STUDIES ON THE SYNTHESIS OF CYCLOHEXYNES FOR INTER- AND INTRAMOLECULAR CYCLOADDITION REACTIONS

by

Cynthia K. Crosswhite
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Signature of Author.....
Department of Chemistry
29 January 2010

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

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

Debts of Gratitude

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To my friends and family

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Submitted to the Department of Chemistry

on 29 January 2010 in Partial Fulfillment of the

Requirements for the Degree of Master of Science

ABSTRACT

Strained cycloalkynes have been of interest to organic chemists for many years due to their exotic structure and their potential utility as synthetic building blocks. This thesis examines the generation of cyclohexyne derivatives and their reactivity in inter- and intramolecular cycloadditions. Several strategies were investigated to generate substrates for the intramolecular trapping of the cyclohexynes. In addition, simple cyclohexyne derivatives were prepared and two cases of intermolecular trapping are reported.

Thesis Supervisor: Rick L. Danheiser

Title: Professor of Chemistry

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Part 1

Introduction and Background

Chapter 1
Cycloalkynes in Cycloaddition Reactions

Introduction

Cycloaddition reactions are among the most powerful transformations available to synthetic chemists.[1] These processes are often the most efficient and reliable methods for preparing cyclic organic compounds with control of regiochemistry and stereochemistry. Our laboratory has had a longstanding interest in the development of new methods for preparing highly substituted rings of various sizes. Among these investigations have been studies of the intramolecular [4+2] cycloaddition of conjugated enynes with various alkenes and alkynes, providing a convergent route to complex polycyclic aromatic systems.[2] As an extension of this cycloaddition methodology, we were interested in examining the application of strained *cyclic alkynes* as 2π components in the reaction. We expected that these unusual alkynes might be exceptionally reactive as the 2π components in cycloaddition reactions. For our synthetic endeavors, we were most interested in six-membered cyclic acetylenes, which are the most widely studied of the strained cycloalkynes. The subject of this thesis is the investigation of employing *cyclohexyne derivatives* as 2π components in various cycloaddition reactions. To introduce this subject I will give brief background on the most well studied cyclic acetylene system, arynes, before giving a more in-depth examination of cycloalkyne chemistry in general.

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[1] Carruthers, W. *Cycloaddition Reactions in Organic Synthesis*; Pergamon Press: New York, 1990.
[2] (a) Danheiser, R. L.; Gould, A. E.; Fernandez de la Pradilla, R.; Helgason, A. L. *J. Org. Chem.* **1994**, *59*, 5514. (b) Wills, M. S. B.; Danheiser, R. L. *J. Am. Chem. Soc.* **1998**, *120*, 9378. (c) Dunetz, J. R.; Danheiser, R. L. *J. Am. Chem. Soc.* **2005**, *127*, 5776.

Arynes: Structure and Reactivity

Benzynes are perhaps the most well-known and extensively reviewed members of the family of strained cycloalkynes.[3] Benzynes are aromatic compounds with a strained π-bond located in the plane of the ring, orthogonal to the aromatic π-system. When compared to a linear alkyne, the triple bond of benzyne is distorted approximately 56° from linearity and elongated by 0.14 Å. Benzynes are soft electrophiles that readily participate in nucleophilic addition reactions, and they are also remarkably reactive 2π components in [2 + 2] and [4 + 2] cycloadditions and ene reactions.

Our laboratory's most recent work with cyclic alkynes has examined the use of arynes as a 2π-component in intramolecular cycloaddition reactions, with special attention given to using conjugated enynes as cycloaddition partners. Eq 1 shows a generalized example of a cycloaddition involving an aryne-enyne system.[4] The direct result of the [4 + 2] cycloaddition is a highly strained cyclic allene intermediate (**2**), which then quickly isomerizes to the more stable aromatic ring (**3**).

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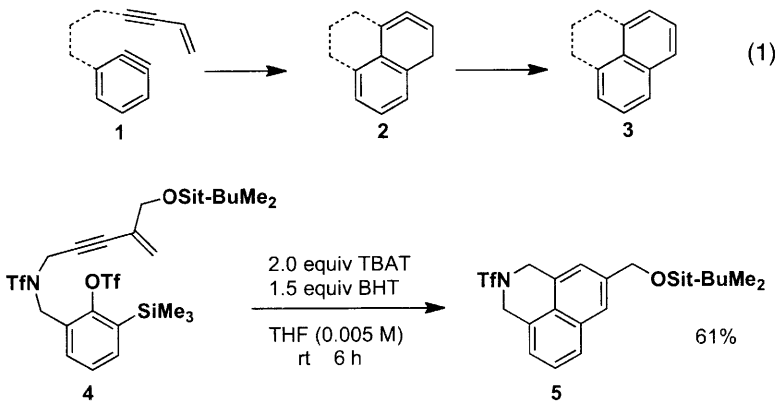
[3] (a) Gilchrist, T. L. In *The Chemistry of the Functional Groups, Suppl. C: The Chemistry of the Triple-Bonded Functional Groups;* Patai, S. Rappaport, Z., Eds.; Wiley: New York, 1994; Ch. 18, pp 1017-1134. (b) Hoffmann, R. W. *Dehydrobenzene and Cycloalkynes*, Verlag Chemie, Weinheim, 1967. (c) Winkler, M.; Wenk, H. H.; Sander, W. In *Reactive Intermediate Chemistry*, Moss, R. A.; Platz, M. S.; Jones, M. Jr., Eds.; Wiley-VCH: Hoboken, NJ, 2004; Ch. 16, pp 741-794. (d) Pellissier, H.; Santelli, M. *Tetrahedron* **2003**, *59*, 701. (e) Wenk, H. H.; Winkler, M.; Sander, W.; *Angew. Chem., Int. Ed. Engl.* **2003**, *42*, 502. (f) Dyke, Alan M.; Hester, Alison J.; Lloyd-Jones, Guy C. *Synthesis* **2006**, 4093.

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



Previous studies have investigated the scope of this aryne cycloaddition with respect to the substitution on the enyne moiety (eq 2). Cycloadditions including several "hetarenynes" have also been developed. The optimized conditions for the reaction of arynes with enynes were also employed in intramolecular aryne-Diels-Alder reactions with simple acyclic dienes, a reaction that previously in the literature had yielded only poor results and only in the case of substrates benefiting from the Thorpe-Ingold effect.[5]

Non-aromatic Cyclic Acetylenes: Structure and Reactivity

The first attempts to generate cyclic alkynes commenced in the early 20th century, beginning in 1933 with the syntheses of cycloheptadecyne and cyclopentadecyne by L. Ruzicka and coworkers.[6] A. T. Blomquist, who had previously completed syntheses of cyclodecyne and cyclononyne, synthesized the smallest isolable cyclic acetylene, cyclooctyne, in 1953.[7] Since then it has been found that smaller cycloalkynes can only be generated and trapped in situ due to the high reactivity of the strained triple bond.

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[5] Buszek, K. R. *Tetrahedron Lett.* **1995**, *36*, 9125.
[6] Ruzicka, L.; Hübrin, M.; Boekenoogen, H. A. *Helv. Chim. Acta.* **1933**, *16*, 498
[7] (a) Blomquist, A. T.; Liu, L. H. *J. Am. Chem. Soc.* **1953**, *75*, 2153. (b) Blomquist, A. T.; Burge, R. E.; Suscy, A. C. *J. Am. Chem. Soc.* **1952**, *74*, 3636. (c) Blomquist, A. T.; Liu, L. H.; Bohrer, J. C. *J. Am. Chem. Soc.* **1952**, *74*, 3643. (d) Blomquist, A. T.; Burge, R. E.; Liu, L. H.; Bohrer, J. C.; Suscy, A. C.; Kleis, J.; *J. Am. Chem. Soc.* **1951**, *73*, 5510. (e) Gleiter, R.; Werz, D. B., in *Science of Synthesis*, **2008**, *43*, 631.

Like arynes, non-aromatic strained cyclic acetylenes are remarkably reactive species that have electrophilic character and participate readily in [2 + 2] and [4 + 2] cycloadditions and other pericyclic reactions.[8] The strain in these systems originates from the steric problem of having four linearly arranged atoms in normal to medium-sized rings. The closing of the linear system removes the degeneracy of the π MOs of the triple bond and electron density is pushed to the outside of the ring. As a result of this bending, the LUMO of the alkyne is stabilized by the efficient mixing of the π* orbitals with the σ* orbitals of the adjoining C-C bonds while the HOMO remains relatively unperturbed (Figure 1).[9]

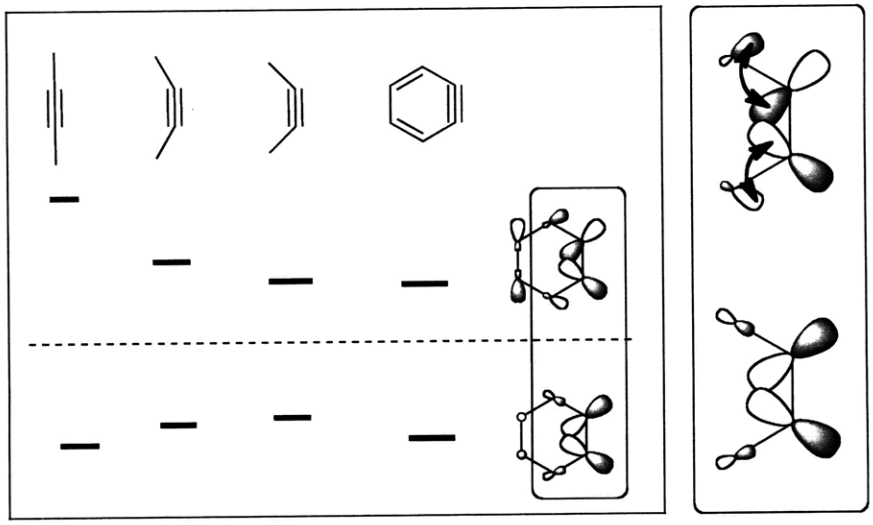


Figure 1: Frontier orbitals and energies for 2-butyne models and benzyne

The figure above shows the frontier molecular orbitals of 2-butyne and various distorted 2-butyne models that mimic the angles and bond lengths present in benzyne. The relative energies of the HOMO and LUMO orbitals in this system, also shown above, were obtained

[8] For reviews of the chemistry of strained cyclic acetylenes including arynes, see (a) Krebs, A.; Wilke, J. *Topics in Curr. Chem.* **1983**, *109*, 189. (b) Meier, H. In *Advances in Strain in Organic Chemistry*, Vol. 1, Halton, B. Ed.; JAI Press: London, 1991; pp 215–272. (c) Hoffman, R. W. *Dehydrobenzene and Cycloalkynes*, Academic Press: New York, 1967.

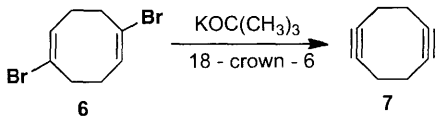
[9] Rondan, N. G.; Domelsmith, L. N.; Houk, K. N. *Tetrahedron Lett.* **1979**, *35*, 3237.

from *ab initio* calculations. The enlarged image on the right shows the mixing of the π^* orbitals with a σ^* orbital that lies only slightly higher in energy, dramatically lowering the LUMO while having a very small effect on the HOMO.

Generation of Strained Cyclic Acetylenes

Large and medium ring systems with less associated strain can often be synthesized by cyclization reactions or via ring enlargement of systems where a triple bond is already in place. Heavily strained cyclic systems, defined as systems in which the deviation at the acetylenic carbon atoms is greater than 10°, can only be prepared when the triple bond is introduced in the last reaction step, usually involving an elimination or cycloelimination process.[8b]

1,2-Elimination is a popular and convenient method for generating cycloalkynes from cycloalkenes. Several variations of this simple but powerful method have been developed, the most basic of which is the dehalogenation of a vinyl halide with base (eq 3).[10] One of the benefits of this method is that it requires only an easily obtainable monofunctionalized ring as the alkyne precursor.



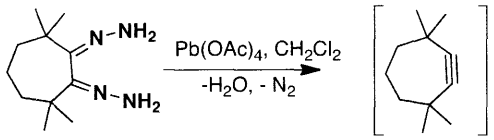
6 7 (3)

More recently, metal-halogen exchange and the use of fluoride ion-induced elimination of a silyl group have become popular methods to synthesize cycloalkynes. These systems do require a more complex 1,2-difunctionalized precursor, but they also offer many advantages; for example, there are a number of convenient fluoride-ion sources that effect efficient displacement of silyl groups under mild conditions. Further discussion and examples of these systems will be

[10] Detert, H.; Rose, B.; Mayer, W.; Meier, H. *Chem. Ber.* **1994**, *127*, 1529.

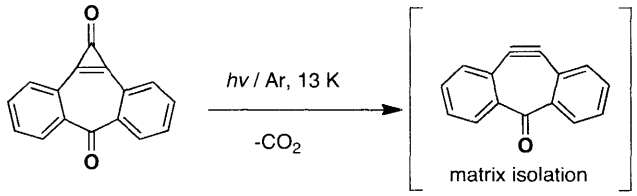
discussed in the next chapter alongside the discussion of previous syntheses of cyclohexyne derivatives.

Other methods to generate strained cycloalkynes include cycloelimination reactions and degradation of 1,2-dihydrazone systems. Dihydrazones of 1,2-cycloalkanediones can be oxidized by various reagents, such as $Pb(OAc)_4$, at low temperatures. These lower temperatures can be an advantage when generating reactive cycloalkynes; in fact, these conditions have been used to great advantage for the preparation of 3,3,7,7,-tetramethylcycloheptyne (eq 4), which dimerizes upon standing at rt.[11] In this example the cycloalkyne was trapped with diphenylisobenzofuran (DPIBF) and the cycloaddition product was used for analysis.



8 9 (4)

In an example of a cycloelimination reaction, cyclopropenone systems can be decarbonylated by either heating or irradiation.[12] As with the dihydrazone systems, an advantage of this method is that it can also be carried out at low temperatures, which has been especially useful for the matrix isolation of short-lived alkynes.



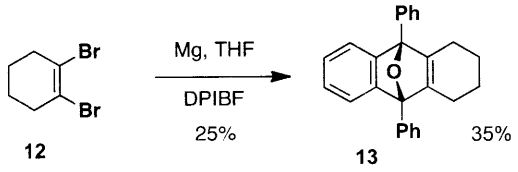
10 11 (5)

[11] Krebs, A.; Kimling, H. *Angew. Chem. Int. Ed.* **1971**, *10*, 509.
[12] Krebs, A.; Cholcha, A.; Müller, M.; Eicher, T.; Pielartzik, H.; Schnöckel, H. *Tetrahedron Lett.* **1984**, *25*, 5027.

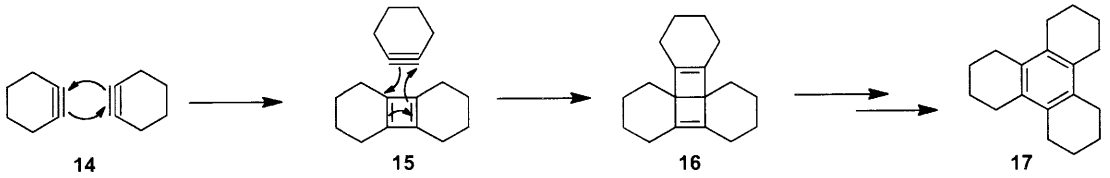
Chapter 2
Previous Syntheses of Cyclohexyne Derivatives

Early Studies of Cyclohexyne

Wittig first synthesized cyclohexyne in 1960 using the metal-induced elimination of a 1,2-dihalide and trapping the resulting alkyne with diphenylisobenzofuran (DPIBF) (eq 6).[13] His later studies demonstrated that cyclohexyne trimerizes in solution; the postulated mechanism for this transformation is shown below in eq 7.

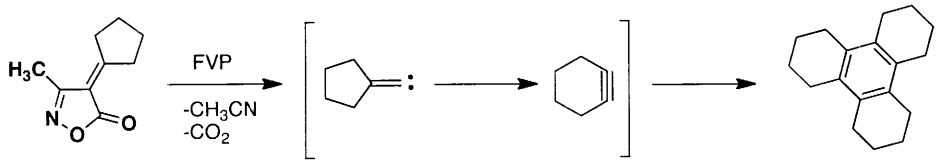


12 13 (6)



14 15 16 17 (7)

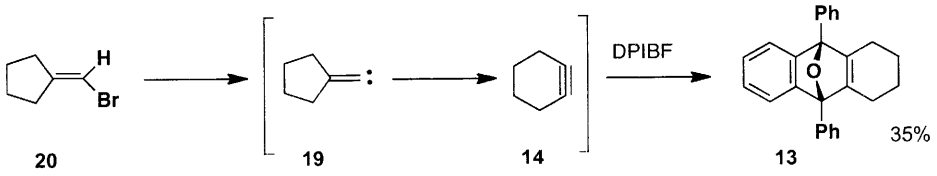
Cyclohexyne has only been characterized using matrix isolation, which was achieved by Wentrup et al. in 1988 using flash vacuum pyrolysis (FVP) (eq 8).[14] In these studies, cyclohexyne was characterized by a pair of IR bands at 2105 and 2090 cm^{-1}.



18 19 14 17 (8)

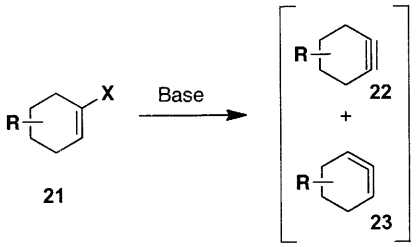
[13] (a) Wittig, G.; Krebs, A.; Pohlke, R. *Angew. Chem.* **1960**, *73*, 324. (b) Wittig, G.; Krebs, A. *Chem. Ber.* **1961**, *94*, 3260.
[14] Wentrup, C.; Blanch, R.; Briehl, H.; Gross, G. *J. Am. Chem. Soc.* **1988**, *110*, 1875.

Several additional syntheses of cyclohexynes have used the rearrangement of bromomethylenecycloalkanes with strong bases, such as potassium *t*-butoxide or $NaNH_2$-*t*-BuONa, leading to the exocyclic carbene intermediate **19**, as shown in eq 9. In 1965, Erickson and Wolinksky used this rearrangement to generate cyclohexyne and, as in the studies by Wittig they trapped the resulting alkyne in situ with DPIBF (eq 9).[15]



(9)

In a departure from cycloaddition trapping, Caubere et al. used this generation method in the presence of nucleophiles to examine the isomerization of various derivatives of cyclohexyne to 1,2-cyclohexadienes (eq 10).[16]



(10)

In these studies and those of Bottini et al. the ratio of *ipso/cine* substitution products, which is postulated to be related to the ratio of cyclohexyne and 1,2-cyclohexadiene in solution, was found to vary depending on the reaction conditions.[17]

Fujita and coworkers used a novel elimination method involving iodonium salts to generate cyclohexynes under milder conditions and to thus avoid the isomerization to allene **23** that occurs in strong base. The purpose of these studies was to examine the intrinsic

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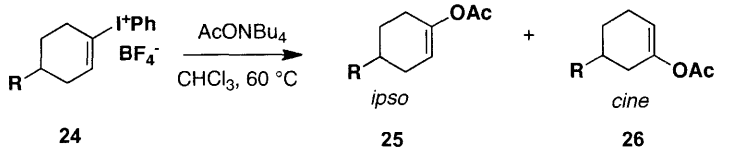
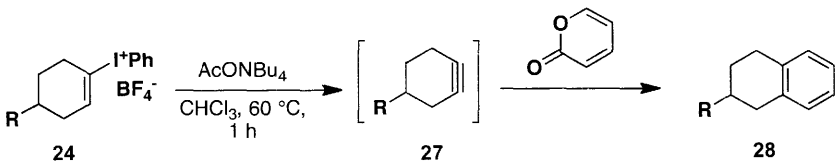
[15] Erickson, K. L.; Wolinsky, J. *J. Am. Chem. Soc.* **1965**, *85*, 1142.
[16] (a) Brunet, J. J.; Caubere, P. *Tetrahedron* **1971**, *27*, 3515. (b) Fixari, B.; Brunet, J. J.; Caubere, P. *Tetrahedron* **1976**, *32*, 927.
[17] (b) Bottini, A. T.; Corson, F. P.; Fitzgerald, R. *Tetrahedron* **1972**, *28*, 4883.

regiochemistry of nucleophilic addition to cyclohexyne species (eq 11). These studies also included two examples of cycloadditions for trapping, shown below in eqs 12 and 13.[18]

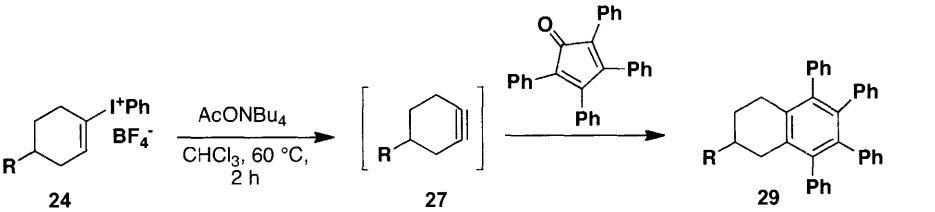


(11)



(12)

R = Me (32%); *t*-Bu (49%)

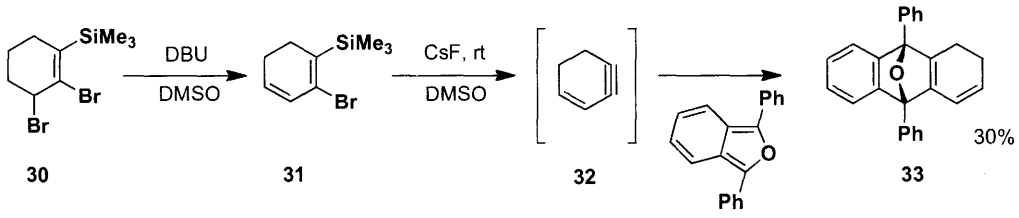


(13)

R = Me (84%); *t*-Bu (91%); Ph (98%)

Cyclohexyne Generation Using Fluoride-Induced 1,2-Elimination

In 1992, R. P. Johnson and W. Shakespeare examined the generation of cyclohexyne derivatives using more modern methods, specifically the fluoride-induced elimination of a 1,2-silylvinyl halide (eq 14).[19]

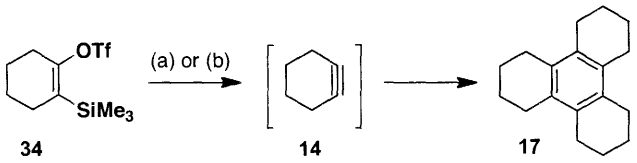


(14)

[18] (a) Fujita, M.; Sakanishi, Y.; Kim, W. H.; Okuyama, T. *Chem. Lett.* **2002**, 908. (b) Fujita, M.; Kim, W. H.; Sakanishi, Y.; Fujiwara, K.; Hirayama, S.; Okuyama, T.; Ohki, Y. Tatsumi, K.; Yoshioka, Y. *J. Am. Chem. Soc.* **2004**, *126*, 7548.

[19] Shakespeare, W. C.; Johnson, R. P. *J. Am. Chem. Soc.* **1990**, *112*, 8578.

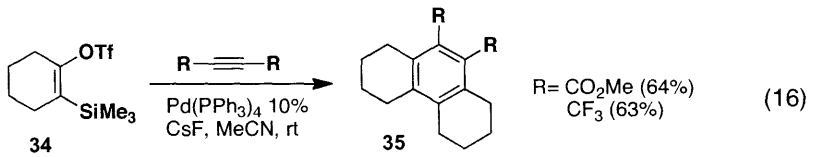
The trimerization of cyclohexyne has been studied recently by Guitián and coworkers using the same generation method. In these studies the cyclotrimerization was metal-catalyzed using palladium or platinum (eq 15).[20]



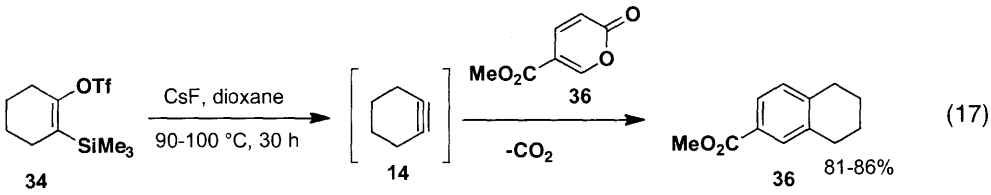
(15)

(a) $Pd(PPh_3)_4$ (10 mol%), CsF, CH_3CN, 20 °C, 64%;
(b) $Pt(PPh_3)_4$ (10 mol%), CsF, CH_3CN, 20 °C, 62%

Guitián et al. also examined the metal catalyzed [2 + 2 + 2] cycloaddition of cyclohexyne and alkynes (eq 16). In addition, they also successfully trapped cyclohexyne in situ in a cycloaddition reaction with an α-pyrone (eq 17).



(16)



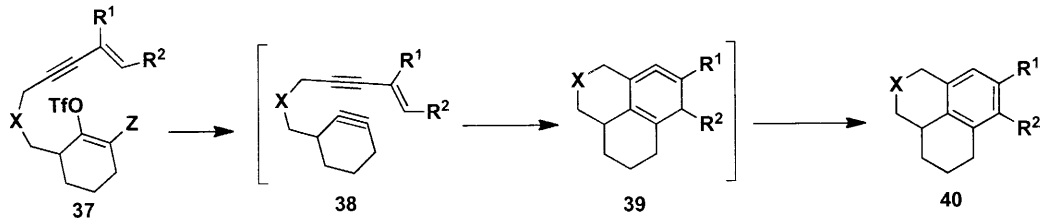
(17)

[20] (a) Atanes, N.; Escudero, S.; Perez, D.; Guitián, E.; Castedo, L. *Tetrahedron Lett.* **1998**, *39*, 3039. (b) Inglesias, B.; Peña, D.; Pérez, D.; Guitián, E.; Castedo, L. *Synlett.* **2002**, *3*, 486. (c) Peña, D.; Iglesias, B.; Quitana, I. Pérez, D.; Guitián, E.; Castedo, L. *Pure App. Chem.* **2006**, *78*, 451.

Chapter 3
Our Synthetic Strategy

Our Goal and Strategy

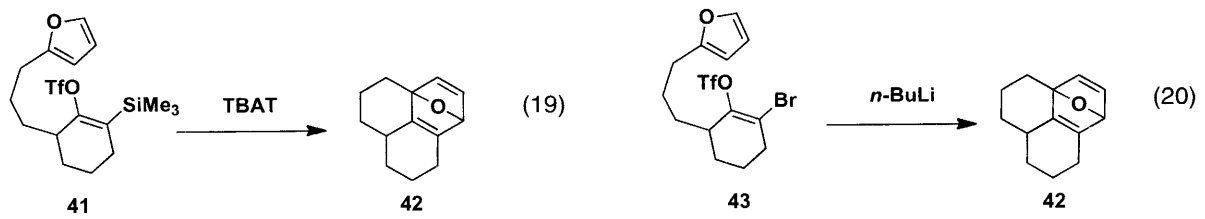
Cyclohexynes have seen almost no applications in organic synthesis. The goal of my research has been to investigate the feasibility of employing *cyclohexyne derivatives* as components in various cycloadditions, including intramolecular enyne cycloadditions in particular. The key step in our strategy for the generation of cyclohexynes involves the 1,2-elimination of a vinyl triflate and a group **Z**, shown below. This strategy would generate the cyclohexyne in situ, to be followed immediately by intramolecular trapping and isomerization (eq 18).



(18)

Thus far we have examined two variants of this strategy, including one in which **Z** is $SiMe_3$ (see **41** below). In this case we would rely on a fluoride-induced 1,2-elimination to generate the desired cycloalkyne intermediate. We have also investigated a strategy where **Z** is Br (**43**), in which case we would use an alkyllithium to promote 1,2-elimination in a similar manner. The latter method is based on previous syntheses of aryne species according to a method developed by Suzuki and coworkers.[21]

[21] Matsumoto, T.; Hosoya, T.; Katsuki, M.; Suzuki, K. *Tetrahedron Lett.* **1991**, *46*, 6735.



41 42 43 42

Because little experimentation has been done with cyclohexyne substrates to date, our interests included examining a variety of possible cycloaddition partners in addition to conjugated enynes. We decided to begin our studies using the furan containing substrates shown above in eq 19 and 20. This type of structure would allow us to examine intramolecular Diels-Alder reactions with the intermediate cycloalkyne using a diene well known to be effective in aryne cycloadditions.

Summary

The chemistry of cyclic alkynes remains an intriguing area of study in modern synthetic chemistry. Apart from their appeal as unique and interesting strained systems these alkynes have significant potential utility for organic synthesis and could provide new methods to generate complex carbocyclic scaffolds.

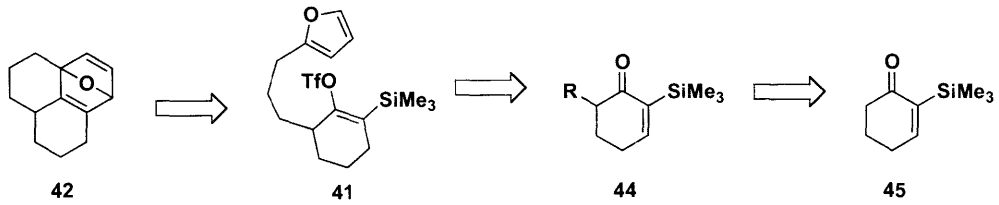
Part II

Studies on the Intramolecular Cycloaddition of Cyclohexynes

Chapter 1
Ketone Alkylation Strategy

Introduction

Our first target was the silyl vinyl triflate **41**, which we hoped to access via a route similar to that taken by Johnson and Guitián in their studies on cyclohexyne reactivity.[19-20] Our initial approach for the synthesis of triflate **41** is shown below in eq 21. Enone **45** would be alkylated to provide **44**, and then conjugate reduction of **44** followed by enolate trapping with a triflating agent was expected to provide our desired vinyl triflate **41**.

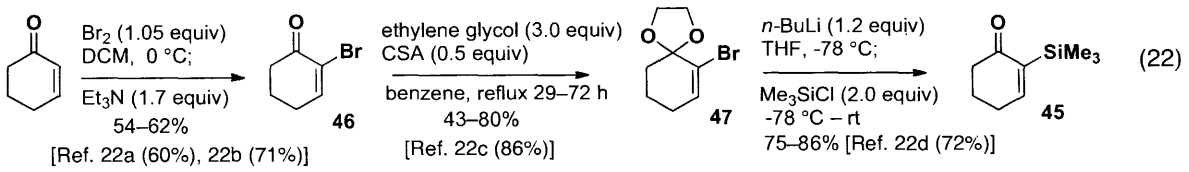


42 **41** **44** **45** (21)

Ketone Alkylation Route to Cyclohexyne Precursors

The alkylation of enolate species is a well-established procedure in organic synthesis. We anticipated that intermediate **44** could be readily prepared from the known enone **45** using standard alkylation reactions. Enone **45** was synthesized in three steps from cyclohexanone according to literature precedent,[22] as shown below in eq 22.

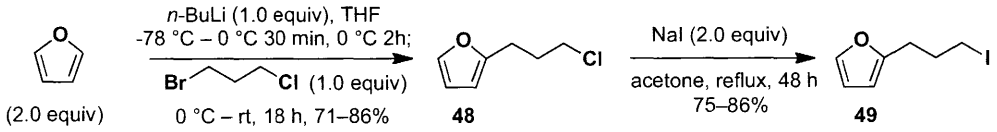
[22](a) Kowalski, C. J.; Weber, A. E.; Fields, K. W. *J. Org. Chem.* **1982**, *47*, 5088. (b) Li, K.; Alexakis, A. *Angew. Chem. Int. Ed.* **2006**, *45*, 7600. (c) Anderson, J. C.; Pearson, David J. *J. Chem. Soc. Perk. T. 1* **1998**, 2023. (d) Shih, C.; Fritzen, E. L.; Swenton, J. S. *J. Org. Chem.* **1980**, *45*, 4462.



(22)

Although the bromination and silyation procedures proceeded in good yield, the ketalization of **46** proved to be a source of frustration. Reactions performed on a scale of less than 1 g proceeded consistently in 70% yield or higher. However, when moving to larger scales the yields became inconsistent and the reaction produced a major side product that could not be identified. Both CSA and TsOH were tested as acids in this reaction, in amounts ranging from 0.1–0.5 equivalents, but the formation of the side product was observed in each case.

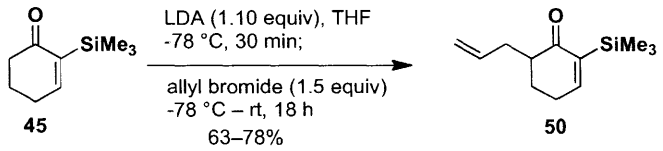
Our desired alkylating agent **49**, a known compound, was also prepared according to literature precedent (eq 23).[23]



(23)

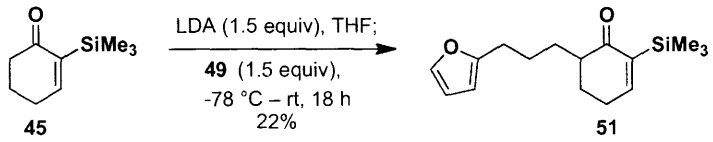
Before we attempted to alkylate enone **45** with iodide **49**, the alkylation procedure was optimized using allyl bromide. Our optimized conditions gave **50** in 63–78% yield (eq 24). Although these yields were acceptable, they nonetheless caused some concern as we were hoping for better results with such an activated alkylating agent.

[23] Rogers, C.; Keay, B. A. *Can. J. Chem.* **1992**, *70*, 2929.



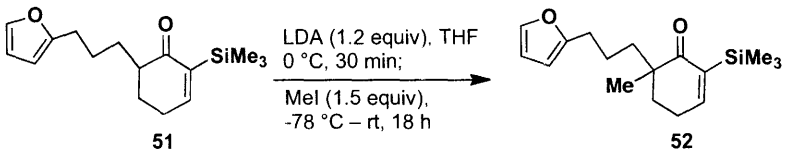
45 50 (24)

Indeed, when these conditions were applied with the desired alkylating agent, iodide **49,** the yield of the reaction remained poor despite our extensive attempts to improve it. Our best conditions produced the desired product in only 22% yield (eq 25). Bases screened included LDA, LiTMP, and LiHMDS, with and without the addition of HMPA. The reaction was also attempted at different temperatures ranging from -78 °C to rt, both with normal and inverse addition of the enolate and alkylating agent. The low yields were consistent with the poor conversion that was seen in these reactions. The reaction did, however, produce few impurities or side products and the unreacted starting material could be recovered and used for further experiments.



45 51 (25)

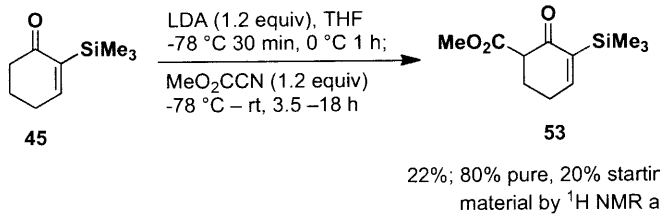
Curious about the reactivity of the alkylated species, we attempted to alkylate enone **51** with methyl iodide (eq 26). Although the reaction did occur, the conversion was again low (ca. 50% by ^{1}H NMR analysis) and the methylated product **52** could not be separated from the starting material.



51 52 (26)

ca. 50% conversion by ^{1}H NMR analysis
compound not isolated

We then attempted to facilitate the alkylation process by incorporating an ester substituent adjacent to the ketone. Mander's reagent (MeO_2CCN) is known to be an effective acylating reagent in these reactions.[24] However, to our surprise enone **45** proved unreactive in acylation chemistry as well, resulting again in low yields and proceeding cleanly but with poor conversion of the original enone (eq 27).

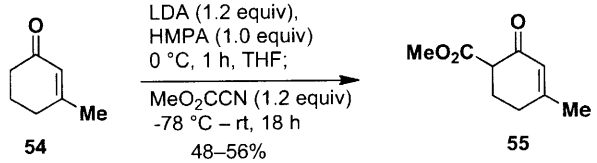


45 53

22%; 80% pure, 20% starting material by ^1H NMR analysis)

(27)

Puzzled by this result, we attempted to acylate 3-methylcyclohexenone as a model to test our methods (eq 28). Although the yields were slightly lower than the closest literature precedent (70% for the acylation of 3-methylcyclohexenone with allyl cyanoformate[25]), we were still seeing a significant increase in reactivity compared to reactions with trimethylsilylcyclohexenone **45**.



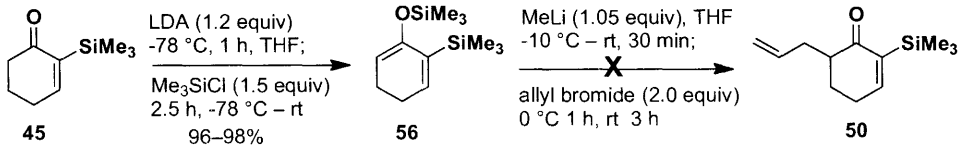
54 55

(28)

To further understand the lack of reactivity of enone **45** we attempted the preparation of the silyl enol ether derivative to examine the ease of enolate formation. This reaction went in quantitative yield with no required purification of the product as shown in eq 29 below.

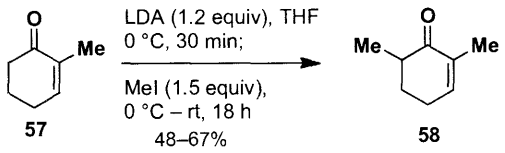
[24] Crabtree, S. R.; Chu, Alex W. L.; Mander, L. C. *Synlett* **1990**, 169.
[25] Mohr, J. T.; Behenna, D. C.; Harned, A. M.; Stoltz, B. M. *Angew. Chem. Int. Ed.* **2005**, *44*, 6924.

However, our attempts to cleave silyl enol ether **56** with methyllithium and then alkylate the resulting lithium enolate resulted only in recovery of the original silyl enol ether with no silyl enol ether cleavage or alkylated enone visible in the crude product by TLC and ^{1}H NMR, implying a surprisingly low reactivity of this enolate precursor.

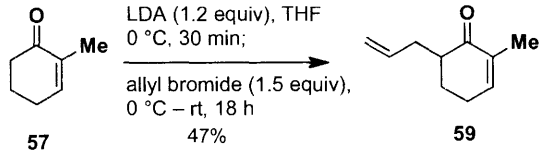


(29)

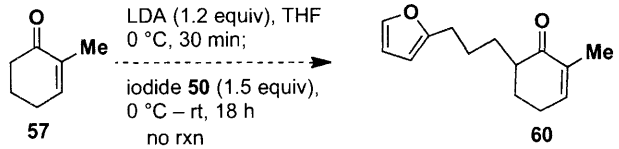
To better understand these results, we wanted to compare the reactivity of enone **45** with a simpler α-substituted cyclohexenone. This led us to attempt alkylations using 2-methylcyclohexenone **57** as a model substrate. This compound was synthesized in two steps from methylcyclohexanone according to a literature procedure.[26] Although methyl enone **57** did react with active alkylating agents in acceptable yield, when we attempted to use iodide **49** as the alkylating agent the reaction produced no significant product (eq 30–32).



(30)



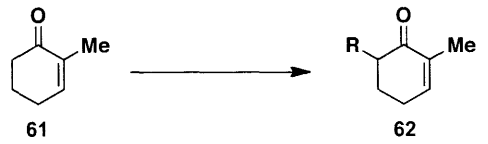
(31)



(32)

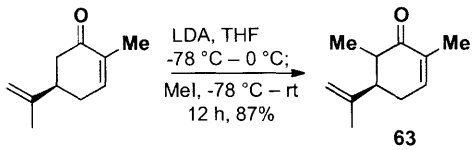
[26] Warnhoff, E. W.; Martin, D. G.; Johnson, W. S. *Org. Syn.* **1957**, *37*, 8.

Although surprising, it should be noted that there are relatively few examples of efficient alkylation reactions of α-substituted cyclohexenones in the prior literature and these alkylations tend to go in variable yields, often producing poor results with unactivated alkylating agents (eq 33).[27]



61 62 (33)

One exception is the alkylation of carvone, which in our hands did proceed well, as expected based on the prior literature (eq 34).[28]



63 (34)

Summary

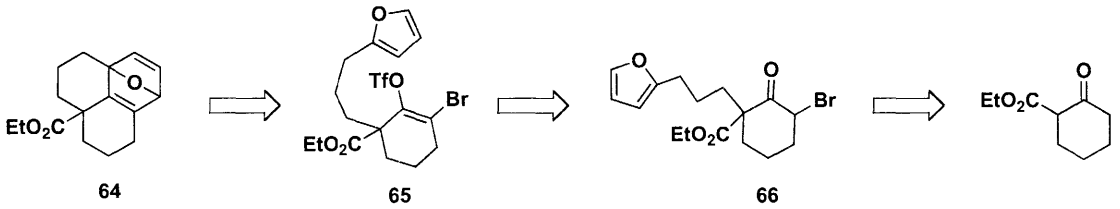
Given the difficulty of alkylating cyclohexenone **45**, we decided to modify our strategy by employing a starting material that would be more amenable to alkylation reactions. In our next approach we decided to simplify the alkylation procedure by starting with a β-keto ester. Keto esters in general are easier to alkylate and react under much milder conditions than those required for our original enone. Our strategy to obtain cyclohexyne precursors using this route is the subject of Chapter 2.

[27] (a) Srikrishna, A.; Pardeshi' V. H.; Satyanarayana, G. *Tetrahedron Lett.* **2007**, *48*, 4087. (b) Yao, M.; Deng, M. *Synthesis* **1993**, 1095.
[28] Srikrishna, A.; Vijaykumar, D. *J. Chem. Soc. Perk. Trans. I.* **2000**, 2583.

Chapter 2:
Keto Ester Alkylation Strategy

Introduction

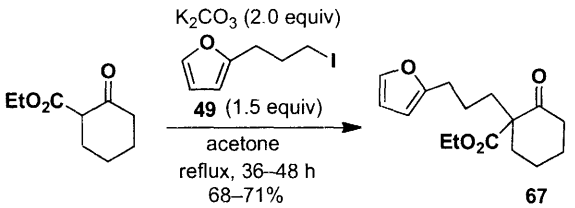
Our keto ester strategy began with the commercially available keto ester shown below in eq 35. In this strategy, our cyclohexyne precursor **65** would be subjected to a *n*-BuLi promoted 1,2-elimination to produce the desired cycloaddition product **64**. The ester component would facilitate the alkylation reactions and then could then be modified or removed as desired. This strategy is based on Suzuki's work on aryne chemistry[29] and we expected it to be effective for the generation of cyclohexyne as well.



64 65 66 (35)

Keto Ester Alkylation Route to Cyclohexyne Precursors

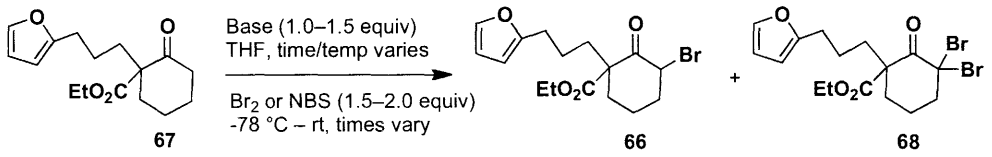
Alkylation of the β-keto ester with our previously generated iodide **49** proceeded in good yield and was easily scaled-up to provide us with convenient access to compound **67** (eq 36).



67 (36)

[29] (a) Masumoto, T.; Hosoya, T.; Katsuki, M.; Suzuki, K. *Tetrahedron Lett.* **1991**, *32*, 6735. (b) Hamura, T.; Hosoya, T.; Yamaguchi, H.; Kuriyama, Y.; Tanabe, M.; Miyamoto, M. Yasui, Y.; Matsumoto, T.; Suzuki, K. *Helv. Chim. Acta* **2002**, *85*, 3589.

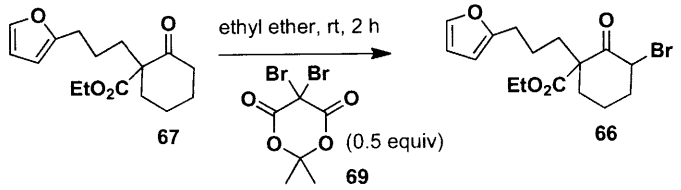
The next step in our strategy required the bromination of keto ester **67**. Finding optimal conditions for this bromination reaction proved troublesome at first. Several bases were screened, including LDA, LiTMP, LHMDS, and KHMDS, using NBS and Br_2 as brominating agents. These reactions resulted in poor conversion of the starting material and production of a major side product that upon isolation proved to be the dibrominated ketone **68** (eq 37). The addition of HMPA to these reactions was moderately successful in suppressing the formation of the doubly brominated product.



(37)

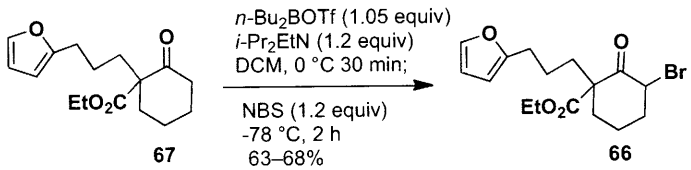
Further attempts to minimize the double bromination included lowering the amount of base to 1.0 equivalent, testing ethyl ether as a solvent, and attempting inverse addition of our enolate to the brominating agent. The yield and conversion of the reaction, however, remained poor. The highest conversion in these reactions was seen with the use of KHMDS as base, resulting in a product mixture containing the dibrominated product (42%) and the desired monobrominated species (53%). The bromination reaction was also attempted with a brominating agent derived from Meldrum's acid, compound **69**[30] shown below (eq 38). By using this procedure[31] we had hoped to improve the efficiency of the reaction by avoiding basic conditions, but the reaction resulted in the production of several side products, including products from bromination of the furan ring, and little to none of desired product.

[30] Snyder, H. R.; Kruse, C. W. *J. Am. Chem. Soc.* **1958**, *80*, 1942.
[31] Bloch, R. *Synthesis* **1978**, 140.



(38)

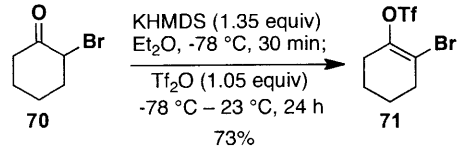
The range of conditions and temperatures that have been used in brominations with reagent **69** vary greatly, and it is therefore possible that with further optimization yields the reaction with this reagent could be improved. This avenue was not further pursued, however, due to the success of our next attempted bromination involving a soft enolization approach. In this procedure we formed the boron enolate and then added that enolate to a slurry of NBS in cold DCM. The reaction proceeded in good yield and provided ample material for triflation experiments (eq 39).



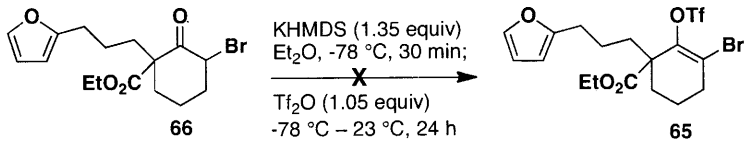
(39)

The next step in our synthetic strategy required the formation of the vinyl triflate **65** from bromo ketone **66**. The closest literature precedent for this reaction is the triflation of 1-bromo-cyclohexanone, **70**, which we were able to repeat in 73% yield (eq 40; literature yield 95%).[32] When these conditions were applied to ketone **66**, however, none of the desired product was obtained. All attempts to effect this reaction were unsuccessful. The reaction was attempted using KHMDS and LDA as the base, with and without the addition of HMPA, and with triflic anhydride and phenyltriflimide as triflating agents (eq 41).

[32] Sünnemann, H. W.; Banwell, M. G.; de Meijere, A. *Eur. J. Org. Chem.* **2007**, 3879.



(40)



(41)

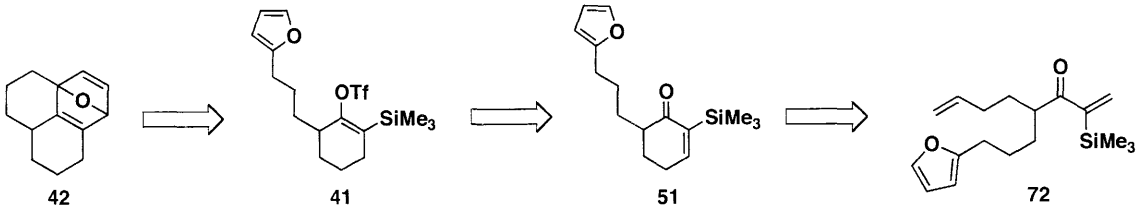
Summary

Our unexpected difficulties in generating the requisite triflate made it necessary to abandon this strategy, causing us to again shift our focus to the fluoride-induced 1,2-elimination of a silyl vinyl triflate to generate cyclohexyne derivatives. Our new strategy towards this goal is described in the next chapter.

Chapter 3
Ring-Closing Metathesis Strategy

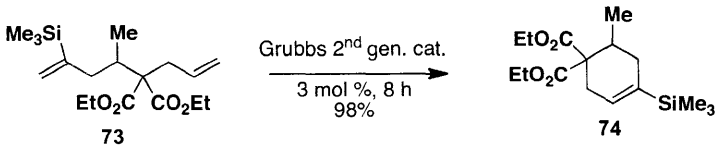
Introduction

Using enone **72** in a ring-closing metathesis (RCM) reaction would generate trimethylsilyl(cyclohexenone) **51** while avoiding the alkylation reactions that were previously problematic. The vinyl triflate could then be generated through the conjugate-reduction and trapping reactions previously planned (eq 42).

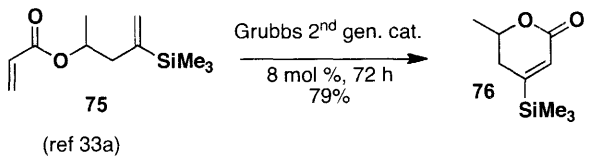


(42)

There is sufficient precedent[33] for ring-closing metathesis reactions involving vinyl silanes (eq 43–45) that we were optimistic about following this strategy to reach our desired enone **51**.

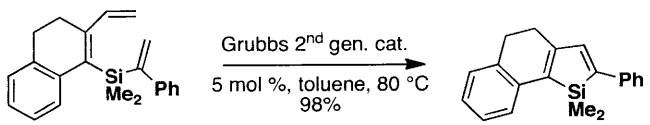


(43)



(44)

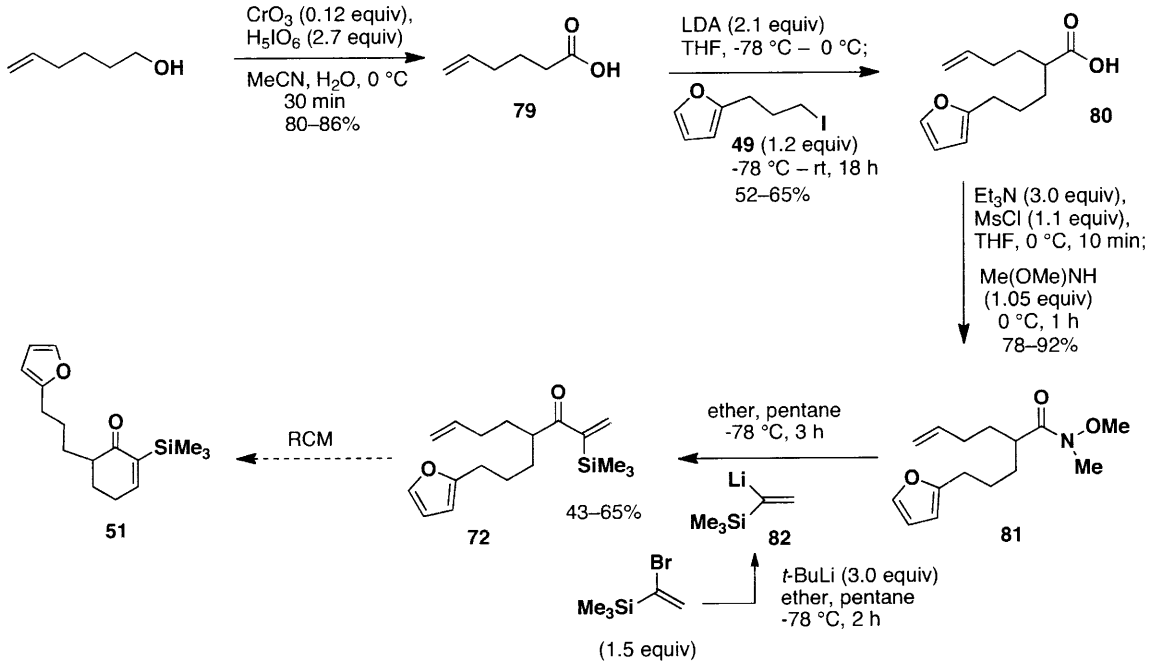
[33] (a) Gouveneur, V.; Schuman, M. *Tetrahedron Lett.* **2002**, *43*, 3513. (b) Matsuda, T.; Yamaguchi, Y.; Murakami, M. *Synlett* **2008**, *4*, 0561.



77 (ref 33b) 78 (45)

Ring-Closing Metathesis Route to Cyclohexyne Precursors

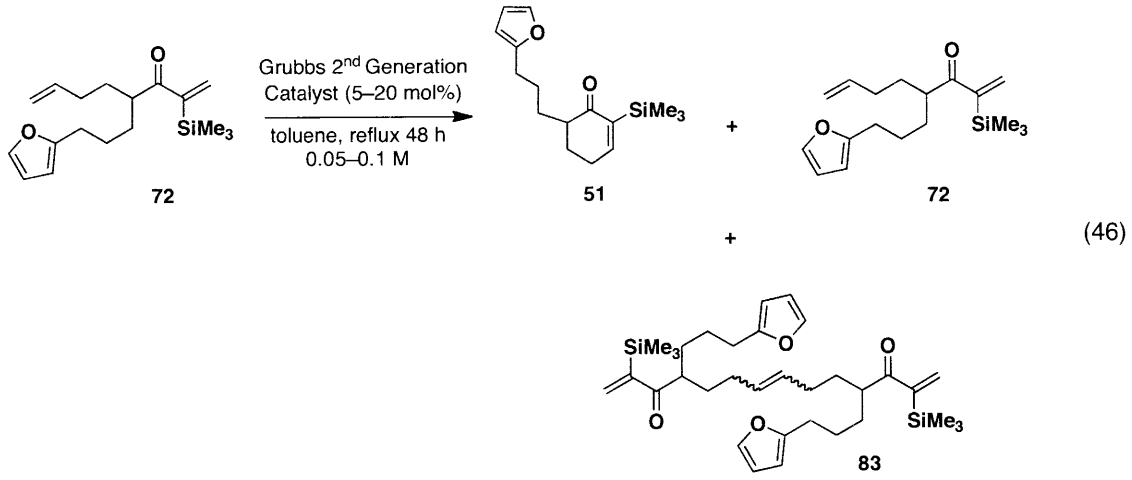
The substrate for the key RCM reaction was expected to be available in 4 steps from 5-hexenol. A catalytic chromium oxide oxidation[34] provided acid **79** in good yield, followed by an alkylation of the acid dianion using our previously prepared alkyl iodide **49**. The resulting acid was then converted to the corresponding Weinreb amide,[35] which was then converted to the desired ketone **72** by reaction with the lithium reagent **81** formed from (1-bromovinyl)trimethylsilane (Scheme 1).



Scheme 1

[34] Zhao, M.; Li, J.; Song, Z.; Desmond, R.; Tschaen, D. M.; Grabowski, E. J. J.; Reider, P. J. *Tetrahedron Lett.* **1998**, *39*, 5323.
[35] Woo, J.; Fenster, E.; Dake, G. R. *J. Org. Chem.* **2004**, *69*, 8984.

With this key intermediate in hand we then tested several different conditions for the ring-closing metathesis. Our first attempts employed 5–20 mol % Grubbs 2nd generation catalyst at concentrations ranging from 0.05–0.1 M. Although some of the desired product was isolated, these reactions did not proceed to completion and the major isolated product was dimer **83** (eq 46). The major components of the dimer mixture were the trans-diastereomers, though all four isomers were visible by GC analysis.

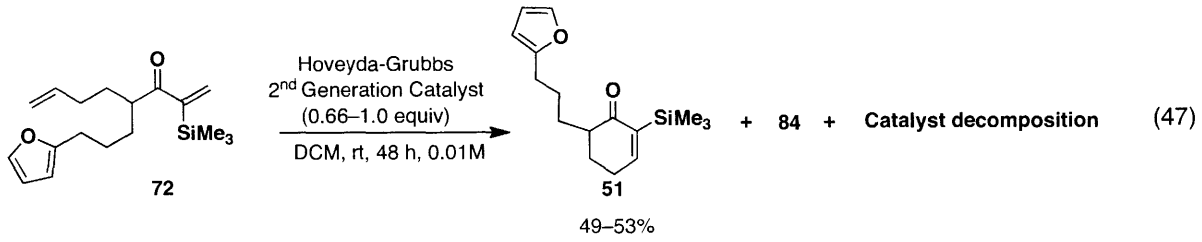


(46)

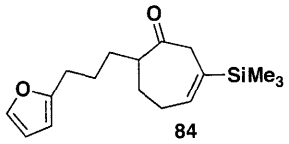
Simultaneously we screened reactions using the Hoveyda-Grubbs 2nd generation catalyst. For these reactions it proved necessary to use 60–100 mol % catalyst to force the reaction to completion. At first this was not considered problematic because the catalyst was expected to be recoverable in high yield.[36] We obtained our desired product, enone **51**, in 49–53% yield, but we also obtained an additional unknown product (**84**) that was present in approximately equal amounts. More problematically, the catalyst appeared to be decomposing during the course of the reaction and could not be recovered (eq 47).

---

[36] (a) Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem Soc.* **2000,** *122,* 8168. (b) Kingsbury, J. S.; Harrity, J. P. A.; Bonitatebus, P. J.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1999**, *121*, 791.



Based on the available analytical data, including ^{1}H NMR, ^{13}C NMR, gCOSY, HMBC, HSQC, GC-MS, and FT-IR spectra, we propose the structure of **84** to be the homologated product shown below.



Compared to the desired enone **51**, compound **84** shows an additional methylene in the ^{13}C NMR and ^{1}H NMR spectra. These two new protons appear as an apparent quartet at ca. 1.65 ppm and do not couple to any other protons on the gCOSY spectrum (Figures 2–3).

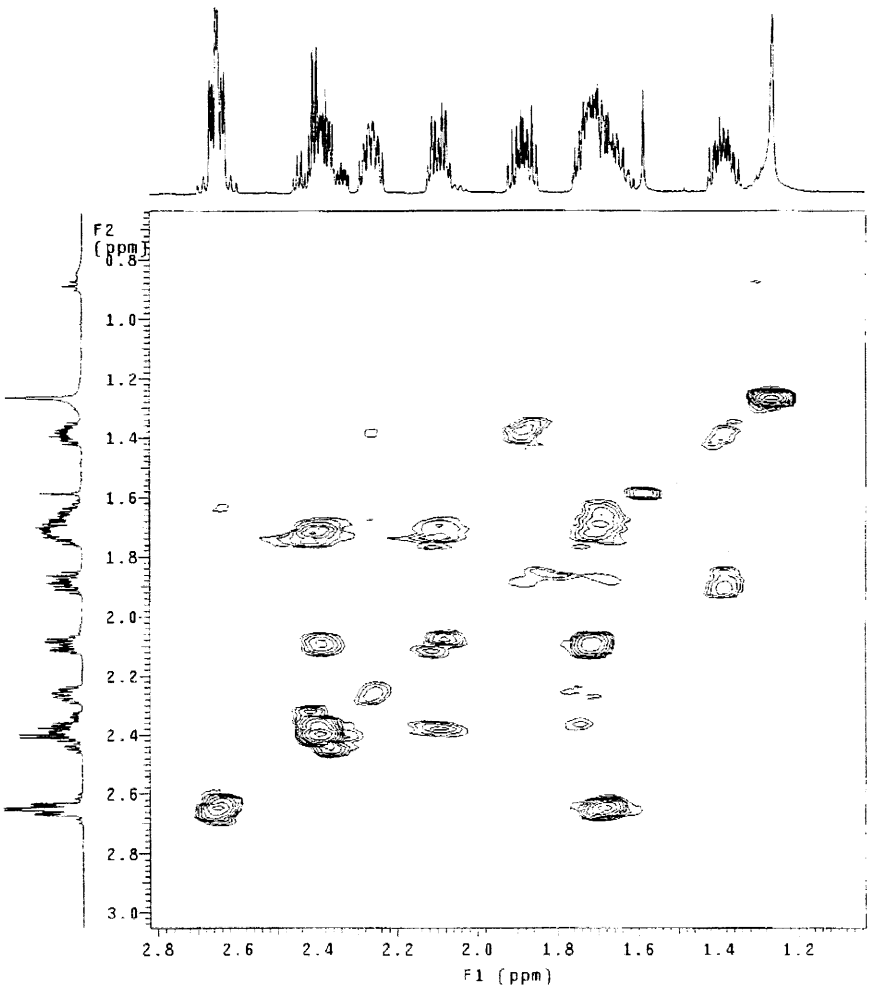


Figure 2: gCOSY spectrum of enone **51** ($CDCl_3$, 500 MHz)

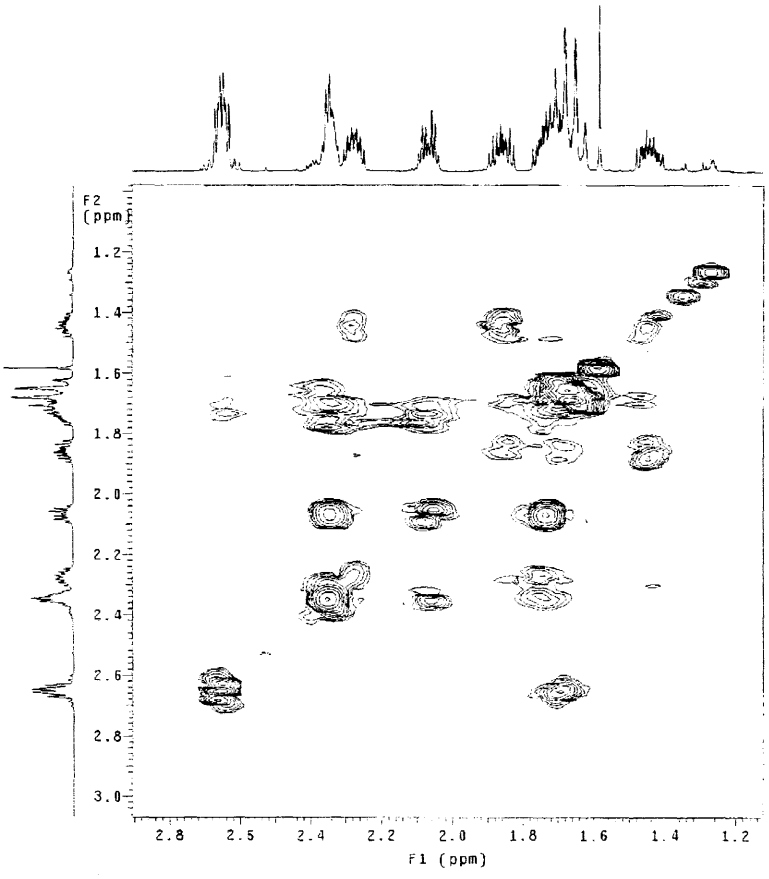
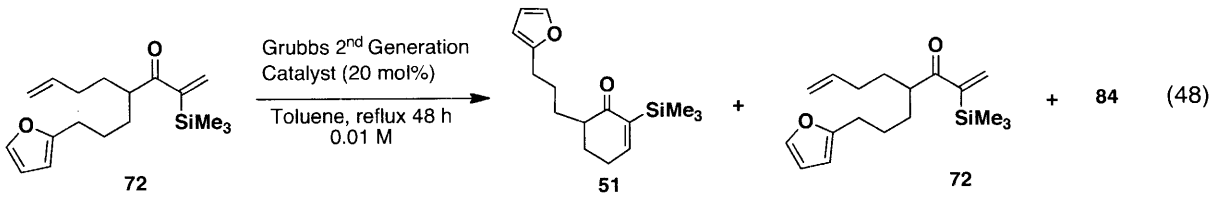


Figure 3: gCOSY spectrum of the unknown **84** ($CDCl_3$, 500 MHz), new app quartet visible at ca 1.65 ppm.

The MS analysis confirms the presence of an additional methylene carbon with a mass ion 14 m/z higher than that seen for the desired enone **51**. This structure is supported by the coupling visible in the HMBC spectrum and with the proton-carbon correlations in the HSQC spectrum as well.

When reexamining the reaction with the 2nd generation Grubbs catalyst at higher dilution (0.01 M), dimer formation was avoided, however, all reactions proceeded with poor conversion (50% or lower), and the same unknown product **84** was visible in the crude product (eq 48).

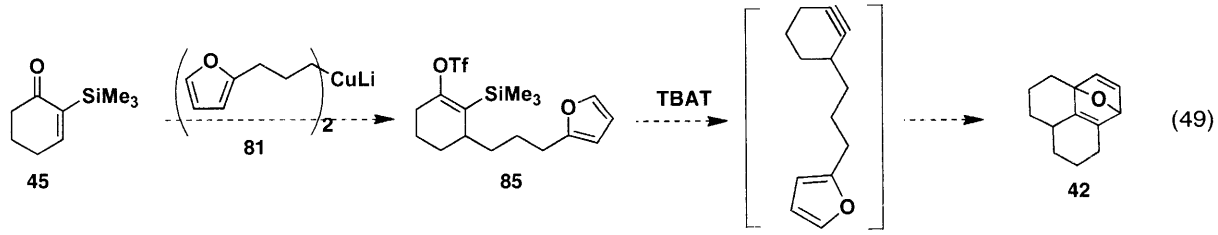


(48)

Vinylsilanes are known to participate effectively in RCM reactions, so it is our hope that this reaction could be improved in future work by removing the complication of the conjugated enone from the system. This could be done easily by reducing the carbonyl group and protecting the resulting alcohol so that the uninhibited vinylsilane could then undergo the RCM reaction. The alcohol could then be oxidized to the ketone and the strategy would continue as planned.

Summary

Although we plan to continue our studies of the RCM route, we are also pursuing a route to cyclohexyne precursors involving conjugate addition and enolate trapping using our previously synthesized trimethylsilylenone **45**. Although precursor **85** is slightly different from our original target, the intermediate after TBAT elimination is the same (eq 49).



(49)

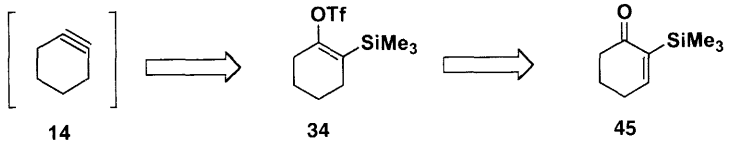
Part III

Studies on the Intermolecular Cycloadditions of Cyclohexyne

Chapter 1
Substrate Generation and Reactivity

Introduction

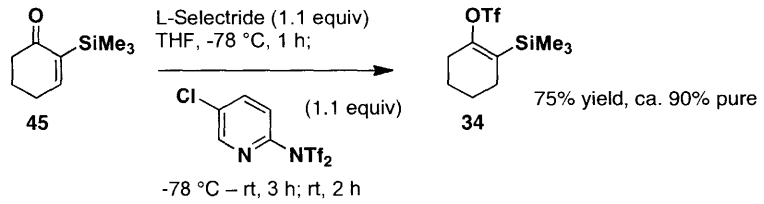
In addition to our interest in intramolecular cycloadditions involving cyclohexynes, the intermolecular cycloadditions of these substrates have also attracted our attention, as there are few studies of the application of these reactions in synthesis to date. Simple cyclohexyne substrates could be formed from triflate compounds such as **34**, which are also easily obtained from our previously generated trimethylsilylenone **45** by conjugate-reduction or addition reactions followed by enolate trapping (eq 50).



14 **34** **45** (50)

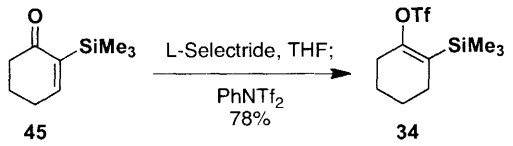
Synthesis of Substrates for Intermolecular Cycloaddition Reactions

Forming the vinyl triflate **34** from the parent enone was successfully carried out using L-Selectride for the reduction, followed by Comins reagent for the triflation. Unfortunately, despite attempts to purify the material there remained an inseparable impurity present in ca 10% in all cases (eq 51). We also tested phenyltriflimide as a triflating agent, but encountered the same problem.



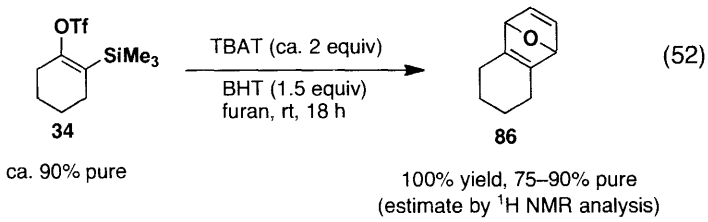
(51)

This reaction was reported to proceed in 78% yield by Guitian et al.[20] (eq 52) in their studies on cyclohexyne, but no detailed procedure was given in this paper and their result could not be replicated in our hands.

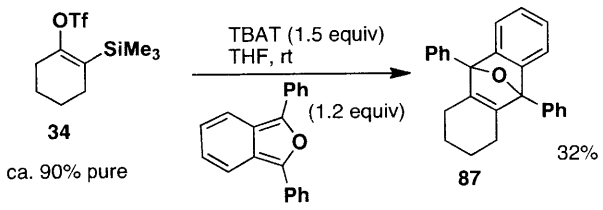


(52)

Triflate **34** has thus far been used in two cycloaddition reactions. The first reaction involved trapping the cyclohexyne intermediate with furan (used as solvent) under conditions typical of the previous aryne trapping work done in our laboratory (eq 53). The next cycloaddition was performed using DPIBF to trap the cyclohexyne intermediate (eq 54). Because DPIBF is a known, very effective diene in Diels-Alder reactions, we intend to optimize the elimination and trapping reactions with this partner before testing other less active systems. Thus far this reaction has only been attempted once and it is expected that yields will significantly increase with better knowledge of the best purification method for this system.

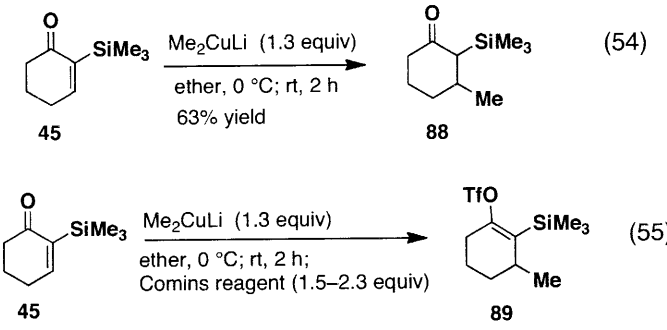


(52)



(53)

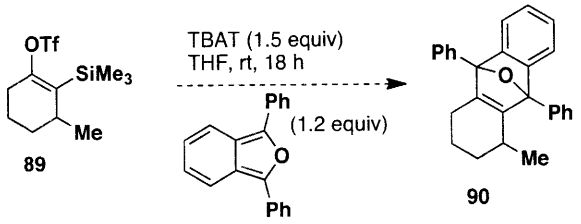
To study cuprate conjugate additions we commenced using simple lithium dimethylcuprate and dimethyl cyanocuprate generated from CuI or CuCN and methyllithium, followed by trapping to generate the triflate compound **86**. Testing the conjugate addition reaction without trapping shows that this reaction proceeds cleanly to completion (eq 54). Trapping the intermediate enolate, however, has proven more difficult and produced several side products that are difficult to separate from the desired compound (eq 55).



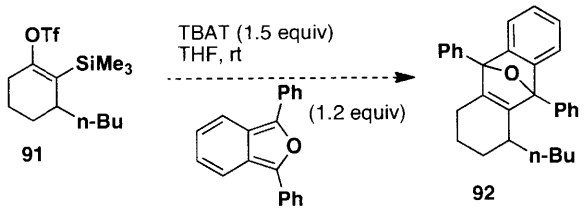
(54)

(55)

We are attempting to optimize this system, and we will next proceed to the dibutylcuprate system. Subsequently these two substrates can also be examined in intermolecular cycloadditions as well (eq 51 and 52).



(56)


OTf
SiMe3
n-Bu
91
TBAT (1.5 equiv)
THF, rt
Ph
O
Ph
(1.2 equiv)
Ph
Ph
O
Ph
n-Bu
92

(57)

Part IV

Experimental Procedures

General Procedures

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

Materials

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

(a) Purified by pressure filtration through activated alumina:

Dichloromethane, diethyl ether, and tetrahydrofuran

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

Toluene

(c) Distilled under argon or vacuum:

Hexamethyl phosphoramide

(d) Distilled under argon from calcium hydride:

Diisopropylamine, triethylamine, diisopropylethylamine, triethylamine, methanesulfonyl chloride, trimethylsilylchloride

(e) Dried under vacuum:

Potassium carbonate was crushed with a mortar and pestle and dried overnight at 0.10 mmHg

(f) Other:

n-Butyllithium and *tert*-Butyllithium were titrated according to the Watson-Eastham method using menthol or BHT in THF at 0 °C with 1,10-phenanthroline as an indicator[37]

Acetone was HPLC grade and distilled from calcium carbonate

Benzene was dried through azeotropic distillation

N,O-dimethylhydroxylamine was obtained immediately before the reaction by distillation of the HCl salt from ethylene glycol and triethanolamine

Molecular sieves (4 Å) were dried under vacuum (0.1 mmHg) at 300 °C for 16 h before use.

Instrumentation

Infrared spectra were obtained using a Perkin Elmer 2000 FT-IR spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were measured with Inova 500 and Bruker 400 MHz spectrometers. ^{1}H NMR chemical shifts are expressed in parts per million (δ) downfield from tetramethylsilane (with the $CHCl_3$ peak at 7.27 ppm used as a standard on the Bruker spectrometers and 7.27 ppm on the Inova). ^{13}C NMR chemical shifts are expressed in parts per million (δ) downfield from tetramethylsilane (with the central peak of $CHCl_3$ at 77.27 ppm used as a standard). High resolution mass spectra (HRMS) were measured on a Bruker Daltonics APEXII 3 telsa Fourier transform mass spectrometer.

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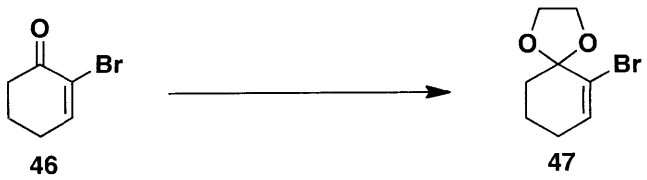
[37] Watson, S. C.; Eastham, J. F. *J. Organomet. Chem.* **1967**, *9*, 165. (b) Ellison, R. A.; Griffin, R.; Kotsonis, F. N. *Organomet. Chem.* **1972**, *369*, 209.

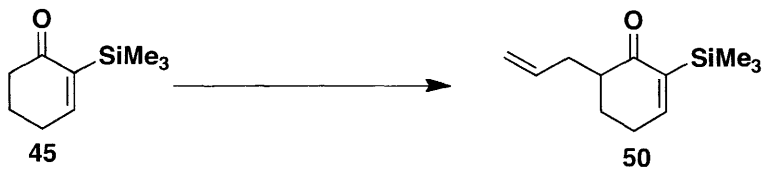


46 47

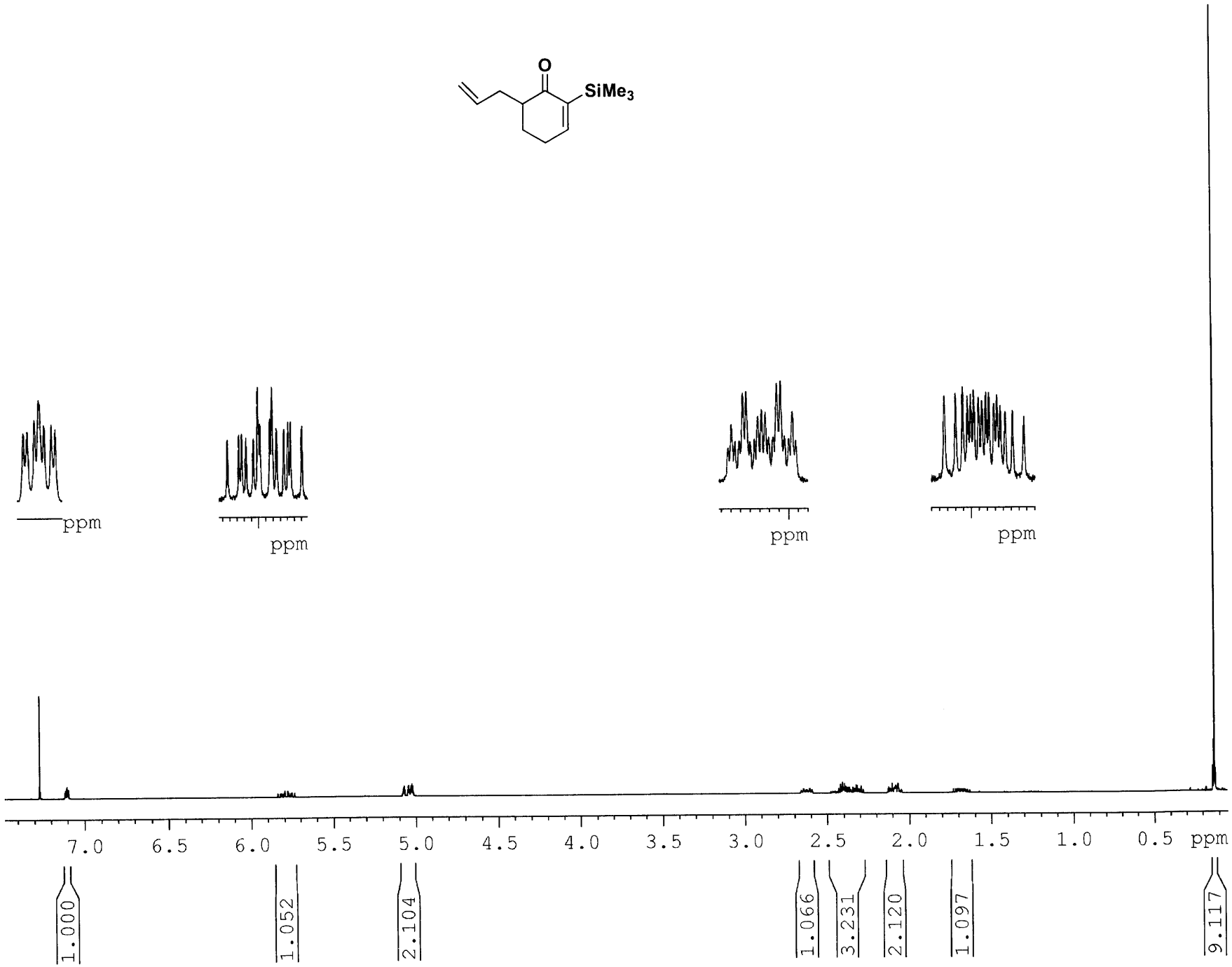
6-Bromo-1,4-dioxaspiro[4.5]dec-6-ene. A 1-L, round-bottomed flask was equipped with a Dean-Stark trap fitted with a reflux condenser and argon inlet. The trap was half-filled with benzene and 4 Å molecular sieves and the flask was charged with enone **46** (5.00 g, 28.6 mmol, 1.0 equiv), ethylene glycol (3.19 mL, 3.55 g, 57.2 mmol, 2.0 equiv), CSA (3.33 g, 14.3 mmol, 0.5 equiv), and 400 mL of benzene. The reaction mixture was heated at reflux for 36 h and then allowed to cool to room temperature. Aq satd $NaHCO_3$ solution (100 mL) was added and the resulting mixture was stirred for 30 min. The aqueous layer was separated and extracted with two 50-mL portions of EtOAc and the combined organic layers were dried over a mixture of $MgSO_4$ and K_2CO_3, filtered, and concentrated to afford 6.29 g of light yellow oil. Column chromatography on 180 g of silica gel (elution with 20% EtOAc-hexanes) provided 5.00 g (80%) of ketal **47** as a colorless oil. Spectral data was identical to that reported previously.[22c]

47 45

2-(Trimethylsilyl)cyclohexenone. A 50-mL, three-necked, round-bottomed flask equipped with an argon inlet and two rubber septa was charged with a solution of ketal **47** (1.980 g, 9.04 mmol, 1.0 equiv) in 25 mL of THF and then cooled at -78 °C while *n*-BuLi (2.59 M in hexane, 4.17 mL, 10.80 mmol, 1.2 equiv) was added dropwise over 7 min. The reaction mixture was stirred at -78 °C for 30 min and then Me_3SiCl (2.29 mL, 1.95 g, 18.08 mmol, 2.0 equiv) was added dropwise over 5 min. After 1 h, the reaction mixture was allowed to warm to room temperature and then stirred for 1 h. Aq satd NH_4Cl solution (5 mL) was added and the resulting mixture was extracted with two 15-mL portions of diethyl ether. The combined organic layers were washed with 15 mL of water and 15 mL of brine, dried over $MgSO_4$, filtered, and concentrated to afford 1.628 g of a light tan oil. Column chromatography on 35 g of silica gel (elution with 20% EtOAc-hexanes) provided 1.31 g (86%) of **45** as a very light tan oil that solidified to a waxy solid upon standing. Spectral data was identical to that reported previously.[22d]



6-Allyl-2-(trimethylsilyl)cyclohex-2-enone. A two-necked, 25-mL, round-bottomed flask equipped with an argon inlet and rubber septum was charged with a solution of 4 mL of THF and diisopropylamine (0.10 mL, 0.069 g, 0.068 mmol, 1.15 equiv). The solution was cooled at 0 °C while *n*-BuLi (2.60 M in hexane, 0.25 mL, 0.65 mmol, 1.10 equiv) was added dropwise over 2 min. After 10 min, the reaction mixture was cooled to -78 °C and a solution of cyclohexenone **45** (0.100 g, 0.60 mmol, 1.0 equiv) in 0.5 mL of THF was added dropwise over 5 minutes. After 30 min, allyl bromide (0.108 g, 0.08 mL, 0.89 mmol, 1.5 equiv) was added rapidly dropwise and the resulting mixture was allowed to warm to room temperature. After 18 h, 20 mL of aq satd NH_4Cl solution was added and the aqueous phase was separated and extracted with two 15-mL portions of diethyl ether. The combined organic layers were washed with 15 mL of water and 15 mL of brine, dried over $MgSO_4$, filtered, and concentrated to afford 0.142 g of tan oil. Column chromatography on 15 g of silica gel (elution with 3% EtOAc-hexanes) provided 0.097 g (78%) of **50** as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.10–7.12 (ddd, J = 4.6, 3.2, 2.8 Hz, 1 H) 5.74–5.84 (dddd, J = 9.0, 8.4, 7.8, 6.4 Hz, 1 H), 5.02–5.09 (m, 2 H), 2.59–2.67 (ddt, J = 14.6, 5.9, 1.4 Hz, 1 H), 2.29–2.43 (m, 3 H), 2.06–2.27 (m, 2 H), 1.63–1.73 (dddd, J = 14.9, 11.3, 9.9, 5.6, 1 H), 0.13 (s, 9 H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 203.9, 157.3, 141.4, 136.5, 116.5, 46.3, 33.8, 27.5, 27.4, 1.3; IR, 3077, 2953, 1663, 1595, 1423, 1339, 1245, 1154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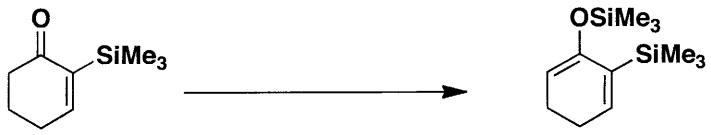
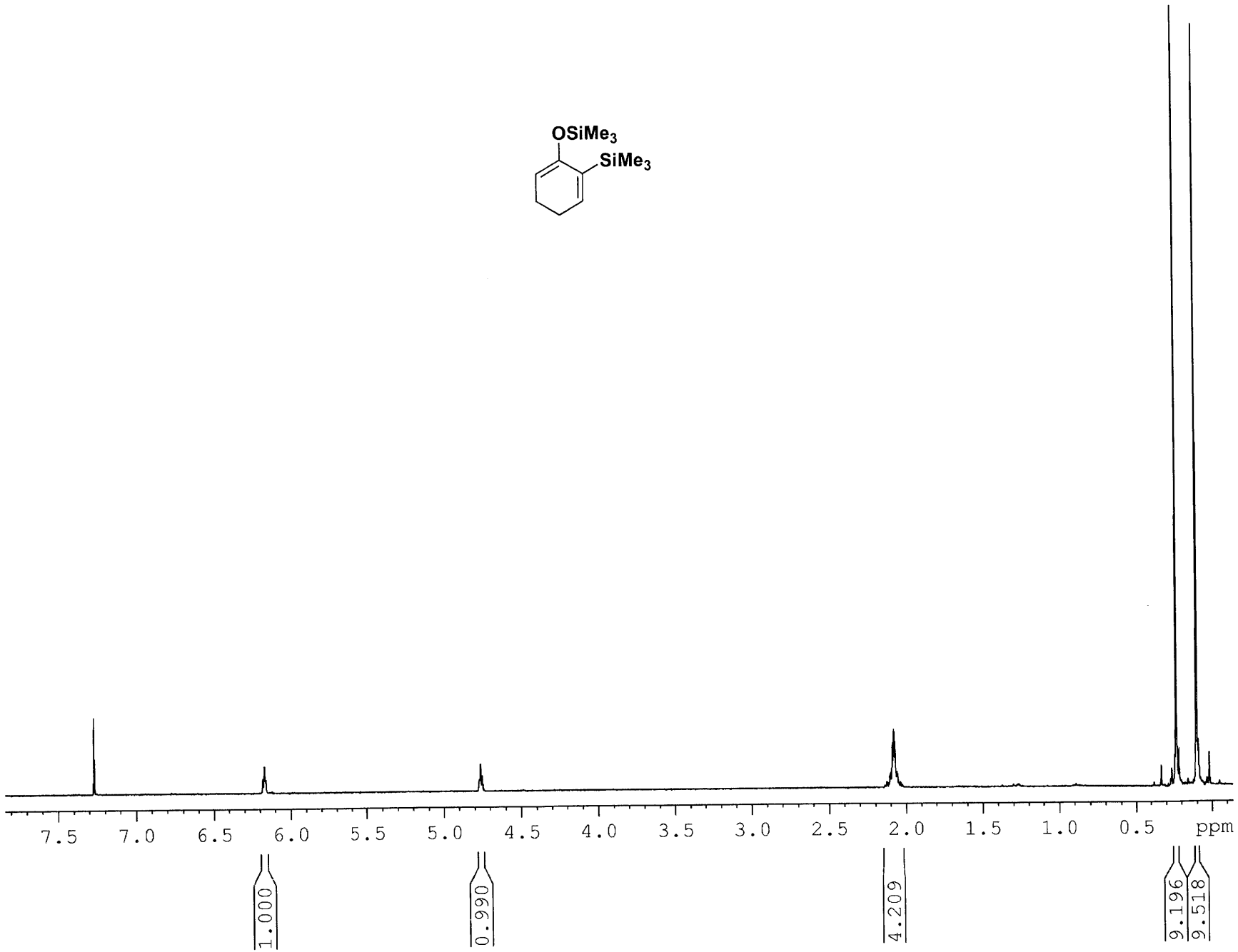
9.117



45 56

2-trimethylsilylcyclohexenone trimethylsilyl enol ether. A 25-mL, two-necked, round-bottomed flask equipped with a rubber septum and argon inlet was charged with a solution of diisopropylamine (0.11 mL, 0.078 g, 0.77 mmol, 1.3 equiv) in 4 mL of THF and cooled at -78 °C while *n*-BuLi (2.60 M in hexane, 0.27 mL, 0.70 mmol, 1.2 equiv) was added dropwise over 3 min. After 30 min, a solution of enone **45** (0.100 g, 0.59 mmol, 1.0 equiv) in 1 mL of THF was added dropwise over 7 min. The reaction mixture was stirred for 1 h and then Me_3SiCl (0.11 mL, 0.096 g, 0.89 mmol, 1.5 equiv) was added rapidly dropwise over 2 min. The reaction mixture was allowed to warm to room temperature, stirred for 1 h, and then concentrated. The resulting yellow residue was diluted with 30 mL of pentane and filtered, and the filtrate was concentrated to yield 0.137 g (96%) of enol ether **56** as a colorless oil that required no further purification: ^{1}H NMR (400 MHz, $CDCl_3$) 6.16–6.19 (m, 1 H), 4.74–4.77 (m, 1 H), 2.02–2.05 (m, 4H) 0.23 (s, 9 H), 0.10 (s, 4H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 152.1, 138.7, 138.2, 98.7, 24.0, 21.9, 0.5, -0.6; IR: 3049, 2957, 2339, 2361, 1628, 1424, 1356, 1319, 1243, 1190, 1089, 1056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4.0
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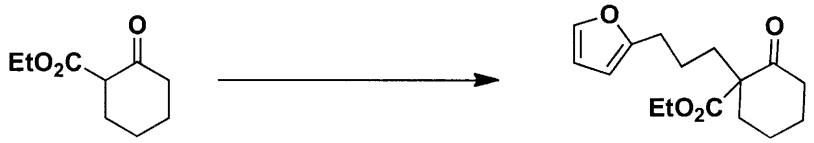
9.196
9.518



67

Ethyl 1-(3-(furan-2-yl)propyl)-2-oxocyclohexane carboxylate. A 100-mL, two-necked, round-bottomed flask equipped with an argon inlet adapter and rubber septum was charged with K_2CO_3 (8.0 g, 58 mmol, 1.8 equiv), 15 mL of acetone, and ethyl 2-oxocyclohexane carboxylate (4.55 mL, 5.00 g, 52.0 mmol, 1.0 equiv). A solution of 2-(3-iodopropyl)furan (8.31 g, 35.2 mmol, 1.1 equiv) in 17 mL of acetone was added in one portion and the resulting solution was heated at reflux for 36 h. The resulting mixture was allowed to cool to rt and then diluted with 20 mL of H_2O and 20 mL of Et_2O. The aqueous phase was separated and extracted with three 10-mL portions of Et_2O, and the combined organic layers were washed with 20 mL of H_2O and 20 mL of brine, dried over $MgSO_4$, filtered, and concentrated to yield 10.79 g of orange oil. Column chromatography on 250 g of silica gel (elution with 0–20% EtOAc-hexanes) provided 6.36 g (71%) of **67** as a light tan oil: FT-IR (film) 2941, 2867, 1713, 1596, 1507, 1451, 1367, 1339, 1308, 1206 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.27–7.28 (dd, J = 1.0, 2.0 Hz, 1 H), 6.25–6.26 (dd, J = 2.0, 3.0 Hz, 1 H), 5.98–5.99 (dq, J = 1.0, 3.0 Hz, 1 H), 4.17–4.22 (qd, J = 1.5, 14.5 Hz, 2 H), 2.60–2.63 (m, 2 H), 2.49–2.53 (dq, J = 3.0, 14.0 Hz, 1 H), 2.42–2.46 (m, 2 H), 1.98–2.03 (m, 1 H), 1.88–1.94 (m, 1 H), 1.52–1.76 (m, 6 H), 1.40–1.46 (m, 1 H), 1.24–1.26 (t, J = 7.5 Hz, 3 H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 208.2, 172.2, 155.9, 140.9, 110.3, 105.2, 61.4, 60.9, 41.3, 36.2, 34.4, 28.2, 27.8, 23.0, 22.8, 14.4

O
O
EtO2C
ppm
ppm
ppm
4.2 ppm
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5 ppm
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3.013
1.604
2.923
1.588
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9.201
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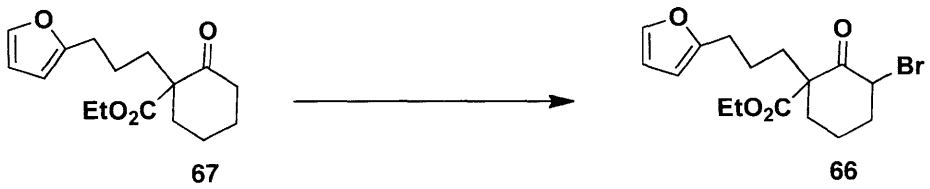
4.162



Ethyl 3-bromo-1-(3-(furan-2-yl)propyl)-2-oxocyclohexane carboxylate. A 50-mL, two-necked, round-bottomed flask equipped with an argon inlet adapter and rubber septum was charged with 10 mL of CH_2Cl_2 and ketone **67** (0.500 g, 1.8 mmol, 1.0 equiv). The solution was cooled at -78 °C and *i*-Pr_2EtN (0.38 mL, 0.279 g, 2.2 mmol, 1.2 equiv) and Bu_2BOTf solution (1.0 M in ether, 1.9 mL, 1.9 mmol, 1.05 equiv) were added. After 15 min, the -78 °C bath was replaced with an ice-water bath and the reaction mixture was stirred at 0 °C for 1 h and then recooled to -78 °C. A 50-mL, two-necked, round-bottomed flask equipped with an argon inlet adapter and rubber septum was charged with NBS (0.351 g, 2.0 mmol, 1.1 equiv) and 5 mL of CH_2Cl_2. The slurry was cooled at -78 °C while the boron enolate solution was added dropwise via cannula over 30 min. After 1 h, 10 mL of brine and 10 mL of satd $Na_2S_2O_3$ were added and the aqueous phase was separated and extracted with two 10-mL portions of CH_2Cl_2. The combined organic layers were washed with 20 mL of brine, dried over $MgSO_4$, filtered, and concentrated to yield 1.468 g of an oily orange solid. Column chromatography on 150 g of silica gel (elution with benzene) provided 0.440 g (68%) of **66** as a light tan oil that was a mixture of two diastereomers (88:12) by ^1H NMR analysis: FT-IR (film) 3449, 3117, 2946, 2360, 1717, 1596, 1507, 1448, 1368, 1218, 1006 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) for major isomer: δ 7.28–7.29 (dd, *J* = 1.0, 2.0 Hz, 1 H), 6.26–6.27 (dd, *J* = 2.0, 3.5 Hz, 1 H), 6.00–6.01 (dq, *J* = 1.0, 3.0 Hz, 1 H), 4.82–4.86 (dd, J = 6.0, 13.0 Hz, 1 H), 4.20–4.25 (qd, *J* = 1.0, 7.0 Hz, 2 H), 2.51–2.65 (m, 4 H), 1.95–2.07 (m, 2 H), 1.60–1.82 (m, 4 H), 1.48–1.52 (m, 2 H), 1.25–1.28 (t, *J* = 7.0 Hz, 3

H). Select shifts for minor isomer: δ 7.29–7.30 (dd, J = 1.0, 2.0 Hz, 1 H), 5.99–6.00 (dq, J = 1.0, 3.0 Hz, 1 H), 4.52–4.54 (m, 1 H), 4.10–4.16 (m, 1 H); the remainder of the peaks overlap with those for the major isomer; ^{13}C NMR (400 MHz, $CDCl_3$): δ 198.5, 171.6, 155.6, 141.0, 110.3, 105.3, 62.0, 61.9, 55.6, 40.1, 36.6, 35.3, 28.3, 23.9, 23.1, 14.4; Calc'd [M + Na] 379.0515, Found 381.0508

O
O
Br
EtO2C
ppm
ppm
4.2
ppm
2.6
ppm
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm
1.104
1.000
0.134
1.139
0.118
2.544
0.147
5.343
0.273
2.276
5.309
2.591
4.107

79

Hex-5-enoic acid.[38] A 500-mL, round-bottomed flask equipped with a glass stopper was charged with periodic acid (24.8 g, 108.8 mmol, 2.7 equiv), chromium trioxide (0.048 g, 0.48 mmol, 0.12 equiv), 1.5 mL of H_2O, and 198 mL of MeCN and the resulting solution was stirred at rt for 2.5 h. A 1-L, three-necked, round-bottomed flask equipped with an argon inlet adapter, rubber septum fitted with a thermocouple probe, and a 250-mL addition funnel was charged with of a solution of hexenol (4.80 mL, 4.0 g, 1.0 equiv) in 1.3 mL H_2O and 169 mL of MeCN and the resulting solution was cooled to 0 °C. The solution of oxidizing agent was transferred to the addition funnel and added to the hexenol solution dropwise over 2 h so that the internal temperature of the reaction mixture remained below 5 °C. The resulting solution was stirred for 1 h at 0 °C and then diluted with 300 mL of satd $NaHPO_4$ solution. The aqueous phase was separated and extracted with three 50-mL portions of toluene and the combined organic layers were washed with 100 mL of a half-satd NaCl solution, 100 mL of satd $NaHSO_4$ solution, and 100 mL of brine, dried over $MgSO_4$, filtered, and concentrated to yield 3.93 g (86%) of acid **79** as a colorless oil. Spectral data was identical to that reported previously.[39]

[38] This procedure is based on the method developed by Zhao, M.; Li, J.; Song, Z.; Desmond, R.; Tschaen, D. M.; Grabowski, E. J.; Reider, P. J. *Tetrahedron Lett.* **1998**, *39*, 5323

[39] Hwu, J. R.; Shiao, S.; Tsay, S. *J. Am. Chem. Soc.* **2000**, *122*, 5899

2-(3-(Furan-2-yl)propyl)hex-5-enoic acid. A 100-mL, 2-necked, round-bottomed flask equipped with an argon inlet adapter and rubber septum was charged with diisopropylamine (2.72 mL, 1.950 g, 19.27 mmol, 2.2 equiv) and 30 mL of THF. The solution was cooled at 0 °C while 7.3 mL of *n*-BuLi solution (2.53 M in hexanes, 18.5 mmol, 2.1 equiv) was added dropwise over 10 min. The resulting solution was then cooled at -78 °C while a solution of carboxylic acid **79** (1.00 g, 8.76 mmol, 1.0 equiv) in 2.5 mL of THF was added over 5 min. The solution was stirred for 30 min and then stirred at 0 °C for 30 min. The reaction mixture was recooled to -78 °C and a solution of 2-(3-iodopropyl)furan (2.14 g, 9.07 mmol, 1.03 equiv) in 2.5 mL of THF was added via syringe over 5 min and the reaction mixture was allowed to warm to rt and stirred for 18 h. Satd aq NH_4Cl solution was added and the aqueous phase was separated and extracted with 10 mL of Et_2O and then acidified to pH 1-2 with 20 mL of 2 N HCl. The aqueous phase was extracted with three 10-mL portions of Et_2O, and the combined organic layers were washed with 50 mL of brine, dried over $MgSO_4$, filtered, and concentrated to yield 2.10 g of deep orange-red oil. Column chromatography on 50 g of silica gel (elution with 10–20% EtOAc-hexanes) gave 1.27 g (65%) of acid **80** as a tan oil: FT-IR (film) 2939 (br), 2361, 2339, 1700, 1641, 1597, 1507, 1457 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 12.15 (br s, 1 H), 7.30–7.31 (dd, J = 1.0, 2.0 Hz, 1 H), 6.28–6.29 (dd, J= 2.0, 3.0 Hz, 1 H), 6.00 (m, 1 H), 5.75–5.83 (ddt, J = 6.5, 10.5, 17.5 Hz, 1 H) 5.02–5.07 (dq, J = 1.5, 17.0 Hz, 1 H), 4.98–4.99 (m, 1 H), 2.65–2.58 (t, J = 7.0 Hz, 2 H), 2.42–2.46 (m, 1 H), 2.09–2.15 (m, 2 H), 1.55–1.80 (m, 6 H); ^{13}C NMR (500

MHz, $CDCl_3$) δ 183.1, 155.8, 141.0, 137.8, 115.5, 110.3, 105.1, 44.8, 31.6, 31.3, 28.0, 25.9; Calc'd [M – H]: 221.1183, Found: 221.1184

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ppm
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ppm
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10
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6
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ppm
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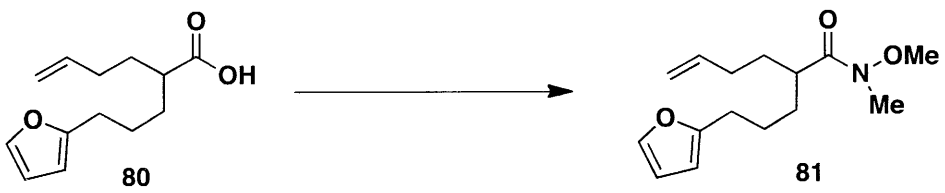
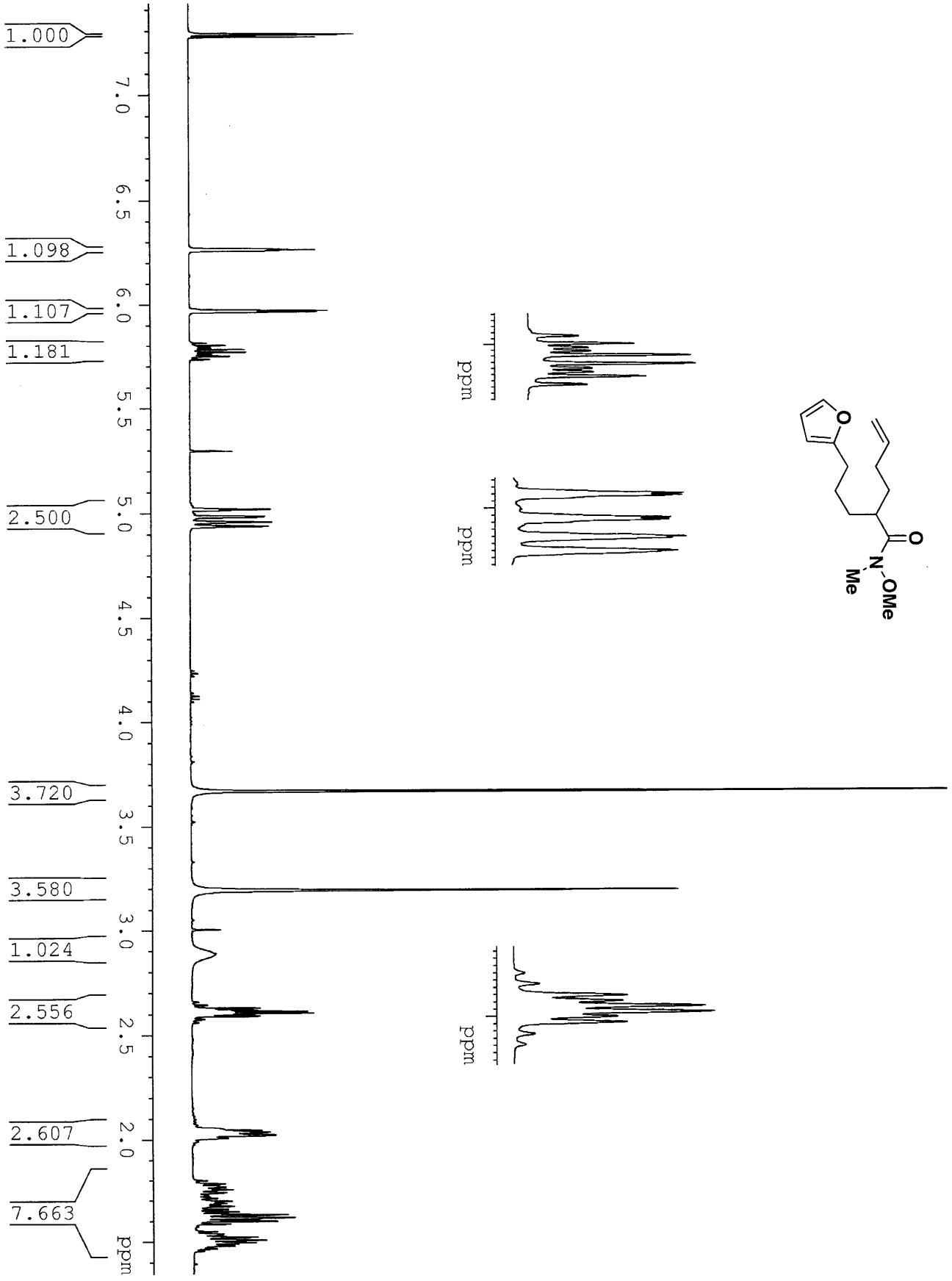


2-(3-(Furan-2-yl)propyl)-N-methoxy-N-methylhex-5-enamide. A 250-mL, round-bottomed flask equipped with an argon inlet adapter and rubber septum was charged with 40 mL of THF and acid **80** (1.0 g, 4.49 mmol, 1.0 equiv). The solution was cooled at 0 °C while triethylamine (1.88 mL, 1.36 g, 13.46 mmol, 3.0 equiv) and methanesulfonyl chloride (0.38 mL, 0.566 g, 4.94 mmol, 1.1 equiv) were each added in one portion. After 10 min, N,O-dimethylhydroxylamine (0.50 mL, 0.441 g, 3.73 mmol, 1.5 equiv) was added and the resulting solution was stirred for 1 h at 0 °C before being diluted with 50 mL of H_2O. The aqueous phase was separated and extracted with three 20-mL portions of Et_2O and the combined organic layers were washed with 50 mL of brine, dried over $MgSO_4$, filtered, and concentrated to yield 1.15 g of yellow oil. Column chromatography on 32 g of silica gel (elution with 20% EtOAc-hexanes) provided 1.00 g (92%) of **81** as a yellow oil: FT-IR (film) 3077, 2937, 2361, 1661, 1596, 1507, 1459, 1416, 1387, 1351 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.28–7.29 (dd, J = 1.0 Hz, 1 H), 6.23–6.26 (m, 1 H), 5.96–5.97 (m, 1 H), 5.73-5.81 (ddt, J = 6.5, 10.0, 17.0 Hz, 1 H), 4.94–5.02 (m, 2 H), 3.67 (s, 3 H), 3.19, (s, 3 H), 2.82–2.93 (br s, 1 H), 2.59–2.63 (m, 2 H), 2.02–2.05 (m, 2 H), 1.46–1.81 (m, 7 H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 177.4, 156.1, 140.9, 138.5, 115.0, 110.2, 105.0, 61.6, 40.1, 32.2, 31.9, 31.8, 28.2, 26.2.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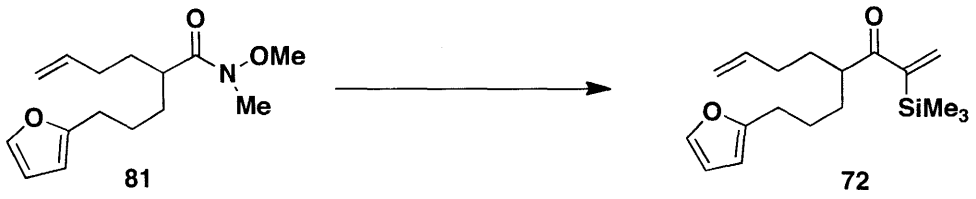
Me



4-(3-(Furan-2-yl)propyl)-2-(trimethylsilyl)octa-1,7-dien-3-one. A 25-mL, two-necked, round-bottomed flask equipped with an argon inlet adapter and rubber septum was charged with 4 mL of Et_2O and (1-bromovinyl)trimethylsilane (0.44 mL, 0.505 g, 2.82 mmol, 1.5 equiv) and cooled at -78 °C while 3.8 mL of *t*-BuLi solution (1.50 M in pentane, 5.64 mmol, 3.0 equiv) was added dropwise over 10 min. After 30 min, the resulting solution was stirred at 0 °C for 30 min and then cooled to -78 °C. A 10-mL pear flask equipped with a rubber septum was charged with amide **81** (0.500 g, 1.88 mmol, 1.0 equiv) and 1 mL of Et_2O and cooled at -78 °C. The vinyllithium solution was then added dropwise to the amide solution via cannula over 10 min. After 3 h, the solution was allowed to warm to 0 °C over 15 min and then diluted with 50 mL of satd NH_4Cl solution. The aqueous phase was separated and extracted with two 20-mL portions of Et_2O, and the combined organic layers were washed with 20 mL of H_2O and 20 mL of brine, dried over $MgSO_4$, filtered, and concentrated to yield 0.611 g of orange oil. Column chromatography on 80 g of silica gel (elution with 30% benzene-hexanes) provided 0.370 g (65%) of **72** as a light tan oil: FT-IR (film) 3076, 2950, 2858, 2361, 2338, 1661, 1507, 1247, 1147 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.28–7.29 (dd, J = 1.0, 1.8 Hz, 1 H), 6.45–6.46 (d, J = 2.0 Hz, 1 H), 6.26–6.27 (dd, J = 2.0, 3.0 Hz, 1 H), 6.14 (d, J = 1.5 Hz, 1 H), 5.96 (m, 1 H), 5.71–5.79 (ddt, J = 6.5, 10.5, 17.5 Hz, 1 H), 4.94–5.00 (m, 2 H), 3.12–3.17 (tt, J = 5.5, 8.0, 1 H), 2.57–2.61 (m, 2 H), 1.90–2.04 (m, 2 H), 1.53–1.59 (app quin, J = 7.5 Hz, 2 H), 1.40–1.50 (m, 2

H), 0.16 (s, 9 H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 210.0, 156.0, 154.9, 141.0, 138.4, 135.6, 115.3, 110.3, 105.1, 45.0, 31.8, 31.7, 28.3, 26.1, -1.0; Calc'd [M + H]: 305.1931, Found: 305.1937

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O
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ppm
ppm
ppm
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ppm
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5.0
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4.0
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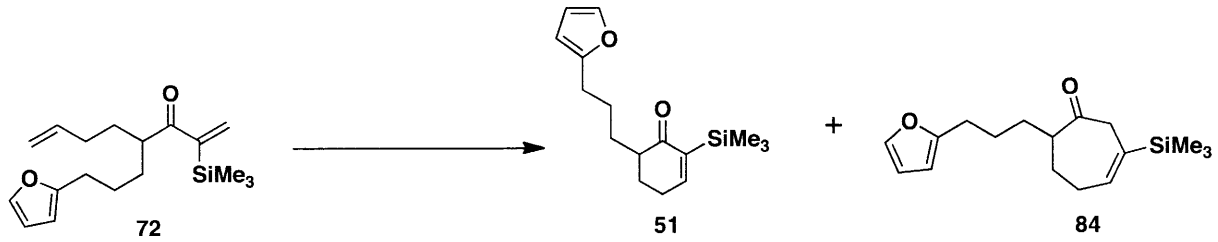

6-(3-(Furan-2-yl)propyl)-2-(trimethylsilyl)cyclohex-2-enone, 7-(3-(furan-2-yl)propyl)-3-(trimethylsilyl)cyclohept-3-enone. A 250-mL, two-necked, round-bottomed flask equipped with an argon inlet adapter and rubber septum was charged with 82 mL of CH_2Cl_2 and enone **72** (0.250 g, 0.82 mmol, 1.0 equiv). The rubber septum was replaced with a glass stopper and Hoveyda-Grubbs 2nd generation catalyst (0.099 g, 0.16 mmol, 0.3 equiv) was added. Additional portions of catalyst (each 0.099 g, 0.16 mmol, 0.3 equiv) were added after 3 h and again after 12 h. The resulting mixture was further stirred for 30 h and then concentrated to yield 0.543 g of a black solid. Column chromatography on 55 g of silica gel (elution with 25–100% CH_2Cl_2-hexanes) provided 0.110 g (49%) of **51** as a yellow oil and 0.097 g (41%) of **84** as a pale tan oil. Compound **51**: FT-IR (film) 2950, 1661, 1596, 1507, 1453, 1423, 1339, 1245, 1154 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29–7.30 (dd, J = 1.0, 2.0 Hz, 1 H), 7.08–7.09 (ddd, J = 1.0, 3.0, 5.5 Hz, 1 H), 6.27–6.28 (dd, J = 2.0, 3.5 Hz, 1 H), 5.99–6.00 (m, 1 H), 2.60–2.70 (m, 2 H), 2.32–2.46 (m, 2 H), 2.23–2.91 (m, 1 H), 2.07–2.12 (dq, J = 5.0, 12.5, 1 H), 1.85–1.92 (ddt, J = 5.5, 11, 24.5 Hz, 1 H), 1.62–1.78 (m, 3 H), 1.35–1.42 (m, 1 H), 0.13 (s, 9 H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 204.8, 157.2, 156.3, 141.6, 140.9, 110.3, 105.0, 46.8, 29.1, 28.4, 28.1, 27.1, 25.8, -1.1; Calc'd [M + H]: 277.1618, Found: 277.3115. Compound **84**: FT-IR (film) 2950, 2862, 1670, 1507, 1367, 1246, 1148 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29–7.30 (dd, J = 1.0, 2.0 Hz, 1 H), 6.46–6.48 (ddd, J = 1.0, 4.0, 4.5 Hz, 1 H), 6.27–6.28 (dd, J = 2.0, 3.5 Hz, 1 H), 5.99–6.00 (m, 1 H), 2.63–2.67 (m, 2 H), 2.29–2.36 (m, 2 H), 2.04–2.09 (dq, J = 5.0, 13 Hz, 1 H), 1.82–1.89

(ddt, J = 5.5, 10.5, 13.5 Hz, 1 H), 1.62–1.77 (m, 6 H), 1.40–1.48 (m, 1 H), 0.08 (s, 9 H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 201.5, 156.4, 141.3, 141.0, 137.6, 110.3, 105.0, 46.8, 29.4, 28.6, 28.4, 25.9, 25.3, 19.5, -1.2; Calc'd [M + Na]: 313.1594, Found: 313.1606

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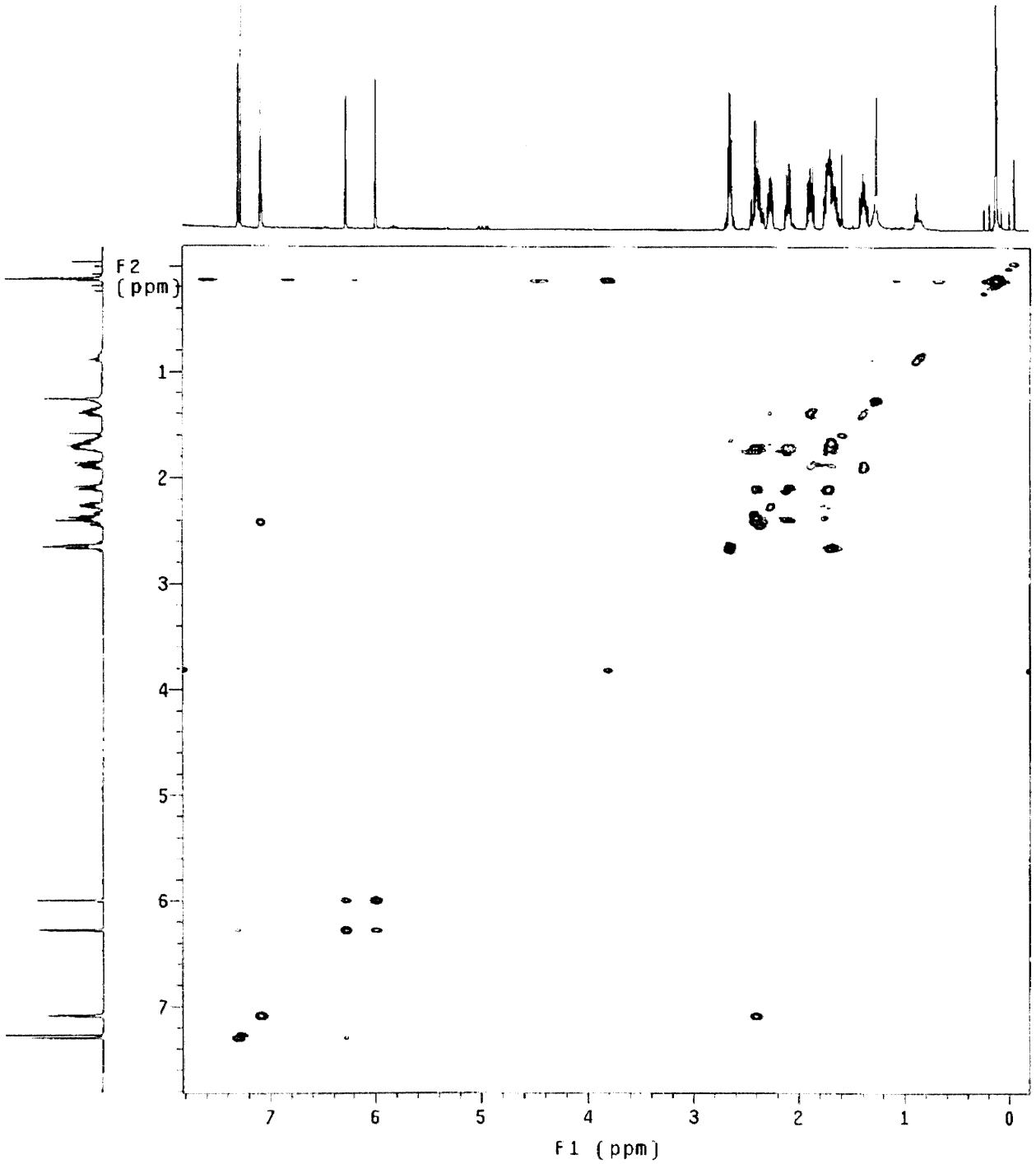
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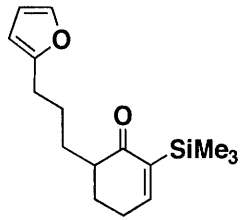
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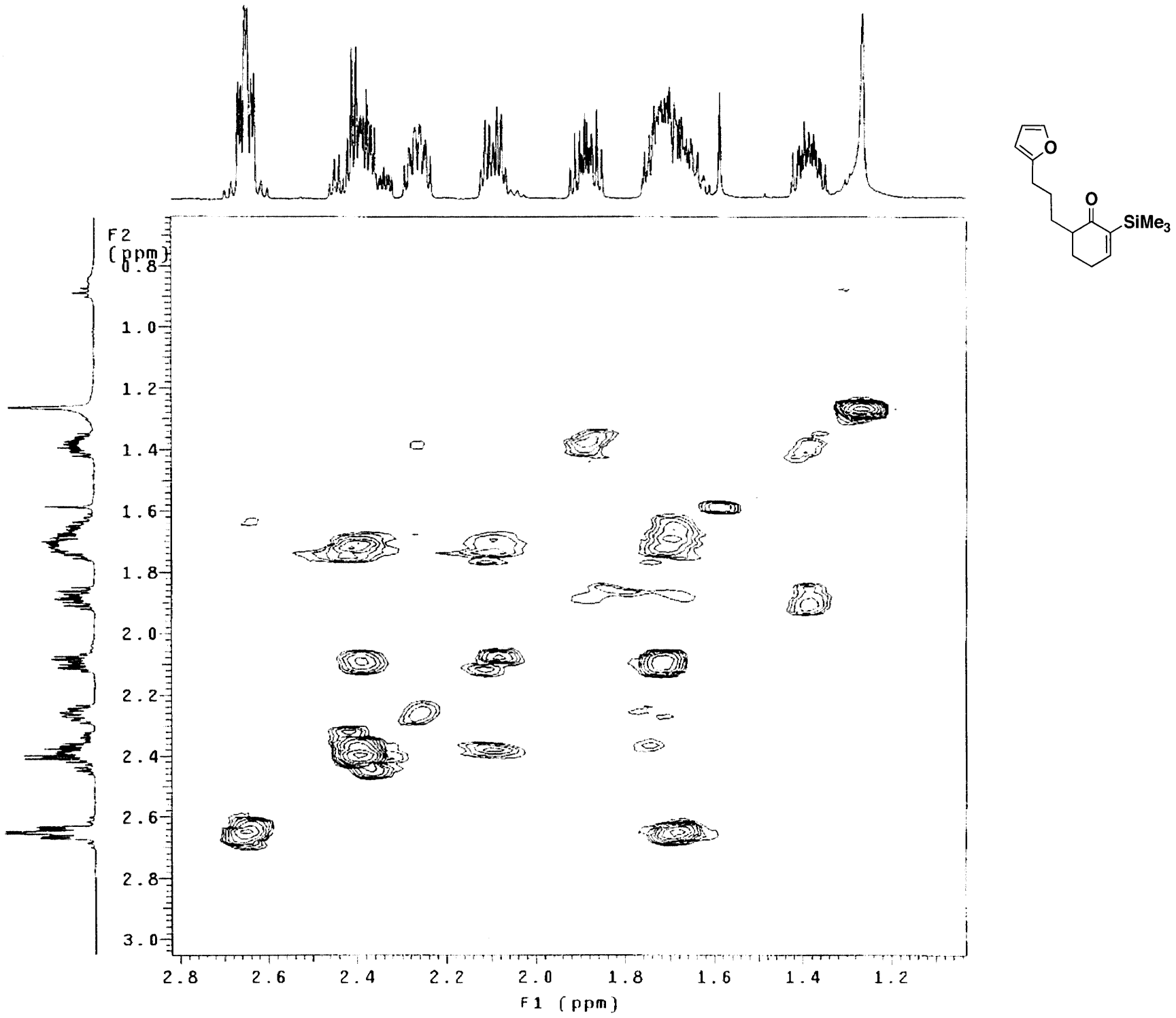
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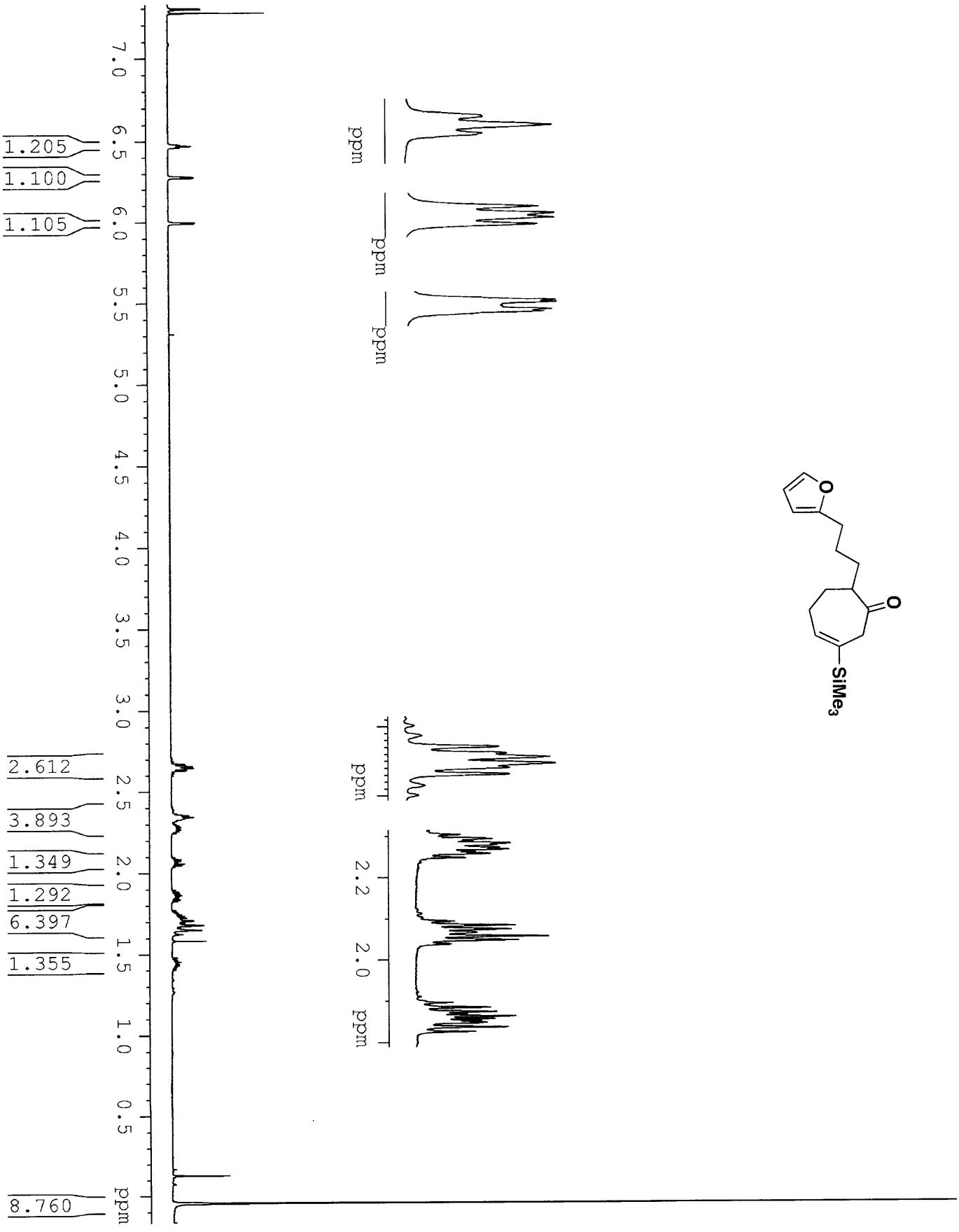
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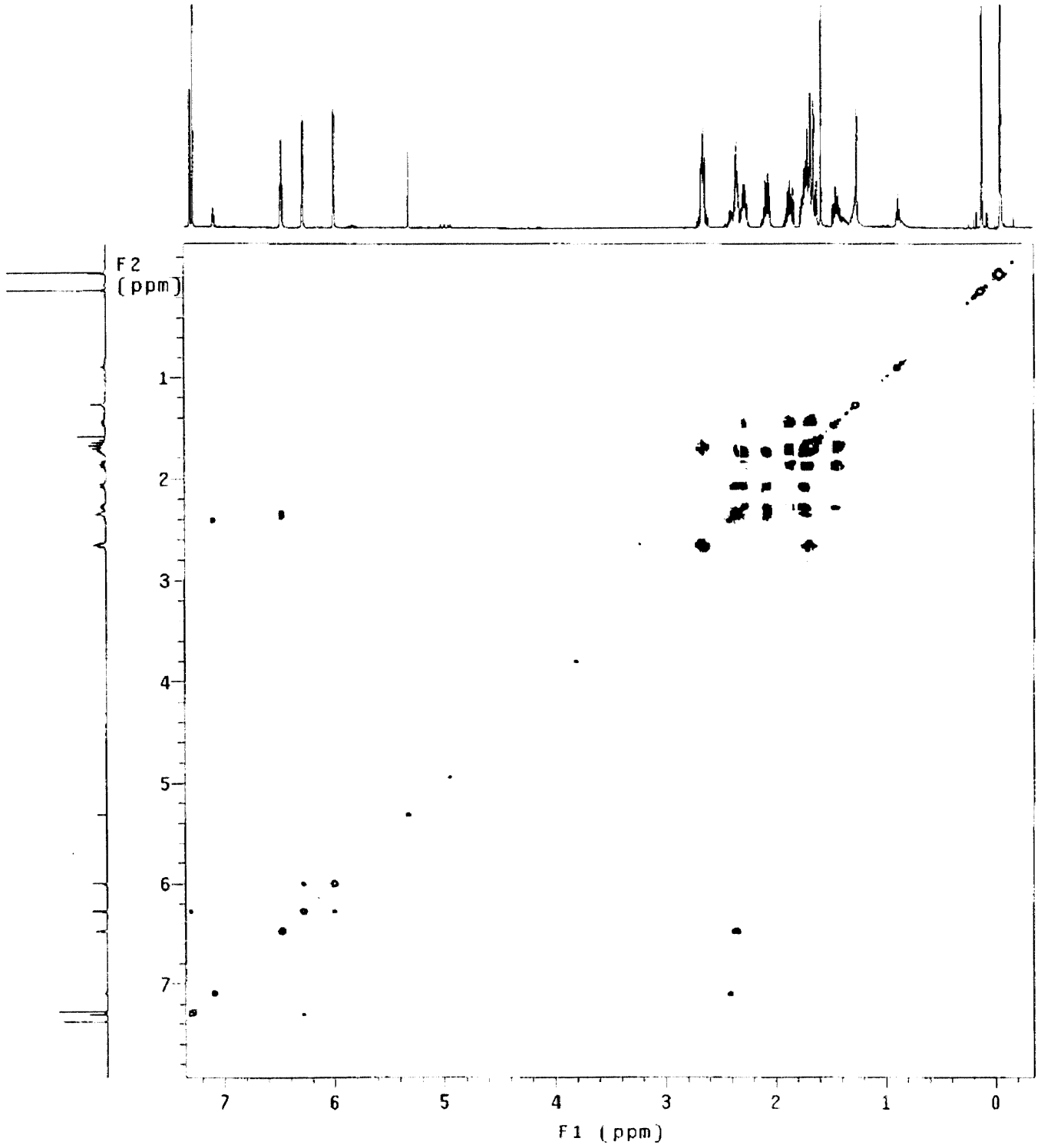
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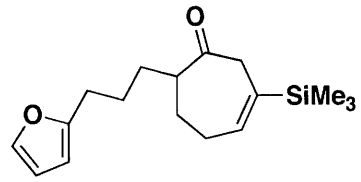
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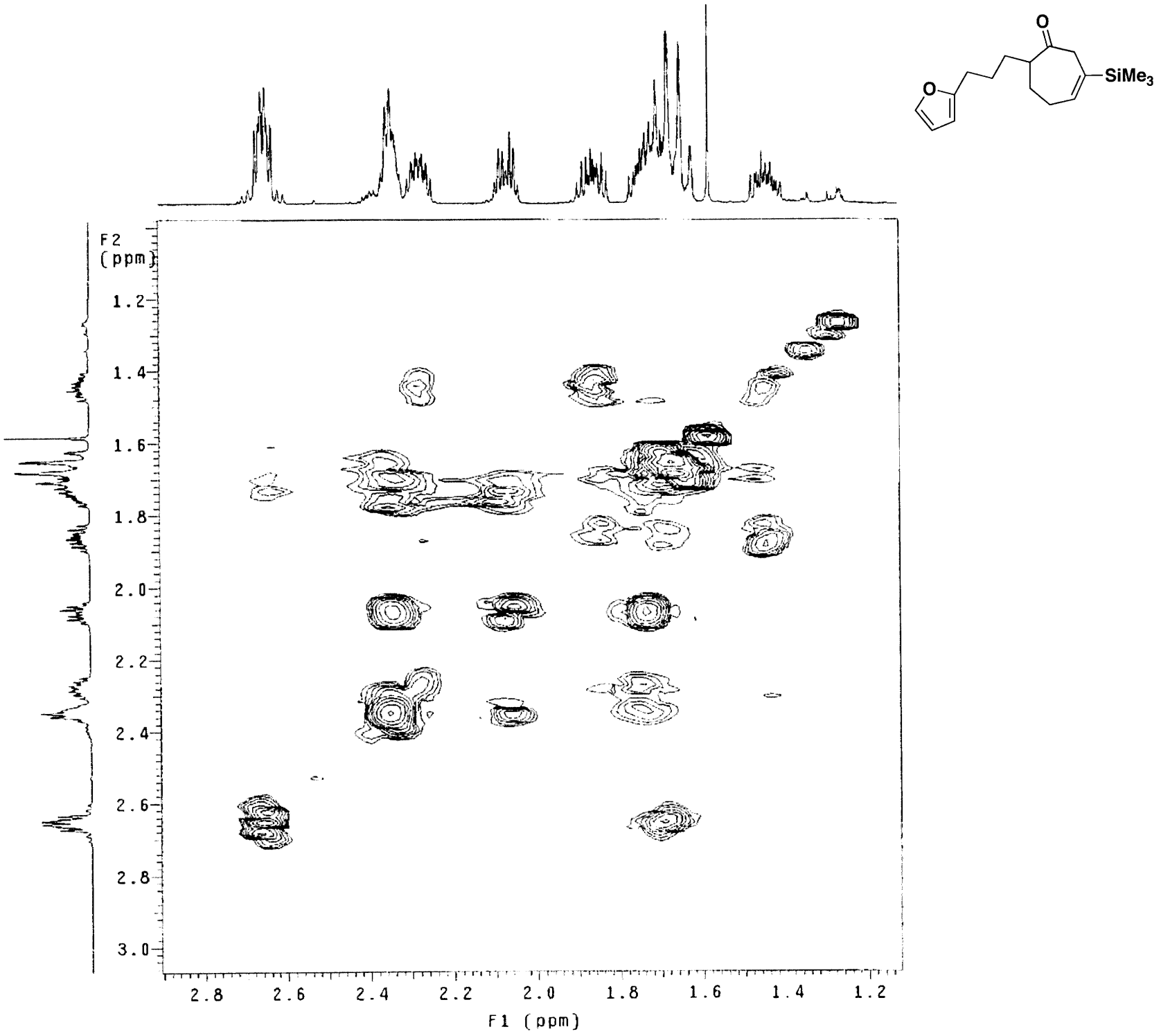
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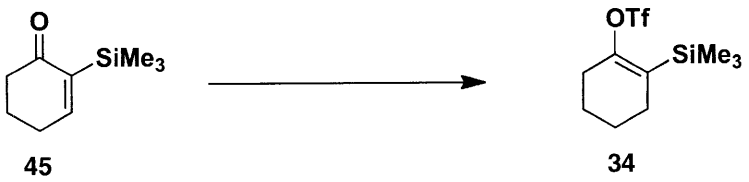

45 34

2-(Trimethylsilyl)cyclohex-1-en-1-yl trifluoromethanesulfonate. A 25-mL, two-necked, round-bottomed flask equipped with an argon inlet adapter and rubber septum was charged with enone **45** (0.132 g, 0.78 mmol, 1.0 equiv) and 1.5 mL of THF and then cooled at -78 °C while L-Selectride solution (1.0 M in THF, 0.86 mL, 0.86 mmol, 1.1 equiv) was added over 4 min. The reaction mixture was stirred for 1 h and then a solution of Comins reagent (0.339 g, 0.86 mmol, 1.1 equiv) in 1.5 mL of THF was added via cannula over 5 min. The resulting solution was allowed to warm to rt over 18 h and then diluted with 5 mL of H_2O and 5 mL of pentane. The aqueous phase was separated and extracted with three 10-mL portions of pentane, and the combined organic layers were washed with two 10-mL portions of 10% NaOH solution and 10 mL of brine, dried over $MgSO_4$, filtered, and concentrated to yield 0.367 g of a tan oil. Chromatography on 8 g of silica gel (elution with 3% EtOAc-hexanes) provided 0.200 g (78%) of triflate **34** as a colorless oil (90% purity by ^{1}H NMR analysis): FT-IR (film) 3077, 2937, 2860, 2662, 1596, 1507, 1459, 1416, 1387, 1351 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.38–2.41 (m, 2 H), 2.18–2.21 (m, 2 H), 1.73–1.78 (tq, J = 3.5, 6.0 Hz, 2 H), 1.55–1.60 (tq, J = 3.5, 6.0 Hz, 2 H), 0.193 (s, 9 H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 154.8, 128.2, 113.8–123.3 (q, J = 317 Hz), 28.5, 23.3, 22.0, -1.0; HRMS pending

OTf
SiMe3

ppm
ppm
ppm
ppm
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5.0
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4.0
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3.0
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ppm
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1.980
2.034
7.215

34 86

1,4,5,6,7,8-Hexahydro-1,4-epoxynaphthalene. A 100-mL, two-necked, round-bottomed flask equipped with an argon inlet adapter and rubber septum was charged with 17 mL of furan and with triflate **34** (0.05 g, ca 90% purity by ^{1}H NMR analysis, 0.17 mmol, 1.0 equiv). A slurry of BHT (0.56 g, 0.25 mmol, 1.5 equiv) and TBAT (0.178 g, 0.33 mmol, 2.0 equiv) in 3 mL of furan was added via cannula over ca. 2 min and the resulting mixture was stirred at rt for 5 h. A second portion of TBAT (0.07 g, 0.13 mmol, 0.8 equiv) was then added and the reaction mixture was stirred at rt for 18 h and then concentrated to yield 0.039 g of red-tan solid. Column chromatography on 10 g of acetone-deactivated silica gel (elution with 3% EtOAc-hexanes) provided 0.024 g (100%) **86** (ca 75–90% purity by ^{1}H NMR estimate) as a tan oil: FT-IR unavailable; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.09 (s, 2 H), 5.14 (s, 2 H), 2.35–2.39 (m, 2 H), 1.82–1.86 (m, 2 H), 1.64–1.67 (m, 2 H), 1.47–1.49 (m, 2 H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 149.2, 143.9, 85.7, 24.4, 23.2; Calc'd [M + H]: 149.0961, Found: 149.0962

7.0
6.5
6.0
5.5
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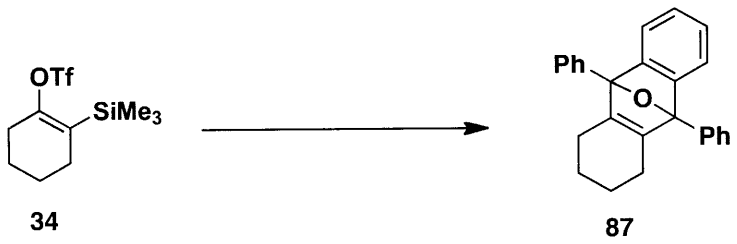

34 87

5,8-Diphenyl-1,2,3,4,9,10-hexahydro-9,10-epoxyanthracene. A 10-mL, two-necked, pear-shaped flask equipped with an argon inlet adapter and rubber septum was charged with triflate **34** (0.066 g, 0.22 mmol, 1.0 equiv), DPIBF (0.088 g, 0.32 mmol, 1.5 equiv), and 1.2 mL of THF. A solution of TBAT (0.173 g, 0.32 mmol, 1.5 equiv) in 1.0 mL of THF was added over 5 min via cannula and the resulting solution was stirred for 18 h and then diluted with 1 mL of EtOAc and 1 mL of Et_2O and cooled at 5 °C. The resulting solution was cooled to 5 °C and after 2 h the crystals of excess TBAT that appeared were separated via vacuum filtration. The filtrate was concentrated to yield 0.076 g of bright yellow oil. Column chromatography on 10 g of silica gel (elution with 0–1% EtOAc-hexanes) afforded 0.019 g (32%) of **87** as a white solid. Spectral data was identical to that reported previously.[40]

[40] Mishimura, T.; Kawamoto, T.; Sasaki, K. Tsurumaki, E.; Hayashi, T. *J. Am. Chem. Soc.* **2007**, *129*, 1492

CYNTHIA K. CROSSWHITE

cynthia.crosswhite@gmail.com
19 Hardwick St. Fl. 2
Cambridge, MA 02141

EDUCATION

Sept. 2007–present **Massachusetts Institute of Technology**, Cambridge, MA
GPA: 4.00/5.00. Master of Science Degree in Organic Chemistry, Expected Feb. 2010

Sept. 2003–June 2007 **Wellesley College**, Wellesley, MA
GPA: 3.71/4.00. Majors: Chemistry and French. *Awards: Magna cum laude*, Honors Degree in Chemistry, Merck Index Women in Chemistry Scholarship Award of Special Recognition, Hypercube Award for Scholastic Excellence in Chemistry, Award for Achievement in Organic Chemistry, First-Year Distinction. *Honors Societies:* Phi Beta Kappa, Sigma Xi

Jan.–June 2006 **Université de Provence: Aix-Marseille I**, Aix-en-Provence, France
Participated in the Wellesley-in-Aix study abroad program. Studies included modern and ancient French literature and French language. All classes taught in French.

RESEARCH EXPERIENCE

Sept. 2007–present **Massachusetts Institute of Technology**, Cambridge, MA
Graduate Research Student, Advisor Rick Danheiser. Worked towards synthesizing cyclohexyne precursors to study the inter- and intramolecular [4 + 2] cycloadditions of cyclohexyne derivatives.

June–August 2007 **Novartis Institutes for Biomedical Research**, Cambridge, MA
Summer Research Student, Metabonomics Division, Advisor: John Gounarides. Worked to optimize simple purification techniques to separate classes of metabolites for quantitative ^{1}H NMR studies.

June 2006–June 2007 **Wellesley College Science Center Research Program**, Wellesley, MA
Undergraduate Research Student, Advisor Julia Miwa. Synthesized 20-residue peptide fragments of the protein ∝-synuclein. Purified by HPLC and characterized by MALDI-TOF MS. Project continued during the academic year as a senior honors thesis.

Spring, Fall 2005 **Chemistry 350 Independent Research Project,** Wellesley, MA
Undergraduate Research Student, Advisor Julia Miwa. Prepared a 12-residue hairpin peptide with a thio-modified tyrosine group. Purified by HPLC.

Summers 2004, 2005 **National Institutes of Health, NIDDK**, Rockville, MD
Undergraduate Research Student, Laboratory of Medicinal Chemistry.
Synthesized analogs of GBR 12909. Prepared synthesized compounds for analytical and biological testing.

Summer 2001 **Naval Research Labs, SEAP Internship Program**, Anacostia, VA
Lab Assistant, Metallurgy Department. Prepared samples of nickel-based metal alloys for future experimentation. Collected data from SEM on prepared samples.

WORK EXPERIENCE

Fall 2004–June 2007 **Wellesley College Campus Police,** Wellesley, MA
Student Supervisor, Fall 2004–June 2007. Created student employee schedule each semester. Trained and supervised campus police student employees. Additional work for campus police as Science Center monitor (2004–2007) and escort van driver (2003–2004).

Spring 2004–June 2007 **Wellesley College Theater,** Wellesley, MA
Theater Assistant, Spring 2004–June 2007. Worked collectively to construct sets for theater productions. Maintained and prepared theater stage, lighting, and sound equipment for college events.

ACTIVITIES AND SKILLS

Spring 2009–present **ChemREFS program.** Served as an intradepartmental mediator and confidential resource for graduate students and postdocs in the MIT Chemistry department.

Spring 2008–present **Group Safety Officer**. Responsible for maintaining a safe lab environment, performing weekly lab inspections, and serving as a resource for safety information.

Skills: Proficient in French; Trained in mediation.