THE SYNTHESIS AND BENZANNULATION REACTIONS OF (TRIALKYLSILYL)VINYLKETENES

by

Wesley F. Austin
B.S., Chemistry
University of California at Berkeley, 2002

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

DOCTOR OF PHILOSOPHY

at the

MASSACHUSETTS INSTITUTE OF TECHNOLOGY
[February 2008]
December 2007

Signature of Author.....
Department of Chemistry
December 18th, 2007

Certified by.....
Rick L. Danheiser
Thesis Supervisor

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

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

Professor Timothy M. Swager.....
Chairman

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

Professor Mohammad Movassaghi.....

Acknowledgements

I would not have been able to complete the work in this thesis without the support of a great many people. I would first like to thank my advisor, Rick Danheiser, for his guidance and commitment to my development. I greatly appreciate the time and effort he has spent for my benefit, and I have learned a great deal from him by working under his direction.

I am also grateful to Professors Tim Swager and Mo Movassaghi, the members of my thesis committee, for their comments and constructive feedback on this thesis, as well as for their assistance and advice during my time at MIT.

I would also like to thank the other members of the Danheiser lab, both past and present, for making this lab an enjoyable place to work. First and foremost are the other members of team TAS-vinylketene, Chris Davie and Yongjun Zhang. Chris is a good friend and has been an invaluable resource, and it was a pleasure to collaborate with him and Yongjun. I also must make particular mention of Martin Hayes for all of his assistance during my first year here. Aimee Crombie, Graham Wright, and Javier Horta have all been excellent colleagues to work with and easy to approach for advice. Josh Dunetz and Charnsak "Touch" Thongsornkleeb were also excellent to work with, and provided hours of endless entertainment.

The current group members are also a wonderful collection of people, and I wish them the best in the future. Kevin Maloney, Xiao Yin Mak, Shaun Fontaine and Julia Robinson have been very helpful to bounce ideas off (and fun to have a beer with) and I will miss seeing them every day. I'll also miss Jenny Fong and her sense of humor and inspiring work ethic. I owe many thanks to Tammy Lam for her help proofreading this thesis and other papers.

Throughout these five years, sports have been instrumental in preserving my sanity, and Kevin deserves mention for his part in arranging most of the teams. I'll miss playing softball with Toxic Waste on summer afternoons (and at NERC). I'd also like to thank the regular players at noon ball, especially PJ, John Naber, Victor Gehling and others. I greatly appreciate Matt Hill for organizing both beach volleyball and court volleyball.

Lastly, I'd like to thank my parents and my wife, without whose unending love and support I never would have graduated.

To my wife Tanya, and to my parents

For their love and support

The Synthesis and Benzannulation Reactions of (Trialkylsilylvinyl)ketenes

By

Wesley F. Austin

Submitted to the Department of Chemistry
on December 13th, 2007 in partial fulfillment of the
requirements for the Degree of Doctor of Philosophy

ABSTRACT

(Trialkylsilyl)vinylketenes ("TAS-vinylketenes") are versatile four-carbon building blocks in a variety of methods for the synthesis of carbocyclic and heterocyclic compounds. This thesis discusses the development of a new benzannulation strategy for the synthesis of phenols based on the reaction of TAS-vinylketenes with lithium ynolates. Studies have shown that the reaction proceeds by formation and electrocyclic ring closure of 3-oxidodienylketene intermediates, followed by an intramolecular 1,3-silyl migration to provide highly substituted 3-siloxy phenols. Further transformations of these products providing efficient access to ortho-benzoquinones and benzofuran, benzoxepine, and benzoxocine ring systems are described. Additionally, unsuccessful attempts to prepare TAS-vinylketenes by the rearrangement of siloxy alkynes and by cross-metathesis are discussed.

Thesis Supervisor: Rick L. Danheiser

Title: Professor of Chemistry

TABLE OF CONTENTS

Part III – New Approaches to the Synthesis of TAS-Vinylketenes

Part IV – Experimental Procedures

Part I

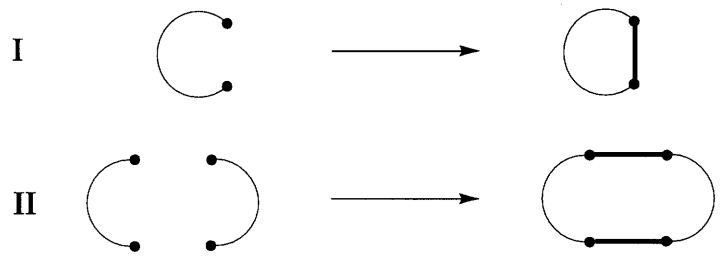
Introduction and Background

Chapter 1

Introduction

The structures of a vast number of natural products and biologically active compounds contain a cyclic system. As a result, it is of no surprise that the development of efficient and effective methods for ring formation is one of the fundamental pursuits of organic chemistry. From a retrosynthetic perspective, strategic approaches to ring systems can be divided into two categories. The more straightforward of the two classes involve cyclization strategies, in which an appropriately substituted molecule reacts intramolecularly with the formation of a single new bond; a generalized example is depicted in Figure 1 (I). While this approach has the advantage of simplicity, it is limited by the fact it is not convergent, and requires starting materials of similar complexity to the desired cyclic compound.

Figure 1. Cyclization and Annulation



In contrast to cyclization, annulation strategies involve the creation of rings by the formation of two new bonds via well-defined methods. These transformations may take place in a single pot, such as cycloadditions, or in multiple reactions, such as the Robinson annulation. Annulation methods are extremely powerful tools for the synthetic chemist, allowing for rapid

assembly of complex cyclic or, in the case of intramolecular annulations, polycyclic compounds in a highly convergent process from substantially less synthetically challenging precursors.

Much of the research conducted in the Danheiser laboratories has centered around the investigation of annulations that provide access to synthetically important ring systems. As a result of these studies, a number of new annulation strategies have been discovered. These transformations generally involve the reaction of an alkene or alkyne with highly unsaturated building blocks such as enynes, allenes, and vinylketenes.

Vinylketenes in particular have been useful as intermediates in annulations due to their readily differentiated polyfunctionality, and investigations into their chemistry have yielded a number of annulations leading to widely varied products. The ketene moiety dominates the reactivity of vinylketenes and, much like other ketenes, vinylketenes participate in [2 + 2] cycloadditions. Alkenes, alkynes, ketones, and imines are all viable partners for these cycloadditions, providing ready access to cyclobutanones, cyclobutenones, β-lactones, and β-lactams, all bearing a vinyl substituent as a very useful handle for further transformations. Previous research in our laboratory has exploited this fact in the development of cascade reactions leading to six- and eight-membered carbocycles, several of which are shown in Scheme 1.

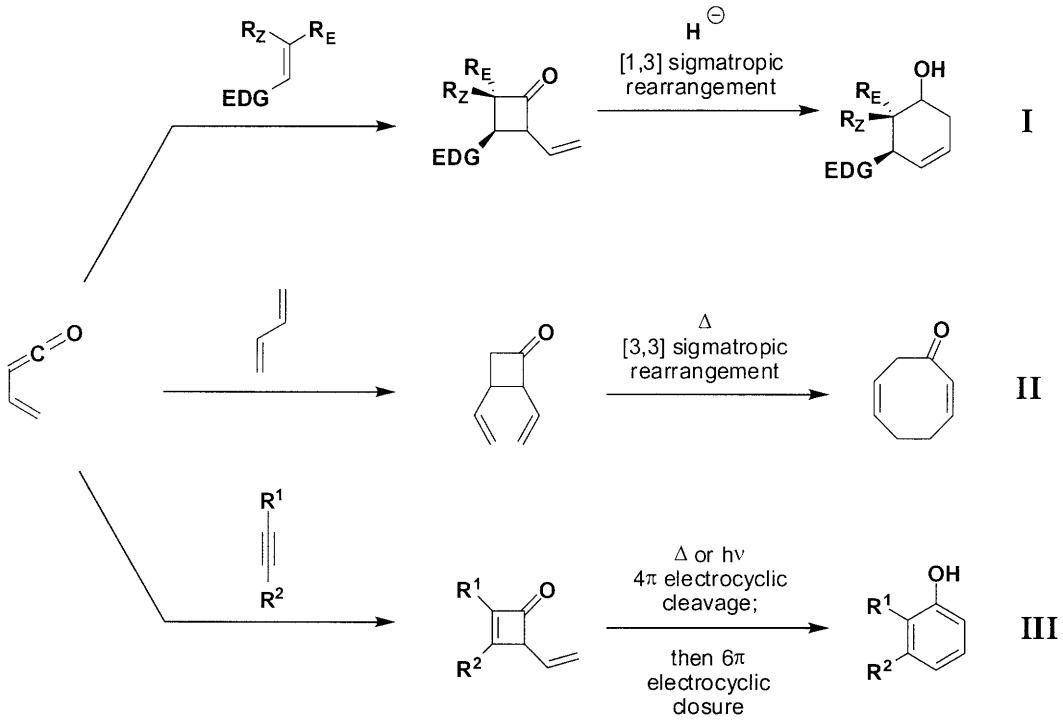
For example, in the annulation leading to cyclohexenols (Scheme 1, I), an electron-rich alkene traps an *in situ* generated vinylketene in a [2 + 2] cycloaddition to form a 2-vinylcyclobutanone. Hydride reduction of the ketone followed by [1,3] sigmatropic rearrangement then provides 3-cyclohexenols.[1] Alternatively, trapping of the vinylketene with a

[1] Danheiser, R. L; Martinez-Davila, C.; Sard, H. *Tetrahedron* **1981**, *37*, 3943.

1,3-diene (Scheme 1, II) affords a 2,3-divinylcyclobutanone, which upon heating undergoes a [3,3] sigmatropic rearrangement to provide a 2,6-cyclooctadienone.[2]

In the most extensively examined of the annulations, reaction of vinylketenes with electron-rich alkynes produces phenols following a series of pericyclic reactions (Scheme 1, III).[3] The vinylketenes involved are generated *in situ* by ring opening of cyclobutenones[4] or by photochemical Wolff rearrangement of α′-diazo-α,β-unsaturated ketones.[5] The preference of vinylketenes for [2 + 2] cycloaddition continues to dominate, affording 4-vinylcyclobutenones upon reaction with the alkyne. Under continued heating or irradiation, this intermediate undergoes ring opening to give a dienylketene, and subsequent 6π electrocyclic ring closure and

Scheme 1. Annulation Reactions of Vinylketenes



[2] Danheiser, R. L.; Gee, S. K.; Sard, H. *J. Am. Chem. Soc.* **1982**, *104*, 7670.
[3] For a review, see: Danheiser, R. L; Dudley, G. B.; Austin, W. F. In *Science of Synthesis;* Danheiser, R. L. Ed.; Thieme, Stuttgart, 2006; Vol. 23, pp 533-555.
[4] (a) Danheiser, R. L.; Gee, S. K. *J. Org. Chem.* **1984**, *49*, 1672. (b) Danheiser, R. L.; Nishida, A.; Savariar, S.; Trova, M. P. *Tetrahedron Lett.* **1988**, *29*, 4917.
[5] Danheiser, R. L.; Brisbois, R. G.; Kowalczyk, J. J.; Miller, R. F. *J. Am. Chem. Soc.* **1990**, *112*, 3093.

tautomerization provides the highly-substituted phenol. This annulation has been employed in the synthesis of a number of biologically active compounds,[6] and studies to expand the scope of the annulation to include the synthesis of highly-substituted anilines are currently underway.

My research has focused on exploring and exploiting the chemistry of vinylketenes bearing a trialkylsilyl substituent at C-2 ("TAS-vinylketenes") on a number of fronts. Part II of this thesis discusses the development of a new benzannulation strategy for the synthesis of highly substituted resorcinol derivatives based on the reaction of TAS-vinylketenes with lithium ynolates, while Part III covers investigations into new methods for the preparation of these valuable four-carbon synthetic building blocks. As an introduction, the next chapter reviews the current body of knowledge regarding the chemistry of TAS-vinylketenes with a particular focus on previous annulation reactions.

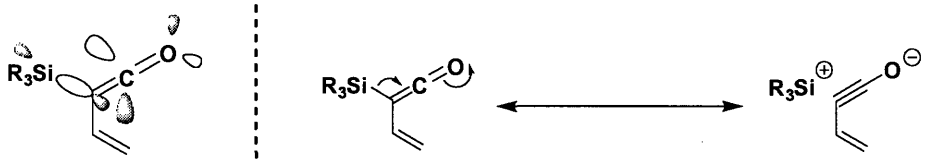
---

[6] Previous natural product syntheses based on this benzannulation strategy: (a) Danheiser, R. L.; Gee, S. K.; Perez, J. J. *J. Am. Chem. Soc.* **1986**, *108*, 806. (b) Kowalski, C. J.; Lal, G. S. *J. Am. Chem. Soc.* **1988**, *110*, 3693. (c) Danheiser, R. L.; Cha, D. C. *Tetrahedron Lett.* **1990**, *31*, 1527. (d) Danheiser, R. L.; Casebier, D. S.; Loebach, J. L. *Tetrahedron Lett.* **1992**, *33*, 1149. (e) Danheiser, R. L.; Casebier, D. S.; Huboux, A. H. *J. Org. Chem.* **1994**, *59*, 4844. (f) Danheiser, R. L.; Helgason, A. L. *J. Am. Chem. Soc.* **1994**, *116*, 9471. (g) Danheiser, R. L.; Trova, M. P. *Synlett* **1995**, 573. (h) Danheiser, R. L.; Casebier, D. S.; Firooznia, F. *J. Org. Chem.* **1995**, *60*, 8341. (i) Dudley, G. B.; Takaki, K. S.; Cha, D. D.; Danheiser, R. L. *Org. Lett.* **2000**, *2*, 3407. (j) Smith, A. B., III; Adams, C. M.; Kozmin, S. S.; Paone, D. V. *J. Am. Chem. Soc.* **2001**, *123*, 5925.

Chapter 2

(Trialkylsilyl)vinylketenes: Versatile Four-Carbon Annulation Units

As mentioned in Chapter 1, the reactivity of vinylketenes is dominated by their participation in [2 + 2] cycloadditions as an electron-deficient 2π component, a mode of reactivity characteristic of ketenes.[7] The longstanding interest of our group in TAS-vinylketenes stems in part from the radically different behavior of *silyl*ketenes compared to most other classes of ketene. While most ketenes are not isolable, and must be generated *in situ* as transient intermediates due to their propensity to dimerize, silylketenes are not susceptible to dimerization and can generally be isolated by distillation (even at elevated temperatures) and in some instances by conventional column chromatography on untreated silica gel. Properly handled, silylketenes can be stored for extended periods with minimal decomposition. For instance, (trimethylsilyl)ketene can be purified by distillation at 82 °C, and can be stored at room temperature for years without decomposition. This exceptional difference in reactivity and stability arises from the influence of a hyperconjugative interaction between the carbon-silicon σ bond and the coplanar carbonyl π^* orbital as depicted below. Inductive donation from the



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

carbon-silicon bond is also expected to provide an additional stabilizing effect. Together these influences reduce the electrophilicity of the carbonyl moiety, rendering the ketene less reactive towards [2 +2] cycloaddition and nucleophilic addition.

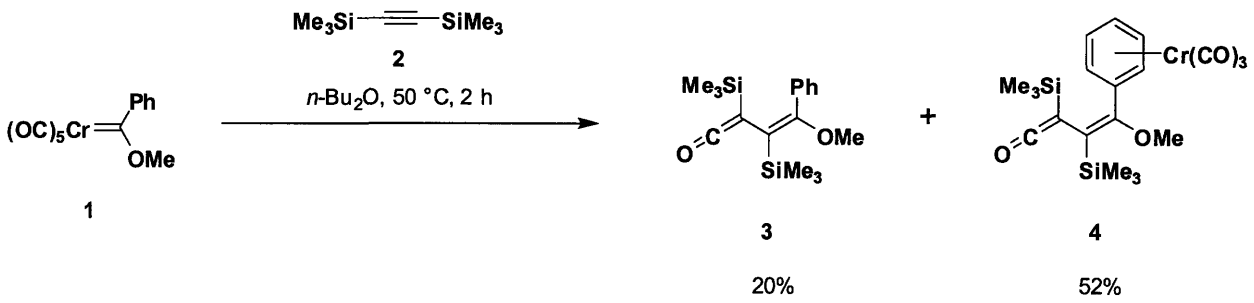
The suppression of the "normal" [2 + 2] cycloaddition reaction pathway of vinylketenes by a silyl substituent allows access to the rich underlying vinylketene functionality, and as a result TAS-vinylketenes tend to behave as electron-rich 1,3-dienes bearing a carbonyl moiety.[8] This unique reactivity pattern, as well as the increased stability of TAS-vinylketenes relative to their counterparts lacking a silyl group, has prompted studies in our laboratory and in others directed towards the discovery of convenient methods for their preparation and for development of new annulation strategies leading to a variety of carbocyclic and heterocyclic compounds.

General Approaches to TAS-Vinylketenes

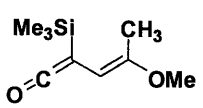
Dötz reported the serendipitous isolation of a stable TAS-vinylketene in 1979. Upon heating chromium carbene **1** in the presence of bis(trimethylsilyl)acetylene (**2**), the free methoxy-substituted TAS-vinylketene **3** was formed in 20% yield, and additionally the chromium complexed ketene **4** was produced in 52% yield.[9] The ketene is proposed to form via a mechanism involving insertion of the chromium carbene into the alkyne followed by insertion of the resulting alkylidene into a carbon monoxide ligand, in a process that follows the initial steps of the Dötz benzannulation. Since this initial example, there have been several scattered

[8] For reviews of the chemistry of silylketenes, see: (a) George, D. M. and Danheiser, R. L. In *Science of Synthesis*; Danheiser, R. L. Ed.; Thieme: Stuttgart, 2006; Vol. 23, 53. (b) Tidwell, T. T. *Ketenes,* 2nd ed.; John Wiley and Sons: Hoboken, NJ, 2006. (c) Pommier, A.; Kocienski, P.; Pons, J.-M. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2105. (d) Schaumann, E.; Scheiblich, S. In *Methoden der Organischen Chemie (Houben Weyl)*; Kropf, E., Schaumann, E., Eds.; Thieme: Stuttgart, Germany, 1993; Vol. E15, parts 2 and 3. (e) Pons, J.-M.; Kocienski, P. J. In *Science of Synthesis*; Fleming, I., Ed.; Thieme: Stuttgart, Germany; Vol. 4, 657.)

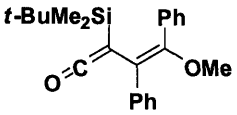
[9] Dötz, K. H. *Angew. Chem. Int. Ed. Eng.* **1979**, *18*, 954.



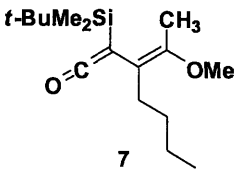
reports of the preparation of TAS-vinylketenes by this route.[10] Several ketenes prepared in this fashion are shown below (**5-7**). Only TAS-vinylketenes bearing 4-alkoxy substituents are accessible due to the nature of the chromium carbene needed for the reaction. The ketenes are produced as a single isomer bearing the alkoxy group *trans* to the ketene for reasons that are not entirely clear.



5



6



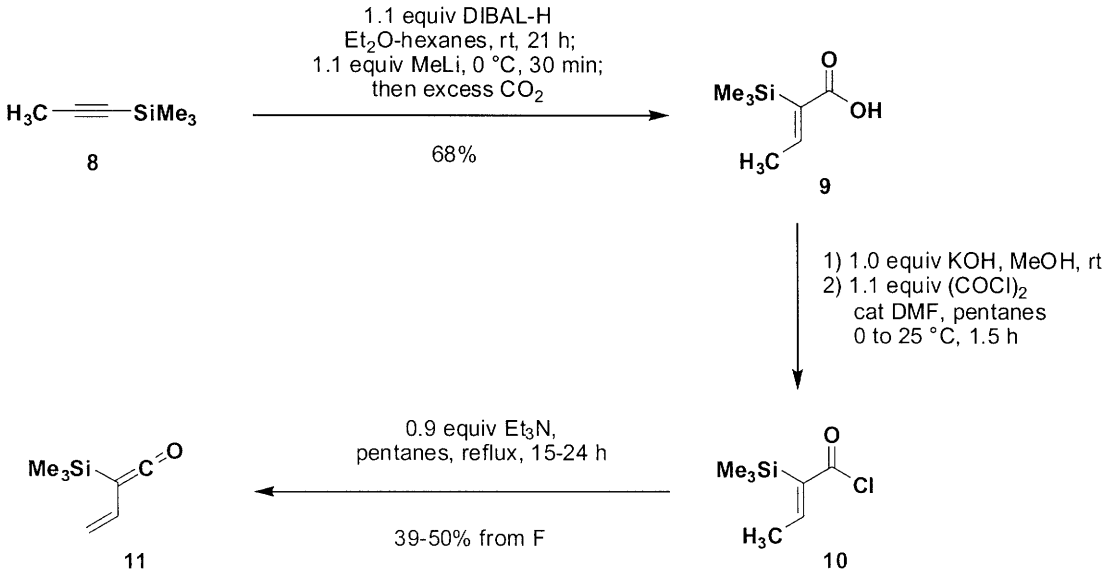
7

In 1980, our laboratory reported the first detailed studies of the chemistry of TAS-vinylketenes, as well as the first synthesis of the parent compound, (trimethylsilyl)vinylketene.[11] Hydroalumination of trimethylsilylpropyne (**8**) with DIBAL-H, activation of the intermediate vinyl alane as the alanate, and carboxylation yielded the α-silyl-α,β-unsaturated acid **9**. The acid was titrated with KOH and converted to the acid chloride **10**, and then, in the key step in this approach, dehydrohalogenation with triethylamine provided (trimethylsilyl)vinylketene (**11**). It is of note, however, that while this dehydrohalogenation strategy is effective for the preparation

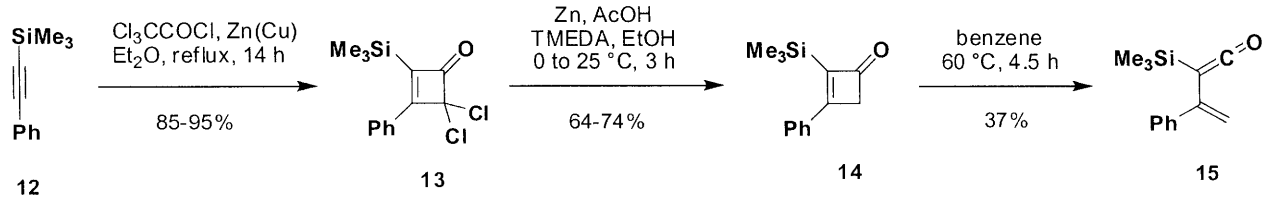
[10] (a) Dötz, K. H.; Fügen-Küster, B. *Chem. Ber.* **1980**, *113*, 1449. (b) Wulff, W. D.; Tang, P.-C. *J. Am. Chem. Soc.* **1984**, *106*, 1132. (c) Wulff, W. D.; Xu, Y.-C. *J. Org. Chem.* **1987**, *52*, 3263. (d) Moser, W. H.; Sun, L.; Huffman, J. C. *Org. Lett.* **2001**, *3*, 3389. (e) Moser, W. H.; Feltes, L. A.; Sun, L.; Giese, M. W.; Farrell, R. W. *J. Org. Chem.* **2006**, *71*, 6542.

[11] Danheiser, R. L.; Sard, H. *J. Org. Chem.* **1980**, *45*, 4810.

of the parent ketene, it is not a general strategy for the preparation of silylketenes bearing substitution on the vinyl moiety, due to regiochemical ambiguities that would be associated with the dehydrohalogenation in some substituted cases.



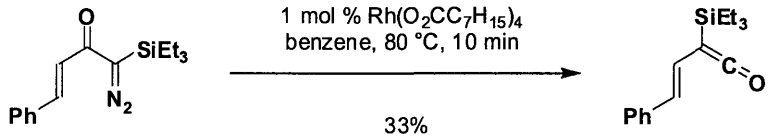
The electrocyclic ring opening of 2-silylcyclobutenones provides a very attractive alternative method to prepare TAS-vinylketenes. Cycloaddition of dichloroketene with phenyl(trimethylsilyl)acetylene (**12**) and subsequent reductive dechlorination of the resulting dichlorocyclobutenone (**13**) affords the requisite cyclobutenone **14**, which upon heating is converted to the TAS-vinylketene **15**.[12] This method is ideally suited for generation of TAS-



[12] Loebach, J. L.; Bennett, D. M.; Danheiser, R. L. *J. Org. Chem.* **1998**, *63*, 8380.

vinylketenes *in situ* as it takes place under mild conditions and no byproducts are formed. Unfortunately, this method is severely limited by the lack of a general approach to the required 2-silylcyclobutenones. While the phenyl group in **12** provides a sufficient directing effect in the cycloaddition with dichloroketene, employment of alkyl substituted silylacetylenes results in a mixture of regioisomeric products. As a result, there are few examples of the preparation of TAS-vinylketenes in this fashion.

The Wolff rearrangement of α′-diazo-α′-silyl-α,β-unsaturated ketones presents another possible approach to the synthesis of TAS-vinylketenes. A number of silylketenes have been prepared by the rhodium- and copper-catalyzed Wolff rearrangement of α-silyl-α-diazo ketones, but the cinnamyl silylketene **17** shown below is the only TAS-vinylketene that has been prepared by metal-catalyzed Wolff rearrangement to date.[13]

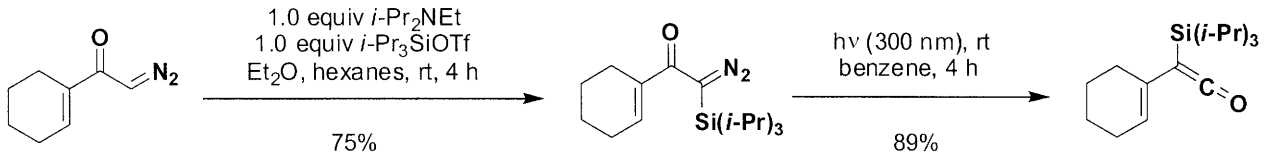


16 **17**

In contrast, a number of TAS-vinylketenes have been prepared via a method developed in our laboratory that relies upon the photochemical variant of the Wolff rearrangement.[10] Silylation of α′-diazo-α,β-unsaturated ketones was conducted employing a modification of the procedure originally reported by Maas.[14] For example, treatment of cyclohexenyl diazo ketone **18** with triisopropylsilyl triflate in the presence of Hünig's base provides the α′-diazo-α′-silyl-α,β-unsaturated ketone **19** in good yield. The employment of diethyl ether-hexanes as the

[13] Marsden, S. P.; Pang, W.-K. *J. Chem. Soc., Chem. Commun.* **1999**, 1199.
[14] (a) Maas, G.; Brückmann, R. *J. Org. Chem.* **1985**, *50*, 2801. (b) Brückmann, R.; Maas, G. *Chem. Ber.* **1987**, *120*, 635. (c) Brückmann, R.; Schneider, K.; Maas, G. *Tetrahedron* **1989**, *45*, 5517.

solvent promotes precipitation of the ammonium triflate salt formed as a byproduct, driving the reaction towards completion and suppressing proto-desilylation of the reaction product by the acidic salt. Irradiation of the α′-diazo-α′-silyl-α,β-unsaturated ketones with 300 nm light at room temperature for 3-4 hours then cleanly produces TAS-vinylketenes such as **20** in good to excellent yield. TAS-vinylketenes bearing a wide variety of di- and trisubstituted double bonds



18 **19** **20**

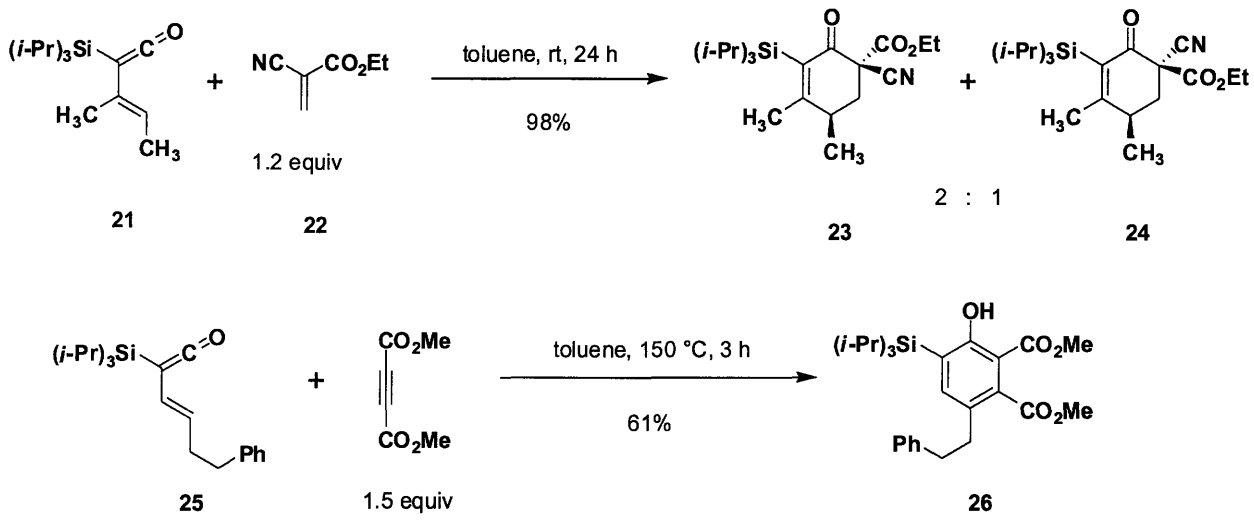
can be prepared in this manner, and a number of examples are presented in the following chapters. However, substituents *cis* to the ketene are not tolerated due to competitive side reactions that occur during irradiation. These undesired pathways will be discussed in greater detail in Part III of this thesis.

Annulation Reactions of TAS-Vinylketenes

One of the earliest applications of TAS-vinylketenes in an annulation strategy was their employment in Diels-Alder [4 + 2] cycloadditions (Scheme 2).[11,12] The ketene behaves as an electron-rich diene and successful reaction requires highly activated electron-deficient dienophiles. Reaction with nitro alkenes or alkenes bearing two electron-withdrawing groups provides cyclohexenones with perfect regiocontrol and a preference for the endo product. An example is shown below in which heating of TAS-vinylketene **21** with cyanoacrylate **22** results in a near quantitative yield of a mixture of diastereomeric annulation products (**23** and **24**). Additionally, employment of dimethyl acetylenedicarboxylate as a dienophile allows access to 3-

hydroxyphthalates such as **26** following tautomerization of the initially formed cyclohexadienone intermediates.

Scheme 2. Diels-Alder Cycloadditions of TAS-Vinylketenes

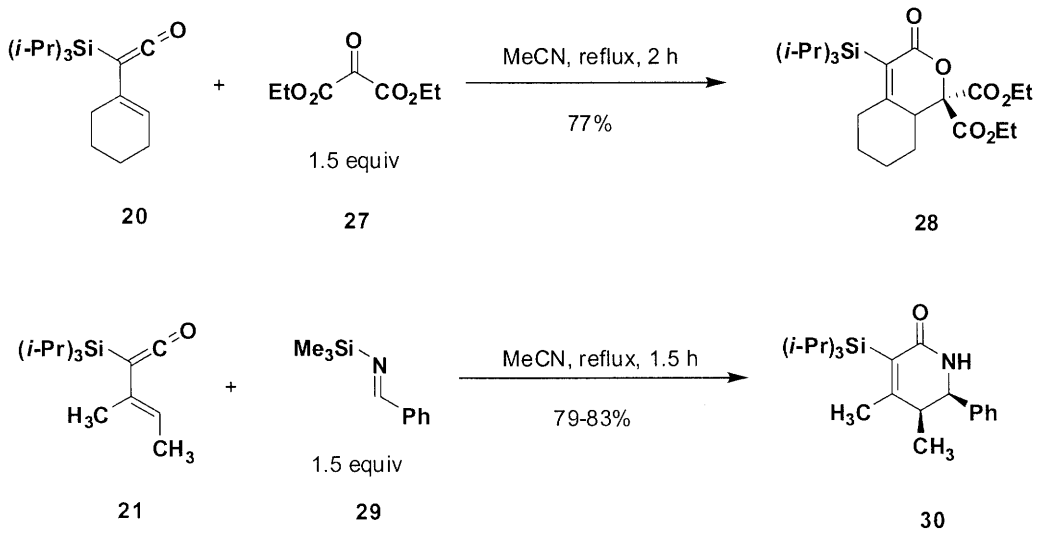


Further research showed that this approach could be extended to hetero-Diels-Alder cycloadditions of TAS-vinylketenes with ketone and imine dienophiles, allowing for rapid and efficient assembly of α,β-unsaturated δ-valerolactones and α,β-unsaturated δ-valerolactams respectively (Scheme 3).[15] Attempts to employ unactivated carbonyl compounds were not fruitful, and to date diethyl oxomalonate (**27**) is the only compound to successfully react, as demonstrated by its reaction with cyclohexenyl TAS-ketene **20** to form the lactone **28**. A wider variety of imines participate in the annulation, and non-enolizable *N*-(trimethylsilyl)imines such as the phenyl imine **29** undergo cycloaddition cleanly. Notably, in contrast to hetero-Diels-Alder reactions utilizing other diene partners, these cycloadditions do not require a Lewis acid promoter. For example, heating imine **29** and dimethyl TAS-vinylketene **21** is sufficient to

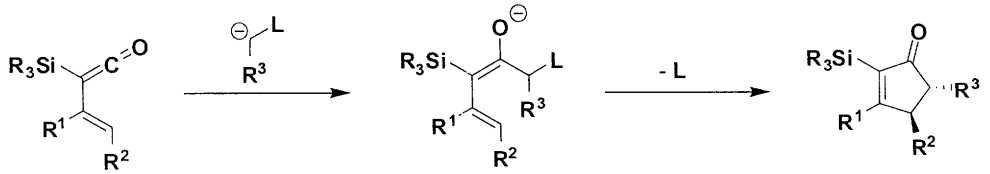
[15] Bennett, D. M.; Okamoto, I.; Danheiser, R. L. *Org. Lett.* **1999**, *1*, 641.

produce lactam **30** in good yield after only 90 minutes. Enolizable imines are not viable partners, however, most likely due to decomposition at the elevated temperatures required for cycloaddition.

Scheme 3. Hetero-Diels-Alder Cycloadditions of TAS-Vinylketenes



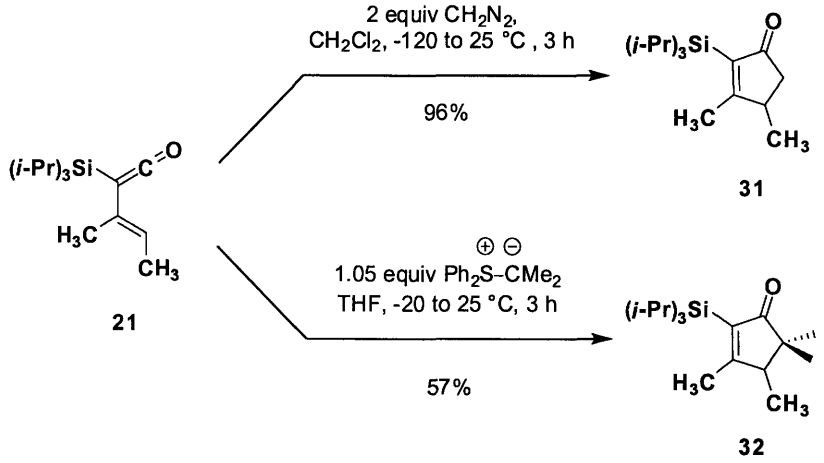
In addition to the development of [4 + 2] annulations, previous research in our laboratory has resulted in the development of a [4 + 1] annulation strategy that utilizes TAS-vinylketenes as a carbonyl compound.[16] Treatment of a TAS-vinylketene with an appropriately substituted "carbenoid reagent" (a nucleophilic carbon atom bearing a leaving group) results in 1,2-addition of the carbenoid to the carbonyl moiety. Loss of the leaving group and cyclization then affords a



[16] (a) Loebach, J. L.; Bennett, D. M.; Danheiser, R. L. *J. Am. Chem. Soc.* **1998**, *120*, 9690. (b) Davie, C. P.; Danheiser, R. L. *Angew. Chem. Int. Ed. Eng.* **2005**, *44*, 5867.

cyclopentenone; the precise mechanism of this process has not been conclusively determined and will be discussed in greater detail in Part III of this thesis. A number of carbenoid reagents have been employed for this reaction; simple diazo alkanes such as diazomethane and (trimethylsilyl)diazomethane react successfully with a variety of TAS-vinylketenes. For instance, cyclopentenone **31** is produced in near quantitative yield upon reaction of TAS-vinylketene **21** with diazomethane. However, in general higher diazo compounds do not react, most likely due to the low nucleophilicity of such compounds. Sulfur ylides, being more nucleophilic, are less limited in this respect and even disubstituted ylides will participate in the annulation providing access to 5,5-disubstituted cyclopentenones such as **32**.

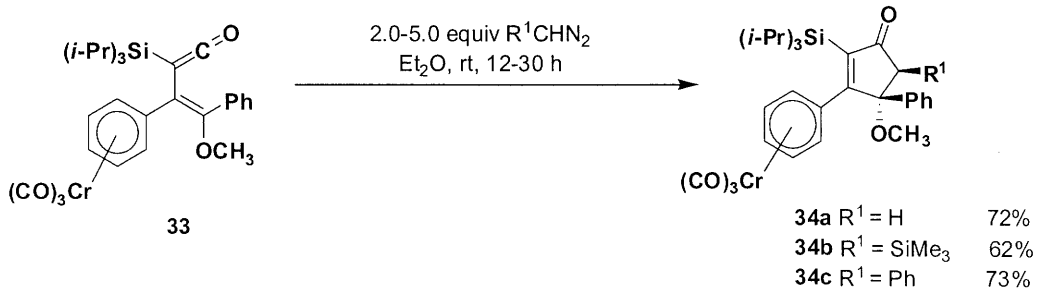
Scheme 4. [4 + 1] Annulation of TAS-Vinylketenes with Carbenoid Reagents



Moser has reported that the scope of this annulation reaction can be expanded to include alkoxy-substituted TAS-vinylketenes such as **33**.[17] Cyclopentenones (**34a-c**) are formed in good yield upon reaction of these ketenes with diazomethane, as well as with phenyl- and trimethylsilyldiazomethane. However, the annulation appears to be less efficient with this type of ketene than with the ketenes previously employed in this annulation, requiring additional

[17] Moser, W. H.; Feltes, L. A.; Sun, L.; Giese, M. W.; Farrell, R. W. *J. Org. Chem.* **2006**, *71*, 6542.

equivalents of the diazo partner. Recently, Sun has demonstrated that similar alkoxy-substituted TAS-vinylketenes react with *tert*-butyl isocyanide to provide products with an exocyclic imine.[18]



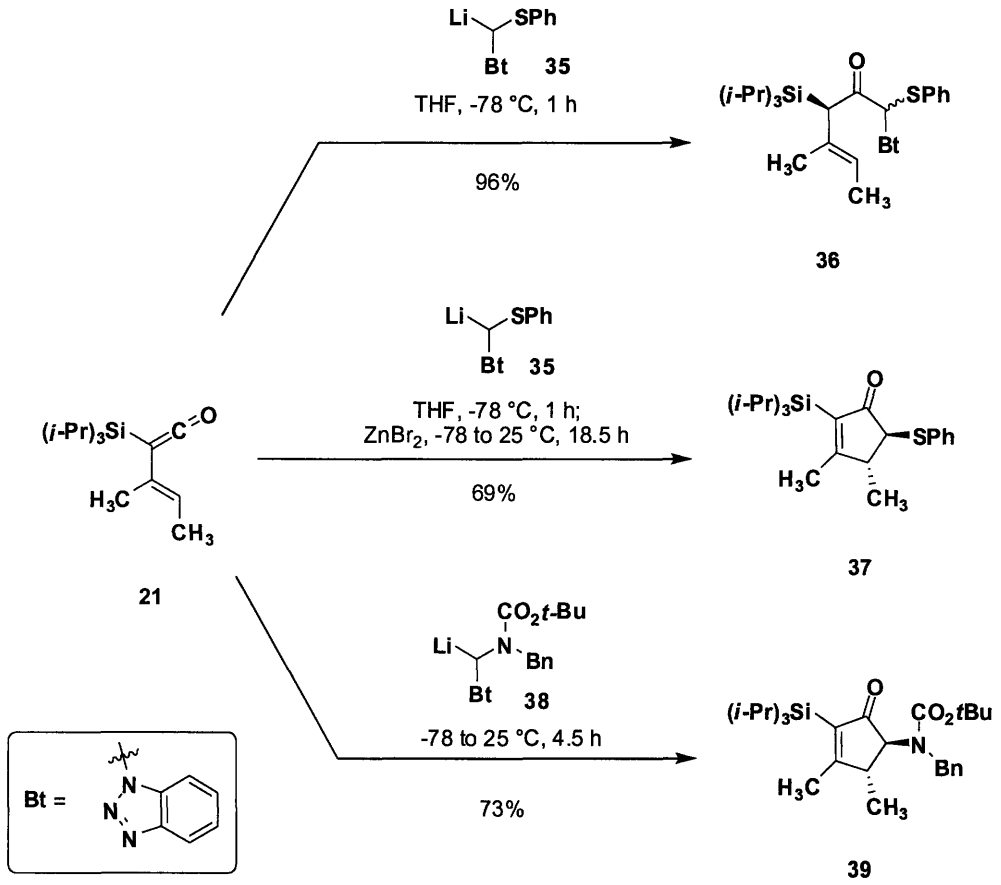
33

34a R^1 = H 72%
34b R^1 = $SiMe_3$ 62%
34c R^1 = Ph 73%

Investigations in our laboratory have revealed that the use of benzotriazolylmethyllithium derivatives as the carbenoid reagents allows for access to a much broader range of substituents at C-5 of the cyclopentenone.[16b] Unlike the annulation with ylides and diazo compounds, the addition products of TAS-vinylketenes and benzotriazolylmethyllithium carbenoids in some cases do not cyclize at room temperature, and Lewis acids are required to promote the ionization of the benzotriazole ("Bt") group required for formation of cyclopentenone products. For example, benzotriazolylmethyllithium **35** smoothly adds to dimethyl TAS-vinylketene **21**, and in the absence of a Lewis acid the enolate intermediate can be quenched to provide **36** in near quantitative yield (Scheme 5). However, warming to room temperature in the presence of zinc bromide converts this intermediate into the cyclopentenone **37**. A variety of heteroatom-substituted carbenoid reagents participate in the annulation and with carbenoids bearing especially strong electron-donating substituents, such as the amino derivative **38**, Lewis acids are not required.

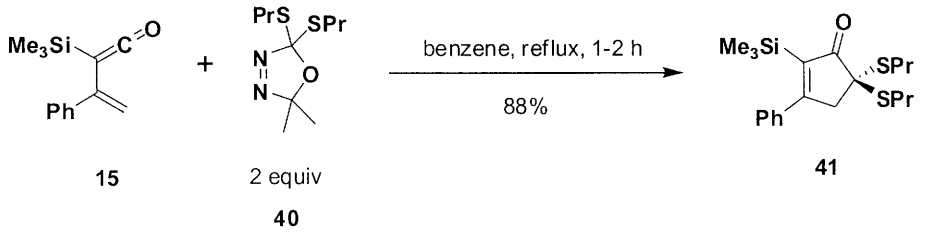
[18] Li, Z.; Moser, W. H.; Deng, R.; Sun. L. *J.Org. Chem.* **2007,** *72*, 10254.

Scheme 5. Benzotriazolylmethyllithium Species as Carbenoid Reagents



In 2003, Rigby showed that in addition to carbenoid reagents, nucleophilic carbenes bearing two alkoxy, alkylthio, or amino substituents will also undergo efficient [4 + 1] cycloaddition.[19] In these cases, the requisite carbenes are generated *in situ* by thermolysis of an appropriate precursor. For instance, upon heating a mixture of the TAS-vinylketene **15** and diazoline **40,** fragmentation of the diazoline provides bis(propylthio)methylenecarbene which adds smoothly to the TAS-vinylketene to provide cyclopentenone **41** in 88% yield.

[19] Rigby, J. H.; Wang, Z. *Org. Lett.* **2003**, *5*, 263.



The majority of my research in the area of TAS-vinylketene annulations was conducted with the goal of developing an annulation strategy centered on their reaction with electron- rich alkynes for the synthesis of electron-rich aromatic compounds, complementary to the previously investigated Diels-Alder type annulations with electron-deficient alkynes mentioned above. This topic will be the focus of Part II of this thesis.

Part II

A Benzannulation Strategy for the Synthesis of Phenols and Heteroaromatic Compounds Based on the Reaction of (Trialkylsilyl)vinylketenes with Lithium Ynolates

Chapter 1

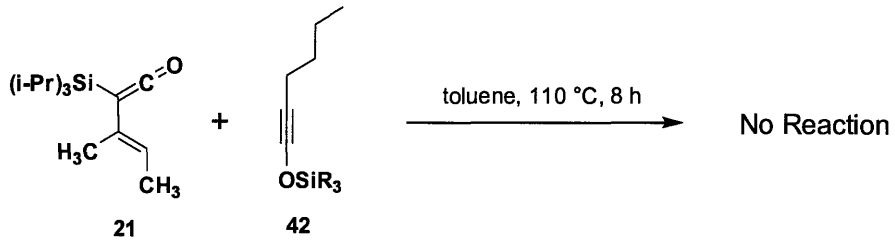
Introduction and Background

Substituted resorcinols are important synthetic targets, and are most commonly prepared by employing linear substitution strategies involving sequential electrophilic substitution and metallation-alkylation reactions. However, a more effective approach involves the application of *benzannulation methods*: convergent strategies in which the aromatic ring system is assembled in a single step from two or more precursors, with all (or most) of the substituents already in place. Benzannulation strategies enjoy significant advantages over conventional linear substitution strategies, especially when applied to the preparation of highly substituted target molecules. For example, benzannulation routes generally avoid the regiochemical ambiguities associated with aromatic substitution reactions, and their intrinsic convergent character facilitates the efficient assembly of highly substituted aromatic compounds that would require long, multistep routes using classical substitution methodology.

The research presented in Part II of this thesis was conducted with the goal of developing a new benzannulation strategy utilizing TAS-vinylketenes that would be complementary to our earlier Diels-Alder strategy and that would allow for the preparation of resorcinols bearing a variety of substituents.

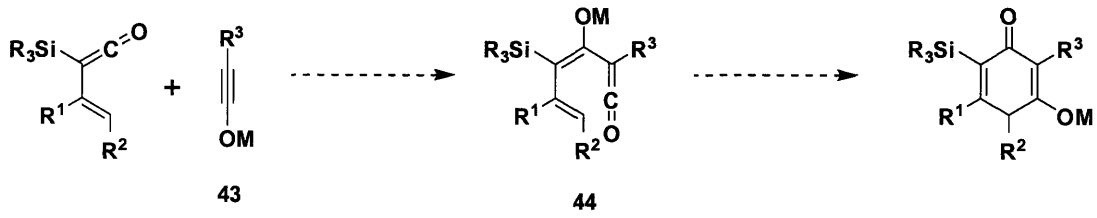
Initial attempts to prepare resorcinol derivatives focused on employment of the [4 + 2] Diels-Alder cycloaddition of TAS-vinylketenes discussed in Part I of this thesis. While this route provides a powerful method for the rapid assembly of cyclohexenones and highly substituted phenol derivatives, it became clear during explorations of the scope that only electron-deficient alkenes and alkynes are viable 2π partners for cycloadditions with TAS-vinylketenes. For example, upon heating a mixture of TAS-vinylketene **21** and the *n*-butyl-

substituted siloxy alkyne **42** in refluxing toluene for 8 h, no reaction was observed and both partners were recovered unchanged.



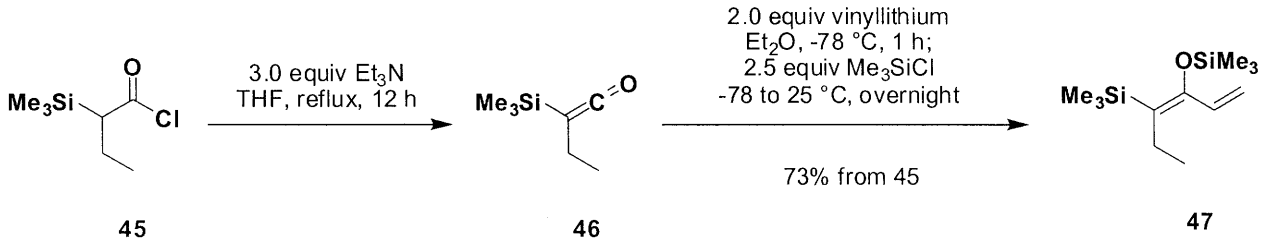
Concept of the Benzannulation

Following this result, we wondered if successful annulation would occur if a more electron-rich and nucleophilic alkyne were employed, such as one analogous to **42** in which the silyl group has been exchanged for a more electropositive metal. We expected that the cycloaddition of an alkyne of type **43** with a TAS-vinylketene would likely occur in a stepwise fashion via a dienylketene intermediate (**44**). In evaluating this possibility, we were confident



that the addition of a nucleophile to the TAS-vinylketene carbonyl would proceed as desired since the reaction of silylketenes with a number of nucleophiles including amines and organometallic compounds are known. For example, in our investigations of the [4 + 1] annulation reaction of TAS-vinylketenes with carbenoid reagents (*vide supra*), we observed that even moderately nucleophilic species such as diazo alkanes are capable of addition to TAS-vinylketenes.

We also expected that the addition reaction would proceed stereoselectively to produce the dienolate isomer **44** required for subsequent cyclization. In this case, the bulky trialkylsilyl group would direct the approach of the nucleophile to the opposite face of the carbonyl, resulting in stereoselective formation of the (*Z*)-enolate required for ring closure. The addition of organolithium reagents to unsymmetrically substituted ketenes has been studied by Tidwell,[20] and several instances of selective addition to silylketenes have been observed. For example, treatment of a solution of ethyl(trimethylsilyl)ketene (**46**) with vinyllithium and trapping with chlorotrimethylsilane forms the (*Z*)-enol ether **47** in better than 73% yield. Similar stereoselective additions are involved in our previously described [4 + 1] annulation reaction.[16]



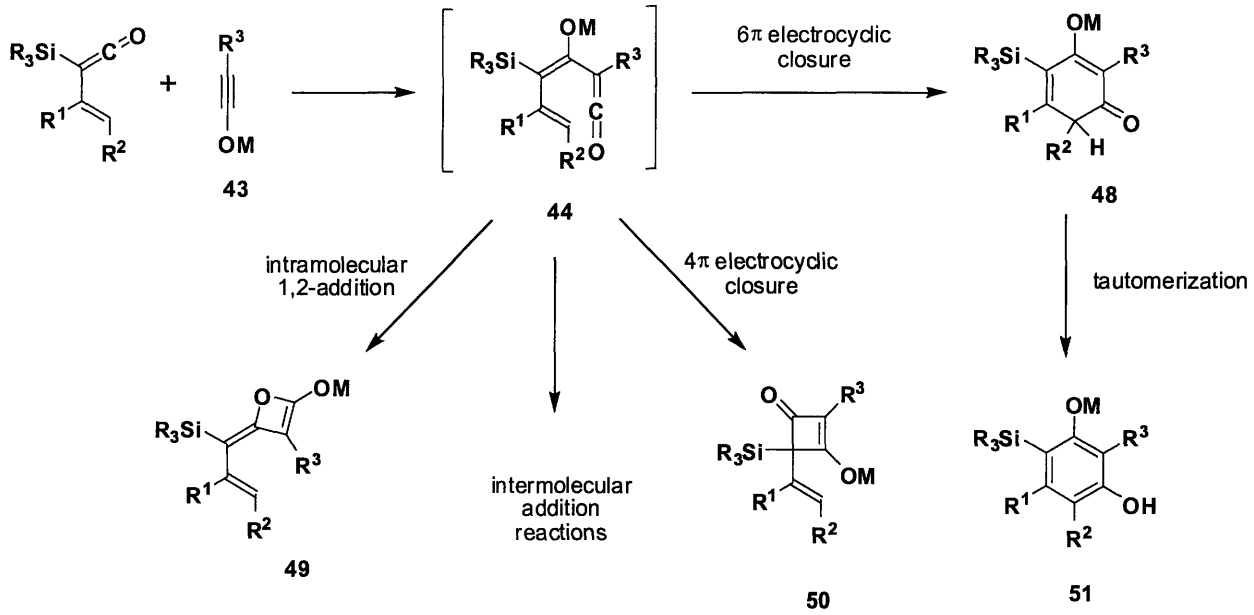
45 **46** **47**

Although we were confident that the reaction of TAS-vinylketenes with ynolates would furnish 3-oxido-dienylketenes of type **44**, the fate of these intermediates was far from certain at the outset of our studies. We hoped that this intermediate would undergo 6π electrocyclic ring closure to provide cyclohexadienes of type **48,** which we expected to rapidly tautomerize to resorcinates of type **51**. However, intermediate **44** is very densely functionalized, bearing diene, ketene and enolate moieties, and there are a number of potential reaction pathways available to it (Scheme 6). In addition to the desired cyclization, several other modes of ring closure are conceivable. For example, the addition of ynolates to aldehydes and ketones leading to the

[20] Baigrie, L. M.; Seiklay, H. R.; Tidwell, T. T. *J. Am. Chem. Soc.* **1985**, *107*, 5391.

formation of β-lactone enolates is well known,[21] and an analogous reaction in this case would give rise to products of type **49**. Alternatively, 4π electrocyclic ring closure would generate the four-membered carbocycle **50**, an enolate derivative of a substituted 1,3-cyclobutanedione.

Scheme 6. Potential Reaction Pathways Available to Dienylketene **44**.



Additionally, **44,** which contains both an electrophilic ketene and a nucleophilic enolate moiety, might be subject to intermolecular processes leading to dimeric and oligomeric products.

Despite these potential complications, we expected that intermediate **44** would most likely undergo the desired 6π electrocyclic ring closure[22] due to an number of important kinetic factors. For instance, the (*Z*)-enolate geometry of **44** enforces close proximity between the C-1 and C-6 carbon atoms at which bond formation is desired, and more importantly, a significant increase in charge stabilization can be expected to develop in the transition state leading to the 1,3-dicarbonyl enolate system in **48.** Furthermore, while the 6π electrocyclic ring closure of

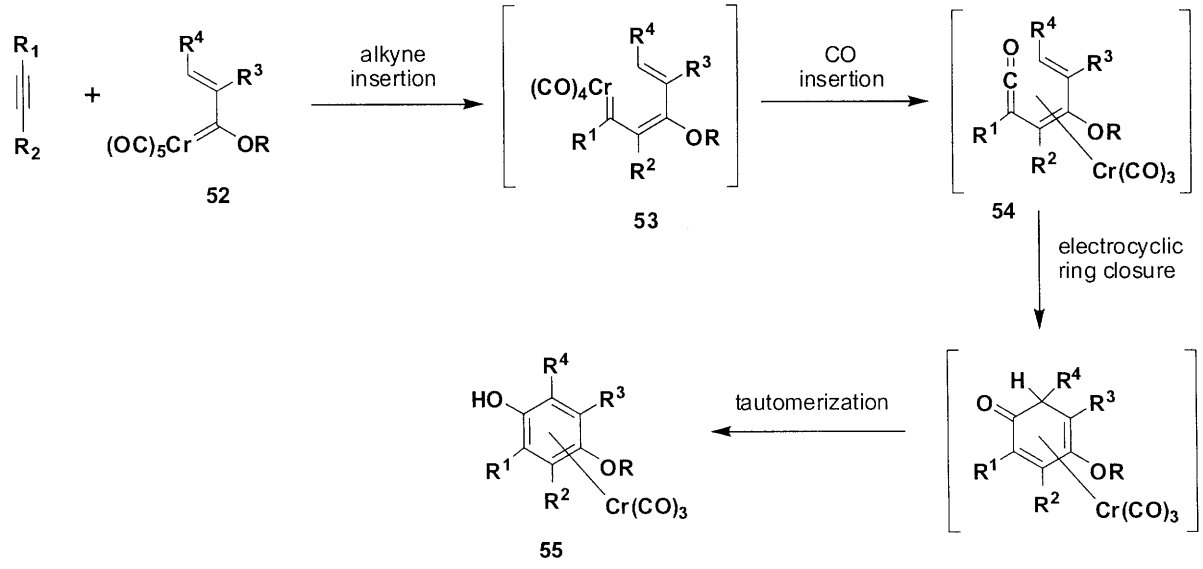
[21] For reviews of the chemistry of ynolates, see: (a) Shindo, M. *Tetrahedron*, **2007**, *63,* 10. (b) Shindo, M. *Synthesis* **2003**, 2275. (c) Shindo, M. *Chem. Soc. Rev.* **1998**, *27*, 367.

[22] For a review, see: (a) Marvell, E. N. *Thermal Electrocyclic Reactions*; Organic Chemistry Series Vol. 43; New York: Academic Press, 1980. (b) Bakulev, V. A. *Russ. Chem. Rev.* **1995**, *64*, 107.

1,3,5-trienes is generally not a rapid process, incorporation of one of the triene π bonds into a ketene greatly increases the rate of cyclization.[23,24]

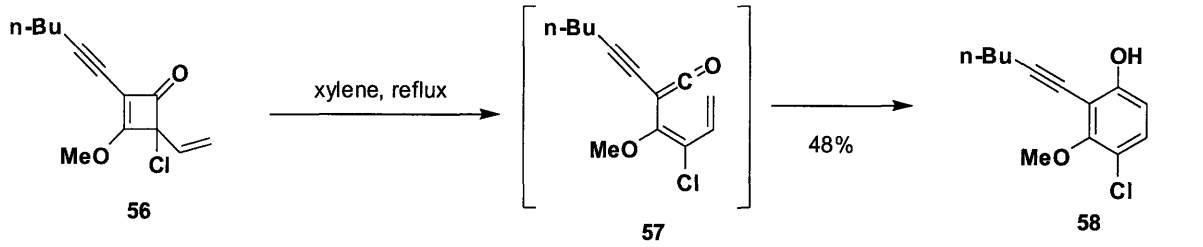
6π Electrocyclic Ring Closure of Dienylketenes

The electrocyclic ring closure of dienylketenes has previously been implicated in a number of approaches to aromatic compounds, perhaps the most famous of which is the Dötz benzannulation.[25] The proposed mechanism for this reaction involves insertion of a vinyl chromium carbonyl complex (**52**) into an alkyne to provide a dienyl chromium carbene (**53**). Insertion into a carbon monoxide ligand then provides the complexed dienylketene **54**, which undergoes electrocyclic ring closure and tautomerization to provide the observed hydroquinone products (**55**).

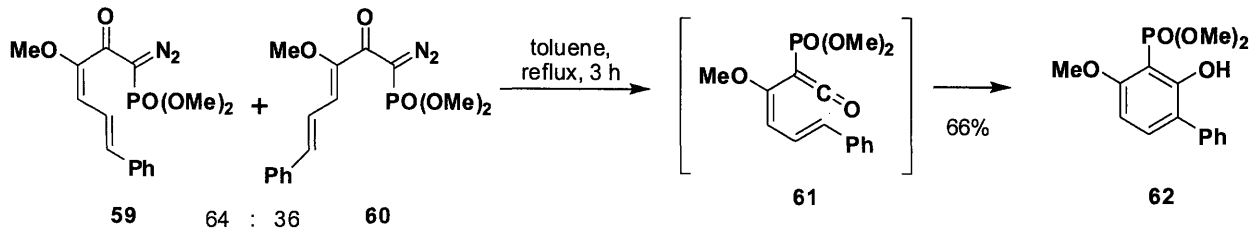


[23] Reviewed in: (a) Moore, H. W.; Decker, O. H. W. *Chem. Rev.* **1986**, *86*, 821. (b) Danheiser, R. L.; Dudley, G. B.; Austin, W. F. In *Science of Synthesis;* Danheiser, R. L. Ed.; Thieme, Stuttgart, 2006; Vol. 23, pp 522-555.
[24] For a review of the of 6π electrocyclization reactions of dienylketenes formed from acid precursors, see: Serra, S.; Fuganti, C.; Brenna, E. *Chem. Eur. J.* **2007**, *13*, 6782.
[25] For reviews of the Dötz benzannulation, see: (a) Dötz, K. H.; Tomuschat, P. *Chem. Soc. Rev.* **1999**, *28*, 187. (b) Dötz, K. H.; Stendel, J., Jr. In *Modern Arene Chemistry*; Astruc, D., Ed.; Wiley-VCH: Weinheim, 2002; pp 250-296

The electrocyclization in this case takes place in the coordination sphere of chromium, though many efficient cyclizations of dienylketenes that take place in the absence of metals are known. In one of many examples, heating 4-vinylcyclobutenone **56** in refluxing xylene produced phenol **58**.[26] This reaction is believed to proceed via dienylketene **57**, a reactive intermediate formed by electrocyclic ring opening of the cyclobutenone. The ketene, as expected, was not observable but instead cyclized rapidly, providing the phenol following tautomerization.



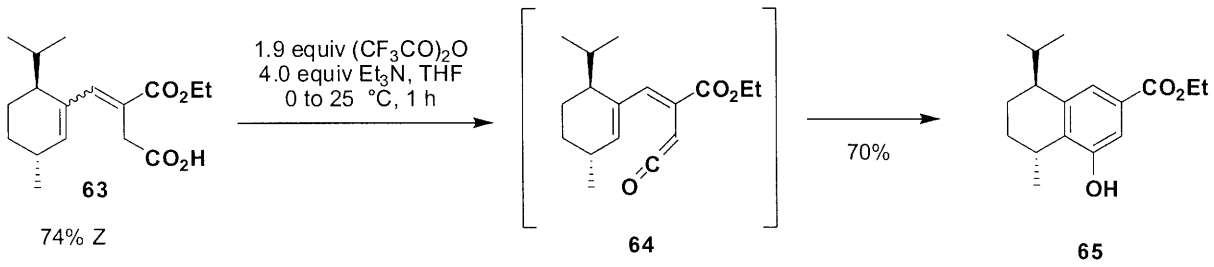
Similarly, a mixture of the stereoisomeric diazo ketones **59** and **60** provided phenol **62** upon thermolysis in refluxing toluene.[27] Wolff rearrangement of **59** provided ketene **61** directly, while the ketene initially formed from diazo ketone **60** had (*Z*)-geometry at the enol ether and was not capable of cyclizing. Instead the ketene is believed to isomerize to **61** via a reversible 4π electrocyclic ring closure, and then proceed to the phenol.



[26] Xu, S. L.; Moore, H. W. *J. Org. Chem.* **1989**, *54*, 4024.
[27] Collomb, D.; Deshays, C.; Doutheau, A. *Tetrahedron* **1996**, *52*, 6665.

In both of these reactions, electrocyclization is not the rate limiting step; elevated temperatures were required for ring opening in the case of the formation of **57** and the Wolff rearrangement in the reaction above. In cases where the ketene can be generated under milder conditions, the cyclization still proceeds very well.

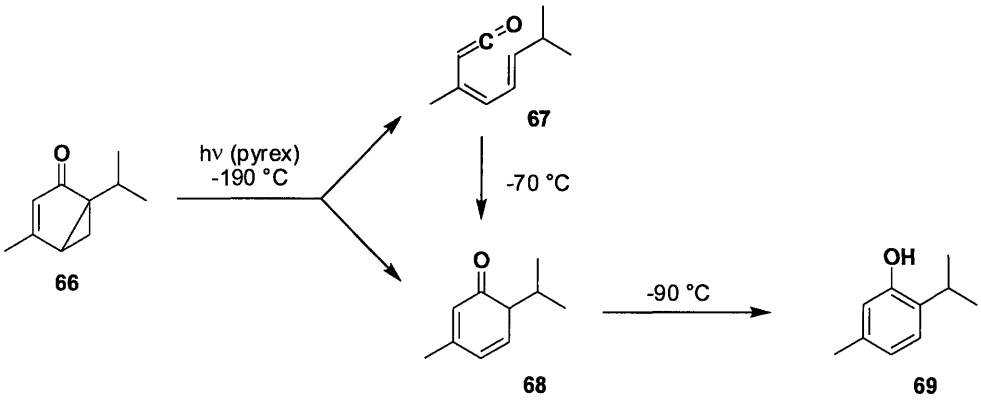
One example of this is the preparation of tetrahydronaphthol **65**. 1,2-Elimination of the mixed anhydride obtained by reaction of (*Z*)-β,γ-unsaturated acid **63** with trifluoroacetic anhydride formed dienylketene **64**. Cyclization at room temperature then produced tetrahydronaphthol **65**.[28]



In perhaps the best example of the facility of the 6π electrocyclic ring closure of dienylketenes, Chapman and co-workers reported an elegant study in which they showed that electrocyclization can take place at very low temperatures.[29] They observed that irradiation of neat umbellulone (**66**) cooled with liquid nitrogen resulted in the formation of two new products: ketene **67** and cyclohexadienone **68** (Scheme 7). Upon warming to -90 °C, **68** tautomerized to thymol (**69**), while the ketene remained unchanged. After further warming to -70 °C, the ketene was converted to **68** by electrocyclic ring closure and then to thymol by tautomerization.

[28] Serra, S.; Fuganti, C. *Tetrahedron Lett.* **2005**, *46*, 4769
[29] Barber, L.; Chapman, O. L.; Lassila, J. D. *J. Am. Chem. Soc.* **1968**, *90*, 5933.

Scheme 7. Mechanistic Paths for Conversion of Umbellulone to Thymol



6π Electrocyclic Ring Closure of 3-Oxido-1,3,5-hexatrienes

The reports cited above provided favorable precedent for the rapid 6π electrocyclic ring closure required in our proposed annulation. Nevertheless, some doubt remained due to the fact that the key dienylketene intermediate **44** is an enolate in addition to being a dienylketene, and prior to our investigation, the cyclization of a dienylketene bearing anionic functionality had not been reported. However, further review of the literature on the chemistry of hexatrienes suggested that the presence of an enolate as part of the cyclizing π system should not hinder the ring closure.[30,31] On the contrary, the presence of a 3-oxido substituent is known to accelerate

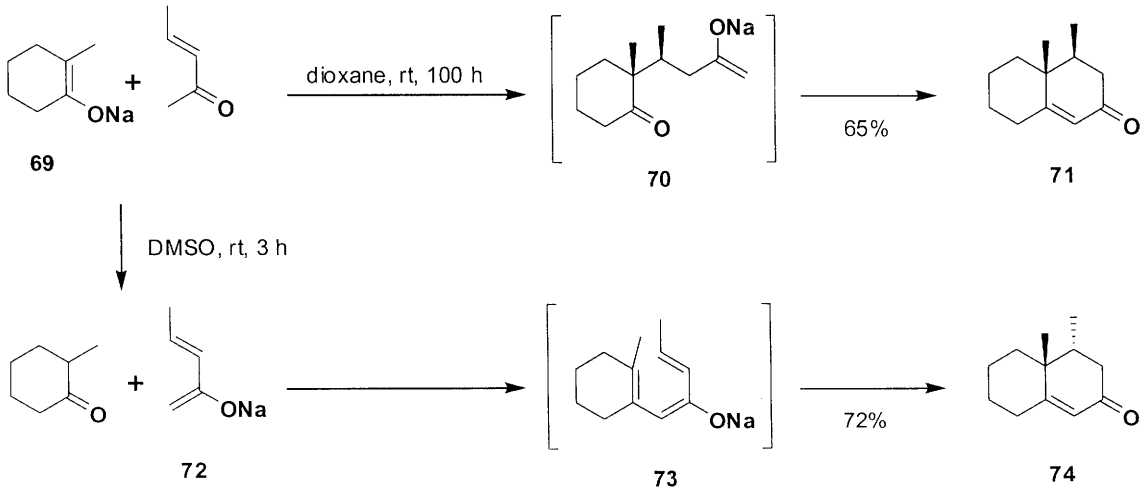
[30] For a discussion of the 6π electrocyclization of 3-oxido-1,3,5-hexatrienes, see: Magnus, P. *Nouv. J. Chem.* **1978**, *2*, 555.

[31] For prior examples of 6π electrocyclization reactions involving enolate derivatives, see: (a) White, J. D.; Skeean, R. W. *J. Am. Chem. Soc.* **1978**, *100*, 6296. (b) White, J. D.; Skeean, R. W.; Trammell, G. L. *J. Org. Chem.* **1985**, *50*, 1939. (c) Magomedov, N. A.; Ruggiero, P. L.; Tang, Y. *J. Am. Chem. Soc.* **2004**, *126*, 1624. (d) Magomedov, N. A.; Ruggiero, P. L.; Tang, Y. *Org. Lett.* **2004**, *6*, 3373 and references cited therein.

electrocyclic ring closure of hexatrienes.[32] This effect is quite pronounced and highly dependent on the location of the oxygen.[33]

Scanio and Starrett first postulated the electrocyclization of 3-oxidotrienes in connection with their investigations of the stereochemical course of the Robinson annulation of 3-penten-2-one.[34] They observed that when 3-penten-2-one was treated with the enolate **69** in dioxane the *cis*-dimethyloctalone **71** was formed. However, when the reaction was performed in DMSO, the *trans*-dimethyloctalone **74** was formed instead. To explain this result, they proposed that **71** is formed by the normal mechanism of the Robinson annulation as shown in Scheme 8. In DMSO, however, rapid proton transfer allowed equilibration of **69** with the cross-conjugated enolate **72**. Aldol condensation and deprotonation then provided the 3-oxidotriene **73**, which was transformed into the octalone **74** by thermally allowed disrotatory electrocyclization and quenching.

Scheme 8. Solvent Effects in the Reaction of Enolate **69** with 3-Penten-2-one.

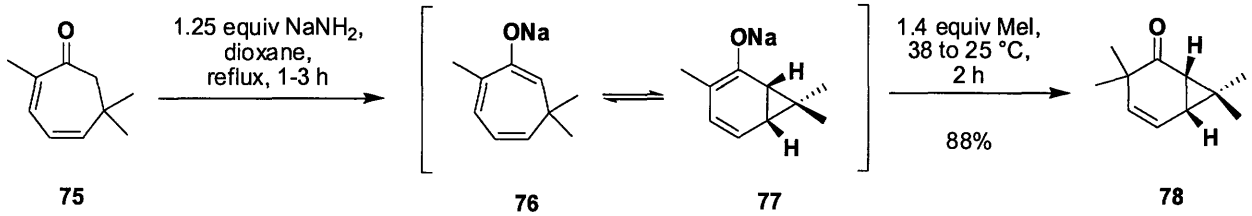


[32] For a discussion of the 6π electrocyclization of 3-oxido-1,3,5-hexatrienes, see: Magnus, P. *Nouv. J. Chem.* **1978**, *2*, 555.

[33] Thermal cyclization of 2-oxido-1,3,5-trienes generally does not take place at ambient temperature; see: (a) White, J. D.; Skeean, R. W. *J. Am. Chem. Soc.* **1978**, *100*, 6296. (b) White, J. D.; Skeean, R. W.; Trammell, G. L. *J. Org. Chem.* **1985**, *50*, 1939.

[34] Scanio, C. J. V.; Starrett, R. M. *J. Am. Chem. Soc.* **1971**, *93*, 1539.

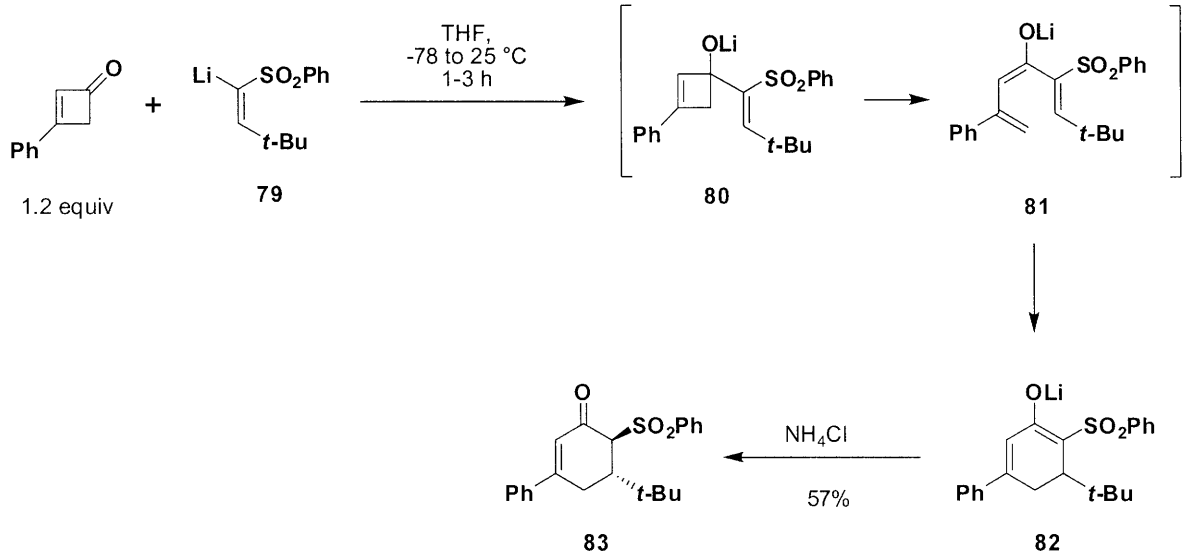
In a more definitive example of electrocyclization, Corey et al. showed that deprotonation of eucarvone (**75**) with sodium amide and trapping with methyl iodide produced the bicyclo[4.1.0]heptenone **78**.[35] A further study showed that the isomerization of enolates **76** and **77** occurred substantially faster than trapping.[36]



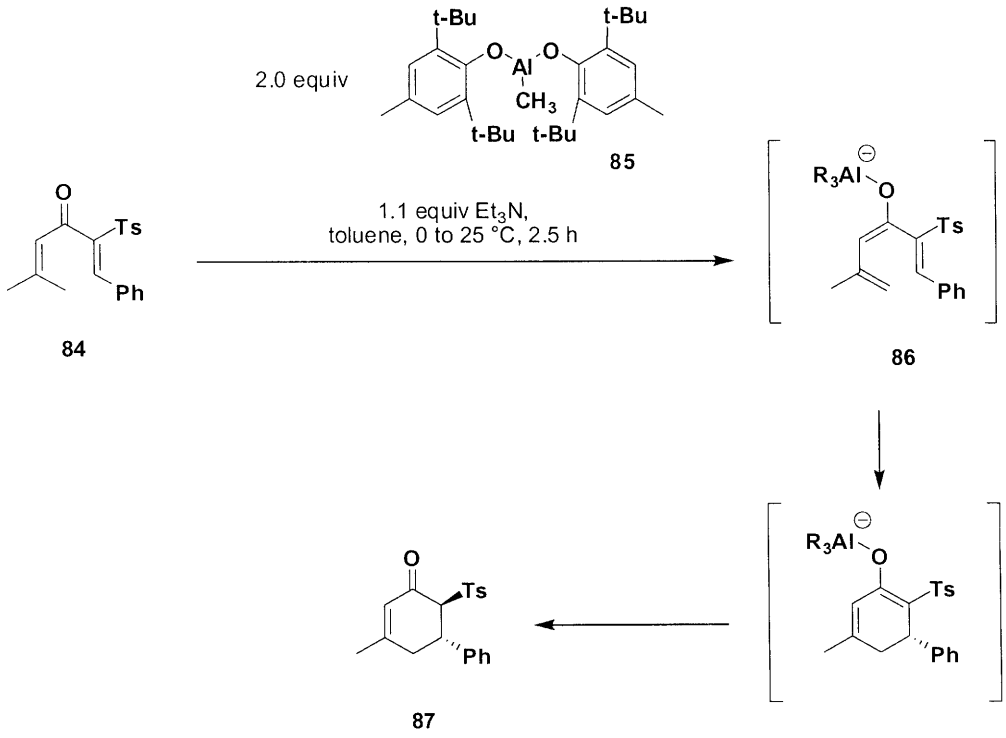
75 **76** **77** **78**

More recently, Magomedov has exploited this type of ring closure in two methods for the preparation of cyclohexenones. In his original approach,[37] addition of a 2-sulfonyl vinyllithium species to a cyclobutenone produced cyclohexenones in a process reminiscent of the Moore and Liebeskind synthesis of phenols and quinones.[38] For example, addition of the vinyllithium species **79** to 3-phenylcyclobutenone provided 3-oxidocyclobutanone **80**, which upon warming underwent electrocyclic ring opening to provide 3-oxido-1,3,5-triene **81**. Six-electron electrocyclic ring closure then produced the stabilized cyclohexenone enolate **82.** Following aqueous workup, the thermodynamically favored *trans*-cyclohexenone **83** was obtained.

[35] Corey, E. J.; Burke, H. J. *J. Am. Chem. Soc.* **1956,** *78*, 174.
[36] Bellamy, A. J.; Crilly, W.; Farthing, J.; Kellie, G. M. *J. Chem. Soc., Perkin Trans. 1* **1974**, 2417.
[37] Magomedov, N. A.; Ruggiero, P. L.; Tang, Y. *J. Am. Chem. Soc.* **2004**, *126*, 1624.
[38] For a review, see: Danheiser, R. L.; Dudley, G. B.; Austin, W. F. In *Science of Synthesis;* Danheiser, R. L. Ed.; Thieme, Stuttgart, 2006; Vol. 23, pp 547-555.

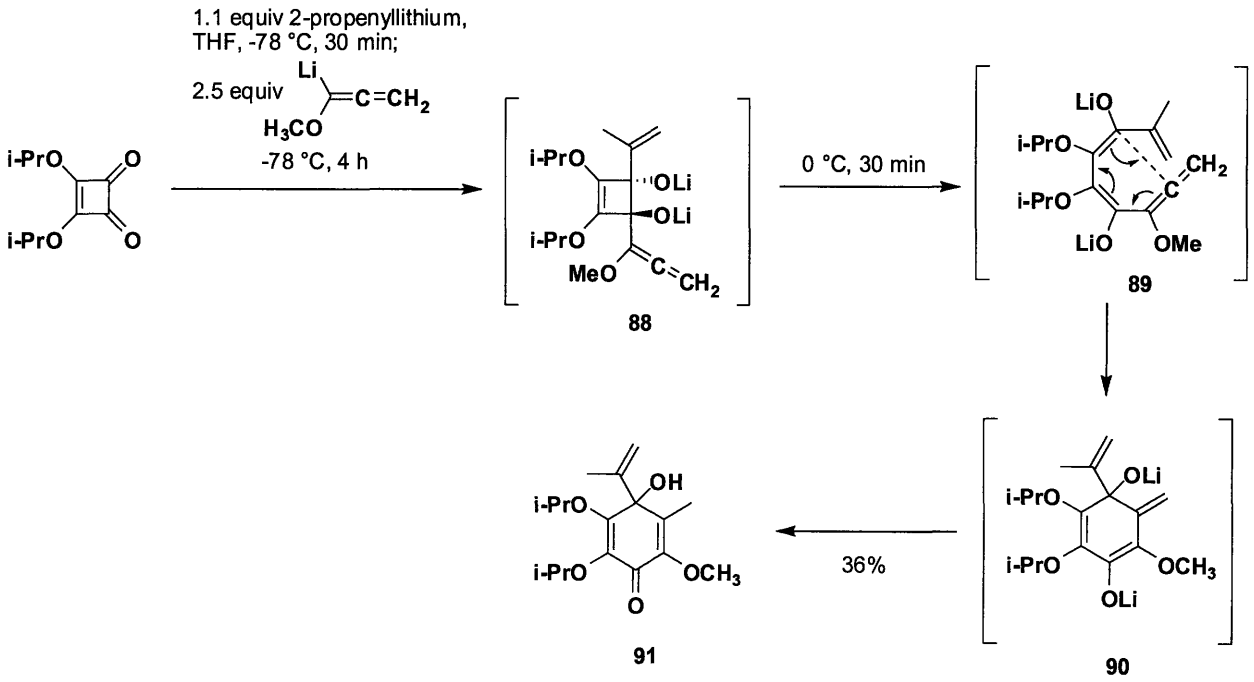


Similarly, enolization of the cross conjugated divinyl ketone **84** with triethylamine in the presence of MAD (**85**) gave the aluminum trienolate **86** which cyclized to provide cyclohexenone **87**.[39] In both of these methods the presence of an electron-withdrawing 2-sulfonyl group is essential for ring closure.



[39] Magomedov, N. A.; Ruggiero, P. L.; Tang, Y. *Org. Lett.* **2004**, *6*, 3373

Paquette has reported related 6π electrocyclizations in which one of the π-bonds is incorporated in an allene. Addition of 2-propenyllithium to diisopropyl squarate, followed by subsequent addition of methoxyallenyllithium, resulted in selective formation of *trans*-cyclobutenone **88** due to steric factors governing the approach of the allenyllithium compound. Upon warming, electrocyclic cleavage of cyclobutenone **88** forms the (*Z*)-polyene **89** which undergoes selective 6π electrocyclic ring closure of the type shown, in preference to 8π electrocyclization or the alternative mode of 6π ring closure. Quenching of **90** then provides the cyclic divinyl ketone **91**.



At the outset of our investigation, we believed that the accelerating effects of the 3-oxido and ketene substituent would reinforce each other and result in an extremely facile triene electrocyclization. We hoped that the cyclization would be sufficiently fast to dominate the other reaction pathways available to the dienylketene and provide good yields of the desired resorcinols.

Chapter 2

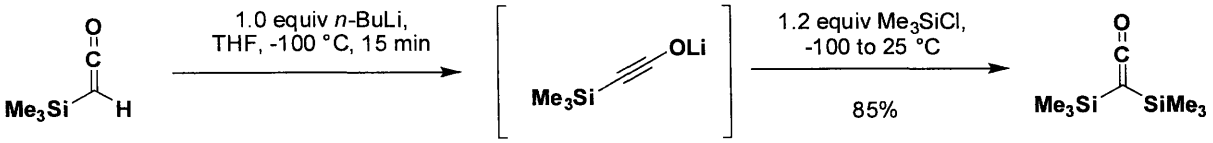
Preparation of the Annulation Substrates

A number of methods potentially could provide access to the substrates required for the investigation of our proposed benzannulation. The first half of this chapter presents a brief review of known methods for the generation of ynolates, the 2π component in our proposed benzannulation. The latter half of the chapter then discusses the specific methods employed for the preparation of the ynolate precursors and the TAS-vinylketenes used in our studies.

General Approaches to the Synthesis of Ynolates

Ynolates, the nucleophilic partner in our benzannulation, are species related to enolates that bear a triple bond in place of the enolate double bond. In contrast to enolates, which are widely used as synthetic intermediates, relatively few reports exist on the preparation and use of ynolates in synthesis. This disparity is due in part to the relative ease of generation of enolates compared to ynolates.

For instance, while enolates are readily prepared by deprotonation of carbonyl compounds, the deprotonation of mono-alkyl ketenes has not been reported. However, Rathke has reported the preparation of bis(trimethylsilyl)ketene upon treatment of trimethylsilylketene with base and trapping with chlorotrimethylsilane.[40] Several bases were examined, and *n*-BuLi

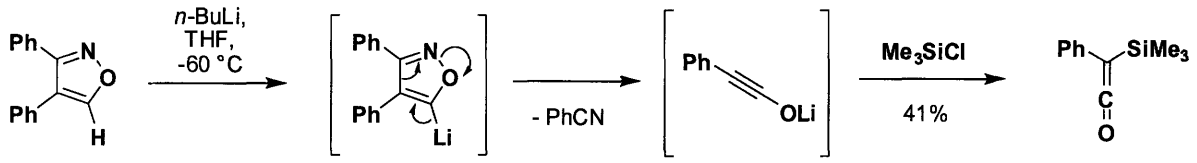


[40] Woodbury, R. P.; Long, N. R.; Rathke, M. W. *J. Org. Chem.* **1978**, *43*, 376.

proved to be the most efficient for ynolate formation, providing the bis-silylketene in 85% yield upon trapping. The successful preparation of silyl ynolates by this method and the absence of a similar preparation of alkyl-substituted ynolates is most likely due to the increased stability and reduced electrophilicity of silylketenes relative to alkylketenes (*vide supra*).

Despite these challenges, the potential synthetic utility of this unique class of compounds has sparked investigations into their chemistry, and recently several convenient and general methods for their generation have been reported.

The first report of ynolates in the literature appeared in 1975 in a communication by Schöllkopf and Hoppe.[41] Diphenyl isoxazole (**92**) was treated with butyllithium followed by chlorotrimethylsilane. However, instead of the expected tri-substituted isoxazole, the product of the reaction was determined to be phenyl(trimethylsilyl)ketene (**94**). To explain this result, Schöllkopf and Hoppe invoked the intermediacy of phenyl ynolate **93**, proposed to form from fragmentation of the lithium isoxazole. Explorations of the scope and generality of this method have not been reported.



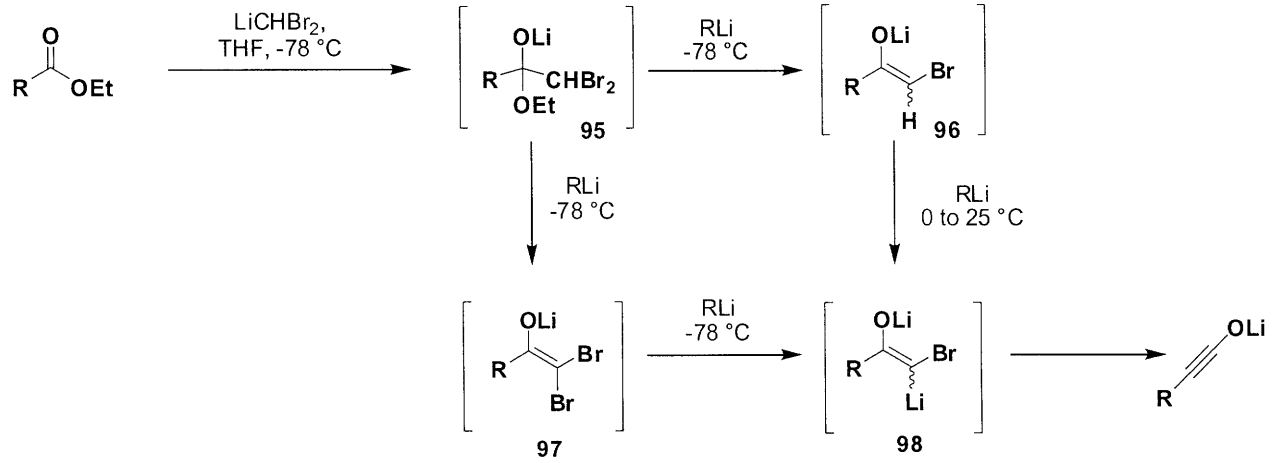
92 **93** **94**

Since this initial paper, a number of reports on the preparation and chemistry of ynolates have appeared and the field has been the subject of a number of reviews.[42] The first

[41] Schöllkopf, U.; Hoppe, I. *Angew. Chem., Int. Ed. Eng.* **1975**, *14*, 765.
[42] Shindo, M. *Tetrahedron* **2007**, *63*, 10. (b) Shindo, M. *Synthesis* **2003**, 2275. (c) Shindo, M. *Chem. Soc. Rev.* **1998**, *27*, 367.

comparatively general route to ynolates to appear was reported by Kowalski in 1982.[43] Treatment of an ester with 2.2 equivalents of $LiCHBr_2$ followed by 5 equivalents of butyllithium provided ynolates which could be trapped with an alcohol to give a homologated ester. The reaction is believed to proceed via the mechanism shown in Scheme 9, in which $LiCHBr_2$ adds to the ester to give the tetrahedral intermediate **95**, for which there are two productive reaction pathways. β-Elimination of ethoxide forms the dibromo enolate **97**, which upon metal-halogen exchange with *n*-BuLi provides the dilithium intermediate **98**. This intermediate can also be reached by metal-halogen exchange of **95**, β-elimination of ethoxide to form the monobromo enolate **96**, and deprotonation by *n*-BuLi or excess $LiCHBr_2$. Upon warming, **98** eliminates lithium bromide and 1,2-rearrangement takes place to afford ynolates in a process analogous to the Hoffman rearrangement of amides.

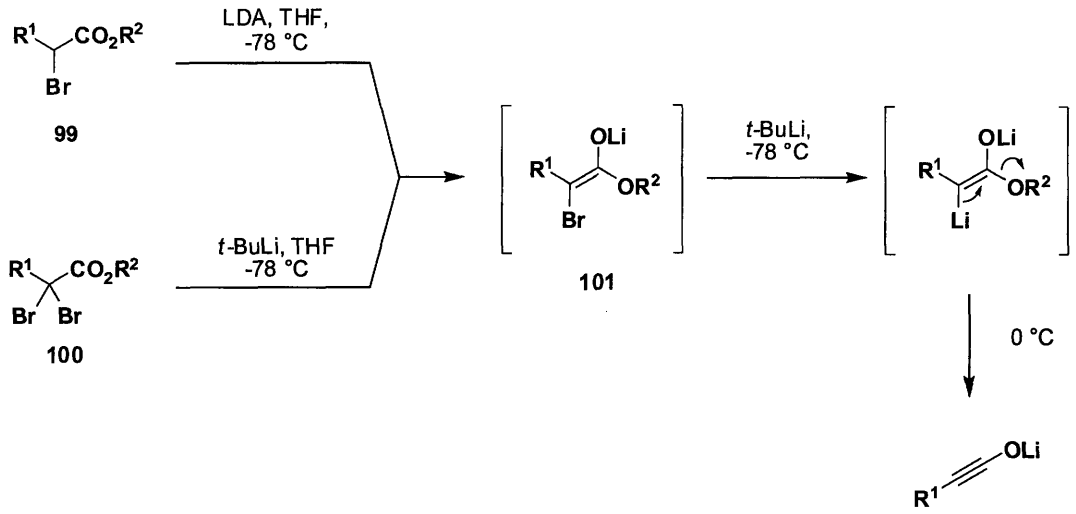
Scheme 9. Mechanism of the Formation of Ynolates from Esters



[43] (a) Kowalski, C. J.; Fields, K. W. *J. Am. Chem. Soc.* **1982,** *104,* 321. (b) Kowalski, C. J.; Haque, M. S.; Fields, K. W. *J. Am. Chem. Soc.* **1985**, *107*, 1429. (c) Kowalski, C. J.; Reddy, R. E. *J. Org. Chem.* **1992**, *57*, 7194. (d) Kowalski, C. J.; Lal, G. S.; Haque, M. S. *J. Am. Chem. Soc.* **1986**, *7127.*

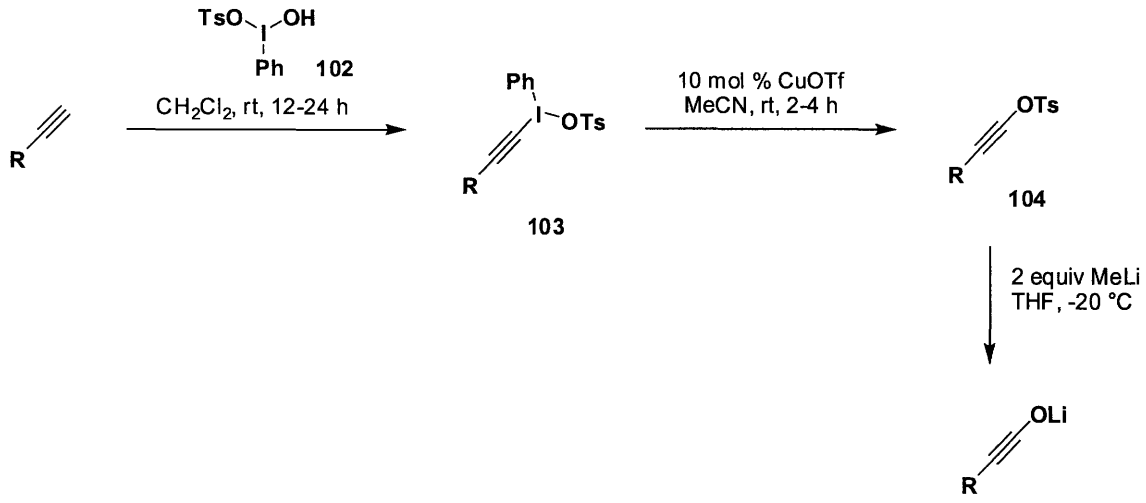
Shindo has reported a similar process based on the cleavage of ester dianions. Metal-halogen exchange of an α-dibromo ester[44] (**100**) or deprotonation of an α-bromo ester[45] (**99**) produces a bromo ester enolate of type **101**. Metal-halogen exchange with excess *t*-BuLi followed by β-elimination of the alkoxide then produces ynolates.

Scheme 10. Formation of Ynolates from α-Bromo and Dibromo Esters

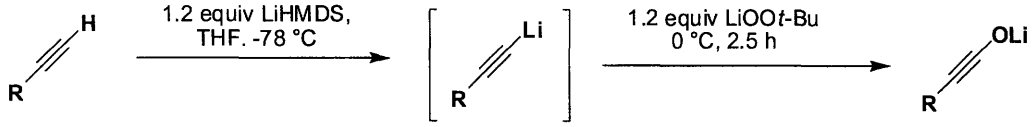


In addition to methods based on ester-derived starting materials, ynolates can also be generated by cleavage of the sulfur-oxygen bond in alkynyl tosylates.[46] Treatment of a terminal alkyne with the hypervalent iodonium reagent **102** provides alkynyl iodonium tosylates (**103**), which upon treatment with catalytic copper triflate form stable alkynyl tosylates (**104**). Reaction of these alkynes with 2 equivalents of methyllithium provides ynolates, which can be trapped with silyl, stannyl, or germyl chlorides in up to 93% yield.

[44] (a) Shindo, M.; Sato, Y.; Shishido, K. *Tetrahedron* **1998**, *54*, 2411. (b) Shindo, M.; Matsumoto, K.; Shishido, K. *Org. Synth.* **2007**, *84*, 11.
[45] Shindo, M. *Tetrahedron Lett.* **1997**, *38*, 4433.
[46] Stang, P. J.; Roberts, K. A. *J. Am. Chem. Soc.* **1986**, *108*, 7125.



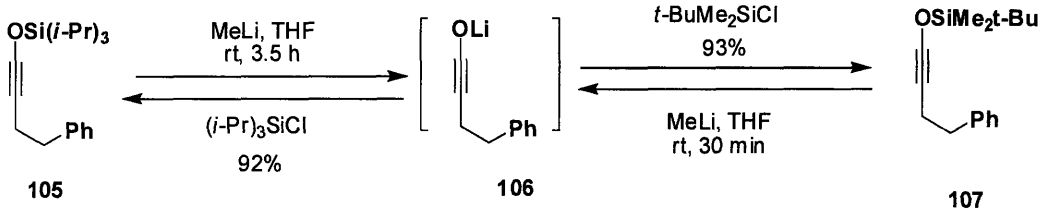
Julia has reported a method for formation of ynolates from alkynes that involves direct oxidation of the terminal carbon.[47] Nucleophilic displacement of *t*-butoxide from LiO*Ot*-Bu by lithium acetylides provides ynolates in excellent yield.



Unfortunately, none of these methods appeared suitable for employment in our benzannulation due to the presence of reaction mixture components such as excess alkyllithium reagents or nucleophilic byproducts that could potentially react competitively with the TAS-vinylketene benzannulation partner. In order to avoid these complications, we centered our initial efforts on the generation of ynolates via cleavage of the silyl ether in siloxy alkynes. This method was first demonstrated in 1986 by Kowalski, who showed that reaction of triisopropylsiloxy alkyne **105** and *t*-butyldimethylsilyl ether **107** with MeLi at rt generates the corresponding ynolate (**106**) which can be trapped as either silyl ether **105** or **107** in excellent yield.[43d] Such an approach is analogous to the regiospecific generation of enolates from silyl

[47] (a) Julia, M.; Saint-Jalmes, V. P.; Verpeaux, J.-N. *Synlett* **1993**, 233. (b) Julia, M.; Saint-Jalmes, V. P.; Plé, K.; Verpeaux, J.-N.; Hollingworth, G. *Bull. Soc. Chim. Fr.* **1996**, *133*, 15.

enol ethers first employed by Stork and Hudrlik.[48] The use of this method, in marked contrast to other methods, offers the distinct advantage that the tetraalkylsilane byproducts of ynolate generation are expected to be inert towards reaction with TAS-vinylketenes or any other intermediates in the benzannulation.



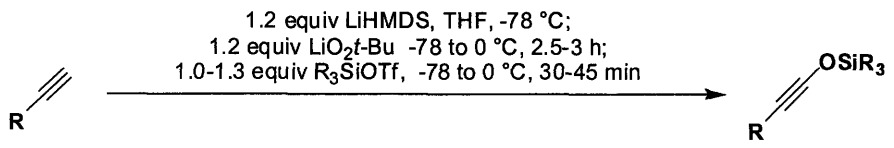
Preparation of the Siloxy Alkyne Partners

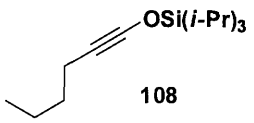
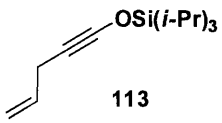
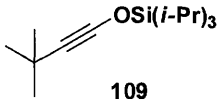
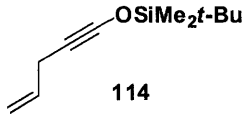
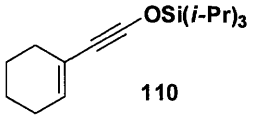
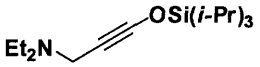
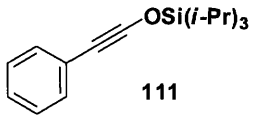
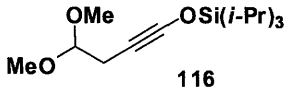
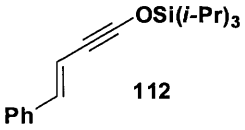
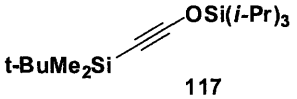
There are a number of reported methods for the preparation of siloxy alkynes, and almost all of them rely upon the silylation of an ynolate. Employed in this manner, siloxy alkynes can be viewed as synthetic equivalents to ynolates, with the particular advantages of allowing for isolation, purification, and storage. Indeed, triisopropylsiloxy alkynes can be purified by distillation at elevated temperatures, and in most cases, by conventional chromatography on silica gel. They can also be stored at 0 °C in a dilute solution for weeks, months, and in some cases even longer with minimal decomposition.

We employed the complementary methods of Kowalski[43] and Julia[46] for preparation of the requisite siloxy alkynes, as both approaches are general and have the distinct advantage of utilizing commercially available starting materials. Generally the method of Julia was preferred to that of Kowalski, being both the more efficient and less time consuming process. As depicted in Table 1, a wide variety of substituents are tolerated in the oxidation and yields are generally

[48] Stork, G.; Hudrlik, P. F. *J. Am. Chem. Soc.* **1968**, *90*, 4464.

Table 1. Preparation of Siloxy Alkynes from Terminal Alkynes



entry	product	yield (%)[a]	entry	product	yield (%)[a]
1	 **108**	86[b]	6	 **113**	69
2	 **109**	84[c]	7	 **114**	48
3	 **110**	87	8	 **115**	77
4	 **111**	60-85[c,d]	9	 **116**	79
5	 **112**	29	10	 **117**	65

[a] Isolated yield. [b] Sweis, R. F.; Schramm, M. P.; Kozmin, S. A. *J. Am. Chem. Soc.* **2004**, *126*, 7442. [c] Sun, J.; Kozmin, S. A. *Angew. Chem., Int. Ed.* **2006**, *45*, 4991. [d] Ref 47a.

good. In some cases, particularly those involving unsaturated siloxy alkynes, we encountered problems during purification by chromatography. Hydrolysis of excess silyl triflate present in the crude reaction product generated acid upon exposure to silica gel and promoted decomposition of the siloxy alkynes. To circumvent this, the crude reaction mixtures were concentrated for several hours at less than 300 mmHg and then rapidly filtered through a short plug of silica gel prior to purification to ensure complete removal of excess silyl triflate.

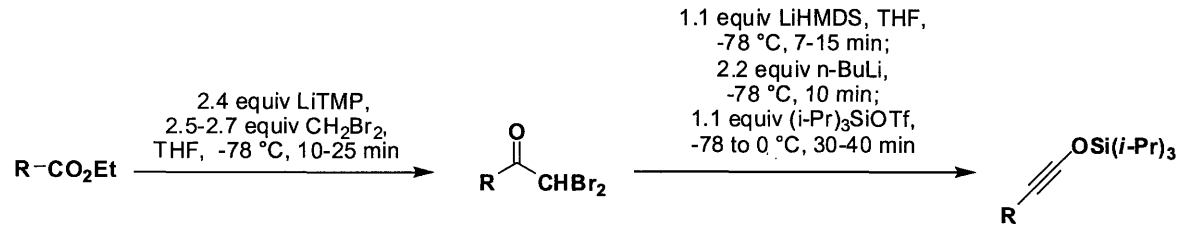
In cases where an appropriately substituted terminal alkyne was not available, we turned instead to the method of Kowalski (Table 2). We elected to use a modification of the original procedure in which the intermediate dibromomethyl ketone was isolated as originally described by Smith in his synthesis of cylindrocyclophane F.[49] In the original one-pot Kowalski procedure excess dibromomethane was present in the reaction mixture and, since this compound can be deprotonated and silylated, excess *n*-butyllithium (5.0 equiv) and silylating agent (5.0 equiv) were required. In the Smith modification, the dibromo ketone resulting from quenching of the dibromo enolate of type **97** is isolated and purified, and the enolate is regenerated by deprotonation with HMDS. Since no CH_2Br_2 is present, far less *n*-BuLi (2.2 equiv) and silylating agent (1.1 equiv) are required for complete conversion to the siloxy alkyne. In practice, purification of the dibromomethyl ketones was challenging due to the presence of monobromo ketones resulting from metal-halogen exchange, and so partially purified mixtures were usually carried on to the next step. Several siloxy alkynes were prepared in this fashion and the yields over the two steps were adequate for our purposes.

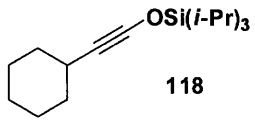
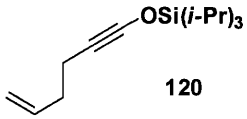
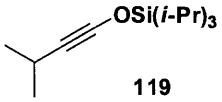
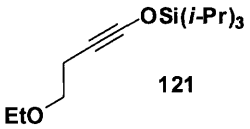
Preparation of the TAS-Vinylketene Partners

As mentioned in Part I, the method best suited for the preparation of the TAS-vinylketenes in terms of yield, generality, and ease of execution is the photochemical variant of the Wolff rearrangement of α′-silyl-α′-diazo-α,β-unsaturated ketones. Along these lines, the TAS-vinylketenes employed in our benzannulation study were prepared by this method via a four step sequence beginning with methyl ketones. The majority of the ketones we required are

[49] Smith, A. B., III; Adams, C. M.; Kozmin, S. A.; Paone, D. V. *J. Am. Chem. Soc.* **2001**, *123*, 5925.

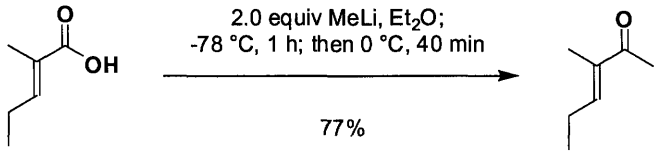
Table 2. Preparation of Siloxy Alkynes from Esters



entry	product	yield (%)[a]	entry	product	yield (%)[a]
1	 **118**	49	3	 **120**	38
2	 **119**	43	4	 **121**	40

[a] Isolated yield over two steps.

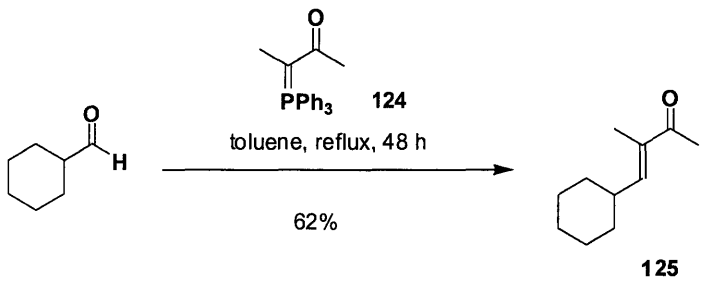
readily available commercially, and the remainder were prepared in a single step from commercial precursors. The known hexenone **123**[50] was prepared from the corresponding acid **122** in 77% yield upon treatment with two equivalents of methyllithium.



122 **123**

Previously unknown enone **125** was prepared from cyclohexane carboxaldehyde via treatment with 1.5 equivalents of the stabilized Wittig reagent **124**.[51] Reaction in refluxing toluene for two days afforded a 92:8 mixture of the (*E*)- and (*Z*)-enones, easily distinguished by

[50] (a) McGreer, D. E.; Chiu, N. W. K.; Vinje, M. G. *Can. J. Chem.* **1965**, *43*, 1398. (b) Marr, D. H.; Stothers, J. B. *Can. J. Chem.* **1965**, *43*, 596.



the characteristic ^{1}H NMR shifts of the single vinyl proton in each (6.40 ppm for (*E*)-enone **125**, 5.45 ppm for the (*Z*)-enone). The isomers could be readily separated by column chromatography on silica gel to yield the desired (*E*)-enone **125** in 62% isolated yield.

There have been a number of reported methods for the preparation of α-diazo ketones from methyl ketones,[52] but the procedure of choice for α,β-unsaturated diazo ketones is the detrifluoroacetylative diazo transfer protocol developed in our laboratory.[53] Generation of the kinetic enolate of the methyl ketone with LiHMDS at -78 °C and trapping with 2,2,2 trifluoroethyl trifluoroacetate provides activated β-diketones. Upon treatment of the crude diketones with methanesulfonyl azide[54] and triethylamine in wet acetonitrile, diazo transfer occurs with concomitant loss of the trifluoroacetyl activating group to give the desired diazo ketones. The process is quite general and provides the expected diazo ketones in good yields (Table 3).

The α'-diazo-α,β-unsaturated ketones were then silylated employing silyl triflates in the presence of Hünig's base, according to a procedure previously employed in our laboratory for

---

[51] For the preparation of this reagent, see: Aitken, A. R.; Atherton, J. I. *J. Chem. Soc. Perkin Trans. 1* **1994**, 1281.

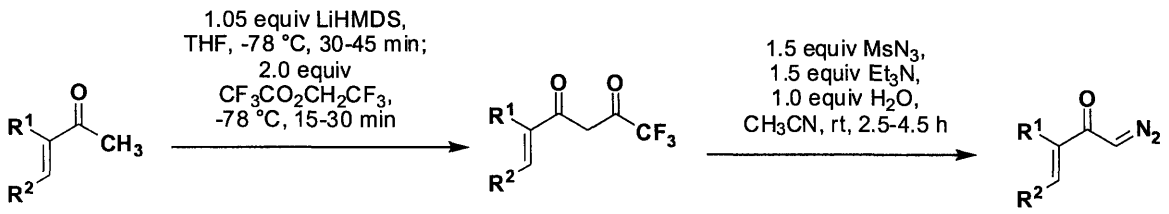
[52] For reviews of the preparation of α-diazo ketones, see: (a) Doyle, M. P.; McKervey, M. A.; Ye, T. Synthesis of α-Diazo Carbonyl Compounds. *Modern Catalytic Methods for Organic Synthesis of Diazo Compounds: from Cyclopropanes to Ylides*; Wiley & Sons: New York, 1998; Chapter 1, pp 1-60. (b) Regitz, M.; Maas, G. *Diazo Compounds: Properties and Synthesis*; Academic Press: Orlando, 1986.

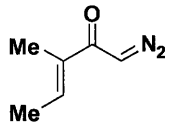
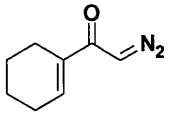
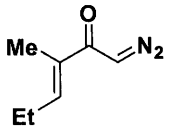
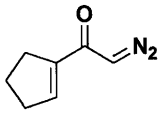
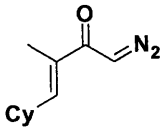
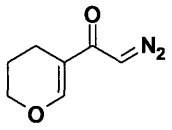
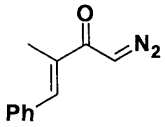
[53] Danheiser, R. L.; Miller, R. F.; Brisbois, R. G.; Park, S. Z. *J. Org. Chem.* **1990**, *55*, 1959.

[54] Prepared by the reaction of methanesulfonyl chloride with 1.5 equiv of NaN_3 in acetone at rt for 1.5-4 h according to the procedure described in Ref 53.

the synthesis of **18** and **126**. The reaction of most of the new diazo ketones proceeded uneventfully, as depicted in Table 4.

Table 3. Preparation of α-Diazo Ketones



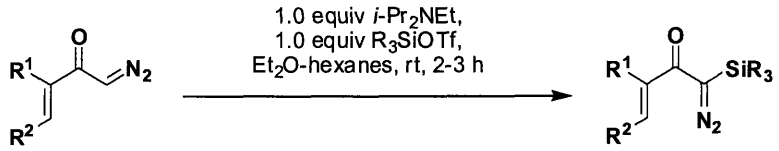
entry	product		yield (%)[a]	entry	product		yield (%)[a]
1		**126**	84[b]	5		**18**	87[b]
2		**127**	76	6		**130**	73
3		**128**	83	7		**131**	47
4		**129**	85				

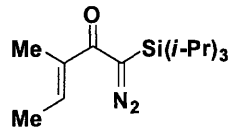
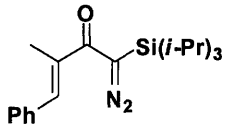
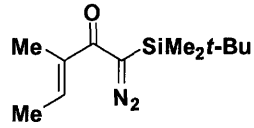
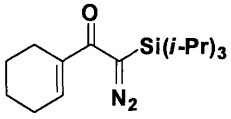
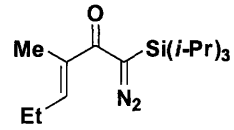
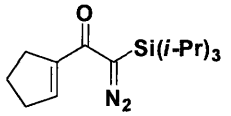
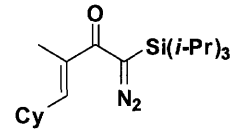
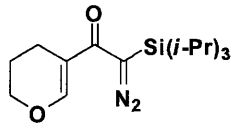
[a] Isolated yield. [b] Ref 53.

Much to our surprise, however, initial attempts to silylate the cyclopentenyl diazo ketone **130** were not successful. Addition of triisopropylsilyl triflate to a stirred solution of **130** and Hünig's base led to the formation of the desired silyl diazo ketone contaminated with a comparable amount of an inseparable byproduct. The similar formation of an unidentifiable byproduct has been observed previously in our laboratory upon attempted silylation of diazo

enones bearing a single β-substituent. We hypothesized in these cases that the initial step in the decomposition pathway was a reversible 1,3-(C→O) silyl shift of the silylated diazo ketone.[55]

Table 4. Preparation of α-Silyl-α-Diazo Ketones



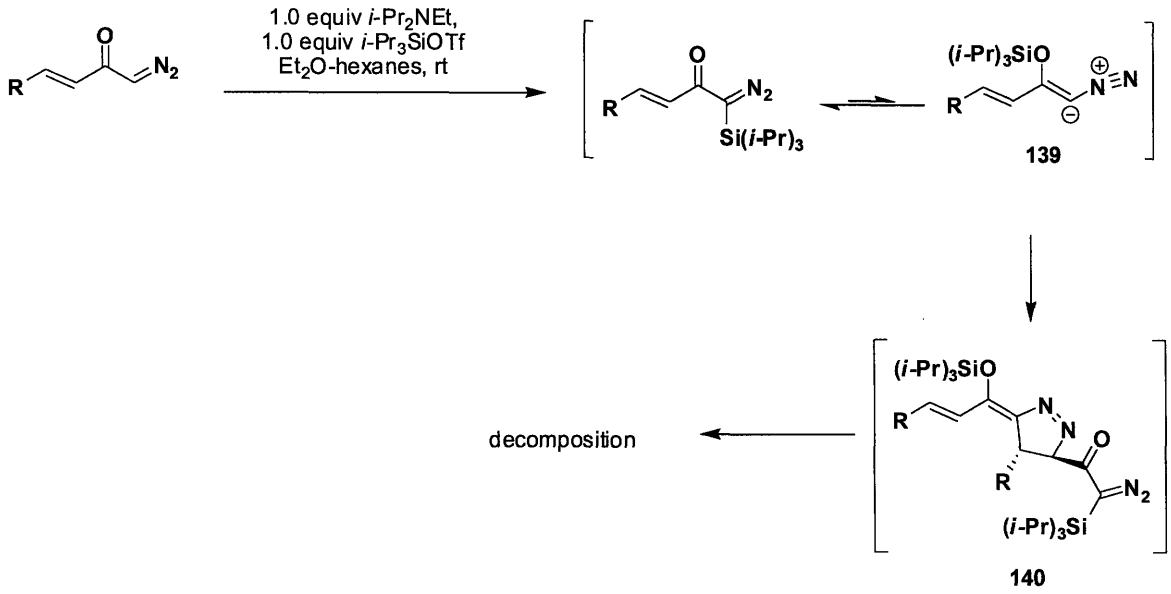
entry	product		yield (%)[a]	entry	product		yield (%)[a]
1		**132**	86-89[b]	5		**136**	68
2		**133**	75	6		**19**	75[b]
3		**134**	76	7		**137**	77
4		**135**	80	8		**138**	–[c]

[a] Isolated yield. [b] Ref 12. [c] Carried on impure - see Table 5, Entry 8.

Such shifts are known, and Maas has shown that the resulting dipole analogous to **139** can be trapped with dipolarophiles such as N-phenylmaleimide.[56] The unknown contaminant may have

[55] Loebach, J. L. Ph. D. Thesis, Massachusetts Institute of Technology, Cambridge, MA, 1995, pp 81-84.
[56] Mumschauer, R.; Maas, G. *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 306.

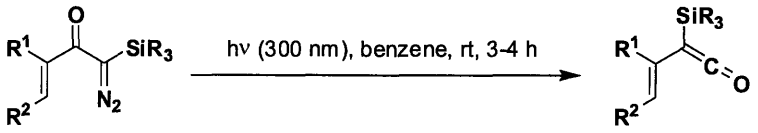
formed by decomposition of a pyrazoline of type **140** formed by the trapping of **139** with the vinyl substituent of a diazo or silyl diazo ketone.

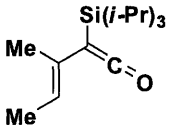
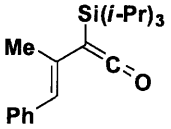
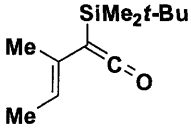
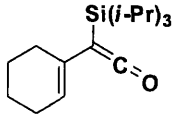
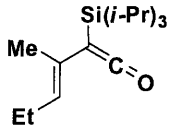
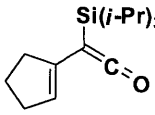
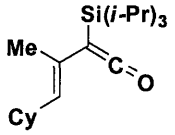
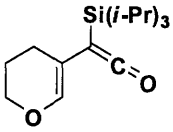


Consistent with this hypothesis, it was found that formation of the byproduct can be minimized by conducting the silylation under conditions of high dilution and employing inverse addition of a preformed solution of diazo ketone and Hünig's base to a stirring solution of silyl triflate.[55] Application of this procedure to the synthesis of cyclopentenyl silyl diazo ketone **137** was successful provided that the reaction mixture was not concentrated prior to purification, and the desired ketone was obtained in 77% yield. It is not clear why this side reaction occurs to a substantial degree in the synthesis of **137** but not in the case of other α,β-substituted diazo enones such as **19**, though we presume that activation of the alkene toward cycloaddition by the additional angle strain of the five-membered ring plays a significant role.

Irradiation of the α′-diazo-α′-silyl-α,β-unsaturated ketones with 300 nm light at rt for 3-4 hours cleanly produced TAS-vinylketenes in good to excellent yield. In this fashion a variety of ketenes were prepared uneventfully, as summarized in Table 5.

Table 5. Synthesis of TAS-Vinylketenes



entry	product		yield (%)[a]	entry	product		yield (%)[a]
1		**21**	79-80[b]	5		**144**	46
2		**141**	64	6		**20**	89[b]
3		**142**	74	7		**145**	66
4		**143**	83	8		**146**	29[c]

[a] Isolated yield. [b] Ref 12. [c] Two steps from **127**, see Table 4, Entry 8.

Chapter 3

Benzannulation via Reaction of TAS-Vinylketenes with Lithium Ynolates

Feasibility of the Annulation

For our initial attempts at benzannulation, we elected to examine the reaction of the cyclohexyl-substituted ynolate and the cyclohexenyl TAS-vinylketene **20** as the annulation partners. In the event, a solution of **118** in THF was stirred at room temperature while one equivalent of methyllithium was added dropwise over several minutes. There were no changes in the appearance of the reaction mixture, but TLC on silica gel allowed for easy monitoring of the progress of the reaction. Staining with $KMnO_4$ showed a decrease in the intensity of the high R_f spot associated with the siloxy alkyne and the formation of an intense baseline spot. This was interpreted to indicate that cleavage of the silyl ether was occurring and consumption of starting material was complete within 3.5 h. At that point, a solution of the ketene **20** in THF was added rapidly via cannula. The reaction mixture developed a yellow color that deepened over several minutes, and TLC showed the formation of a single new product that produced a very dark spot upon staining with PMA. Due to the presence of byproducts with $R_f = 0$, disappearance of the ynolate could not be monitored by TLC. As a result, the reaction mixture was allowed to stir for one hour at room temperature to ensure complete reaction. Aqueous workup with ammonium chloride and purification by column chromatography on silica gel yielded a product whose ^{13}C NMR data indicated the presence of the expected aromatic system, displaying resonances for four aromatic carbons between 110 and 135 ppm, and two characteristic oxygen-substituted aryl carbons at approximately 153 ppm. We were concerned, however, that the ^{1}H NMR data obtained for the new compound was not in accord with that for the expected annulation product.

In particular, we expected the two phenolic protons of **147** to exhibit similar ^{1}H NMR shifts, while the downfield resonances for the annulation product appeared at 4.71 and 6.19 ppm (Figure 2).

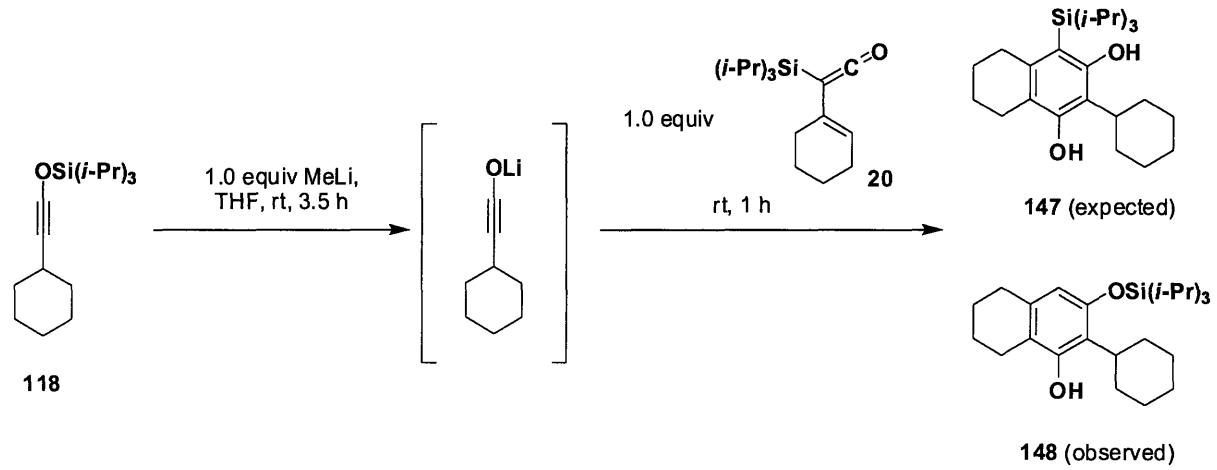
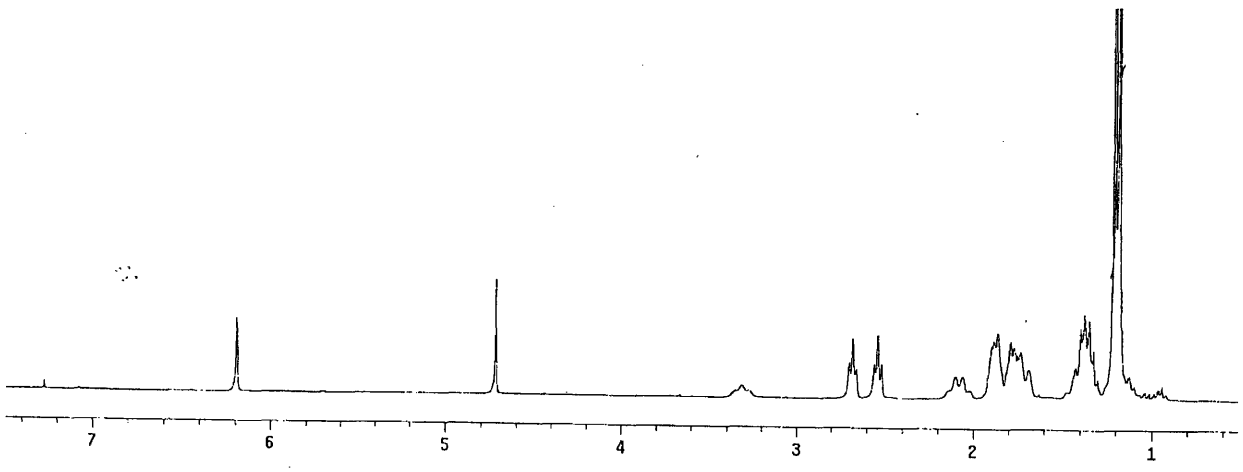


Figure 2. Proton NMR Spectra of Annulation Product **148.**

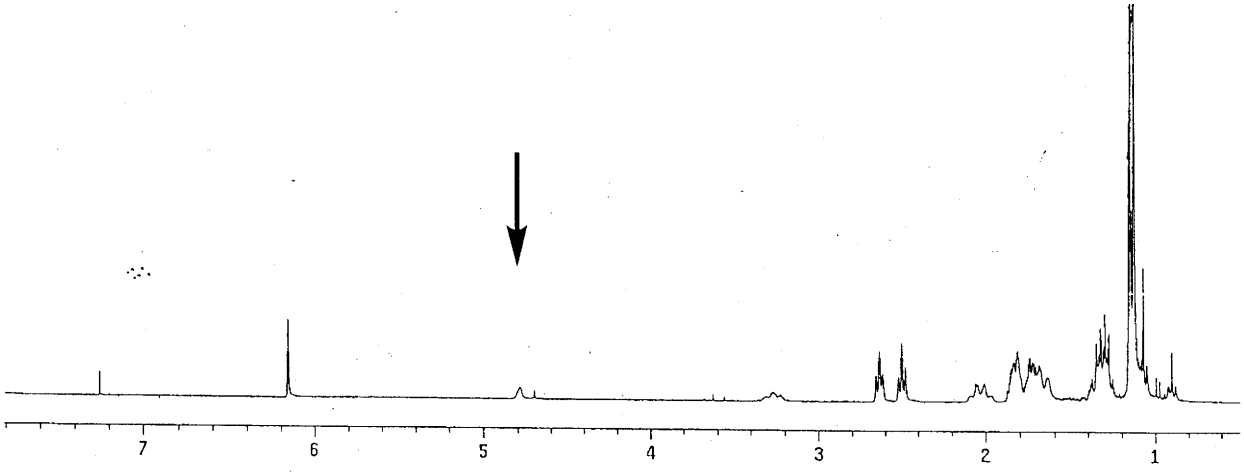


Identification of the Annulation Product

To establish whether both of the downfield resonances were due to phenolic hydrogen atoms, the annulation product was dissolved in D_2O and stirred for 15 minutes. ^{1}H NMR

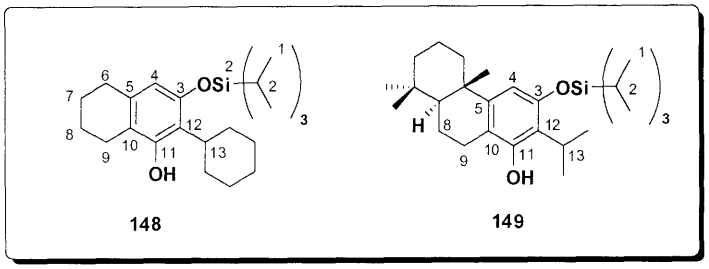
analysis of the resulting product showed that only the proton that appeared at 4.71 ppm exhibited exchange with deuterium (Figure 3). As a result of this experiment, the actual product of the

Figure 3. Proton NMR Spectra of Annulation Product **148** After Deuterium Exchange.



annulation was assigned as the 3-siloxyphenol **148** resulting from the migration of the triisopropylsilyl group from carbon to the adjacent oxygen. A complete assignment of the spectral data of **148**, and comparison with the known reference compound **149**[6h] is shown in Table 6. Table 7 presents data for the less complex annulation product assigned as **150**, which permits a closer comparison to the known compound **151**.[5] The structure of **151** was previously established unambigously on the basis of close examination of the ^{1}H and ^{13}C NMR shifts and comparison to similar compounds.

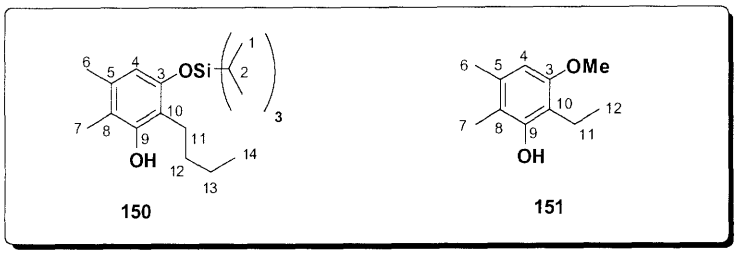
Table 6. Spectral Data for Phenols **148** and **149**.



	^{1}H NMR spectra (δ)	
	148	**149**
C-1	1.18 (d)	1.11 (d)
C-2	1.37 (m)	1.10-1.75 (m)
C-4	6.19 (s)	6.31 (s)
C-6	2.68 (app t)	-
C-7	1.70-2.16 (m)	2.35-2.75 (m)
C-8	1.70-2.16 (m)	1.85-2.15 (m)
C-9	2.54 (app t)	2.35-2.75 (m)
C-13	3.25 (m)	3.56 (sept)
OH	4.71 (s)	4.61 (s)

	^{13}C NMR spectra (δ)	
	148	**1**
C-3, C-11	152.2	152.9
	153.3	153.0
C-4, C-10, C-12	111.2	107.0
	115.4	113.7
	120.3	120.4
C-5	135.5	148.7
C-1	18.5	17.9
C-2	13.5	13.0

Table 7. Spectral Data for Phenols **150** and **151**.

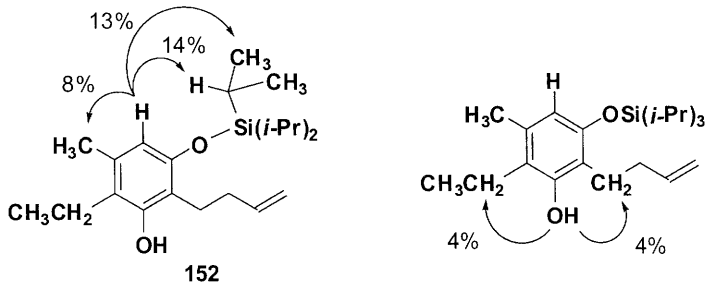


	^{1}H NMR spectra (δ)	
	150	**151**
C-1	1.13 (d)	-
C-2	1.28-1.36 (m)	-
C-4	6.28 (s)	6.33 (s)
C-6	2.20 (s)	2.25 (s)
C-7	2.10 (s)	2.11 (s)
C-11	2.63 (t)	2.62 (q)
C-12	1.36-1.55 (m)	1.12 (t)
C-13	1.36-1.55 (m)	-
C-14	0.95 (t)	-
OH	4.65 (s)	4.72 (s)

	^{13}C NMR spectra (δ)	
	150	**151**
C-3, C-9	152.6	151.9
	153.0	155.4
C-4, C-8, C-10	112.7	104.9
	114.7	114.5
	116.7	115.3
C-5	135.1	134.8
C-1	18.9	-
C-2	13.8	-
C-6	21.0	16.6
C-7	14.9	13.8
C-11	32.4	20.3

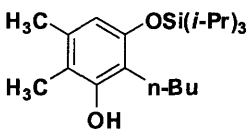
Additional support for our assignment of the product structure was obtained by nOe studies of the related annulation product **152**, shown in Figure 4. Irradiation of the single aromatic proton at 6.27 ppm in **152** resulted in enhancement of the singlet methyl resonance appearing at 2.23 ppm and both the methyl and methine resonances of the triisopropylsilyl group. In a separate experiment, irradiation of the phenolic proton (4.71 ppm) resulted in a modest enhancement of the methylenes assigned as part of the ethyl substituent and the butenyl substituent. Taken together, these results confirm the regiochemistry of the annulation products as that shown, and also support our assignment of the annulation products as silyl ethers.

Figure 4. NOE Studies of Phenol **152**

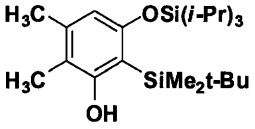


All of the other annulation products were assigned as the silyl ethers analogous to **148** and **152** based on the similarity of their spectral data to that of the products discussed above. The diagnostic ^{1}H resonances for the aryl proton and phenolic proton, as well as key IR absorbances for several examples are given in Table 8. The anomalous IR data and phenolic proton chemical shift observed for phenol **157** was attributed to an intramolecular hydrogen bond between the hydroxyl and the oxygen of the side chain ether.

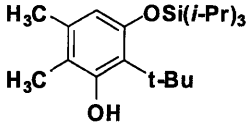
Table 8. Spectral Data for Selected Annulation Products



150

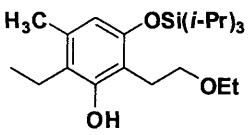


153

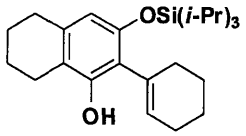


154

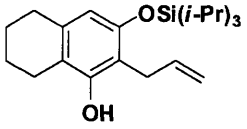
155



156



157

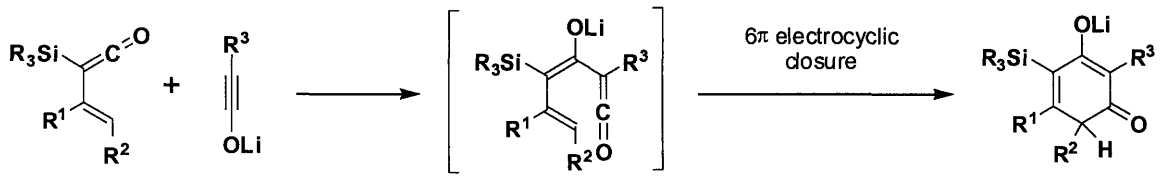


158

	150	153	154	155	156	157	158
Aryl-H (ppm)	6.28	6.25	6.22	6.36	6.25	6.13	6.23
Aryl-OH (ppm)	4.65	4.96	5.13	4.97	8.05	5.56	5.01
IR (cm^{-1})	3621 1617 1577	3603 1601 1558	3622 1610 1567	3552 1621 1570	3327 1615 1574	3512 1618 1574	3550 1618 1578

Mechanism of the Benzannulation

The formation of aromatic products requires addition of the ynolate to the TAS-vinylketene and ring closure. For reasons discussed in Chapter 1, we believe the initial stages of the benzannulation follow the pathway depicted below in which C-acylation of the ynolate is followed by 6π electrocyclic ring closure. We cannot entirely exclude the formation of a isomeric form of cyclohexadiene **161** by a Diels-Alder [4 + 2] cycloaddition of the ynolate with the TAS-vinylketene. However, the electronic requirements for cycloaddition make this path unlikely, as the cycloaddition of TAS-vinylketenes requires electron-deficient dienophiles.



159 160

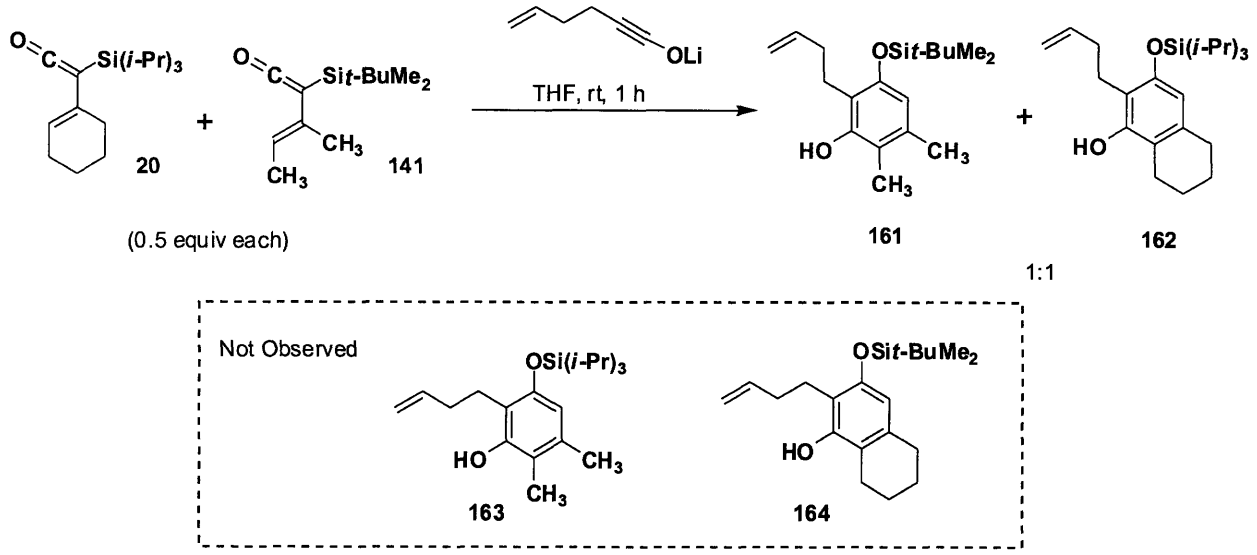
We were initially less certain of the mechanism by which the cyclohexadiene **160** was transformed to the observed siloxy phenol final products. We suspected that the formation of silyl ether products instead of the expected resorcinols was the result of an intramolecular C→O silyl shift, rather than an intermolecular silyl transfer, and to confirm our suspicions a crossover experiment was conducted (Scheme 11). In this experiment, a 1:1 mixture of triisopropylsilyl ketene **20** and (*tert*-butyldimethylsilyl)ketene **141** was reacted with one equivalent of the ynolate derived from alkyne **120**. NMR and GC-MS analysis of the crude reaction mixture showed the presence of only two aromatic products, assigned as **161** and **162,** each bearing the silyl group and substituents corresponding to a single ketene reactant. Neither **163** or **164**, the phenols that would result from intermolecular silyl group transfer, were detected in the crude product of the reaction.

As a result of this experiment, we believe that the observed siloxy phenols are formed by a series of tautomerizations and proton transfers culminating in an irreversible 1,3-(C→O) silyl shift as shown in Scheme 12 below. Silyl shifts in α-silyl ketones to form silyl enol ethers are well known processes,[57] and related rearrangements involving silylcyclohexadienones have been observed in our laboratory[12] and others.[58] In one recent example, Moser showed that upon heating ketene **165** at 165 °C in acetonitrile, the siloxy naphthol **167** was formed. He proposed

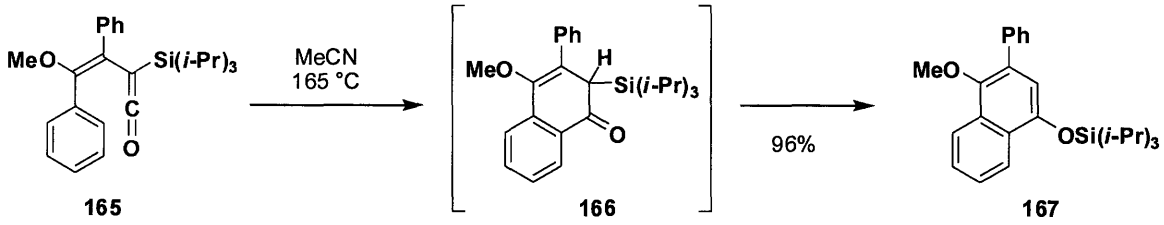
[57] For a recent theoretical study and leading references, see: Takahashi, M.; Kira, M. *J. Am. Chem. Soc.* **1999**, *121*, 8597.

[58] (a) Moser, W. H.; Sun, L.; Huffman, J. C. *Org. Lett.* **2001**, *3*, 3389. (b) Fogel, L.; Hsung, R. P.; Wulff, W. D.; Sommer, R. D.; Rheingold, A. L. *J. Am. Chem. Soc.* **2001**, *123*, 5580. (c) Chamberlin, S.; Wulff, W. D. *J. Org. Chem.* **1994**, *59*, 3047.

Scheme 11. Results of a Crossover Experiment



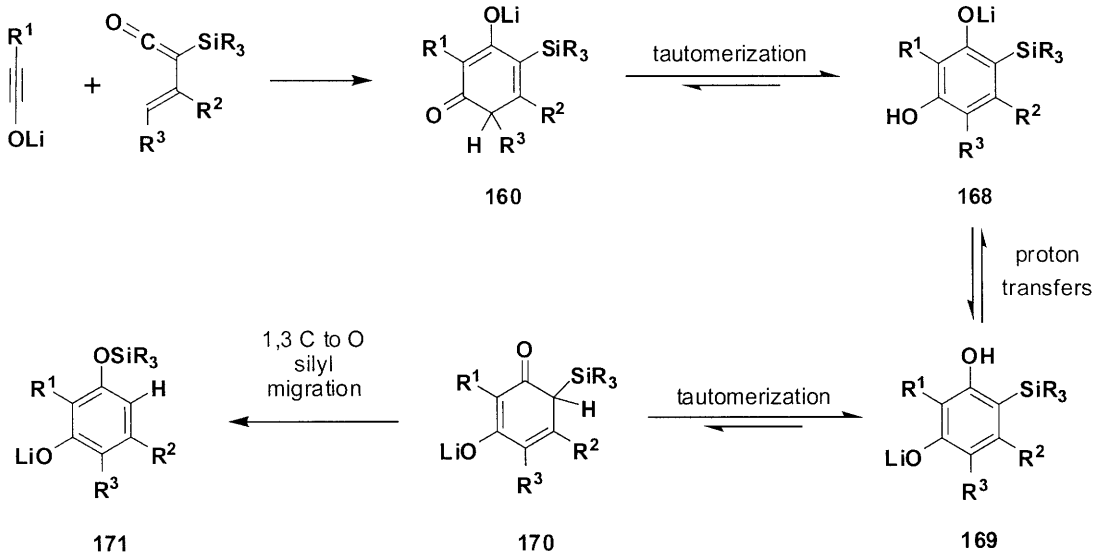
that the mechanism for formation of the observed product involves electrocyclization of the ketene followed by 1,5 hydride shift to provide cyclohexadiene **166**. A 1,3 C→O silyl shift then forms the naphthohydroquinone.



Similarly, we believe that the 3-siloxyphenolate product **171** is formed from a 2,4-cyclohexadienone of type **170**, itself formed by a series of reversible proton transfer and tautomerization steps. Tautomerization of the initially formed electrocyclization product provides the monolithium resorcinate salt **168**, which we propose equilibrates with its isomer, **169**. The relatively small difference in pK_{a1} and pK_{a2} values for the hydroxyl groups in

resorcinol (9.2 and 10.9 in water)[59] suggests that interconversion of the monolithium salts **168** and **169** may proceed via disproportionation to form a mixture of the corresponding resorcinol and its dilithium derivative. Tautomerization of **169** produces the 6-silyl-2,4-cyclohexadienone **170** which then aromatizes via an irreversible 1,3-silyl shift.

Scheme 12. Mechanism of Formation of the Observed Annulation Product



In an effort to further probe the mechanism of the annulation, the trialkylsilyl-substituted siloxy alkyne **117** was prepared. As expected, cleavage of the silicon-oxygen bond by methyllithium was substantially faster than cleavage of the carbon-silicon bond, providing the *t*-butyldimethylsilyl-substituted ynolate under the conditions employed in our previous benzannulations. Reaction of this ynolate with TAS-vinylketene **21** provided a mixture of two phenols, each bearing a single aromatic hydrogen, in a ratio varying from 73:27 to 50:50 and in combined yields of ca. 40-60%. While both of these compounds were sensitive to purification, column chromatography on acetone-deactivated silica gel in the presence of triethylamine

[59] Blanco, S. E.; Almandoz, M. C.; Ferretti, F. H. *Spectrochim. Acta, Part A* **2005**, *61*, 93 and references cited therein.

yielded samples of sufficient purity to permit identification. Comparison of the ^{1}H NMR spectra of 2-*tert*-butyldimethylsilylphenol[60] (**174**) and *tert*-butyldimethyl(phenoxy)silane[61] (**173**) revealed that the methyl resonances of a carbon-bound *tert*-butyldimethylsilyl group are farther downfield than those of an oxygen-bound group (Table 9). By analogy we assigned the major product of the benzannulation as either O-TBDMS ether **172a** or **172b**, and the minor product as the *ortho*-TBDMS phenol **173**. To date we have been unable to unambiguously distinguish between these two possibilities.

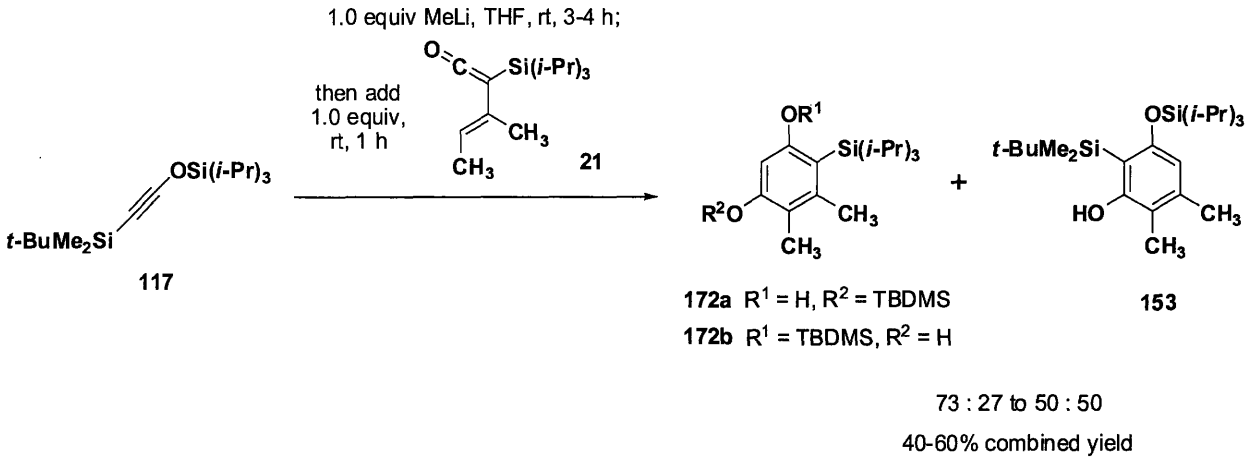
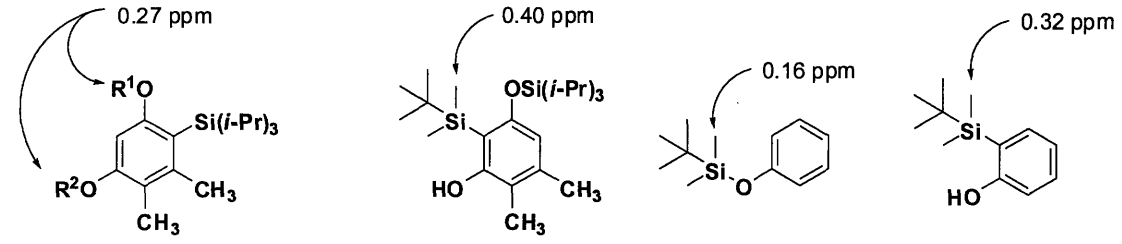


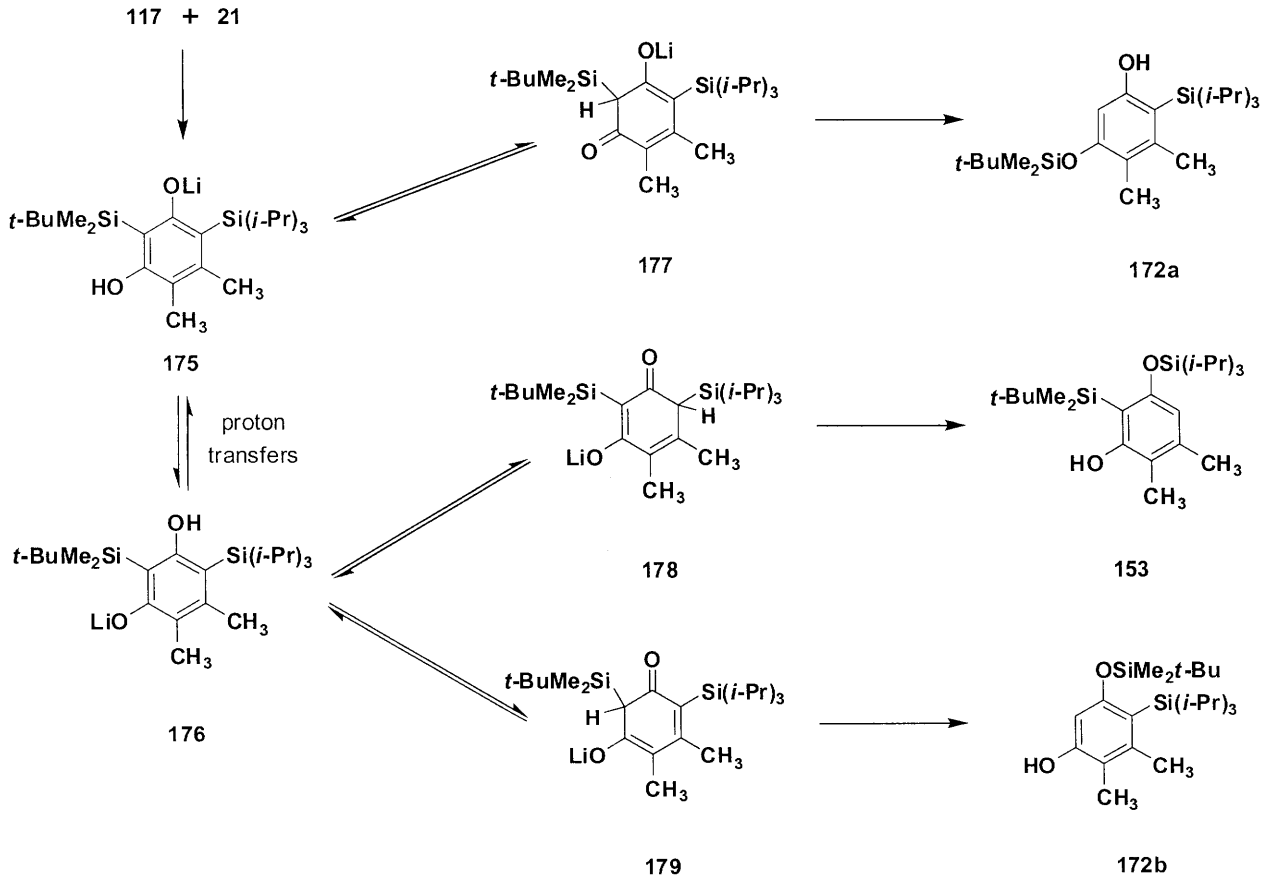
Table 9. Methyl ^{1}H NMR Shifts of TBDMS Groups



[60] Fukui, M.; Ikeda, T.; Oishi, T. *Chem. Pharm. Bull.* **1983**, *31*, 466.
[61] Sinhababu, A. K.; Kawase, M.; Borchardt, R. T. *Synthesis* **1988**, 710.

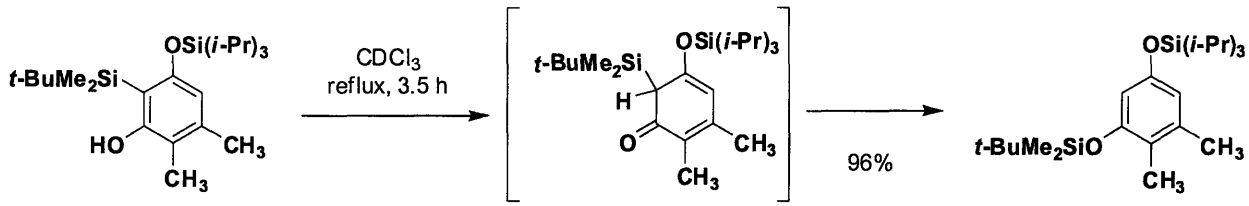
The formation of these products provides support for our proposal of the mechanism of the annulation. Scheme 13 outlines how this mechanism could give rise to **172** and **153**. Compound **153** is believed to form by the same pathway as other annulation products via cyclohexadiene **178** which then undergoes 1,3 C→O silyl shift to form **153** (following aqueous workup). Intermediate **176** is also capable of tautomerizing to form an isomeric cyclohexadiene **179**, which can form **172b** following silyl migration and quenching. Alternatively, tautomerization of **175** can form cyclohexadiene **177**, which may be transformed into **172a** following silyl migration and aqueous workup. As mentioned above, we have been unable to

Scheme 13. Mechanism for Formation of Phenols **172** and **153**



determine whether the major product is **172a** or **172b**, though we tend to favor **172a** since the 1,3-silyl shift of **179** to form **172b** is expected to be difficult due to steric interactions with the TIPS group.

It is of note that while either silyl group can migrate, only products resulting from a single silyl shift are observed. For example, migration of the TBDMS group in **153** is conceivable (via tautomerization to **180**, see below), and yet we do not observe the formation of **181** under the conditions of the annulation. By comparison, C→O migration of the *tert*-butyldimethylsilyl group in phenol **153** requires heating for several hours in refluxing benzene or chloroform to proceed to completion.[62] These results suggest that silyl migration occurs substantially faster in compounds bearing an oxido substituent such as **177**, **178**, and **179** than in compounds such as **180** in which the C-5 oxygen is less electron rich. Alternatively, the energy barrier for silicon migration in penta-substituted cyclohexadienones such as **177**, **178**, and **179** may be smaller than that for tetra-substituted analogs due to relief of additional intramolecular non-bonded interactions present in the ground state of the more substituted cyclohexadienones.



153 **180** **181**

[62] A related thermal 1,3 carbon to oxygen shift in a 2-*tert*-butyldimethylsilyl-substituted phenol has recently been reported: Eastham, S. A.; Ingham, S. P.; Hallett, M. R.; Herbert, J.; Quayle, P.; Raftery, J. *Tetrahedron Lett.* **2006**, *47*, 2299.

Scope of the Benzannulation

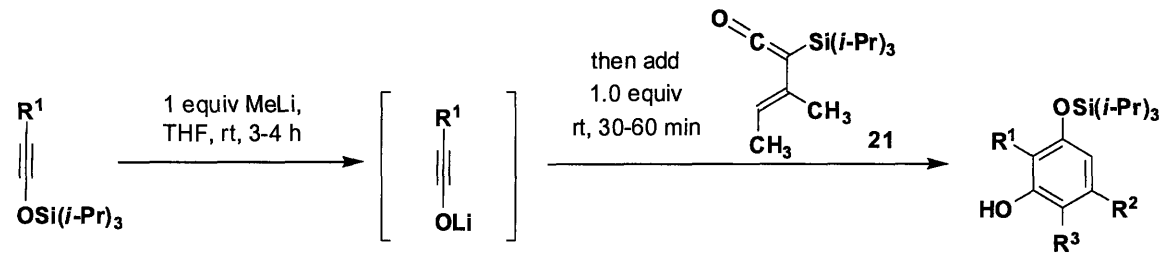
The previous chapter outlined the synthesis of a number of TAS-vinylketenes and siloxy alkynes, and these were used to investigate the scope of the benzannulation. As shown in Table 10, our initial efforts were directed at determining the steric constraints, if any, on the scope of the reaction with respect to the ynolate substituent (R^1). In a series of experiments, the dimethyl-substituted ketene **21** was reacted with ynolates bearing increasingly bulky substituents. In addition to the *n*-butyl substituted alkyne mentioned previously, isopropyl and *tert*-butyl alkynes were found to be well tolerated and the size of the substituent has little effect upon the yield. However, we found that the presence of a conjugated aryl substituent resulted in a moderate decrease in yield.

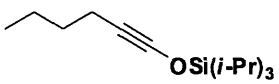
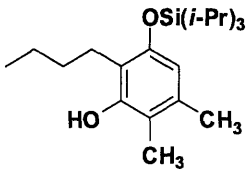
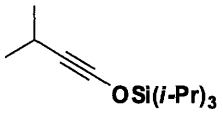
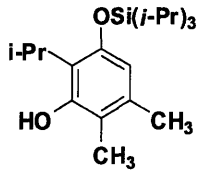
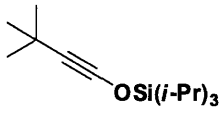
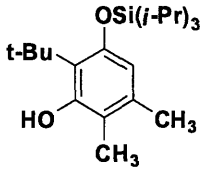
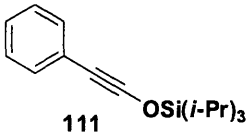
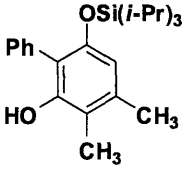
We continued our explorations by examining the annulation of TAS-vinylketenes bearing differential substitution on the vinyl moiety, as shown in Table 11. As we expected, the aromatic products were formed with perfect regiocontrol. We were gratified to see that the presence of a bulkier substituent on C-4 of the TAS-vinylketene, at what will become the terminus of the dienylketene intermediate, did not inhibit cyclization or even greatly affect the yield of the annulation (see entry 1 and entry 2). In addition, siloxy alkynes bearing ether and unconjugated alkene functionality react successfully, albeit in slightly diminished yields in the case of the former. However, the annulation reaction of vinyl-substituted siloxy alkynes, similar to that of aryl-substituted siloxy alkynes, proceeds in only moderate yield.

We were also interested in the use of this reaction for the preparation of polycyclic compounds, and to this end we turned our attention to TAS-vinylketenes in which the vinyl component is embedded in a carbocyclic system. As shown in Table 12, the reaction of TAS-vinylketene **20** with ynolates results in the formation of tetrahydronaphthols in generally good

yields. As observed previously, the steric bulk of the ynolate substituent appears to have little effect on the yield of the annulations, while vinyl substituents react in somewhat lower yields.

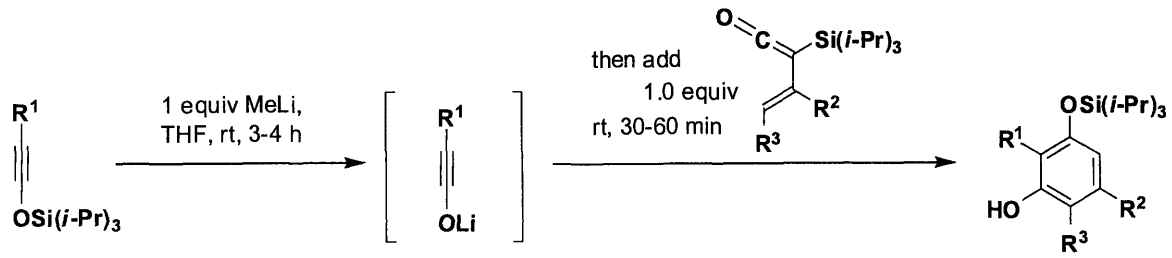
Table 10. Benzannulation Reactions of TAS-Vinylketene **21**

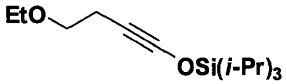
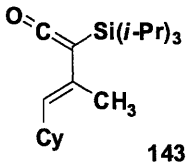
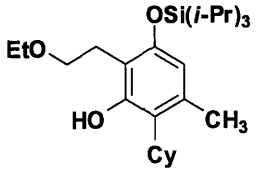
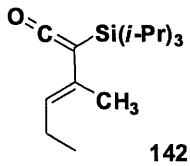
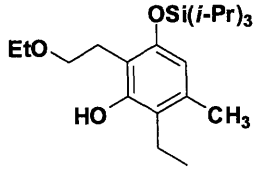
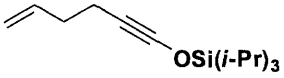
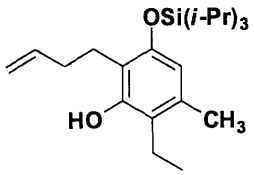
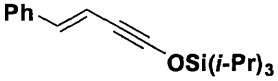
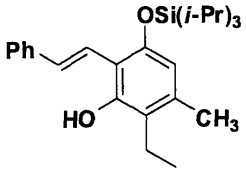


entry	alkyne	product		yield (%)[a]
1	 **108**		**150**	51-62
2	 **119**		**182**	65
3	 **109**		**154**	55
4	 **111**		**155**	30

[a] Isolated yield of products purified by column chromatography.

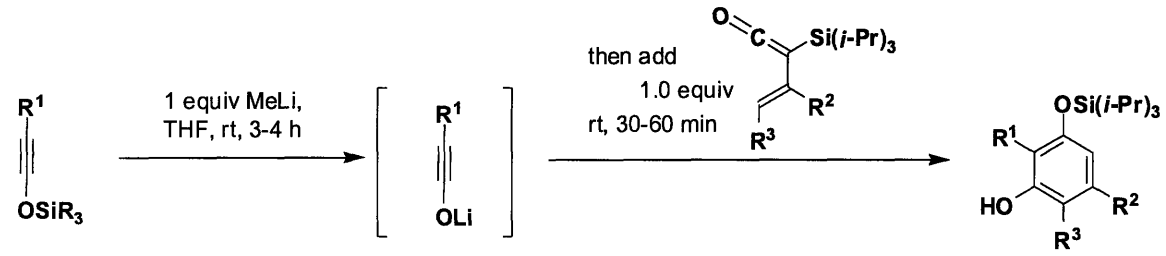
Table 11. Benzannulation Reactions of Differentially Substituted TAS-Vinylketenes

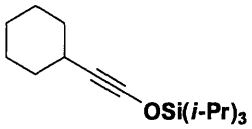
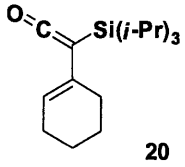
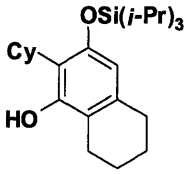
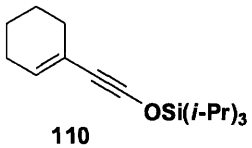
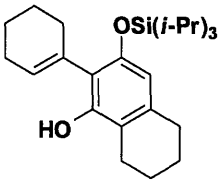
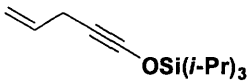
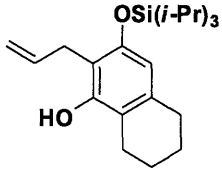
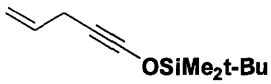
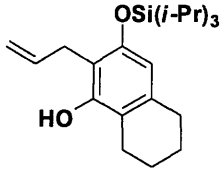
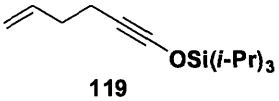
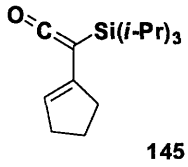
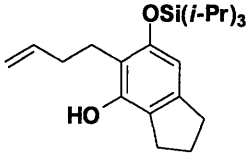


entry	alkyne	ketene	product		yield (%)[a]
1	 **121**	 **143**		**183**	44-46
2	**121**	 **142**		**156**	46
3	 **120**	**142**		**152**	68-70
4	 **112**	**142**		**184**	37

[a] Isolated yield of products purified by column chromatography.

Table 12. Benzannulation Reactions of Cyclic TAS-Vinylketenes

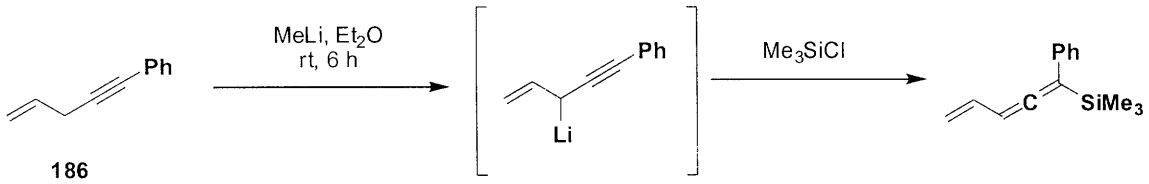


entry	alkyne	ketene	product		yield (%)[a]
1	 **118**	 **20**		**148**	67-71
2	 **110**	**20**		**157**	43
3	 **113**	**20**		**158**	26
3	 **114**	**20**		**158**	44-48
4[b]	 **119**	 **145**		**185**	<20

[a] Isolated yield of products purified by column chromatography.

[b] Ketene 7a was added at -78 and the mixture was allowed to warm to rt over 2 h

Difficulties encountered during formation of the allyl ynolate from triisopropylsiloxy alkyne **113** resulted in the low yield of the annulation product **158** (entry 3). During generation of a typical ynolate the reaction mixture remains colorless to pale yellow, with less color generally associated with higher yields. Upon addition of methyllithium to **107**, the reaction mixture became pink and slowly turned dark red upon further reaction. We suspected that the color was due to the formation of an extended π system by competitive deprotonation of the allylic methylene. A literature report of the metallation of 1-phenyl-4-penten-1-yne (**186**) with methyllithium under similar conditions supports our hypothesis.[63] To minimize the impact of



186

this competing reaction, the *tert*-butyldimethylsiloxy alkyne **114** was employed. Cleavage of the smaller silyl group occurs at a much faster rate, and is complete within 30 minutes, resulting in yields nearly double that of annulation with **113**. In general, however, triisopropylsiloxy alkynes are preferred to the TBDMS analogs due to their increased stability towards purification and storage.

In view of the success of the annulation for the synthesis of tetrahydronaphthols, we were surprised to find that the analogous formation of indanes from TAS-vinylketene **145** was not successful. Upon addition of the ketene to a solution of the ynolate derived from siloxy alkyne **119**, multiple products were observed by TLC, and ^{13}C NMR analysis of the crude product showed no aromatic carbons. As mentioned in Chapter 1, the preparation of this ketene was complicated by the unusually high reactivity of the cyclopentene alkene moiety. We believe

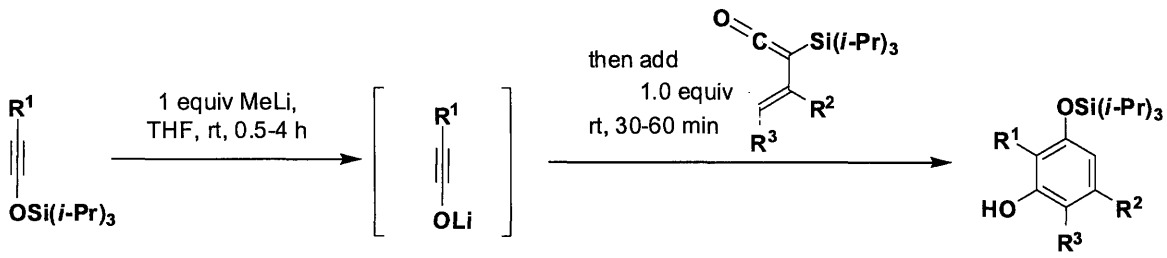
[63] Klein, J.; Brenner, S.; Medlik, A. *Isr. J. Chem.* **1971**, *9*, 177.

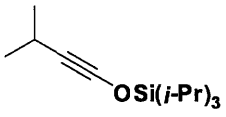
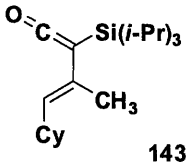
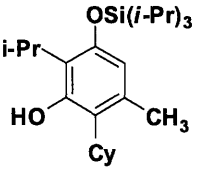
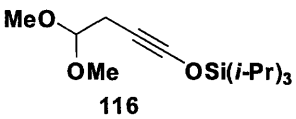
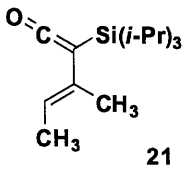
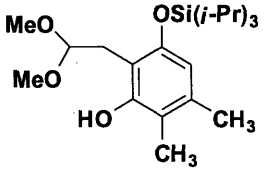
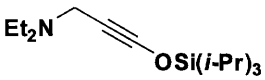
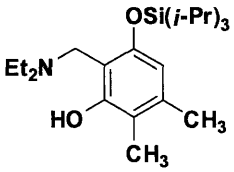
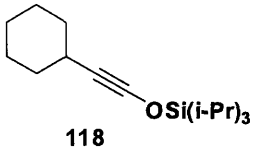
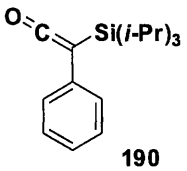
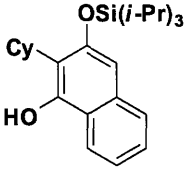
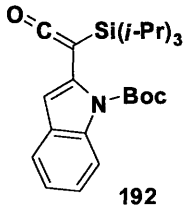
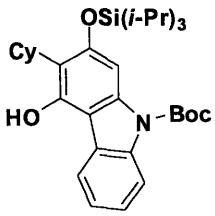
that the activation of this bond by ring strain promotes intermolecular reactions of the dienylketene intermediate that compete with the desired electrocyclization. The desired annulation product could be observed upon attempting the annulation at high dilution and low temperature. However, yields were low and so the synthesis of indanes by this approach was abandoned.

Several other annulations were not successful, a few examples of which are shown in Table 13. For example, entry one depicts an unusual case in which the desired annulation product was formed in fair yield, accompanied by a byproduct of approximately equal mass. The byproduct was found to be a dienyl ketone containing structural elements of both reaction partners, suggesting that it forms by a pathway that diverges from the usual mechanism at some point following addition of the ynolate to the TAS-vinylketene. Unfortunately, determination of the precise structure and mechanism of formation of this compound has so far proved elusive. We were surprised by the outcome of this reaction as the same ynolate and the same ketene have been shown to participate successfully in the annulation with other partners (see Tables 10 and 11). Additionally, the substituents are not located near each other in space and are not expected to interact with each other.

Anomalous cases aside, there are two systematic constraints on the reaction partners that successfully react in the annulation. The first and foremost is that in contrast to the successful reactions of TAS-*vinyl*ketenes, TAS-*aryl*ketenes do not participate in the benzannulation. For example, attempted reaction of phenyl(silyl)ketene **190**, in which the vinyl component is embedded in the framework of an aromatic system, resulted only in the formation of mixtures of unidentifiable compounds. This outcome was not entirely unexpected, as 6π electrocyclic ring

Table 13. Limitations of the Annulation



entry	alkyne	ketene	product		yield (%)[a]
1	 **119**	 **143**		**187**	34
2	 **116**	 **21**		**188**	<20
3	 **115**	**21**		**189**	trace
3	 **118**	 **190**		**191**	–
4	**118**	 **192**		**193**	–

[a] Isolated yield of products purified by column chromatography.

closure of the arylvinylketene intermediate expected in these cases requires a disruption of the aromaticity of the aryl system, presumably retarding the rate of such an electrocyclization. In fact, calculations suggest that the incorporation of one of the bonds of a triene into an aromatic system increases the barrier to electrocyclization by about 8 kcal/mol.[22b] As discussed in Chapter 1, we believe that successful benzannulation requires an extremely facile electrocyclic ring closure. In its absence, (as in the case of annulations involving TAS-arylketenes) several alternative reaction pathways can compete, resulting in the formation of complex mixtures. We also investigated TAS-heteroarylketenes such as indole derivative **192** in the hope that electrocyclization of the intermediates formed from these compounds would not be as affected due to the reduced aromaticity of heteroaryl systems relative to aryl systems. Unfortunately, the annulation with these systems also failed.

The primary limitation on the range of acceptable siloxy alkynes appears to arise not from the annulation itself, but instead from the method of generation. The siloxy alkynes employed must tolerate the basic and nucleophilic conditions of ynol ether cleavage. The low yields of phenols when allyl siloxy alkyne **113** was employed (*vide supra*) represent one example of this limitation. Despite donation from the siloxy substituent, the alkyne moiety is electron withdrawing and in combination with an additional activating element, such as a sp^2 carbon in the case of **113** or heteroatom in the case of siloxy alkyne **115,** the adjacent carbon can be deprotonated, resulting in low yields.

It should be noted that we have found that the quality of methyllithium used for the generation of the ynolate is very important for the success of the desilylation step. The methyllithium used in the annulation was handled using Schlenk techniques and stored at -5 to 0 °C in the dark. After transfer to a Schlenk flask, the methyllithium was titrated for alkyllithium

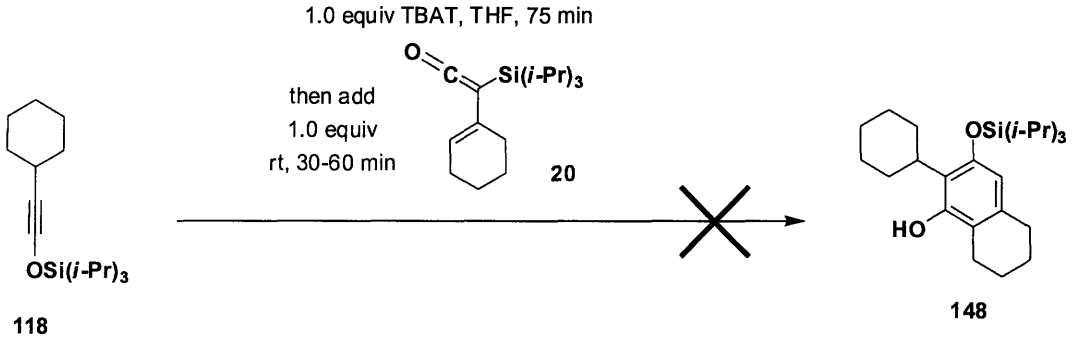
content according to the Watson-Eastham method using BHT in THF with 1,10 phenanthroline as an indicator.[64] The total base content was determined by quenching an aliquot of methyllithium with excess cold isopropanol and titrating to a phenolphthalein endpoint with HCl. Using commercially available methyllithium, we have observed strong bottle-to-bottle variations in the yields of our annulation products, though we have not been able to tie these variations to any specific impurity in the methyllithium solution. We have observed no correlation between annulation yield and appearance of precipitate in the methyllithium solution or the amount of alkoxide present. Generally, material from a "good" bottle of methyllithium will continue to provide annulation products in high yields over time, though occasionally sharp decreases in obtained yields have been observed. So far we have purchased methyllithium from both Aldrich and Alfa Aesar but neither supplier regularly produces excellent material for our purposes.

Alternative Approaches to Benzannulation

To address some of the constraints on the scope of the annulation that arise due to ynolate generation, we investigated several alternate methods with the hope of finding a milder alternative to methyllithium. An immediately obvious possibility was cleavage of the silicon-oxygen bond of siloxy alkynes with fluoride. Treatment of a mixture of butyl-substituted siloxy alkyne **108** and dimethyl-substituted TAS-vinylketene **21** with one equivalent of TBAF in THF at room temperature resulted in complete consumption of both reaction partners within 10 minutes. However, analysis of the crude reaction mixture by GCMS indicated that none of the desired phenol was present. Initially we believed that this result may have been due to the water present in TBAF, and complications resulting from the nucleophilc addition of the fluoride to the

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

ketene. To this end, we elected to employ tetrabutylammonium triphenyldifluorosilicate (TBAT), an anhydrous, nonhygroscopic, and less basic fluoride source, and generate the ynolate prior to addition of the ketene. Siloxy alkyne **118** was treated with a single equivalent of TBAT and after 1.5 h with ketene **20** was added. TLC showed the formation of decomposition products prior to addition of the ketene, and following addition of the ketene nothing that could potentially be the desired product was observed. We do not entirely understand the origins of failure of these approaches. One possibility is "naked" ynolates with dissociated ammonium counterions are less stable or react in a different fashion as compared to lithium derivatives.

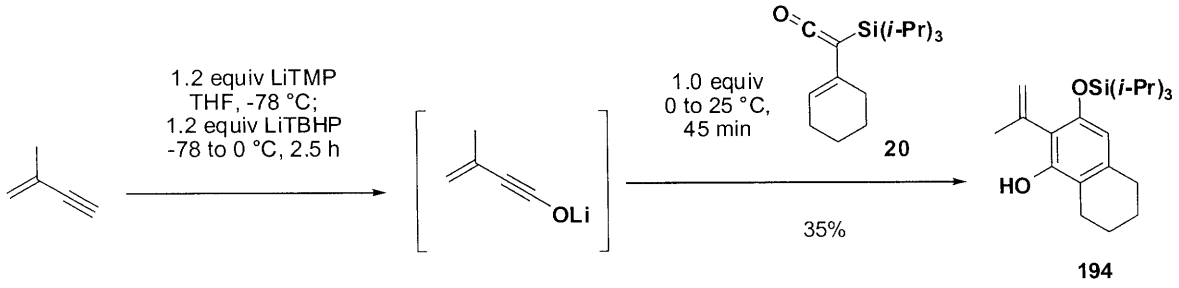


Based on a report of its application to the cleavage of silyl enol ethers,[65] we also investigated the use of KOEt in place of methyllithium. Analysis by TLC showed incomplete consumption of the siloxy alkyne **119** after 4 h at room temperature and formation of several new products. As a result of these experiments, we concluded that methyllithium is the best reagent for the generation of an ynolate from a siloxy alkyne.

In an alternate approach, we also considered the possibility of performing the annulation with an ynolate generated in situ from a terminal alkyne. As discussed in Chapter 2, the presence of nucleophilic reagents and byproducts present as a result of most methods for generation of ynolates can complicate the application of these methods in our annulation. We

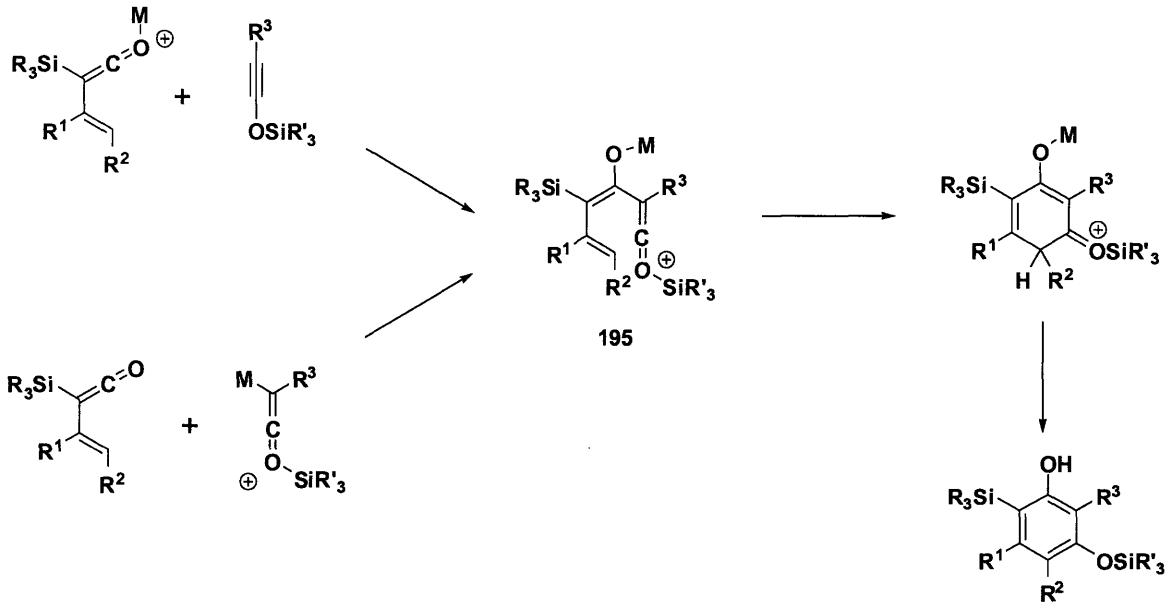
[65] Yu, W.; Jin, Z. *Tetrahedron Lett.* **2001**, *42*, 369.

initially elected to generate the required ynolates by cleavage of the silyl ether with methyllithium to avoid these complications. However, some substrates incorporate functionality that might be sensitive to methyllithium, and so we investigated alternative methods for ynolate generation. In considering other possibilities, the methods of Kowalski and Shindo were excluded since they the require the use of excess alkyllithium reagents. Julia's method requires only a slight excess of an amine base, though it also generates a full equivalent of *t*-butoxide for each equivalent of ynolate. However, we were hopeful that upon addition of the TAS-vinylketene to this mixture, the ynolate would add to the ketene carbonyl substantially faster than the amine or alkoxide nucleophiles. In the event, we were encouraged by the observations of a small amount of the desired annulation product in our initial experiments. Several variations of the original Julia conditions were attempted during optimization, including reduction in the amount of base and peroxide and the use of LiTMP instead of LiHMDS. Unfortunately, despite our best efforts we were not able to obtain a reasonable yield of the desired annulation products. In the most successful case, deprotonation of 3-methylbutenyne with LiTMP and oxidation with LiOO*t*-Bu yielded an ynolate that was trapped with cyclohexenyl TAS-vinylketene **20.** Purification then yielded phenol **194** in 35% yield. In view of the modest yield obtained for this reaction, further investigation of this variant of the annulation was not pursued.

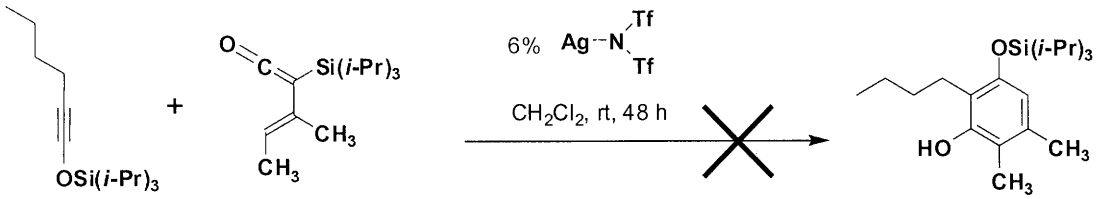


We have also investigated an alternative approach to the synthesis of phenols from TAS-vinylketenes that does not rely on ynolates. We believed that while siloxy alkynes do not react with TAS-vinylketenes, in the presence of Lewis acids addition might occur. There are two possible mechanisms for an annulation of this type, depending on whether complexation of the Lewis acid occurs with the TAS-vinylketene or with the siloxyalkyne. In the former case, coordination of the acid to the ketene carbonyl would activate it toward addition of the electron-rich alkyne, resulting in an oxido-triene of type **195**. Cyclization and tautomerization then would provide the aromatic system. Alternatively, coordination of the Lewis acid to the siloxy alkyne could potentially activate it for nucleophilic attack on the TAS-vinylketene. Kozmin has observed that the presence of catalytic amounts of silver triflimide promotes a formal [2 + 2] cycloaddition of siloxy alkynes and enones. On the basis of NMR experiments confirming formation of a siloxy alkyne-silver triflimide complex and other observations, Kozmin suggests

Scheme 14. Potential Pathway for Acid Promoted Benzannulation



that the observed cyclobutenes are formed by conjugate addition of the alkyne complex to the enone followed by intramolecular trapping of the ketenium ion. In our investigation, treatment of a mixture of siloxy alkyne **108** and TAS-vinylketene **21** with catalytic silver triflimide resulted in the formation of a complex mixture of products, and NMR analysis of the crude reaction mixture indicated that none of the desired phenol had been formed. A substantial amount of TAS-vinylketene **21** remained, even after 2 days, suggesting that the products formed resulted from decomposition of the siloxy alkyne. The failure of this case may arise from a mismatch of reactivity between the presumably soft nucleophilic alkyne complex and the hard carbonyl. Several other Lewis and protic acids were screened including lithium triflimide, zinc iodide, titanium (IV) chloride, and even trifluoromethane sulfonimide, but in all cases only extensive decomposition was observed.



108 21 150

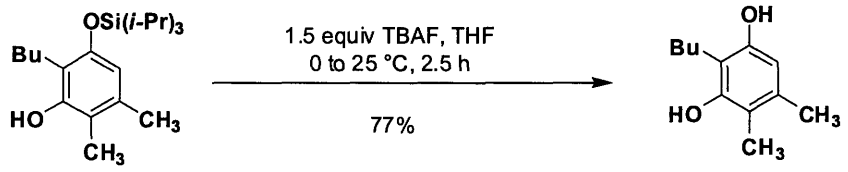
Chapter 4

Synthetic Elaboration of the Benzannulation Products

As mentioned previously, one of the reasons that we were interested in developing a new annulation targeting resorcinols is the number of natural products and biologically active compounds that incorporate this type of ring system. With the successful development of the annulation reaction allowing convenient access to these highly substituted products, we sought to further extend the utility of this strategy by examining the synthetic elaboration of the annulation products. We were particularly interested in investigating cyclizations that could be employed in tandem with our annulation to provide benzo-fused oxygen heterocycles.

Functional Group Transformations

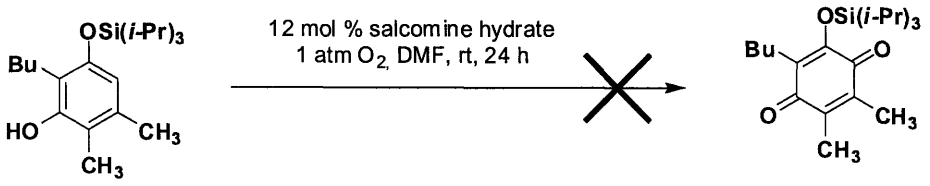
For our initial investigation, we focused on some straightforward transformations of the annulation products. As expected, the 3-(triisopropylsiloxy)phenol **150** could be readily desilylated upon treatment with TBAF in THF at rt for 2.5 h to provide the expected resorcinol **196**.



150 **196**

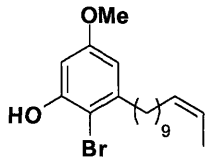
An initial attempt to oxidize phenol **150** to the corresponding *para*-quinone (**197**) was unsuccessful. No reaction was observed upon stirring a solution of the phenol in DMF under an

oxygen atmosphere for 24 h in the presence of salcomine.[66] The mechanism for oxidation of phenols under these conditions requires delivery of oxygen by the cobalt catalyst. We believe that non-bonded interactions between the bulky salcomine-oxygen complex and the large



150 **197**

3-triisopropylsiloxy substituent are preventing close approach of the complex to C-4. This conclusion is supported by the report of the successful oxidation of 3-methoxyphenol **198** under similar conditions,[67] as well as both the successful oxidation of more electron rich[68] and electron poor[69] compounds.

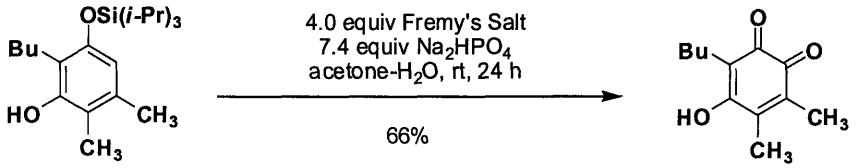


198

In order to circumvent this complication, we decided to employ Fremy's salt [potassium nitrosodisulfonate, $(KSO_3)_2NO$]. The oxidation of phenols to quinones with Fremy's salt[70] follows a mechanism similar to oxidation with salcomine and O_2, but we expected this smaller oxidant to not be as affected by steric constraints. Upon treatment of phenol **150** with

[66] Van Dort, H. M.; Guersen, H. J. Recl. Trav. Chim. Pays-Bas **1967**, *86*, 520. (b) Vogt, L. H., Jr.; Wirth, J. G.; Finkbeiner, H. L. *J. Org. Chem.* **1969**, *34*, 273 (c) DeJonge, C. R. H. I.; Hageman, H. J.; Hoentjen, G.; Mus, W. J. *Org. Synth.*, **1988**, *57*, 78.
[67] Fukuyama, Y.; Kiriyama, Y.; Kodama, M. *Tetrahedron Lett.* **1993**, *34*, 7637.
[68] Lipshutz, B. H.; Lower, A.; Berl, V.; Schein, K.; Wetterich, F. *Org. Lett.* **2005**, *7*, 4095.
[69] Dockal, E. R.; Cass, Q. B.; Brocksom, T. J.; Brocksom, U.; Correa, A. G. *Synth. Commun.* **1985**, *15*, 1033.
[70] For a review, see: Zimmer, H.; Lankin, D. C.; Horgan, S. W. *Chem. Rev.* **1971**, *71*, 229.

$(KSO_3)_2NO$ in Na_2HPO_4-buffered aqueous acetone at rt for 24 h, a new product was formed. Upon isolation and purification, this product was assigned as the *ortho*-quinone **199** resulting from oxidation to form the desired *para*-quinone followed by an unexpected deprotection.



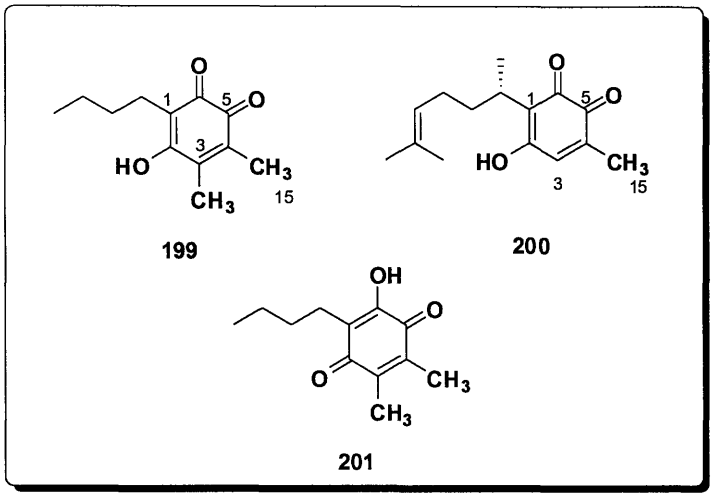
150 **199**

The structural assignment of this product was made based on analysis of IR and ^1H and ^{13}C NMR data and comparison with the known compound rigidone (**200**).[71] The NMR data alone was consistent with both hydroxyquinone **199** and the isomeric 1,4-*para*-quinone **201**. Fortunately, the *para*-quinone should possess an intramolecular hydrogen bond between the hydroxyl group and adjacent carbonyl, resulting in a strong IR absorbance at ~1560 cm^{-1}.[70] Such an absorption was not observed in the IR spectrum of the isolated compound, which instead exhibited the expected quinone at 1650 cm^{-1} and two additional absorbances at 1633 and 1620 cm^{-1} which could not be attributed to a *para*-quinone. As a result of these observations, the product of the oxidation was assigned as **199**.

Hydroxyquinone **199** exhibits a characteristic resonance in the ^1H NMR spectrum for an electron-deficient hydroxyl appearing at 6.94 ppm, in adequate agreement with that of rigidone (7.10 ppm). Furthermore, the ^{13}C NMR spectrum shows resonances consistent with an enol, two carbonyl groups and two other sp^2 carbons, all in excellent agreement with those observed for rigidone (Table 14).

[71] Freyer, A. J.; Patil, A. D.; Killmer, L.; Zuber, G.; Myers, C.; Johnson, R. K. *J. Nat. Prod.* **1997**, *60*, 309.

Table 14. Spectral Data and Assignments of Quinone **199** and Rigidone



	^{13}C NMR spectra (δ)	
	199	**200**
C-1	121.8	124.6
C-2	150.8	151.0
C-3	136.3	135.8
C-4	143.9	140.5
C-5	184.0	184.3
C-6	187.6	187.6
C-15	14.1	14.7

In addition to these transformations, we envision many other possible synthetic applications of the annulation products. For example, we expect that the electron-rich aromatic system is ideally suited for electrophilic aromatic substitution at the unsubstituted C-4 position, potentially providing access to fully functionalized resorcinol derivatives. Alternatively, triflation of the unprotected phenol and palladium catalyzed cross-coupling should allow access to anilines and tetra-substituted phenols.

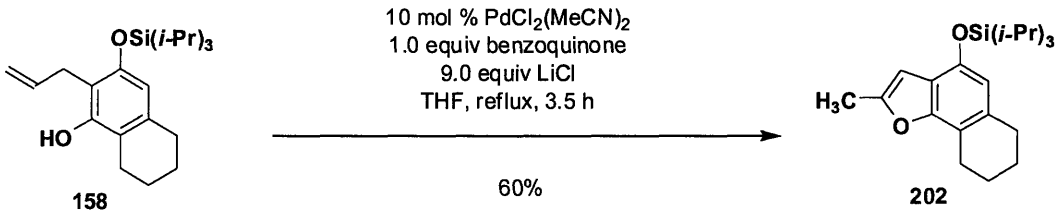
Synthesis of Benzo-fused Oxygen Heterocycles

In addition to exploring functional group transformations of our benzannulation products, we also explored the application of the product phenols to the synthesis of heterocycles. Benzo-fused oxygen heterocycles such as benzofurans, benzopyrans, and benzoxepines are employed commercially in a number of applications, including uses as herbicides, dyes, and pharmaceuticals, and the development of new approaches to these compounds is of significant importance in organic chemistry. As a result, we began to investigate the application of our

benzannulation products in intramolecular ring forming reactions. The utility of *ortho*-substituted phenols in the synthesis of heterocycles is well documented, and we expected that with careful selection of the ynolate partner in our benzannulation, phenols suitably functionalized for subsequent cyclization could be prepared. Such a tandem annulation-cyclization strategy provides a convenient route for the rapid assembly of benzo-fused heterocycles.

One of the most intriguing potential applications of the benzannulation products is in palladium catalyzed cyclizations of *ortho*-allyl phenols such as **158**. The transformations of such compounds into benzofurans, dihydrobenzofurans, and benzopyrans have been reported,[72] and application of these methods to annulation products bearing appropriate *ortho* functionality could potentially produce an array of heterocyclic derivatives bearing a highly-substituted benzene ring.

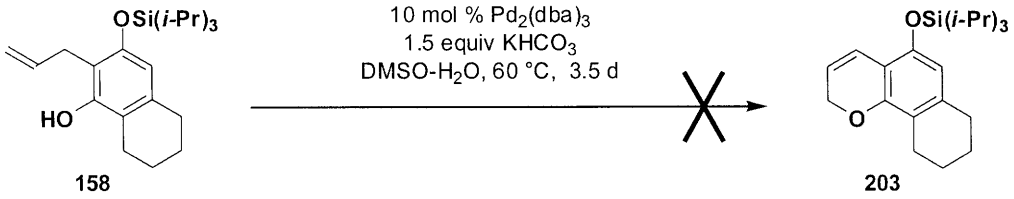
First, we elected to examine the formation of benzofurans under conditions originally employed by Hegedus for the cyclization of *ortho*-allylanilines to indoles.[73] Reaction of *ortho*-allylphenol **158** with 10 mol% of the acetonitrile complex of palladium chloride in the presence of benzoquinone as an oxidant provided the desired tricyclic product **202** in 60% yield.



Most conditions for palladium (II)-catalyzed ring closure of *ortho*-allyl phenols lead to the formation of five-membered rings. However, Larock has shown that under certain conditions

[72] For a recent review, see: Zeni, G.; Larock, R. C. *Chem. Rev.* **2004**, *104*, 2285.
[73] Hegedus, L. S.; Allen, G. F.; Bozell, J. J.; Waterman, E. L. *J. Am. Chem. Soc.* **1978**, *100*, 5800.

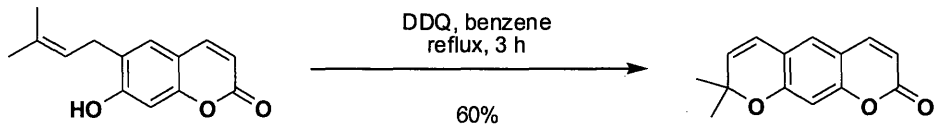
the product of 6-endo cyclization can be obtained selectively.[74] For example, heating an *ortho*-allylphenol with $Pd(dba)_2$ and potassium bicarbonate in wet DMSO for 3 days in a flask open to air provides chromenes in 60-80% yield. Electron-rich phenols, as well as phenols bearing a variety of substitution patterns on the allyl moiety react smoothly. However, our attempts to promote the cyclization of phenol **158** with the related catalyst $Pd_2(dba)_3$ under otherwise identical conditions were not successful. After 36 hours, no reaction was observed, and after 3.5 days, only decomposition had occurred. We were surprised by the low reactivity of the phenol under these conditions, as the dipalladium precatalyst can be expected to be more reactive and more susceptible to oxidation due to the increased ratio of palladium to dibenyzlideneacetone.



Larock has reported that $Pd(OAc)_2$ is also a useful catalyst for this transformation, though he observes that $Pd(dba)_2$ is superior for electron-rich phenols. However, our attempts to convert **158** to **203** with catalytic $Pd(OAc)_2$ resulted in decomposition of phenol **158**. Gagné reported that $Pd(OAc)_2$ catalyzes the conversion of *ortho*-3-methyl-2,6-heptadienyl phenol to the corresponding 2,2-disubstituted chromene in the presence of benzoquinone.[75] Unfortunately, upon applying these conditions to phenol **158**, we found that benzofuran **202** is formed instead.

[74] Larock, R. C.; Wei, L.; Hightower, T. R. *Synlett* **1998**, 522.
[75] Koh, J. H.; Mascarenhas, C.; Gagné, M. R. *Tetrahedron* **2004**, *60*, 7405.

Following these failures, we investigated an alternate method for the synthesis of chromenes that does not involve the use of palladium. Kim et al. have reported that oxidation of demethylsuberosin (**204**) with DDQ provides the six-membered cyclic ether **205**.[76]



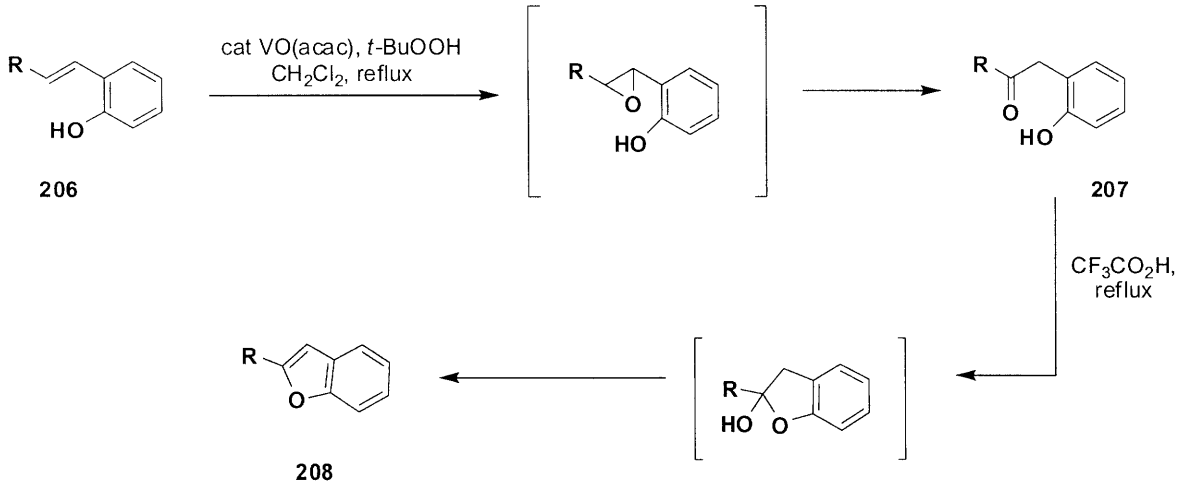
204 **205**

Unfortunately, our attempts to oxidize phenol **158** with one equivalent of DDQ in refluxing benzene were not successful. In these experiments little reaction was observed and most of the phenol was unchanged after periods of up to 4 days. This difference in reactivity is presumably due to the absence of the stabilizing effects of methyl substitution on the carbocationic intermediate formed by hydride abstraction.

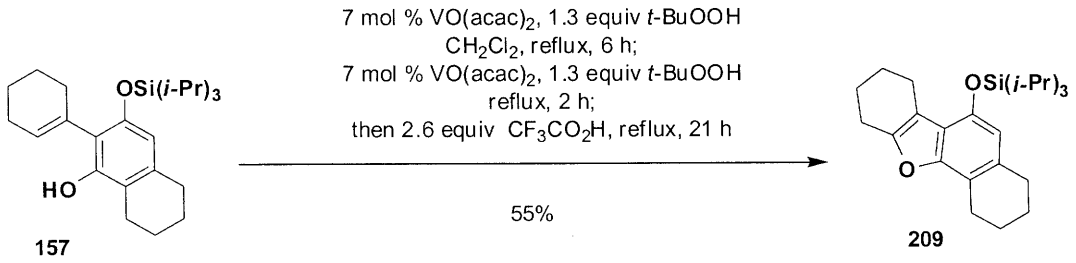
A recent publication by Lattanzi discussing a preparation of benzofurans caught our attention, as this method utilizes ortho-vinyl rather than ortho-allyl-substituted phenols.[77] Lattanzi reported that oxidation of phenols bearing a β-alkyl *ortho*-vinyl substituent with *tert*-butylhydroperoxide and catalytic vanadium acetoacetate, followed by treatment with trifluoroacetic acid, provides 2-alkylbenzofurans. The authors propose that the mechanism of the reaction follows the course shown below. Coordination of the phenolic hydroxyl group in **206** to the vanadium complex activates the complex, resulting in a significant rate enhancement of epoxidation. Coordination of the vanadium complex to the epoxide then promotes selective

[76] Kim, S.; Ko, H.; Son, S.; Shin, K. J.; Kim, D. J. *Tetrahedron Lett.* **2001**, *42*, 7641.
[77] (a) Lattanzi, A; Scettri, A. *Synlett* **2002**, 942-946. (b) Lattanzi, A. Senatore, A.; Massa, A.; Scettri, A. *J. Org. Chem.* **2003**, *68*, 3691.

cleavage of the benzylic carbon-oxygen bond and rapid 1,2-hydride migration then provides *ortho*-hydroxybenzyl ketones **207.** These compounds can be isolated and purified, or treated



with acid in the same pot to promote an intramolecular condensation forming 2-alkylbenzofurans (**208**). While this report only investigated phenols bearing an *ortho*-β-alkyl-substituted vinyl group, we saw no reason that this method could not be extended to include the more highly substituted phenols produced by our annulation. We were pleased to find that upon treatment of cyclohexenyl-substituted phenol **157** with vanadium acetoacetate and *t*-butylhydroperoxide, followed by trifluoroacetic acid, the desired tetracycle **209** was obtained in 55% yield.



Ring closing metathesis ("RCM") presents another extremely attractive approach to ring formation and has found widespread use in organic synthesis following the development of air-stable, functional group-tolerant catalyst systems. In fact, many cyclic ethers and lactones have

been prepared in this fashion, and this field has been recently reviewed.[78] The use of RCM for the synthesis of benzo-fused heterocycles is especially favorable due to the configurational constraints enforced upon a cyclizing system by incorporation of a benzene ring.

With this precedent, we were confident that RCM of dienes derived from the annulation products would be successful and provide benzo-fused heterocycles of varying ring sizes. To this end, the annulation products **152** and **158** were alkylated with allyl bromide in the presence of potassium carbonate and catalytic sodium iodide. These reactions proceeded quite slowly, presumably due to steric hindrance from the two *ortho* substituents. However, after 36 hours in refluxing acetone the desired RCM precursors were obtained in adequate yield.

As expected, the ring closing metathesis was extremely successful. Heating a 0.005 M solution of diene **210** in the presence of 5 mol% of Grubbs' second generation ruthenium catalyst (**212**) led to the formation of the benzo[*b*]oxepine **214** in 96% yield. Similarly, heating of **211** with **212** produced benzo[*b*]oxocine **213** in near quantitative yield.

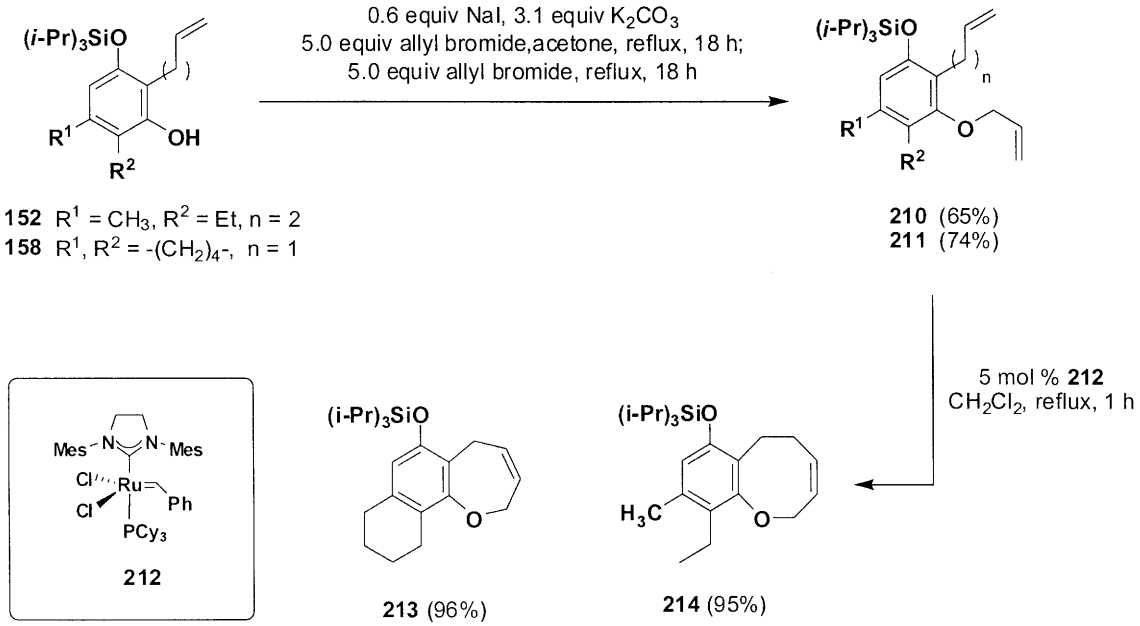
Conclusion

In conclusion, we have shown that TAS-vinylketenes react with lithium ynolates in a regiocontrolled benzannulation process that provides efficient access to highly substituted phenols. In conjunction with transition-metal catalyzed cyclization reactions, this strategy can be employed for the synthesis of a variety of benzofused oxygen heterocycles, including benzofurans, benzo[*b*]oxocines, and benzo[*b*]oxepines.

---

[78] (a) Chattopadhyay, S. K.; Karmakar, S.; Biswas, T.; Majumdar, K. C.; Rahaman, H.; Roy, B. *Tetrahedron* **2007**, *63*, 3919. (b) Deiters, A.; Martin, S. F. *Chem. Rev.* **2004**, *104*, 2199.

Scheme 15. Allylation and Ring Closing Metathesis of the Benzannulation Products



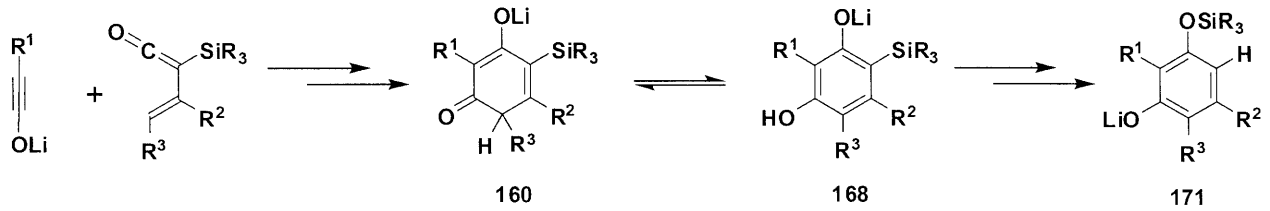
Part III

New Approaches to the Synthesis of TAS-Vinylketenes

Chapter 1

Introduction and Background

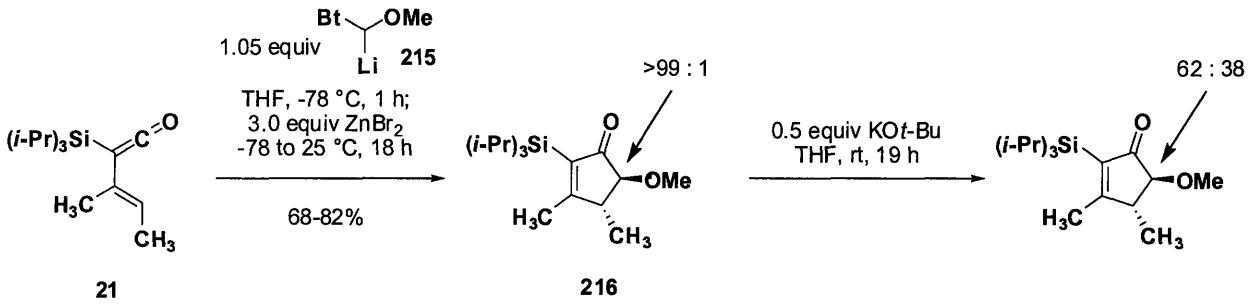
The previous sections of this thesis detailed the results of our investigations directed toward the development of an annulation strategy for the synthesis of 3-siloxyphenols from TAS-vinylketenes and ynolates. One step in the mechanism of this transformation involves the tautomerization of cyclohexadienone **160** to the resorcinate **168**. As a result, only ketenes



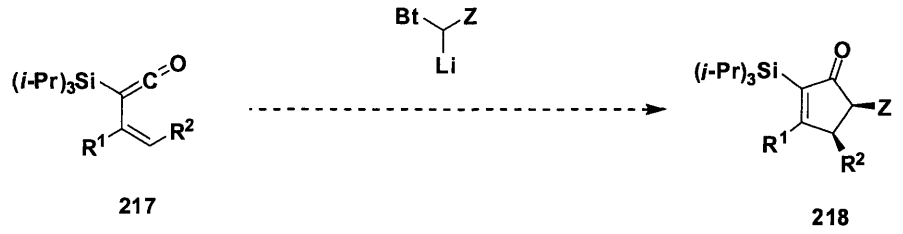
bearing a hydrogen atom at C-4 can successfully participate in the benzannulation. It is also of note that during the annulation any stereochemical information about the TAS-vinylketenes is lost. We expect that (*E*)- or (*Z*)-substituted ketenes will react to provide identical products.

This is not the case for other TAS-vinylketene based annulations. Previous research into the [4 + 1] annulation of (*E*)-substituted TAS-vinylketenes with carbenoid reagents showed that the products are formed with generally high selectivity for the *trans*-substituted cyclopentenones. Some examples of this transformation are described in Part I, Chapter 2, and an additional example is shown below. Control experiments indicated that the observed distribution of annulation products does not reflect the thermodynamic ratio of diastereomers. For instance, reaction of TAS-vinylketene **21** with **215** and treatment of the intermediate resulting from carbenoid addition with zinc bromide produced the *trans*-substituted cyclopentenone **216**. The *cis* diastereomer was not observed in the crude reaction product. Exposure of **216** to 0.5 equiv of potassium *tert*-butoxide in THF produced a 62:38 mixture of the *trans*- and *cis*-substituted

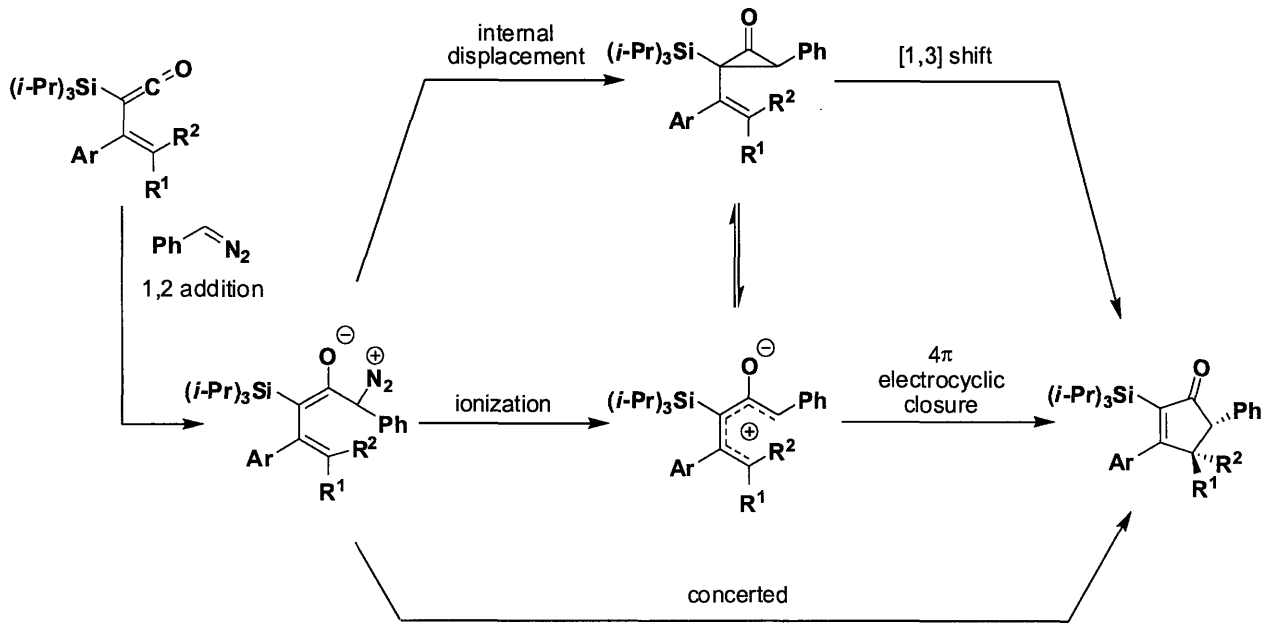
cyclopentenones, suggesting that the selective formation of *trans* isomers in the [4 + 1] annulation is the result of kinetic control.



Scheme 16 depicts several potential mechanistic pathways that are consistent with the stereochemical outcome of the reaction. We expect that the transformation of TAS-vinylketenes to cyclopentenones with carbenoid reagents is stereospecific, and that employment of (*Z*)-substituted TAS-vinylketenes of type **217** will provide *cis*-substituted cyclopentenones.

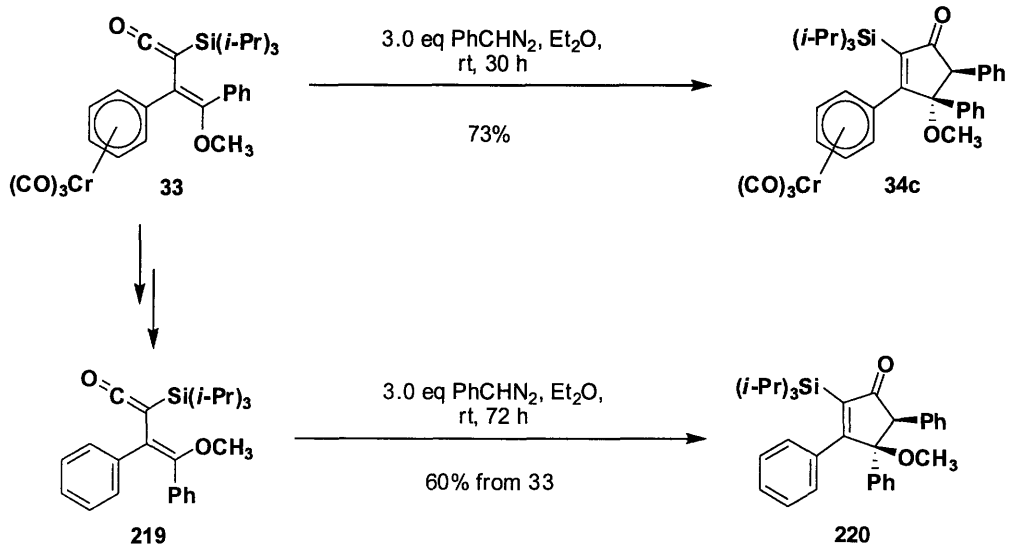


Scheme 16. Possible Mechanistic Pathways for the [4 + 1] Annulation



Support for our belief that the [4 + 1] annulation with **217** should provide *cis*-disubstituted products is provided by a recent report by Moser on the application of our annulation to TAS-vinylketenes bearing two C-4 substituents.[17] As mentioned in Part I of this thesis, he was able to show that the diastereoselective annulation we observed with ketenes bearing a single substitutent at C-4 occurred in these cases as well. While nearly all of the ketenes used in this study bear an (*E*)-methoxy substituent, Moser did examine a pseudo-"matched pair" of isomers, differing only in the stereochemistry of the double bond and the presence in one compound of a chromium tricarbonyl fragment. Upon treatment with phenyldiazomethane, both silylketenes react stereoselectively to yield the *cis*- and *trans*-substituted cyclopentenones, respectively (Scheme 17).

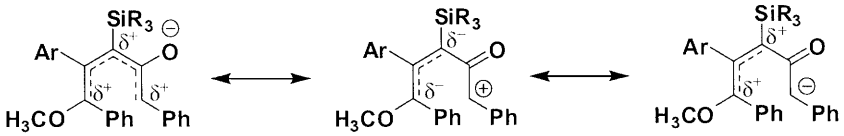
Scheme 17. Stereoselective [4 + 1] Annulation of Ketenes **33** and **219**



Moser observed that the reaction of these two pseudo-isomers occurs with a distinct difference in rate, and he proposes that the reaction occurs via 4π electrocyclic ring closure of an intermediate pentadienylic cation. He suggests that the difference in reactivity between **33** and **219** is due to the greater ability of phenyl rings bearing chromium fragments to stabilize positive charge at the benzylic position, as evidenced by the ability of such fragments to promote rate accelerations in Nazarov cyclizations.

While the 4π electrocyclic ring closure of an intermediate pentadienyl cation may indeed play a role in the mechanistic pathway, the ability of the chromium fragment to stabilize positive charge is unlikely to greatly affect the rate of formation of the proposed pentadienyl cation intermediate or its rate of closure. Positive charge in a pentadienyl cation would be expected at the 1-, 3-, and 5-carbons (**221**), rather than at C-4 where additional stabilization by the chromium fragment would take effect. In addition, these intermediates are zwitterionic rather than cationic,

and electrocyclic ring closure generates an unsaturated ketone directly, rather than an oxy-allyl cation, further reducing the requirement for carbocation stabilization.

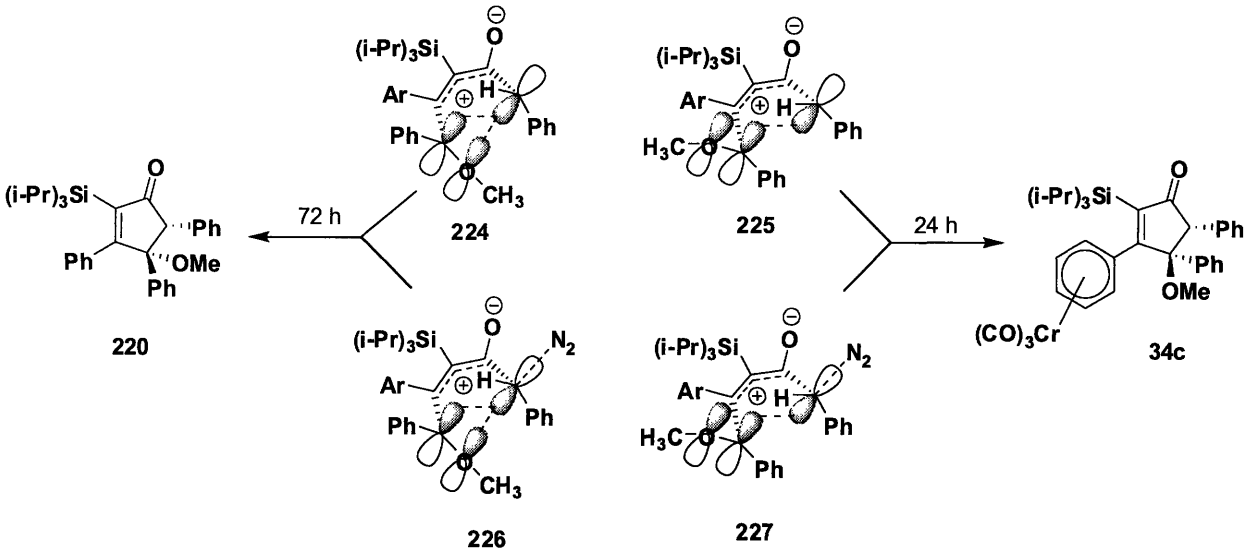


221 222 223

We propose an alternative explanation for the faster rate of cyclization of **33** relative to **219** based on the work of Houk and co-workers. Houk has investigated the torquoselectivity of 4π electrocyclic ring openings and closings. His calculations of the transition state energy for electrocyclic closure of pentadienylic cations bearing electron donating groups indicate that the activation energy is substantially lower for cases where the donating group occupies an "outside" position relative to the analogous systems where the donor occupies an "inside" position.[79] The authors suggest that this differentiation is a result of a destabilizing interaction between the non-bonding electrons of the donating group and the electrons of the incipient σ bond. These interactions will be expected to retard the cyclization of the "alkoxy-inside" intermediate, as depicted in Scheme 18, whether it occurs following ionization (**224**) or with concomitant departure of the diazo leaving group (**226**). This should result in a slower rate for the reaction of "alkoxy-inside" vinylketenes relative to the corresponding "alkoxy-outside" vinylketenes (**225** or **227**) thus explaining the rate difference observed by Moser and co-workers.

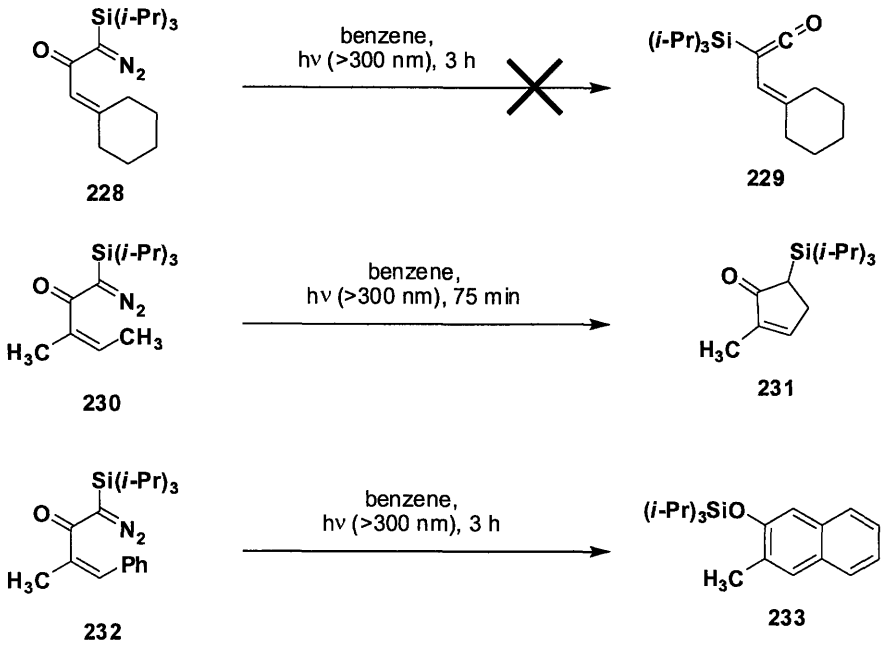
[79] Kallel, E. A.; Houk, K. N. *J. Org. Chem.* **1989**, *54*, 6006.

Scheme 18. Orbital Interactions During Ring Closure of Annulation Intermediates

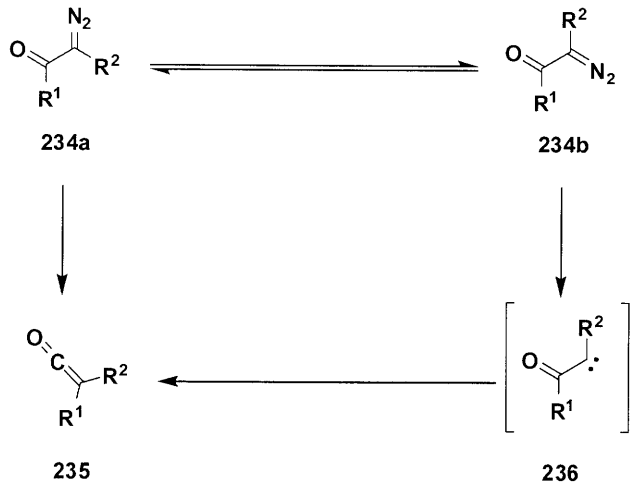


While observations of the reaction of **33** and **219**, the pseudo-"matched pair" of TAS-vinylketenes, provide encouraging precedent, to date the lack of a general method for the synthesis of TAS-vinylketenes bearing (*Z*)-substituents has hindered our ability to investigate this aspect of the [4 + 1] annulation. As discussed in Part II, Chapter 2, the most general approach to substituted TAS-vinylketenes is the photo-Wolff rearrangement of α′-diazo-α′-silyl-α,β-unsaturated ketones. We have attempted several times to apply this method to the preparation of TAS-vinylketenes bearing (*Z*)-substituents, but all attempts have met with failure. As shown in Scheme 19, irradiation of silyl diazo ketones bearing (*Z*)-substituted vinyl substituents results in decomposition or the formation of products resulting from intramolecular C-H insertion.

Scheme 19. Products of Irradiation of (*Z*)-Substituted Silyl Diazo Ketones



There are several possible mechanisms for the Wolff rearrangement of α-diazo ketones. The rearrangement can occur in a concerted fashion if the migrating group occupies a position anti-periplanar to the nitrogen leaving group. Alternatively, extrusion of nitrogen can form a ketocarbene which subsequently rearranges to the ketene. We expect that silyl diazo ketones adopt an s-*E* ground state conformation (**234b**, $R^2 = SiR_3$) in which the large trialkylsilyl group is adjacent to the small carbonyl group rather than R^1. In this conformation, concerted migration and elimination is not possible and irradiation is expected to form the singlet carbene of type **236**. This carbene can undergo typical carbene reactions or Wolff rearrangement. For silyl diazo enones bearing (*Z*)-substituents on the double bond, insertion of the carbene into nearby



C-H bonds successfully competes with Wolff rearrangement and results in formation of the cyclic products observed. In the absence of such a substituent, rearrangement to provide TAS-vinylketenes dominates.

As a result of these observations, we believe that the synthesis of (*Z*)-substituted TAS-vinylketenes by this route is not possible. We therefore began to investigate other possible methods for the general preparation of TAS-vinylketenes substituted at any position. These studies form the basis of this part of my thesis.

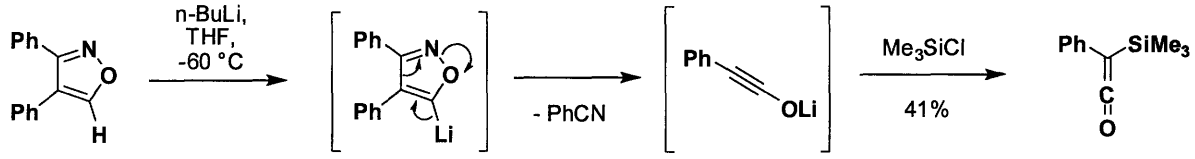
Chapter 2

Investigations of Siloxy and Alkoxy Alkynes as TAS-Vinylketene Precursors

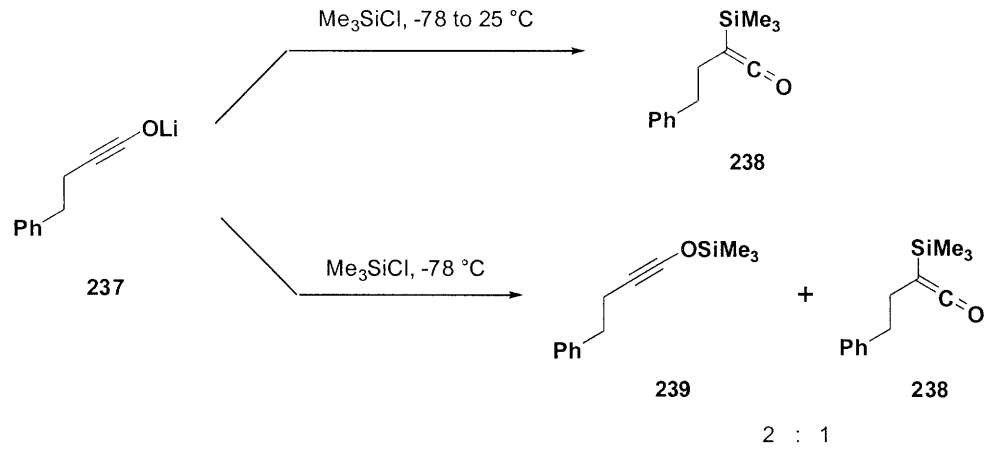
All previously known methods for the preparation of TAS-vinylketenes are not well suited for the synthesis of derivatives in which the vinyl moiety bears substituents cis to the ketene. For instance, the photo-Wolff strategy employed to prepare the (*E*)-alkenyl TAS-vinylketenes described in Part II of this thesis forms only products derived from C-H insertion when applied to enones with alkyl or aryl substituents *cis* on the double bond to the carbonyl group. In the case of TAS-vinylketenes generated by electrocyclic opening of cyclobutenones, the geometry about the vinyl double bond is determined by the torquoselectivity of the electrocyclic ring opening.[80] As this selectivity is determined by the electronic nature of the cyclobutenone C-4 substituents, this strategy cannot form the basis for a general route to *cis*-substituted TAS-vinylketenes. TAS-vinylketenes bearing *cis* substituents have been prepared by the reaction of silyl alkynes with chromium carbene complexes,[10] but as mentioned in Part I, Chapter 2, only TAS-vinylketenes bearing *trans*-alkoxy groups can be prepared by this process. Similarly, *ortho*-alkyl TAS-arylketenes cannot be reached by photo-Wolff rearrangement due to C-H insertion, and the substrates that would be required for their formation from cyclobutenones would be extremely difficult to prepare.

[80] Niwayama, S.; Kallel, E. A.; Sheu, C.; Houk, K. N. *J. Org. Chem.* **1996**, *61*, 2517.

As a result, we began to consider other strategies that might allow the preparation of TAS-vinyl and arylketenes bearing wide variety of substituents and that would be applicable to the stereoselective synthesis of both (*E*)- and (*Z*)-vinyl derivatives. We were particularly interested in the possibility of preparing these ketenes by the silylation of ynolates bearing unsaturated substituents. While studying methods for the preparation of siloxy alkynes in connection with our investigations of the benzannulation reaction, we came across scattered reports of the formation of ketenes upon reaction of ynolates with chlorotrimethylsilane. In one early example, Schöllkopf and Hoppe showed that treatment of phenyl ynolate (**93**) with chlorotrimethylsilane produced (trimethylsilyl)phenylketene (**94**).[41] Kowalski later showed that

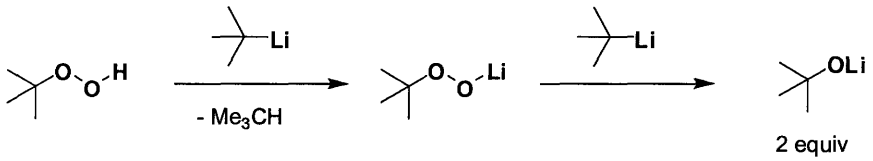


ynolates are kinetically silylated on oxygen, but that siloxy alkynes bearing small silyl groups isomerize to the more stable ketene upon warming. For instance, treatment of ynolate **237** with chlorotrimethylsilane at -78 °C and warming to room temperature afforded ketene **238**. However, when the reaction mixture was quenched prior to warming, a 2:1 mixture of siloxy alkyne **239** and ketene **238** was obtained instead.[43d]

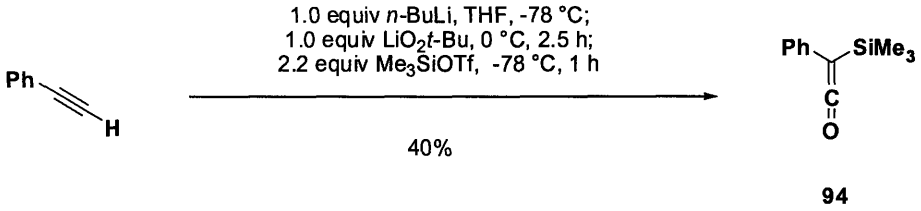


We expected that it should be possible to trap vinyl- and aryl-substituted ynolates generated by the method of Julia with trimethylsilyl groups to provide TAS-ketenes. However, one could imagine several concerns about the viability of this method. In particular, we were concerned that when ynolates are produced by the method of Julia, they are produced as mixtures also containing alkoxides and amines. These by-products could potentially react with and destroy the desired TAS-ketenes.

In Julia's standard conditions for synthesis of siloxy alkynes, a lithium acetylide is treated with 1.2 equiv of LiOO*t*-Bu, both generated separately with a slight excess of LiHMDS. In order to provide the best chance of success for the preparation of ketenes, we experimented with several alternatives to the standard conditions of the Julia oxidation with the intent of limiting the presence of nucleophiles. Using phenylacetylene as a model case, we attempted to generate the lithium acetylide and LiOO*t*-Bu by using *t*-BuLi in place of LiHMDS, but reactions employing these conditions formed phenyl(trimethylsilyl)acetylene as the major product. We believe that *t*-BuLi reacts with LiOO*t*-Bu at a rate comparable to deprotonation of *t*-BuOOH, and therefore insufficient LiOO*t*-Bu remains to completely oxidize the acetylide. Upon addition of chlorotrimethylsilane the residual acetylide is converted to the silyl alkyne.



In subsequent experiments, we continued to employ alkyllithium reagents for the generation of the acetylide, and returned to the use of LiHMDS for the preparation of LiOO*t*-Bu. The most favorable conditions for TAS-vinylketene synthesis that we discovered are shown below. The acetylide was formed with 1.0 equiv of *n*-BuLi and oxidized with 1.0 equiv of LiOO*t*-Bu, and the ynolate that resulted was treated with 2.2 equiv of Me_3SiOTf at -78 °C for 1 h. We hoped that the excess silyl triflate would silylate any nucleophiles at -78 °C prior to rearrangement of the siloxy alkyne to the ketene. Unfortunately, we were not able to improve upon the yields of ketene observed by Schöllkopf and Hoppe.

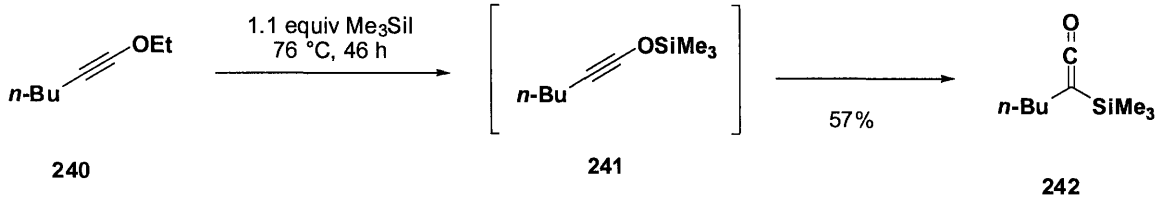


94

Despite these unsatisfactory results, we decided to continue our investigations into this silyl migration strategy using alternate tactics. We believed that if trimethylsiloxy alkynes bearing unsaturated substituents were formed in the absence of nucleophiles, acceptable yields of TAS-ketenes might be obtained by their rearrangement. Several reports of the formation of silylketenes upon treatment of alkoxy alkynes with iodotrimethylsilane provide encouraging precedent for this approach.[81] For instance, Sakurai reported that treatment of ethoxyhexyne

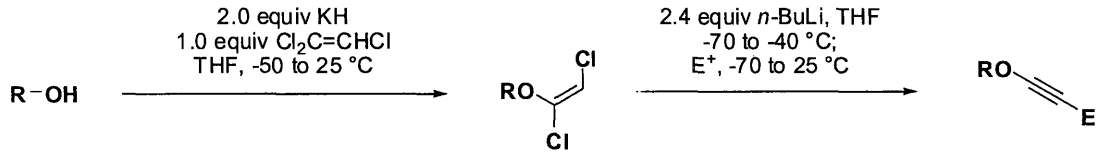
[81] (a) Sakurai, H; Shirahata, A.; Sasaki, K.; Hosomi, A. *Synthesis* **1979**, 740. (b) Kalganov, B. E.; Efimova, I. V.; Kazankova, M. A.; Lutsenko, I. F. *Zh. Obshch. Khim.***1985**, *55*, 708. (c) Pons, J.-M.; Kocieński, P. *Tetrahedron Lett.* **1989**, *30*, 1833. (d) Pommier, A.; Pons, J.-M. *Synthesis* **1994**, 1294. (e) Kocieński, P.; Pelotier, B.; Pons, J.-

(**240**) with a slight excess of iodotrimethylsilane formed *n*-butyl(trimethylsilyl)ketene (**242**) in 57% yield.[80a] This reaction is believed to proceed by silylation of the ether oxygen and nucleophilic dealkylation to form the siloxy alkyne **241**, followed by rearrangement to form the ketene.[82]



240 **241** **242**

The 2-alkyl-1-alkoxy alkynes that are required for the above transformation can be prepared in several different ways, with the most common method involving alkylation of an alkoxy acetylide which is often generated in situ by elimination from an appropriate precursor. For example, Greene has shown that reaction of a potassium alkoxide with trichloroethylene forms dichlorovinyl ethers of type **243** which can be isolated or used in situ for the next step. Upon addition of *n*-BuLi, metal-halogen exchange, elimination and deprotonation provides acetylides which can be trapped with various electrophiles.[83]



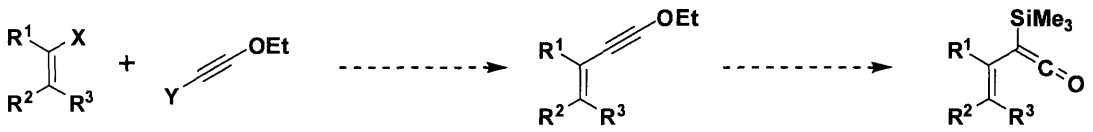
243

M.; Prideaux, H. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1373. (f) Ponomarev, S. V.; Zolotareva, A. S.; Leontev, Y.; Petrosyan, V. S. *Russ. Chem. Bull., Int. Ed.* **2001**, *50*, 1088.

[82] For a theoretical study, see: Oblin, M.; Fotiadu, F.; Rajzmann, M.; Pons, J.-M. *J. Chem. Soc., Perkin Trans. 2* **1997**, 1621.

[83] (a) Moyano, A.; Charbonnier, F.; Greene, A. E. *J. Org. Chem.* **1987**, *52*, 2919. (b) Kann, N.; Bernardes, B. Greene, A. E. *Org. Synth.* **1996**, *74*, 13.

Unfortunately, this method is not readily adaptable to the preparation of the vinyl- and aryl-substituted ethoxy alkynes that we were principally interested in. Instead, we expected that the most general and convenient approach to the alkynes we desired would be cross coupling reactions of ethoxy alkyne or its derivatives. This approach is especially attractive because in



addition to providing TAS-vinyl and TAS-arylketenes upon reaction with iodotrimethylsilane, ethoxy alkynes also generally undergo a retro-ene reaction upon heating[84] to form vinylketenes. In cases where R^3 is unsaturated, the resulting dienylketene would be expected to cyclize rapidly, providing a new aromatic system (see Part II, Chapter 1). This type of transformation would provide a particularly attractive method for the preparation of polycyclic aromatic compounds.

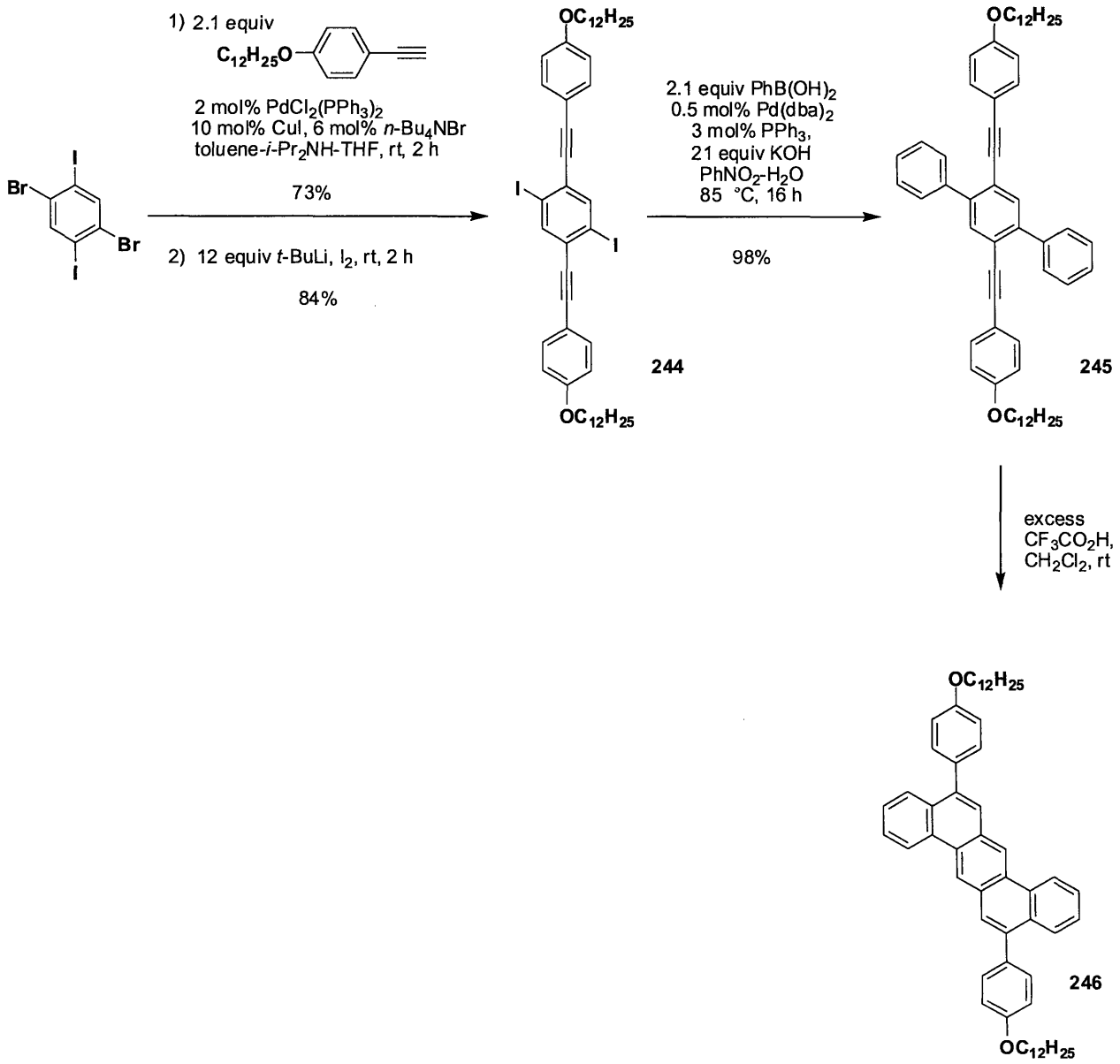
Fused polycyclic aromatic compounds[85] such as **246** possess interesting electronic properties and have the potential to be applied commercially as sensors and in electronic devices. Therefore, the development of efficient syntheses of these types of molecules has attracted considerable attention. For instance, Swager has reported the synthesis of several terphenyls that bear alkynes capped with electron-rich aryl substituents, and his group has demonstrated the use of these molecules in the synthesis of fused aromatic compounds.[86] In one example, terphenyl **245** was prepared by a sequence of reactions starting with 1,4-dibromo-2,5-diiodobenzene. A chemoselective Sonogashira coupling reaction between the tetrahalobenzene and 4-

[84] (a) Ficini, J. *Bull. Soc. Chim. Fr.* **1954**, 1367. (b) Niewenhuis, J.; Arens, J. F. *Recl. Trav. Chim. Pays-Bas* **1958**, *77*, 761. (c) van Daalen, J. J.; Kraak, A.; Arens, J. F. *Recl. Trav. Chim. Pays-Bas* **1961**, *80*, 810. (d) Moyano, A.; Pericas, M. A.; Serratosa, F.; Valenti, E. *J. Org. Chem.* **1987**, *52*, 5532.

[85] Harvey, R. G. *Polycyclic Aromatic Hydrocarbons*; Wiley-VCH: New York, 1997.

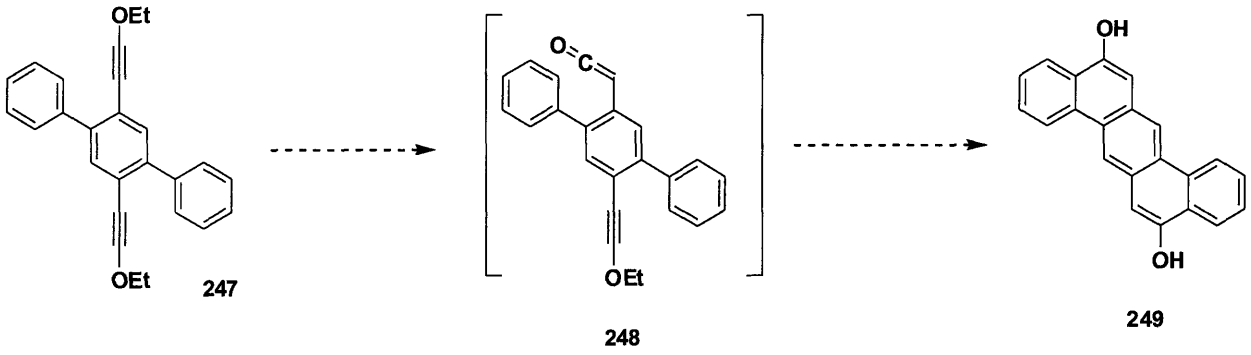
[86] Goldfinger, M. B.; Crawford, K. B.; Swager, T. M. *J. Am. Chem. Soc.* **1997**, *119*, 4578. (b) Goldfinger, M. B.; Crawford, K. B.; Swager, T. M. *J. Org. Chem.* **1998**, *63*, 1676. (c) Tovar, J. D.; Swager, T. M. *J. Organomet. Chem.* **2002**, *653*, 215.

(dodecyloxy)ethynylbenzene produced a dibromide that was converted into diiodide **244** by metal-halogen exchange and trapping with iodine. A palladium-catalyzed Suzuki cross coupling with phenylboronic acid then produced terphenyl **245**, which cyclized to **246** upon treatment with acid.



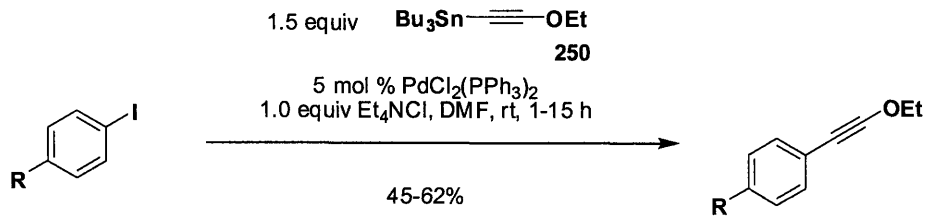
We envisioned that similar fused aromatic systems could be prepared by the cyclization of diarylketenes formed in situ from related terphenyls bearing alkoxy alkynes. Heating of

terphenyl **247** should provide the dibenzanthracene **249** via the intermediacy of diarylketenes such as **248**. Such an approach would provide advantages for the preparation of polymeric fused aromatic systems in that no reagents are required and ethylene gas is the only by-product.

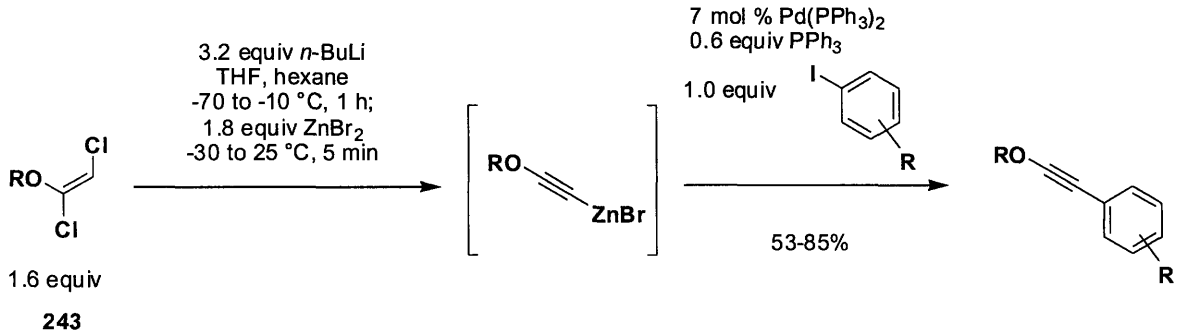


Prior to investigating the preparation of polycyclic aromatic compounds and TAS-aryl- and TAS-vinylketenes, we first needed to be able to synthesize the required aryl- and vinyl-substituted alkoxy alkynes. Unfortunately, while the coupling reactions of most alkynes are well established, the preparation of aryl- and vinyl-substituted alkoxy alkynes by the same strategy is less well known. The first coupling reaction of an alkoxy alkyne was reported in 1978 by Vermeer, who found that reaction of lithium diphenyl cuprate with 2-iodo-1-ethoxyethyne produces phenyl ethoxyacetylene in 60% yield.[87] Most known cases of alkoxy alkyne coupling reactions use aryl or vinyl iodides as electrophiles and alkynyl metal compounds as nucleophiles. For instance, Yamanaka has reported the preparation of aryl ethoxy alkynes, including phenyl ethoxyacetylene, by Stille coupling of alkynyl stannane **250** with aryl iodides catalyzed by $PdCl_2(PPh_3)_2$.[88] Iodobenzene derivatives bearing a variety of *para*-substituents ranging from electron-withdrawing to mildly electron-donating react successfully, though derivatives bearing strongly donating groups do not.

[87] Verboom, W.; Westmijze, H.; Bos, H. J. T.; Vermeer, P. *Tetrahedron Lett.* **1978**, 19, 1441.
[88] (a) Sakamoto, T.; Yasuhara, A.; Kondo, H.; Yamanaka, H. *Synlett* **1992**, 502. (b) Sakamoto, T.; Yasuhara, A.; Kondo, Y.; Yamanaka, H. *Chem. Pharm. Bull.* **1994**, *42*, 2032.



Himbert has reported that aryl alkoxy alkynes can also be prepared by Negishi coupling of alkynyl zinc species. Transmetallation of lithium acetylides generated by Greene's method with $ZnBr_2$ followed by palladium-catalyzed coupling with aryl iodides provides the desired alkynes in 53-85% yield.[89] However, excess triphenylphosphine is required to prevent polymerization of the product promoted by palladium, and *ortho*-substituted aryl halides do not

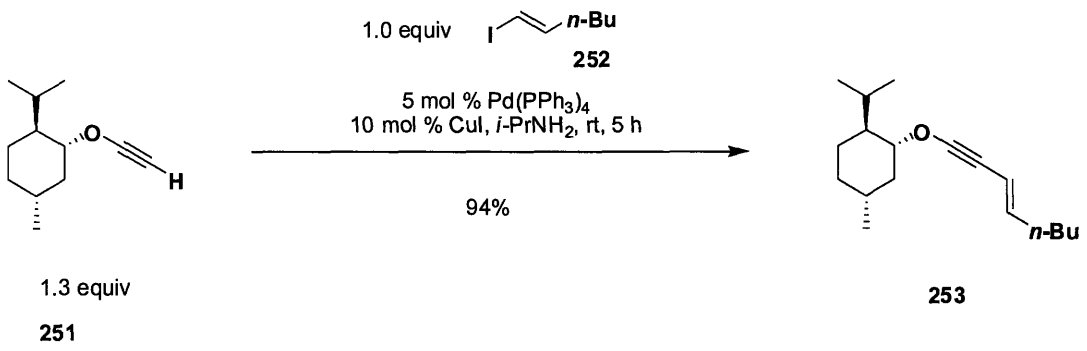


participate successfully. Wang has reported similar coupling reactions of zinc acetylides with vinyl iodides in yields that range from 21-49%, although the modest yields were attributed at least partially to the sensitivity of the product enynes to purification.[90]

We focused our attention on preparing these aryl- and vinyl-substituted alkynyl ethers via the Sonogashira coupling reaction because in this approach terminal alkoxy alkynes can be used directly, and it is not necessary to prepare an alkynyl metal derivative in a prior step. Unfortunately, Sonogashira coupling of alkoxy-substituted alkynes is not as straightforward as that of other terminal alkynes. For instance, Yamanaka observed that attempted coupling of

[89] Löffler, A.; Himbert, G. *Synthesis* **1992**, 495.
[90] Tarli, A.; Wang, K. K. *J. Org. Chem.* **1997**, *62*, 8841.

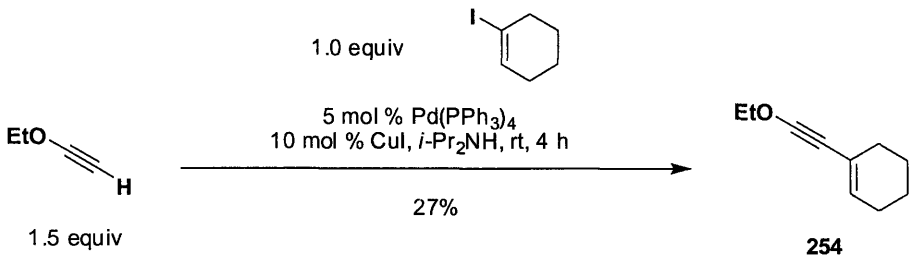
iodobenzene and ethoxyacetylene with catalytic $PdCl_2(PPh_3)_2$ and CuI in triethylamine resulted only in the formation of polymeric products. In contrast, Dussalt has recently reported the coupling of two alkynyl ethers (both bearing a bulky alkoxy substituent) with several vinyl iodides.[91] In one example, enyne **253** was obtained in 94% yield upon stirring a solution of alkyne **251** and (*E*)-1-iodohexene (**252**) in isopropylamine in the presence of catalytic $Pd(PPh_3)_4$ and CuI.



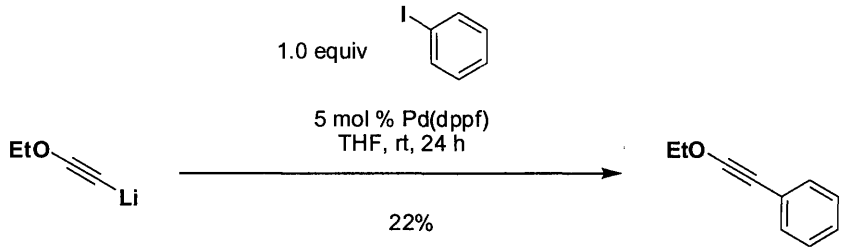
For our purposes, we preferred to prepare enynes bearing primary alkoxy groups. Our attempts to prepare these compounds were only partially successful. Upon subjecting ethoxyacetylene and 1-iodohexene to the conditions of Dussalt, we obtained varying mixtures of the desired enyne and the ethyl ether resulting from hydration of the alkyne moiety in low yield. A series of TLC experiments implicated ammonium salts formed in the reaction as the promoter of product decomposition in the presence of water. We experimented with various workup and purification conditions in pursuit of a method that would provide the pure alkyne. We found that when the reaction was run in diisopropylamine instead of isopropylamine, the ammonium salts were only sparingly soluble. Filtration of the reaction mixture through Celite and purification provided enyne **254** in 27% yield.

---

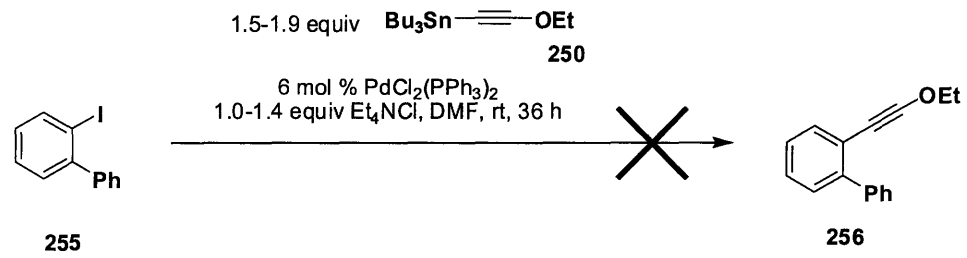
[91] (a) Dussalt, P. H.; Sloss, D. G.; Symonsbergen, D. J. *Synlett*, **1998**, 1387. (b) Dussalt, P. H.; Han, Q.; Sloss, D. G.; Symonsbergen, D. J. *Tetrahedron*, **1999**, 1437.



Due to these challenges, we turned our attention to other cross coupling reactions in search of higher yielding alternatives. We were particularly interested in methods that do not form acid by-products. Kumada coupling of lithium ethoxy acetylide with iodobenzene catalyzed by Pd(dppf) [generated in situ by the reaction of $PdCl_2$(dppf) with *n*-BuLi] proceeded in poor yield, though pure (phenyl)ethoxyacetylene could be obtained and formation of the ester resulting from hydrolysis was not observed.

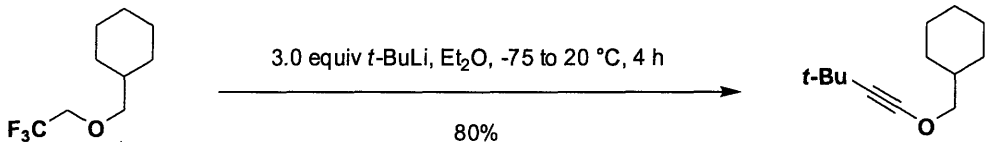


While Yamanaka had reported successful coupling of *para*-substituted aryl iodides, we had initially avoided Stille couplings due to the toxicity of the alkynyl stannane reagents. Following the failure of other methods, we began investigation of these conditions. As successful coupling of *para*-substituted aryl iodides was known, we turned our attention directly to iodides bearing *ortho*-substitution. Unfortunately, subjecting biphenyl iodide **255** to conditions the reported by Yamanaka resulted only in low yields of a new product that did not display the characteristic IR absorbance of alkoxy alkynes (~2250 cm^{-1}).



255 256

At this point, we decided in light of the difficulty in preparing the required substrates to discontinue our investigation into the preparation of TAS-vinylketenes, TAS-arylketenes, and polycyclic aromatic compounds. We believe that the strategy for the synthesis of these molecules is sound, and should a convenient approach to the required alkoxy alkyne precursors appear it may warrant further investigation. One possibility we have not explored is an alternate route to alkoxy alkynes first reported by Nakai, which introduces the eventual alkyne substitutent as a alkyllithium species rather than as an electrophile.[92] In one more recent example, reaction of 2,2,2-trifluoroethyl ether **257** with 3 equiv of *t*-BuLi formed alkoxy alkyne **258** in 80% yield.[93] Overaddition occurs when phenyllithium is added to ethyl 2,2,2-trifluoroethyl ether,[85] but it is conceivable that vinyllithium species may react with **257** in the same fashion as alkyllithium reagents to provide the desired vinyl-substituted alkoxy alkynes.



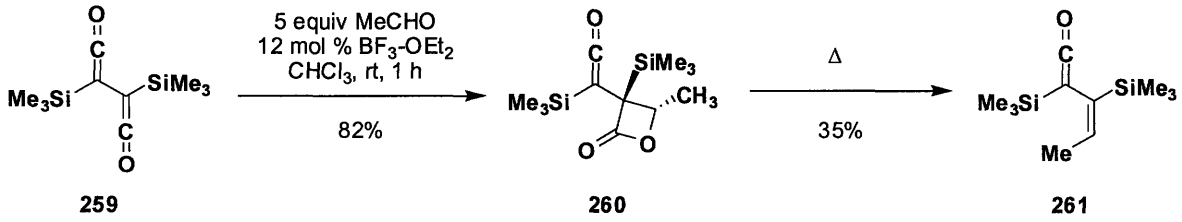
257 258

[92] Tanaka, K.; Shiraishi, S.; Nakai, T.; Ishikawa, N. *Tetrahedron Lett.* **1978**, *19*, 3106
[93] Casson, S. Kocienski, P. *Synthesis* **1993**, 1133.

Chapter 3

Cross-Metathesis of (Trialkylsilyl)vinylketenes

Nearly all of the TAS-vinylketenes that are known to date have been prepared by methods in which the ketene portion of the molecule is formed, either simultaneously with the vinyl moiety or from precursors bearing an appropriately substituted alkene. In fact there is only a single report of the preparation of a TAS-vinylketene from a ketene bearing precursor.[94] Tidwell reported that Lewis acid catalyzed [2 + 2] cycloaddition of acetaldehyde to bisketene **259** formed the lactone **260**. Upon heating in a gas chromatograph, decarboxylation occurred to form 8.9 mg of a TAS-vinylketene assumed to be the (*Z*)-methyl-substituted ketene **261**.



259 **260** **261**

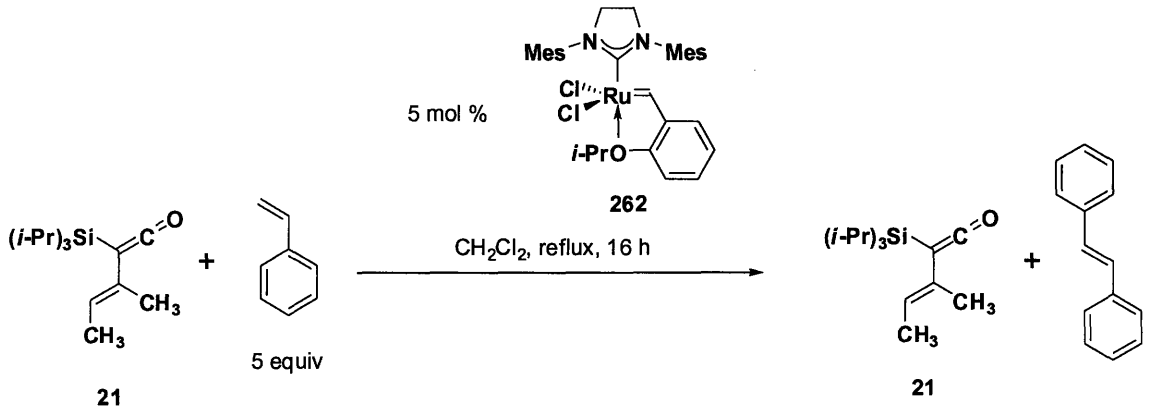
We believed that cross-metathesis could provide a powerful method for the derivatization of TAS-vinylketenes. There have been a number of reports of the preparation of substituted alkenes from less complex alkenes by cross-metathesis,[95] and the conditions for metathesis with ruthenium catalysts are quite mild and tolerate a wide variety of functional groups, including ketones.

---

[94] Colomvakos, J. D.; Egle, I.; Ma, J.; Pole, D. L.; Tidwell, T. T.; Warkentin, J. *J. Org. Chem.* **1996**, *61*, 9522.

[95] For recent reviews of the cross-metathesis of alkenes, see: (a) Chatterjee, A. K. In *Handbook of Metathesis;* Grubbs, R. H., Ed.; Wiley-VCH: Weinheim, 2003; Vol. 2, pp 246-295. (b) Connon, S. J.; Blechert, S. *Angew. Chem. Int. Ed. Engl.* **2003,** *42*, 1900. (c) Chatterjee, A. K.; Choi, T.-L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360. (d) Grubbs, R. H. *Tetrahedron* **2004**, *60*, 7117. (e) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem. Int. Ed. Engl.* **2005**, *44*, 4490.

For our initial foray into this area, we elected to probe the stability of TAS-vinylketenes to the cross-metathesis conditions using the readily available TAS-vinylketene **21.** A solution of ketene **21** and five equivalents of styrene in CH_2Cl_2 containing 5 mol% of the Grubbs-Hoyveda ruthenium metathesis catalyst (**262**) was heated at reflux for 8 hours. Monitoring the progress of the reaction by TLC on silica gel indicated that styrene was consumed and the only product formed in significant amounts was stilbene. The intensity of the spot associated with the ketene starting



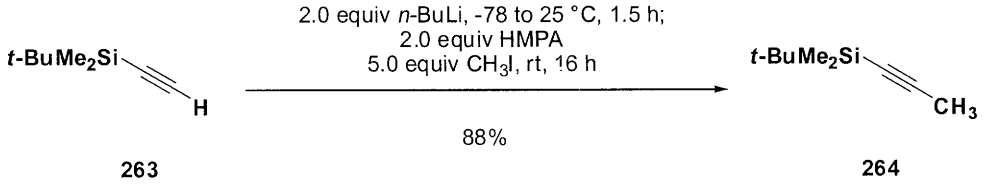
material did not appreciably change during the reaction. These results were confirmed by ^1H NMR analysis, which showed the crude reaction product to be almost entirely stilbene and ketene **21**. We were very pleased with these observations as they indicated that the ketene moiety of **21** was stable in the presence of the ruthenium catalyst and did not interfere with the self-metathesis of styrene. Based on this encouraging result, we set out to prepare a TAS-ketene bearing an unsubstituted alkene for further investigations.

Preparation of (*tert*-Butyldimethylsilyl)vinylketene

At the outset of our studies, (trimethylsilyl)vinylketene was the only known TAS-vinylketene lacking substituents on the vinyl group. While this was a viable candidate for the

ketene partner in our investigations, we felt that additional steric shielding about the ketene moiety provided by a larger silyl group would decrease the potential for undesired reactions. Additionally, we expected that the sequence of reactions used to prepare (trimethylsilyl)vinylketene (**11**, see Part I, Chapter 2) would be readily adaptable to the preparation of any unsubstituted TAS-vinylketene, and for these reasons elected to employ (*tert*-butyldimethylsilyl)vinylketene as the ketene partner in our next cross-metathesis experiments.

The previously reported synthesis of ketene **11** began with 1-trimethylsilylpropyne.[11] However, the TBDMS analog, propyne **272** was not commercially available, though it had been previously prepared by silylation of 1-propynyllithium.[96] For reasons of convenience, we elected instead to synthesize **264** from acetylene **263**. Deprotonation of the terminal alkyne with *n*-butyllithium and trapping of the resulting acetylide with iodomethane in the presence of HPMA provided the desired alkyne in 88% yield. The boiling points and silica gel retention factors of **263** and **264** are nearly identical so all reagents were used in excess, ensuring complete conversion of the acetylene to the propyne.

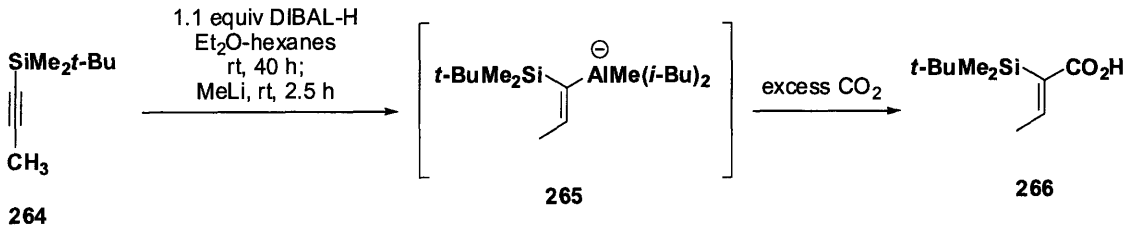


263 **264**

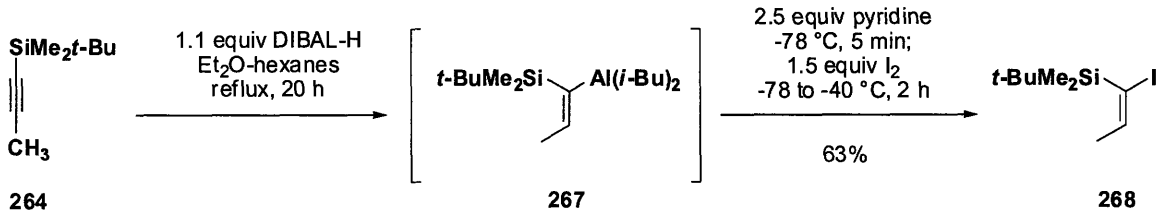
We initially planned to prepare the α-silyl-α,β-unsaturated acid from the alkyne in a single step in a fashion analogous to the transformation of trimethylsilylpropyne to the unsaturated acid **9** (see page 11). Unfortunately, this method produced low yields of acid **266,**

[96] For the previous preparation of **272**, see: Fitzmaurice, N. J.; Jackson, W. R.; Perlmutter, P. *J. Organomet. Chem.* **1985**, *285*, 375.

and substantial amounts of alkyne **264** had been converted instead to the *cis* alkene resulting from hydrolysis of the alane or alanate intermediate. These results showed that despite the additional steric bulk of the silyl group, hydroalumination of the alkyne proceeded with excellent regiocontrol. Unfortunately, the steric environment presented by the geminal alane and silyl substitutent severely hindered further reaction.

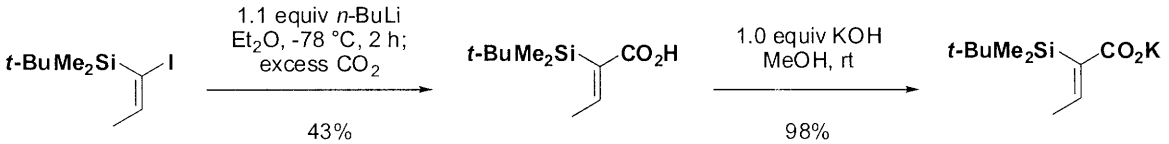


In order to obtain acid **266**, we decided carboxylation of a more nucleophilic vinyllithium species would provide better results. We expected that the vinyllithium compound we required could be formed by metal-halogen exchange of a vinyl iodide, itself prepared from an alanate. To this end, the alane resulting from hydroalumination was treated with 2.5 equiv pyridine and quenched with iodine to give the desired iodide **268** in moderate yield. The pyridine in this reaction may play a dual role, serving as both a nucleophilic catalyst for activation of the iodine, and potentially coordinating activator of the alane.



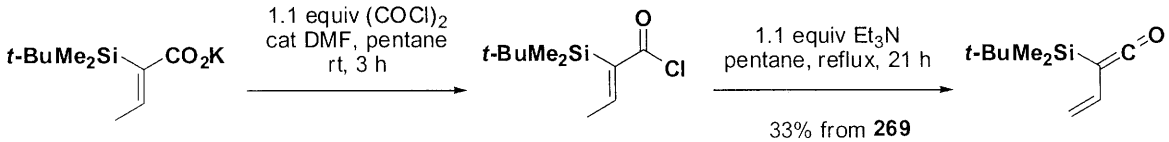
Vinyl iodide **268** was then subjected to metal-halogen exchange with 1.1 equiv of *n*-butyllithium, and the vinyllithium species was added dropwise onto dry ice. The acid was obtained in the low, though acceptable yield of 45%. Addition of gaseous carbon dioxide to the

reaction mixture cannot be employed as vinyllithium species of this type are capable of conjugate addition to the α,β-unsaturated acid salts resulting from carboxylation.[97] Though treatment with potassium hydride and oxalyl chloride would potentially form the acyl chloride we require in a single step, we elected instead preform the potassium salt. Acid **266** was dissolved in methanol and titration with KOH in the presence of phenolphthalein provided the potassium salt **269**.



268 **266** **269**

Treatment of this salt with oxalyl chloride in the presence of catalytic DMF for 3 hours resulted in formation of acyl chloride **270**. The crude acyl chloride was added dropwise to a solution of triethylamine, and after heating at reflux overnight, a heterogeneous solution was formed. Purification by filtration and distillation provided ketene **271**.



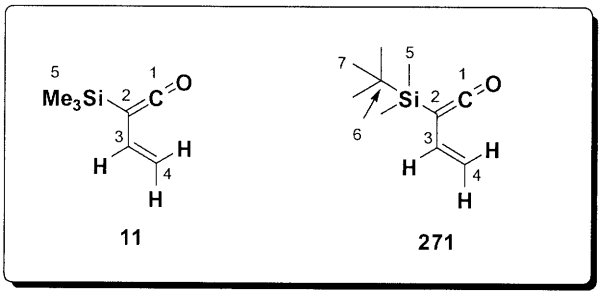
269 **270** **271**

The assignment of the dehydrohalogenation product as ketene **271** follows from consideration of its spectral characteristics and comparison with known ketene **11**.[11] The diagnostic silyl ketene IR absorbance near 2080 cm^{-1} is observed, as are the characteristic ^{13}C NMR shifts (75 MHz, $CDCl_3$) of approximately 180 ppm for the carbonyl and about 20 ppm for

[97] Cooke, M. P., Jr. *J. Org. Chem.* **1987**, *52*, 5729.

the ketene β-carbon. The remaining carbon resonances are consistent with those expected for a TBDMS group and a two sp^2 hybridized carbons. The chemical shifts, integrations and coupling constants of peaks in the ^1H NMR spectrum (500 MHz, $CDCl_3$), summarized in Table 15, are also consistent with what would be expected for ketene **271**.

Table 15. Spectral Data for TAS-Vinylketenes **11** and **271**

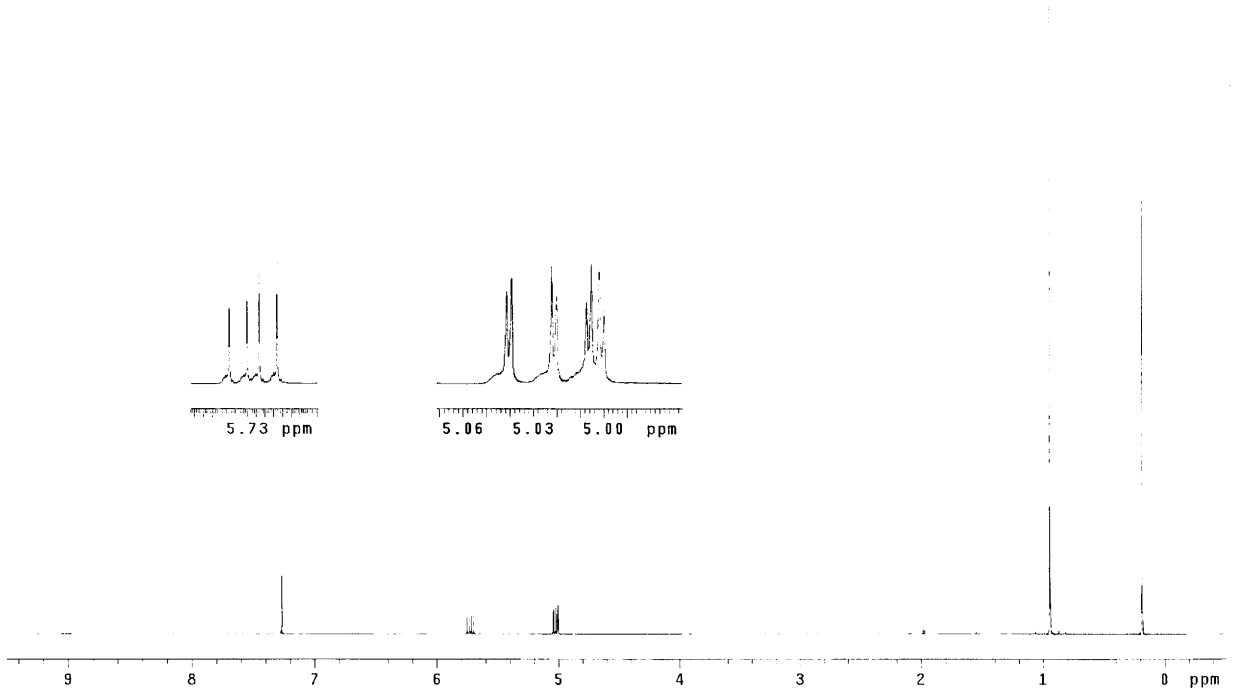


	^1H NMR spectra (δ)	
	11	**271**
C-3	5.92 (dd, J = 17, 10 Hz)	5.71 (dd, J = 17, 10 Hz)
C-4	4.88 (dd, J = 17, 1 Hz)	5.02 (dd, J = 17, 1 Hz)
	4.82 (dd, J = 10, 1 Hz))	5.01 (dd, J = 10, 1 Hz)
C-5	0.25 (s)	0.17 (s)
C-7	-	0.93 (s)

	^{13}C NMR spectra (δ)	
	11	**271**
C-1	183.7	184.1
C-2	22.2	19.8
C-3	125.1	125.8
C-4	111.9	113.4
C-5	-0.9	-5.5
C-6	-	19.1
C-7	-	26.6

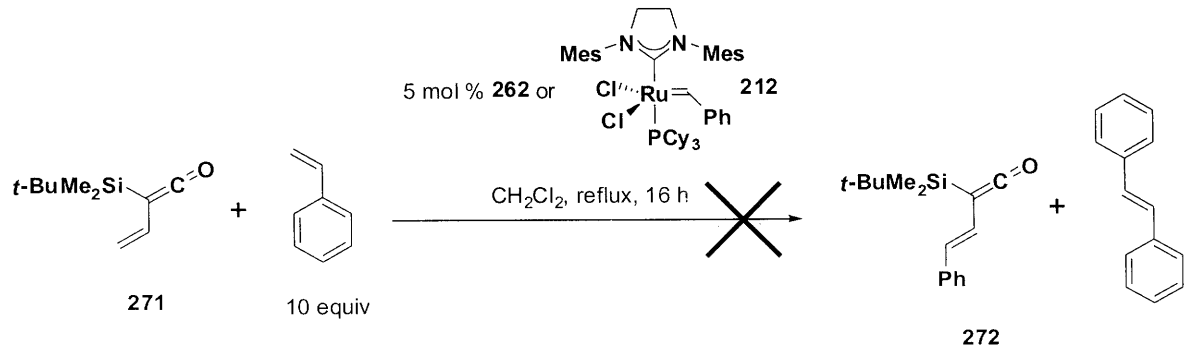
	IR spectra (cm^{-1})
11	2960, 2085, 1610
271	2956, 2085, 1610

Figure 5. ^{1}H NMR Spectrum of Ketene **271**

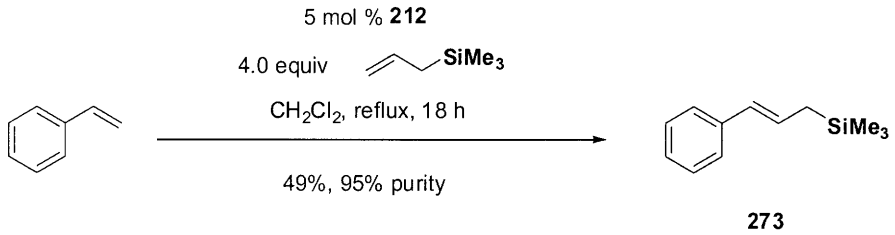


Cross-Metathesis of TAS-Vinylketenes

With ketene **271** in hand, we turned our attention to its application in cross-metathesis reactions. For our initial experiments, the ketene was dissolved in CH_2Cl_2 containing ten equivalents of styrene and 5 mol% of ruthenium catalyst. However, none of the desired product was observed when either Grubbs second generation (**212**) or Grubbs-Hoyveda (**262**) metathesis catalysts were employed. Surprisingly, the self metathesis of styrene was also not observed.

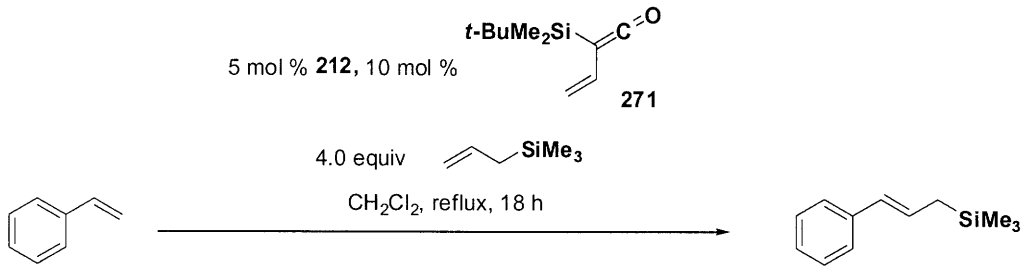


In order to confirm that the above results were due to the presence of vinylketene **271** and not other factors, a control experiment was conducted. Styrene was reacted with four equivalents of allyltrimethylsilane in the presence of 5 mol% of catalyst **212**. Following 18 hours at reflux in CH_2Cl_2, the cross-metathesis product **273** was obtained in 49% yield (95% purity).



273

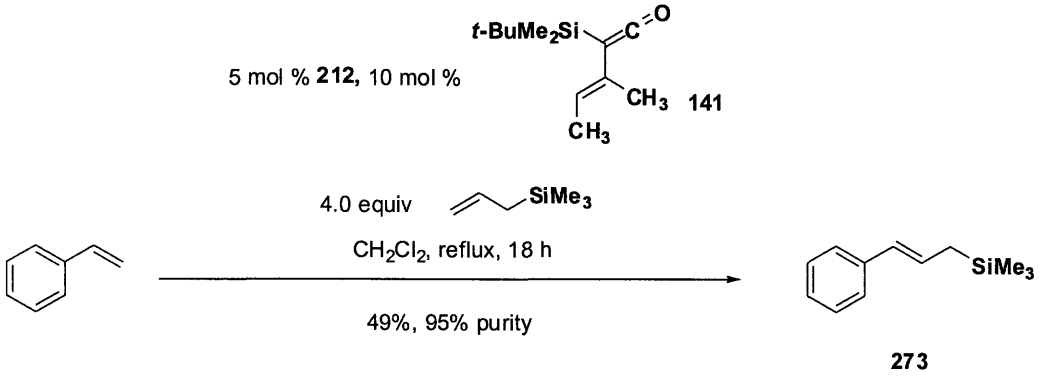
The observation of successful metathesis in this case but not in the cases involving ketene **271** supported our suspicion that the ketene was capable of destructively inactivating the ruthenium catalysts. To prove conclusively that this was the case, a solution of 5 mol% of catalyst **212** was incubated for 10 minutes with 10 mol% of **271**. Following this, the mixture was added to a solution of styrene and four equivalents of allyltrimethylsilane and heated at reflux for 18 hours. No cross-metathesis products were observed, confirming our suspicion.



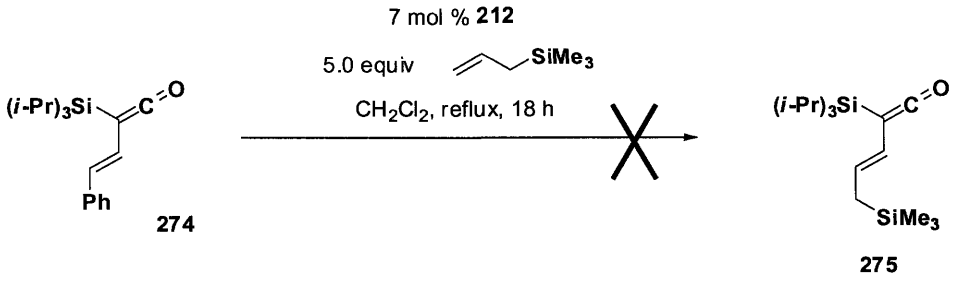
273

This was at odds with our previous observations that the TIPS ketene **21** did not interfere with the self metathesis of styrene. The different outcome in this case could conceivably result from the presence of a bulkier silyl group or the substitution on the vinyl moiety. To determine

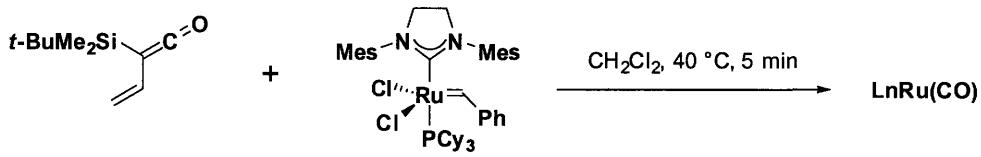
which was the case, the metathesis catalyst **212** was incubated with the TBDMS ketene **141**, and the cross-metathesis of styrene was attempted under identical conditions as employed previously. In this case, the cross-metathesis product was obtained in identical yield and purity as when the metathesis was carried out in the absence of any ketene. These results suggest that the initial step in deactivation of the ruthenium catalysts **212** and **262** is metathesis of the vinyl substituent.



We hoped that the use of a β-substituted TAS-vinylketene such as **274**[12] would slow down metathesis at the vinyl carbon and prevent accumulation of the ruthenium carbene intermediates that may be responsible for the destruction of the catalyst. Unfortunately, under similar reaction conditions, ketene **274** inactivates metathesis catalyst **212** as well. The rate of catalyst destruction by **274** is slower than that of **271**, as evidenced by the observation of small amounts of the self-metathesis product of allyltrimethylsilane in this case despite the presence of a full equivalent of ketene.



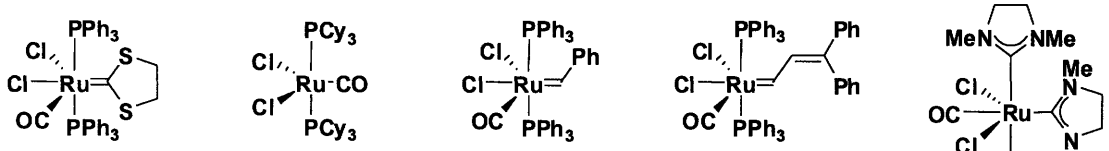
In order to gain additional information about the mechanism of inactivation, a solution of the metathesis catalyst **212** was treated with one equivalent of TAS-vinylketene **271**. IR analysis of the resulting mixture showed a strong absorbance at 1941 cm^{-1}, indicative of the formation of a ruthenium carbonyl complex. Several examples of known ruthenium carbonyl complexes are presented in Figure 6 for comparison.



271 **212**

1.0 equiv

Figure 6. Carbonyl IR Absorbances for **276**,[98] **277**,[99] **278**,[100] **279**,[101] and **280**.[102]

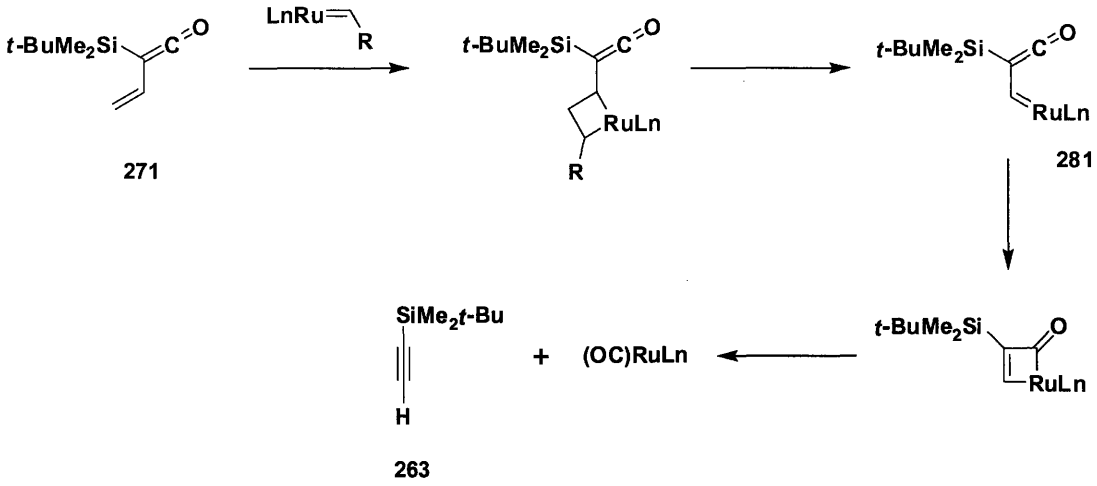


276 1945 cm^{-1} **277** 1934 cm^{-1} **278** 1965 cm^{-1} **279** 1955 cm^{-1} **280** 1938 cm^{-1}

It is possible that this complex could be formed via an intramolecular electrocyclization of α-ketenyl carbene **281**, followed by an extrusion of the silylacetylene **271**. However, IR spectroscopy of the reaction mixture following inactivation of **212** with **271** could not confirm the presence of alkyne **263**. Determination of the precise mechanism by which catalyst

[98] Roper, W. R; Wright, A. H. *J. Organomet. Chem.* **1982**, *233*, C59.
[99] Drouin, S. D.; Amoroso, D.; Yap, G. P. A.; Fogg, D. E. *Organometallics* **2002**, *21*, 1042.
[100] Baker, L.-J.; Clark, G. R.; Rickard, C. E. F.; Roper, W. R.; Woodgate, S. D.; Wright, L. J. *J. Organomet. Chem.* **1998**, *551*, 247.
[101] Harlow, K. J.; Hill, A. F.; Welton, T. *J. Chem. Soc., Dalton Trans.* **1999**, 1911.
[102] Hitchcock, P. B.; Lappert, M. F.; Pye, P. L. *J. Chem. Soc., Dalton Trans.* **1978**, 826.

inactivation occurs will be prohibitively complex and, as a result, we decided to discontinue our investigations into the synthesis of TAS-vinylketenes by this method.



Part IV

Experimental Procedures

General Procedures.

All reactions were performed in flame-dried glassware under a positive pressure of argon. Reaction mixtures were stirred magnetically. 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 0.05 mmHg (vacuum pump) unless otherwise indicated.

Materials.

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

(a) Distilled under argon from calcium hydride

Triisopropylsilyl trifluoromethanesulfonate, triisopropylchlorosilane, triethylsilyl trifluoromethanesulfonate, trimethylchlorosilane, methanesulfonyl chloride, hexanes, pentane, benzene, diisopropylethylamine, triethylamine, and 1,1,1,3,3,3-hexamethyldisilazane.

(b) Purified by pressure filtration through activated alumina

Dichloromethane, diethyl ether, tetrahydrofuran

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

Toluene

(d) Alkyllithiums

Methyllithium and *n*-butyllithium were titrated according to the Watson-Eastham method using BHT in THF with 1,10 phenanthroline as an indicator.[62]

(e) LiHMDS solution

THF solutions of LiHMDS (1.0 M) were prepared by reaction of HMDS in THF with *n*-BuLi.[103]

(f) Anhydrous tert-Butyl hydroperoxide solution

Anhydrous solutions of *tert*-butylhydroperoxide in toluene were prepared by the method of Sharpless.[104]

Chromatography.

Analytical 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 radiation, (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 solution of 10% phosphomolybdic acid in methanol followed by heating to ca. 200 °C, (f) immersion of the plate in an aqueous solution of 6% ammonium molybdate and 1% cerium(IV) sulfate containing 12% concentrated sulfuric acid followed by heating to ca. 200 °C, (g) immersion of the place in an aqueous solution of 5% sodium hydroxide containing 1% potassium permanganate and 6% potassium carbonate followed by heating to ca 200 °C.

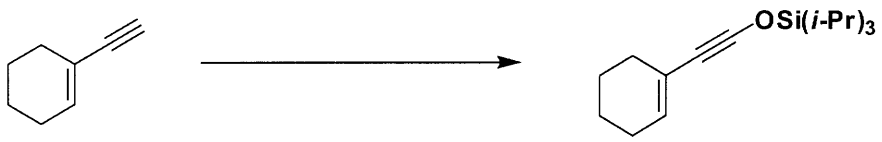
---

[103] Sample procedure: a 25-mL, two-necked, round-bottomed flask, equipped with a rubber septum and argon inlet adapter was charged with a solution of HMDS (4.2 mL, 3.2 g, 20 mmol) in 8.7 mL of THF and cooled at 0 °C while 8.7 mL of *n*-BuLi solution (2.31 M in hexanes, 19 mmol) was added and stirred 5 min.

[104] Hill, J. G.; Rossiter, B. E.; Sharpless, K. B. *J. Org. Chem.* **1983**, *48*, 3607.

Instrumentation.

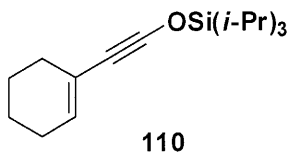
Melting points were determined with a Fisher-Johns melting point apparatus and are uncorrected. Infrared spectra were obtained using a Perkin Elmer 2000 FT-IR spectrophotometer. ^{1}H NMR spectra were recorded on Varian XL-300 (300 MHz), Varian Unity 300 (300 MHz) and Varian Inova 500 (500 MHz) spectrometers. ^{1}H NMR chemical shifts are expressed in parts per million (δ) downfield to TMS (with the residual solvent peak used as a standard). ^{13}C NMR spectra were recorded on Varian XL-300 (75 MHz), Varian Unity 300 (75 MHz) and Varian Inova 500 (125 MHz) spectrometers. ^{13}C NMR chemical shifts are expressed in parts per million (δ) downfield to TMS (with the residual solvent peak used as a standard). High resolution mass spectra were measured in a Bruker Daltonics APEXII 3 tesla fourier mass spectrometer.



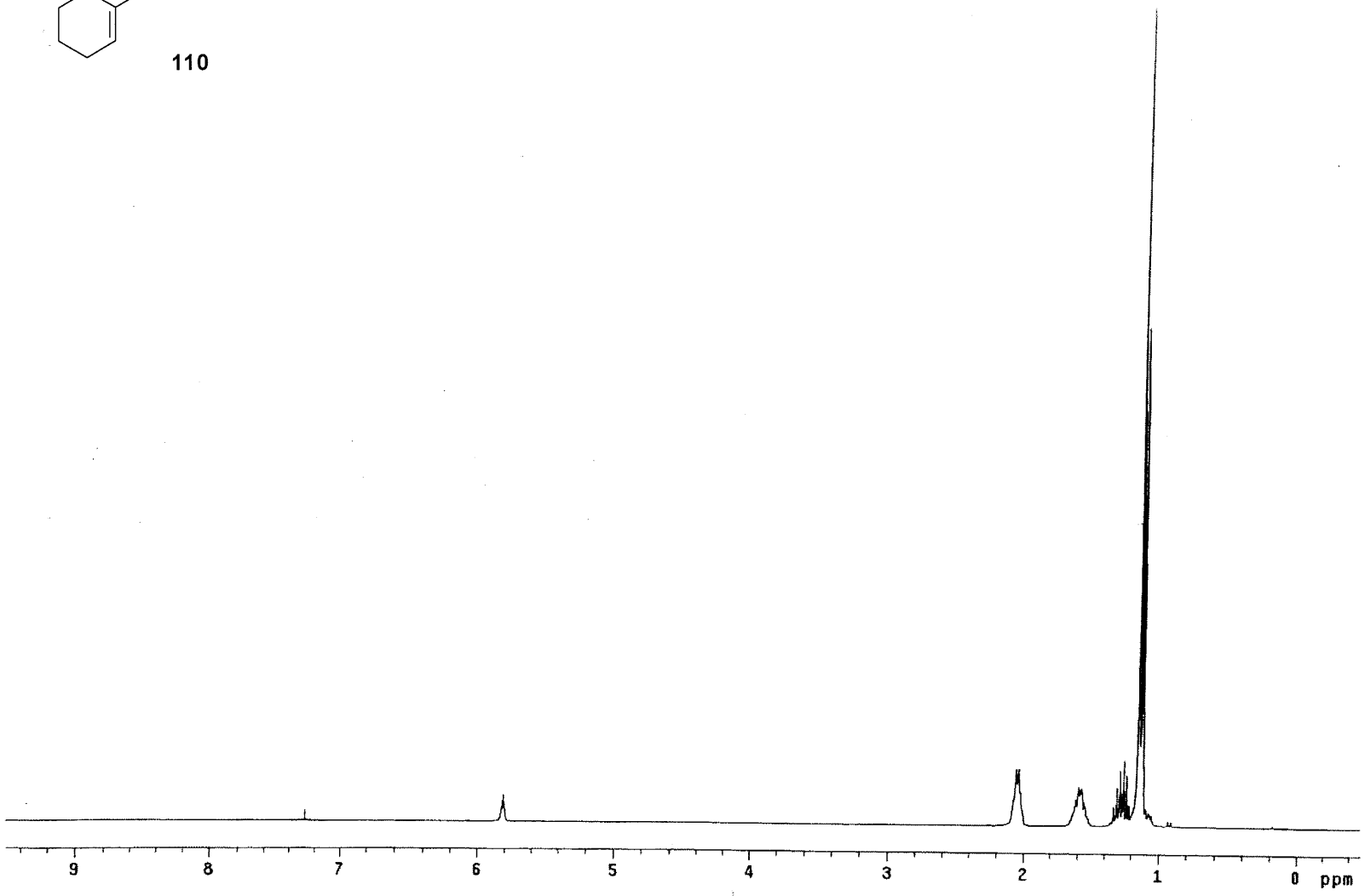
110

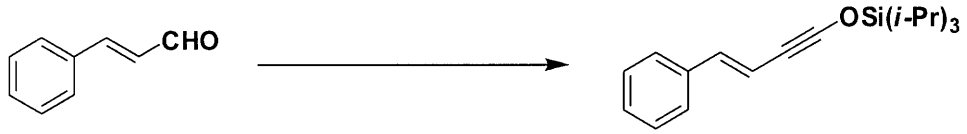
2-(1-Cyclohexenyl)-1-triisopropylsiloxy-ethyne (110).

A 100-mL, round-bottomed, three-necked flask equipped with a rubber septum, glass stopper, and an argon inlet adapter was charged with a solution of 1-ethynylcyclohexene (0.30 mL, 0.27 g, 2.6 mmol) in 10 mL of THF and cooled at -78 °C while 3.1 mL of freshly prepared LiHMDS solution (1.0 M, 3.1 mmol) was added rapidly dropwise. A 100-mL, round-bottomed, three-necked flask equipped with a rubber septum, glass stopper, and an argon inlet adapter was charged with 0.83 mL of a solution of TBHP in toulene (3.7 M, 3.1 mmol). The solution was diluted with 10 mL of THF and cooled at -78 °C while 3.3 mL of freshly prepared LiHMDS solution (1.0 M, 3.3 mmol) was added rapidly dropwise. The resulting solution was added to the lithiated alkyne solution via cannula over 5 min (the flask was rinsed with 5 mL of THF). The dry ice bath was replaced with an ice water bath and the mixture was stirred for 2.5 h, and then recooled at -78 °C before triisopropylsilyl trifluoromethanesulfonate (0.90 mL, 1.0 g, 3.3 mmol) was added rapidly dropwise. The mixture was stirred 10 min, and then the dry ice bath was replaced with an ice water bath and the mixture was stirred for 40 min. The mixture was recooled at -78 °C and diluted with 50 mL of hexanes, and then poured into 30 mL of a satd aq $NaHCO_3$ solution. The aqueous phase was separated and extracted with two 30-mL portions of hexanes, and then the combined organic phases were washed with 30 mL of water and 30 mL of brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure (20 mmHg, ca 0.5 h; then 0.3 mmHg ca 2 h). The resulting orange oil was filtered through 5 g of silica gel with the aid of 125 mL hexanes to yield 0.643 g (90%) of the siloxy alkyne **110** as a colorless oil: IR (hexanes) 2958, 2873, 2258, 1466 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.79-5.84 (m, 1 H), 1.99-2.10 (m, 4 H), 1.50-1.67 (m, 4 H), 1.20-1.34 m (3 H), 1.13 (d, J = 6.9 Hz, 18 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 129.9, 121.2, 94.8, 35.1, 30.7, 25.8, 22.9, 22.0, 17.5, 12.1.



110





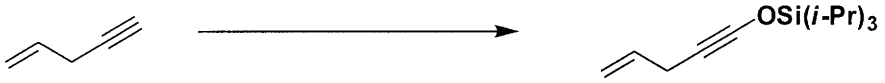
112

(*E*)-4-Phenyl-1-(triisopropylsiloxy)-3-buten-1-yne (112).

A 250-mL, three-necked, round-bottomed flask equipped with a rubber septum, glass stopper, and an argon inlet adapter and charged with dibromomethyl triphenylphosphonium bromide (7.483 g, 14.5) in 80 mL of THF and stirred at rt while KO*t*-Bu (1.609 g, 14.3 mmol) was added portionwise over 5 min. Cinnamaldehyde (0.94 mL, 0.99 g, 7.6 mmol) was added and the mixture was stirred 10 min, cooled to -78 °C, and additional KO*t*-Bu (4.203 g, 37.4 mmol) was added portionwise over 5 min. The mixture was stirred for 15 min and then poured into 60 mL of brine. The aqueous phase was extracted with two 50-mL portions of Et_2O and the combined organics were dried with Na_2SO_4, filtered, and concentrated. The resulting black oil was filtered through 30 g of silical gel with 500 mL hexanes anc concentrated to yield 0.962 g of a yellow oil. Column chromatography on 30 g of silica gel (elution with 10% benzene-hexanes) yielded 0.895 g of a yellow oil, estimated to be 95% pure by ^{1}H NMR. A 100-mL, three-necked, round-bottomed flask equipped with a rubber septum, glass stopper, and an argon inlet adapter was charged with a solution of the crude alkyne (0.882 g, 6.9 mmol) in 20 mL of THF and cooled at -78 °C while 8.3 mL of freshly prepared LiHMDS solution (1.0 M, 8.3 mmol) was added dropwise over 30 s. A 50-mL, three-necked, round-bottomed flask equipped with a rubber septum, glass stopper, and an argon inlet adapter was charged with 2.3 mL of *t*-BuOOH solution (3.7 M in toluene, 8.5 mmol) and 10 mL of THF and cooled at -78 °C while 9.0 mL of freshly prepared LiHMDS solution (1.0 M, 9.0 mmol) was added rapidly dropwise over 30 s. The resulting solution was then transferred via cannula over 5 min into the solution of lithium acetylide (the flask was rinsed with 5 mL of THF). The dry ice-acetone bath was replaced with an ice-water bath and the reaction mixture was stirred at 0 °C for 2.5 h. The resulting solution was cooled to -78 °C and *i*-Pr_3SiOTf (2.4 mL, 2.7 g, 8.9 mmol) was added rapidly dropwise via syringe. The reaction mixture was stirred for 10 min at -78 °C and 30 min at 0 °C, and then was cooled at -78 °C and diluted with 50 mL of hexanes. The resulting solution was poured into 40 mL of satd aq $NaHCO_3$ solution, and the aqueous phase was separated and extracted with two

30-mL portions of hexanes. The combined organic phases were washed with 50 mL of water and 50 mL of brine, dried over Na_2SO_4, filtered, concentrated (0.3 mmHg, 90 min), and then filtered through 5 g of silica gel with the aid of 125 mL of hexanes and concentrated to afford 0.824 g of a yellow oil. Purification by column chromatography on 30 g of silica gel (elution with hexanes) yielded 0.643 g (29%) of siloxy alkyne **112** with spectral characteristics identical to those previously reported for this compound.[105]

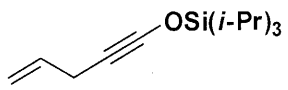
[105] Siloxy alkyne **112** has been previously prepared from ethyl cinnimate in 50% yield by the method of Kowalski. See reference 43d.



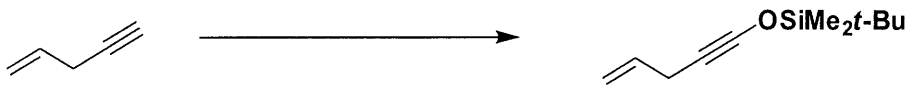
113

1-(Triisopropylsiloxy)-4-penten-1-yne (113).

A 50-mL, three-necked, round-bottomed flask equipped with a rubber septum, glass stopper, and an argon inlet adapter was charged with a solution of 1-penten-4-yne (0.243 g, 3.68 mmol) in 10 mL of THF and cooled at -78 °C while 4.4 mL of freshly prepared LiHMDS solution (1.0 M, 4.4 mmol) was added dropwise over 30 s. A 100-mL, three-necked, round-bottomed flask equipped with a rubber septum, glass stopper, and an argon inlet adapter was charged with 2.3 mL of *t*-BuOOH solution (3.7 M in toluene, 8.5 mmol) and 10 mL of THF and cooled at -78 °C while 4.8 mL of freshly prepared LiHMDS solution (1.0 M, 4.8 mmol) was added rapidly dropwise over 30 s. The resulting solution was then transferred via cannula over 5 min into the solution of lithium acetylide (the flask was rinsed with 5 mL of THF). The dry ice-acetone bath was replaced with an ice-water bath and the reaction mixture was stirred at 0 °C for 2.5 h. The resulting solution was cooled to -78 °C and *i*-Pr_3SiOTf (1.3 mL, 1.5 g, 9.1 mmol) was added rapidly dropwise via syringe. The reaction mixture was stirred for 10 min at -78 °C and 30 min at 0 °C, and then was cooled at -78 °C and diluted with 30 mL of hexanes. The resulting solution was poured into 30 mL of satd aq $NaHCO_3$ solution, and the aqueous phase was separated and extracted with two 15-mL portions of hexanes. The combined organic phases were washed with 30 mL of water and 30 mL of brine, dried over Na_2SO_4, filtered, concentrated (0.3 mmHg, 90 min), and then filtered through 5 g of silica gel with the aid of 125 mL of hexanes and concentrated to afford 0.824 g of a yellow oil. Purification by column chromatography on 30 g of silica gel (elution with hexanes) yielded 0.603 g (69%) of siloxy alkyne **113** as a colorless oil: IR (neat) 3086, 2869, 2282, 1642, 1464 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.84 (ddt, *J* = 13.6, 10.0, 6.8 Hz, 1 H), 5.30 (app dq, *J* = 16.8, 1.9 Hz, 1 H), 5.04 (app dq, *J* = 10.1, 1.8 Hz, 1 H), 2.87 (app dt, *J* = 5.2, 1.8 Hz, 2 H), 1.22-1.33 (m, 3 H), 1.14 (d, *J* = 7.3 Hz, 18 H); ^{13}C NMR (75 MHz, C_6D_6) δ 135.7, 115.3, 89.7, 27.8, 22.4, 18.1, 12.5.



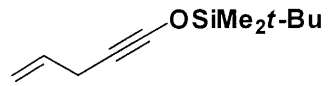
113



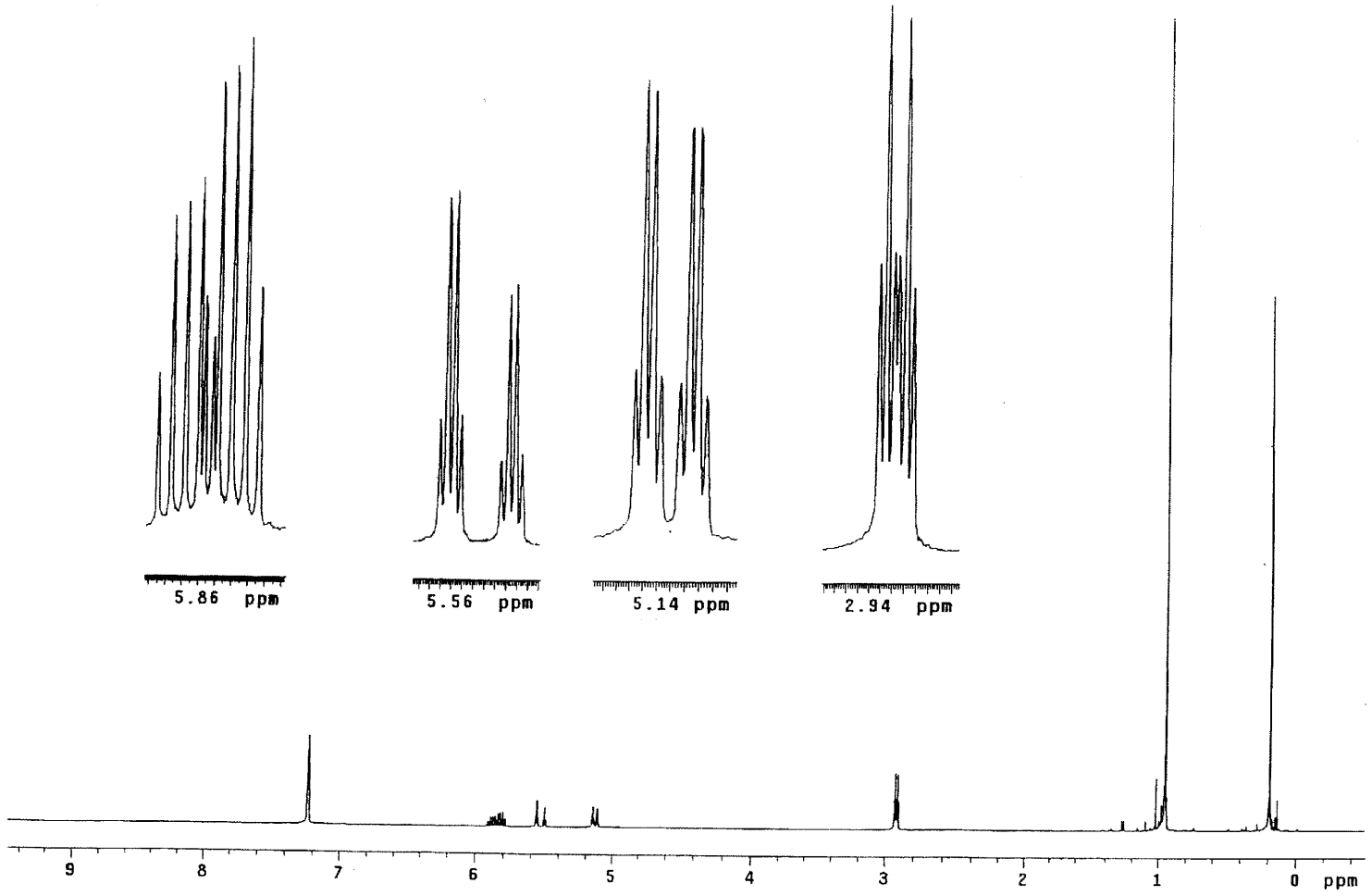
114

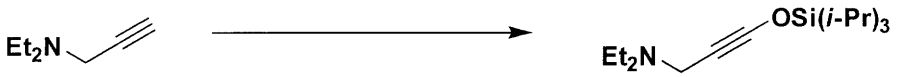
1-(*tert*-Butyldimethylsiloxy)-4-penten-1-yne (114).

A 100-mL, three-necked, round-bottomed flask equipped with a rubber septum, glass stopper, and an argon inlet adapter was charged with a solution of 1-penten-4-yne (0.463 g, 7.00 mmol) in 20 mL of THF and cooled at -78 °C while 8.4 mL of freshly prepared LiHMDS solution (1.0 M, 8.4 mmol) was added dropwise over 30 s. A 100-mL, three-necked, round-bottomed flask equipped with a rubber septum, glass stopper, and an argon inlet adapter was charged with 2.3 mL of *t*-BuOOH solution (3.7 M in toluene, 8.5 mmol) and 15 mL of THF and cooled at -78 °C while 9.1 mL of freshly prepared LiHMDS solution (1.0 M, 9.1 mmol) was added rapidly dropwise over 1 min. The resulting solution was then transferred via cannula over 5 min into the solution of lithium acetylide (the flask was rinsed with 5 mL of THF). The dry ice-acetone bath was replaced with an ice-water bath and the reaction mixture was stirred at 0 °C for 2.5 h. The resulting solution was cooled to -78 °C and *t*-$BuMe_2SiOTf$ (2.1 mL, 2.4 g, 9.1 mmol) was added rapidly dropwise via syringe. The reaction mixture was stirred for 10 min at -78 °C and 30 min at 0 °C, and then was cooled at -78 °C and diluted with 75 mL of hexanes. The resulting solution was poured into 50 mL of satd aq $NaHCO_3$ solution, and the aqueous phase was separated and extracted with two 25-mL portions of hexanes. The combined organic phases were washed with 50 mL of water and 50 mL of brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford 1.932 g of an orange oil. Purification by bulb-to-bulb distillation (50-60 °C bath temperature, 0.15-0.20 mmHg) yielded 0.653 g (48%) of siloxy alkyne **114** as a colorless oil: IR (neat) 3086, 2958, 2861, 2284, 1643, 1472, 1253 cm^{-1}; ^1H NMR (300 MHz, C_6D_6) δ 5.84 (ddt, J = 16.9, 10.0, 5.0 Hz, 1 H), 5.51 (app dq, J = 16.9, 2.0 Hz, 1 H), 5.12 (app dq, J = 9.9, 2.0 Hz, 1 H), 2.90 (app dt, J = 5.1, 1.9 Hz, 2 H), 0.95 (s, 9 H), 0.19 (s, 6 H); ^{13}C NMR (75 MHz, C_6D_6) δ 135.1, 114.7, 88.8, 28.2, 25.3, 21.9, 18.3, -5.9.



114

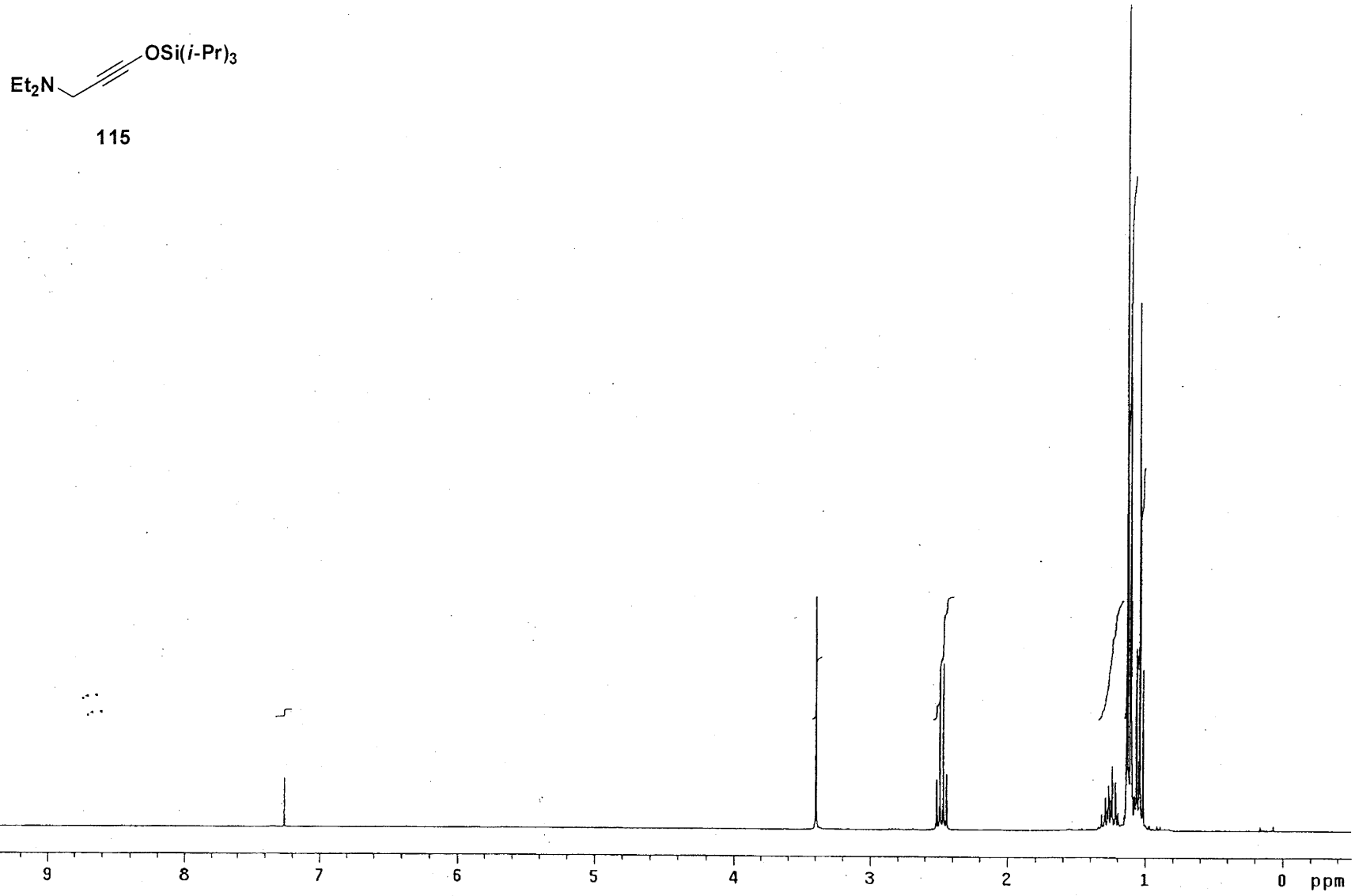


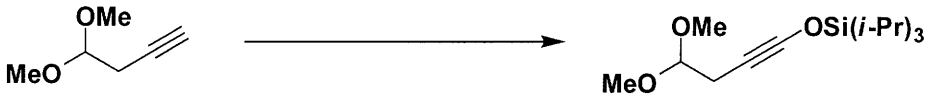


115

3-(Diethylamino)-1-(Triisopropylsiloxy)-1-propyne (115).

A 100-mL, two-necked, round-bottomed flask equipped with a rubber septum and argon inlet adapter was charged with a solution of 3-diethylamino-1-propyne (0.63 mL, 0.51 g, 4.6 mmol) in 15 mL of THF and cooled at -78 °C while 5.5 mL of LiHMDS solution (1.0 M in THF, 5.5 mmol) was added rapidly dropwise over 30 s. Simultaneously, a 20-mL, two-necked, round-bottomed flask equipped with a rubber septum and argon inlet adapter was charged with a solution of *tert*-butyl hydroperoxide (4.0 M in toluene, 1.4 mL, 5.6 mmol) in 10 mL of THF and cooled at -78 °C while 6.0 mL of LiHMDS solution (1.0 M in THF, 6.0 mmol) was added rapidly dropwise over 30 s. The resulting solution was added to the acetylide solution via cannula over 3 min, and the dry ice-acetone bath was replaced with an ice water bath and the mixture was stirred for 2.5 h. The mixture was recooled to -78 °C, TIPSOTf (1.6 mL, 1.8 g, 6.0 mmol) was added in one portion, the reaction mixture was stirred for 10 min at -78 °C, and then for 45 min at 0 °C. The mixture was recooled at -78 °C, diluted with 50 mL of hexanes, and then poured into a separatory funnel containing 50 mL of satd aq $NaHCO_3$ solution. The aq phase was extracted with two 25-mL portions of hexanes, and then the combined organic phases were washed with 75 mL of water and 75 mL of satd aq NaCl solution, dried over $MgSO_4$, filtered, and concentrated to yield 1.497 g of a orange oil. Bulb-to-bulb distillation (110-115 °C bath temperature, 0.2-0.3 mmHg) yielded 0.990 g (77%) of siloxy alkyne **115** as a pale yellow oil: IR (neat) 2945, 2868, 2265, 1654, 1609 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.39 (s, 2 H), 2.48 (q, J = 7.2 Hz, 4 H), 1.19-1.33 (m, 3H), 1.12 (d, J = 6.9 Hz, 18H) 1.04 (t, J = 7.2 Hz, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 90.7, 47.4, 39.8, 17.9, 17.6, 13.2, 12.0.

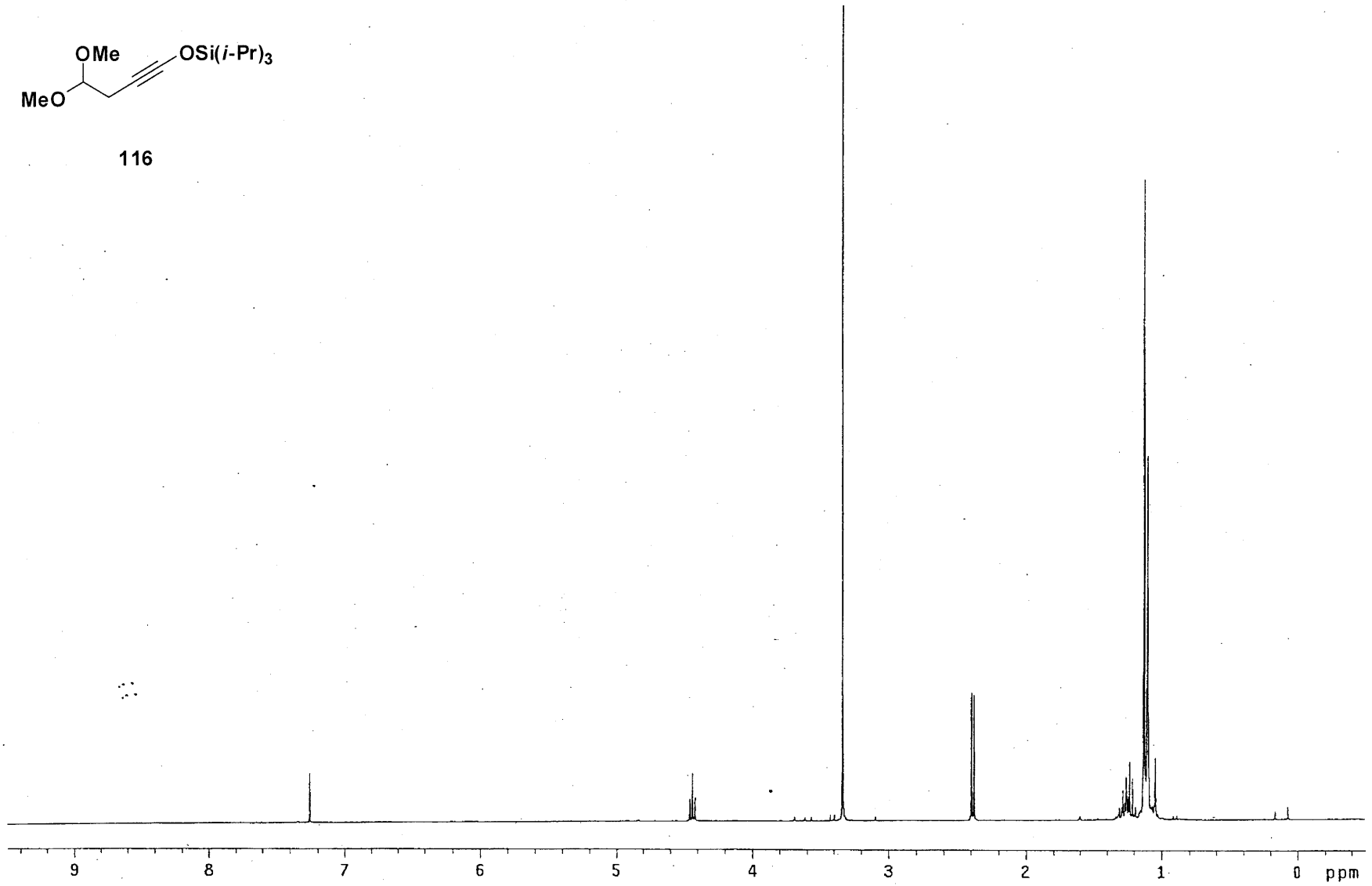

OSi(i-Pr)3
Et2N
115
9
8
7
6
5
4
3
2
1
0
ppm

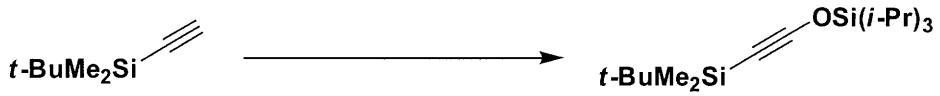


116

4,4-Dimethoxy-1-triisopropylsiloxy-1-butyne (116).

A 100-mL, round-bottomed, two-necked flask equipped with a rubber septum and an argon inlet adapter was charged with a solution of 4,4-dimethoxy-1-butyne (0.502 g, 4.4 mmol) in 15 mL of THF and cooled at -78 °C while 5.4 mL of freshly prepared LiHMDS solution (1.0 M, 5.4 mmol) was added rapidly dropwise. A 50-mL, round-bottomed, two-necked flask equipped with a rubber septum and an argon inlet adapter was charged with 1.35 mL of a solution of TBHP in toulene (4.0 M, 5.4 mmol). The solution was diluted with 10 mL of THF and cooled at -78 °C while 5.9 mL of freshly prepared LiHMDS solution (1.0 M, 5.9 mmol) was added rapidly dropwise. The resulting solution was added to the lithiated alkyne solution via cannula over 5 min (the flask was rinsed with 5 mL of THF). The dry ice bath was replaced with an ice water bath and the mixture was stirred for 2.5 h, and then recooled at -78 °C before triisopropylsilyl trifluoromethanesulfonate (1.6 mL, 1.8 g, 5.9 mmol) was added in rapidly dropwise. The mixture was stirred 10 min, and then the dry ice bath was replaced with an ice water bath and the mixture was stirred for 30 min. The mixture was recooled at -78 °C and diluted with 50 mL of hexanes, and then poured into 30 mL of a satd aq $NaHCO_3$ solution. The aqueous phase was separated and extracted with two 50-mL portions of hexanes, and the combined organic phases were washed with 75 mL of water and 75 mL of brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure (20 mmHg, ca 0.5 h; then 0.3 mmHg ca. 1 h). Bulb-to-bulb distillation (bath temp 100-110 °C, 0.25-0.30 mmHg) yielded 1.116 g of a colorless oil. Further concentration (bath temp 100-110 °C, 0.25-0.30 mmHg) yielded 0.997 g (79%) of the siloxy alkyne **116** as a colorless oil: IR (hexanes) 2946, 2869, 2285, 1464 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.42 (t, J = 5.8 Hz, 1 H), 3.32 (s, 6 H), 2.37 (d, J = 5.9 Hz, 2 H), 1.21-1.30 (m, 3 H), 1.10 (d, J = 6.7 Hz, 18 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 103.7, 87.9, 53.1, 25.6, 22.4, 17.5, 12.0; ; HRMS-ESI (*m/z*): $[M + H]^+$ calcd for $C_{15}H_{30}O_3Si$, 287.2037; found, 287.2030.


OMe
OSi(i-Pr)3
MeO
116
9
8
7
6
5
4
3
2
1
0
ppm



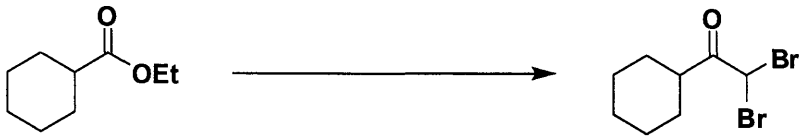
117

2-*tert*-Butyldimethylsilyl-1-(triisopropylsiloxy)-ethyne (117).

A 100-mL, two-necked, round-bottomed flask equipped with a rubber septum and argon inlet adapter was charged with a solution of *tert*-butyldimethylsilylacetlyene (0.68 mL, 0.51 g, 3.6 mmol) in 15 mL of THF and cooled at -78 °C while 5.5 mL of LiHMDS solution (1.0 M in THF, 5.5 mmol) was added rapidly dropwise over 30 s. Simultaneously, a 50-mL, two-necked, round-bottomed flask equipped with a rubber septum and argon inlet adapter was charged with a solution of *tert*-butyl hydroperoxide (4.0 M in toluene, 1.4 mL, 5.6 mmol) in 10 mL of THF and cooled at -78 °C while 6.0 mL of LiHMDS solution (1.0 M in THF, 6.0 mmol) was added rapidly dropwise over 30 s. The resulting solution was added to the acetylide solution via cannula over 3 min, and then the dry ice-acetone bath was replaced with an ice water bath and the mixture was stirred for 2.5 h and the dry ice bath was replaced. TIPSOTf (1.6 mL, 1.8 g, 6.0 mmol) was added in one portion, the mixture was stirred 15 min, and then the dry ice-acetone bath was again replaced with an ice water bath and the stirring was continued for 45 min. The mixture cooled at -78 °C, and diluted with 50 mL of hexanes, and then poured into a separatory funnel containing 40 mL of satd aq $NaHCO_3$ solution. The aq phase was separated and extracted with two 25-mL portions of hexanes, and then the combined organic phases were washed with 75 mL of water and 75 mL of satd aq NaCl solution, dried over Na_2SO_4, filtered, and concentrated (0.2-0.3 mmHg, 2 h) to yield 1.323 g of an orange oil. Bulb-to-bulb distillation (90-100 °C bath temperature, 0.2-0.3 mmHg) yielded 0.739 g (65%) of siloxy alkyne **117** as a colorless oil with spectral characteristics identical to those previously reported:[106] IR (neat) 2184 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.20-1.30 (m, 3 H), 1.13 (d, J = 6.8 Hz, 18 H), 0.90 (s, 9 H), 0.03 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 107.9, 27.8, 26.4, 17.5, 17.0, 12.1, -3.6.

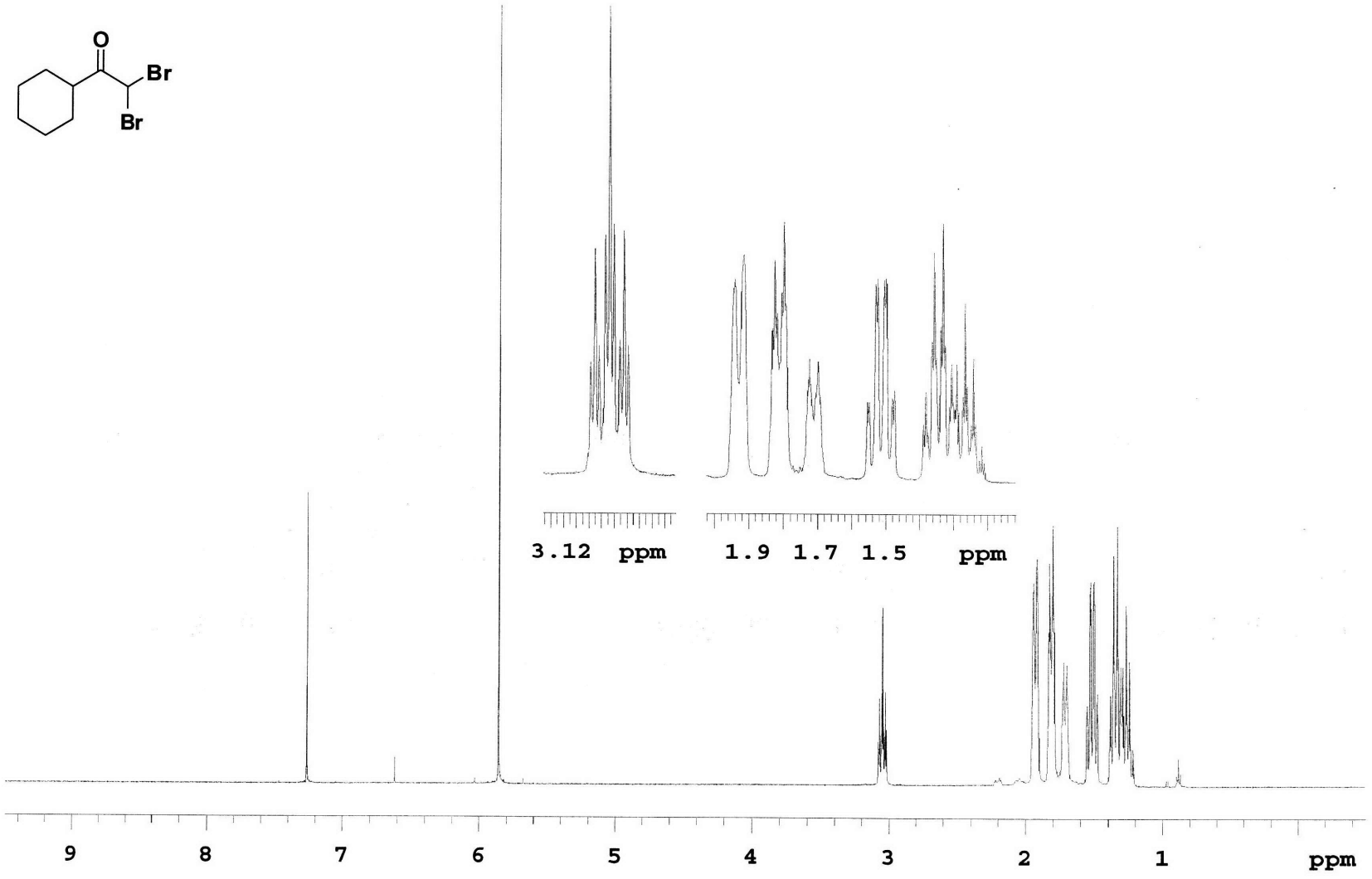
---

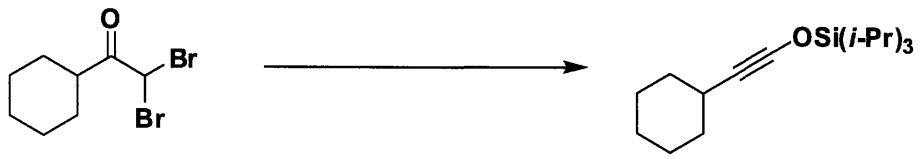
[106] Siloxy alkyne **117** has been previously prepared from (*tert*-butyldimethylsilyl)ketene in 50% yield. See: Akai, S.; Kitagaki, S.; Naka, T.; Yamamoto, K.; Tsuzuki, Y.; Matsumoto, K.; Kita, Y. *J. . Chem. Soc., Perkin Trans. 1.* **1996**, 1705.



2-Cyclohexyl-1,1-dibromo-2-ethanone.

A 100-mL, three-necked, round-bottomed flask equipped with a rubber septum, a glass stopper and an argon inlet was charged with ethyl cyclohexanecarboxylate (0.344 g, 2.20 mmol), dibromomethane (0.39 mL, 0.966 g, 5.6 mmol), and 8 mL of THF and cooled at –78 °C in a dry ice-acetone bath. A 50-mL, two-necked, round-bottomed flask was charged with 2,2,6,6-tetramethylpiperidine (1.00 mL, 0.837 g, 5.93 mmol) and 10 mL of THF and cooled at 0 °C in an ice-water bath while 2.2 mL of *n*-butyllithium solution (2.35 M in hexanes, 5.2 mmol) was added rapidly. The resulting solution was stirred for 5 min, added to the 100-mL flask via cannula over 20 min (the flask was rinsed with 2 mL of additional THF), and then stirred at –78 °C an additional 25 min. The reaction mixture was then cannulated into 25 mL of 1.2 M aq HCl over 5 min. The aqueous phase was extracted with two 20-mL portions of hexanes, and the combined organic phases were washed with 50 mL of water and 50 mL of satd aq NaCl solution, dried over $MgSO_4$, filtered, and concentrated to give 0.622 g of brown oil. Column chromatography on 40 g of silica gel (gradient elution 0-1% EtOAc-hexanes) gave 0.558 g of a pale yellow oil which was further purified by column chromatography on 10 g of silica gel (elution with hexanes) to give 0.508 g (81%) of 2-cyclohexyl-1,1-dibromo-2-ethanone as a colorless oil: IR (neat) 2935, 2855, 1720 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.87 (s, 1 H), 3.06 (tt, J = 11.5, 3.4 Hz, 1 H), 1.90-1.96 (m, 2 H), 1.78-.185 (m, 2 H), 1.68-1.74 (m, 1 H), 1.47-1.56 (m, 2 H), 1.20-1.39 (m, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.4, 45.2, 42.5, 30.7, 25.6, 25.6.


O
Br
Br
3.12 ppm
1.9 1.7 1.5 ppm
9
8
7
6
5
4
3
2
1
ppm

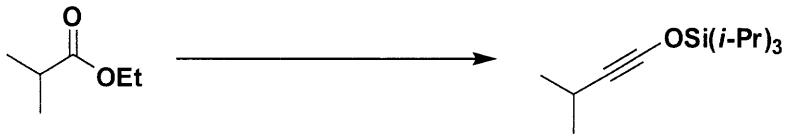


118

2-Cyclohexyl-1-(triisopropylsiloxy)-1-ethyne (118).

A 50-mL, three-necked, round-bottomed flask equipped with a glass stopper, rubber septum, and argon inlet adapter was charged with a solution of 1,1-dibromo-2-cyclohexyl-2-ethanone (0.503 g, 1.8 mmol) in 50 mL of THF and cooled at –78 °C in a dry ice-acetone bath. A 25-mL, two-necked, round-bottomed flask equipped with a rubber septum and argon inlet adapter was charged with a solution of HMDS (0.45 mL, 0.34 g, 2.1 mmol) in 6 mL of THF and cooled at 0 °C in an ice-water bath while 0.79 mL of *n*-butyllithium solution (2.35 M in hexanes, 1.9 mmol) was added rapidly via syringe. The resulting mixture was stirred for 5 min, and then transferred via cannula over 6 min into the solution of dibromo ketone (the flask was rinsed with an additional 1 mL of THF). The resulting solution was stirred for 14 min at –78 °C, and then 1.65 mL of *n*-butyllithium solution (2.35 M in hexanes, 3.9 mmol) was added dropwise over 5 min. The reaction mixture was stirred at –78 °C for 10 min and then (*i*-Pr)$_3$SiOTf (0.48 mL, 0.55 g, 1.8 mmol) was added in one portion. After 10 min, the dry ice-acetone bath was replaced with an ice-water bath and stirring was continued at 0 °C for 30 min. The reaction mixture was diluted with 20 mL of hexanes and poured into 10 mL of satd aq $NaHCO_3$. The aqueous phase was separated and extracted with three 10-mL portions of hexanes, and then the combined organic phases were washed with two 30-mL portions of water and 30 mL of brine, dried over Na_2SO_4, filtered, and concentrated (0.2 mmHg, 1 h). The yellow oil was filtered through 4 g of silica gel with the aid of 125 mL of hexanes, and the filtrate was concentrated to afford 0.429 g of a colorless oil. Purification column chromatography on 30 g of silica gel (elution with hexanes) yielded 0.305 g (61%) of siloxy alkyne **118** with spectral characteristics identical to those previously reported.[107]

[107] Siloxy alkyne **118** has been previously prepared from cyclohexane carboxylate in 68% yield by the one-pot procedure of Kowalski. See reference 43d.



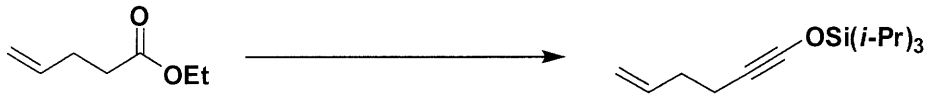
119

3-Methyl-1-(triisopropylsiloxy)-1-butyne (119).

A 250-mL, three-necked, round-bottomed flask equipped with a rubber septum, a glass stopper and an argon inlet was charged with ethyl isobutyrate (0.869 g, 7.5 mmol), dibromomethane (1.45 mL, 3.59 g, 20.7 mmol), and 35 mL of THF and cooled at –78 °C in a dry ice-acetone bath. A 100-mL, two-necked, round-bottomed flask was charged with 2,2,6,6-tetramethylpiperidine (3.4 mL, 2.9 g, 20 mmol) and 35 mL of THF and cooled at 0 °C in an ice-water bath while 7.6 mL of *n*-butyllithium solution (2.35 M in hexanes, 18 mmol) was added rapidly. The resulting solution was stirred 5 min, and then added to the 100-mL flask via cannula over 30 min and stirred at –78 °C an additional 25 min. The reaction mixture was then cannulated into 50 mL of 1.2 M aq HCl over 5 min. The aqueous phase was extracted with two 50-mL portions of hexanes, and the combined organic phases were washed with 50 mL of water and 50 mL of satd aq NaCl solution, dried over $MgSO_4$, filtered, and concentrated to give 0.622 g of brown oil. Column chromatography on 100 g of silica gel (elution with 2% EtOAc-hexanes) gave 1.409 g of a yellow oil estimated to be ca. 90% dibromo ketone by ^1H NMR. A 250-mL, three-necked, round-bottomed flask equipped with a glass stopper, rubber septum, and argon inlet was charged with a solution of the crude dibromo ketone (1.397 g) in 25 mL of THF and cooled at –78 °C in a dry ice-acetone bath. A 100-mL, three-necked, round-bottomed flask equipped with a glass stopper, rubber septum, and argon inlet was charged with a solution of 1,1,1,3,3,3-hexamethyldisilazane (1.45 mL, 1.11 g, 6.87 mmol) in 20 mL of THF and cooled at 0 °C in an ice-water bath while 2.6 mL of *n*-butyllithium solution (2.35 M in hexanes, 6.1 mmol) was added over 5 s. The resulting mixture was stirred for 5 min, and then cooled at -78 °C and added to the dibromo ketone solution via cannula over 10 min (the flask was rinsed with an additional 5 mL of THF) and stirred an additional 13 min at –78 °C, after which 5.4 mL of *n*-butyllithium solution (2.35 M in hexanes, 13 mmol) was added dropwise via syringe over 5 min. The reaction mixture was stirred for 10 min, and then TIPSOTf (1.54 mL, 1.76 g, 5.73 mmol) was added in one portion and the resulting solution was stirred at –78 °C for 10 min, and then the dry ice-acetone bath was exchanged with an ice-water bath and stirring was continued an

additional 30 min, after which the flask was returned to a dry ice-acetone bath and cooled to –78 °C. The reaction mixture was diluted with 50 mL of hexanes and 25 mL of satd aq $NaHCO_3$, and then the dry ice-acetone bath was removed and the reaction mixture was allowed to warm to rt. The aqueous phase was extracted with three 50-mL portions of hexanes, and then the combined organic phases were washed with two 50-mL portions of water and 50 mL of a saturated NaCl solution, dried over Na_2SO_4, filtered, and concentrated. The resulting yellow oil was further concentrated at 0.2 mmHg for 2 h to afford yellow oil which was filtered through 6 g of silica gel with the aid of 150 mL of hexanes and concentrated to yield 1.131 g of a colorless oil. Purification by column chromatography on 60 g of silica gel (elution with hexanes) yielded 0.771 g (43%) of the siloxyacetylene **119** as a colorless oil with spectral characteristics identical to those previously reported for this compound.[108]

[108] Siloxy alkyne **118** has been previously prepared from ethyl isobutyrate in 49% yield by the one-pot procedure of Kowalski. See: Danheiser, R. L.; Helgason, A. L. *J. Am. Chem. Soc.* **1994**, *116*, 9471.



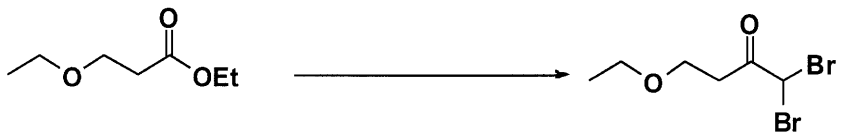
120

1-(Triisopropylsiloxy)-5-hexen-1-yne (120).

A 250-mL, three-necked, round-bottomed flask equipped with a rubber septum, a glass stopper and an argon inlet was charged with ethyl 5-pentenoate (1.013 g, 7.9 mmol), dibromomethane (1.5 mL, 3.7 g, 21 mmol), and 35 mL of THF and cooled at –78 °C in a dry ice-acetone bath. A 100-mL, two-necked, round-bottomed flask was charged with 2,2,6,6-tetramethylpiperidine (3.5 mL, 2.9 g, 21 mmol) and 35 mL of THF and cooled at 0 °C in an ice-water bath while 7.8 mL of *n*-butyllithium solution (2.39 M in hexanes, 19 mmol) was added rapidly. The resulting solution was stirred 5 min, and then cooled at -78 °C and added to the 100-mL flask via cannula over 15 min. The resulting solution was stirred at –78 °C an additional 15 min and then cannulated into 50 mL of 1.2 M aq HCl over 5 min. The aqueous phase was extracted with two 75-mL portions of hexanes, and the combined organic phases were washed with two 50-mL portions of water and 50 mL of satd aq NaCl solution, dried over $MgSO_4$, filtered, and concentrated. The resulting brown oil was filtered through 8 g of silica gel with the aid of 300 mL of hexanes and concentrated to afford 1.434 g of a brown oil. Column chromatography on 100 g of silica gel (gradient elution with 1-2% EtOAc-hexanes) gave 1.191 g of a pale brown oil estimated to be 85-90% dibromo ketone by ^{1}H NMR. A 250-mL, three-necked, round-bottomed flask equipped with a glass stopper, rubber septum, and argon inlet was charged with a solution of the crude dibromo ketone (1.184 g) in 20 mL of THF and cooled at –78 °C in a dry ice-acetone bath. A 100-mL, three-necked, round-bottomed flask equipped with a glass stopper, rubber septum, and argon inlet was charged with a solution of 1,1,1,3,3,3-hexamethyldisilazane (1.2 mL, 0.92 g, 5.7 mmol) in 15 mL of THF and cooled at 0 °C in an ice-water bath while 2.0 mL of *n*-butyllithium solution (2.39 M in hexanes, 4.8 mmol) was added rapidly. The resulting mixture was stirred for 5 min, and then cooled at -78 °C and added to the dibromo ketone solution via cannula over 10 min (the flask was rinsed with an additional 5 mL of THF) and stirred an additional 10 min at –78 °C, after which 4.3 mL of *n*-butyllithium solution (2.39 M in hexanes, 10 mmol) was added dropwise via syringe over 5 min. The reaction mixture was stirred for 10 min, TIPSOTf (1.25 mL, 1.4 g, 4.6 mmol) was added in one portion

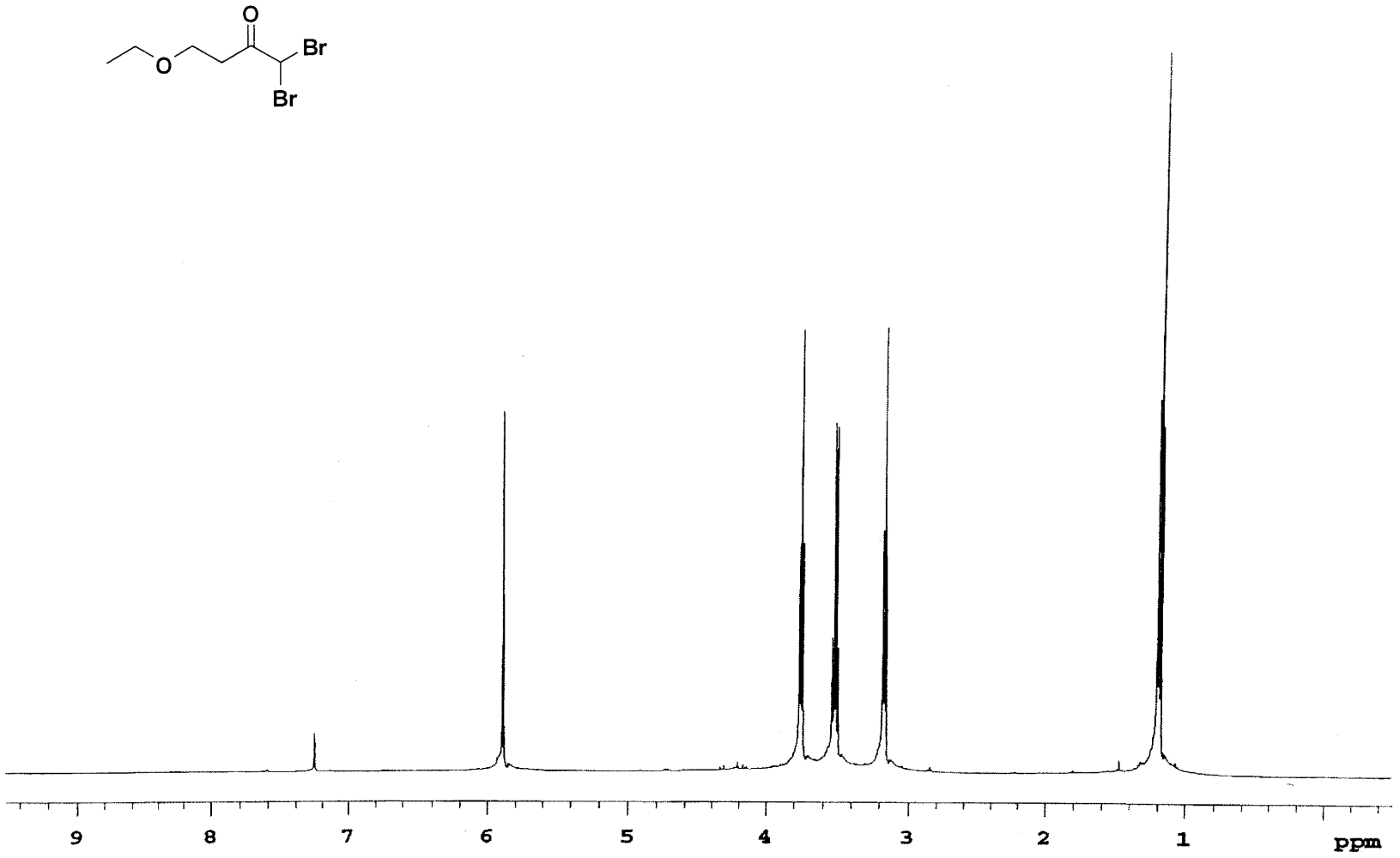
and the resulting solution was stirred at –78 °C for 10 min. The dry ice-acetone bath was exchanged with an ice-water bath and stirring was continued an additional 30 min, after which the flask was returned to a dry ice-acetone bath and cooled to –78 °C. The reaction mixture was diluted with 50 mL of hexanes and 25 mL of satd aq $NaHCO_3$, and then the dry ice-acetone bath was removed and the reaction mixture was allowed to warm to rt. The aqueous phase was extracted with three 20-mL portions of hexanes, and then the combined organic phases were washed with two 50-mL portions of water and 50 mL of a saturated NaCl solution, dried over Na_2SO_4, filtered, and concentrated. The resulting yellow oil was further concentrated at 0.2 mmHg for 2 h to afford a yellow oil which was filtered through 5 g of silica gel with the aid of 200 mL of hexanes and concentrated to yield 0.984 g of a colorless oil. Purification by column chromatography on 60 g of silica gel (elution with hexanes) yielded 0.747 g (38%) of the siloxy acetylene **120** as a colorless oil with spectral characteristics identical to those previously reported for this compound.[109]

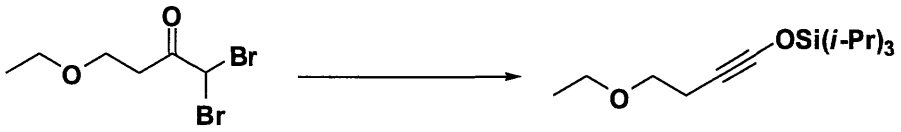
[109] Siloxy alkyne **120** has been previously prepared from 5-hexen-1-yne in 84% yield by the method of Julia. See: Zhang, L.; Kosmin, S. A. *J. Am. Chem. Soc.* **2004**, *126*, 10204.



1,1-Dibromo-4-ethoxy-2-butanone.

A 250-mL, three-necked, round-bottomed flask equipped with a glass stopper, rubber septum, and argon inlet adapter was charged with a solution of dibromomethane (1.9 mL, 4.7 g, 27 mmol) and ethyl 3-ethoxypropionate (1.5 mL, 1.4 g, 9.7 mmol) in 50 mL THF and cooled at –78 °C in a dry ice-acetone bath. A 100-mL, three-necked, round-bottomed flask equipped with a glass stopper, rubber septum, and argon inlet adapter was charged with 2,2,6,6-tetramethylpiperidine (4.5 mL, 3.8 g, 27 mmol) and 50 mL of THF and cooled at 0 °C in an ice-water bath while *n*-butyllithium solution (10.0 mL, 2.34 M in hexane, 23.4 mmol) was added rapidly via syringe. The resulting solution was stirred for 5 min and then transferred via cannula over 15 min to the 250-mL flask. The reaction mixture was stirred at –78 °C for 10 min, and then 75 mL of 1.2 M HCl solution was added. The aqueous phase was separated and extracted with two 50-mL portions of hexanes, and the combined organic phases were washed with 100 mL of water and 100 mL of satd aq NaCl solution, dried over $MgSO_4$, filtered, and concentrated to give 2.367 g of a dark brown oil. Column chromatography on 100 g of silica gel (elution with 10% EtOAc—hexanes) afforded 1.797 g (67%) of 1,1-dibromo-4-ethoxy-2-butanone as a yellow-orange oil: IR (neat) 2976, 2931, 2871, 1724 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.89 (s, 1 H), 3.75 (t, J = 6.3 Hz, 2 H), 3.52 (q, J = 7.0 Hz, 2 H), 3.17 (t, J = 6.3 Hz, 2 H), 1.20 (t, J = 7.0 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.6, 67.4, 66.3, 44.2, 36.7, 15.8; HRMS-ESI (*m/z*): $[M + Na]^+$ calcd for $C_6H_{10}O_2Br_2$, 294.8940; found, 294.8948.


O
Br
O
Br
9
8
7
6
5
4
3
2
1
ppm

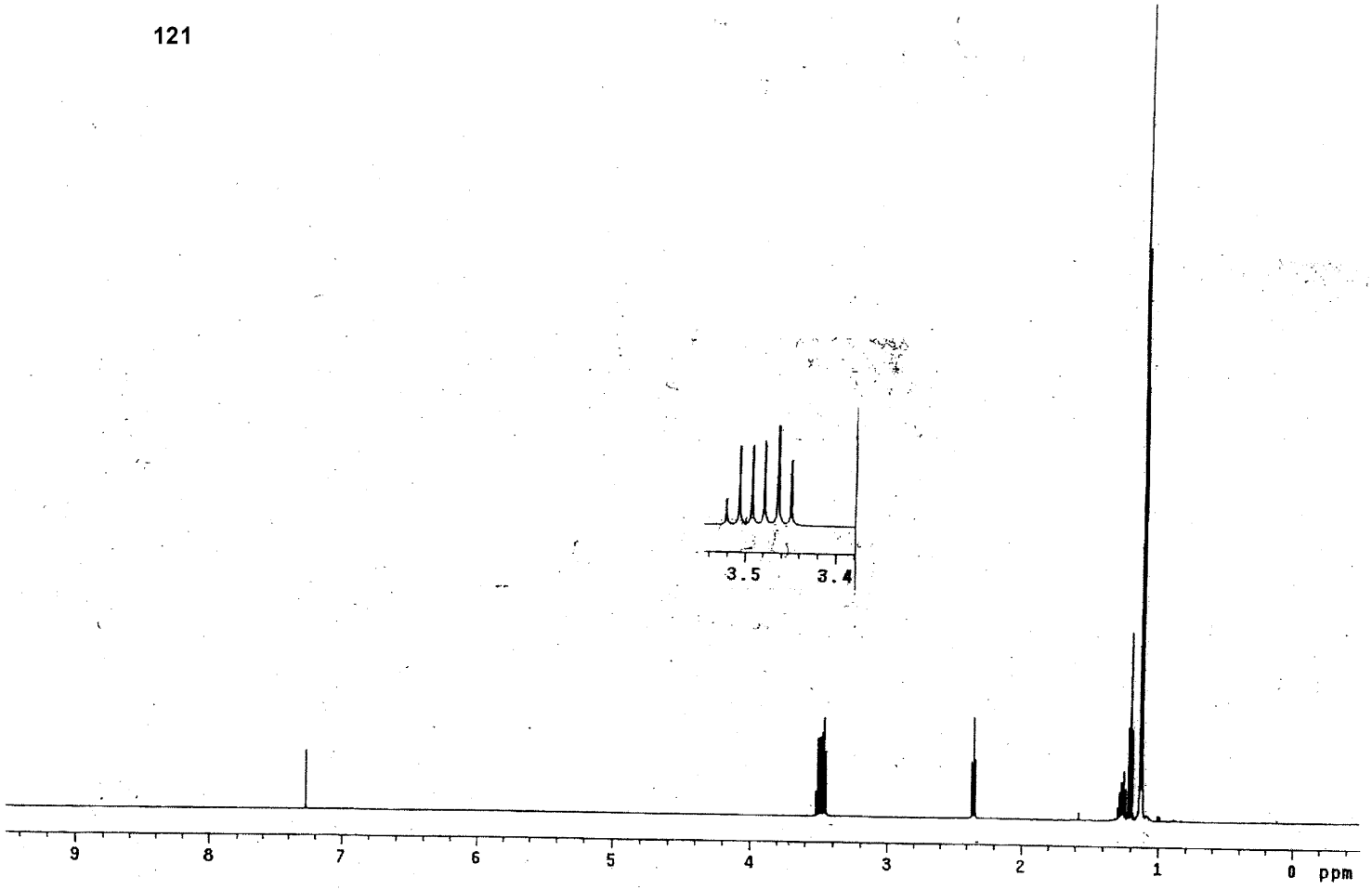


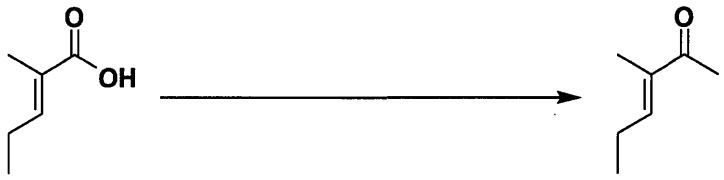
121

4-Ethoxy-1-(triisopropylsiloxy)-1-butyne (121).

A 250-mL, three-necked, round-bottomed flask equipped with a glass stopper, rubber septum, and argon inlet adapter was charged with a solution of 1,1-dibromo-4-ethoxy-2-butanone (1.190 g, 4.34 mmol) in 50 mL of THF and cooled at –78 °C in a dry ice-acetone bath. A 100-mL, three-necked, round-bottomed flask equipped with a glass stopper, rubber septum, and argon inlet adapter was charged with a solution of HMDS (1.1 mL, 0.84 g, 5.2 mmol) in 40 mL of THF and cooled at 0 °C in an ice-water bath while *n*-butyllithium solution (2.34 M in hexanes, 1.95 mL, 4.56 mmol) was added rapidly via syringe. The resulting mixture was stirred for 5 min, and then transferred via cannula over 12 min into the solution of dibromo ketone (the flask was rinsed with an additional 10 mL of THF). The resulting solution was stirred for 7 min at –78 °C, and then *n*-butyllithium solution (2.34 M in hexanes, 4.1 mL, 9.6 mmol) was added dropwise over 4 min. The reaction mixture was stirred at –78 °C for 8 min and then (*i*-Pr)$_3$SiOTf (1.1 mL, 1.3 g, 4.1 mmol) was added in one portion. After 5 min, the dry ice-acetone bath was replaced with an ice-water bath and stirring was continued at 0 °C for 25 min. The reaction mixture was diluted with 150 mL of hexanes, 0.1 mL of water was added, and the resulting mixture was stirred for 15 min and then dried over Na_2SO_4. The resulting solution was filtered through a glass frit, concentrated, and the residue was taken up in ca. 5 mL of benzene, filtered through a glass frit, and concentrated to yield 1.613 g of an orange oil. Purification via bulb-to-bulb distillation (bath temperature 90-150 °C, 0.5 mmHg) followed by column chromatography on 40 g of silica gel (elution with 2% EtOAc-hexanes) yielded 0.665 g (60%) of siloxy alkyne **121** as a yellow oil: IR (neat) 2947, 2869, 2282, 1464, 1376 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.50 (q, J = 7.0 Hz, 2 H), 3.48 (t, J = 7.3 Hz, 2 H), 2.35 (t, J = 7.5 Hz, 2 Hz), 1.25 (septet, J = 7.0 Hz, 3 H), 1.20 (t, J = 7.0 Hz, 3 H), 1.12 (d, J = 7.0 Hz, 18 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 87.6, 70.4, 66.3, 27.3, 18.8, 17.6, 15.4, 12.0; HRMS-ESI (*m/z*): $[M + Na]^+$ calcd for $C_{15}H_{30}O_2Si$ 293.1907; found, 293.1898.

121



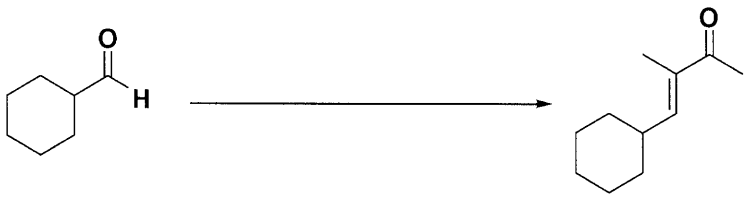


123

(*E*)-3-Methyl-3-hexen-2-one (123).

A 250-mL, three-necked, round-bottomed flask fitted with an argon inlet adapter, rubber septum, and glass stopper was charged with a solution of *trans*-2-methyl-2-pentenoic acid (1.512 g, 13.24 mmol) in 150 mL of Et_2O and cooled at -78 °C in a dry ice-acetone bath. Methyllithium solution (1.49 M in Et_2O, 18 mL, 27 mmol) was added rapidly via syringe, and the resulting mixture was allowed to stir for 1 h. The dry ice-acetone bath was replaced with an ice-water bath, and the reaction mixture was stirred at 0 °C for 40 min and then transferred by cannula into a 500-mL, one-necked, round-bottomed flask fitted with a rubber septum containing 150 mL of 0.12 M aq HCl. The organic phase was separated and washed with two 50-mL portions of satd aq Na_2CO_3 solution and 50 mL of satd aq NaCl solution, dried over $MgSO_4$, filtered, and concentrated by atmospheric distillation (bath temperature 60 °C) through an 8-cm Vigreux column to a volume of ca. 2 mL. The residue was purified via bulb-to-bulb distillation at atmospheric pressure (bath temperature 150-175 °C) to yield 1.148 g (77%) of 3-methyl-3-hexen-2-one (**123**) as a pale yellow oil with spectral characteristics consistent with those previously reported:[110] IR (neat) 3047, 2969, 1670, 1641 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.59 (tq, J = 7.2, 1.3 Hz, 1 H), 2.28 (s, 3 H), 2.24 (app quintet, J = 7.4 Hz, 2 H), 1.73 (s, 3 H), 1.05 (t, J =7.6 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.0, 145.4, 137.3, 25.5, 22.6, 13.3, 11.1.

[110] Enone **123** has been previously prepared by aldol condensation of methyl ethyl ketone with propionaldehyde (see: McGreer, D. E.; Chiu, N. W. K.; Vinje, M. G. *Can. J. Chem.* **1965**, *43*, 1398) and by decomposition of 1-acetyl-3,5-dimethyl-1-pyrazoline (see: Marr, D. H.; Stothers, J. B. *Can. J. Chem.* **1965**, *43*, 596) though yields were not reported in either instance.



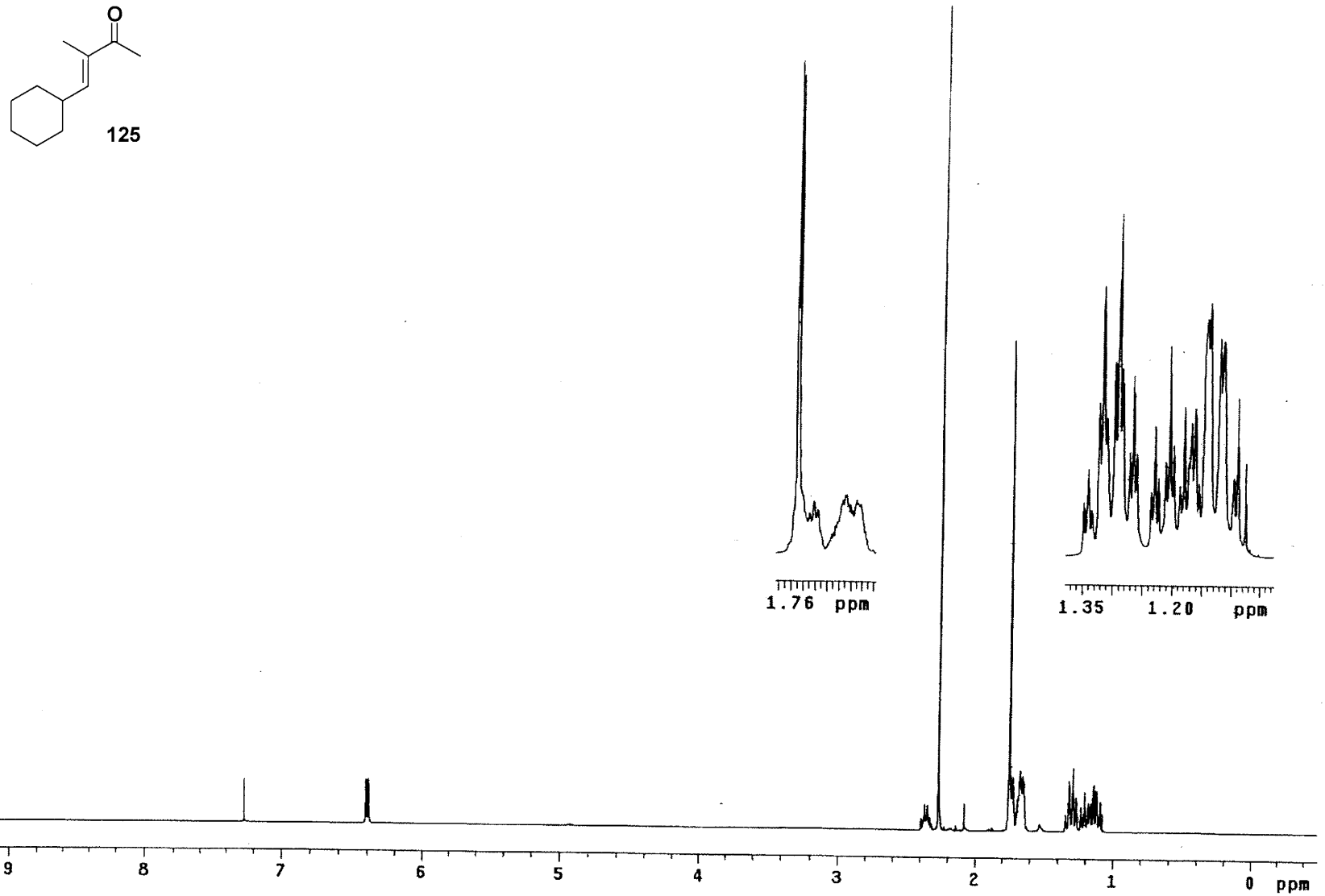
125

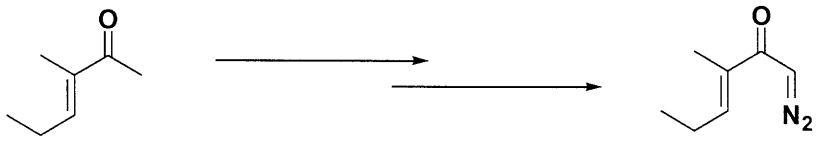
4-Cyclohexyl-3-methyl-(*E*)-3-buten-2-one (125).

A 250-mL, three-necked, round-bottomed flask equipped with a glass stopper, rubber septum, and argon inlet adapter was charged with a solution of 3-(triphenylphosphoranylidene)butan-2-one[111] (4.316 g, 12.99 mmol) and cyclohexane carboxaldehyde (1.20 mL, 1.11 g, 9.90 mmol) in 125 mL of toluene. The rubber septum was replaced with a glass stopper and the reaction mixture was heated at reflux for 48 h. The reaction mixture was allowed to cool to room temperature and then concentrated at reduced pressure to afford 7.019 g of a tan solid.[112] This material was dissolved in 50 mL of EtOAc and concentrated onto 20 g of silica gel which was added to the top of a column of 150 g of silica gel and eluted with 5% EtOAc-hexanes to provide 1.017 g (62%) of 4-cyclohexyl-3-methyl-(*E*)-3-buten-2-one (**125**) as a colorless oil: IR (neat) 3001, 2927, 2852, 1669, 1641, 1448 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.40 (app dd, J = 9.2, 1.2 Hz, 1 H), 2.30-2.41 (m, 1 H), 2.27 (s, 3 H), 1.64-1.76 (m, 7 H), 1.05-1.37 (m, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.6, 149.0, 135.9, 38.4, 32.2, 26.1, 25.8, 25.6, 11.4; HRMS-ESI (*m/z*): $[M + Na]^+$ calcd for $C_{11}H_{18}O$, 189.1250; found, 189.1249.

111 Aitken, A. R.; Atherton, J. I. *J. Chem. Soc. Perkin Trans. 1* **1994**, 1281.

112 The crude product contained a 92:8 mixture of (*E*)- and (*Z*)-enones.


O
125
1.76 ppm
1.35 1.20 ppm
9 8 7 6 5 4 3 2 1 0 ppm

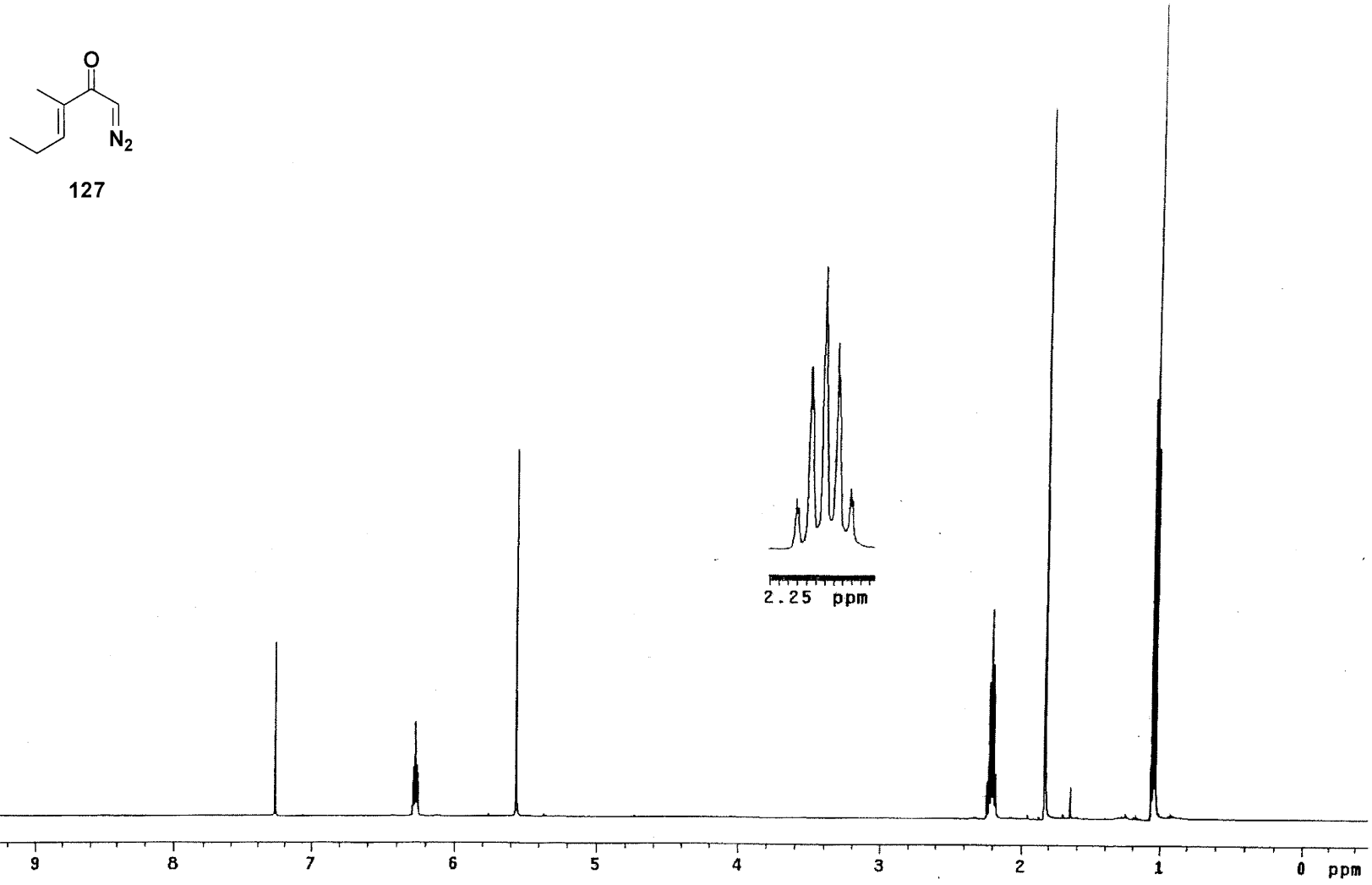


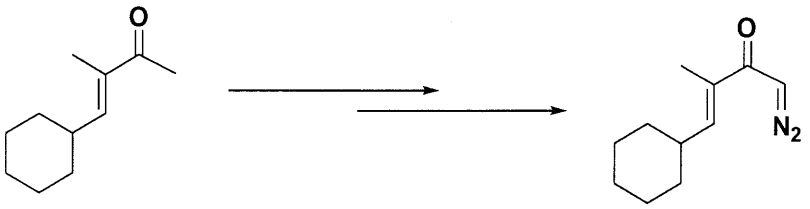
123 127

1-Diazo-3-methyl-(*E*)-3-hexen-2-one (127).

A 100-mL, three-necked, round-bottomed flask equipped with a 25-mL pressure-equalizing addition funnel, rubber septum, and an argon inlet adapter was charged with a solution of HMDS (3.1 mL, 2.4 g, 15 mmol) in 30 mL of THF and then cooled at 0 °C in an ice water-bath while 6.2 mL of *n*-butyllithium solution (2.34 M in hexanes, 15 mmol) was added rapidly dropwise. After 30 min, the resulting solution was cooled at –78 °C in a dry ice-acetone bath while a solution of (*E*)-3-methyl-3-hexen-2-one (**123**, 1.50 g, 13.4 mmol) in 15 mL of THF was added dropwise over 30 min (the addition funnel was rinsed with 5 mL of additional THF). The reaction mixture was stirred at –78 °C for 1.25 h, and then 2,2,2-trifluoroethyl trifluoroacetate (3.6 mL, 5.3 g, 27 mmol) was added rapidly by syringe in one portion. After 45 min, the reaction mixture was poured into a separatory funnel containing 50 mL of 5% aq HCl solution and 30 mL of Et_2O. The organic phase was washed with 50 mL of water, the combined aqueous phases were extracted with two 25-mL portions of Et_2O, and then the combined organic phases were washed with 30 mL of a saturated NaCl solution, dried over Na_2SO_4, filtered, and concentrated at reduced pressure to give 5.353 g of a brown oil which was diluted with 30 mL of CH_3CN and transferred to a 100-mL, three-necked, round-bottomed flask equipped with a 25-mL pressure equalizing-addition funnel, rubber septum, and an argon inlet adapter. Water (0.241 mL, 0.241 g, 13.4 mmol) and Et_3N (2.8 mL, 2.0 g, 20 mmol) were added via syringe, and then a solution of methanesulfonyl azide (2.461 g, 20.1 mmol) in 20 mL of CH_3CN was added dropwise over 2 min (the addition funnel was rinsed with an additional 5 mL of CH_3CN). The resulting solution was stirred at room temperature for 3 h and then concentrated to a volume of ca. 15 mL. The residue was diluted with 50 mL of Et_2O and washed with four 30-mL portions of 10% aq NaOH solution and three 25-mL portions of water, and then the combined aqueous phases were extracted with 50 mL of Et_2O. The combined organic layers were washed with 30 mL of saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford 1.808 g of yellow oil. Column chromatography on 120 g of silica gel (gradient elution with 5-10% EtOAc-

hexanes) provided 1.411 g (76%) of diazo ketone **127** as a yellow oil: IR (neat) 3088, 2969, 2936, 2876, 2101, 1644, 1603 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.24 (tq, J = 7.2, 1.2 Hz, 1 H), 5.57 (s, 1 H), 2.18 (app quintet, J = 7.5 Hz, 2 H), 1.80 (s, 3 H), 1.02 (t, J = 7.5 Hz, 3 H); ^{13}C NMR: (75 MHz, $CDCl_3$) δ 189.0, 144.1 135.1, 53.0, 22.2, 13.3, 12.2; HRMS-ESI (*m/z*): M^+ calcd for $C_7H_{10}N_2O$, 138.0788; found, 138.0787.


O
N2
127
2.25 ppm
9
8
7
6
5
4
3
2
1
0 ppm

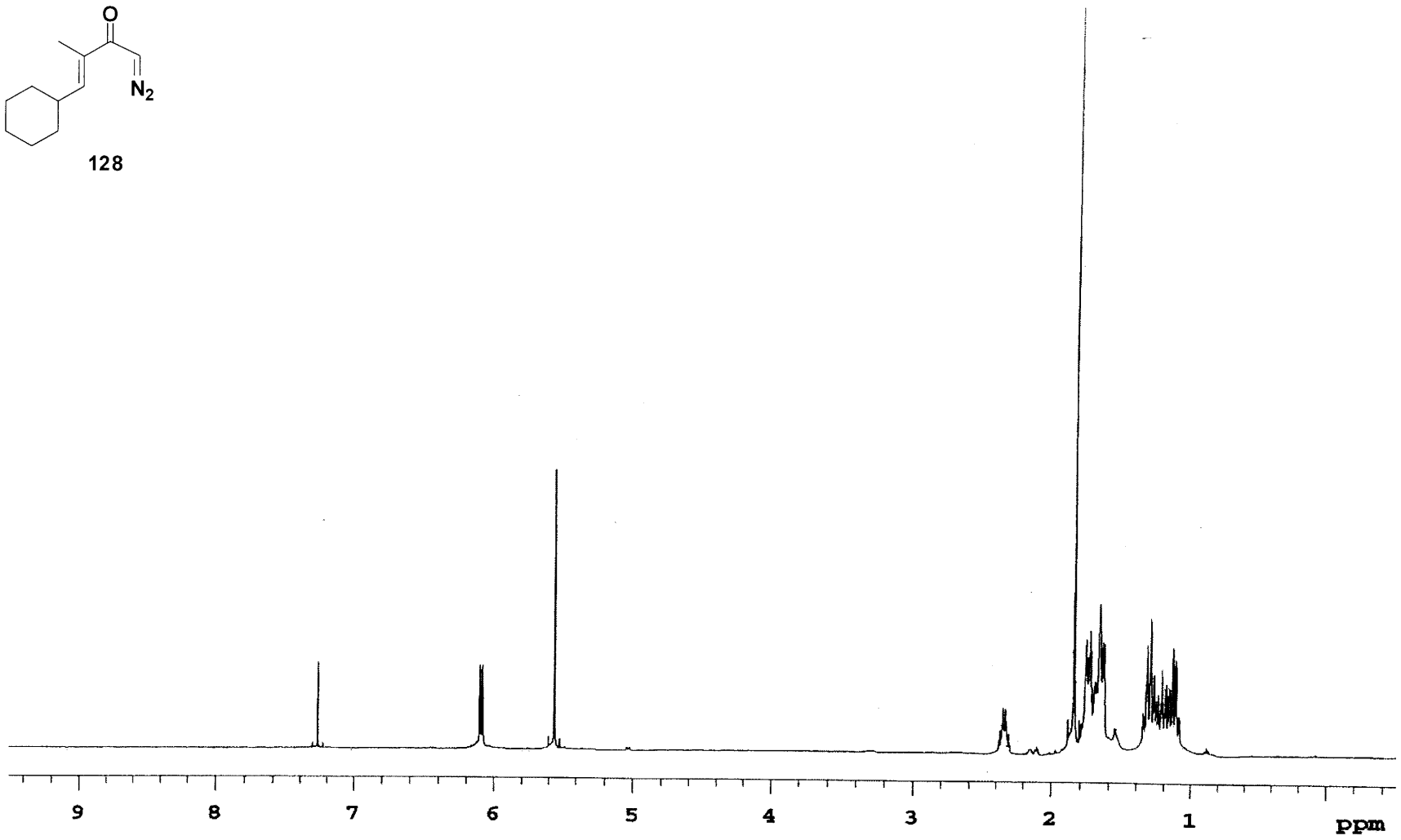


125 128

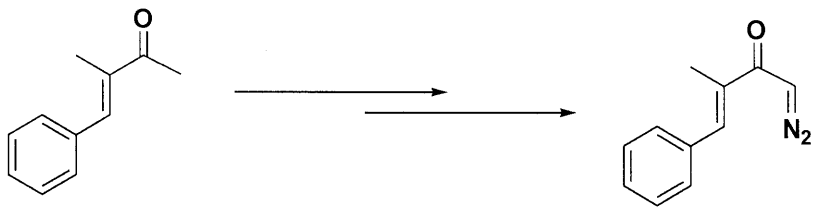
4-Cyclohexyl-1-diazo-3-methyl-(*E*)-3-buten-2-one (128).

A 100-mL, three-necked, round-bottomed flask equipped with a 25-mL pressure-equalizing addition funnel, rubber septum, and an argon inlet adapter was charged with a solution of HMDS (1.50 mL, 1.15 g, 7.16 mmol) in 20 mL of THF and then cooled at 0 °C in an ice-water bath while 2.80 mL of *n*-butyllithium solution (2.34 M in hexane, 6.55 mmol) was added rapidly dropwise. After 15 min, the resulting solution was cooled at –78 °C in a dry ice-acetone bath while a solution of ketone **125** (1.007 g, 6.06 mmol) in 10 mL of THF was added dropwise over 6 min (the addition funnel was rinsed with 5 mL of additional THF). The reaction mixture was stirred at –78 °C for 1 h, and then 2,2,2-trifluoroethyl trifluoroacetate (1.60 mL, 2.342 g, 11.95 mmol) was added rapidly by syringe in one portion. After 1 h, the reaction mixture was poured into a separatory funnel containing 25 mL of 5% aq HCl solution and 30 mL of Et_2O. The aqueous phase was extracted with two 25-mL portions of Et_2O, and the combined organic phases were washed with 25 mL of saturated NaCl solution, dried over Na_2SO_4, filtered, and concentrated at reduced pressure to give 2.304 g of a brown oil, which was diluted in 20 mL of CH_3CN and transferred to a 100-mL, three-necked, round-bottomed flask equipped with a 25-mL pressure-equalizing addition funnel, rubber septum, and an argon inlet adapter. Water (0.110 mL, 0.110 g, 6.11 mmol) and Et_3N (1.25 mL, 0.908 g, 8.97 mmol) were added via syringe, and a solution of methanesulfonyl azide (1.113 g, 9.19 mmol) in 10 mL of CH_3CN was added dropwise over 15 min (the addition funnel was rinsed with an additional 2 mL of CH_3CN). The resulting solution was stirred at room temperature for 2.2 h and then concentrated to a volume of ca. 10 mL. The residue was diluted with 30 mL of Et_2O and washed with three 25-mL portions of 10% aq NaOH solution, 30 mL of water, and 30 mL of saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford 1.132 g of yellow oil. Column chromatography on 60 g of silica gel (elution with 7.5% EtOAc-hexanes) provided 0.970 g (83%) of the diazo ketone **128** as yellow crystals, mp 52-55 °C: IR ($CHCl_3$) 3019, 2929, 2853, 2107, 1643, 1602, 1358,

1337, 1216 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.09 (d, J = 9.3 Hz, 1 H), 5.56 (s, 1 H), 2.29-2.39 (m, 1 H), 1.62-1.86 (m, 7 H), 1.06-1.35 (m, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 189.3 143.7, 133.8, 53.1, 37.9, 32.3, 26.1, 25.8, 12.4; HRMS-ESI (*m/z*): $[M + Na]^+$ calcd for $C_{11}H_{16}N_2O$, 215.1155; found, 215.1154.



128

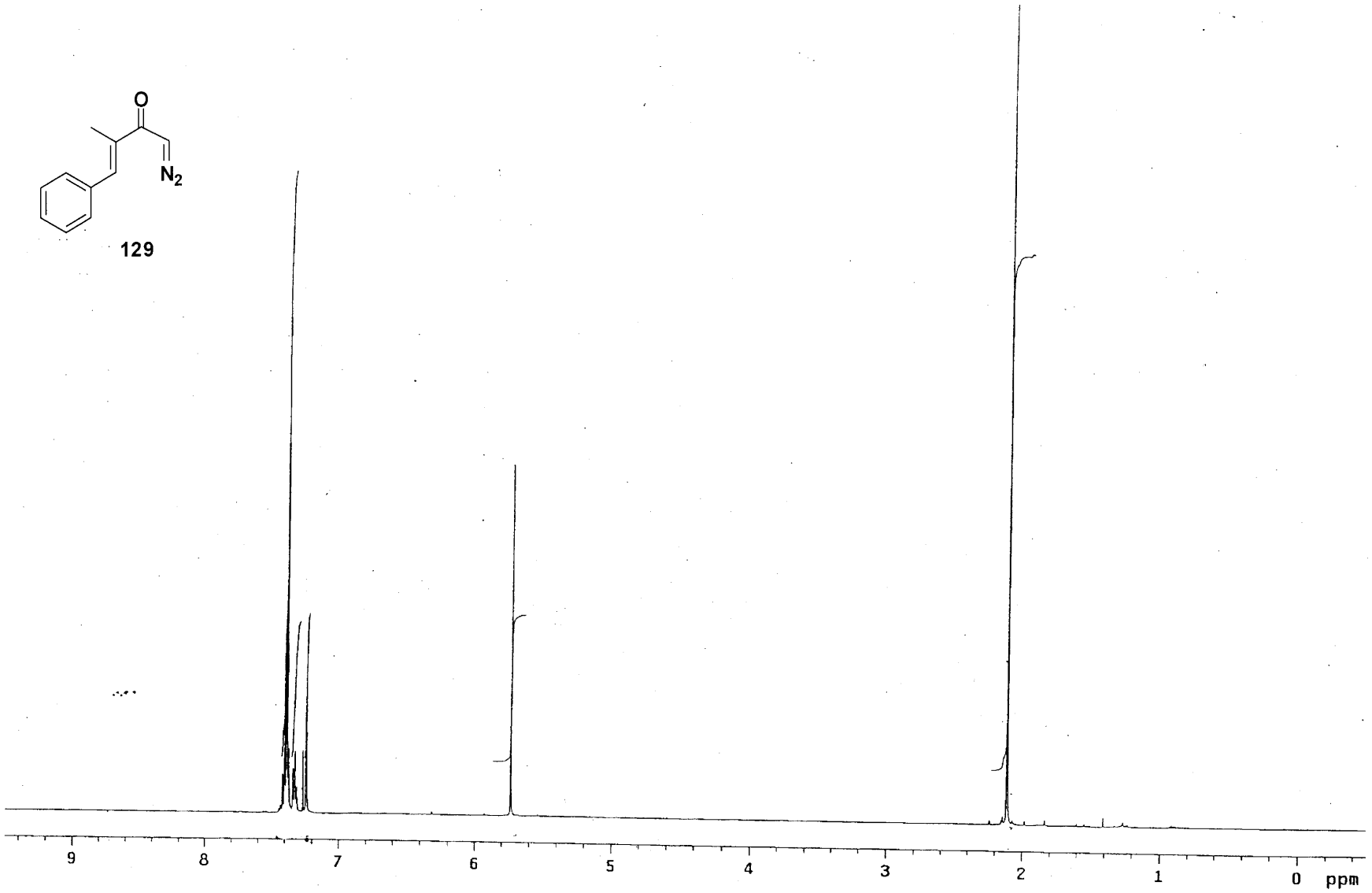


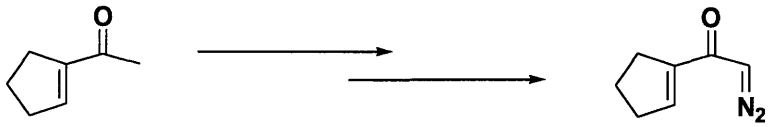
129

1-Diazo-3-methyl-4-phenyl-(*E*)-3-buten-2-one (129).

A 100-mL, three-necked, round-bottomed flask equipped with a 10-mL pressure-equalizing addition funnel, rubber septum, and an argon inlet adapter was charged with a solution of HMDS (1.3 mL, 1.0 g, 6.2 mmol) in 20 mL of THF and then cooled at 0 °C in an ice water-bath while 2.6 mL of *n*-butyllithium solution (2.32 M in hexanes, 6.0 mmol) was added rapidly dropwise. After 5 min, the resulting solution was cooled at –78 °C in a dry ice-acetone bath while a solution of 3-methyl-4-phenyl-(*E*)-3-buten-2-one (0.878 g, 5.5 mmol) in 8 mL of THF was added dropwise over 2 min (the addition funnel was rinsed with 1 mL of additional THF). The reaction mixture was stirred at –78 °C for 40 min, and then 2,2,2-trifluoroethyl trifluoroacetate (1.5 mL, 2.2 g, 11.4 mmol) was added rapidly by syringe in one portion. After 20 min, the reaction mixture was poured into a separatory funnel containing 30 mL of 0.6M HCl solution. The aqueous phase was separated and extracted with two 20-mL portions of Et_2O, and then the combined organic phases were washed with 30 mL of a saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated at reduced pressure to give 3.918 g of a yellow oil which was diluted with 25 mL of CH_3CN and transferred to a 100-mL, three-necked, round-bottomed flask equipped with a 10-mL pressure equalizing-addition funnel, rubber septum, and an argon inlet adapter. Water (0.100 mL, 0.100 g, 5.55 mmol) and Et_3N (1.15 mL, 0.835 g, 8.25 mmol) were added via syringe, and then a solution of methanesulfonyl azide (1.00 g, 8.27 mmol) in 8 mL of CH_3CN was added dropwise over 2 min (the addition funnel was rinsed with an additional 1 mL of CH_3CN). The resulting solution was stirred at room temperature for 4.5 h and then concentrated. The residue was diluted with 40 mL of Et_2O and washed with three 20-mL portions of 10% aq NaOH solution, two 20-mL portions of water, and one 30-mL portion of brine. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated to afford 0.855 g (85%) of the diazo ketone **129** as yellow crystals: mp 88-91 °C; IR (hexanes) 3054, 2108, 1608, 1421 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.38-7.42 (m, 4 H), 7.30-7.35 (m, 1 H),

7.25 (d, J = 1.2 Hz, 1 H), 5.74 (s, 1 H), 2.11 (d, J = 1.4 Hz, 3 H); ^{13}C NMR: (75 MHz, $CDCl_3$) δ 189.1, 135.9, 135.8, 135.2, 129.8, 128.5, 53.9, 14.1.


O
N2
129
9
8
7
6
5
4
3
2
1
0
ppm

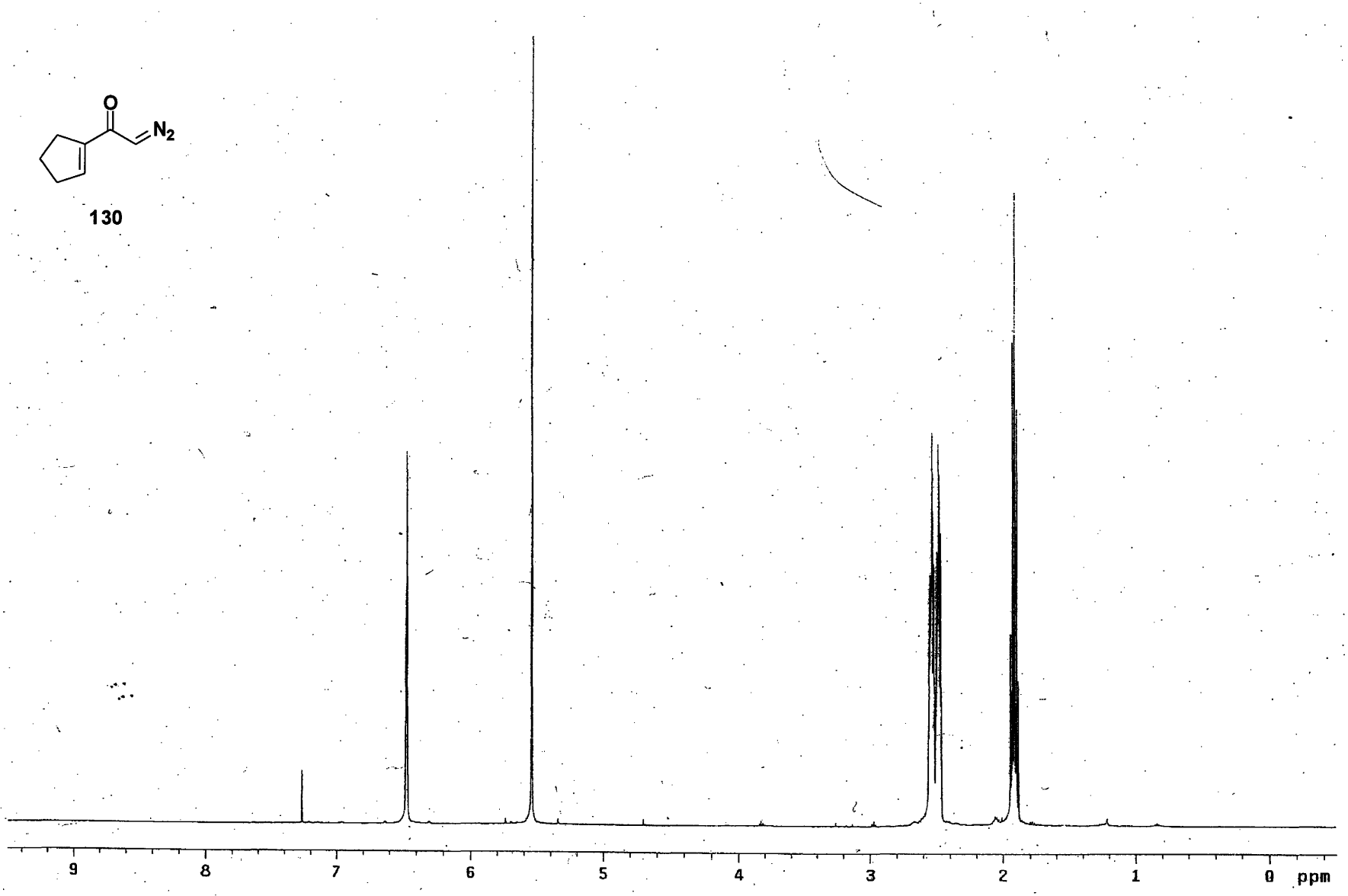


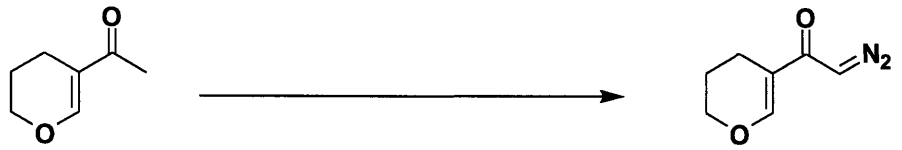
130

1-(1-Cyclopentenyl)-2-diazo-1-ethanone (130).

A 50-mL, three-necked, round-bottomed flask equipped with a 25-mL pressure-equalizing addition funnel, rubber septum, and argon inlet adapter was charged with a solution of 1,1,1,3,3,3-hexamethyldisilylazane (2.05 mL, 1.57 g, 9.71 mmol) in 20 mL of THF and then cooled at 0 °C in an ice—water bath while *n*-butyllithium solution (2.35M in hexanes, 4.15 mL, 9.75 mmol) was added rapidly dropwise. After 5 min, the resulting solution was cooled at –78 °C in a dry ice—acetone bath while a solution of 1-acetyl-1-cyclopentene (0.974 g, 8.84 mmol) in 8 mL THF was added dropwise over 3 min (the addition funnel was rinsed with 2 mL of additional THF). The reaction mixture was stirred at –78 °C for 37 min, and then 2,2,2-trifluoroethyl trifluoroacetate (2.40 mL, 3.51 g, 17.9 mmol) was added rapidly by syringe. After 20 min, the reaction mixture was poured into a separatory funnel containing 25 mL of 5% aq HCl solution and 30 mL of Et_2O. The aqueous phase was extracted with two 25-mL portions of Et_2O, and then the combined organic phases were washed with 25 mL of a saturated NaCl solution, dried over Na_2SO_4, filtered, and concentrated at reduced pressure to give 2.951 g of a dark brown oil, which was diluted with 30 mL CH_3CN and transferred to a 100-mL, three-necked, round-bottomed flask equipped with a 25-mL pressure-equalizing addition funnel, rubber septum, and an argon inlet adapter. Water (0.159 mL, 0.159 g, 8.83 mmol) and Et_3N (1.85 mL, 1.343 g, 13.27 mmol) were added via syringe, and then a solution of methanesulfonyl azide (1.539 g, 12.71 mmol) in 20 mL CH_3CN was added dropwise over 15 min (the addition funnel was rinsed with 2 mL of additional CH_3CN). The resulting solution was stirred at room temperature for 2.75 h and then concentrated to a volume of ca. 10 mL. The residue was diluted with 50 mL of Et_2O and washed with three 25-mL portions of 10% aq NaOH solution and 25 mL of water, and then the combined aqueous phases were extracted with two 25-mL portions of Et_2O. The combined organic layers were washed with 50 mL of satd aq NaCl, dried over $MgSO_4$, filtered, and concentrated to afford 1.418 g of a red-brown oil. Column chromatography on 75 g of silica gel (gradient elution with 10-20% EtOAc-hexanes) provided 0.878 g (73%) of

the diazo ketone **130** as orange crystals, mp 28-30 °C: IR (neat) 3123, 2961, 2842, 2105, 1625, 1596, 1382, 1362, 1325, 1117, 947 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.47 (s, 1 H), 5.54 (s, 1 H), 2.54 (m, 2 H), 2.49 (m, 2 H), 1.97 (quintet, J = 7.5 Hz, 2 H); ^{13}C NMR: (125 MHz, $CDCl_3$) δ 184.4, 144.0 139.7, 53.8, 33.7, 31.4, 23.1; HRMS-EI (*m/z*): $[M - H]^+$ calcd for $C_7H_8N_2O$, 135.0558; found, 135.0558.


O
N2
130
9
8
7
6
5
4
3
2
1
0
ppm

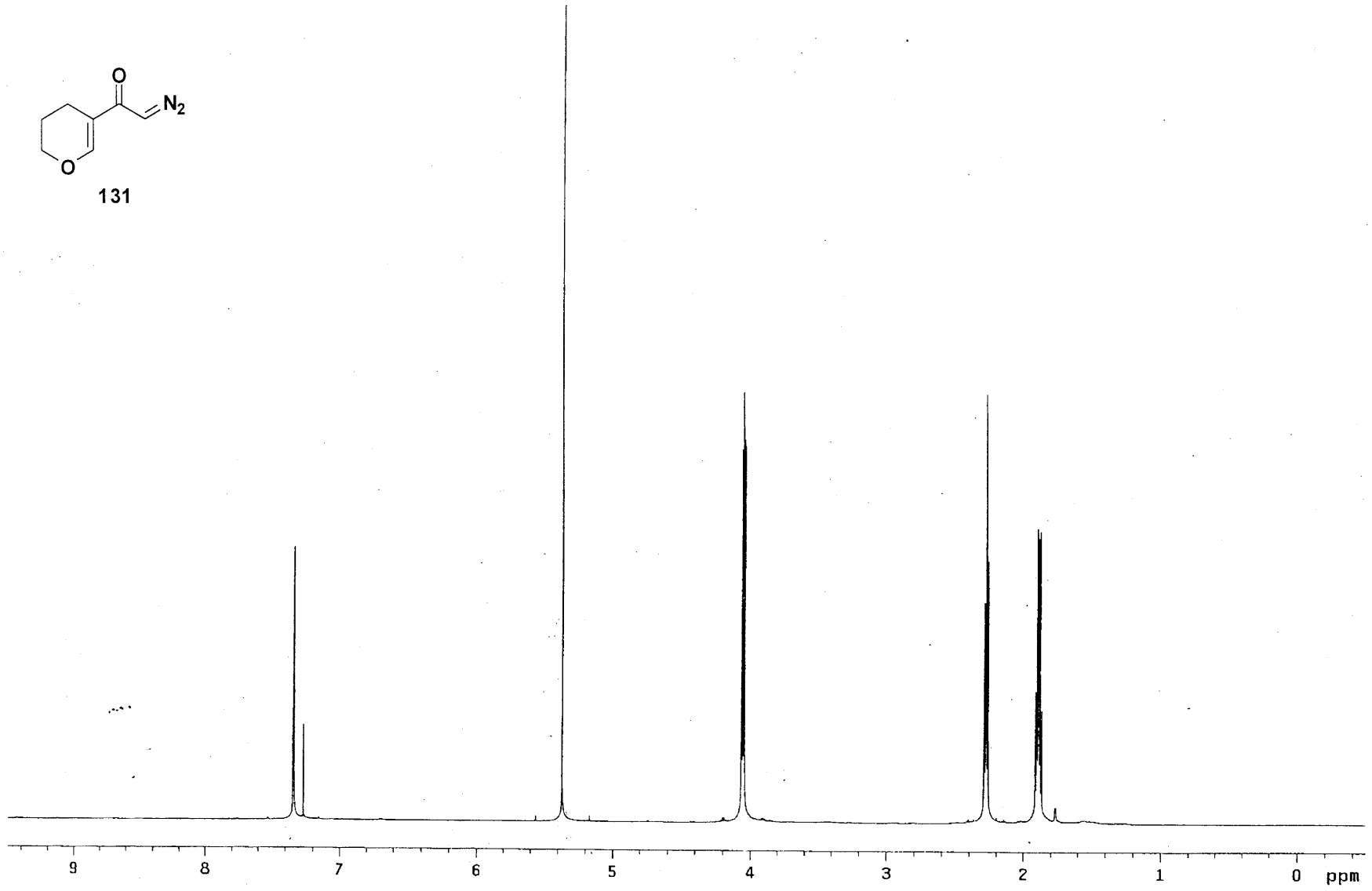


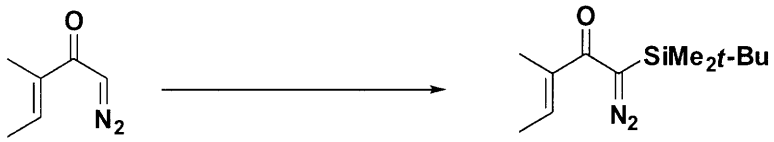
131

2-Diazo-1-(3,4-dihydro-2H-pyran-5-yl)ethanone (131).

A 100-mL, three-necked, round-bottomed flask equipped with a 25-mL pressure-equalizing addition funnel, rubber septum, and an argon inlet adapter was charged with a solution of HMDS (2.0 mL, 1.5 g, 9.5 mmol) in 25 mL of THF and then cooled at 0 °C in an ice water-bath while 3.3 mL of *n*-butyllithium solution (2.45 M in hexanes, 8.1 mmol) was added rapidly dropwise. After 30 min, the resulting solution was cooled at –78 °C in a dry ice-acetone bath while a solution of 3-acetyl-4*H*-5,6-dihydropyran (1.008 g, 8.0 mmol) in 15 mL of THF was added dropwise over 5 min. The reaction mixture was stirred at –78 °C for 45 min, and then 2,2,2-trifluoroethyl trifluoroacetate (2.1 mL, 3.1 g, 16 mmol) was added rapidly by syringe in one portion. After 15 min, the reaction mixture was poured into a separatory funnel containing 40 mL of 5% aq HCl solution and 20 mL of Et_2O. The aqueous phase was extracted with two 20-mL portions of Et_2O, and then the combined organic phases were washed with 25 mL of water and 25 mL of a saturated NaCl solution, dried over Na_2SO_4, filtered, and concentrated at reduced pressure to give 2.369 g of a brown oil which was diluted with 30 mL of CH_3CN and transferred to a 100-mL, three-necked, round-bottomed flask equipped with a 25-mL pressure equalizing-addition funnel, rubber septum, and an argon inlet adapter. Water (0.144 mL, 0.144 g, 8.0 mmol) and Et_3N (1.7 mL, 1.2 g, 12 mmol) were added via syringe, and then a solution of methanesulfonyl azide (1.465 g, 12 mmol) in 10 mL of CH_3CN was added dropwise over 3 min. The resulting solution was stirred at room temperature for 3 h and then concentrated to a volume of ca. 10 mL. The residue was diluted with 50 mL of Et_2O and washed with four 30-mL portions of 10% aq NaOH solution and three 25-mL portions of water, and then the combined aqueous phases were extracted with two 20-mL portions of Et_2O. The combined organic layers were washed with 30 mL of saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford a yellow oil. Column chromatography on 60 g of silica gel (gradient elution with 30-50% EtOAc-hexanes) provided 0.577 g (47%) of diazo ketone **131** as a yellow solid, mp 25-27 °C: IR (CH_2Cl_2) 3054, 2987, 2104 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.34 (s, 1 H), 5.37 (s, 1 H),

4.05 (app t, J = 5.3 Hz, 2 H), 2.28 (app t, J = 6.3 Hz, 2 H), 1.89 (app q, J = 6.2 Hz, 2 H); ^{13}C NMR: (75 MHz, $CDCl_3$) δ 185.8, 152.1 114.1, 67.1, 51.9, 21.3, 19.3; HRMS-ESI (*m/z*): [M + Na]$^+$ calcd for $C_7H_8N_2O_2$, 175.0478; found, 175.0483.

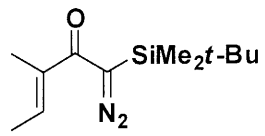

O
N2
O
131
9
8
7
6
5
4
3
2
1
0
ppm



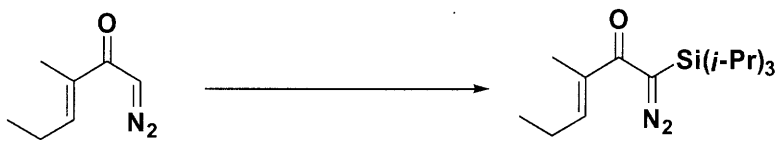
126 133

1-(*tert*-Butyldimethylsilyl)-1-diazo-3-methyl-1-(*E*)-3-penten-2-one (133).

A 50-mL, two-necked, round-bottomed flask equipped with a rubber septum, glass stopper, and argon inlet adapter was charged with a solution of diazo ketone **126** (0.500 g, 4.03 mmol) in 20 mL of 1:1 Et_2O-hexanes and cooled at 0 °C while *i*-Pr_2EtN (0.71 mL, 0.53 g, 4.1 mmol) was added dropwise over 1 min. After 3 min, *t*-$BuMe_2SiOTf$ (0.93 mL, 1.1 g, 4.1 mmol) was added dropwise over 1 min, and the resulting solution was allowed to slowly warm to 10 °C over 2.5 h, and then stirred at rt for an additional 30 min. The reaction mixture was filtered through Celite with the aid of 10 mL of hexanes, and the filtrate was concentrated to afford 1.048 g of an orange oil. Column chromatography on 60 g of silica gel (elution with 2% EtOAc-1% NEt_3-hexanes) provided 0.716 g (75%) of silyl diazo ketone **133** as a yellow oil: IR (neat) 2929, 2858, 2066, 1615 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.13 (qq, *J* = 6.9, 1.4 Hz, 1 H), 1.81 (app quint, *J* = 1.1 Hz, 3 H), 1.76 (dq, *J* = 6.7, 1.1 Hz, 3 H), 0.94 (s, 9 H), 0.23 (s, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.4, 136.7, 130.5, 51.6, 21.7, 26.9, 19.3, 13.9, 13.3, -6.0.



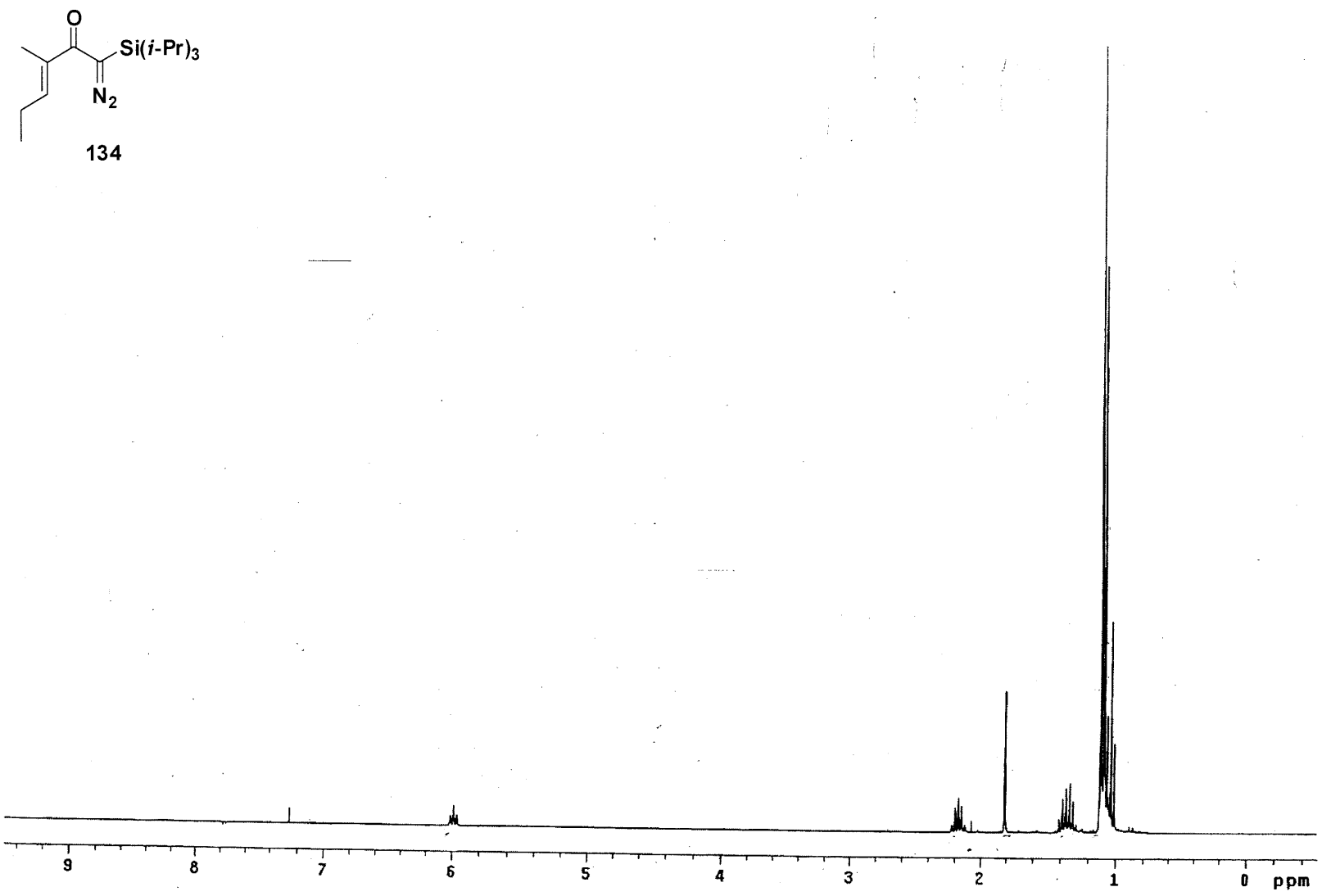
133

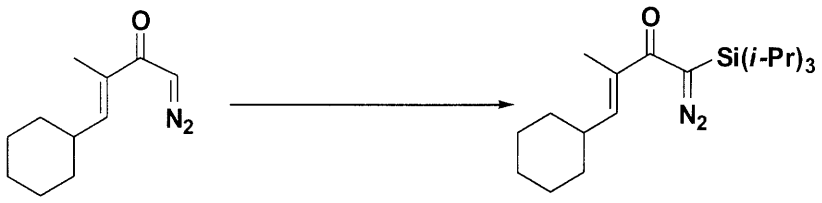


127 134

1-Diazo-3-methyl-1-(triisopropylsilyl)-(*E*)-3-hexen-2-one (134).

A 50-mL, three-necked, round-bottomed flask equipped with a rubber septum, glass stopper, and argon inlet adapter was charged with a solution of diazo ketone **127** (0.145 g, 1.05 mmol) in 10 mL of 1:1 Et_2O-hexanes and *i*-Pr_2EtN (0.19 mL, 0.141 g, 1.09 mmol) was added dropwise over 1 min. After 2 min, TIPSOTf (0.28 mL, 0.319 g, 1.04 mmol) was added dropwise over 1 min, and the resulting solution was stirred at room temperature for 2.2 h. The reaction mixture was filtered through Celite with the aid of 50 mL of 1:1 Et_2O-hexanes, and the filtrate was concentrated to afford 0.343 g of an orange oil. Column chromatography on 20 g of silica gel (elution with 1% EtOAc-1% NEt_3-hexanes) provided 0.234 g (76%) of silyl diazo ketone **134** as a yellow oil: IR (neat) 2946, 2867, 2064, 1617, 1463, 921 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.99 (tq, J = 7.5, 1.5 Hz, 1 H), 2.11-2.15 (m, 2 H), 1.81 (s, 3 H), 1.35 (m, 3 H), 1.10 (d, J = 7.3 Hz, 18 H), 1.04 (t, J = 7.6 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.3, 137.1, 134.6, 50.2, 21.7, 18.7, 18.0, 13.4, 11.7; HRMS-ESI (*m/z*): $[M + Na]^+$ calcd for $C_{16}H_{30}ON_2Si$, 317.2020; found, 317.2026.

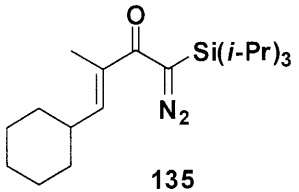

O
Si(i-Pr)3
N2
134
9
8
7
6
5
4
3
2
1
0
ppm



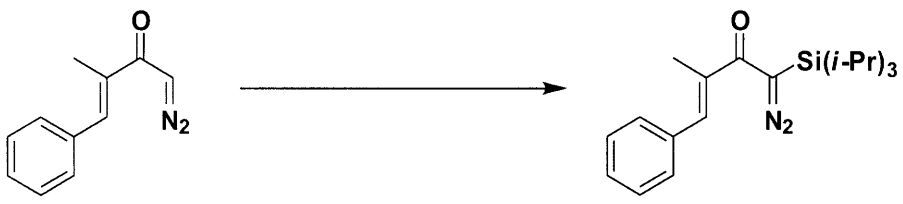
128 135

4-Cyclohexyl-1-diazo-3-methyl-1-(triisopropylsilyl)-(*E*)-3-buten-2-one (135).

A 100-mL, three-necked, round-bottomed flask equipped with a rubber septum, glass stopper, and argon inlet adapter was charged with a solution of diazo ketone **128** (1.003 g, 5.22 mmol) in 60 mL of 1:1 Et_2O-hexane and $(i\text{-Pr})_2EtN$ (0.91 mL, 0.675 g, 5.22 mmol) was added dropwise by syringe over 1 min. After 2 min, $(i\text{-Pr})_3SiOTf$ (1.40 mL, 1.596 g, 5.21 mmol) was added dropwise over 1 min, and the resulting solution was stirred at room temperature for 2.5 h. The reaction mixture was filtered through Celite with the aid of 100 mL of 1:1 Et_2O-pentane, and the filtrate was concentrated to afford 1.870 g of an orange oil. Column chromatography on 60 g of silica gel (elution with 2% EtOAc-1% NEt_3-hexanes) provided 1.458 g (80%) of silyl diazo ketone **135** as a yellow oil: IR (neat) 2927, 2866, 2064, 1743, 1615, 1464, 1448, 882 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.81 (dd, J = 9.3, 1.2 Hz, 1 H), 2.28-2.37 (m, 1 H), 1.83 (d, J = 1.4 Hz, 3 H), 1.63-1.77 (m, 4 H), 1.02-1.42 (m, 27 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.0, 141.3, 133.4, 50.9, 38.0, 32.8 26.6, 26.3, 19.2, 14.0, 12.2; HRMS-ESI (*m/z*): $[M + H]^+$ calcd for $C_{20}H_{36}ON_2OSi$, 371.2489; found, 371.2483.



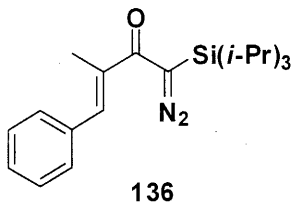
135



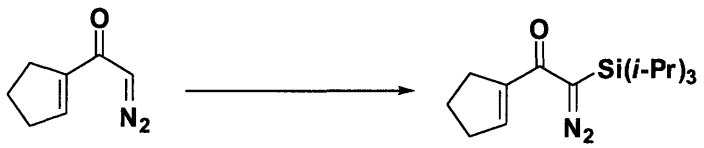
129 136

1-Diazo-3-methyl-4-phenyl-1-triisopropylsilyl-(3*E*)-buten-2-one (136).

A 50-mL, two-necked, round-bottomed flask equipped with a rubber septum, glass stopper, and argon inlet adapter was charged with a solution of diazo ketone **129** (0.733 g, 3.9 mmol) in 25 mL of Et_2O and 10 mL of hexanes and *i*-Pr_2EtN (0.70 mL, 0.52 g, 4.0 mmol) was added dropwise over 1 min. After 5 min, *i*-Pr_3SiOTf (1.1 mL, 1.3 g, 4.1 mmol) was added in one portion, and the resulting solution stirred at room temperature for 2 h. The reaction mixture was filtered through Celite with the aid of hexanes, and the filtrate was concentrated to afford 1.419 g of an orange oil. Column chromatography on 40 g of silica gel (elution with 3% EtOAc-1% NEt_3-hexanes) provided 0.917 g (68%) of silyl diazo ketone **136** as a yellow oil: IR (hexanes) 2946, 2065, 1614, 1464 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.37-7.43 (m, 4 H), 7.30-7.34 (m, 1 H), 6.95 (d, J = 1.5 Hz, 1 H), 2.13 (d, J = 1.5 Hz, 3 H), 1.42 (septet, J = 7.6 Hz, 3 H), 1.16 (d, J = 7.5, 18 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.4, 136.7, 135.8, 132.9, 129.6, 128.6, 128.2, 51.1, 18.7, 15.5, 11.8.



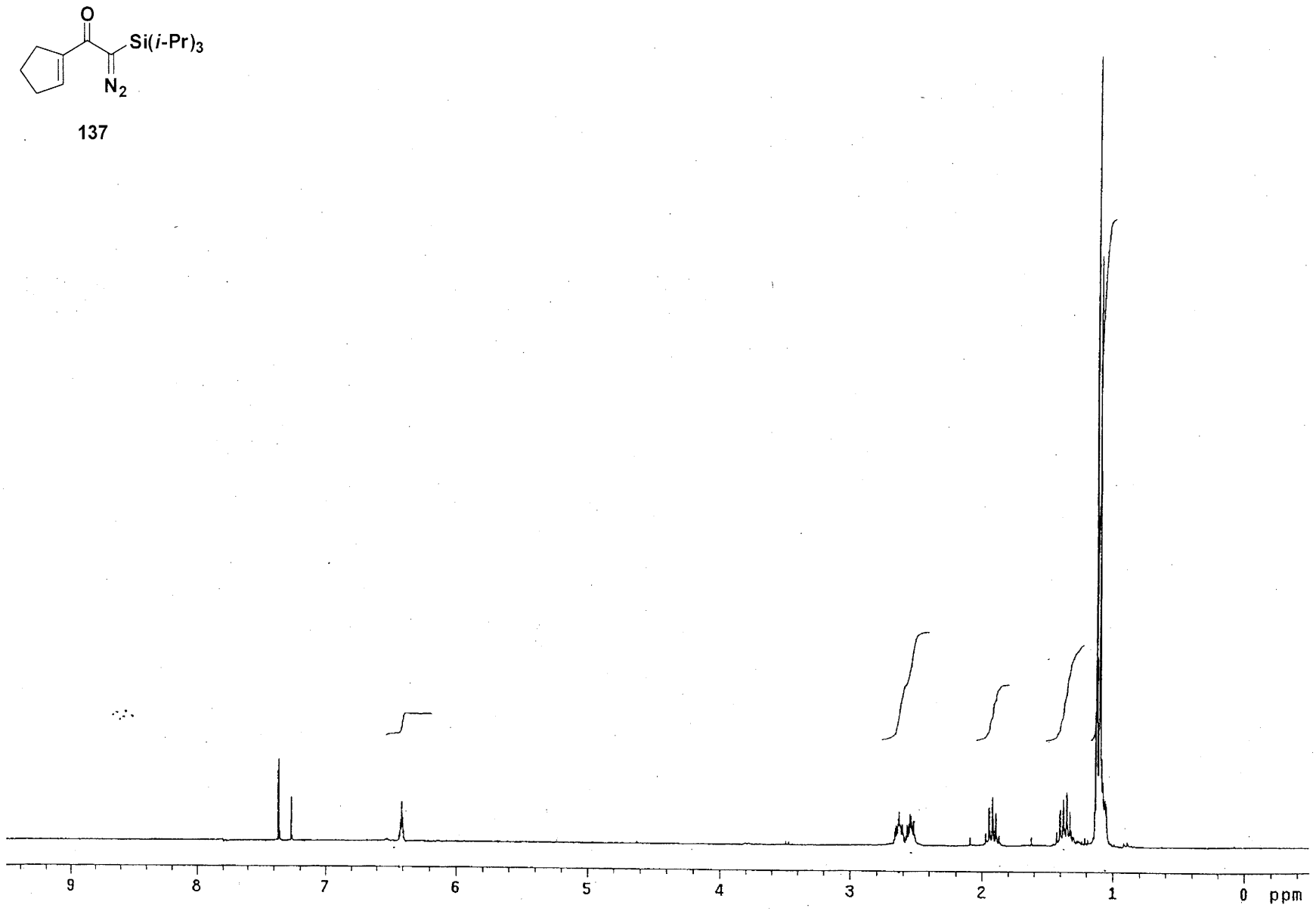
136

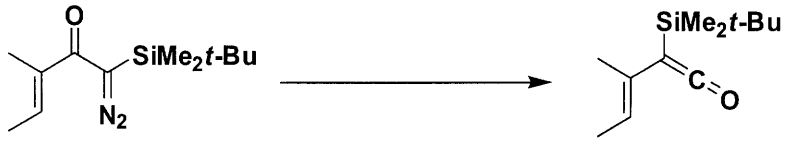


130 137

1-(1-Cyclopentenyl)-2-diazo-2-triisopropylsilyl-ethanone (137).

A 500-mL, three-necked, round-bottomed flask equipped with a glass stopper, rubber septum, and argon inlet adapter was charged with a solution of TIPSOTf (1.93 mL, 2.20 g, 7.18 mmol) in 75 mL of Et_2O and 125 mL of hexanes and cooled at 0 °C in an ice-water bath. A 100-mL, three-necked, round-bottomed flask equipped with a glass stopper, rubber septum, and argon inlet adapter was charged with a solution of diazo ketone **130** (0.979 g, 7.19 mmol) in 40 mL of Et_2O and cooled at 0 °C in an ice-water bath while *i*-Pr_2NEt (1.25 mL, 0.928 g, 7.18 mmol) was added in one portion. The resulting solution was allowed to stir for 5 min, and then was transferred dropwise via cannula over 20 min to the triflate solution (the flask was rinsed with 10 mL of Et_2O). The reaction mixture was stirred at 0 °C for 2.5 h, and then was filtered through a plug of Celite with the aid of 50 mL of hexanes and concentrated under reduced pressure at 0 °C to a volume of ca. 75 mL. The resulting solution was filtered through a plug of Celite with the aid of 20 mL of hexanes, and then concentrated under reduced pressure at 0 °C to a volume of ca. 10 mL. Column chromatography on 60 g of silica gel (elution with 3% EtOAc-1% NEt_3-hexanes cooled at 0 °C in an ice-water bath) yielded 1.616 g (77%) of the silyl diazo ketone **137** as a yellow oil: IR (neat) 2946, 2867, 2061, 1723, 1624, 1602 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.38-6.41 (m, 1 H), 2.50-2.65 (m, 4H), 1.92 (quintet, J = 7.6 Hz, 2 H), 1.36 (septet, J = 7.5 Hz, 3 H), 1.11 (d, J = 7.3 Hz, 18 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.8, 143.7, 137.8, 50.8, 33.8, 33.0, 22.7, 18.7, 11.7; HRMS-EI (*m/z*): $[M + Na]^+$ calcd for $C_{16}H_{28}OSiNa$, 315.1863; found, 315.1870.

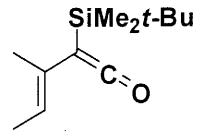

O
Si(i-Pr)3
N2
137
9
8
7
6
5
4
3
2
1
0
ppm



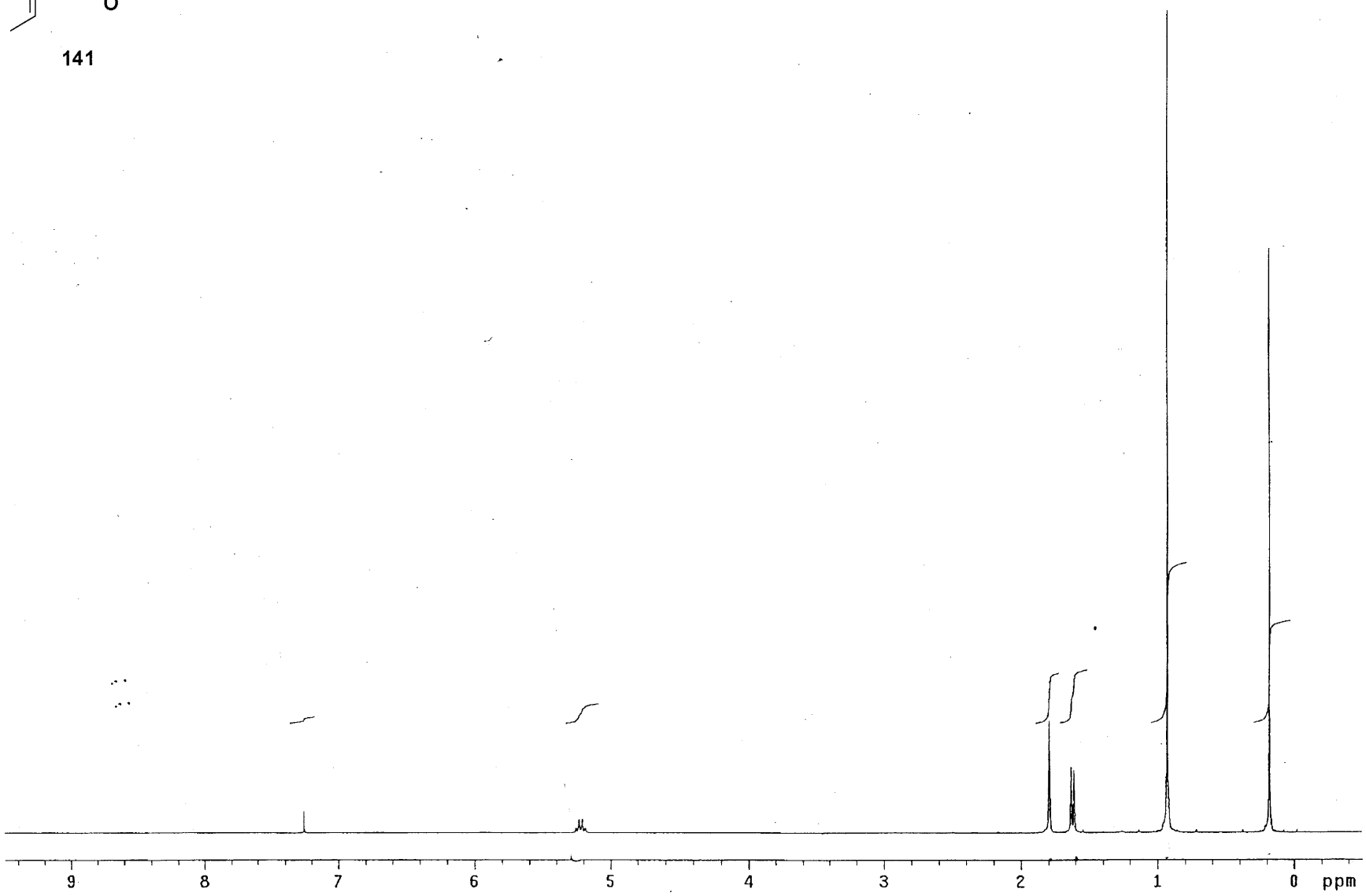
133 141

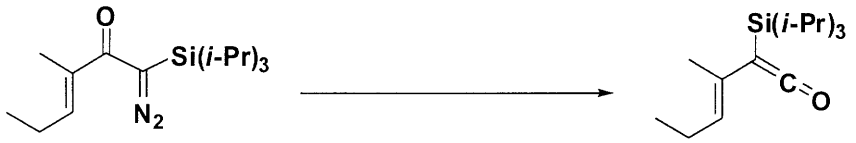
2-(*tert*-butyldimethylsilyl)-(*E*)-2-(1-Methyl-1-propenyl)ketene (141).

A solution of silyl diazo ketone **133** (0.693 g, 2.91 mmol) in 30 mL of benzene was distributed evenly between two 30-cm quartz tubes fitted with rubber septa. A second rubber septum (inverted) was secured with vinyl tape to each tube to ensure a good seal, and the reaction mixtures were degassed (three freeze-pump-thaw cycles at –196 °C, <0.5 mmHg) and then irradiated with 300 nm light in a Rayonet reactor for 3 h. The resulting solutions were combined and concentrated at reduced pressure to afford 0.513 g of a yellow oil. Column chromatography on 30 g of silica gel (elution with hexanes) provided 0.393 g (64%) of ketene **141** as a yellow oil: IR (neat) 2930, 2859, 2077, 1647 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.22 (qq, J = 7.0, 1.3 Hz, 1 H), 1.80 (app quintet, J = 1.1 Hz, 3 H), 1.62 (dq, J = 6.7, 1.0 Hz, 3 H), 0.93 (s, 9 H), 0.18 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 184.6, 124.1, 120.3, 27.0, 25.3, 19.3, 19.2, 14.2, -4.3.



141

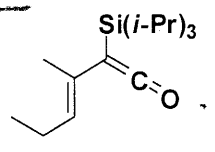




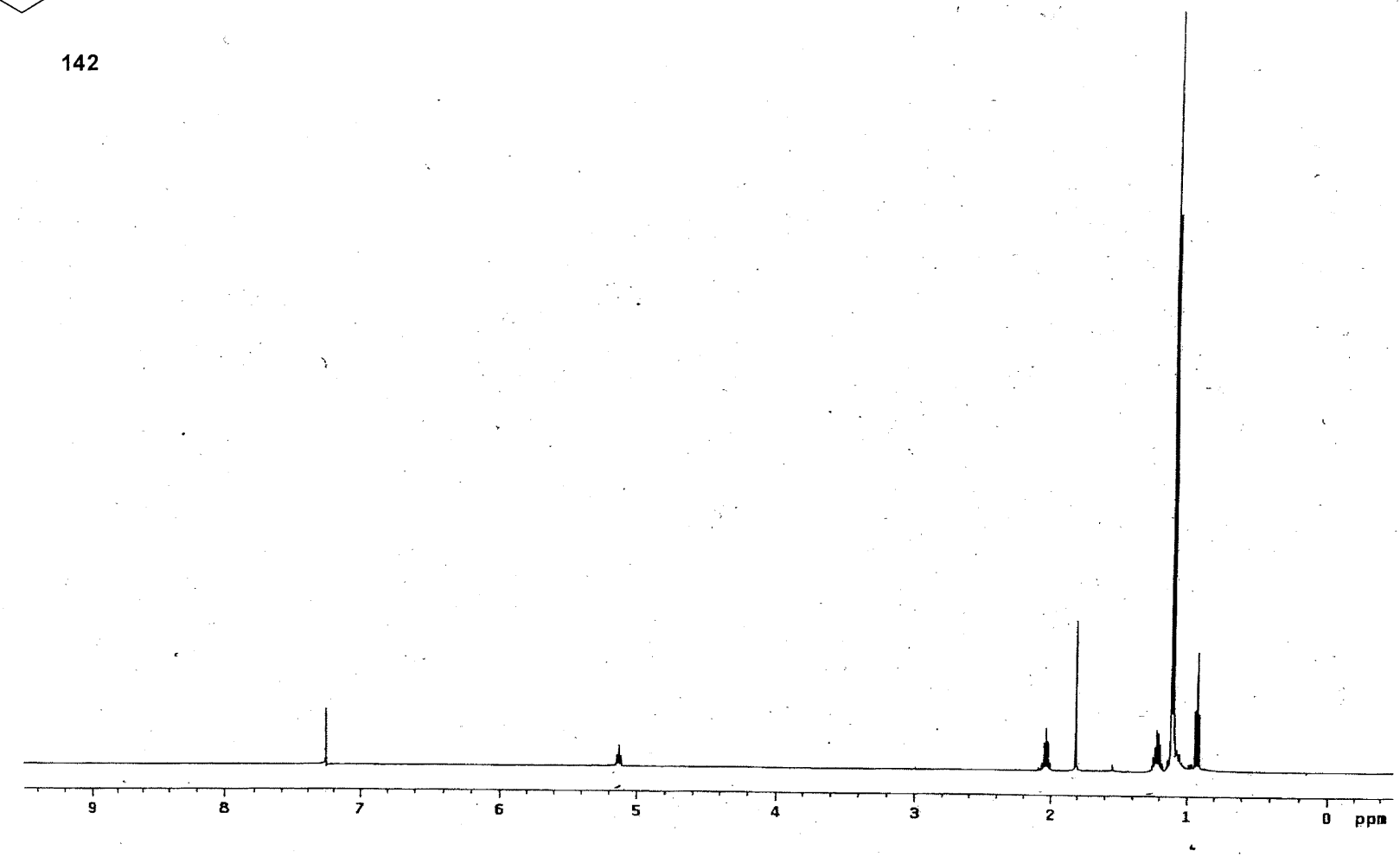
134 142

2-(1-Methyl-(*E*)-1-butenyl)-2-(triisopropylsilyl)ketene (142).

A 25-cm Vycor tube sealed with a rubber septum was charged with a solution of diazo ketone **134** (0.225 g, 0.76 mmol) in 8 mL of benzene. A second rubber septum (inverted) was secured to the tube with vinyl tape to ensure a good seal, and the reaction mixture was degassed (three freeze-pump-thaw cycles at –196 °C, <0.5 mmHg) and then irradiated at room temperature with 300 nm light in a Rayonet reactor for 4 h. The resulting solution was concentrated to afford 0.220 g of a yellow oil. Column chromatography on 10 g of silica gel (elution with hexanes) provided 0.150 g (74%) of ketene **142** as a yellow oil: IR (neat) 2946, 2868, 2725, 2077, 1643, 1463, 1382, 882 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.13 (t, J = 7.4 Hz, 1 H), 2.04 (app quintet, J = 7.5 Hz, 2 H), 1.81 (s, 3 H), 1.17-1.27 (m, 3 H), 1.10 (d, J = 7.3 Hz, 18 H), 0.93 (t, J = 7.5 Hz, 3 H) ^{13}C NMR (125 MHz, $CDCl_3$): δ 185.5, 128.1, 123.3, 23.4, 22.6, 19.6, 19.3, 15.0, 13.3; HRMS-ESI (*m/z*): $[M + H]^+$ calcd for $C_{16}H_{30}OSi$, 267.2139; found, 267.2147.



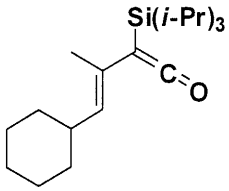
142



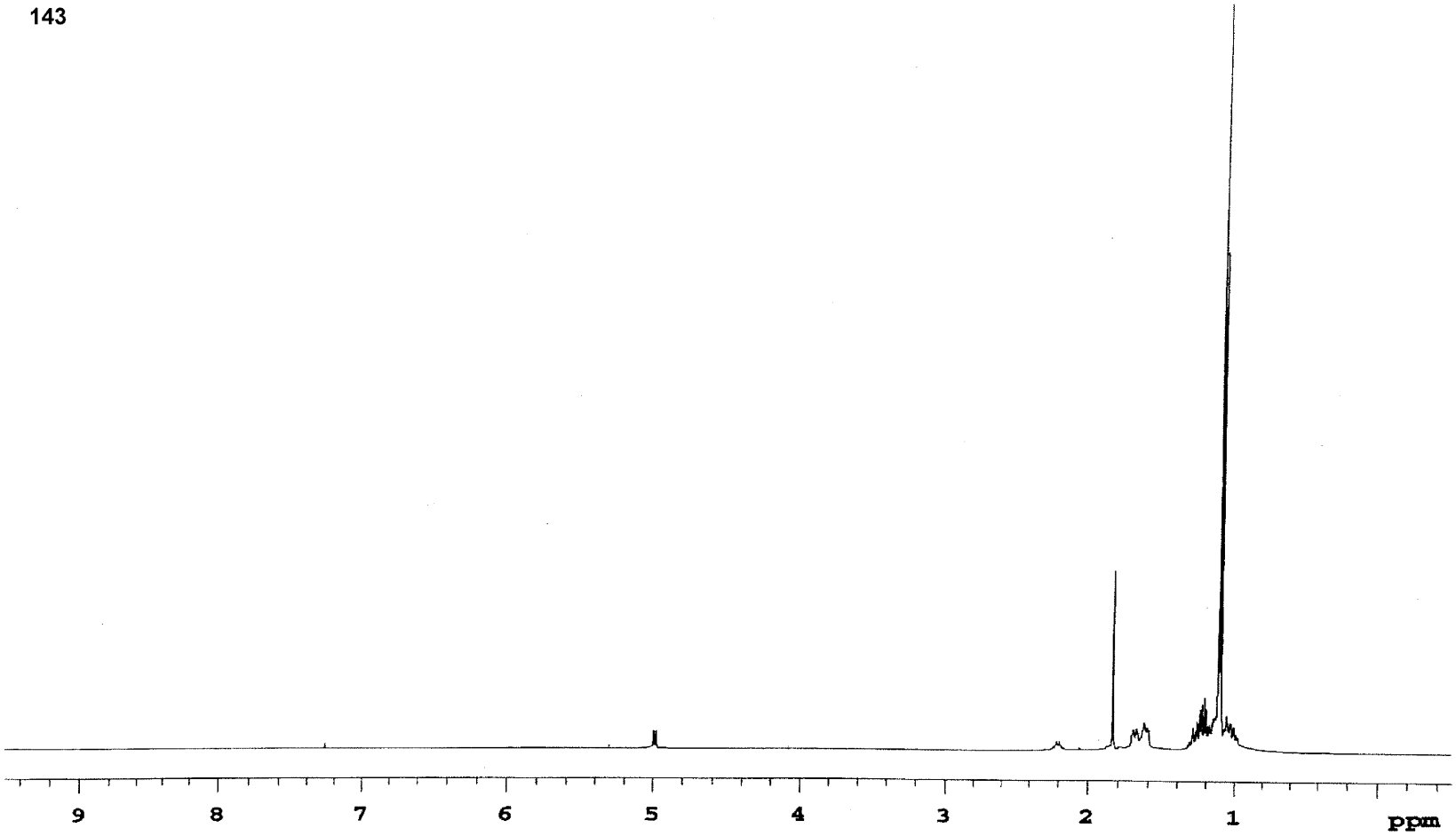
135 143

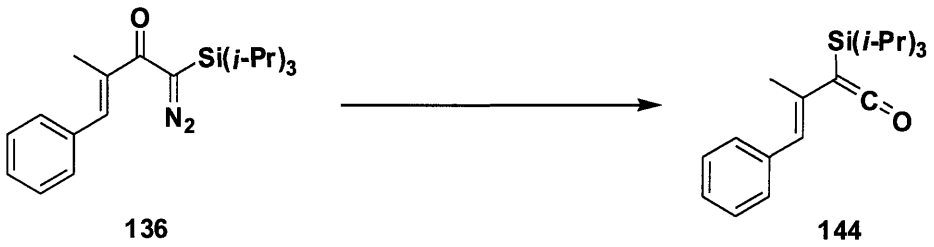
(*E*)-2-(1-Methyl)-2-cyclohexylethenyl)-2-(triisopropylsilyl)ketene (143).

A solution of silyl diazo ketone **135** (1.444 g, 4.14 mmol) in 40 mL of benzene was distributed evenly between two 25-cm Vycor tubes fitted with rubber septa. A second rubber septum (inverted) was secured with vinyl tape to each tube to ensure a good seal, and the reaction mixtures were degassed (three freeze-pump-thaw cycles at –196 °C, <0.5 mmHg) and then irradiated with 300 nm light in a Rayonet reactor for 4 h. The resulting solutions were combined and concentrated at reduced pressure to afford 1.470 g of a yellow oil. Column chromatography on 30 g of silica gel (elution with hexanes) provided 1.104 g (83%) of ketene **143** as a yellow oil: IR (neat) 2925, 2867, 2077, 1642, 1644, 1647, 1382, 883 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.98 (dd, J = 9.1, 1.2 Hz, 1 H), 2.15-2.25 (m, 1 H), 1.84 (d, J = 1.2 Hz, 3 H), 1.58-1.72 (m, 4 H), 0.98-1.34 (m, 27 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 185.1, 132.1, 121.6, 37.9, 33.6, 26.3, 26.2, 23.0, 19.4, 18.9, 12.8; HRMS-ESI (*m/z*): $[M + H]^+$ calcd for $C_{20}H_{36}OSiNa$, 343.2428; found, 343.2433.



143

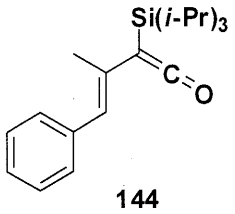




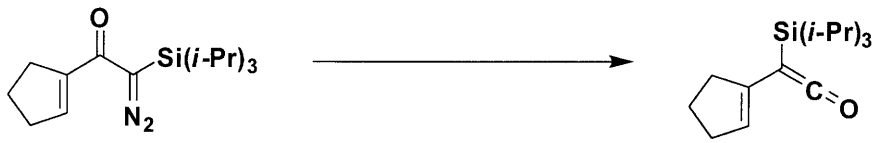
136 144

(*E*)-2-(1-Methyl-2-phenylethenyl)-2-(triisopropylsilyl) ketene (144).

A solution of silyl diazo ketone **136** (0.789 g, 2.30 mmol) in 30 mL of benzene was distributed evenly between two 30-cm quartz tubes fitted with rubber septa. A second rubber septum (inverted) was secured with vinyl tape to each tube to ensure a good seal, and the reaction mixtures were degassed (three freeze-pump-thaw cycles at –196 °C, <0.5 mmHg) and then irradiated with 300 nm light in a Rayonet reactor for 3 h. The resulting solutions were combined and concentrated at reduced pressure to afford 1.002 g of a yellow oil. Column chromatography on 100 g of silica gel (elution with hexanes) provided 0.334 g (46%) of ketene **144** as a yellow oil: IR (neat) 2946, 2074, 1627, 1464 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.39 (t, J = 8.1 Hz, 2 H), 7.26 (app d, J = 7.6 Hz, 3 H), 6.31 (s, 1 H), 2.15 (s, 3 H), 1.41 (septet, J = 7.6 Hz, 3 H), 1.25 (d, J = 7.3 Hz, 18 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 184.5, 139.0, 129.3, 128.6, 128.5, 126.4, 124.8, 25.9, 21.1, 19.1, 13.1; HRMS-ESI (*m/z*): $[M + H]^+$ calcd for $C_{20}H_{30}OSi$ 315.2139; found, 315.2131.



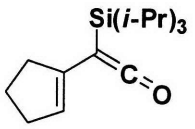
144



137 145

2-(1-Cyclopentenyl)-2-triisopropylsilyl ketene (145).

A solution of silyl diazo ketone **137** (1.596 g, 5.46 mmol) in 40 mL of benzene was distributed evenly between two 25-cm Vycor tubes fitted with rubber septa. A second rubber septum (inverted) was secured with vinyl tape to each tube to ensure a good seal, and the reaction mixtures were degassed (three freeze-pump-thaw cycles at –196 °C, <0.5 mmHg) and then irradiated with 300-nm light in a Rayonet reactor for 4 h. The resulting solutions were combined and concentrated at reduced pressure to afford 1.372 g of a rust-colored oil. Column chromatography on 50 g of silica gel (elution with hexanes) provided 0.958 g (66%) of ketene **145** as a yellow oil: IR (neat) 3374, 2867, 2082, 2024, 1751, 1623 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.34-5.38 (m, 1 H), 2.32-2.44 (m, 4 H), 1.89 (quintet, J = 7.3 Hz, 2 H), 1.24 (septet, J = 7.1 Hz, 3 H); 1.12 (d, J = 7.0 Hz, 18 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 185.4, 130.2, 123.4, 37.6, 33.4, 23.2, 18.8, 17.0, 12.6.

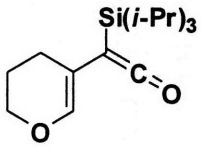


145

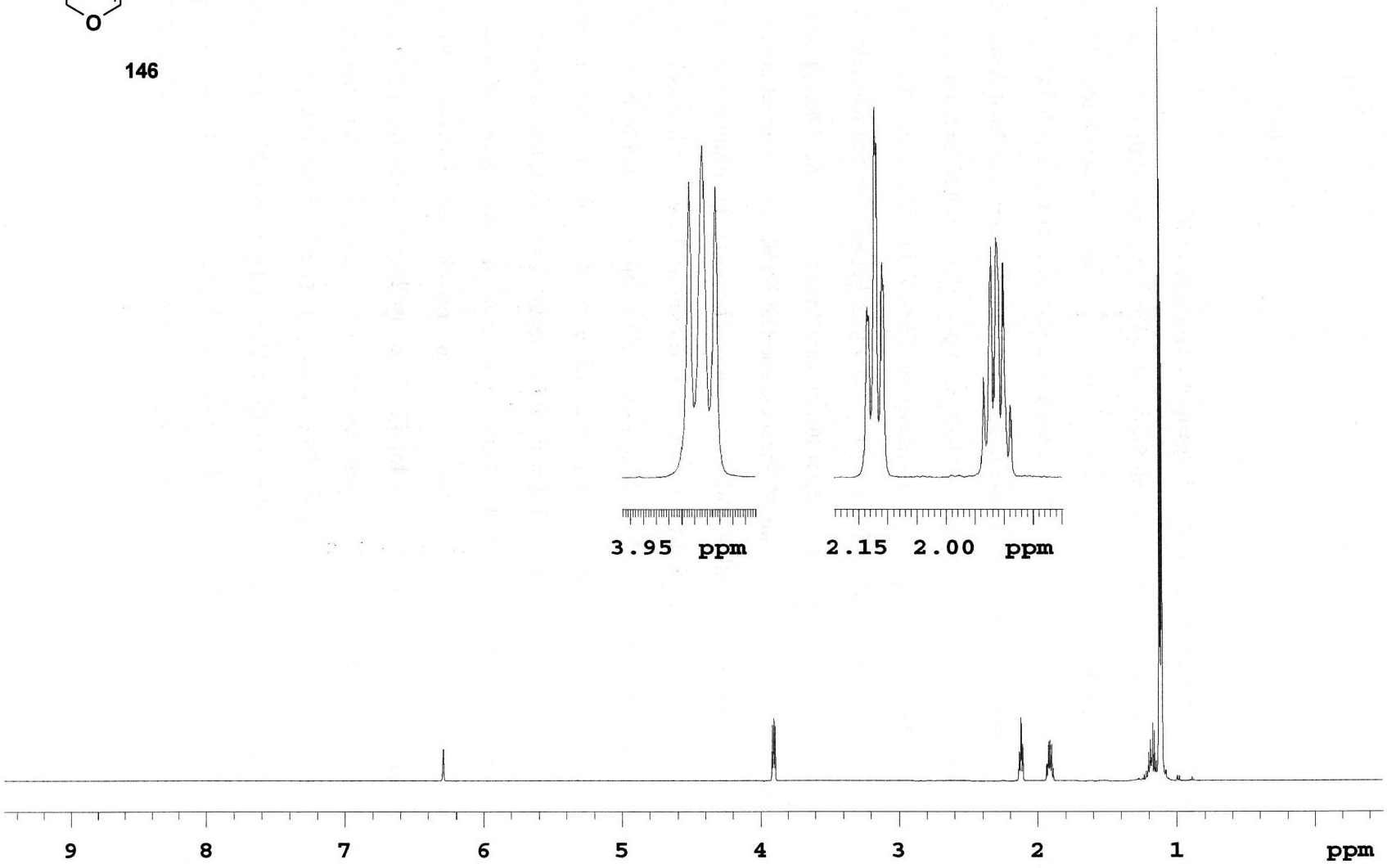
131 146

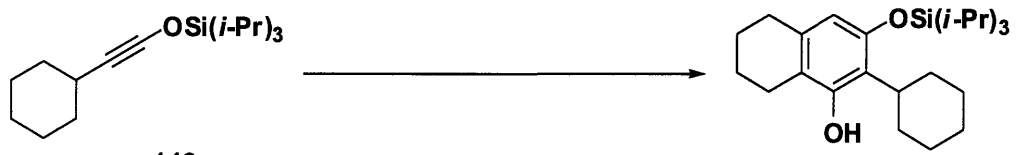
2-(3,4-Dihydro-2H-pyran-5-yl)-2-triisopropylsilylketene (146).

A 50-mL, three-necked, round-bottomed flask equipped with a rubber septum, glass stopper, and argon inlet adapter was charged with a solution of diazo ketone **131** (0.577 g, 3.8 mmol) in 15 mL of Et_2O. The reaction mixture was stirred at rt while *i*-Pr_2EtN (0.7 mL, 0.5 g, 4 mmol) was added dropwise over 1 min and the resulting solution was then stirred for 5 min. A 250-mL, three-necked, round-bottomed flask equipped with a rubber septum, glass stopper, and argon inlet adapter was charged with a solution of TIPSOTf (1.02 mL, 0.1.16 g, 3.8 mmol) in 60 mL of 1:2 Et_2O-hexanes and cooled at 0 °C. The diazo ketone solution was added dropwise via cannula over 25 min, and the resulting solution was stirred for 2.5 h. The reaction mixture was filtered through Celite with the aid of hexanes, and the filtrate was concentrated to a volume of ca 20 mL, and then diluted with 40 mL of hexanes. The resulting solution was concentrated to a volume of ca 3 mL and applied to the top of a column of 30 g of silica gel. Elution with 5% EtOAc-1% NEt_3-hexanes provided 0.885 g of a yellow oil, estimated to be 90-95% silyl diazo ketone **135** by ^1H NMR. This mixture was diluted with 34 mL of benzene and partitioned between two 25-cm Vycor tube sealed with rubber septa. A second rubber septum (inverted) was secured to the tube with vinyl tape to ensure a good seal, and the reaction mixture was degassed (three freeze-pump-thaw cycles at –196 °C, <0.5 mmHg) and then irradiated at room temperature with 300 nm light in a Rayonet reactor for 4 h. The resulting solution was concentrated to afford 1.009 g of a yellow oil. Column chromatography on 20 g of silica gel (elution with hexanes) provided 0.296 g (29% overall from diazo ketone **131**) of ketene **146** as a yellow oil: IR (CH_2Cl_2) 3054, 2868, 2077 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.29 (s, 1 H), 3.90 (app t, J = 5.2 Hz, 2 H), 2.12 (app td, J = 6.4, 1.2 Hz, 2 H), 1.88-1.94 (m, 2 H), 1.17 (sept, J = 6.4 Hz, 3 H), 1.11 (d, J = 6.7 Hz, 18 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 183.9, 140.9, 102.0, 65.3, 27.0, 23.2, 18.8, 15.5, 12.7.



146

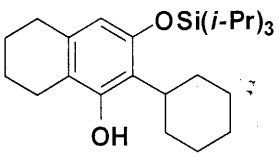




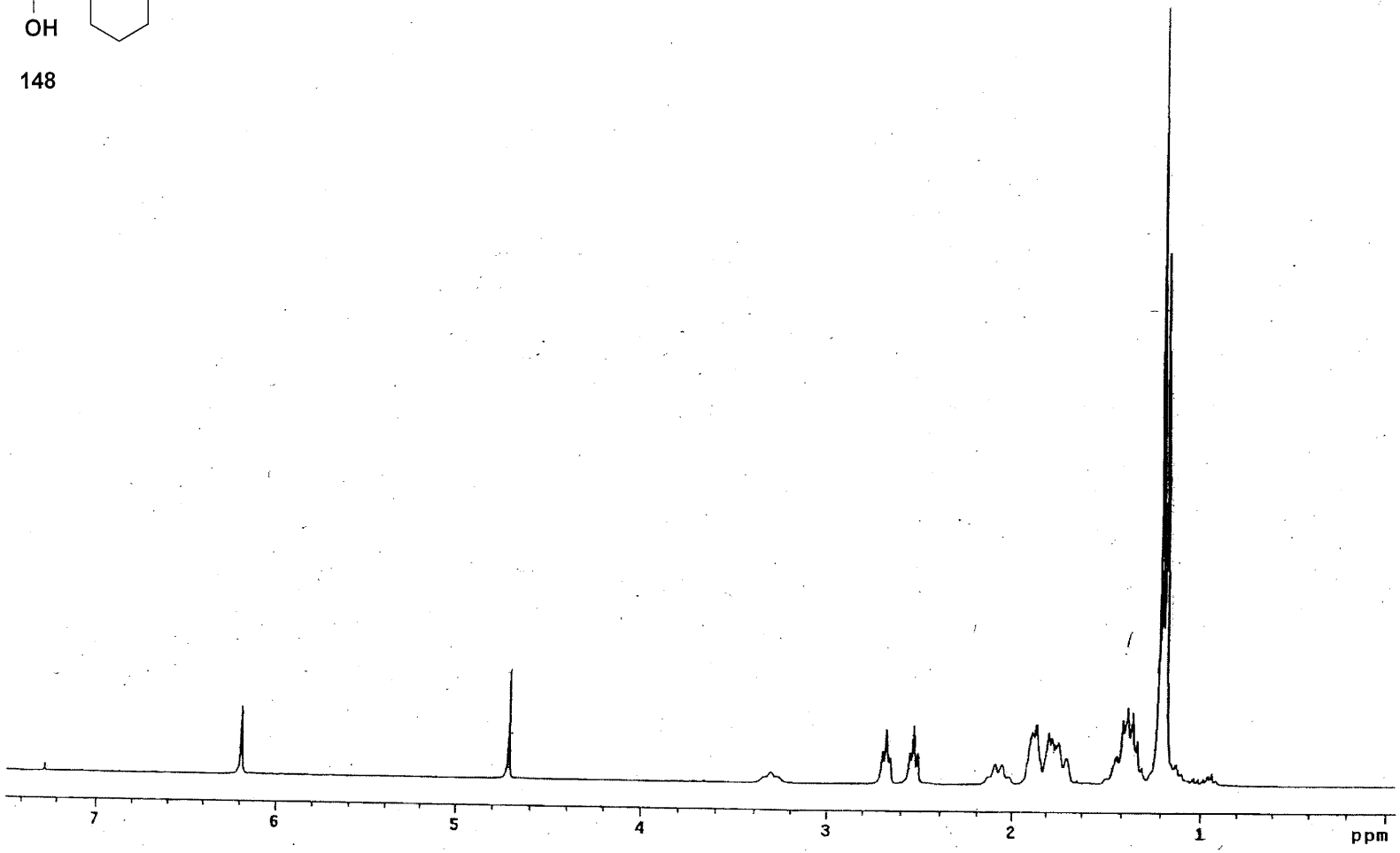
118 148

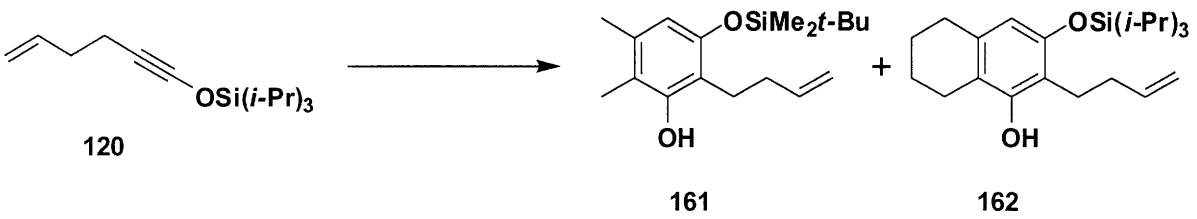
2-Cyclohexyl-5,6,7,8-tetrahydro-3-(triisopropylsiloxy)-1-napthol (148).

A 25-mL, two-necked, round-bottomed flask equipped with a rubber septum and an argon inlet adapter was charged with siloxy alkyne **118** (0.149 g, 0.531 mmol) and 3 mL of THF. MeLi solution (1.48 M in Et_2O, 0.36 mL, 0.53 mmol) was added dropwise via syringe over 30 s, and the resulting solution was stirred at room temperature for 4 h. A solution of ketene **20** (0.149 mg, 0.539 mmol) in 1 mL of THF was added via cannula (the flask was rinsed with 1 mL of THF), and the resulting solution was stirred for an additional 2 h. The reaction mixture was then poured into a separatory funnel containing 10 mL of satd aq NH_4Cl. The aqueous phase was extracted with two 5-mL portions of Et_2O, and then the combined organic phases were washed with 10 mL of water and 10 mL of brine, dried over $MgSO_4$, filtered, and concentrated to afford 0.296 g of a yellow oil. Column chromatography on 30 g of silica gel (elution with 1% EtOAc—hexanes) provided 0.151 g (71%) of tetrahydronapthol **148** as a yellow oil: IR (CH_2Cl_2) 3054, 2987, 1422 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.19 (s, 1 H), 4.71 (s, 1 H), 3.31 (m, 1 H), 2.68 (app t, J = 6.0, 2 H), 2.54 (t, J = 6.0, 2 H), 2.01-2.14 (m, 2 H), 1.83-1.93 (m, 4 H), 1.66-1.80 (m, 5 H), 1.31-1.46 (m, 6 H), 1.18 (d, J = 6.9, 18 H); ^{13}C NMR (75 MHz, r. t., $CDCl_3$): δ 153.3, 152.2, 135.5, 120.3, 115.4, 111.2, 35.7, 30.7, 29.8, 27.9, 26.7, 23.3, 23.2, 22.7, 18.5, 13.5; HRMS-EI (*m/z*): $[M + H]^+$ calcd for $C_{25}H_{43}O_2Si$, 403.3027; found, 403.3032.



148

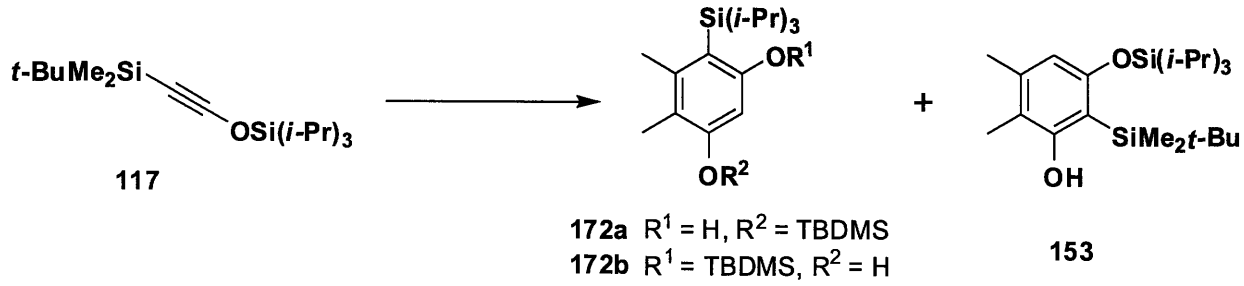




120 161 162

Crossover Experiment.

A 10-mL, two-necked, round-bottomed flask equipped with a rubber septum and argon inlet adapter was charged with a solution of siloxy alkyne **120** (0.249 g, 0.99 mmol) in 3 mL of THF and stirred at room temperature while 0.62 mL of MeLi solution (1.61 M in Et_2O, 1.0 mmol) was added. The resulting mixture was stirred for 4.5 h, and then a solution of (*tert*-butyldimethylsilyl)ketene **20** (0.104 g, 0.49 mmol) and (triisopropylsilyl)ketene **141** (0.137 g, 0.49 mmol) in 2.5 mL of THF was added over 10 sec. The mixture was stirred 1 h and then diluted with 10 mL of Et_2O and washed with 10 mL of satd aq NH_4Cl solution. The aqueous phase was extracted with two 5-mL portions of Et_2O. The organic phase was washed with 10 mL of water and 15 mL of brine, dried over $MgSO_4$, filtered, and concentrated to yield 0.441 g of a yellow oil. An aliquot of this material was analyzed by GCMS which indicated the presence of phenols **161** and **162**. No product corresponding to the crossed-over compounds, phenols **163** and **164,** was observed.

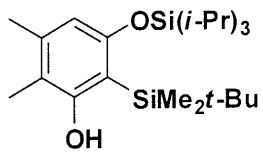


5-(*tert*-Butyldimethylsiloxy)-3,4-dimethyl-2-(triisopropylsilyl)phenol (172a) or 5-(*tert*-butyldimethylsiloxy)-2,3-dimethyl-4-(triisopropylsilyl)phenol (172b) and 2-(*tert*-butyldimethylsilyl)-5,6-dimethyl-3-(triisopropylsiloxy)phenol (153).

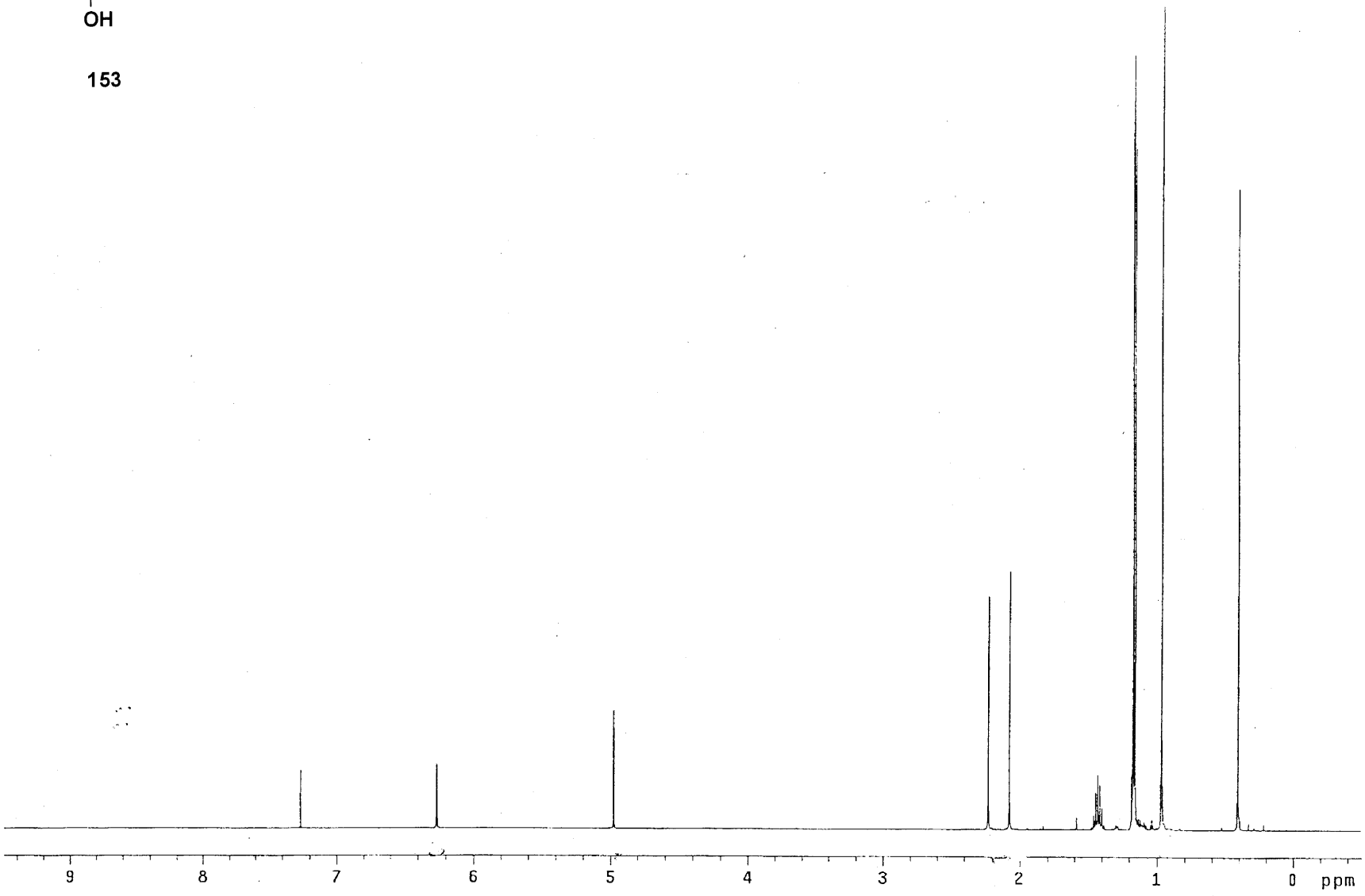
Reaction of siloxy alkyne **117** (0.250 g, 0.800 mmol) with MeLi solution (1.63 M in Et_2O, 0.50 mL, 0.82 mmol) and ketene **21** (0.205 g, 0.812 mmol) in 5 mL of THF according to the general procedure provided 0.501 g of orange oil. NMR analysis of this material indicated the presence of two aromatic products **172** and **153** in a ratio of 66:34 and an estimated combined yield of 40-60%. Pure samples of each compound could not be obtained without significant losses due to the presence of impurities with similar chromatographic properties and the fact that both compounds underwent partial decomposition upon attempted purification by chromatography under a variety of conditions. A pure sample of **153** was obtained by the following procedure. Column chromatography on 20 g of silica gel deactivated with acetone and triethylamine (elution with 5% EtOAc-1% Et_3N-hexanes) provided 0.120 g of a yellow oil which was applied to the top of a column of 5 g of acetone-deactivated silica gel and eluted with 0-1% EtOAc-hexanes to yield 0.047 g (14%) of phenol **153** as a white solid, mp 92-95 °C: IR (CH_2Cl_2) 3603, 3053, 2948, 2948, 2868, 1601, 1469 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.25 (s, 1 H), 4.96 (s, 1 H), 2.21 (s, 3 H), 2.06 (s, 3 H), 1.42 (sept, J = 7.6 Hz, 3 H), 1.15 (d, J = 7.6 Hz, 18 H), 0.95 (s, 9 H), 0.40 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.3, 160.1, 139.5, 113.7, 112.6, 108.5, 27.5, 20.9, 18.8, 18.6, 14.0, 11.5, -0.9; HRMS-ESI (*m/z*): $[M + H]^+$ calcd for $C_{23}H_{44}O_2Si_2$, 409.2953; found, 409.2957.

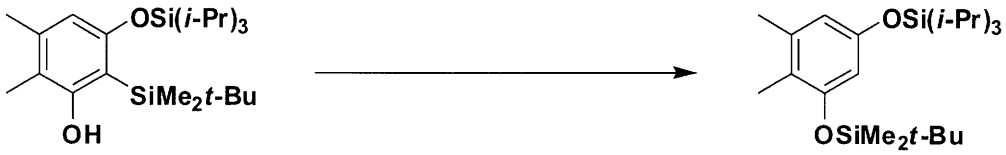
A pure sample of **173** could not be obtained, but a sample of sufficient purity for identification of NMR characteristics was obtained by the following procedure. The crude

product of another run of the benzannulation was first partially purified by column chromatography on 20 g of silica gel deactivated with acetone and triethylamine (elution with 5% EtOAc-1% Et_3N-hexanes) to afford 0.133 g of a red oil. This material was dissolved in 10 mL of Et_2O, washed with five 5-mL portions of satd aqueous NH_4Cl solution, dried over $MgSO_4$, filtered, and concentrated to afford 0.069 g of a sample of the major benzannulation product assigned as either **173a** or **173b** (ca. 80% purity) as a yellow oil: ^1H NMR (500 MHz, $CDCl_3$) δ 6.20 (s, 1 H), 4.87-5.00 (br s, 1 H), 2.31 (s, 3 H), 2.08 (s, 3 H), 1.66 (sept, J = 7.5 Hz, 3 H), 1.09 (d, J = 7.5 Hz), 1.00 (s, 9 H), 0.27 (s, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.1, 154.8, 146.8, 117.7, 115.7, 104.3, 27.6, 23.1, 20.4, 19.3, 14.5, 12.1, -2.7.



153

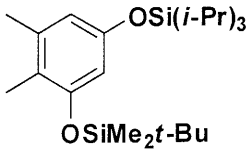




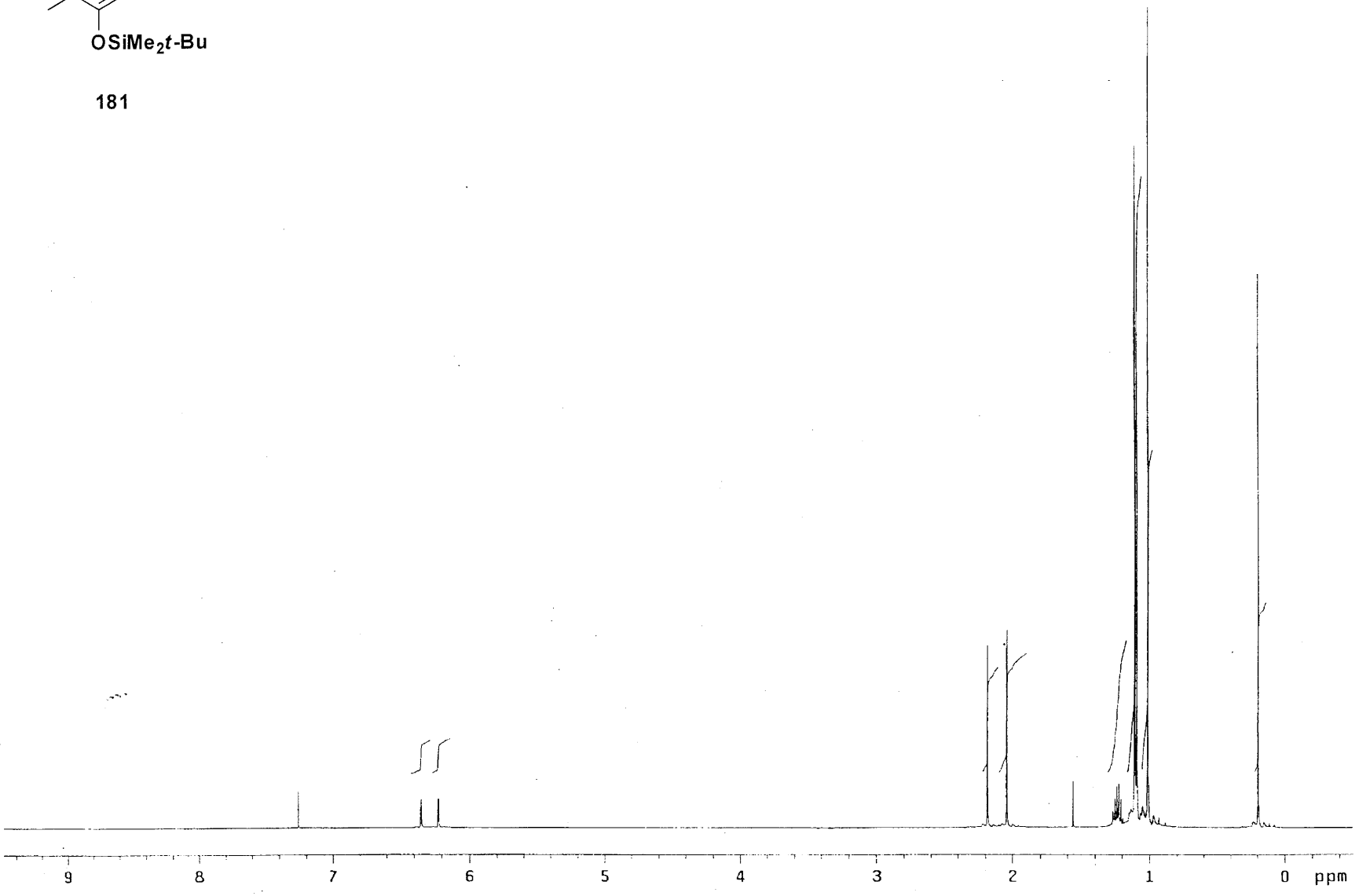
153 181

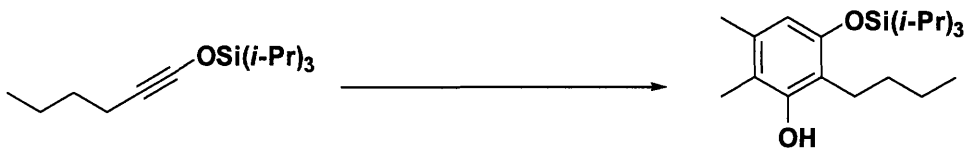
4,5-Dimethyl-3-*tert*-butyldimethylsiloxy-1-triisopropylsiloxy-benzene.

A 5-mm glass tube was charged with a solution of phenol **153** (0.026 g, 0.064 mmol) in 0.70 mL of $CDCl_3$. The reaction mixture was heated at reflux for 3.5 h then allowed to cool and concentrated to yield 0.025 g (96%) of **181** as a pale yellow oil: IR (neat) 2945, 2866, 1603, 1473, 1333 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) d 6.35 (d, J = 2.4, 1 H), 6.22 (d, J = 2.4, 1 H), 2.18 (s, 3 H), 2.04 (s, 3 H), 1.22 (m, 3 H), 1.10 (d, J = 7.3, 18 H), 1.01 (s, 9 H), 0.19 (s, 6 H); ^{13}C NMR d 154.6, 154.3, 139.0, 120.5, 115.3, 108.9, 26.5, 21.2, 19.0, 18.7, 13.4, 12.6, -3.6; HRMS-ESI (*m/z*): $[M + H]^+$ calcd for $C_{23}H_{44}O_2Si_2$, 409.2953; found, 409.2959.



181

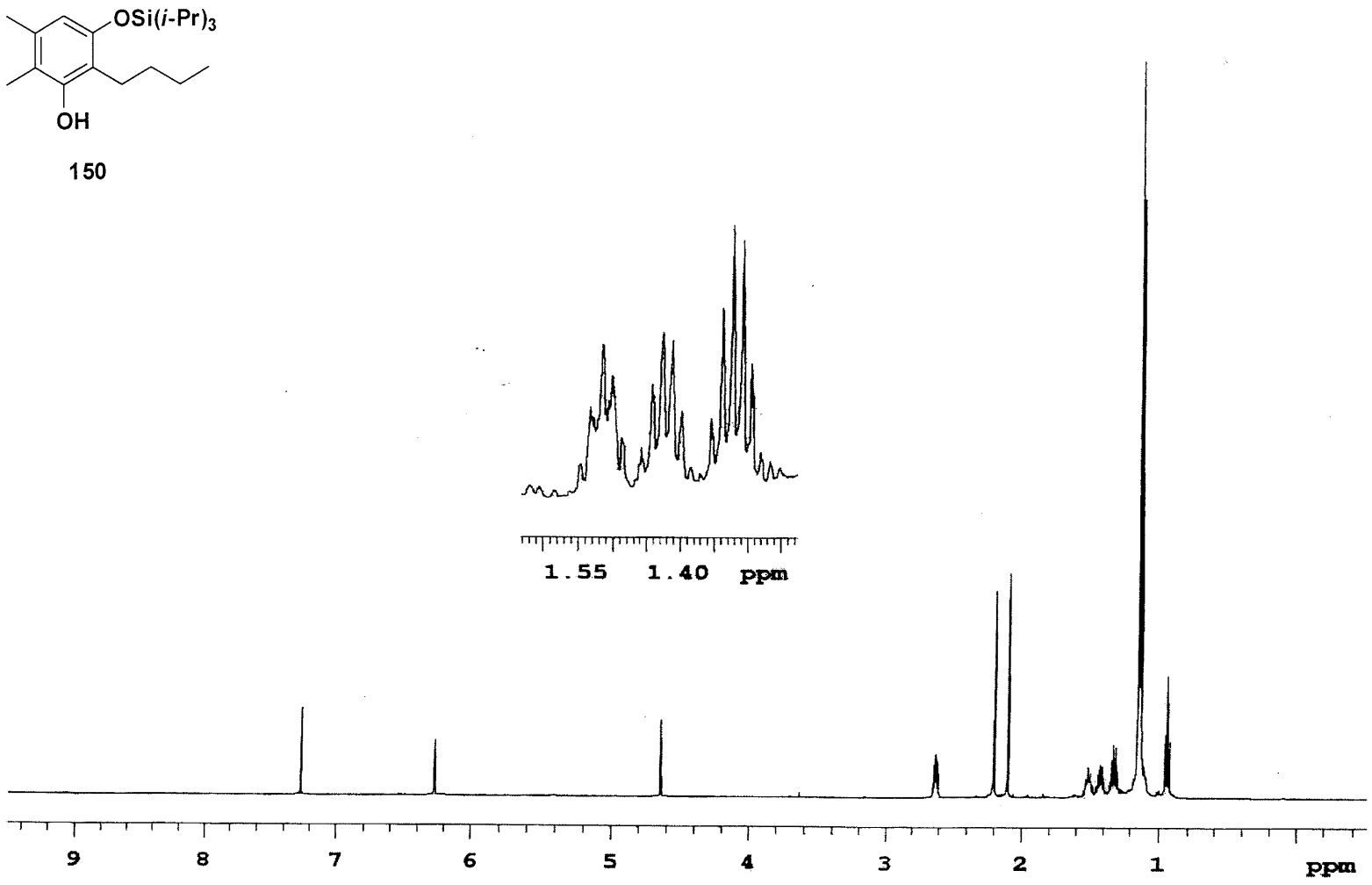


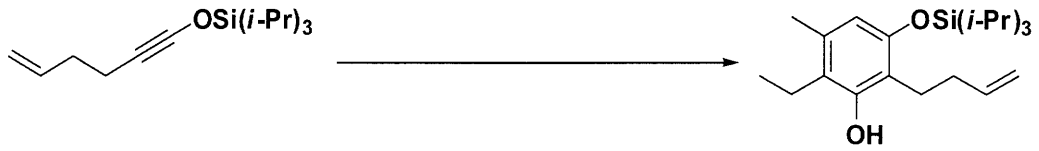


108 150

2-Butyl-5,6-dimethyl-3-(triisopropylsiloxy)phenol (150).

A 25-mL, two-necked, round-bottomed flask equipped with a rubber septum and argon inlet adapter was charged with siloxy alkyne **108** (0.314 g, 1.23 mmol) and 5 mL of THF. MeLi solution (1.53 M in Et_2O, 0.81 mL, 1.2 mmol) was added dropwise via syringe over 2 min, and the resulting solution was stirred at room temperature for 4 h. A solution of ketene **21** (0.313 g, 1.24 mmol) in 2 mL of THF was added via cannula in one portion (the flask was rinsed with 1 mL of THF), and the resulting solution was stirred for an additional 1 h. The reaction mixture was poured into 10 mL of satd aq NH_4Cl, the aqueous phase was separated and extracted with two 10-mL portions of Et_2O, and the combined organic phases were washed with 20 mL of water and 20 mL of saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford 0.547 g of a yellow oil. Column chromatography on 25 g of silica gel (elution with 5% EtOAc-hexanes) provided 0.220 g (51%) of phenol **150** as a yellow oil: IR (neat) 3621, 2945, 2867, 1618, 1577, 1498, 1464, cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.27 (s, 1 H), 4.66 (s, 1 H), 2.64 (t, J = 7.2 Hz, 2 H), 2.21 (s, 3 H), 2.11 (s 3 H), 1.22-1.58 (m, 7 H), 1.15 (d, J = 6.9 Hz, 18 H), 0.96 (d, J = 7.5 Hz, 3 H), 1.32 (sept, J = 7.2 Hz, 3 H) 1.13 (d, J = 7.5 Hz, 18 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.5, 152.0, 134.6, 116.2, 114.2, 112.4, 32.1, 24.4, 23.6, 20.7, 18.6, 14.6, 13.6, 11.8; HRMS-ESI (m/z): $[M + Na]^+$ calcd for $C_{21}H_{38}O_2Si$, 373.2533; found, 373.2544.


OSi(i-Pr)3
OH
150
1.55
1.40
ppm
9
8
7
6
5
4
3
2
1
ppm

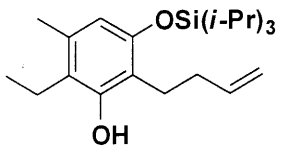


120

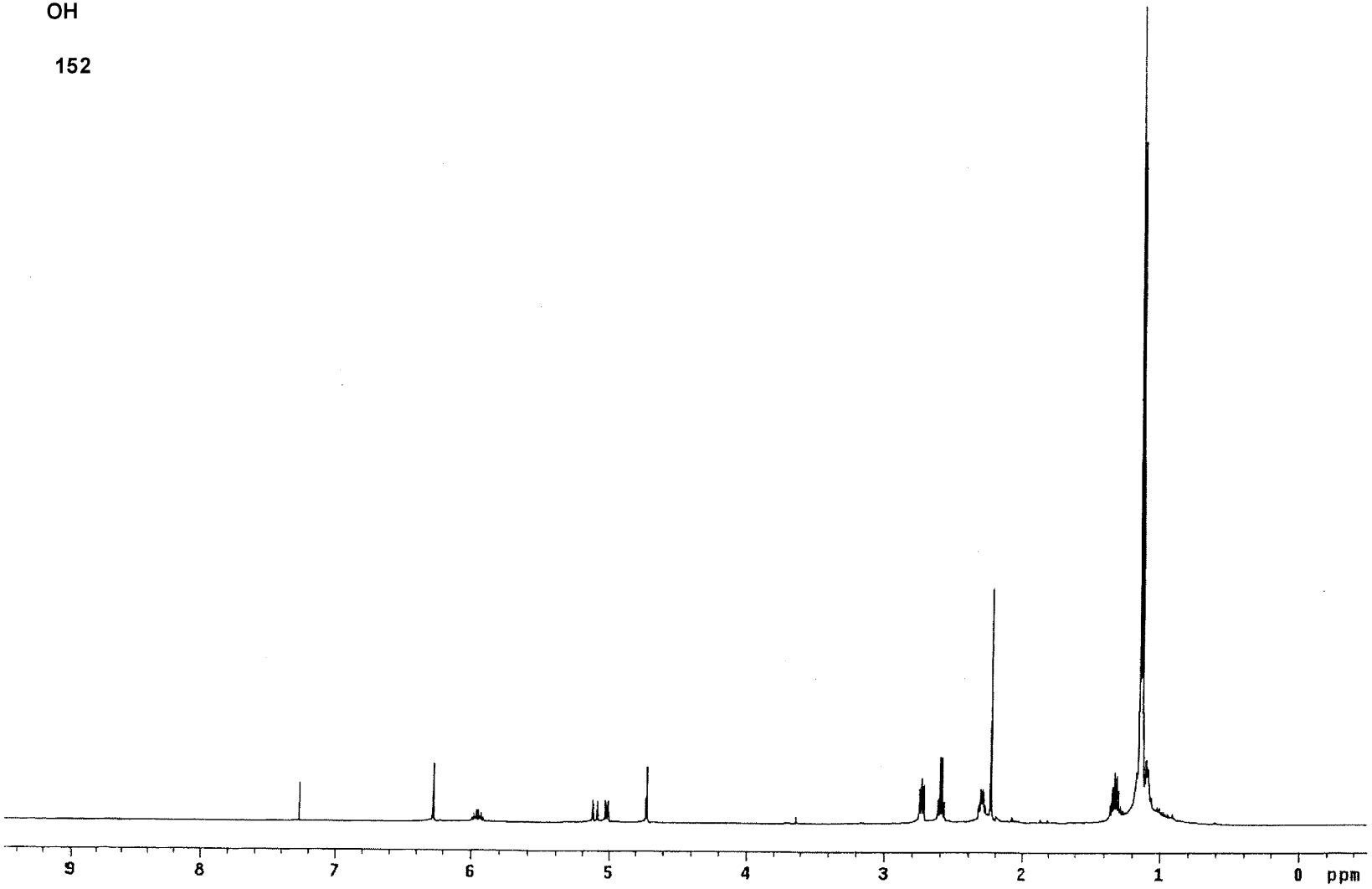
152

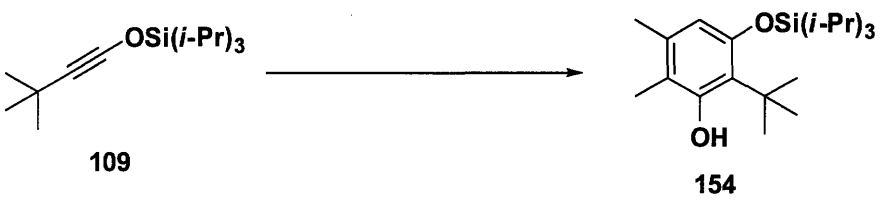
6-Ethyl-5-methyl-2-(3-butenyl)-3-(triisopropylsiloxy)phenol (152).

A 25-mL, two-necked, round-bottomed flask equipped with a rubber septum and argon inlet adapter was charged with siloxy alkyne **120** (0.150 g, 0.594 mmol) and 3 mL of THF. MeLi solution (1.48 M in Et_2O, 0.40 mL, 0.59 mmol) was added dropwise via syringe over 30 s, and the resulting solution was stirred at room temperature for 4 h. A solution of ketene **142** (0.158 g, 0.593 mmol) in 1 mL of THF was added via cannula in one portion (the flask was rinsed with 1 mL of THF), and the resulting solution was stirred at rt for an additional 2.5 h. The reaction mixture was poured into 5 mL of satd aq NH_4Cl, and the aqueous phase was separated and extracted with two 5-mL portions of Et_2O. The combined organic phases were washed with 10 mL of water and 10 mL of satd NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford 0.290 g of a yellow oil. Column chromatography on 30 g of silica gel (elution with 2% EtOAc-hexanes) provided 0.145 g (68%) of phenol **152** as a yellow oil: IR (neat) 3620, 2945, 2868, 1614, 1575, 1462 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.27 (s, 1 H), 5.95 (tdd, J = 6.8, 10.2, 17.1 Hz, 1 H), 5.10 (dd, J = 17.1, 1.5 Hz, 1 H), 5.01 (dd, J = 10.1, 1.2 Hz, 1 H), 4.71 (d, J = 1.8 Hz, 1 H), 2.73 (7, J = 7.8 Hz, 2 H) 2.59 (q, J = 7.3 Hz, 2 H), 2.30 (q, J = 7.9 Hz, 3 H), 2.23 (s, 3 H), 1.32 (sept, J = 7.2 Hz, 3 H) 1.06-1.18 (m, 21 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.9, 152.7, 139.6, 134.8, 121.4, 116.0, 115.6, 113.0, 34.2, 24.7, 20.24, 20.19, 18.9, 14.5, 13.8; HRMS-ESI (*m/z*): $[M + Na]^+$ calcd for $C_{22}H_{38}O_2Si$, 385.2553; found, 385.2542.



152

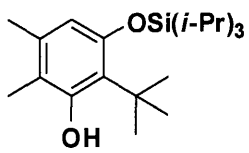




109 154

5,6-Dimethyl-2-*tert*-butyl-3-(triisopropylsiloxy)phenol (154).

A 10-mL, two-necked, round-bottomed flask equipped with a rubber septum and argon inlet adapter was charged with siloxy alkyne **109** (0.198 g, 0.778 mmol) and 3 mL of THF. MeLi solution (1.63 M in Et_2O, 0.49 mL, 0.80 mmol) was added dropwise via syringe over 30 sec, and the resulting solution was stirred at room temperature for 3.5 h. A solution of ketene **21** (0.200 g, 0.792 mmol) in 1 mL of THF was added via cannula in one portion (the flask was rinsed with 1 mL of THF), and the resulting solution was stirred for an additional 1 h. The reaction mixture was poured into 5 mL of satd aq NH_4Cl, the aqueous phase was separated and extracted with two 5-mL portions of Et_2O, and the combined organic phases were washed with 10 mL of water and 10 mL of saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford 0.389 g of an orange oil. Column chromatography on 20 g of silica gel (elution with 2% EtOAc-hexanes) provided 0.180 g of a yellow oil. Further purification on a second column of 20 g of silica gel (elution with 25% benzene-hexanes) afforded 0.151 g (55%) of phenol **154** as a pale yellow oil: IR (neat) 3622, 2947, 2868, 1610, 1567, 1484 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.22 (s, 1 H), 5.13 (s, 1 H), 2.17 (s, 3 H), 2.07 (s 3 H), 1.57 (s, 9 H), 1.37 (sept, J = 7.5 Hz, 3 H) 1.15 (d, J = 7.5 Hz, 18 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.2, 153.8, 134.8, 121.5, 115.6, 114.3, 36.7, 32.5, 20.8, 18.6, 13.9, 11.9; HRMS-ESI (*m/z*): $[M + H]^+$ calcd for $C_{21}H_{38}O_2Si$, 351.2714; found, 351.2719.

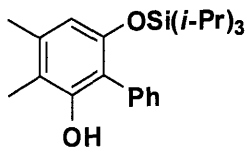


154

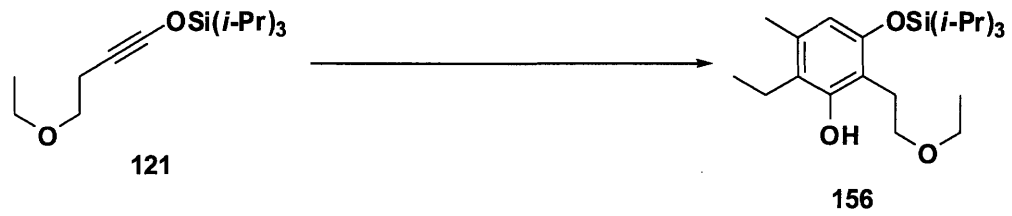
111 155

5,6-Dimethyl-2-phenyl-3-(triisopropylsiloxy)phenol (155).

A 10-mL, two-necked, round-bottomed flask equipped with a rubber septum and argon inlet adapter was charged with siloxy alkyne **111** (0.200 g, 0.729 mmol) and 3 mL of THF. MeLi solution (1.63 M in Et_2O, 0.46 mL, 0.75 mmol) was added dropwise via syringe over 30 sec, and the resulting solution was stirred at room temperature for 4 h. A solution of ketene **21** (0.1850 g, 0.733 mmol) in 1 mL of THF was added via cannula in one portion (the flask was rinsed with 1 mL of THF), and the resulting solution was stirred for an additional 1 h. The reaction mixture was poured into 5 mL of satd aq NH_4Cl, the aqueous phase was separated and extracted with two 5-mL portions of Et_2O, and the combined organic phases were washed with 10 mL of water and 10 mL of saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford 0.389 g of an orange oil. Column chromatography on 15 g of silica gel (elution with 20% benzene-hexanes) afforded 0.080 g (30%) of phenol **155** as a pale yellow oil: IR (neat) 3552, 2942, 2867, 1621, 1570, 1463 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.42-7.49 (m, 2 H), 7.32-7.39 (m, 3 H), 6.36 (s, 1 H), 4.97 (s, 1 H), 2.26 (s, 3 H), 2.15 (s 3 H), 1.01-1.14 (m, 3 H) 0.92 (d, J = 7.5 Hz, 18 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.5, 151.0, 137.4, 134.0, 131.4, 131.4, 129.2, 129.2, 128.0, 117.4, 115.1, 112.4, 20.6, 18.1, 13.0, 11.7; HRMS-ESI (*m/z*): $[M + H]^+$ calcd for $C_{23}H_{34}O_2Si$, 371.2401; found, 371.2412.



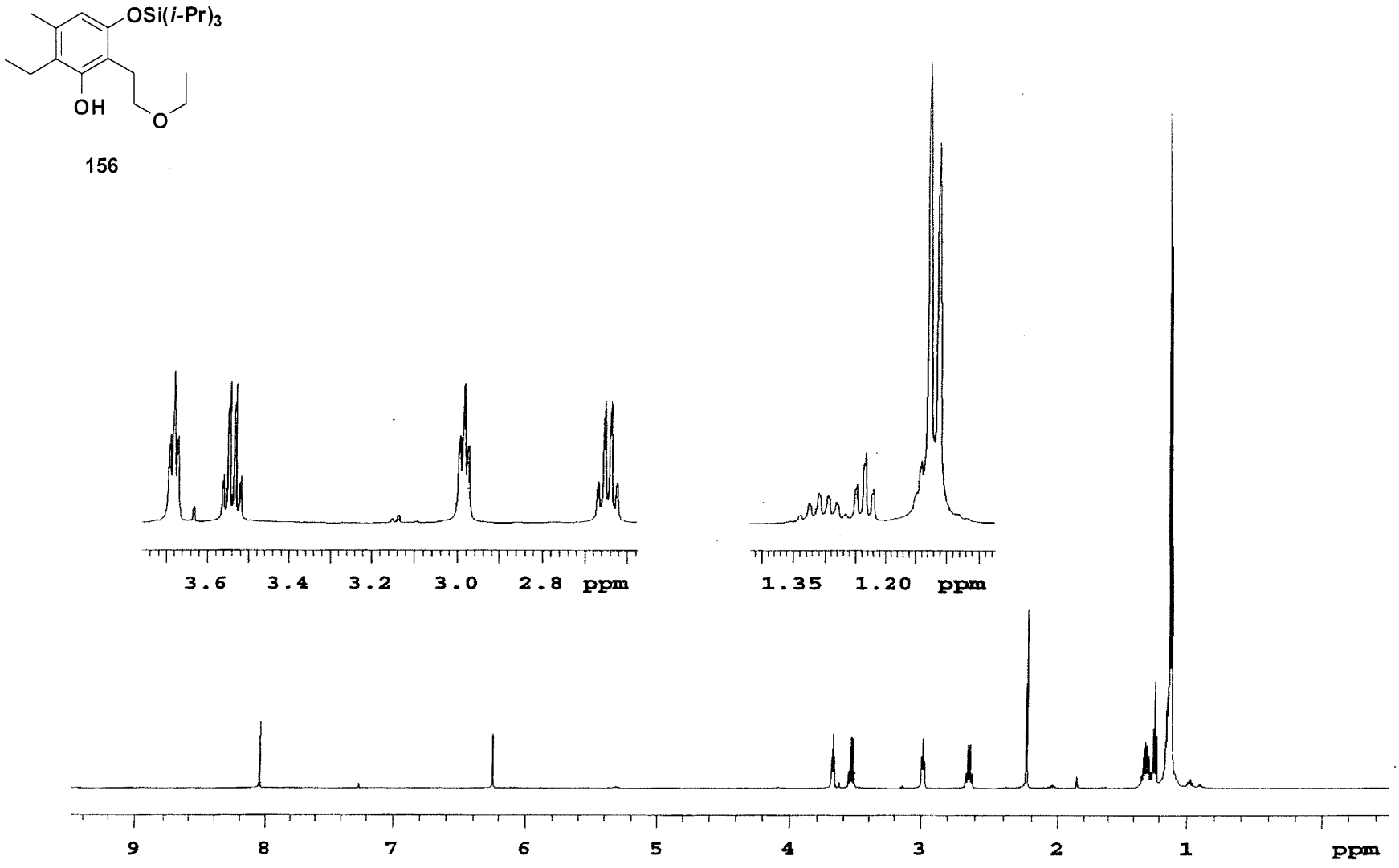
155

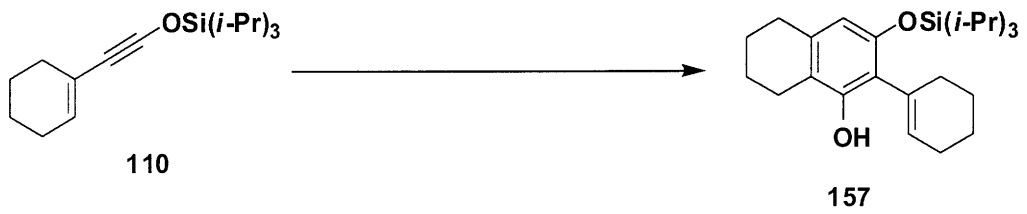


121 156

2-(2-Ethoxyethyl)-6-ethyl-5-methyl-3-(triisopropylsiloxy)phenol (156).

A 25-mL, two-necked, round-bottomed flask equipped with a rubber septum and argon inlet adapter was charged with siloxy alkyne **121** (0.154 g, 0.569 mmol) and 3 mL of THF. MeLi solution (1.51 M in Et_2O, 0.38 mL, 0.57 mmol) was added dropwise via syringe over 30 s, and the resulting solution was stirred at room temperature for 4 h. A solution of ketene **142** (0.151 g, 0.567 mmol) in 1 mL of THF was added via cannula in one portion (the flask was rinsed with 1 mL of THF), and the resulting solution was stirred at rt for an additional 2.5 h. The reaction mixture was poured into 5 mL of satd aq NH_4Cl, and the aqueous phase was separated and extracted with two 5-mL portions of Et_2O. The combined organic phases were washed with 10 mL of water and 10 mL of saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford 0.216 g of yellow oil. Column chromatography on 30 g of silica gel (elution with 0-2% EtOAc-hexanes) provided 0.100 g (46%) of phenol **156** as a yellow oil: IR (neat) 3327, 2945, 2867, 1615, 1574, 1499, 1462 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.05 (s, 1 H), 6.25 (s, 1 H), 3.68 (t, J = 5.6 Hz, 2 H), 3.51 (q, J = 7.0 Hz, 2 H), 2.99 (t, J = 5.3 Hz, 2 H), 2.64 (q, J = 7.5 Hz, 2 H) 2.24 (s, 3 H), 1.30 (septet, 3 H), 1.23 (t, J = 6.9 Hz, 3 H) 1.10-1.15 (m, 21 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.3, 152.1, 135.6, 124.1, 115.9, 112.4 73.2, 67.7, 25.9, 20.4, 20.1, 18.9, 15.7, 14.7, 13.8; HRMS-ESI (*m/z*): $[M + Na]^+$ calcd for $C_{22}H_{40}O_3Si$, 403.2639; found, 403.2658.

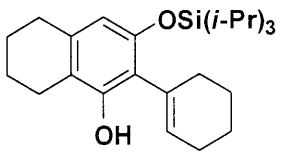

OSi(i-Pr)3
OH
O
156
3.6
3.4
3.2
3.0
2.8
ppm
1.35
1.20
ppm
9
8
7
6
5
4
3
2
1
ppm



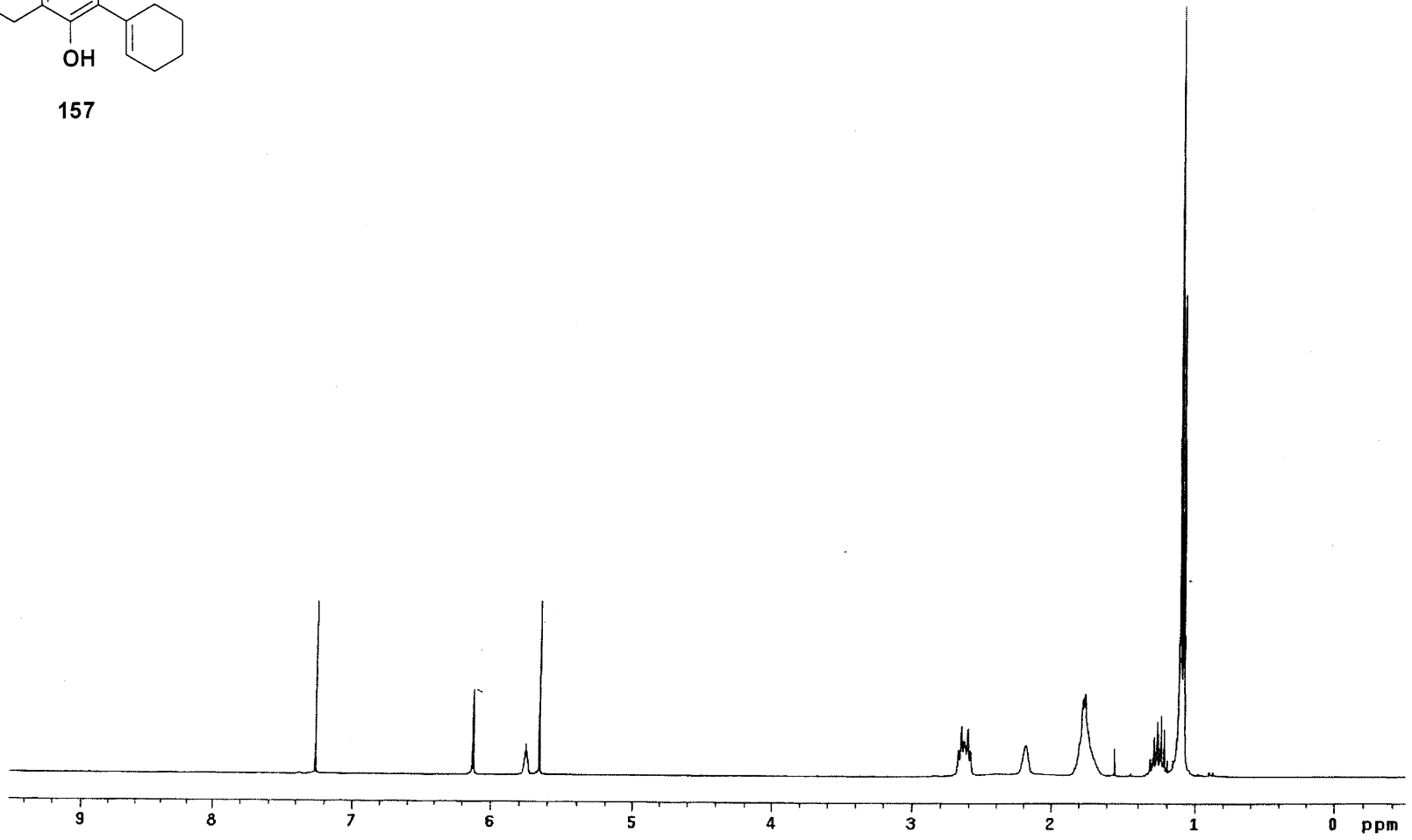
110 157

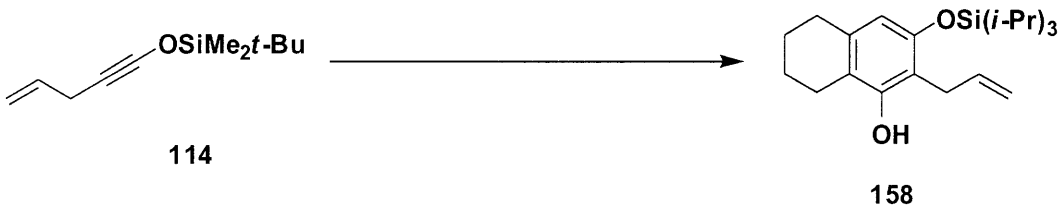
2-(1-Cyclohexenyl)-5,6,7,8-tetrahydro-3-(triisopropylsiloxy)-1-napthol (157).

A 25-mL, two-necked, round-bottomed flask equipped with a rubber septum and argon inlet adapter was charged with siloxy alkyne **110** (0.200 g, 0.718 mmol) and 3 mL of THF. MeLi solution (1.47 M in Et_2O, 0.49 mL, 0.72 mmol) was added dropwise via syringe over 10 s, and the resulting solution was stirred at room temperature for 3.5 h. A solution of ketene **20** (0.200 g, 0.718 mmol) in 1 mL of THF was added via cannula in one portion (the flask was rinsed with 1 mL of THF), and the resulting solution was stirred for an additional 75 min. The reaction mixture was poured into 5 mL of satd aq NH_4Cl soln, the aqueous phase was separated and extracted with two 3-mL portions of Et_2O, and the combined organic phases were washed with 5 mL of water and 5 mL of saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford 0.399 g of a yellow oil. Column chromatography on 30 g of silica gel (10-40% EtOAc-hexanes) provided 0.125 g (43%) of phenol **157** as a yellow oil: IR (neat) 3512, 2958, 2860, 1618, 1574, 1465 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.13 (s, 1 H), 5.73-5.78 (s, 1 H), 5.56 (s, 1 H), 2.56-2.69 (m, 4 H), 2.15-2.24 (m, 3 H), 1.65-1.85 (m, 9 H), 1.20-1.35 (sept, J = 7.4 Hz, 3 H), 1.10 (d, J = 7.2 Hz, 18 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.2, 150.6, 137.0, 133.9, 129.3, 118.4, 115.9, 110.3, 29.6, 28.6, 25.3, 22.84, 22.77 (2 C), 22.6, 21.8, 18.3, 13.5; HRMS-EI (*m/z*): $[M + Na]^+$ calcd for 423.2690; found, 423.2693.



157



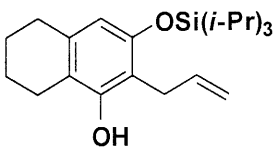


114

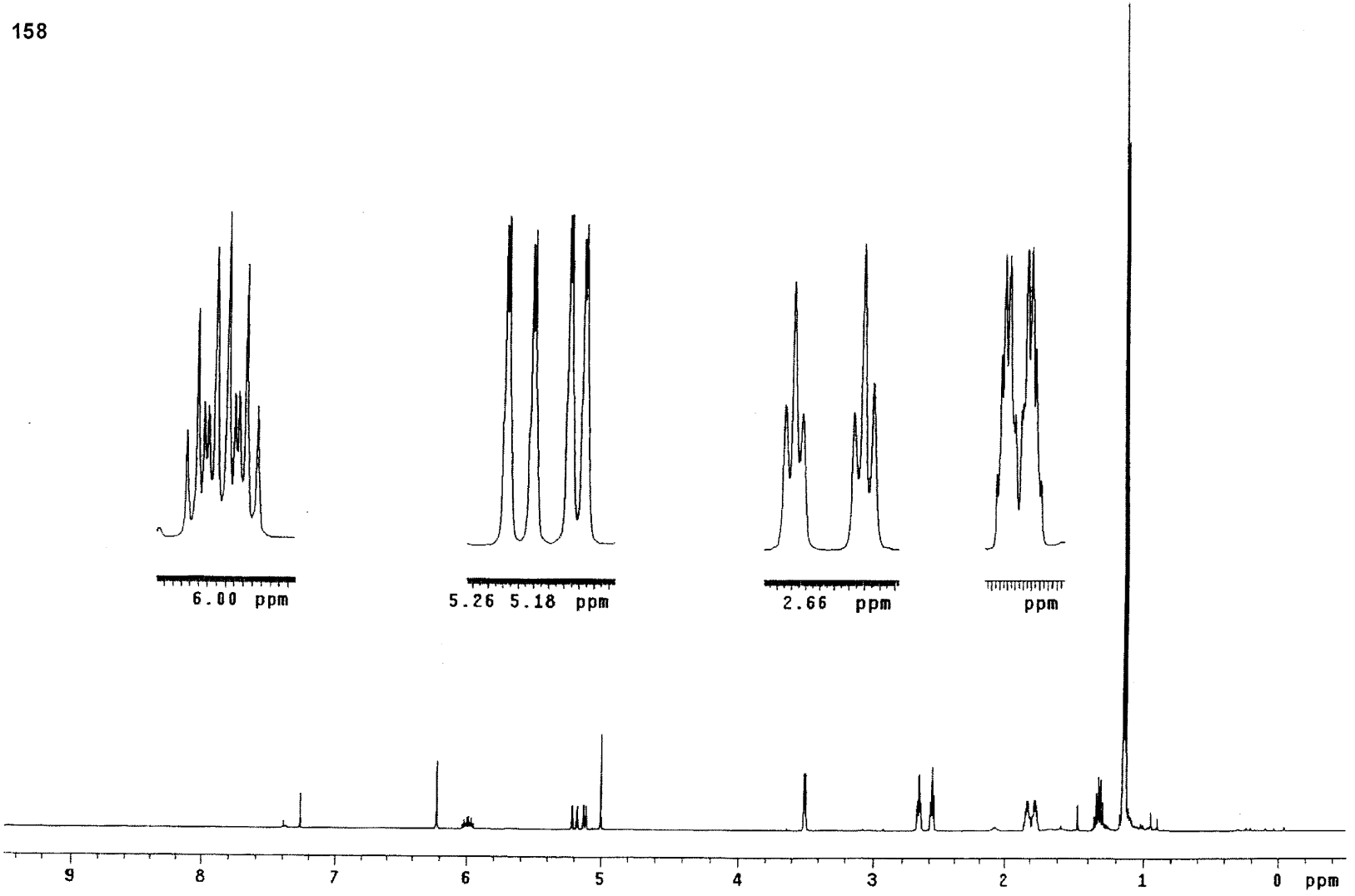
158

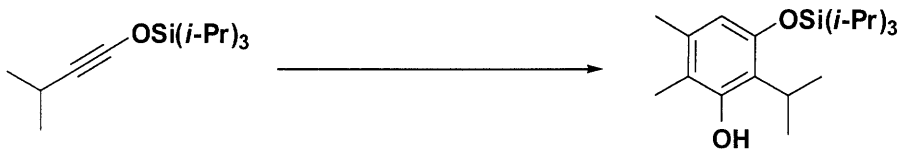
2-(3-Propenyl)-5,6,7,8-tetrahydro-3-(triisopropylsiloxy)-1-napthol (158).

A 25-mL, two-necked, round-bottomed flask equipped with a rubber septum and argon inlet adapter was charged with siloxy alkyne **114** (0.890 g, 4.53 mmol) and 6 mL of THF. MeLi solution (1.53 M in Et_2O, 3.0 mL, 4.6 mmol) was added dropwise via syringe over 10 s, and the resulting solution was stirred at room temperature for 30 min. A solution of ketene **20** (1.267 g, 4.551 mmol) in 3 mL of THF was added via cannula in one portion (the flask was rinsed with 1 mL of THF), and the resulting solution was stirred for an additional 70 min. The reaction mixture was poured into 20 mL of satd aq NH_4Cl soln, the aqueous phase was separated and extracted with two 10-mL portions of Et_2O, and the combined organic phases were washed with 20 mL of water and 20 mL of saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford 2.034 g of a yellow oil. Column chromatography on 100 g of silica gel (25% benzene-hexanes) provided 0.788 g (48%) of phenol **158** as a yellow oil: IR (neat) 3550, 3077, 2942, 2866, 1618, 1578, 1495, 1426 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.23 (s, 1 H), 6.00 (ddt, J = 17.2, 10.0, 6.2 Hz, 1 H), 5.20 (app dq, J = 17.3, 1.7 Hz, 1 H), 5.12 (app dq, J = 9.9, 1.7 Hz, 1 H), 5.01 (s, 1 H), 3.51 (app dt, J = 6.2, 1.6 Hz, 2 H), 2.67 (t, J = 6.1 Hz, 2 H), 2.58 (t, J = 6.1 Hz, 2 H), 1.71-1.88 (m, 4 H), 1.25-1.39 (m, 3 H), 1.15 (d, 7.2 Hz, 18 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.3, 151.9, 137.0, 136.5, 116.3, 115.7, 112.5, 110.8, 31.8, 29.9, 28.6, 23.7, 22.8, 18.3, 13.3; HRMS-ESI (*m/z*): $[M + Na]^+$ calcd for $C_{25}H_{43}O_2Si$, 383.2377; found, 383.2380.



158

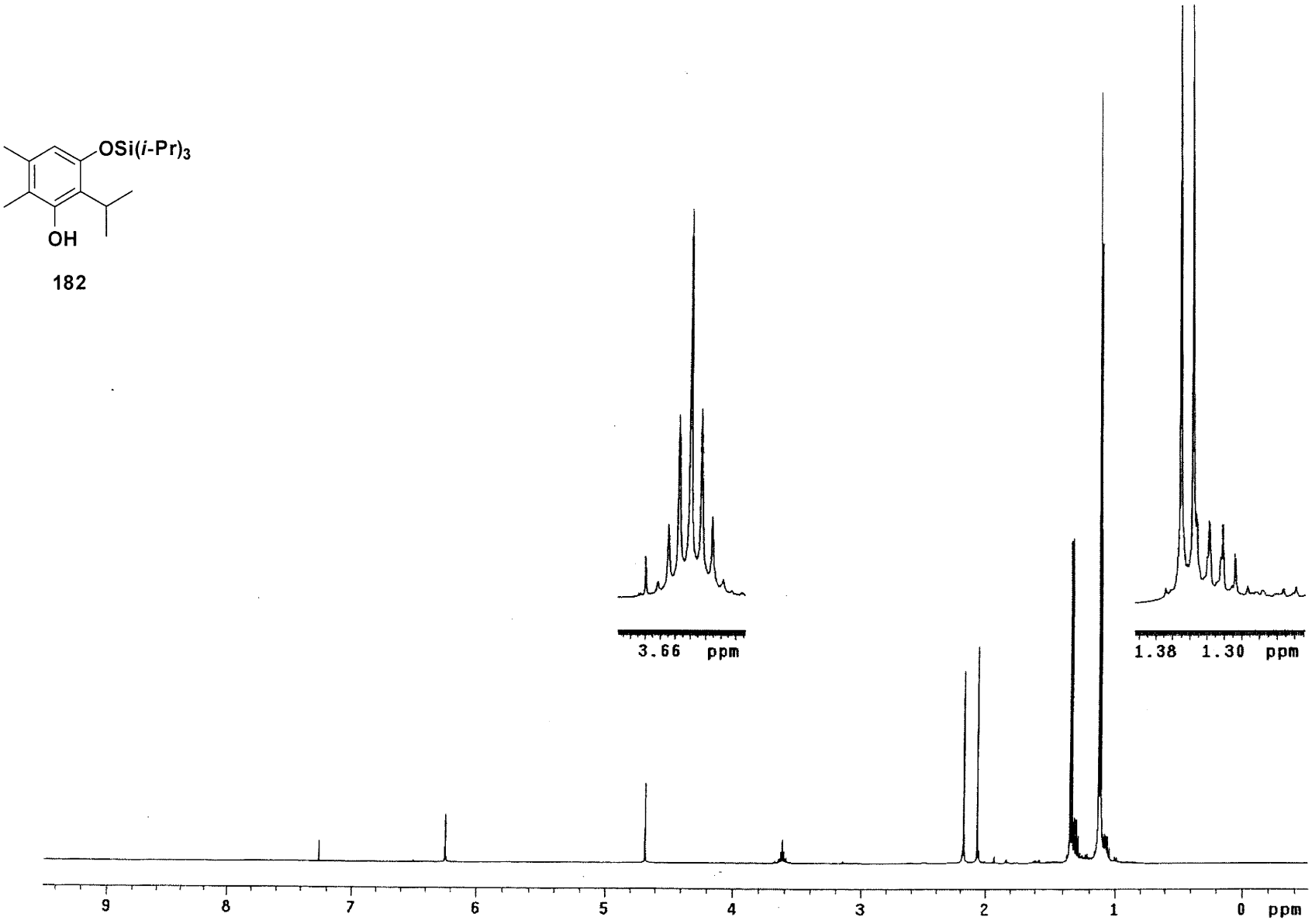


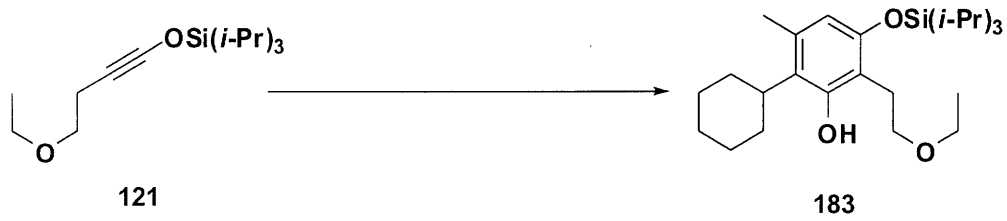


119 182

5,6-Dimethyl-2-isopropyl-3-(triisopropylsiloxy)phenol (182).

A 25-mL, two-necked, round-bottomed flask equipped with a rubber septum and argon inlet adapter was charged with siloxy alkyne **119** (0.171 g, 0.711 mmol) and 6 mL of THF. MeLi solution (1.42 M in Et_2O, 0.50 mL, 0.71 mmol) was added dropwise via syringe over 30 s, and the resulting solution was stirred at room temperature for 4 h, and then diluted with 10 mL of THF. A solution of ketene **21** (0.179 g, 0.709 mmol) in 3 mL of THF was added via cannula in one portion (the flask was rinsed with 1 mL of THF), and the resulting solution was stirred for an additional 2 h. The reaction mixture was poured into 30 mL of satd aq NH_4Cl, the aqueous phase was separated and extracted with two 20-mL portions of Et_2O, and the combined organic phases were washed with 20 mL of water and 20 mL of saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford 0.356 g of a yellow oil. The oil was diluted with 10 mL of CH_2Cl_2 and concentrated onto 1.5 g of silica gel which was transferred to the top of a column of 30 g of silica gel and eluted with 2% EtOAc-hexanes to provide 0.165 g (65%) of phenol **182** as a yellow oil: IR (neat) 3621, 3573, 2946, 1615, 1574, 1493, 1464 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.24 (s, 1 H), 4.68 (s, 1 H), 3.62 (septet, J = 7.2 Hz, 1 H), 2.18 (s, 3 H), 2.07 (s, 3 H), 1.34 (d, J = 7.2 Hz, 6 H), 1.32 (sept, J = 7.2 Hz, 3 H) 1.13 (d, J = 7.5 Hz, 18 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.5, 151.8, 134.5, 121.1, 114.5, 112.6, 24.7, 21.1, 20.5, 18.4, 13.4, 11.4; HRMS-ESI (*m/z*): $[M + Na]^+$ calcd for $C_{20}H_{36}O_2Si$, 359.2377; found, 359.2392.

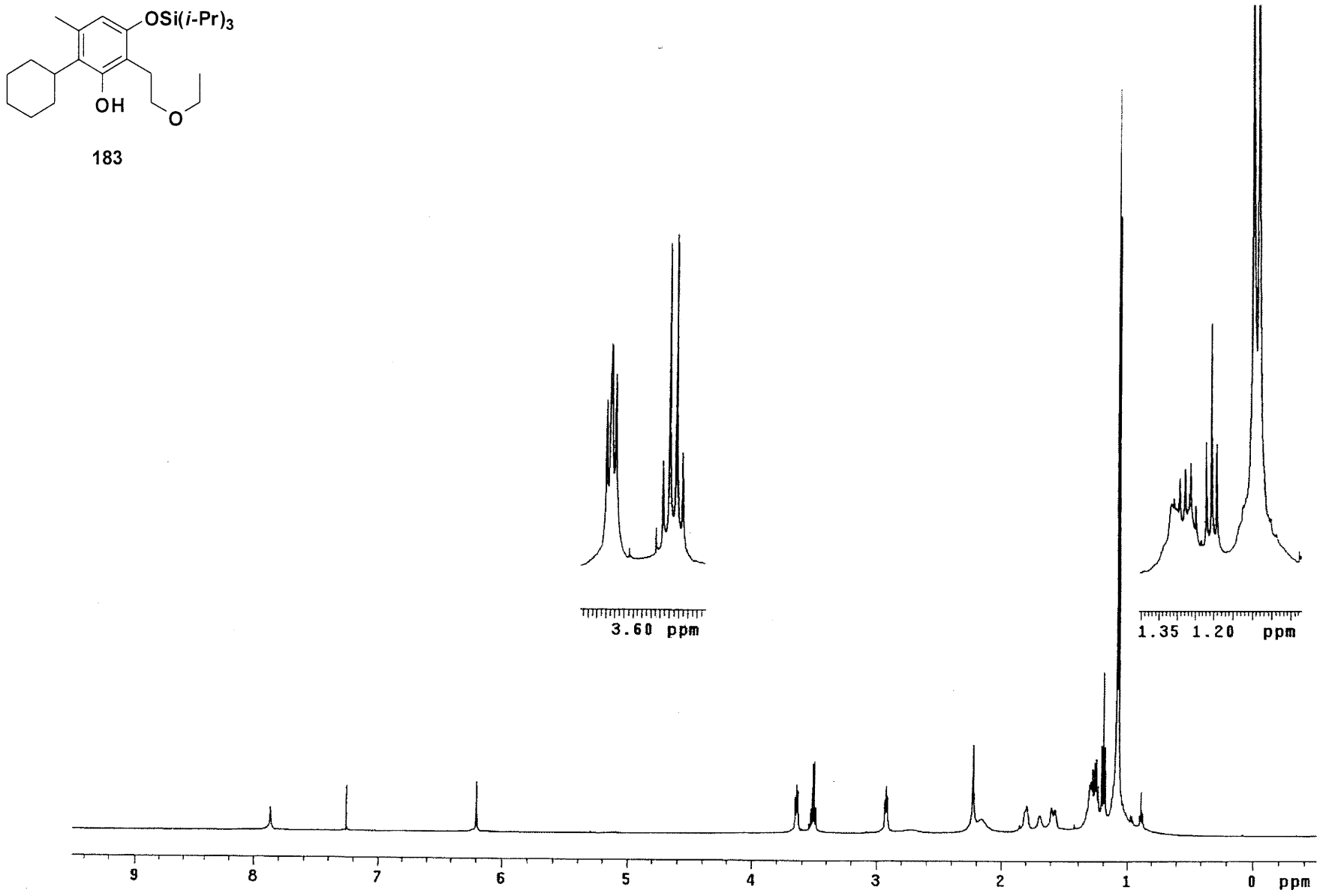

OSi(i-Pr)3
OH
182
3.66 ppm
1.38 1.30 ppm
9
8
7
6
5
4
3
2
1
0 ppm

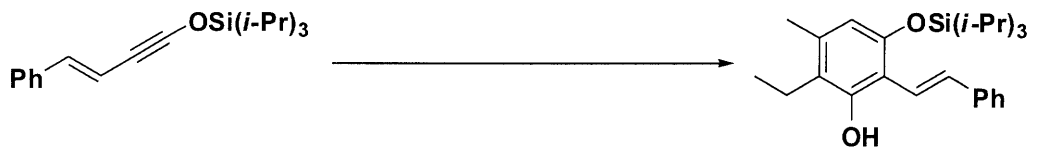


121 183

6-Cyclohexyl-2-(2-ethoxyethyl)-5-methyl-3-(triisopropylsiloxy)-phenol (183).

A 25-mL, two-necked, round-bottomed flask equipped with a rubber septum and an argon inlet adapter was charged with siloxy alkyne **121** (0.149 g, 0.551 mmol) and 3 mL of THF. MeLi solution (1.51 M in Et_2O, 0.37 mL, 0.559 mmol) was added dropwise via syringe over 30 s, and the resulting solution was stirred at room temperature for 4 h. A solution of ketene **143** (0.177 g, 0.552 mmol) in 1 mL of THF was added via cannula (the flask was rinsed with 1 mL of THF), and the resulting solution was stirred for an additional 2 h. The reaction mixture was then poured into a separatory funnel containing 10 mL of a satd aq NH_4Cl solution with the aid of 1 mL of Et_2O. The aqueous phase was extracted with two 5-mL portions of Et_2O, and the combined organic phases were washed with 10 mL of water and 10 mL of brine, dried over $MgSO_4$, filtered, and concentrated to afford 0.296 g of a yellow oil. Column chromatography on 30 g of silica gel (elution with 1% EtOAc-hexanes) provided 0.109 g (46%) of phenol **183** as a yellow oil: IR (CH_2Cl_2) 3301, 3053, 2926, 2867, 1610, 1566, 1422 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.87 (s, 1 H), 6.20 (s, 1 H), 3.65 (t, J = 5.2, 2 H), 3.51 (q, J = 7.0, 2 H), 2.93 (t, J = 5.5, 2 H), 2.10-2.25 (m, 4 H), 1.76-1.87 (m, 3 H), 1.66-1.73 (m, 2 H). 1.54-1.63 (m, 3 H), 0.98-1.38 (m, 26 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 156.4, 152.0, 135.4, 126.7, 117.0, 112.9, 73.1, 67.7, 40.3, 30.9, 28.4, 27.0, 25.9, 22.0, 18.9, 15.7, 13.7; HRMS-ESI (*m/z*): $[M + H]^+$ calcd for $C_{25}H_{43}O_2Si$: 435.3289; found: 435.3275.

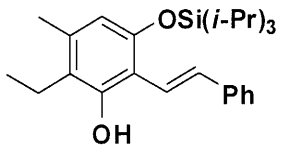

OSi(i-Pr)3
OH
O
183
3.60 ppm
1.35 1.20 ppm
9
8
7
6
5
4
3
2
1
0 ppm



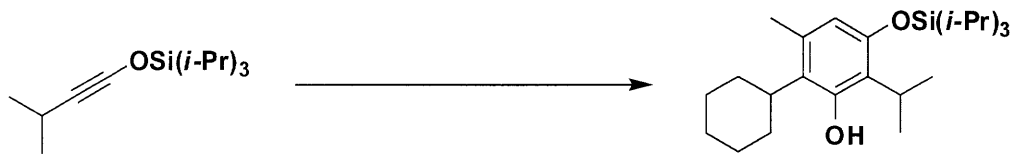
112 184

6-Ethyl-5-methyl-2-[(1*E*)-2-phenylethenyl]-3-(triisopropylsilyloxy)phenol (184).

A 25-mL, two-necked, round-bottomed flask equipped with a rubber septum and argon inlet adapter was charged with siloxy alkyne **112** (0.226 g, 0.752 mmol) and 3 mL of THF. MeLi solution (1.50 M in Et_2O, 0.50 mL, 0.75 mmol) was added dropwise via syringe over 30 sec, and the resulting solution was stirred at room temperature for 4 h. A solution of ketene **142** (0.200 g, 0.750 mmol) in 1 mL of THF was added via cannula in one portion (the flask was rinsed with 1 mL of THF), and the resulting solution was stirred for an additional 1 h. The reaction mixture was poured into 5 mL of satd aq NH_4Cl, the aqueous phase was separated and extracted with two 5-mL portions of Et_2O, and the combined organic phases were washed with 10 mL of water and 10 mL of saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford 0.416 g of an orange oil. Column chromatography on 15 g of silica gel (elution with 25-38% benzene-hexanes) afforded 0.111 g (37%) of phenol **184** as a pale yellow oil: IR (neat) 3552, 2942, 2867, 1621, 1570, 1463 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.50 (d, J = 7.7 Hz, 2 H), 7.37 (t, J = 7.7 Hz, 2 H), 7.31 (d, J = 17.1 Hz, 1 H), 7.25-7.29 (m, 1 H), 7.03 (d, J = 17.1, 1 H), 6.28 (s, 1 H), (s, 1 H), 2.64 (q, J = 7.5 Hz, 2 H), 2.26 (s, 3 H), 1.29 (sept, J = 7.6 Hz, 3 H) 1.15 (t, J = 7.6 Hz, 3 H), 1.11 (d, J = 7.4 Hz, 18 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.0, 151.6, 137.5, 136.4, 131.3, 128.6, 127.4, 126.1, 122.7, 121.5, 113.3, 112.5, 19.5, 19.4, 18.0, 13.7, 12.9; HRMS-ESI (*m/z*): M^+ calcd for $C_{26}H_{38}O_2Si$, 410.2636; found, 410.2646.



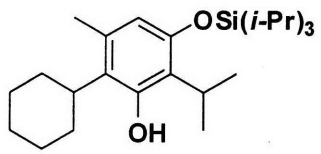
184



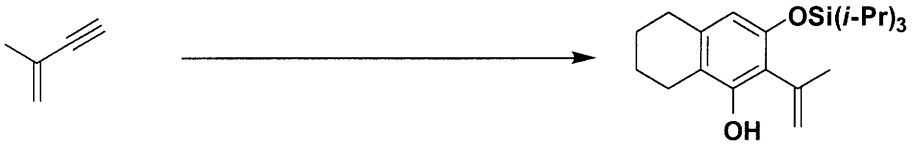
119 187

6-Cyclohexyl-2-isopropyl-5-methyl-3-(triisopropylsiloxy)-phenol (187).

A 25-mL, two-necked, round-bottomed flask equipped with a rubber septum and argon inlet adapter was charged with siloxy alkyne **119** (0.143 g, 0.595 mmol) and 3 mL of THF. MeLi solution (1.49 M in Et_2O, 0.40 mL, 0.60 mmol) was added dropwise via syringe over 30 sec, and the resulting solution was stirred at room temperature for 4 h. A solution of ketene **143** (0.191 g, 0.596 mmol) in 1 mL of THF was added via cannula in one portion (the flask was rinsed with 1 mL of THF), and the resulting solution was stirred for an additional 2 h. The reaction mixture was poured into 5 mL of satd aq NH_4Cl, the aqueous phase was separated and extracted with two 5-mL portions of Et_2O, and the combined organic phases were washed with 10 mL of water and 10 mL of saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford 0.395 g of a yellow oil. Column chromatography on 60 g of silica gel (gradient elution with 0-2% EtOAc-hexanes) afforded 0.173 g of material which was further purified by column chromatography on 30 g of silica gel (10% benzene-hexanes) to afford 0.082 g (34%) of phenol **187** as a pale yellow oil: IR (neat) 3638, 2927, 2867, 1609, 1565, 1453 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.22 (s, 1 H), 4.87 (s, 1 H), 3.64 (sept, J = 7.3 Hz, 1 H), 2.76-2.88 (br s, 1 H), 2.24 (s, 3 H), 1.92-2.03 (m, 2 H), 1.84-1.90 (m, 2 H), 1.71-1.80 (m, 4 H), 1.26-1.42 (m, 2 H), 1.37 (d, J = 7.5 H, 6 H), 1.34 (t, J = 7.5 Hz, 3 H), 1.15 (d, J = 7.4 Hz, 18 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.2, 152.1, 134.5, 124.6, 122.2, 113.7, 40.0, 31.5, 28.4, 27.1, 25.0, 21.8, 21.7, 18.9, 13.9.



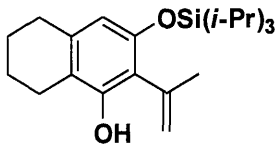
187



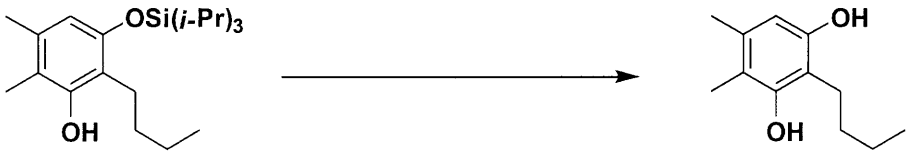
194

2-(2-Propenyl)-5,6,7,8-tetrahydro-3-(triisopropylsiloxy)-1-napthol (194).

A 25-mL, two-necked, round-bottomed flask equipped with a rubber septum and an argon inlet adapter was charged with a solution of 3-methyl-3-buten-1-yne (0.080 mL, 0.056 g, 0.84 mmol) in 3 mL of THF and cooled at -78 °C while 1.0 mL of freshly prepared LiTMP solution (1.0 M, 4.4 mmol) was added dropwise over 30 s. A 10-mL, two-necked, round-bottomed flask equipped with a rubber septum and an argon inlet adapter was charged with 0.27 mL of *t*-BuOOH solution (3.7 M in toluene, 1.0 mmol) and 3 mL of THF and cooled at -78 °C while 1.1 mL of freshly prepared LiTMP solution (1.0 M, 1.1 mmol) was added rapidly dropwise over 30 s. The resulting solution was then transferred via cannula over 1 min into the solution of lithium acetylide (the flask was rinsed with 1 mL of THF). The dry ice-acetone bath was replaced with an ice-water bath and the reaction mixture was stirred at 0 °C for 2.5 h. A solution of ketene **20** in 3 mL of THF was added over 30 s, and the resulting mixture was stirred at rt for 45 min, and then poured into 10 mL of satd aq NH_4Cl. The aq phase was extracted with two 10-mL portions of Et_2O, and the combined organic phases were washed with 20 mL of water and 20 mL of brine, dried over $MgSO_4$, filtered, and concentrated to yield 0.532 g of an orange oil. This material was diluted with CH_2Cl_2 and concentrated onto 2 g of silica gel and applied to the top of a column of 40 g of silica gel. Gradient elution (0-10% EtOAc-hexanes) provided 0.287 g of a yellow oil. Further purification by column chromatography on 40 g of silica gel (elution with 25% benzene-hexanes) yielded 0.106 g (35%) of phenol **194** as a yellow oil: IR (CH_2Cl_2) 3506, 3053, 2945, 1616, 1570, 1494 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.17 (s, 1 H), 5.73 (s, 1 H), 5.46 (s, 1 H), 5.05 (s, 1 H), 2.68 (t, J = 6.1 Hz, 2 H), 2.64 (t, J = 6.1 Hz, 2 H), 2.11 (s, 3 H), 1.74-1.85 (m, 4 H), 1.30 (sept, J = 7.3 Hz, 3 H), 1.13 (d, J = 7.3 Hz, 18 H); ^{13}C NMR (75 MHz, C_6D_6) δ 150.9, 150.1, 141.9, 137.5, 117.8, 117.4, 116.2, 110.5, 30.1, 23.9, 23.3, 23.24, 23.22, 18.3, 13.3; HRMS-ESI (*m/z*): $[M + H]^+$ calcd for $C_{22}H_{36}O_2Si$, 361.2557; found, 261.2545.



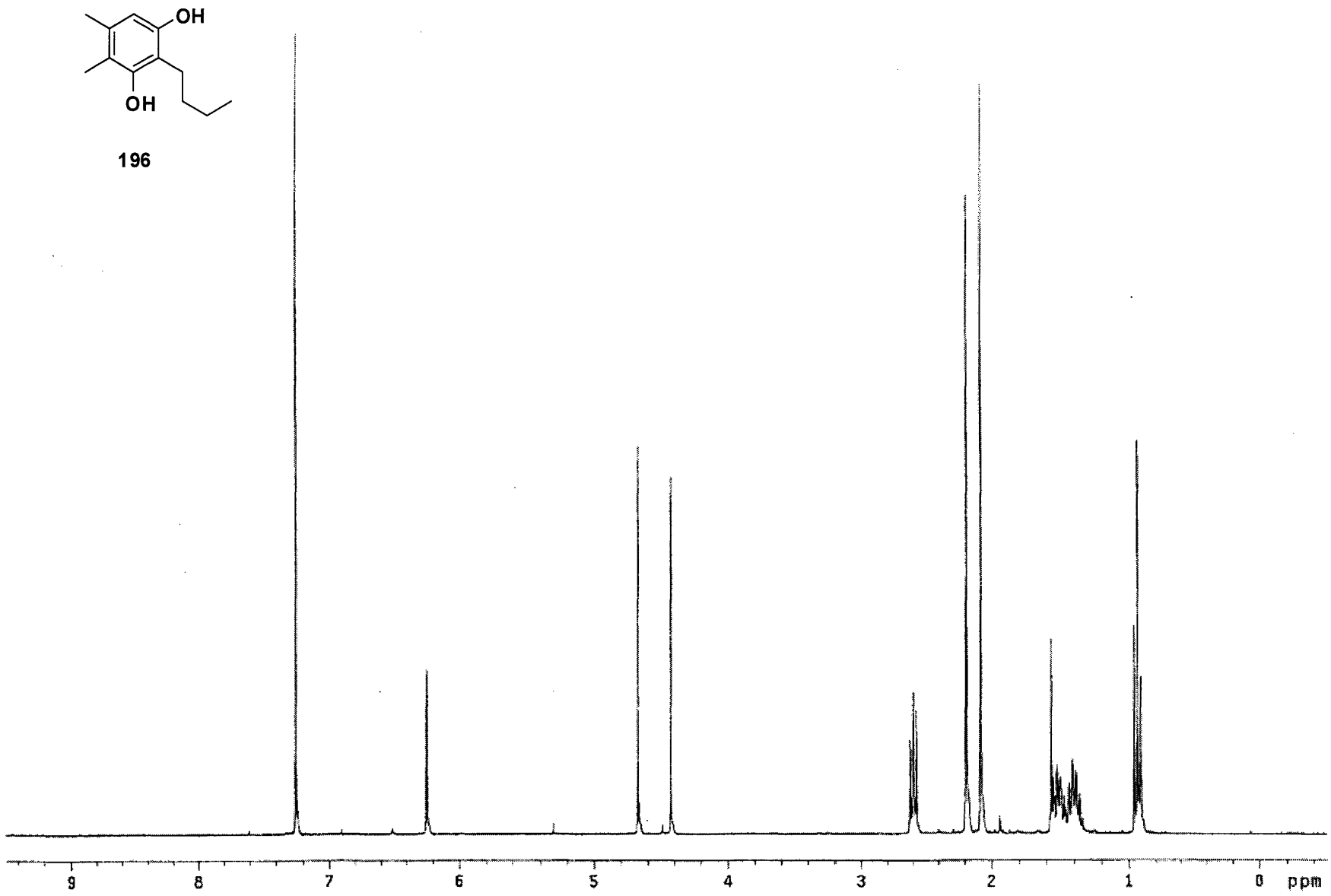
194

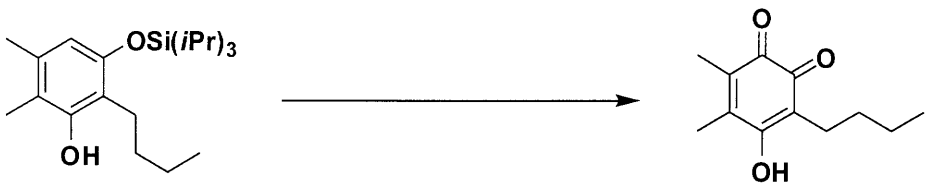


150 196

2-Butyl-5,6-dimethylresorcinol (196).

A 10-mL, two-necked, round-bottomed flask equipped with a rubber septum and argon inlet adapter was charged with a solution of phenol **150** (0.200 g, 0.570 mmol) in 2 mL of THF and stirred at 0 °C while 0.85 mL of TBAF solution (1.0 M in THF, 0.85 mmol) was added. The reaction mixture was allowed to warm slowly to rt over 2h, stirred an additional 30 min, and then partitioned between 5 mL Et_2O and 5 mL water. The aq phase was extracted with 5 mL of Et_2O, and the combined organic phases were washed with 5 mL of brine, dried over $MgSO_4$, filtered, and concentrated to yield 0.303 g of an orange-brown oil. Column chromatography on 15 g of silica gel (elution with 10% EtOAc-hexanes) afforded 0.086 g (77%) of the resorcinol **196** as a white solid, mp 126-129 °C: IR (neat) 3426, 3054, 2987, 1631, 1422 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.25 (s, 1 H), 4.67 (s, 1 H), 4.43 (s, 1 H), 2.59 (t, J = 7.6 Hz, 2 H), 2.19 (s, 3 H), 2.08 (s, 3 H), 1.33-1.57 (m, 4 H), 0.93 (t, J = 7.2 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.6, 151.8, 135.5, 114.2, 112.5, 109.3, 31.8, 23.5, 23.1, 20.3, 14.3, 11.6; HRMS-ESI (*m/z*): $[M + H]^+$ calcd for $C_{12}H_{18}O_2$, 195.1385; found, 195.1386.

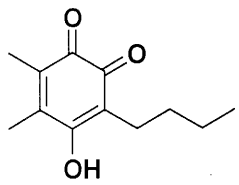

OH
OH
196
9
8
7
6
5
4
3
2
1
0
ppm



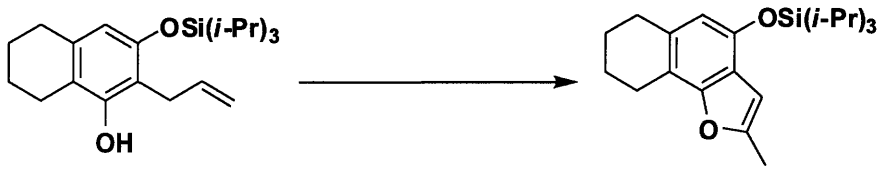
150 199

3-Butyl-4-hydroxy-5,6-dimethyl-*ortho*-quinone (199).

A 100-mL, two-necked, round-bottomed flask equipped with a rubber septum and 50-mL addition funnel equipped with an argon inlet adapter was charged with a solution of phenol **150** (0.187 g, 0.533 mmol) in 30 mL of acetone and stirred at room temperature while a solution of Na_2HPO_4 (0.56 g, 3.9 mmol) and potassium nitrosodisulfonate (0.575 g, 2.1 mmol) in 20 mL of water was added dropwise over 3 min. The resulting solution was stirred for 24 h and then extracted with three 30-mL portions of EtOAc. The combined organic phases were dried over $MgSO_4$, filtered, and concentrated to afford 0.163 g of an orange oil which was diluted with hexanes and concentrated onto 0.450 g of silica gel. This material was applied to the top of a column of 15 g of silica gel and eluted with 0-10% EtOAc-hexanes to provide 0.146 of an orange oil. Further concentration (0.2-0.3 mmHg, rt, 1 h) followed by additional column chromatography on 10 g of silica gel (elution with 5% EtOAc-hexanes) yielded 0.073 g (66%) of quinone **199** as fluorescent orange crystals, mp 63-68 °C: IR (KBr) 3392, 2956, 2928, 2859, 1650, 1633, 1620, 1365; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.94 (s, 1 H), 2.39-2.46 (m, 2 H), 2.04 (t, J = 1.1 Hz, 3 H), 2.03 (t, J = 1.1 Hz, 3 H), 1.26-1.49 (m, 4 H), 0.90 (t, J = 7.1 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 187.6, 184.0, 150.8, 143.8, 136.3, 121.8, 30.7, 23.01, 22.95, 14.1, 13.1, 11.8; HRMS-ESI (*m/z*): $[M + H]^+$ calcd for $C_{12}H_{16}O_3$, 209.1172; found, 209.1171.



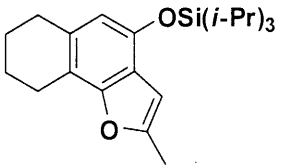
199



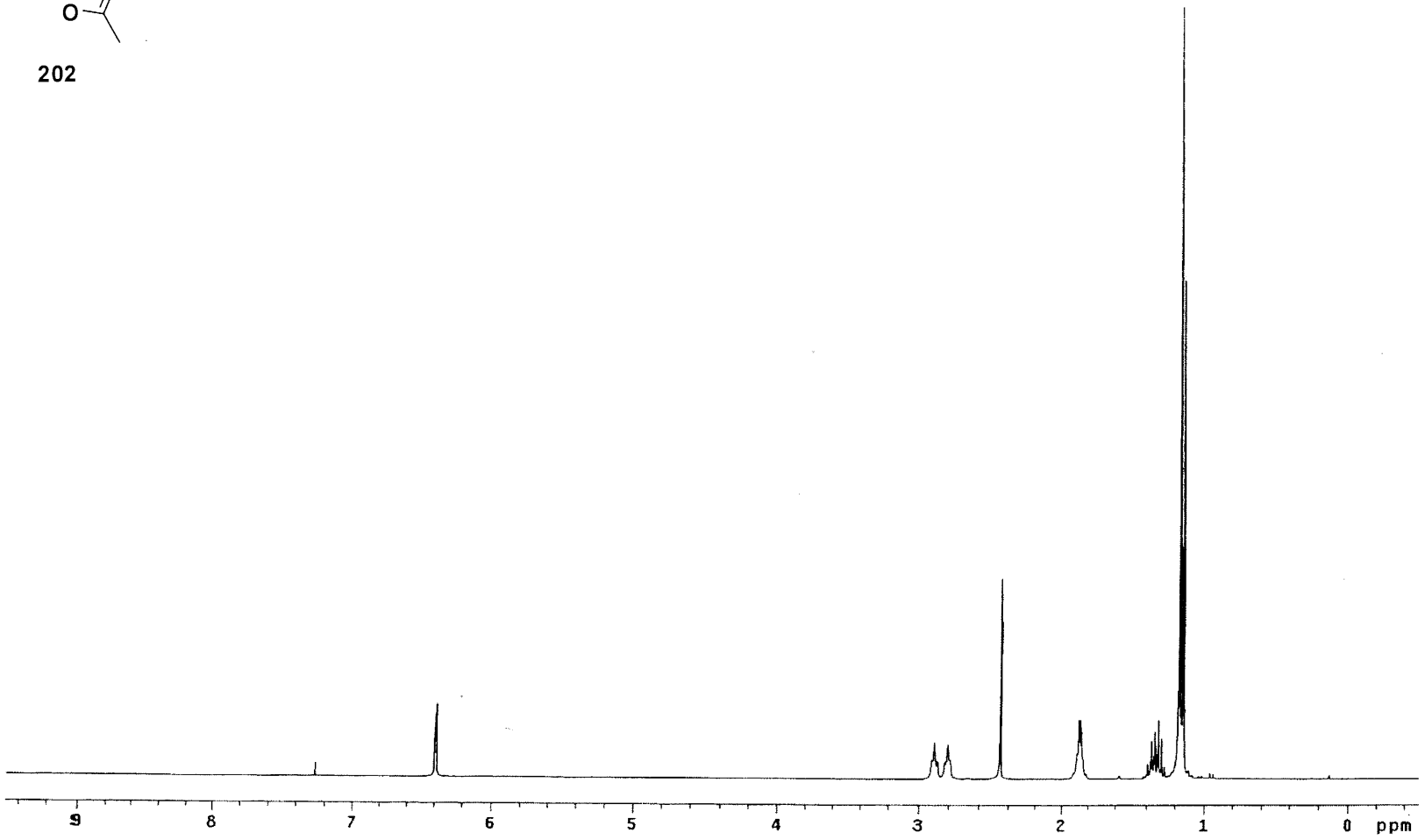
158 202

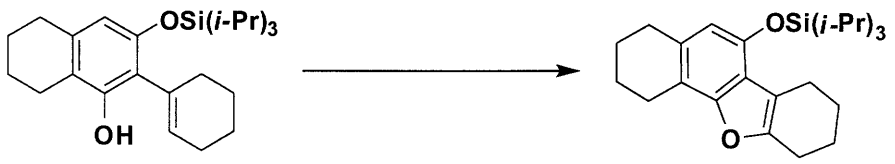
2-Methyl-6,7,8,9-tetrahydro-4-(triisopropylsiloxy)naphtho[1,2-b]furan (202).

A 25-mL, two-necked, round-bottomed flask equipped with a rubber septum and cold-finger condenser fitted with an argon inlet adapter was charged with a solution of $PdCl_2(MeCN)_2$ (0.016 g, 0.062 mmol), LiCl (0.211 g, 4.98 mmol), and benzoquinone (0.061 g, 0.564 mmol) in 8 mL of THF. A solution of phenol **158** (0.200 g, 0.555 mmol) in 2 mL of THF was added in one portion, the rubber septum was replaced by a glass stopper, and the resulting mixture was heated at reflux for 3.5 h and then allowed to cool to room temperature. The reaction mixture was filtered through 5 g of silica gel with the aid of 75 mL of hexanes and then concentrated to yield 0.220 g of a mixture of a black solid and orange oil. This material was diluted with 10 mL of Et_2O and concentrated onto 0.5 g of silica gel which was transferred to the top of a column of 20 g of silica gel and eluted with 25% benzene-hexanes to provide 0.119 g (60%) of tetrahydronaphthofuran **202** as a yellow oil: IR (neat) 2943, 2866, 1622, 1592, 1508, 1463, 1446 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.38-6.41 (m, 2 H), 2.86-2.93 (m, 2 H), 2.77-2.84 (m, 2 H), 2.45 (d, J = 1.1 Hz, 3 H), 1.81-1.91 (m, 4 H), 1.27-1.41 (m, 3 H), 1.16 (d, J = 6.9 Hz, 18 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.8, 153.0, 146.3, 132.6, 119.1, 113.7, 112.5, 110.6, 29.7, 23.7, 22.9, 22.7, 18.3, 14.3, 13.1; HRMS-ESI (*m/z*): $[M + Na]^+$ calcd for $C_{22}H_{34}O_2Si$, 381.2220; found, 381.2236.



202

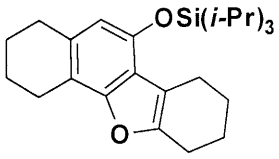




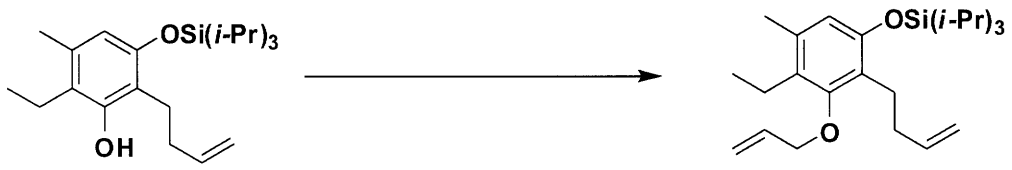
157 209

5-Triisopropylsiloxy-1,2,3,4,7,8,9,10-octahydrobenzo[d]naphtho[1,2-b]furan (209).

A 10-mL, one-necked, round-bottomed flask equipped with a rubber septum and argon inlet needle was charged with a solution of phenol **157** (125 mg, 0.311 mmol) in 2 mL of CH_2Cl_2 and stirred at rt while $VO(acac)_2$ (6 mg, 0.02 mmol) was added. The mixture was stirred for 5 min, and then 0.100 mL of anhydrous TBHP solution (4.0 M in toluene, 0.400 mmol) was added, the rubber septum was replaced by a cold finger condenser, and the mixture was heated at reflux for 4.5 h. Additional $VO(acac)_2$ (6 mg, 0.02 mmol) and TBHP (4.0 M in toluene, 0.100 mL, 0.400 mmol) were added and heating was continued for 2 h, and then TFA (0.060 mL, 92 mg, 0.81 mmol) was added and the reaction mixture was heated at reflux an additional 21 h, and then allowed to cool and concentrated to afford 0.260 g of a viscous blue-green oil. The oil was diluted with CH_2Cl_2 and concentrated onto 0.6 g of silica gel which was transferred to the top of a column of 20 g of silica gel and eluted with 5% benzene-hexanes to provide 0.068 mg (55%) of tetracycle **209** as a yellow oil: IR (neat) 2940, 1618, 1592, 1507, 1463, 1448 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.30 (s, 1 H), 2.80-2.87 (m, 4 H), 2.74-2.78 (m, 2 H), 2.68-2.72 (m, 2 H), 1.77-1.92 (m, 8 H), 1.34 (sept, J = 7.8 Hz, 3 H), 1.14 (d, J = 7.5 Hz, 18 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.9, 151.9, 148.1, 132.8, 118.2, 114.1, 113.2, 112.2, 30.2, 24.2 (2 C), 23.8, 23.54, 23.48, 23.2, 23.1, 18.9, 14.0; HRMS-ESI (*m/z*): $[M + H]^+$ calcd for $C_{25}H_{38}O_2Si$, 399.2714; found, 399.2716.



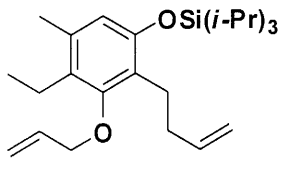
209



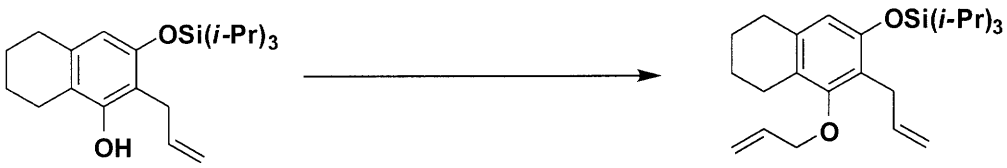
152 210

2-Propenyl 2-(3-butenyl)-6-ethyl-5-methyl-3-triisopropylsiloxy-phenyl ether (210).

A 10-mL, one-necked, round-bottomed flask equipped with a rubber septum and argon inlet needle was charged with K_2CO_3 (0.100 g, 0.723 mmol) and NaI (0.021 g, 0.14 mmol) and flame dried under vacuum. The flask was back-filled with argon and allowed to cool to rt, and then a solution of phenol **152** (0.083 g, 0.23 mol) in 2 mL of acetone was added. The mixture was stirred for 5 min, allyl bromide (0.100 mL, 0.140 g, 1.16 mmol) was added, the septum was replaced by a cold finger condenser, and the reaction mixture was heated at reflux for 18 h. Additional allyl bromide was added (0.100 mL, 0.140 g, 1.16 mmol), and heating was continued for an additional 18 h, and then the reaction mixture was allowed to cool to rt and partitioned between 5 mL of Et_2O and 5 mL of water. The aq phase was extracted with two 5-mL portions of Et_2O, the combined organic phases were dried over $MgSO_4$, filtered, and concentrated to yield 0.132 g of an orange oil. The oil was diluted with hexanes and concentrated onto 0.3 g of silica gel which was transferred to the top of a column of 10 g of silica gel and eluted with 0-10% benzene-hexanes to provide 0.060 g (65%) of allyl ether **210** as a yellow oil: IR (neat) 3077, 2945, 2867, 1640, 1603, 1569, 1479 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.41 (s, 1 H), 6.11 (ddt, J = 17.2, 10.4, 5.2, 1 H) 5.91 (ddt, J = 17.1, 10.2, 6.6, 1 H), 5.46 (app dq, J = 17.1, 1.7 Hz, 1 H), 5.26 (app dq, J = 10.4, 1.5 Hz, 1 H), 5.04 (app dq, J = 17.1, 1.7 Hz, 1 H), 4.96 (dm, J = 10.1 Hz, 1 H), 4.30 (dt, J = 5.2, 1.6 Hz, 2 H), 2.63-2.71 (m, 2 H), 2.58 (q, J = 7.5, 2 H), 2.25-2.34 (m, 2 H), 2.23 (s, 3 H), 1.22-1.36 (m, 3 H), 1.08-1.14 (m, 21 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.6, 152.7, 139.4, 134.8, 134.6, 128.5, 123.3, 116.7, 116.4, 114.3, 75.3, 34.4, 24.9, 20.1, 19.6, 18.4, 15.0, 13.4; HRMS-ESI (*m/z*): $[M + H]^+$ calcd for $C_{25}H_{42}O_2Si$, 403.3027; found, 403.3017.



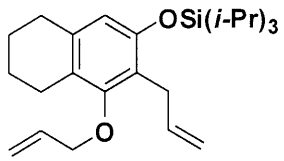
210



158 211

2-Propenyl 2-(2-Propenyl)-3-triisopropylsiloxy-5,6,7,8-tetrahydronaphthyl ether (211).

A 10-mL, one-necked, round-bottomed flask equipped with a rubber septum and argon inlet needle was charged with K_2CO_3 (0.100 g, 0.723 mmol) and NaI (0.021 g, 0.14 mmol) and flame dried under vacuum. The flask was back-filled with argon and allowed to cool to rt, and then a solution of naphthol **158** (0.083 g, 0.23 mol) in 2 mL of acetone was added. The mixture was stirred for 5 min, allyl bromide (0.100 mL, 0.140 g, 1.16 mmol) was added, the septum was replaced with a cold finger condenser, and the reaction mixture was heated at reflux for 18 h. Additional allyl bromide was added (0.100 mL, 0.140 g, 1.16 mmol), and heating was continued for an additional 18 h, and then the reaction mixture was allowed to cool to rt and partitioned between 5 mL of Et_2O and 5 mL of water. The aq phase was extracted with two 5-mL portions of Et_2O, the combined organic phases were dried over $MgSO_4$, filtered, and concentrated to yield 0.171 g of a yellow oil. The oil was diluted with hexanes and concentrated onto 0.3 g of silica gel which was transferred to the top of a column of 10 g of silica gel and eluted with 5-10% benzene-hexanes to provide 0.068 g (74%) of allyl ether **211** as a yellow oil: IR (neat) 3078, 2942, 2867, 1637, 1605, 1573, 1477, 1425 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.35 (s, 1 H), 6.11 (ddt, J = 17.1, 10.5, 5.3, 1 H) 6.00 (ddt, J = 17.1, 10.0, 6.0, 1 H), 5.43 (app dq, J = 17.2, 1.7 Hz, 1 H), 5.24 (app dq, J = 10.5, 1.5 Hz, 1 H), 4.99 (app dq, J = 17.1, 1.8 Hz, 1 H), 4.94 (app dq, J = 10.1, 1.7 Hz, 1 H), 4.38 (dt, J = 5.3, 1.6 Hz, 2 H), 3.41 (dt, J = 6.0, 1.6 Hz, 2 H), 2.64-2.71 (m, 4 H), 1.72-1.78 (m, 4 H), 1.24-1.36 (m, 3 H), 1.11 (d, J = 7.1 Hz, 18 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.3, 152.6, 137.9, 136.4, 134.6, 130.3, 123.1, 121.1, 116.8, 114.4, 73.4, 29.8, 29.2, 23.7, 23.4, 23.3, 18.4, 13.3; HRMS-ESI (*m/z*): $[M + H]^+$ calcd for $C_{25}H_{40}O_2Si$, 401.2870; found, 401.2861.

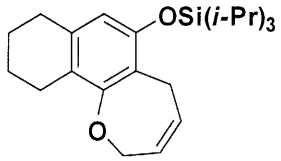


211

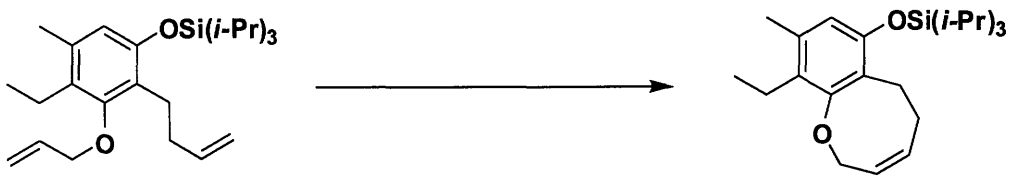
211 213

6-Triisopropylsiloxy-2,5,8,9,10,11-hexahydronaphtho[1,2-*b*]oxepine (213).

A 50-mL, one-necked, round-bottomed flask equipped with a rubber septum and argon inlet needle was charged with the Grubbs second generation ruthenium metathesis catalyst **212**, (0.006 g, 0.007 mmol). The flask was evacuated, backfilled with argon, and then charged with 20 mL of CH_2Cl_2. A solution of allyl ether **211** (0.056 g, 0.14 mmol) in 10 mL of CH_2Cl_2 was added, the septum was replaced with a cold finger reflux condenser with an argon inlet and the reaction mixture was heated at reflux for 1 h, and then allowed to cool and concentrated to yield 0.080 g of a brown oil. Column chromatography on 5 g of silica gel (elution with 1% EtOAc-hexanes) afforded 0.050 g (96%) of the oxopine **213** as a yellow oil: IR (neat) 2944, 2867, 1609, 1572, 1481 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.34 (s, 1 H), 5.77-5.88 (m, 1 H), 5.40 (dm, J = 11.3, 1 H), 4.52 (app quint, J = 2.4, 2 H), 3.51 (dd, J = 5.3, 2.0 Hz, 2 H), 2.62-2.69 (m, 4 H), 1.70-1.80 (m, 4 H), 1.21-1.34 (m, 3 H), 1.11 (d, J = 7.0 Hz, 18 H), ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.3, 150.4, 136.2, 127.7, 126.6, 124.5, 122.4, 114.9, 69.9, 29.8, 23.4, 23.3, 23.2, 23.1, 18.3, 13.3; HRMS-ESI (*m/z*): $[M + H]^+$ calcd for $C_{23}H_{36}O_2Si$, 373.2557; found, 373.2567.



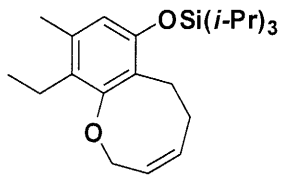
213



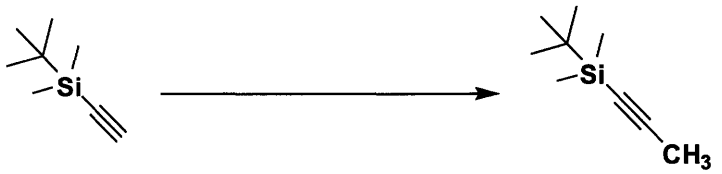
210 214

10-Ethyl-9-methyl-3-triisopropylsiloxy-5,6-dihydro-2H-benzo[*b*]oxocine (214).

A 50-mL, one-necked, round-bottomed flask equipped with a rubber septum and argon inlet needle was charged with the Grubbs second generation ruthenium metathesis catalyst **212**, (0.005 g, 0.006 mmol). The flask was evacuated, backfilled with argon, and then charged with 15 mL of CH_2Cl_2. A solution of allyl ether **214** (0.044 g, 0.11 mmol) in 10 mL of CH_2Cl_2 was added, the septum was replaced with a cold finger reflux condenser with an argon inlet and the reaction mixture was heated at reflux for 1 h, and then allowed to cool and concentrated to yield 0.053 g of a brown oil. Column chromatography on 5 g of silica gel (elution with 1% EtOAc-hexanes) afforded 0.039 g (95%) of the oxocine **214** as a yellow oil: IR (neat) 2944, 2867, 1603, 1569, 1465 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.41 (s, 1 H), 5.81 (dtt, J = 11.4, 6.7, 1.5 Hz, 1 H), 5.40 (dtt, J = 11.3, 4.5, 1.2 Hz, 1 H), 4.68 (dd, J = 4.6, 1.3, 2 H), 2.97 (d, J = 6.3 Hz, 1 H), 2.94 (d, J = 4.8 Hz, 1 H), 2.60-2.69 (m, 2 H), 2.59 (q, J = 7.5 Hz, 2 H), 2.23 (s, 3 H), 1.21-1.35 (m, 3 H), 1.11 (d, J = 7.0 Hz, 18 H), 1.12 (t, J = 7.2 Hz, 3 H) ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.8, 152.0, 134.7, 133.5, 128.2, 125.3, 122.4, 116.0, 71.9, 28.0, 25.7, 19.9, 19.6, 18.4, 14.9, 13.3; HRMS-ESI (*m/z*): $[M + H]^+$ calcd for $C_{25}H_{38}O_2Si$, 375.2714; found, 375.2713.



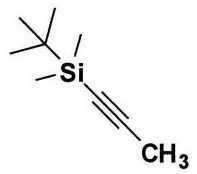
214



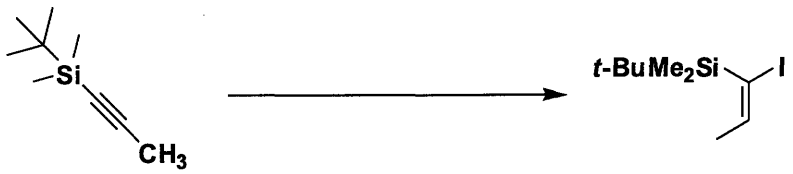
263 264

1-(*tert*-Butyldimethylsilyl)-1-propyne (264).

A 250-mL, two-necked, round-bottomed flask equipped with an argon inlet adapter and a rubber septum was charged with a solution of (*tert*-butyldimethylsilyl)acetylene (4.30 g, 30.6 mmol) in 100 mL of THF and cooled at -78 °C while *n*-BuLi solution (2.68 M in hexanes, 23 mL, 62 mmol) was added. The mixture was stirred at rt for 90 min, and then recooled at -78 °C while HMPA (11 mL, 11 g, 63 mmol) and iodomethane (9.5 mL, 22 g, 150 mmol) were added sequentially. The resulting mixture was stirred at rt overnight and then poured into 100 mL of water. The aqueous phase was separated and extracted with three 50-mL portions of Et_2O, and then the combined organic phases were washed with 100 mL of water and 100 mL of brine, dried over $MgSO_4$, filtered, and concentrated (0 °C, 30 mmHg) to afford 13 g of a yellow oil. Short-path distillation (40 mmHg, 65-73 °C) afforded 4.158 g (88%) of the alkyne **264** as a colorless oil with spectral characteristics consistent with those previously reported:[96] IR (neat) 2182, 1471, 1463 cm^{-1}; ^1H NMR (300 MHZ, $CDCl_3$) δ 1.88 (s, 3 H), 0.92 (s, 9 H), 0.07 (s, 6 H); ^{13}C NMR (75 MHz, CDCl3) δ 103.6, 82.0, 26.3, 16.7, 5.1, -4.3.



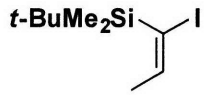
264



264 268

(*E*)-1-Iodo-1-(*tert*-butyldimethylsilyl)-1-propene (268).

A 100-mL, one-necked, round-bottomed flask fitted with a rubber septum and an argon inlet needle was charged with a solution of alkyne **264** (3.608 g, 23.37 mmol) in 26 mL of Et_2O and stirred at rt while 26 mL of DIBAL solution (1.0 M in hexanes, 26 mmol) was added rapidly dropwise. The septum was replaced with a cold-finger condenser with an integrated argon inlet and the reaction mixture was heated at reflux for 20 h, and then allowed to cool to rt. The condenser was replaced with a rubber septum and the reaction mixture was transferred by cannula to a 250-mL, two-necked, round-bottomed flask fitted with an argon inlet adapter and a 50-mL addition funnel with the aid of 10 mL of Et_2O, and cooled at -78 °C while pyridine (4.7 mL, 4.6 g, 58 mmol) was added in one portion. The resulting mixture was stirred for 5 min, and then a solution of iodine (9.2 g, 36 mmol) in 50 mL of Et_2O was added dropwise over 15 min. The reaction mixture was stirred for 1.75 h during which time the bath temperature was allowed to rise to -40 °C. The resulting solution was recooled at -78 °C and poured into 75 mL of 10% NaOH and 75 mL ice. The aqueous phase was separated and extracted with 50 mL of Et_2O, and the combined organic phases were washed with 100 mL of satd $NaHCO_3$ solution. The resulting mixture consisted of three phases: an aqueous phase, an organic phase, and an emulsion. The organic phase and aqueous phases were separated, the emulsion was broken with 50 mL of 1.2 M HCl, and the resulting organic phase was separated. The combined organic phases were washed with 100 mL of brine, dried over MgSO4, filtered, and concentrated to yield 6.707 g of a yellow oil. Column chromatography on 120 of silica gel (elution with hexanes) yielded 4.186 g (63%) of iodide **268** as a peach oil: IR (neat) 1591, 1463 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.42 (q, J = 7.4 Hz, 1 H), 1.70 (d, J = 7.4 Hz, 3 H), 0.98 (s, 9 H), 0.29 (s, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.1, 103.3, 27.4, 22.0, 19.1, -0.9; HRMS-EI (*m/z*): M^+ calcd for $C_9H_{19}ISi$, 282.0295; found, 282.0293.

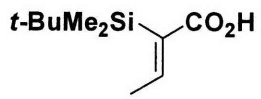


268

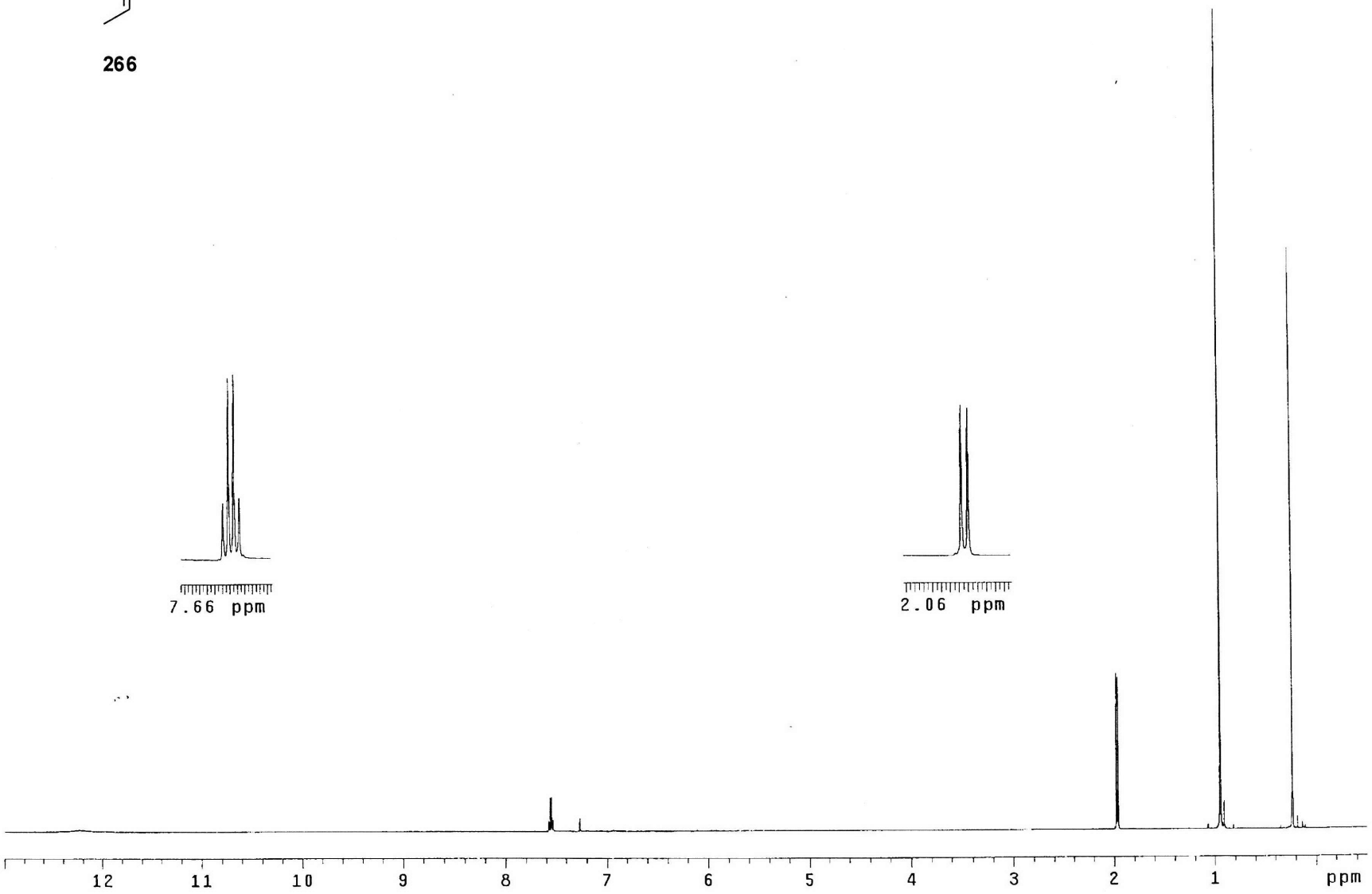
268 266

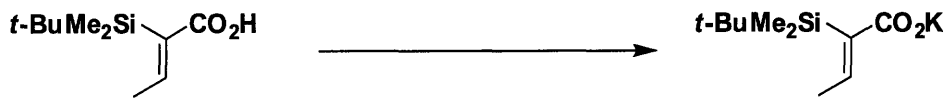
(*Z*)-2-(*tert*-Butyldimethylsilyl)-2-butenoic acid (266).

A 250-mL, two-necked, round-bottomed flask fitted with a rubber septum and an argon inlet adapter was charged with a solution of iodide **268** (4.150 g, 14.70 mmol) in 50 mL of Et_2O and stirred at -78 °C while 6.2 mL of *n*-butyllithium solution (2.57 M in hexanes, 16 mmol) was added over 5 min. The mixture was stirred for 2 h and then diluted with 50 mL of Et_2O. Three 250-mL, one-necked, round-bottomed flasks fitted with rubber septa were filled half-full of crushed dry ice, and one-third of the vinyllithium solution was added dropwise via cannula to each of the flasks. The flasks were allowed to stand until all of the dry ice had sublimed and the resulting solutions were combined and washed with 100 mL of 1.2 M HCl. The aqueous phase was extracted with two 50-mL portions of Et_2O and the combined organic phases were washed with 100 mL of brine, dried over $MgSO_4$, filtered, and concentrated to afford 4.014 g of a yellow oil. This material was dissolved in 50 mL of CH_2Cl_2 and concentrated onto 10 g of silica gel that was applied to the top of a column of 120 g of silica gel. Elution with 10% EtOAc-hexanes yielded 0.608 g of acid **266** as white plates and an additional 1.095 g of impure acid. The impure acid was dissolved in 25 mL of CH_2Cl_2 and concentrated onto 3 g of silica gel that was applied to the top of a column of 120 g of silica gel. Elution with 10% EtOAc-hexanes yielded 0.665 g of acid **266** as white plates. Total yield, 1.273 g (43%), mp 83-86 °C: IR (neat) 1678, 1599, 1463 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 11.75-11.96 (br s, 1 H), 7.56 (q, J = 7.4 Hz, 1 H), 1.97 (d, J = 7.4 Hz, 3 H), 0.95 (s, 9 H), 0.24 (s, 6 H) ; ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.5, 156.1, 133.1, 27.3, 19.0, 18.5, -2.5; HRMS-ESI (*m/z*): $[M + Na]^+$ calcd for $C_{10}H_{20}O_2Si$, 223.1125; found, 223.1129.



266

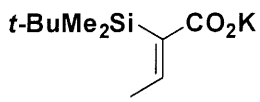




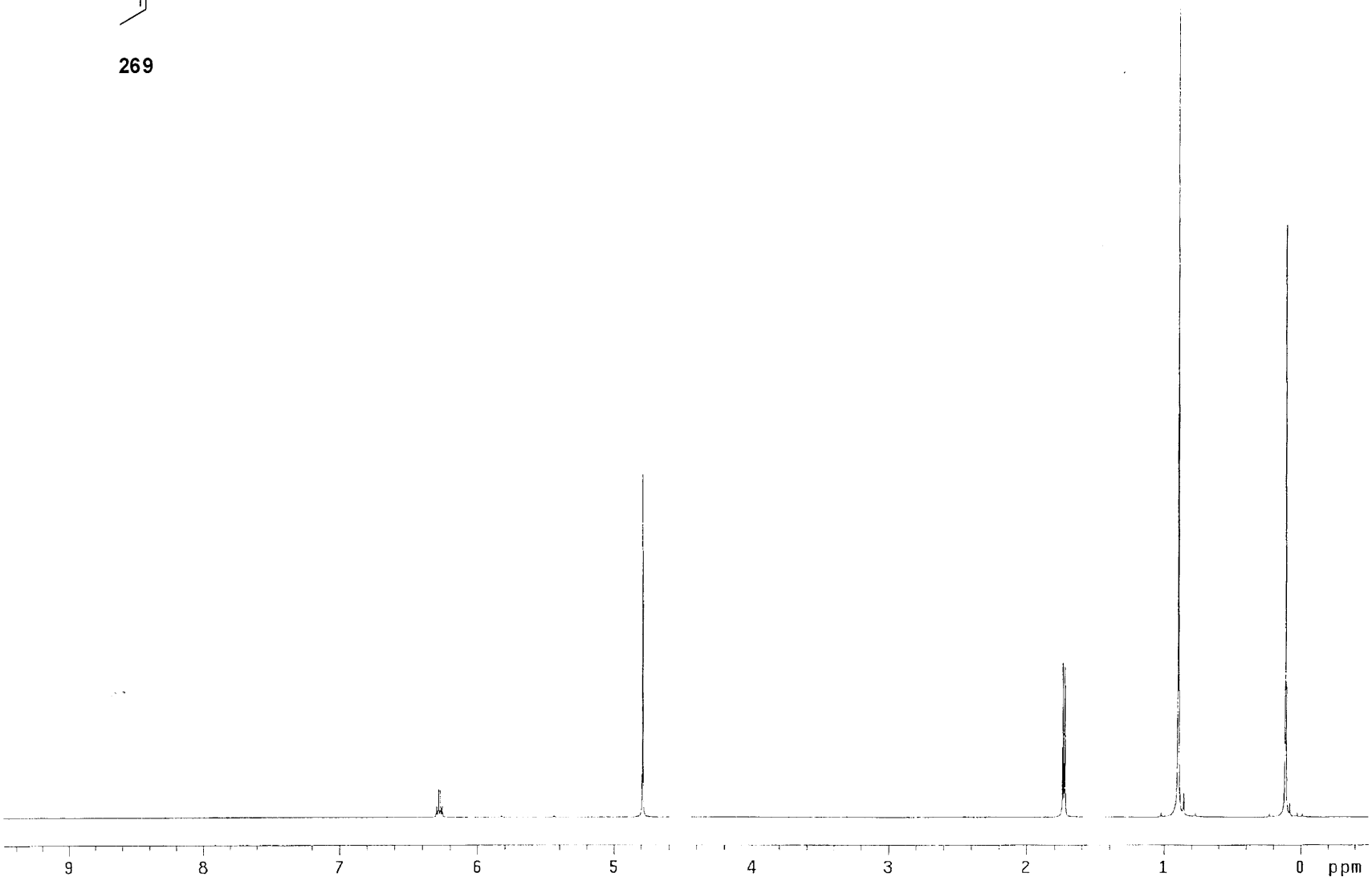
266 269

Potassium (*Z*)-2-(*tert*-butyldimethylsilyl)-2-butenoate (269).

A 250-mL round-bottomed, one-necked flask open to the atmosphere was charged with a a solution of 0.007 g of phenolphthalein in 75 mL of methanol and stirred at room temperature while a solution of acid **266** in 25 mL of methanol was added. A solution of KOH in methanol (0.5 M, ca. 12 mL) was added carefully dropwise until the reaction mixture developed a persistent pink color, and the reaction mixture was concentrated under reduced pressure. The residue was diluted with 50 mL of benzene and concentrated under reduced pressure, and this was repeated three additional times. The resulting solid was dried under vacuum (0.2 mmHg) at 90 °C for 5 h to afford 1.401 g (98%) of salt **269** as a pale purple powder: IR (KBr) 3156, 2929, 1527, 1375 cm^{-1}; ^1H NMR (500 MHz, D_2O) δ 6.28 (q, J = 7.0 Hz, 1 H), 1.73 (d, J = 7.1 Hz, 3 H), 0.90 (s, 9 H), 0.11 (s, 6 H); ^{13}C NMR (125 MHz, D_2O) δ 187.0, 145.3, 141.9, 29.7, 21.3, 20.7, -1.1; HRMS-ESI (*m/z*): $[M + H]^+$ calcd for $C_{10}H_{19}KO_2Si$, 239.0864; found, 239.0887.



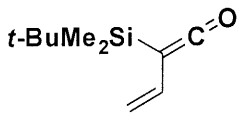
269



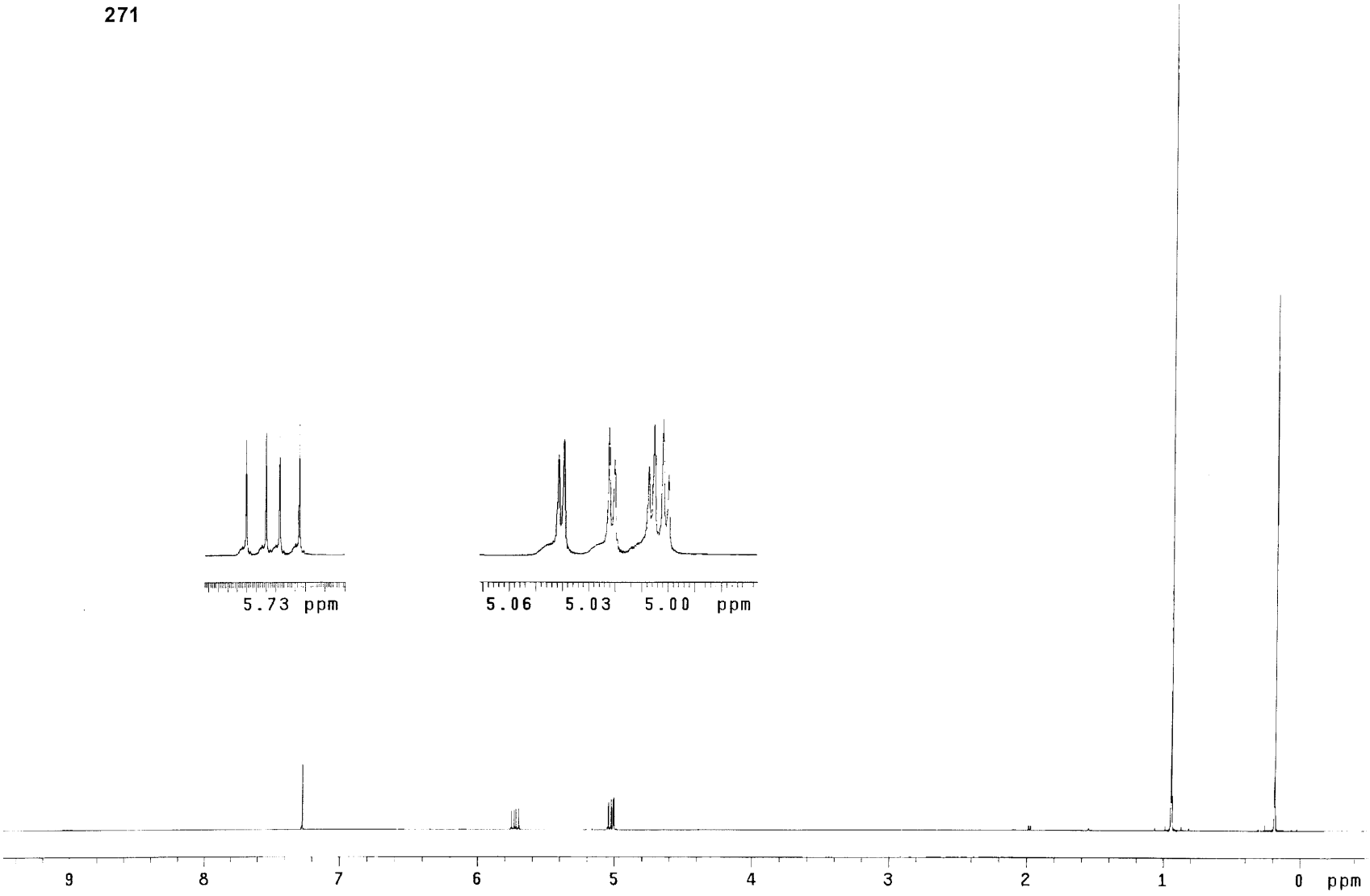
269 271

(*tert*-Butyldimethylsilyl)vinylketene (271).

A 100-mL, three-necked, round-bottomed flask equipped with a rubber septum, 50-mL pressure-equalizing addition funnel, and an argon inlet adapter was charged with a suspension of potassium salt **269** (1.273 g, 5.34 mmol) in 25 mL pentane. Two drops of DMF were added and the reaction mixture was cooled at 0 °C while a solution of oxalyl chloride (0.50 mL, 0.74 g, 5.8 mmol) in 25 mL of pentane was added dropwise over 10 min. The resulting solution was allowed to stir for 3 h at rt and then filtered through a plug of Celite under nitrogen and the remaining solid was washed with 10 mL of pentane. Concentration afforded 1.192 g of crude acid chloride as a brown oil. A 100-mL, one-necked, round-bottomed flask equipped with a rubber septum with an argon inlet needle was charged with a solution of triethylamine (0.81 mL, 0.59 g, 5.8 mmol) in 25 mL of pentane. The rubber septum was replaced with a 50-mL pressure-equalizing addition funnel bearing a rubber septum with an argon inlet needle. The addition funnel was charged with a solution of all of the crude acid chloride in 25 mL of pentane and this solution was added to the the triethylamine solution dropwise over 30 min. The addition funnel was replaced with a cold-finger condenser with an integrated argon inlet and the reaction mixture was heated at reflux for 16 h, during which time the mixture concentrated to a volume of ca. 2 mL. The residue was diluted with 50 mL of pentane and heated at reflux an additional 5 h, and then allowed to cool and filtered through a plug of Celite. The filtrate was concentrated to afford a yellow semi-solid which was suspended in pentane and filtered through a plug of Celite and concentrated to yield 1.039 g of an orange oil. Short path distillation (22 °C, 0.4 mmHg) yielded 0.323 g (33% overall from salt **269**) of the ketene as a yellow oil: IR (neat) 2956, 2859, 2085, 1606 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.72 (dd, J = 17.1, 10.2 Hz, 1 H), 5.02 (dd, J = 17.1, 1.0 Hz), 5.01 (dd, J = 10.2, 1.0 Hz, 1 H), 0.94 (s, 9 H), 0.18 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 184.1, 125.8, 113.4, 26.6, 19.8, 19.1, -5.5.



271



WESLEY AUSTIN

240 FRANKLIN ST #6 • CAMBRIDGE, MA 02139
PHONE (617) 253-1835 • E-MAIL WES.AUSTIN@MIT.EDU

OBJECTIVE

A research and development position utilizing my expertise in experimental design and problem solving in the synthesis of organic molecules.

EDUCATION

2002-2007 **Ph. D. in Organic Chemistry, *Massachusetts Institute of Technology***
Thesis Advisor: Prof. Rick Danheiser
Thesis title: "Synthesis and Annulation Reactions of Trialkylsilylvinylketenes"

1998-2002 **B. S., Chemistry, *University of California at Berkeley***

RESEARCH EXPERIENCE

2002-2007 **Graduate Research Assistant, *Massachusetts Institute of Technology***
Advisor: Prof. Rick L. Danheiser
- Developed a new benzannulation strategy for the synthesis of highly substituted resorcinols based on the reaction of lithium ynolates and (trialkylsilyl)vinylketenes.
- Currently investigating new methods for the synthesis of (trialkylsilyl)vinylketenes that may allow for general Z-substitution and the application of these ketenes to [4+1] annulation reactions.

2002 **Research Internship, *Cibus Genetics***
Advisor: Dr. Peter Beetham
- Conducted research aimed at developing a procedure for isolation of DNA from plants with high lipid content..

2001-2002 **Undergraduate Research Assistant, *University of California at Berkeley***
Advisor: Prof. Dirk Trauner
- Synthesized centrosymmetric small molecules and studied their desymmetrization with pig liver esterase.

2000 **Research Internship, *The Burnham Institute***
Advisor: Prof. Dorit Hanien.
- Investigated methods for the isolation and purification of tensin from insect cells for use in binding and cell motility studies.

1998 **Intern, *Mycogen Corporation***
- Toxin Discovery and Molecular Biology departments. Maintained cell culture library, stocks of growth media and other stock solutions and assisted other researchers using previously designed protocols.

ADDITIONAL EXPERIENCE

2005-Present **Program Director, *MIT Chemistry Outreach Program***
Direct volunteer recruitment, training and assignments for 20-25 school visits per year. Also manage relations with interested schools and give presentations about the program to visiting high school teachers.

2003-2005 **Volunteer, *MIT Chemistry Outreach Program***
Traveled to New England area high schools and gave demonstrations to educate and excite the students about chemistry.

2002-2006 **Graduate Teaching Assistant, *Massachusetts Institute of Technology***
Taught general chemistry and introductory organic chemistry to sections of 15-30 undergraduate students. (Recipient of the MIT Excellence in Teaching by a Graduate Student Award)
Answered student questions, created answer keys, and maintained course website for graduate-level asymmetric synthesis course.

PUBLICATIONS

Austin, W. F.; Zhang, Y.; Danheiser, R. L. " A Benzannulation Strategy for the Synthesis of Phenols and Heteroaromatic Compounds Based on the Reaction of (Trialkylsilyl)vinylketenes with Lithium Ynolates" *Tetrahedron* In Press.

Austin, W. F.; Kowalczyk, J. J.; Dudley, G. B.; Danheiser, R. L. "Alkylideneketenes." In *Science of Synthesis*; Danheiser R. L. Ed.; Thieme: Stuttgart, 2006; Vol. 23, 245.

Danheiser, R. L.; Dudley, G. B.; Austin, W. F. "Alkenylketenes." In *Science of Synthesis*; Danheiser R. L. Ed.; Thieme: Stuttgart, 2006; Vol. 23, 493.

Austin, W. F.; Zhang, Y.; Danheiser, R. L. "Reaction of (Trialkylsilyl)vinylketenes with Lithium Ynolates: A New Benzannulation Strategy", *Org. Lett.* **2005**, *7*, 3905.

Böhm, C.; Austin, W. F.; Trauner, D. "Enzymatic Desymmetrization of a Centrosymmetric Diacetate", *Tetrahedron: Asymmetry* **2003**, *14*, 71.

REFERENCES

Prof. Rick L Danheiser
MIT-Dept. of Chemistry
77 Massachusetts Ave
Room 18-298
Cambridge, MA 02139
(617) 253-1842
danheisr@mit.edu

Prof. Sylvia T. Ceyer
MIT-Dept. of Chemistry
77 Massachusetts Ave
Room 6-217
Cambridge, MA 02139
(617) 253-4537
stceyer@mit.edu

Prof. Timothy M. Swager
MIT-Dept. of Chemistry
77 Massachusetts Ave
Room 18-597
Cambridge, MA 02139
(617) 253-4423
tswager@mit.edu