I. INTRAMOLECULAR [4+2] CYCLOADDITIONS OF
CONJUGATED YNONES AND RELATED SPECIES.
II. STUDIES DIRECTED TOWARD THE TOTAL SYNTHESIS OF
GLYCINOECLEPIN A.

By

JASON MICHAEL DIFFENDAL
B.S., Chemistry
Villanova University, 1997

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

September 2002

Signature of Author..

<div style="text-align:right">

Department of Chemistry
July 25, 2002

</div>

Certified by ....

<div style="text-align:right">

Rick L. Danheiser
Thesis Supervisor

</div>

Accepted by ....

<div style="text-align:right">

Robert W. Field
Departmental Committee on Graduate Studies

</div>

This doctoral thesis has been examined by a committee of the Department of Chemistry as follows:

Professor Timothy F. Jamison ....
Chairman

Professor Rick L. Danheiser ....
Thesis Supervisor

Professor Daniel S. Kemp...

Acknowledgments

First and foremost, I would like to thank my research advisor, Rick L. Danheiser for everything he has done for me these past five years. Rick has been an excellent mentor and I am grateful for the opportunity to have worked in his laboratory. Rick is also a superb teacher and I learned an enormous amount of chemistry from him. I also owe Rick a big (very big) thank-you for his time and effort spent proofreading and editing this thesis.

The rest of the thanks will start from the beginning. I thank my parents for their unwavering love and support in all of my endeavors. Without them I could never even dream to be where I am today.

I also thank my fiancée, Angel. She has been with me every step of the way, to Boston and back again. She has been a source of unending support and love throughout these past ten years.

I have been blessed with some of the best chemistry teachers a student could ask for. For my introduction to chemistry, I thank Mr. Jim Ferris. His enthralling chemistry course at Pius led me down the path to an exciting career. Dr. Saul Shupack's unique teaching style and constant guidance during my first year at Villanova made it clear to me I made the right choice. His was the first laboratory in which I worked. I also thank Dr. Barry Selinski and Dr. Joe Bausch for the opportunities to have worked in their laboratories.

I also thank Grant Spoors for the opportunity to work with him as a summer intern at SmithKline Beecham for two summers. That experience is what prompted my desire to return to the pharmaceutical industry.

I also wish to thank the members of the Danheiser Group at MIT for the camaraderie these past years. They made MIT a fun place to be and I owe much to all of them. I thank Chris Mellon who was my first baymate for the leadership during my first year at MIT. Also I thank Kevin Shea, Greg Dudley, Matt Martin, Rob Niger, Dawn Bennett, Yoshi Ikeura, and Hiro Shinokubo for their friendship and for looking after me in the lab.

I also thank the current Danheiser Group members for their support and friendship: Dave Amos, Aimee Crombie, Martin Hayes, Charnsak Thongsornkleeb, Chris Davie, Graham Wright, Josh Dunetz, Christian Peschko, and Y. J. Zhang.

I also thank all of my MIT colleagues for the fun we've had. Dana Buske, Michele Harris, Luis Melean, Tim Long, J. D. Tovar, Brian Hodous, and everyone else: it's been a great time.

I also extend thanks to everyone who helped me with this thesis, whether proofreading the text or discussing the chemistry.

I wish you all the best of luck in your future endeavors. I will always remember you as I think fondly of my MIT years.

To the three most important people in my life:

Mom, Dad, and Angel

I. INTRAMOLECULAR [4+2] CYCLOADDITIONS OF CONJUGATED YNONES AND RELATED SPECIES.
II. STUDIES DIRECTED TOWARD THE TOTAL SYNTHESIS OF GLYCINOECLEPIN A.

by
Jason Michael Diffendal

Submitted to the Department of Chemistry
on July 25, 2002 in partial fulfillment of the
requirements for the degree of Doctor of Philosophy

ABSTRACT

The intramolecular [4 + 2] cycloaddition reactions of α,β-alkynyl carbonyl compounds are described. This reaction, the first heterocyclic variant of the enyne cycloaddition reaction, affords a product with a dihydroisobenzofuran ring system. For this reaction, we propose a mechanism in which a highly strained heterocyclic allene intermediate undergoes an unusual rearrangement leading to a 3-furfuryl carbene. A 1,2-*C-H* insertion then produces the polycyclic furan product. A detailed analysis of the scope and mechanism of this reaction is presented. The synthetic utility of the method for the synthesis of complex organic molecules is illustrated by two sequences demonstraing further transformations of the dihydroisobenzofuran products. A two-step formal benzannulation process generates a tetrahydroanthracene derivative. Ozonolysis of a 7-oxabicycloheptene derivative prepared from a dihydroisobenzofuran affords a product that contains the core oxabicyclo[6.2.1]undecane ring system of eleutherobin and the sarcodictyin family of natural products.

Glycinoeclepin A is the natural hatching stimulus agent of the soybean cyst nematode. A new strategy for the synthesis of an advanced A-ring intermediate in the total synthesis of this important compound is presented. This strategy provides the key A-ring enyne intermediate in seven steps from 2,2-dimethylcyclohexanedione, utilizing a novel acid-catalyzed cyclization reaction of a hydroxy enedione.

Thesis Supervisor: Rick L. Danheiser

Title: Professor of Chemistry

Table of Contents

Part II: Studies Directed Toward the Total Synthesis of Glycinoeclepin A

Chapter 1: Background and Significance

Chapter 2: The "A-Ring" of Glycinoeclepin A

Chapter 3: New Approaches to the Synthesis of an A-Ring Enyne Intermediate

Part III: Experimental Section

Part I

Intramolecular [4 + 2] Cycloadditions of Conjugated Ynones and Related Species

Chapter 1

Introduction and Background: Intramolecular [4 + 2] Cycloadditions of Enynes and Arenynes

**Importance of Cycloadditions in Organic Synthesis**

Cycloadditions are arguably the most powerful ring-forming reactions in organic synthesis.[1] The convergence, regioselectivity, and stereoselectivity of many cycloadditions contribute to their importance as synthetic strategies. These reactions have been employed as pivotal steps in the synthesis of numerous natural products and commercially significant organic compounds. Both intermolecular and intramolecular cycloadditions are valuable; however, the intramolecular transformations allow for the design of highly convergent synthetic strategies, as multiple rings can be formed in one step from acyclic precursors.

Research in our laboratory has focused on the development of new types of cycloaddition reactions. In particular, we have investigated the intramolecular cycloadditions of highly unsaturated, conjugated molecules which afford dihydroaromatic and aromatic polycyclic compounds. This part of the thesis is devoted to my studies of the intramolecular [4 + 2] cycloadditions of heteroenynes. This chapter will focus on previous studies of intramolecular [4 + 2] cycloadditions of conjugated enynes that are background to my work.

---

[1] Carruthers, W. *Cycloaddition Reactions in Organic Synthesis*; Pergamon Press: New York, 1990.

Inspiration for the new cycloaddition strategies investigated in our laboratory came from the discovery of novel cycloaromatization reactions,[2] which involve the thermal cyclization of highly unsaturated molecules to form high-energy aromatic biradical species (Scheme 1).

Scheme 1
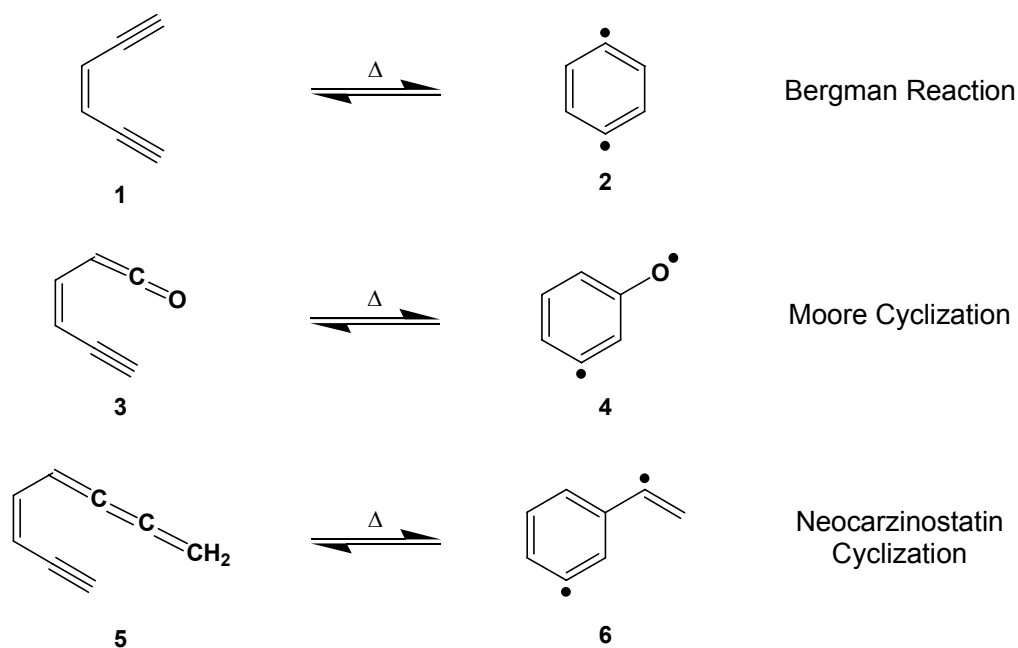
The mechanism of action of the enediyne antitumor antibiotics[3] and neocarzinostatin[4] involves the formation of biradicals which can cleave DNA and thereby promote cell death. Several research groups have investigated the synthetic utility of

[2] For reviews, see: (a) Grissom, J. W.; Gunawardena, G. U.; Klingsberg, D.; Huang, D. *Tetrahedron* **1996**, *52*, 6453. (b) Gleiter, R.; Kratz, D. *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 842.
[3] For reviews, see: (a) *Enediyne Antibiotics as Antitumor Agents*; Borders, D. B.; Doyle, T. W., Eds.; Marcel Dekker: New York, 1995. (b) Smith, A. L.; Nicolaou, K. C. *J. Med. Chem.* **1996**, *39*, 2103. (c) Nicolaou, K. C. The Enediyne Antibiotics. In *Modern Acetylene Chemistry*; Stang P. J.; Diederich, F., Eds.; Wiley-VCH: New York, 1995; pp 203-283.

these reactions.[5]   Because cycloaromatization reactions are cyclization processes, in which only a single new bond is formed, strategies incorporating cycloaromatizations are much less convergent than annulation strategies,[6] in which two new bonds are formed in one process.   It was thus our desire to develop annulation strategies based on highly unsaturated conjugated molecules, reminiscent of these cycloaromatizations.

Intramolecular [4 + 2] Cycloadditions of Enynes: Early Studies

Our laboratory became interested in the [4 + 2] cycloadditions of conjugated enynes in the early 1990s. Enyne cycloadditions have several important advantages over other cycloaddition methodologies for the formation of aromatic and dihydromatic products. The enynes are considerably easier to assemble than the α-pyrones, triazines, or highly-functionalized dienes required in other methods. A wide range of substrates can be synthesized utilizing commercially available acetylene components and a wide range of versatile alkyne condensation[7] and cross-coupling[8] reactions. In addition, the enyne cycloadditions provide the aromatic or dihydroaromatic products directly without additional elimination or cycloreversion steps.

[4] For reviews, see: (a) *Neocarzinostatin: The Past, Present, and Future of an Anticancer Drug*; Maeda, H.; Edo, K.; Ishida, N., Eds.; Springer: New York, 1997. (b) Goldberg, I. H. *Acc. Chem. Res.* **1991**, *24*, 191. (c) Myers, A. G.; Arvedson, S. P.; Lee, R. W. *J. Am. Chem. Soc.* **1996**, *118*, 4725.

[5] For reviews, see: (a) Wang, K. K.; *Chem. Rev.* **1996**, *96*, 207. (b) Ref. 2a.

[6] An annulation is defined as a ring-forming process 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.

[7] For general procedures for a wide range of reactions involving alkynes, see: (a) Brandsma, L.; Verkruijsse, H. D. *Synthesis of Acetylenes, Allenes and Cumulenes*; Elsevier: Amsterdam, 1981. (b) Brandsma, L. *Preparative Acetylenic Chemistry*, 2nd ed.; Elsevier: Amsterdam, 1988.

[8] (a) Diederich, F.; Stang, P. J. *Metal Catalyzed Cross-Coupling Reactions*; Wiley-VCH: New York, 1998. (b) Winterfeldt, E. Acetylenes in Synthesis. In *Modern Synthetic Methods*; Scheffold, R., Ed.; VCH: New York, 1992; Vol. 6; pp. 104-226.

A review of the literature reveals several prior examples of intramolecular [4 + 2] cycloaddition reactions of conjugated enynes. The related [4 + 2] cycloadditions of conjugated "arenynes" (aryl-substituted alkynes) will be discussed in a subsequent section of this chapter.

The first example of an intramolecular enyne cycloaddition appeared in 1945 with Johnson's report on the reaction of propargylic alcohol **7** with acetylenedicarboxylic acid (**8**) to give phthalide **10** (Scheme 2).[9]

Scheme 2
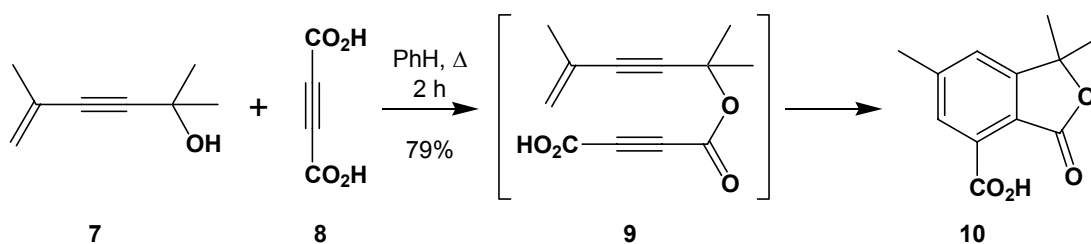
In 1959, Nazarov reported the serendipitous discovery of several enyne cycloadditions involving propargyl ethers, and proposed that dienyl cations such as **12** are intermediates in these reactions (Scheme 3).[10] Hakopian determined that cycloadditions of related ethers proceed most efficiently when the "enynophile" triple bond is substituted with an electron-withdrawing group.[11] We believe these results suggest that the cycloadditions may be concerted processes involving the LUMO of the enynophile π-bond.

---

[9] Johnson, A. W. *J. Chem. Soc.* **1945**, 715.
[10] Nazarov, I. N.; Verkholetova, G. P.; Torgov, I. V. *J. Gen. Chem. USSR* **1959**, *29*, 3277.

Scheme 3

11   12   13   14
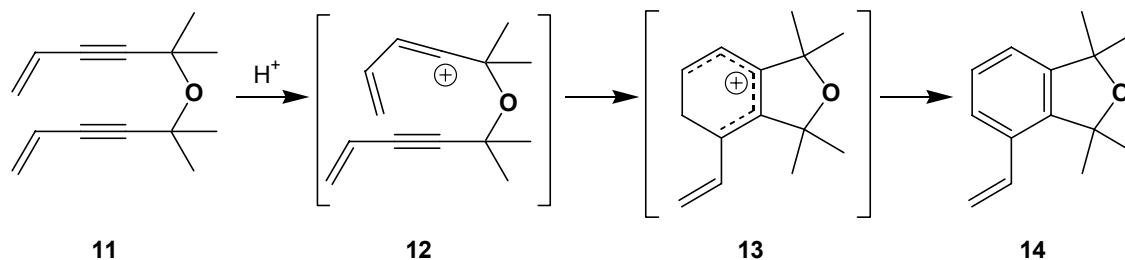
In 1993, simultaneous with our work, Hoffmann and coworkers reported a detailed investigation of various intramolecular enyne cycloadditions utilizing acetal substrates such as **15** that possess olefinic enynophiles.[12] As shown in Scheme 4, the authors proposed a mechanism involving the intermediacy of dienyl cation **18**, although they failed to cite the fact that Nazarov had previously suggested this mechanism to account for a closely related reaction (*vide supra*).[13] Hoffmann proposes that cycloaddition of dienyl cation **18** forms allyl cation **19**; elimination of a proton then generates the observed products **16** and **17**.

---

[11] (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.
[12] Hoffmann, H. M. R.; Krumwiede, D.; Mucha, B.; Oehlerking, H. H.; Prahst, G. W. *Tetrahedron* **1993**, *49*, 8999.
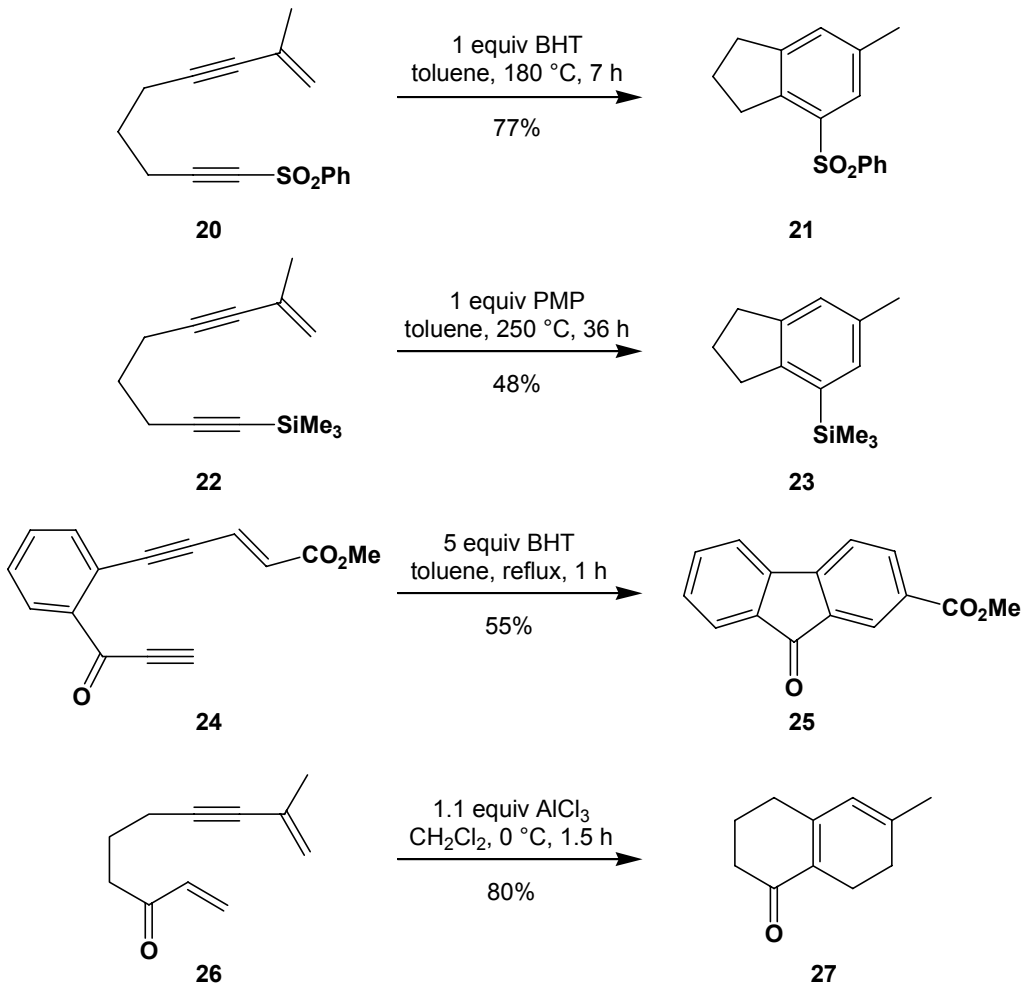
Scheme 4
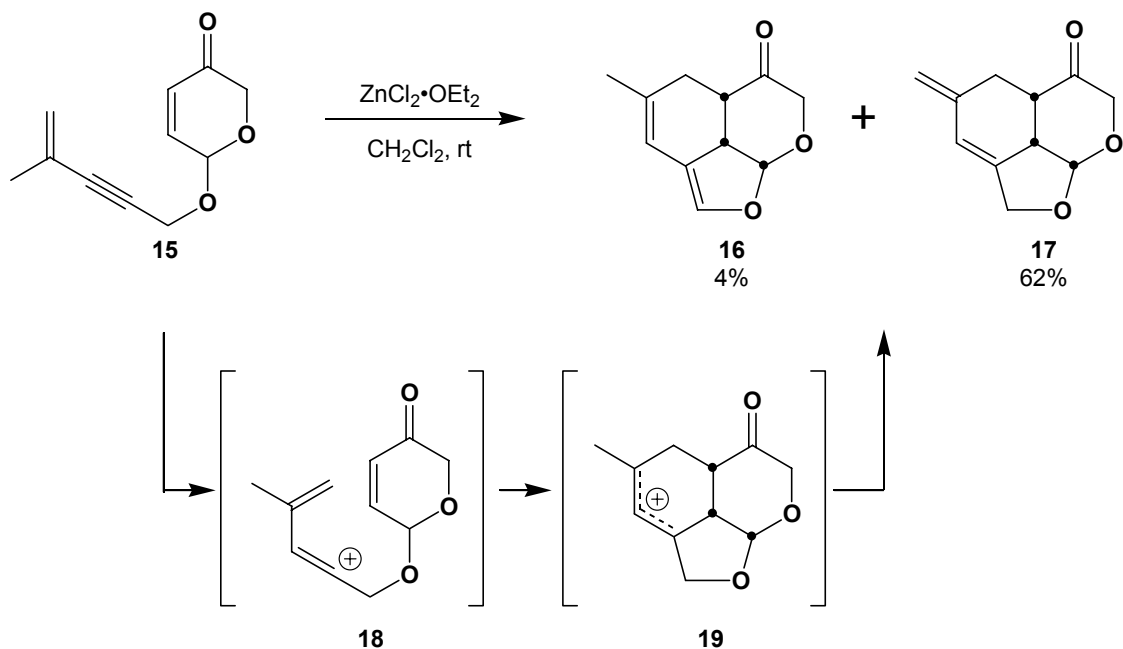
In 1994, our laboratory reported the first systematic investigation of the scope and mechanism of the intramolecular $[4 + 2]$ cycloaddition of conjugated enynes.[14,15] As illustrated with the examples shown in Scheme 5, it was found that the enyne cycloaddition provides an efficient route to a variety of polycyclic aromatic and dihydroaromatic systems. Notably, both protic and Lewis acids were found to promote the reaction, in some cases utilizing only catalytic amounts.

[13] Later, Miller et al. proposed a similar mechanism for an intermolecular enyne cycloaddition. See: Miller, B.; Ionescu, D. *Tetrahedron Lett.* **1994**, *35*, 6615.

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

[15] For a more detailed discussion of the background, scope, and mechanism of the enyne cycloaddition, see: (a) Gould, A. E. Ph.D. Thesis, Massachusetts Institute of Technology, Cambridge, MA, June 1996. (b) Palucki, B. L. Ph.D. Thesis, Massachusetts Institute of Technology, Cambridge, MA, June 1997. (c) Helgason, A. E. Ph.D. Thesis, Massachusetts Institute of Technology, Cambridge, MA, June 1994.

Scheme 5

As shown in Scheme 6, the [4 + 2] cycloaddition of conjugated enynes with alkynes could occur through a number of potential pathways. The mechanism of the enyne [4 + 2] cycloaddition can be separated into two discrete stages. The first stage involves the formation of the new six-membered ring via a high-energy cyclic allene (**31**), biradical intermediate (**32**), or cationic species (**33**). The second stage of the overall process furnishes the observed aromatic product **36** through any of a number of pathways.

Scheme 6
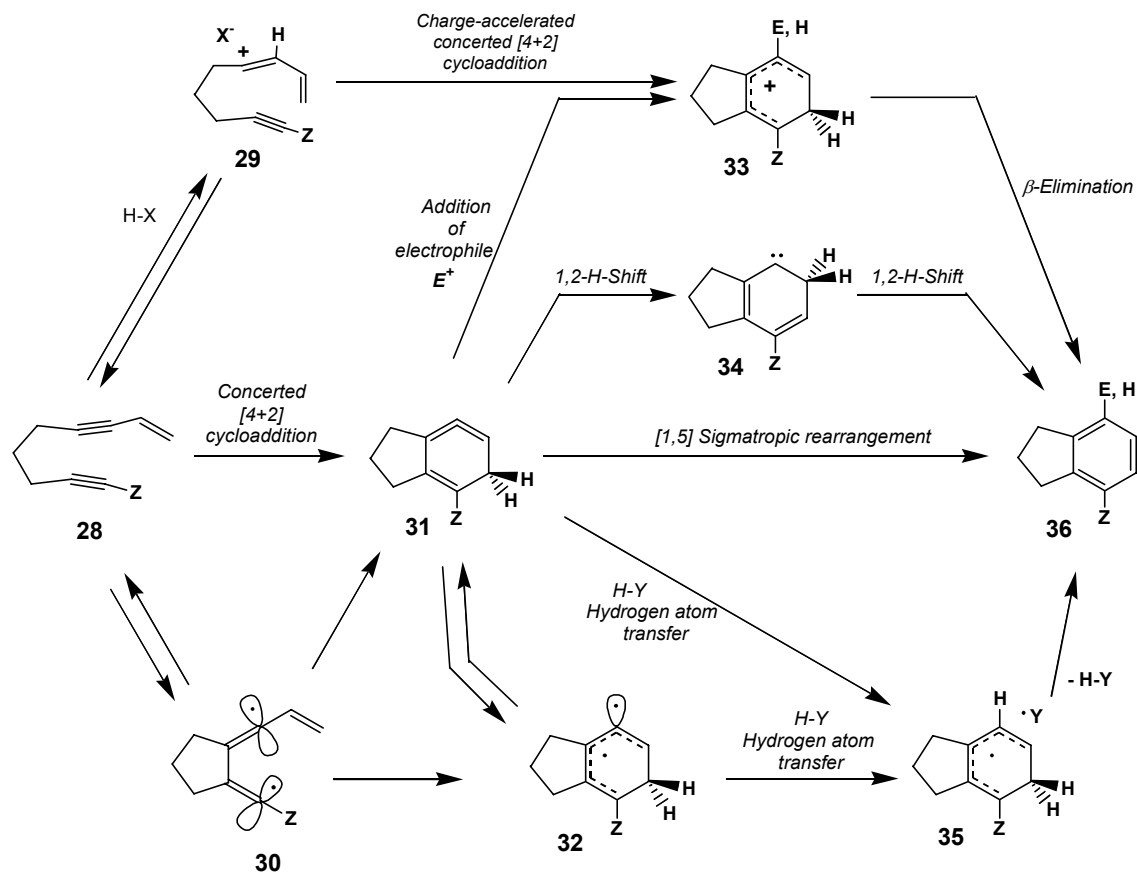
Based on our studies (*vide infra*), we believe that in many cases the reaction proceeds through direct formation of the cyclic allene **31** via a concerted [4 + 2] cycloaddition, particularly when the "enynophile" triple bond is substituted with an electron-withdrawing group. The presence of the electron-withdrawing group lowers the energy of the alkyne LUMO, thus lowering the activation energy for a concerted cycloaddition. Calculations of the relative energies of cyclic allenes and the corresponding biradicals (*vide infra*) suggest that at elevated temperature the cyclic allene **31** could be in equilibrium with the biradical species **32**. In substrates that lack an electron-withdrawing group on the enynophile, the HOMO – LUMO gap is much larger,

and a second pathway to cyclic allene **31** becomes competitive. This pathway involves stepwise formation of **31** via initial cyclization to the biradical **30**. In summary, we believe it is likely that different mechanisms may be at work depending on the exact nature of the cycloaddition substrate.

In the acid-catalyzed enyne cycloaddition reactions we have studied, the enynophile π-bonds are substituted with a carbonyl group. In these reactions we believe that protonation of the carbonyl group lowers the energy of the alkyne LUMO and consequently reduces the activation energy for cycloaddition.

With regard to the mechanism for isomerization of cyclic allene **31** to the ultimately observed aromatic product (**36**), we believe that the presence of a hydrogen atom or proton donor favors *intermolecular* pathways (via **32** and **33**) that convert the cyclic allene or biradical intermediate to **36**. Discussion of recent work probing the intermediacy of carbene **34** will be deferred to a later section of this chapter.

In considering the energetic feasibility of the enyne cycloaddition, a simplistic calculation based on average bond energies[16] indicates that a process in which two acetylene π bonds (ca. 51 kcal/mol each) are broken and two carbon-carbon single bonds (ca. 84 kcal/mol each) are formed is exothermic. This examination of bond energies, however, fails to account for the ring strain of the allene. Based on Janoschek's calculation of the heat of formation of 1,2,4-cyclohexatriene[17] and Benson group

---

[16] Mean bond energy values at 25 °C. March, J. *Advanced Organic Chemistry*, 4th ed.; Wiley: New York, 1992, p 24.

[17] Janoschek, R. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 476.

additivities,[18] we calculated the enthalpy of reaction (ΔH_R) for the intermolecular version of the enyne cycloaddition to be -29.7 kcal/mol.[14]

Cyclic Allenes and Isoaromatic Species

   As discussed in the previous section, we believe that cyclic allenes are key intermediates in the [4 + 2] cycloaddition of conjugated enynes.   The cyclic allenes produced in cycloadditions with alkyne "enynophiles" are 1,2,4-cyclohexatrienes (e.g., **37**), highly reactive species which are difficult, if not impossible, to observe directly. Simpler cyclic allenes, such as 1,2-cyclohexadiene (**38**), have been the subject of numerous experimental and theoretical investigations.[19]

37   **38**
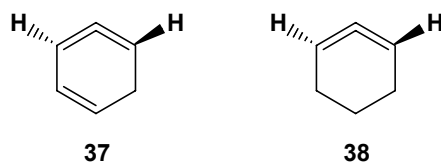
   The equilibrium geometry for allene is linear with orthogonal pairs of substitutents.   An allene incorporated into a ring of nine or more atoms is relatively unstrained.   As the ring size decreases, the linear allene becomes twisted and bent until the energy gained by π bonding is insufficient to offset the increased strain.   Ring constraints exert torsion toward a planar arrangement of substituents and lower the energy barrier to π-bond rotation, which results in the interconversion of enantiomers of chiral cyclic allenes.

---

[18] (a) Benson, S. W. *Thermodynamic Kinetics*; Wiley: New York, 1976. (b) Cohen, N.; Benson, S. W. *Chem. Rev.* **1993**, *93*, 2419.
[19] For reviews, see: (a) Hopf, H. *Classics in Hydrocarbon Chemistry*; Wiley-VCH: New York, 2000; pp 182-187. (b) Balci, M.; Taskesenligil, Y. In *Advances in Strained and Interesting Organic Molecules*; Halton, B., Ed.; JAI Press: Greenwich, CT, 2000; Vol. 8, pp 43-81. (c) Johnson, R. P. *Chem. Rev.* **1989**, *89*, 1111.

The six-membered cyclic allene **38** is considerably strained; the allene bond angle is distorted from 180° to approximately 134°.[17] The smallest unsubstituted carbocyclic allene that has been isolated is 1,2-cyclononadiene.[20] Eight-[21] and seven-membered[22] carbocyclic allenes have been generated and trapped.

In the enyne cycloaddition reactions which utilize an alkene as the enynophile, the ultimate product formed is a dihydroaromatic species, and the cyclic allene intermediate involved is a 1,2-cyclohexadiene derivative. 1,2-Cyclohexadienes (e.g., **38**) are highly reactive species that participate in numerous types of reactions, including $[2+2]$ cycloadditions, $[4+2]$ cycloadditions with both cyclic and acyclic dienes, dimer formation, tetramer formation, and reactions with nucleophiles at the central carbon.[18,23,24,25,26]

Considerable controversy has erupted over the exact nature of the structure of 1,2-cyclohexadiene (**38**). There are five possible electronic configurations of this species: the strained, chiral allene **38**, and four planar achiral carbocycles containing an allyl system with an sp^2-hybridized carbon at the center: a singlet biradical **39**, a triplet biradical **40**, and two zwitterions **41** and **42**. Early studies by a number of groups,[23,27]

[20] (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) Skattebøl, L. *Tetrahedron Lett.* **1961**, *2*, 167. (c) Skattebøl, L.; Solomon, S. *Org. Synth.* **1960**, *49*, 35.

[21] Price, J. P.; Johnson, R. P. *Tetrahedron Lett.* **1986**, *27*, 4679.

[22] Balci, M.; Jones, W. M. *J. Am. Chem. Soc.* **1980**, *102*, 7607.

[23] (a) Moore, W. R.; Moser, W. *J. Am. Chem. Soc.* **1970**, *92*, 5469. (b) Moore, W. R.; Moser, W. *J. Org. Chem.* **1970**, *35*, 908.

[24] (a) Bottini, A. T.; Corson, F. P.; Fitzgerald, R.; Frost, K. A. *Tetrahedron* **1972**, *28*, 2883. (b) Bottini, A. T.; Hilton, L. L.; Plott, J. *Tetrahedron* **1975**, *31*, 1997.

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

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

[27] Greenberg, A.; Liebman, J. L. *Strained Organic Molecules*; Academic Press: New York, 1978; p 126.

including low-level theoretical calculations,[28] led to the conclusion that zwitterion **41** or **42** is the lowest-energy species.
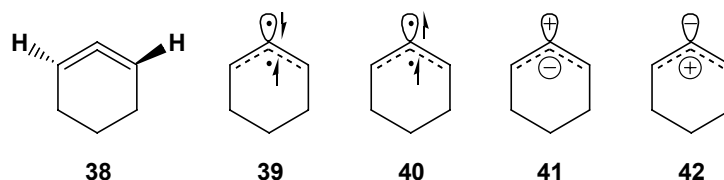
Further studies of the chemistry of 1,2-cyclohexadiene led Bottini to favor the formation of an initial bent allene (**38**) which rapidly isomerizes to the biradical **40**.[24] Balci trapped optically active **38** at low temperatures, and found that racemization becomes competitive with trapping at 80 °C, suggesting a low barrier for racemization.[22] Wentrup[29] trapped 1,2-cyclohexadiene in an argon matrix at 11 K and observed that its infrared spectrum shows an allene stretch at 1886 cm^{-1}. Although this frequency differs by 70 cm^{-1} from that for a "normal" allene, this spectrum is consistent with the presence of an allene moiety. Johnson[30] has performed *ab initio* MCSCF//3-21G calculations on 1,2-cyclohexadiene and found the chiral allene structure (**38**) to be the lowest energy species. Many recent experimental and theoretical studies (*vide infra*) support Johnson's conclusion that the cyclic allene structure is indeed the lowest energy species.

Various methods have been reported for the synthesis of 1,2-cyclohexadiene and its derivatives, including base-induced β-elimination of vinyl halides,[31] fluoride-induced

[28] Dillon, P. W.; Underwood, G. R. *J. Am. Chem. Soc.* **1974**, *96*, 779.
[29] Wentrup, C.; Gross, G.; Maquestiau, A.; Flammery, R. *Angew. Chem., Int. Ed. Engl.* **1983**, *27*, 542.
[30] (a) Schmidt, M. W.; Angus, R. O.; Johnson R. P. *J. Am. Chem. Soc.* **1982**, *104*, 6838. (b) Angus, R. O.; Schmidt, M. W.; Johnson, R. P. *J. Am. Chem. Soc.* **1985**, *107*, 532.
[31] (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.

β-elimination of an α-silyl vinyl halide,[32] and ring-opening of a variety of substituted bicyclo[3.1.0]hexanes. [23,29,33]

In enyne cycloadditions that involve alkynes as enynophiles, the ultimate product formed is an aromatic compound, and the cyclic allene intermediate involved is a 1,2,4-cyclohexatriene derivative, an *"isoaromatic"* compound. This type of cyclic allene has been the subject of experimental and theoretical investigations. In 1987, Miller and Shi reported the generation and trapping of the cyclic allene **44**. Dehydrohalogenation of vinyl bromide **43** provided **45** and **46**, which are believed to arise from [4 + 2] cycloaddition of **44** with diphenylisobenzofuran (DPIBF) (Scheme 7).[34] Miller and Shi noted that in the absence of DPIBF, nucleophilic addition of *tert*-butoxide to **44** takes place to afford enol ether **47**.

Scheme 7

---
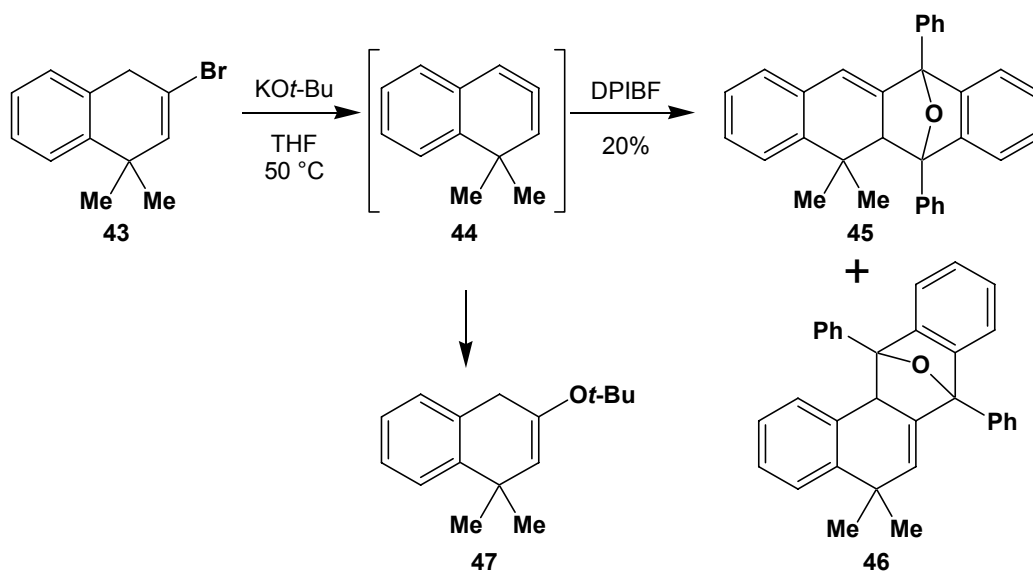
[32] (a) Shakespeare, W. C.; Johnson, R. P. *J. Am. Chem. Soc.* **1990**, *112*, 8578. (b) Sütbeyaz, Y.; Ceylan, M.; Secen, H. *J. Chem. Res. (S)* **1993**, 293.
[33] Runge, A.; Sander, W. *Tetrahedron Lett.* **1986**, *27*, 5835.

In 1992, Christl and coworkers reported the generation of isonaphthalene (**49**) and isobenzene (**53**) from dihalocyclopropanes **48** and **52**, and the trapping of these allenes with styrene to afford **51** and **55**, respectively (Scheme 8).[35] Christl proposed that these reactions proceed via biradicals **50** and **54** which then close to afford the observed cyclobutanes.

Scheme 8
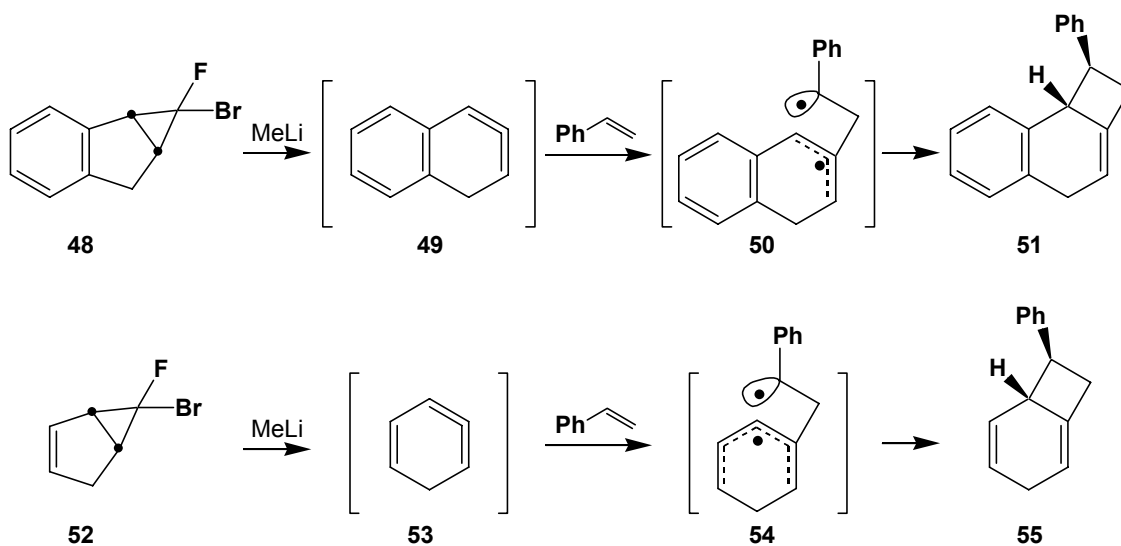
Janoschek has performed AM1 calculations on isobenzene (**53**) which suggest that the allenic structure for this species is lower in energy than the biradical.[17] Later, Christl, Engels, and coworkers performed high-level MR-CI+Q calculations on 1,2-cyclohexadiene (**38**), isobenzene (**53**), and isonaphthalene (**49**), and found that in all three cases, the strained allenic structure is lowest in energy (Scheme 9).[36] In the case of

[34] Miller, B.; Shi, X. *J. Am. Chem. Soc.* **1987**, *109*, 578.
[35] Christl, M.; Braun, M.; Müller, G. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 473.
[36] Engels, B.; Schöneboom, J. C.; Münster, A. F.; Groetsch, S.; Christl, M. *J. Am. Chem. Soc.* **2001**, *124*, 287.

isobenzene, the allenic structure was found to be lower in energy than the singlet biradical by about 9 kcal/mol, with the triplet biradical lying 2-3 kcal/mol higher than the singlet. In the case of isonaphthalene (**49**), the singlet biradical is higher in energy than the allene by about 11 kcal/mol. The authors explain this difference by the fact that the allene is slightly less strained in isonaphthalene than isobenzene because of the increased bond length of the ring fusion bond compared to the corresponding bond in isobenzene. This is a consequence of the aromatic delocalization of the π bond in isonaphthalene.

Scheme 9
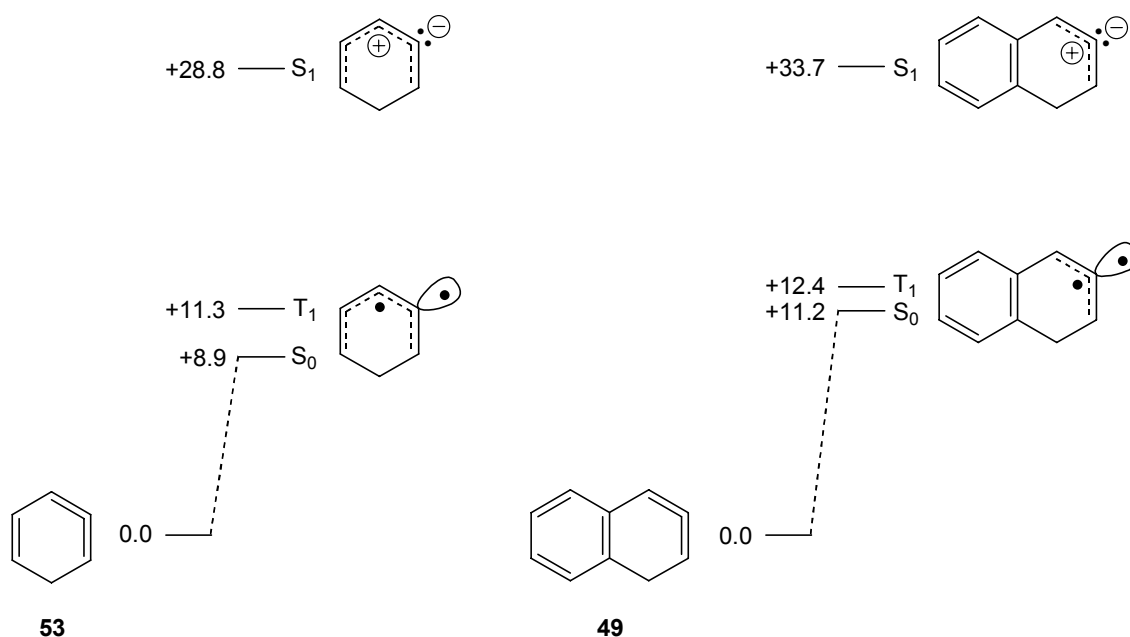
In contrast to the extensive studies on carbocyclic allenes, to date only limited reports have appeared on heterocyclic allenes. In 1987, Schreck and Christl reported the synthesis of 1-oxa-3,4-cyclohexadiene (**56**), and the trapping of this heterocyclic allene in

both [4 + 2] and [2 + 2] cycloaddition processes.[37] Two years later, Christl and Braun reported the generation and trapping of the isomeric 1-oxa-2,3-cyclohexadiene (**57**).[38] Christl observed that when allene **57** was generated in the presence of styrene and other dienes, [2 + 2] adducts were the major or exclusive products, with reaction occurring at the electron-rich enol ether double bond. Interestingly, in the case of furan, a [4 + 2] cycloadduct was the major product, with reaction occurring at the double bond of the allene farther from oxygen.
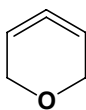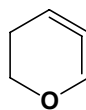
56   **57**

Heterocyclic allenes with an additional double bond in the ring are even less well known. Shevlin has reported the generation of 1-aza-2,3,5-cyclohexatriene (**60**)[39] and 1-thia-2,3,5-cyclohexatriene (**64**)[40] by condensation of C-13-enriched atomic carbon with pyrrole and thiophene in a carbon arc reaction at 77 K (Scheme 10).
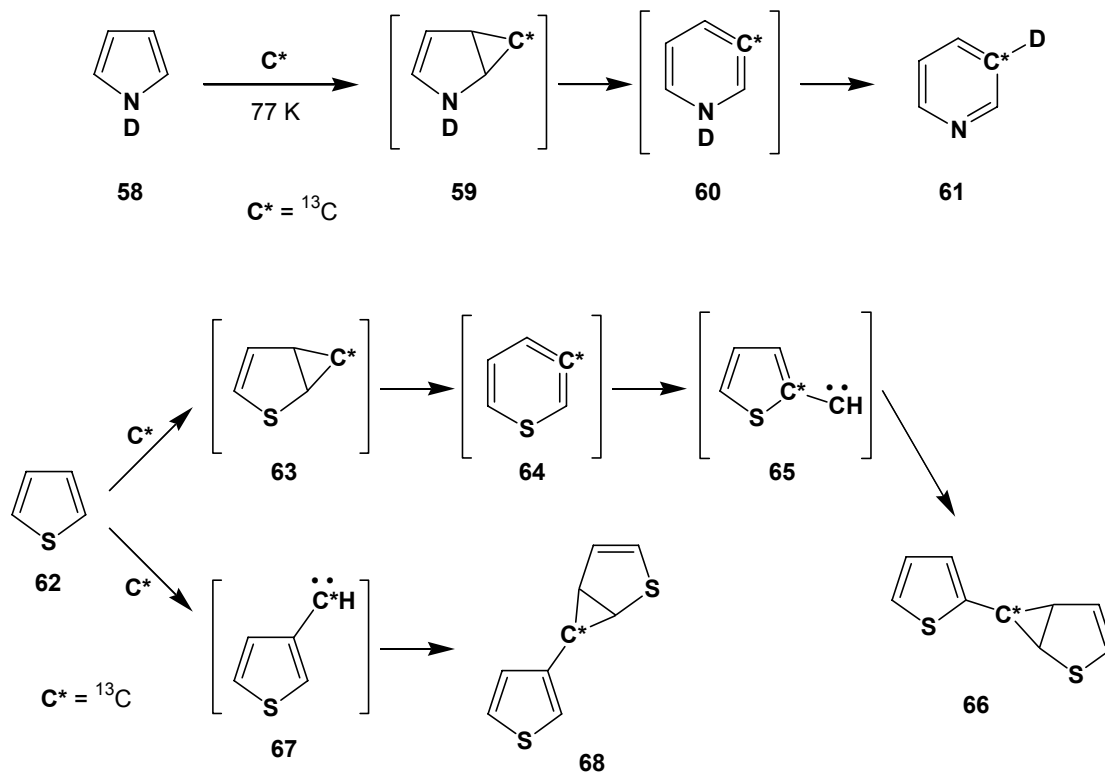
[37] Schreck, M.; Christl, M. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 690.
[38] Christl, M.; Braun, M. *Chem. Ber.* **1989**, *122*, 1939.
[39] Emanuel, C. J.; Shevlin, P. B. *J. Am. Chem. Soc.* **1994**, *116*, 5991.
[40] Pan, W.; Balci, M.; Shevlin, P. B. *J. Am. Chem. Soc.* **1997**, *119*, 5035.

Scheme 10

C* = ^{13}C

The authors subjected furan to this same carbon arc reaction, and report that furan "reacts rather differently." The only product isolated was unsaturated aldehyde **71**, which they suggest comes directly from ring-opening of intermediate **70** (Scheme 11).[39,41] However, furan may indeed react similarly to pyrrole and thiophene, producing 1-oxa-2,3,5-cyclohexatriene **72** as an intermediate in the formation of **71**.

---

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

Scheme 11
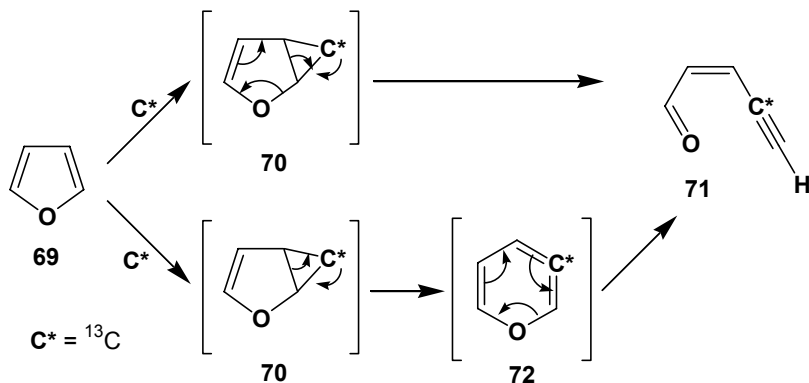
Christl, Engels, and coworkers have generated 1-oxa-2,3,5-cyclohexatriene (dehydropyran, **73**); however, all attempts to trap this allene in a cycloaddition failed, and they observed only nucleophilic addition at the carbon of the allene farthest from oxygen.[36] MR-CI+Q calculations on **73** and dehydrochromene **74** suggest that in both cases, the allenic structures are again the lowest energy electronic configurations, but the zwitterionic structures, identified based on the calculated shapes of the frontier orbitals, are close in energy to the cyclic allenes. In **73**, the zwitterion lies only about 1 kcal/mol higher than the allene, whereas in **74** the zwitterion lies about 5 kcal/mol higher than the allene (Scheme 12). This is in contrast to the corresponding carbocyclic systems (Scheme 9), where the zwitterions are about 30 kcal/mol higher in energy that the allenes.

Scheme 12

+15.6 —— S_1
+14.3 —— T_1

+10.4 —— T_1
+9.6 —— S_1

+5.4 —— S_0

0.0   +1.0 —— S_0

0.0

73   **74**
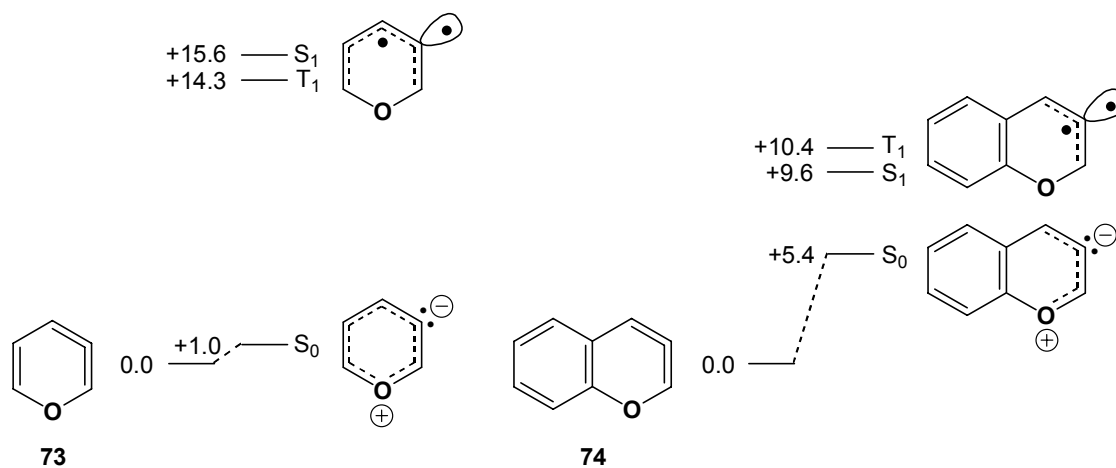
The authors offer a rationalization for the calculated values. Inclusion of an oxygen atom in the ring allows for the possibility of a conjugated π system with six electrons, a situation which is not possible in the carbocyclic analog. In this situation, the positive charge is more delocalized, thus lowering the energy of the zwitterions.

Although nucleophilic addition to heterocyclic allene **73** has been observed, trapping experiments with cycloaddition partners so far have been unsuccessful. The increased polarity of the cyclic allene, due to the contribution of the zwitterion structure, likely favors the addition of a nucleophile over cycloaddition.

Recently, Sheridan and Khasanova reported the generation of cyclic allene **76** and the characterization of **76** by infrared and ultraviolet spectroscopy. Irradiation of 2-benzofurylchlorocarbene (**75**) at 366 nm in a nitrogen matrix at 10 K produced a compound with spectral data matching that calculated for 2-chlorodehydrochromene (**76**). Warming to 32 K in the presence of HCl afforded a new compound with spectral data consistent with that calculated for pyrylium salt **77** (Scheme 13). To our knowledge, this

is the first example of the characterization and subsequent trapping of a dehydropyran

derivative, and lends experimental support to the proposed zwitterionic structure.

Scheme 13
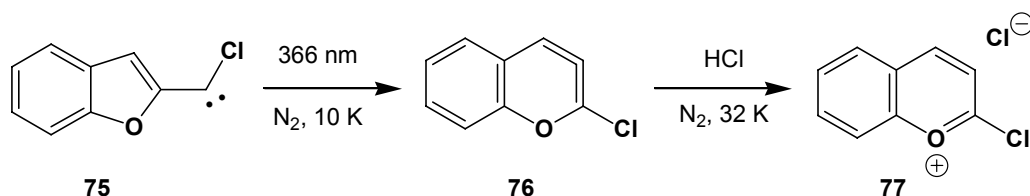
Though the carbon arc reaction is not synthetically useful, there are other methods

currently used for the generation of heterocyclic allenes. The more practical reactions

involving base-induced elimination of vinyl halides[36,42] and ring-opening of substituted

bicyclo[3.1.0]hexanes[37,38] have been used to provide 1-oxa-2,3-cyclohexadiene **56**,

1-oxa-3,4-cyclohexadiene **57**, and 1-oxa-2,3,5-cyclohexatriene **73**.

Arenyne Cycloadditions

Closely related to the [4 + 2] cycloadditions of conjugated enynes is the class of

analogous cycloadditions in which the double bond of the enyne component is

incorporated in an aromatic or heteroaromatic ring. These "arenyne cycloadditions,"

which we believe are mechanistically related to the enyne cycloaddition, have been the

[42] (a) Jamart-Grégorie, B.; Grand, V.; Ianelli, S.; Nardelli, M.; Caubére, P. *Tetrahedron Lett.* **1991**, *31*, 7603. (b) Jamart-Grégorie, B.; Mercier-Girardot, S.; Ianelli, S.; Nardelli, M.; Caubére, P. *Tetrahedron* **1995**, *51*, 1973. (c) Ianelli, S.; Nardelli, M.; Belletti, D.; Jamart-Grégorie, B.; Mercier-Girardot, S.; Caubère, P. *Acta Cryst.* **1996**, *C52*, 237. (d) Ruzziconi, R.; Naruse, Y.; Schlosser, M. *Tetrahedron* **1991**, *47*, 4603.

subject of considerable attention recently. Interestingly, the first example of an arenyne cycloaddition may date back to the 19th century.

In 1898, Michael and Bucher reported[43] that condensation of phenylpropiolic acid (**78**) in refluxing acetic anhydride produces not the desired anhydride **80**, but rather a different anhydride whose structure was eventually assigned to be **79** (Scheme 14). In the years since this discovery, the mechanism of this transformation has been the subject of much discussion. In 1994, we proposed that the conversion of **80** to **79** may in fact proceed via a [4 + 2] cycloaddition involving the enyne moiety embedded in the arenyne **80**.

Scheme 14

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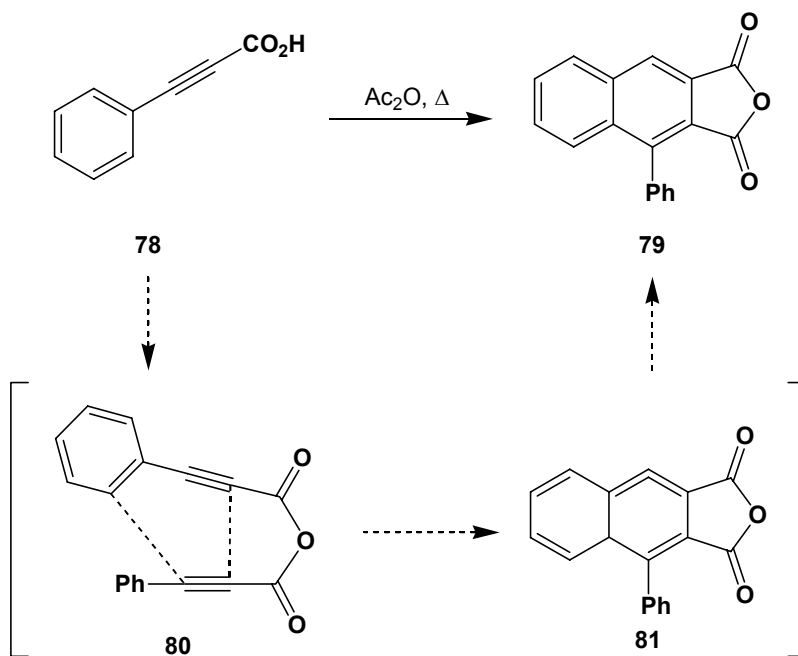
[43] Michael, A.; Bucher, J. E. *Am. Chem. J.* **1898**, *20*, 89.

No further examples of this class of reactions appeared until 1947 when Baddar[44] began his systematic investigation of the regiochemical course of the Michael-Bucher reaction. Though Baddar's studies revealed that these reactions do not proceed with significant regioselectivity, this work did serve to demonstrate the generality of the Michael-Bucher reaction.

Over the course of the next several decades, scattered reports appeared on the Michael-Bucher reaction, demonstrating milder conditions to effect the reaction, and extending the scope of the process to include terminal alkynes as 2π components.[45,46,47] Other studies focused on the mechanism of the Michael-Bucher reaction. In 1969, Whitlock reported studies with deuterium-labeled substrates, and proposed a mechanism involving a cationic intermediate.[48] Though this mechanism was consistent with the observed products, Whitlock's results did not rule out other possible mechanisms.

Recently, there has been a surge of new interest in the arenyne cycloaddition reaction. A number of groups began investigations of arenyne cycloadditions after Schmittel and coworkers in 1995 reported their serendipitous discovery of a new example

[44] (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. G.; 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.

[45] (a) Brown, D.; Stevenson, R. *Tetrahedron Lett.* **1964**, *5*, 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. (f) Cadby, P. A.; Hearn, M.T. W.; Ward, A. D. *Aust. J. Chem.* **1973**, *26*, 557.

[46] Campbell, A. D.; Grimmett, M. R. *Aust. J. Chem.* **1963**, *16*, 854.

[47] (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.

[48] Whitlock. H. W., Jr.; Wu, E.-M.; Whitlock, B. J. *J. Org. Chem.* **1969**, *34*, 1857.

of the reaction during their studies on Myers-Saito cyclizations.[49] A typical example of the Myers-Saito (C^2-C^7) cyclization is shown in Scheme 15 (pathway *a*), and involves formation of biradical **83** which is converted to **84** by hydrogen atom transfer from 1,4-cyclohexadiene (CHD). Schmittel and coworkers discovered that incorporation of an additional aryl substituent on the alkyne of a typical cyclization substrate induces a complete switch to a novel C^2-C^6 reaction motif (pathway *b*). This "Schmittel cyclization" proceeds via biradical **86** to provide indene **87**, the product of a formal ene reaction.[50,51] Schmittel suggests that the reaction of **85** follows this new pathway due to the stabilization of the vinyl radical in **86** by the additional phenyl group. Interestingly, calculations indicate that the average C^2-C^7 distance in these cyclization substrates is 2.96 Å, whereas the C^2-C^6 distance is between 3.3 and 3.5 Å.[52,53] The additional stabilization of the intermediate **86** must reduce the activation energy of the transition state leading to **86** (Hammond postulate), such that this pathway becomes energetically viable.

[49] Schmittel, M.; Strittmatter, M.; Kiau, S. *Tetrahedron Lett.* **1995**, *28*, 4975.

[50] Hock, H. A.; Kirk, B. E.; Taylor, D. R. *J. Chem. Soc. Perkin Trans. 1* **1974**, 1209.

[51] Recent calculations by Musch and Engels suggest that the "intramolecular ene" pathway is energetically competitive with the biradical pathway for substrates which incorporate a bulky (but not radical-stabilizing) substituent at the alkyne terminus. See: Musch, P. W.; Engels, B. *J. Am. Chem. Soc.* **2001**, *123*, 5557.

[52] Schmittel, M.; Keller, M.; Kiau, S.; Strittmatter, M. *Chem. Eur. J.* **1997**, *3*, 807.

[53] Reaction energetics were also calculated at the AM1 level. See: Engels, B.; Lennartz, C.; Hanrath, M.; Schmittel, M.; Strittmatter, M. *Angew. Chem. Int. Ed. Engl.* **1998**, *37*, 1960.

Scheme 15
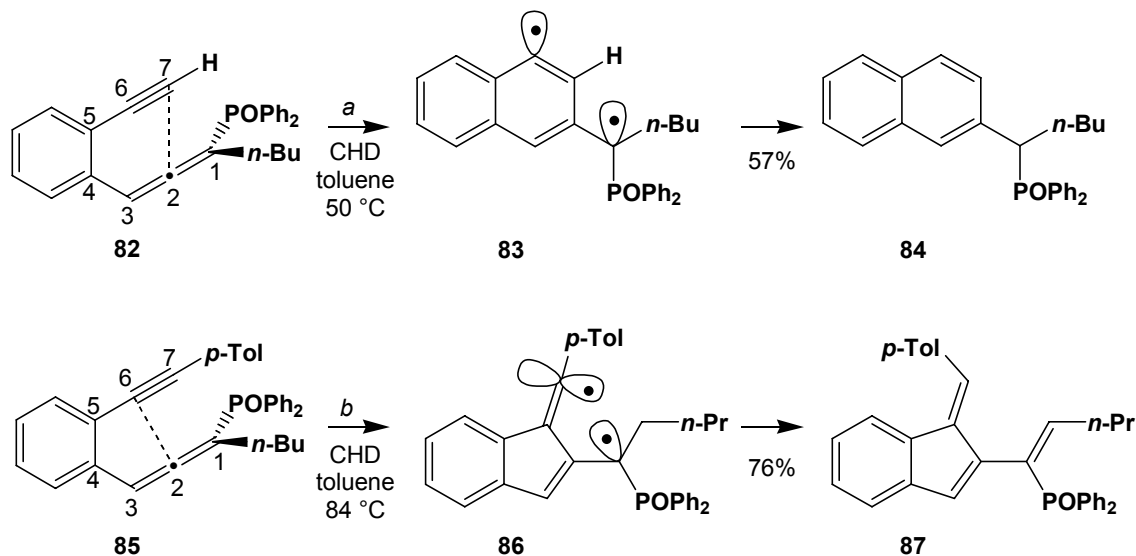
Soon thereafter, Schmittel reported[52] that upon replacing the alkyl substituent on the allene moiety with an aryl group (e.g., **88**), the reaction proceeds as expected along the C^2-C^6 pathway to form biradical **89**. The vinyl radical then cyclizes onto the tethered aromatic ring to afford, after hydrogen atom transfer, the benzofluorene **90** (Scheme 16).[54] This overall transformation is a formal [4 + 2] cycloaddition, specifically an intramolecular Diels-Alder reaction[55] in which the diene is a vinylbenzene[56] and the dienophile is an acetylene.

---

[54] (a) Schmittel, M.; Strittmatter, M.; Vollmann, K.; Kiau, S. *Tetrahedron Lett.* **1996**, *37*, 999. (b) Schmittel, M.; Strittmatter, M.; Kiau, S. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1843. (c) Schmittel, M.; Maywald, M.; Strittmatter, M. *Synlett* **1997**, 165. (d) Schmittel, M.; Kiau, S. *Liebigs Ann.* **1997**, 733.

[55] For reviews of intramolecular Diels-Alder reactions, see: (a) Roush, W. R. In *Comprehensive Organic Synthesis*, Trost, B. M.; Fleming, I., Eds.; Pergamon: New York, 1991, Vol. 5, Chapter 4.4, pp 513-550. (b) Roush, W. R. In *Advances in Cycloaddition*; Curran, D. P., Ed.; JAI Press: Greenwich, CT, 1990, Vol. 2, pp 91 ff. (c) Craig, D. *Chem. Soc. Rev.* **1987**, *16*, 187. (d) Ciganik, E. *Org. React.* **1984**, *32*, 1. (e) D. F. Taber, *Intramolecular Diels–Alder and Ene Reactions*; Springer-Verlag: New York, 1984. (f) Fallis, A. G. *Can. J. Chem.* **1984**, *62*, 183. (g) Brieger, G.; Bennett, J. N. *Chem. Rev.* **1980**, *80*, 63. (h) Bear, B. R.; Sparks, S. M.; Shea, K. J. *Angew. Chem. Int. Ed. Engl.* **2001**, *40*, 821.

[56] For reviews, see: (a) Wagner-Jauregg, T. *Synthesis* **1980**, 165. (b) Wagner-Jauregg, T. *Synthesis* **1980**, 769. For additional examples of intramolecular Diels-Alder reactions of styrenes with alkynes, see: (c) Baba, A.; Oda, T.; Taketomi, S.; Notoya, K.; Nishimura, A.; Makino, H.; Sohida, T. *Chem. Pharm. Bull.*

Scheme 16
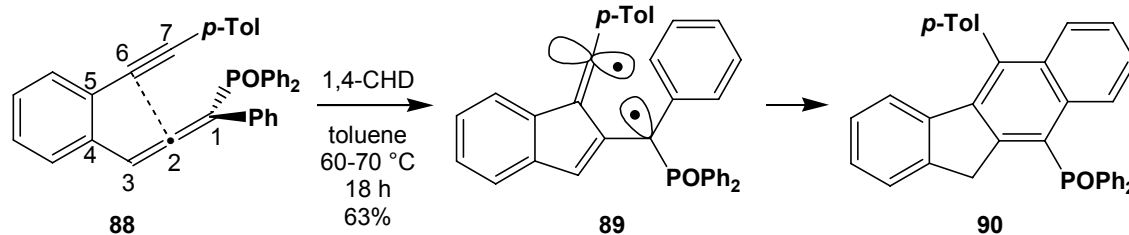
Schmittel's work on these novel reactions was initially focused on structures of the general type **85**, and later was extended to substrates of the type **91-93**.[57]   In the context of this work it was found that the Schmittel cyclization can be suppressed by ring strain effects. As shown in Scheme 17, cyclopentene **91** reacts to give only the Myers-Saito product **94**, despite the presence of a phenyl substituent at the alkyne terminus which usually favors the Schmittel cyclization pathway. Compounds **92** and **93**, which incorporate six- and seven-membered rings, respectively, react exclusively according to the Schmittel cyclization pathway.

Scheme 17
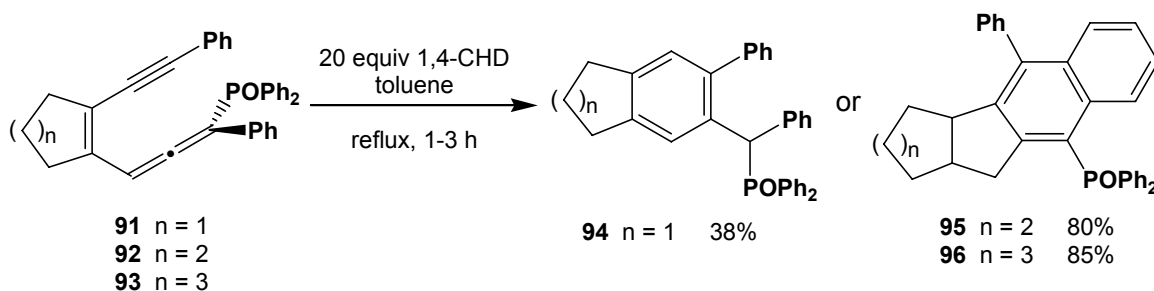
1999, *47*, 369. (d) Kashima, T.; Tanoguchi, M.; Arimoto, M.; Yamaguchi, H. *Chem. Pharm. Bull.* **1991**, *39*, 192. (e) Kanematsu, K.; Tsuruoka, M.; Takaoka, Y.; Sasaki, T. *Heterocycles* **1991**, *32*, 859. (f) Revesz, L.; Meigel, H. *Helv. Chim. Acta* **1988**, *71*, 1697.
[57] Schmittel, M.; Steffen, J.-P.; Auer, D.; Maywald, M. *Tetrahedron Lett.* **1997**, *37*, 6177.

Schmittel also found that substrates in which the allene is replaced by a ketenimine[58] or a carbodiimide[59] react in an analogous fashion to form the expected heterocycles. Further studies extended the scope of the reaction to include carbonyl-substituted allenes.[60]

Schmittel has extended the scope of the C^2-C^6 cyclization motif to include reactions of the propargylic alcohols which are the synthetic precursors to his earlier enyne-allene substrates.[61] For example, heating propargyl alcohol **97**, containing two different phenylacetylene moieties, affords two regioisomeric products **99** and **101** resulting from reaction according to both possible cycloaddition pathways (Scheme 18).
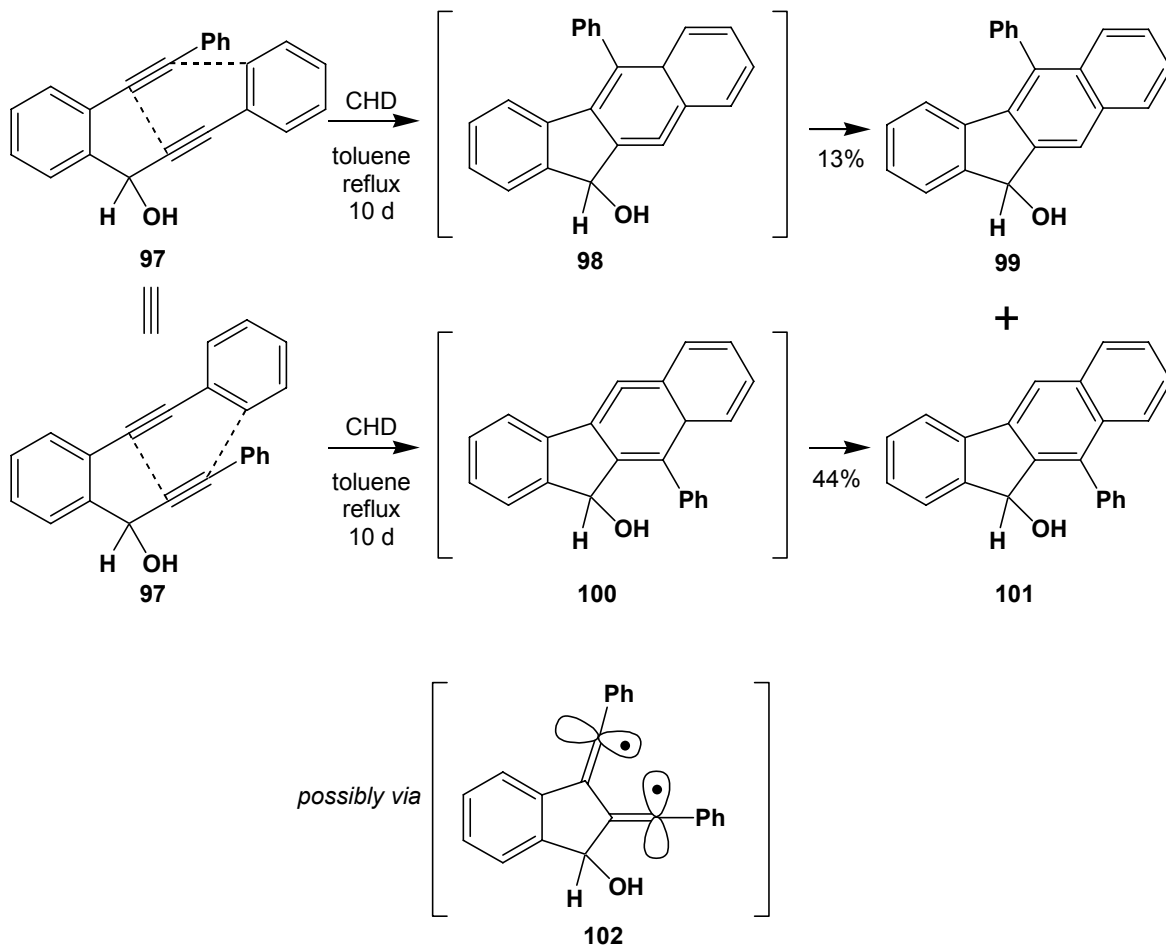
[58] Schmittel, M.; Steffen, J.-P.; Ángel, M. Á. W.; Engels, B.; Lennartz, C.; Hanrath, M. *Angew. Chem. Int. Ed. Engl.* **1998**, *37*, 1562.

[59] Schmittel, M.; Steffen, J.-P.; Engels, B.; Lennartz, C.; Hanrath, M. *Angew. Chem. Int. Ed. Engl.* **1998**, *37*, 2371.

[60] Schmittel, M.; Strittmatter, M. *Tetrahedron* **1998**, *54*, 13751.

[61] Schmittel, M.; Strittmatter, M.; Schenk, W. A.; Hagel, M. *Z. Naturforsch.* **1998**, *53b*, 1015.

Scheme 18

For the cycloaddition of **97**, Schmittel suggests two possible mechanistic pathways. A concerted $[4+2]$ cycloaddition would directly form cyclic allene intermediates **98** and **100**; a stepwise pathway via biradical **102** would provide the same cyclic allene intermediates (*vide supra*). However, Schmittel's initial experiments do not provide adequate evidence to distinguish between the two pathways.

The attempted cycloaddition of **103**, in which a phenyl has been replaced with a *tert*-butyl group, affords no cycloadduct **105** but only unreacted **103** (Scheme 19). The *tert*-butyl group's inability to stabilize the adjacent vinyl radical in biradical **104** would

cause the intermediate **104** to be higher in energy than **102**. Alternately, biradical **104** could form reversibly, but cyclization to **105** could be impeded due to steric reasons.

Scheme 19
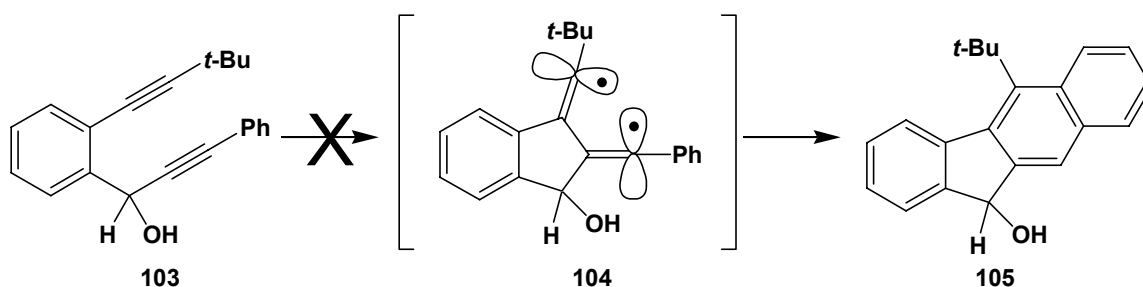
Subsequent to Schmittel's first report, a number of groups have published investigations of formal cycloadditions involving arenynes and alkynes.

Domínguez, Saá, and coworkers have described the cycloadditions of non-conjugated benzotriynes (e.g., **106**), in which an alkynyl group is substituted for one of the phenyl groups of Schmittel's arenyne cycloaddition substrates. As expected, the formal $[4 + 2]$ cycloaddition proceeds to give the cycloadduct **108** in good yield, presumably via biradical intermediate **107** (Scheme 20).[62] Theoretical studies support a mechanism involving initial formation of the biradical **107**, followed by fast intramolecular coupling to generate a strained cyclic allene which then evolves to the observed benzo[*b*]fluorene derivatives.[63]

[62] Rodriguez, D.; Castedo, L.; Domínguez, D.; Saá, C. *Tetrahedron Lett.* **1999**, *40*, 7701.
[63] Rodriguez, D.; Navarro, A.; Castedo, L.; Domínguez, D.; Saá, C. *Org. Lett.* **2000**, *2*, 1497.

Scheme 20
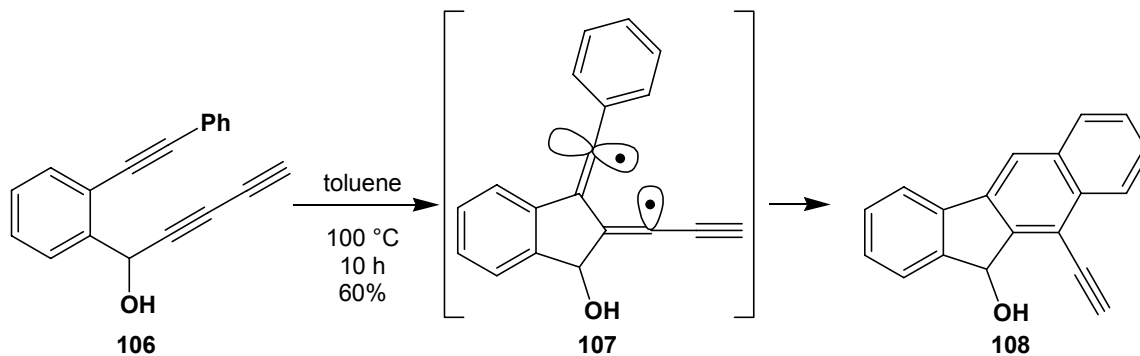
Deuterium incorporation studies were conducted to probe the conversion of the cyclic allene to the aromatic product. Cycloaddition in the presence of CH_3OD led to deuterated product (>95% D), whereas the use of CD_3OH led to no incorporation of deuterium. The authors interpret these results as indicative of a protonation step in the transformation of the cyclic allene to the final product.

In later work, Domínguez and Saá report the essentially the same reaction on ketones corresponding to the alcohols involved in the previous study.[63] These substrates react at much lower temperatures to afford the expected benzofluorenone products (Scheme 21). The authors attribute this greater reactivity to conformational and electronic effects imposed by the sp^2-hybridized carbon of the carbonyl group.

Scheme 21
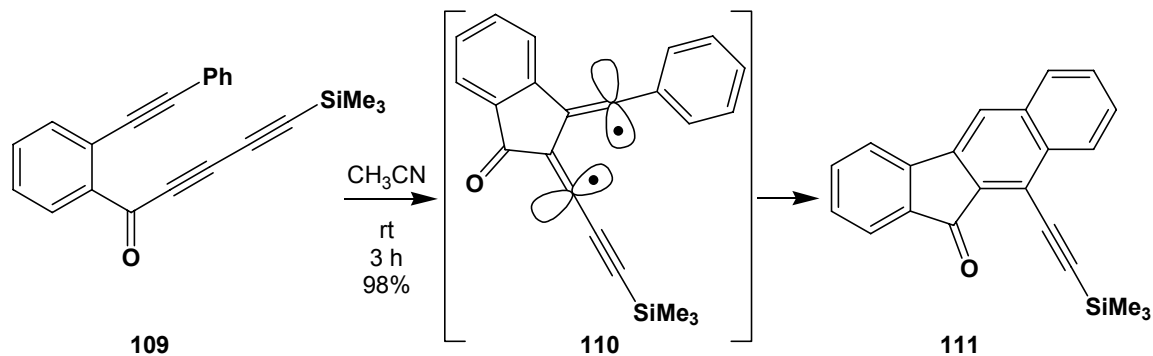
Echavarren and coworkers[64] have investigated the application of related arenyne cycloadditions to the synthesis of benzo[*b*]fluorene natural products of the kinamycin family.[65] Interestingly, these reactions produce mixtures of the desired benzo[*b*]fluorenes **113** with rearranged benzo[*a*]fluorenes of type **114** (Scheme 22).
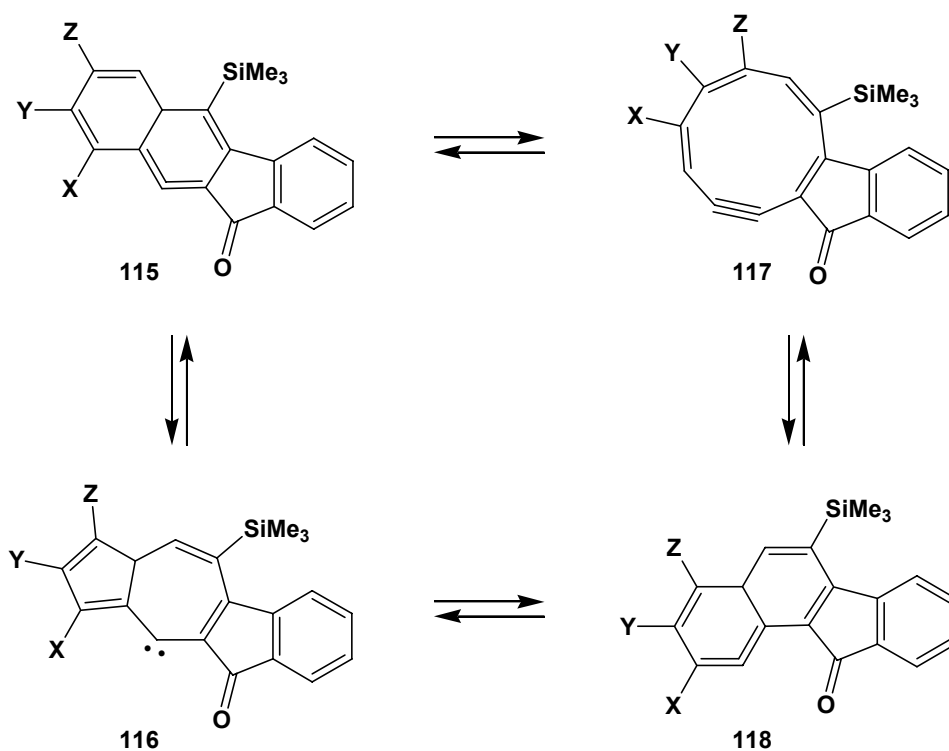
Scheme 22

---
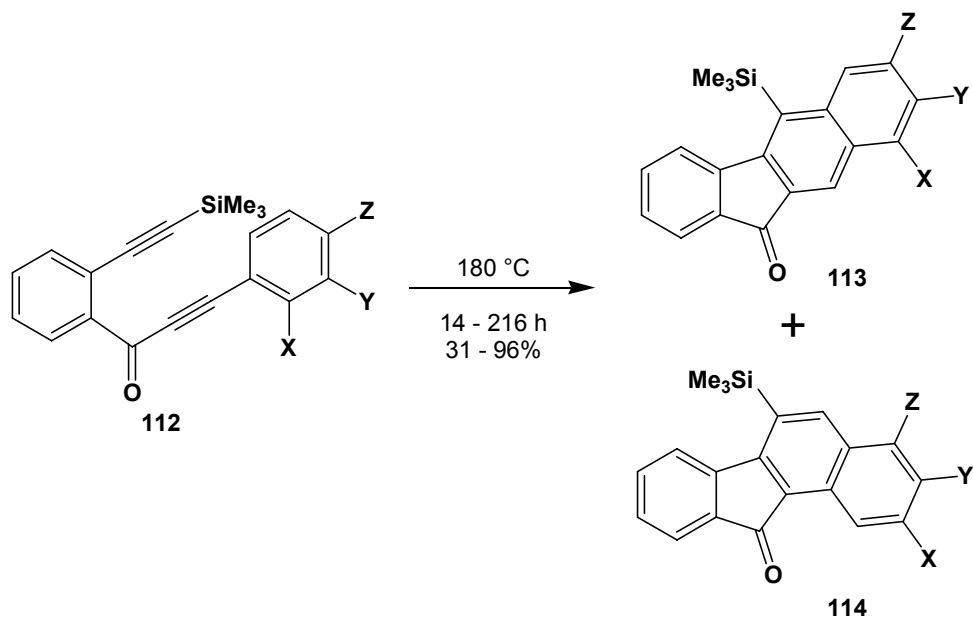
[64] Atienza, C.; Mateo, C.; de Frutos, O.; Echavarren, A. M. *Org. Lett.* **2001**, *3*, 153.
[65] For a review of the biosynthesis of the kinamycins, see: Gould, S. J. *Chem. Rev.* **1997**, *97*, 2499.

The authors explain these results by invoking the equilibrium of cyclic allenes **115** and **118**, which they propose can interconvert by two pathways: electrocyclic ring opening to dehydro[10]annulene **117** followed by electrocyclization, or rearrangement to carbene **116** followed by 1,2-C-C insertion (Scheme 23). No experimental evidence was provided to distinguish between the pathways.

Scheme 23

In subsequent work, Domínguez and Saá have observed this same skeletal rearrangement in the cycloaddition of propiolic amide **119**, which affords two regioisomeric cycloadducts **120** and **121** (Scheme 24).[66] The authors suggest the intermediacy of dehydro[10]annulene **123** in this reaction, analogous to **117** proposed

earlier by Echavarren (Scheme 23). Interestingly, the benzo[*b*]fluorene **120** is the exclusive product when the reaction is run in the presence of phenol, although in the absence of phenol, the rearranged benzo[*a*]fluorene **121** is the exclusive product. The lack of an effective proton or hydrogen atom donor disfavors isomerization of cyclic allene **122** to **120**, thus allowing rearrangemenet to take place to the energetically favored cyclic allene **124** (calculated to be 1.4 kcal/mol more stable than **122**). The authors do not comment on the mechanism of isomerization of **124** to **121** in the absence of phenol, though either toluene or an intermediate in the reaction could serve as a hydrogen atom donor.

Scheme 24
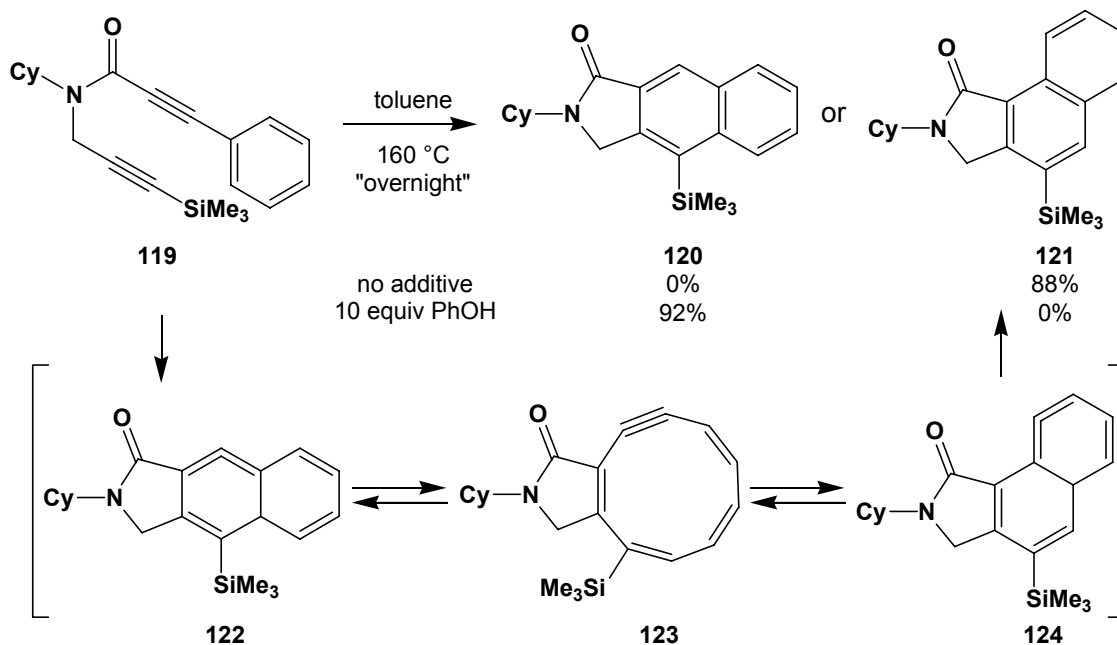
[66] Rodriguez, D.; Navarro-Vázquez, A.; Castedo, L.; Domínguez, D.; Saá, C. *J. Am. Chem. Soc.* **2001**, *123*, 9178.

The authors note that in reactions conducted in the absence of phenol, "*the addition of radical hydrogen donors such as 1,4-cyclohexadiene or γ-terpinene had no effect although radical paths for cyclic allenes had been observed. It seems that cyclic allenes much prefer ionic proton abstraction.*"[66] This observation is consistent with their deuterium incorporation study conducted earlier (*vide infra*).

Additional studies by Domínguez and Saá on substrates similar to Echavarren's revealed similar rearrangements.[67] The also found that the use of toluene instead of benzene led to little difference in the results, "showing that the presence of possible radical hydrogen donors plays at most a minor role in the final aromatization step." Notably, the use of triethylamine as solvent led to quantitative yields of the cycloadduct. The authors attribute this result to the triethylamine "acting as a catalytic base for the aromatization step."

The cycloadditions of arenynes with arynes is a related process which has also been explored. In 1997, Guitián and coworkers reported the cycloaddition of arenyne **125** with benzyne to form a cyclic allene (**126**) or biradical intermediate (**127**), which then cyclizes onto the pendant alkyne moiety to ultimately furnish benzo[*a*]pyrene (**129**) (Scheme 25).[68]

[67] Rodriguez, D.; Navarro-Vázquez, A.; Castedo, L.; Domínguez, D.; Saá, C. *Tetrahedron Lett.* **2002**, *43*, 2717.

[68] Cobas, A.; Guitián, E.; Castedo, L. *J. Org. Chem.* **1997**, *62*, 4896.

Scheme 25

125 THF, rt 30% **129**

126 **127** **128**
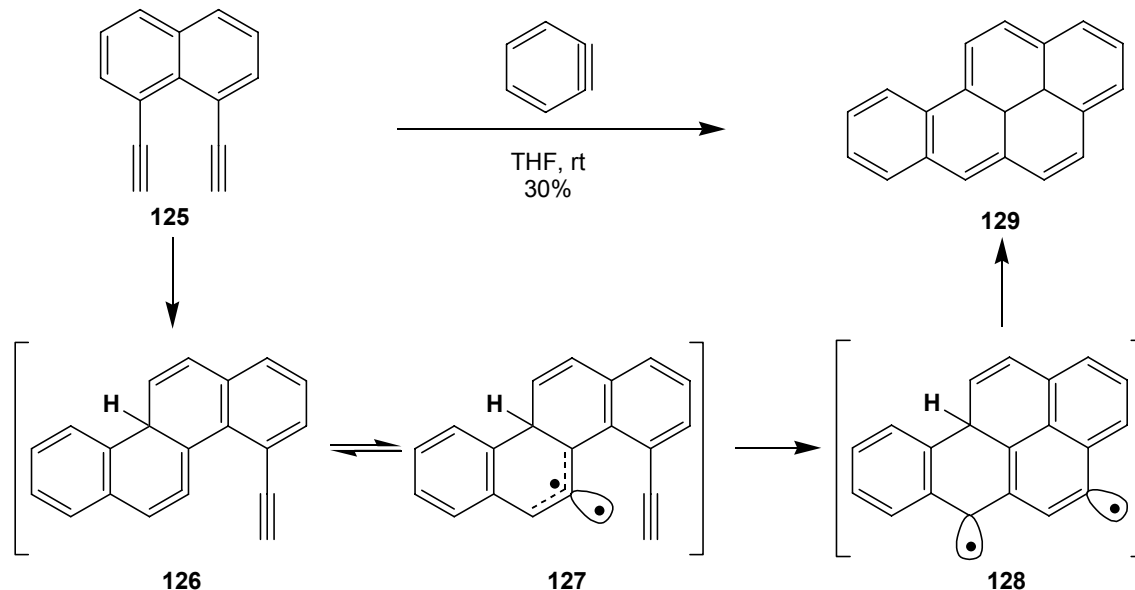
In studies concurrent with Schmittel's early work, Ueda and coworkers discovered an intramolecular [4 + 2] cycloaddition of a diyne with an alkyne to afford an aryne intermediate (though the authors refer to the intermediate as a "didehydrobenzene diradical").[69] Thus, the cycloaddition of **130** at room temperature, in the presence of excess anthracene as a trapping agent, affords a mixture of **134** (8%) and **135** (72%), presumably via arynes **132** and **133** (Scheme 26). In the absence of anthracene, only 5% of the corresponding arene was isolated, along with 6% of a compound resulting from cycloaddition of the aryne intermediate to benzene (the solvent).

[69] (a) Miyawaki, K.; Suzuki, R.; Kawano, T.; Ueda, I. *Tetrahedron Lett.* **1997**, *38*, 3943. (b) Ueda, I.; Sakurai, Y.; Kawano, T.; Wada, Y.; Futai, M. *Tetrahedron Lett.* **1999**, *40*, 319.

Scheme 26
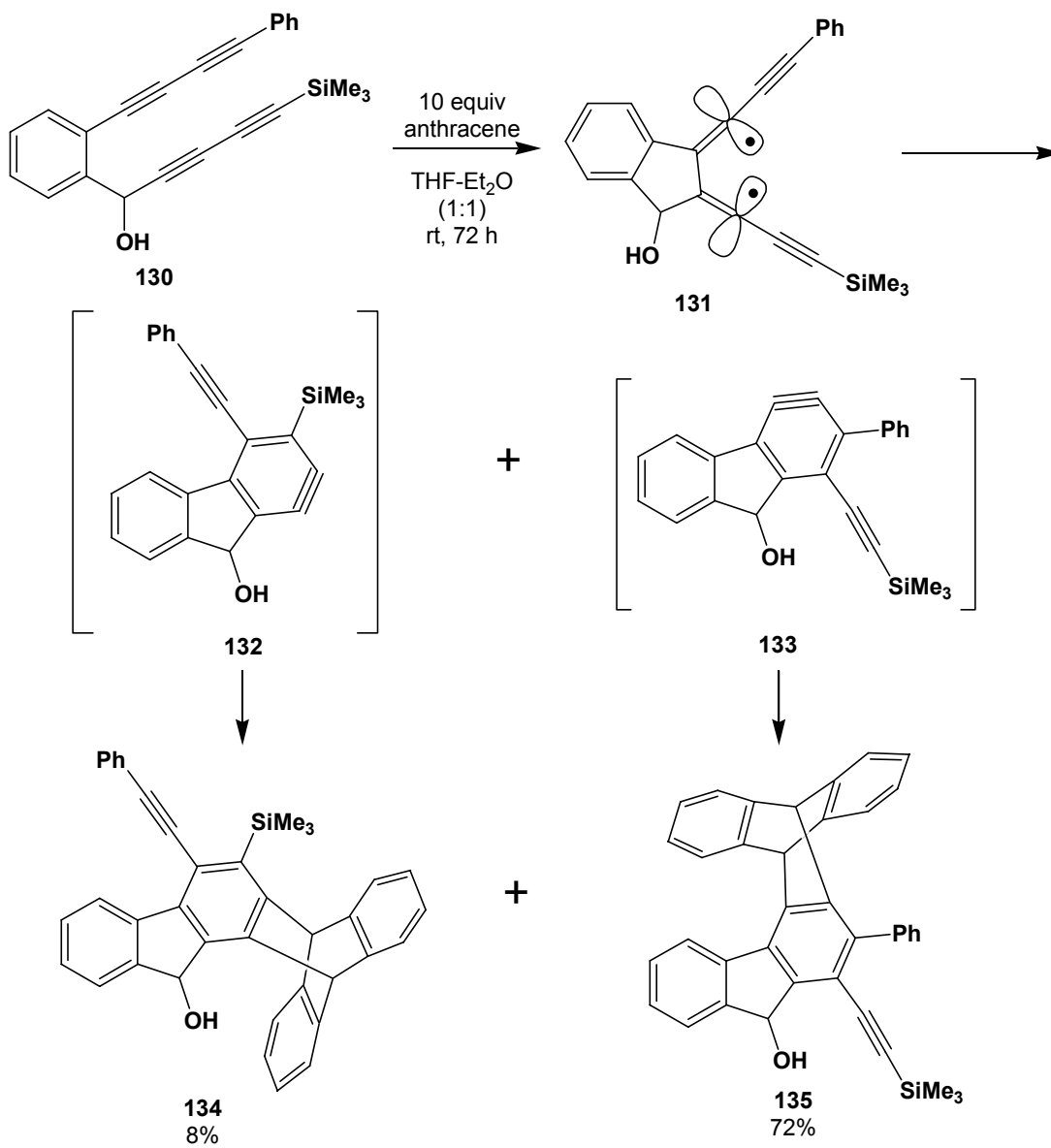
Ueda and coworkers subsequently extended this chemistry to substrates in which the resulting aryne intermediate undergoes further cyclization with a pendant alkyne to furnish a condensed polyaromatic species,[70] similar to the earlier work of Guitián.

---

[70] (a) Miyawaki, K.; Kawano, T.; Ueda, I. *Tetrahedron Lett.* **1998**, *39*, 6923. (b) Miyawaki, K.; Kawano, T.; Ueda, I. *Tetrahedron Lett.* **2000**, *41*, 1447.

An interesting reaction pertinent to the mechanism of arenyne cycloadditions was serendipitously discovered by Oppolzer during attempted intramolecular Diels-Alder reaction of the styrene **136** to give **139** (Scheme 27).[71] Diels-Alder reactions involving styrene derivatives as 4π components are known to be somewhat difficult due to the disruption of aromaticity of the benzene ring in the transition state for cycloaddition.[56] In this particular substrate, an alternative pathway involving cyclization to form biradical **140** becomes energetically competitive; the benzylic stabilization of the incipient radicals in the transition state lowers the activation energy for this pathway. In this instance, the biradical intermediate **140** does not react according to a typical arenyne cycloaddition pathway. Cyclization of the secondary radical onto the pendant phenyl ring would result in a bridgehead alkene, a violation of Bredt's rule.[72] Cyclization of the tertiary radical probably does not take place due to geometric constraints; it may simply be too far from the phenyl ring. Instead, **140** undergoes a radical combination to afford the observed products **137** and **138**, resulting in a formal [2 + 2] cycloaddition. The initial cyclization step in this reaction is reminiscent of the first step of an arenyne cycloaddition, which forms an intermediate biradical that is stabilized by the presence of aryl groups.

[71] Oppolzer, W.; Loosli, H.-R. *Helv. Chim. Acta* **1974**, 57, 2605. (b) Oppolzer, W. *Helv. Chim. Acta* **1974**, 57, 2610.

[72] (a) For a recent report, see: Bear, B.R.; Sparks, S.M.; Shea, K.J; *Angew. Chem. Int. Ed. Engl.* **2001**, 40, 821. For reviews, see: (b) Keese, R.; Luef, W. In *Topics in Stereochemistry*, Eliel, E. L.; Wilen, S. H., Eds.; Wiley: New York, 1991; Vol. 20, pp 231-318. (c) Warner, P. M. *Chem. Rev.* **1989**, 89, 1067. (d) Broden, W. T. *Chem. Rev.* **1989**, 89, 1099. (e) Krause, G. A.; Yon, Y. S.; Thomas, P. J.; Laramay, S.; Liras, S.; Hanson, J. *Chem. Rev.* **1989**, 89, 1591. (f) Szeimies, G. In *Reactive Intermediates*; Abranovitch, R. A., Ed.; Plenum: New York, 1983; Vol. 3, pp. 299-366. (g) Shea, K. J. *Tetrahedron* **1980**, 36, 1683.

Scheme 27

136

o-dichlorobenzene
180 °C
72 h

137
30%

+

138
26%

139
not observed

140
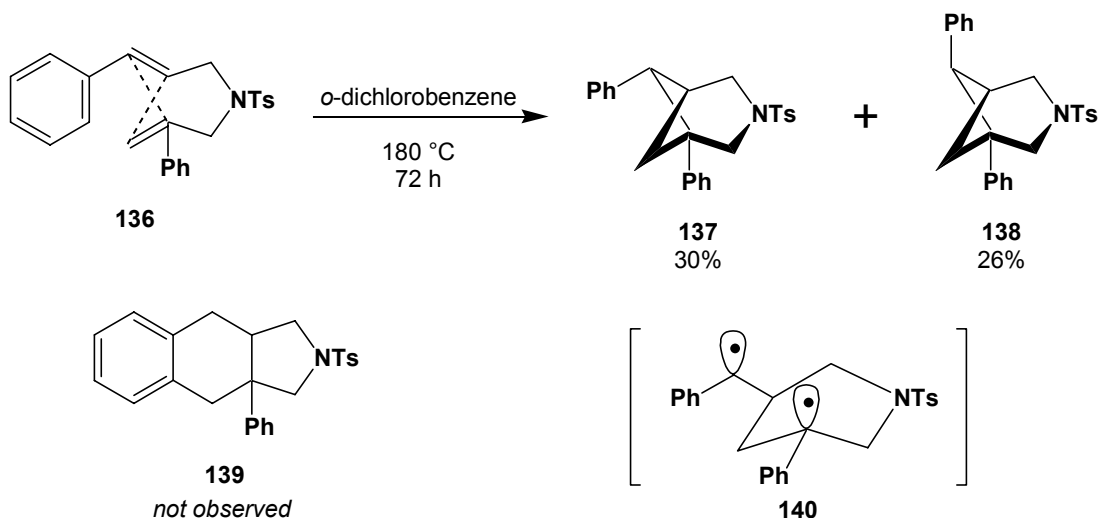
## Intramolecular Enyne [4 + 2] Cycloadditions: Recent Work

As mentioned earlier, our group reported the first systematic investigation of the scope and mechanism of the intramolecular enyne [4 + 2] cycloaddition.[14] Since that publication, researchers in our group have undertaken additional experiments to probe the mechanism and expand the scope of the reaction.[73] In addition, several other research groups have also seized upon the opportunities presented by these powerful cycloadditions.

A number of additional examples of the enyne cycloaddition have been investigated in our laboratory, including two cases where the enynophile is a trisubstituted alkene (**141** and **143**).[73] The products resulting from this cycloaddition (**142** and **144**) retain the configuration of the double bond, thus providing evidence that

---

[73] (a) Gould, A. E.; Palucki, B. L.; Fernández de la Pradilla, R.; Helgason, A. L.; Yli-Kauhaluoma, J.; Hayes, M. E.; Dunetz, J. R.; Danheiser, R. L. Manuscript in preparation. (b) Gould, A. E.; Palucki, B. L.;

the cycloaddition is suprafacial with respect to the enyne moiety (Scheme 28).[74] This

leads to the conclusion that the cycloaddition occurs through either a concerted

mechanism or a stepwise mechanism involving a very rapid cyclization step. In addition,

the cycloaddition of substrate **145** afforded exclusively the *endo* product **146**, indicating

that the cycloaddition proceeds with high *endo* selectivity (Scheme 28).
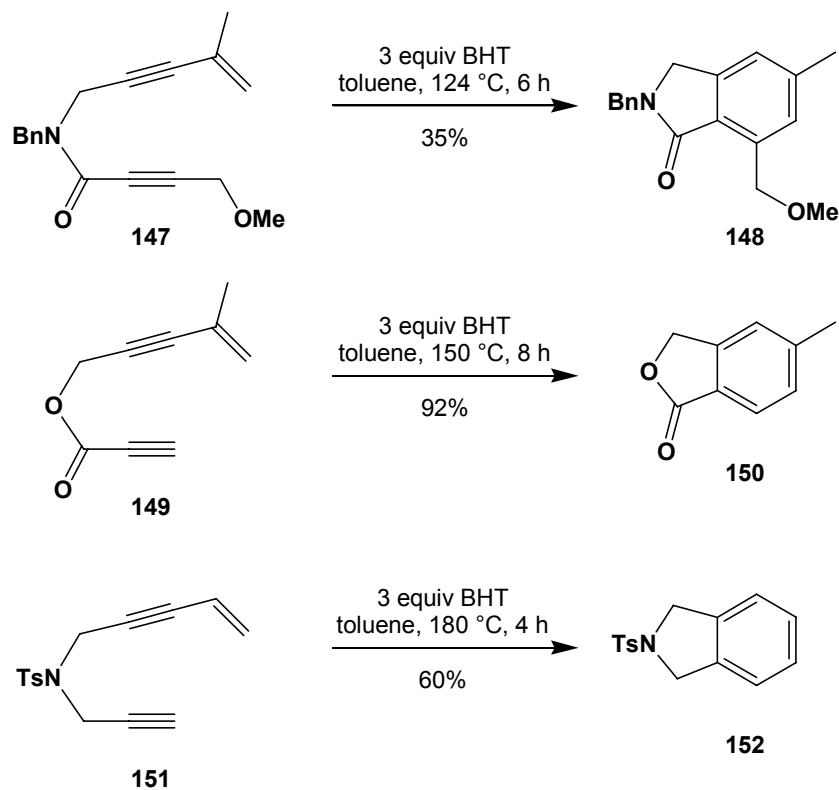
Scheme 28
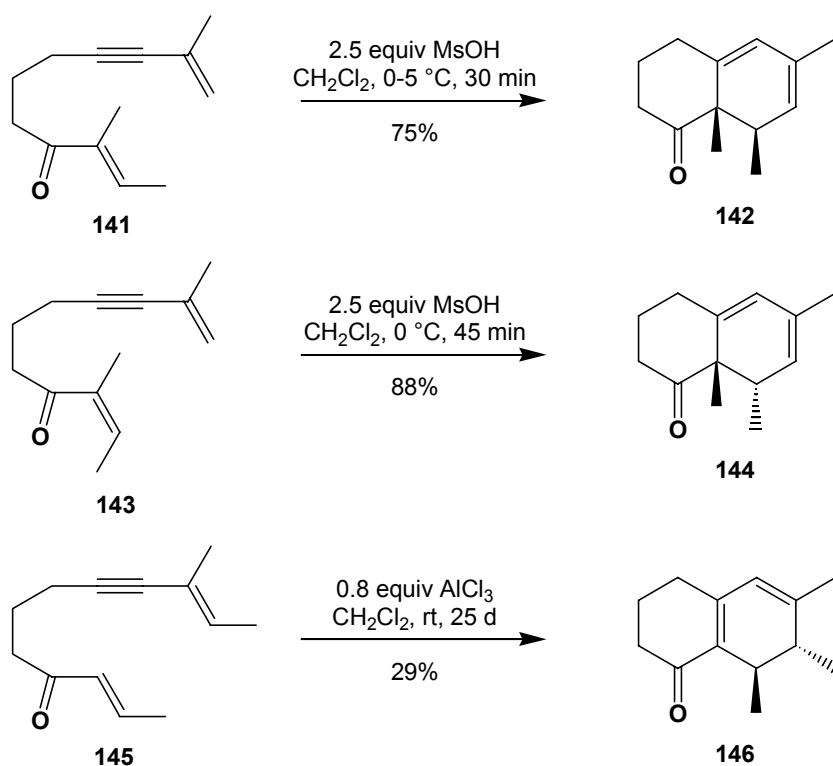
A number of other enynes have been synthesized in our laboratory and undergo

cycloaddition successfully. In addition to previous examples with all-carbon and

---

Fernández de la Pradilla, R.; Helgason, A. L.; Yli-Kauhaluoma, J.; Danheiser, R. L. Manuscript in preparation.
[74] This is in agreement with Miller's recent work on intermolecular enyne cycloadditions. See: Ionescu, D.; Silverton, J. V.; Dickinson, L. C.; Miller, B. *Tetrahedron Lett.* **1996**, *37*, 1559.

ketone-containing tethers (Scheme 5), it has been shown that amides, esters, and substituted amines also can be incorporated as functionality in the tether (Scheme 29).

Scheme 29

Echavarren has reported the cycloaddition of an enyne tethered to an acetylene via a rigid naphthalene scaffold.[75] Thus, enyne **153** undergoes cycloaddition at 150 °C in 6 hours to afford the cycloadduct **154** (Scheme 30). In this report, the authors provide no mechanistic discussion on the cycloaddition.

---

[75] González, J. J.; Francesch, A.; Cárdenas, D. J.; Echavarren, A. M. *J. Org. Chem.* **1998**, *63*, 2854.

Scheme 30

153 → 0.01 equiv hydroquinone
xylene, 150 °C, 6 h

65%

154
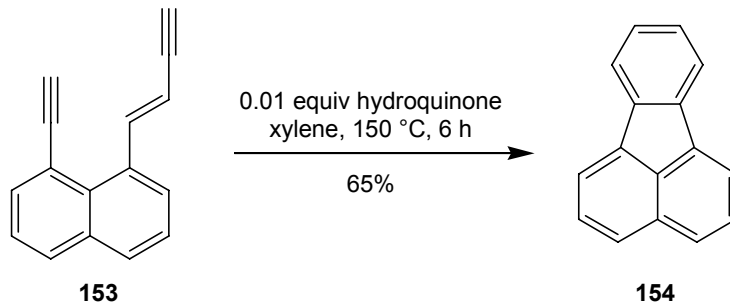
Johnson and coworkers have demonstrated cycloadditions of enynes **155** and **158** and diyne **163** under flash vacuum thermolysis conditions.[76] Compounds **157**, **161**, and **165** isolated from these reactions support the intermediacy of a cyclic allene (Scheme 31). In the case of **157**, cycloreversion of allene **156** results in loss of ethylene to provide the observed product. The formation of **161** and **165** likely results from a six-electron electrocyclic ring opening of the cyclic allene intermediates.

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

Scheme 31
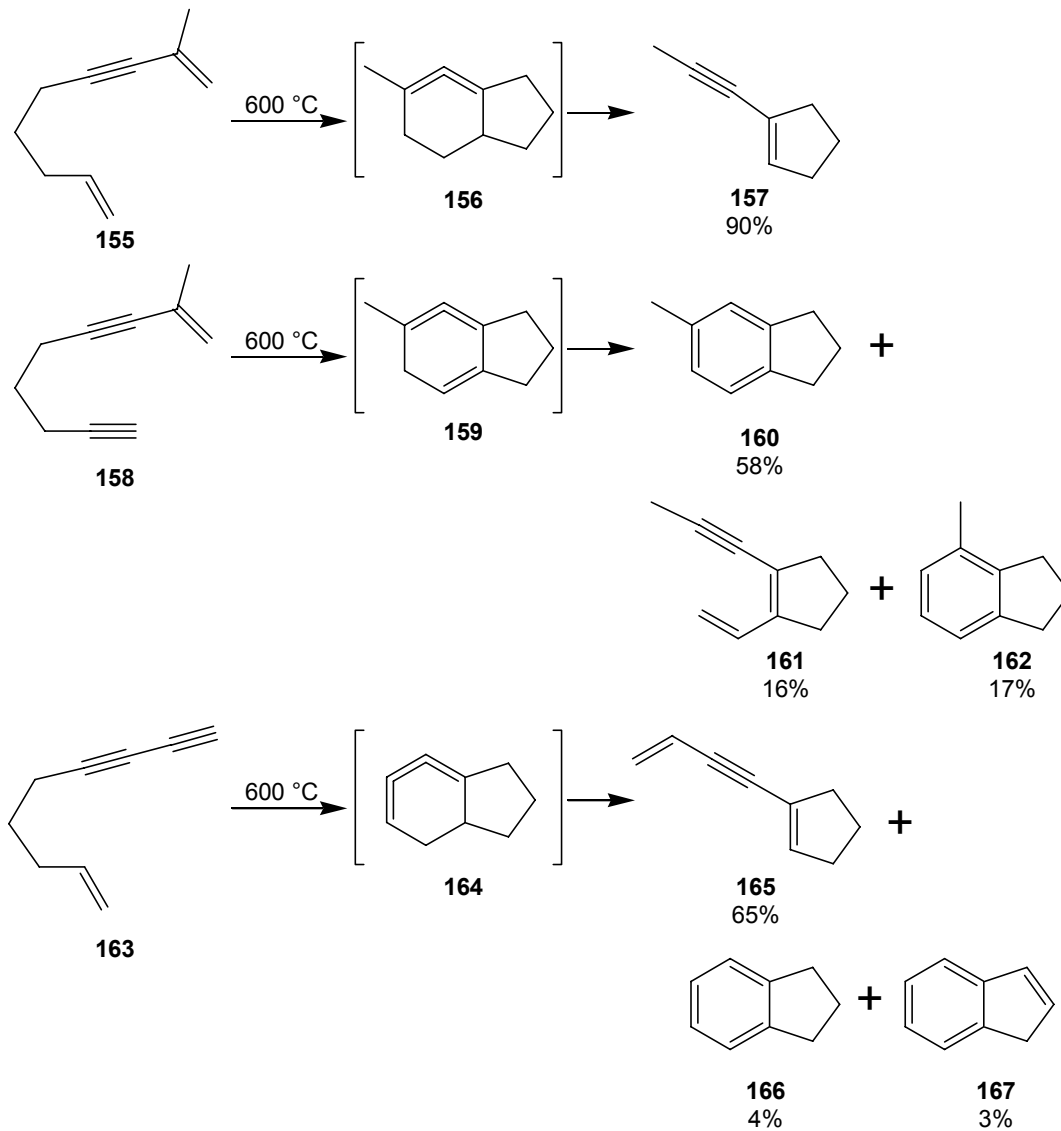
Johnson and coworkers also explored the intramolecular [4 + 2] cycloaddition of 1,3,8-nonatriyne (**168**), which produces aryne intermediate **169**, and ultimately furnishes indan and indene via hydrogen transfer (Scheme 32).[77] Mechanistic support for a [4 + 2] cycloaddition was provided by deuterium labeling studies.

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

Scheme 32

168   600 °C   [169]   166 82% + 167 13%
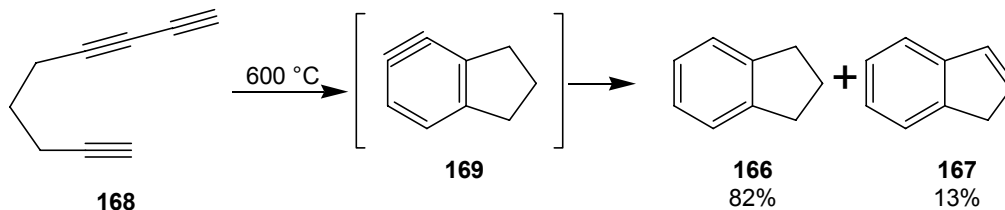
Johnson has also reported reaction energetics derived from *ab initio* calculations for the intermolecular version of the enyne cycloaddition.[78] He reported the enthalpy of reaction (ΔH_R) based on *ab initio* calculations to be -25.4 kcal/mol, similar to our previous calculation of -29.7 kcal/mol (*vide supra*).

Recently, Ananikov has calculated the potential energy surfaces for both intermolecular and intramolecular cycloadditions of prototypical enyne substrates, and has calculated the structures of transition states and intermediates.[79] The calculations for the transformation of cyclic allene **53** to the observed aromatic product were restricted to unimolecular processes, and revealed two possible pathways, shown in Scheme 33. The first pathway involves a 1,3-hydrogen shift, but this leads to *cis*, *cis*, *trans*-1,3,5-cyclohexadiene (**170**) or "Möbius benzene."[80] The second pathway proceeds via a 1,2-hydrogen shift, producing carbene intermediate **171**, which undergoes a second 1,2-hydrogen shift to form benzene.

---

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

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

[80] Johnson, R. P.; Daoust, K. J. *J. Am. Chem. Soc.* **1996**, *118*, 7381.

Scheme 33

170   170   53   171
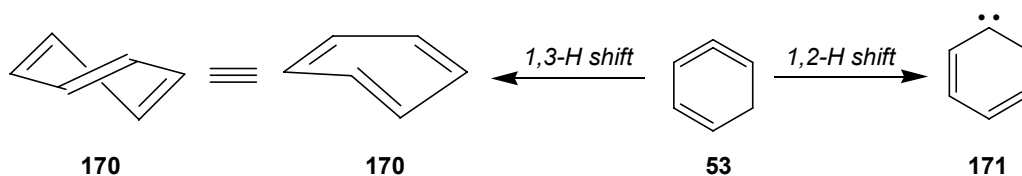
The carbene **171** is calculated to be lower in energy than Möbius benzene (**170**) by 4.0 kcal/mol. Although these calculations suggest that, in the gas phase, isomerization of isobenzene to benzene can involve intramolecular hydrogen shifts, we believe that in solution phase reactions with hydrogen atom or proton donor additives, the allene isomerization proceeds via intermolecular pathways.

After Ananikov's report, Martin Hayes in our laboratory conducted a deuterium-labeling study to probe the possibility that carbenes such as **171** are intermediates in the isomerization of the cyclic allene to the aromatic product. To this end, enyne **172** was synthesized and subjected to the typical cycloaddition conditions. The product resulting from intermolecular aromatization pathways should be **174**, whereas the pathway involving carbene **175** should provide a mixture of **174** and **176**. In the event, the reaction afforded only **174**, in which no deuterium shift occurred (Scheme 34).[81] The same product was obtained in the absence of BHT, albeit in lower yield. This result provides strong evidence against the possibility of a carbene intermediate in the isomerization of the cyclic allene to the observed aromatic product.

---

[81] Hayes, M. E., Massachusetts Institute of Technology, unpublished results.

Scheme 34
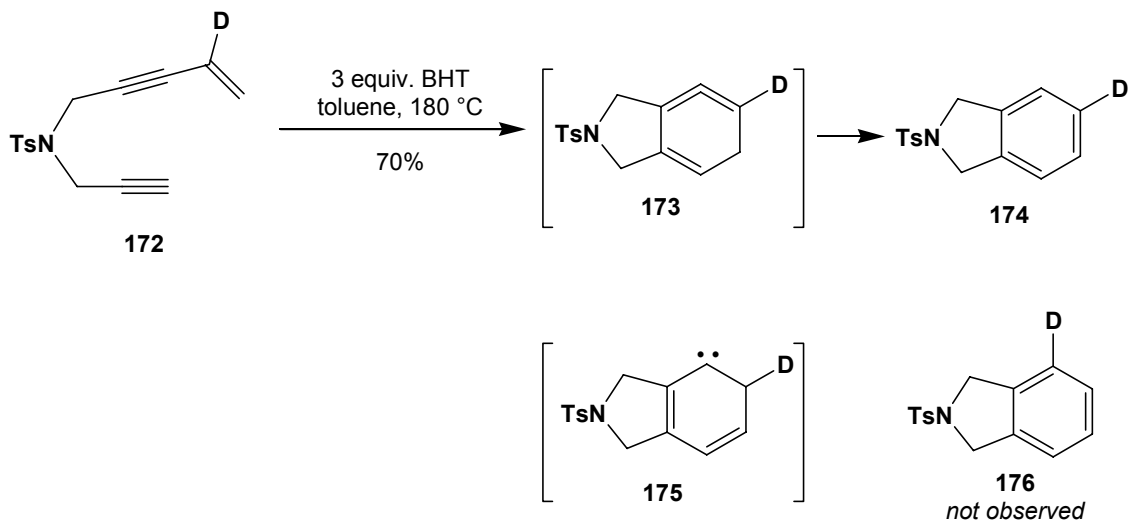
Summary

The intramolecular $[4+2]$ cycloadditions of conjugated enynes represent an important new entry into the arsenal of cycloadditions for the synthetic organic chemist. The related formal $[4+2]$ cycloadditions of arenynes are also potentially useful tools for the synthesis of condensed polycycles; however, unlike the enyne cycloadditions, cycloadditions of substituted arenynes have exhibited some lack of regiocontrol, which is a drawback for their application to natural products synthesis. The expansion of the enyne cycloaddition methodology to "heteroenynes" will be discussed in detail in the following chapters.

Chapter 2

Introduction and Background: Intramolecular [4 + 2] Cycloadditions of Heteroenynes

Importance of Heterocyclic Compounds

Heterocyclic compounds[82] are widely distributed in nature, and they play essential roles in all living cells. There are a vast number of pharmacologically active heterocyclic compounds; while some are natural products, the majority of compounds currently in clinical use are synthetic, with finely-tuned activity.

Other common uses for heterocyclic compounds include pesticides, insecticides, herbicides, flavorings, fragrances, dyes, copolymers, solvents, and photographic sensitizers and developers. In addition, many heterocyclic compounds are important synthetic intermediates. The range of chemical transformations in which heterocycles participate is growing rapidly, including their use in the synthesis of specific functionalized non-heterocyclic structures.

A practically limitless number of structurally diverse, novel heterocyclic compounds with a wide range of physical, chemical, and biological properties, and possessing a wide range of stability and reactivity characteristics, are imaginable.

This chapter will review the extension of the enyne cycloaddition methodology to "heteroenynes," compounds of the type **177** in which one of the carbon atoms of the alkene is replaced by a heteroatom (Scheme 35). Specifically, the intramolecular [4 + 2]

---

[82] (a) *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R.; Rees, C. W., Eds.; Pergamon: New York, 1984. (b) *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R.; Rees, C. W.; Scriven, E. F. V., Eds.; Pergamon: New York, 1996. (c) *Handbook of Heterocyclic Chemistry*; Katritzky, A. R.; Pozharskii, A. F.; Pergamon: New York, 2000.

cycloadditions of 1-oxaenynes (e.g., **179**) with alkynes will be discussed. Our proposed mechanism for the transformation involves the heterocyclic allene intermediate **180**, which ultimately furnishes the observed dihydroisobenzofuran product **181**.

Scheme 35
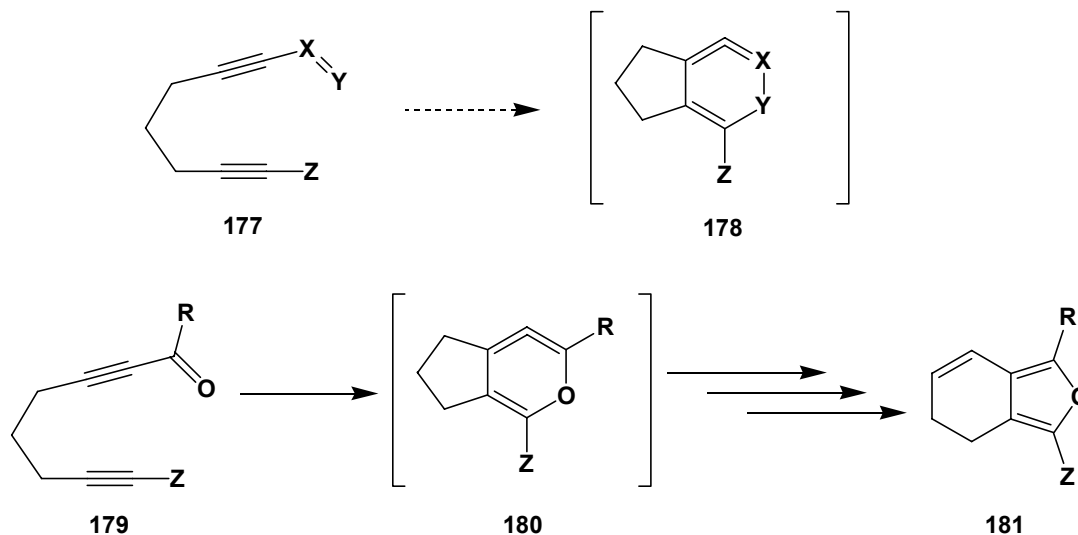
My work, which will be detailed in Chapter 3, involves the cycloaddition of several additional 1-oxaenynes. We were particularly interested in additional studies to probe the mechanism of the transformation, and we sought to demonstrate the utility of the dihydroisobenzofuran products, which are valuable as synthetic intermediates and are incorporated in a number of natural products of biological importance (*vide infra*).

Significance of Furans in Organic Synthesis

Furans are the most common of the five-membered heterocycles in nature and in organic synthesis. Polysubstituted furans are found as key structural units in many natural products and pharmaceuticals. Most naturally-occurring furans are of botanical

origin, though furans have also been isolated from fungi and mammals.[83] In addition to their biological significance, furans are commonly utilized as building blocks in organic synthesis,[84] where they function as dienes in cycloadditions,[85] as masked carboxylic acids,[86] and as 1,4-diketone equivalents.[87] Furans are also utilized in the food industry as natural and artificial flavors, fragrances, and preservatives.[88]

Due to the many applications of furans, the synthesis of polysubstituted furans continues to be of great import to organic chemists, and has led to the development of an extensive array of synthetic approaches to the furan skeleton.[89] Despite the numerous methods available for the synthesis of furans, relatively few general methods are applicable to the construction of 3,4-substituted or 3,4-fused derivatives. Previous routes to 3,4-fused polycyclic furans include Kanematsu's furan ring transfer strategy[90] and others.[91] The intramolecular cycloaddition of oxaenynes is a new entrant to this area, providing 3,4-fused furans directly. Cleavage of the six-membered ring in the product

---

[83] (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. *Biochim. Biophys. Acta* **1984**, *793*, 429.

[84] For an overview, see: Lipshutz, B. H. *Chem. Rev.* **1986**, *86*, 795.

[85] For recent reviews, see: (a) Kappee, C. O.; Murphree, S. S.; Padwa, A. *Tetrahedron* **1997**, *53*, 14179. (b) Wright, D. L. *Chem. Innov.* **2001**, *31*, 17.

[86] 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.

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

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

[89] For recent reviews, see: (a) Gilchrist, T. L. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2491. (b) Gilchrist, T. L. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2849. (b) Gilchrist, T. L. *J. Chem. Soc., Perkin Trans. 1* **1998**, 615. (c) Gilchrist, T. L. *Contemp. Org. Synth.* **1995**, *2*, 337. (d) Gilchrist, T. L. *Contemp. Org. Synth.* **1994**, *1*, 205.

[90] (a) Yamaguchi, Y.; Yamada, H.; Hayakawa, K.; Kanematsu, K. *J. Org. Chem.* **1987**, *52*, 2040. (b) Baba, Y.; Sakamoto, T.; Kanematsu, K. *Tetrahedron Lett.* **1994**, *35*, 5677. (c) Wu, H.-J.; Lin, S.-H.; Lin, C.-C. *Heterocycles* **1994**, *38*, 1507.

[91] For a review on the synthesis of substituted furans, see: Hou, X. L.; Cheung, H. Y.; Hon, T. Y.; Kwan, P. L.; Lo, T. H.; Tong, S. Y.; Wong, H. N. C. *Tetrahedron* **1998**, *54*, 1955.

reveals monocyclic tetrasubstituted furans which are otherwise difficult to assemble using conventional routes.

Diels-Alder Reactions of 1-Oxabutadienes

We will begin with a discussion of the related cycloadditions of 1-oxabutadienes. The first example of a Diels-Alder reaction involving an oxabutadiene appeared in 1938 with Sherlin's report of the thermal dimerization of acrolein.[92]   Since that initial discovery, extensive investigations of the Diels-Alder reactions of 1-oxabutadienes have been reported by many groups, and numerous reviews have provided a thorough analysis of the scope, mechanism, and synthetic utility of these reactions.[93,94,95,96]

The hetero Diels-Alder reaction of α,β-unsaturated aldehydes and ketones **182** with electron rich or unactivated olefins **183** (Scheme 36) gives access to 2-substituted dihydropyrans **184** which are useful precursors to a variety of natural products. The use of alkynes **185** as dienophiles affords pyrans **186**.   Theoretical calculations on this inverse-electron-demand cycloaddition (LUMO-controlled with respect to the heterodiene) are consistent with the observed formation of the 2-substituted dihydropyran regioisomer.   These calculations also support the preferred *endo* approach of the dienophile in a concerted asynchronous transformation, i.e., in the transition state, the new carbon-carbon bond is more fully formed than the new carbon-oxygen bond. Exceptions to the predicted regioselectivity all involve poorly matched substrates

[92] Sherlin, S. M.; Berlin, A. Y.; Serebrennikova, T. A.; Rabinovitch, R. F. *J. Gen. Chem. USSR* **1938**, *8*, 22.
[93] Tietze, L. F.; Kettschau, G. *Top. Curr. Chem.* **1997**, *189*, 1.
[94] Boger, D. L.; Weinreb, S. M. *Hetero Diels-Alder Methodology in Organic Synthesis*; Academic Press: New York, 1987.
[95] Desimoni, G.; Tacconi, G. *Chem. Rev.* **1975**, *75*, 651.
[96] For a theoretical treatment, see: Park, Y. S.; Lee, B. S.; Lee, I. *New J. Chem.* **1999**, *23*, 707.

(electron-deficient dienes with electron-deficient dienophiles).[95] Electron-withdrawing groups attached to the carbon α to the carbonyl enhance the reactivity of the heterodiene by lowering the energy of the LUMO. In addition, substitutents on the α carbon also stabilize the cisoid conformation of the heterodiene.

Scheme 36
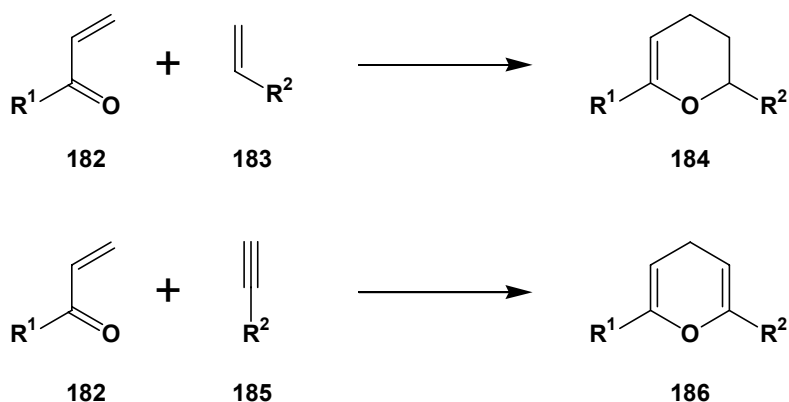
Thermal hetero Diels-Alder reactions of 1-oxabutadienes with alkenes and alkynes typically require temperatures of 150 to 200 °C. In these reactions, the competing dimerization or polymerization of the heterodienes is often a serious side reaction. The addition of a radical inhibitor or the use of an excess of the oxabutadiene has often moderated these side reactions. Recently, Lewis acid catalysis,[97] high pressure techniques,[98] and microwave activation[99] have all come into common use as facilitators of the hetero Diels-Alder reactions of 1-oxabutadienes.

---

[97] (a) David B. Gorman, D. B.; Tomlinson, I. A. *Chem. Commun.* **1998**, 25. (b) Merour, J.-Y.; Bourlot, A.-S.; Desarbe, E. *Tetrahedron Lett.* **1995**, *36*, 3527. (c) Snider, B. B.; Phillips, G. B. *J. Org. Chem.* **1983**, *48*, 2789.

[98] (a) Matsumoto, K.; Sera, A. *Synthesis* **1986**, 999. (b) Dauben, W. G.; Krabbenhoft, H. O. *J. Org. Chem.* **1977**, *42*, 282. (c) Dauben, W. G.; Kozikowski, A. P. *J. Am. Chem. Soc.* **1974**, *96*, 3664. (d) Firestone, R. A.; Smith, G. M. *Chem. Ber.* **1989**, *122*, 1089.

The intramolecular cycloadditions of oxabutadienes proceed even more efficiently than intermolecular reactions, and intramolecular Diels-Alder reactions of *activated* oxabutadienes with electron-rich, unactivated, and even electron-poor dienophiles are all well known.[100] Intramolecular cycloaddition substrates incorporating electron-withdrawing groups at the α carbon display exceptional regio- and stereoselectivity, and exhibit enhanced reactivity, in certain cases even undergoing cycloaddition at room temperature. In general, the stereochemistry of the reacting oxabutadiene system, the nature of the tether, and the substitution pattern of the alkene dienophile all affect the rate, stereoselectivity, and regioselectivity of the cycloaddition.[101] Reports of *unactivated* oxabutadienes participating in intramolecular Diels-Alder reactions are limited due to the competition between the desired cycloaddition and the intramolecular ene reaction.[102]

In recent years, asymmetric versions of both intermolecular and intramolecular Diels-Alder reactions of oxabutadienes have been reported. The use of chiral auxiliaries[103] and substrates with stereogenic centers[104] has been investigated. In

[99] Diaz-Ortiz, A.; Diez-Berra, E.; de la Hoz, A.; Prieto, P.; Moreno, A. *J. Chem. Soc., Perkin Trans. 1* **1994**, 3595.

[100] For reviews of intramolecular Diels-Alder reactions, see: (a) Roush, W. R. In *Comprehensive Organic Synthesis*, Trost, B. M.; Fleming, I., Eds.; Pergamon: New York, 1991, Vol. 5, Chapter 4.4, pp 513-550. (b) Roush, W. R. In *Advances in Cycloaddition*; Curran, D. P., Ed.; JAI Press: Greenwich, CT, 1990, Vol. 2, p 91 ff. (c) Craig, D. *Chem. Soc. Rev.* **1987**, *16*, 187. (d) Ciganik, E. *Org. React.* **1984**, *32*, 1. (e) D. F. Taber, *Intramolecular Diels–Alder and Ene Reactions*; Springer-Verlag: New York, 1984. (f) Fallis, A. G. *Can. J. Chem.* **1984**, *62*, 183. (g) Brieger, G.; Bennett, J. N. *Chem. Rev.* **1980**, *80*, 63. (h) Bear, B. R.; Sparks, S. M.; Shea, K. J. *Angew. Chem. Int. Ed. Engl.* **2001**, *40*, 821.

[101] 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.

[102] (a) For an example under thermal 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.

[103] For examples, see: (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.

[104] For an example, see: Tietze, L. F.; Geissler, H.; Fennen, J.; Brumby, T.; Brand, S.; Schulz, G. *J. Org. Chem.* **1994**, *59*, 182.

addition, the use of chiral Lewis acids not only promotes the cycloaddition but also provides enantioenriched compounds from racemic precursors.[105]

## The Heteroenyne [4 + 2] Cycloaddition of Ynones and Related Species

Our laboratory recently reported the first example of a heterocyclic variant of the enyne cycloaddition, the intramolecular [4 + 2] cycloaddition of conjugated ynones.[106] Analogous to the enyne cycloaddition, the heteroenyne cycloaddition occurs to give highly strained heterocyclic allenes **180** (Scheme 37).   In cycloadditions involving conjugated enynes, the cyclic allene intermediate can isomerize to furnish an aromatic product; however, in the cycloaddition of oxaenynes, such an isomerization of the heterocyclic allene intermediate cannot occur.   Two conceivable pathways providing products incorporating a six-membered oxygen heterocycle lead to pyran **187** or pyrylium cation **188**.   Neither of these two products was isolated from the reaction; instead, the dihydrosiobenzofuran **181** was the only characterizable product.   Although furan formation was not expected, it opened the door to exciting possibilities for the application of this reaction in organic synthesis.[107]

---

[105] Maruoka, K. In *Catalytic Asymmetric Synthesis*, 2nd Ed.; Ojima, I., Ed.; Wiley-VCH: New York, 2000; Chapter 8A.

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

[107] For full details of the discovery and exploration of this new reaction, see: Wills, M. S. B. Ph.D. Thesis, Massachusetts Institute of Technology, Cambridge, MA, June 1998.

Scheme 37
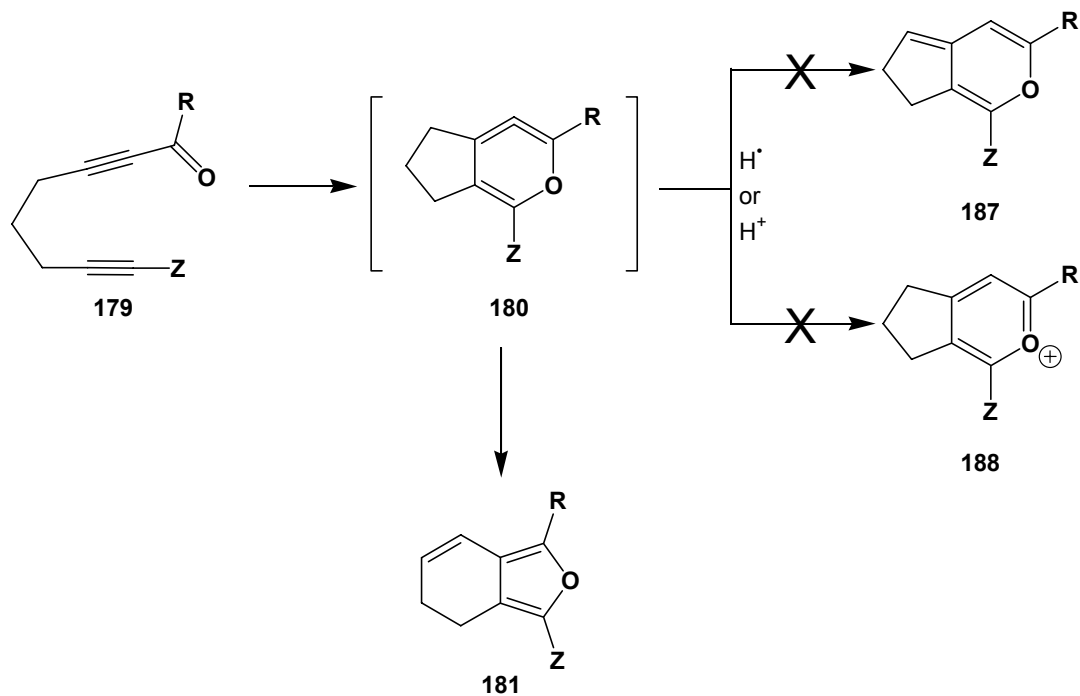
Scheme 38 shows the mechanism proposed for this fascinating reaction. The alkynone **189** undergoes an intramolecular [4 + 2] cycloaddition to produce the strained heterocyclic allene **190**. An unusual 1,2-carbon shift then generates the furylcarbene intermediate **191** with concomitant release of ring strain and formation of the aromatic furan ring. This carbene can undergo a variety of reactions depending on the substrate, the most common of which is the facile insertion into an adjacent C-H bond to afford the dihydroisobenzofuran **192**.

Scheme 38
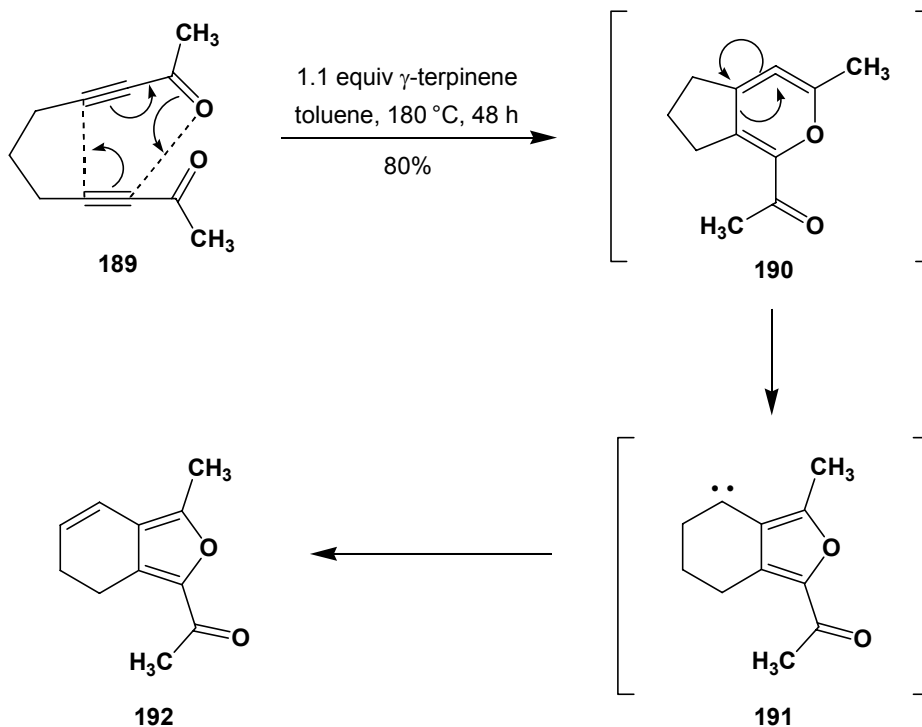
Dr. Wills' initial exploration of this new reaction focused mainly on simple substrates such as **187**. The conditions for effecting the cycloaddition reaction involve heating a degassed 0.1 M solution of the substrate in toluene in the presence of 1.1 equiv of γ-terpinene, a cyclohexadiene derivative. The choice of solvent and the concentration of the reaction solution were selected based on previous work performed on the related enyne cycloaddition (*vide supra*). Since the use of these conditions provided the furan products in good yields, Dr. Wills did not examine the use of different solvents or other reaction concentrations.

The use of γ-terpinene exerts a strong effect on the efficiency of the desired transformation. In reactions conducted without this additive or with a substoichiometric amount, yields of the furan product fell by 10-15%. We believe that γ-terpinene acts as a

radical inhibitor and prevents polymerization of the oxaenyne substrates at the elevated reaction temperatures. Dr. Wills explored the use of phenolic additives that could function as radical inhibitors, but found that these were not as effective. This result is interesting since phenolic additives improve the yields of enyne cycloadditions. In the cycloadditions of conjugated enynes, phenolic additives may improve the efficiency of the reaction by facilitating the isomerization of the cyclic allene intermediate to the aromatic product; however, in the cycloadditions of oxaenynes, such as isomerization cannot occur.

The following three Tables summarize Dr. Wills' experiments. Interpretation of the results from these experiments will be deferred until later in this chapter in conjunction with the discussion of the mechanism of the reaction, and in Chapter 3 in relation to additional experiments aimed at extending the scope of the reaction.

Table 1 delineates Dr. Wills' investigation of a variety of substituted alkynes as the 2π component of the reaction.

Table 1
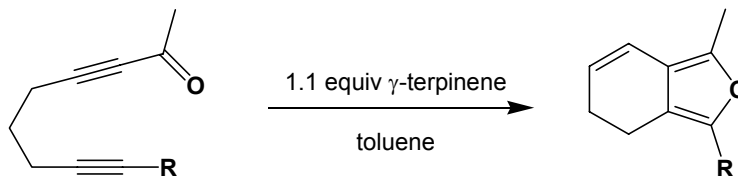
Entry	R	Substrate	Cycloadduct	Conditions	Yield
1	C(O)CH$_3$	**189**	**192**	180 °C, 48 h	80%
2	C$_6$H$_5$	**193**	**194**	180 °C, 48 h	70%
3	C$_6$H$_4$p-OMe	**195**	**196**	180 °C, 77 h	52%
4	C$_6$H$_4$p-NO$_2$	**197**	**198**	180 °C, 48 h	81%
5	SiMe$_3$	**199**	**200**	220 °C, 72 h	50%
6	C≡CEt	**201**	**202**	180 °C, 6 h	56%
7	H	**203**	**204**	220 °C, 48 h	2-10%
8	SPh	**205**	**206**	180 °C, 48 h	0%
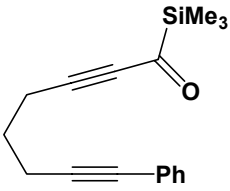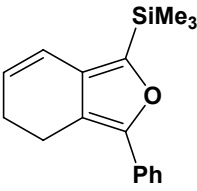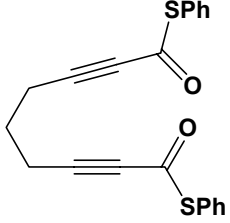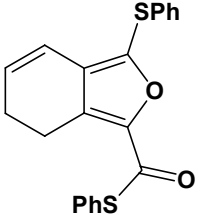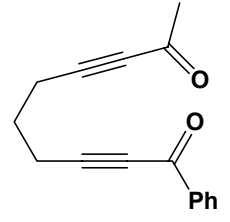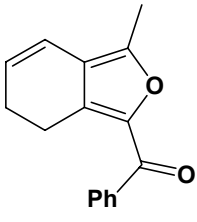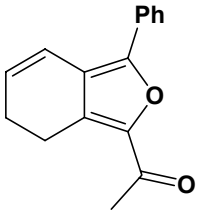
Dr. Wills also studied two substrates which deviated from the typical 3-carbon tether. Table 2 summarizes the results of these experiments.
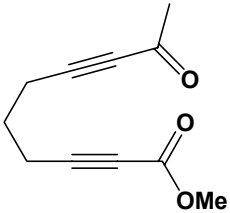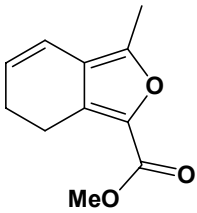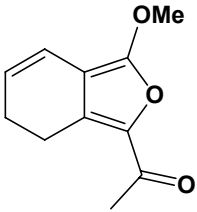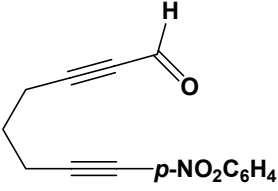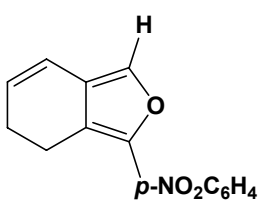
Table 2
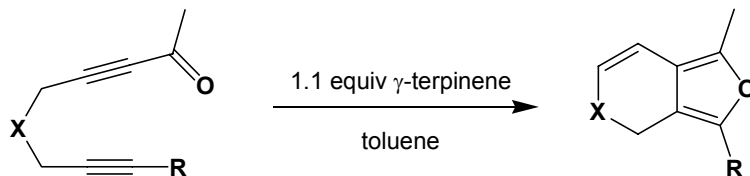
Entry	R	X	Substrate	Cycloadduct	Conditions	Yield
1	$C(O)CH_3$	CH_2CH_2	**207**	**208**	220 °C, 72 h	20%
2	$SiMe_3$	TsN	**209**	**210**	111 °C, 16 h	64%

A number of experiments were conducted to probe variations in the 4π component of the cycloaddition, including a series of competition experiments in which a single substrate incorporates two different heteroenynes that can both react as 4π components in the cycloaddition. Table 3 outlines the results of these investigations.

Table 3

Entry	Substrate	Cycloadduct	Conditions	Yield
1	**211**	**212**	180 °C, 20 h	36%
2	**213**	**214**	180 °C, 45 h	0%
3	**215**	**216**	180 °C, 48 h	59%
		217	180 °C, 48 h	9%

| Entry	Substrate	Cycloadduct	Conditions	Yield
4	**218**	**219**	180 °C, 48 h	51%
		220	180 °C, 48 h	0%
5	**221**	**222**	180 °C, 48 h	10%

Mechanism of the Heteroenyne Cycloaddition

In addition to her initial investigation into the scope of the reaction, Dr. Wills undertook a few experiments to probe the mechanism of the cycloaddition. As shown earlier (Scheme 38), the proposed mechanism involves initial [4 + 2] cycloaddition to form a strained cyclic allene **190**, followed by a 1,2-sigmatropic rearrangement to a 3-furylcarbene **191**, and subsequently a facile 1,2-C-H insertion to furnish the dihydroisobenzofuran system **192**.

The [4 + 2] cycloaddition step has precedent in the related [4 + 2] cycloadditions of conjugated enynes. As discussed in Chapter 1, enynes and arenynes have been the subject of numerous recent studies that indicate a cycloaddition process occurs under thermal conditions. Theoretical studies support the existence of a cyclic allene or biradical intermediate in the enyne and arenyne cycloaddition reactions, and recent theoretical and experimental studies of heterocyclic allenes demonstrate their transient existence. Reactions of enynes under flash vacuum thermolysis conditions produce products which support the intermediacy of a cyclic allene, as their formation likely results from a six-electron electrocyclic ring opening of the cyclic allene.

Dr. Wills conducted similar investigations involving flash vacuum thermolysis conditions to determine whether the oxaenyne systems would provide products consistent with the intermediacy of cyclic allenes. Thus, substrate **193** was heated to 600 °C in an FVP oven and the expected cycloadduct **194** was isolated in 39% yield along with the cyclopentene **224** in 28% yield (Scheme 39). Cyclopentene **224** could be formed via a six-electron electrocyclic ring opening of the heterocyclic allene intermediate **223**; thus the isolation of **224** supports the existence of cyclic allene **223** as an intermediate in the cycloaddition. It is worth noting that products resulting from an electrocyclic ring-opening of the cyclic allene intermediate are not observed in solution-phase reactions even at 220 °C; we believe that the electrocyclic ring-opening pathway is accessible only at the high temperatures typically utilized in FVP experiments.

Scheme 39
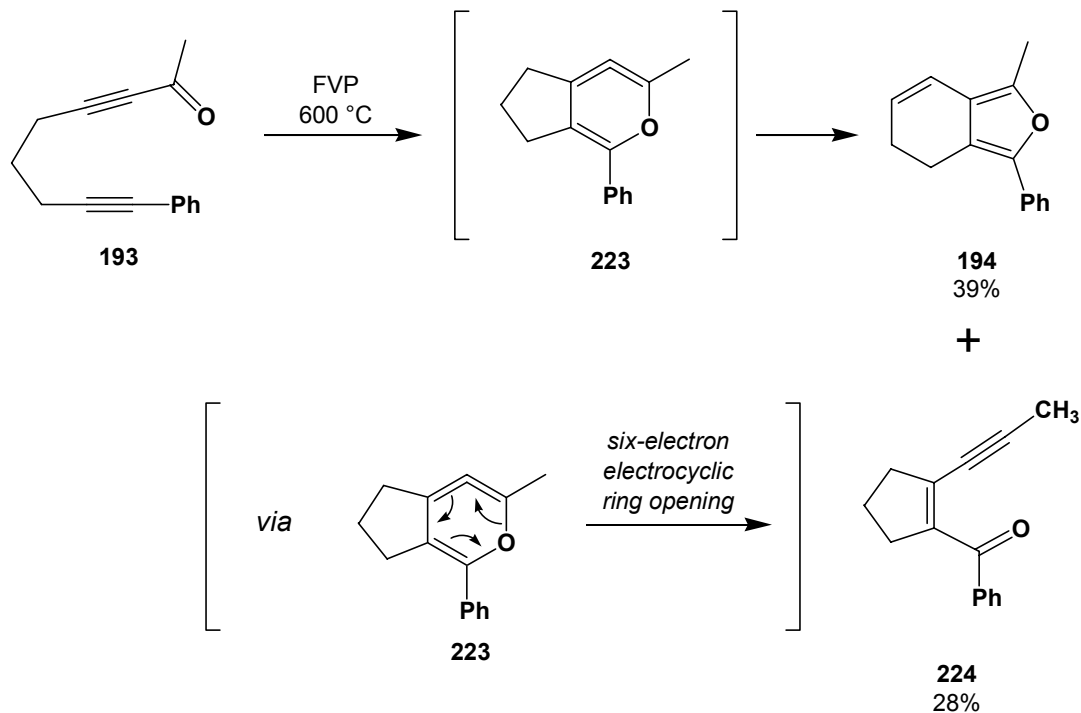
The second step in the proposed mechanism involves a 1,2-sigmatropic rearrangement of the strained heterocyclic allene **190** to form the 3-furylcarbene **191**. Precedent for this rearrangement is found in the literature of certain strained π systems which undergo rearrangements to carbenes.

Examples of the rearrangement of strained bridgehead olefins to carbenes are shown in Scheme 40. In all three cases, the strained olefins were generated *in situ*, and in two cases (**225**[108] and **227**[109]) evidence for the carbene was provided by trapping experiments. In the case of olefin **229**,[110] the isolation of the corresponding nortricyclene **231** provides evidence for the intermediacy of carbene **230**.

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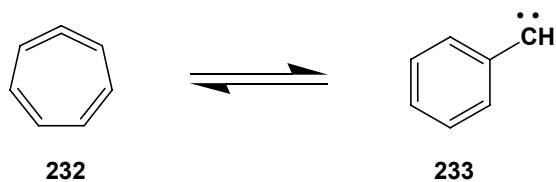[109] Eaton, P. E.; Hoffmann, K-L. *J. Am. Chem. Soc.* **1987**, *109*, 5285.
[110] Barton, T. J.; Yeh, M.-H. *Tetrahedron Lett.* **1987**, *28*, 6421.

Scheme 40

225 → 226

227 → 228

229 → 230 → 231
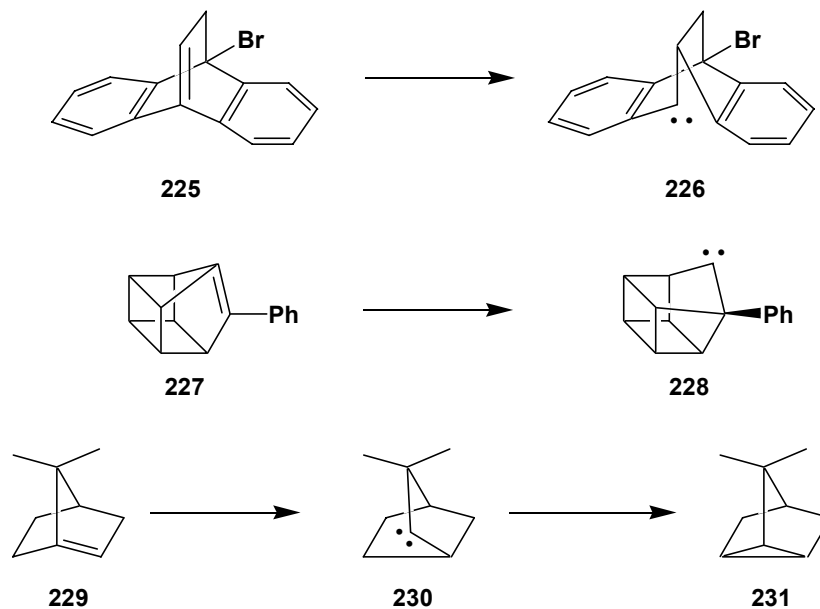
In addition, the well-known interconversion of cycloheptatetraene **232** and phenylcarbene **233** is a closely related process (Scheme 41).[111]

Scheme 41

232 ⇌ 233

Perhaps the most relevant and closely related literature precedent for the generation of a furylcarbene from a strained heterocyclic allene are the

---

[111] (a) Geise, C. M.; Hadad, C. M. *J. Org. Chem.* **2002**, *67*, 2532 and references therein. (b) Gaspar, P. P.; Hsu, J-P.; Chari, S.; Jones, M., Jr. *Tetrahedron* **1985**, *41*, 1479 and references therein.

1-aza-2,3,5-cyclohexatriene[112] and 1-thia-2,3,5-cyclohexatriene[113] rearrangements discovered by Shevlin, which were previously discussed in Chapter 1 (see Scheme 10).

Dr. Wills attempted to trap the carbene intermediate in the heteroenyne cycloaddition by using DMSO as the reaction solvent (Scheme 42). In the event, thermolysis of **189** produced none of the product (**234**) expected from intermolecular trapping of the carbene **191**, likely due to the facility of the intramolecular 1,2-C-H insertion pathway available for this carbene.

Scheme 42
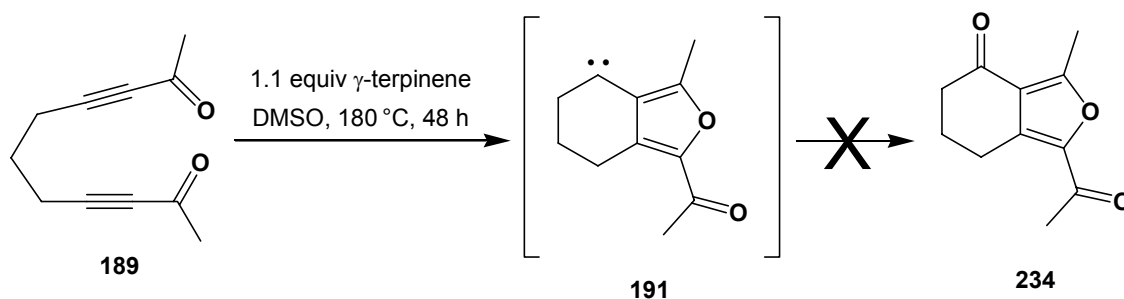
An alternative plan was developed to provide evidence to support the intemediacy of a carbene in the cycloaddition. The cycloaddition of the custom-designed substrate **235** was expected to provide carbene **237** upon cycloaddition and rearrangement. Because the carbene **237** cannot undergo 1,2-C-H insertion, a characteristic fragmentation was expected to transpire which would generate the tetrasubstituted furan **238** (Scheme 43). In the event, heating **235** at 150 °C for 16 hours provided furan **238** in

[112] Emanuel, C. J.; Shevlin, P. B. *J. Am. Chem. Soc.* **1994**, *116*, 5991.
[113] Pan, W.; Balci, M.; Shevlin, P. B. *J. Am. Chem. Soc.* **1997**, *119*, 5035.

35% yield. The isolation of this fragmentation product lends support to the proposed carbene intermediate in the reaction.

Scheme 43
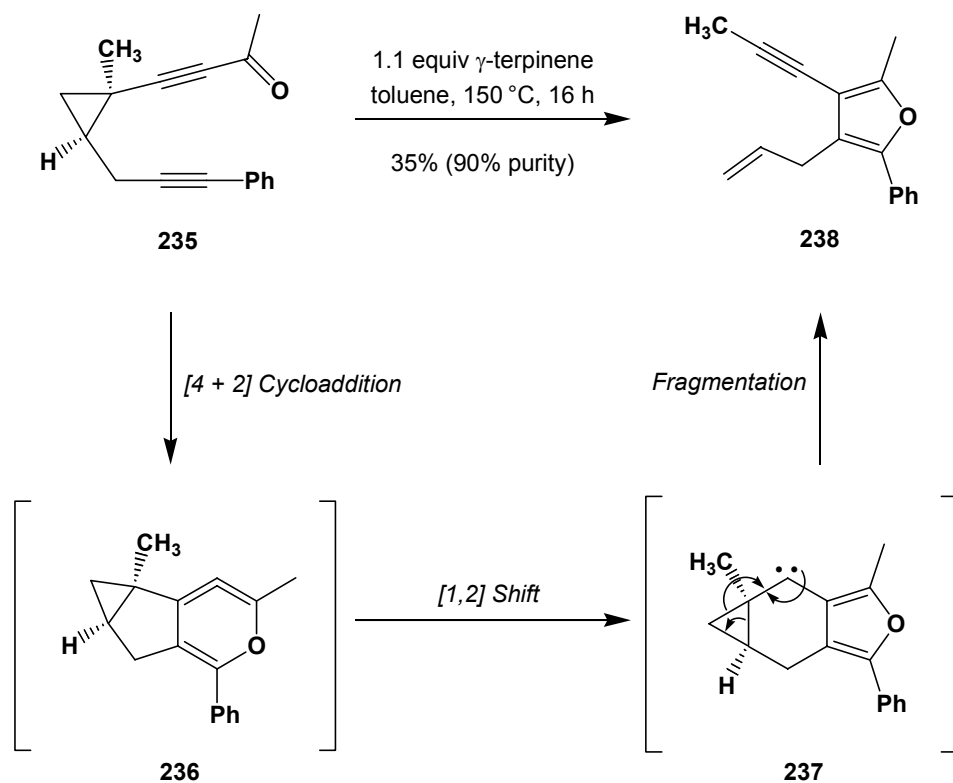
The final step in the proposed mechanism, the 1,2-C-H insertion, finds precedent in the literature of numerous carbene C-H insertion reactions.[114] Specifically, 2-furylcarbenes have been found to undergo C-H insertion reactions as well as fragmentations and cyclopropanations.[115,116] Examples of 3-furylcarbenes in the

---

[114] (a) 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. (b) For a recent review of stable carbenes, see: Bourissou, D.; Guerret, O.; Gabbaï, F. P.; Bertrand, G. *Chem. Rev.* **2000**, *100*, 39.

[115] (a) Roser, C.; Albers, R.; Sander, W. *Eur. J. Org. Chem.* **2001**, 269. (b) Khasanova, T.; Sheridan, R. S. *J. Am. Chem. Soc.* **2000**, *122*, 8585. (c) Khasanova, T.; Sheridan, R. S. *J. Am. Chem. Soc.* **1998**, *120*, 233.

literature are scarce; all instances of 3-furylcarbenes as reactive intermediates are those in which no C-H insertion pathways are available.[117] We believe that, due to the availability of a 1,2-C-H insertion pathway, the carbene intermediates generated in the heteroenyne cycloaddition undergo rapid 1,2-C-H insertions to generate the observed dihydroisobenzofuran products.

Goals for Further Studies

The initial studies by Dr. Wills established the utility of the heteroenyne cycloaddition for the preparation of a range of dihydroisobenzofurans. At the conclusion of her studies, a number of questions concerning the scope, mechanism, and synthetic utility of the reaction remained unanswered. The focus of my work, which will be discussed in Chapter 3, has been the design and execution of additional experiments with the aim of addressing the following specific concerns.

- Dr. Wills investigated substrates in which the all-carbon tethers contain no substitutents. We believed that a suitably substituted tether could enhance the reactivity of the substrate due to steric or conformational effects. Thus the construction of a substrate having a substituted carbon backbone was a top priority.

(d) Kirmse, W.; Lelgemann, R.; Friedrich, K. *Chem. Ber*. **1991**, *124*, 1853. (e) Albers, R.; Sander, W. *Liebigs Ann*. **1997**, 897. (f) Sander, W.; Albers, R.; Komnick, P.; Wandel, H. *Liebigs Ann*. **1997**, 901. (g) Hoffman, R. V.; Schecter, H. *J. Am. Chem. Soc*. **1978**, *100*, 7934. (h) Hoffman, R. V.; Schecter, H. *J. Am. Chem. Soc*. **1971**, *93*, 5940.

[116] For a recent example of a novel rearrangement of 2-pyrrolocarbenes, see: Frey, L. F.; Tillyer, R. D.; Ouellet, S. G.; Reamer, R. A.; Grabowski, E. J. J.; Reider, P. J. *J. Am. Chem. Soc*. **2000**, *122*, 1215.

[117] (a) Khasanova, T.; Sheridan, R. S. *Org. Lett*. **1999**, *1*, 1091. (b) Ref. 115d. (c) Hoffmann, R. V.; Oprhanides, G. G.; Schecter, H *J. Am. Chem. Soc*. **1978**, *100*, 7927.

- Dr. Wills explored only a single substrate that incorporates a heteroatom in the tether. The enhanced reactivity of this substrate, as well as similar results with enyne substrates incorporating a heteroatom in the tether, stimulated us to explore additional substrates of this type.

- Dr. Wills' preliminary results indicated that alkynyl aldehydes do not function as heteroenynes in the cycloaddition. However, aldehydes should function as activating groups on the "heteroenynophile," the 2π component of the cycloaddition. We planned to explore such cycloadditions to determine if aldehydes can indeed activate the heteroenynophile.

- Although Dr. Wills' single attempt to use an alkynyl aldehyde as a heteroenyne failed, we sought to reinvestigate the use of alkynyl aldehydes as heteroenynes. If indeed they could be made to function as 4π components in the cycloaddition, one could then access 2-unsubstituted furans directly via the heteroenyne cycloaddition. This would be a valuable extension of the methodology.

- Dr. Wills' single attempt to intercept the carbene intermediate in the reaction afforded the expected fragmentation product in low yield. We believed that another example of the interception of the carbene intermediate would offer additional evidence in support of our proposed mechanism. In addition, we have been interested in intercepting the carbenes intramolecularly with reactive functional groups to generate new functionality and additional ring systems.

- Dr. Wills noted that in a substrate incorporating a four-atom tether, the yield of the reaction dropped dramatically, and a successful reaction required a higher temperature. This result is consistent with the increased entropy associated with a

longer tether. We planned to examine an additional substrate with a four-atom tether to gain additional data on the entropic effects of tether length.

The next chapter will detail my studies of the cycloaddition of several additional 1-oxaenynes, which provide additional insight on the mechanism of the transformation and demonstrate the utility of the dihydroisobenzofuran products obtained from the reaction.

Chapter 3

Scope, Mechanism, and Synthetic Utility of [4 + 2] Cycloadditions of Conjugated Ynones and Related Species

As mentioned previously, the study of the cycloaddition of several selected oxaenyne substrates was the focus of my work on this project. We sought to investigate several unexplored facets of the reaction to advance our understanding of the scope and mechanism of the heteroenyne cycloaddition. In addition, we planned to demonstrate the synthetic utility of this version of the heteroenyne cycloaddition by exploiting the dihydroisobenzofuran products as synthetic intermediates in the construction of complex carbocyclic compounds.

In this chapter, the three main strategies we employed for the construction of the oxaenyne functionality will be described. Next, each new cycloaddition study will be described in detail, including the rationale for the selection of the substrate, the particulars of the synthesis of the requisite oxaenyne, the outcome of the cycloaddition, and the interpretation of the results in comparison to other heteroenyne cycloaddition reactions. In the final section, two sequences demonstrating further transformations of dihydroisobenzofuran products will be reported.
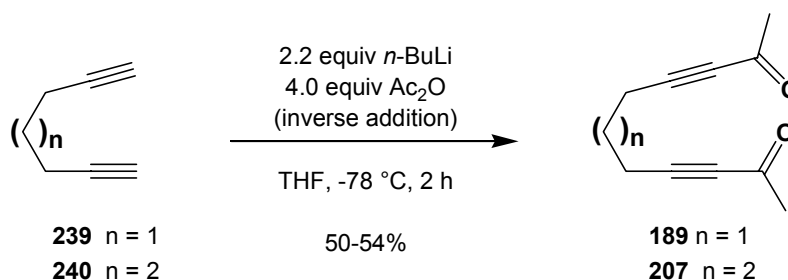
Strategies for the Synthesis of α,β-Alkynyl Carbonyl Compounds

We have employed three general strategies for the synthesis of oxaenyne cycloaddition substrates.[118] Two of these strategies were utilized by Dr. Wills for the synthesis of cycloaddition substrates involved in her studies. These approaches will be illustrated here with examples from her work. The third strategy was not employed by Dr. Wills but represents a very useful approach to heteroenyne cycloaddition substrates.

(a) Synthesis of Oxaenynes by Acylation of Acetylenes

One common and simple approach to α,β-alkynyl carbonyl compounds involves the direct installation of the carbonyl group onto a terminal acetylene. Using this approach, Dr. Wills generated a series of alkynyl methyl ketones via acylation of the lithium salt of an acetylene with acetic anhydride (Scheme 44).

Scheme 44

2.2 equiv *n*-BuLi
4.0 equiv Ac$_2$O
(inverse addition)

THF, -78 °C, 2 h

50-54%

239 n = 1
240 n = 2

189 n = 1
207 n = 2

Although this approach is straightforward and expeditious, it suffers from a few shortcomings. The modest yield typically observed in these reactions stems from

---

[118] For general procedures for a wide range of reactions involving alkynes, see: (a) Brandsma, L.; Verkruijsse, H. D. *Synthesis of Acetylenes, Allenes and Cumulenes*; Elsevier: Amsterdam, 1981. (b) Brandsma, L. *Preparative Acetylenic Chemistry*, 2nd ed.; Elsevier: Amsterdam, 1988.

incomplete acylation of the alkynes, which is due to proton transfer to the lithium acetylide from the enolizable ketone product. In addition, the potential exists for attack on the ketone product by the lithium acetylide, generating a tertiary alcohol byproduct. To minimize these side reactions, an inverse addition technique is used in which the lithium acetylide derivative is added to an excess of acetic anhydride.

In addition to acylation of lithium acetylides with acetic anhydride, there are a number of other methods for direct acylation of acetylenes.[119] One of the most popular and widely used approaches is the addition of lithium or magnesium acetylides to Weinreb amides.[120] Other common procedures include coupling of alkynylzinc reagents with acyl chlorides, pioneered by Negishi,[121] and addition of alkynylsilanes to acid chorides under Lewis acid catalysis.[122] Procedures involving boron trifluoride etherate[123] have been investigated, and recently microwave-assisted couplings of alkynes and aroyl chlorides catalyzed by copper (I) species have been reported.[124]

The direct acylation of lithium acetylides was successfully employed for the synthesis of one of the oxaenynes described later in this chapter. However, another limitation of this approach is the requirement that substrates possess no functionality reactive toward strong bases or nucleophiles. For this reason, we were forced to use alternate methods for the synthesis of other substrates.

---

[119] For a recent review on the synthesis of ketones from acyl chlorides, see: Dieter, K. R. *Tetrahedron* **1999**, *55*, 4177.

[120] Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815.

[121] Negishi, E.; Bagheri, V.; Chatterjee, S. Fen-Tair, L.; Miller, J.; Stoll, A. T. *Tetrahedron Lett.* **1983**, *24*, 5181.

[122] Birkofer, L.; Ritter, A.; Uhlenbrauck, H. *Chem. Ber.* **1963**, *96*, 3280. (b) Stang, P. J.; Ladika, M. *Synthesis* **1981**, 29.

[123] Brown, H. C.; Racherla, U. S.; Singh, S. M. *Tetrahedron Lett.* **1984**, *25*, 2411.

(b) Synthesis of Oxaenynes by Oxidation of Propargylic Alcohols

A second common approach to α,β-alkynyl ketones and aldehydes involves the oxidation of the corresponding propargylic alcohols. A number of general methods for the oxidation of propargylic alcohols are known.[125] Dr. Wills chose to employ exclusively the Dess-Martin periodinane[126] as an effective oxidizing agent for both secondary and primary propargylic alcohols. This very mild reagent was the oxidant of choice because it could be deployed in the presence of a variety of functional groups.

Propargylic alcohols are attractive as ketone precursors in the synthesis of oxaenynes for several reasons. Following installation and protection of the alcohol, a number of functional groups can be incorporated into the substrate utilizing a wide variety of reaction conditions. In many cases, these reactions would not be possible in the presence of the ketone itself.

The deprotection and oxidation steps that reveal the oxaenyne are frequently carried out under mild conditions, and therefore are often compatible with sensitive functionality elsewhere in the molecule. In many cases, the installation of the ketone via direct acylation would not be possible in the presence of this sensitive functionality.

A sequence demonstrating this approach is shown in Scheme 45. The alkyne **241** incorporating a protected alcohol can be converted to the alkynyl ester **242** in good yield. After installation of the ester, the free alcohol **243** is revealed and oxidized to afford the alkynyl ketone **218**.

[124] Wang, J.; Wei, B.; Hu, Y.; Liu, Z.; Fu, Y. *Synth. Commun.* **2001**, *31*, 3527.

[125] Ebenezer, W. J.; Wight, P. In *Comprehensive Organic Functional Group Transformations*; Pattenden, G., Ed.; Pergamon: New York, 1995; Vol. 3; p 78, 275.

[126] (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. (c) Ireland, R. E.; Liu, L. *J. Org. Chem.* **1993**, *58*, 2899. (d) Boeckman, R. K. Jr.; Shao, P.; Mullins; J. J. *Org. Synth.* **1999**, *77*, 141.

Scheme 45
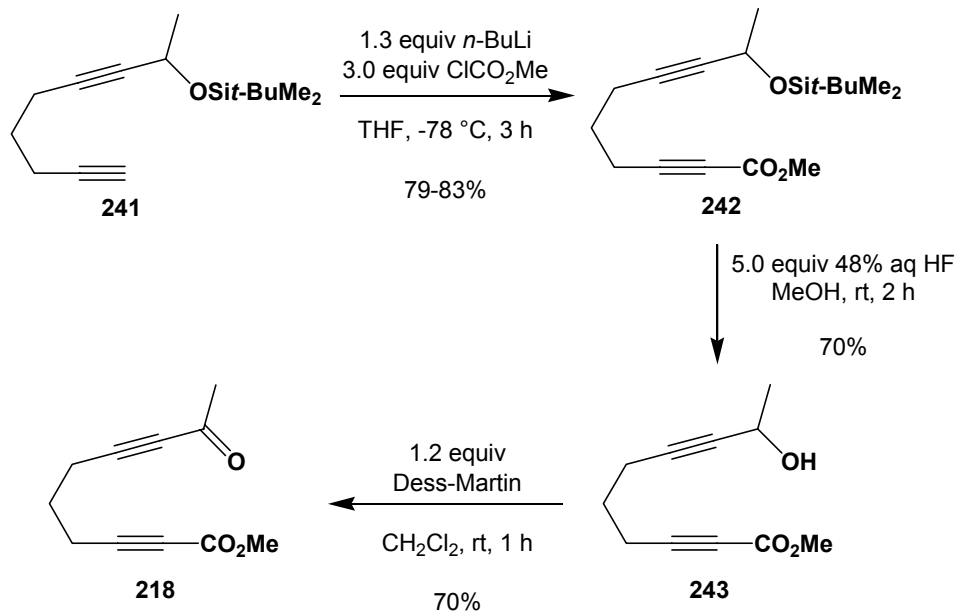
In addition, certain transformations can be carried out in the presence of the free alcohol. As shown in Scheme 46, the phenyl sulfide moiety is installed in the presence of the deprotonated alcohol to give **245** in moderate yield. Subsequent oxidation of the alcohol with the Dess-Martin reagent gives the alkynyl ketone **205**.

Scheme 46
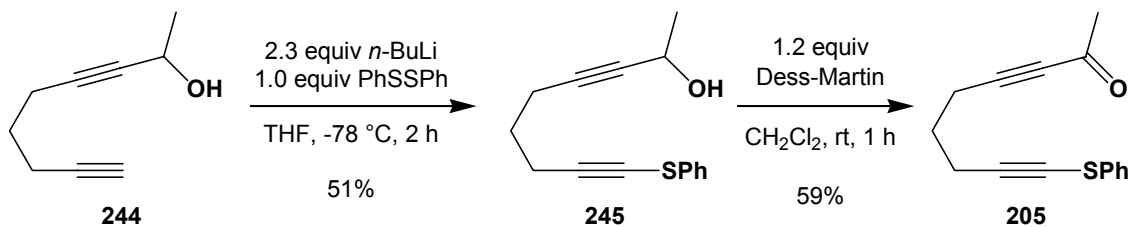
As demonstrated with these examples, the flexibility imparted by the utilization of propargylic alcohols makes this approach complementary to the direct acylation strategy

described above. We have utilized propargylic alcohols as oxaenyne precursors in the synthesis of several substrates as described later in this chapter.

(c) Synthesis of Oxaenynes by Ozonolysis of Enynes

A third strategy for the synthesis of oxaenynes involves the chemoselective ozonolysis of conjugated enynes. Derivatives of isopropenylacetylene, upon oxidative cleavage by ozone under typical ozonolysis conditions (including reductive workup), afford alkynyl ketones **247** (Scheme 47). This transformation requires that the operator stop the reaction after reaction of the alkene but before oxidation of the alkyne. Most alkenes are more reactive to ozone than alkynes,[127] and so the reaction is essentially a titration with ozone. Ozonolysis indicators allow one to visually determine the endpoint of the desired oxidation.[127]

We utilized Sudan Red (**248**, Solvent Red 23) as our indicator of choice because it is known that its reactivity toward ozone is intermediate between 1,1-dialkylalkenes and disubstituted alkynes.[128] Since the alkene reacts before Sudan Red, the reaction solution is an intense red color during ozonolysis of the alkene. After the alkene is completely consumed, the Sudan Red begins to react with the ozone. The oxidation products of the indicator are a pale purple color, so when the intense red color has disappeared, the reaction is stopped and ozone is purged from the reaction solution. The ozonide intermediates are then quenched as desired.

---

[127] Bailey, P. S. *Ozonation in Organic Chemistry*; New York: Academic Press, 1978; Vol. 1.

Scheme 47

Sudan Red (**248**)
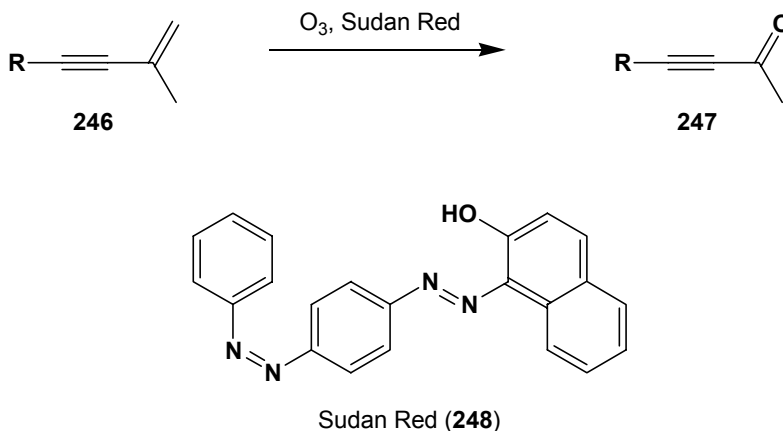
This very selective alkene oxidation method is employed in the synthesis of one substrate discussed later in this chapter.

Cycloaddition of a Heteroenyne with a Substituted Tether

Initial work by Dr. Wills centered primarily on substrates containing all-carbon tethers synthesized from commercially available 1,6-heptadiyne. These substrates contained no substituents on atoms of the tether that links the oxaenyne and oxaenynophile. However, many of our projected applications of this methodology will require complex heteroenyne substrates with substituents and/or functional groups adorning the tether that links the reacting moieties. Therefore, we were interested in examining the effect on the cycloaddition of tethers with substituents.

---

[128] Veysoglu, T.; Mitsecher, L. A.; Swayze, J. K. *Synthesis* **1980**, 807.

It is well known that the rate and efficiency of a variety of cyclization processes are significantly affected by steric and conformational effects in the tether linking the reactive functional groups.[129]

One of the first observations of the effect of substitutents on ring formation was made by Beesley, Thorpe, and Ingold in 1915.[130] Commonly referred to as the "Thorpe-Ingold effect," this effect was originally thought to be due to steric strain, and is often confused with the "reactive rotamer effect" (*vide infra*). The Thorpe-Ingold effect is a steric effect imposed on bonding angles about a particular carbon atom by the steric repulsion of attached groups. In acyclic chains, the C-C-C bond angle was estimated to be greater than a "normal" tetrahedral angle (109°28') because steric factors force the methylene groups, which are bigger than hydrogens, apart. This leads to decreased nonbonded interactions between the two methylene groups.[131] Replacing the hydrogens with bulkier substitutents should therefore decrease the C-C-C bond angle. For example, the C-C-C bond angle for malonic acid is 110°, while in dimethylmalonic acid, the angle is 106.2°. The opposite trend is seen for geminal substitutents on small rings: the C-C-C bond angle for cyclopropanedicarboxylic acid is 118.4°.[132]
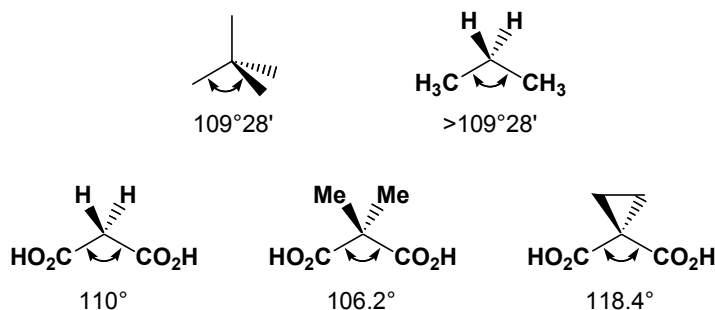
[129] For a review, see: Samnes, P. G.; Weller, D. J. *Synthesis* **1995**, 1205.
[130] Beesley, R. M.; Ingold, C. K.; Thorpe, J. F. *J. Chem. Soc.* **1915**, *105*, 1080.
[131] Ingold, C. K. *J. Chem. Soc.* **1921**, 305.
[132] Kirby, A. J.; Lloyd, G. J. *J. Chem. Soc., Perkin Trans. 2* **1976**, 1753.

Accordingly, Thorpe-Ingold effect refers specifically to the facility of ring formation due to the consequence of changing bond angles by substitution, typically called "angle compression."

The "*gem*-dialkyl effect" refers to the acceleration of a reaction due to the substitution of two alkyl groups for two geminal hydrogen atoms on one of the carbon atoms in a chain that links two reacting centers.[133,134] This effect was initially thought to be caused by angle compression, i.e., an extension of the Thorpe-Ingold effect. However, the *gem*-dialkyl effect actually is due to a combination of factors; angle compression is a small contributor,[135] but the main effect is the introduction of conformational changes into the system. These conformational effects are called the "reactive rotamer effect."

The "reactive rotamer effect," first proposed by Bruice and Pandit in 1960,[136] is based on the hypothesis that reaction rate is dependent on the concentration of the reactive conformer (rotamer) of the molecule. In order for cyclization to occur intramolecularly between atoms **X** and **Y** at the termini of a polymethylene chain, the atoms must be able to move toward one another as well as adopt a favorable stereoelectronic approach toward the transition state. This proximity condition requires rotation about the bonds of the tether from the more stable (and therefore more highly populated) *anti* conformation of the chain to the higher energy *gauche* conformation (situation *A*). The substitution of a carbon atom of the chain with one or two alkyl groups causes additional steric interactions that increase the energy of the *anti* conformation, making it comparable in energy to the *gauche* conformation, and thus allow the *gauche*

[133] Brown, R. F.; van Gulick, N. M. *J. Org. Chem.* **1956**, *21*, 1046.
[134] Kirby, A. J. *Adv. Phys. Org. Chem.* **1980**, *17*, 183.
[135] Keese, R.; Meyer, M. *Tetrahedron* **1993**, *49*, 2055.

conformation to become more highly populated (situation *B*). The increased population of the reactive (*gauche*) conformer facilitates the cyclization.[137]
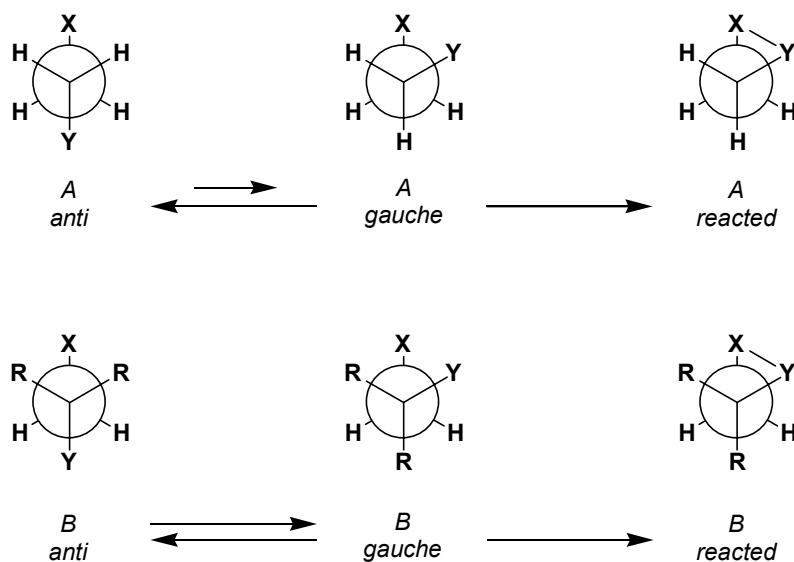
These conformational interactions cause the ground state energy of the molecule to be raised, and therefore the activation energy for the reaction becomes lower. This is often called the "facilitated transition state hypothesis."[138]

The Thorpe-Ingold effect, *gem*-dialkyl effect, and reactive rotamer effect all involve substitution of atoms in a connecting chain between two reactive centers. "Steric buttressing" is a related strategy for the steric promotion of cyclizations and intramolecular cycloadditions. This involves designed attempts at restricting the available conformational space that reacting groups can occupy in order to force them to be closer in space. The inclusion of apparently innocuous groups, typically methyl groups, into a molecule limits the freedom of the rest of the molecule to occupy that

[136] Bruice, T. C.; Pandit, U. K. *J. Am. Chem. Soc.* **1960**, *82*, 5858.
[137] (a) Jung, M. E.; Marquez, R. *Tetrahedron Lett.* **1997**, *38*, 6521. (b) Jung, M. E.; Gervay, J. *J. Am. Chem. Soc.* **1991**, *113*, 224. (c) Sternbach, D. D.; Rossana, D. M.; Onan, K. D. *Tetrahedron Lett.* **1985**, *26*, 591.
[138] Parrill, A. L.; Dolata, J. P. *Tetrahedron Lett.* **1994**, *35*, 7319.

space, and in some cases forces reacting partners to remain closer together.[139] Steric

buttressing is also the term given to the effect observed when functionality added to a

substrate distorts the ground state of the molecule to become more like the transition

state, thereby increasing the ground state energy and consequently lowering the activation

energy for reaction.[140,141]

We expected that a substrate such as **249** (Scheme 48) with substituents on the

tether would exhibit enhanced reactivity in the cycloaddition compared to the

corresponding substrate **189** lacking such substitution.

Scheme 48
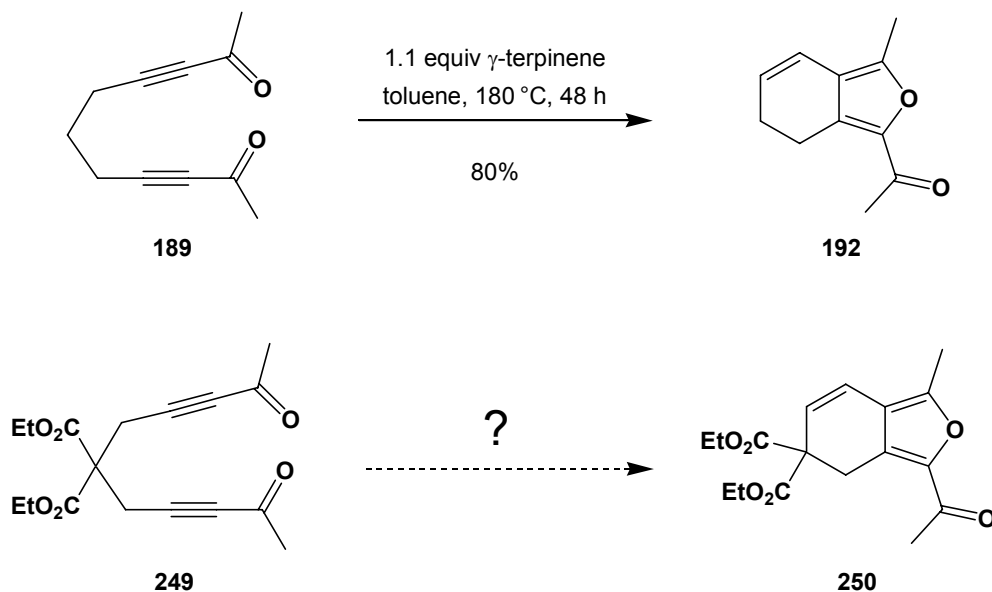
[139] Klein, L. L. *J. Org. Chem.* **1985**, *50*, 1770.
[140] Gisby, G. P.; Royall, S. E.; Sammes, P. G. *J. Chem. Soc., Perkin Trans. 1* **1982**, 169.
[141] Grigg, R.; Heaney, F.; Makandra, J.; Surendrakumar, S.; Thornton-Pett, M.; Warnock, W. J. *Tetrahedron* **1991**, *47*, 4007.

Our retrosynthetic analysis of diketone **249** suggested the use of diethyl malonate as an inexpensive and readily available starting material. We planned a double alkylation of diethyl malonate with a propargyl derivative containing a synthetic precursor to the necessary ketone functionality.

We chose the known propargylic chloride derivative **253**[142] as the alkylating agent incorporating the masked methyl ketone. The synthesis of **253** (Scheme 49) began with lithiation of propargyl chloride with *n*-butyllithium at -90 °C.[143] Low temperature is required because 3-lithiopropargyl chloride undergoes elimination to form allenylidenecarbene at higher temperatures. Addition of acetaldehyde affords the propargylic alcohol **252**, which we found to decompose when subjected to prolonged storage at 4 °C. Therefore, immediate silylation with *tert*-butyldimethylsilyl chloride was effected,[144] providing the requisite protected alcohol **253** to be used for the alkylation of diethyl malonate.

Scheme 49

---
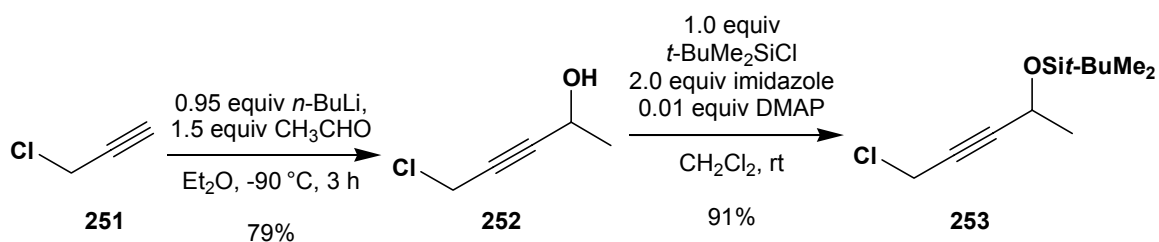
[142] Chen, C.-C.; Fan, J.-S.; Shieh, S.-J.; Lee, G.-H.; Peng, S.-M.; Wang, S.-L.; Liu, R.-S. *J. Am. Chem. Soc.* **1996**, *118*, 9279.

[143] Brandsma, L.; Verkruijsse, H. D. *Synthesis of Acetylenes, Allenes and Cumulenes*; Elsevier: Amsterdam, 1981; p 65.

[144] For a range of conditions used for the protection of alcohols as silyl ethers, see: Greene, T. W.; Wutz, P. G. M. *Protecting Groups in Organic Synthesis*, 3rd ed.; John Wiley & Sons: New York: 1999; pp 113-148.

The key alkylation reaction[145] (Scheme 50) was carried out in tetrahydrofuran with sodium hydride and a catalytic amount of sodium iodide. Although the unoptimized yield for this step was only 40%, the reaction was done on sufficient scale to provide ample material for the rest of the sequence. It was later determined that like alcohol **252**, the silyl ether **253** is also not stable to storage for prolonged periods. This leads us to believe that decomposition of **253** during the alkylation reaction is one possible cause of the low yield observed for that step. In addition, a major byproduct of the reaction is the monoalkylation product, which, if necessary, can be recycled by further alkylation with additional **253**.

Scheme 50
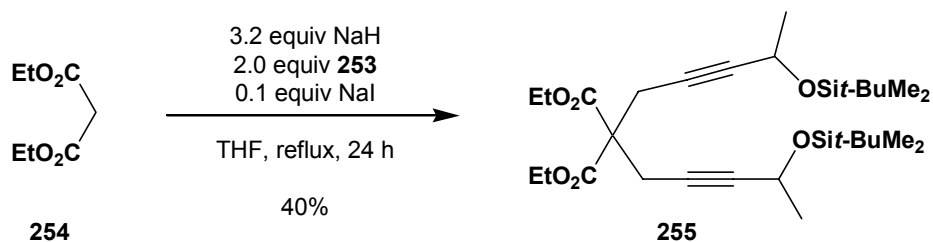
Subsequent cleavage of the silyl ethers of **255** with tetra-*n*-butylammonium fluoride in THF at 0 °C proceeded in 87% yield to provide diol **256**.[146] Oxidation of the alcohols in **256** with the Dess-Martin periodinane then gave the desired bis-alkynone **249** in 88% yield (Scheme 51).

[145] For a similar alkylation of diethyl malonate with a propargylic halide, see: Llerena, D.; Aubert, C.; Malacria, M. *Tetrahedron Lett.* **1996**, *37*, 7027.
[146] For a range of conditions used for the cleavage of silyl ethers, see: Greene, T. W.; Wutz, P. G. M. *Protecting Groups in Organic Synthesis*, 3rd ed.; John Wiley & Sons: New York: 1999; pp 113-148.

Scheme 51
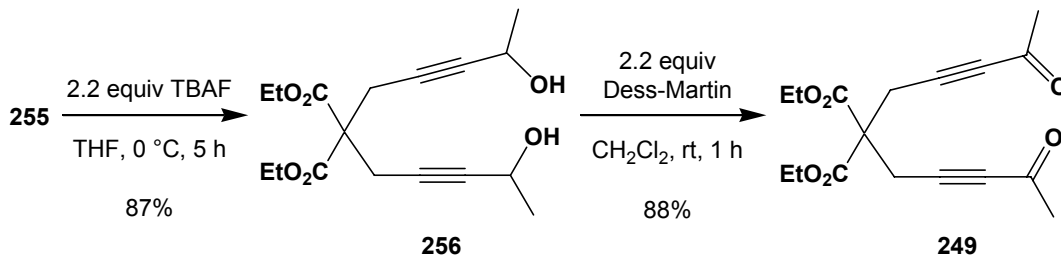
We initially thought that the cycloaddition of **249** might proceed in refluxing toluene. However, under these conditions, no cycloadduct was observed, and **249** was recovered unchanged. This was disappointing because Dr. Wills observed cycloadditions of ynones at temperatures as low as 120 °C with substrates incorporating a heteroatom in the tether (See Table 2, Entry 2 in the previous chapter). Apparently, the steric or conformational effects exerted by the *gem*-disubstituted carbon in the tether were not as great as those exerted by the substituted nitrogen. However, we were pleased to find that that the cycloaddition of **249** proceeds quite well at 180 °C in 24 h under our typical conditions to afford the dihydroisobenzofuran **250** in 89% yield. The standard reaction conditions (including the additive γ-terpinene; see Chapter 2) employed by Dr. Wills were used in order to ensure valid comparison with reactions of substrates studied previously.

Scheme 52

90
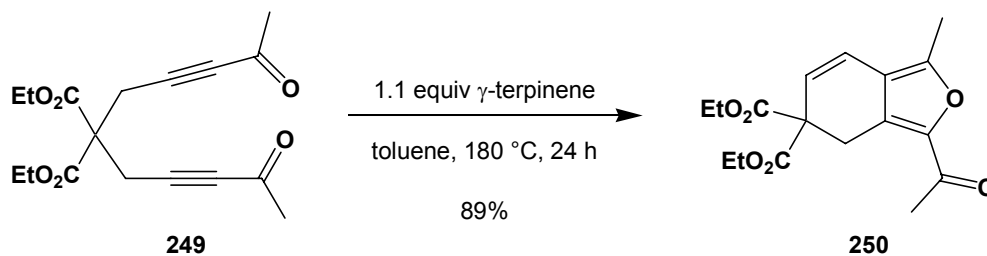
The structure for cycloadduct **250** was assigned by comparison of its spectral data to that of the earlier dihydrobenzofuran **192**. In particular, the IR stretch at 1670 cm^{-1} corresponds to the ketone carbonyl, and is consistent with the stretch at 1660 cm^{-1} associated with the ketone in compound **192**. The IR spectrum also exhibits an additional stretch at 1734 cm^{-1} corresponding to the ester carbonyls. Signals for four quaternary aromatic carbons of the furan nucleus in the ^{13}C NMR match closely those of **192**. The carbon resonance at 55.0 ppm corresponds to the central carbon of the malonate system. The molecular formula of the cycloadduct is confirmed by elemental analysis.

Comparing this cycloaddition to that of the corresponding substrate **189** which lacked substitution on atoms of the tether (Scheme 48), we observe that the reaction of **249** occurs at about twice the rate of the previous system. Therefore, we conclude that, as predicted, steric and/or conformational effects cause a notable acceleration of the reaction.

Cycloaddition of a Heteroenyne with an Aldehyde Activating the Heteroenynophile

Although Dr. Wills did not investigate the use of alkynyl aldehydes as 2π components for the heteroenyne cycloaddition, she did attempt to employ an alkynyl aldehyde as the 4π heteroenyne component in the reaction. As mentioned previously, attempts to effect this cycloaddition were not fruitful. As shown in Scheme 53, the cycloaddition of alkynyl ketone **197** proceeds in good yield at 180 °C, but the alkynyl aldehyde **221** affords only traces of cycloadduct.

Scheme 53

	1.1 equiv γ-terpinene	
	toluene, 180 °C, 48 h	

197 R = Me
221 R = H

198 R = Me   81%
222 R = H   2-10%
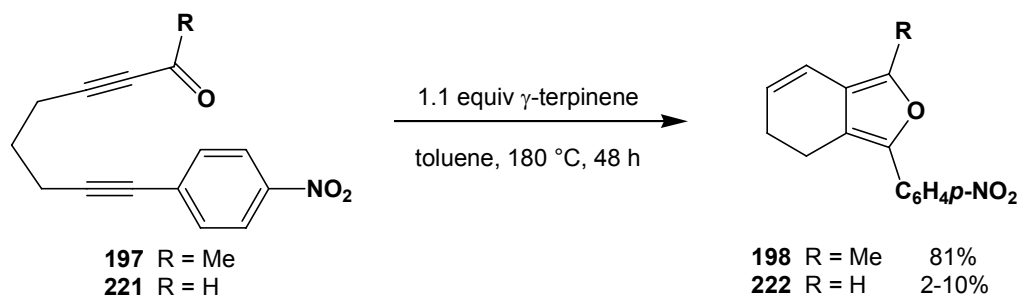
Interestingly, cycloaddition of the acylsilane **211** proceeds at 180 °C to afford the expected silylfuran, albeit in only 36% yield (Scheme 54). Since the silylfuran readily undergoes protodesilylation upon exposure to weak acid, α,β-alkynyl acylsilanes[147] can serve as aldehyde equivalents as 4π components in the heteroenyne cycloaddition.

Scheme 54

	1.1 equiv γ-terpinene	
	toluene, 180 °C, 20 h	
	36%	

211   **212**
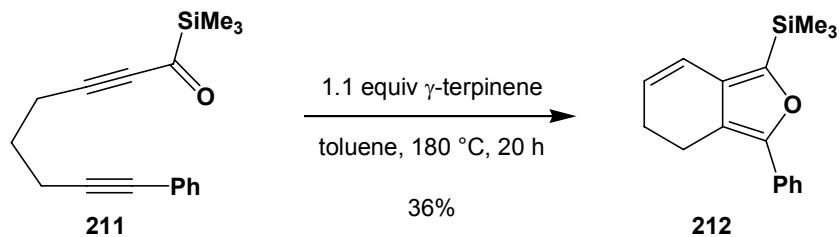
It was later determined from control experiments that acylsilanes such as **211** are not stable to the reaction conditions; Dr. Wills recovered only 48% of a model alkynyl acylsilane after heating it in toluene at 180 °C for 20 h.

In considering the reason for failure of the cycloaddition involving alkynyl aldehyde **221**, we imagined either the alkynyl aldehyde was not stable to the high

temperatures employed in the reaction and thus decomposed prior to cycloaddition, or was simply relatively unreactive as a heteroenyne. To shed some light on this question, we investigated a substrate (**257**) which incorporates an alkynyl ketone and an alkynyl aldehyde (Scheme 55). The outcome of this cycloaddition would provide valuable information with respect to the relative reactivity of alkynyl aldehydes and ketones as 4π and 2π components in the heteroenyne cycloaddition.

Scheme 55
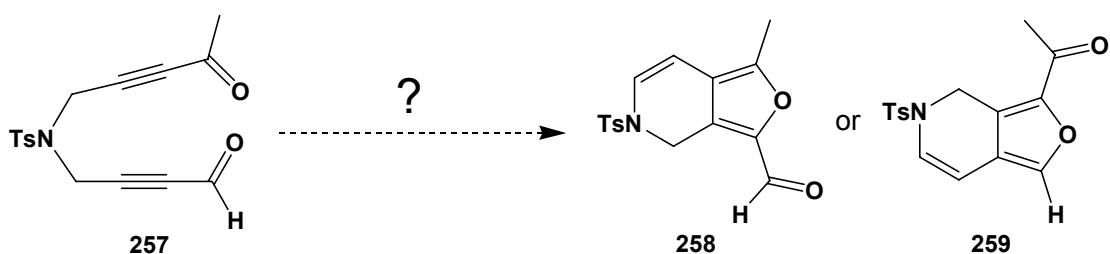
Dr. Wills had previously demonstrated that incorporation of a nitrogen atom substituted as a *p*-toluenesulfonamide allowed the cycloaddition to proceed at a much lower temperature (Scheme 56) as compared to the all-carbon system. We therefore decided to focus our attention on the keto aldehyde **257** with the expectation that cycloaddition would occur under relatively mild conditions, thus minimizing decomposition of the sensitive aldehyde functionality.

---

[147] For a recent review of synthetic approaches to acylsilanes, see: Najera, C.; Yus, M. *Org. Prep. Proced.*

Scheme 56

199 X = CH₂
209 X = NTs

1.1 equiv γ-terpinene
toluene

X = CH₂, 220 °C, 72 h
X = NTs, reflux, 16 h

200 X = CH₂   50%
210 X = NTs   64%
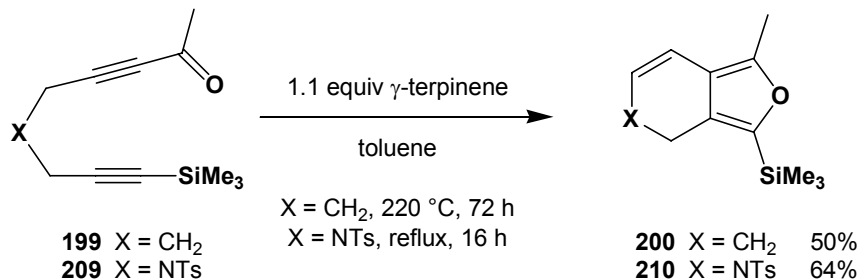
While considering synthetic strategies for keto aldehyde **257**, we discovered that *N,N*-dipropargyl-*p*-toluenesulfonamide (**261**) is a known compound,[148] and we realized that it could be used in a variety of reactions analogous to those in which Dr. Wills utilized 1,6-heptadiyne.

The ready availability of the inexpensive starting materials encouraged us to prepare **261** on a large scale. *p*-Toluenesulfonamide (**260**) is double-alkylated with propargyl chloride using potassium carbonate and a catalytic amount of sodium iodide in refluxing acetone to afford diyne **261** in 80% yield (Scheme 57). In this fashion we synthesized multigram quantities of diyne **261** in short order. The major byproduct in this reaction is the monoalkylated sulfonamide which is easily separated by column chromatography due to the large difference in polarity between it and the desired product.

Int. **1995**, *27*, 383.
[148] Oppolzer, W.; Pimm, A.; Stammen, B.; Hume, W. E. *Helv. Chim. Acta* **1997**, *80*, 623.

Scheme 57

TsNH₂ — (4.0 equiv HC≡CCH₂Cl, 0.5 equiv NaI, 6.0 equiv K₂CO₃, acetone, reflux, 72 h, 80%) → TsN

260   **261**
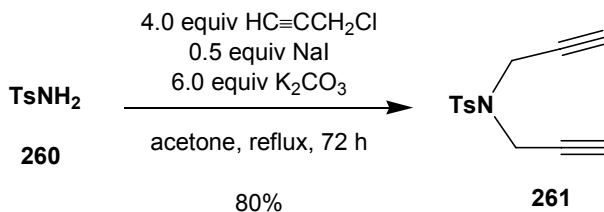
The next step in the sequence involved the functionalization of only one of the alkyne units. Such a transformation had been previously accomplished on 1,6-heptadiyne by Dr. Wills, and so we were confident this transformation was possible with **261**. As in previous cases, we expected that the difunctionalized derivative would be the major byproduct, though it should be easily separable from the desired product. In the event, treatment of the diyne **261** with 1.0 equiv of *n*-BuLi followed by excess acetaldehyde afforded the secondary propargylic alcohol **262** in 70% yield (Scheme 58). Without protecting the alcohol, we functionalized the remaining terminal alkyne in **262** by treatment with 2.3 equiv of *n*-BuLi followed by excess paraformaldehyde, which afforded diol **263** in a modest 31% yield. We were not concerned about competing reaction at oxygen, because the acetal that would be formed should be easily hydrolyzed during an acidic workup. This two-step sequence thus provided the unsymmetrical diol **263** in an expeditious manner without the use of protecting groups.

The remaining transformation for the synthesis of the cycloaddition substrate **257** involved the oxidation of the diol **263**. The Dess-Martin reagent was again quite effective, providing the keto aldehyde **257** in 94% yield.

Scheme 58
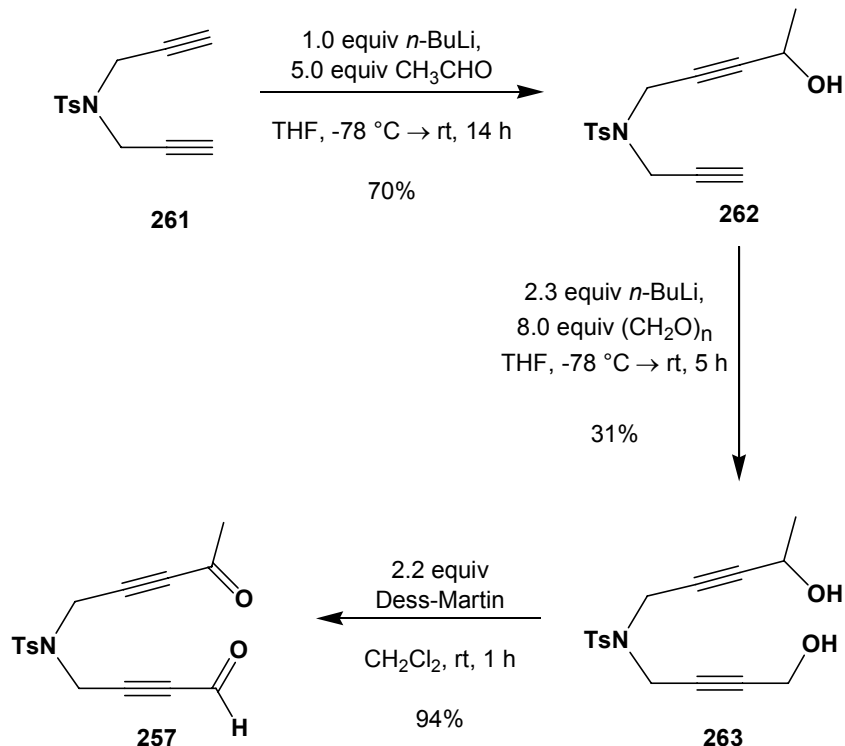
Our prediction for the temperature requirements for the cycloaddition of **257** was based the successful cycloaddition at 111 ℃ of a related substrate with a nitrogen atom in the tether (**209**, Scheme 56), explored by Dr. Wills.

We expected that **257** would undergo cycloaddition at a temperature somewhat lower than 111 ℃ since **257** contains an electron-withdrawing formyl group attached to the heteroenynophile triple bond. Because a primary concern was the decomposition of the alkynyl aldehyde at high reaction temperatures, we elected to run the cycloaddition reaction at 85 ℃. This also allowed more convenient monitoring of the reaction by thin layer chromatography than with sealed tube reactions, and permitted us to raise the temperature to 111 °C if the cycloaddition was sluggish. We were pleased to find that

thermolysis of **257** for 24 hours at 85 ºC afforded an off-white solid in 68% yield (Scheme 59).

The ^{1}H NMR analysis of the crude solid obtained from the reaction revealed that, as predicted, the aldehyde functioned effectively as the activating group on the heteroenynophile to produce the expected cycloadduct **258**. However, a signal at 7.17 ppm, characteristic of a proton attached at the 2-position of a furan, was also observed in the ^{1}H NMR spectrum of the crude product. The infrared spectrum of the reaction product, which displayed a ketone carbonyl stretch at 1646 cm^{-1} and an aldehyde stretch at 1673 cm^{-1}, confirmed our suspicion that the alkynyl aldehyde did indeed react as a heteroenyne to give a small amount of the cycloadduct **259** (Scheme 59). The ratio of the **258** to **259** was determined to be 87:13 based on integration of ^{1}H NMR signals.

Scheme 59
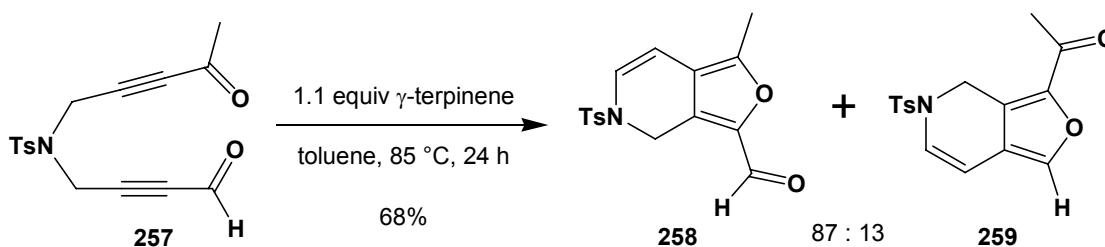
Cycloaddition of an Alkynyl Aldehyde as the Heteroenyne

The demonstration of the feasibility of employing alkynyl aldehydes as 4π components in the heteroenyne cycloaddition was an important extension to the methodology. Three naturally-occurring and biologically active furans containing a

2-unsubstituted, 3,4-fused furan in their skeleton are shown below. Xestoquinone[149] and halenaquinone,[150] isolated from marine sponges, are inotropic agents and protein tyrosine kinase inhibitors. Viridin[151] is a steroidal antibiotic and exhibits anti-fungal activity.

Xestoquinone (264)   *Halenaquinone* (265)   *Viridin* (266)
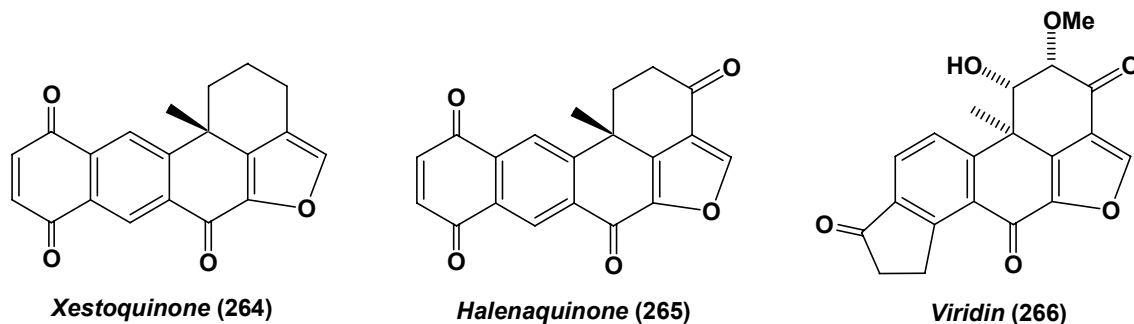
Our strategies targeting these natural products had initially required the use of acylsilanes as aldehyde equivalents in the heteroenyne cycloaddition. The discovery that alkynyl aldehydes can function as oxaenynes allowed us to simplify our synthetic strategies targeting these natural products. For example, the alkynyl aldehyde **267** would be expected to afford furan **268**, containing all of the carbon atoms of the xestoquinone skeleton (Scheme 60).

Scheme 60

267   268
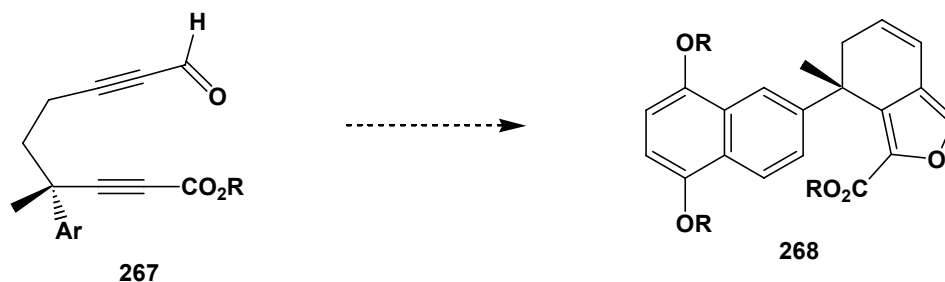
[149] Nakamura, H.; Kobayashi, J.; Kobayashi, M.; Ohizuma, Y.; Hirata, Y. *Chem. Lett.* **1985**, 713.
[150] Scheuer, P. J.; Roll, D. M.; Matsumoto, G. K.; Clardy, J. *J. Am. Chem. Soc.* **1983**, *105*, 6177.
[151] For a review, see: Hanson, J. R. *Nat. Prod. Rep.* **1995**, 381.

Having established that alkynyl aldehydes can function as 4π components in the heteroenyne cycloaddition, we desired to explore this chemistry further to gain additional insight into the reaction of these systems. Alkynyl aldehyde **269** would be expected to undergo cycloaddition with one of the alkynyl aldehydes necessarily participating as a heteroenyne (Scheme 61).

Scheme 61
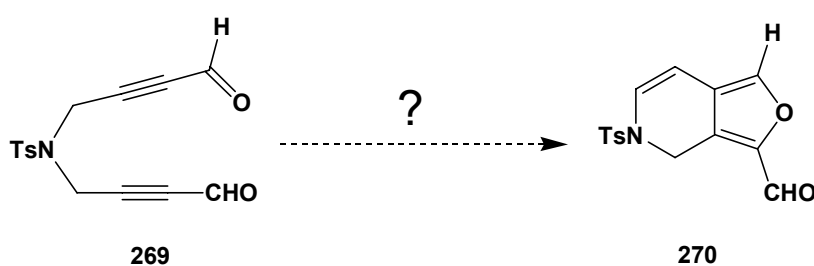
The requisite cycloaddition substrate **269** was easily synthesized in two steps from the previously prepared dipropargylsulfonamide **261**. Reaction of diyne **261** with 2.5 equiv of *n*-BuLi followed by quenching with excess paraformaldehyde afforded the symmetrical diol **271**. As in the synthesis of our previous aldehyde substrate, oxidation with the Dess-Martin reagent proceeded quite efficiently, providing **269** in 94% yield (Scheme 62).

Scheme 62
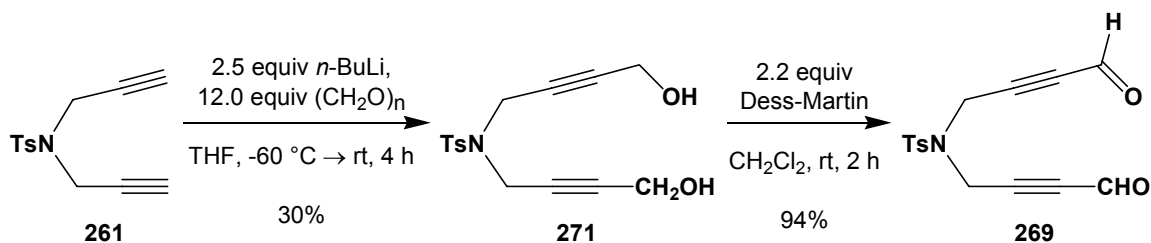
An alternative route to diol **271** was also developed in which alkylation of *p*-toluenesulfonamide with the known[143] propargylic chloride derivative 4-chlorobut-2-yn-1-ol (ClCH$_2$C≡CCH$_2$OH) provided **271** in 72% yield.

Our experience with the successful cycloaddition of **257** at 85 °C encouraged us to explore a lower temperature for the cycloaddition of **269**. As before, the use of toluene as solvent permitted us to raise the temperature as high as 111 °C if necessary. We were ecstatic to find that cycloaddition of **269** proceeded smoothly in 24 h at 70 °C to afford a single product in 52% yield (Scheme 63). A later cycloaddition of this same substrate was conducted at 111 °C for 24 h and afforded the same product in 75% yield.

Scheme 63
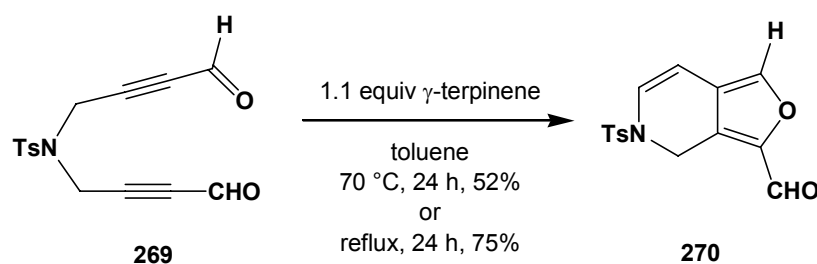
The spectral data for **270** was very similar to that of the closely-related furan **258** (Scheme 59) which differs by a methyl group. The characteristic carbonyl stretch in the infrared spectrum appears at 1681 cm^{-1} for **270** (1673 cm^{-1} for **258**), and the characteristic singlet in the ^{1}H NMR spectrum for the furan proton appears at 7.22 ppm for **270** (7.17 ppm for **258**). Elemental analysis is consistent with the structure assigned to compound **270**.

Heteroenyne Cycloaddition with Further Transformation of the Carbene Intermediate

One aspect of the heteroenyne cycloaddition we wished to investigate further was the proposed intermediacy of a carbene in the mechanism of the reaction. As discussed in Chapter 2, Dr. Wills' attempts at intermolecular trapping of this intermediate failed, and her only success at demonstrating the participation of carbene species in the reaction involved the tandem cycloaddition-rearrangement-fragmentation process outlined in Scheme 64 (see also Chapter 2, Scheme 43). We believed that another example of the interception of the carbene intermediate would offer further evidence in support of our proposed mechanism.

Scheme 64
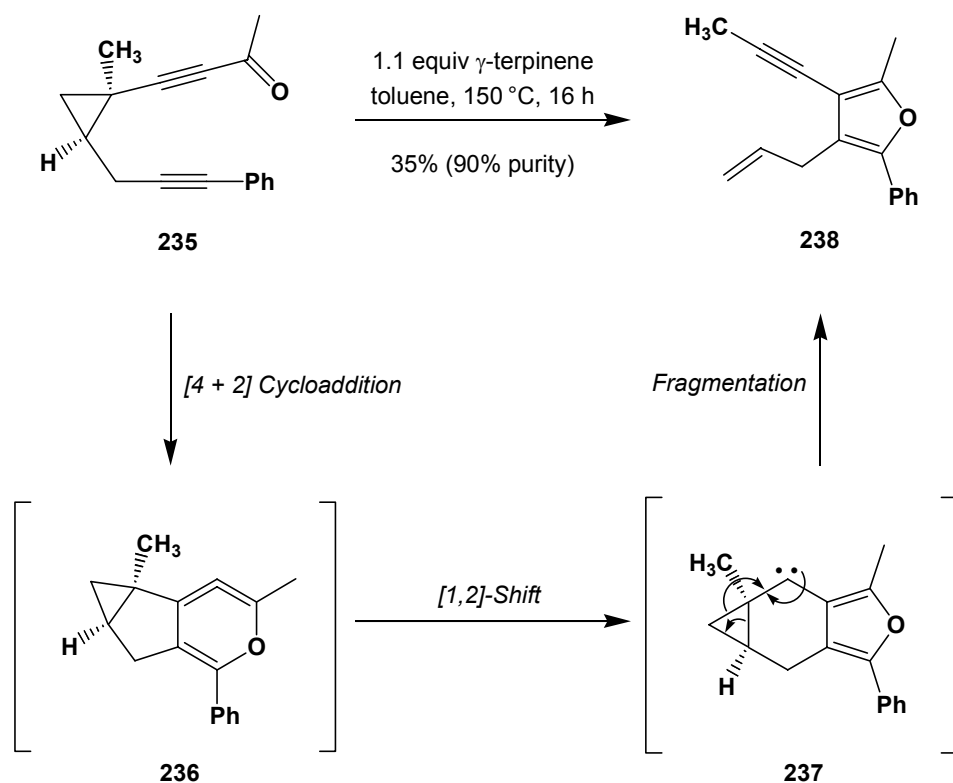
More importantly, we wanted to develop variants of the heteroenyne cycloaddition that would provide access to compounds with additional useful functionality on the new six-membered ring. Specifically, we have been interested in intercepting the carbenes intramolecularly with reactive functional groups to generate new functionality and additional ring systems.

We selected dithiane **272** as the next cycloaddition substrate for our investigation of the feasibility of intercepting the carbene intermediate prior to 1,2-C-H insertion. In addition to the interesting mechanistic insights the cycloaddition of **272** might provide, it would also serve as an example of the exploitation of the carbene intermediate.

According to our proposed cycloaddition mechanism, the cycloaddition and rearrangement of oxaenyne **272** should provide carbene **273** (Scheme 65). It is known that sulfur ylides are readily formed by the reaction of nucleophilic sulfides with carbenes.[152,153] Consequently, we expected that in **273**, the neighboring sulfur atom should add to the carbene to form the sulfonium ylide **274**. We anticipated that this zwitterion would undergo β-elimination to form dithiepine **275**, relieving ring strain and neutralizing the separation of charge.

[152] Jones, W. M. Rearrangements of Carbenes and Nitrenes. In *Rearrangements in Ground and Excited States*, de Mayo, P., Ed.; Academic Press: New York, 1980; Vol. 1, pp 95-160.
[153] For a recent review on the reactions of heteroatoms with carbenes, see: Padwa, A.; Hornbuckle, S. F. *Chem. Rev.* **1991**, *91*, 263.

Scheme 65

272   ?   **275**
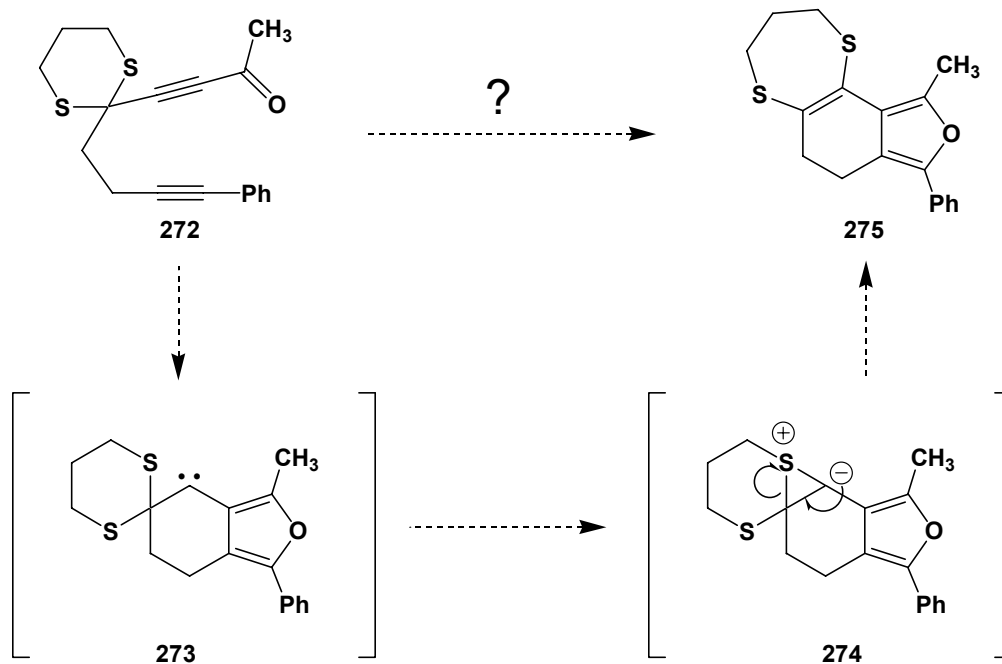
273   **274**

Precedent for our proposed intramolecular capture of the carbene (**273**→**274**) can be found in recent work by Kim and Cho (Scheme 66).[154] The thermolysis of *N*-aziridinylimine **276** forms the 1,4-dithiepine **278**, presumably via the carbene **277**.

Scheme 66

276   toluene, reflux, 12 h   88%   **277**   **278**

---
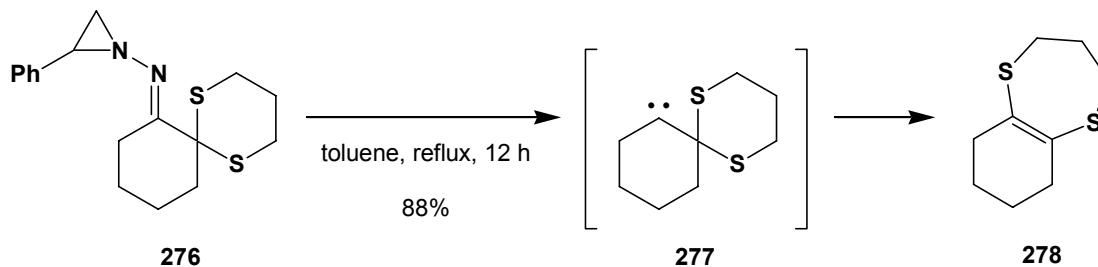
[154] Kim, S.; Cho, C. M. *Heterocycles* **1994**, *38*, 1971.

As discussed earlier, substituents effects are important in facilitating cyclization processes. The incorporation of a disubstituted carbon in the tether of this substrate could provide further insight into the steric and conformational effects of substituents on the cycloaddition. The effect of positioning the thioketal on a carbon other than the central atom of the tether might also be revealing.

Our retrosynthetic analysis of alkynyl ketone **272** suggested the use of the known alkynyldithiane **281**[155] as a key building block. Oxidation of commercially available 3-trimethylsilylpropargyl alcohol (**279**) provides the unstable propiolic aldehyde **280**, which is not purified but immediately subjected to thioketalization with propanedithiol and catalytic *p*-toluenesulfonic acid (Scheme 67). The alkynyldithiane **281** is a stable solid which according to the literature can be purified via column chromatography. However, in our hands chromatography provided a yellow oil of inferior purity. Our preferred method for purification of this compound involves sublimation, which affords pure **281** as a yellow solid, mp 47.0-48.0 °C.

Scheme 67

---
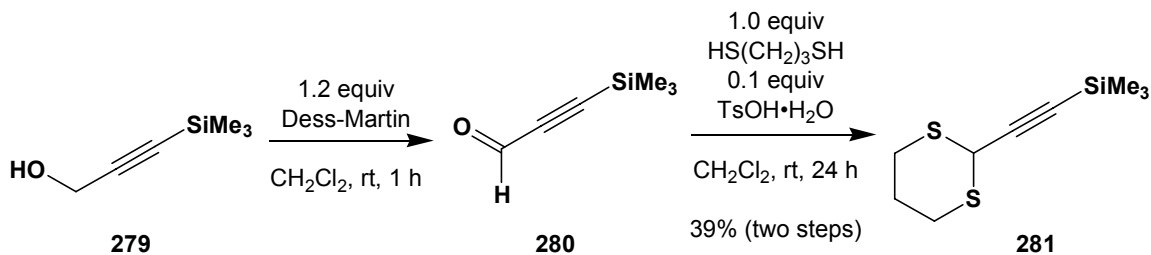
[155] (a) Andersen, N. H.; Denniston, A. D.; McCrae, D. A. *J. Org. Chem.* **1982**, *47*, 1145. (b) Johnson, W. S.; Frei, B.; Gopalan, A. S. *J. Org. Chem.* **1981**, *46*, 1512.

Our plan for the synthesis of the cycloaddition substrate next called for alkylation of dithiane **281** with the homopropargyl iodide **284**. This known compound[156] was prepared in excellent yield by a two-step sequence beginning with butynol, involving installation of the phenyl ring on the alkyne and conversion of the alcohol to the iodide. The Sonogashira coupling of iodobenzene with 3-butyn-1-ol according to the procedure of Linstrumelle[157] provided **283** in 99% yield. Conversion of alcohol **283** to the iodide was effected with Ph₃P and I₂ to give **284** in 76% yield (Scheme 68).[156]

Scheme 68
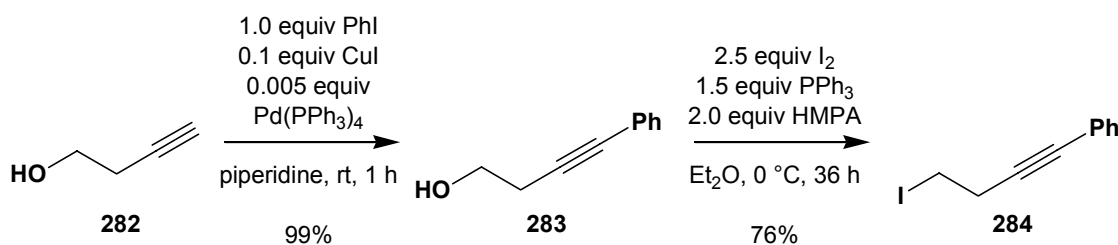
Lithiation of the dithiane **281** and alkylation of the lithiodithiane with the iodide **284** was expected to produce the dithiane **285**. Because homopropargyl halides often undergo elimination to form enynes, we were concerned about competing elimination in this alkylation reaction. Our fears were unfounded, however: in the event, alkylation of **281** afforded diyne **285** in 99% yield (Scheme 69).

[156] Molander, G. A.; Retsch, W. H. *J. Org. Chem.* **1998**, *63*, 5507.
[157] Alami, M.; Ferri, F.; Linstrumelle, G. *Tetrahedron Lett.* **1993**, *34*, 6403.

Scheme 69
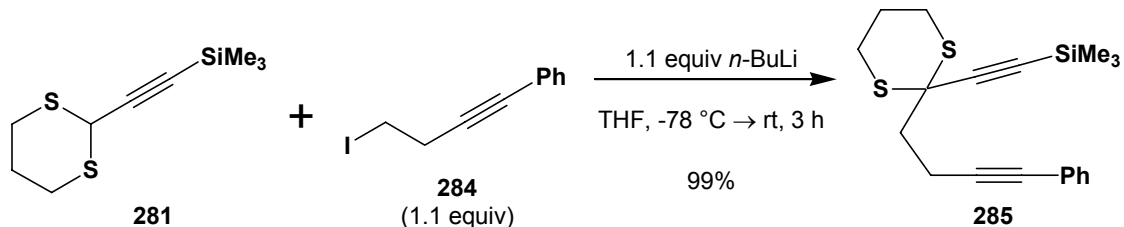
Scheme 70 outlines the remaining steps in our synthesis. The desilylation of **285** and subsequent acylation of **286** would give the oxaenyne **272**. The removal of the trimethylsilyl group was cleanly accomplished with catalytic potassium carbonate in methanol to afford terminal acetylene **286** in 85% yield. The acylation of **286** with *n*-butyllithium and acetic anhydride proceeded to give ketone **272** in 36% yield.

Scheme 70
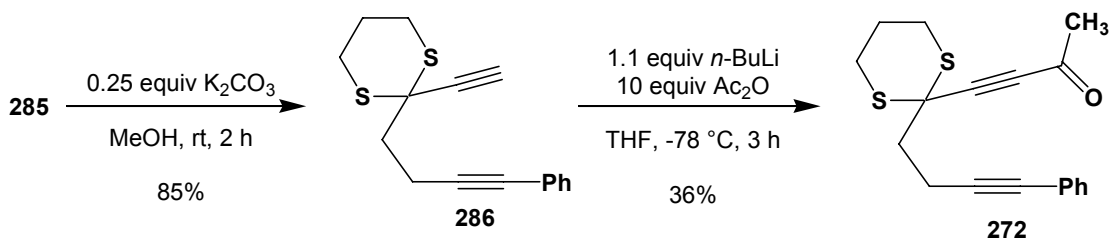
With the alkynyl ketone **272** in hand, we were ready to attempt the cycloaddition. As in previous cases, we had little experience to suggest what temperature would be required for the successful cycloaddition of this heteroenyne. Hoping that the thioketal would exert some steric or conformational effects on the substrate and thus lower the activation energy required for cycloaddition, we initially attempted the reaction at

111 °C. We were pleased to find that under these conditions the cycloaddition proceeded

in 24 h to afford a single product in 59% yield (Scheme 71).

Scheme 71
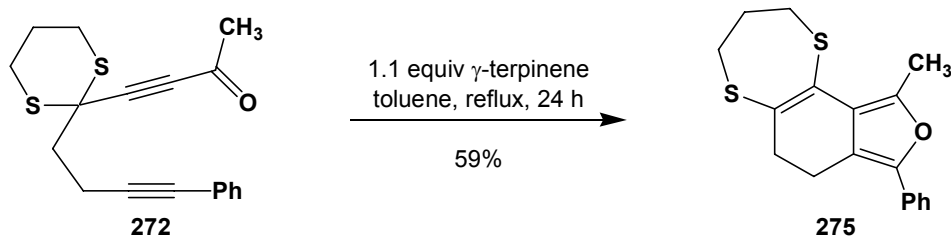
The molecular formula of the product was established by elemental analysis.

Identification of this compound as the expected 1,4-dithiepine **275** was confirmed by

comparison of its spectral data to other dihydroisobenzofurans and dithiepines.   In

particular, the C=C stretch at 1544 cm^{-1} in the infrared spectrum of **275** matches that of

known dithiepines.[158] The two alkenyl carbons and nine aromatic carbons are consistent

with the spectral data for the phenyl-substituted dihydrosiobenzofuran motif present in

cycloadducts synthesized by Dr. Wills (see Chapter 2, Table 1). As determined from the

DEPT spectrum, the presence of one methyl and five methylene carbons, as well as the

three resonances resulting from the methine carbons of the phenyl ring, supports the

structure of tricyclic compound **275**.

---

[158] Afonso, C. A. M.; Barros, M T.; Maycock, C. D. *Tetrahedron* **1999**, *55*, 801.

Cycloaddition of a Heteroenyne with a Tether Containing an Aromatic Ring

As mentioned previously, one of the limitations of the heteroenyne cycloaddition we hoped to address in the current study was the low yields observed with substrates incorporating tethers consisting of four carbon atoms. As shown in Scheme 72, the cycloaddition of **189** proceeds at 180 °C and affords **192** in 80% yield, but the cycloaddition of **207** requires 220 °C and affords the cycloadduct **208** in only 20% yield.

Scheme 72
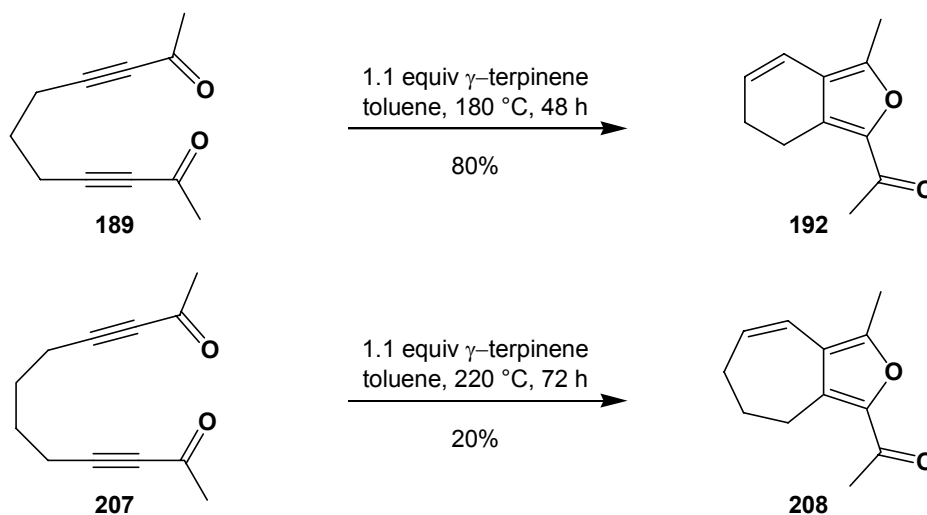
We decided to next focus our attention on the diketone **286**, which we expected would provide the cycloadduct **287** according to our proposed mechanism. In addition to demonstrating whether a benzo-fused system could be generated by our reaction, the cycloaddition of this substrate was predicted to occur at a lower temperature than that required for **207** due to the incorporation of a tether which contains two geometrically-constrained sp^2-hybridized carbons in an aromatic ring (Scheme 73).

Scheme 73

286   **287**
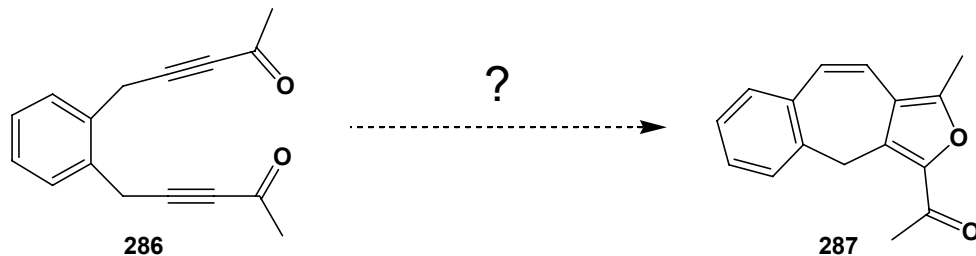
The synthesis of heteroenyne **286** was not as straightforward as we had hoped.

Initially, we envisioned a short three-step sequence (Scheme 74) exploiting the symmetry

of the starting material to effect two transformations in each step. Beginning with

α,α'-dibromo-*o*-xylene (**288**), we envisaged S_N2 displacement of the benzylic bromide by

trimethylsilylacetylide, to afford **289**. Subsequent removal of the trimethylsilyl groups

would provide **290**, and acylation with acetic anhydride would furnish the desired

diketone **286**.

Scheme 74

288   **289** R = SiMe₃   **286**

290 R = H
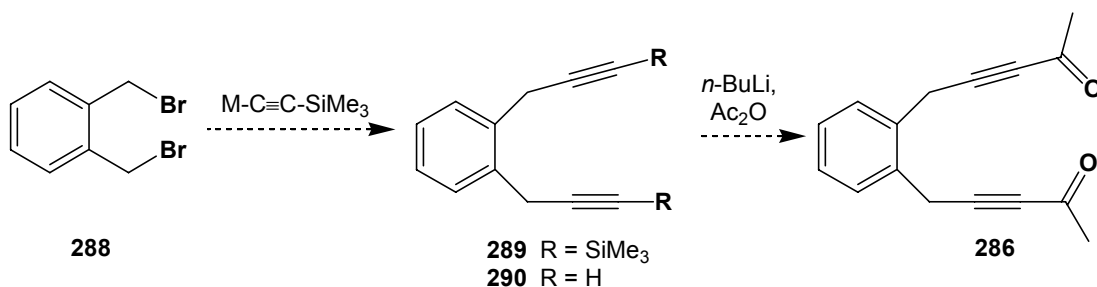
A variety of conditions were explored for the conversion of **288** to **289**. Initial

attempts with lithium acetylides failed, and led to recovered starting material. Likewise,

the use of acetylenic Grignard reagents also failed to provide the desired compounds.

Finally, use of a copper acetylide,[159] prepared from the corresponding Grignard and CuBr•SMe$_2$, gave the desired diyne **289** in 88% isolated yield with no chromatography necessary (Scheme 75). Although diyne **290** is a known compound,[160] previous reports of its synthesis did not involve desilylation of **289**. Numerous attempts to desilylate **289** proved fruitless.

Scheme 75
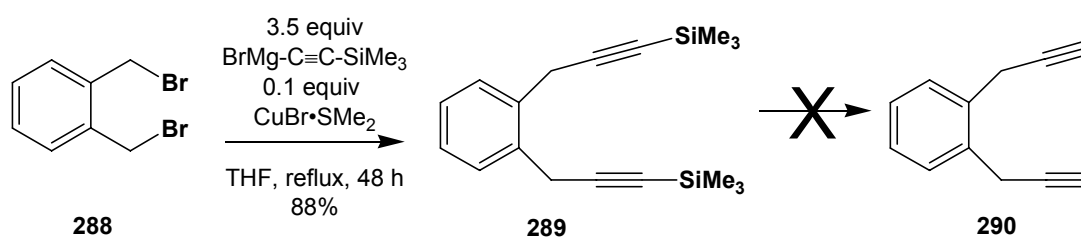
One can imagine a few reasons for the failure of this desilylation. Diyne **289** is a "skipped arenyne,"[161] a class of acetylenes prone to undergo isomerization to allenes. This "prototropic propargylic rearrangement" is typically a base-catalyzed process in which a propargylic proton is transferred from the propargylic carbon to the distal alkyne carbon.[162] Typical conditions to effect the rearrangement involve the use of bases such as alkali metal amides, alkylmetals, potassium *tert*-butoxide, or sodium dimsyl. In some cases, acids have also been found to catalyze the rearrangement. Typical conditions for the reaction involve aliphatic or alcoholic solvents and temperatures from 25 to 200 °C.

[159] Rossi, R.; Carpita, A.; Lippolis, V.; Benetti, M. *Gazz. Chim. Ital.* **1990**, *120*, 783.
[160] (a) Müller, P.; Rodriguez, D. *Helv. Chim. Acta* **1983**, *66*, 2540. (b) Bowes, C. M.; Montecalvo, D. F.; Sondheimer, F. *Tetrahedron Lett.* **1973**, *34*, 3181.
[161] For recent investigations of skipped enynes, see: Gleiter, R.; Merger, R. Nuber, B. *J. Am. Chem. Soc.* **1992**, *114*, 8921 and references cited therein.
[162] Wotiz, J. H. Propargylic Rearrangements. In *Chemistry of Acetylenes*. Viehe, H. G., Ed.; Marcel Dekker: New York, 1969; pp 365-424.

Certain substrates, especially skipped enynes and dienes, undergo particularly facile rearrangements under mild conditions such as contact with basic alumina or triethylamine.

Examples of this type of propargylic rearrangement taking place under purely thermal conditions are relatively rare in the literature.[163] The thermal rearrangement is thought to be a unimolecular process. One proposal involves a 1,3-H shift, but a more likely scenario is a two-step process involving the intermediacy of a cyclopropene. It has been observed that cyclopropenes can rearrange at temperatures of 220 °C to afford propyne and a small amount of allene.

The product resulting from propargylic rearrangement of diyne **290** is *o*-bis(allenyl)benzene, which has been reported in the literature as an unstable oil.[160b] It is quite likely that if isomerization occurred to form the bis-allene, facile side reactions could destroy the compound.

Attempts at desilylation using basic reagents such as tetra-*n*-butylammonium fluoride, potassium carbonate in methanol, and potassium fluoride all failed, although no isomerization products could be isolated due to decomposition of the substrate. In an attempt to avoid basic reagents, we investigated the use of HF, but reactions of **289** with this reagent also failed to provide **290**. Desilylation methods involving silver nitrate and potassium cyanide also decomposed the material. In addition to the literature reports, we later obtained experimental evidence to indicate that compounds similar to **290** are not very stable. We believe conditions that effect desilylation of silylalkyne **289** probably cause decomposition of diyne **290**.

Consideration of different approaches led us to design a sequence in which a four-carbon alkynone precursor would be installed in one reaction, thus avoiding the need for preparation and isolation of the unstable diyne **290**. The known TBDMS ether derivative of 1-butyn-3-ol (**291**) was prepared in 83% yield according to the literature procedure.[164] Reaction of dibromide **288** with the Grignard reagent derived from **291** under our optimized conditions afforded diyne **292** in 73% yield (Scheme 76). We also noted that some decomposition of **292** occurred upon storage at 4 °C.

Scheme 76
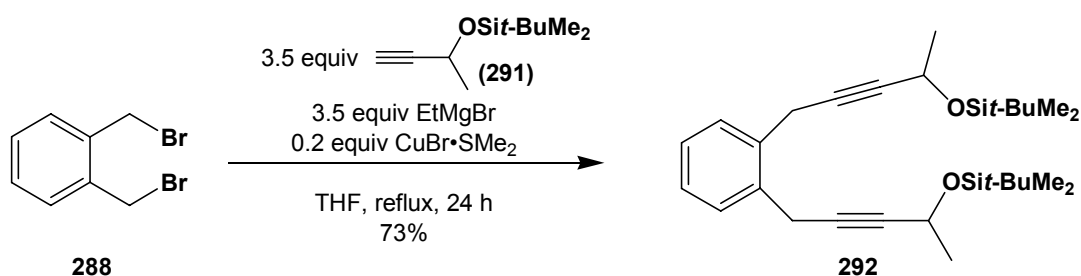
Although this route was promising, we decided to focus on an even shorter route to **286** involving isopropenylacetylene as the alkynone precursor. The Grignard reagent derived from isopropenylacetylene was smoothly alkylated with **288** to provide the bis-enyne **293** in 59% yield (Scheme 77). As observed with the related compound **292**, storage of **293** results in slow decomposition. Ozonolysis[128] with Sudan Red indicator as described earlier provided the diketone **286** in 67% yield.

[163] Huntsman, W. D. Rearrangements Involving Allenes. In *The Chemistry of Ketenes, Allenes, and Related Compounds*. Patai, S., Ed.; John Wiley and Sons: New York, 1980; pp 521-667.
[164] Cotterill, A. S.; Gill, M.; Gimenez, A.; Milanovic, N. M. *J. Chem. Soc., Perkin Trans. 1* **1994**, 3269.

Scheme 77
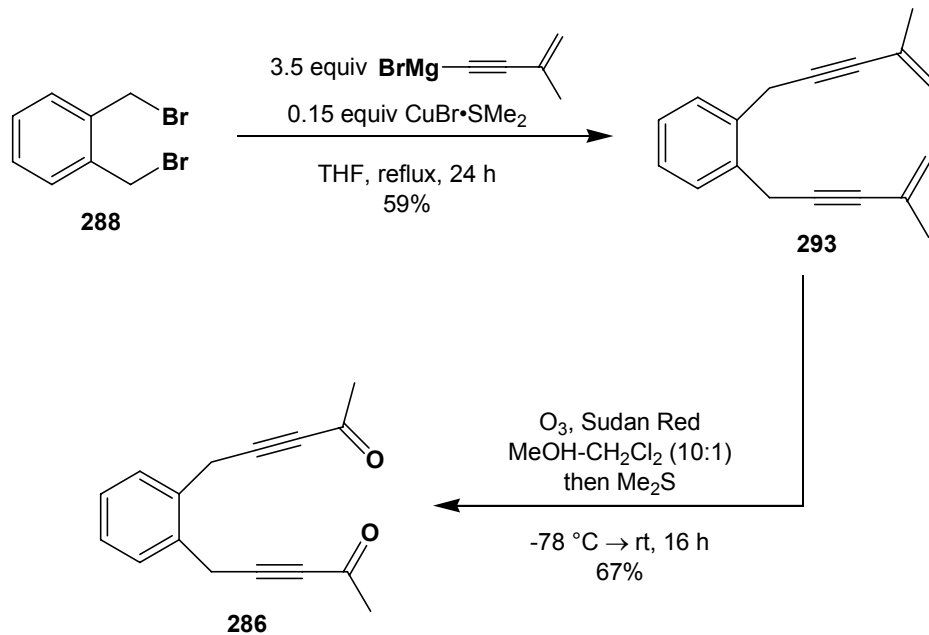
Cycloaddition of this heteroenyne was first attempted in refluxing toluene but the reaction proceeded very slowly. At 150 °C, the substrate was fully consumed in 48 h, and provided a mixture of two products (Scheme 78). The expected tricyclic furan **287** was isolated in only 20% yield, while the major product, isolated in 60% yield, was identified as the benzoisochromene **294**.
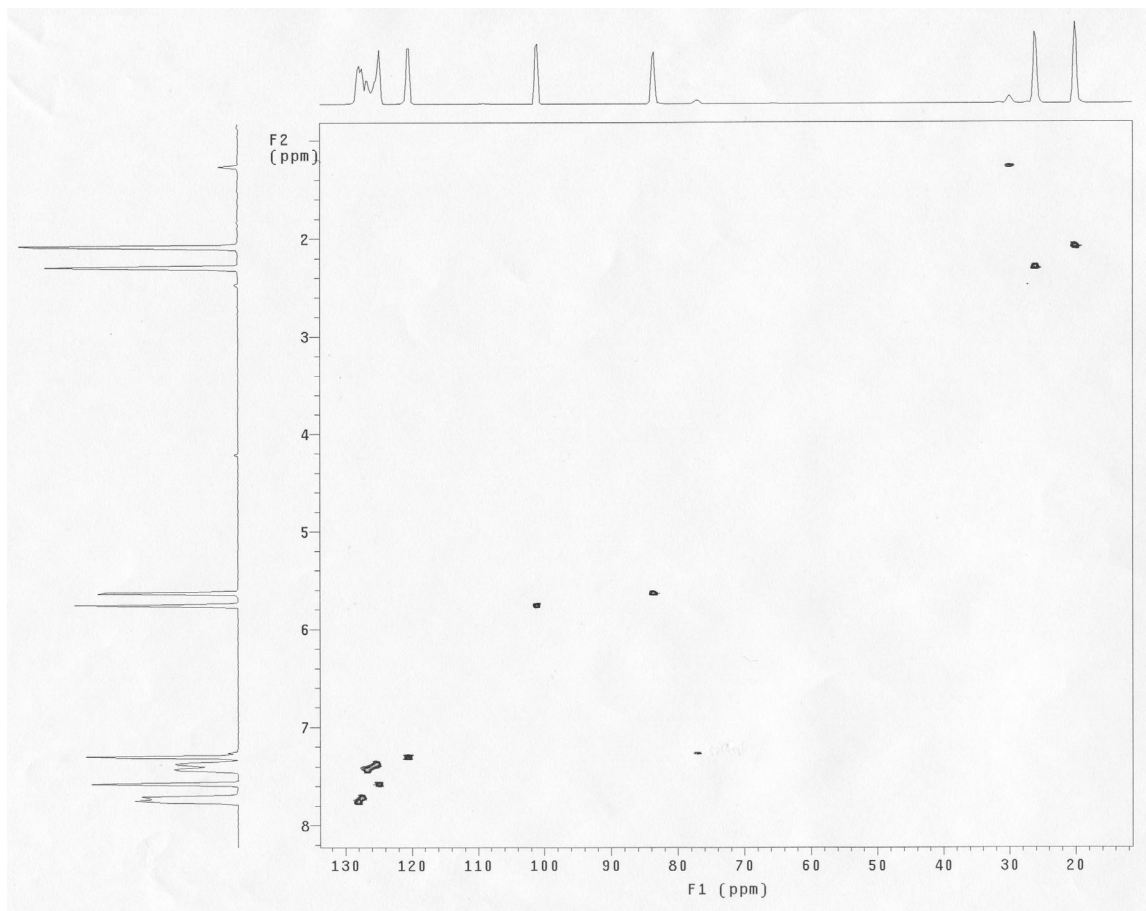
Scheme 78
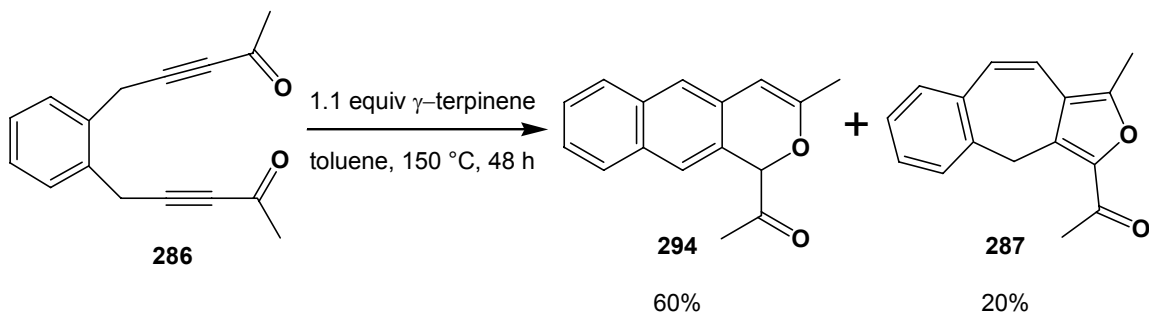
The structure of the furan **287** isolated from the reaction was confirmed by comparison of its NMR and IR spectra to those of furans generated from other oxaenyne cycloadditions. In particular, the two alkene carbons and the methylene carbon provided diagnostic signals in the ^{13}C NMR spectrum, and the coupled vinyl protons appeared where expected in the ^{1}H NMR spectrum at 6.77 and 6.60 ppm.

The structure determination for compound **294** was much more complicated. The infrared spectrum of compound **294** displays a carbonyl stretch at 1726 cm^{-1}, indicative of a non-conjugated ketone. The ^{1}H NMR spectrum of **294** includes four singlets, each integrating as one proton, corresponding to the three uncoupled vinylic protons and the single proton adjacent to the pyran oxygen atom. Several 2-D NMR experiments were undertaken to help elucidate the structure of the cycloadducts. A DEPT experiment showed that no methylene carbons are present, but the compound contains one sp^{3}-hybridized methine carbon. Heteronuclear multiple quantum correlation (HMQC) and heteronuclear multiple bond correlation (HMBC) experiments were performed, and the data generated by these powerful experiments allowed us to map the complete structure of the molecule.
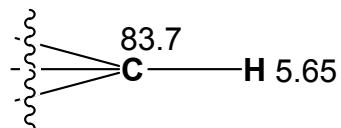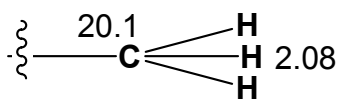
The HMQC experiment is a heteronuclear correlation experiment which allows one to determine one-bond carbon-hydrogen connectivity.

Figure 1. HMQC Spectrum of 294

The HMQC spectrum shown in Figure 1 allows us to generate the structure fragments depicted in Scheme 79. In conjunction with data from the DEPT spectrum, the data from the HMQC spectrum allowed us to determine that a methyl group with a carbon resonance at 20.1 ppm contains protons with a resonance at 2.08 ppm, and a second methyl group with a carbon resonance at 26.1 ppm contains protons with resonances at 2.29 ppm.   In addition, we could determine that the carbon with a resonance of 83.7 ppm has an attached proton occurring at 5.65 ppm, and the carbon with a resonance at 101.2 ppm has an attached proton occurring at 5.76 ppm.

Scheme 79

20.1
C
H
H 2.08
H

83.7
C
H 5.65

26.1
C
H
H 2.29
H

101.2
C
H 5.76
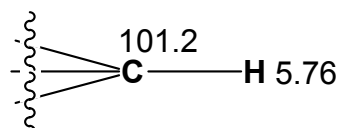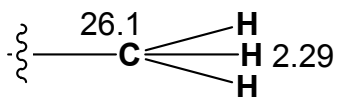
The HMBC experiment is a more powerful heteronuclear correlation experiment that allows one to correlate protons with a carbon atom two bonds away (i.e., the carbon atom adjacent to the one to which the protons are directly attached). It thus allows mapping of two-bond connectivity.

Figure 2. HMBC Spectrum of 294
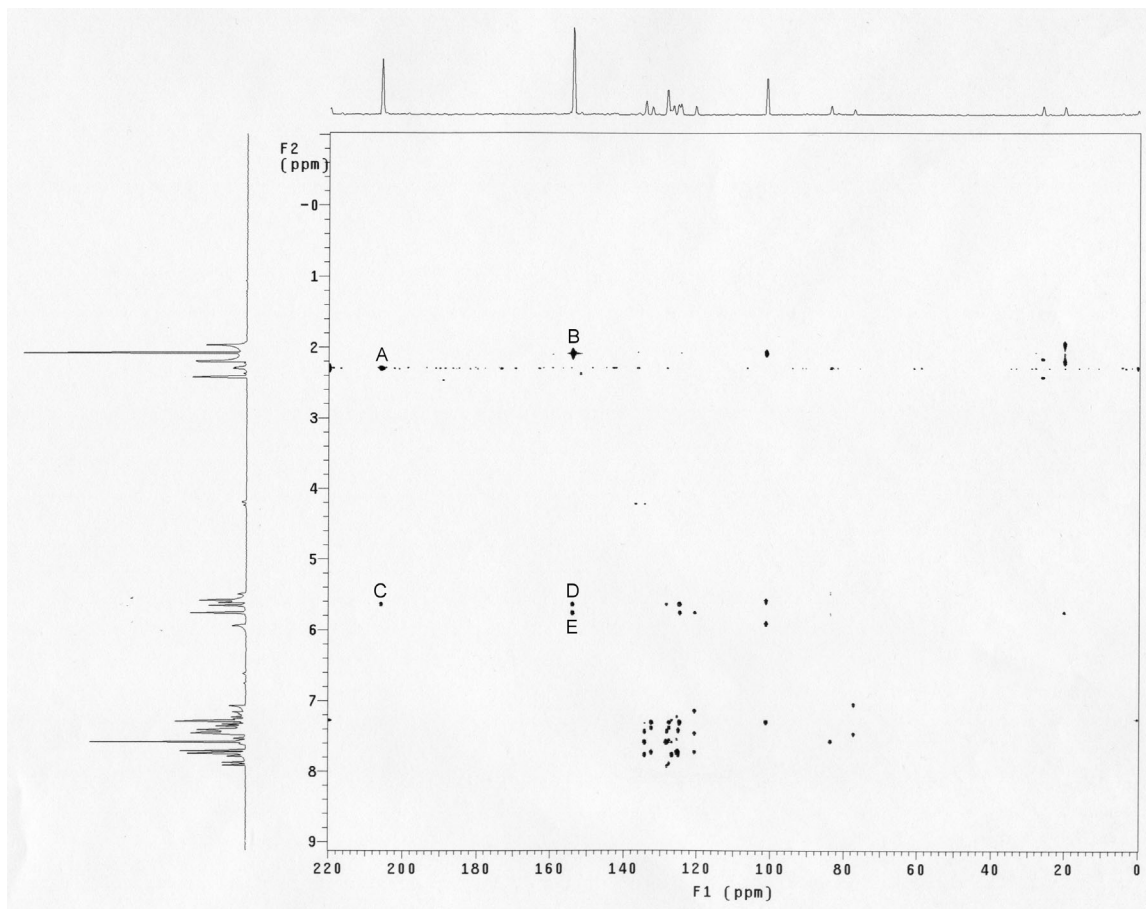
Based on IR and ^{13}C data, we were first able to assign the resonance at 205.8 ppm to the carbon of the carbonyl group. From this starting point, all resonances could be assigned relative to this carbon. Shown in Figure 2 is the HMBC spectrum for **294**. The cross-peaks *A* and *C* indicate that protons at 2.29 ppm and 5.65 ppm are attached to carbon atoms adjacent to the carbonyl carbon. In conjunction with the HMQC data (Scheme 79), this allowed us to assign the protons at 2.29 ppm as belonging to the methyl ketone, and the proton at 5.65 ppm as being attached to a methine carbon. The cross-peak *B* indicates that the other methyl group in the molecule is attached to the carbon with a resonance at 153.8 ppm. The DEPT spectrum indicated that no protons were

117

attached to this particular carbon. Cross-peaks **D** and **E** both correspond to the carbon with a resonance at 153.8 ppm, and in conjunction with the previous data confirm the carbons with resonances at 153.8 and 83.7 ppm are adjacent to an ether oxygen atom (HMBC cross-peaks can occur even if a heteroatom links two carbon atoms). Assembling all of this spectral information, we were able to construct the structural fragment shown in Scheme 80.

Scheme 80
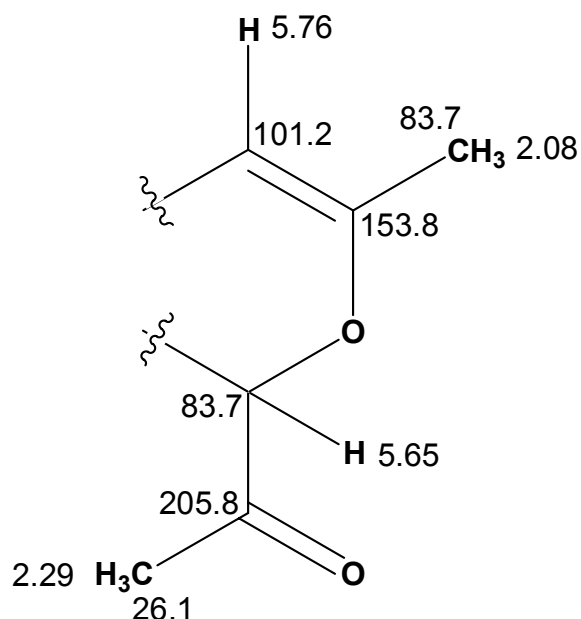
With this basic framework in place, we were able to assign the remaining carbons in the molecule (all of which are sp^2-hybridized) and their attached hydrogens in a similar manner based on the 2-D NMR spectra and coupling patterns observed in the ^1H NMR spectrum.

The formation of the anomalous byproduct **294** was quite intriguing. We envisaged a number of possible mechanisms by which this product might be formed. As

depicted in Scheme 81, direct [4 + 2] cycloaddition of **286** was expected to give the cyclic allene **295**. The isolation of the "normal" tandem cycloaddition-rearrangement product **287**, presumably formed from **295** via our proposed mechanism (see Chapter 2), suggests that this cyclic allene is indeed generated in the thermolysis of substrate **286**.
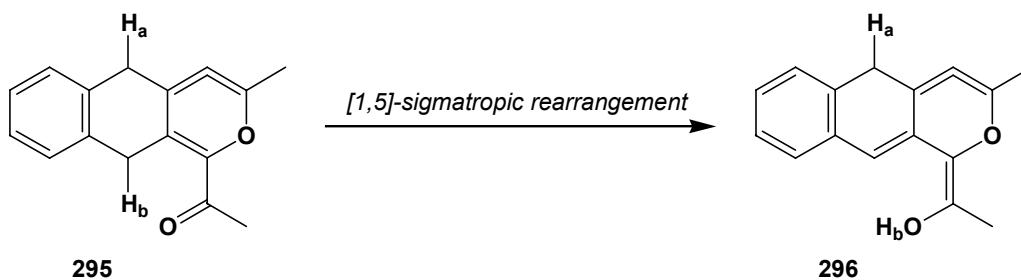
Scheme 81
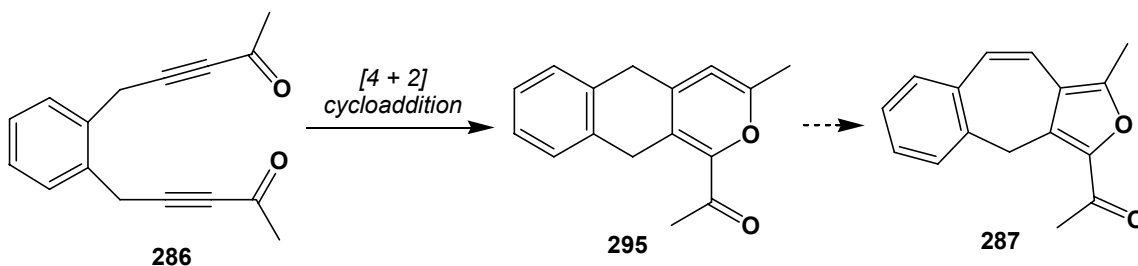
In order for the cyclic allene **295** to be an intermediate in the formation of benzoisochromene **294**, a series of hydrogen atom or proton transfers, including one which results in deconjugation of the enone, are required. The isomerization of this cyclic allene to the aromatic benzoisochromene product could involve a hydrogen atom or proton transfer process similar to that which occurs in the enyne cycloaddition (*vide supra*).

Scheme 82 depicts the conversion of cyclic allene **295** to enol **296** via a [1,5]-sigmatropic rearrangement. The resultant cyclic allene could undergo further isomerizations (*vide infra*) to ultimately furnish the benzoisochromene **294**. However, we believe this mechanism for the formation of **294** is not likely since the [1,5]-shift does not relieve the significant strain associated with the cyclic allene.

Scheme 82


295 → [1,5]-sigmatropic rearrangement → 296

Scheme 83 illustrates two isomerization pathways involving hydrogen atom transfers available to the biradical **297** which might be generated from cyclic allene **295**. Because the vinylic radical is the higher energy radical, both pathways involve initial hydrogen atom abstraction of H_c from the terpinene additive, the solvent, or from other intermediates by this radical, to then afford intermediate **298**. Pathway *a*, involving initial loss of H_a, would lead to **299**, a product not observed in the reaction. Alternatively, intramolecular hydrogen atom transfer of H_b onto the ketone oxygen would afford enol **300** as shown in pathway *b*. Subsequent hydrogen atom abstraction of H_a and tautomerization would then provide the observed benzoisochromene **294**. We believe that this intramolecular hydrogen atom transfer mechanism is most likely operating in the reaction.
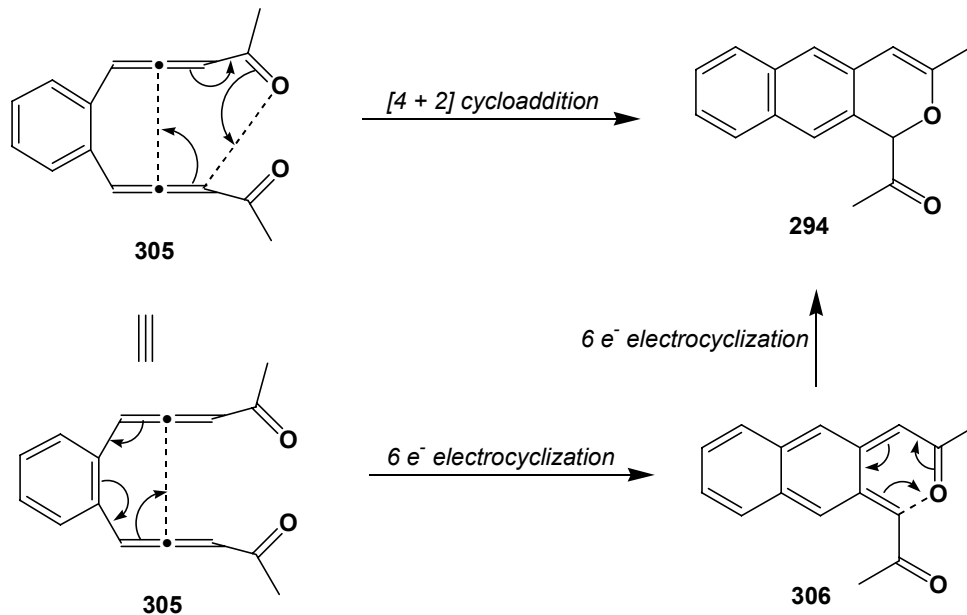
Scheme 83
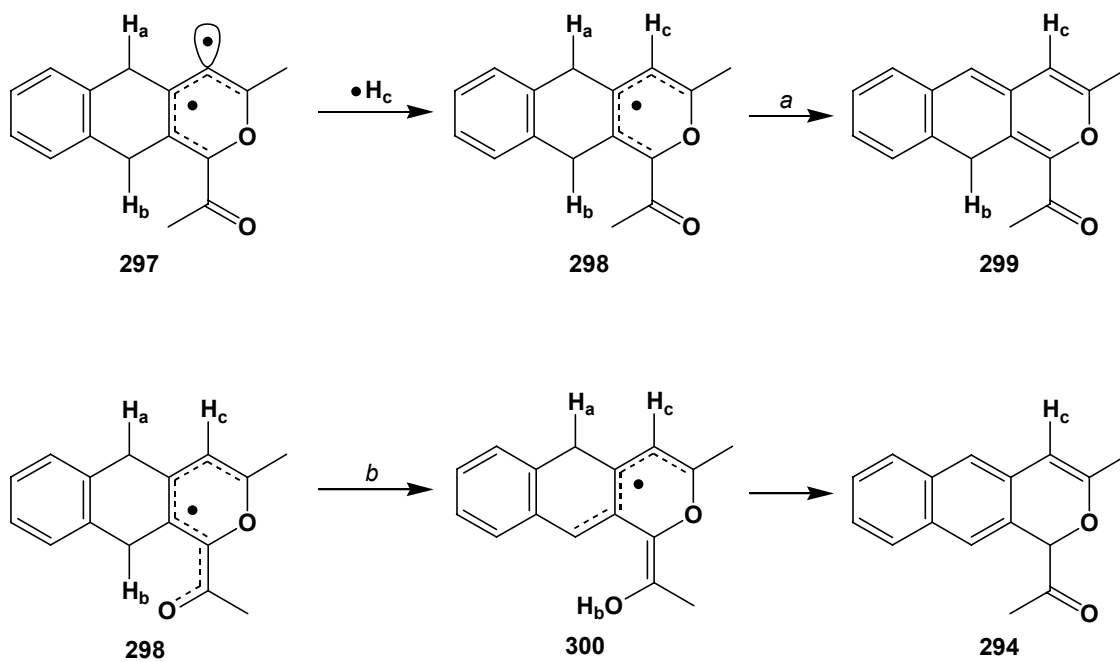
As discussed in Chapter 1, calculations suggest that heterocyclic allenes are close in energy to the corresponding zwitterionic species, which are much lower in energy than the corresponding biradicals. Scheme 84 shows two isomerization pathways available to zwitterion **301** corresponding to cyclic allene **295**. The first step in this case involves protonation of the vinylic anion of **301** to provide the pyrylium cation **302**. Deprotonation at the more acidic site (H_b) then affords the carbonyl ylide **303**, and subsequent elimination of H_a leads to enolate **304**, protonation of which affords the observed product **294**.

Scheme 84


301   302   303

294   304
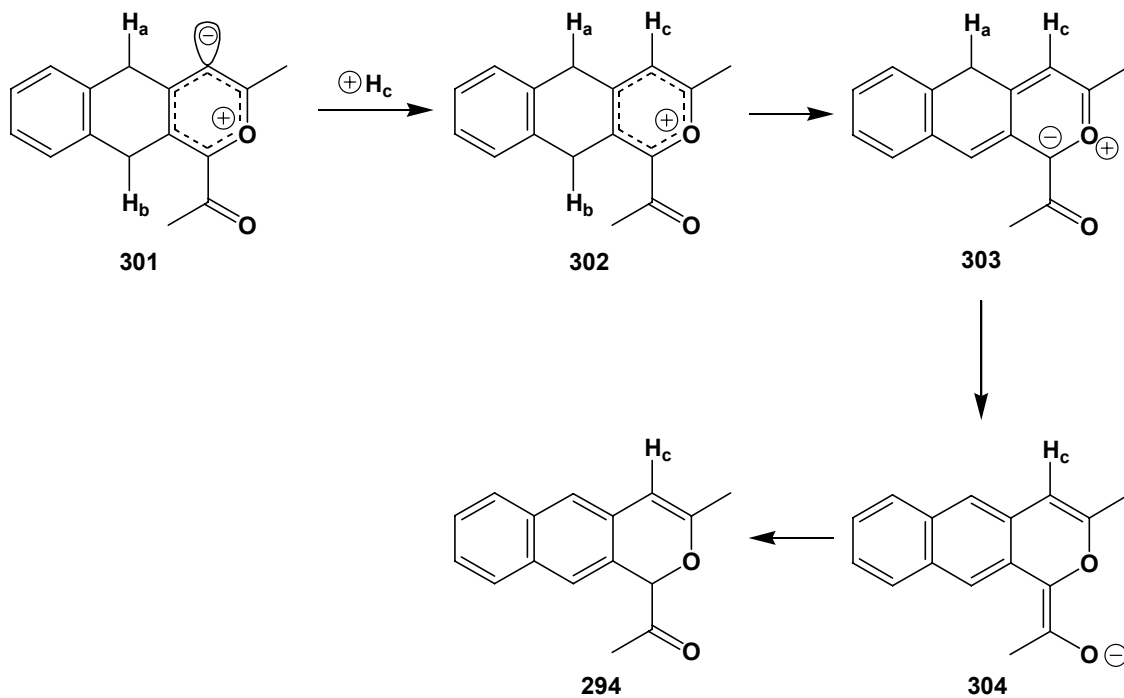
Other possible pathways for formation of **294** involve not an initial cycloaddition to a cyclic allene, but rather the isomerization of one or both benzylic alkynes to allenes via prototropic propargylic rearrangement (*vide supra*). Isomerization of both alkynes in **286** would generate the bis-allenone **305**. As shown in Scheme 85, [4 + 2] cycloaddition of **305** could provide benzoisochromene **294** directly. Alternately, two sequential six-electron electrocyclizations could form the same product via orthoquinodimethane **306**.

Scheme 85

Alternatively, isomerization of only one of the benzylic alkynes in **286** would generate the mono-allene **307** shown in Scheme 86. Two possible [4 + 2] cycloaddition pathways are available to this intermediate, leading to **308** or **299**. Cyclic allene **308** resembles the cyclic allene **295** above, differing only by the position of a double bond, and could further react by hydrogen atom transfer or protonation pathways similar to those described above to generate the observed benzoisochromene **294**. Pyran **299** is not observed in the reaction.

Scheme 86

307   [4 + 2] cycloaddition   308

307   [4 + 2] cycloaddition   299
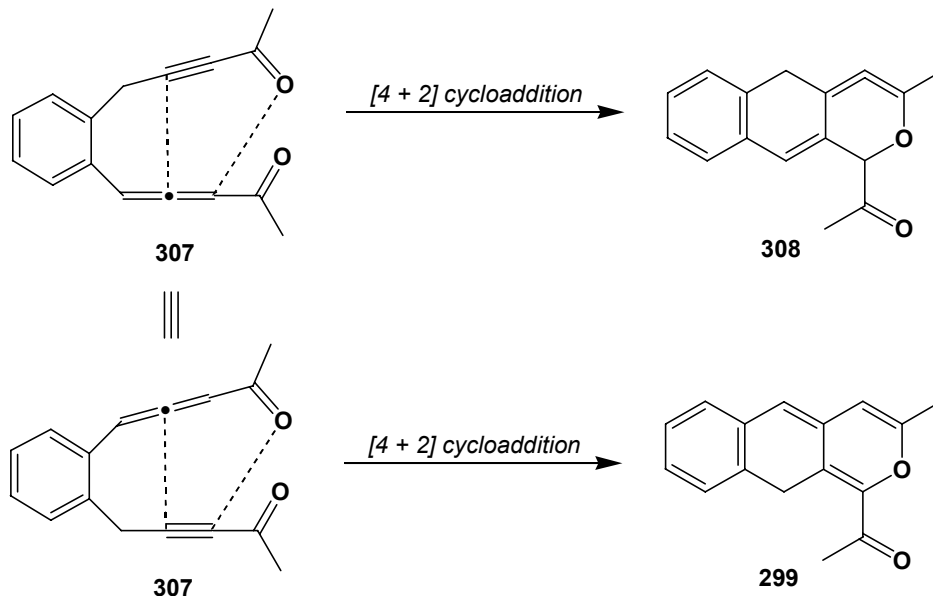
To investigate the prototropic propargylic rearrangement of benzylic alkyne **286** (Scheme 87), we treated **286** with potassium *tert*-butoxide in DMSO, conditions which are known to convert alkynes such as **286** to allenes.[165] Surprisingly, this very fast reaction afforded pyran **299**, a product different from **294**, the benzoisochromene isolated from the thermal reaction of **286**! As shown in Scheme 87, **299** likely arises from a hetero Diels-Alder cycloaddition of the mono-allene **307** discussed above. An alternative mechanism involves [4 + 2] cycloaddition of bis-allene **305** to form **294** followed by base-promoted isomerization to the observed product (**299**). This alternative is ruled out by the finding that **294** is recovered unchanged upon exposure to potassium *tert*-butoxide under the conditions in Scheme 87.

---

[165] For an example, see: Van Dongen, J. P. C. M.; De Jong, A. J.; Selling, H. A.; Montijn, P. P.; Van Boom, J. H.; Brandsma, L. *Recl. Trav. Chim. Pays-Bas* **1967**, *86*, 1077.
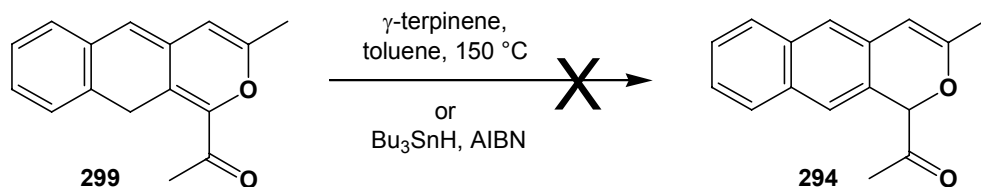
Scheme 87
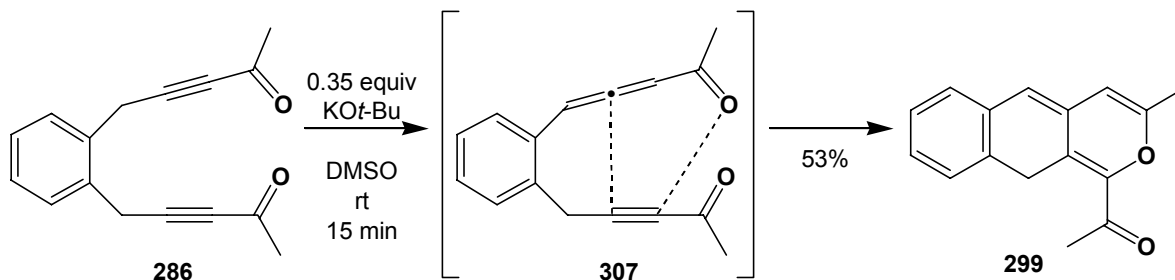
The spectral data of the product of the reaction is consistent with the structure **299**. Diagnostic data was obtained from the DEPT spectrum, which indicated the presence of an sp^3-hybridized methylene carbon. In addition, the infrared spectrum exhibits a stretch at 1668 cm^{-1} indicative of an unsaturated ketone, and the ^{1}H NMR spectrum includes signals resulting from two uncoupled vinyl protons appearing as singlets at 6.59 and 6.45 ppm.

We next examined the interconversion of benzoisochromene **294**, the product of the thermal reaction, with pyran **299**, the product of the base-catalyzed reaction, believing that this might shed light on the mechanism of formation of these products. These experiments also would indicate if **299** is an intermediate in the formation of **294**, or vice versa.

Heating **299** under the reaction conditions used for the cycloaddition did not provide **294**, and **299** was recovered. Though this result provides support against the intermediacy of **299** in the pathway leading to **294**, the experiment did not rule out the possibility that radical intermediates in the thermal cycloaddition could promote the isomerization of **299** to **294**. Therefore, we subjected **299** to hydrogen atom transfer conditions (tributyltin hydride and AIBN), but again **299** was recovered unchanged.

Scheme 88

Although there are many potential pathways for the formation of the observed product **294**, we believe the most likely mechanistic pathway involves intramolecular hydrogen atom transfer as shown in Scheme 83, pathway *b*. Considering all of the pathways presented above involving removal of H_b from cyclic allene **295**, this is the only one in which the removal of H_b appears to provide a lower energy intermediate, as the resulting radical **300** is further stabilized by conjugation with the phenyl ring.

We considered several experiments involving deuterium labeling of the alkynyl ketone **286** in an attempt to probe the mechanism further. However, we believe that none of the labeling experiments we imagined would provide conclusive evidence for any one of these mechanisms to the exclusion of the others.

Experiments Probing the Reactivity of Alkynyl Esters as Heteroenynes

Our next investigation involved oxaenynes in which the carbonyl of the 4π component was incorporated as an ester. Dr. Wills had examined the cycloaddition of one compound of this type, the unsymmetrical keto ester **218** (Scheme 89; see also Chapter 2, Table 3).

Scheme 89
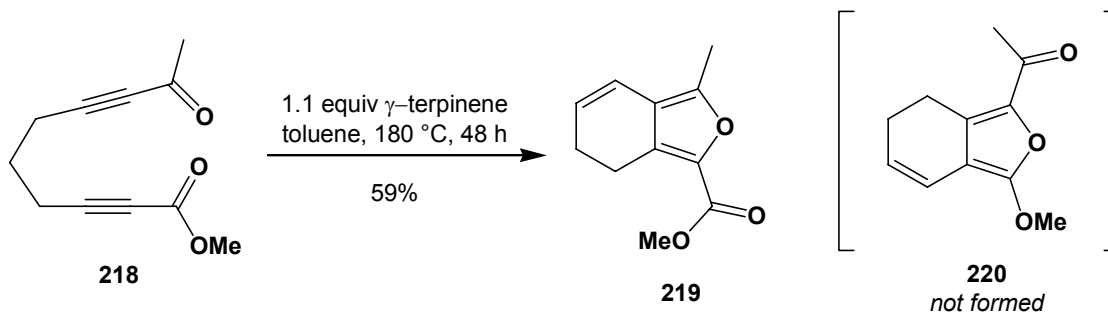
In the reaction of **218**, it was predicted that the alkynyl ketone would be the more reactive heteroenyne, and thus no cycloadduct **220** resulting from reaction of the alkynyl ester as the 4π component was expected to form. Although alkynyl esters are less reactive than alkynyl ketones as heteroenynes due to resonance effects of the ester oxygen atom, we wished to determine if an alkynyl ester could function as the 4π component in the cycloaddition in a situation where there was no alternative cycloaddition pathway.

The first substrate we selected for this study was the alkynyl ester **309**. Preparation of the compound was straightforward, starting with the bis-lithiation of 1,6-heptadiyne followed by quenching with methyl chloroformate. However, under our typical cycloaddition conditions, no cycloadduct was observed, even at 220 °C (Scheme 90), and the starting material was recovered.

Scheme 90
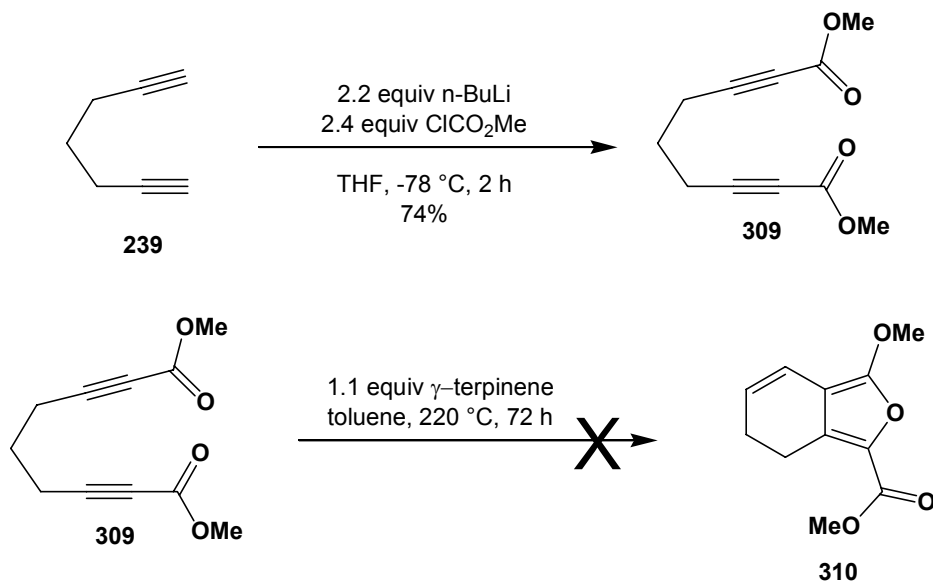
Our previous studies suggested that the replacement of a carbon atom of the tether with a substituted nitrogen atom would lower the activation energy of the reaction (*vide supra*). We therefore investigated the cycloaddition of ester **311** that incorporates a sulfonamide in the tether. The synthesis of **311** was carried out in an analogous manner to that of ester **309**, in this case beginning with *N,N*-dipropargylsulfonamide **261** (see Scheme 57). To our dismay, this compound did not undergo cycloaddition, even after thermolysis for 45 hours at 180 °C (Scheme 91), and again the ester was recovered.

Scheme 91

128
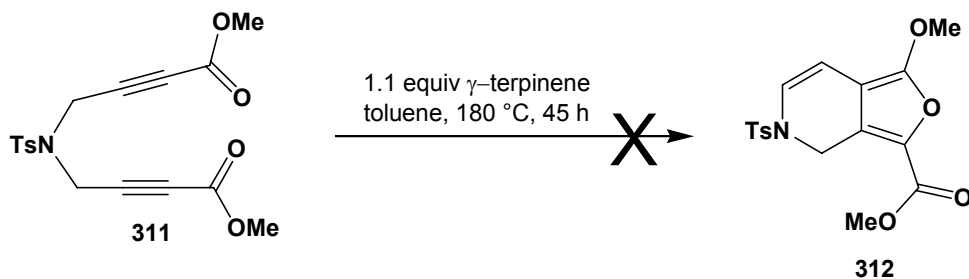
Due to the resonance delocalization of the electrons in the ester system, enoate esters are poor substrates for hetero Diels-Alder reactions, requiring harsh conditions to effect cycloaddition.[166] Therefore is not surprising that alkynyl esters are similarly unsuitable as heteroenynes in the heteroenyne cycloaddition.

Cycloadditions of Compounds with the Activating Group Contained in the Tether

We next investigated the cycloaddition of compounds of type **316** that incorporate an electron-withdrawing activating group within the tether. Analogous enyne substrates of this type had previously been shown to undergo the enyne cycloaddition (see Chapter 1). The synthesis of the ester **316** (Scheme 92) began with the propargyl alcohol THP derivative **313**, prepared according to the procedure of Larock.[167] Acylation with acetic anhydride provided the ketone **314**. Removal of the tetrahydropyranyl group with pyridinium *p*-toluenesulfonate in ethanol afforded the unstable alcohol **315**, and immediate esterification with propiolic acid afforded heteroenyne **316** in 46% yield over the two steps.

[166] Boger, D. L.; Weinreb, S. M. *Hetero Diels-Alder Methodology in Organic Synthesis*; Academic Press: New York, 1987; p 169.
[167] Larock, R.; Liu, C. L. *J. Org. Chem.* **1983**, *48*, 2151.

Scheme 92
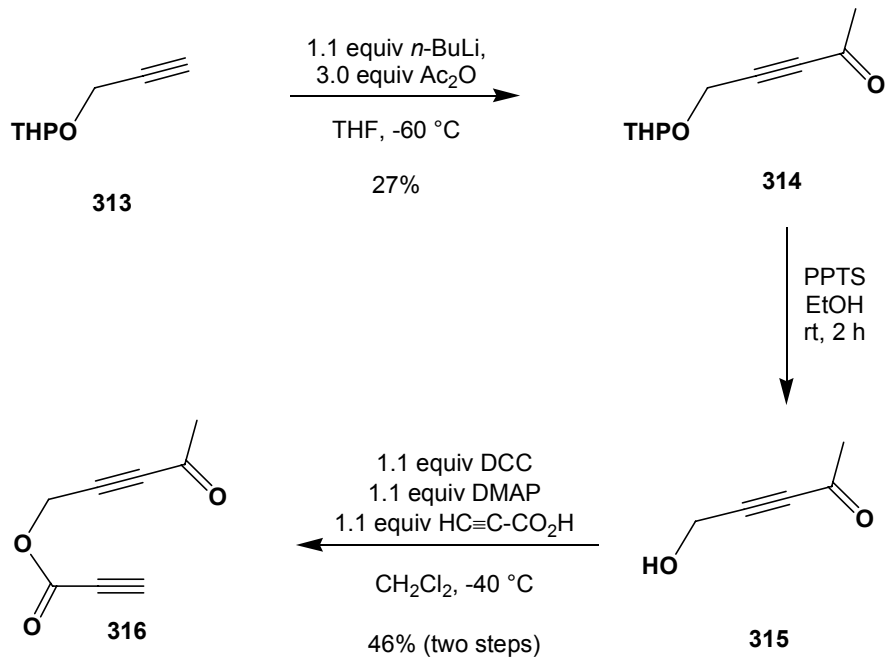
The cycloaddition of heteroenyne **316** was expected to afford lactone **317**. Unfortunately, reaction at 210 °C for 4 h led to complete decomposition of the starting material and provided none of the desired product (Scheme 93). Only a small amount of an uncharacterizable byproduct was isolated from the black tar.

Scheme 93
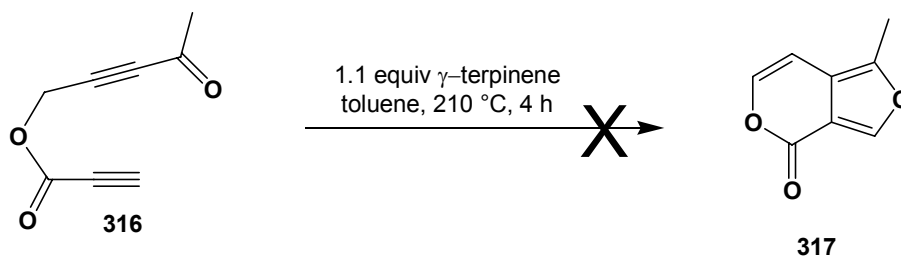
Later attempts at cycloadditions of this type involved **320** which could be prepared in fewer steps. As shown in Scheme 94, esterification of hexynediol **318** with propiolic acid, followed by oxidation, afforded the heteroenyne **320**.

Scheme 94
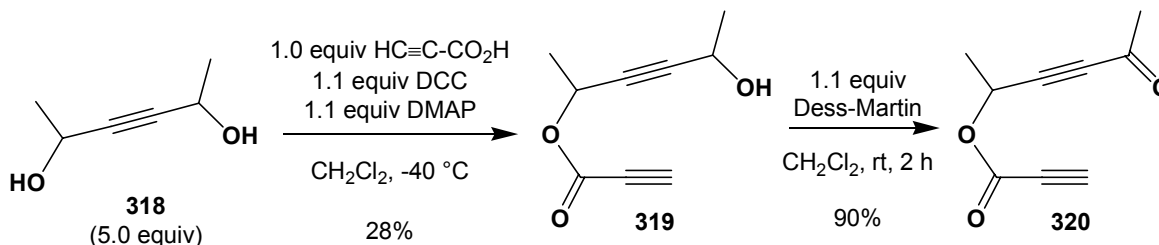
We expected that the addition of the methyl group on the tether might have a steric or conformational effect (*vide supra*) and lower the activation energy required for cycloaddition. Unfortunately, cycloaddition of **320** was again unsuccessful (Scheme 95). Thermolysis of **320** for 90 h in refluxing toluene afforded none of the desired cycloadduct **321** although all of the starting material was consumed.

Scheme 95
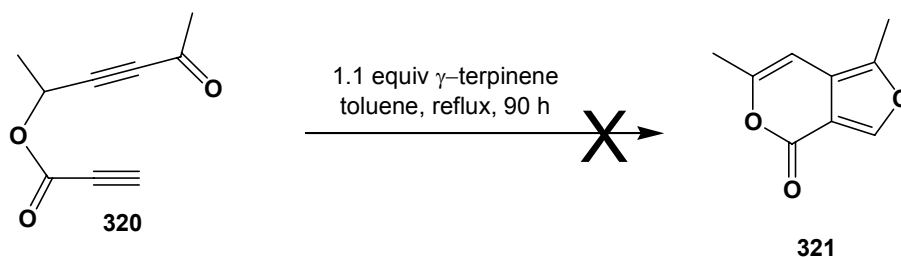
One possible reason for the failure of **316** and **320** to undergo the desired transformation might involve the preferred s-*cis* conformation of the ester, a result of

opposing dipoles in the molecule. Although one might suppose that this conformational effect could inhibit the reaction, cycloadditions of enynes incorporating tethers of this type have been successful. Therefore, we believe that this conformational effect should not hinder the cycloaddition.

A second potential reason for the failure of the cycloaddition is the requirement that a terminal alkyne function as a heteroenynophile. Although terminal alkynes function as enynophiles in the enyne cycloaddition, it is possible that they are not suitable heteroenynophile partners in cycloadditions with oxaenynes. Another possibility is that the desired product and/or cyclic allene intermediate is unstable due to the increased strain or electronic effects caused by the carbonyl functionality in the six membered ring.

Synthetic Utility of the Dihydroisobenzofuran Products of the Heteroenyne Cycloaddition

Isobenzofurans[168] are important molecules and their dihydro and tetrahydro derivatives are common systems incorporated in a wide variety of natural products of biological importance. Previous routes to 3,4-fused polycyclic furans include Kanematsu's furan ring transfer strategy.[169,170]

We were very interested in demonstrating the utility of our cycloaddition for the synthesis of complex molecules. The reactive furan moiety incorporated in our cycloadducts allows them to undergo transformations to generate other functionalized

---

[168] For a review of isobenzofurans and their applications in synthesis, see: Rodrigo, R. *Tetrahedron* **1988**, *44*, 2093.

[169] (a) Yamaguchi, Y.; Yamada, H.; Hayakawa, K.; Kanematsu, K. *J. Org. Chem.* **1987**, *52*, 2040. (b) Baba, Y.; Sakamoto, T.; Kanematsu, K. *Tetrahedron Lett.* **1994**, *35*, 5677. (c) Wu, H.-J.; Lin, S.-H.; Lin, C.-C. *Heterocycles* **1994**, *38*, 1507.

systems which could be useful intermediates in the total synthesis of natural products. Scheme 96 outlines two such transformations based on initial Diels-Alder reaction of tetrahydroisobenzofuran **322**. Cleavage of the either the ring junction C=C bond or a C-O bond then provides access to important types of polycyclic systems. A number of elimination or deoxygenation methods exist for cleaving the oxygen bridge, thus creating aromatic or dihydroaromatic products. The overall transformation in this case is an example of an aromatic annulation. Substitution patterns on the polycyclic product could be tailored to suit a variety of targets by variation in the heteroenyne cycloaddition substrate used to make **322** and the dienophile for the furan Diels-Alder reaction. Alternatively, cleavage of the carbon-carbon double bond via oxidation would lead to cyclic ethers of the type **325**.

Scheme 96

---
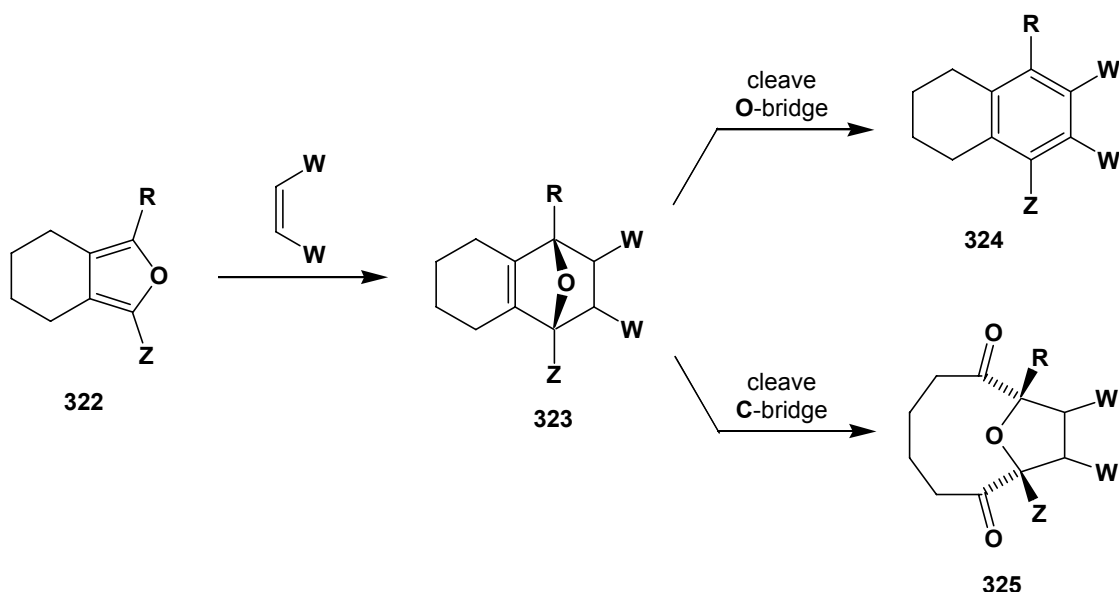
[170] Other approaches are discussed in a recent review on the synthesis of substituted furans. See: Hou, X. L.; Cheung, H. Y.; Hon, T. Y.; Kwan, P. L.; Lo, T. H.; Tong, S. Y.; Wong, H. N. C. *Tetrahedron* **1998**, *54*,

It is worth noting that the oxabicyclo[6.2.1]undecane ring system formed from the approach involving cleavage of the carbon bridge is the core ring system found in the tubulin polymerizing agents[171] eleutherobin (**326**) and the sarcodictyins.[172] The cycloaddition of a suitably substituted oxaenyne and subsequent transformation according to the carbon bridge cleavage plan outlined above could provide rapid access to this family of natural products as well as approaches to analogs.
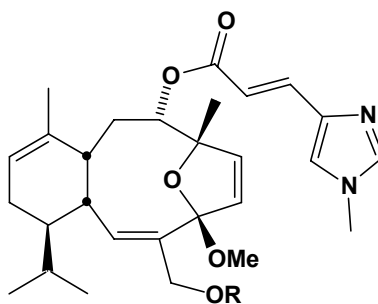
Eleutherobin (326)

A demonstration of a transformation involving the cleavage of the oxygen bridge is shown in Scheme 97. The tetrahydroisobenzofuran **327** is easily prepared by hydrogenation of **219** under standard conditions with hydrogen and palladium on carbon. This reaction proceeded quite efficiently to give **327** in 92% yield. Exposure of **327** to benzyne generated from **328** by the method of Kitamura[173] afforded the 1,4-endoxide **329** in 89% yield. Deoxygenation with low-valent titanium according to Wong's protocol[174]

1955.

[171] For reviews of the tubulin polymerizing agents and their use as anticancer treatments, see: (a) von Angerer, E. *Curr. Opin. Drug Disc. Dev.* **2000**, *3*, 575. (b) Nicolaou, K. C.; Hepworth, D.; King, N. P.; Finlay, M. R. V. *Pure Appl. Chem.* **1999**, *71*, 989.

[172] For a review of the biological activity and total syntheses of eleutherobin and the sarcodictyins, see: Nicolaou, K. C.; Pfefferkorn, J.; Xu, J.; Winssinger, N.; Oshima, T.; Kim, S.; Hosokawa, S.; Vourloumis, D.; van Delft, F.; Li, T. *Chem. Pharm. Bull.* **1999**, *47*, 1199.

[173] Kitamura, T.; Yamane, M.; Inoue, K.; Todaka, M.; Fukatsu, N.; Meng, Z.; Fujiwara, Y. *J. Am. Chem. Soc.* **1999**, *121*, 11674.

[174] For a review, see: Wong, H. N. C. *Acc. Chem. Res.* **1989**, *22*, 145.

afforded tetrahydroanthracene **330**. The tetrahydroanthracene product is the result of a two-step formal benzannulation sequence.

Scheme 97
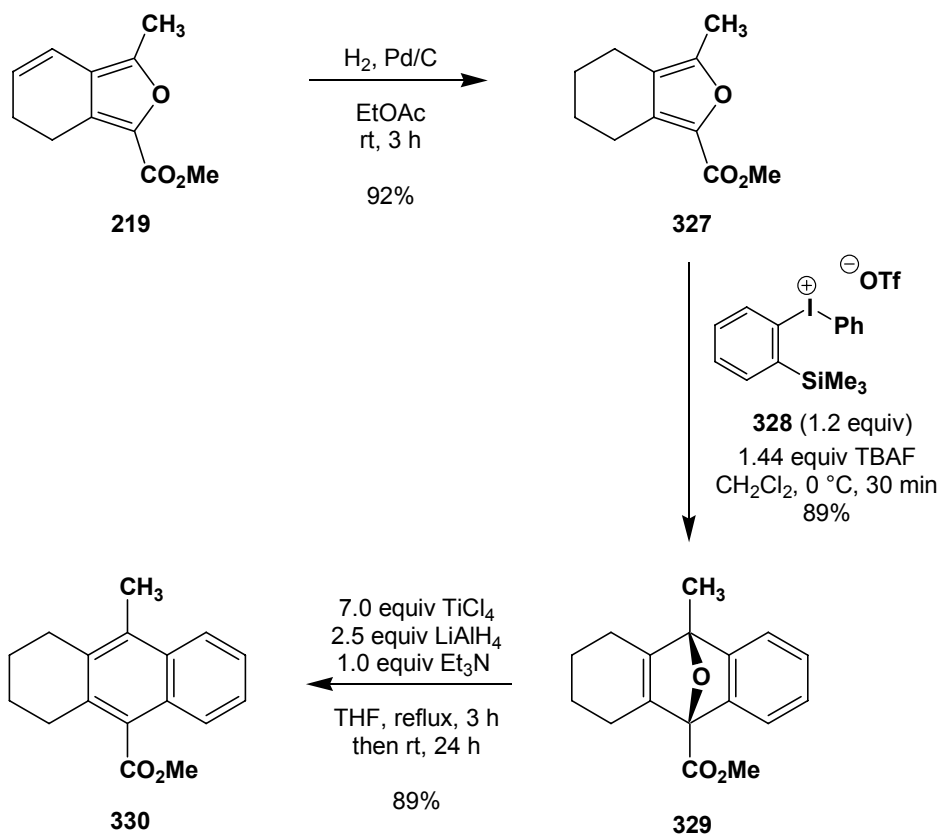
An approach involving the cleavage of the carbon bridge is shown in Scheme 98. Hydrogenation of dihydroisobenzofuran **200** affords the corresponding tetrahydroisobenzofuran, which is not purified but immediately subjected to the action of maleic anhydride in benzene for 44 h, to afford cycloadduct **331** as a mixture of diastereomers. In this step, the silylfuran is protodesilylated, probably via acid formed by the hydrolysis of maleic anhydride by adventitious water. Unfortunately, under conditions which rigorously exclude water from the reaction, the Diels-Alder

cycloaddition does not take place. This indicates that the silyl moiety attached to the furan prevents cycloaddition, possibly because of steric hindrance. It was found that in an analogous compound incorporating the diphenylmethylsilyl group in place of the trimethylsilyl group, the bulkier silyl group is also cleaved, but the Diels-Alder cycloaddition requires 96 hours for completion. This is consistent with our hypothesis that the silyl group is cleaved before the cycloaddition, as the diphenylmethylsilyl group should be cleaved more slowly than the trimethylsilyl group.

The oxidative cleavage of the oxabicyclo[2.2.1]heptene moiety in **331** with ozone[175] and reductive workup with dimethyl sulfide affords anhydride **332**. For isolation and characterization purposes, the anhydride was transformed to the corresponding diester **333** by sequential treatment with methanol and diazomethane. The diester **333** is produced in 37% overall yield (from **200**). The relative stereochemistry of the single diastereomer isolated from the reaction was assigned based on ^{1}H NMR coupling constants. The coupling constant between the bridgehead proton and the adjacent proton is 7.6 Hz, indicative of a *trans* relationship. The two protons α to the esters show a coupling constant of 7.9 Hz, again indicative of a *trans* relationship.

---

[175] For related approaches, see Donohoe, T. J.; Raoof, A.; Linney, A. D.; Helliwell, M. *Org. Lett.* **2001**, *3*, 861 and references therein.

Scheme 98
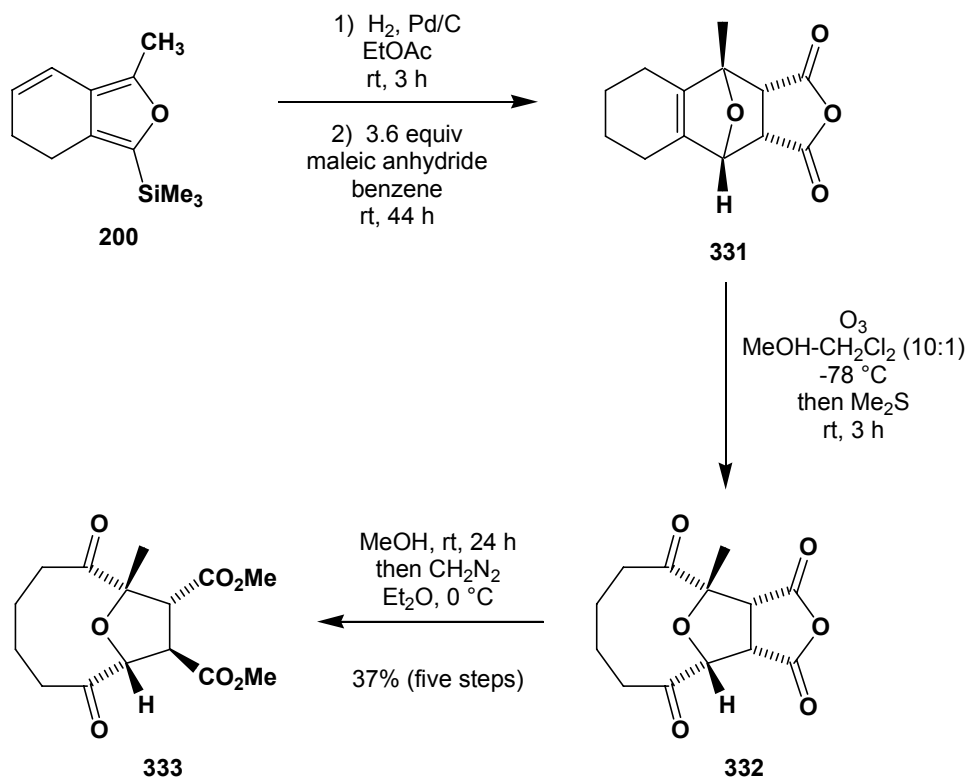
This five-step sequence demonstrates the feasibility of an approach involving cleavage of the carbon bridge in the Diels-Alder adducts of tetrahydroisobenzofurans for the synthesis of compounds containing the oxabicyclo[6.2.1]undecane ring system.

Mechanism of the [4 + 2] Cycloaddition of Conjugated Oxaenynes

Previous studies by Dr. Wills and one of the experiments presented in this chapter provide substantial evidence for our proposed mechanism for the transformation of the cyclic allene intermediate to the observed furan product.

However, a key question that remains unanswered is the mechanism of the first stage of the transformation, in which the oxaenyne substrate **179** forms the six-membered heterocyclic allene intermediate **180**. Analogous to the enyne and arenyne cycloadditions

137

discussed in Chapter 1 (Scheme 6), there are two potential pathways for the formation of the heterocyclic allene intermediate **180**, involving a concerted [4 + 2] cycloaddition, or a cyclization pathway via biradical intermediate **334**. As discussed earlier (Chapter 1), the current evidence favors the concerted pathway for [4 + 2] cycloadditions of conjugated enynes, and the stepwise mechanism for the related cycloadditions of arenynes. At present, either pathway appears consistent with our results for the [4 + 2] cycloadditions of conjugated oxaenynes.

Scheme 99
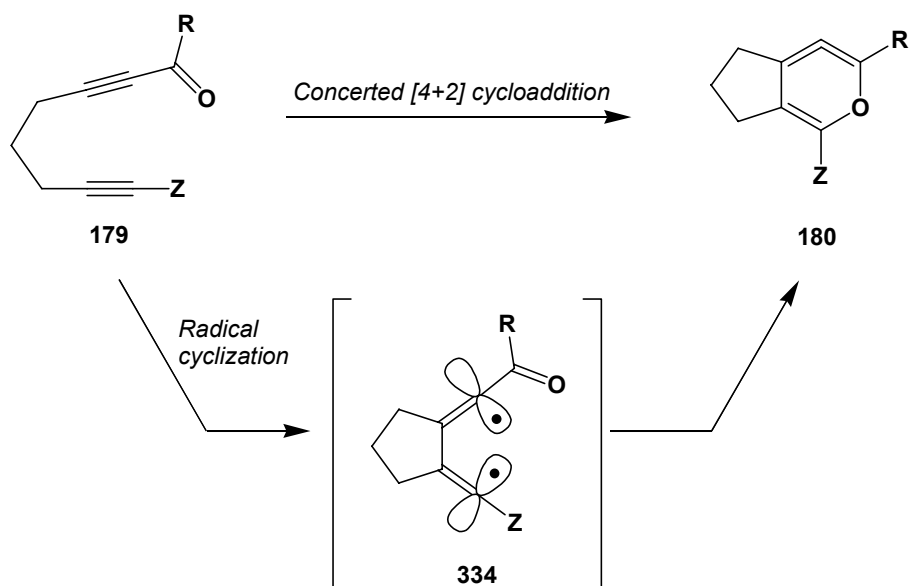
In evaluating the *stepwise pathway* for the enyne, arenyne, and oxaenyne cycloadditions, an important consideration is the stability of the intermediate biradical that is taking form in the transition state for the cyclization. The bond dissociation

energy[176] (relative to methane) for a benzylic hydrogen atom is 17 kcal/mol, while for an allylic hydrogen atom the value is 19 kcal/mol. For a hydrogen atom α to a carbonyl, the value is 11 kcal/mol. Thus we conclude that the biradical intermediate **334** is reasonable but not as stabilized as the biradical intermediates in the arenyne cycloaddition. In contrast, experimental evidence and theoretical studies suggest such a pathway does not occur in the enyne cycloaddition.

With regard to the comparison of *concerted pathways* for the three classes of cycloadditions, important considerations include the nature of the bonds broken and formed in the concerted process, and the relative strain associated with the resultant cyclic allenes. With regard to changes in bond strengths, the oxaenyne cycloaddition should be less favorable by ca. 30 kcal/mol as compared to the enyne cycloaddition. This is primarily due to the fact that a C=O bond is lost in the former process where a weaker C=C bond is sacrificed in the latter cycloaddition. This would appear to make the concerted pathway less favorable for heteroenynes as compared to enynes. However, one must take into account that this deficiency may be offset by the additional stabilization of heterocyclic allenes due to the contribution of the aromatic zwitterionic structures, which are not possible in the case of the carbocyclic allenes (see Chapter 1). In addition, we believe the concerted pathway is higher in energy for the arenyne cycloaddition due to the disruption of aromaticity in the benzene ring, while this would not be the case for the heteroenyne cycloaddition.

As discussed in Chapter 2, the hetero Diels-Alder reactions of enones typically proceed most efficiently as inverse electron demand cycloadditions incorporating

---

[176] (a) Bordwell, F. G.; Zhang, X.-M.; Alnajjar, M. S. *J. Am. Chem. Soc.* **1992**, *114*, 7623. (b) Bordwell, F.

electron-rich dienophiles. In contrast, the oxaenyne cycloaddition proceeds most readily when the heteroenynophile is substituted with an electron-withdrawing group, and at a slower rate when the heteroenynophile is substituted with an electron-donating group, a situation which facilitates inverse electron demand cycloadditions.

Although we cannot prove that the oxaenyne cycloaddition proceeds through a concerted pathway, as opposed to a mechanism involving a biradical cyclization, we believe that the experimental evidence suggests that [4 + 2] cycloadditions of conjugated oxaenynes probably occurs as a *normal electron demand* concerted cycloaddition, reminiscent of the thermal dimerization of α,β-unsaturated carbonyl compounds.

An accurate comparison of the relative energies of these two potential pathways would likely require a high-level theoretical treatment. Further studies are required in order to shed light on this step of the mechanism.

Summary

Many of the questions about the heteroenyne cycloaddition of oxaenynes we set out to investigate have been answered. Most notably, we extended the scope of the heteroenyne cycloaddition to include the use of alkynyl aldehydes as heteroenynes, which provide dihydroisobenzofuran products lacking a substituent on a carbon of the furan moiety. In addition, we determined that substrates incorporating substituted nitrogens or disubstituted carbons as atoms in the tether proceed more efficiently to produce the expected cycloadducts at faster rates and/or at lower temperatures. We have also gained additional experimental evidence for the intermediacy of a carbene in the cycloaddition,

G.; Zhang, X.-M. *Acc. Chem. Res.* **1993**, *26*, 570.

as well as discovering an interesting transformation of benzylic heteroenynes. Finally, we have also demonstrated the synthetic utility of the heteroenyne cycloaddition by the transformation of two cycloadducts to complex carbocyclic compounds.

Part II

Studies Directed Toward the

Total Synthesis of Glycinoeclepin A

Chapter 1

Background and Significance

Heterodera glycines: The Soybean Cyst Nematode

Nematodes are roundworms of the phylum Nematoda and are found in the soil and water.[177] Nematodes are the most abundant animals on earth – it is estimated that there are five billion of them in the upper three inches of an acre of soil.   These organisms are parasitic to a number of plants and animals. Nematodes infect many of the plants and animals on which humans depend for food, and therefore they are a serious contributing factor in the global problem of starvation and food shortage.

Nematodes of the genus *Heterodera* have been particularly serious pests because they feed on a number of economically important crops. In addition, their larvae are covered by a cyst, which provides protection from adverse environmental conditions, and allows them to remain viable in the soil for a number of seasons.[178] The cyst nematodes generally have a limited number of host plants. This specificity is thought to be due to the fact that hatching of larvae is dependent upon key stimulants from the host plant. This insight into the nematode life cycle was first realized in 1922 when Baunacke found that extracts from potatoes could stimulate the emergence of larvae from the cysts of the potato cyst nematode.[179]

---

[177] (a) Perry, R. N., Wright, D. J., Eds. *The Physiology and Biochemistry of Free-living and Plant-parasitic Nematodes*; CAB International: New York, 1998. (b) Chitwood, B. G.; Chitwood, M. B. *Introduction to Nematology*; University Park Press: Baltimore, 1974. (c) Decker, H. *Plant Nematodes and Their Control (Phytonematology)* (translated from Russian); Amerind: New Delhi, 1980; p 128.
[178] Whitehead, A. G. In *Cyst Nematodes*; NATO ASI, Series A, Vol 121; Lamberti, F. and Taylor, C. E., Eds.; Plenum: New York, 1985; p 413.
[179] Baunacke, W. E. *Arb. Biol. Bund Anst. Land-u. Forstw.* **1922**, *11*, 185.

The soybean cyst nematode (*Heterodera glycines*) has attracted considerable attention because it parasitizes a number of economically important plants, such as soybeans, kidney beans, and adzuki beans. This nematode causes *daizu iwo byo* ("yellow dwarf disease") in soybean plants which leads to severe inhibition in plant growth. The infected plants produce very few flowers and seeds, and their leaves lack pigments and drop early. The nematode not only attacks the plant's cells and blocks its vital transport channels, but it also renders the plants susceptible to viruses, bacteria, and fungi. *H. glycines* is widespread in Japan, the United States, Canada, and South America, and accounts for most of the $2.5 billion in crops lost each year to nematodes.[180]

The application of traditional toxic pesticides is standard practice in the agricultural industry to control and kill many types of agricultural pests.[178,181] However, the chemicals used are broad spectrum pesticides and typically are employed in high concentrations, which has caused these substances to bioaccumulate in the environment. Furthermore, as pests develop resistance to these chemicals, their effectiveness is diminishing. These factors have created a need for new strategies to control agricultural pests.

Currently, the main strategy employed to combat the soybean cyst nematode involves the use of crop rotation and nematode-resistant varieties of soybean.[181b] Unfortunately, strains of soybean cyst nematodes exist which are not affected by the

---

[180] (a) Sasser, J. N.; Frackman, D. W. In *Vistas on Nematology*; Veech, J.A.; Dickson, D. W., Eds.; Society of Nematologists, Inc.: Hyattsville, 1987. (b) Noel, G. R. In *Biology and Management of the Soybean Cyst Nematode*; Riggs, R.D.; Wrather, J. A.; APS Press: St. Paul, MN, 1992.

[181] (a) Atkinson, H. J.; Lilley, C. J.; Urwin, P. E.; McPherson, M. J. Engineering Resistance to Plant-parasitic Nematodes. In *The Physiology and Biochemistry of Free-living and Plant-parasitic Nematodes*; Perry, R. N., Wright, D. J., Eds. CAB International: New York, 1998; pp 381-413. (b) Illinois SCN Coalition. http://www.ilscncoalition.org/manage7.ace (Accessed June 2002).

nematode-resistant soybeans, and over time these nematodes will become more predominant.

Alternative Approaches to Pest Control

The application of a combination of different approaches to the problem of pest control, commonly referred to as integrated pest management (IPM), has gained favor as an alternative to the large-scale use of toxic pesticides.[182] Among the strategies employed in IPM are the use of pest predators such as parasites, bacteria, and viruses in concert with limited applications of pesticides. This latter category involves the use of rationally designed synthetic pest control agents as well as behavior-modifying substances, known as semiochemicals.

Semiochemicals are usually highly selective and highly active substances.[183] They can be divided into two classes: pheromones and allelochemicals. Pheromones are substances used by members of a species to communicate with each other. A common use of these compounds in pest control is the employment of sex pheromones to attract insects to traps containing insecticides. Allelochemicals are substances produced by one species with an effect on a different species. There are two classes of allelochemicals: allomones and kairomones. With allomones, the result is favorable to the emitter, but not to the receiving species (e.g., plant defense agents such as azadirachtin[184]). Kairomones, however, produce a result that is favorable to the receiving species, but not to the emitter. Semiochemicals typically exhibit high levels of activity in the environment, and are

---

[182] For example, see: Bellus, D. *Chimia* **1991**, *45*, 154.
[183] For an overview, see: *Semiochemicals, Their Role in Pest Control*; Nordlung, D. A.; Jones, R. L.; Lewis, W. J., Eds.; John Wiley & Sons: New York, 1981.

usually species-specific. Since both pheromones and kairomones are generally not toxic to pests, they are more likely to not be toxic towards the ecosystem as compared to classical pesticides. This makes semiochemicals attractive candidates as pest control agents.

In the battle against the soybean cyst nematode, a strategy involving kairomones or pheromones could be extremely effective. The high selectivity and high activity could allow for the elimination of this pest using a minimal amount of the compound and without harmful effects to the environment.

Isolation and Biological Activity of Glycinoeclepin A

The biological activity of glycinoeclepin A and its potential use as a pest control agent can best be understood by looking at the life cycle of *H. glycines*. The life of cyst nematodes begins when the eggs hatch into larvae and proceed to invade the host plant.[185] The host plant provides the nourishment for the developing nematode during its four-week life cycle. Following fertilization, the female fills with eggs and dies. Her body becomes a cyst which protects the eggs until the optimal conditions for hatching are present. These cysts are resistant to adverse seasonal conditions and can remain viable for three or more years.

In 1966, Tsutsumi and Sakurai showed that, as is the case with the potato cyst nematode, host plant extracts are potent stimulants for the hatching of the larvae of the

---

[184] Azadirachtin is a natural product found in the seeds of the neem tree and used in India to control insects. Scientists believe the neem tree produces azadirachtin as a deterrent to insect attacks.
[185] Opperman, C. H.; Dong, K.; Chang, S. In *Advances in Molecular Plant Nematology*; NATO ASI, Series A, Vol 268; Lamberti, F.; De Giorgi, C. and Bird, D. M., Eds.; Plenum: New York, 1985; p 65.

soybean cyst nematode.[186] This exciting discovery offered the potential ability to control the hatching of this pest, and prompted the search for the exact nature of the stimulant. In 1967, Tadashi Masamune undertook the monumental task of isolating and identifying this important compound.[187]

Fifteen years later, in 1982, Masamune reported the first breakthrough in this heroic effort: the isolation of 50 μg of the *p*-bromophenacyl ester (*p*-BPE) of a substance that stimulated the hatching of the soybean cyst nematode.[188] The source of the compound was a 113-kg sample of dried and powdered kidney bean roots collected from a 1-hectare field. This material was extracted and purified numerous times to give fractions that were tested for activity by bioassay. When the 50 μg sample[189] isolated by Masamune and co-workers was tested, it was found to stimulate hatching of the cyst nematode eggs, *in vitro*, at a level of 10^{-11} to 10^{-12} g/mL! Unfortunately, the small amount of isolated compound was only adequate for preliminary analyses. Mass spectrometry established the molecular formula, and ^{1}H NMR revealed the types of oxygen functionality in the sample. To complete the structural assignment of this fascinating compound, designated as glycinoeclepin A, a larger amount of sample was required, and the isolation process had to be repeated on a larger scale.

The structure of glycinoeclepin A (**335**) was finally established in 1987. Over 1,000 kg of dried and powdered kidney bean roots were harvested from a 10-hectare field and purified to give 1.25 mg of glycinoeclepin A as its *p*-bromophenacyl ester (*p*-BPE)

---

[186] Tsutsumi, M.; Sakura, K. *Japn. J. Appl. Ent. Zool.* **1966**, *10*, 129.
[187] Masamune, T. In *Natural Products and Biological Activities; A Naito Foundation Symposium*; University of Tokyo Press; Elsevier: New York, 1986; p 25.
[188] Masamune, T.; Anetai, M.; Takasugi, M.; Katsui, N. *Nature* **1982**, *297*, 495.
[189] Sample is isolated as its *p*-BPE and hydrolyzed before testing.

(336).[190] This sample was characterized using several spectroscopic methods (including mass spectrometry and various NMR techniques) and was assigned the structure shown below.[190a,191] The assignment was confirmed by X-ray analysis of a single crystal of glycinoeclepin A *p*-BPE.[17] The hydrolysis of glycinoeclepin A *p*-BPE (336) afforded the natural product (335) which was found to be active, *in vitro*, at the 10^{-12} g/mL level.
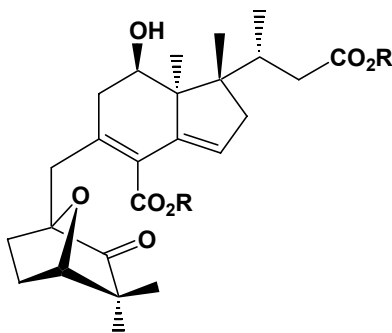
R = H *Glycinoeclepin A* (335)
R = CH$_2$COC$_6$H$_4$*p*-Br (336)

Potential Use of Glycinoeclepin A as a Pest-Control Agent

Researchers found that exposure of the cysts to a solution of glycinoeclepin A stimulated the hatching of the larvae from the cysts. It was observed from bioassays that the larvae which emerge from cysts treated with glycinoeclepin A are active, whereas the larvae from untreated cysts are less active and appeared in smaller numbers.

The ability of glycinoeclepin A to stimulate the hatching of the soybean cyst nematode has led to great interest in its potential use as a pest control agent. It could be envisioned that application of glycinoeclepin A on the fields in the spring, before the

---

[190] (a) Fukuzawa, A.; Furusaki, A.; Ikura, M; Masamune, T. *J. Chem. Soc., Chem. Commun.* **1985**, 222. (b) Masamune, T.; Anetai, M.; Fukuzawa, A.; Takasugi, M.; Matsue, H.; Kobayashi, K.; Ueno, S.; Katsui, N. *Bull Chem. Soc. Jpn.* **1987**, *60*, 981.

soybeans are planted, should cause the larvae to hatch from the cysts. Since no host plant would be present, the nematodes would have no food source, and would then die. Thus the possibility exists that glycinoeclepin A could be used as an *environmentally benign* nematode control agent.

A major obstacle to implementing this strategy that needs to be addressed is the lack of a suitable source of glycinoeclepin A. Nature does not appear to be a feasible source of material, but chemical synthesis could provide the quantities necessary for testing and, eventually, application of glycinoeclepin A. Therefore, it comes as no surprise that the combination of the potential utility of this molecule as a pest control agent and its challenging chemical structure have made it an interesting target for total synthesis. Work in this area has resulted in three total syntheses (see Chapter 2), a biomimetic synthesis of a close derivative, and several papers on synthetic approaches[192] and structure-activity relationships of analogs.

Summary

Glycinoeclepin A is a potential environmentally-benign pest control agent for the management of soybean cyst nematodes. Though three total syntheses of this important molecule have been completed to date, all of them are rather lengthy and not particularly efficient. Part II of this thesis focuses on the total synthesis of a section of this important molecule. Chapter 2 outlines previous routes to glycinoeclepin A, and introduces our convergent strategy, which should provide an effective route to this significant

[191] (a) Masamune, T.; Fukuzawa, A.; Furuzaki, A.; Ikura, M.; Matsue, H.; Kaneko, T.; Abiko, A.; Sakamoto, N.; Tanimoto, N.; Murai, A. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 1001. (b) Takasugi, M.; Fukuzawa, A.; Masamune, T. *J. Synth. Org. Chem. Jpn.* **1988**, *46*, 416.

compound. The development and deployment of a new, concise route to the A-ring enyne section of glycinoeclepin A will be detailed in Chapter 3.

---

[192] For synthetic approaches to the D-ring side chain, see: Okawara, H.; Nii, Y.;Miwa, A.; Sakakibara, M. *Tetrahedron Lett.* **1987**, *28*, 2597.

Chapter 2

The "A-Ring" of Glycinoeclepin A

The objective of our research in this area has been the development of an *efficient* and *practical* synthesis of glycinoeclepin A. While three previous total syntheses of this molecule have been reported to date,[190,191,192] we believe that none of them are truly *practical* (that is, able to provide useful quantities of the material in an *efficient* manner). Further biological studies on the feasibility of glycinoeclepin A as a pest control agent would require tens or hundreds of milligrams of glycinoeclepin A, and the commercialization of the compound or an analog would require much more. The goal of our research has been to develop a synthesis consisting of 20 or fewer steps in the longest linear sequence.

Retrosynthetic Analysis

Our retrosynthetic plan is outlined in Scheme 100. As convergent strategies are the most efficient synthetic strategies, we chose to divide the molecule into two roughly equal-sized fragments, CD-ring precursor **339** and A-ring enyne **340**. The crucial transformation in our strategy involves a tandem propargylic rearrangement-asymmetric inverse electron-demand intramolecular vinylallene [4 + 2] cycloaddition.[193] This key step was developed by retrosynthetically disconnecting the hydrindane skeleton into a

[190] Murai, A.; Tanimoto, N.; Sakamoto, N.; Masamune, T. *J. Am. Chem. Soc.* **1988**, *110*, 1985.
[191] Mori, K.; Watanabe, H. *Pure Appl. Chem.* **1989**, *61*, 543.
[192] Corey, E. J.; Houpis, I. N. *J. Am. Chem. Soc.* **1990**, *112*, 8997.

molecule (**338**) containing a latent vinylallene (in the form of a propargylic alcohol) tethered to an enol ether.

Scheme 100

Glycinoeclepin A (**335**)

337

340 + **339** **338**
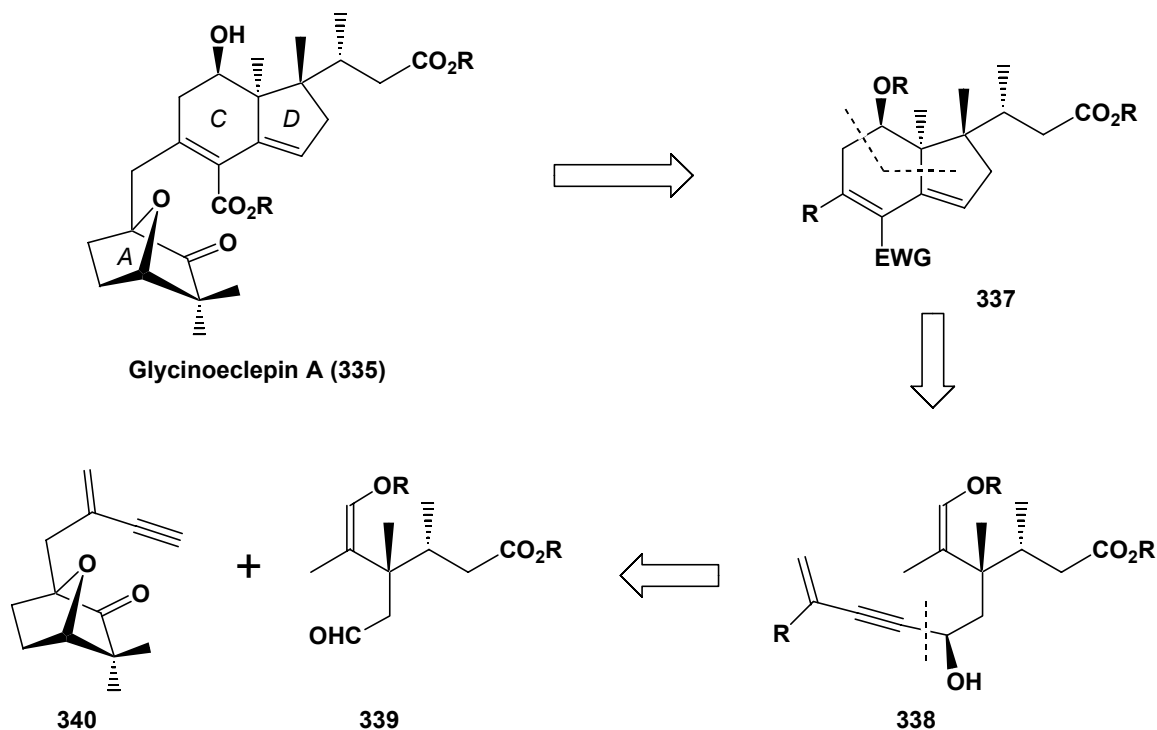
This part of the thesis will be devoted to the discussion of our group's efforts to synthesize the requisite oxabicyclo[2.2.1]heptane A-ring enyne intermediate **340**. The aldehyde **339**, precursor to the CD-ring system, has already been synthesized in a stereoselective manner via a ten-step route developed by Dr. Matthew W. Martin.[194]

---

[193] For a discussion of this key transformation and studies on this phase of the synthesis, see: Martin, M. W. Ph.D. Thesis, Massachusetts Institute of Technology, Cambridge, MA, February 2000.

[194] For a full account of the synthesis of the CD-ring precursor aldehyde **341**, see: Martin, M. W. Ph.D. Thesis, Massachusetts Institute of Technology, Cambridge, MA, February 2000.

7-Oxabicyclo[2.2.1]heptanes

Derivatives of 7-oxabicyclo[2.2.1]heptane are widespread in nature, and a number of synthetic methods have been developed to access this core structure.[195] In addition, because these molecules and their unsaturated derivatives undergo a variety of interesting reactions, they are useful synthetic intermediates for the organic chemist. Furthermore, a number of methods have been developed for the production of enantiomerically pure 7-oxabicycloheptanes, making them useful chirons.

Perhaps the oldest example of a natural product incorporating this key skeletal unit is cantharidin (**341**). First isolated in crystalline form by Robiquet in 1810, cantharidin is found in cantharide beetles and at one time was thought to be an aphrodisiac. A number of related compounds, including palasonin (**342**), are inhibitors of protein phosphatases PP1, PP2A, and PP2B. The natural herbicide 1,4-cineole (**343**), first described by Wallach in 1907, is formed by acid-promoted elimination of water and cyclization of 1,8-terpin (*p*-menthane-1,8-diol, **344**).

cantharidin (**341**)   palosonin (**342**)   1,4-cineole (**343**)   1,8-terpin (**344**)

---
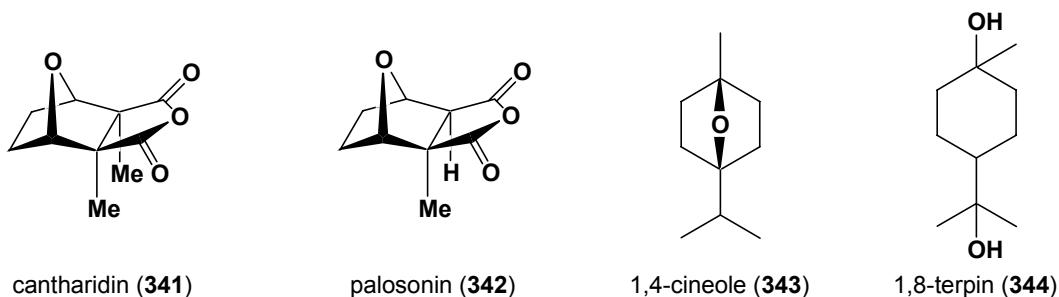
[195] For recent reviews, see: (a) Lautens, M.; Chiu, P. *Topics. Curr. Chem.* **1997**, *190*, 1. (b) Vogel, P.; Cossy, J.; Plumet, J.; Arjona, O. *Tetrahedron* **1999**, *55*, 12521.

7-Oxabicycloheptanes via Cycloaddition Approaches

As discussed in Part I of this thesis, cycloaddition reactions are powerful transformations that allow for the design of highly convergent synthetic strategies. Thus, it is not surprising that some of the most expeditious and frequently employed routes to the oxabicycloheptane skeleton involve the use of cycloadditions. Two common cycloaddition approaches to the oxabicycloheptane system involve the retrosynthetic disconnections shown in Scheme 101.

Scheme 101
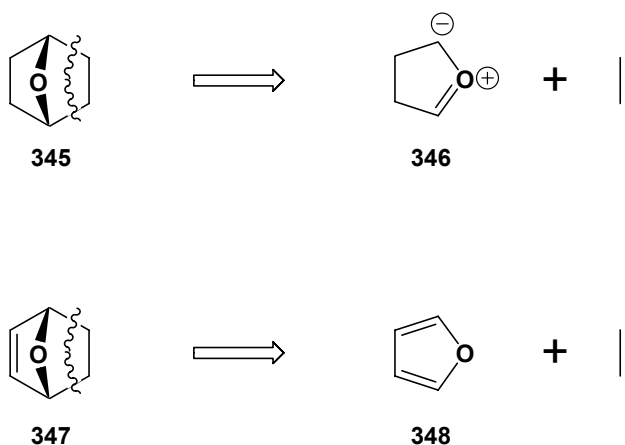
Disconnection of 7-oxabicycloheptane **345** gives rise to carbonyl ylide **346** as the partner for a 1,3-dipolar cycloaddition with an alkene. Retrosynthetic analysis of the 7-oxabicycloheptene **347**, itself a useful intermediate and easily transformed into **345**, leads to a [4 + 2] cycloaddition of furan with an alkene. Both of these approaches have been used for the construction of oxabicycloheptane derivatives.[195]

The reaction between furan and maleic anhydride was first investigated by Diels and Alder in 1929.[196] At room temperature the reaction gives rise to the *exo* adduct **350**, the structure of which was first demonstrated by Woodward and Baer in 1948.[197] In 1962, Anet and coworkers determined that the *endo* adduct **351** forms concurrently at low temperatures, but after a period of time, only the *exo* adduct is observed.[198] As shown in Scheme 102, kinetic data on the cycloaddition of furan with maleic anhydride indicate that the *endo* adduct **351** is formed faster than the *exo* adduct **350**, but also undergoes cycloreversion faster.[199]

Scheme 102

$k_1 = 1.60 \times 10^{-5}\ \text{Lmol}^{-1}\text{s}^{-1}$

$k_{-1} = 4.40 \times 10^{-6}\ \text{s}^{-1}$

350

$k_2 = 7.29 \times 10^{-3}\ \text{Lmol}^{-1}\text{s}^{-1}$

$k_{-2} = 4.37 \times 10^{-2}\ \text{s}^{-1}$

348   **349**

351
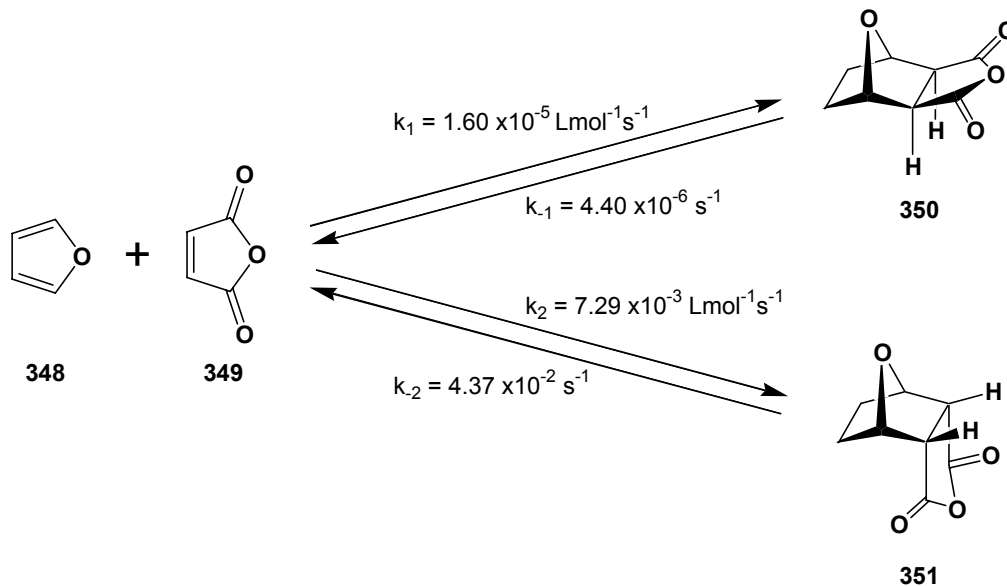
Due to the aromaticity of furan, its cycloadducts are thermally sensitive and often revert to the starting materials. Through the use of very reactive dienophiles, respectable

[196] Diels, O.; Alder, K. *Chem. Ber.* **1929**, *62*, 554.
[197] Woodward, R. B.; Baer, H. *J. Am. Chem. Soc.* **1948**, *70*, 1161.

yields of cycloadducts can be formed. Application of high-pressure techniques[200] and the use of Lewis acid promoters[201] that activate the dienophile can facilitate the cycloaddition of furans. In some cases even unactivated dienophiles add to furan.[202]

Padwa has developed an approach to oxabicycloheptanes in which carbonyl ylides undergo 1,3-dipolar cycloadditions with a variety of dipolarophiles. Scheme 103 depicts an example of this methodology as applied to the synthesis of the pterosin family of sesquiterpenes.[203]   This methodology has also been extended to generate fused 7-oxabicycloheptanes via intramolecular carbonyl ylide cycloadditions with pendant alkenes.

Scheme 103

352   353   354
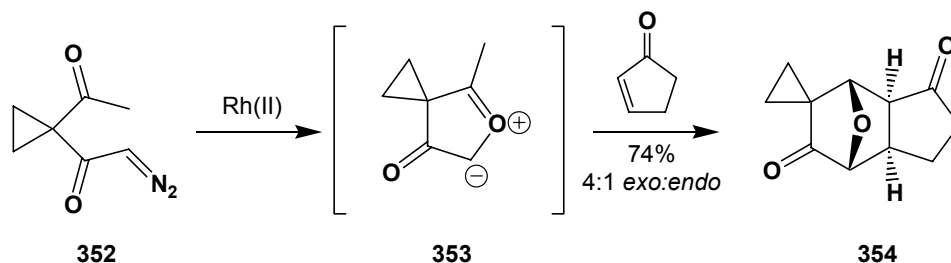
[198] Anet, F. A. L. *Tetrahedron Lett.* **1962**, *3*, 1219.
[199] Lee, M. W.; Herndon, W. C. *J. Org. Chem.* **1978**, *43*, 518.
[200] (a) Dauben, W. G.; Krabbenhoft, H. O. *J. Am. Chem. Soc.* **1976**, *98*, 1992. (b) Butz, T.; Sauer, J. *Tetrahedron: Asymmetry* **1997**, *8*, 703.
[201] (a) Grieco, P. A.; Nunes, J. J.; Gaul, M. D. *J. Am. Chem. Soc.* **1990**, *112*, 4595. (b) Waldmann, H. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1306.
[202] (a) Newman, M. S.; Addor, R. W. *J. Am. Chem. Soc.* **1955**, *77*, 3789. (b) Matsumoto, K.; Ikemi, Y.; Hashimoto, S.; Lee, H. S. Okamoto, Y. *J. Org. Chem.* **1986**, *51*, 3729.
[203] Curtis, E. A.; Sandananyaka, V. P.; Padwa, A. *Tetrahedron Lett.* **1995**, *36*, 1989.

7-Oxabicycloheptanes via Cyclization Approaches

A number of general methods exist for the formation of the 7-oxabicycloheptane system that do not involve a cycloaddition reaction. Most of these approaches take advantage of the nucleophilicity of an oxygen atom for the cyclization step. Scheme 104 depicts the retrosynthetic analysis of the S_N1-type approach, which involves the formation and cyclization of a 4-hydroxycyclohexyl cation **355**, and the S_N2-type approach, which involves a cyclohexanol **356** with a leaving group at the 4-position. An example of each of these approaches will be discussed below.

Scheme 104
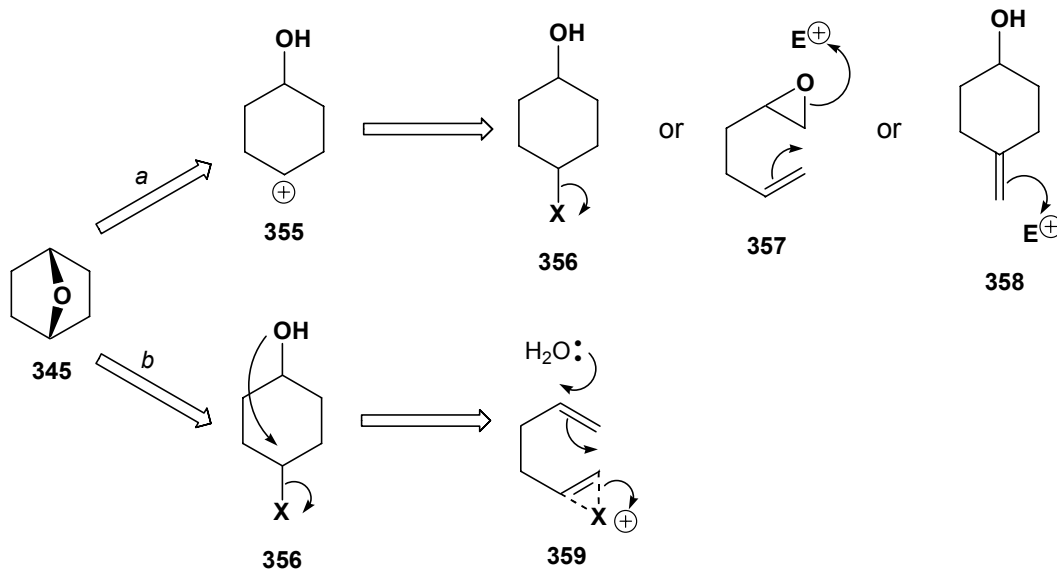
Retrosynthetic pathway *a* involves the intermediacy of a 4-hydroxycyclohexyl cation **355**. Two examples of this approach, shown in Scheme 105, involve the ionization of a leaving group from **356**, in these cases via acid-catalyzed ring-opening of epoxides. Alkenes **360** and **363** are epoxidized to oxiranes **361** and **364** respectively,

which can then be treated with acid catalysts to induce ring-opening with concomitant cyclization to afford the oxabicyclic products **362** and **365**.

Scheme 105
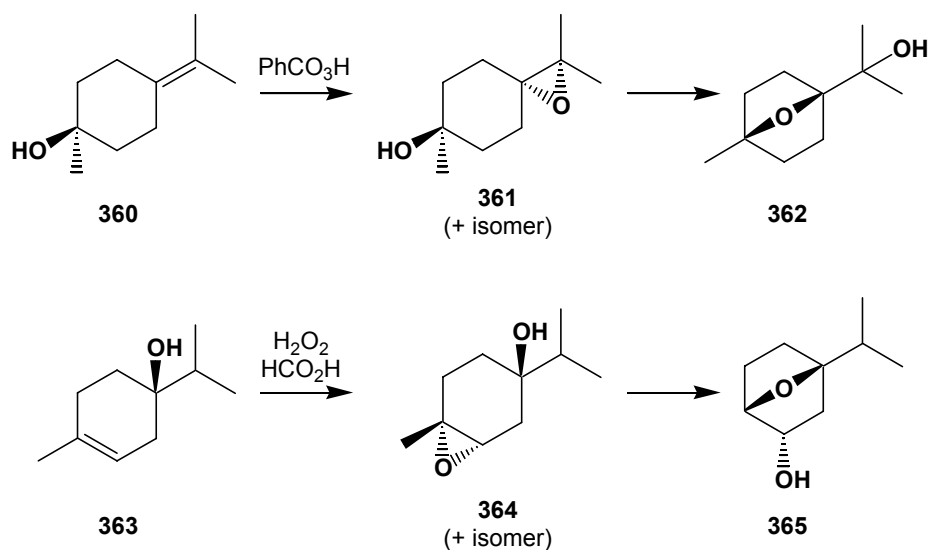
A similar approach included in this category involves the acid-catalyzed rearrangement of cyclopropyl epoxides shown in Scheme 106. Cyclopropyl epoxide **366** can rearrange to cation **367**, ultimately providing allylic alcohol **368**. This approach was employed by Corey in his biomimetic synthesis of 12-deoxyglycinoeclepin.[204]

Scheme 106
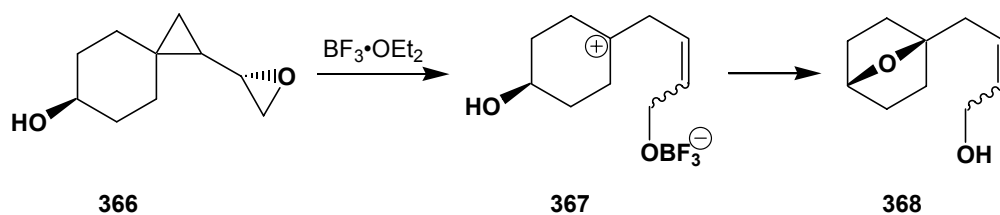
An alternative approach for the formation of the 4-hydroxycyclohexyl cation **355** involves addition of an electrophile to a 4-alkylidenecyclohexanol **358**. There are numerous examples of this approach involving primarily iodoetherification and oxymercuration processes. Several examples will be discussed later in conjunction with the review of previous strategies for the synthesis of glycinoeclepin A.

Cationic cyclization of butenyl-substituted epoxide **357** has also been employed to generate the 4-hydroxycyclohexyl cation **355**. Scheme 107 outlines an example of this approach.

Scheme 107
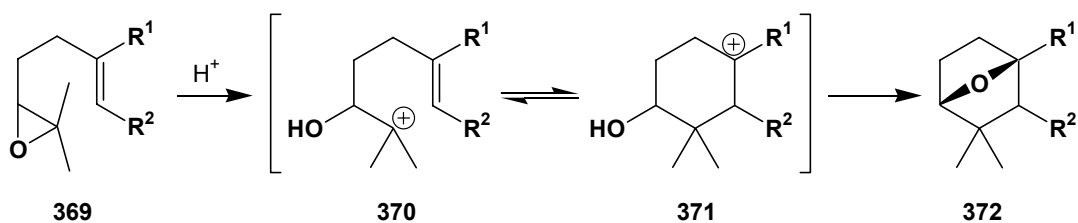
The acid-promoted ring-opening of epoxide **369** generates carbocationic intermediate **370** which undergoes cation-π cyclization, generating a 4-hydroxycyclohexyl cation **371**. This cation then is trapped by the internal hydroxyl group to form the oxabicycloheptane ring system **372**.

Retrosynthetic pathway *b* involves nucleophilic displacement of a leaving group on **356** by the nucleophilic oxygen atom. An example of this approach involves a rather

---

[204] Corey, E. J.; Hong, B.-C. *J. Am. Chem. Soc.* **1994**, *116*, 3149.

unusual oxidative cyclization reaction.[205] As shown in Scheme 108, thallium tris(perchlorate) adds to the terminal double bond of geraniol (**373**) and triggers a cation-π cyclization (**374→375**); trapping of the resultant cation by water then gives intermediate **376**. The hydroxyl group then intramolecularly displaces the thallium species bound to the 4-position of the ring to afford the oxabicyclic compound **377**.

Scheme 108
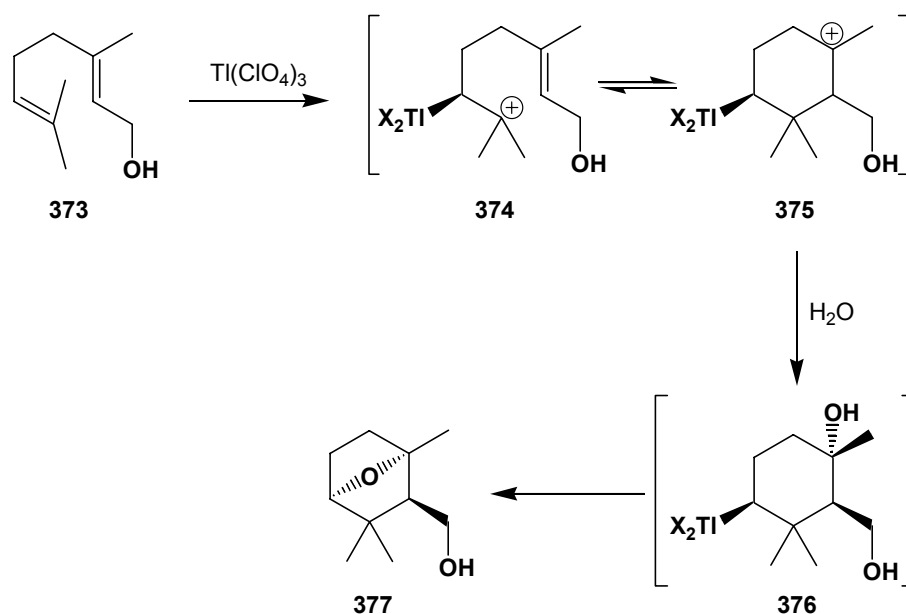
Previous Strategies for the Construction of the Glycinoeclepin A-Ring

As mentioned above, three previous total syntheses of glycinoeclepin A have been reported to date. This section will outline, for each total synthesis, the retrosynthetic disconnection leading to A-ring and CD-ring fragments, the approach employed for the

[205] (a) Yamada, Y.; Sanjoh, H.; Iguchi, K. *J. Chem. Soc., Chem. Commun.* **1976**, 997. (b) Aziz, M.; Rouessac, F. *Bull. Chim. Soc. Fr.* **1988**, 555.

construction of the A-ring component, and the reaction sequence employed to attach it to the CD-ring building block.

(a) Murai Strategy

The first total synthesis of glycinoeclepin A, published by Murai and coworkers,[190] employed an alkylation strategy to attach the A-ring iodide **378** to the CD-ring partner **379** (Scheme 109).

Scheme 109

Glycinoeclepin A (335)   378   379
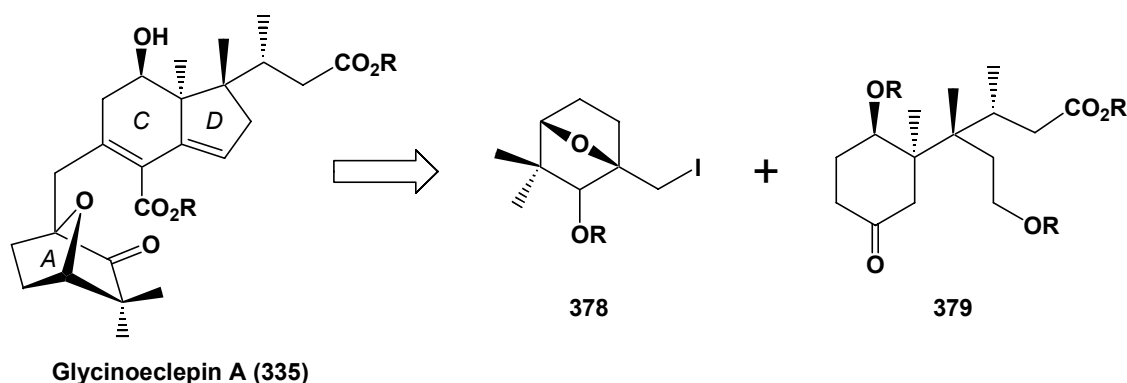
The A-ring iodide **378** incorporates the easily-identifiable retron for an iodoetherification reaction. Thus, the synthesis of **378** was a fairly straightforward process, as outlined in Scheme 110. The chiral hydroxy ketone **381**[206] is clearly a key intermediate in this route. Enantioselective reduction of 2,2-dimethyl-1,3-cyclohexanedione (**380**)[207] using Baker's yeast afforded **381** in 67% yield with a reported 94.3% enantiomeric excess. Protection of the alcohol and α-methylenation gave enone

[206] Mori, K.; Mori, H. *Organic Syntheses*; Wiley & Sons: New York, 1993; Collect. Vol. VIII, 312.
[207] Jacobson, B. M.; Soteropoulos, P.; Bahadori, S. *J. Org. Chem.* **1988**, *53*, 3247.

382. Reduction of the ketone with sodium trimethoxyborohydride followed by acid hydrolysis of the ethoxyethyl ether afforded diol **383** in 86% yield over two steps. The diol **383** was treated with *N*-iodosuccinimide to effect the intramolecular iodoetherification, providing iodide **384** in 79% yield.

Scheme 110
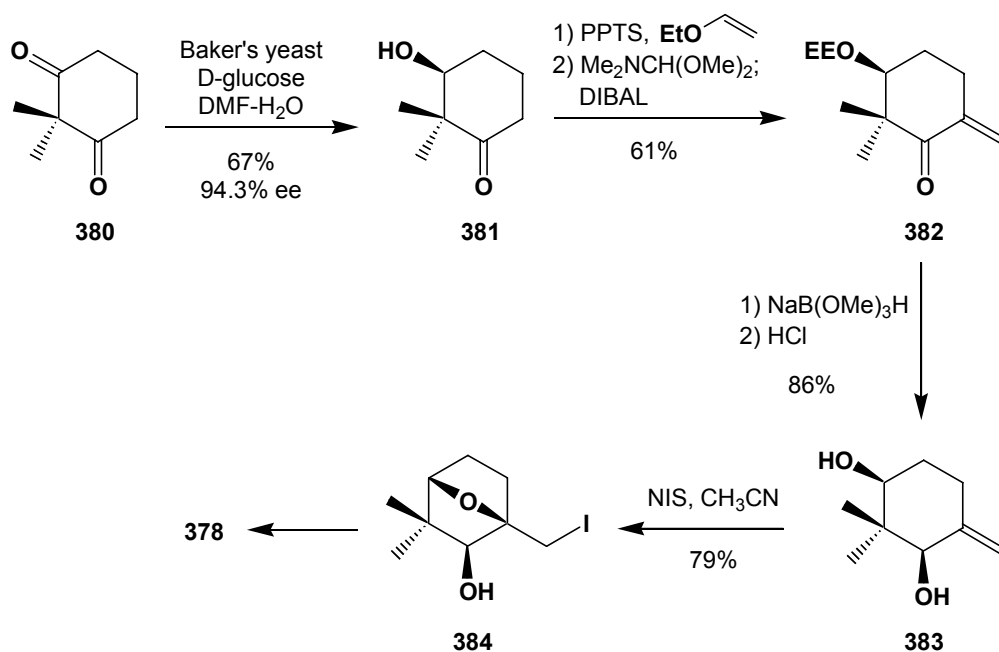
All attempts at alkylation of the ketone **385** with primary iodide **378** met with failure (Scheme 111). Quite possibly, the neopentylic iodide is too sterically congested to undergo intermolecular displacement.

Scheme 111

378   **385**   **386**
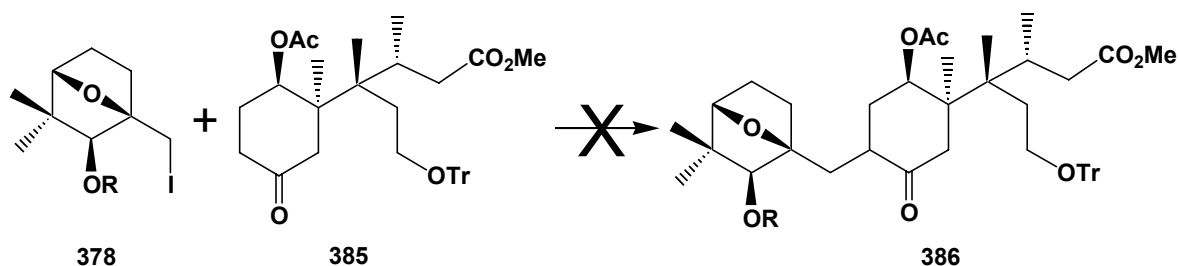
Because this intermolecular alkylation strategy failed, the authors decided to attempt an intramolecular alkylation as depicted in Scheme 112. Ester **387** was synthesized and, upon treatment with potassium fluoride and 18-crown-6, the desired lactone **388** was formed.[208]

Scheme 112

KF
18-crown-6

76%

387   **388**
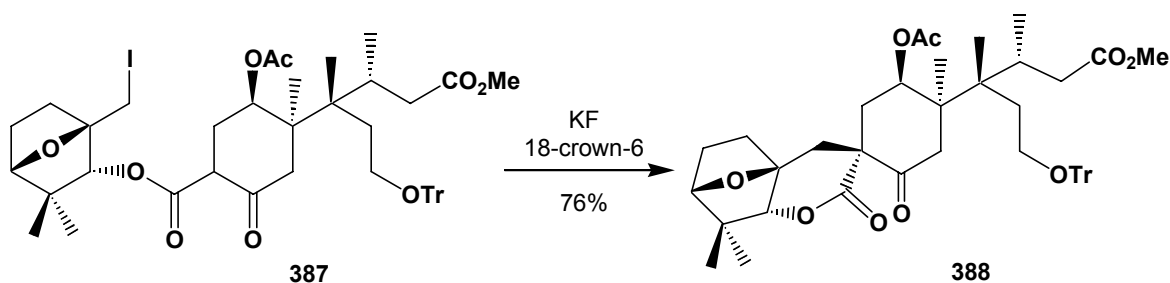
(b) Mori Strategy

In 1989, Mori and Watanabe published the second total synthesis of glycinoeclepin A.[191] In an approach similar to that of Murai, Mori's A-ring strategy (Scheme 113) employed Baker's yeast reduction of **380**. Protection of the alcohol and aldol condensation with acetaldehyde afforded enone **389**. Reduction of the ketone and

---

[208] The configuration of the A-ring alcohol in **387** is opposite to that in **378**. All attempts at alkylation with the ester derived from **378** met with failure. The isomeric alcohol precursor to **387** was obtained by an oxidation and then reduction of **378**.

protection of the resultant alcohol set the stage for the key NIS-promoted iodoetherification, which afforded the oxabicyclic iodide **390**. Further elaboration of this compound to **392** was to set the stage for its use as an aldol partner in a coupling to a CD-ring precursor.

Scheme 113
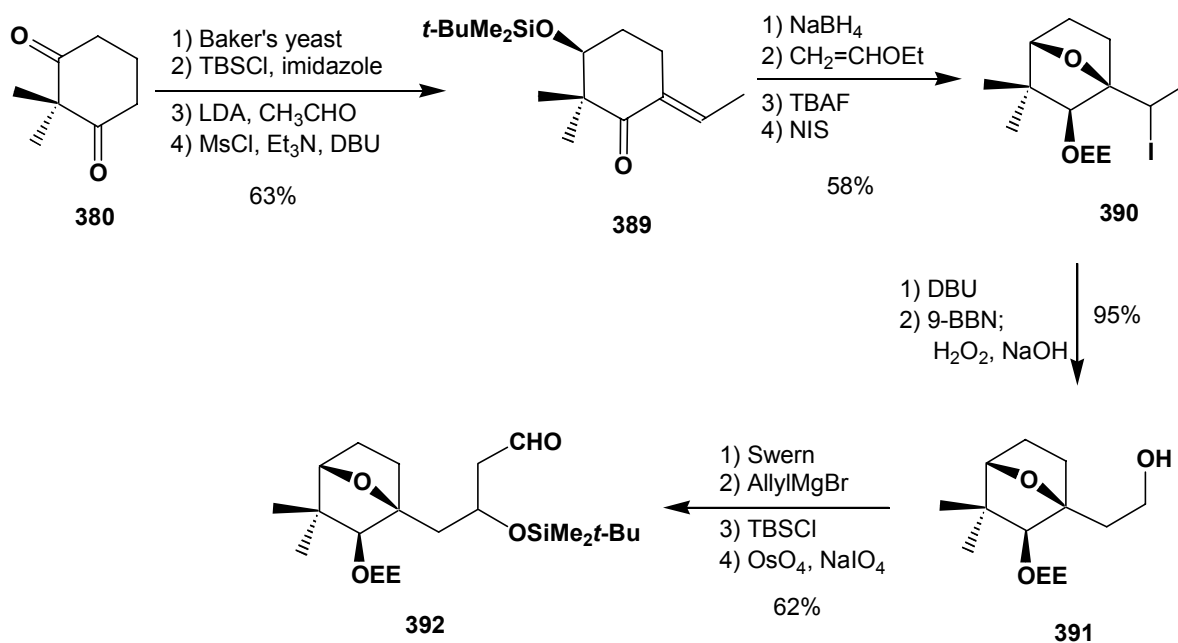
(c) Corey Strategy

The third total synthesis of glycinoeclepin A was completed by Corey and Houpis in 1990.[192] Corey's plan for coupling A-ring and CD-ring intermediates relied upon a Stille reaction involving vinyl triflate **396** (Scheme 114). The A-ring synthesis again began with dione **380**, but in this instance Corey chose a catalytic enantioselective reduction of the ketone with catecholborane and the oxazaborolidine catalyst **393**.[209] Protection of the resultant alcohol **381** furnished ketone **394**, which was then formylated

by treatment with sodium hydride and ethyl formate to generate **395**. Conversion of this formyl derivative to the vinyl triflate **396** required for the Stille reaction was accomplished with sodium hydride and *N*-phenyltriflimide.

Scheme 114
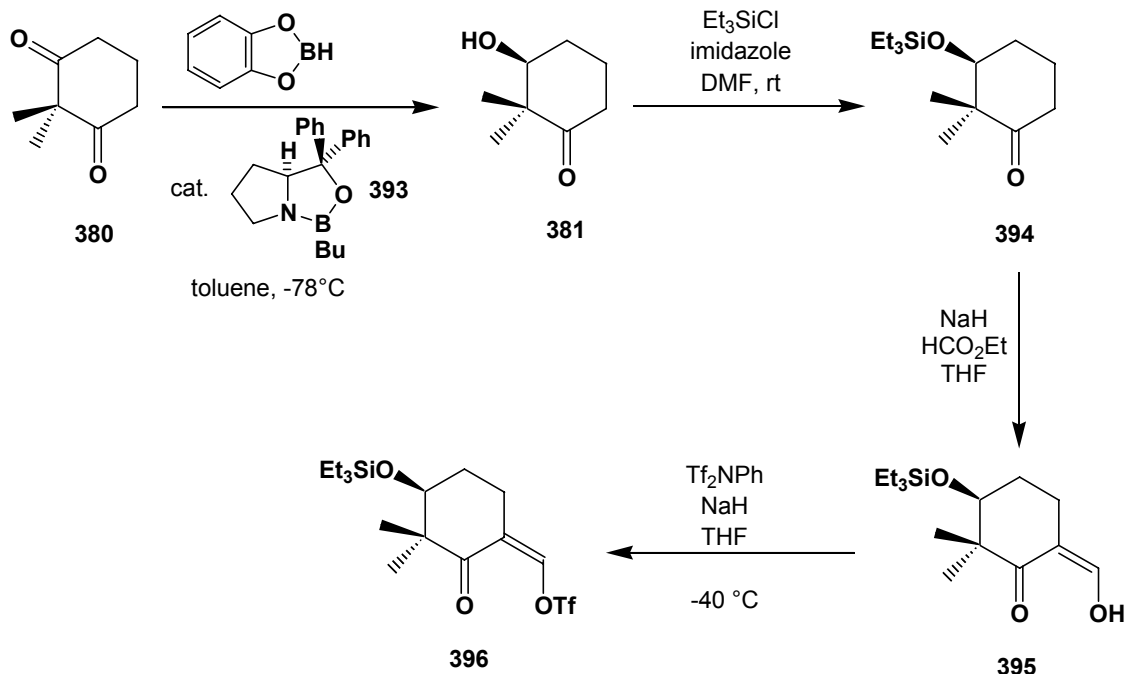
Stille coupling of vinyl triflate **396** with stannane **397** provided **398** with the complete A-C-D carbocyclic system in place. However, the A-ring still required a further elaboration to form the oxabicyclic system. As shown in Scheme 115, a series of functional group manipulations afforded alcohol **399**, which was cyclized by oxymercuration with mercury(II) oxide/mercury(II) trifluoroacetate. The subsequent demercuration of the organomercurial species was accomplished with dibutyltin hydride.

---

[209] Corey, E. J.; Bakshi, R. K. *Tetrahedron Lett.* **1990**, *31*, 611.

Deprotection and oxidation of the A-ring alcohol then afforded **400**, complete with the oxabicyclic A-ring fully elaborated.

Scheme 115
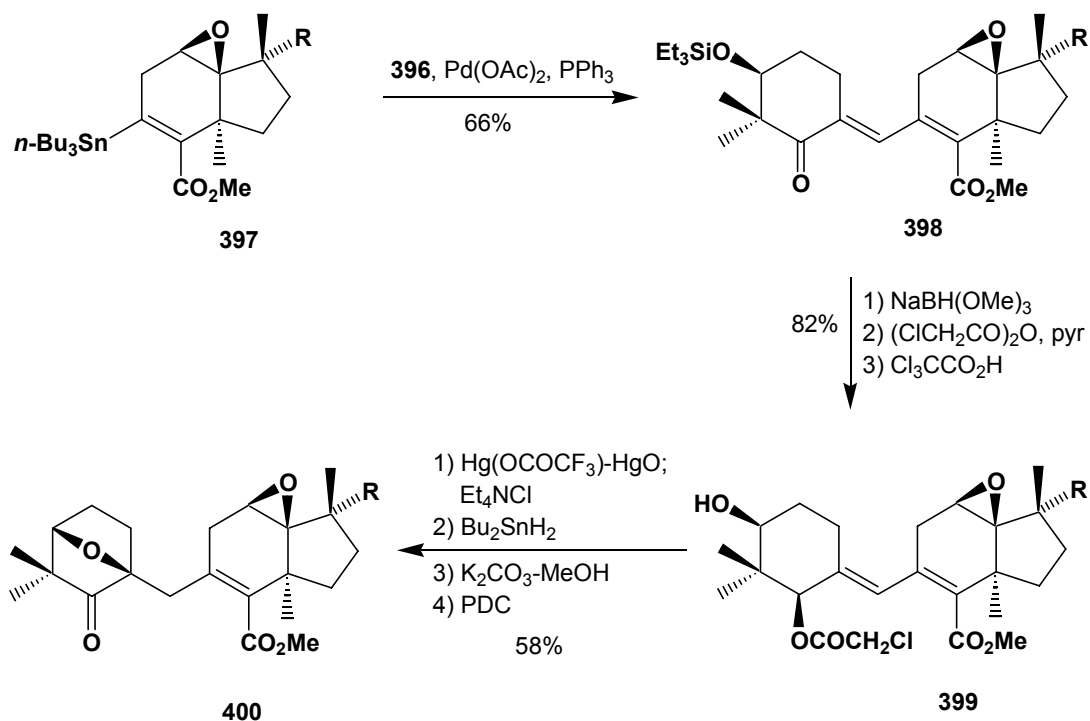
Our First-Generation Synthesis of the A-Ring Enyne

As mentioned earlier, synthesis of a key CD-ring intermediate was completed in our laboratory by Dr. Matthew Martin, and studies on the key rearrangement-cycloaddition step required access to an A-ring enyne intermediate. At that stage in our research, the priority was to synthesize the A-ring enyne by any route adequate at providing reasonable quantities of an A-ring building block.

Dr. Christophe Mellon developed the retrosynthetic analysis shown in Scheme 116 which led to our "first-generation" synthesis of the A-ring enyne **340**. The actual target molecule for this synthetic strategy was the protected alcohol **401**. It was planned that deprotection of the alcohol and oxidation to the ketone would take place after the rearrangement-cycloaddition step, concurrent with other functional group transformations required for completion of the synthesis.

Two key transformations dictated most of the strategy developed for this route. First was the desire to create the oxabicyclic system in **401** via an oxymercuration/demercuration protocol similar to the one used by Corey in his synthesis of glycinoeclepin A.[192] Second was the insight that the enyne moiety could be created from the methyl ketone **402** by vinyl triflate formation and Sonogashira coupling with trimethylsilylacetylene.

The 4-alkylidenecyclohexanol **404** would be the substrate for the oxymercuration reaction. The synthesis of **404** was based on an aldol strategy, in which the aldehyde partner would incorporate a latent ketone at the α position which could be unmasked to provide ketone in **402** after the oxymercuration. The known β-alkoxy aldehyde **406** was selected because it could be easily prepared from commercially available ethyl lactate.

Scheme 116
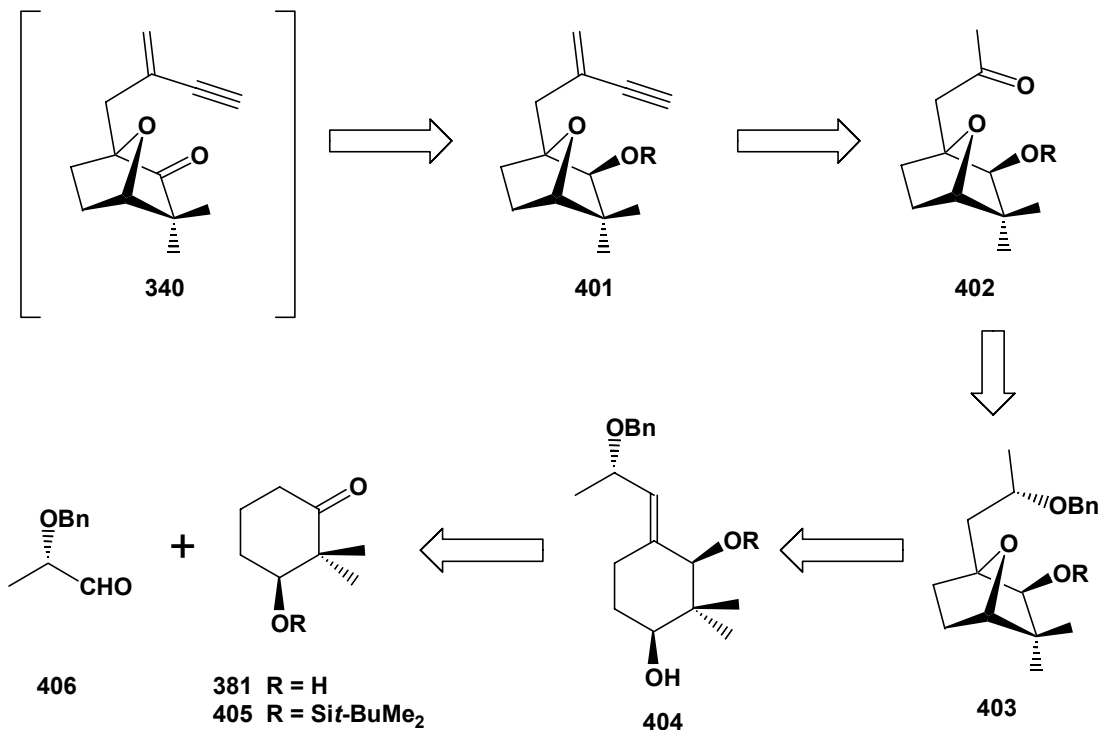
Aldehyde **406** was prepared from ethyl lactate via a three-step procedure according to the protocol of Heathcock (Scheme 117).[210] Protection of the alcohol in **407** as the benzyl ether using silver (II) oxide-promoted etherification with benzyl bromide, followed by reduction of the ester to the alcohol with lithium aluminum hydride, afforded **408** in 42% yield over two steps. Swern oxidation proceeded in excellent yield afford the aldehyde **406** necessary for the aldol reaction.

---

[210] Takai, K.; Heathcock, C. H. *J. Org. Chem.* **1985**, *50*, 3247.

Scheme 117
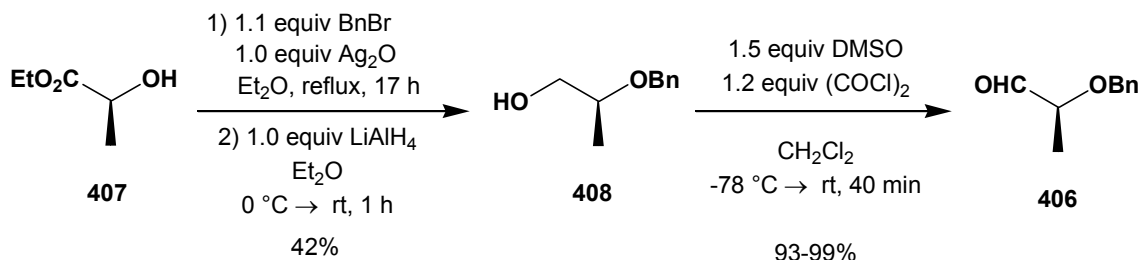
The aldol reaction between aldehyde **406** and ketone **405** and *in situ* elimination of the intermediate alcohol **409** provided a mixture of compounds from which enone **410** could be isolated in 36% yield. Optimization of this sequence by Dr. Yoshinori Ikeura revealed that the yield could be greatly improved if the aldol reaction and elimination were performed as two separate steps. As illustrated in Scheme 118, treatment of ketone **405** with LDA followed by addition of aldehyde **406** at -60 °C and warming of the reaction mixture to -45 °C provided **409**. Formation of the mesylate with methanesulfonyl chloride and triethylamine followed by elimination with DBU afforded the desired enone **410** in 76% overall yield from **405**. Under these optimized conditions, enone **410** was formed exclusively as the *E*-isomer as determined by analysis of the ^{1}H NMR spectrum.[211]

---

[211] In preliminary experiments, a mixture of *E*- and *Z*-isomers was obtained. ^{1}H NMR analysis of the two isomers revealed that the C-7 vinyl protons appear at 6.4 ppm and 5.6 ppm for the major and minor isomers, respectively. The downfield shift for the vinyl proton in the major isomer results from its orientation in the deshielding region of the adjacent carbonyl group. The major isomer was therefore assigned the *E*-configuration.

Scheme 118
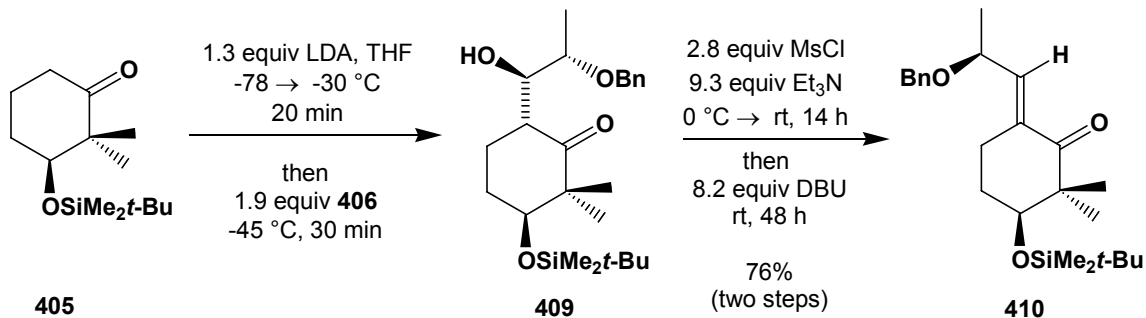
Enone **410** was next converted to alcohol **412** by a three step sequence (Scheme 119). Reduction of the ketone carbonyl was accomplished following the Luche protocol to yield the expected allyl alcohol. Protection of the alcohol by esterification with pivaloyl chloride afforded **411** in 96% yield over two steps. Cleavage of the silyl ether with TBAF and acetic acid in refluxing THF then gave the 4-alkylidenecyclohexanol **412**.

Scheme 119
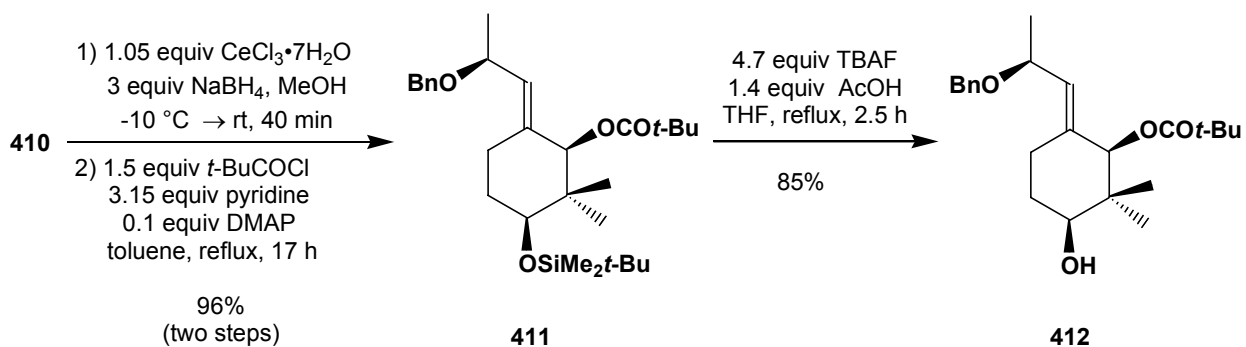
As outlined in Scheme 120, intramolecular oxymercuration with mercury (II) oxide and mercury (II) trifluoroacetate, followed by *in situ* demercuration of the

organomercurial intermediate with sodium borohydride, provided the desired oxabicyclic

compound **413** in 83% yield.

Scheme 120
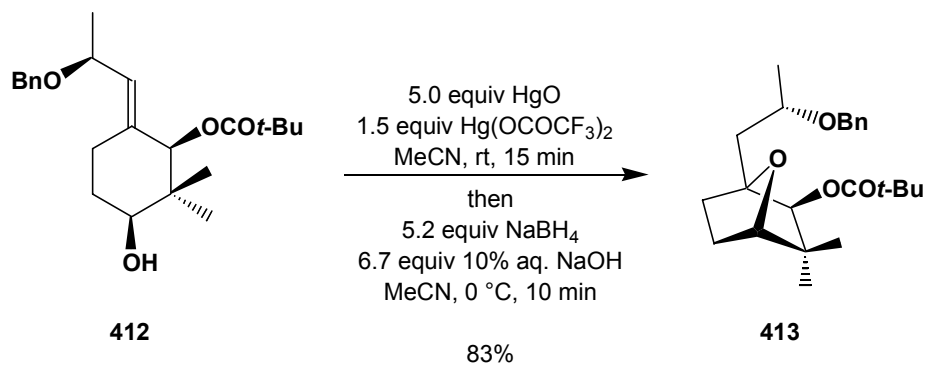
Debenzylation and Dess-Martin oxidation of the resultant alcohol provided ketone

414.   Formation   of   vinyl   triflate   **415**   and   Sonogashira   coupling   with

(trimethylsilyl)acetylene then afforded the desired silylenyne **416** (Scheme 121).

Scheme 121
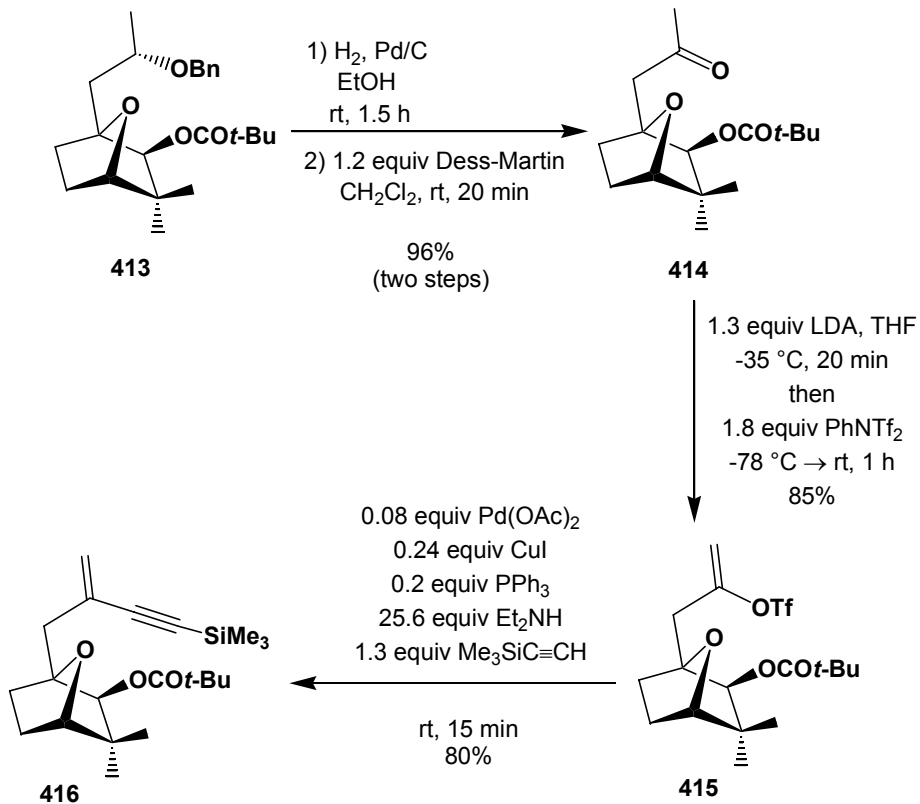
The alkynylsilane **417** was desilylated under standard conditions with TBAF in THF to afford enyne **418** (Scheme 122). This compound, with the ring ketone protected as the pivalate ester of the corresponding alcohol, was used in initial studies of the tandem propargylic rearrangement – intramolecular vinylallene Diels-Alder reaction.

Scheme 122
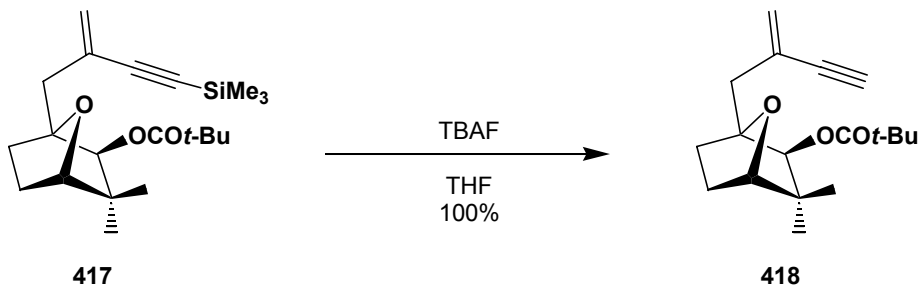
Summary

The three published routes and our first-generation synthetic strategy for the synthesis of the A-ring portion of glycinoeclepin A have been described. As discussed in this chapter, there are a number of useful strategies for the synthesis of 7-oxabicycloheptane derivatives. The three published routes to the A-ring of glycinoeclepin A all involve electrophilic cyclization strategies for the cyclization of the bicyclic system. Dr. Christophe Mellon and Dr. Yoshinori Ikeura in our group have employed an oxymercuration strategy for their synthesis of the A-ring enyne intermediate **418** via a 12-step route.

The next chapter will detail my unsuccessful attempts at streamlining this route utilizing similar electrophilic cyclization tactics, and the development and optimization of a novel acid-catalyzed cyclization route which has provided the A-ring enyne **340** in only six steps from the alcohol **381**.

Chapter 3

New Approaches to the Synthesis of an
A-Ring Enyne Intermediate

As discussed in the previous chapter, Drs. Mellon and Ikeura developed a 12-step sequence for the production of the A-ring enyne intermediate **418**. This accomplishment was important because it provided sufficient quantities of material for initial studies of the tandem propargylic rearrangement – intramolecular vinylallene Diels-Alder reaction, the key step in our total synthesis.

However, the lengthy 12-step route to A-ring enyne **418** detracts from the overall efficiency of our total synthesis of glycinoeclepin A, especially in comparison to the 10-step route to the more complex CD-ring precursor. The development of a shorter route to the A-ring intermediate **340** was desirable.

We envisioned a number of alternative strategies for construction of the A-ring enyne intermediate, including streamlined versions of our first-generation route which incorporate changes to the protecting group strategies. This chapter will detail my work on the modification of our first-generation route, and the development of a new cyclization strategy which provides the enyne **340** from the hydroxy ketone **381** in only six steps.

A Modified Rearrangement-Cycloaddition Strategy

The A-ring enyne **418** used in the initial cycloaddition studies contains a protected form of the A-ring ketone which would therefore require eventual unmasking. It was envisioned that the deprotection of the pivalate ester and oxidation to the ketone would

take place after the key cycloaddition step, concurrent with other reductive and oxidative functional group transformations required for elaboration of functionality on the CD-ring portion of the molecule.

Optimization studies (Scheme 123) by Dr. Yoshinori Ikeura on the key rearrangement-cycloaddition reaction led to the discovery that the reaction proceeds more efficiently when the propargylic mesylate **421** is used instead of the carbonate **419**. Critical to the success of this reaction is the use of the A-ring ketone in place of the more sterically demanding protected alcohol.[212]

Scheme 123

---
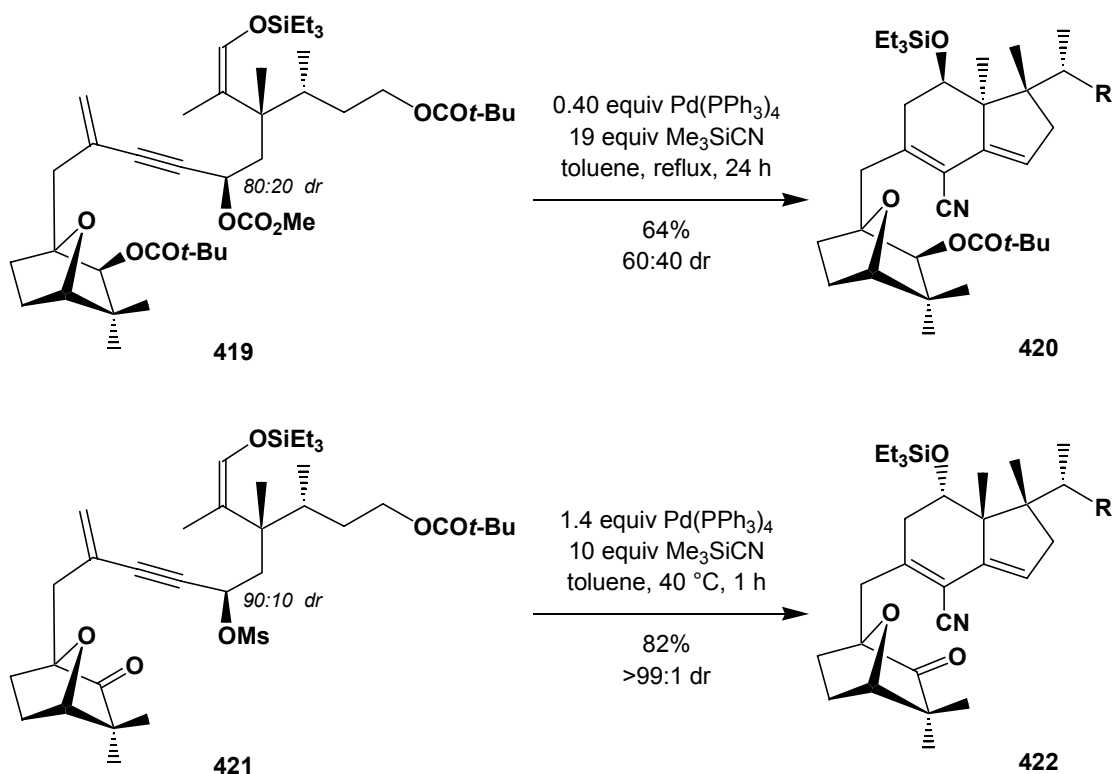
[212] Although the reaction of **423**→**424** provided the undesired diastereomer, the cycloaddition proceeded quite well in the presence of the A-ring ketone. Dr. Hiroshi Shinokubo later developed improved conditions for this reaction which gives the desired diastereomer as the major (60:40) product.

175

The mesylate **421** was derived from propargylic alcohol **424**, which was obtained with excellent diastereoselectivity from the reaction of the lithium acetylide derived from **340** with aldehyde **423** (Scheme 124). Importantly, the lithium acetylide is a stable species which does not undergo self-condensation under the reaction conditions.

Scheme 124
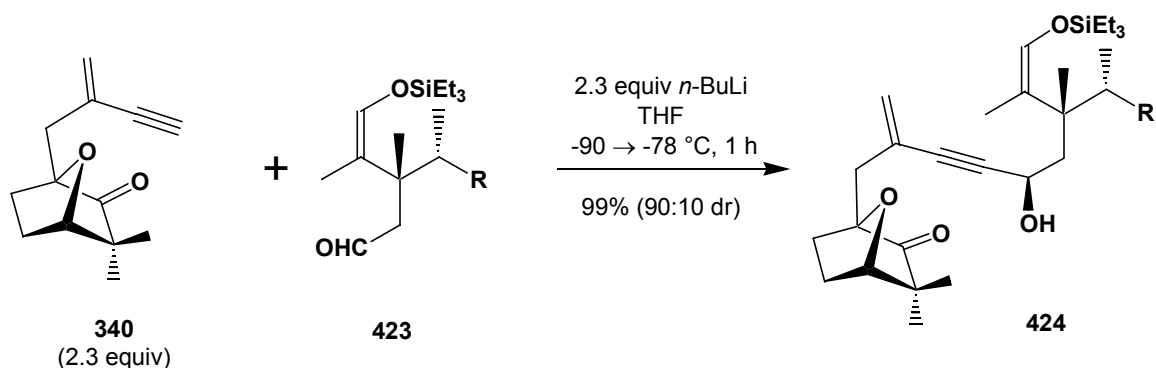
The ketone **340** was obtained from the Mellon-Ikeura A-ring intermediate **418** (Scheme 125) by a two-step deprotection-oxidation sequence. With these two additional steps, the route to the A-ring enyne intermediate **340** totals 14 steps in the longest linear sequence. Clearly a shorter route was required.

Scheme 125

176
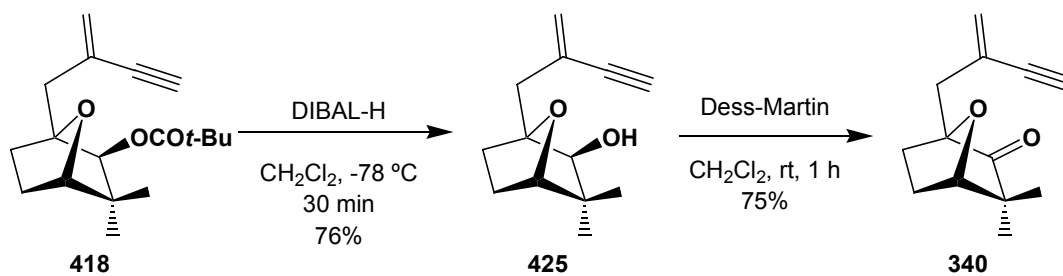
Streamlined Approaches to the A-Ring Enyne via Electrophilic Cyclization

As summarized in Scheme 126, our first-generation route to the A-ring enyne **429** incorporated a reduction-protection sequence prior to the cyclization, and a deprotection-oxidation sequence afterward.

Scheme 126
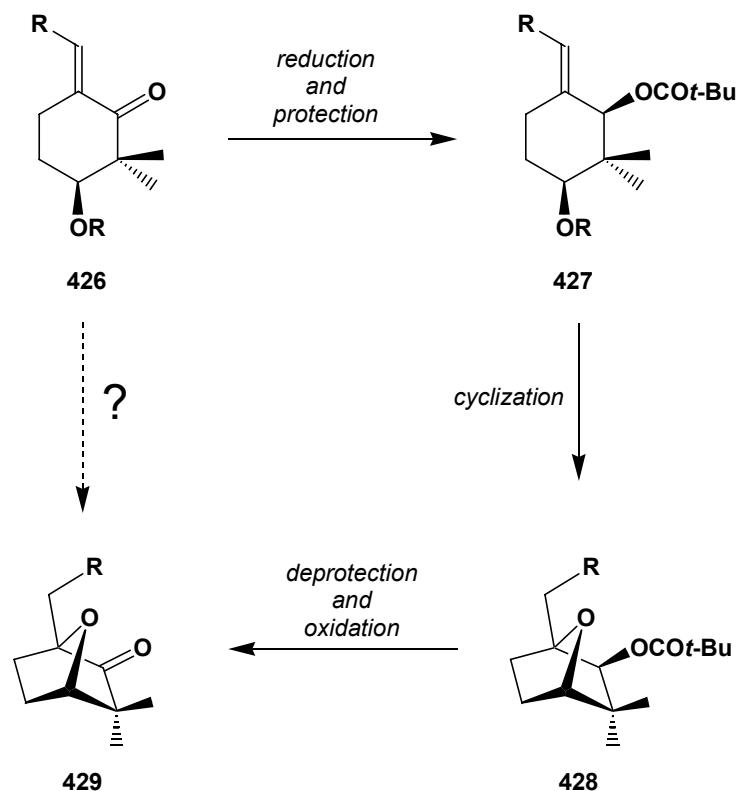
If we could eliminate these potentially unnecessary functional group manipulations of the ring ketone, we could potentially access the A-ring enyne **429** in 10 steps, four fewer than the first-generation route. Initially, we wished to retain from our first-generation route oxymercuration of the 4-alkylidenecyclohexanol (*vide supra*) as the key cyclization step. However, we noted that successful implementation of this new

strategy would require the oxymercuration reaction to be carried out on the double bond of an enone (instead of the double bond of a protected allylic alcohol).

We were concerned that the electron-deficient double bond of the enone would be unreactive toward electrophilic reagents such as mercury (II) salts. We noted that Corey's total synthesis of glycinoeclepin A involves an oxymercuration on a dienoate ester as the key cyclization step (see Chapter 2, Scheme 115). In addition to Corey's oxymercuration of unsaturated esters, a few scattered reports of oxymercuration of enoate esters can be found in the literature.[213] However, a thorough review of the literature revealed no examples of oxymercuration of enones.

Our initial exploration focused on electrophilic cyclizations because these reactions were straightforward. The required 4-alkylidenecyclohexanol **431** was prepared from **430** by desilylation with TBAF in THF. Subjecting **431** to the same oxymercuration conditions successfully employed by Dr. Mellon led only to recovery of unchanged starting material (Scheme 127).

Scheme 127

---
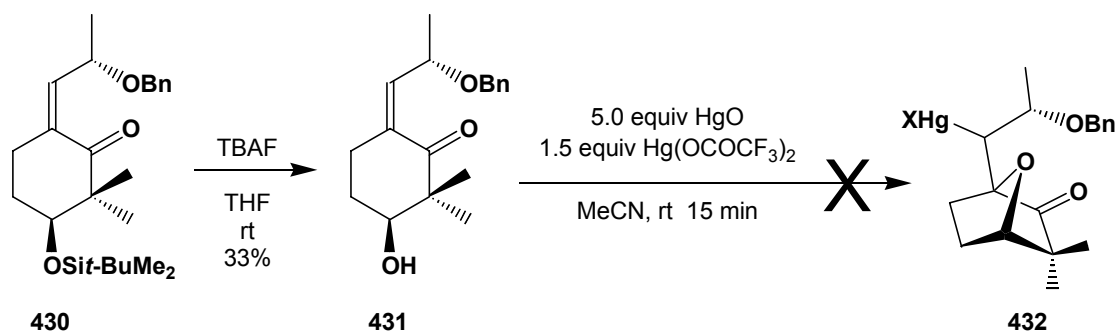
[213] (a) Anelli, P. L.; Beltrami, A.; Lolli, M.; Uggeri, F. *Synth. Comm.* **1993**, *23*, 2639. (b) Gouzoules, F. H.; Whitney, R. A. *J. Org. Chem.* **1986**, *51*, 2024.

Not surprisingly, examination of the reactivity of enone **431** toward other electrophilic reagents led to the same disappointing results. Electrophiles such as Br_2, I_2, NIS, and ICl and did not promote the desired reactions, and starting material was recovered in each case (Scheme 128).

Scheme 128
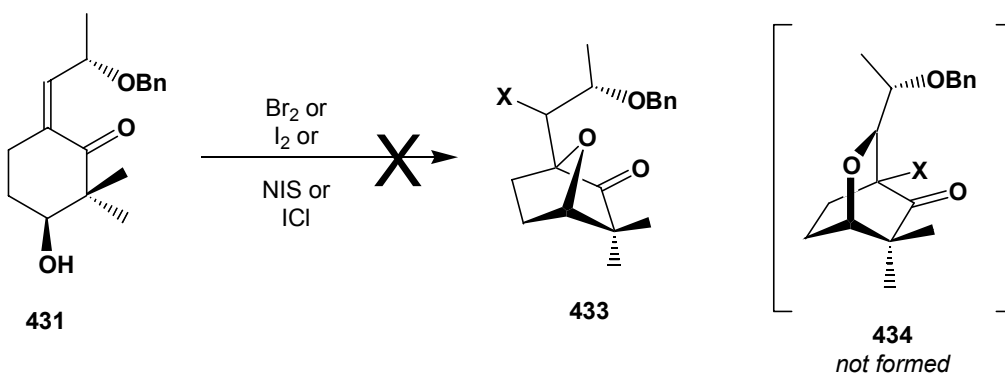
The known examples of oxymercuration of enoates afford products that result from formal 1,4-addition of the hydroxyl group to the enoate, via an intermediate α-mercurial ester. The formation of the desired oxabicyclo[2.2.1]heptane would require the reaction of the hydroxyl group at the α carbon of the enone, although this regiochemistry may be disfavored if the transition state involves significant cationic character at that carbon. The electronically-favored addition of the hydroxyl group at the β carbon should provide oxabicyclo[2.2.2]octane **434**, although we observe none of this alternative product from the reaction of **431** with various electrophiles. We conclude that **433** is disfavored electronically, while **434** is disfavored geometrically.

After our plan to shorten the first-generation route by elimination of functional group manipulations met with failure, we considered several related similar alternative

strategies. We imagined that the lack of reactivity of the enone toward electrophiles might be overcome by converting the carbonyl to an unprotected alcohol, as in Murai's approach (See Chapter 2, Scheme 110). Though this plan would result in a savings of two synthetic steps, the synthesis of the enyne **340** would still require 12 steps. We considered this number too high, and so turned our attention to alternative strategies.

Concurrent with my work on electrophilic cyclizations of enone **431**, Dr. Hiroshi Shinokubo studied the oxymercuration of dienone **435**, which should afford **436** (Scheme 129). We envisaged that a two-step sequence involving demercuration and Sonogashira coupling with trimethylsilylacetylene would then furnish the desired enyne.

Scheme 129
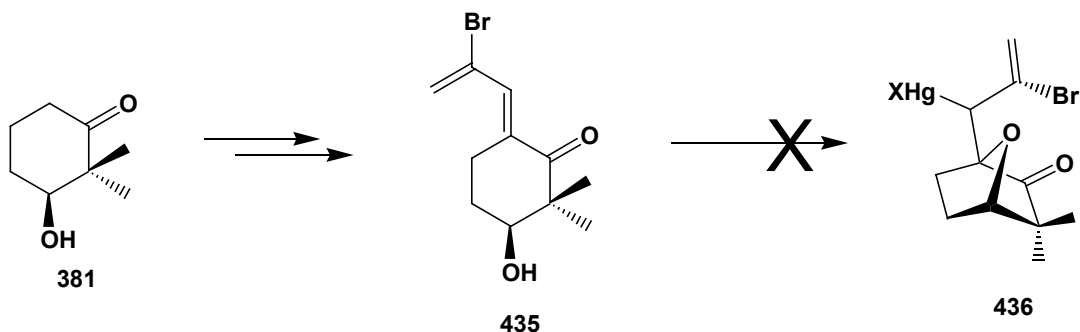
As with enone **431**, the dienone **435** failed to undergo oxymercuration. Although the desired transformation was unsuccessful, Dr. Shinokubo made an important discovery during the synthesis of **435** (Scheme 130). His synthesis involved the aldol reaction of 2-bromoacrolein with ketone **381** incorporating an unprotected hydroxyl group. Importantly this reaction provided the desired aldol product **437** in 68% yield; no ring-opened product (**438**) resulting from retro-aldol reaction was observed. This important

observation allowed us to eliminate protection and deprotection involving the hydroxyl group on **381** in future strategies.

Scheme 130
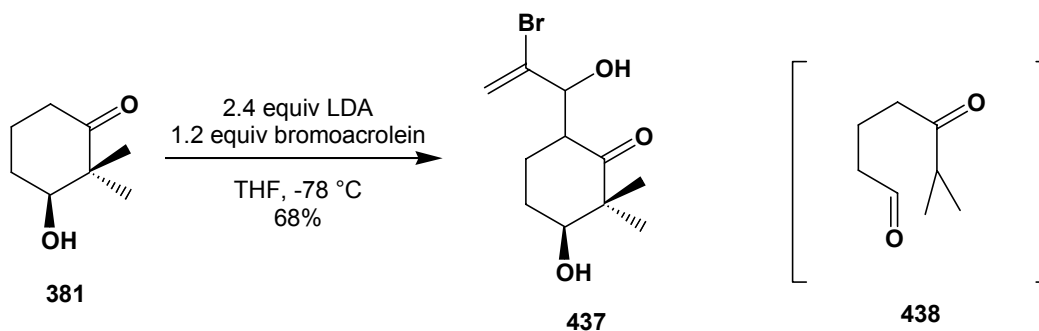
Further contemplation of cyclization approaches to the oxabicyclic A-ring intermediate led us to consider the cyclization of enedione **439** (Scheme 131). In contrast to the electrophilic cyclization approaches investigated previously, this cyclization strategy utilizes a nucleophilic conjugate addition of the hydroxyl oxygen.

The 1,4-additions of heteroatom nucleophiles to α,β-unsaturated carbonyl compounds are well documented in the literature.[214] Many examples have been reported for the addition of an oxygen nucleophile to α,β-unsaturated enones,[215] most of which involve catalytic base to deprotonate the hydroxyl group. Examples of the acid-catalyzed version of the reaction typically involve the use of Lewis acids. In addition, the conjugate addition of heteroatom nucleophiles to quinones and related species has been

---

[214] For an overview of 1,4-additions of oxygen nucleophiles, see: (a) Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis*; Pergamon: New York, 1992. (b) Little, R. D.; Masjedizadeh, M. R.; Wallquist, O.; McLoughlin, J. I. *Org. React.* **1995**, *47*, 315.

[215] For recent examples, see: Berkessel, A. In *Methoden der Organischen Chemie (Houben-Weyl)*, 4th ed.; Helmchen, G.; Hoffmann, R. W.; Mulzer, J.; Schaumann, E., Eds.; Thieme: New York, 1995; Vol. E21e, pp 4818-4856.

well-documented.[216] Several examples in the literature demonstrate the feasibility of 1,4-additions of alcohols to enediones.[217]

We imagined this approach might overcome the difficulties encountered previously with electrophilic cyclizations involving enones. Cyclization of alcohol **439** should furnish the oxabicyclic ketone **440**. We planned to elaborate this methyl ketone to enyne **340** in a manner analogous to that used by Dr. Mellon on a related substrate (see Chapter 2, Scheme 121).

Scheme 131
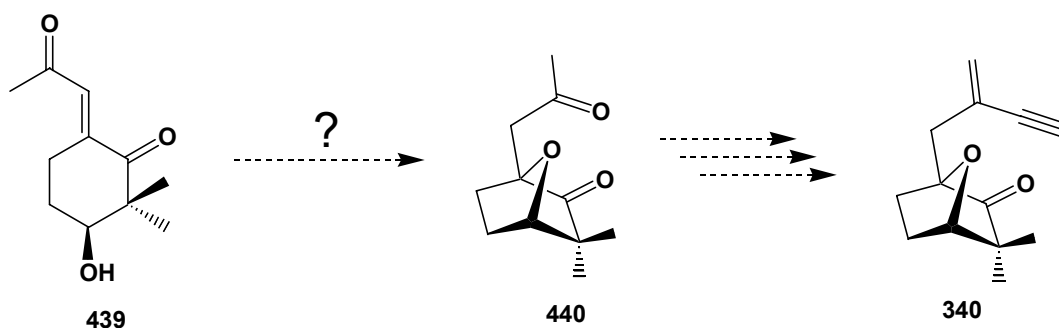
Our strategy for the synthesis of enedione **439** paralleled the route used by Dr. Shinokubo for the production of aldol condensation product **435** above. For all of the investigations described below, we used racemic hydroxy ketone **381** which is considerably easier to prepare than the enantiopure version. Aldol reaction of **381** with methacrolein furnished **441** as a mixture of diastereomers. No attempt was made to assign stereochemistry of these isomers since the stereogenic centers would become

[216] Ulrich, H.; Richter, R. In *Methoden der Organischen Chemie (Houben-Weyl)*, 4th ed.; Müller, E., Ed.; Verlag: Stuttgart, 1977; Vol. VII/3a, pp 660-674.

sp^2-hybridized in a subsequent step. Ozonolysis of **441** provided the diol **442**. The yield

of the aldol reaction was typically in the 80-90% range; however, the ozonolysis step

proceeded in fair yield. This is likely due to the intermediate ozonide or molozonide

beng intercepted by an intramolecular hydroxyl group instead of methanol. Because **441**

was difficult to separate from unreacted starting material, we conducted the two-step

sequence without purification of the intermediate **441**, and in this manner we isolated diol

442 in 42% yield over two steps (Scheme 132).

Scheme 132
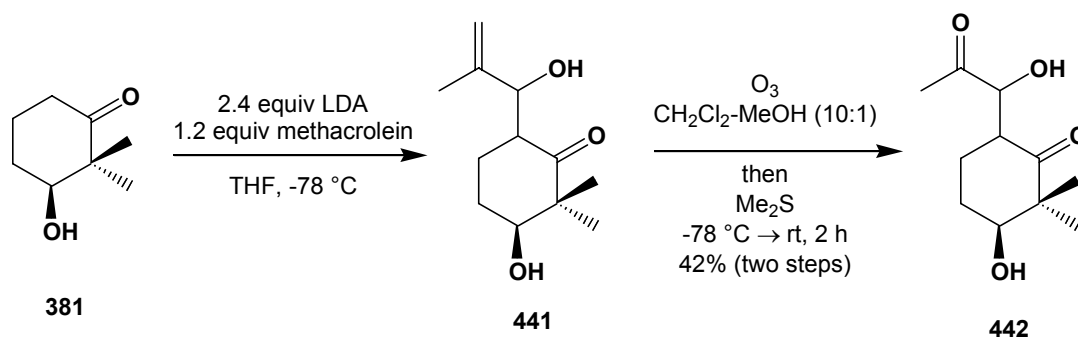
The elimination to afford the desired enedione was first attempted with dilute

sulfuric acid in ethanol. Under these conditions, the reaction affords only the enol ether

443 (Scheme 133). The formation of **443** likely results from ketalization of the methyl

ketone followed by elimination of ethanol. This ketalization-elimination sequence could

occur before or after elimination of the hydroxyl group.

---

[217] (a) Burke, S. D.; Letourneau, J. J.; Matulenko, M. A. *Tetrahedron Lett.* **1999**, *40*, 9. (b) Smith, A. B.; Fukui, M. *J. Am. Chem. Soc.* **1987**, *109*, 1269. (c) Sachchar, S. P.; Tripathi, N. N.; Singh, A. K. *Indian J. Chem., Sect. B.***1987**, *26*, 493.

The spectral data obtained for the product of this reaction is consistent with the structure of **443**. In particular, three vinylic proton resonances in the ^{1}H NMR spectrum in conjunction with the single unsaturated ketone stretch in the IR spectrum provide strong evidence for the assigned structure.

Scheme 133
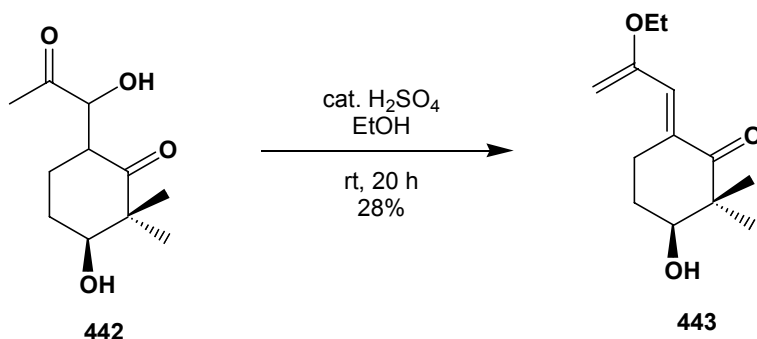
A Serendipitous Discovery

To avoid formation of the enol ether, we turned our attention to the use of non-alcoholic solvents for the acid-catalyzed elimination of **442**. We selected benzene as a non-polar solvent and camphorsulfonic acid as an acid commonly used for elimination reactions which is soluble in benzene. Reaction of **442** with 0.25 equiv of CSA in benzene for 24 h at rt provided not the expected enedione **439**, but rather the bicyclic compound **440**! The spectral data for the product of the reaction is consistent with the oxabicyclic structure **440**, based on comparison to spectral data of many other similar compounds previously prepared in our group in conjunction with this project. Particularly diagnostic in the ^{1}H NMR spectrum is the bridgehead proton resonance at 4.30 ppm, and the resonances of the diastereotopic methylene protons on the sidechain at

184

3.04 and 2.90 ppm which show a distinctive splitting pattern. In addition, the IR spectrum displays a broad carbonyl stretch at 1733 cm^{-1}, corresponding to both non-conjugated ketone carbonyl groups. It should be noted that at this stage we have no evidence for the stereochemical relationship of **442** and **440**, and we are assuming that the configuration at C3 is retained in the bicyclic product.

Scheme 134

0.25 equiv CSA

benzene
rt, 24 h
20-40%

442

439

440
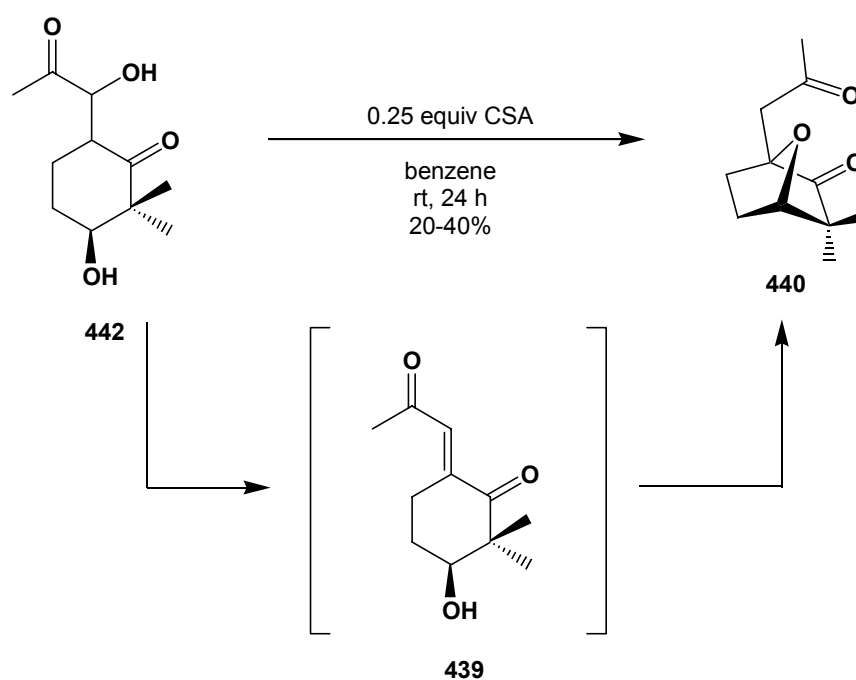
Optimization of the Cyclization and Mechanistic Studies

In subsequent experiments we found that the yield of this cyclization ranged from 20% to 40% when carried out under near-identical conditions. We conducted an extensive study to optimize the reaction, investigating the effect of different solvents, reaction concentrations, acid catalysts, amounts of acid catalyst, and temperature. From these studies, we were able to conclude that the reaction suffers from a number of serious

185

problems which together result in the low and variable yields observed for the transformation.

The optimized conditions are shown in Scheme 135. The use of 1.0 equiv of PPTS in refluxing benzene gave the desired oxabicyclic ketone **440** in 31-37% yield. Alternately, 1.0 equiv of quinolinium camphorsulfonate (QCS) in benzene at 40 °C for 48 h gave the desired product in similar yield (35-37%), but resulted in a cleaner reaction with easier purification. These results were promising and could be adequate for the production of sufficient quantities of the A-ring enyne component.

Scheme 135
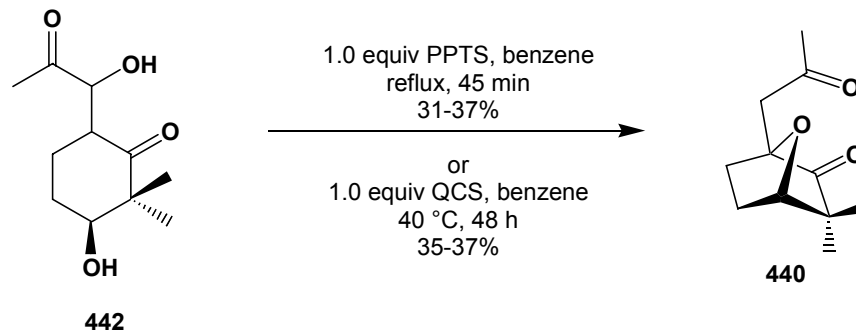
Under these optimal conditions the main byproduct we observe in the reaction is the endocyclic enone **444**. The structure of this compound was determined based on NMR and IR spectral data. The enone **444** exhibits two ketone IR absorptions, at 1669 and 1712 cm^{-1}, indicating one saturated ketone and one unsaturated ketone, as well as the expected OH stretch at 3449 cm^{-1}. This byproduct was isolated in up to 24% yield from reactions run under the optimal conditions shown above. The endocyclic enone **444** was observed in all reactions in varying amounts based on TLC analysis.

444
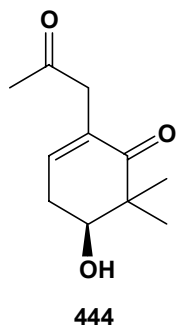
In the case of cyclizations run at temperatures above 50 °C, a second byproduct is observed in the reaction, identified as benzofuran **445** by NMR and IR spectral data. This compound exhibits no carbonyl IR stretches, but ^{1}H NMR shows three methyl groups and three aromatic hydrogens. The ^{13}C NMR spectrum is similar to the spectrum of many known benzofurans of this type, displaying eight aromatic carbon resonances. Three additional aliphatic carbon resonances are observed, corresponding to the three methyl groups. This byproduct could be isolated in up to 30% yield from reactions run under the PPTS conditions shown in Scheme 135.

445
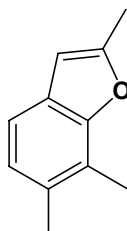
Our attempts to optimize the key cyclization led us to explore a variety of acids as promoters of the reaction. We investigated camphorsulfonic acid (CSA), pyridinium *p*-toluenesulfonate (PPTS), *p*-toluenesulfonic acid (TsOH), and quinolinium camphorsulfonate (QCS). All of these acids are soluble in benzene; however, the time for complete dissolution can be lengthy. All four of these acids were found to promote the reaction. The fastest reaction rates were observed with CSA. The use of quinolinium

camphorsulfonate gave good yields of the cycloadduct with no formation of benzofuran in reactions run at 40 °C.

Many of our initial runs were done under heterogeneous conditions, such that the acid never completely dissolved in the solvent. In these reactions, dark brown decomposition material was observed on the surface of the acid shortly after the reaction began. Later reactions were run with the acid pre-dissolved in the solvent before the substrate was added. In these reactions, the bulk solution turned a darker color than in the heterogeneous reactions, but there were no brown solids present in the reaction mixture. However, we have concluded that this variation in reaction conditions does not have a significant effect on the yield of the reaction.

We determined the optimal concentration of substrate and acid catalyst in the reaction to be 0.02 M. At lower concentrations (0.005 M in substrate) the reaction becomes very sluggish, while at higher concentrations (0.1 M in acid), insolubility of the acid becomes a problem unless higher temperatures are used. It appears that reaction concentration only affects the rate of the reaction.

We also varied the amount of the catalyst used. Increasing the amount of acid from 0.1 equiv to 5.0 equiv led only to the expected increase in the rate of the reaction, but no effect on the outcome of the reaction or distribution of products was observed.

With the goal of further improving the efficiency of the key cyclization, we have undertaken studies aimed at obtaining a better understanding of the mechanism of formation of the bicyclic diketone **440** as well as the key byproducts of the reaction. This section summarizes our preliminary findings to date; further work in this area is being continued by Charnsak Thongsornkleeb in our laboratory.

Table 4 presents our findings with regard to the interconversion of various intermediates and products of the reaction. Important points include:

- Endocyclic enone **444** is formed irreversibly. Under conditions similar to the normal reaction it does not produce either bicyclic diketone or benzofuran.

- The benzofuran **445** forms irreversibly. Under conditions similar to the normal reaction it does not produce either bicyclic diketone or endocyclic enone.

- Bicyclic diketone **440** forms the endocyclic enone under the conditions similar to the normal reaction.

Table 4. Interconversion Experiments[a]
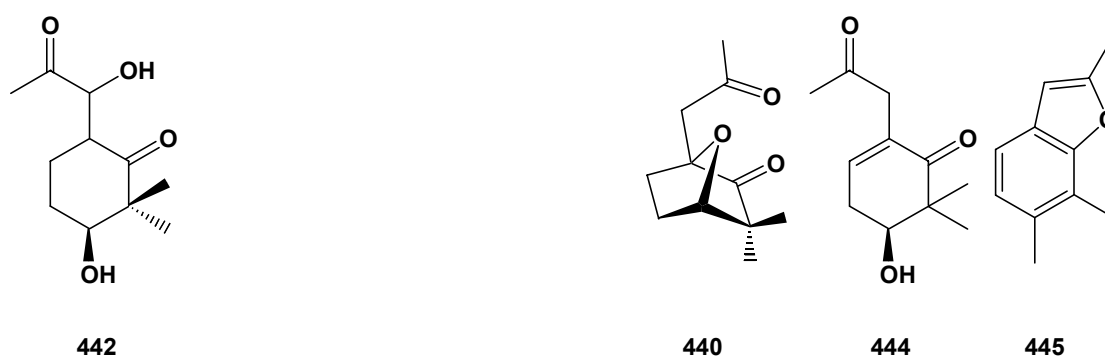
| | | **442** | | **440** | **444** | **445** |

Entry	Starting Material	Conditions	**440**	**444**	**445**
1	**442**	QCS, 40 °C, 48 h	YES	YES	--
2	**442**	PPTS, 80 °C, 45 min	YES	YES	YES
3	**440**	PPTS, 111 °C, 2 h, 100+ eq H_2O	--	YES	--
4	**444**	PPTS, 111 °C, 2 h	*no reaction*		
5	**444**	PPTS, 111 ºC, 2 h, 100+ eq H_2O	*no reaction*		
6	**445**	PPTS, 111 ºC, 2 h	*no reaction*		

[a]All reactions were run in benzene or toluene at a concentration of 0.02M using 1.0 equiv of the indicated acid. The formation of **440**, **444**, and **445** was monitored by TLC analysis.

It should be noted that the effect of water in these interconversion experiments has not been fully examined at this time. Certain reactions run with excess water present may not accurately simulate the normal reaction conditions. Further studies of the effect of water are currently underway.

Based on the preliminary results presented in Table 4, the following scheme outlines our current thoughts with regard to the mechanism of formation of the desired bicyclic diketone and the two principal byproducts of the reaction. Elimination of water can form the exocyclic enone **439** which can cyclize to produce the desired bicyclic diketone **440**. In competition with this process, isomerization to the endocyclic enone can take place, for example, via the dienol. In addition, the bicyclic product **440** can undergo ring-opening after protonation to also afford the endocyclic enone **444**.

Scheme 136

442

439

444

440
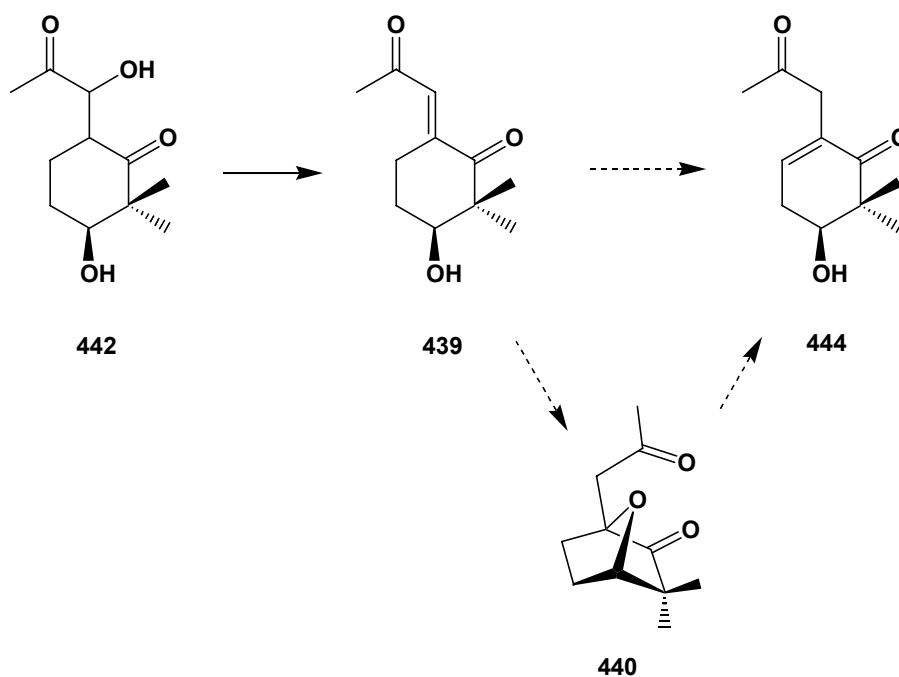
A more complicated question involves the mechanism for formation of the benzofuran byproduct. We believe that this compound is generated via a 1,2-methyl shift involving an intermediate such as **446**; methyl migration then produces a highly stabilized carbocation and elimination furnishes the aromatic benzofuran.

Routes to this intermediate (**446**) can be envisioned beginning with either the bicyclic product **440**, or the endocyclic enone **444**; however, preliminary experiments (Table 4) indicate that these compounds do not afford benzofuran upon exposure to PPTS. As noted earlier, these preliminary experiments were not carried out under conditions which accurately simulate the normal reaction, and so we cannot rule out the possibility that **440** or **444** give rise to benzofuran **445** under the normal reaction conditions.

Further studies on the mechanism will focus on the proposed exocyclic enone intermediate **439**. When the reaction of diol **442** is carried out with 1.0 equiv of PPTS in benzene at reflux in the presence of 4Å MS, a mixture of the desired bicyclic product **440**, endocyclic enone **444**, and a new enone was isolated. This latter compound appears to be the exocyclic enone **439** (stereochemical assignment tentative).

Surprisingly, exposure of this enone to PPTS in refluxing toluene led to isomerization to the endocyclic enone **444**, and none of the expected bicyclic diketone was observed to form. Further studies are needed to examine the role of water in this cyclization.

Scheme 137
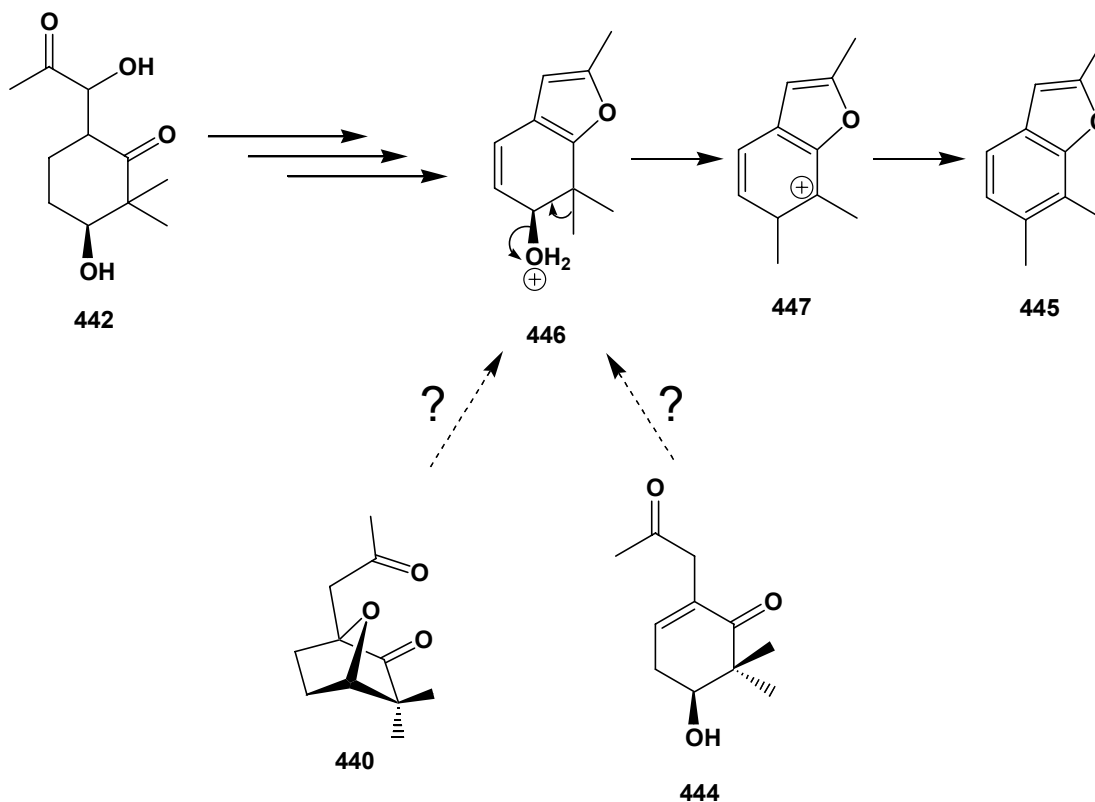
Further work by Charnsak Thongsornkleeb is underway to answer a number of remaining questions concerning this complex reaction. The remainder of this chapter describes our progress with the remaining steps of this approach to the synthesis of the A-ring enyne intermediate.

Construction of the Enyne

After a number of optimization reactions, we accumulated a sufficient quantity of the bicyclic ketone **440** to begin exploring the conversion of this compound to the key A-ring building block **340**. Our plan involved conversion of the methyl ketone to the vinyl triflate and cross-coupling, a strategy similar to one employed by Dr. Mellon on a

related substrate (see Chapter 2). However, exposure of the ketone **440** to LDA and PhNTf$_2$ led to an intramolecular aldol reaction producing tricyclic compound **448** (Scheme 138). Although this aldol reaction should be reversible, no vinyl triflate **449** was observed.

Scheme 138
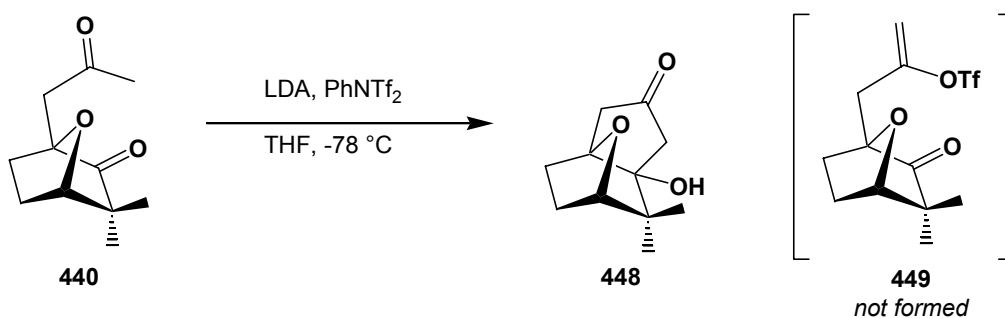
Concurrent with our studies of routes based on bicyclic ketone **440**, we also investigated alternative strategies involving other precursors to the desired enyne. For example, we hypothesized that the use of amide **451** instead of the methyl ketone **440** (Scheme 139) could eliminate the need to form vinyl triflate **449**, as addition of lithium acetylide to the amide **451** would provide ynone **452**, which could then be olefinated[218] under a variety of conditions.

---

[218] For an example of the construction of an enyne via olefination of an ynone, see: Hoffmann, H. M. R.; Krumwiede, D.; Mucha, B.; Oehlerking, H. H.; Prahst, G. W. *Tetrahedron* **1993**, *49*, 8999.

Scheme 139

450　　　　451　　　　452　　　　340
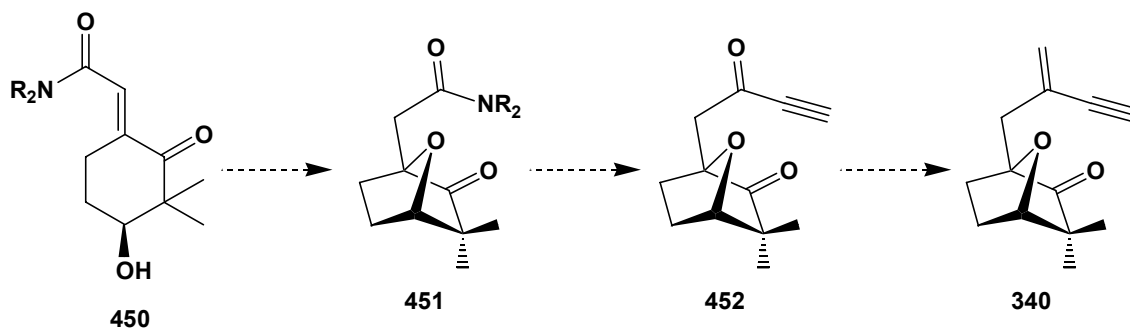
The study of this amide strategy was carried out by Charnsak Thongsornkleeb and focused on the use of the glyoxylic amide **455** (Scheme 140),[219] which was expected to function similarly to a Weinreb amide[220] for acetylide addition. Production of the hemiacetal **454** was carried out in a two-step procedure beginning with fumaroyl chloride, as shown in Scheme 140. Addition of fumaroyl chloride to excess morpholine provided the bis-amide, ozonolysis of which provided the hemiacetal **454** in 83% overall yield.[221] We were unable to prepare the glyoxylic amide **455** either from the hemiacetal or via any other means.

[219] For a recent example of the use of glyoxylic amide derivatives as electrophiles, see: Kiegiel, K.; Jurczak, J. *Tetrahedron Lett.* **1999**, *40*, 2009.
[220] Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815.
[221] For a recent example of the synthesis of the hemiacetal of a glyoxylic amide derivative, see: Bauer, T.; Jezewski, A.; Chapuis, C.; Jurczak, J. *Tetrahedron: Asymmetry* **1996**, *7*, 1385.

Scheme 140
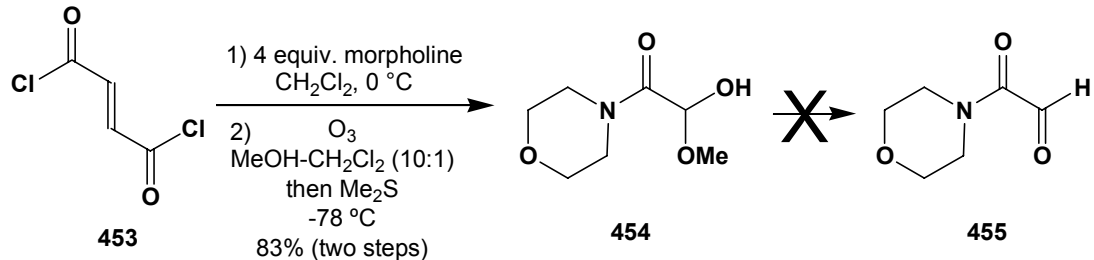
However, an acid-catalyzed aldol reaction utilizing hemiacetal **454** directly looked promising. A model reaction using ketone **456** afforded the aldol condensation product **457** in 42% yield (Scheme 141).

Scheme 141
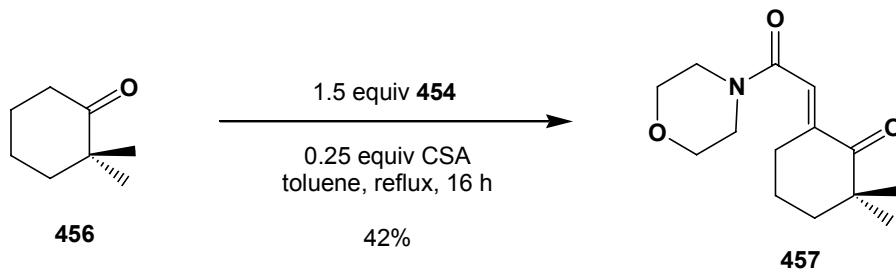
In fact, we hoped that immediately following the acid-catalyzed aldol condensation with hydroxyl ketone **381**, acid-catalyzed cyclization would occur to furnish bicyclic amide **451** in one pot.

Scheme 142
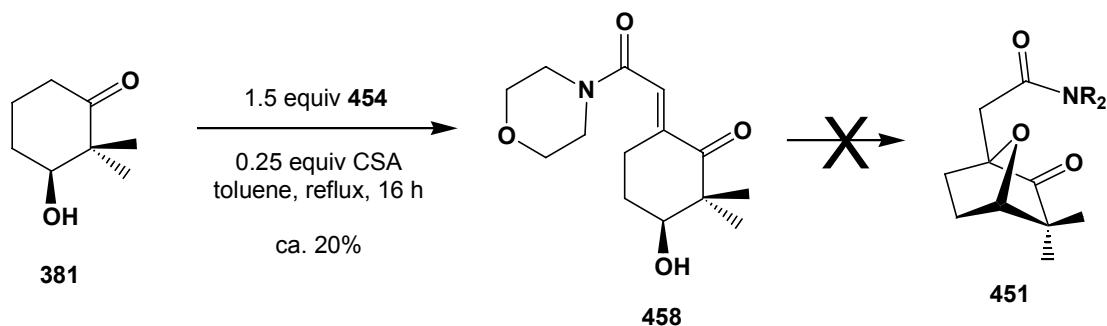
In the event, aldol condensation proceeded in low yield to afford **458** (Scheme 142). No cyclization product **451** was observed, and subsequent attempts to effect the cyclization to afford bicyclic amide **451** met with failure. Apparently the amide functionality, which is not as electron-withdrawing as the ketone, cannot facilitate the conjugate addition as the ketone does. Forced to abandon this promising alternative, we turned our attention back to the methyl ketone **440**. We focused on methods for the conversion of the methyl ketone to the desired A-ring enyne **340**.

As vinyl triflate formation was not possible under kinetic conditions (*vide supra*), we also explored thermodynamic conditions, utilizing triflic anhydride and various amine bases. It was our hope that the formation of the internal vinyl triflate would be disfavored by steric congestion and the desired regioisomer would be produced. Unfortunately, no vinyl triflate was formed from these reactions and the ketone **440** was recovered unchanged.

We next envisioned an addition-elimination strategy as shown in Scheme 143. The addition of lithium acetylide to the ketone, followed by a regioselective elimination, could provide a two-step route to the enyne **340**.

Scheme 143

440 → 459 → 340
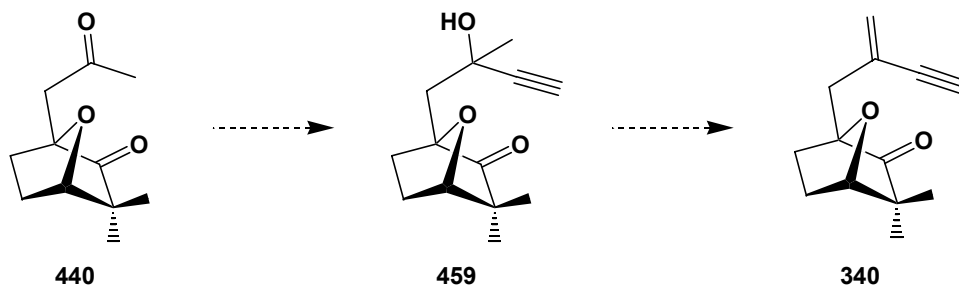
For ease of operation during small-scale reactions, we elected examine the feasibility of this route using trimethylsilylacetylide, expecting that on larger scale, lithium acetylide could be employed in an analogous fashion. To our delight, the acetylide addition afforded propargylic alcohol **460** in 80% yield (Scheme 144). In some cases, addition of lithium acetylides to methyl ketone proceeds in poor yield due to competing enolization. In these instances cerium acetylides are often used.[222] However, in this case we recovered no starting material from the reaction.

Scheme 144

1.4 equiv **Li-C≡C-SiMe₃**

THF, -78 °C, 30 min

80%

440 → 460

---
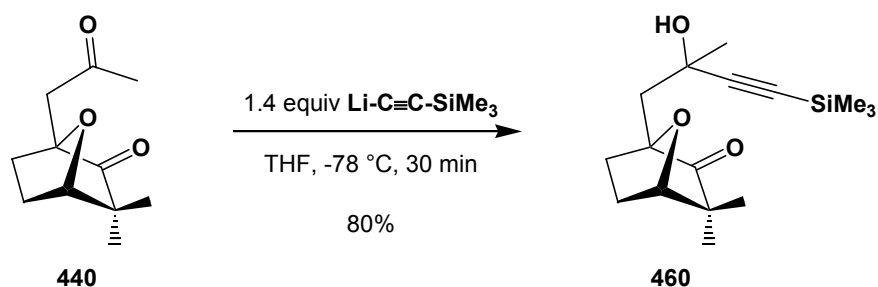
[222] Imamoto, T.; Takiyama, N.; Nakamura, K.; Hatajima, T.; Kamiya, Y. *J. Am. Chem. Soc.* **1989**, *111*, 4392.

We expected that our regioselective elimination strategy might be somewhat problematic. It is known that, under conditions that favor E_1 pathways, the more substituted (Zaitsef) product is typically the major product. Our desired product, the less substituted (Hofmann) product, is formed by E_1 pathways only under exotic conditions.[223] We expected that E_2 pathways could favor the Hofmann product due to steric hindrance of removal of the neopentyl-like methylene protons.

Elimination of mesylates is a strategy that has been used in our group for the production of enynes for studies of the enyne cycloaddition (See Part I, Chapter 1). Although elimination of the mesylate would likely favor the Zaitsef product, it was a straightforward beginning for our elimination studies. However, attempts at formation of the mesylate and *in situ* elimination with a variety of amine bases including triethylamine and DBU led to imcomplete reactions. As determined by ^{1}H NMR analysis of the crude reaction mixtures, these reactions yielded mixtures of the Zaitsef and Hofmann products.

Attempts to synthesize the tosylate and phenyl carbonate derivatives of the alcohol were unsuccessful. We had hoped that these leaving groups, having less ionic character than the mesylate, would favor an E_2 pathway.

Success was finally achieved by utilizing the Burgess reagent (Scheme 145).[224] Addition of 1.1 equiv of the reagent to a THF solution of the tertiary alcohol at rt effected clean conversion to a mixture of enynes in 15 min. A statistical mixture of enynes (ca. 60:40 based on analysis of the ^{1}H NMR spectrum of the crude material) was formed in

[223] For an overview of elimination reactions, see: March, J. *Advanced Organic Chemistry*, 4th ed.; Wiley: New York, 1992; pp 982-1010.
[224] Burgess, E. M.; Penton, H. R., Jr.; Taylor, E. A.; Williams, W. M. *Org. Synth.* **1977**, *56*, 40.

which **461** was the major isomer. The desired enyne **461** could be separated from the minor isomer via preparative HPLC, and was isolated in 40% yield.

Scheme 145
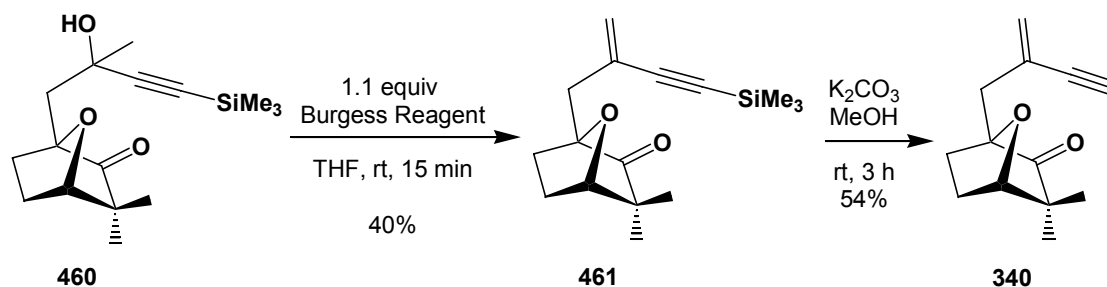
A simple desilylation reaction was all that remained for the synthesis of the enyne **340**. This reaction was carried out with catalytic potassium carbonate in methanol, and provided the enyne **340** in 54% yield.

Summary

A novel acid-catalyzed cyclization strategy was developed for the synthesis of the enyne **340** in only 6 steps from the hydroxy ketone **381**. This route, though it has drawbacks, is a significant improvement over the first-generation route for the synthesis of enyne **340** which required 14 steps. Further studies are ongoing for the development of even more efficient routes and the final completion of the total synthesis of glycinoeclepin A.

Part III

Experimental Section

General Procedures

All reactions were performed in flame-dried or oven-dried glassware under a positive pressure of argon unless otherwise indicated. Reaction mixtures, with the exception of sealed-tube reactions, were stirred magnetically unless otherwise indicated. Air- and moisture-sensitive liquids and solutions were transferred via syringe or cannula and were introduced into reaction vessels through rubber septa. Reaction product solutions and chromatography fractions were concentrated using a Büchi rotary evaporator at ca. 20 mmHg and then at ca. 0.1 mmHg (vacuum pump) unless otherwise indicated.

Materials

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

Tetrahydrofuran and diethyl ether were distilled from sodium benzophenone ketyl or dianion or purified by pressure filtration through activated alumina.

Methylene chloride and toluene were distilled from calcium hydride or purified by pressure filtration through activated alumina.

Dimethyl sulfoxide and dimethylformamide were EM Dri-Solv grade and used as received.

Diethylamine, diisopropylamine, trimethylsilyl chloride, and pyridine were distilled from calcium hydride.

Acetic anhydride was distilled from quinoline.

Acetaldehyde, methyl chloroformate, γ-terpinene, propargyl chloride, 1-butyn-3-ol, and methacrolein were distilled under an argon atmosphere.

Copper (I) iodide was continuously extracted with tetrahydrofuran for 18 h.[225]

α,α'-Dibromo-*o*-xylene was recrystallized from chloroform.

Paraformaldehyde was dried under vacuum over phosphorum pentoxide for 48 h.

Alkyllithium reagents were titrated in tetrahydrofuran or hexane at 0 °C with *sec*-butanol or menthol using 1,10-phenanthroline as an indicator.[226]

Ozone was generated using a Welsbach ozone generator.

Diazomethane was generated from *N*-nitroso-*N*-methylurea according to the procedure of Arndt.[227]

Chromatography

Analytical and preparative thin layer chromatography was performed on Merck precoated glass-backed silica gel 60 F-254 0.25 mm plates. Visualization was effected by one or more of the following techniques: (a) ultraviolet illumination, (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, (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, (e) immersion of the plate in a 10% solution of phosphomolybdic acid in ethanol followed by heating to ca. 200 °C, (f) immersion of the plate in an aqueous solution of 6% ammonium molybdate and 1%

---

[225] Taylor, R. J. K. *Organocopper Reagents: A Practical Approach*; Oxford University Press: Oxford, 1994; pp 39-40.

[226] Watson, S. C.; Eastham, J. F. *J. Organomet. Chem.* **1967**, *9*, 165.

cerium(IV) sulfate containing 12% concentrated sulfuric acid followed by heating to ca. 200 °C.

Column chromatography was performed on EM Science silica gel 60 (35-75 um) or Silicycle silica gel 60 (230-400 mesh).

Instrumentation

Melting points were determined with a Fisher-Johns melting point apparatus and are uncorrected.

^{1}H NMR spectra were measured with Varian XL-300 (300 MHz), Unity-300 (300 MHz), and Inova-500 (500MHz) spectrometers with $CDCl_3$ as solvent unless otherwise indicated. ^{1}H NMR chemical shifts are expressed in parts per million (δ) relative to tetramethylsilane, with the $CHCl_3$ peak at 7.26 ppm used as reference.

^{13}C NMR spectra were measured with Varian XL-300 (75 MHz), Unity-300 (75 MHz), and Inova-500 (125MHz) spectrometers with $CDCl_3$ as solvent unless otherwise indicated. ^{13}C NMR chemical shifts are expressed in parts per million (δ) relative to tetramethylsilane, with the central peak of $CDCl_3$ at 77.23 ppm used as reference.

Infrared spectra were obtained on a Perkin-Elmer 1320 grating spectrophotometer, a Perkin-Elmer 1600 Fourier Transform spectrophotometer, or a Perkin-Elmer 2000 Fourier Transform spectrophotometer.

High-resolution mass spectra were obtained on a Finnegan MATT-8200 spectrometer or a Bruker Daltonics APEX 3 Tesla Fourier Transform spectrometer.

---

[227] Arndt, F. *Organic Syntheses*; Wiley & Sons: New York, 1943; Collect. Vol. 2, p 165.

Low-resolution mass spectra were obtained on an HP 5890 Series II Gas Chromatograph with an HP 5971 Mass Selective Detector.

Elemental analyses were performed by Complete Analysis Laboratories, Inc. of Parsippany, New Jersey.

Note on Compounds Previously Prepared in Our Group

Compounds **199** and **200** were previously prepared by Dr. Melanie S. B. Wills[228] and are reported here with modified experimental details and updated spectral and analytical data.

Methyl 1-methyl-4,5-dihydroisobenzofuran-3-carboxylate (**219**) was prepared in six steps according to procedures described by Dr. Wills.[228]

---

[228] Wills, M. S. B. Ph.D. Thesis, Massachusetts Institute of Technology, Cambridge, MA, June 1998.

254   **255**
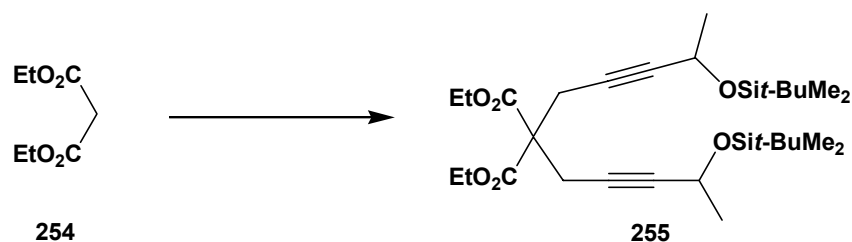
Diethyl 2,2-bis(4-*t*-butyldimethylsilyloxypent-2-ynyl)malonate (255).

A 100-mL three-necked, round-bottomed flask equipped with a rubber septum, glass stopper, and argon inlet adapter, was charged with diethyl malonate (0.688 g, 0.652 mL, 4.30 mmol) and 40 mL of tetrahydrofuran. Sodium hydride (60% dispersion in mineral oil, 0.360 g, 9.01 mmol) was added slowly over 3 min. 4-*t*-Butyldimethylsilyloxy-1-chloro-2-pentyne[229] (2.00 g, 8.59 mmol) was added via syringe over 3 min and the reaction mixture was heated at reflux for 5 h. The resulting solution was cooled and additional sodium hydride (60% dispersion in mineral oil, 0.180 g, 4.50 mmol) and sodium iodide (0.064 g, 0.43 mmol) were added, and the reaction mixture was heated at reflux for an additional 19 h. The resulting solution was then cooled to rt, saturated aqueous NH_4Cl (10 mL) was added, and the aqueous layer was washed with three 10-mL portions of ether, and the combined organic layers were washed with 10 mL of brine, dried over $MgSO_4$, filtered, and concentrated to afford 1.68 g of a yellow oil which was purified by column chromatography on 40 g of silica gel (gradient elution with 0-10% MTBE-hexane) to afford 0.940 g (40%) of **255** as a colorless oil.

[229] Chen, C.-C.; Fan, J.-S.; Shieh, S.-J.; Lee, G.-H.; Peng, S.-M.; Wang, S.-L.; Liu, R.-S. *J. Am. Chem. Soc.* **1996**, *118*, 9279.

IR (film):	2930, 2857, 2238, 1741, 1207, 1102 cm^{-1}.
^{1}H NMR (500 MHz, CDCl$_3$):	δ 4.44 (qt, J = 6.5 Hz, 1.7 Hz, 2H), 4.18 (qd, J = 7.1 Hz, 1.8 Hz, 4H), 2.94 (d, J = 1.5 Hz, 4H), 1.33 (d, J = 6.4 Hz, 6H), 1.24 (t, J = 7.2 Hz, 6H), 0.87 (s, 18H), 0.09 (s, 6H), 0.08 (s, 6H).
^{13}C NMR (125 MHz, CDCl$_3$):	δ 169.0, 86.2, 77.8, 62.0, 59.19, 56.8, 26.0, 25.8, 22.9, 18.4, 14.3, -4.4, -4.8.
MS (*m/z*):	552 (M+).

255
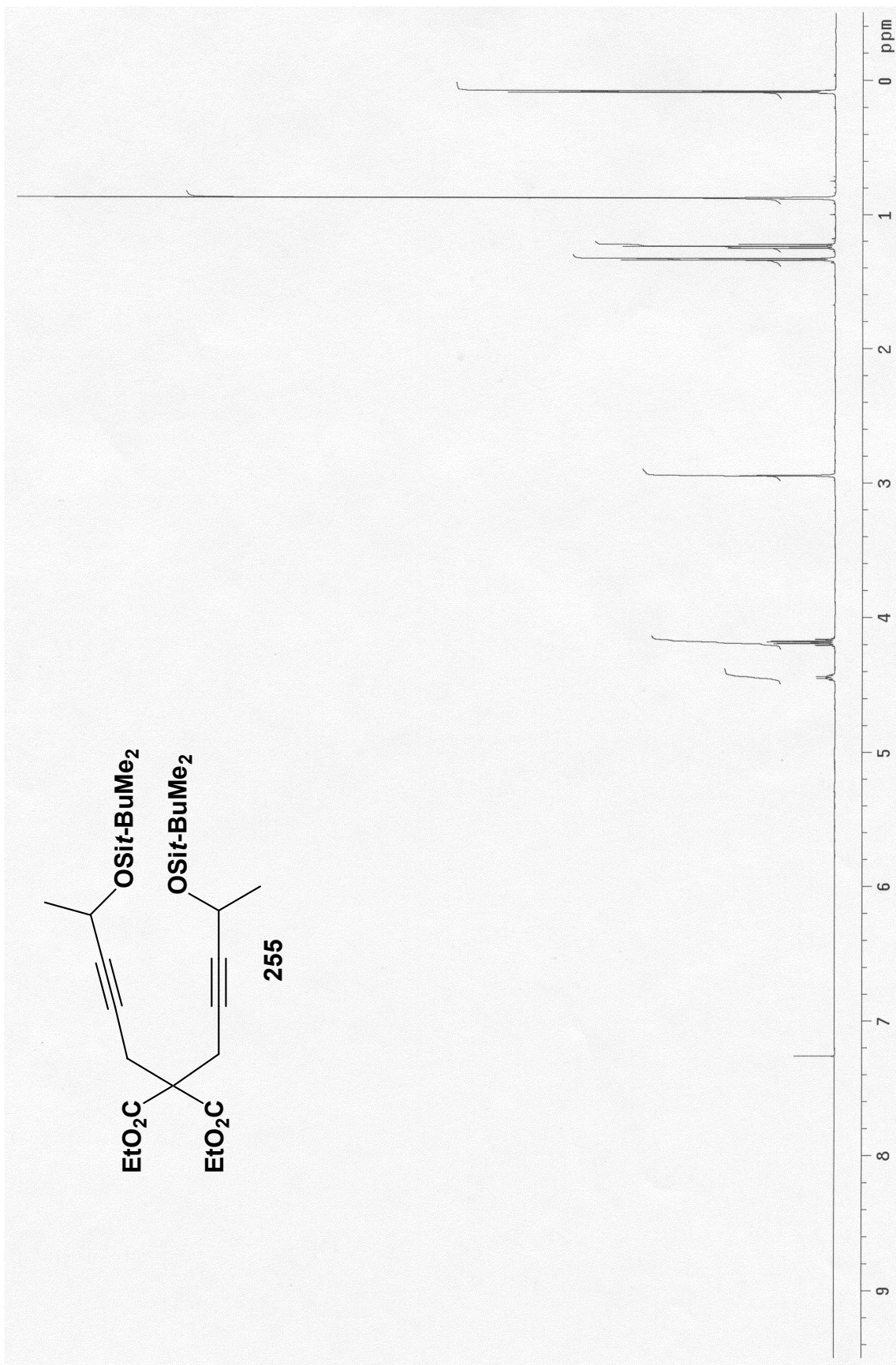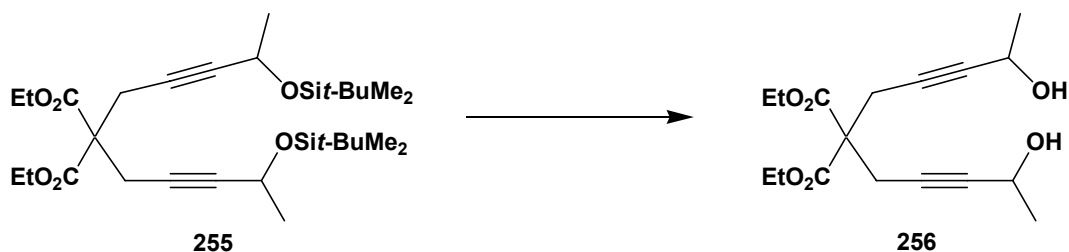
Diethyl 2,2-bis(4-hydroxypent-2-ynyl)malonate (256).

A 25-mL, round-bottomed flask equipped with a rubber septum with argon inlet needle was charged with 15 mL of tetrahydrofuran and diethyl 2,2-bis(4-*t*-butyldimethylsilyloxypent-2-ynyl)malonate (**255**) (0.823 g, 1.56 mmol) and then cooled to 0 °C. Tetra-*n*-butylammonium fluoride (1.0 M solution in tetrahydrofuran, 3.44 mL, 3.44 mmol) was added via syringe over 2 min, and the reaction mixture stirred 5 h at 0 °C. Saturated aqueous NH$_4$Cl (10 mL) was added, and the aqueous layer was separated and washed with three 10-mL portions of ether, and the combined organic layers were washed with 10 mL of brine, dried over MgSO$_4$, filtered, and concentrated to afford 0.573 g of a yellow oil which was purified by column chromatography on 25 g of silica gel (gradient elution with 40-70% MTBE-hexane) to afford 0.440 g (87%) of **256** as a colorless oil.

IR (film):	3484, 2988, 2251, 1718, 1197, 1156 cm^{-1}.
^{1}H NMR (500 MHz, CDCl$_3$):	δ 4.42 (q, *J* = 6.5 Hz, 2H), 4.18 (q, *J* = 7.1 Hz, 4H), 3.05 (s, 2H), 2.92 (d, *J* = 1.5 Hz, 4H), 1.35 (d, *J* = 6.7 Hz, 6H), 1.22 (t, *J* = 7.1 Hz, 6H).
^{13}C NMR (125 MHz, CDCl$_3$):	δ 169.2, 86.0, 78.3, 62.2, 58.2, 56.8, 24.5, 22.9, 14.2.
MS (*m/z*):	324 (M+).

256
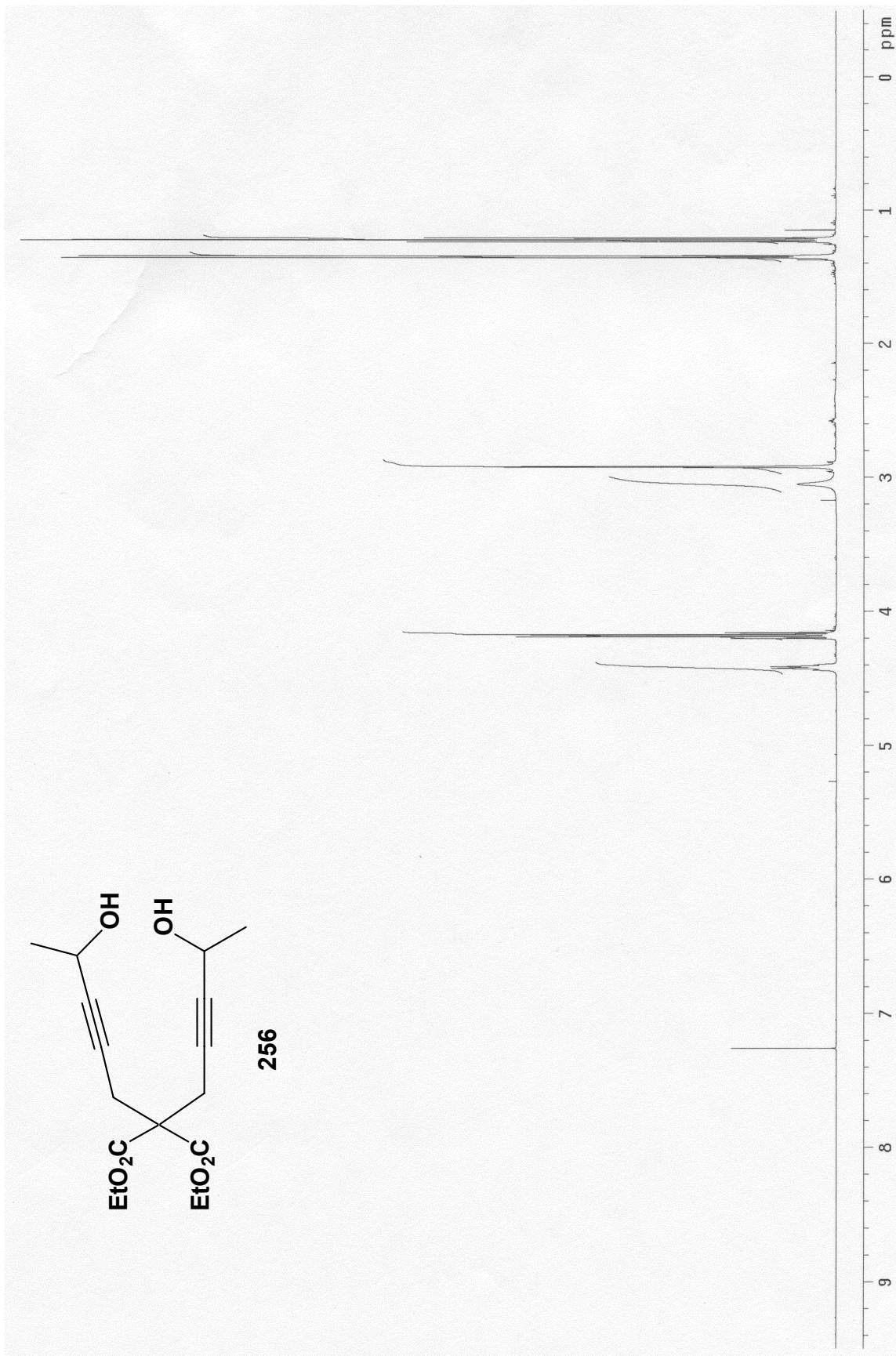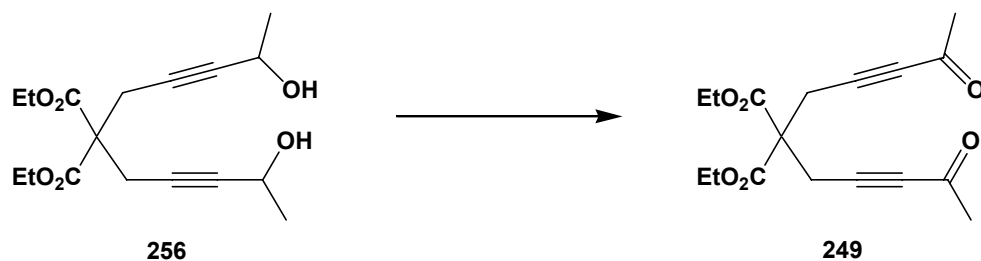
Diethyl 2,2-bis(4-oxopent-2-ynyl)malonate (249).

A 50-mL, round-bottomed flask equipped with a rubber septum with argon inlet needle was charged with diethyl 2,2-bis(4-hydroxypent-2-ynyl)malonate (**256**) (0.440 g, 1.36 mmol), 30 mL of dichloromethane, and Dess-Martin periodinane (1.27 g, 2.98 mmol). The solution was stirred at 25 °C for 1 h and then concentrated by rotary evaporation. The residue was diluted with 20 mL of diethyl ether and 20 mL of saturated NaHCO₃ solution, and 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 NaHCO₃ and saturated Na₂S₂O₃ solution, 30 mL of saturated NaCl solution, dried over MgSO₄, filtered, and concentrated to afford 0.400 g of a yellow oil. Column chromatography on 20 g of silica gel (gradient elution with 20-50% MTBE-hexane) afforded 0.381 g (88%) of **249** as a colorless oil.

IR (film):	2984, 2213, 1737, 1679, 1206, 1195 cm^{-1}.
^{1}H NMR (500 MHz, CDCl₃):	δ 4.24 (q, J = 7.1 Hz, 4H), 3.13 (s, 4H), 2.30 (s, 6H), 1.26 (t, J = 7.1 Hz, 6H).
^{13}C NMR (125 MHz, CDCl₃):	δ 184.1, 167.9, 86.5, 83.9, 62.8, 56.0, 33.0, 23.5, 14.2.
MS (*m/z*):	320 (M+).

249
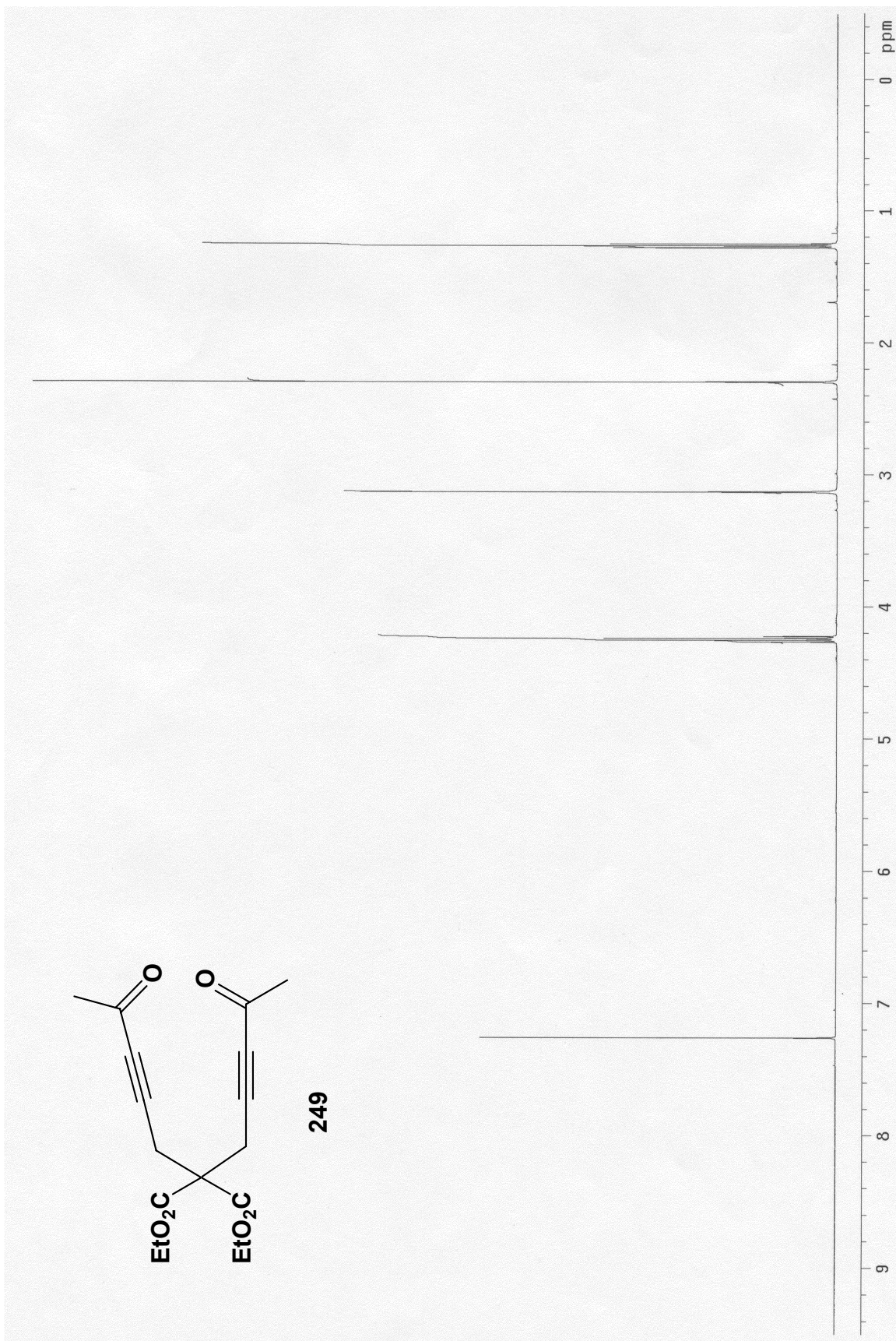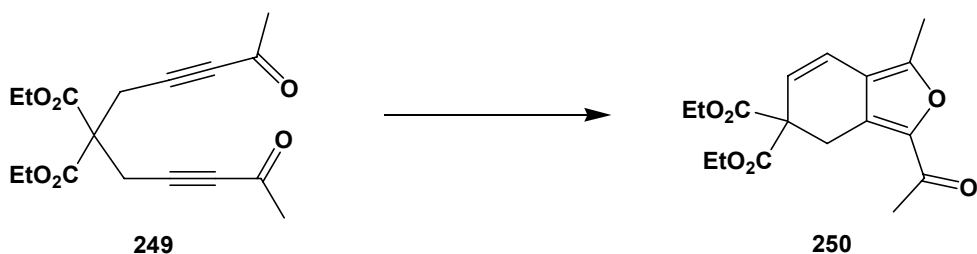
Diethyl 3-acetyl-1-methyl-4*H*-isobenzofuran-5,5-dicarboxylate (250).

An oven-dried threaded Pyrex tube (ca. 10 mL capacity) equipped with a rubber septum and argon inlet needle was charged with diyne **249** (0.153 g, 0.478 mmol), 2.5 mL of toluene, and γ-terpinene (0.092 mL, 0.078 g, 0.525 mmol). The solution was degassed by four freeze-pump-thaw cycles, and the tube was then sealed with a Teflon cap. The sealed tube was placed in a preheated oil bath at 180 °C for 24 h, and then allowed to cool to rt. Concentration gave 0.276 g of a brown oil, which was purified by column chromatography on 10 g of silica gel (gradient elution with 0-50% MTBE-hexane) to afford 0.136 g (89%) of **250** as a colorless oil.

IR (film):	3000, 2926, 1734, 1670, 1594, 1561, 1255, 1235 cm^{-1}.
^{1}H NMR (500MHz, CDCl$_3$):	δ 6.52 (d, J = 9.8 Hz, 1H), 6.04 (d, J = 9.8 Hz, 1H), 4.18 (q, J = 7.0 Hz, 2H), 3.54 (s, 2H), 2.44 (s, 3H), 2.33 (s, 3H), 1.24 (t, J = 7.0 Hz, 6H).
^{13}C NMR (125 MHz, CDCl$_3$):	δ 188.0, 170.0, 150.3, 146.1, 126.9, 123.8, 120.2, 118.3, 62.1, 55.0, 27.1, 27.0, 14.2, 12.4.
Anal. Calcd. for C$_{17}$H$_{20}$O$_6$:	C, 63.74; H, 6.29.
Found:	C, 63.82; H, 6.41.

250

261 → **262**
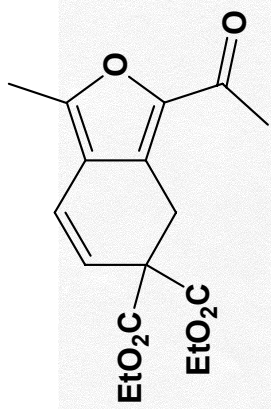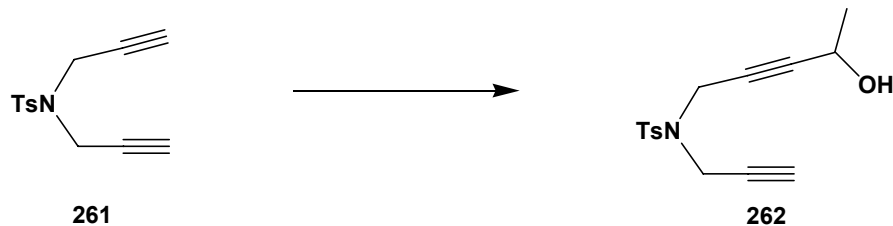
_N_-(4-hydroxypent-2-ynyl)-_N_-prop-2-ynyl-_p_-toluenesulfonamide (262).
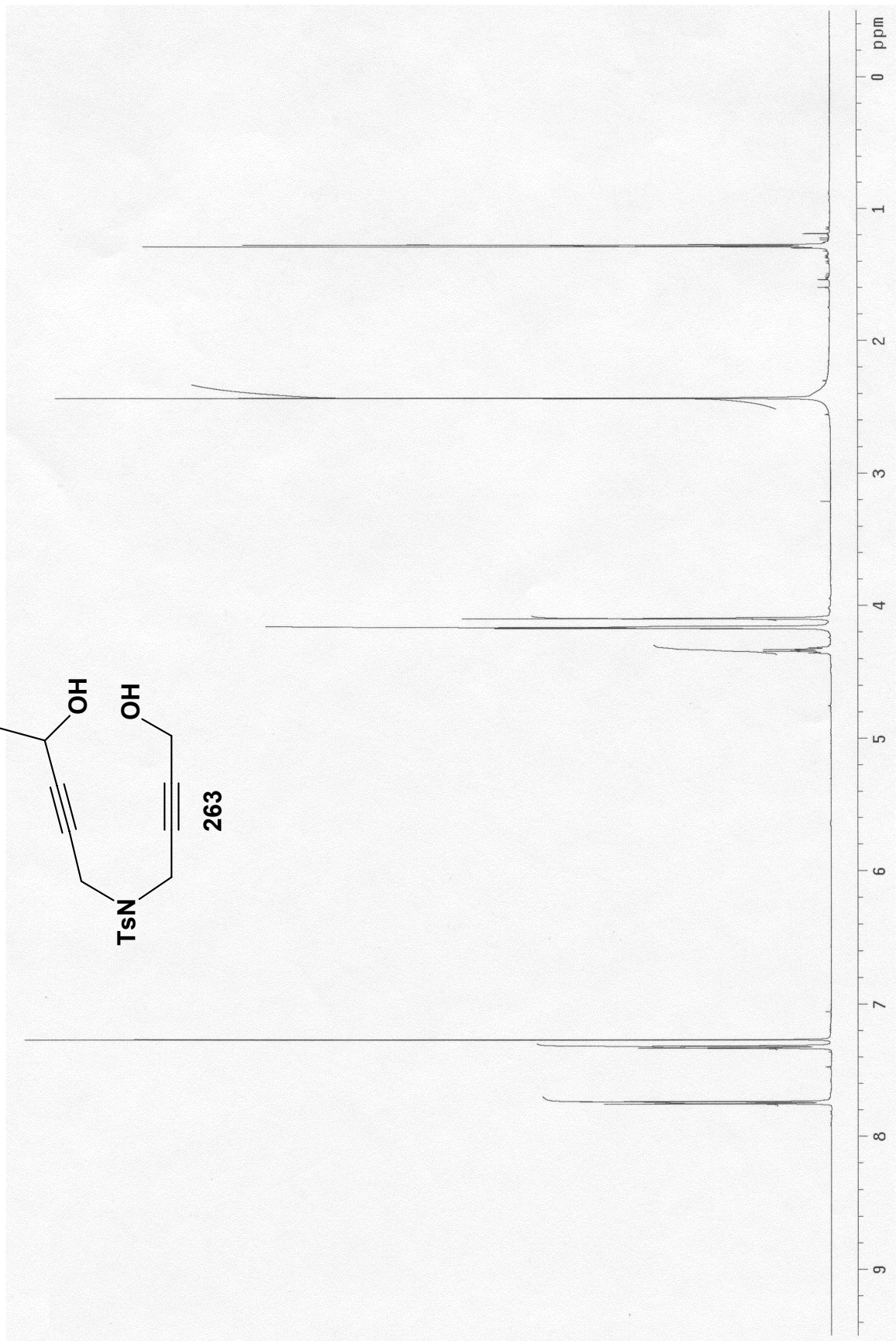
A 50-mL, three-necked, round-bottomed flask equipped with a rubber septum, glass stopper, and argon inlet adapter, was charged with 17 mL of tetrahydrofuran and _N,N_-dipropargylsulfonamide[230] (0.547 g, 2.21 mmol), and cooled to -78 °C. _n_-Butyllithium (2.30 M solution in hexanes, 0.960 mL, 2.21 mmol) was added dropwise via syringe over 3 min and the resulting solution was allowed to warm to 10 °C over 1.5 h. Acetaldehyde (0.487 g, 0.618 mL, 11.1 mmol) was added in one portion via syringe and the reaction mixture was allowed to warm to rt over 14 h. Saturated aqueous NH_4Cl (10 mL) was then added, and the aqueous layer was separated and washed with three 10-mL portions of ether. The combined organic layers were washed with 10 mL of brine, dried over $MgSO_4$, filtered, and concentrated to give 0.938 g of an orange oil which was purified by column chromatography on 30 g of silica gel (gradient elution with 40-80 % MTBE-hexane) to give 0.429 g (70%) of **262** as a colorless oil.

IR (neat):	3420, 3275, 3040, 2975, 2920, 2110, 1590, 1350, 1160 cm^{-1}.
^{1}H NMR (500 MHz, CDCl$_3$):	δ 7.71 (d, _J_ = 8.5 Hz, 2H), 7.31 (d, _J_ = 8.2 Hz, 2H), 4.34 (m, 1H), 4.19 (d, _J_ = 1.5 Hz, 2H), 4.14 (d, _J_ = 2.4 Hz, 2H), 2.43 (s, 3H), 2.17 (t, _J_ = 2.4 Hz, 1H), 1.28 (d, _J_ = 6.7 Hz, 3H).

---

[230] Oppolzer, W.; Pimm, A.; Stammen, B.; Hume, W. E. _Helv. Chim. Acta_ **1997**, _80_, 623.

¹³C NMR (125 MHz, CDCl₃):	δ 144.2, 135.4, 129.7, 128.1, 88.0, 75.5, 76.4, 74.2, 58.2, 36.6, 36.5, 24.1, 21.7.
MS (*m/z*):	291 (M+).

262
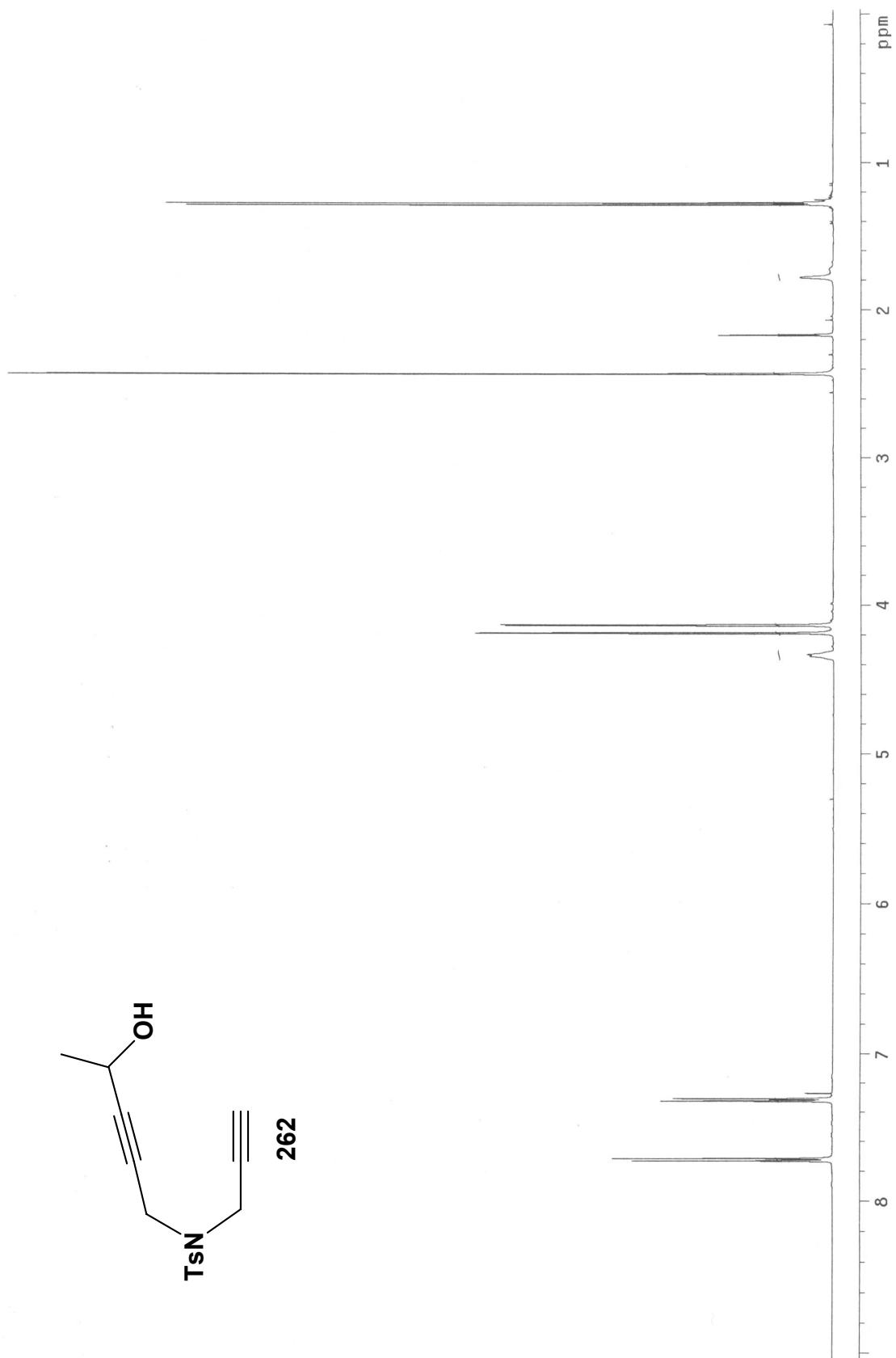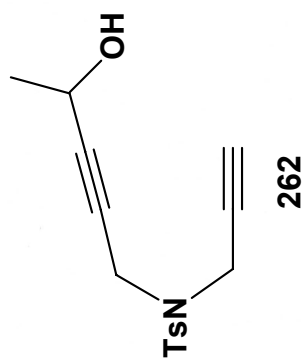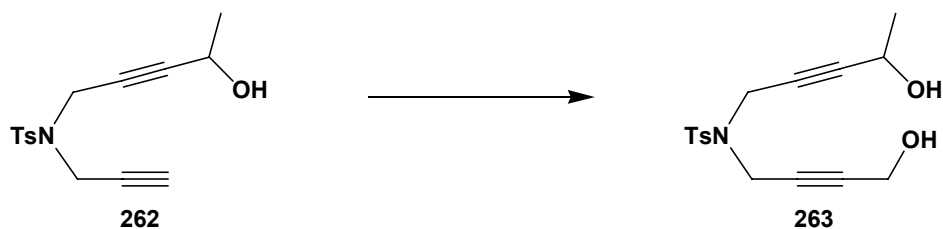
N-(4-hydroxybut-2-ynyl)-N-(4-hydroxypent-2-ynyl)-p-toluenesulfonamide (263).

A 50-mL, three-necked, round-bottomed flask equipped with a rubber septum, glass stopper, and argon inlet adapter, was charged with 15 mL of tetrahydrofuran and N-(4-hydroxypent-2-ynyl)-N-prop-2-ynyl-p-toluenesulfonamide (**262**) (0.350 g, 1.26 mmol), and cooled to -78 °C. n-Butyllithium (2.30 M solution in hexanes, 1.26 mL, 2.90 mmol) was added dropwise via syringe over 4 min and the solution was stirred for 30 min. Paraformaldehyde (0.303 g, 10.1 mmol) was added in one portion and the reaction mixture was allowed to warm to rt over 5 h. Saturated aqueous NH_4Cl (10 mL) was added, and the aqueous layer was washed with three 10-mL portions of ether, then the combined organic layers were washed with 10 mL of brine, dried over $MgSO_4$, filtered, and concentrated to give 0.315 g of an orange oil which was purified by column chromatography on 25 g of silica gel (gradient elution with 60-80 % MTBE-hexane) to give 0.127 g (31%) of **263** as a colorless oil.

IR (film):	3386, 2979, 2930, 2361, 2335, 1348, 1162 cm^{-1}.
^{1}H NMR (500 MHz, CDCl$_3$):	δ 7.74 (d, J = 8.2 Hz, 2H), 7.31 (d, J = 7.9 Hz, 2H), 4.33 (qt, J = 6.7, 1.7 Hz, 1H), 4.17 (d, J = 1.8 Hz, 2H), 4.16 (t, J = 1.8 Hz, 2H), 4.09 (t, J = 1.8 Hz, 2H), 2.42 (s, 3H), 2.40 (br s, 2H), 1.27 (d, J = 6.7 Hz, 3H).

¹³C NMR (125 MHz, CDCl₃):	δ 144.3, 135.6, 129.7, 128.3, 87.9, 84.3, 78.6, 76.8, 58.2, 58.2, 50.9, 37.3, 24.1, 21.7.
MS (*m/z*):	303 (M-H₂O+).

263

263 → **257**
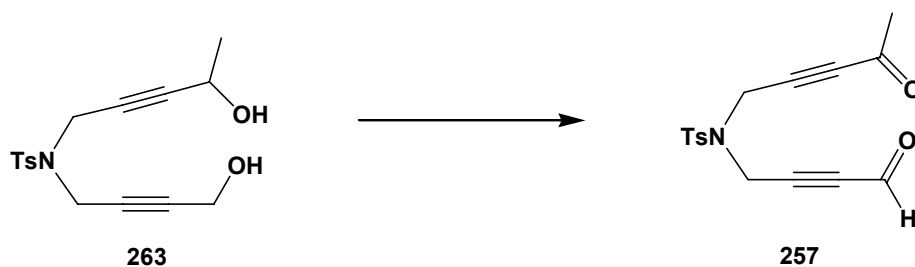
N-(4-oxobut-2-ynyl)-N-(4-oxopent-2-ynyl)-p-toluenesulfonamide (257).

A 50-mL, round-bottomed flask equipped with a rubber septum with argon inlet needle was charged with N-(4-hydroxybut-2-ynyl)-N-(4-hydroxypent-2-ynyl)-p-toluenesulfonamide (**263**) (0.105 g, 0.327 mmol), 10 mL of dichloromethane, and Dess-Martin periodinane (0.305 g, 0.719 mmol). The solution was stirred at 25 °C for 1 h and then concentrated and diluted with 10 mL of diethyl ether and 10 mL of saturated NaHCO$_3$ solution. The aqueous layer was separated and extracted with two 20-mL portions of diethyl ether. The combined organic phases were washed with two 20-mL portions of a 1:1 mixture of saturated NaHCO$_3$ and saturated Na$_2$S$_2$O$_3$ solution, 30 mL of saturated NaCl solution, dried over MgSO$_4$, filtered, and concentrated to afford 0.093 g of a yellow oil. Column chromatography on 10 g of silica gel (gradient elution with 20-50% MTBE-hexane) afforded 0.085 g (81%) of **257** as a pale yellow oil.

IR (film):	3030, 2968, 2923, 2873, 2251, 2211, 1676, 1597, 1352, 1162 cm^{-1}.
^{1}H NMR (300 MHz, CDCl$_3$):	δ 9.01 (s, 1H), 7.72 (d, J = 8.5 Hz, 2H), 7.33 (d, J = 8.0 Hz, 2H), 4.35 (d, J = 2.5 Hz, 2H), 4.31 (d, J = 3.0 Hz, 2H), 2.42 (s, 3H), 2.20 (s, 3H).
^{13}C NMR (125 MHz, CDCl$_3$):	δ 183.4, 175.8, 145.1, 134.5, 130.0, 128.0, 88.0, 85.3, 84.9, 83.0, 37.2, 37.2, 32.5, 21.7.

257
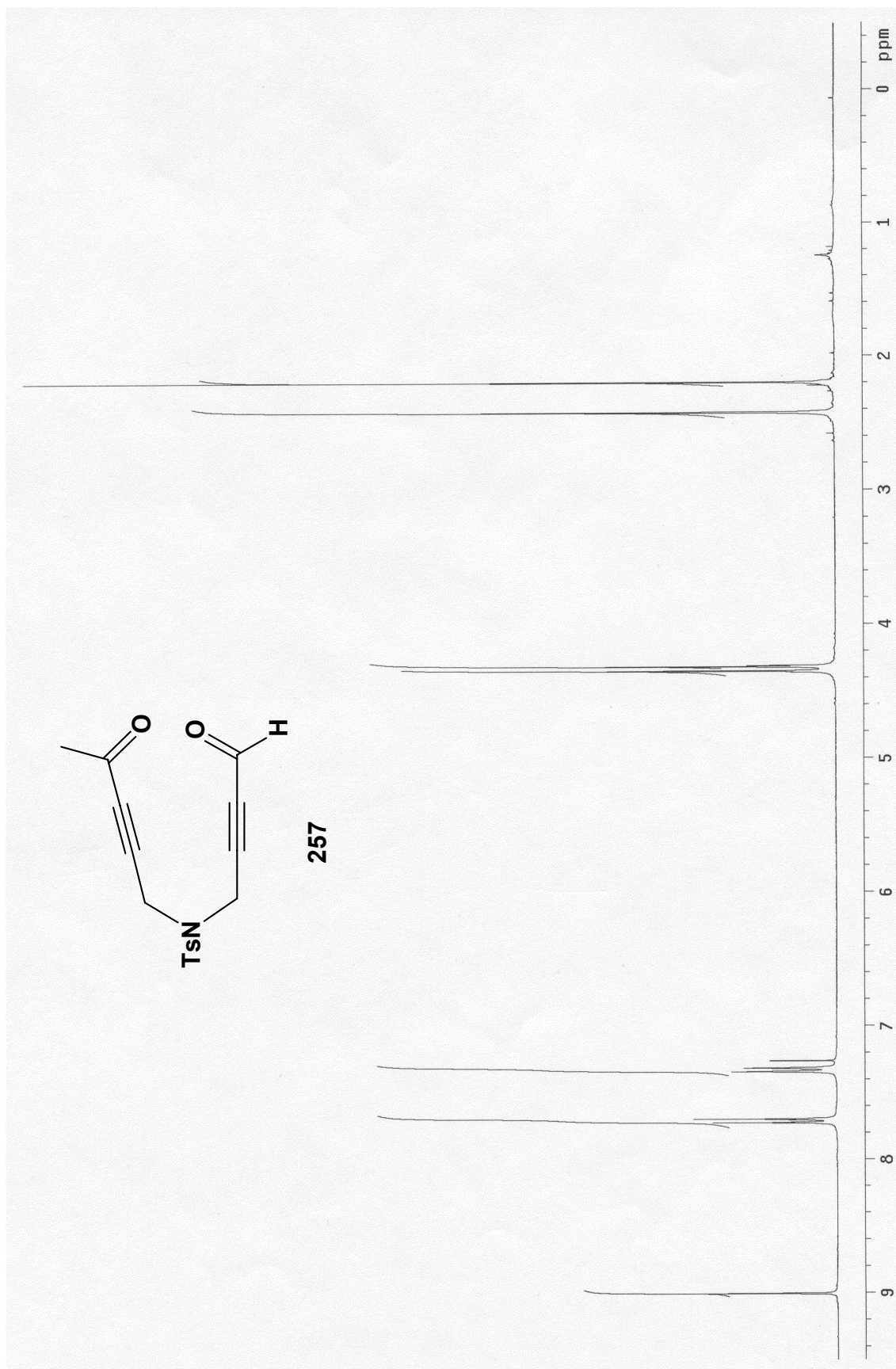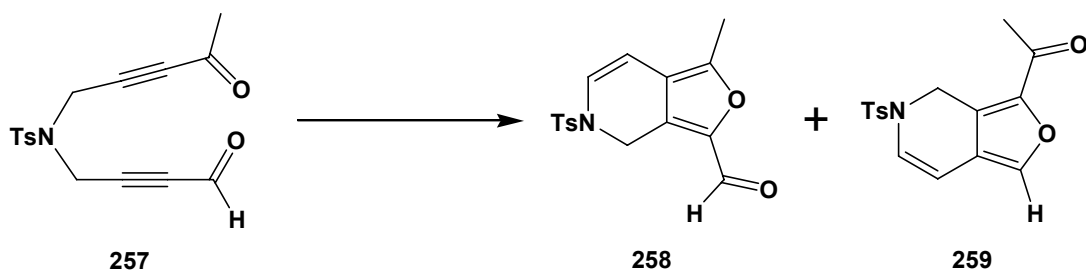
3-Formyl-1-methyl-5-(*p*-toluenesulfonyl)-4,5-dihydrofuro[3,4-*c*]pyridine (258) and

3-Acetyl-5-(*p*-toluenesulfonyl)-4,5-dihydrofuro[3,4-*c*]pyridine (259).

A 10-mL, one-necked, round-bottomed flask equipped with a rubber septum and argon inlet needle was charged with the diyne **257** (0.086 g, 0.27 mmol), 3 mL of toluene, and γ-terpinene (0.053 mL, 0.045 g, 0.30 mmol). The solution was degassed with a stream of argon for 1 h, and the septum was then replaced with a water-jacketed condenser and argon inlet adapter. The reaction mixture was heated at reflux (111 °C) for 24 h, and then allowed to cool to rt. Concentration gave 0.122 g of an orange oil which was purified by column chromatography on 8 g of silica gel (gradient elution with 30% diethyl ether-pentane) to give 0.058 g (68%) of an inseparable mixture of **258** and **259** as a yellow oil (87:13 by gas chromatographic analysis).

For the mixture:

IR (film):	3055, 2986, 1673, 1646, 1594, 1565, 1358, 1169 cm^{-1}.
HRMS(EI) Calcd. for C$_{16}$H$_{15}$NO$_4$S:	317.0722.
Found:	317.0718.
Anal. Calcd. for C$_{16}$H$_{15}$NO$_4$S:	C, 60.55; H, 4.76; N, 4.41.
Found:	C, 60.05; H, 4.22; N, 4.10.

For **258**:

^{1}H NMR (500 MHz, CDCl$_3$):	δ 9.57 (s, 1H), 7.72 (d, *J* = 8.2 Hz, 2H), 7.32 (d, *J* = 7.9 Hz, 2H), 6.76 (d, *J* = 8.2 Hz, 1H), 5.57 (d, *J* = 7.9 Hz, 1H), 4.81 (s, 2H), 2.42 (s, 3H), 2.29 (s, 3H).
^{13}C NMR (125 MHz, CDCl$_3$) :	δ 188.8, 144.7, 137.1, 134.2, 130.2, 127.5, 125.5, 119.8, 116.3, 110.3, 97.6, 41.5, 21.8, 12.5.

For **259** (partial):

^{1}H NMR:	δ 7.17 (s, 1H), 2.37 (s, 3H), 2.26 (s, 3H).
^{13}C NMR:	δ 42.2, 26.6.

259

+

258

260 → **271**

(with structures: TsNH$_2$ **260** converting to the bis-ynyl product **271** bearing Ts-N with two butynyl chains terminating in OH and CH$_2$OH)
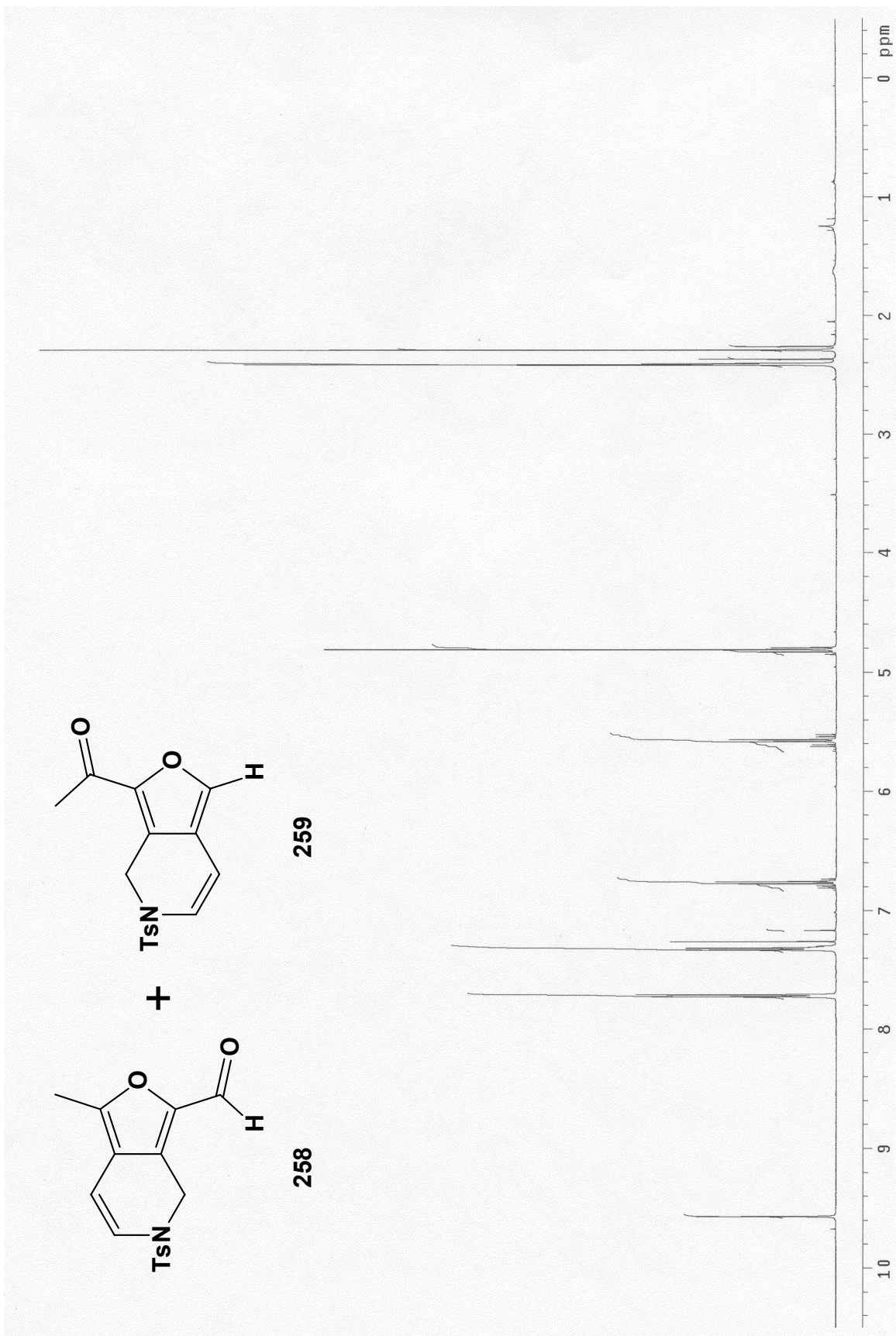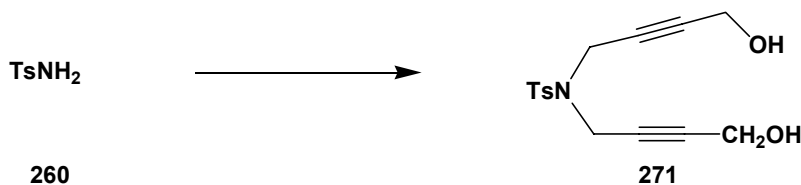
N,N-bis(4-hydroxybut-2-ynyl)-p-toluenesulfonamide[231] (271).

A 50-mL, round-bottomed flask equipped with a water-jacketed condenser fitted with an argon inlet adapter was charged with 30 mL of acetone, p-toluenesulfonamide (**260**) (0.786 g, 4.59 mmol), 4-chlorobut-2-yn-1-ol[232] (1.20 g, 11.5 mmol), and potassium carbonate (1.59 g, 11.5 mmol), and then heated at reflux for 72 h. The resulting brown mixture was concentrated in vacuo and the residue partitioned between 25 mL of H$_2$O and 25 mL of MTBE. The aqueous layer was extracted with three 10-mL portions of MTBE, and the combined organic layers were washed with 10 mL of brine, dried over MgSO$_4$, filtered, and concentrated to give 1.95 g of a brown oil which was purified by column chromatography on 25 g of silica gel (gradient elution with 50-100 % MTBE-hexane) to give **271** as an off-white solid which was recrystallized from CHCl$_3$ to afford 1.015 g (72%) of a white solid, mp 93.0-94.0 °C.

IR (CH$_2$Cl$_2$):	3404, 3000, 2926, 2359, 2342, 1716, 1346, 1161 cm^{-1}.
^{1}H NMR (500 MHz, CDCl$_3$):	δ 7.75 (d, J = 8.2 Hz, 2H), 7.33 (d, J = 8.2 Hz, 2H), 4.18 (s, 4H), 4.10 (s, 4H), 2.44 (s, 3H), 2.06 (s, 2H).
^{13}C NMR (125 MHz, CDCl$_3$):	δ 144.3, 135.6, 129.6, 128.4, 84.3, 78.6, 51.0, 37.4, 21.8.

---

[231] This compound has previously been prepared using 4-bromobut-2-yn-1-ol. See Gleiter, R; Ritter, J.; Irngartinger, H.; Lichtenthaeler, J. *Tetrahedron Lett.* **1991**, *32*, 2883.

[232] Brandsma, L.; Verkruijsse, H. D. *Synthesis of Acetylenes, Allenes, and Cumulenes*; Elsevier: Amsterdam, 1981; p 65.

MS (*m/z*): 289 (M-H$_2$O+).

271
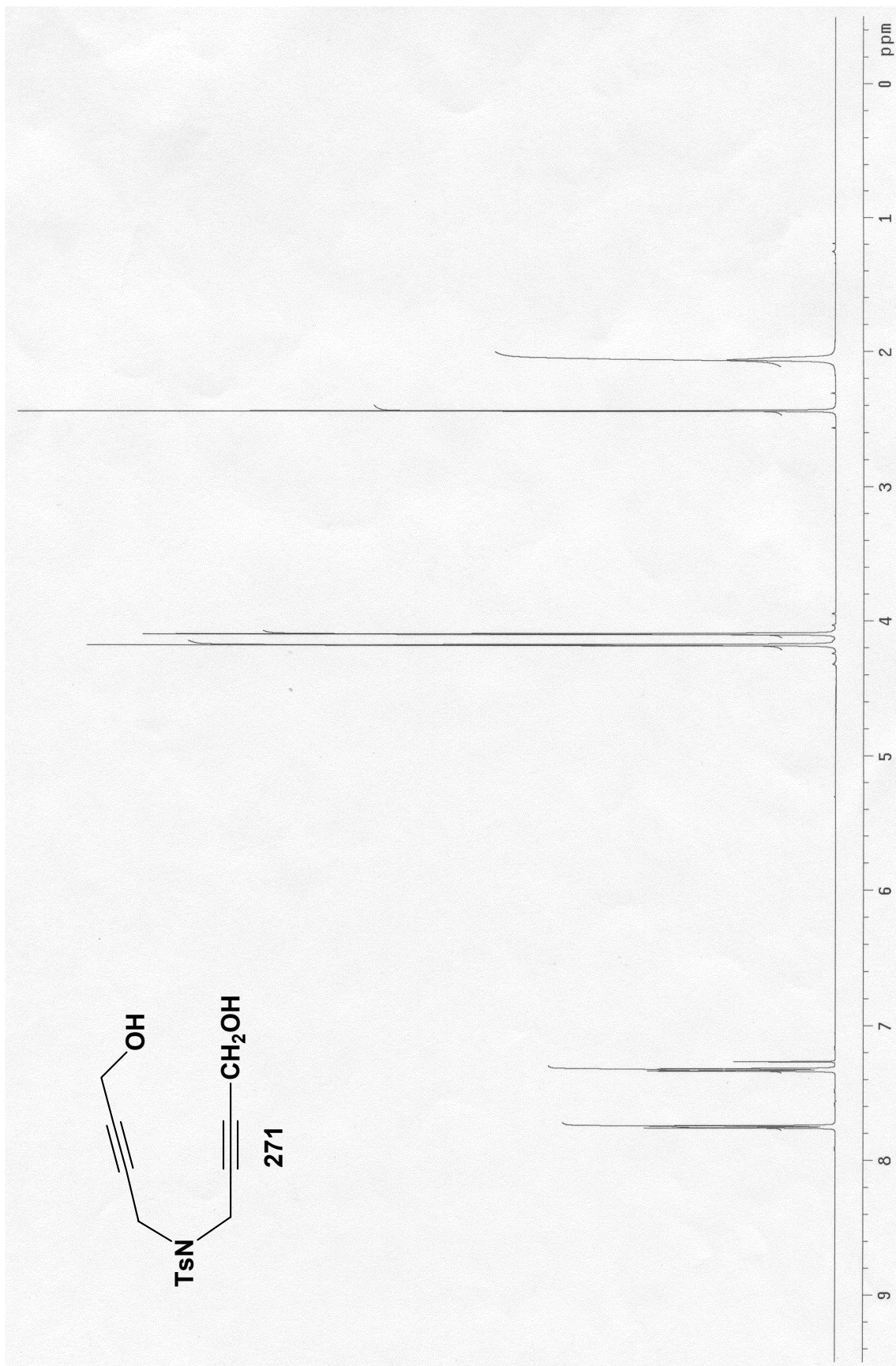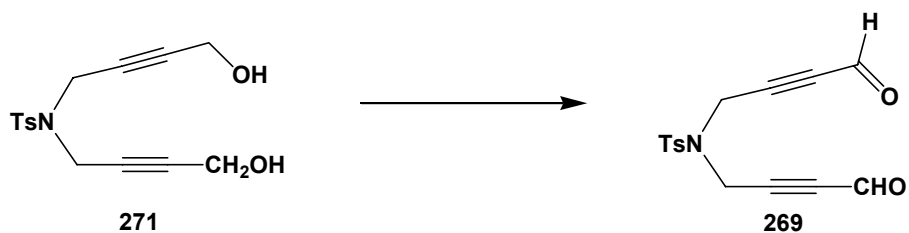
N,N-bis(4-oxobut-2-ynyl)-p-toluenesulfonamide (269).

A 50-mL, round-bottomed flask equipped with a rubber septum with argon inlet needle was charged with *N,N*-bis(4-hydroxybut-2-ynyl)-p-toluenesulfonamide (**271**) (0.401 g, 1.30 mmol), 30 mL of dichloromethane, and Dess-Martin periodinane (1.22 g, 2.87 mmol). The solution was stirred at 25 °C for 1 h and then 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 0.456 g of a yellow oil. Column chromatography on 20 g of silica gel (gradient elution with 20-50% MTBE-hexane) afforded 0.370 g (94%) of **269** as a pale yellow oil.

IR (film):	3055, 2973, 2871, 2743, 2254, 2200, 1673, 1352, 1164 cm^{-1}.
^{1}H NMR (500 MHz, CDCl$_3$):	δ 9.01 (s, 2H), 7.71 (d, J = 8.2 Hz, 2H), 7.33 (d, J = 8.2 Hz, 2H), 4.36 (s, 4H), 2.42 (s, 3H).
^{13}C NMR (125 MHz, CDCl$_3$):	δ 175.7, 145.3, 134.3, 130.1, 128.0, 87.8, 85.0, 37.3, 21.7.

269

269 → **270**
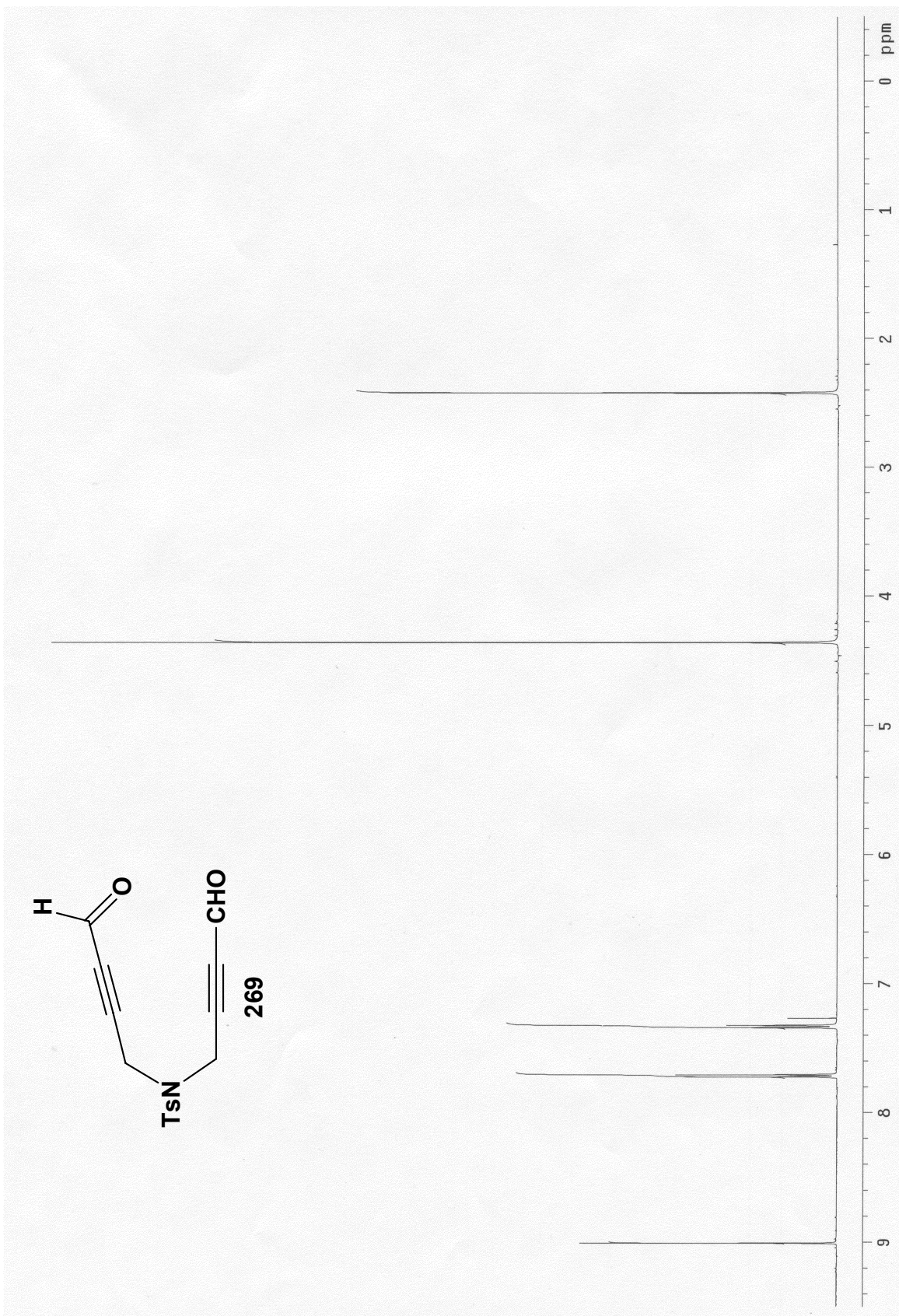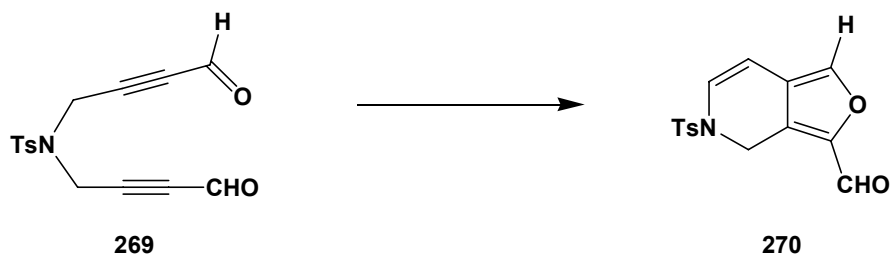
3-Formyl-5-(*p*-toluenesulfonyl)-4,5-dihydrofuro[3,4-*c*]pyridine (270).

A 10-mL, one-necked, round-bottomed flask equipped with a rubber septum and argon inlet needle was charged with the diyne **269** (0.176 g, 0.581 mmol), 5 mL of toluene, and γ-terpinene (0.095 g, 0.112 mL, 0.639 mmol). The solution was degassed with a stream of argon for 1 h, and the septum was then replaced with a water-jacketed condenser and argon inlet adapter. The reaction mixture was heated at reflux (111 °C) for 24 h, and then allowed to cool to rt. Concentration gave 0.212 mg of a brown oil, which was purified by column chromatography on 15 g of silica gel (gradient elution with 10-40% MTBE-hexane) to give 0.132 g (75%) of **270** as a white solid, mp 130.0-131.0 °C.

IR (film):	3054, 2986, 1681, 1594, 1548, 1359, 1171 cm^{-1}.
^{1}H NMR (500 MHz, CDCl$_3$):	δ 9.64 (d, $J = 0.6$ Hz, 1H), 7.69 (d, $J = 8.2$ Hz, 2H), 7.29 (d, $J = 7.9$ Hz, 2H), 7.22 (d, $J = 0.6$ Hz, 1H), 6.79 (d, $J = 7.9$ Hz, 1H), 5.61 (d, $J = 8.2$ Hz, 1H), 4.82 (s, 2H), 2.38 (s, 3H).
^{13}C NMR (125 MHz, CDCl$_3$):	δ 179.6, 146.5, 144.8, 139.3, 134.2, 130.3, 127.5, 126.9, 120.2, 97.1, 41.5, 21.8.
Anal. Calcd. for C$_{15}$H$_{13}$NO$_4$S:	C, 59.39; H, 4.32; N, 4.62.
Found:	C, 59.28; H, 4.34; N, 4.54.

270

281 → **285**
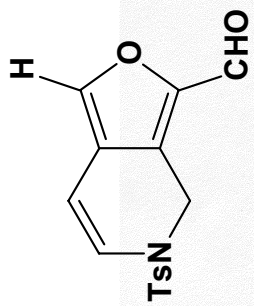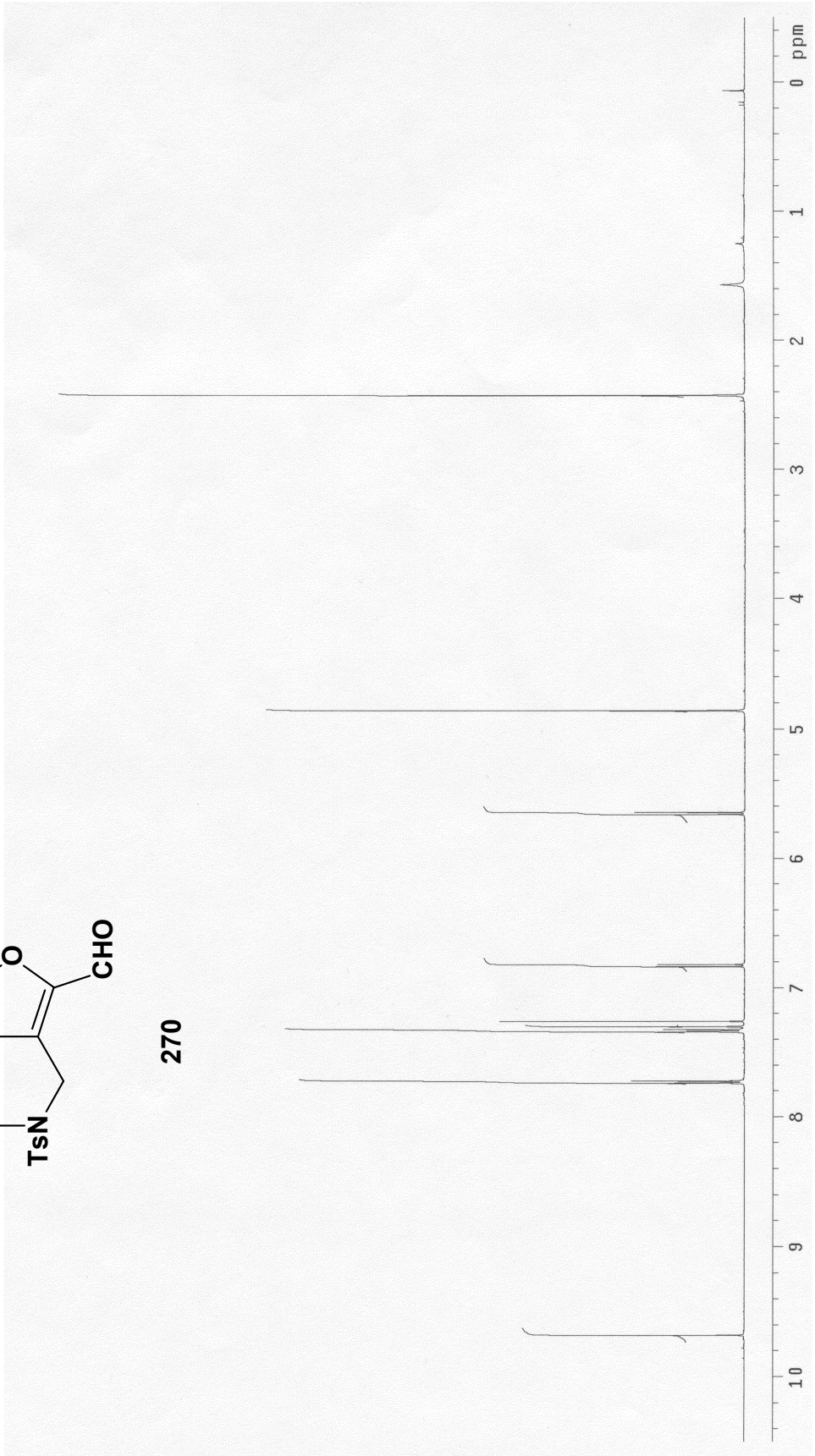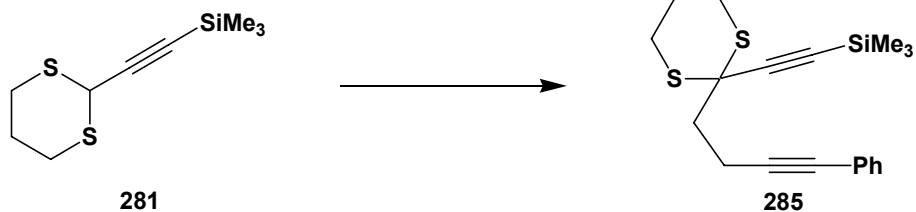
2-(Trimethylsilylethynyl)-2-(4-phenylbut-3-ynyl)-1,3-dithiane (285).

A 100-mL, three-necked, round-bottomed flask equipped with a rubber septum, glass stopper, and argon inlet adapter, was charged with 25 mL of tetrahydrofuran and 2-(trimethylsilylethynyl)-1,3-dithiane[233] (0.147 g, 0.679 mmol) and cooled to -78 °C. *n*-Butyllithium (2.60 M solution in hexanes, 0.287 mL, 0.747 mmol) was added dropwise via syringe over 2 min, and the resulting yellow solution was allowed to warm to -50 °C over 1 h. The reaction mixture was cooled to -78 °C and 4-iodo-1-phenyl-1-butyne[234] (0.191 g, 0.747 mmol) was added via syringe over 1 min. The reaction mixture was allowed to warm to rt over 2.5 h, and then quenched by the addition of saturated aqueous NH_4Cl (10 mL). The aqueous layer was separated and extracted with three 10-mL portions of diethyl ether, and the combined organic phases were washed with 30 mL of saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford 0.243 g of a yellow oil which was purified by column chromatography on 20 g of silica gel (gradient elution with 0-10% MTBE-hexane) to afford 0.232 g (99%) of **285** as a yellow oil.

IR (film): 2955, 2905, 2234, 2156 cm^{-1}.

[233] Andersen, N.H.; Denniston, A. D.; McCrae, D. A. *J. Org. Chem.* **1982**, *47*, 1146.
[234] Ozaki, S.; Mitoh, S.; Ohmori, H. *Chem. Pharm. Bull.* **1995**, *43*, 1435.

|	
^{1}H NMR (500 MHz, CDCl$_3$):	δ 7.40-7.42 (m, 2H), 7.28-7.30 (m, 3H), 3.33 (t, $J =$ 12.5 Hz, 2H), 2.81-2.85 (m, 4H), 2.32 (t, $J = 8.5$ Hz, 2H), 2.17 (d, $J = 14.0$ Hz, 1H), 1.86 (q, $J = 14.0$ Hz, 1H), 0.24 (s, 9H).
^{13}C NMR (125 MHz, CDCl$_3$):	δ 131.7, 128.4, 127.9, 123.8, 103.1, 92.5, 88.9, 81.4, 46.1, 40.5, 28.9, 25.8, 15.5, 0.3.
MS (*m/z*):	344 (M+).

285
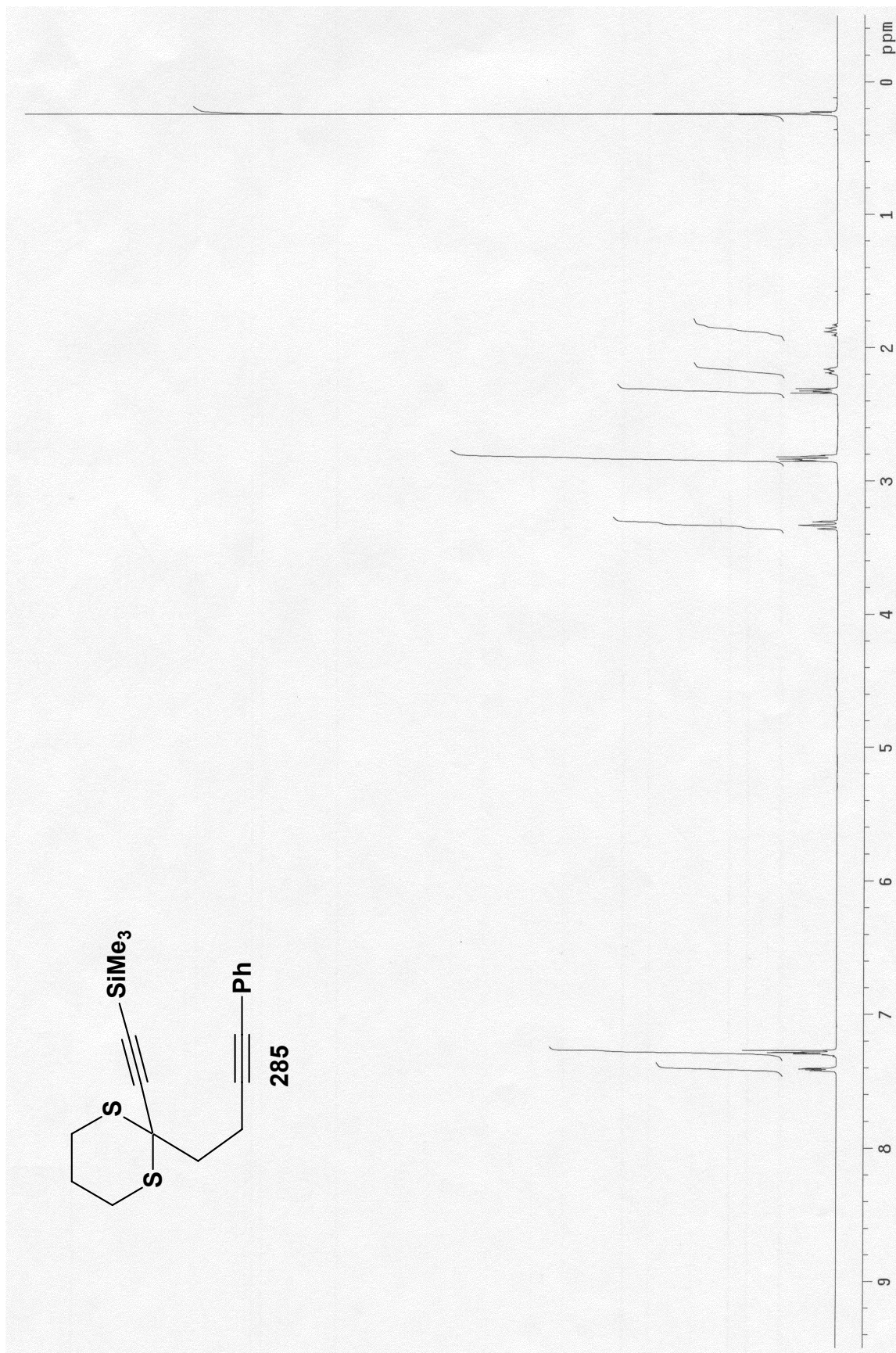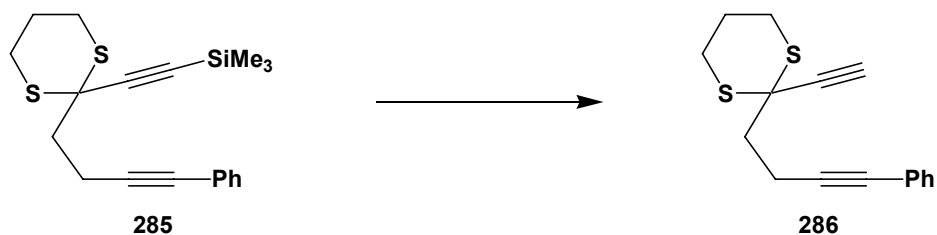
2-Ethynyl-2-(4-phenylbut-3-ynyl)-1,3-dithiane (286).

A 50-mL, round-bottomed flask equipped with a Teflon stir bar was charged with 2-(trimethylsilylethynyl)-2-(4-phenylbut-3-ynyl)-1,3-dithiane (**285**) (0.745 g, 2.73 mmol), 15 mL of methanol, 5 mL of CH_2Cl_2, and K_2CO_3 (0.100 g, 0.72 mmol), and stirred at rt for 2 h. The reaction mixture was concentrated, and the residue was suspended in 10 mL of CH_2Cl_2, washed with two 5-mL portions of saturated aqueous NH_4Cl and 5 mL of brine, dried over $MgSO_4$, filtered, and concentrated to afford 0.600 g of a yellow oil which was purified by column chromatography on 20 g of silica gel (gradient elution with 0-20% MTBE-hexane) to afford 0.502 g (85%) of **286** as a pale yellow oil.

IR (film):	3286, 3054, 2906, 2359, 2233 cm^{-1}.
^{1}H NMR (500 MHz, CDCl$_3$):	δ 7.39-7.41 (m, 2H), 7.27-7.29 (m, 3H), 3.39-3.33 (m, 2H), 2.91 (s, 1H), 2.81-2.86 (m, 4H), 2.36-2.33 (m, 2H), 2.16-2.20 (m, 1H), 1.83-1.91 (m, 1H).
^{13}C NMR (125 MHz, CDCl$_3$):	δ 131.8, 128.4, 127.9, 123.8, 88.7, 82.5, 81.5, 75.3, 45.2, 40.6, 28.8, 25.7, 15.5.
MS (*m/z*):	272 (M+).

286
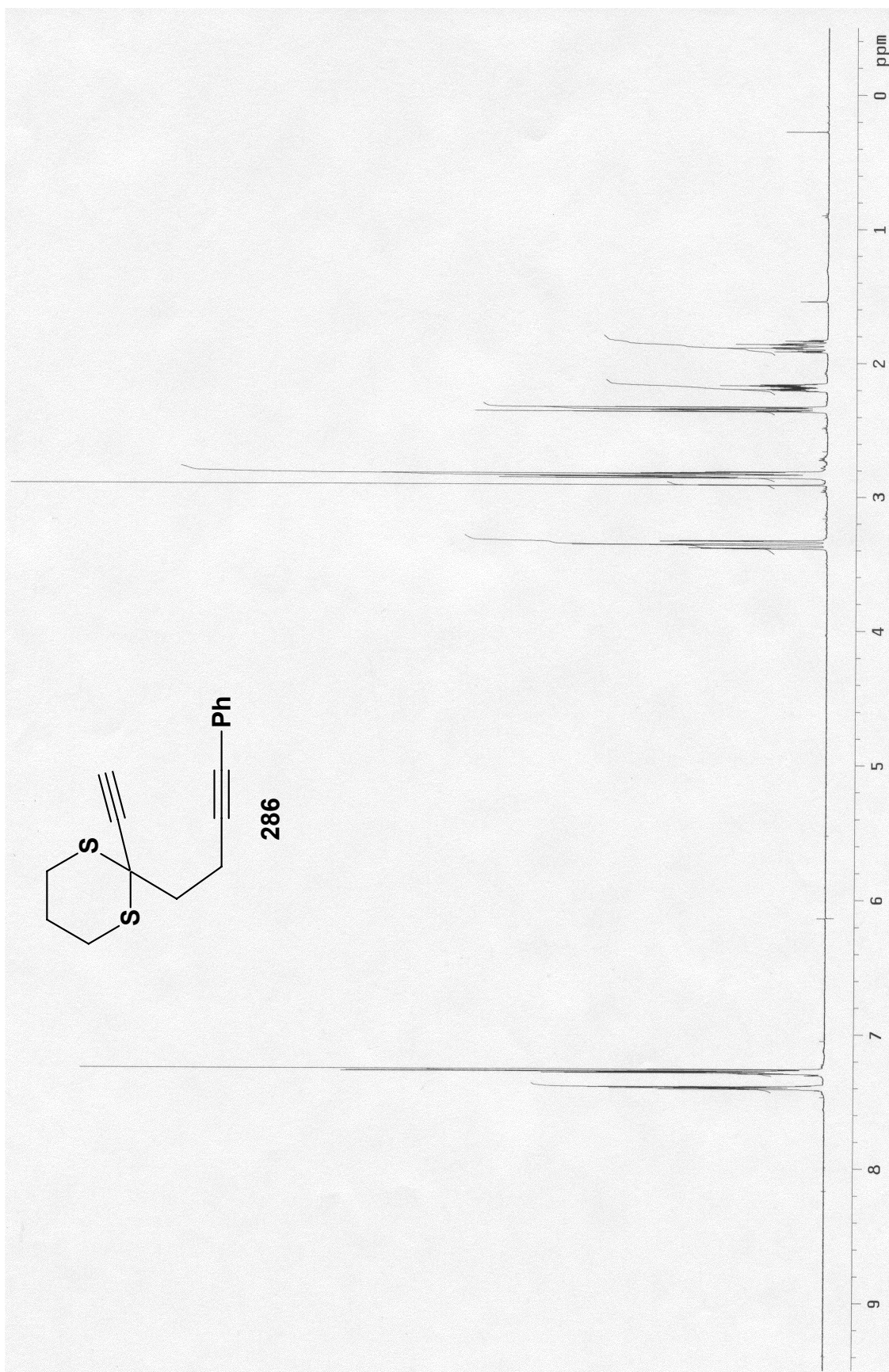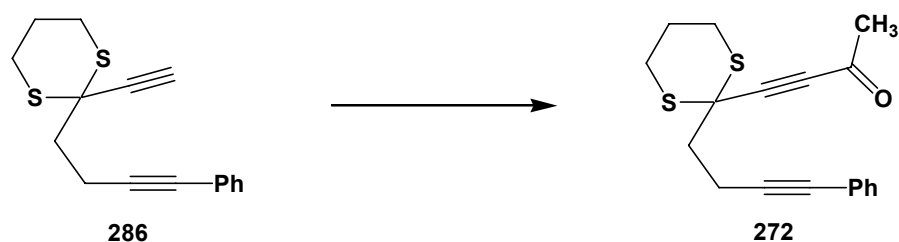
2-(3-Oxobut-1-ynyl)-2-(4-phenylbut-3-ynyl)-1,3-dithiane (272).

A 50-mL, three-necked, round-bottomed flask equipped with an argon inlet adapter, glass stopper, and rubber septum, was charged with 2-ethynyl-2-(4-phenylbut-3-ynyl)-1,3-dithiane (**286**) (0.486 g, 1.78 mmol) and 20 mL of tetrahydrofuran, and cooled at -78 °C with a dry ice-acetone bath. *n*-Butyllithium (2.60 M in hexanes, 0.750 mL, 1.95 mmol) was added dropwise via syringe over 3 min and the resulting mixture was stirred at -78 °C for 1 h. A 50-L, three-necked, round-bottomed flask equipped with an argon inlet adapter, rubber septum, and glass stopper was charged with acetic anhydride (1.82 g, 1.68 mL, 17.8 mmol) and 10 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 30 min, and the resulting mixture was then stirred at -78 °C for 3 h. The reaction mixture was diluted with 10 mL of a 10:1 mixture of saturated aqueous NH$_4$Cl and concentrated NH$_4$OH, and then allowed to warm to rt. The aqueous layer was separated and extracted with two 10-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 0.360 g of a yellow oil. Column chromatography on 20 g of silica gel (gradient elution with 0-10% MTBE-hexanes) afforded 0.202 g (36%) of **272** as a yellow oil.

IR (film):	3054, 2907, 2200, 2158, 1674 cm^{-1}.
^{1}H NMR (500 MHz, CDCl$_3$):	δ 7.37-7.41 (m, 2H), 7.27-7.31 (m, 3H), 3.28-3.34 (m, 2H), 2.79-2.85 (m, 4H), 2.39 (s, 3H), 2.33-2.36 (m, 2H), 2.17-2.22 (m, 1H), 1.83-1.92 (m, 1H).
^{13}C NMR (125 MHz, CDCl$_3$):	δ 184.3, 131.7, 128.4, 128.0, 123.6, 89.0, 88.2, 86.2, 81.8, 44.4, 40.1, 33.2, 28.8, 25.3, 15.5.
MS (*m/z*):	314 (M+).

272
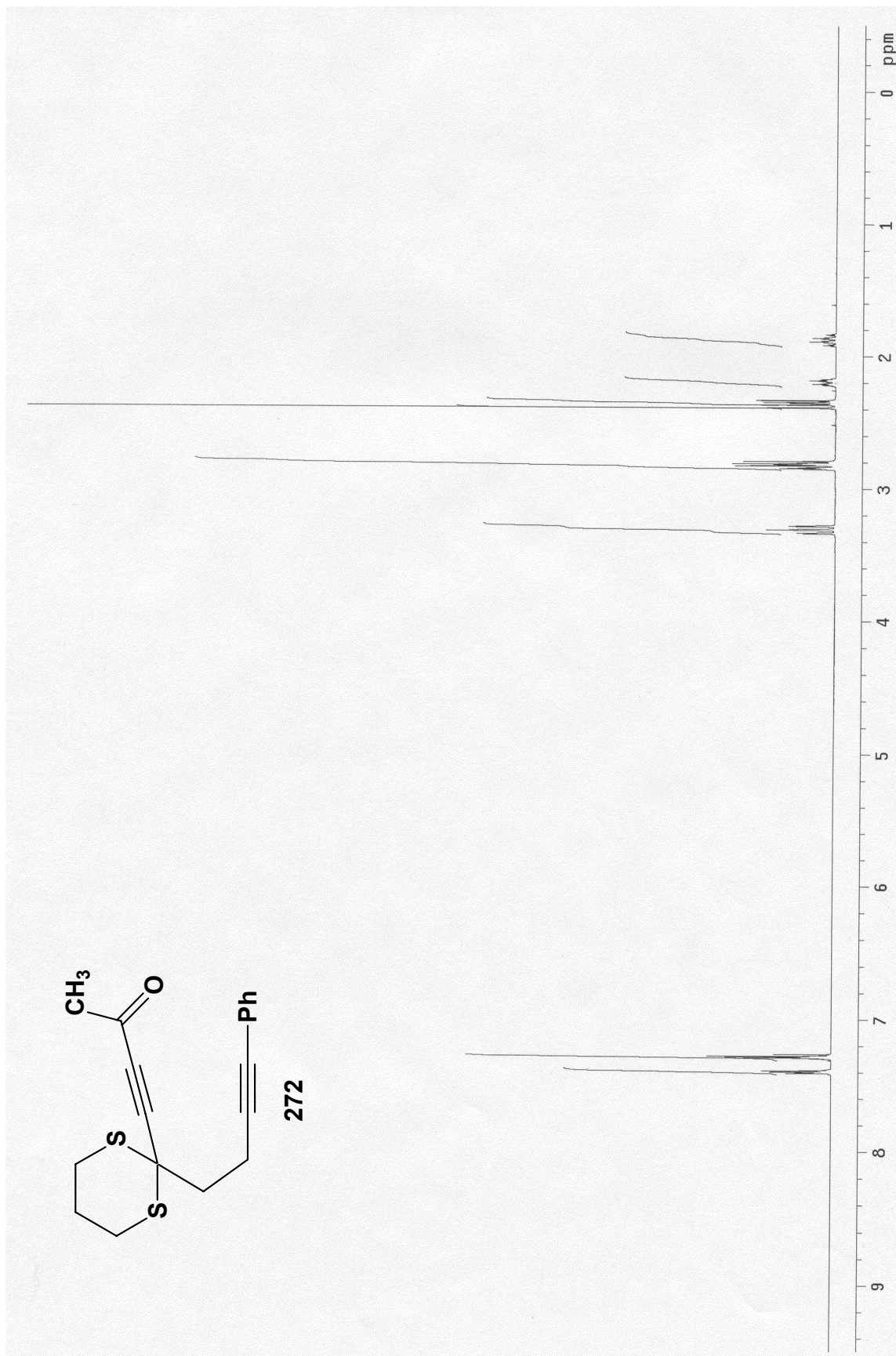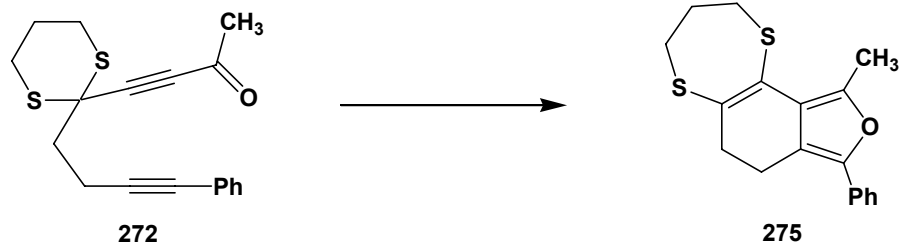
10-Methyl-8-phenyl-3,4,6,7-tetrahydro-2*H*-[1,4]dithiepino[2,3-*e*]isobenzofuran (275).

A 10-mL, one-necked, round-bottomed flask equipped with a rubber septum and argon inlet needle was charged with the diyne **272** (0.155 g, 0.493 mmol), 5 mL of toluene, and γ-terpinene (0.095 mL, 0.080 g, 0.542 mmol). The solution was degassed with a stream of argon for 1 h, and the septum was then replaced with a water-jacketed condenser and argon inlet adapter. The reaction mixture was heated at reflux (111 °C) for 24 h, and then allowed to cool to rt. Concentration gave 0.148 g of a brown oil, which was purified by column chromatography on 20 g of silica gel (gradient 0-30% diethyl ether-pentane) to afford 0.091 g (59%) of **275** as a yellow oil.

IR (film):	3054, 2986, 1600, 1544, 1266 cm^{-1}.
^{1}H NMR (500MHz, CDCl$_3$):	δ 7.54-7.56 (m, 2H), 7.36-7.40 (m, 2H), 7.21-7.25 (m, 1H), 3.21 (app quintet, J = 6.0 Hz, 4H), 2.80 (t, J = 7.0 Hz, 2H), 2.62 (s, 3H), 2.48 (t, J = 7.0 Hz, 2H), 2.20 (app quintet, J = 5.8 Hz, 2H).
^{13}C NMR (125 MHz, CDCl$_3$):	δ 145.9, 143.8, 133.0, 131.5, 128.7, 126.7, 124.9, 123.5, 121.5, 117.6, 35.5, 32.5, 32.2, 31.2, 21.0, 14.7.
Anal. Calcd. for C$_{18}$H$_{18}$OS$_2$:	C, 68.75; H, 5.77; S, 20.39.
Found:	C, 68.59; H, 5.84; S, 20.69.

275

288   **293**
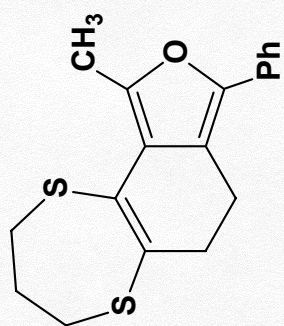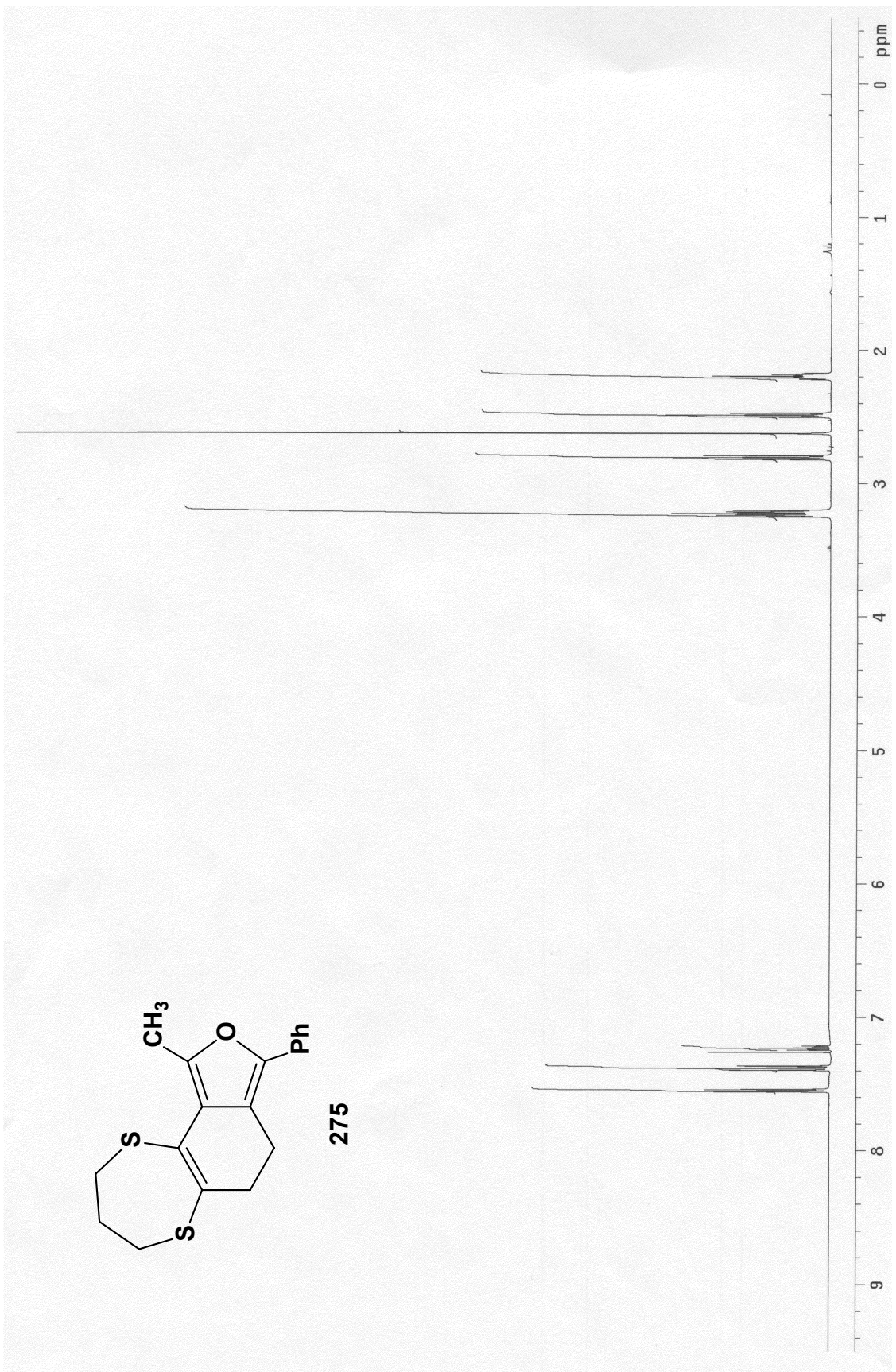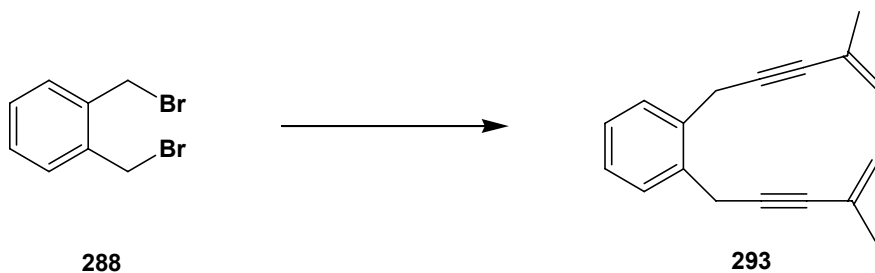
1,2-Bis(4-methylpent-4-en-2-ynyl)benzene (293).

A 100-mL, three-necked, round-bottomed flask equipped with a rubber septum, argon inlet adapter, and glass stopper, was charged with 30 mL of tetrahydrofuran and CuBr•SMe$_2$ (0.117 g, 0.57 mmol). A 50-mL, two-necked, pear flask equipped with a rubber septum, and argon inlet adapter, was charged with 20 mL of tetrahydrofuran and 2-methyl-1-buten-3-yne (1.26 mL, 0.876 g, 13.3 mmol) and cooled to 0 °C. EtMgBr (3.1 M in Et$_2$O, 4.28 mL, 13.3 mmol) was added dropwise via syringe over 5 min, and the gray solution was stirred for 15 min at 0 °C. The cooling bath was removed and the gray solution was stirred for 1 h at rt. This solution was then transferred via cannula over 5 min into the rapidly stirred mixture of CuBr•SMe$_2$ in THF. A 25-mL, two-necked, pear flask equipped with a rubber septum, and argon inlet adapter, was charged with 10 mL of tetrahydrofuran and α,α'-dibromo-*o*-xylene (**288**) (1.00 g, 3.79 mmol) and the mixture was stirred for 5 min to dissolve the solid. This solution was then transferred via cannula over 5 min into the solution of copper acetylide, with the aid of two 1-mL rinses of tetrahydrofuran. The glass stopper was replaced with a water-jacketed condenser and the reaction mixture was heated at reflux for 24 h. The reaction mixture was then allowed to cool to rt and poured into a separatory funnel containing saturated aqueous NH$_4$Cl (20 mL). The aqueous phase was separated and extracted with two 20-mL portions of ether.

The combined organic phases were washed with 20 mL of brine, and dried over MgSO$_4$, filtered, and concentrated to give 0.700 g of a brown oil. Column chromatography on 50 g of silica gel (elution with hexane) provided 0.424 g (48%) of the diyne **293** as a colorless oil.
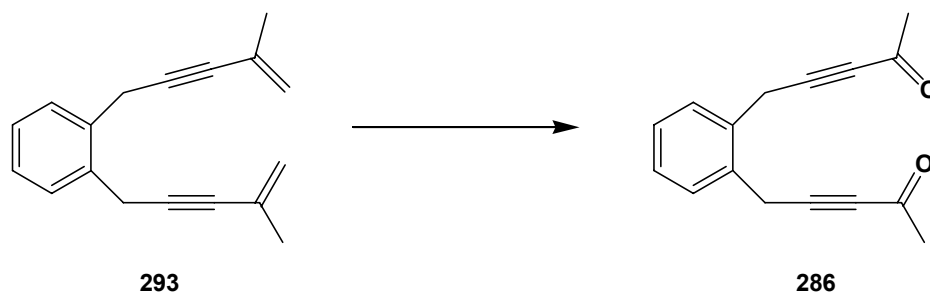
IR (film):	3095, 3022, 2955, 2922, 2227, 1615, 895 cm^{-1}.
^{1}H NMR (500 MHz, CDCl$_3$):	δ 7.46-7.49 (m, 2H), 7.26-7.29 (m, 2H), 5.27-5.29 (m, 2H), 5.19-5.21 (m, 2H), 3.75 (s, 4H), 1.91-1.93 (m, 6H).
^{13}C NMR (125 MHz, CDCl$_3$):	δ 134.7, 128.9, 127.4, 127.2, 121.2, 85.9, 84.5, 23.9, 23.5.
MS (*m/z*):	234 (M+).

293

293 → **286**
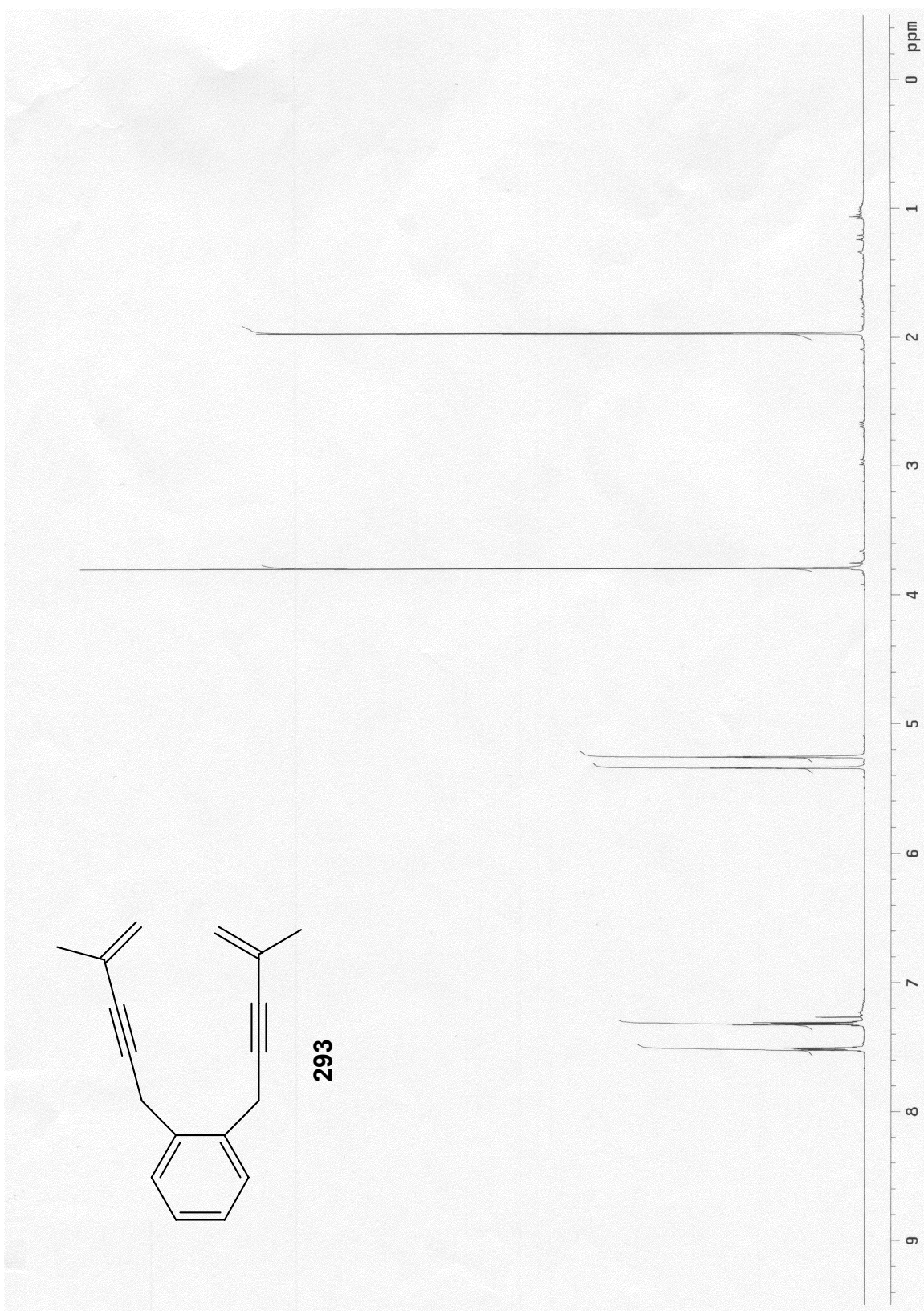
1,2-Bis(4-oxo-2-pentynyl)benzene (286).

A 100-mL, round-bottomed flask was charged with 27 mL of CH_2Cl_2, 3 mL of MeOH, and the bis-enyne **293** (0.377 g, 1.61 mmol). Sudan Red indicator was added until the solution became bright red, and the flask was then cooled to -78 °C. A stream of ozone was bubbled through the solution via pipet with stirring until the red color disappeared (a pale purple color was visible). The solution was degassed with a stream of argon for 15 min at -78 °C, then Me_2S (0.508 g, 0.600 mL) was added via syringe. The pale yellow solution was allowed to warm to rt over 14 h, and then concentrated to afford 0.347 g of a yellow oil which was purified by column chromatography on 30 g of silica gel (gradient elution with 20-40% MTBE-hexane) to afford 0.267 g (67%) of bis-ynone **286** as a very pale yellow oil.

IR (film):	3002, 2917, 2212, 1673 cm^{-1}.
^{1}H NMR (300 MHz, CDCl$_3$):	δ 7.37-7.41 (m, 2H), 7.29-7.33 (m, 2H), 3.79 (s, 4H), 2.36 (s, 6H).
^{13}C NMR (75 MHz, CDCl$_3$):	δ 184.5, 132.5, 129.5, 128.3, 89.3, 83.3, 33.0, 23.4.
MS (*m/z*):	238 (M+).

286
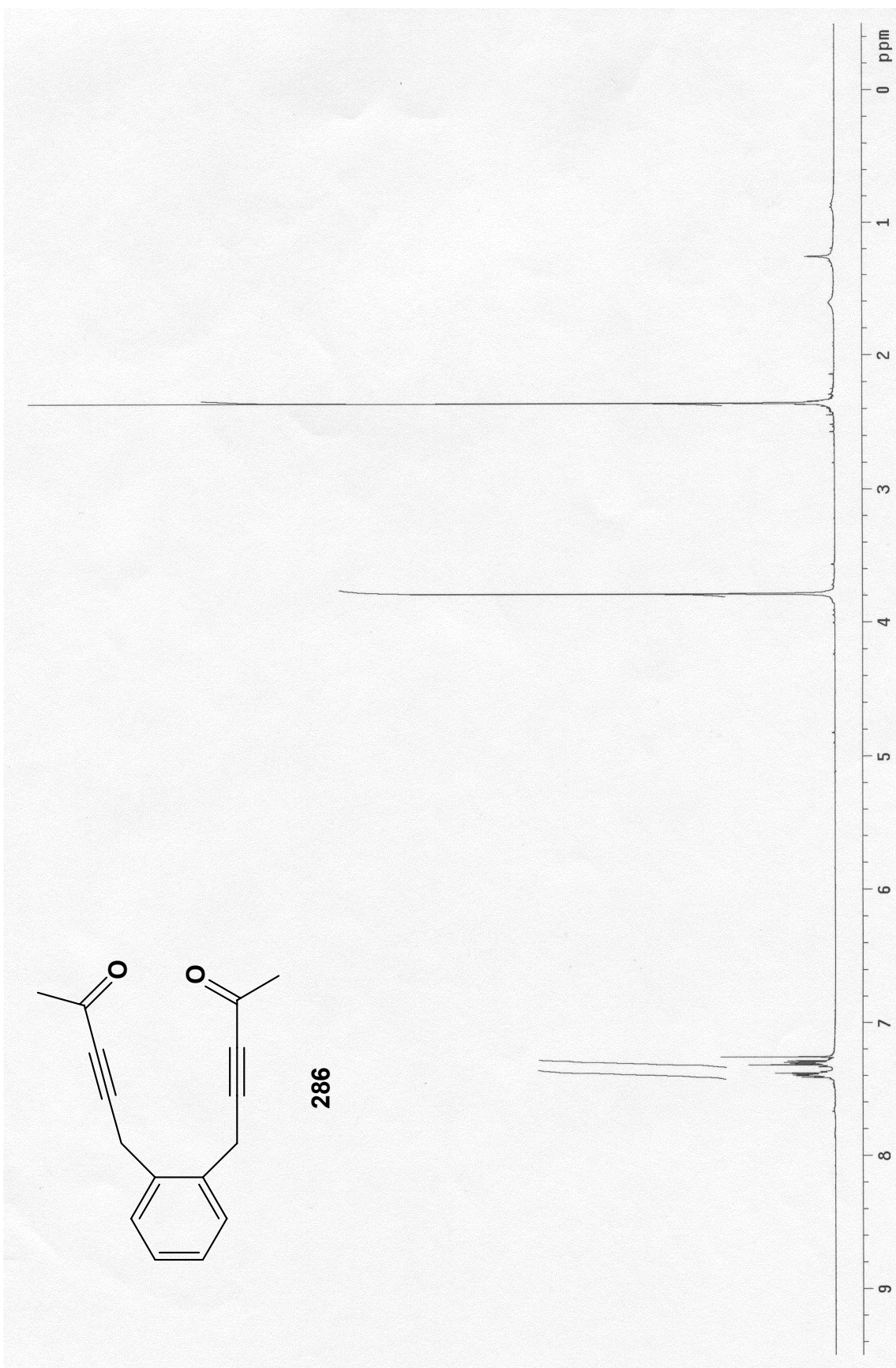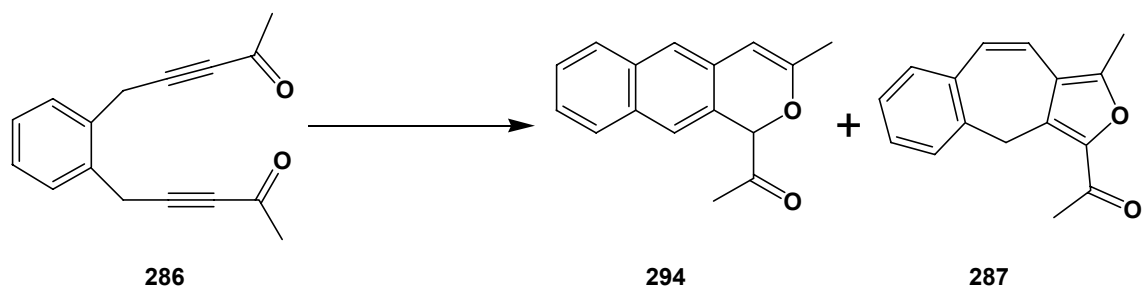
1-Acetyl-3-methyl-1*H*-benzo[*g*]isochromene (294) and

3-Acetyl-1-methyl-4*H*-benzo[4,5]cyclohepta[1,2-*c*]furan (287).

An oven-dried, threaded, Pyrex tube (ca. 20 mL capacity) equipped with a rubber septum and argon inlet needle was charged with diyne **286** (0.257 g, 1.08 mmol), 11 mL of toluene, and γ-terpinene (0.209 mL, 0.178 g, 1.19 mmol). The solution was degassed by four freeze-pump-thaw cycles, and the tube was then sealed with a Teflon cap. The sealed tube was placed in a preheated oil bath at 150 °C for 48 h, then allowed to cool to rt. Concentration gave a brown oil which was purified on 25 g of silica gel (gradient elution with 0-20% MTBE-hexane) to give 0.206 g (80%) of an inseparable mixture of **294** and **287** as an off-white solid, mp 98.0-101.0 °C (76:24 ratio by gas chromatographic analysis).

For the mixture:

IR (film):	3054, 2986, 1726, 1655, 1097, 1072 cm^{-1}.
Anal. Calcd. for C$_{16}$H$_{14}$O$_2$: Found:	C, 80.65; H, 5.92. C, 80.78; H, 5.91.

For **294**:

^{1}H NMR (500 MHz, CDCl$_3$):	δ 7.75 (d, *J* = 7.9 Hz, 1H), 7.71 (d, *J* = 8.2 Hz, 1H), 7.57 (s, 1H), 7.42 (td, *J* = 7.9, 1.2 Hz, 1H), 7.37 (td,

	J = 8.2, 1.2 Hz, 1H), 7.29 (s, 1H), 5.75 (s, 1H), 5.63 (s, 1H), 2.29 (s, 3H), 2.08 (s, 3H).
^{13}C NMR (125 MHz, CDCl$_3$):	δ 205.8, 153.9, 134.2, 132.4, 128.4, 128.1, 127.5, 126.8, 125.4, 125.0, 124.7, 120.6, 101.2, 83.8, 26.1, 20.2.

For **287**:

^{1}H NMR (500 MHz, CDCl$_3$):	δ 7.34-7.37 (m, 1H), 7.23-7.27 (m, 1H), 7.20-7.23 (m, 2H), 6.77 (d, J = 11.6 Hz, 1H), 6.60 (d, J = 11.6 Hz, 1H), 4.21 (s, 2H), 2.48 (s, 3H), 2.35 (s, 3H).

287

+

294
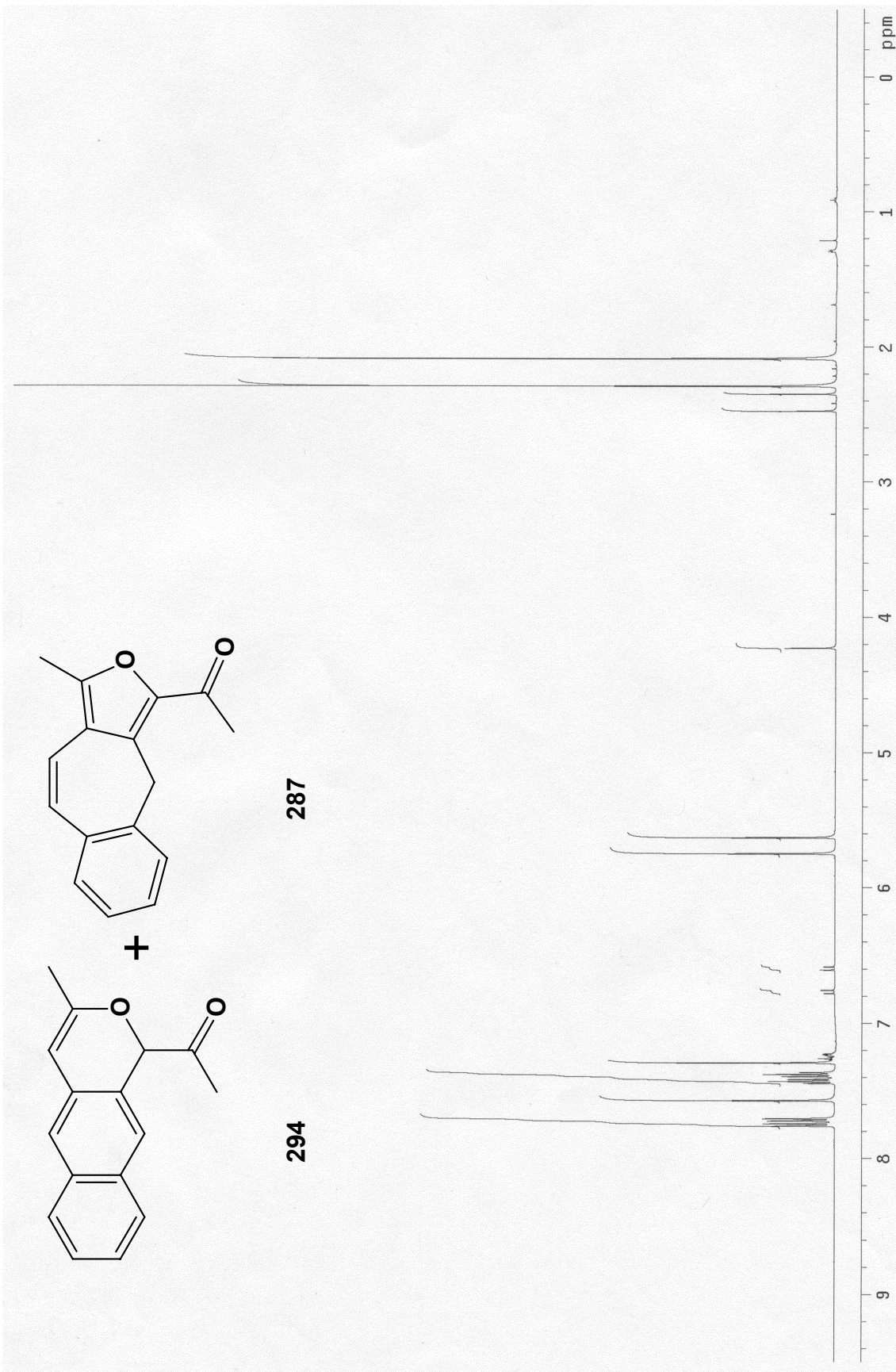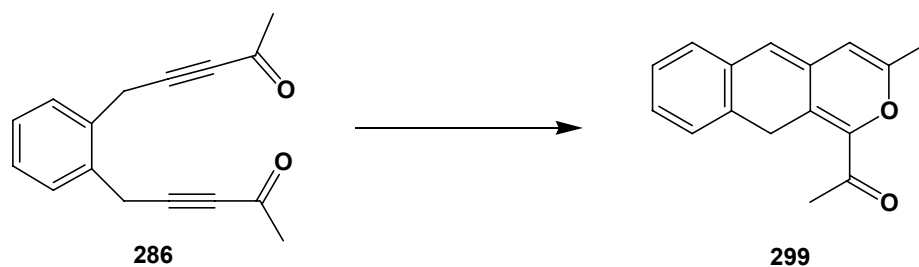
1-Acetyl-3-methyl-10*H*-benzo[*g*]isochromene (299).

A 10-mL, oven-dried, round-bottomed flask equipped with an argon inlet adapter was charged with diyne **286** (0.091 g, 0.284 mmol), and 5 mL of dimethyl sulfoxide. Potassium *t*-butoxide (0.003 g, 0.028 mmol) was added, and the solution immediately turned deep red. The reaction mixture was stirred for 5 min at rt, and then poured into a separatory funnel containing saturated aqueous NH_4Cl (5 mL) and 20 mL of diethyl ether. The aqueous layer was separated and extracted with two 15-mL portions of diethyl ether. The combined organic phases were washed with 10 mL of saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford 0.052 g of a brown oil, which was purified by column chromatography on 10 g of silica gel (gradient elution with 0-50% MTBE-hexane) to give 0.048 g (53%) of **299** as a yellow solid, mp 96.0-98.0 °C.

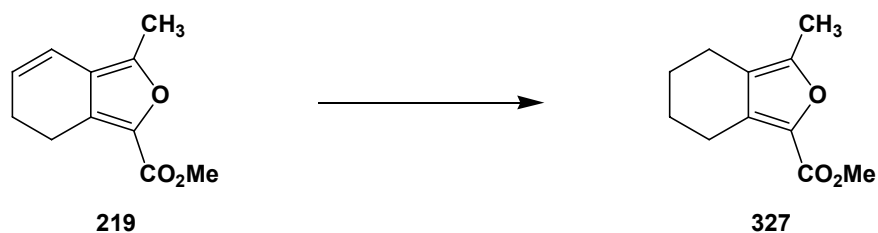|	
IR (CH_2Cl_2):	2054, 2987, 2924, 1720, 1668 cm^{-1}.
^{1}H NMR (500 MHz, CDCl$_3$):	δ 7.81 (d, *J* = 7.6 Hz, 1H), 7.56 (d, *J* = 7.9 Hz, 1H), 7.40 (td, *J* = 7.3, 0.9 Hz, 1H), 7.23 (td, *J* = 7.3, 0.9 Hz, 1H), 6.59 (s, 1H), 6.45 (s, 1H), 4.17 (s, 1H), 2.35 (s, 3H), 2.26 (s, 3H).
^{13}C NMR (125 MHz, CDCl$_3$):	δ 202.4, 150.7, 148.9, 144.9, 131.2, 128.4, 127.3, 122.0, 121.7, 120.4, 120.2, 106.7, 104.8, 48.0, 29.6, 19.8.

Anal. Calcd. for $C_{16}H_{14}O_2$:   C, 80.65; H, 5.92.
Found: C, 80.46; H, 5.95.

299

219 → 327
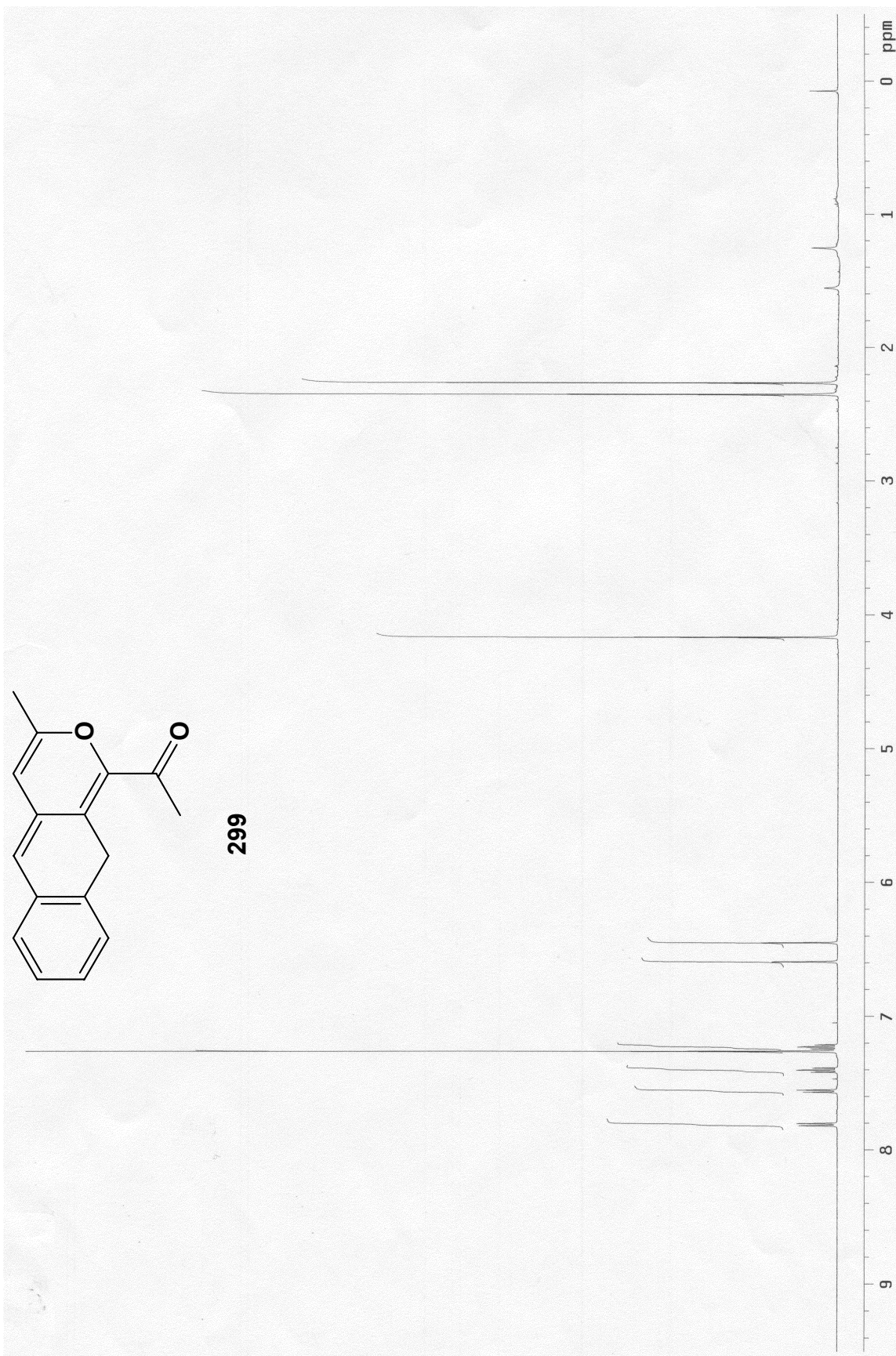
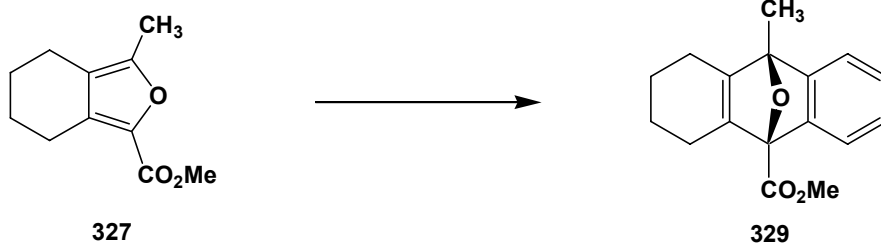**Methyl 1-methyl-4,5,6,7-tetrahydroisobenzofuran-3-carboxylate (327).**

A 25-mL, round-bottomed flask was charged with dihydroisobenzofuran **219** (0.201 g, 1.05 mmol), 15 mL of ethyl acetate, and 0.040 g of 10% palladium on carbon. The flask was fitted with a three-way stopcock and a balloon filled with hydrogen gas was attached. The flask was purged twice with hydrogen and stirred under an atmosphere of hydrogen for 30 min. The reaction mixture was filtered through a pad of celite and concentrated to give 0.190 g of a colorless oil which was purified on 25 g of silica gel (gradient elution with 0-30% MTBE-hexane) to give 0.187 g (92%) of **327** as a white solid. An analytical sample was obtained by recrystallization from hexane to give a white solid, mp 52.0-53.0 °C.

IR (CH$_2$Cl$_2$):	3054, 2987, 1709, 1422, 1267, 1157 cm^{-1}.
^{1}H NMR (500 MHz, CDCl$_3$):	δ 3.85 (s, 3H), 2.78 (br s, 2H), 2.40 (br s, 2H), 2.24 (s, 3H), 1.68-1.71 (m, 4H).
^{13}C NMR (125 MHz, CDCl$_3$):	δ 160.1, 151.0, 136.7, 134.3, 119.5, 51.5, 22.9, 22.7, 22.6, 20.3, 12.3.
Anal. Calcd. for C$_{11}$H$_{14}$O$_3$:	C, 68.02; H, 7.27.
Found:	C, 68.13; H, 7.25.

327

327 → **329**
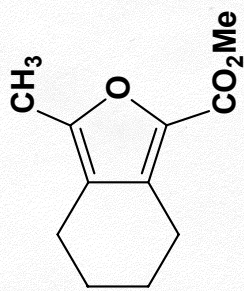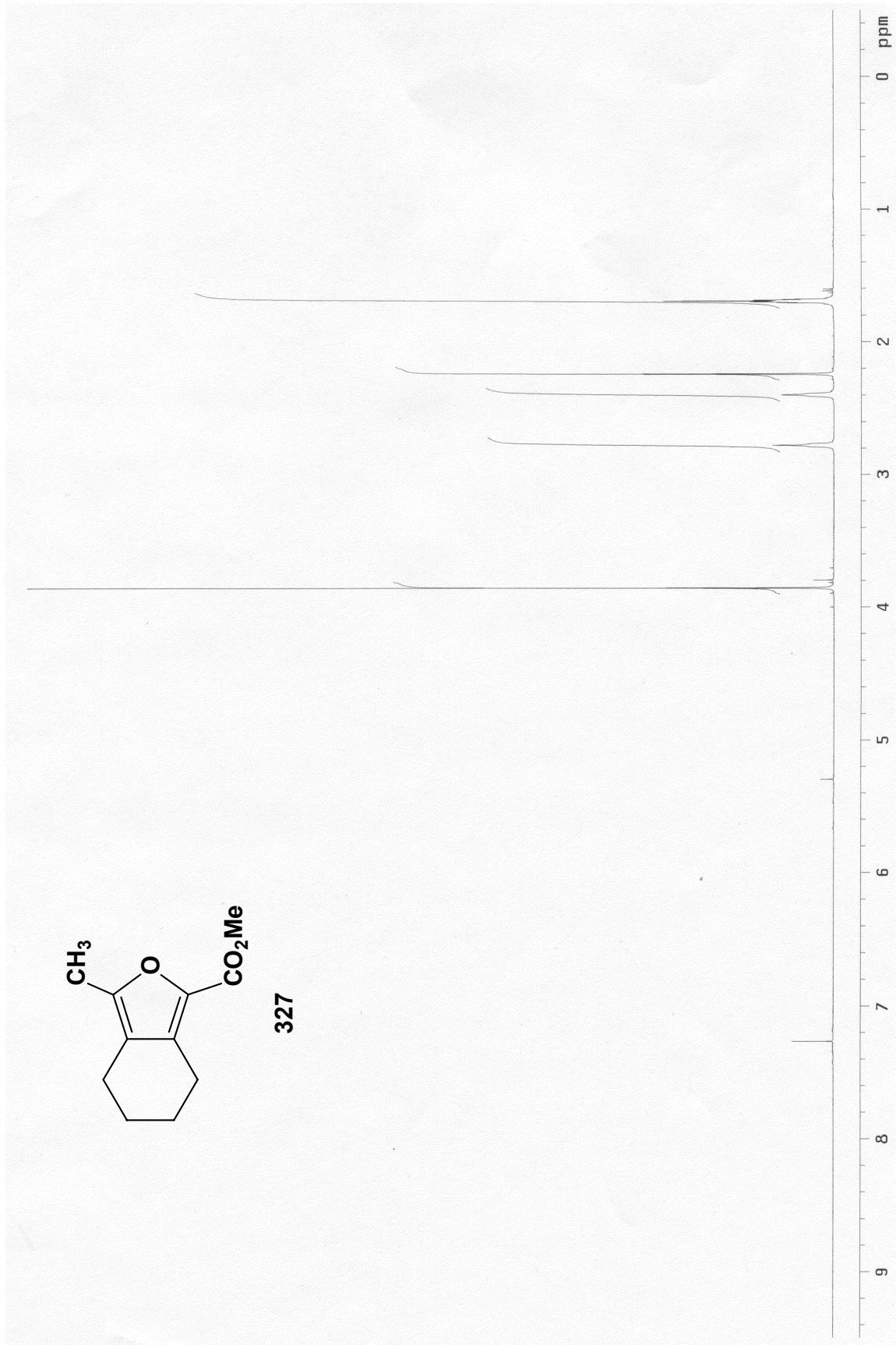
**Methyl 10-methyl-1,3,4,10-tetrahydro-9,10-epoxyanthracene-9(2H)-carboxylate (329).**

A 50-mL, round-bottomed flask equipped with an argon inlet adapter was charged with tetrahydroisobenzofuran **327** (0.159 g, 0.819 mmol), (phenyl)[o-(trimethylsilyl)phenyl]iodonium triflate (0.493 g, 0.982 mmol), and 15 mL of methylene chloride and cooled to 0 °C in an ice bath. Tetra-n-butylammonium fluoride (1.0 M in THF, 1.18 mL, 1.18 mmol) was then added dropwise via syringe over 3 min. The ice bath was removed and the reaction mixture was allowed to warm to rt, and stirred for 30 min. The reaction mixture was quenched by the addition of 5 mL of water. The aqueous layer was separated and extracted with three 10-mL portions of methylene chloride. The combined organic phases were washed with 20 mL of saturated NaCl solution, dried over Na_2SO_4, filtered, and concentrated to give 0.220 g of a pale yellow oil. Column chromatography on 25 g of silica gel (gradient elution with 0-40% MTBE-hexane) provided 0.199 g (90%) of endoxide **329** as a colorless oil.
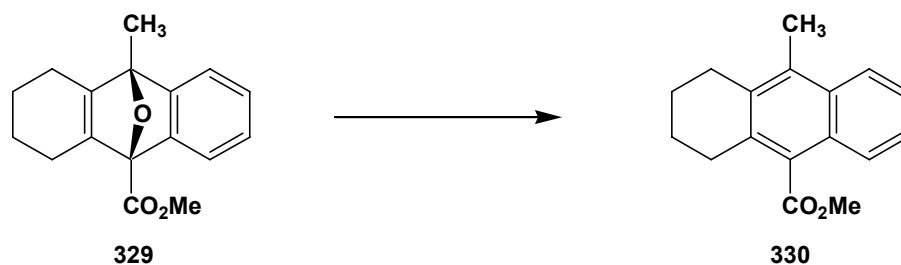
IR (CH_2Cl_2):	3054, 2986, 1720, 1422, 1267, 896, 747 cm^{-1}.
^{1}H NMR (500 MHz, CDCl$_3$):	δ 7.36-7.38 (m, 1H), 7.12-7.14 (m, 1H), 6.97-7.03 (m, 2H), 3.95 (s, 3H), 2.20-2.33 (m, 2H), 1.97-2.06 (m, 1H), 1.85 (s, 3H), 1.70-1.79 (m, 1H), 1.55-1.66 (m, 2H), 1.34-1.44 (m, 2H).

¹³C NMR (125 MHz, CDCl₃):   δ 168.4, 150.8, 149.7, 148.6, 148.6, 125.6, 125.0, 119.0, 118.1, 90.0, 52.6, 22.3, 22.3, 22.2, 21.7, 13.4, 4.0.

MS (*m/z*):   270 (M+).

329

329 → **330**
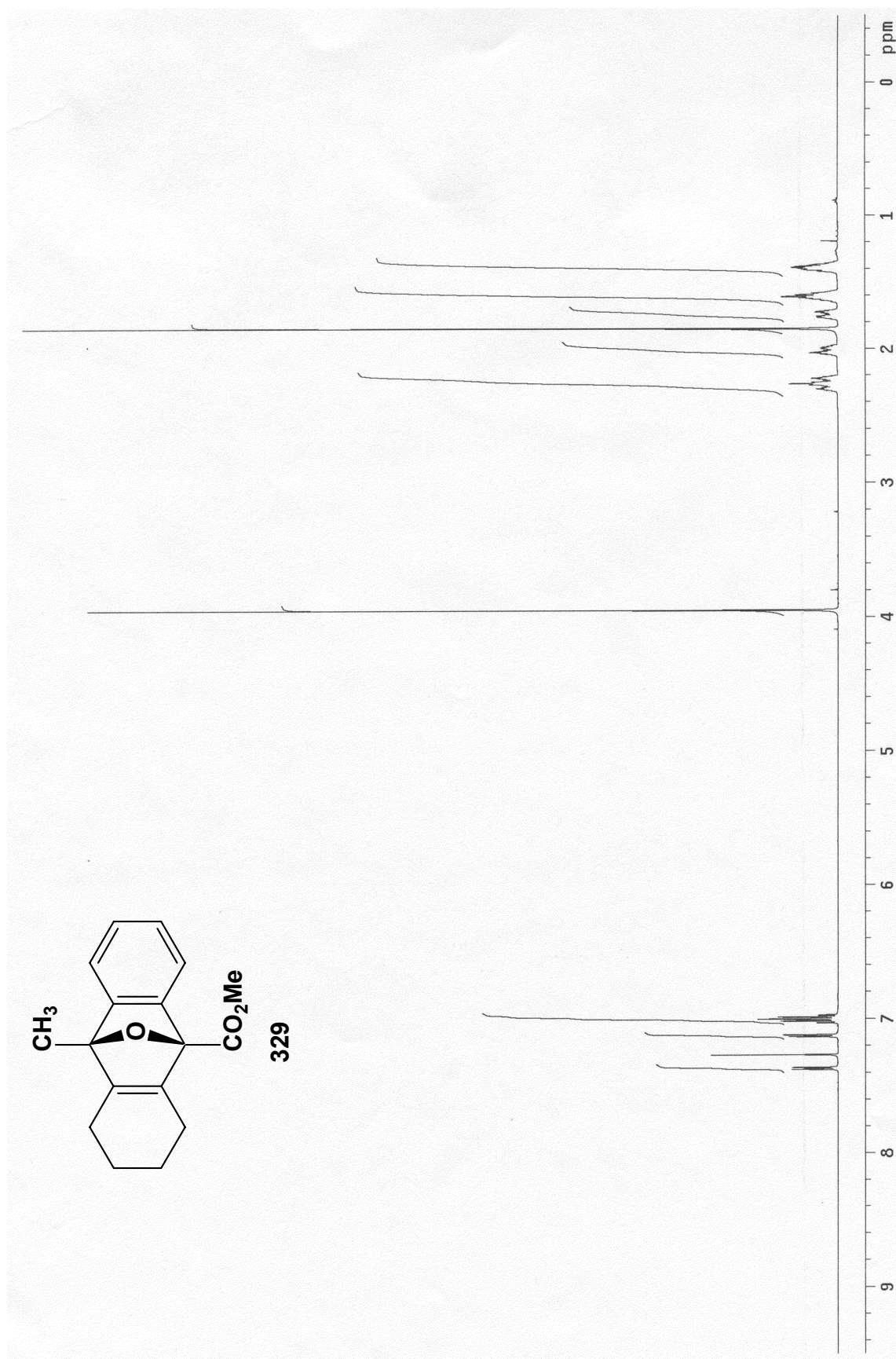
Methyl 10-methyl-1,2,3,4-tetrahydro-anthracene-9-carboxylate (330).

A 100-mL, three-necked, round-bottomed flask equipped with an argon inlet adapter, glass stopper, and rubber septum, was charged with titanium tetrachloride bis-tetrahydrofuran complex (1.47 g, 4.43 mmol) under a blanket of argon provided through an inverted funnel. The flask was cooled to 0 °C in an ice bath, and 15 mL of tetrahydrofuran was added slowly via syringe over 10 min. A suspension of lithium aluminum hydride (0.60 g, 1.58 mmol) in 7 mL of tetrahydrofuran was prepared in a 25-mL pear flask was then transferred dropwise via cannula over 3 min into the reaction mixture with the aid of three 3-mL THF rinses. A solution of triethylamine (0.64 g, 0.88 mL, 0.633 mmol) in 5 mL of THF was then added dropwise via cannula over 3 min with the aid of a 2-mL tetrahydrofuran rinse. The reaction mixture was heated at reflux for 30 min, and then cooled to rt. The 1,4-endoxide (**329**) was added via cannula as a solution in 10 mL of THF, followed by a 2-mL THF rinse. The resulting black solution was stirred at rt for 24 h. The reaction mixture was then poured into a 250-mL Erlenmeyer flask containing 100 mL of 20% (w/w) aqueous potassium carbonate and stirred for 15 min. The mixture was then filtered, 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 0.192 g of a yellow oil.

Column chromatography on 25 g of silica gel (gradient elution with 0-20% MTBE-hexane) provided 0.143 g (89%) of **330** as a white solid, mp 133.0-134.0 °C.
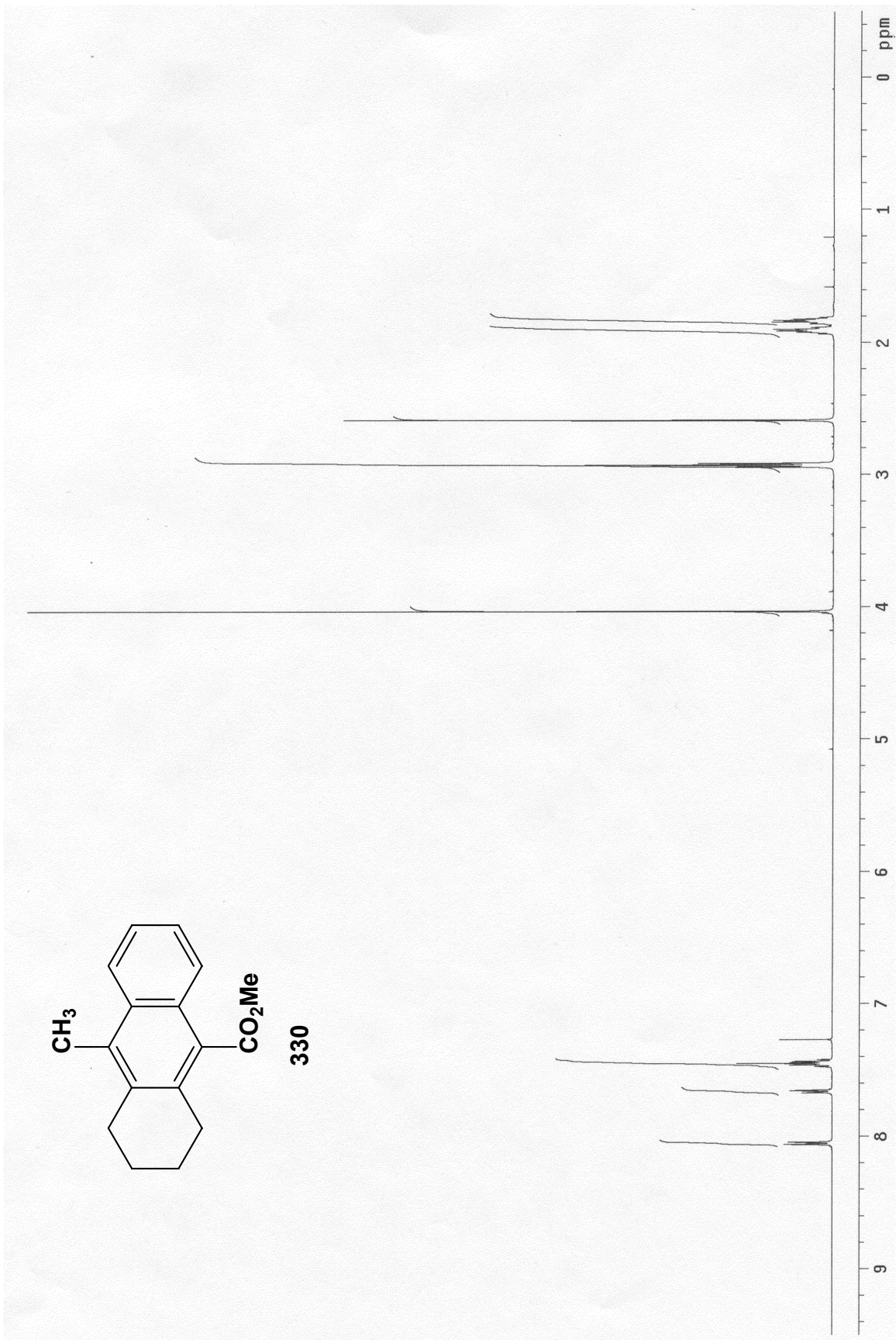
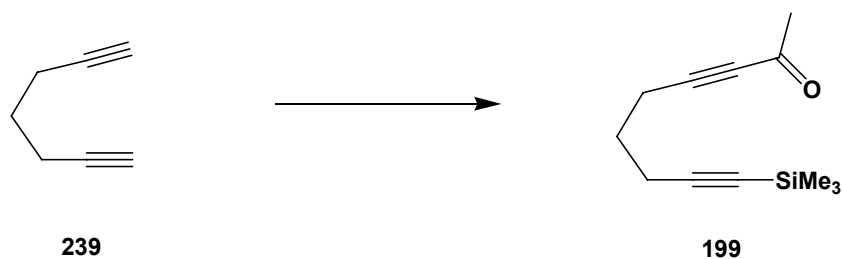|	
IR (neat):	2933, 2861, 1718, 1559, 1505, 1437, 1250, 1212, 1169 cm^{-1}.
^{1}H NMR (500 MHz, CDCl$_3$):	δ 8.04-8.06 (m, 1H), 7.65-7.67 (m, 1H), 7.42-7.47 (m, 2H), 4.03 (s, 3H), 2.91-2.94 (m, 4H), 2.59 (s, 3H), 1.88-1.93 (m, 2H), 1.81-1.86 (m, 2H).
^{13}C NMR (125 MHz, CDCl$_3$):	δ 171.2, 133.7, 133.4, 133.1, 131.1, 129.1, 128.3, 125.9, 125.5, 124.9, 124.1, 52.4, 28.6, 28.4, 23.5, 22.7, 14.6.
Anal. Calcd. for C$_{17}$H$_{18}$O$_2$: Found:	C, 80.28; H, 7.13. C, 80.47; H, 7.02.

330

239   199

9-(Trimethylsilyl)-nona-3,8-diyn-2-one (199).

A 1-L, three-necked, round-bottomed flask equipped with rubber septum, glass stopper, and argon inlet adapter, was charged with 1,6-heptadiyne (**239**) (3.99 g, 43.4 mmol) and 600 mL of tetrahydrofuran, and the resulting solution was cooled at 0 °C using an ice-water bath. EtMgBr (3.04 M in diethyl ether, 28.5 mL, 86.7 mmol) was added dropwise via syringe over 5 min. The resulting mixture was stirred at 0 °C for 90 min and then trimethylsilyl chloride (5.50 mL, 4.71 g, 43.4 mmol) was added via syringe dropwise over 5 min. The reaction mixture was stirred at 0 °C for 1 h and then allowed to warm to rt and stirred at rt for 1 h. The resulting solution was diluted with saturated aqueous NH_4Cl (100 mL) and the aqueous layer was separated and extracted with three 50-mL portions of diethyl ether. The combined organic phases were washed with two 50-mL portions of saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford 4.62 g of a colorless oil. Column chromatography on 100 g of silica gel (gradient elution with 0-4% diethyl ether-pentane) provided 6.35 g of a colorless oil which was shown by ^{1}H NMR analysis to be a mixture of the desired 1-(trimethylsilyl)-1,6-heptadiyne and 1,9-bis(trimethylsilyl)-1,6-heptadiyne. This material was used in the next step without further purification.

A 1-L, three-necked, round-bottomed flask equipped with an argon inlet adapter and rubber septum was charged with diyne prepared above and 550 mL of

tetrahydrofuran, and cooled at -78 °C in a dry ice-acetone bath. *n*-Butyllithium (2.49 M in hexanes, 15.9 mL, 39.7 mmol) was added dropwise via syringe over 3 min and the resulting mixture was stirred at -78 °C for 1 h. A 1-L, three-necked, round-bottomed flask equipped with an argon inlet adapter, rubber septum, and glass stopper was charged with acetic anhydride (16.0 mL, 17.3 g, 170 mmol) and 100 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 30 min, and the resulting mixture was then stirred at -78 °C for 3 h. The reaction mixture was diluted with 50 mL of a 10:1 mixture of saturated aqueous NH_4Cl and concentrated NH_4OH, and then allowed to warm to rt. The aqueous layer was separated and extracted with two 100-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 a yellow oil. Column chromatography on 100 g of silica gel (gradient elution with 0-4% MTBE-hexane) provided 2.25 g (25% overall for two steps) of ketone **199** as a colorless oil.

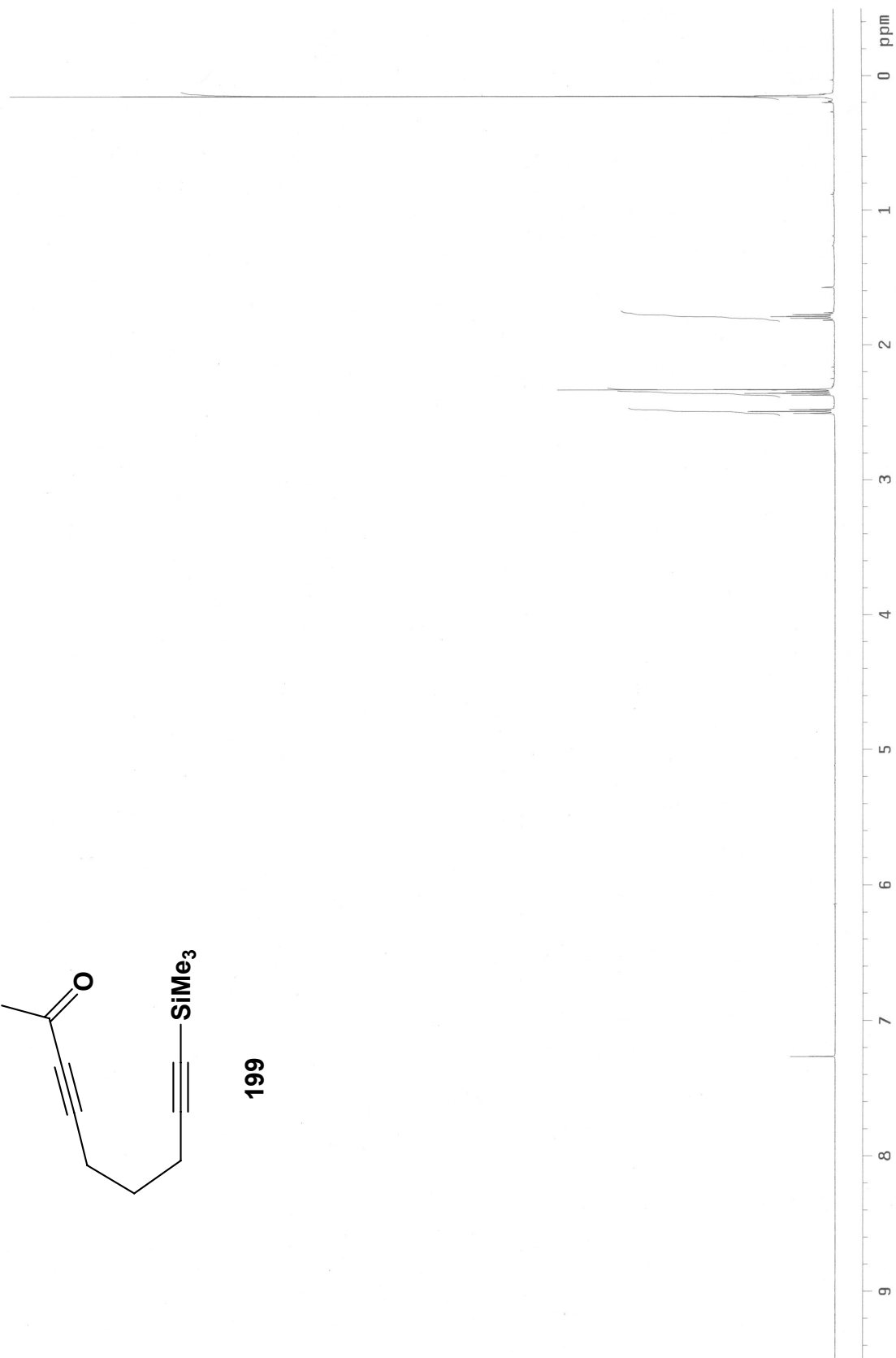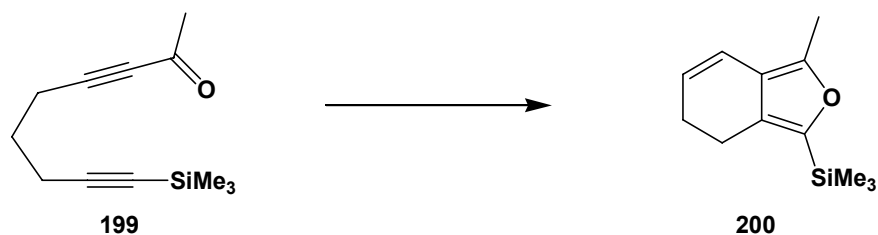|	
IR (film):	2940, 2890, 2200, 2160, 1650 cm^{-1}.
^{1}H NMR (500 MHz, CDCl$_3$):	δ 2.49 (t, J = 7.0 Hz, 2H), 2.36 (t, J = 7.0 Hz, 2H), 2.33 (s, 3H), 1.79 (quintet, J = 7.0 Hz, 2H) 0.15 (s, 9H).
^{13}C NMR (125 MHz, CDCl$_3$):	δ 185.5, 105.5, 93.0, 86.1, 81.9, 33.0, 26.9, 19.3, 18.2, 0.3.
MS (*m/z*):	191 (M-CH$_3$+).
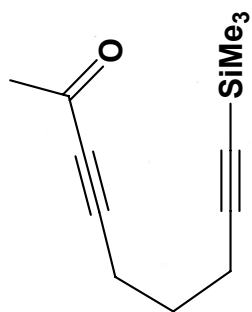
199

**1-Methyl-3-trimethylsilyl-4,5-dihydroisobenzofuran (200).**

An oven-dried threaded Pyrex tube (ca. 160 mL capacity) equipped with a rubber septum and argon inlet needle was charged with diyne **199** (1.60 g, 7.76 mmol), 78 mL of toluene, and γ-terpinene (1.37 mL, 1.16 g, 8.54 mmol). The solution was degassed by four freeze-pump-thaw cycles, and the tube was then sealed with a Teflon cap. The sealed tube was placed in a preheated oil bath at 220 °C for 60 h, and then allowed to cool to rt. Concentration gave 2.89 g of a brown oil, which was purified by column chromatography on 50 g of silica gel (gradient elution with 0-10% MTBE-hexane) to afford 1.40 g (87%) of **200** as a colorless oil.

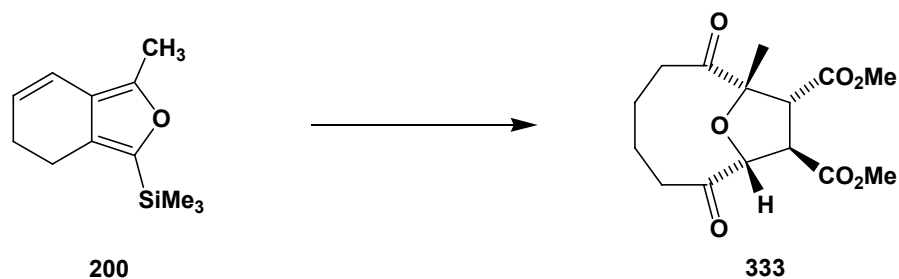|	
IR (film):	3030, 2950, 1640, 1540 cm^{-1}.
^{1}H NMR (500 MHz, CDCl$_3$):	δ 6.36 (dt, J = 9.5, 1.2 Hz, 1H), 5.75 (dt, J = 9.7, 4.3 Hz, 1H), 2.67 (t, J = 7.5 Hz, 2H), 2.26-2.33 (m, 2H), 2.27 (s, 3H), 0.27 (s, 9H).
^{13}C NMR (75 MHz, CDCl$_3$):	δ 150.0, 149.1, 131.3, 124.7, 118.9, 116.9, 23.8, 19.4, 11.8, -1.2.
Anal. Calcd. for C$_{12}$H$_{18}$OSi:	C, 69.84; H, 8.79.
Found:	C, 69.64; H, 8.94.

200

200 → **333**
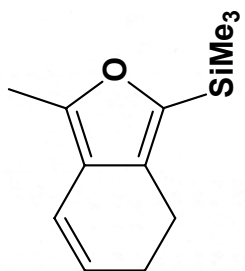
Dimethyl 1-methyl-2,7-dioxo-11-oxa-bicyclo[6.2.1]undecane-9,10-dicarboxylate (333).

A 50-mL, round-bottomed flask equipped with a Teflon stir bar was charged with dihydroisobenzofuran **200** (1.02 g, 4.93 mmol), 25 mL of ethyl acetate, and 0.100 g of 10% palladium on carbon. The flask was fitted with a three-way stopcock and a balloon filled with hydrogen gas was attached. The flask was purged twice with hydrogen and stirred under an atmosphere of hydrogen for 3 h. The reaction mixture was filtered through a pad of celite and concentrated to give 0.536 g of a colorless oil which was taken on to the next step without further purification.

A 25-mL, round-bottomed flask was charged with the furan prepared above (0.205 g, 0.983 mmol) and 10 mL of benzene. Maleic anhydride (0.116 g, 1.18 mmol) was added, and the solution was stirred at 25 °C for 24 h. Additional maleic anhydride (0.232 g, 2.36 mmol) was added, and the reaction mixture stirred at 25 °C for an additional 20 h. The resulting solution was concentrated to a brown oil which solidified upon refrigeration. The brown solid was dissolved in a mixture 54 mL of MeOH and 6 mL of CH_2Cl_2, and the flask was then cooled to -78 °C. A stream of ozone was bubbled through the solution via pipet with stirring until a pale blue color persisted. The solution was degassed with a stream of argon for 15 min at -78 °C, and then Me_2S (0.339 g, 0.400

mL) was added via syringe. The colorless solution was allowed to warm to rt over 3 h, and then concentrated to a pale yellow oil. This oil was dissolved in 20 mL of MeOH and stirred at 25 °C for 24 h. The solution was then transferred to a brand new 125-mL Erlenmeyer flask and 25 mL of diethyl ether was added. The flask was cooled to 0 °C, and a solution of diazomethane in diethyl ether was added via flame-polished pipet dropwise until a yellow color persisted. The yellow solution was stirred at 0 °C for 20 min, and then glacial acetic acid was added dropwise until the solution was approximately pH 6. The solution was then concentrated to give 0.246 g of a yellow oil which was purified by column chromatography on 40 g of silica gel (gradient elution with 40-80% MTBE-hexane) to afford 0.206 g (37% over five steps) of **333** as a white solid, mp 88.0-89.0 °C.
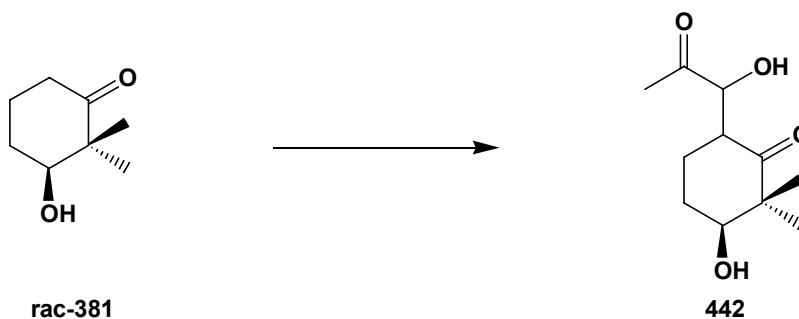
IR (CH_2Cl_2):	3054, 2987, 1751, 1717, 1437, 1422, 1264 cm^{-1}.
^{1}H NMR (500 MHz, CDCl$_3$):	δ 4.99 (d, $J = 7.6$ Hz, 1H), 4.03 (d, $J = 7.9$ Hz, 1H), 3.72 (s, 3H), 3.68 (s, 3H), 3.47 (app t, $J = 7.6$ Hz, 1H), 3.36-3.41 (m, 1H), 3.11-3.16 (m, 1H), 2.21-2.26 (m, 1H), 2.13-2.18 (m, 1H), 2.01-2.09 (m, 1H), 1.75-1.89 (m, 2H), 1.51-1.59 (m, 1H), 1.36 (s, 3H).
^{13}C NMR (125 MHz, CDCl$_3$):	δ 212.6, 212.3, 171.6, 170.4, 92.0, 85.2, 52.8, 52.3, 51.9, 48.3, 35.1, 34.2, 24.8, 23.5, 19.4.
Anal. Calcd. for $C_{15}H_{20}O_7$: Found:	C, 57.69; H, 6.45. C, 57.53; H, 6.43.

333
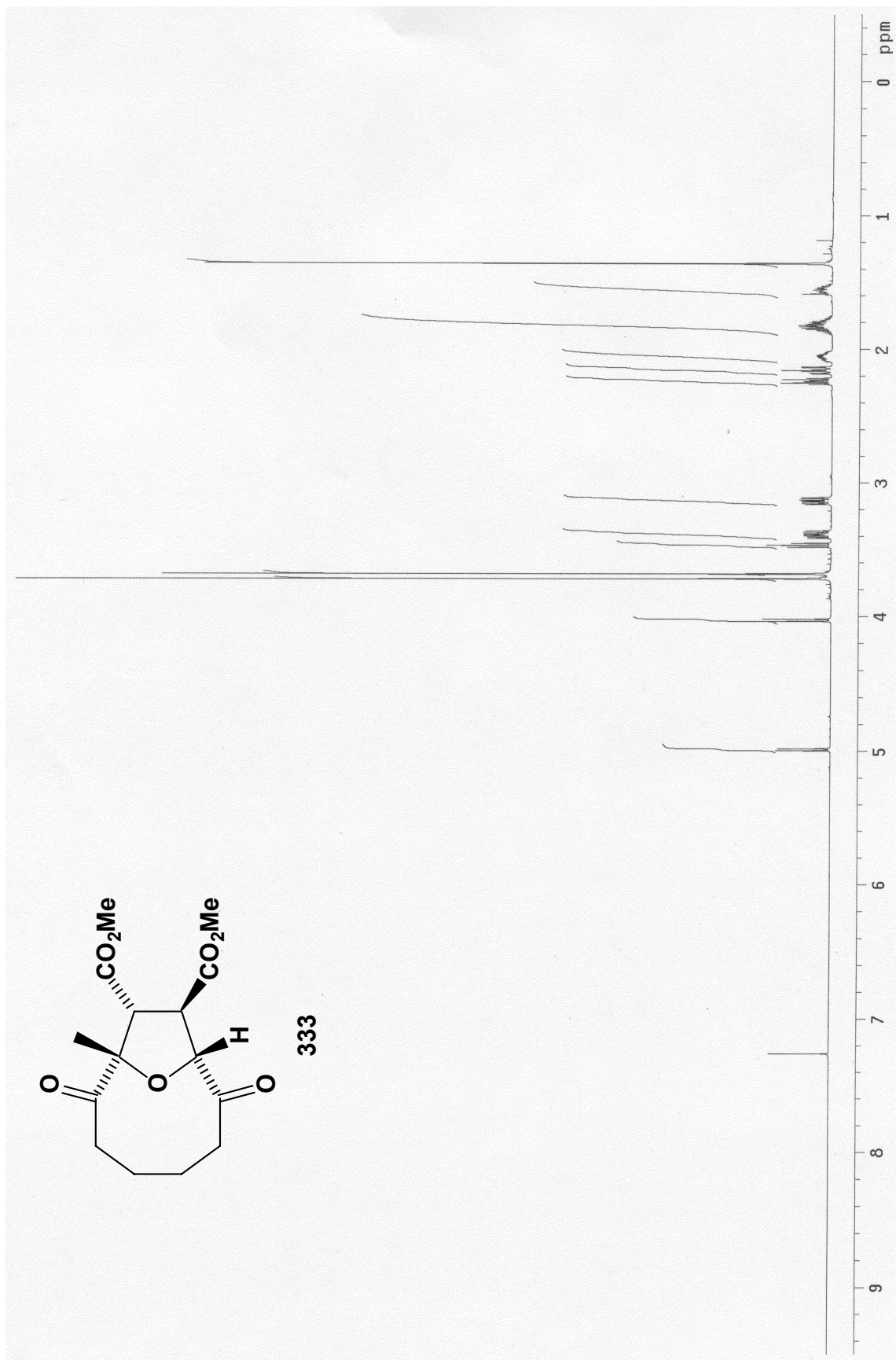
3-Hydroxy-6-(1-hydroxy-2-oxopropyl)-2,2-dimethylcyclohexanone (442).

A 100-mL, three-necked, round-bottomed flask equipped with a rubber septum, glass stopper, and argon inlet adapter, was charged with 20 mL of tetrahydrofuran and diisopropylamine (1.07 g, 1.48 mL, 10.5 mmol), and cooled to 0 °C. *n*-Butyllithium (2.52 M solution in hexanes, 3.86 mL, 9.72 mmol) was added dropwise via syringe over 5 min, and the resulting yellow solution was stirred at 0 °C for 30 min.

A 10-mL, two-necked, pear flask was charged with 5 mL of tetrahydrofuran and 3-hydroxy-2,2-dimethylcyclohexanone (**381**) (0.576 g, 4.05 mmol) and cooled to -78 °C. This solution was added to the solution of LDA via cannula over 8 min, and the flask was then rinsed with 1 mL of tetrahydrofuran. The resulting yellow solution was stirred at -78 °C for 30 min.

A 10-mL, two-necked, pear flask was charged with 5 mL of tetrahydrofuran and methacrolein (0.341 g, 0.402 mL, 4.86 mmol) and cooled to -78 °C. This solution was then added to the reaction flask via cannula over 3 min, and the resulting colorless solution (containing a white precipitate) was stirred at -78 °C for 2 h. The reaction mixture was quenched by the addition of saturated aqueous NH₄Cl (10 mL). The aqueous layer was separated and extracted with three 10-mL portions of MTBE, and the combined organic phases were washed with 30 mL of saturated NaCl solution, dried over

MgSO$_4$, filtered, filtered, and concentrated to afford 0.807 g of a yellow oil which was used in the next step without further purification.

A 100-mL, pear flask was charged with 36 mL of CH$_2$Cl$_2$, 4 mL of MeOH and the yellow oil prepared above. A solution of Sudan Red in 1 mL of CH$_2$Cl$_2$ was added until the solution in the reaction flask was deep red. The flask was cooled to -78 °C and a stream of ozone was bubbled through the solution via pipet with stirring until the red color disappeared. The solution was degassed with a stream of argon for 15 min at -78 °C, and then Me$_2$S (1.35 g, 1.60 mL, 21.8 mmol) was added via syringe. The pale yellow solution was allowed to warm to rt over 14 h, and then concentrated to afford 0.842 g of a yellow oil which was purified by column chromatography on 40 g of silica gel (gradient elution with 80-100% MTBE-hexane) to afford 0.568 g (65%) of diol **442** (mixture of diastereomers) as a colorless oil.

IR (film):	3423, 2972, 2938, 1702, 1252, 1134, 1066 cm^{-1}.
^{1}H NMR (500 MHz, CDCl$_3$):	δ 3.86-3.90 (m, 2H), 3.83 (dd, J = 8.2, 3.1 Hz), 3.50-3.60 (m, 3H), 3.41 (dq, 13.3, 3.1 Hz), 3.33 (dq, 12.8, 3.1 Hz), 2.30 (s, 3H), 2.28 (s, 3H), 2.25-2.34 (m, 2H), 1.91-2.09 (m, 4H), 1.72-1.83 (m, 2H), 1.90-1.96 (m, 2H), 1.22 (s, 3H), 1.15 (s, 3H), 1.13 (s, 3H), 1.11 (s, 3H).
^{13}C NMR (125 MHz, CDCl$_3$):	δ 216.2, 214.7, 210.9, 210.1, 78.8, 78.1, 77.9, 76.6, 52.0, 50.8, 49.6, 48.8, 29.5, 27.9, 26.3, 25.9, 25.0, 23.7, 24.2, 21.0, 20.7, 18.8.

442
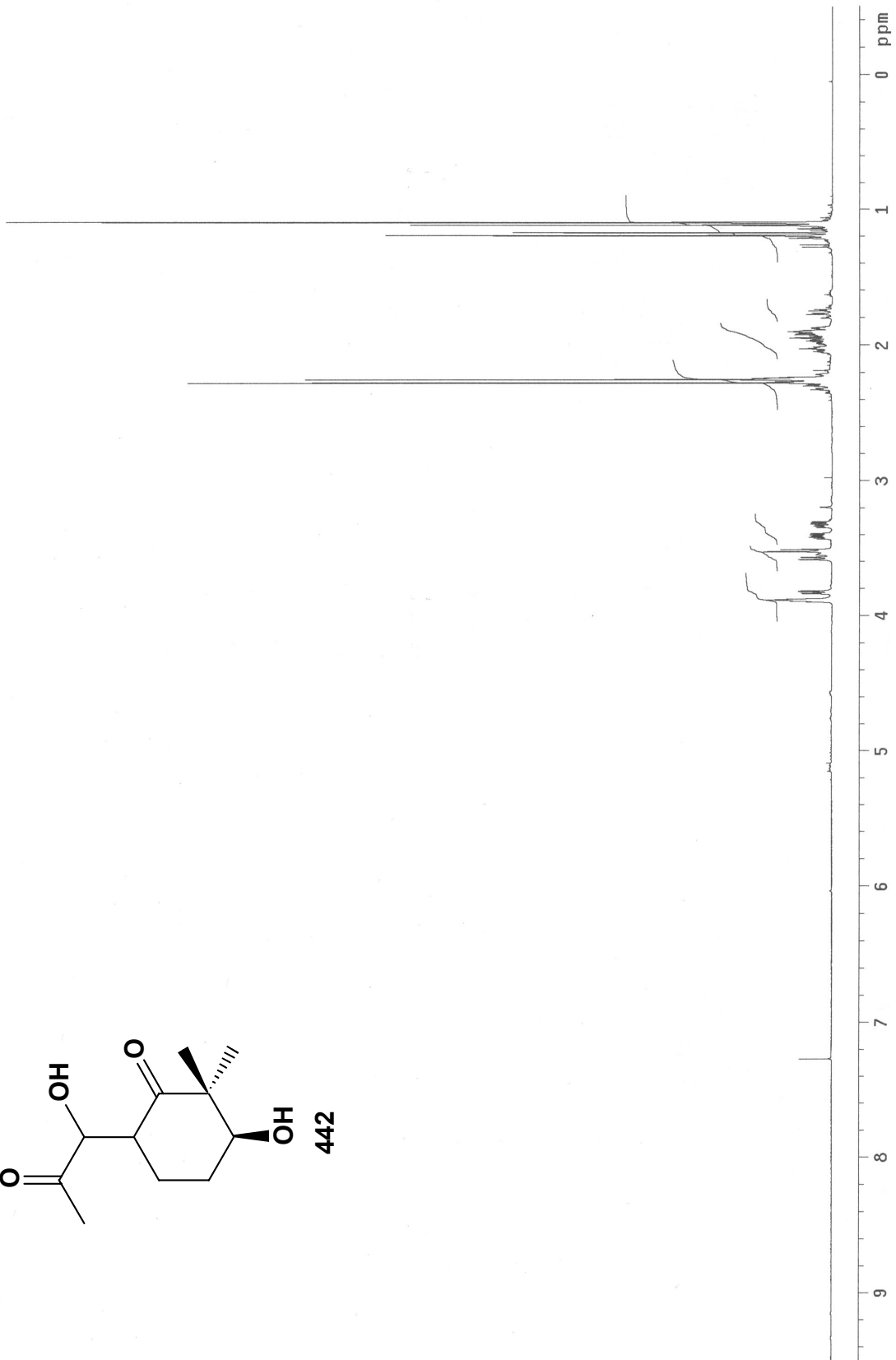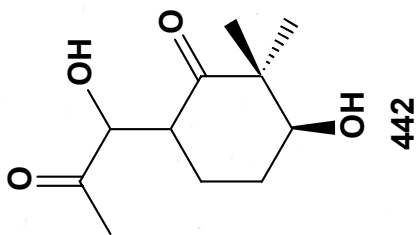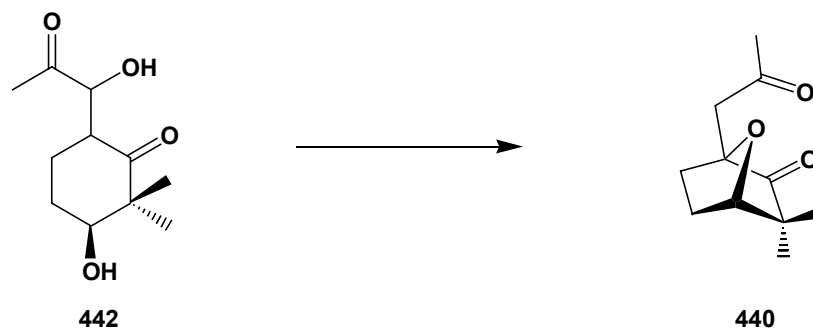
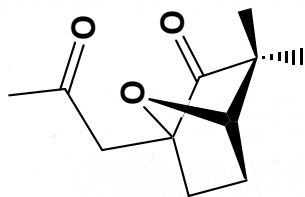**3,3-Dimethyl-1-(2-oxopropyl)-7-oxabicyclo[2.2.1]heptan-2-one (440).**

A 250-mL, one-necked, round-bottomed flask equipped with a reflux condenser fitted with an argon inlet adapter was charged with 100 mL of benzene and quinolinium camphorsulfonate (1.13 g, 3.13 mmol). The mixture was heated at reflux until the solid dissolved (ca. 15 min), and then was allowed to cool to rt. A solution of 3-hydroxy-6-(1-hydroxy-2-oxopropyl)-2,2-dimethylcyclohexanone (**442**) (0.672 g, 3.13 mmol) in 57 mL of benzene was added via pipet over 1 min, and the reaction mixture was heated at 40 °C for 48 h. The reaction mixture was allowed to cool to rt and the solid was filtered and washed with three 10-mL portions of MTBE. The filtrate was washed with three 25-mL portions of saturated NaHCO$_3$ solution, three 25-mL portions of 0.1 M aqueous HCl, and 25 mL of brine, dried over MgSO$_4$, filtered, and concentrated to give 0.518 g of a brown oil. Column chromatography on 30 g of silica gel (gradient elution with 10-30% MTBE-hexane) gave impure product, which was further purified by column chromatography on 30 g of silica gel (isocratic elution with 20% MTBE-hexane) to afford 0.230 g (37%) of **440** as a pale yellow oil.

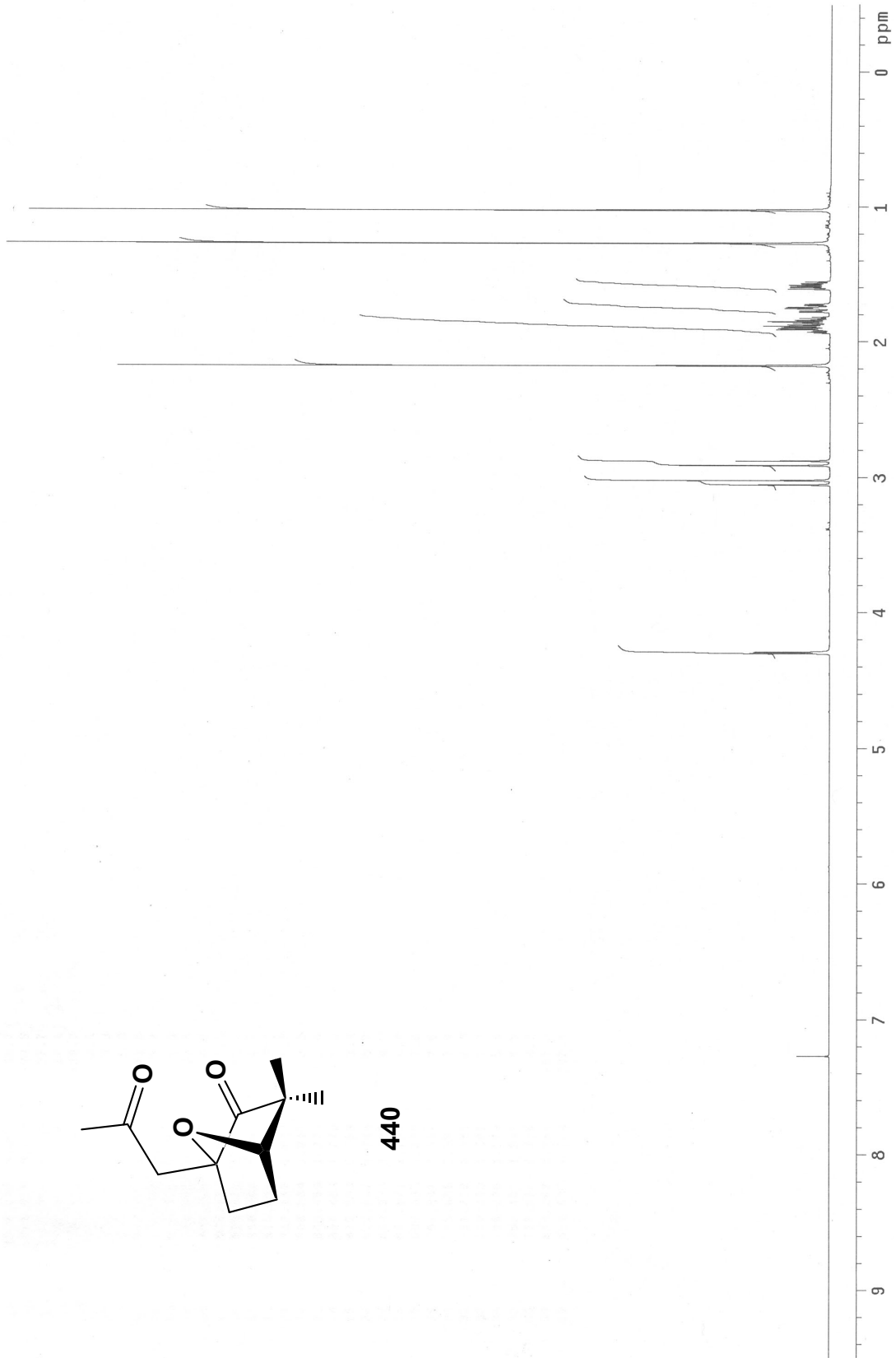IR (CH$_2$Cl$_2$):   2986, 1733, 1267, 1046 cm^{-1}.

¹H NMR (500 MHz, CDCl₃):

δ 4.30 (d, *J* = 4.9 Hz, 1H), 3.04 (d, *J* = 16.8 Hz, 1H), 2.90 (d, *J* = 16.5 Hz, 1H), 2.18 (s, 3H), 1.82-1.94 (m, 2H), 1.72-1.78 (m, 1H), 1.56-1.61 (m, 1H), 1.27 (s, 3H), 1.02 (s, 3H).
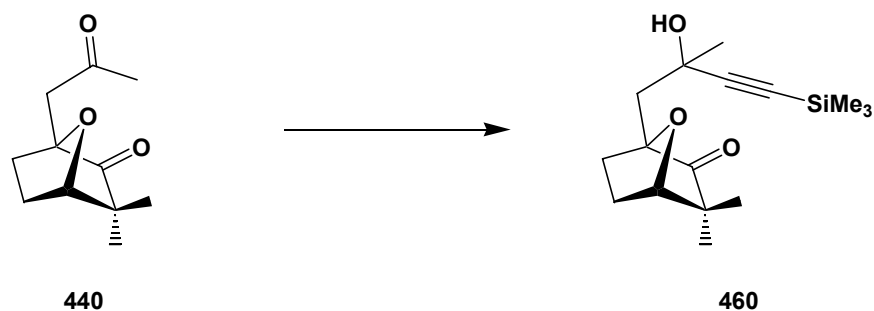
¹³C NMR (125 MHz, CDCl₃):

δ 217.0, 204.1, 85.7, 84.4, 49.4, 43.1, 31.1, 30.0, 25.0, 23.3, 23.1.

MS (*m/z*):

196 (M+).

440

440 → 460

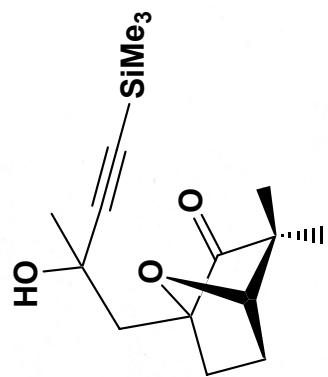**1-(2-Hydroxy-2-methyl-4-trimethylsilylbut-3-ynyl)-3,3-dimethyl-7-oxa-**

bicyclo[2.2.1]heptan-2-one (460).

A 25-mL, two-necked, pear flask was charged with 5 mL of tetrahydrofuran and trimethylsilylacetylene (0.089 g, 0.127 mL, 0.902 mmol) and cooled to -78 °C. To this solution was added a solution of *n*-BuLi (2.40M in hexanes, 0.351 mL, 0.842 mmol) via syringe over 1 min, and the resulting solution was stirred for 10 min at -78 °C. A 100-mL, three-necked, round-bottomed flask equipped with an argon inlet adapter, rubber septum, and glass stopper, was charged with the oxabicyclic ketone **440** (0.118 g, 0.601 mmol) and 15 mL of tetrahydrofuran, and cooled to -78 °C. The lithium acetylide solution was then transferred via cannula into the reaction mixture over 3 min. The reaction mixture was stirred for 15 min at -78 °C and then quenched by the addition of saturated aqueous NH$_4$Cl (5 mL). The resulting mixture was allowed to warm to rt over 30 min, and the aqueous layer was separated and extracted with three 10-mL portions of MTBE. The combined organic phases were washed with 20 mL of saturated NaCl solution, dried over MgSO$_4$, filtered, and concentrated to afford a 0.166 g of a colorless oil. Purification by column chromatography on 30 g of silica gel (gradient elution with 10-20% MTBE-hexane) afforded 0.142 g (80%) of **460** as a colorless oil.

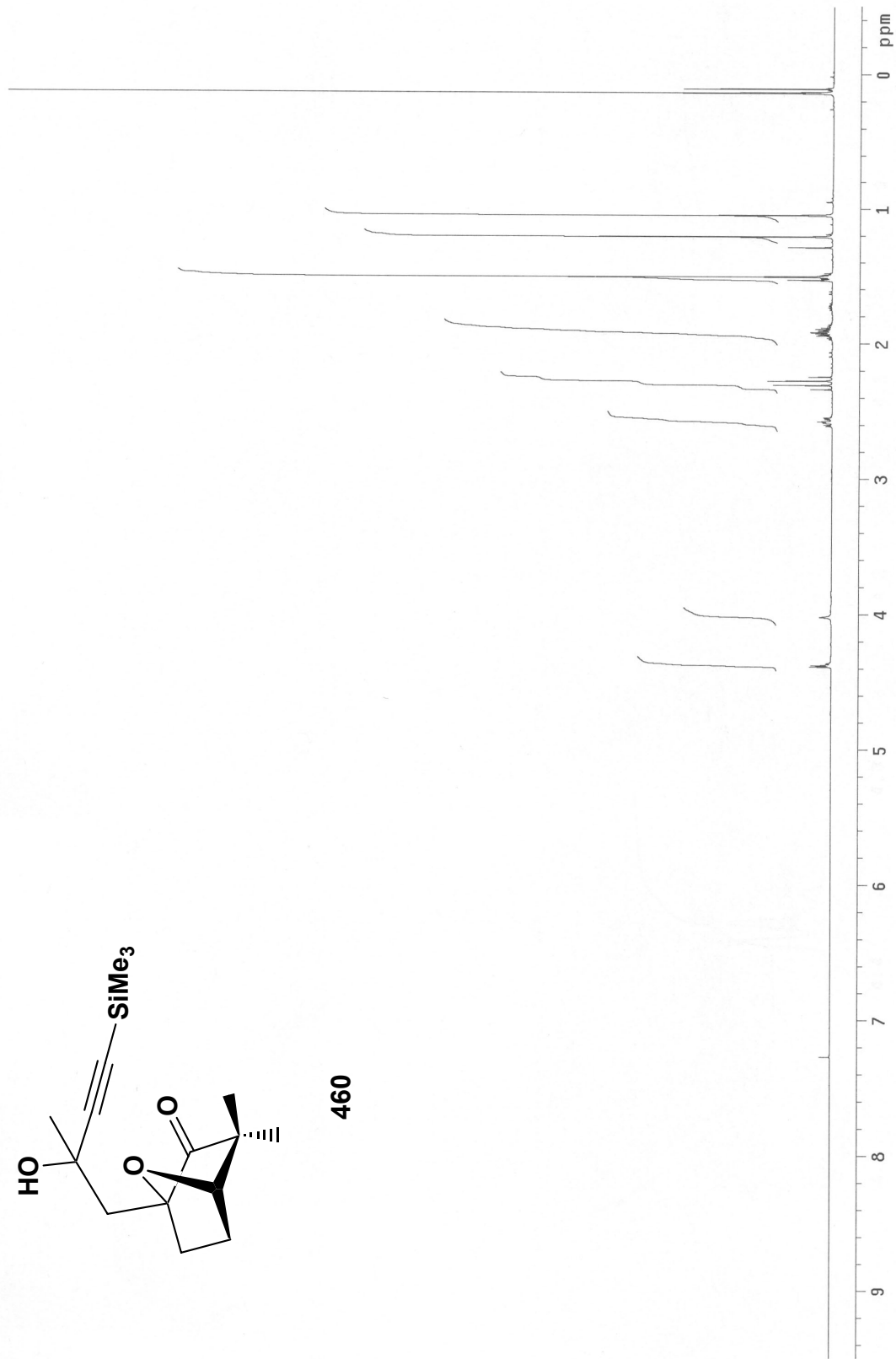IR (film): 3528, 2967, 2168, 1763, 1464, 1385, 1251, 1140, 1018 cm^{-1}.

^{1}H NMR (500 MHz, CDCl$_3$): δ 4.38 (d, J = 4.5 Hz, 1H), 4.10 (s, 1H), 2.54-2.62 (m, 1H), 2.32 (d, J = 15.0 Hz, 1H), 2.26 (d, J = 15.0 Hz, 1H), 1.85-1.97 (m, 2H), 1.49-1.54 (m, 1H), 1.51 (s, 3H), 1.21 (s, 3H), 1.05 (s, 3H), 0.14 (s, 9H).
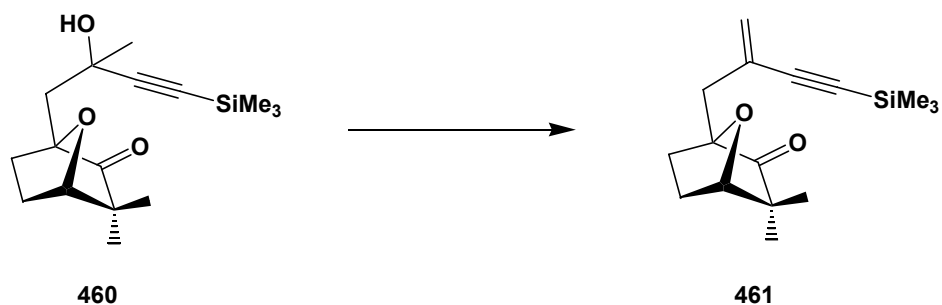
^{13}C NMR (125 MHz, CDCl$_3$): δ 217.4, 109.7, 87.8, 84.9, 84.7, 66.6, 49.0, 40.5, 31.6, 29.1, 25.1, 23.4, 20.3, 0.0.

HRMS(ESI) Calcd. for C$_{16}$H$_{26}$O$_3$Si: 317.1543 (M+Na).
Found: 317.1540.

460

460 461

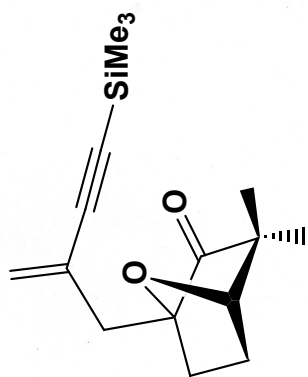**3,3-Dimethyl-1-(2-methylene-4-trimethylsilylbut-3-ynyl)-7-oxa-bicyclo[2.2.1]heptan-2-one (461)**

A 25-mL, one-necked, round-bottomed flask equipped with an argon inlet adapter was charged with alcohol **460** (0.069 g, 0.234 mmol) and 3 mL of tetrahydrofuran and cooled to 0 °C. A 10-mL, pear flask equipped with a rubber septum with argon inlet needle was charged with the Burgess reagent (0.072 g, 0.304 mmol) and 3 mL of tetrahydrofuran and this solution was then transferred via cannula to the solution of the alcohol over 2 min. The reaction mixture was stirred for 12 h at rt, and then quenched by addition of 5 mL of water. The aqueous layer was separated and extracted with three 5-mL portions of MTBE, and the combined organic phases were washed with 10 mL of saturated NaCl solution, dried over MgSO$_4$, filtered, and concentrated to afford a 0.101 g of a colorless oil. Purification by preparative HPLC on a Waters Prep Nova Pak HR column, 6 μ silica, 19 mm x 30 cm (isocratic elution with 4% EtOAc-hexane) afforded 0.026 g (40%) of **461** as a colorless oil.

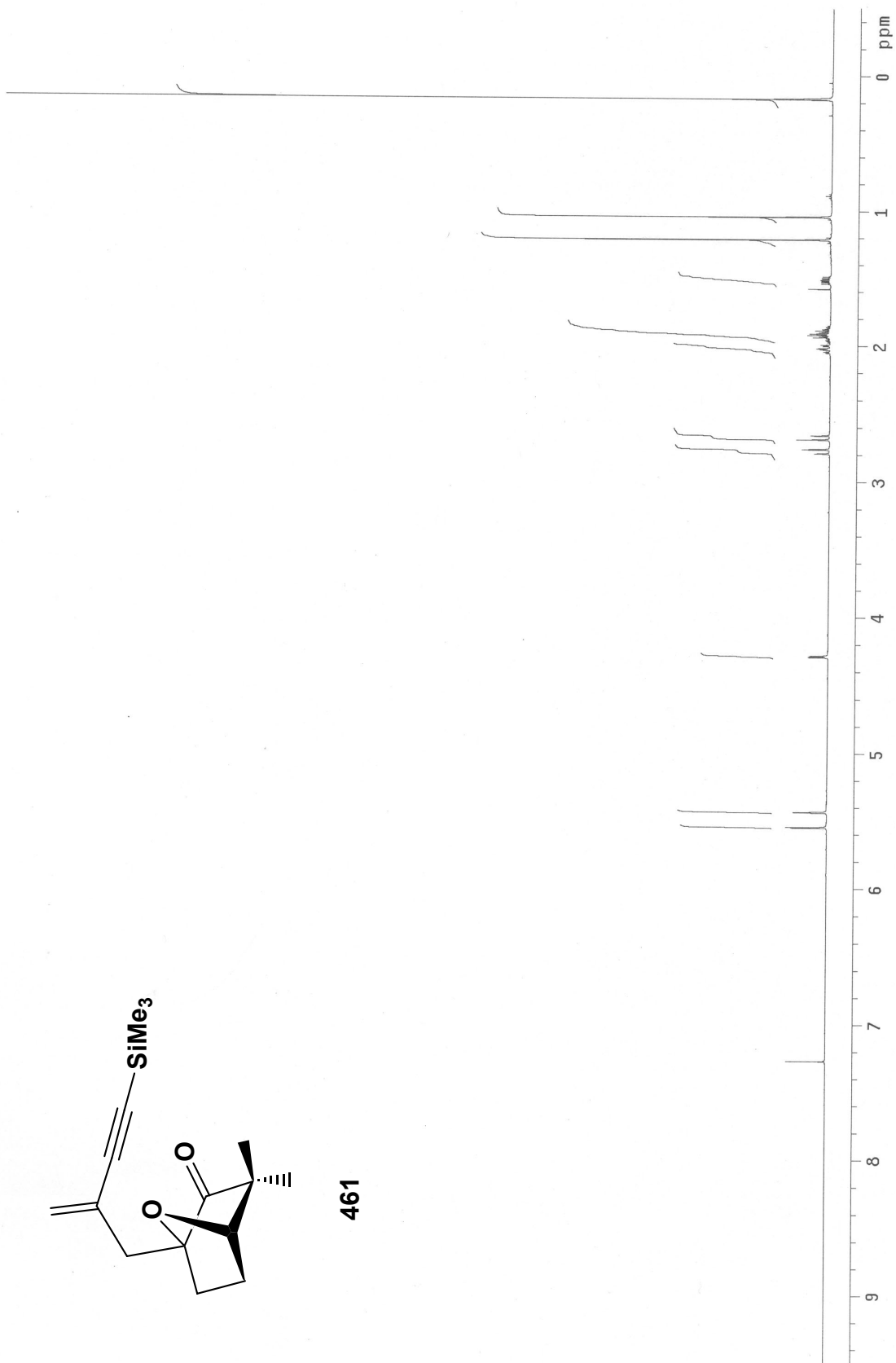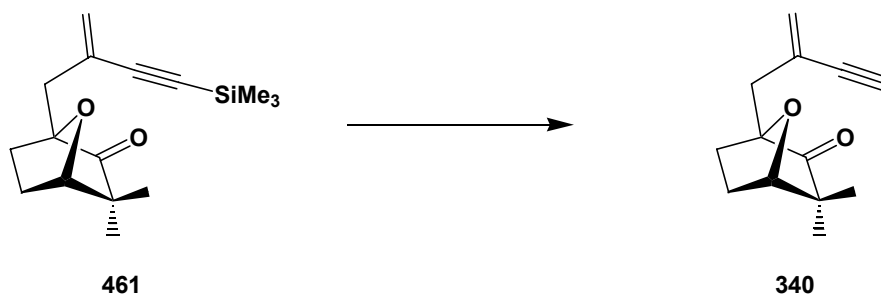|	
IR (CH$_2$Cl$_2$):	2966, 2870, 2146, 1761, 1463, 1384, 1250, 1018 cm^{-1}.
^{1}H NMR (500 MHz, CDCl$_3$):	δ 5.55 (d, J = 1.8 Hz, 1H), 5.43 (dd, J = 1.8 Hz, 0.9 Hz, 1H), 4.29 (d, J = 4.9 Hz, 1H), 2.77 (d, J = 15.0

Hz, 1H), 2.67 (dd, J = 15.0, 0.9 Hz, 1H), 1.99-2.05 (m, 1H), 1.85-1.97 (m, 2H), 1.48-1.54 (m, 1H), 1.21 (s, 3H), 1.04 (s, 3H), 0.17 (s, 9H).

^{13}C NMR (125 MHz, CDCl$_3$):   δ 217.2, 126.5, 126.3, 106.1, 87.9, 87.8, 83.9, 49.5, 36.1, 29.1, 25.5, 23.2, 20.3, 0.1.

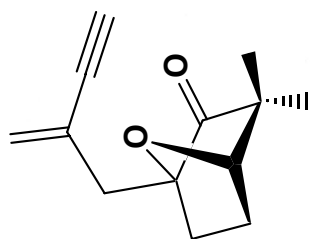**461**

461 → **340**

3,3-Dimethyl-1-(2-methylenebut-3-ynyl)-7-oxabicyclo[2.2.1]heptan-2-one (340).

A 25-mL, round-bottomed flask equipped with an aron inlet adapter was charged with the alkynylsilane **461** (0.084 g, 0.304 mmol) and 10 mL of methanol. Potassium carbonate (0.011 g, 0.080 mmol) was added and the reaction mixture was stirred for 3 h at rt. The resulting solution was concentrated to afford 0.102 g of an orange oil and purified by column chromatography on 20 g of silica gel (isocratic elution with 5% Et_2O-pentane) to afford 0.35 g (54%) of enyne **340** as a colorless oil.

IR (CH_2Cl_2):	3273, 2973, 2870, 1760, 1610, 1463, 2130, 1071, 1018, 854 cm^{-1}.
^{1}H NMR (500 MHz, CDCl$_3$):	δ 5.60 (d, J = 1.8 Hz, 1H), 5.47 (d, J = 1.2 Hz, 1H), 4.31-4.33 (m, 1H), 2.93 (s, 1H), 2.82 (d, J = 14.4 Hz, 1H), 2.66 (d, J = 14.6 Hz, 1H), 1.89-1.95 (m, 3H), 1.50-1.54 (m, 1H), 1.21 (s, 3H), 1.05 (s, 3H).
^{13}C NMR (125 MHz, CDCl$_3$):	δ 217.3, 127.4, 125.4, 88.1, 84.7, 84.0, 77.6, 49.4, 36.0, 29.4, 25.3, 22.9, 20.1.

340