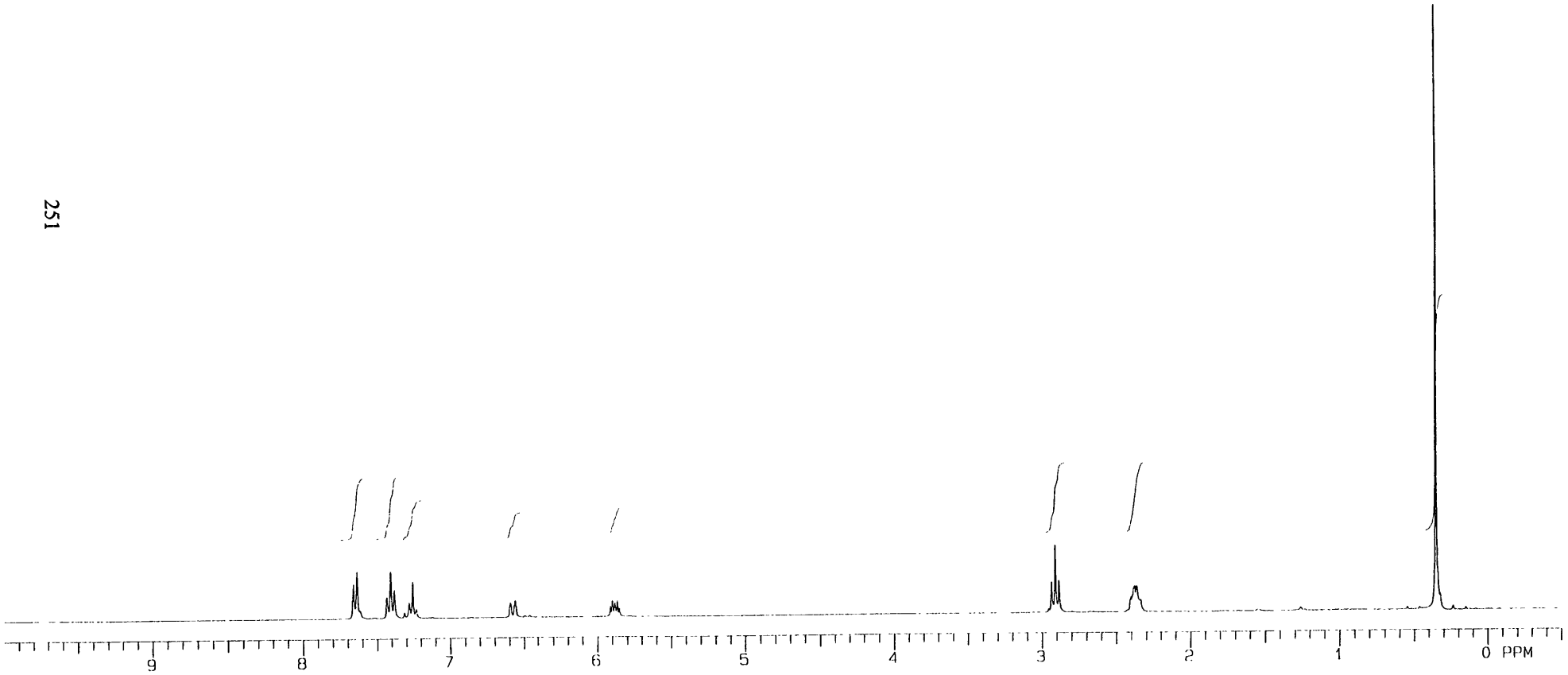
4,5-Dihydro-2-phenyl-9-(trimethylsilyl)-isobenzofuran (284)

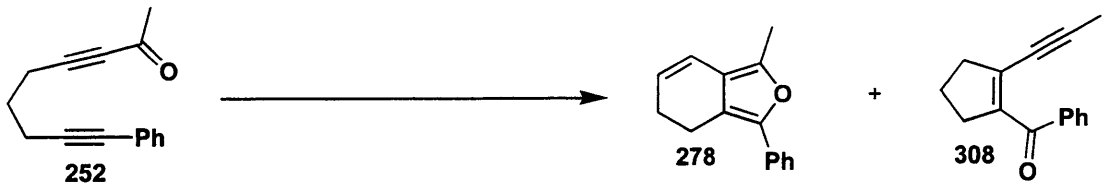
A threaded Pyrex tube (ca. 25-mL capacity) with a side arm equipped with a nitrogen inlet adapter was charged with acyl silane **268** (0.052 g, 0.194 mmol), 2 mL of toluene, and γ-terpinene (0.037 mL, 0.032 g, 0.213 mmol). The solution was degassed with a stream of argon for 1 h and then the tube was sealed with a threaded Teflon cap. The reaction mixture was heated in a 180 °C oil bath for 20 h and then allowed to cool to room temperature. Concentration gave 0.090 g of a brown oil. Column chromatography on 18 g of silica gel (elution with 1% triethylamine-hexane) provided 0.018 g (36%) of furan **284** as a colorless oil.

IR (film)	3010, 2960, 2940, 2920, 1600, 1490, 1450, 1400, 1310, 1250, 1180, 1090, 1060, 1010, 980, 830, and 750cm^{-1}.
^{1}H NMR (500 MHz, $CDCl_3$)	7.64 (d, J = 7.6 Hz, 2H), 7.41 (app t, J = 7.8 Hz, 2H), 7.26 (t, J = 7.4 Hz, 1H), 6.59 (d of t, J = 9.8 Hz, J = 1.9 Hz, 1H), 5.88 (d of t, J = 9.8 Hz, J = 4.5 Hz, 1H), 2.91 (t, J = 7.5 Hz, 2H), 2.43-2.37 (m, 2H), and 0.32 (s, 9H).
^{13}C NMR (75 MHz, $CDCl_3$)	152.2, 149.8, 133.0, 132.0, 128.4, 126.7, 125.1, 124.9, 120.1, 116.3, 23.9, 19.8, and –0.7.



284



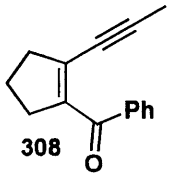


1-Benzoyl-2-(1-propyne)-cyclopentene (308)

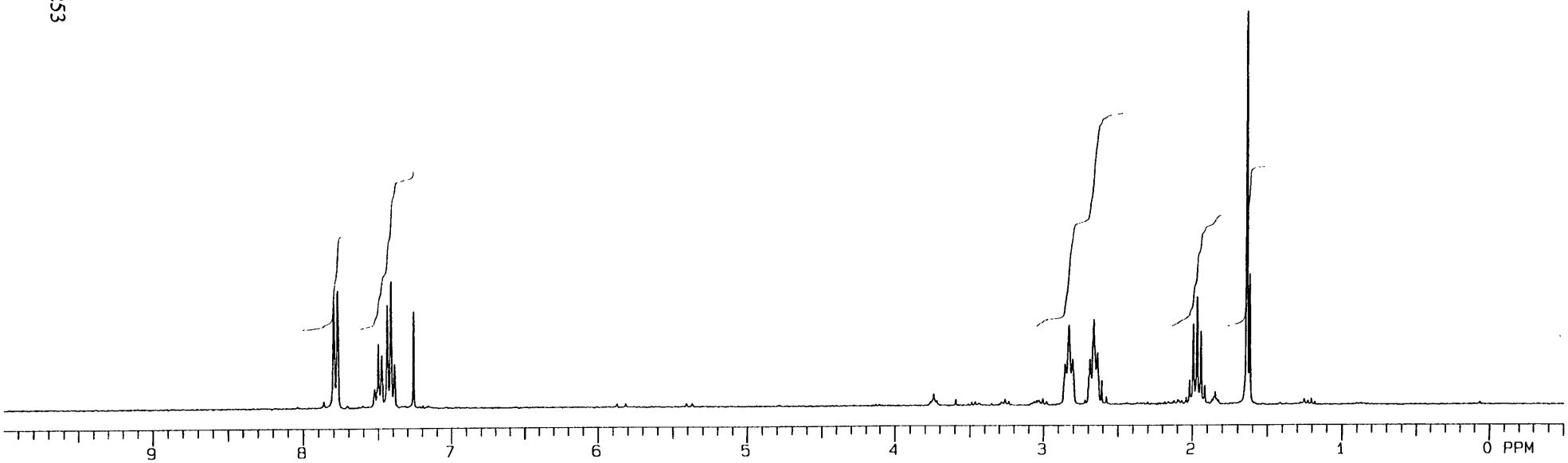
A 50-mL Schlenk flask was charged with ynone **252** (0.097 g, 0.461 mmol) and 8 mL of benzene. The solution was degassed with a stream of argon for 15 min and the flask was placed in a liquid nitrogen bath. While the solution froze (ca. 5 min), the flash vacuum pyrolysis apparatus was assembled, the oven was heated to a temperature of 600 °C, and the heating tape on the exit arm of the apparatus was heated to a temperature of 330 °C. The flask was then attached to the FVP apparatus, the system was evacuated (0.1 mmHg), and the Schlenk trap of the apparatus was cooled in a liquid nitrogen bath. The reaction flask was then heated at 240-245 °C at 0.1 mmHg until no material remained in the flask (ca. 15 min). The system was vented to the atmosphere and allowed to cool to room temperature. The material collected in the Schlenk trap was concentrated to afford 0.096 g of an orange oil. Column chromatography on 6 g of silica gel (gradient elution with 10% diethyl ether-pentane) provided 0.027 g (28%) of ketone **308** as an orange oil and 0.038 g (38%) of furan **278** as a colorless oil

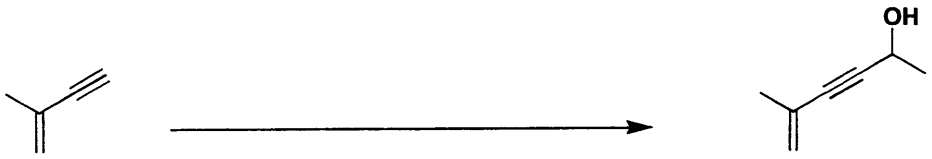
Data for ketone **308**:

IR (film)	3040, 3020, 2940, 2900, 2840, 2220, 1630, 1580, 1440, 1350, 1260, 1230, 1170, 1140, 1060, and 1020cm^{-1}.
^{1}H NMR (300 MHz, $CDCl_3$)	7.78 (d, J = 7.5 Hz, 2H), 7.51 (t, J = 7.3 Hz, 1H), 7.44 (app t, J = 7.4 Hz, 2H), 2.83 (t, J = 7.5 Hz, 2H), 2.66 (t, J = 7.6 Hz, 2H), 1.97 (app quintet, J = 7.5 Hz, 2H), and 1.64 (s, 3H).
^{13}C NMR (300 MHz, $CDCl_3$)	195.4, 145.1, 138.2, 133.3, 132.1, 129.3, 127.8, 97.3, 76.0, 39.7, 34.6, 22.3, and 4.4.



308



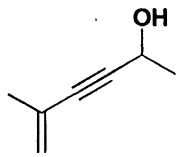


352 353

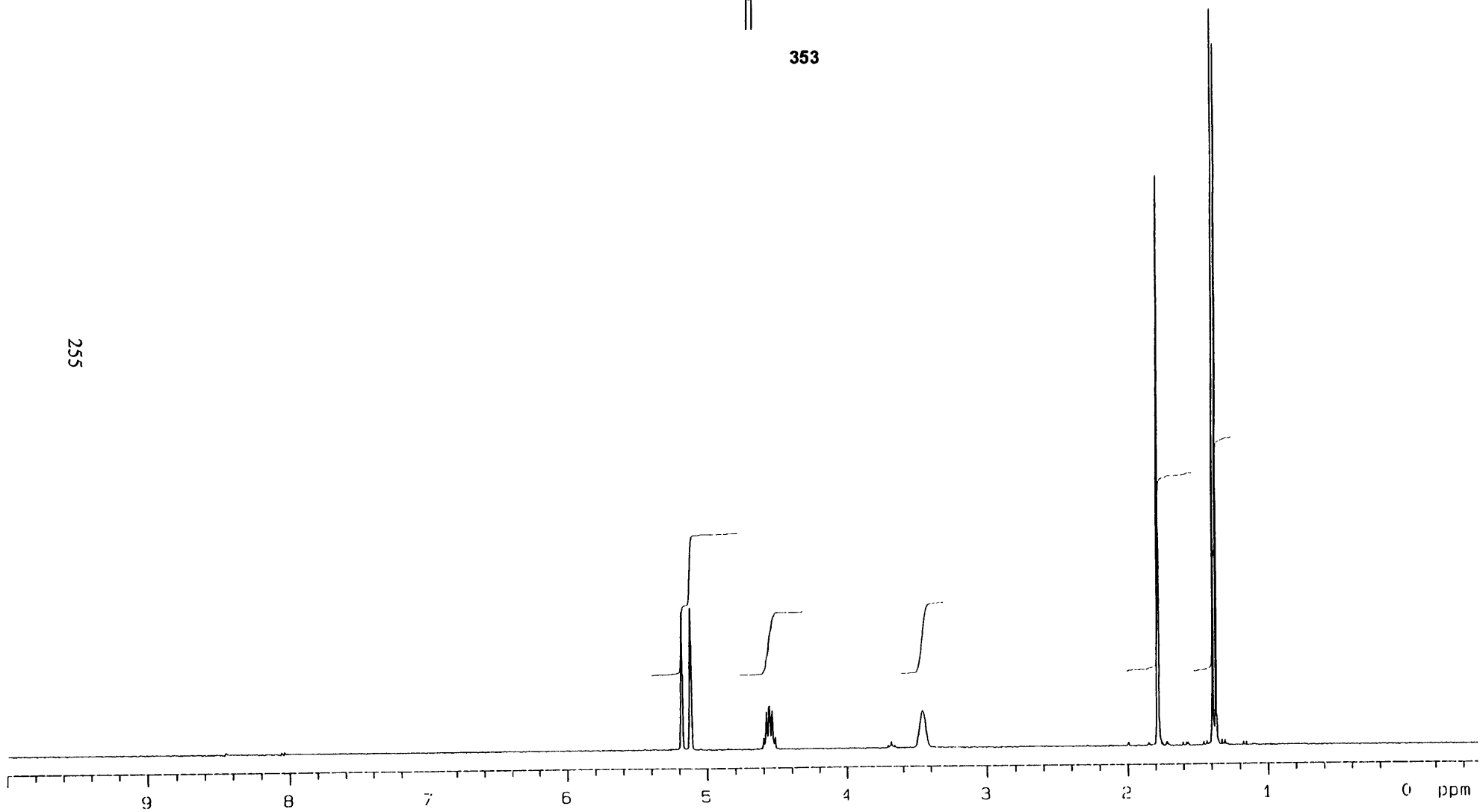
5-Methyl-hex-3-yn-5-en-2-ol (353)

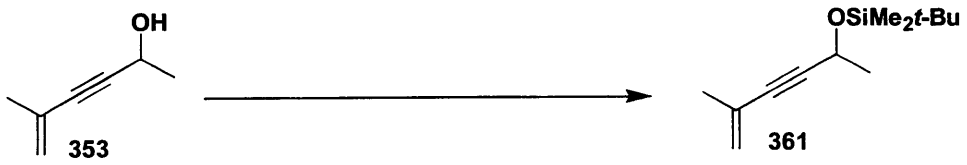
A 250-mL, three-necked, round-bottomed flask equipped with rubber septum, glass stopper, and argon inlet adapter was charged with 2-methyl-but-1-en-3-yne (**352**) (4.76 mL, 3.31 g, 50.0 mmol) and 166 mL of tetrahydrofuran and the resulting solution was cooled at 0 °C using an ice-water bath. An ethylmagnesium bromide solution (1.0 M in tetrahydrofuran, 50.0 mL, 50.0 mmol) was added dropwise via syringe over 10 min. The resulting mixture was stirred at 0 °C for 2 h and then acetaldehyde (10.42 mL, 8.21 g, 200.0 mmol) was added via syringe over 2 min. The reaction mixture was stirred at 0 °C for 20 min, diluted with 30 mL of saturated NH_4Cl solution, and allowed to warm to room temperature. The aqueous layer was separated and extracted with three 40-mL portions of diethyl ether. The combined organic phases were washed with 40 mL of saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford 6.02 g of a yellow oil. Column chromatography on 60 g of silica gel (elution with 15% ethyl acetate-hexane) provided 4.80 g (87%) of propargylic alcohol **353** as a colorless oil.

IR (film)	3310, 2980, 2970, 2920, 2860, 2210, 1620, 1440, 1420, 1360, 1320, 1280, 1110, 1040, 1000, 920, 890, and 850 cm^{-1}.
^1H NMR (300 MHz, $CDCl_3$)	5.19 (br s, 1H), 5.12 (app quintet, J = 1.7 Hz, 1H), 4.56 (quart, J = 6.7 1H), 3.46 (br s, 1H), 1.78 (app t, J = 1.6 Hz, 3H), and 1.38 (d, J = 6.7 Hz, 3H).
^{13}C NMR (75 MHz, $CDCl_3$)	126.2, 121.7, 90.1, 84.7, 58.2, 24.0, and 23.1.



353

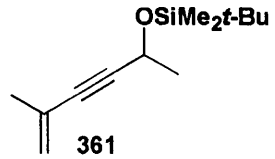




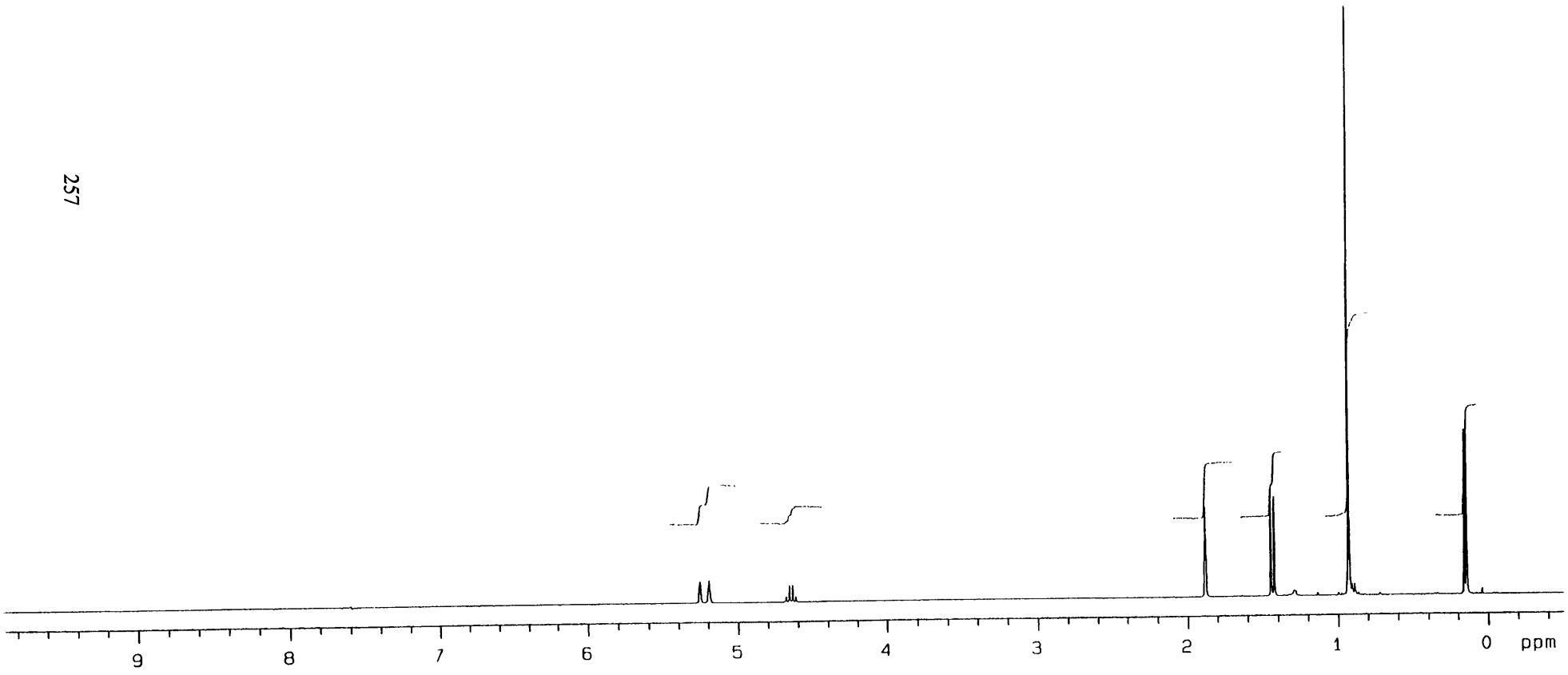
2-Methyl-5-(*tert* -butyldimethylsilyloxy)-hex-1-en-3-yne (361)

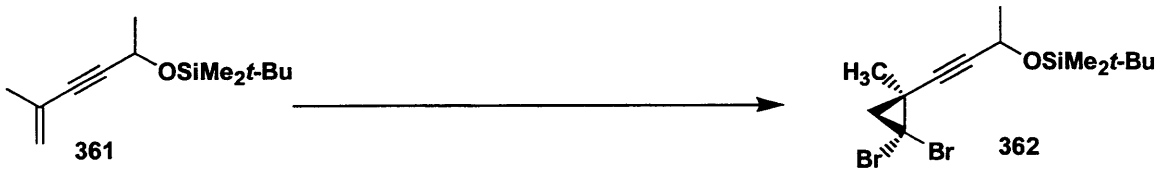
A 50-mL, round-bottomed flask equipped with rubber septum and argon needle inlet was charged with alcohol **353** (4.79 g, 43.5 mmol), 30 mL of dichloromethane, and imidazole (3.55 g, 52.2 mmol). Once the imidazole had dissolved, the solution was cooled at 0 °C using an ice-water bath and *tert* -butyldimethylsilylchloride (7.21 g, 47.9 mmol) was added in one portion. The solution was stirred at 0 °C for 4 h then it was allowed to warm to room temperature over 16 h. The reaction solution was diluted with 30 mL of saturated NH_4Cl solution and then aqueous layer was separated and extracted with three 30-mL portions of dichloromethane. The combined organic phases were washed with 30 mL of saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford 9.70 g of a yellow oil. Column chromatography on 110 g of silica gel (elution with 2% ethyl acetate-hexane) provided 9.10 g (93%) of **361** as a colorless oil.

IR (film)	2970, 2940, 2920, 2880, 2840, 1600, 1460, 1390, 1370, 1340, 1320, 1270, 1250, 1120, 1100, 1070, 1000, 950, 900, 830, and 770 cm^{-1}.
^1H NMR (300 MHz, $CDCl_3$)	5.24 (br s, 1H), 5.18 (app quintet, J = 1.6 Hz, 1H), 4.63 (quart, J = 6.6 1H), 1.86 (app t, J = 1.6 Hz, 3H), 1.41 (d, J = 6.6 Hz, 3H), 0.91 (s, 9H), 0.13 (s, 3H), and 0.12 (s, 3H).
^{13}C NMR (75 MHz, $CDCl_3$)	126.6, 121.3, 90.9, 84.5, 59.3, 25.8, 25.3, 23.3, 18.2, -4.6, and –4.9.



361

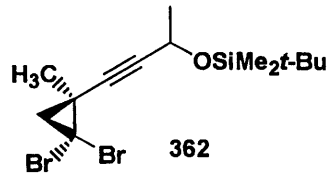




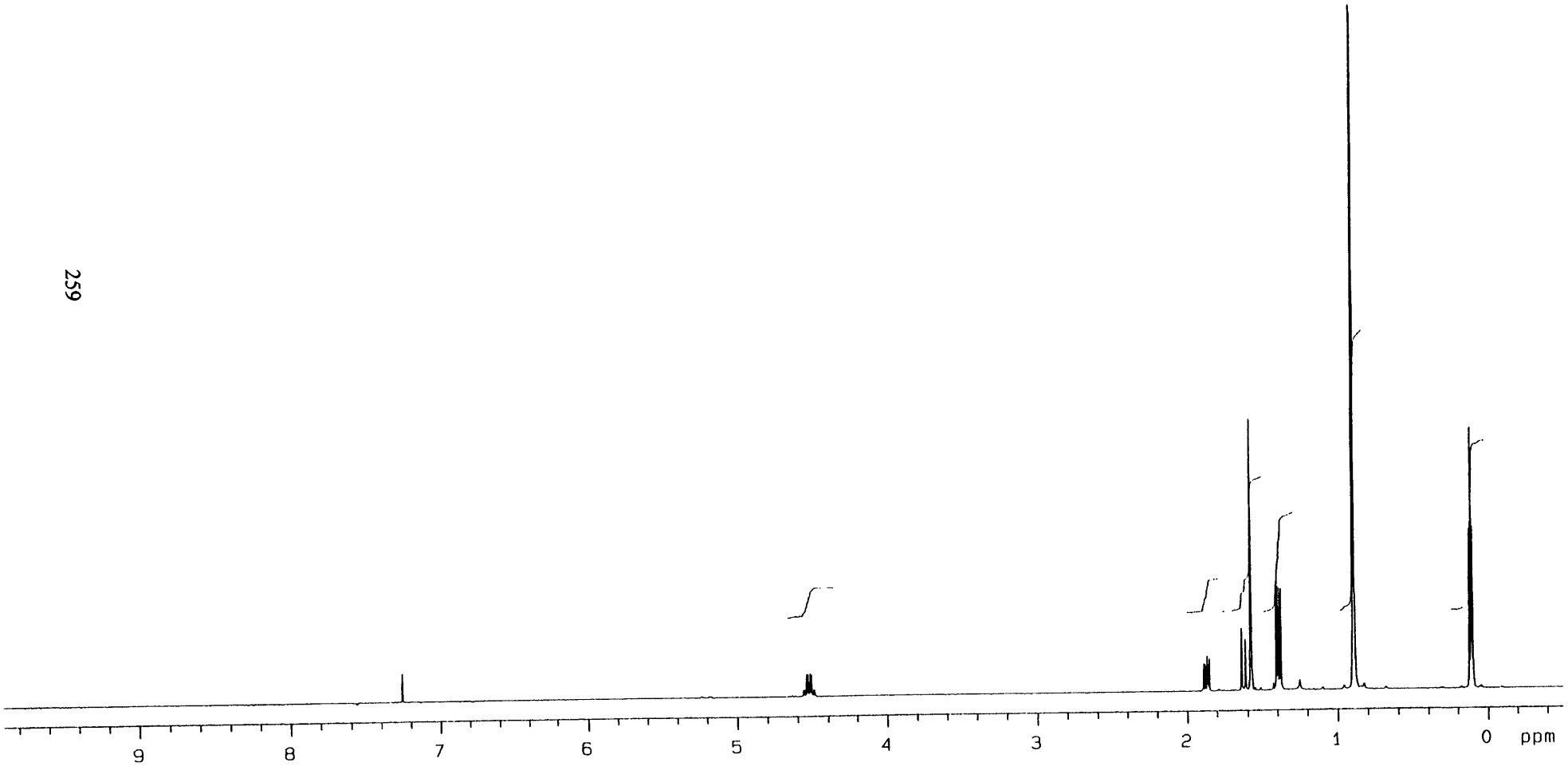
2-Methyl-2-{[3-(*tert*-butyldimethylsilyloxy)]-but-1-yn}-1,1-dibromocyclopropane (362)

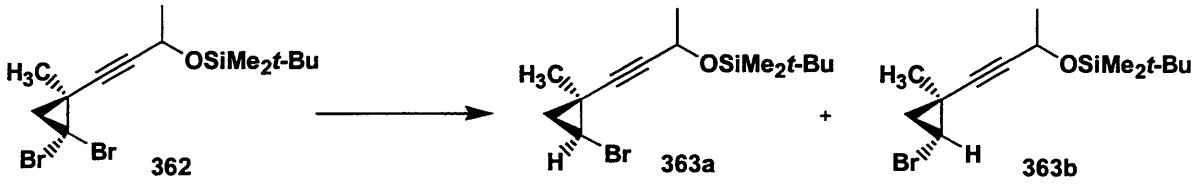
A 100-mL, round-bottomed flask equipped with rubber septum, glass stopper and argon inlet was charged with enyne **361** (8.50 g, 37.8 mmol), 57 mL of pentane and cooled at 0 °C using an ice-water bath. Potassium *tert*-butoxide (6.37 g, 56.7 mmol) was added in one portion followed by the dropwise addition of bromoform (4.96 mL, 14.34g, 56.7 mmol) over 7 min. The solution was stirred at 0 °C for 20 min then it was allowed to warm to room temperature over 17 h. The reaction solution was diluted with 30 mL of water and then aqueous layer was separated and extracted with three 30-mL portions of diethyl ether. The combined organic phases were washed with 30 mL of saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford 17.7 g of a brown oil. Column chromatography on 220 g of silica gel (elution with 3% ethyl acetate-hexane) provided 6.08 g (41%) of cyclopropane **362** as a brown oil.

IR (film)	2940, 2920, 2840, 2820, 2200, 1600, 1450, 1430, 1360, 1330, 1310, 1240, 1120, 1100, 1070, 1030, 1000, 960, 920, 830, 760, and 700 cm^{-1}.
^1H NMR (300 MHz, $CDCl_3$)	4.56 (quart, J = 6.9 1H), 1.89 (d, J = 7.1 Hz, 1H), 1.63 (d, J = 7.1 Hz, 1H), 1.60 (s, 3H), 1.42 (d, J = 6.9 1H), 0.92 (s, 9H), 0.14 (s, 3H), and 0.13 (s, 3H).
^{13}C NMR (75 MHz, $CDCl_3$)	84.1, 83.6, 59.1, 36.8, 34.7, 25.8, 25.4, 24.0, 23.7, 18.2, -4.6, and –4.9.



362





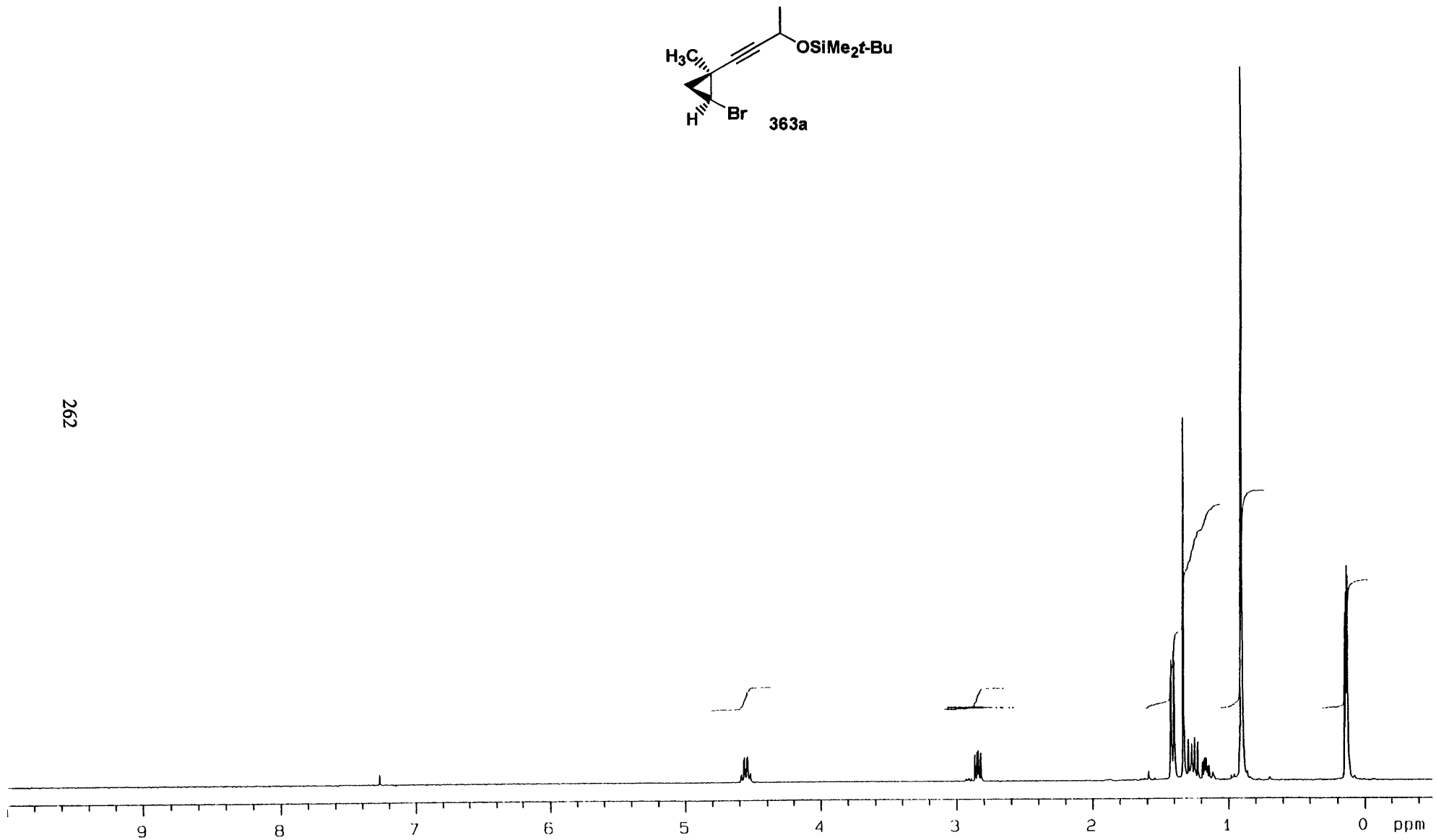
cis-1-Bromo-2-methyl-2-{[3-(_tert_-butyldimethylsilyloxy)]-but-1-yn}-cyclopropane (363a)
trans-1-Bromo-2-methyl-2-{[3-(_tert_-butyldimethylsilyloxy)]-but-1-yn}-cyclopropane (363b)

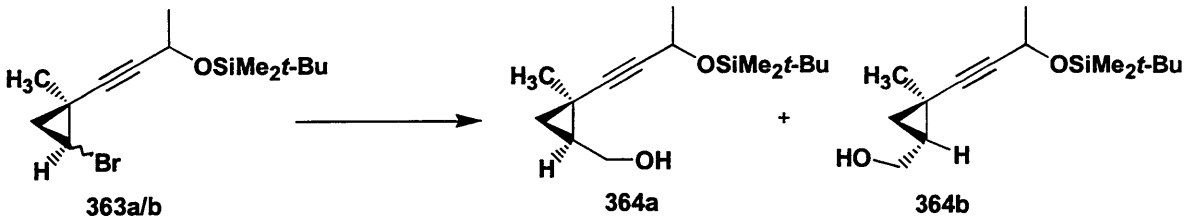
A 250-mL, round-bottomed flask equipped with rubber septum, glass stopper and argon inlet was charged dibromocyclopropane **362** (6.08 g, 15.3 mmol), 154 mL of tetrahydrofuran and cooled at -95 °C using a toluene-liquid nitrogen bath. A *n*-butyllithium solution (2.38 M in hexanes, 7.09 mL, 16.9 mmol) was added dropwise over 14 min. After stirring at -95 °C for 15 min, ethanol (2.70 mL, 2.12 g, 46.0 mmol) was added dropwise over 4 min. The solution stirred at -95 °C for 15 min then the cooling bath was removed and the solution stirred at room temperature for 3 h. The reaction solution was diluted with 30 mL of saturated NH_4Cl and then aqueous layer was separated and extracted with three 30-mL portions of diethyl ether. The combined organic phases were washed with 40 mL of saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford 10.1 g of a brown oil. Column chromatography on 250 g of silica gel (elution with 1% ethyl acetate-hexane) provided 3.81 g (78%) of a mixture of cyclopropanes **363a** and **363b** as a brown oil in an approximately 6:1 isomer ratio by ^1H NMR analysis. A sample of the major isomer was isolated by additional column chromatography.

Data for the major isomer **363a**:

IR (film)	2940, 2920, 2840, 2220, 1450, 1430, 1360, 1340, 1260, 1240, 1200, 1140, 1100, 1040, 1000, 950, 830, and 770 cm^{-1}.
^1H NMR (500 MHz, $CDCl_3$)	4.57 (quart, J = 6.5 1H), 2.84 (dd, J = 7.3, J = 5.1, 1H), 1.41 (d, J = 6.5 Hz, 3H), 1.34 (s, 3H), 1.23-1.29 (dd, J = 7.5, J = 5.1, 1H), 1.19-1.15 (dd, J =

	7.5, J = 7.3, 1H), 0.91 (s, 9H), 0.15 (s, 3H), and 0.13 (s, 3H).
^{13}C NMR (75 MHz, $CDCl_3$)	85.0, 82.6, 59.1, 27.2, 25.8, 25.6, 25.4, 23.5, 18.2, 15.5, -4.9, and –4.5.


H3C
OSiMe2t-Bu
H
Br
363a
9
8
7
6
5
4
3
2
1
0
ppm



cis-1-Hydroxymethyl-2-methyl-2-{[3-(_tert_-butyldimethylsilyloxy)]-but-1-yn}-cyclopropane (364a)
trans-1-Hydroxymethyl-2-methyl-2-{[3-(_tert_-butyldimethylsilyloxy)]-but-1-yn}-cyclopropane (364b)

A 50-mL, round-bottomed flask equipped with rubber septum, glass stopper and argon inlet was charged with a mixture of bromocyclopropanes **363a** and **363b** (0.961 g, 3.02 mmol) and 30 mL of tetrahydrofuran and cooled at -78 °C using a dry ice-acetone bath. A *n*-butyllithium solution (2.55 M in hexanes, 1.42 mL, 3.62 mmol) was added dropwise over 4 min. After stirring at -78 °C for 15 min, the golden yellow solution was warmed at -30 °C using a dry ice-acetone bath.

A 25-mL, round-bottomed flask equipped with glass stopper and argon inlet was charged with paraformaldehyde (0.815 g, 27.2 mmol) then the glass stopper was removed and the flask was connected to the -30°C alkyl lithium solution via tygon tubing. The glass stopper on the 50-mL flask was then replaced by a tetrahydrofuran bubbler and the argon inlet on the 50-mL flask was closed. The 25-mL flask was then placed in a 160 °C oil bath. The formaldehyde gas produced was bubbled into the alkyl lithium solution via a steady stream of argon. After 1 h, the alkyl lithium solution had turned pale yellow and cloudy. The tubing was disconnected and the reaction solution was diluted with 5 mL of saturated NH_4Cl. The resulting solution was then poured into a seperatory funnel containing 30 mL saturated NH_4Cl and 30 mL diethyl ether. The aqueous layer was separated and extracted with three 30-mL portions of diethyl ether. The combined organic phases were washed with 40 mL of saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford 1.05 g of a yellow oil. Column chromatography on 40 g of silica gel (gradient elution with 5-30% ethyl acetate-hexane) provided 0.534 g (65%)

of a mixture of cyclopropanes **364a** and **364b** as a brown oil in an approximately 6:1 ratio based on the isomer ratio of the starting material.

Spectral data for the mixture:

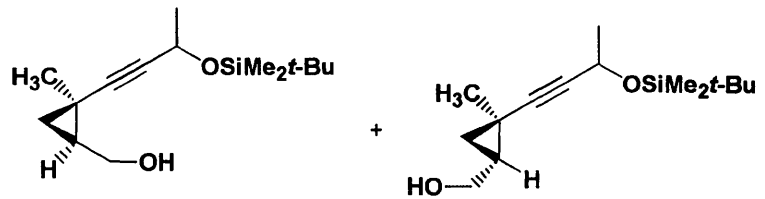
IR (film)	3350, 2960, 2940, 2920, 2910, 2210, 1450, 1430, 1330, 1250, 1110, 1100, 1070, 950, 930, 820, and 770 cm^{-1}.
^{1}H NMR (500 MHz, $CDCl_3$)	4.47 (quart, J = 6.4 1H), 3.83-3.81 (br s, 1H), 3.54-3.52 (m, 1H), 1.83 (br s, 1H), 1.34(d, J = 6.4 Hz, 3H), 1.25 (s, 3H), 1.18-1.15 (m, 1H), 0.87 (s, 9H), 0.8-0.6 (m, 2H), 0.15 (s, 3H), and 0.13 (s, 3H).

Spectral Data for **364 a**:

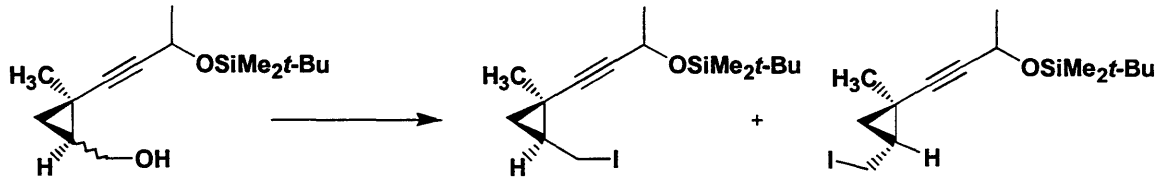
^{13}C NMR (75 MHz, $CDCl_3$)	86.1, 80.9, 64.6, 59.1, 28.7, 25.8, 25.7, 24.6, 20.4, 18.2, 11.6, -4.9, and –4.6.

Spectral Data for **364b** (partial):

^{13}C NMR (75 MHz, $CDCl_3$)	28.6



364a (Major Isomer) **364b** (Minor Isomer)



cis-1-Iodomethyl-2-methyl-2-{[3-(_tert_-butyldimethylsilyloxy)]-but-1-yn}-cyclopropane (365a)
trans-1-Iodomethyl-2-methyl-2-{[3-(_tert_-butyldimethylsilyloxy)]-but-1-yn}-cyclopropane (365b)

A 250-mL, round-bottomed flask equipped with rubber septum, glass stopper, and argon inlet adapter was charged with a mixture of alcohols **364a** and **364b** (1.05 g, 3.93 mmol), 66 mL of diethyl ether, and 20 mL of acetonitrile. Triphenylphosphine (1.54 g, 5.89 mmol) was added in one portion followed by imidazole (0.401 g, 5.89 mmol) and iodine (1.49 g, 5.89 mmol). After stirring at room temperature for 1 h, the solution was diluted with 10 mL of saturated $NaHCO_3$ solution. After stirring for an additional 5 min, small portions of iodine were added until the organic layer remained brown. The aqueous layer was separated and extracted with two 30 mL-portions of diethyl ether. The combined organic extracts were washed with 30 mL of saturated $Na_2S_2O_3$, 30 mL of saturated NaCl solution, dried over Na_2SO_4, filtered, and concentrated to afford 2.02 g of a brown oil. Column chromatography on 75 g of silica gel (elution with 3% ethyl acetate-hexane) provided 1.00 g (68%) of a mixture of iodides **365a** and **365b** as a colorless oil in an approximately 6:1 ratio based on the isomer ratio of the starting material.

Spectral data for the mixture:

IR (film)	2960, 2920, 2860, 2840, 2220, 1460, 1440, 1370, 1350, 1250, 1170, 1120, 1100, 1070, 1000, 940, 830, and 780 cm^{-1}.
^1H NMR (500 MHz, $CDCl_3$)	4.51 (quart, J = 6.6 1H), 3.32-3.27 (m, 2H), 1.34 (d, J = 6.6 Hz, 3H), 1.25 (s, 3H), 0.95-0.93 (m, 2H),

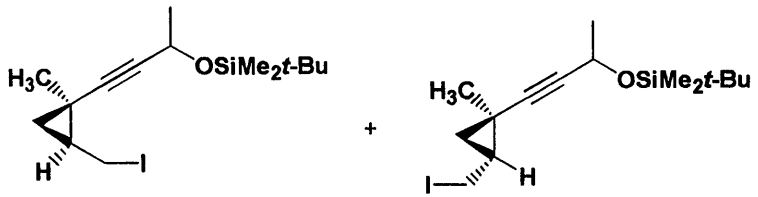
0.90 (s, 9H), 0.65-0.62 (m, 1H), 0.13 (s, 3H), and 0.12 (s, 3H).

Spectral data for **365a**:

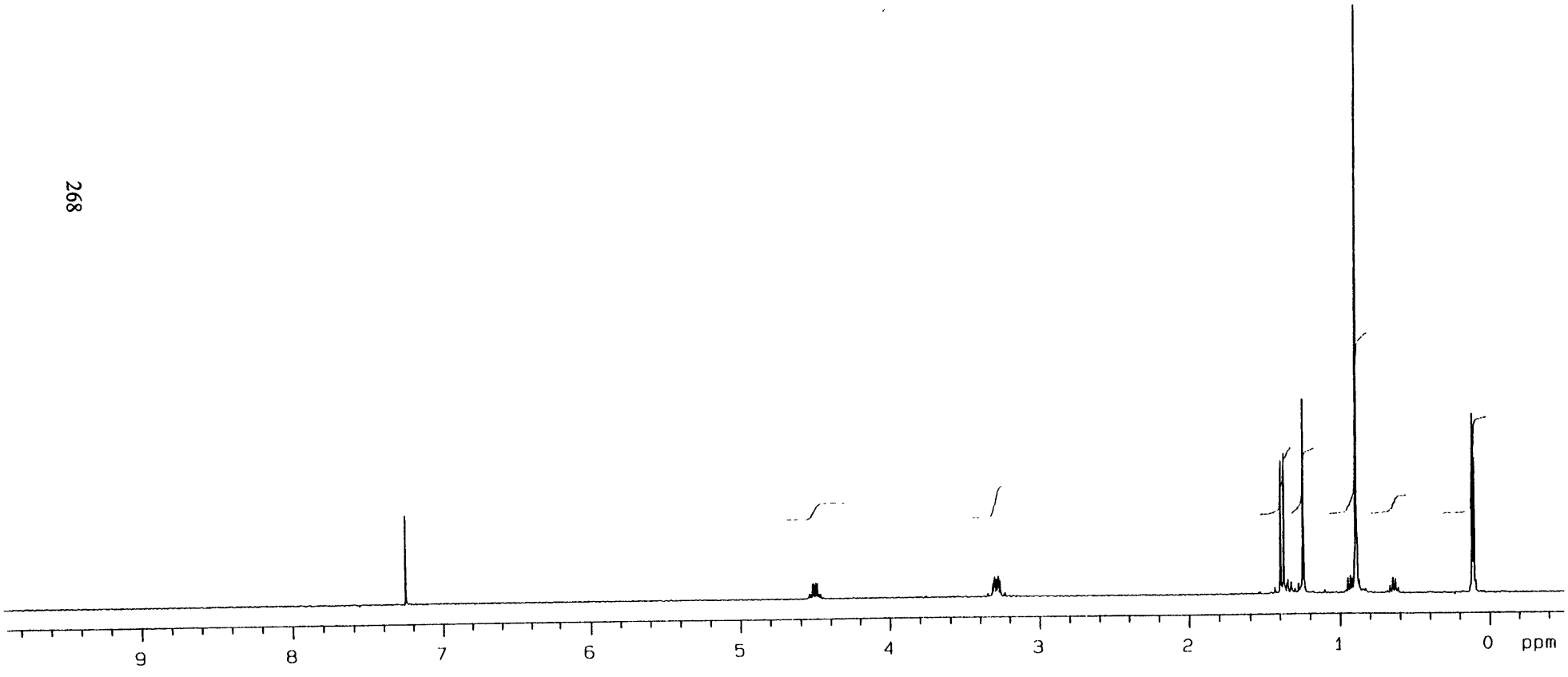
^{13}C NMR (75 MHz, $CDCl_3$) 84.3, 81.9, 59.2, 29.7, 29.6, 26.0, 25.8, 24.4, 18.9, 18.2, 12.3, -4.9, and –4.6.

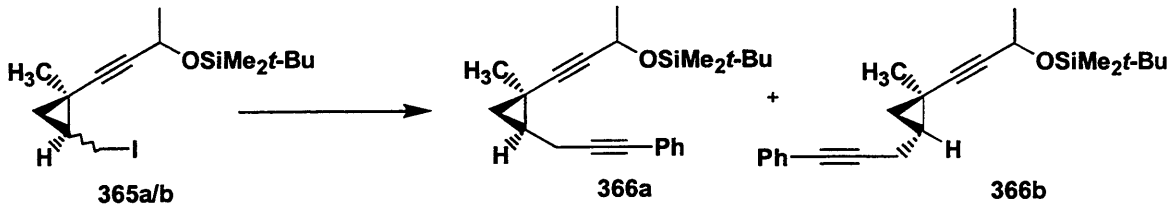
Spectral data for **365b** (partial):

^{13}C NMR (75 MHz, $CDCl_3$) 26.0, 25.7, and 24.4.



365a (Major Isomer) **365b** (Minor Isomer)





cis-2-Methyl-1-(3-phenyl-prop-2-yn)-2-{[3-(_*tert*_ -butyldimethylsilyloxy)]-but-1-yn}-cyclopropane (366a)
trans-2-Methyl-1-(3-phenyl-prop-2-yn)-2-{[3-(_*tert*_ -butyldimethylsilyloxy)]-but-1-yn}-cyclopropane (366b)

A 50-mL, round-bottomed flask equipped with rubber septum with an argon inlet needle was charged with phenylacetylene (0.277 mL, 0.257 g, 2.51 mmol) and 17 mL of tetrahydrofuran. The solution was cooled at -78 °C using a dry ice-acetone bath then a *n*-butyllithium solution (2.38 M in hexanes, 1.06 mL, 2.51 mmol) was added dropwise over 4 min. After stirring at -78 °C for 15 min, a solution of iodides **365a** and **365b** (0.950 g, 2.51 mmol) in 2 mL hexamethylphosphoamide was added via cannula over 10 min. The cooling bath was removed and the solution stirred at room temperature for 18 h. The solution was diluted with 15 mL of saturated NH_4Cl solution then the aqueous layer was separated and extracted with two 30-mL portions of diethyl ether. The combined organic extracts were washed with 40 mL of saturated NaCl solution, dried over Mg_2SO_4, filtered, and concentrated to afford 1.15 g of a yellow oil. Column chromatography on 100 g of silica gel (elution with 2% ethyl acetate-hexane) provided 0.706 g (80%) of a mixture of cyclopropanes **366a** and **366b** as a yellow oil in an approximately 6:1 ratio based on the isomer ratio for the starting material.

Spectral data for the mixture:

IR (film)	3060, 2960, 2920, 2880, 2800, 2120, 1600, 1490, 1470, 1430, 1370, 1350, 1240, 1120, 1100, 1080, 1000, 960, 830, 780 and 760 cm^{-1}.
^1H NMR (500 MHz, $CDCl_3$)	7.42-7.38 (m, 2H), 7.31-7.26 (m, 3H), 4.51 (quartet, J = 6.5 Hz, 1H), 2.70 (dd, J = 17.4 Hz, J = 6.4 Hz, 1H), 2.42 (dd, J = 17.4 Hz, J = 7.6 Hz, 1H), 1.38 (d, J = 6.5 Hz, 3H), 1.28 (s, 3H), 1.12-1.15 (m. 1H),

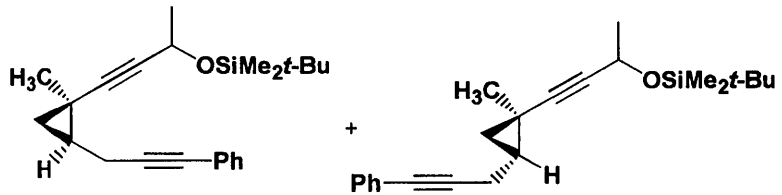
0.91 (s, 9H), 0.85-0.83 (m, 1H), 0.67-0.65 (m, 1H), 0.12 (s, 3H), and 0.11 (s, 3H).

Spectral data for **366a**:

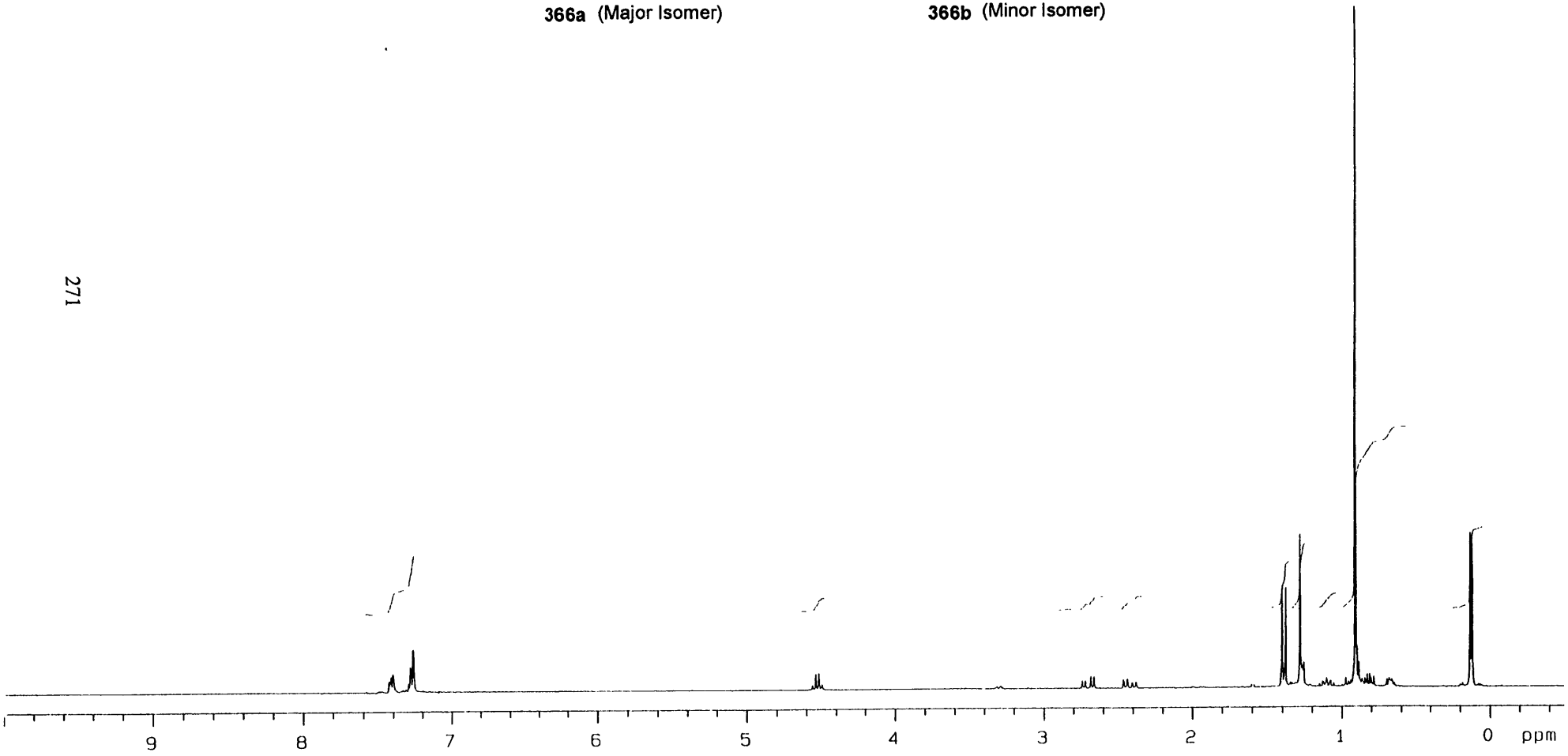
^{13}C NMR (75 MHz, $CDCl_3$) 131.6, 128.2, 127.5, 124.1, 89.2, 86.1, 81.5, 80.7, 59.3, 25.8, 25.4, 24.6, 22.0, 21.3, 18.3, 14.1, 13.0, -4.8, and -4.4.

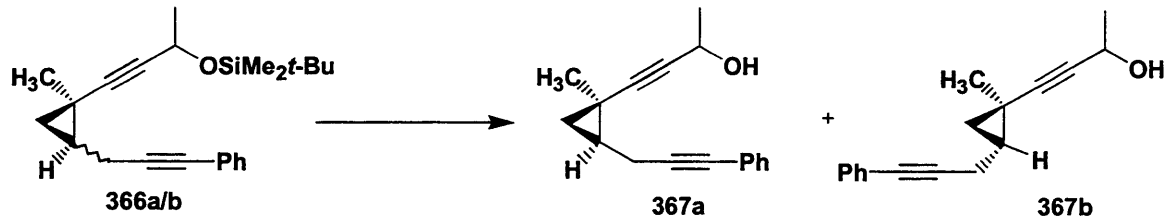
Spectral data for **366b** (partial):

^{13}C NMR (75 MHz, $CDCl_3$) 31.6, 25.5, 24.6, 22.7, 22.0, and 21.2.



366a (Major Isomer) **366b** (Minor Isomer)





***cis*-2-(1-Butyn-3-ol)-2-methyl-1-(3-phenyl-prop-2-yn)-cyclopropane (367a)**

***trans*-2-(1-Butyn-3-ol)-2-methyl-1-(3-phenyl-prop-2-yn)-cyclopropane (367b)**

A 100-mL, round-bottomed flask equipped with rubber septum, glass stopper, and argon inlet adapter was charged with a mixture of cyclopropanes **366a** and **366b** (0.650 g, 1.85 mmol) and 137 mL of tetrahydrofuran. The solution was cooled at 0 °C using a water-ice bath then a tetrabutylammonium fluoride solution (1.0 M in tetrahydrofuran, 9.25 mL, 9.25 mmol) was added dropwise over 7 min. After stirring at 0 °C for 1 h, the solution was diluted with 10 mL of saturated NH_4Cl solution. The aqueous layer was separated and extracted with three 20-mL portions of diethyl ether. The combined organic extracts were washed with 40 mL of saturated NaCl solution, dried over Mg_2SO_4, filtered, and concentrated to afford 0.503 g of a yellow oil. Column chromatography on 50 g of silica gel (elution with 15% ethyl acetate-hexane) provided 0.355 g (81%) of a mixture of alcohols **367a** and **367b** as a yellow oil in an approximately 6:1 ratio based on ^{1}H NMR analysis.

Spectral data for the mixture:

IR (film)	3360, 3060, 2980, 2920, 2880, 2220, 1600, 1490, 1440, 1400, 1370, 1330, 1300, 1170, 1120, 1050, 980, 870, and 760 cm^{-1}.

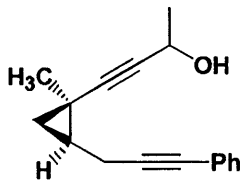
Spectral data for **367a**:

^{1}H NMR (500 MHz, $CDCl_3$)	7.41-7.38 (m, 2H), 7.33-7.27 (m, 3H), 4.50 (quartet, J = 6.2 Hz, 1H), 2.66 (dd, J = 17.6 Hz, J = 5.9 Hz, 1H), 2.44 (dd, J = 17.6 Hz, J = 7.3 Hz, 1H), 1.83 (br s, 1H), 1.41 (d, J = 6.2 Hz, 3H), 1.27 (s, 3H), 1.14-1.12 (m. 1H), 0.83-0.81 (m, 1H), and 0.72-0.66 (m, 1H).

^{13}C NMR (75 MHz, $CDCl_3$)	131.8, 128.2, 127.6, 124.1, 89.1, 87.1, 81.1, 80.8, 58.7, 25.1, 24.6, 22.1, 20.5, 12.2, and 8.2.

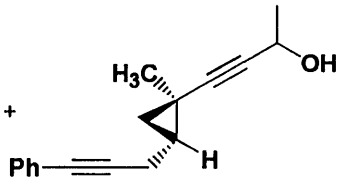
Spectral Data for **367b** (partial):

^{1}H NMR (500 MHz, $CDCl_3$)	7.41-7.38 (m, 2H), 7.33-7.27 (m, 3H), 4.50 (quartet, J = 6.2 Hz, 1H), 3.32 (m, 1H), 3.23 (m, 1H), 1.25 (s, 3H), 0.99-0.93 (m, 1H).
^{13}C NMR (75 MHz, $CDCl_3$)	30.1, 26.5, and 12.4.

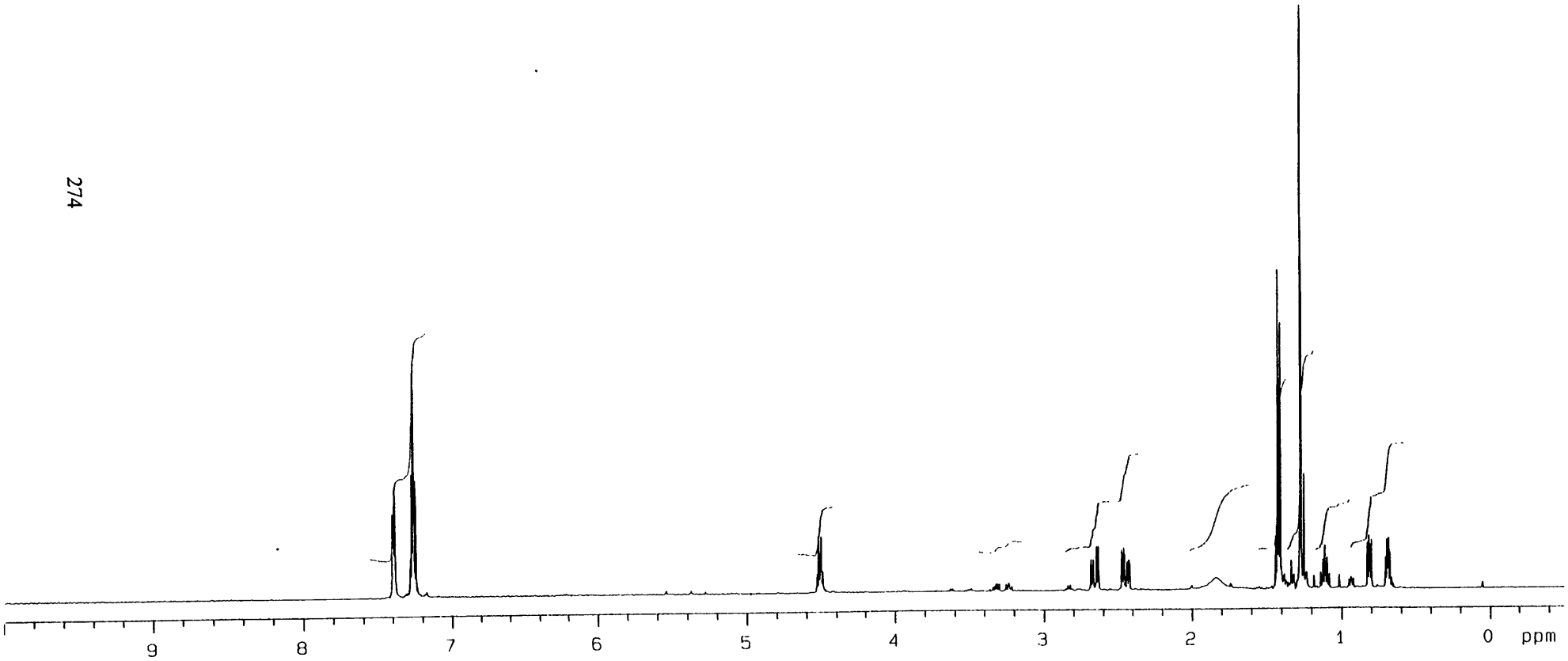


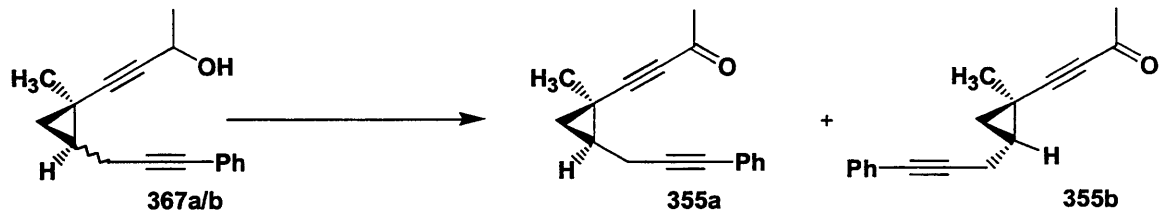
367a (Major Isomer)

+



367b (Minor Isomer)





***cis*-2-(1-Butyn-3-one)-2-methyl-1-(3-phenyl-prop-2-yn)-cyclopropane (355a)**

***trans*-2-(1-Butyn-3-one)-2-methyl-1-(3-phenyl-prop-2-yn)-cyclopropane (355b)**

A 25-mL, round-bottomed flask equipped with rubber septum with argon inlet needle was charged with a mixture of cyclopropanes **367a** and **367b** (0.253 g, 1.07 mmol) and 12 mL of dichloromethane. Sodium acetate (0.877 g, 10.70 mmol) and pyridinium chlorochromate (1.61 g, 7.47 mmol) were then added and the solution was stirred at 25 °C for 2.5 h. The solution was filtered through a 5g column of silica gel using dichloromethane as the eluant. The fractions containing product were collected and concentrated down to afford 0.202 g of a yellow oil. Column chromatography on 20g of silica gel (gradient elution with 5-10% ethyl acetate/hexane) provided 0.151 g (60%) of a mixture of ketones **355a** and **355b** as a yellow oil in an approximately 6:1 ratio based on ^{1}H NMR analysis.

Spectral Data for the mixture:

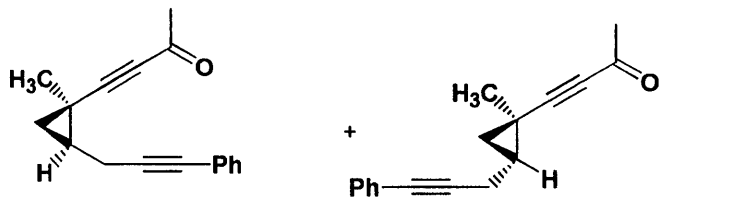
IR (film)	2940, 2900, 2190, 1660, 1570, 1440, 1430, 1350, 1310, 1230, 1190, 1090, 1010, 930, and 740 cm^{-1}.

Spectral Data for **355a**:

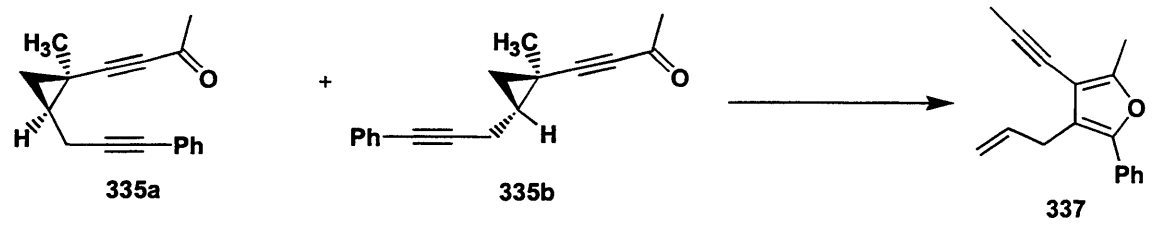
^{1}H NMR (500 MHz, $CDCl_3$)	7.38-7.34 (m, 2H), 7.26-7.22 (m, 3H), 2.66 (dd, J = 17.5 Hz, J = 6.6 Hz, 1H), 2.49 (dd, J = 17.5 Hz, J = 7.1 Hz, 1H), 2.27 (s, 3H), 1.32 (s, 3H), and 1.10-0.80 (m, 3H).
^{13}C NMR (75 MHz, $CDCl_3$)	184.2, 131.4, 128.0, 127.5, 123.5, 97.4, 87.1, 81.1, 79.6, 27.2, 27.1, 23.0, 21.0, 12.7, and 6.5.

Spectral Data for **355b** (partial):

^{1}H NMR (500 MHz, $CDCl_3$)	7.38-7.34 (m, 2H), 7.26-7.22 (m, 3H), 3.31-3.22 (m, 2H), 2.29 (s, 3H), 1.29 (s, 3H), and 1.09-1.01 (m, 1H).
^{13}C NMR (75 MHz, $CDCl_3$)	32.5, 31.3, 23.4, 23.3, and 18.2.



355a (Major Isomer) **355b** (Minor Isomer)



2-Methyl-5-phenyl-4-(prop-2-en)-3-(prop-1-yn)-furan (337)

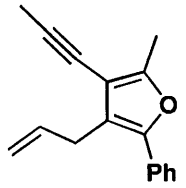
A threaded Pyrex tube (ca. 25-mL capacity) with a side arm equipped with a nitrogen inlet adapter was charged with an approximately 6:1 mixture of cyclopropanes **335a** and **335b** (0.086 g, 0.364 mmol), 3.6 mL of toluene, and γ-terpinene (0.071 mL, 0.060 g, 0.401 mmol). The solution was degassed with a stream of argon for 1 h and then the tube was sealed with a threaded Teflon cap. The reaction mixture was heated in a 150 °C oil bath for 16 h and then allowed to cool to room temperature. Concentration gave 0.62 g of an orange oil. Column chromatography on 15 g of silica gel (elution with hexane) provided 0.024 g (35%) of furan **337** as a yellow oil (purity 90-95% by ^{1}HNMR).

A pure sample of furan **337** was obtained as follows. A 5-mL, pear flask equipped with rubber septum with argon inlet needle was charged with impure furan **337** (0.024 g, 0.102 mmol) and 1 mL of dichloromethane. Dicobaltoctacarbonyl (0.038 g, 0.112 mmol) was added in one portion and then the solution stirred at 25 °C for 6 h. The solution was filtered through a pad of celite using dichloromethane as the eluant. The filtrate was then concentrated to 0.062g of a green/black solid. Column chromatography on 5 g of silica gel (elution with hexane) provided 0.047 g of the cobalt complexed furan as a green/black solid.

A 5-mL, pear flask equipped with rubber septum with argon inlet needle was then charged with the complexed furan (0.047 g, 0.090 mmol) and 1 mL of tetrahydrofuran. 3 drops of *t*-butyl alcohol were added followed by 4-methylmorpholine N-oxide (0.032 g, 0.270 mmol) and the solution stirred at 25 °C for 18 h. The solution was diluted with 2

mL of water then the aqueous layer was separated and extracted with two 5-mL portions of diethyl ether. The combined organic extracts were washed with 15 mL of saturated NaCl solution, dried over Mg_2SO_4, filtered, and concentrated to afford 0.025 g of a yellow oil. Column chromatography on 5 g of silica gel (elution with hexane) provided 0.017 g (64%) of furan **337** as a yellow oil.

IR (film)	3060, 3040 3020, 2960, 2980, 2860, 1600, 1570, 1480, 1440, 1370, 1240, 1220, 1180, 1140, 1080, 1010, 990, 960, 900, and 780 cm^{-1}.
^1H NMR (500 MHz, $CDCl_3$)	7.57 (d, J = 7.8 Hz, 2H), 7.38 (app t, J = 7.4 Hz, 2H), 7.26 (d, J = 7.4 Hz, 1H), 6.05 (m, J = 12.8 Hz, J = 15.5 Hz, J = 4.7 Hz, 1H), 5.09 (m, J = 12.8 Hz, J = 15.5Hz, J = 2.2 Hz, 2H), 3.39 (d, J = 4.7 Hz, 2H), 2.40 (s, 3H), and 2.07 (s, 3H).
^{13}C NMR (75 MHz, $CDCl_3$)	154.0, 147.1, 135.4, 131.1, 128.5, 126.5, 125.2, 124.5, 119.9, 115.5, 90.0, 70.5, 29.1, 12.8, and 4.5.



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