I. TOTAL SYNTHESIS OF DAN SHEN DITERPENOID QUINONES

II. SYNTHESIS AND CHEMISTRY OF (TRIALKYLSILYL)VINYLKETENES

by

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To Mom and Dad
with love

I. TOTAL SYNTHESIS OF DAN SHEN DITERPENOID QUINONES

II. SYNTHESIS AND CHEMISTRY OF (TRIALKYLSILYL)VINYLKETENES

by

Jennifer L. Loebach

Submitted to the Department of Chemistry
on May 4, 1995 in partial fulfillment of the
requirements for the Degree of Doctor of Philosophy

ABSTRACT

Part I:

The preparation of gram quantitites of three naturally occurring and biologically active quinones has been accomplished using an aromatic annulation strategy developed in these laboratories based on the photochemical Wolff rearrangement. In only five steps, (+)-Danshexinkun A was synthesized in optically active form via the annulation of a chiral silyloxyacetylene with an α-diazo ketone. Cyclization of (+)-danshexinkun A then afforded (-)-dihydrotanshinone I, which could be easily dehydrogenated to tanshinone I.

Part II:

Silylketenes exhibit dramatically different properties from those found for most ketenes. A widely applicable and productive route to a variety of *substituted* (trialkylsilyl)vinylketenes has been developed based on the photochemical Wolff rearrangement of α-silyldiazo ketones. These vinylketenes have been found to be remarkabley robust substances which are stable to silica gel purification and heating in C_6D_6 at 80 °C for several days.

A systematic investigation of the reactivity of these vinylketenes has been conducted to demonstrate their use as versatile four carbon building blocks. Substituted (silyl)vinylketenes have been shown to undergo Diels-Alder reactions with activated olefinic and acetylenic dienophiles. These vinylketenes also participate in a novel [4 + 1] cycloaddition which provides a new route to 5-membered carbocyclic compounds.

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

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Part I

Total Synthesis of Dan Shen Diterpenoid Quinones Isolated from *Salvia Miltorrhizia*

CHAPTER 1

INTRODUCTION AND BACKGROUND

Introduction: Dan Shen Diterpenoid Quinones

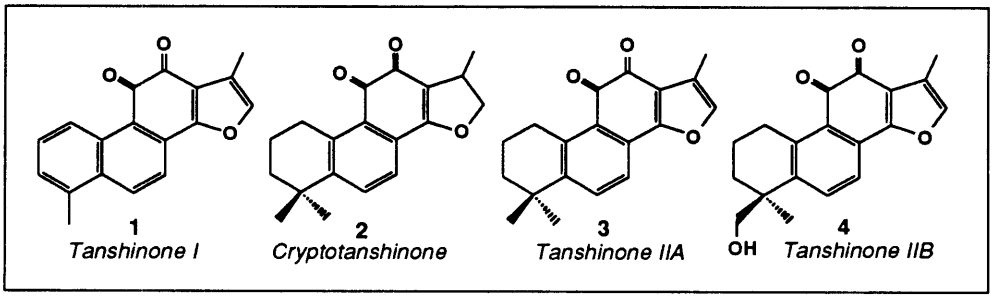
Dan Shen is regarded as one of the most important drugs in Chinese traditional medicine.[1] Obtained from the dried root of the Chinese red-rooted sage *Salvia miltiorrhiza*, today Dan Shen is used clinically for the treatment of heart disease, menstrual disorders, miscarriage, hypertension, and viral hepatitis.[1b] Dan Shen also displays antipyretic, antineoplastic, antimicrobial, and anti-inflammatory properties, and exhibits strong activity against collagen-induced platelet aggregation.[1b,2] Previously it has been shown that Dan Shen's broad spectrum of biological activity is due to a number of interesting abietane diterpenoid quinones.[2-3]

To date, more than 50 related diterpenes have been isolated from Dan Shen. In 1934, Nakao and Fukushima first reported the isolation of three orange-red pigments from *Salvia miltiorrhiza* and named these compounds tanshinone I, II, and III.[4] (The Wades-Giles system for Romanizing Chinese characters spells the drug "Tan-Shin"; the correct pinyin pronunciation is "Dan-Shen", however the names for this class of compounds stem from the older spelling, hence: tanshinones). Takiura found that tanshinone III was actually a mixture of tanshinone II and cryptotanshinone (**2**). The structure of tanshinone I (**1**) was determined by von Wessely[5] in 1940, and the following year Takiura elucidated the structure of cryptotanshinone (**2**).[6] Later, it was discovered by Takiura that in fact, the

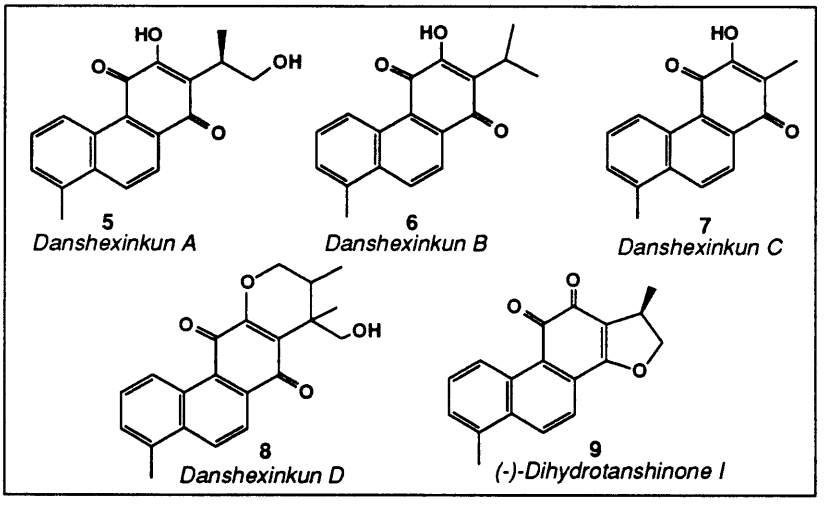
---

1. (a) Duke, J. A.; Ayensu, E. S. *Medicinal Plants of China*; Reference Publications, Inc.: Algonac, MI, 1985; Vol. 2, p 381. (b) *Pharmacology and Applications of Chinese Materia Medica*; Chang, J. M.; But, P. P. H. Eds.; World Scientific Publishing Co.: Singapore, 1986; Vol. 1, pp 255-268.
2. For additional references documenting the biological activity of Dan Shen, see: (a) Footnotes 3-5 in Lee, Choang, T. F.; Chow, H. F.; Chui, K. Y.; Hon, P. M.; Tan, F. W.; Yang, Y.; Zhong, Z. P.; Lee, C. M.; Sham, H. L.; Chan, C. F.; Cui, Y. X.; Wong, H. N. C. *J. Org. Chem.* **1990**, *55*, 3537.
3. Thomson, R. H. *Naturally Occurring Quinones*; Chapman & Hall: London, 1987; Vol. 3, pp 624-629 and references cited therein.
4. Nakoa, M.; Fukushima, T. *J. Pharm. Soc. Japan* **1934**, *54*, 154.
5. von Wessely, F.; Wang, S. *Ber* **1940**, *79*, 19.
6. Takiura, K. *J. Pharm. Soc. Japan* **1941**, *61*, 482.

originally isolated tanshinone II was composed of two compounds: tanshinone IIA (**3**) and IIB (**4**).[3] In 1962, elucidation of the structure of tanshinone IIA (**3**) was achieved by Takiura[7] and in 1968, Thomson published the structure of tanshinone IIB (**4**),[8] thereby completing the assignment of structures for the major Dan Shen pigments.



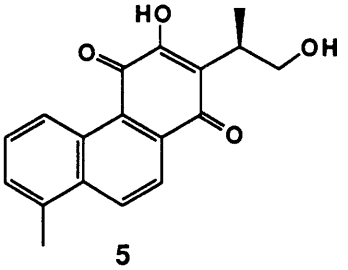
Unfortunately, subsequent biological studies of these individual components of the drug revealed that their activity did not reproduce all of the activity of the crude extract, so efforts were then focused on the isolation of the less abundant components of Dan Shen. Chinese chemists isolated the related compounds danshexinkun A (**5**), B (**6**), C (**7**), and D (**8**), and (-)-dihydrotanshinone I (**9**).[9]



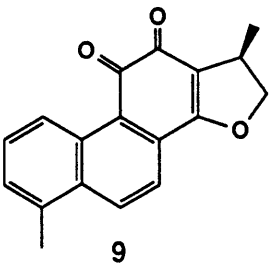
7. Takiura, K. T.; Koizumi, K. *Chem. Pharm. Bull.* **1962**, *10*, 112.
8. Baille, A. C.; Thomson, R. H. *J. Chem. Soc. (C)* **1968**, 48.
9. (a) **5-7:** Fang, C. N.; Chang, P.-L.; Hsu, T.-P. *Acta Chem. Sinica* **1976**, *34*, 197. (b) **8:** Lou, H.-W.; Wu, B.-J.; Wu, Mu, M.-Y.; Yong, Z. G.; *Acta Pharm. Sinica* **1985**, *20*, 542. (c) **9:** Qian, M.-K.; Yng, B.-J.; Gu, W.-H.; Chen, Z.-X.; Chen, X.-D.; Ye, X.-Q. *Acta Chem. Sinica* **1978**, *36*, 199.

Several of the purified Dan Shen components have been screened for biological activity. The tanshinones **1**, **2**, and **3** as well as danshexinkun A (**5**) and (-)-dihydrotanshinone I (**9**) are effective coronary vasodilators.[10] Antiplatelet aggregation activity is reported for tanshinones **1**, **2**, **3**, and (-)-dihydrotanshinone I (**9**).[11] (-)-Dihydrotanshinone I is highly active against the dermatophytic fungi *Trichophyton rubrum, T. mentagrophytes, T. tonsulans* var. *sulfureum, Microsporum gyseum, Sabourandites canis, and Epidermophyton floccosum.*[12] In the same report, cryptotanshinone (**2**), (-)-dihydrotanshinone (**9**), and tanshinone IIB (**4**) were all found to be active in vitro against *Staphylococcuc aureus* and gram positive bacteria. Despite the bioactivity reported for many of the pure individual compounds isolated from *Salvia Miltiorrhiza*, none approaches the medical properties of the crude drug mixture. Unfortunately, further identification of the most active components has been frustrated by the extreme scarcity of some of these substances.

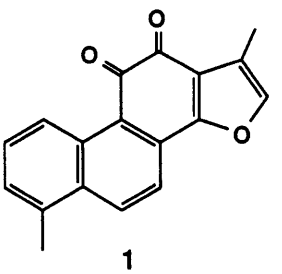
The three diterpenes shown below - danshexinkun A (**5**), (-)-dihydrotanshinone I (**9**), and tanshinone I (**1**) - were selected as target structures for our synthetic investigation.



5
Danshexinkun A



9
(-)-Dihydrotanshinone I



1
Tanshinone I

The aim of this study was two-fold. One goal was to perfect the recently developed "second generation" version[13b] of our annulation strategy and examine its application for

10. Chen, C.-C.; Chen, H.-T.; Chen, Y.-P.; Hsu, H.-Y.; Hsieh, T.-C. *Taiwan Pharm. Assoc.* **1986**, *38*, 226.
11. Onitsuka, M.; Fujiu, M.; Shinma, N.; Maruyama, H. B. *Chem. Pharm. Bull.* **1983**, *34*, 1670.
12. Honda, G.; Koezuka, Y.; Tabata, M. *Chem. Pharm. Bull.* **1988**, *36*, 408.
13. (a) Danheiser, R. L.; Nishida, A.; Savariar, S.; Trova, M. P. *Tetrahedron Lett.* **1988**, 4917. (b) Danheiser, R. L.; Brisbois, R. G.; Kowalczyk, J. J.; Miller, R. F. *J. Am. Chem. Soc.* **1990**, *112*, 3093.

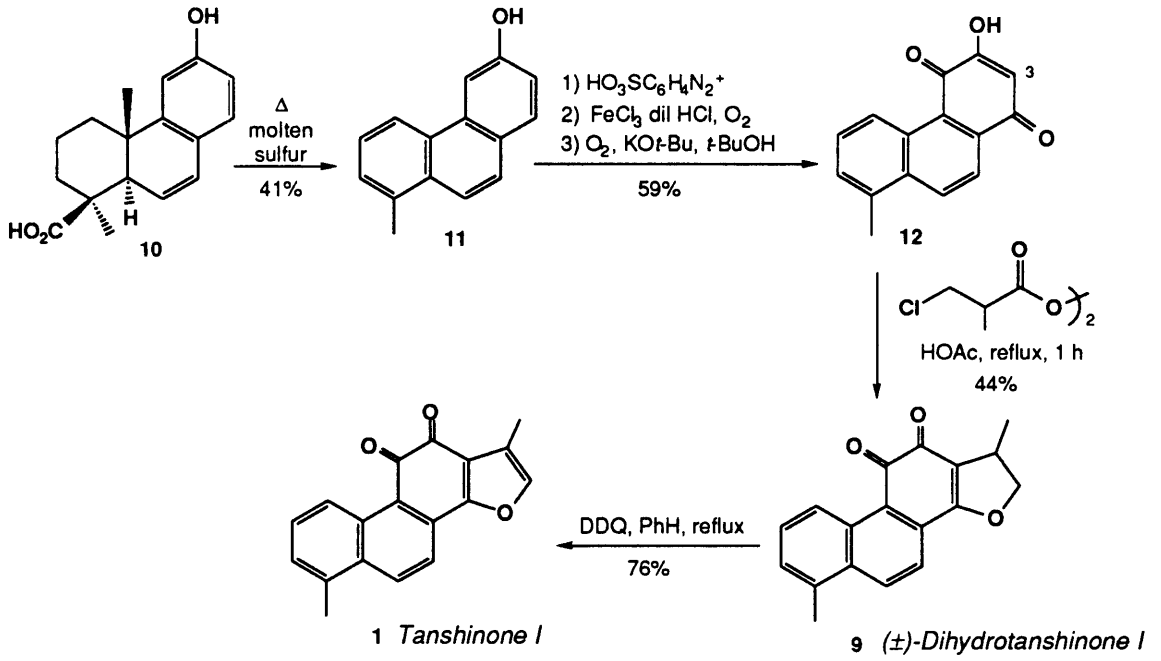
the synthesis of the tricyclic aromatic system found in compounds **5**, **9**, and **1**. A second goal was to develop efficient syntheses of these compounds practical enough to support the preparation of gram quantities of each diterpene, thus facilitating the evaluation and exploitation of their biological activity. Initial studies by David Casebier, a former member of the Danheiser group, had previously led to a route to diterpenes **5**, **9**, and **1**.[14] My research goals included the optimization of each synthesis, the complete characterization of all synthetic intermediates and the final natural products, and the preparation of gram quantities of the target diterpenes.

Previous Syntheses of Danshexinkun A (5), (-)-Dihydrotanshinone I (9), and Tanshinone I (1)

Despite great interest in the isolation of natural products from Dan Shen, no total syntheses of danshexinkun A (**5**) and relatively few total syntheses of tanshinone I (**1**) and dihydrotanshinone I (**9**) have been reported. Prior to 1968, there were several unsuccessful synthetic attempts on the tanshinones.[15] In 1968, the synthesis of the incorrect isomer of tanshinone I was reported by King.[16] Later that same year, Baille and Thomson reported the successful partial synthesis of several tanshinones.[8] As outlined in Scheme 1, tanshinone I (**1**) was produced from 8-methyl-3-phenanthrol (**11**) which was obtained in 41% yield via the destructive distillation of podocarpic acid (**10**) from molten sulfur.[17] The tricyclic intermediate **11** was oxidized to the hydroxy-*para*-quinone **12** and the furan ring was then constructed via the introduction of an isopropenyl group at C-3 using β-chloro-α-methyl propionyl peroxide followed by cyclization. Treatment of the resulting (±)-dihydrotanshinone I (**9**) with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) effected dehydrogenation to afford quinone **1** which was identical with tanshinone I.

14. Casebier, D. S. Ph.D. Dissertation, Massachusetts Institute of Technology, 1990.
15. Tanaka, S.; Kawai, S. *J. Chem. Soc. Japan* **1959**, *80*, 1183.
16. King, T. J.; Read, G. *J. Chem. Soc.* **1968**, 5090.
17. Sherwood, I. R.; Short, W. F. *J. Chem. Soc.* **1938**, 1006.

Scheme 1



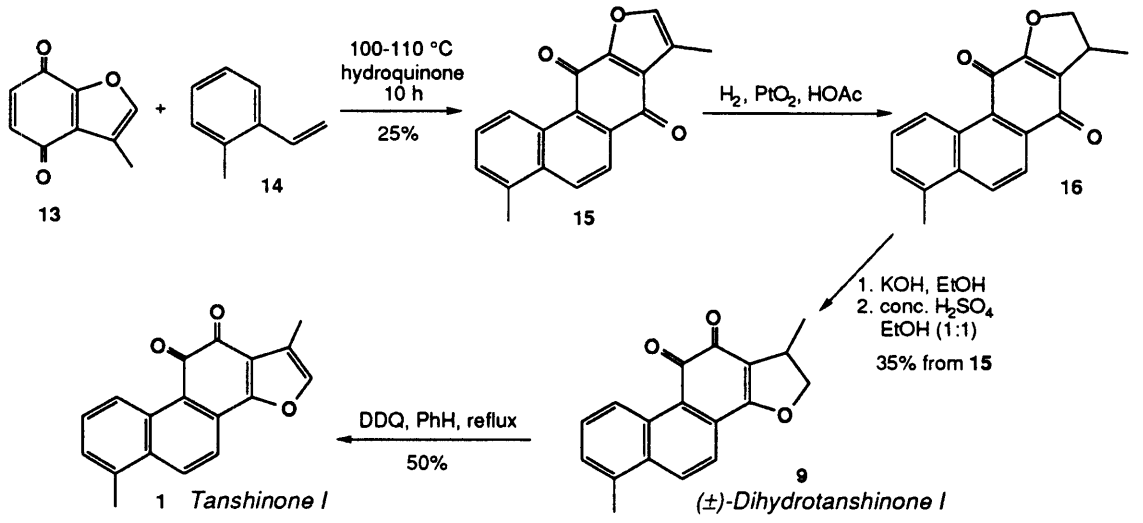
Although this route begins with an expensive natural product as the starting material, the target compounds are synthesized in only a few steps. Tanshinone I (**1**) is produced in six steps from podocarpic acid **10** in 8% overall yield, and (±)-dihydrotanshinone I (**9**) is prepared in five steps beginning with **10** (11% overall yield).

In 1969, Kakisawa reported the first *total* synthesis of tanshinone I (**1**) utilizing a Diels-Alder strategy to build-up the tanshinone framework (Scheme 2).[18] The thermal cycloaddition of 3-methylbenzofuran-4,7-quinone (**13**) (obtained in two steps from 2-acetylresorcinol[19]) and *o*-methylstyrene (**14**) afforded in 25% yield the Diels-Alder adduct **15**. Kakisawa reported the formation of five colored products by tlc analysis in this reaction, but was only able to successfully identify two of the products. The tetracyclic quinone **15** was determined to be the major product, and the regioisomeric Diels-Alder adduct was noted as a minor product. Hydrogenation of the furan ring in **15** using platinum oxide in acetic acid afforded **16**. Hydrolysis employing alcoholic potassium

18. Inouye, Y.; Kakisawa, H. *Bull. Chem. Soc. Japan* **1969**, *42*, 3318.
19. Walley, W. B. *J. Chem. Soc.* **1951**, 3229.

hydroxide followed by heating with concentrated sulfuric acid in ethanol then provided (±)-dihydrotanshinone I (**9**) in 9% overall yield from quinone **13**. (±)-Dihydrotanshinone I (**9**) was dehydrogenated with DDQ in 50% yield to produce tanshinone I (**1**) in 4% overall yield. This Diels-Alder approach, although admirably convergent, suffers from very low yields and the need to rearrange the *para* to the *ortho* quinone.

Scheme 2



Recently, Snyder and coworkers have synthesized a number of tanshinones (but not specifically dihydrotanshinone I (**9**) and tanshinone I (**1**)) using an ultrasound Diels-Alder strategy.[20] Their strategy is similar to that reported by Kakisawa but employs an *ortho*-quinone as the dienophile. This modification eliminates extra steps late in the synthesis and provides a concise, efficient route for the construction of the tanshinone framework.

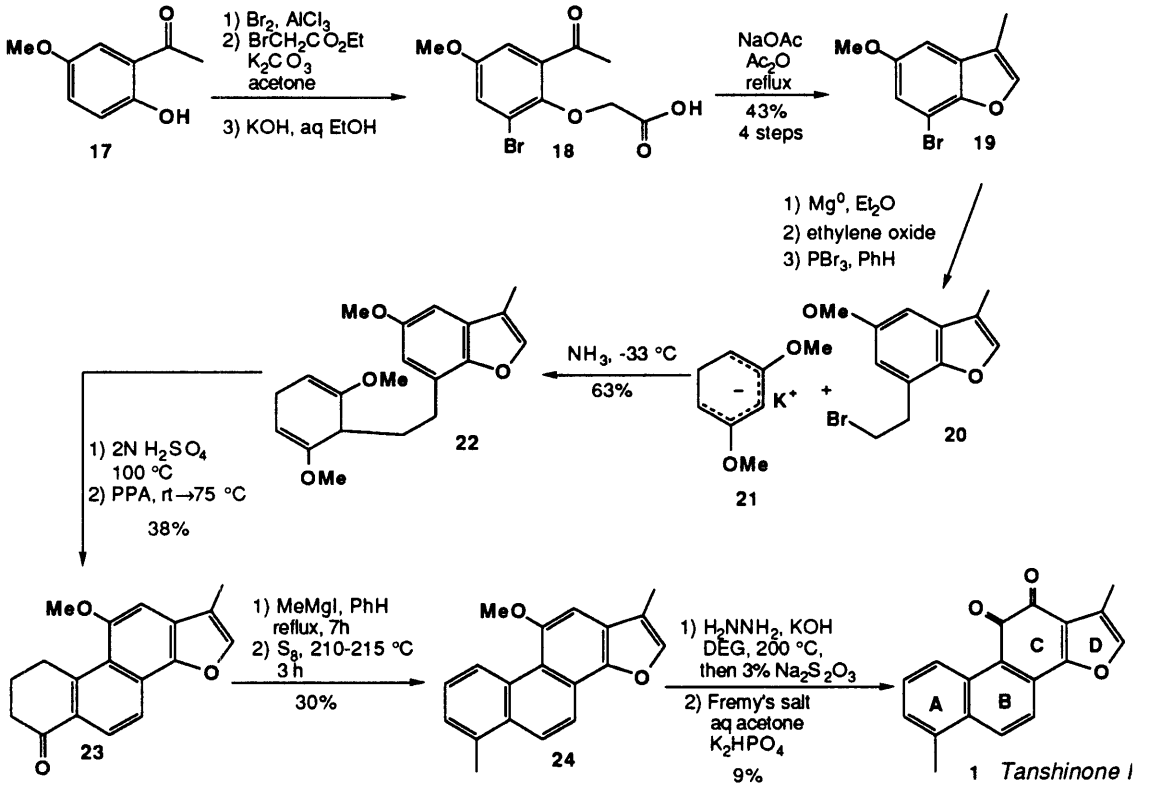
Imai has published a very different approach for the ring construction of tanshinone I (**1**).[21] His strategy assembles the ring skeleton via the sequence C→D→A→B (Scheme 3). Commercially available 2'-hydroxy-5'-methoxyacetophenone (**17**) was first brominated to provide a "handle" for further elaboration, and the furan ring was then

20 (a) Lee, J.; Snyder, J. K. *J. Org. Chem.* **1990**, *55*, 4995 (b) Lee, J.; Li, J.-H.; Oya, S.; Snyder, J. K. *J. Org. Chem.* **1992**, *55*, 5301.

21. Imai, S. *J. Sci. Hiroshima Univ. Ser. A* **1971**, *35*, 171.

formed using an intramolecular Perkin reaction. Alkylation of the Grignard reagent derived from **19** with ethylene oxide gave a primary alcohol which was converted to **20** by treatment with PBr_3. The pentadienyl anion derived from resorcinol dimethyl ether by Birch reduction was alkylated with **20** to yield the ACD intermediate **22**. Acid catalyzed cleavage of the methyl enol ethers and intramolecular Friedel-Crafts reaction generated the B-ring. The ketone **23** was treated with methyl Grignard reagent and then dehydrogenated using powdered sulfur. Cleavage of the methyl ether and oxidation with Fremy's salt afforded tanshinone I (0.4 % overall yield).

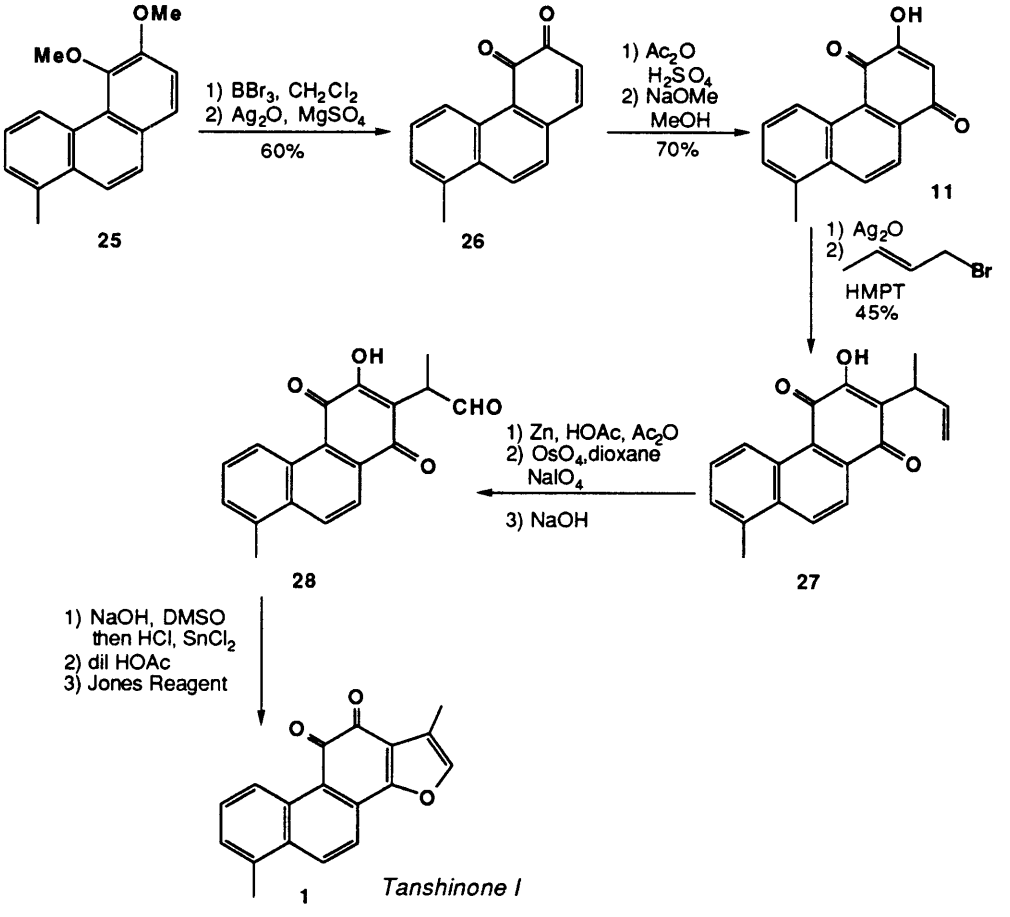
Scheme 3



Althought this is a lengthy synthesis (14 steps) for tanshinone I (**1**) in comparison to the previous examples, this approach for the construction of the ring skeleton employs some clever transformations which involve minimal deprotection and manipulation of functional groups.

The most recent synthesis of tanshinone I (**1**) was reported by Huot and Brassard (Scheme 4).[22] Their route started with the phenanthrene catechol dimethyl ether **25**, which was synthesized from *p*-vanillin in nine steps in 16% overall yield. Cleavage of the methyl ethers and oxidation to the *ortho*-quinone was accomplished in 60% yield to produce **26**, which was converted to the hydroxy *para*-quinone **11**. Following the formation of the silver salt of **11**, treatment with crotyl bromide and heating produced **27** via a [3,3] sigmatropic rearrangement of the crotyl ether. Zinc metal was employed to reduce the quinone, and the three hydroxyl groups were protected as acetate esters. Oxidative cleavage of the olefin generated the aldehyde and subsequent alcohol deprotection yielded "quinonal" **28** which upon closure of the furan ring was transformed to tanshinone I (**1**).

Scheme 4



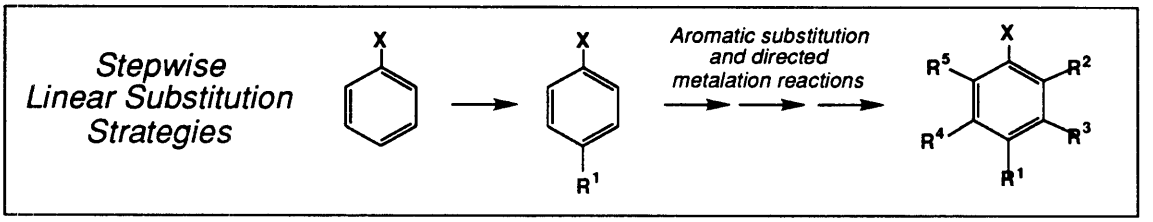
22. Huot, R.; Brassard, P. *Can. J. Chem.* **1974**, *52*, 88.

This is the longest route to tanshinone I (**1**), employing 21 steps starting from *p*-vanillin and resulting in 0.8% yield overall. This route requires two steps for the conversion from the *ortho*- to *para*-quinone and several steps to incorporate the furan ring.

It is important to note that although we have chosen to present the published syntheses of three Dan Shen natural products, considerable synthetic efforts have been focused on several of the other interesting diterpenoid quinones that have been isolated from *Salvia miltiorrhiza.* These efforts have utilized many of the strategies mentioned above as well as other new innovative methods.[23]

Annulation Strategies for the Assembly of Aromatic Compounds

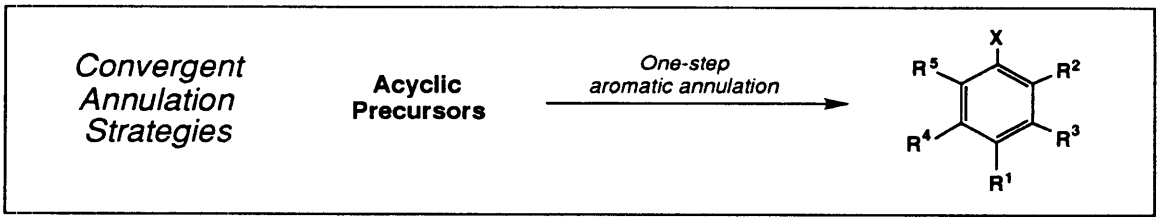
For the most efficient synthesis of highly substituted aromatic compounds, a convergent and regiospecific strategy is required. Classical synthetic approaches to substituted benzenoid compounds most often have employed *linear substitution strategies.* Readily available aromatic derivatives are modified in a stepwise approach via electrophilic and nucleophilic substitution reactions and more recently, directed-metal alkylation reactions.[24] Disadvantages of some of these classical approaches include: (1) vigorous



reaction conditions which may require additional protection/deprotection steps; (2) a lack of convergent character, leading to lengthy routes; (3) problems of regiocontrol when

23. (a) Tateishi, M.; Kusumi, T.; Kakisawa, H. *Tetrahedron*, **1971**, *27*, 237. (b) Kakisawa, H.; Tateishi, M.; Kusumi, T. *Tetrahedron. Lett.* **1968**, 3783.
24. (a) Gawley, R. E.; Rein, K. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I.; Eds.; Pergamon Press: Oxford, 1991, Vol. 1 pp. 459-476. (b) Snieckus, V. *Chem. Rev.* **1990**, 879. (c) Gschwend, H. W.; Rodriguez, H. R. *Org. React.* **1979**, *26*, 1. (d) Townsend, C. A.; Davus, S. G.; Christensen, S. B.; Link, L. C.; Lewis, C. P. *J. Am. Chem. Soc.* **1981**, *22*, 3923. (e) Narasimhan, N. S.; Mali, R. S. *Top. Cur. Chem.* **1987**, *138*, 63.

carrying out reactions on substituted aromatic systems. A more effective approach to highly substituted aromatic compounds involves the application of *annulation methods*: convergent strategies in which the aromatic system is assembled in a single step, with all or most of the substituents in place. Aromatic annulation methods often enjoy significant advantages over classical linear substitution strategies. Annulation methods avoid many of the regiochemical ambiguities associated with classical substitution methods. Often, it is possible to synthesize aromatic compounds with substitution patterns that would normally not be accessible via the classical substitution approach.

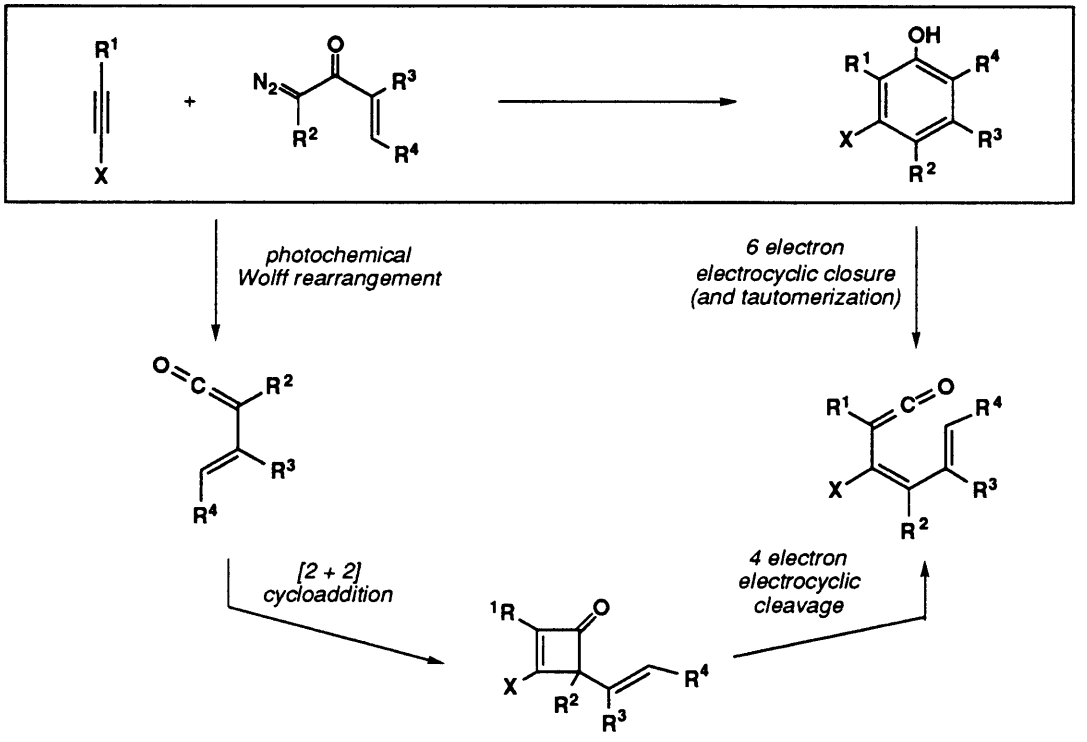


Aromatic Annulation Strategies Based on Vinylketenes

A powerful aromatic annulation strategy has been developed in our laboratory that is based on the addition of a vinylketene to an activated (heterosubstituted) or unactivated acetylene.[13] The reaction involves the generation of the vinylketene via the 4π electrocyclic ring opening of a cyclobutenone. Recently, a "second-generation" version of this annulation strategy has been developed which greatly expands the scope of the method.[13b] In particular, this variant allows access to a variety of *polycyclic* aromatic and heteroaromatic systems which were not previously available using the cyclobutenone-based strategy. This new method is based on the generation of a vinylketene or an arylketene using the photochemical Wolff rearrangement of an α-diazo ketone. Scheme 5 outlines the overall mechanistic course of the reaction. Irradiation of the α-diazo ketone induces Wolff rearrangement to produce an aryl- or vinylketene which then combines in a [2 + 2]

cycloaddition with the acetylene. Further irradiation (or in some cases thermolysis) results in 4π electrocyclic ring cleavage of the cyclobutenone ring to produce a dienylketene which undergoes 6π electrocyclization to afford a 2,4-cyclohexadienone, which upon tautomerization produces the desired aromatic product.

Scheme 5

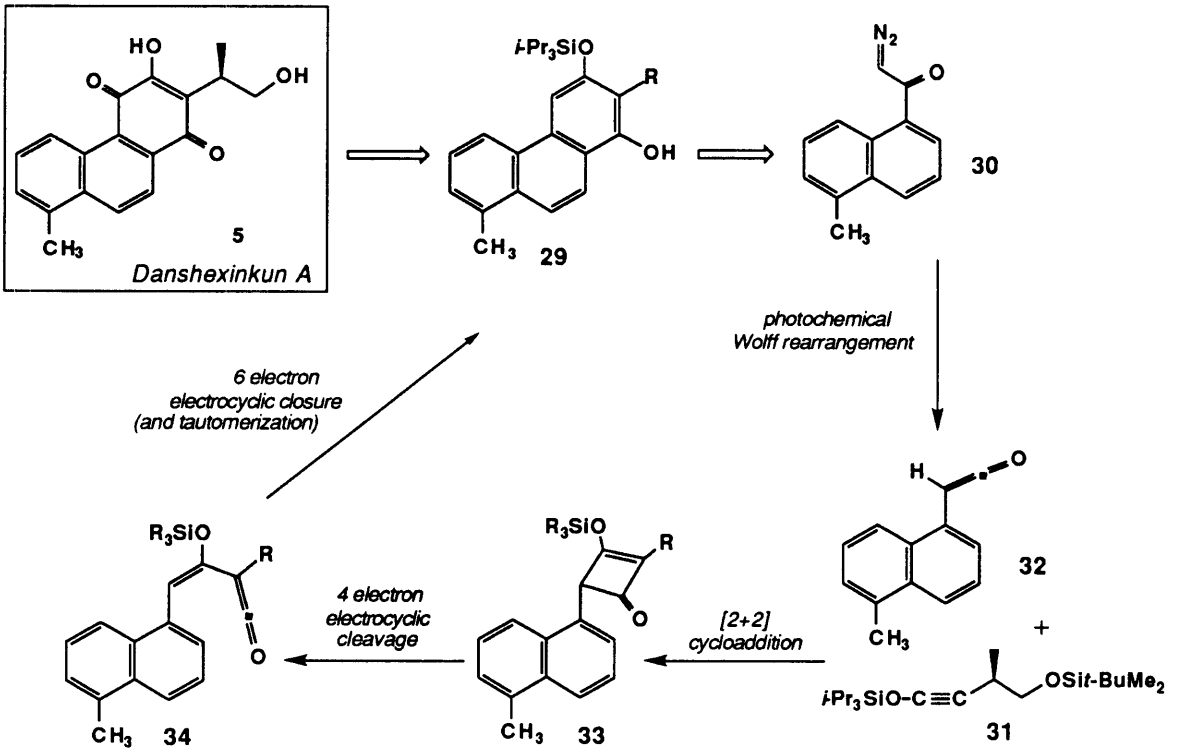


Synthesis of Diterpenoid Quinones Based on the Aromatic Annulation Strategy

The pivotal step in our synthetic approach to the Dan Shen diterpenoids employs the "second-generation" aromatic annulation strategy. The following retrosynthetic analysis (Scheme 6) outlines our plan for the application of the annulation strategy to the assembly of the key tricyclic intermediate **29**, a precursor to (+)-danshexinkun A (**5**), (-)-dihydrotanshinone I (**9**), and tanshinone I (**1**). Irradiation of the α-diazo ketone **30** triggers a photochemical Wolff rearrangement to generate the arylketene **32**, which upon [2 + 2] cycloaddition with acetylene **31** would yield the cyclobutenone **33**. Photochemical or

thermal cleavage of this cyclobutenone would lead to ketene **34**, and electrocyclic ring closure and tautomerization would then produce the desired tricyclic phenol **29** which could be elaborated to afford danshexinkun A (**5**), dihydrotanshinone I (**9**), and tanshinone I (**1**).

Scheme 6



Our approach is a particularly attractive route for the efficient assembly of this tricyclic system and offers the potential flexibility to access a number of other Dan Shen diterpenoid quinones.[14,25]

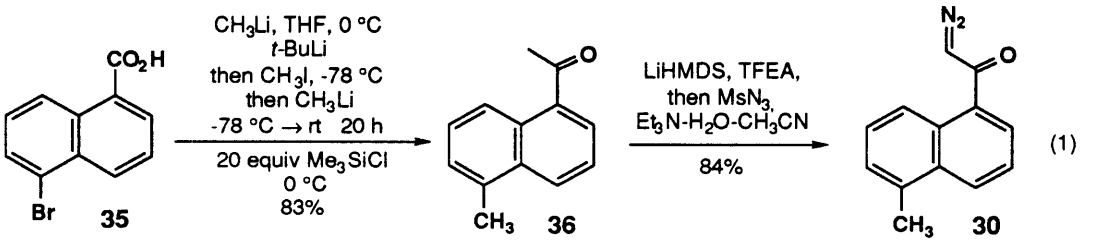
25. Danheiser, R. L.; Casebier, D. S.; Huboux, A. H. *J. Org. Chem.* **1994**, *59*, 4844.

CHAPTER 2

TOTAL SYNTHESIS OF DANSHEXINKUN A, DIHYDROTANSHINONE I, AND TANSHINONE I

Synthesis of the α-Diazo Ketone Intermediate

The α-diazo ketone **30** required for the key aromatic annulation step was prepared starting from 5-bromo-1-napthoic acid (**35**), a known compound which can be prepared on a large scale by treating 1-napthoic acid with bromine in hot acetic acid according to the procedure of Shoesmith and Rubli.[26] The bromo acid **35** was converted to the ketone **36** via the following one-pot procedure (eq 1). The bromo acid **35** was first deprotonated with methyllithium to produce the carboxylate salt. Treatment of this salt with 2.1 equivalents of *t*-butyllithium effected halogen-metal exchange, and then 1.2 equivalents of the alkylating agent methyl iodide were added followed by 2.0 equivalents of methyllithium. After stirring for 20 h at room temperature, the reaction mixture was cooled at 0 °C and quenched with 20 equivalents of chlorotrimethylsilane. Upon workup with dilute hydrochloric acid, the ketone **36** was produced in 83-86% yield after purification by column chromatography.

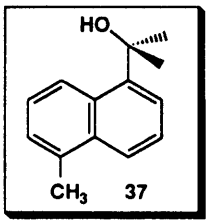


(1)

In the original study conducted by Casebier, this transformation was effected via the treatment of a solution of lithium 5-methyl-1-napthoate with 3.0 equivalents of

26. Shoesmith, J. B.; Rubli, H. *J. Chem. Soc.* **1927**, 3098.

methyllithium. The reaction was quenched directly by slow addition to dilute hydrochloric acid with rapid stirring. However, this procedure was found to be difficult to reproduce without a significant amount (~30%) of the tertiary alcohol **37** being formed due to the slow hydrolysis rate of methyllithium relative to the breakdown of the tetrahedral intermediate into the methyl ketone and addition of methyllithium to the unmasked carbonyl group.



37

Tertiary alcohol formation has been reported as the most common side reaction observed during the conversion of an acid to a ketone with a organolithium reagent.[27] The amount of alcohol formed has been noted to be erratic and unpredictable. Methods devised to minimize the formation of this side product include: quenching the reaction by addition to dilute acid with rapid stirring and using several fresh portions of hydrolyzing medium; employing exactly one equivalent of organolithium reagent with preformed lithium carboxylates; using tetrahydrofuran as the solvent to increase carboxylate solubility; and adding ethyl acetate or ethyl formate before hydrolysis to react with any remaining organolithium reagent. After considerable study, we found that the carboxylate salt was smoothly converted into the desired ketone by using the "Rubottom procedure"[28] which involves quenching the reaction mixture with a large excess of chlorotrimethylsilane. Any excess methyllithium reagent reacts quickly with the chlorotrimethylsilane and thereby leaves no organometallic reagent to react with the ketone. This method provided the methyl ketone **36** in 83-86% yield after purification by column chromatography.

Conversion of the ketone **36** to the α-diazo derivative **30** was then achieved by employing the improved "detrifluoroacetylative" diazo transfer method recently developed

27. Review: Jorgenson, M. *J. Org. React.* **1970**, *18*,1.
28. Rubottom, G. M.; Kim, C.-W. *J. Org. Chem.* **1983**, *48*, 1550.

in our laboratory.[29] The original Casebier procedure for this step used only 1.2 equivalents each of triethylamine and methanesulfonyl azide as well as a saturated sodium bicarbonate wash in the workup. The reaction conditions were modified to conform to the published method[29] and 1.5 equivalents each of triethylamine and methanesulfonyl azide were used. Also, it was found that the 10% sodium hydroxide wash stipulated in the original procedure[29] was indeed necessary to remove the sulfonamide byproduct which was not separated from the diazo ketone when sodium bicarbonate was used.

The α-diazo ketone **30** exhibited strong characteristic IR absorptions at 2100 cm^{-1} (CN_2 stretching frequency) and 1615 cm^{-1} (carbonyl stretching frequency) and was obtained as bright yellow needles, mp 84-85 °C, in 84% yield. This α-diazo ketone **30** was found to be stable to storage for extended periods of time (ca. 3 y at 0 °C).

Synthesis of the Siloxyacetylene Annulation Component

Siloxyalkyne **31** was selected as the acetylene component for the pivotal aromatic annulation step. Due to the ease of cleavage of a silyl ether group compared to an alkyl ether group, siloxy derivatives are usually the preferred alkynes for our aromatic annulation[13] although both serve as effective ketenophiles. Siloxyalkynes can be conveniently prepared from carboxylic esters using the Kowalski reaction.[30a,b] The requisite optically active siloxyalkyne **31**[30c] was prepared from commercially available (S)-(+)-methyl 3-hydroxy-2-methylpropionate (**38**) via (a) protection with *t*-butyldimethylsilyl chloride, followed by (b) sequential treatment with lithiodibromomethane (generated in situ from the treatment of dibromomethane with lithium tetramethylpiperidide), excess *n*-butyllithium, and triisopropylsilyl chloride according to the procedure of Kowalski (Scheme 7).

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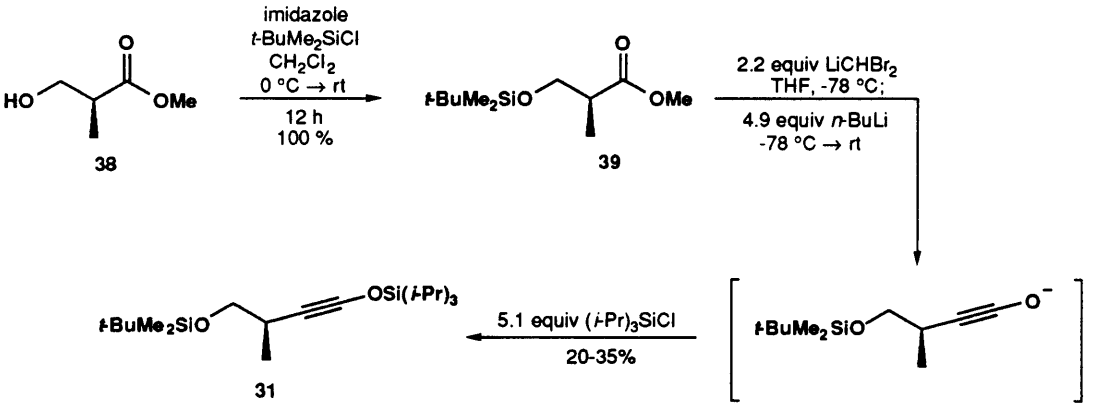
29. (a) Danheiser, R. L.; Miller, R. F.; Brisbois, R. G.; Park, S. Z.; *J. Org. Chem.* **1990**, *55*, 1959. (b) Brisbois, R. G., Ph. D. Thesis, Massachusetts Institute of Technology, 1990.
30. a) Kowalski, C. J.; Lal, G. S.; Haque, M. S. *J. Am. Chem. Soc.* **1986**, *108*, 7127. (b) Kowalski, C. J.; Lal, G. S. *J. Am. Chem. Soc.* **1988**, *110*, 3693. (c) Evans, D. A.;; Sacks, C. E.; Kleschick, W. A.; Taber, J. R. *J. Am. Chem. Soc.* **1979**, *101*, 6789.

Scheme 7

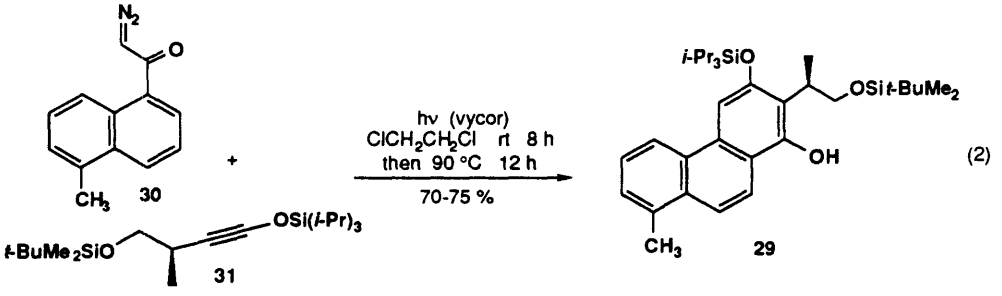


Casebier's yields for this reaction generally ranged from 47-53%. The isolated yields that I obtained for pure siloxyacetylene were low (20-35%). This was believed to be primarily due to the competitive formation of the isomeric silylketene identified by the IR stretching frequency at ~2100 cm^{-1} (C=O stretching). Chromatographic purification was complicated by the presence of this silylketene, which has a very similar R_f to that of the siloxyacetylene, and it was often necessary to run multiple (3-4) purification columns in order to obtain uncontaminated siloxyacetylene **31**. The siloxyacetylene was stable to storage in a solution of dichloromethane at 15 °C for several weeks; however after that time, chromatography was necessary to purify the product before use. With the siloxyacetylene in hand, our efforts were now focused on the pivotal aromatic annulation reaction.

Aromatic Annulation Step

The key annulation step was accomplished as shown in equation 2 by irradiating, in a vycor tube, a degassed 0.35 M solution of the diazo ketone **30** and 1.4 equivalents of the siloxyalkyne **31** in 1,2-dichloroethane with a low-pressure mercury lamp (254 nm). After 8 h, tlc analysis indicated that consumption of the diazo ketone **30** was complete. At this point, two major products were evident by tlc analysis: the desired annulation product and

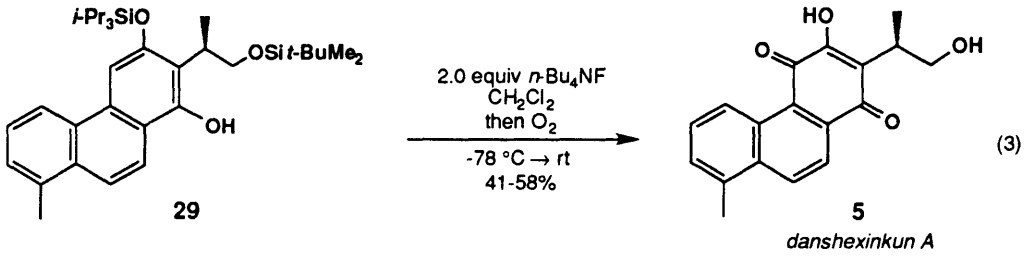
what was presumed to be the intermediate aryl cyclobutenone **33** (see Scheme 6, p. 13). Polymer build-up on the inside of the vycor tube tends to impede the transmittance of light and therefore the completion of the reaction. The reaction mixture was diluted with additional dichloroethane and driven to completion by heating at reflux for 12 h. Concentration and chromatographic purification furnished the tricyclic phenol **29** as a yellow oil, $[\alpha]_D$ 28.3 ° (*c* = 0.12, $CHCl_3$) in 70-75% yield. The ^1H NMR spectrum of the tricyclic phenol **29** exhibited a characteristic phenolic proton peak at 9.89 ppm as well as a broad IR absorption at 3200 cm^{-1} (O-H stretching). The number of equivalents of siloxyalkyne used for this annulation was decreased from the amount used in the original Casebier study (2.0 to 1.4 equivalents) without affecting the yield of the reaction.



(2)

Synthesis of Danshexinkun A

Cleavage of the silyl ether protective groups and oxidation to produce danshexinkun A (**5**) was achieved in a single operation by exposure of **29** to the action of 2.2 equivalents of tetra-*n*-butylammonium fluoride in tetrahydrofuran (-78 °C to rt, 12 h) in the presence of oxygen (eq 3). After a number of procedures were tried, the optimal conditions for purification were found to be low temperature recrystallization from diethyl ether which furnished (+)-danshexinkun A (**5**) in 41-58% yield as orange crystals, mp 200-201 °C (lit 200 °C),[9a] $[\alpha]_D$ +30 ° (*c* = 0.01 $CHCl_3$). It is likely that a considerable amount of material was lost during the purification. In earlier studies Casebier had obtained the diterpene in 91% yield following a similar protocol.



(3)

Synthetic (+)-danshexinkun A (**5**) was characterized by ^{1}H NMR, ^{13}C NMR and IR spectroscopy. The ^{1}H NMR spectrum of synthetic (+)-danshexinkun A (Figure 1) was identical in all respects with the spectrum we obtained for an authentic sample of natural (+)-danshexinkun A provided to us by Dr. Henry N. C. Wong (Table 1). We are grateful to Professor Wong (Chinese University of Hong Kong) for providing us with authentic samples of (+)-danshexinkun A, (-)-dihydrotanshinone I, and tanshinone I. The spectral properties (^{1}H NMR 300 MHz, $CDCl_3$) of synthetic (+)-danshexinkun A also closely matched the published data (^{1}H NMR 60 MHz, $CDCl_3$).[9a]

Recently, the enantiomer of (+)-danshexinkun A, (-)-danshexinkun A, has been isolated from *Salvia miltiorrhiza*.[31] To date, no ^{13}C NMR data has been published for (+)-danshexinkun A, therefore we have compared our ^{13}C NMR spectral data for synthetic (+)-danshexinkun A to that reported for the enantiomer and found them to be in good agreement (Table 2).

The melting point of our synthetic material (200-201 °C) was in excellent agreement with the value we measured for natural (+)-danshexinkun A (198-200 °C) and with the published value (200 °C).[9a] A mixed sample of synthetic and natural (+)-danshexinkun A was prepared by grinding equivalent amounts of each compound together. The mixed melting point of this sample was observed at 197-200 °C. We had also planned to measure a mixed melting point of a sample prepared from a *solution* of synthetic and natural

31. Ikeshiro, Y.; Hashimoto, I.; Iwamoto, Y.; Mase, I.; Tomita, Y. *Phytochemistry*, **1991**, *30*, 2791.

material. Unfortunately, due to the decompositition of the very small amount of authentic natural (+)-danshexinkun we had obtained, we were not able to conduct this experiment.

To our knowledge, the optical rotation of (+)-danshexinkun A has not been published in the literature. The specific rotation measured for our synthetic (+)-danshexinkun A was $[\alpha]_D$ +30.0° (c = 0.01, $CHCl_3$). The magnitude of this value agrees with the specific rotation measured (at a higher concentration) for (-)-danshexinkun A $[\alpha]_D$ -33.0 (c = 0.09, $CHCl_3$).[31] An attempt was made to measure the optical rotation of the authentic sample of (+)-danshexinkun A provided to us by Dr. Wong. The specific rotation was found to be $[\alpha]_D$ +12.5° (c = 0.2, $CHCl_3$). However, the purity of this sample at this point at the time of the measurement is uncertain since when checked a few days later it was found to have partially decomposed. Due to the small amount of sample available, we were unable to repurify this material.

Although Fang and coworkers did not report the optical rotation of natural danshexinkun A or its absolute stereochemistry,[9a] we believe that it must be the S isomer. Other researchers have referred to natural danshexinkun A as the S isomer,[31] and this absolute configuration is consistent with that found in a number of related diterpene quinones isolated from the same plant. In particular, as discussed below, we have converted our synthetic (+)-danshexinkun A into (-)-dihydrotanshinone I, the absolute stereochemistry of which was established by comparison of its optical rotation to that of the natural product of known absolute configuration.

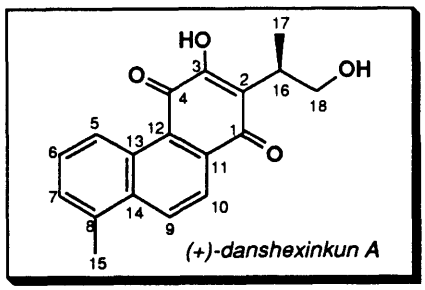


Table 1: ^{1}H NMR (300 MHz, $CDCl_3$) Spectral Data for Danshexinkun A

	Synthetic (+)-Danshexinkun A	Natural (+)-Danshexinkun A
1	-	-
2	-	-
3	8.05 (br, s)	8.05 (br, s)
4	-	-
5	9.43 (d, J = 9Hz)	9.42 (d, J = 9 Hz)
6	7.64 (dd, J = 7, 9 Hz)	7.63 (dd, J = 7, 9 Hz)
7	7.48 (d, J = 7 Hz)	7.46 (d, J = 7 Hz)
8	-	-
9	8.43 (d, J = 9 Hz)	8.42 (d, J = 7 Hz)
10	8.27 (d, J = 9 Hz)	8.26 (d, J = 9 Hz)
11	-	-
12	-	-
13	-	-
14	-	-
15	2.74 (s)	2.75 (s)
16	3.51 (m)	3.47 (m)
17	1.34 (d, J = 7 Hz)	1.32 (d, J = 7Hz)
18α	4.01 (dd, J = 8, 11 Hz)	3.98 (dd, J = 8, 11 Hz)
18β	3.87 (dd, J = 5, 11 Hz)	3.89 (dd, J = 5, 11 Hz)

Table 2: ^{13}C NMR Spectral Data for Danshexinkun A

	Synthetic (+)-Danshexinkun A (75 MHz, $CDCl_3$)	Natural (-)-Danshexinkun A[31] (100.4 MHz, $CDCl_3$-CD_3OD)
1	185.4	186.5
2	122.2	122.7
3	156.8	156.3
4	184.3	184.4
5	125.1	126.0
6	129.7	130.5
7	129.4	129.6
8	135.5	135.7
9	131.9	132.4
10	122.0	122.6
11	130.2	130.8
12	124.8	125.4
13	134.7	135.6
14	133.0	134.0
15	19.3	19.9
16	32.7	33.4
17	14.6	14.9
18	63.7	65.4

Synthesis of (-)-Dihydrotanshinone I

As described by Fang et al., the treatment of (+)-danshexinkun A (**5**) with concentrated sulfuric acid resulted in cyclization to afford (-)-dihydrotanshinone I (eq 4).[9a] After column chromatography, (-)-dihydrotanshinone I (**9**) was isolated in 65% yield as red needles, mp 221-222 °C (lit 224-225 °C).[11]

The specific rotation of synthetic (-)-dihydrotanshinone I was determined to be $[\alpha]_D$ -300 ° (c = 0.01, $CHCl_3$). This is in good agreement with the literature value reported for the natural product $[\alpha]_D$ -328° (c = 0.11, $CHCl_3$).[11] Due to the small amount of natural dihydrotanshinone we were able to obtain, we did not measure its optical rotation.

The ^1H NMR spectrum of synthetic (-)-dihydrotanshinone I (Figure 2) was compared to a spectrum we measured for the authentic sample and found to be in excellent agreement (Figure 2 and Table 3). The ^{13}C NMR spectral data for synthetic (-)-dihydrotanshinone I (**9**) (75 MHz, $CDCl_3$) closely matched the spectral data published for natural (-)-dihydrotanshinone I (100.4 MHz, $CDCl_3$-CD_3OD)[31] (Table 4). Resonances for the *ortho*-quinone carbonyls were observed at 184.3 and 175.7 ppm.

The melting point of a natural (-)-dihydrotanshinone I provided to us by Dr. Wong was 209-211 °C, somewhat lower compared to the literature value (224-225 °C)[11] and the value measured for our synthetic sample (221-222 °C). Examination of the ^1H NMR spectra of the authentic sample reveals the presence of trace impurities which probably account for the lower melting point.

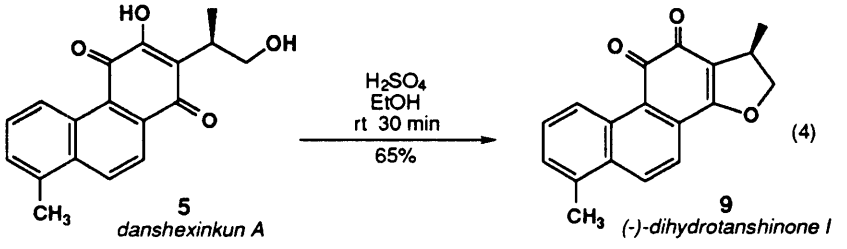
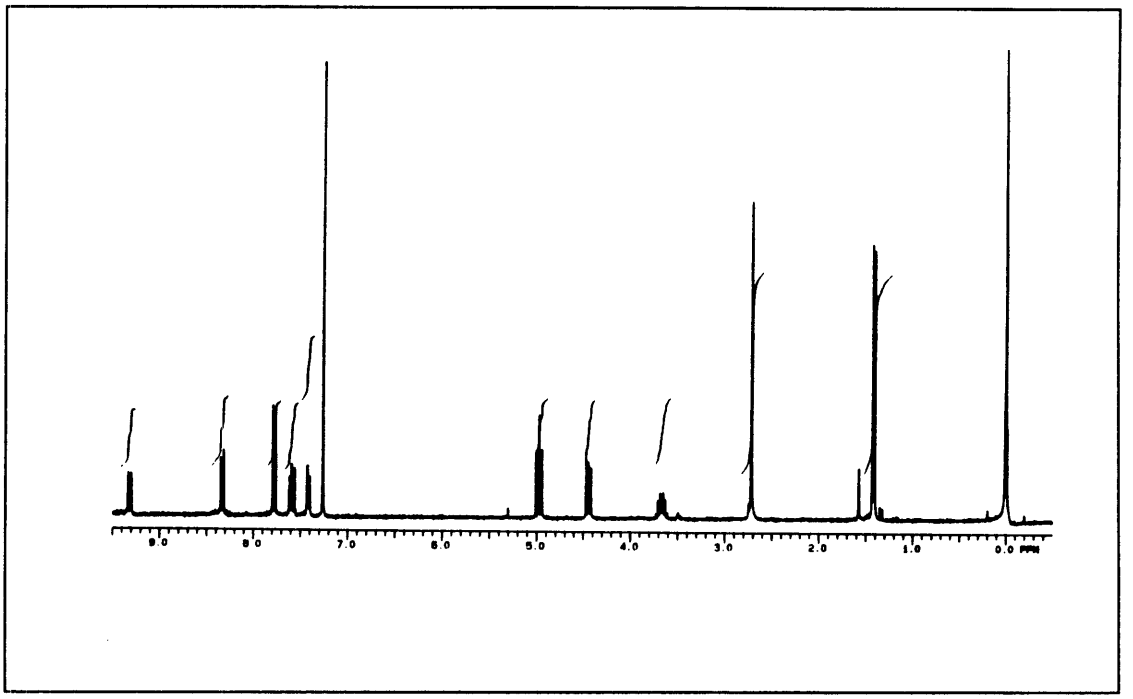
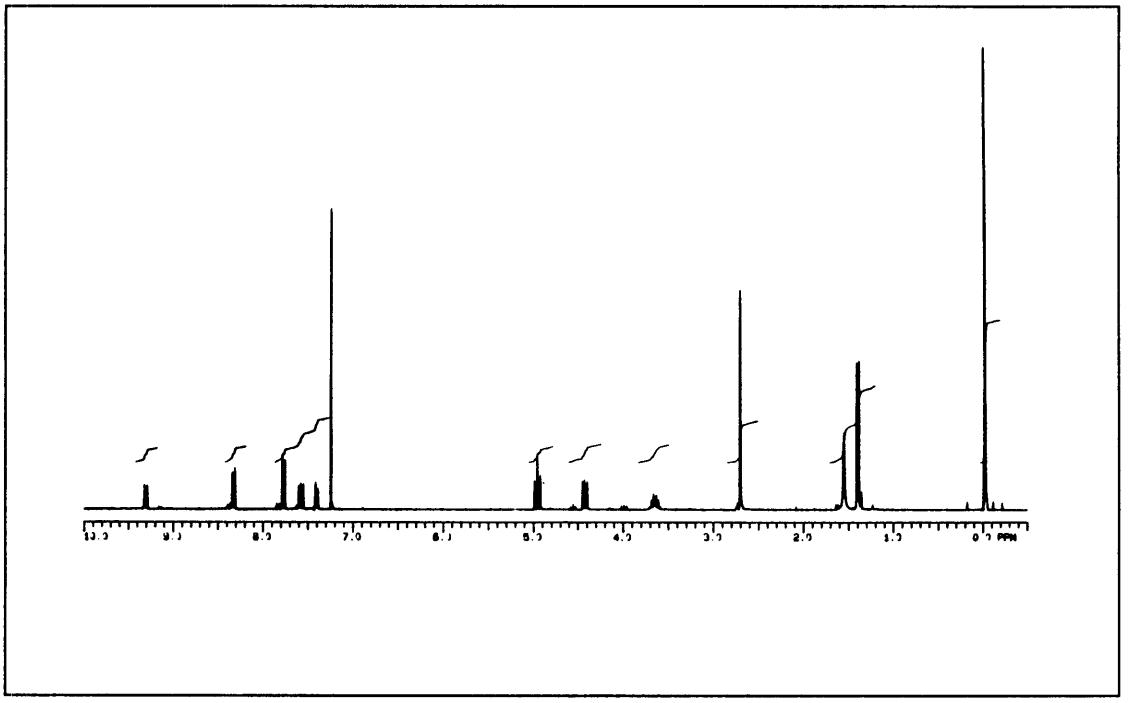


Figure 2: ^1H NMR Spectrum of Synthetic (-)-Dihydrotanshinone I in $CDCl_3$



^1H NMR Spectrum of Authentic (-)-Dihydrotanshinone I in $CDCl_3$



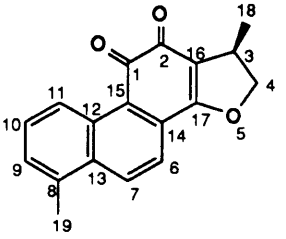


Table 3: ^{1}H NMR (300 MHz, $CDCl_3$) Spectral Data for Dihydrotanshinone I

	Synthetic (-)-Dihydrotanshinone I	Natural (-)-Dihydrotanshinone I
1	-	-
2	-	-
3	3.67 (ddq, J = 7, 10, 7 Hz)	3.65 (ddq, J = 7, 10, 7 Hz)
4α	4.44 (dd, J = 6, 10 Hz)	4.42 (dd, J = 6, 10 Hz)
4β	4.98 (app t, J = 10 Hz)	4.96 (app t, J = 10 Hz)
5	-	-
6	7.79 (d, J = 8 Hz)	7.77 (d, J = 9 Hz)
7	8.33 (d, J = 9 Hz)	8.33 (d, J = 8 Hz)
8	-	-
9	7.42 (d, J = 7 Hz)	7.40 (d, J = 7 Hz)
10	7.59 (dd, J = 7, 9 Hz)	7.58 (dd, J = 7, 9 Hz)
11	9.32 (d, J = 9 Hz)	9.31 (d, J = 9 Hz)
12	-	-
13	-	-
14	-	-
15	-	-
16	-	-
17	-	-
18	1.42 (d, J = 7 Hz)	1.40 (d, J = 7 Hz)
19	2.72 (s)	2.70 (s)

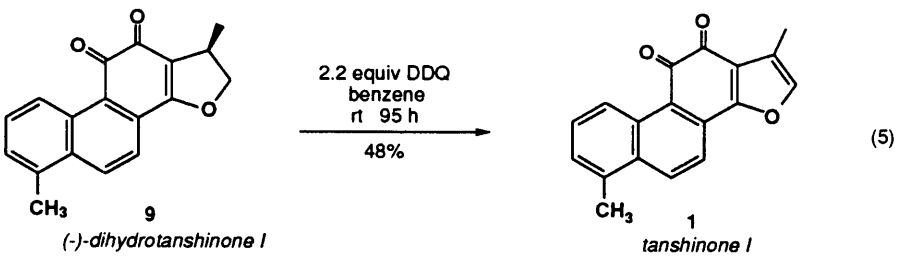
Table 4: ^{13}C NMR Spectral Data for Dihydrotanshinone I

	Synthetic (-)-Dihydrotanshinone I (75 MHz, $CDCl_3$)	Natural (-)-Dihydrotanshinone I[31] (100.4 MHz, $CDCl_3$-CD_3OD)
1	184.3	184.3
2	175.7	175.7
3	34.7	34.8
4	81.6	81.7
5	-	-
6	120.3	120.3
7	132.0	131.8
8	134.9	135.0
9	128.8	128.9
10	130.4	130.4
11	125.0	125.1
12	134.8	134.8
13	132.1	132.2
14	128.2	128.3
15	126.1	126.2
16	118.4	118.4
17	170.6	170.4
18	18.8	18.8
19	19.9	19.8

Synthesis of Tanshinone I

Dehydrogenation of (-)-dihydrotanshinone I (**9**) was accomplished by treatment with DDQ in benzene at room temperature to furnish tanshinone I (eq 5). Column chromatography afforded tanshinone I (**1**) in 48% yield (74% yield based on recovered starting material) as dark red needles, mp 226-227 °C (lit. 233-234 °C).[11] The melting point measured for an authentic sample of the natural product provided by Dr. Wong was 223-224 °C. ^{1}H NMR spectral data of both synthetic and authentic tanshinone I were essentially identical (Figure 3 and Table 5) and in excellent agreement with the published data.[11] ^{13}C NMR data for synthetic tanshinone I exhibited carbonyl resonances at 183.4 and 175.5 ppm. This spectral data was found to be consistent with published data for similar *ortho*-quinone compounds.[31]

Due to a limited amount of synthetic material, this final transformation was tried only once and afforded tanshinone I in 48% yield. However, Casebier was able to effect this final step in 97% yield using similar DDQ conditions (1.9 equiv, benzene, rt, 36 h) and this is considered to be the optimized yield for this step.[14]



(5)

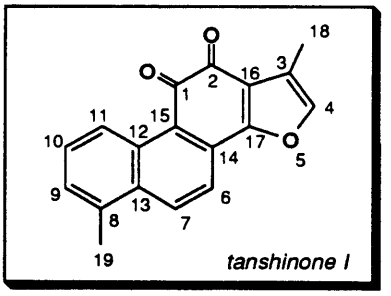
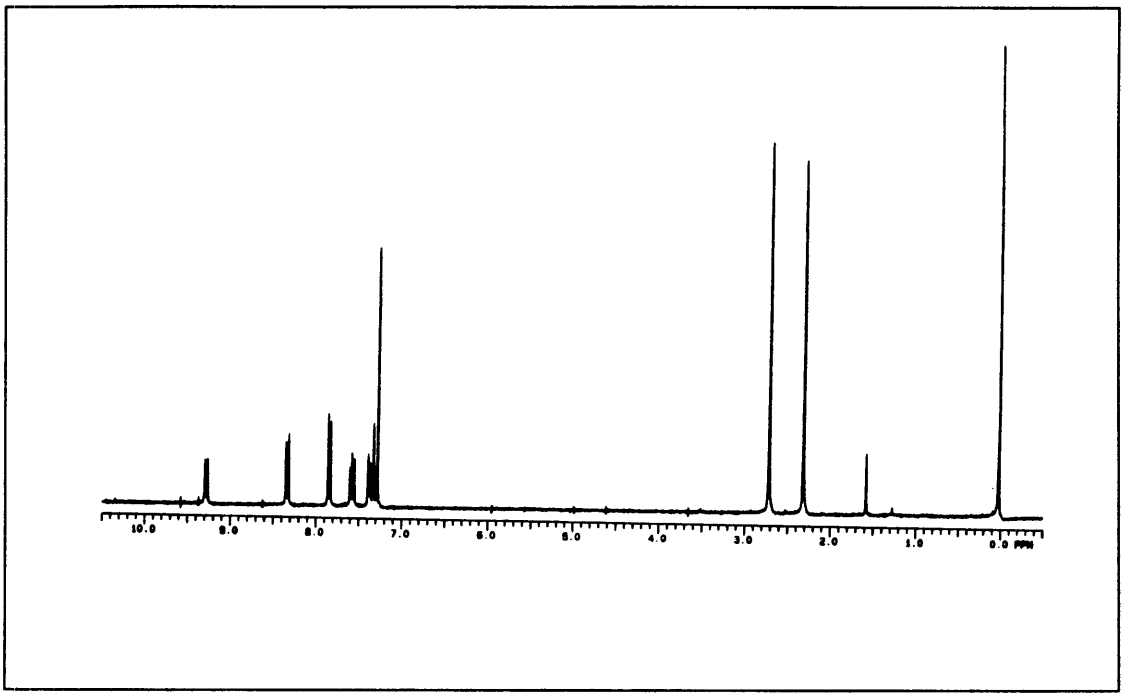


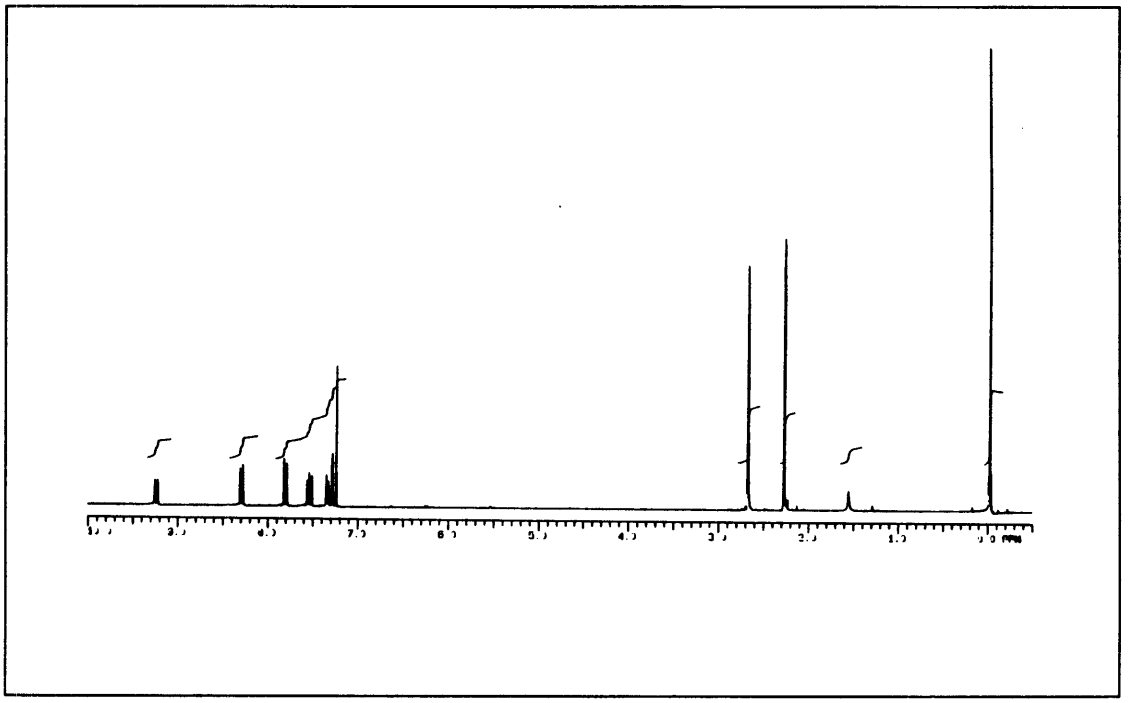
Table 5: ^{1}H NMR (300 MHz, $CDCl_3$) Spectral Data for Tanshinone I

	Synthetic Tanshinone I	Natural Tanshinone I
1	-	-
2	-	-
3	-	-
4	7.22 (s)	7.28 (s)
5	-	-
6	7.78 (d, J = 9 Hz)	7.81 (d, J = 8 Hz)
7	8.27 (d, J = 9 Hz)	8.30 (d, J = 9 Hz)
8	-	-
9	7.32 (d, J = 7 Hz)	7.34 (d, J = 7 Hz)
10	7.52 (dd, J = 7, 9 Hz)	7.54 (dd, J = 7, 9 Hz)
11	9.22 (d, J = 9 Hz)	9.24 (d, J = 9 Hz)
12	2.25 (s)	2.27 (s)
13	2.66 (s)	2.67 (s)

Figure 3: ^1H NMR Spectrum of Synthetic Tanshinone I in $CDCl_3$



^1H NMR Spectrum of Authentic Tanshinone I in $CDCl_3$



This is the first reported total synthesis of (+)-danshexinkun A (**5**). Only five steps are required to produce (+)-danshexinkun A in 37-46% overall yield from 1-napthoic acid. The synthesis of (-)-dihydrotanshinone I (**9**) establishes for the first time the absolute stereochemistry of the furan ring. Our route to (-)-dihydrotanshinone I requires five steps and affords the natural product under optimized conditions in 24-30% overall yield. From (-)-dihydrotanshinone I (**9**), only one additional step is needed to produce tanshinone I in 23-29% overall yield.

Part II

Synthesis and Chemistry of (Trialkylsilyl)vinylketenes ("TAS-Vinylketenes")

Part II of this thesis will focus on the synthesis and chemistry of (trialkylsilyl)vinylketenes ("TAS-vinylketenes"). The development of a general and efficient method for the preparation of these compounds based on the photochemical Wolff rearrangement of α-silyldiazo ketones is presented as well as the results of an investigation of their utility as four-carbon building blocks in new cycloaddition and annulation strategies. The background relevant to our results will be presented in two parts: *Chapter 1* - an introduction to the chemistry of *vinylketenes* with a discussion of their preparation, reactivity, and use in synthesis, followed by *Chapter 2* - an introduction to the chemistry of *silylketenes* with a discussion of their preparation, stability, and use in synthesis.

CHAPTER 1

INTRODUCTION AND BACKGROUND: VINYLKETENES

Introduction

Since the early part of this century, ketenes have been studied extensively and their utility as versatile synthetic intermediates has been exploited for a variety of useful transformations. Pioneering studies on ketene chemistry were conducted in the laboratory of Staudinger.[32] These early investigations focused on the development of synthetic routes to simple alkyl and arylketenes as well as the systematic examination of their chemistry, including reactions such as dimerization, polymerization, and their addition reactions with nucleophiles. Over the years, interest concerning the synthetic, mechanistic, and theoretical aspects of ketene chemistry has increased greatly.[33]

Vinylketenes were suspected as intermediates in chemical reactions as far back as 1941.[34] Relatively few vinylketenes have been isolated and characterized[35] due to their natural tendency towards dimerization, polymerization, and oxidation. However, many vinylketenes have been identified as transient intermediates in a number of reactions, and also may be generated *in situ* for reaction with various substrates.

Generation of Vinylketenes

Presently, a number of methods exist for the preparation of vinylketenes. In most cases the vinylketene is not isolated, but immediately reacts with a ketenophile present in the reaction mixture.

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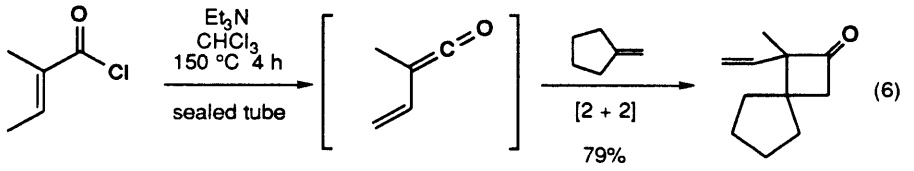
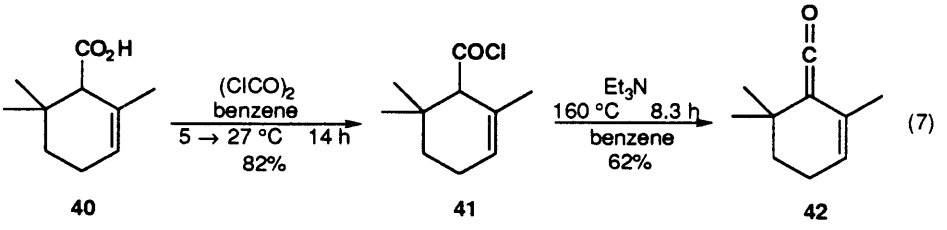
32. (a) Staudinger, H. *Chem. Ber.* **1905**, *38*, 1735. (b) Staudinger, H.; Ott, E. *Chem. Ber.* **1908**, *41*, 2208. (c) Staudinger, H.; Anthes, E.; Schneider, H. *Chem. Ber.* **1913**, *46*, 3539.
33. For recent reviews in the area of ketene chemistry, see: (a) "The Chemistry of Ketenes, Allenes, and Related Compounds", Patai, S. Ed.; John Wiley and Sons: New York, 1980; and references cited therein. (b) Hyatt, J. A.; Raynolds, P. W. *Org. React.* **1994**, *45*, 159. (c) Schaumann, E., Scheiblich, S. In *Methoden der organischen Chemie (Houben Weyl);* Kropf, H., Schaumann, E., Eds.; George Thieme; Stuttgart, 1993; Vol. E15/3, pp 2818-2880, 2933-2957.
34. Smith, L. I.; Hoehn, H. H. *J. Am. Chem. Soc.* **1941**, *63*, 1181.
35. (a) Wuest, J. D.; Madonik, A. M.; Gordon, D. C. *J. Org. Chem.* **1977**, *42*, 2111. (b) Dötz, K. H. *Ang. Chem. Int. Ed. Engl.* **1979**, *18*, 954. (c) Dötz, K. H.; Fugen-Kosterm, B. *Chem. Ber.* **1980**, *113*, 1449. (d) Danheiser, R. L.; Sard, H. *J. Org. Chem.* **1980**, *45*, 4810.

A classical approach to the synthesis of ketenes involves the dehydrohalogenation of an acid chloride. Payne applied this method for the first time to an α,β-unsaturated acid chloride in 1966.[36] In this early work, isopropenylketene was generated from 3-methyl-2-butenoyl chloride with trimethylamine in the presence of ethyl vinyl ether. Both the ketene dimer and [2 + 2] ketene-olefin cycloadduct were isolated. Since this initial study, a variety of vinylketenes have been prepared employing the dehydrohalogenation strategy.[37] For example, Dreiding and coworkers have utilized the dehydrohalogenation method for the synthesis of alkylvinylketenes and studied [2 + 2] vinylketene-olefin cycloadditions (eq 6).[37d]



(6)

In 1977, Wuest reported the first isolation and characterization of a vinylketene.[35a] Treatment of the acyl chloride **41** with triethylamine in benzene at 160 °C produced the sterically shielded vinylketene **42** which was isolated by distillation at reduced pressure as a yellow-orange liquid in 51% overall yield from **40** (eq 7).



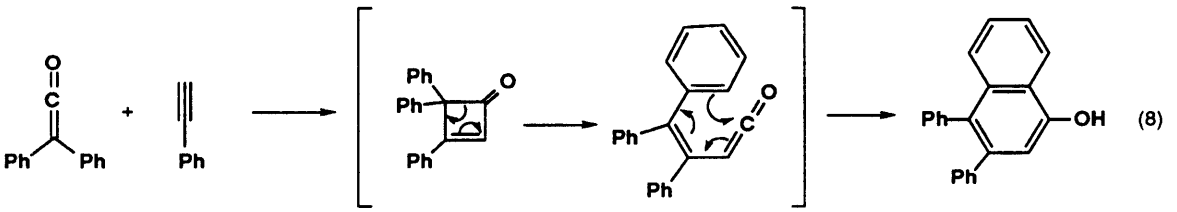
(7)

36. Payne, G. B. *J. Org. Chem.* **1966**, *31*, 718.

37. For several examples of the generation of vinylketenes via dehydrohalogenation, see: (a) Gelin, R.; Gelin. S.; Dohnazon, R. *Tetrahedron Lett.* **1970**, 3657. (b) Hickmott, P. W.; Miles, G. J.; Sheppard, G.; Urbani, R.; Yoxall, C. T. *J. Chem. Soc., Perkin Trans. 1* **1973**, 1514. (c) Rey, M.; Roberts, S.; Dieffenbacher, A.; Dreiding, A. S. *Helv. Chim. Acta* **1970**, *53*, 417. (d) Rey, M.; Dunkelblum, E.; Allain, R.; Dreiding, A. S. *Helv. Chim. Acta* **1970**, *53*, 2159. (e) Dondoni, A. *Heterocycles* **1980**, 1547. (f) Wuest, J. D. *Tetrahedron* **1980**, *36*, 2291. (g) Huston, R.; Rey, M.; Dreiding, A. S. *Helv. Chim. Acta* **1982**, *65*, 451. (h) Holder, R.; Dreiding, A. S. *Helv. Chim. Acta* **1983**, *66*, 2330. (i) Danheiser, R. L.; Martinez-Davila, C.; Sard, H. *Tetrahedron* **1981**, *37*, 3943. (j) Danheiser, R. L.; Gee, S. K.; Sard, H. *J. Am. Chem. Soc.* **1982**, *104*, 7670.

Unfortunately, the dehydrohalogenation method suffers in general from limitations due to the triethylamine hydrochloride produced as a byproduct. This amine salt has been noted to catalyze the polymerization of ketenes[38] and isomerize the β,γ-double bond of 2-vinylcyclobutanones (products resulting from vinylketene-olefin [2 + 2] cycloadditions) into conjugation with the carbonyl.[37h]

An alternative method for generating vinylketenes involves the electrocyclic ring opening of cyclobutenones which can be effected under either thermal[39] or photochemical[40,45] conditions. In 1939, Smith and Hoehn observed the formation of α-naphthols when diphenylketene was heated with mono- and disubstituted acetylenes.[41] Woodward and Arens later suggested the participation of cyclobutenones as intermediates in this reaction (eq 8).[42]



(8)

In the 1950's, Roberts et al. reported the thermal racemization of the optically active cyclobutenone **43**, which proceeds via a reversible electrocyclic ring opening (eq 9).[43,44]

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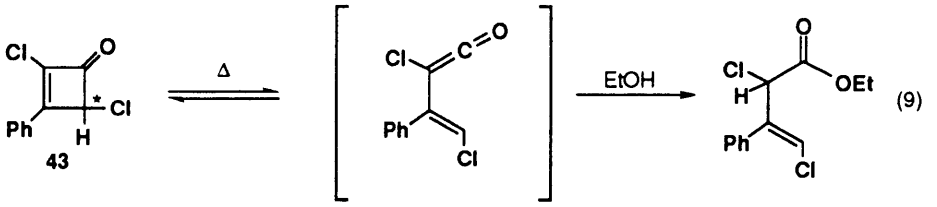
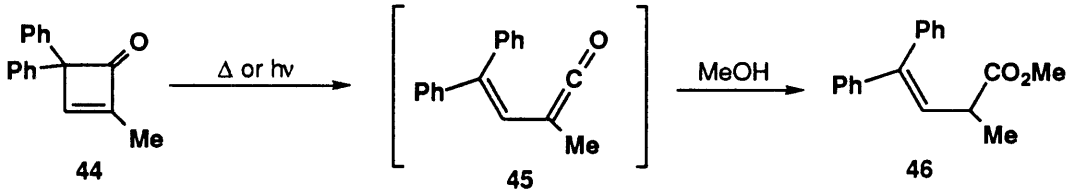
38. For example, see (a) Brady, W. T.; Waters, O. H. *J. Org. Chem.* **1967**, *32*, 3703. (b) Hansford, W. E.; Sauer, J. C. *Org. React.* **1946**, *3*, 108.
39. For recent reviews, see: (a) Durst, T.; Brean, L. In *Comprehensive Organic Synthesis;* Trost, B. M., Ed.; Pergamon Press: Oxford, 1991, Vol. 5, pp. 688-691. (b) Moore, H. W.; Decker, O. H. W. *Chem. Rev.* **1986**, *86*, 821. (c) Bellus, D.; Ernst, B. *Angew. Chem., Intl. Ed. Engl.* **1988**, 797. (d) Marvell, E. N. In *Thermal Electrocyclic Reactions*, Academic Press: New York, 1980, pp. 124-190.
40. For a discussion of the mechanistic differences which prevail under photochemical conditions, see: Kikuchi, O. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 1669.
41. (a) Smith, L. I.; Hoehn, H. H. *J. Am. Chem. Soc.* **1939**, *61*, 2619. (b) Smith, L. I.; Hoehn, H. H. *J. Am. Chem. Soc.* **1941**, *63*, 1175.
42. (a) Druey, J.; Jenny, E. F.; Schenker, K.; Woodward, R. B. *Helv. Chim. Acta* **1962**, *45*, 600. (b) Nieuwenhius, J.; Arens, J. F. *Recl. Trav. Chim. Pays-Bas* **1958**, *77*, 1153. (c) Arens, J. F. *Adv. Org. Chem.* **1960**, *2*, 191.
43. (a) Jenny, E. F.; Roberts, J. D. *J. Am. Chem. Soc.* **1956**, *78*, 2005. (b) Silversmith, E. F.; Kitahara, Y.; Roberts, J. D. *J. Am. Chem. Soc.* **1958**, *80*, 4088. (c) Silversmith, E. F.; Kitahara, Y.; Caserio, M. C.; Roberts, J. D. *J. Am. Chem. Soc.* **1958**, *80*, 5840.
44. For more examples of thermal electrocyclic ring opening to generate vinylketenes, see: refs. 13a, 37j, and (a) Maahs, G. *Angew. Chem., Int. Ed. Engl.* **1963**, *2*, 690. (b) Maahs, G. *Justus Liebigs Ann. Chem.* **1965**, *686*, 55.



(9)

Alternatively, the photochemical irradiation of cyclobutenones is known to promote electrocyclic cleavage to generate vinylketenes at room temperature. These mild photochemical conditions have been employed for the generation of a variety of vinylketenes.[45] For example, Mayr reported that cyclobutenone **44** opens under both thermal conditions (refluxing cyclohexane, 81 °C) and photolytic conditions (irradiation in carbon tetrachloride at 10 °C) to afford the vinylketene intermediate **45.** This intermediate was observed by its characteristic ketene band at 2097 cm^{-1} in the infrared spectrum and the appearance of a yellow color which disappeared upon the addition of methanol to produce the ester **46**.[46]



(10)

Mayr has also reported the synthesis and trapping of methylprenylketene **48** via the electrocyclic ring opening of 2,4,4-trimethylcyclobutenone (**47**). Cycloaddition of this vinylketene with ethyl vinyl ether produced a mixture of stereoisomeric cyclobutanones (eq 11).[45f]

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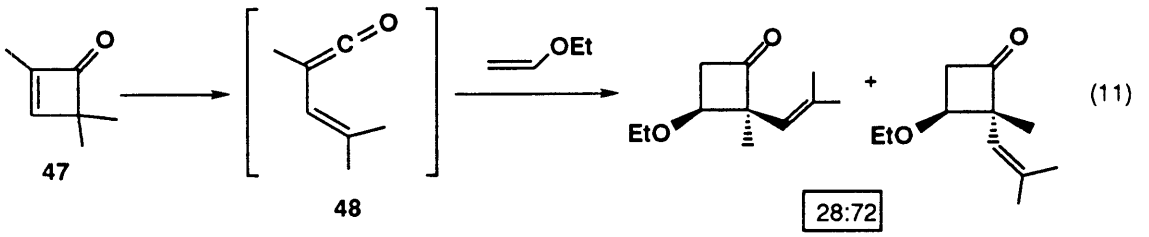
45. For more examples of photochemical electrocyclic ring opening to generate vinylketenes, see: (a) Barton, D. H. R. *Helv. Chim. Acta* **1959**, *42*, 2604. (b) Baldwin, J. E.; McDaniel, M. C. *J. Am. Chem. Soc.* **1968**, *90*, 6118. (c) Chapman, O. L.; Lassila, J. D. *J. Am. Chem. Soc.* **1968**, *90*, 2449. (d) Arnold, D. R.; Hedaya, E.; Merritt, V. Y.; Karnischky, L. A.; Kent, M. E. *Tetrahedron Lett.* **1972**, 3917. (e) Huisgen, R.; Mayr, H. *J. Chem. Soc., Chem. Comm.* **1976**, 55. (f) Huisgen, R.; Mayr, H. *J. Chem. Soc., Chem. Comm.* **1976**, 57.

46. Mayr, H. *Angew. Chem., Intl. Ed. Engl.* **1975**, *14*, 500.



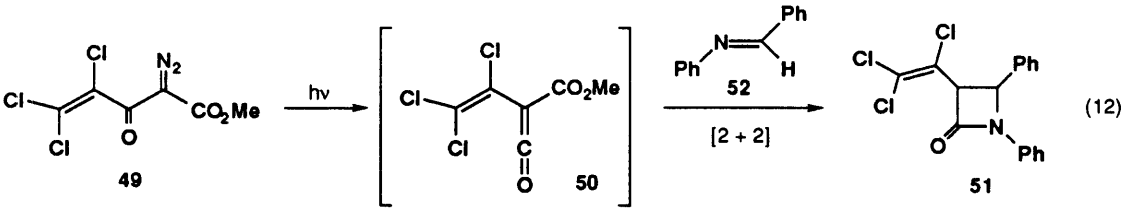
The electrocyclic ring opening of cyclobutenones is often preferred over other methods to generate vinylketenes because it does not produce a detrimental salt and allows the ketene to be generated at low effective concentrations which helps minimize ketene dimerization. In general, cyclobutenone ring opening serves as a mild and efficient method for the preparation of vinylketenes.

As mentioned above, vinylketenes are often observed spectroscopically as reactive intermediates.[47] In our laboratory, Kollol Pal conducted studies on the reversibility of the photochemical generation of vinylketenes from cyclobutenones. Upon irradiation of a solution of a particular cyclobutenone in perdeuterobenzene at temperatures ranging from 0 to 25 °C, Pal was able to observe the presence of a vinylketene by ^{1}H NMR spectroscopy.[47a]

Vinylketenes have also been obtained via the photochemical Wolff rearrangement[48] of α,β-unsaturated diazo ketones. As shown below in equation 12, irradiation of the diazo ketone **49** initially afforded the vinylketene **50** which was then trapped in a [2 + 2] cycloaddition with imine **52** to yield the β-lactam **51**.[49] This is an attractive method for vinylketene generation since the photochemical Wolff rearrangement can be induced at room temperature and produces nitrogen gas as the only byproduct. Our laboratory has also generated vinylketenes from α-diazo ketones via the photochemical Wolff

47. (a) Pal, K., Ph. D. Thesis, Massachusetts Institute of Technology, Cambridge, MA 1987, pp. 69-77. (b) Trahanovsky, W. S.; Suber, B. W.; Wilkes, M. C.; Preckel, M. M. *J. Am. Chem. Soc.* **1982**, *104*, 6779.
48. For reviews of the photochemical Wolff rearrangement, see: (a) Meier, H.; Zeller, K. P. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 32. (b) Ando, W. In *The Chemistry of the Diazonium and Diazo Groups;* Patai, S., Ed.; John Wiley and Sons: New York, 1978; Part 1, p. 458. (c) Regitz, M.; Maas, G. In *Diazo Compounds: Properties and Synthesis*; Academic Press: Orlando, FL, 1986; p. 185. (d) Gill, G. B. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, **1991**, Vol. 3, p. 891.
49. Roedig, A.; Fahr, E.; Aman, H. *Chem. Ber.* **1964**, *97*,77.

rearrangement in our recently developed aromatic annulation strategy as discussed in Part I of this thesis.[13b] Irradiation of pyrazoles has also been shown to generate α-diazo ketones which upon further irradiation afford vinylketenes as well.[50]



(12)

In summary, three methods to produce vinylketenes have been described: dehydrohalogenation of α,β-unsaturated acid chlorides, electrocyclic ring opening of cyclobutenones, and photochemical Wolff rearrangement of α,β-unsaturated diazo ketones. There are also a number of vapor phase pyrolysis methods[51] as well as other photochemical methods (that do not involve the irradiation of cyclobutenones or diazo compounds) by which specific vinylketenes have been generated.[52]

Reactions of Vinylketenes

(1) Addition of Nucleophiles to Vinylketenes

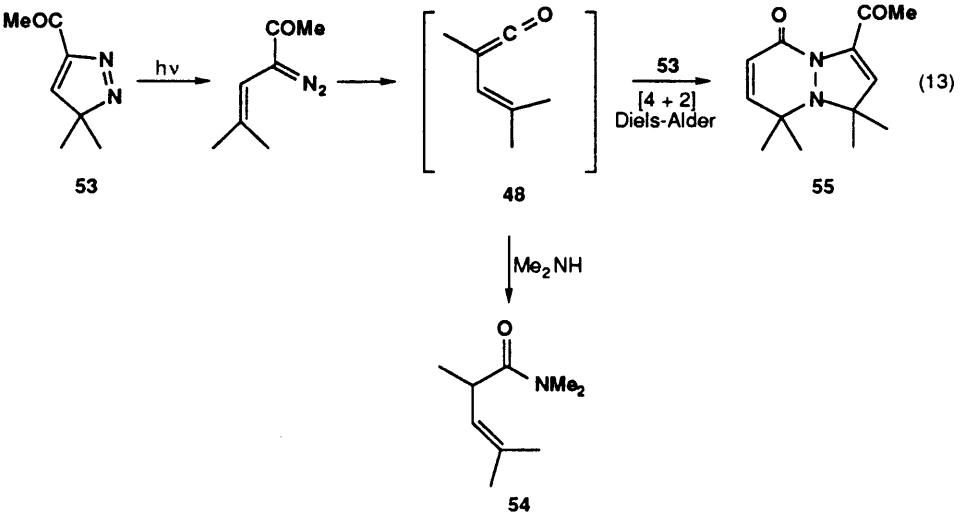
In general, ketenes undergo addition reactions with nucleophiles such as water, alcohols, amines, and carboxylic acids to yield acids, esters, amides, and anhydrides respectively. Oftentimes there are simpler routes to these products and therefore

50. (a) Franck-Neumann, M.; Buchecker, C. *Tetrahedron Lett.* **1973**, 2875. (b) Day, A. C.; McDonald, A. N.; Anderson, B. F.; Bartczak, T. J.; Hodder, O. J. R. *J. Chem. Soc., Chem. Comm.* **1973**, 247.

51. (a) Brown, R. F. C.; Butcher, M. *Aust. J. Chem.* **1969**, *22*, 1457. (b) Rousseau, G.; Bloch, R.; LePerchec, P.; Conia, J. M. *J. Chem. Soc., Chem. Comm.* **1973**, 795. (c) Schiess, P.; Radimerski, P. *Helv. Chim. Acta* **1974**, *57*, 2583. (d) Schiess, P.; Heitzmann, M. *Angew. Chem. Int. Ed. Engl.* **1977**, *16*, 469. (e) Terlouw, J. K.; Burgers, P. C.; Holmes, J. L. *J. Am. Chem. Soc.* **1979**, *101*, 225. (f) Holmes, J. L.; Terlouw, J. K.; Vijfhuizen, P. C.; Campo, C. A. *Org. Mass Spectrom.* **1979**, *14*, 204. (g) Mohmand, S.; Hirabayashi, T.; Bock, H. *Chem. Ber.* **1981**, *114*, 2609.

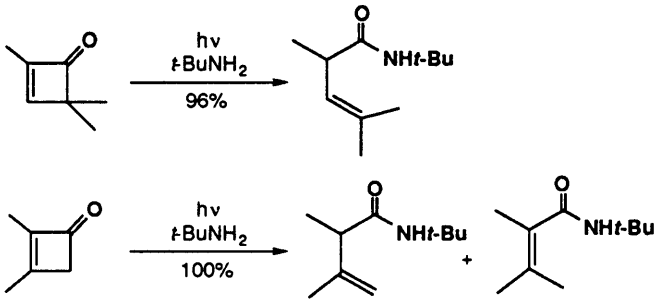
52. (a) Chapman, O. L.; McIntosh, C. L.; Pacansky, J. *J. Am. Chem. Soc.* **1873**, *95*, 244. (b) McIntosh, C. L.; Chapman, O. L. *J. Am. Chem. Soc.* **1973**, *95*, 247. (c) Pong, R. G. S.; Shirk, J. S. *J. Am. Chem. Soc.* **1973**, *95*, 248. (d) Collins, P. M.; Hart, H. *J. Chem. Soc. (C)* **1967**, 1197. (e) Griffiths, J.; Hart, H. *J. Am. Chem. Soc.*, **1968**, *90*, 5296. (f) Barton, D. H. R.; Quinkert, *J. Chem. Soc.*, **1960**, 1. (g) Quinkert, G. *Angew. Chem., Int. Ed. Eng.* **1965**, *4*, 211. (h) Quinkert, K. R.; Schmieder, G.; Dürner, G.; Hache, K.; Stegk, A.; Barton, D. H. R. *Chem. Ber.* **1977**, *110*, 3583.

nucleophilic additions to ketenes are not used a great deal synthetically. However, the addition of nucleophiles is frequently used to confirm if a ketene was generated under the reaction conditions. In the case presented below (eq 13), the photochemical generation of vinylketene **48** was established after the addition of dimethylamine to the reaction mixture produced amide **54**.[50b]



Similarily, Kollol Pal used this method in our laboratory to intercept vinylketenes generated from the photochemical electrocyclic ring opening of cyclobutenones (Scheme 8). In these studies, *tert*-butylamine was employed as the nucleophile because it does not contain a chromophore and therefore, would not interfere with the photochemical transformation. As shown below, the amine served as a very effective trap for the vinylketenes.[47a]

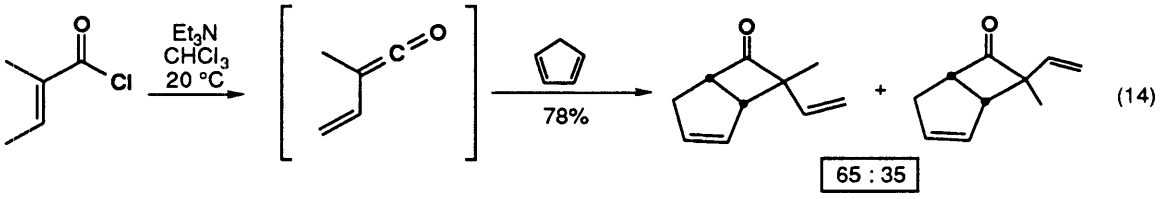
Scheme 8



(2) [2 + 2] Cycloadditions of Vinylketenes in Synthesis

The regiospecific [2 + 2] cycloaddition of ketenes with olefins is a common, synthetically useful reaction which provides one of the most efficient routes for the synthesis of four-membered rings. Mechanistically, the [2 + 2] cycloaddition is described as a [π2s + π2a] process, in which the ketene reacts in an antarafacial mode and the ketenophile in a suprafacial mode. For cycloadditions of this type, ketenes are ideal antarafacial components since one of their carbon atoms is an *sp* hybridized carbonyl carbon which offers a minimum amount of steric hindrance. This results in a significant decrease in the degree of crowding in the transition state favoring the [2 + 2] mode of reaction.

A number of groups have utilized the [2 + 2] cycloaddition of vinylketenes in the preparation of 2-vinylcyclobutanones.[53] For example, Dreiding reported the generation of methylvinylketene via *in situ* dehydrohalogenation and trapped it with a number of simple olefins as illustrated below (eq 14).[37d,h]



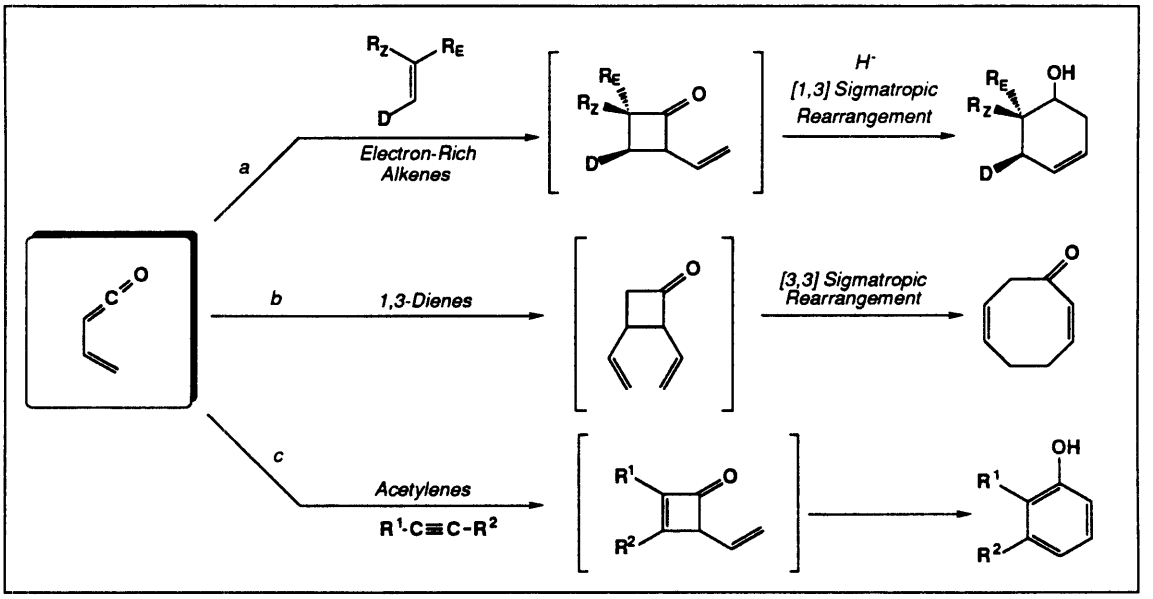
(14)

(3) Annulation Strategies Based on Vinylketene [2 + 2] Cycloadditions

Over the past 15 years, several new annulation methods have been developed which exploit the [2 + 2] reactivity of vinylketenes with both alkenes and acetylenes. Our laboratory has been particularly interested in employing vinylketenes as four-carbon components for the development of new synthetic approaches to a variety of carbocyclic and heterocyclic systems (Scheme 9).

53. For examples, see: Ref 13, 37d,h,i,j, and 45f.

Scheme 9



In 1981, our laboratory reported a new annulation approach to the synthesis of 3-cyclohexenol derivatives via an alkoxy-accelerated rearrangement of vinylcyclobutanes (*pathway a*).[37i] The vinylketenes required for this method were produced via dehydrohalogenation of α,β-unsaturated acid chlorides (using triethylamine in chloroform) in the presence of excess ketenophile. The vinylketene generated reacts in a [2 + 2] fashion with the olefin to produce a 2-vinylcyclobutanone, which upon addition of a suitable nucleophile then undergoes an alkoxy-accelerated [1,3]-sigmatropic rearrangement to produce the 3-cyclohexenol. Overall, this process constitutes a powerful [4 + 2] annulation which utilizes the four-carbon vinylketene unit for the synthesis of six-membered carbocycles.

As outlined above (*pathway b*), the [4 + 4] annulation approach developed in our laboratory for the synthesis of cyclooctadienone derivatives employs a 1,3-diene as one four-carbon unit and a vinylketene as the second four-carbon unit.[37j] For this reaction, the vinylketene is generated either by thermal electrocyclic cyclobutenone cleavage or via 1,4-dehydrohalogenation of an α,β-unsaturated acid chloride. The vinylketene produced then undergoes a regiospecific [2 + 2] cycloaddition with the conjugated diene to yield a 2,3-

divinylcyclobutanone derivative. At elevated reaction temperatures, this divinylcyclobutanone rearranges to produce the eight-membered annulation product. Both Dreiding[37g,54] and Tranhanovsky[47b] have reported this type of annulation strategy with a vinylketene and cyclopentadiene which upon [2 + 2] cycloaddition rearranges to afford bicyclo[4.2.1]nonadienones.

An annulation route to highly substituted aromatic systems based on the [2 + 2] cycloaddition of vinylketenes and acetylenes (Scheme 9; *pathway c*) has been developed in our laboratories.[13] This annulation method is described in detail in Part I of this thesis. Related methodology for the synthesis of quinones has been developed independently in the laboratories of Liebeskind[55] and Moore[56] using vinylketenes generated from modified squaric acid derivatives

In 1975, Dötz[57] reported a transition metal-mediated aromatic annulation that employs Fischer carbenes for the synthesis of 1,4-hydroquinones. The mechanism of this reaction (outlined in Scheme 10) involves the generation of a vinylketene intermediate which is stabilized by complexation with chromium. Vinylketenes have been confirmed as intermediates in this reaction through nucleophilic trapping experiments and the isolation of stable compounds in several cases.[57b]

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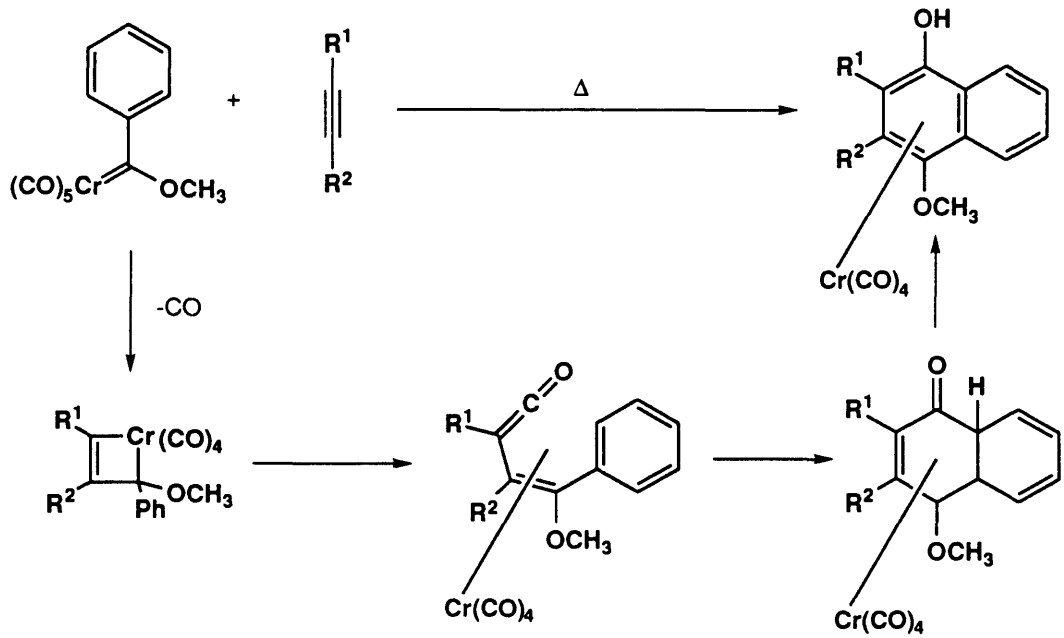
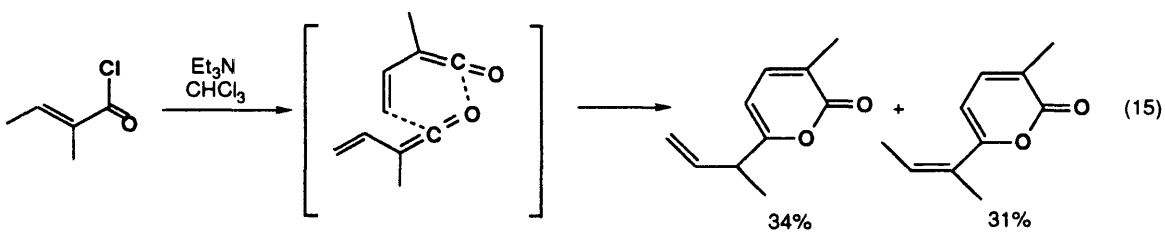
54. Huston, R.; Rey, M.; Dreiding, A. S. *Helv. Chim. Acta* **1984**, *67*, 1506.
55. Liebeskind, L. S.; Iyer, S.; Jewell, C. F., Jr. *J. Org. Chem.* **1986**, *51*, 3065.
56. (a) Perri, S. T.; Foland, L. D.; Decker, O. H.; Moore, H. W. *J. Org. Chem.* **1986**, *51*, 3067. (b) Perri, S. T.; Moore, H. W. *Tetrahedron Lett.* **1987**, *28*, 4507. (c) Moore, H. W.; Perri, S. T. *J. Org. Chem.* **1988**, *53*, 996.
57. For reviews, see: (a) Dötz, K. H.; Fischer, H.; Hofmann, P.; Kriessel, F. R.; Schubert, U.; Weiss, K. *Transition Metal Carbene Complexes*; Verlag Chemie International: Deerfield Beach, FL, 1984. (b) Dötz, K. H. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 587. (c) Wulff, W. D. In *Advances in Metal-Organic Chemistry*; Liebskind, L. S., Ed.; JAI Press Inc.: Grenwich, CT, 1989; Vol. 1. (d) Wulff, W. D. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, 1991, Vol 5, pp. 1089-1106.

Scheme 10



(4) Dimerization of Vinylketenes

The ease of preparation and isolation of ketenes is very dependent upon their reactivity, particularly towards dimerization. Many ketenes are known to dimerize quite readily.[33a,b] For example, ketene can be handled as a pure colorless liquid at -78 °C yet dimerizes exothermically below room temperature to afford a [2 + 2] cycloadduct.[33b] Vinylketenes also dimerize, but produce [4 + 2] cycloaddition products as shown below. Dreiding and coworkers described vinylketene dimerization as a new method to make α-pyrones in the early 1970's (eq 15).[37d]

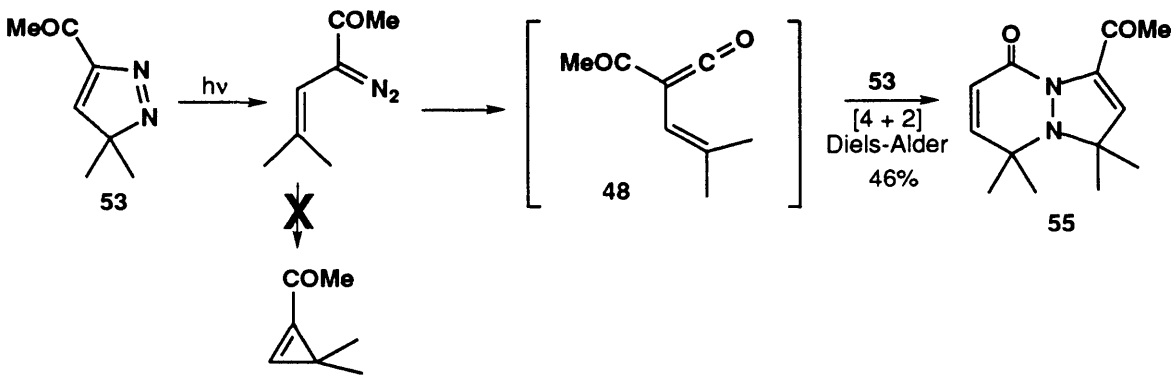


(15)

(5) [4 + 2] Cycloadditions of Vinylketenes

Due to the normal tendency of vinylketenes to form [2 + 2] cycloadducts with olefins, limited examples of the direct use of vinylketenes as [4 + 2] enophiles exist. In 1973, Day observed the reaction of the vinylketene **48** as the four-carbon diene in an unexpected Diels-Alder reaction with the N=N bond of the diazo compound **53** (Scheme 11).[50b]

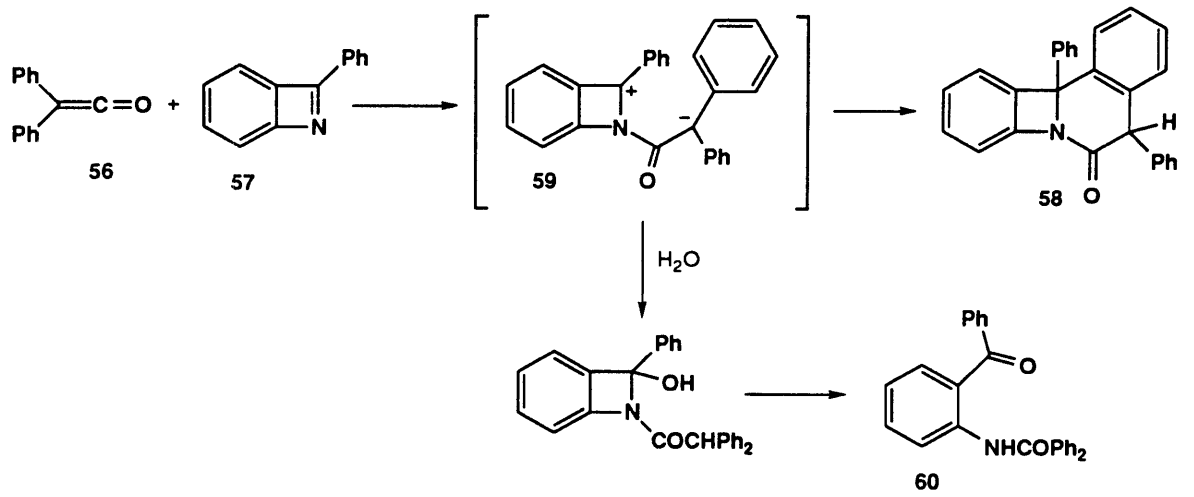
Scheme 11



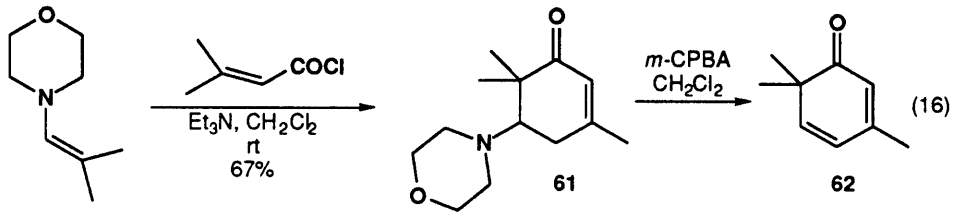
Similarily, diphenylketene **56** has been shown to react with the highly strained imine, 2-phenylbenzazete (**57**) in a [4 + 2] fashion to afford the cycloadduct **58** (Scheme 12).[58] This transformation is presumed to occur via a stepwise mechanism. Experiments have demonstrated trapping of the zwitterionic intermediate **59** with water to produce the amidoketone **60**. Control experiments have also been conducted to show that the amidoketone **60** does not arise by hydration of the final product **58** or by the addition of diphenylacetic acid to the azete **57**.

58. Rees, C. W.; Somanathan, R.; Storr, R. C.; Woolhouse, A. D. *J. Chem. Soc., Chem. Comm.* **1976**, 125.

Scheme 12



More recently, Dreiding has demonstrated the cycloaddition of alkyl- and aldo-vinylketenes to enamines to afford [4 + 2] cycloadducts (eq 16).[59] Upon mild oxidation the cyclohexenone **61** undergoes a Cope-type elimination to yield cyclohexadienone **62**.



To date, the utility of vinylketenes as synthetic intermediates has been well established and their reactivity in [2 + 2] cycloadditions has proven to be useful in the synthesis of a variety of cyclic systems. However questions still remain such as: "Is it possible to prepare stable, isolable vinylketene derivatives?" "Can the [2 + 2] reactivity of vinylketenes be suppressed?" and "Can vinylketenes function in other types of synthetically useful cycloaddition and annulation processes?" Answers to these questions will be the focus of the remaining chapters of this thesis.

59. Berge, J. M.; Rey, M.; Dreiding, A. S. *Helv. Chim. Acta* **1982**, *65*, 2230.

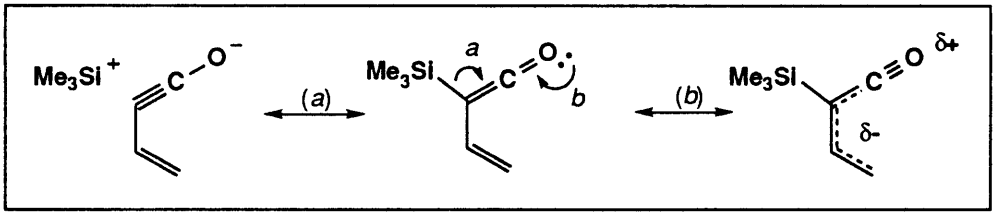
CHAPTER 2

INTRODUCTION AND BACKGROUND: (TRIALKYSILYL)KETENES ("TAS-KETENES")

The objective of the studies described in the remainder of this thesis was to develop a general method for the synthesis of TAS-vinylketenes and to investigate their utility as four-carbon components in new annulation strategies. This chapter reviews the chemistry of simple (trialkylsilyl)ketenes and explains the basis for our expectation that TAS-vinylketenes might be stable compounds that would function as useful four-carbon building blocks in synthesis.

Properties of TAS-Ketenes

Silylketenes exhibit dramatically different properties from those found for most ketenes.[60] Silyl substituents have the unique ability to stabilize ketenes and suppress their natural tendency to dimerize and undergo [2 + 2] cycloadditions.[61] This stabilization has been attributed to an electron-releasing effect of the silicon-carbon σ-bond. Hyperconjugative donation of this σ–bond to the ketene π-system renders the carbonyl less electrophilic and less reactive toward cycloadditions and nucleophilic addition reactions (*a*).



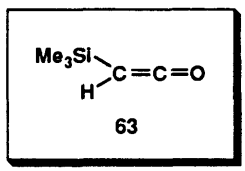
60. Reviews: (a) Colvin, E. *Silicon in Organic Synthesis* Butterworths: London, 1982; Chapter 14. (b) Moreau, J.-L. "Organometallic Derivatives of Allenes and Ketenes" In The Chemistry of Ketenes, Allenes, and Related Compounds; Patai, S. Ed.; Wiley: New York, 1980, pp 401-413. (c) Tidwell, T. *Ketenes* John Wiley & Sons, Inc. New York, 1995; 348-365.

61. For theoretical calculations regarding the stability and reactivity of these compounds, see (a) Gong, L; Mc Allister, M. A.; Tidwell, T. T. *J. Am. Chem. Soc.* **1991**, *113*, 6021. (b) Allen. A. D.; Tidwell, T. T. *Tetrahedron Lett.* **1991**, *32*, 847.

Thus far, the use of silylketenes in synthesis has been relatively limited, and the majority of studies have been conducted on the "parent derivative", (trimethylsilyl)ketene. Our laboratory reported the first synthesis of a (silyl)*vinyl*ketene and its participation in Diels-Alder reactions in 1980.[35d] In these reactions, the vinylketene behaves as an electron-rich diene in which the carbonyl oxygen exerts a strong directing effect thus controlling the regiochemical course of the cycloadditions (*b*).

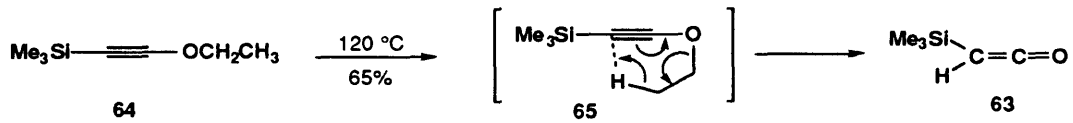
Preparation of (Trimethylsilyl)ketene and Other TAS-Ketene Derivatives

(Trimethylsilyl)ketene (**63**) is a colorless liquid that boils at 82 °C. It is unusually stable for an aldoketene with respect to polymerization and decomposition. Samples of (trimethylsilyl)ketene can be stored neat under nitrogen at room temperature for several years without decomposition.



63

In 1965, (trimethylsilyl)ketene was first prepared via the silylation of ethoxyacetylene to afford **64** followed by the thermally induced elimination of ethylene at 120 °C as illustrated below.[62]

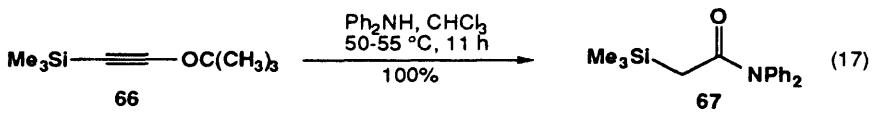


64 **65** **63**

A recent improvement in this method has been reported which involves the thermal decomposition of (*tert*-butoxytrimethylsilyl)ethyne (**66**) (eq 17).[63] Elimination

62. Shchukovskaya, L. L.; Pal'chik, R. I.; Lazarev, A. N. *Dokl. Akad. Nauk SSSR* **1965**, *164*, 357.
63. Valenti, E.; Pericas, M. A.; Serratosa, F. *J. Org. Chem.* **1990**, *55*, 395.

of 2-methylpropene from **66** occurred slowly at temperatures as low as 50 °C and instantaneously at 100-110 °C to produce (trimethylsilyl)ketene in 63% isolated yield. Alternatively, the silylketene was generated and trapped quantitatively with a nucleophilic amine (eq 17). The starting alkyne **66** can be obtained either via the silylation of *tert*-butoxyethyne[63] or via a β-elimination/silylation process beginning with (Z)-1-bromo-*tert*-butoxyethene.[64]

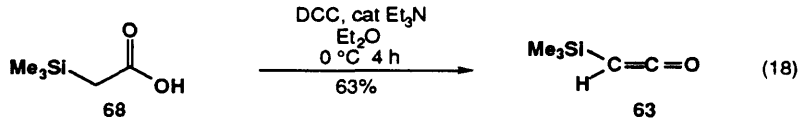


66 67 (17)

The main advantage of the thermal elimination of (*tert*-butoxytrimethylsilyl)ethyne is that the silylketene can be generated at considerably lower temperatures and in the presence of nucleophiles. The increased bulk of the *t*-butoxy substituent helps prevent polymerization reactions and electrophilic attack which are side reactions that commonly occur when the silylketene is generated from the less bulky (trimethylsilyl)ethoxyacetylene (**64**). On the other hand, ethoxyacetylene is commercially available and more readily accessible than the *t*-butoxy derivative. Anhydride pyrolysis is another method that has been applied for the preparation of **63**, although, this method reportedly affords (trimethylsilyl)ketene in low yield.[65a,b]

Olah has prepared (trimethylsilyl)ketene via the dehydration of commercially available (trimethylsilyl)acetic acid (**68**) (eq 18).[66] Dehydration of this acid using dicyclohexylcarbodiimide (DCC) and a catalytic amount of trimethylamine gave the silylketene in 63% yield.

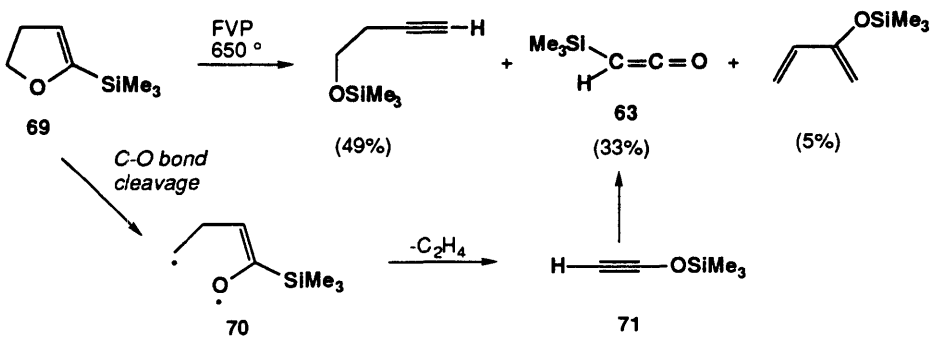
64. Pericas, M. A.; Serratosa, F.; Valenti, E. *Tetrahedron* **1987**, *43*, 2311.
65. (a) Kostyuk, A. S.; Boyadzhan, Zh. G.; Zaitseva, G. S.; Sergeev, V. N.; Savel'eva, N. I.; Baukov, Y. I.; Lutsenko, I. F. *Zh. Obshch. Khim.* **1979**, *49*, 1543. (b) Kotstyuk, A. S.; Dudukina, O. V.; Burlachenko, G. S.; Baukov, Y. I.; Lutsenko, I. F. *Zh. Obshch. Khim.* **1969**, *39*, 467. (c) Lutsenko, I. F.; Baukov, Y. I.; Kostyuk, A. S.; Savelyeva, N. I.; Krysina, V. K. *J. Organomet. Chem.* **1969**, *17*, 241.
66. Olah, G. A.; Wu, A.; Farooq, O. *Synthesis* **1989**, 568.



(18)

Barton has observed the formation of (trimethylsilyl)ketene in 33% yield as a minor product formed during the pyrolysis of (trimethylsilyl)-4,5-dihydrofuran (**69**) (Scheme 13).[67] Formation of the silylketene is rationalized to proceed via homolytic C-O bond cleavage of **69** to form the diradical species **70.** Following the expulsion of ethylene, (trimethylsilyloxy)acetylene (**71**) is produced and then undergoes salt-promoted isomerization to (trimethylsilyl)ketene (**63**).

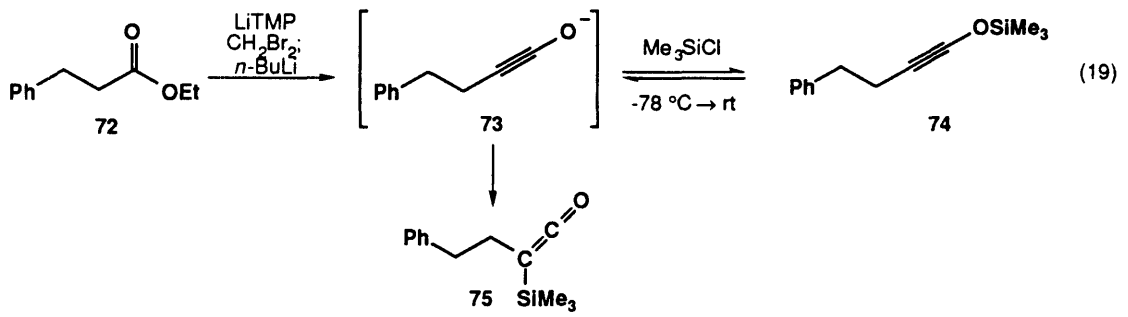
Scheme 13



Kowalski has reported this same type of siloxyacetylene isomerization to produce a silylketene. The ester **72** was homologated using the Kowalski method[68] and the ynolate anion generated was trapped with chlorotrimethylsilane at -78 °C. The reaction mixture was allowed to warm to room temperature to afford silylketene **75** as the only product (eq 19). When the same ynolate was trapped at -78 °C and the reaction mixture quenched with aqueous bicarbonate at -78 °C, a mixture of the siloxyacetylene **74** and silylketene **75** (2:1 ratio) was produced. It appears that silylation kinetically occurs on oxygen, but that isomerization to the more stable ketene occurs when the reaction is

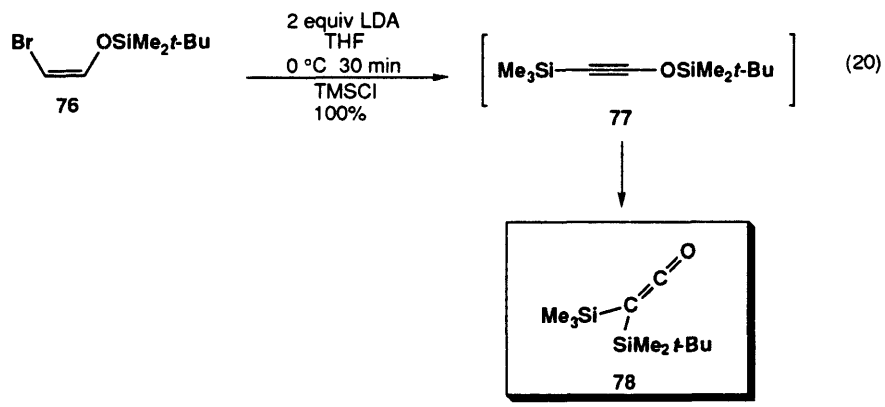
67. Barton, T. J.; Groh, B. L. *J. Am. Chem. Soc.* **1985,** *107,* 7221.
68. Kowalski, C. J.; Haque, M. S.; Fields, K. W. *J. Am. Chem. Soc.* **1985**, *107,* 1429.

quenched at ambient temperature.[69] This siloxyacetylene isomerization is limited to small trialkylsilyl groups (i.e. Me_3Si, Et_3Si). Siloxyacetylenes with bulkier silyl groups (such as *i*-Pr_3Si) do not isomerize to afford the silylketene.



(19)

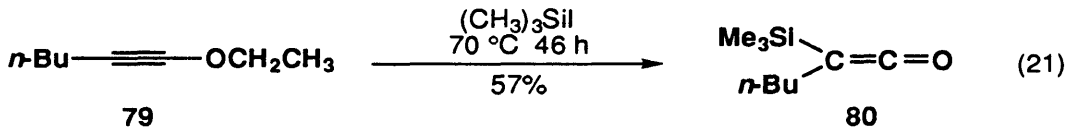
While exploring the synthetic utility of (*Z*)-haloalkenes, Pirrung and Hwu reported the quantitative conversion of alkene **76** to siloxyacetylene **77** (eq 20).[70] However, upon close examination of Pirrung and Hwu's IR data, it was realized that the compound isolated was not the siloxyacetylene **77,** but was rather the silylketene **78** produced by isomerization of the initially formed siloxyacetylene.[71]



(20)

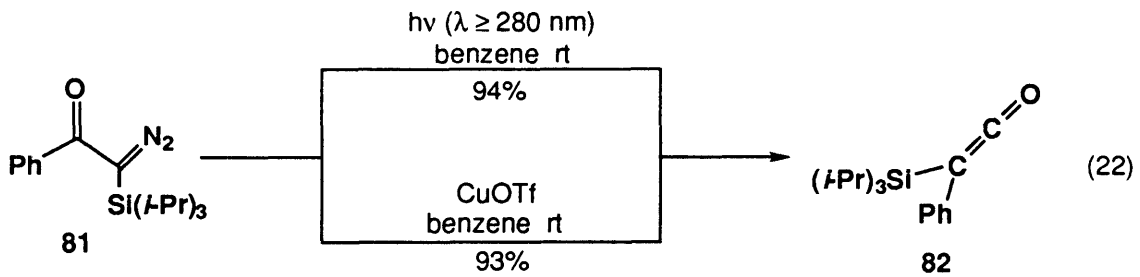
69. Kowalski, C. J.; Sankar Lal, G.; Haque, M. S. *J. Am. Chem. Soc.* **1986,** *108,* 7127.
70. Pirrung, M. C.; Hwu, J. R. *Tetrahedron Lett.* **1983,** *24,* 565.
71. Danheiser, R. L.; Nishida, A.; Savariar, S.; Trova, M. P. *Tetrahedron Lett.* **1988,** *29,* 4917.

In 1979, Sakurai reported the first "satisfactory" method to make higher alkyl-substituted TAS-ketenes via the strategy shown below (eq 21).[72] The alkoxyalkyne **79** was reacted with a slight excess of iodotrimethylsilane (generated *in situ* from hexamethyldisilane and iodine) to produce the alkyl(silyl)ketene **80** in moderate yield.



79 **80** (21)

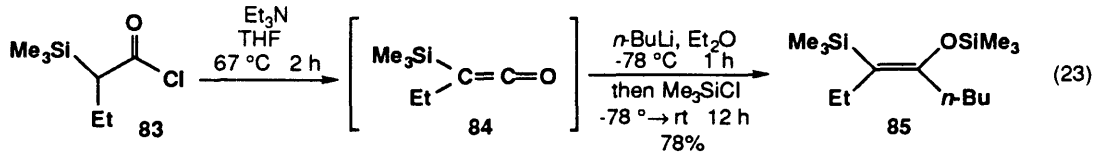
Alkyl- and arylsilylketenes have also been generated via the Wolff rearrangement of corresponding α-silyldiazo ketones (eq 22).[73] Wolff rearrangement has been induced under photochemical conditions and using transition metal catalysis to afford silylketenes in moderate to high isolated yields. This transformation has also been effected on a variety of α-silyldiazo ketones with different trialkylsilyl groups.



81 **82** (22)

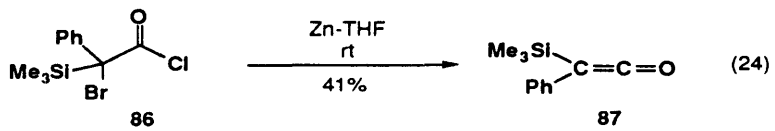
Dehydrohalogenation, although a common method for ketene generation, does not produce (trimethylsilyl)ketene in good yield.[65b,c] However, this method has been an effective strategy for the synthesis of higher alkyl TAS-ketenes. For example, Tidwell has generated (trimethylsilyl)ethylketene (**84**) in this fashion in the course of his studies on the stereospecific generation of silyl enol ethers from ketenes (eq 23).[74]

72. Sakurai, H.; Shirahata, A.; Sasaki, K.; Hosomi, A. *Synthesis* **1979**, 740.
73. (a) Maas, G.; Brückmann R. *J. Org. Chem.* **1985**, *50*, 2802. (b) Brückmann, R.; Schneider, K.; Maas, G. *Tetrahedron*, **1989**, *45*, 5517.
74. Baigrie, L. M.; Seiklay, H. R.; Tidwell, T. T. *J. Am. Chem. Soc.* **1985**, *107*, 5391.



(23)

Zinc dehydrohalogenation has been employed by Brady for the synthesis of (trimethylsilyl)phenylketene **87** (eq 24).[75a] Phenyl(trimethylsilyl)bromoacetyl chloride (**86**) was stirred with activated zinc at room temperature. After removal of the zinc salts, the silylketene **87** was isolated by vacuum distillation in 41% yield. Dehydrohalogenation using triethylamine was also attempted for the preparation of this ketene but was unsuccessful due to carbon-silicon bond cleavage.



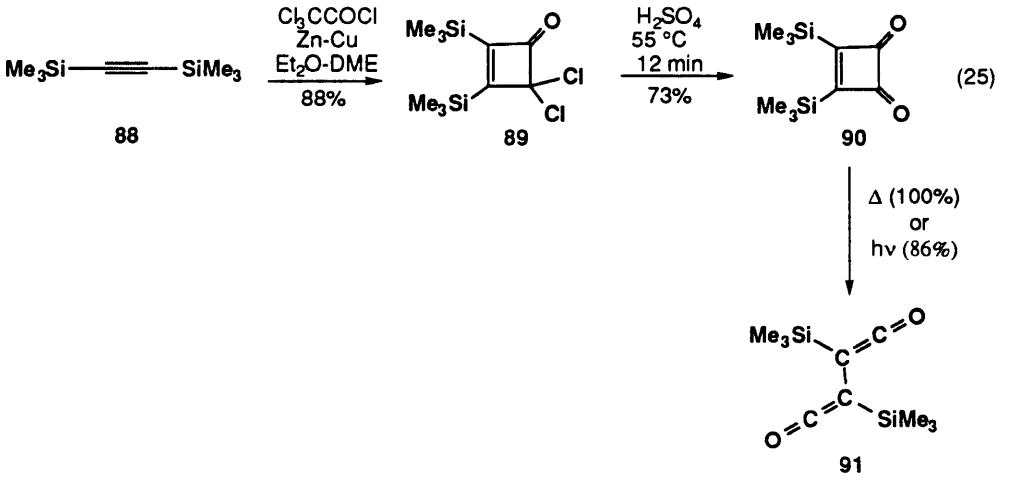
(24)

Dötz[75b,c] and Wulff[75d] have also isolated substituted TAS-vinylketenes in low to moderate yields via the reaction of Fischer carbene complexes with silyl substituted acetylenes.

Tidwell has prepared stable and persistent bis(silyl)-substituted bisketenes by electrocyclic ring opening of cyclobutenediones (eq 25).[76] Cycloaddition of bis(trimethylsilyl)acetylene (**88**) with dichloroketene (generated from trichloroacetyl chloride using zinc-copper couple) gave dichlorocyclobutenone **89,** which upon treatment with concentrated sulfuric acid was hydrolyzed to afford cyclobutenedione **90** in 64% yield over two steps. Ring opening of **90** could be induced either thermally ($CDCl_3$, 100 °C, 1 h, sealed tube) or photochemically (hν, λ=350 nm, 5 °C, 48 min) to give

75. (a) Brady, W. T.; Cheng, T. C. *J. Organomet. Chem.* **1977**, *137*, 287. (b) Dötz, K. H. *Angew. Chem. Int. Ed. Engl.* **1979**, 954. (c) Dötz, K. H.; Mühlemeier, J.; Trenkle, B. *J. Organomet. Chem.* **1985**, *289*, 257. (d) Tang, P.-C.; Wulff, W. D. *J. Am. Chem. Soc.* **1984**, *106*, 1132.
76. (a) Zhao, D.-C.; Tidwell, T. T. *J. Am. Chem. Soc.* **1992**, *114*, 10980. (b) Zhao, D.-C.; Allen, D.; Tidwell, T. T. *J. Am. Chem. Soc.* **1993**, *115*, 10097.

bis(trimethylsilyl)bisketene (**91**) in excellent yield. This method has also been used to prepare other bis(trialkylsilyl)-substituted bisketenes.



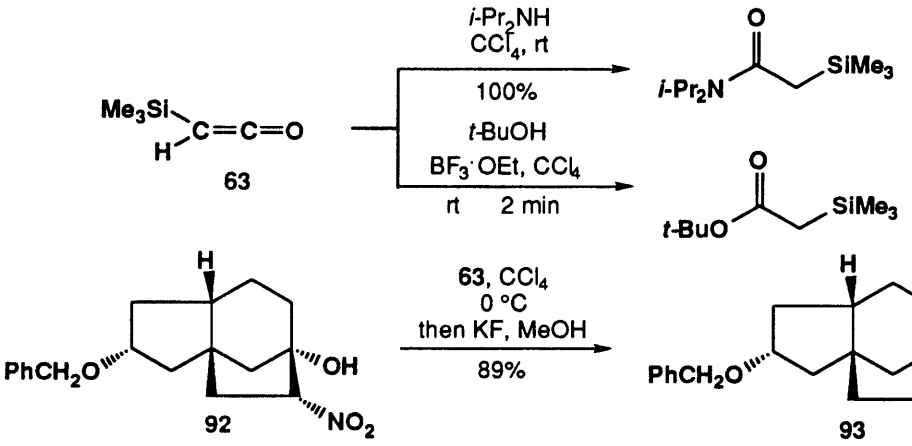
Reactions of TAS-Ketenes

(1) Nucleophilic Additions

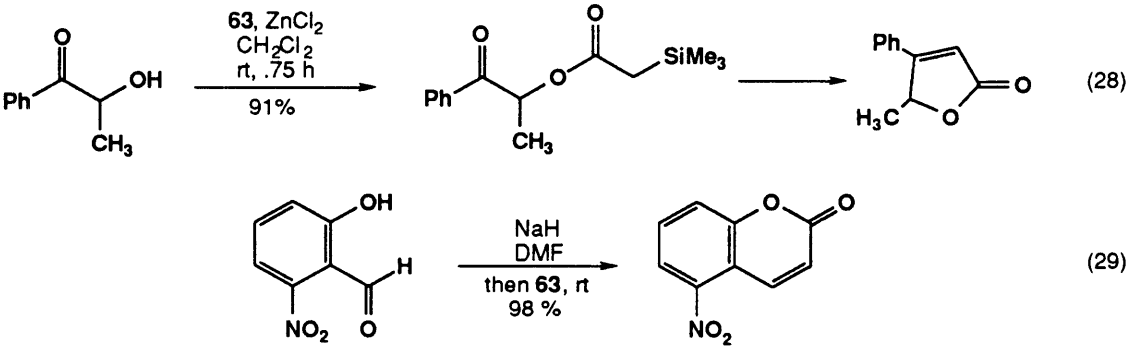
TAS-ketenes have been shown to readily undergo nucleophilic additions.[61b,77] Ruden has reported the use of (trimethylsilyl)ketene as a potent acylating agent for both amines and alcohols.[77a] (Trimethylsilyl)ketene reacted almost instantaneously with hindered amines to form α-silyl amides in quantitative yield (eq 26), whereas, the reaction with alcohols such as *tert*-butanol was much slower (CCl_4, 48 h, rt, 80% yield). However, $BF_3{\cdot}OEt_2$ has been found to strongly catalyze the addition of alcohols to (trimethylsilyl)ketene. The hindered tertiary alcohol **92,** which could not be acylated using standard reagents such as benzoyl chloride, acetyl chloride, and acetic anhydride (even in the presence of DMAP), was successfully acetylated with (trimethylsilyl)ketene. Desilylation was effected via the action of potassium fluoride in methanol to produce the acetate **93** directly (eq 27).[78]

77. (a) Ruden, R. A. *J. Org. Chem.* **1974**, *39*, 3607. (b) Lebedev, S. A.; Gervits, L. L.; Ponomarev, S. V.; Lutsenko, I. F. *J. Gen. Chem. USSR* **1976**, *46*, 592. (c) Ponomarev, S. V.; Erman, M. B.; Lebedev, S. A.; Pechurina, S. Ya.; Lutsenko, I. F. *J. Gen. Chem. USSR* **1971**, *41*, 122.

78. (a) Danheiser, R. L. In *Strategy and Tactics in Organic Synthesis,* Lindberg, T., Ed.; Academic Press, Inc.: Orlando, Florida, 1984; Vol. 1, Chapter 2. (b) Danheiser, R. L. Ph. D. Thesis, Harvard University, 1978.

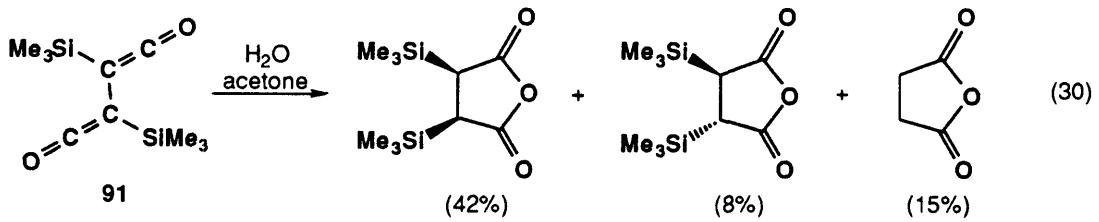


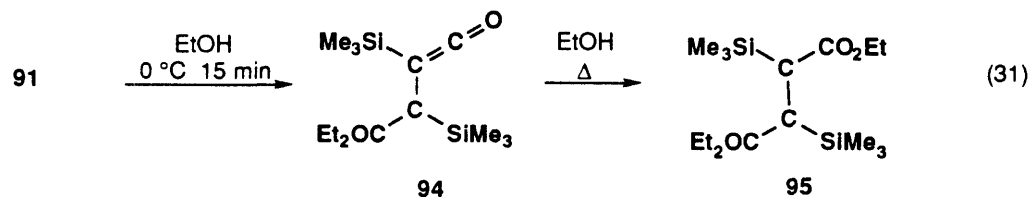
Kita has found that a high degree of functionality in the substrate can be tolerated when the addition of alcohols to (trimethylsilyl)ketene is catalyzed by zinc halides. These functional groups include: carbonyls, acetals, thioacetals, epoxides, and olefins.[79] In contrast, $BF_3{\cdot}OEt_2$ catalysis resulted in partial product desilylation with alcohols containing carbonyl groups and also caused cleavage of acetal groups. The synthetic utility of functionalized α-silylacetates has been demonstrated for the synthesis of butenolides (eq 28). Similarly, Taylor has found that (trimethylsilyl)ketene is useful in the synthesis of coumarins (eq 29).[80]



79. Kita, Y.; Sekihachi, J. Hayashi, ; Y.; Da, Y.-Z.; Yamamoto, M.; Akai, S. *J. Org. Chem.* **1990,** *55*, 1108.
80. Taylor, R. T.; Cassell, R. A. *Synthesis* **1982**, 672.

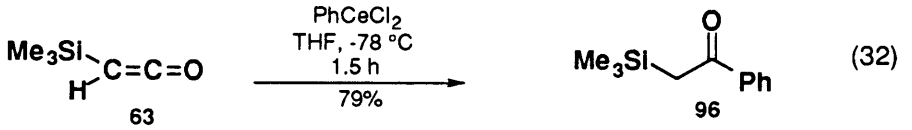
Tidwell has studied the addition of nucleophiles to (trialkylsilyl)ketenes and bis(trialkylsilyl)bisketenes.[61b,76] The reaction of bisketene **91** with water afforded the mixture of anhydride products shown below (eq 30). Treatment of **91** with ethanol at 0 °C formed the monoketene **94**, and an additional equivalent of ethanol reacts under thermal conditions to produce the diester **95** (eq 31).



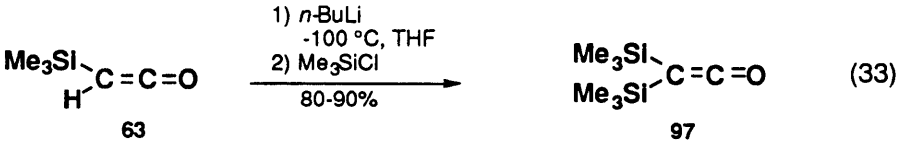


α-Silyl ketones have been prepared by Kita in a one-pot procedure by the addition of (trimethylsilyl)ketene to organocerium reagents followed by quenching with aqueous ammonium chloride or alkyl halides (eq 32).[81] Organolithium reagents are not suitable for this reaction because proton abstraction is preferred over nucleophilic addition. In fact, the addition of (trimethylsilyl)ketene to a 0.01 M *n*-butyllithium solution at -100 °C followed by quenching with chlorotrimethylsilane afforded in high yield the bis silylketene **97** (eq 33).[82] Attempts to trap the ynolate with other electrophiles were unsuccessful.

81. Kita, Y.; Matsuda, S.; Kitagaki, S. Tsuzuki, Y. Akai, S. *Synlett.* **1991**, 401.
82. Woodbury, R. P.; Long, N. R.; Rathke, M. W. *J. Org. Chem.* **1978**, *43*, 376.

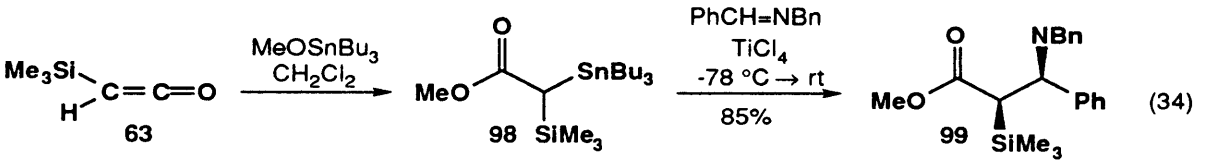


(32)



(33)

As an extension of the α-silyl ketone methodology, Kita has shown that alkoxystannanes add to (trimethylsilyl)ketene, and the resulting α-(tributylstannyl)acetate **98** can be added to aldehydes and aldimines in the presence of $TiCl_4$ (eq 34).[83] Notably, the reaction with aldimines leads to the stereospecific preparation of *syn*-β-amino-α-silyl esters which can be further elaborated to useful *syn*-amino diol derivatives.

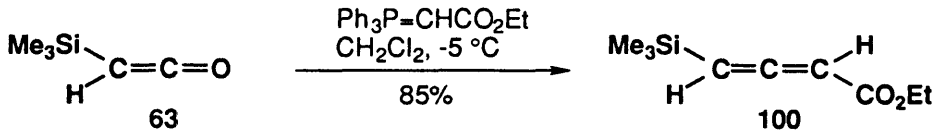


(34)

(2) Wittig and Related Reactions

(Trimethylsilyl)ketene has been used for the preparation of allenes.[77a,84] For example, olefination of silylketene **63** with a stabilized phosphorus ylide, carboethoxymethylenetriphenylphosphorane, afforded the silyl-substituted allenic ester **100** in 85% yield (eq 35).[77a] This Wittig-type reaction occurred only with stabilized phosphorus ylides, and unstabilized ylides were found to form complex mixtures. When this reaction was conducted at room temperature, a mixture of the allene **100** and the isomeric unconjugated (trimethylsilyl)acetylenic ester was formed. Acetylene formation presumably occurs via isomerization promoted by the basic ylide.

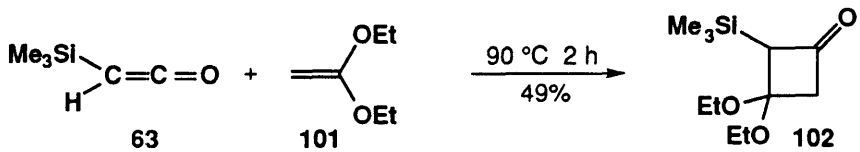
83. Akai, S.; Tsuzuki, Y.; Matsuda, S.; Kitagaki, S.; Kita, Y. *J. Chem. Soc. Perkin Trans. I* **1992**, 2813.
84. Orlov, V. Yl; Lebedev, S. A.; Ponomarev, S. V.; Lutsenko, I. F. *J. Gen. Chem. USSR* **1975**, *45*, 696.



(35)

(3) [2 + 2] Cycloadditions

Silyl substitution greatly diminishes the natural tendency of ketenes to undergo [2 + 2] cycloadditions. As a result, cycloadditions of (trimethylsilyl)ketene with simple olefins and dienes have been unsuccessful.[77a,85] However, silylketenes do participate in [2 + 2] cycloadditions with a few highly electron-rich olefins. Baukov first reported the reaction of (trimethylsilyl)ketene with ketene diethyl acetal (**101**). Equivalent amounts of the reactants were mixed together and heated. The cycloadduct **102** was formed in moderate yield (eq 36).[86] Brady has described similar [2 + 2] cycloadditions involving (trimethylsilyl)ketene and tetraalkoxyethylenes.[85]

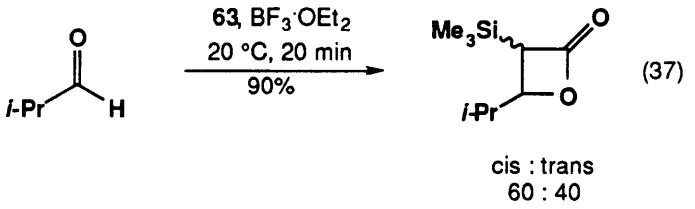


(36)

(Trimethylsilyl)ketene also undergoes [2 + 2] cycloadditions with aldehydes to afford β-lactones.[87] Baukov[87a,b] first reported the $BF_3{\cdot}OEt_2$ catalyzed cycloaddition of (trimethylsilyl)ketene with saturated aldehydes which results in mixtures of both *cis* and

85. Brady, W. T.; Saidi, K. *J. Org. Chem.* **1980**, *45*, 729.
86. Zaitseva, G. S.; Baukov, Y. I.; Mal'tsev, V. V.; Lutsenko, I. F. *Zh. Obshch. Khim.* **1974**, *44*, 1415.
87. (a) Zaitseva, G. S.; Vinokurova, N. G. Baukov, Y. I. *Zh. Obshch. Khim.* **1975**, *45*, 1398. (b) Zaitseva, G. S.; Vasil'eva, L. I.; Vinokurova, N. G.; Safronova, O. A.; Baukov, Y. I. *Zh. Obshch. Khim.* **1978**, *48*, 1363. (c) Mead, K. T.; Yang, H-L. *Tetrahedron Lett.* **1989**, *30*, 6829. (d) Mead, K. T.; Samuel, B. *Tetrahedron Lett.* **1988**, *29*, 6573. (e) Brady, W. T.; Saidi, K. *J. Org. Chem.* **1979**, *44*, 733. (f) Maruoka, K.; Concepcion, A. B.; Yamamoto, H. *Synlett* **1992**, 31.

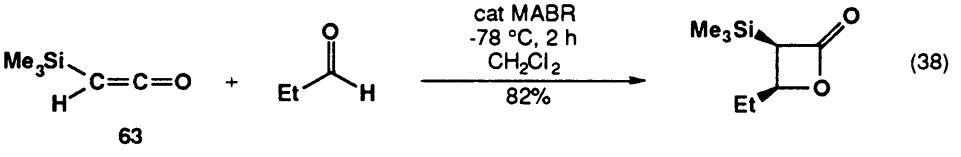
trans-2-oxetanones (eq 37). Ketones do not to undergo [2 + 2] cycloadditions with silylketene **63**.



(37)

Later, Brady reported cycloadditions of TMS-ketene and both saturated and α,β-unsaturated aldehydes in the presence of $BF_3 \cdot OEt_2$. The reaction of the α,β-unsaturated aldehydes with silylketene **63** afforded 2-oxetanones as indicated by IR; however, upon distillation a [1,3]-shift of the organosilyl group occurred accompanied by ring opening to yield trimethylsilyl dienoate esters.[87e]

Recently, a method for the stereoselective preparation of cis-substituted β-lactones using the exceptionally bulky Lewis acid catalyst methylaluminum bis(4-bromo-2,6-di-*tert*-butylphenoxide) (MABR) has been described by Yamamoto.[87f] This method is reported to work well for reactions of **63** with alkyl, aryl, and unsaturated aldehydes (eq 38). When stoichiometric amounts of the catalyst were employed, desilylation occurred followed by ring opening to afford (*Z*)-alkenoic acids.



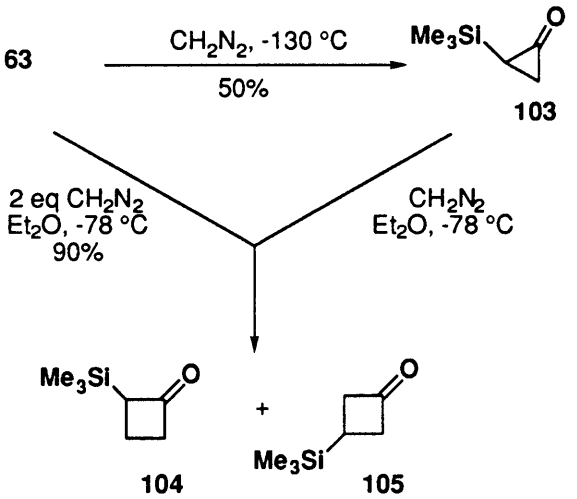
(38)

(4) Cyclopropane and Cyclobutane Formation

Baukov has shown that diazomethane adds to trimethylsilylketene to give two types of products: silyl-substituted cyclopropanones and cyclobutanones (Scheme

14).[88a,b] The treatment of (trimethylsilyl)ketene with an ethereal solution of an equimolar amount of diazomethane at -130 °C produced (trimethylsilyl)cyclopropanone (**103**) in 50% yield. The 3-membered ring product **103** was then reacted with a second equivalent of diazomethane, and upon warming to -78 °C, ring expansion occurred to yield a mixture of 2- and 3-(trimethylsilyl)cyclobutanones **104** and **105**. Alternatively, these isomeric 4-membered ring products were formed directly with two equivalents of diazomethane at -78 °C in 90% yield in a 40:60 ratio, with the 3-substituted product favored. Treatment of the isomeric (trimethylsilyl)cyclobutanone mixture with methanol makes it possible to obtain the pure 3-substituted isomer in 84% yield.[89] This [2 + 1] cycloaddition with (trimethylsilyl)ketene has also been effected with trimethylsilyldiazomethane,[88d,e] and the cycloaddition has been performed with other (trimethylsilyl)arylketenes as well.[88f]

Scheme 14

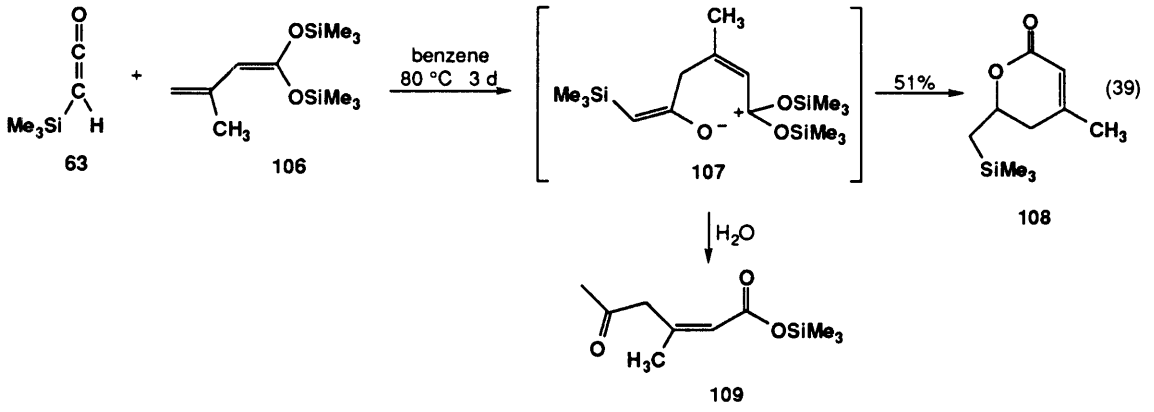


(5) [4 + 2] Cycloadditions

88. (a) Zaitseva, G. S.; Bogdanova, G. S.; Baukov, Y. I.; Lutsenko, I. F.; *J. Organomet. Chem.* **1976,** *121,* C1-C22. (b) Zaitseva, G. S.; Bogdanova, G. S.; Baukov, Y. I.; Lutsenko, I. F. *Zh. Obshch. Khim.* **1978,** *48,* 131. (c) Zaitseva, G. S.; Krylova, G. S.; Perelydina, O. P.; Baukov, Y. I.; Lutsenko, I. F. *Zh. Obshch. Khim.* **1981,** *51,* 2252. (d) Zaitseva, G. S.; Kisim, A. N.; Fedorenko, E. N.; Nosova, V. M.; Livantsova, L. I.; Baukov, Y. I. *J. Gen. Chem.* **1987,** *57,* 1836. (e) Zaitseva, G. S.; Lutsenko, I. F.; Kisin, A. V.; Baukov, Y. I.; Lorberth, J. *J. Organomet. Chem.* **1988,** *345,* 253. (f) Brady, W. T.; Cheng, T. C. *J. Organomet. Chem.* **1977,** *137,* 287.

89. Tarakanova, A. V.; Baranova, S. V.; Boganov, A. M.; Sefirov, N. S. *Zh. Org. Khim.* **1986,** *22,* 1095.

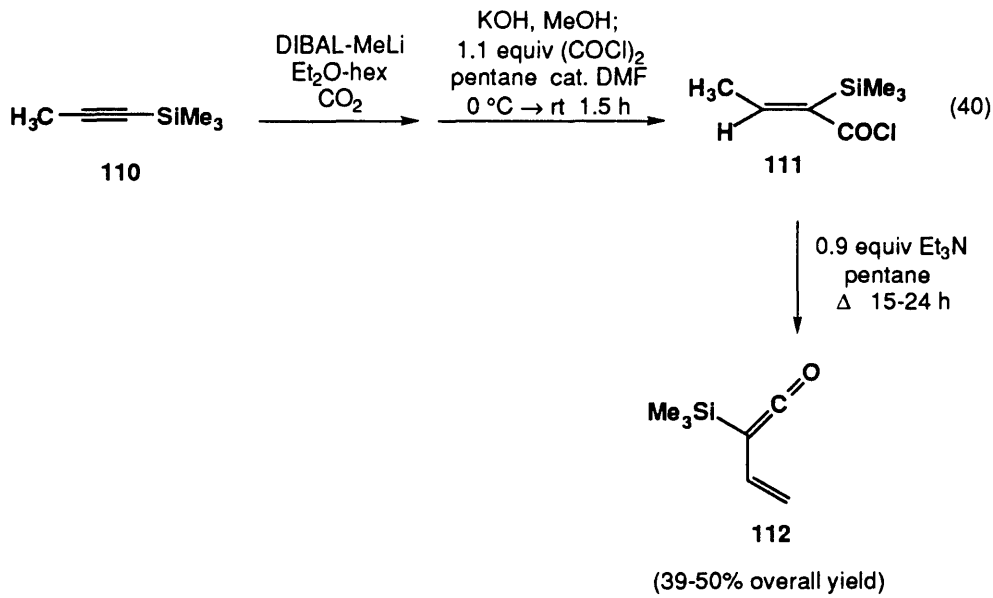
In 1993, Shioiri reported the first [4 + 2] cycloaddition reaction of a silylketene with an electron rich diene. Silylketene **63** reacted smoothly with diene **106** in refluxing benzene to afford the 2-pyranone **108** (eq 39). Other aldoketenes with different trialkylsilyl groups have been shown to be good heterodienophiles for this cycloaddition. This transformation is a stepwise process with initial nucleophilic attack by diene **106** on the *sp*-hybridized ketene carbonyl to produce the zwitterionic intermediate **107**. Hydrolysis of the reaction mixture at this point resulted in the isolation of ester **109** with loss of the original ketene trialkylsilyl group. Prolonged reaction times or higher temperatures promoted cyclization and upon hydrolysis the α,β-unsaturated lactone **108** was obtained.[90]



Preparation of (Trimethylsilyl)vinylketene

(Trimethylsilyl)vinylketene (**112**) was first prepared in our laboratories via a dehydrohalogenation reaction as outlined in the equation below.[35d]

90. Ito, T.; Aoyama, T.; Shioiri, T. *Tetrahedron Lett.* **1993**, *34*, 6583.



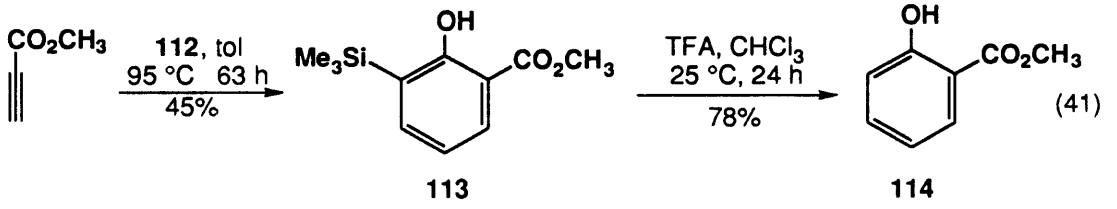
Treatment of 1-(trimethylsilyl)propyne **110**[91] with diisobutylaluminum hydride and methyllithium (0 °C, 0.5 h) in ether-hexane,[92] followed by reaction of the resulting vinylalanate with anhydrous carbon dioxide yielded (*Z*)-2-(trimethylsilyl)-2-butenoic acid in 68% yield. Exposure of the potassium salt of the acid to oxalyl chloride in pentane containing a catalytic amount of dimethylformamide then produced the acid chloride **111** which was dehydrohalogenated without further purification. Thus, a solution of **111** in pentane was added dropwise over 1-2 h to a solution of 0.9 equivalents of triethylamine in pentane at 25 °C, and the resulting mixture was heated at reflux for 15-24 h and then filtered with the aid of pentane. Solvent was evaporated at -50 °C (0.5 mmHg), and the residue was distilled at 25 °C (1 mmHg) and then again at 5 mmHg into a receiver cooled at -78 °C. In this manner (trimethylsilyl)vinylketene (**112**) was obtained as a yellow-green liquid in 39-50% overall yield (from **110**). (Trimethylsilyl)vinylketene is a relatively stable, isolable compound, and the purified vinylketene can be stored under nitrogen in solution at 0 °C without appreciable decomposition for 1-2 weeks.

91. (a) Eisch, J. J.; Damasevitz, G. A. *J. Org. Chem.* **1976**, *41*, 2214. (b) Uchida, K.; Utimoto, K.; Nozaki, H. *J. Org. Chem.* **1976**, *41*, 2215.
92 Zweifel, G.; Steele, R. B. *J. Am. Chem. Soc.* **1967**, *89*, 2754.

[4 + 2] Cycloadditions of (Trimethylsilyl)vinylketene

(Trimethylsilyl)vinylketene (**112**) does not enter into typical [2 + 2] cycloadditions with electron rich olefins. Instead, it was found that (trimethylsilyl)vinylketene participates in [4 +2] Diels-Alder reactions with a variety of olefinic and acetylenic dienophiles. Ghosez later reported a similar [4 + 2] strategy which employs *N*-silylated silylvinylketenimines which undergo cycloadditions with olefinic and acetylenic dienophiles.[93]

Our studies with (trimethylsilyl)vinylketene (**112**) illustrate the directing effect of the carbonyl group in controlling the regiochemical course of the cycloadditions. For example, reaction of silylvinylketene **112** with methyl propiolate produced methyl 3-(trimethylsilyl)salicylate (**113**) with the expected regiochemical orientation. Protodesilylation of this adduct with trifluoroacetic acid afforded methyl salicylate (**114**) in 78% yield (eq 41).

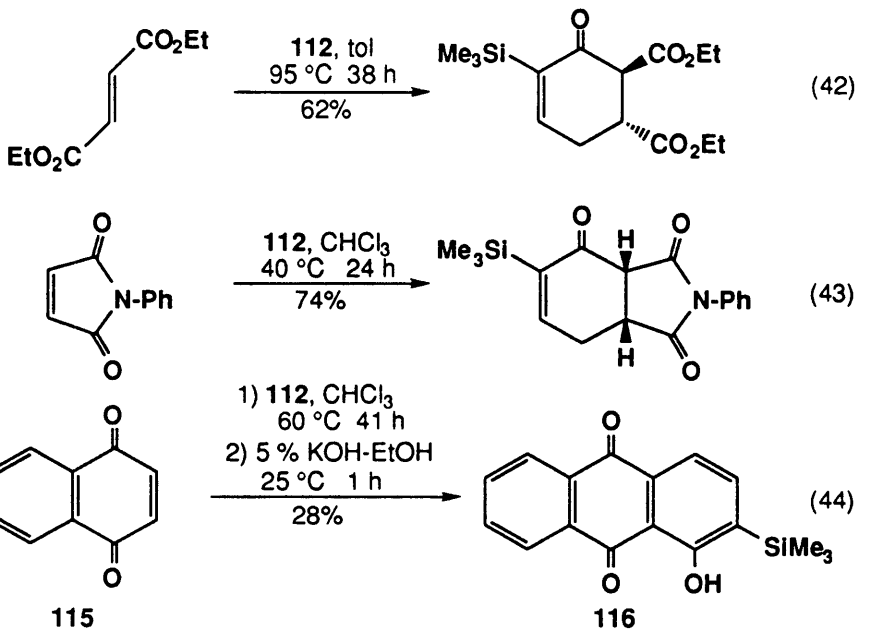


(41)

113 **114**

Diels-Alder addition of silylvinylketene **112** to olefinic dienophiles furnished cyclohexenone derivatives as shown in equations 42 and 43. The addition of **112** to naphthoquinone (**115**) afforded a mixture of several cycloadducts which could then be oxidized to a single anthraquinone **116** (eq 44).

93. Differding, E.; Vandevelde, O.; Roekens, B.; Van, T.; Ghosez, L. *Tetrahedron Lett.* **1987**, *28*, 397.



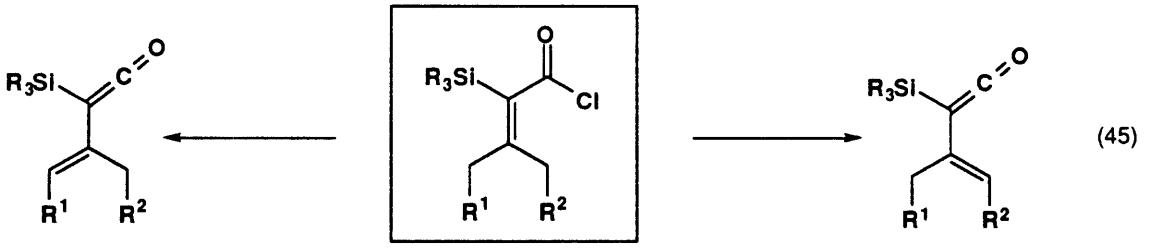
Unfortunately, at the time of the original investigation, no efficient and general route to *substituted* TAS-vinylketenes was available. We have now developed a widely applicable and productive route to substituted TAS-vinylketenes based on the photochemical Wolff rearrangement of α-silyldiazo ketones, as discussed in detail in Chapter 3.

CHAPTER 3

SYNTHETIC APPROACHES TO SUBSTITUTED TAS-VINYLKETENES

TAS-Vinylketenes via a Photochemical Wolff Rearrangement Strategy

One limitation of using the dehydrohalogenation method discussed in Chapter 2 for the synthesis of (trimethylsilyl)vinylketene is the inability of this method to provide a general route to *substituted* TAS-vinylketene derivatives. The application of this method to the preparation of substituted TAS-vinylketenes is complicated by the regiochemical ambiguity associated with the elimination step (eq 45).

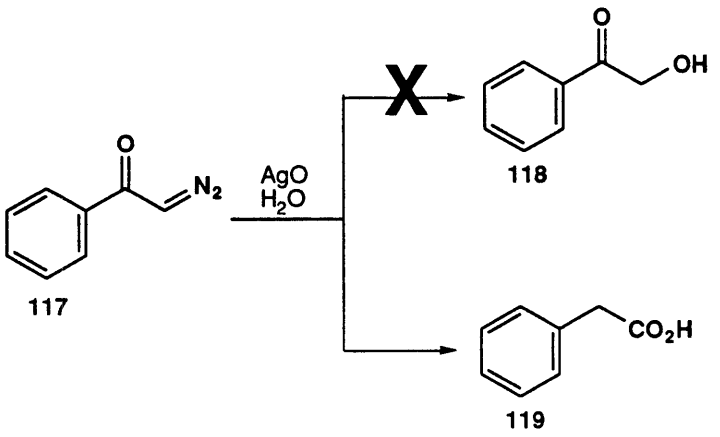


(45)

In general, the Wolff rearrangement of α-diazo ketones is an attractive option for ketene generation since nitrogen is the only byproduct of the reaction, and the α-diazo ketone substrates are usually very readily available. The aromatic annulation strategy developed in our laboratory[13] has established that the photochemical Wolff methodology can be applied for the generation of vinylketenes, and Maas has also utilized this rearrangement for the generation of (trialkylsilyl)aryl- and (trialkylsilyl)alkylketenes from α-silyldiazo ketones (see eq 22, p. 57).[73] Consequently, it was our expectation that the photochemical Wolff rearrangement of α'-silyl-α'-diazo-α,β-unsaturated ketones might serve as a general and synthetically very useful method for the generation of TAS-vinylketenes.

At the beginning of the twentieth century, the Wolff rearrangement was discovered accidentally by Ludwig Wolff. Wolff found that treatment of diazoacetophenone **117** with

water and silver oxide did not produce the expected α-hydroxy ketone **118**, but instead afforded the rearrangement product phenylacetic acid **119** (eq 46).[94] A few years later, Schröter published his results of an analogous study.[95]



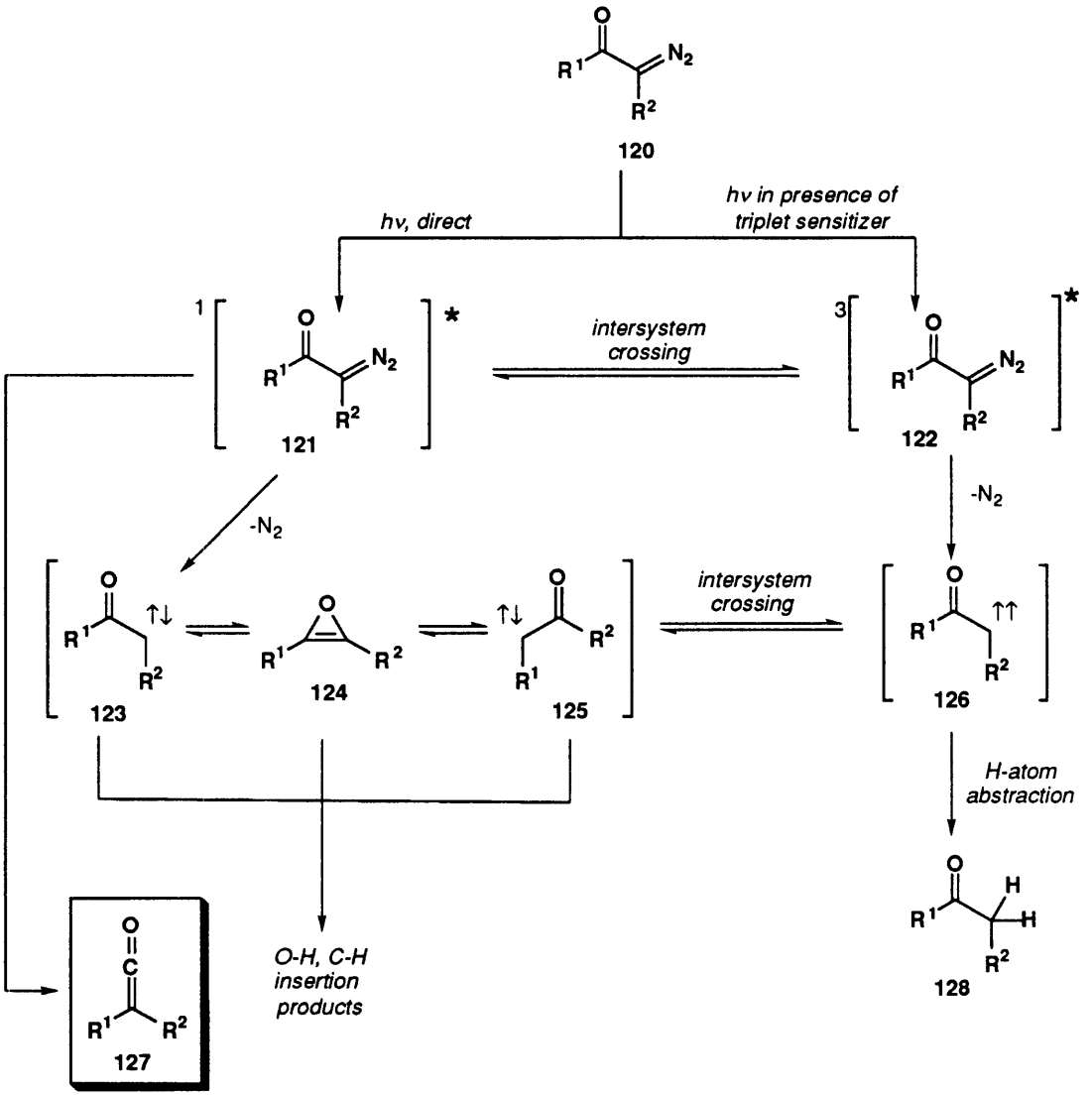
(46)

Twenty years passed before the Wolff rearrangement became a synthetically useful reaction. This was mainly due to a lack of convenient methods for the preparation of the α-diazo ketone starting materials. However, the discovery that α-diazo ketones could be easily synthesized via the acylation of diazoalkanes with acid chlorides[96] led to the development of the Wolff rearrangement as a valuable reaction in preparative organic synthesis. The reaction is commonly employed for Arndt-Eistert homologation of acid chlorides, ring contraction strategies, as well as for ketene generation. Wolff rearrangement can be induced under thermal or metal catalyzed conditions as initially described by Wolff. Alternatively, Horner discovered in 1951 that the Wolff reaction can also be initiated photochemically.[97,48] This photochemical method of ketene generation is often the procedure of choice since the rearrangement can be induced at room temperature.

94. (a) Wolff, L. *Justus Liebigs Ann. Chem.* **1902**, *325*, 129; **1904**, *333*, 1; **1912**, *394*, 23.
95. Schröter, *Chem. Ber.* **1909**, *42*, 2346.
96. (a) Arndt, F.; Eistert, B.; Partale, W. *Chem. Ber.* **1927**, *60*, 1364. (b) Arndt, F.; Amend, J. *Chem. Ber.* **1928**, *61*, 1122.
97. Horner, L.; Spietschka, E.; Gross, A. *Liebigs. Ann. Chem.* **1951**, *573*, 17.

Although the mechanism of the photochemical Wolff rearrangement has been studied extensively, there is no widespread agreement on the mechanistic details connecting reactants to products.[98] It is entirely possible that more than one mechanism is involved in the Wolff rearrangement of different systems. Several possible mechanistic pathways are illustrated in Scheme 15.

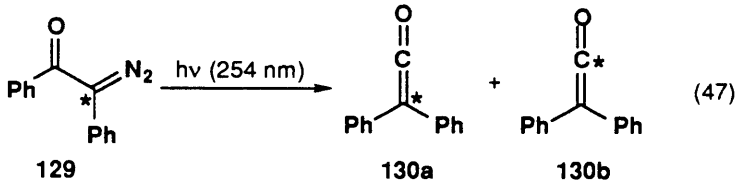
Scheme 15



98. (a) Murai, H.; Satarik, I.; Torres, M.; Strauz, O. P. *J. Am. Chem. Soc.* **1988**, *110*, 1025. (b) Mc Mahon, R. J.; Chapman, O. L.; Hayes, R. A.; Hess, T. C.; Krimer, H.-P. *J. Am. Chem. Soc.* **1985**, *107*, 7597, and references contained therein.

The pivotal question is whether the expulsion of nitrogen and substitutent migration occur in a *stepwise* (via a ketocarbene) or *concerted* fashion under photochemical conditions. A widely held view is that direct photolysis of an α-diazo ketone produces the singlet excited state of the compound and brings about Wolff rearrangement (**121** → **127**).[48c] In fact, triplet-sensitized photolysis often suppresses Wolff rearrangement and favors typical ketocarbene reactions such as H-abstraction and C-H and O-H insertion. Migration of the R^1 substitutent is known to occur in the singlet carbene species **121** but not in the triplet carbene intermediate **122**.[99] Spin inversion may occur in both directions when the singlet-triplet splitting is relatively small.

Evidence exists for the loss of nitrogen from the diazo ketone to form an intermediate singlet ketocarbene (**123**).[100] Also, isotopic labeling experiments have been carried out to prove that an isomerization can occur between ketocarbene **123** and oxirene **124** and carbene **125**. For example, irradiation of the isotopically labeled diazo ketone **129** resulted in ca. 30% scrambling of the ^{13}C label (eq 47).[101] However, it should be noted that the presence of an antiaromatic oxirene intermediate would only affect the synthesis of a ketene if the aim was to prepare isotopically labeled material, since otherwise both carbene **123** and **125** rearrange to the same ketene product.



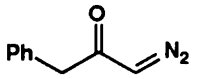
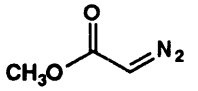
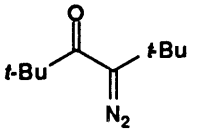
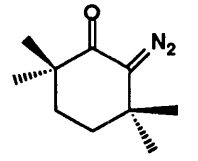
(47)

One well established fact is that the efficiency of the Wolff rearrangement depends on the ground state conformation of the α-diazo ketone. Wolff rearrangement is favored by the s-Z conformation of the diazo ketone (e.g. **120**), in which the migrating group (R^1)

99. Tomiokla, H.; Okuno, H.; Izawa, Y. *J. Org. Chem.* **1980**, *45*, 5278.
100. (a) Meyer, H.; Zeller, K.-P. *Angew. Chem.* **1975**, *87*, 52. (b) Meyer, H.; Zeller, K.-P. *Angew. Chem. Int. Ed. Engl.* **1975**, *14*, 32.
101. (a) Fenwick, J.; Frater, G.; Ogi, K.; Strausz, O. P. J. *J. Am. Chem. Soc.* **1973**, *95*, 124. (b) de Montellano, O. J. *J. Am. Chem. Soc.* **1980**, *102*, 7373.

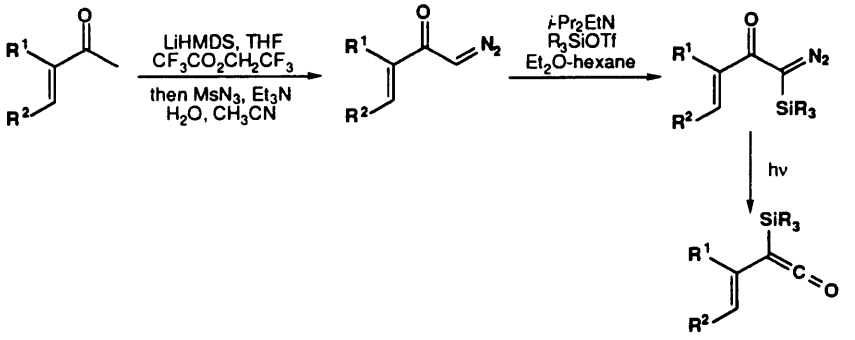
is trans to the nitrogen leaving group that is then displaced by backside attack. The relative efficiency at which several diazo ketones undergo rearrangement is illustrated in Table 6.[48c]

Table 6

Diazo Ketone	Major Conformer	% Yield of Photo-Wolff Rearrangement Products
	s-Z (96% at -40 °C)	97
	s-Z (54% at -40 °C)	44
	s-E	<3
	s-Z	96

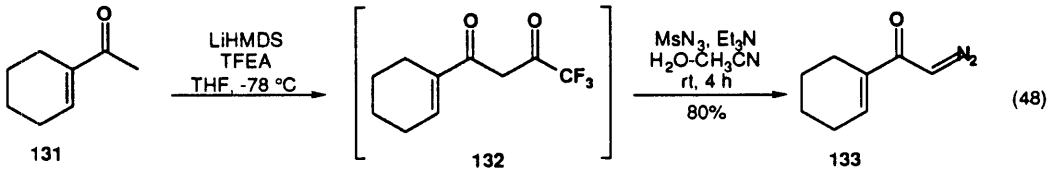
In summary, the ability of the photochemical Wolff rearrangement to efficiently provide ketenes under mild conditions from the requisite α-diazo ketones suggested that this might be a very suitable method for synthesizing TAS-vinylketenes. Our general route for the synthesis of TAS-vinylketenes is illustrated below (Scheme 16). An attractive feature of this approach is that α-diazo ketones can usually be obtained in one step from methyl ketones in high yield via diazo transfer.[29] Silylation using a modification of the procedure of Maas[73] followed by irradiation to induce Wolff rearrangement should then afford TAS-vinylketenes.

Scheme 16



Synthesis of α-Diazo Ketones

All of the α-diazo ketones in this study were prepared using the "detrifluoroacetylative" diazo transfer strategy previously developed in our laboratory.[29] This is a particularly valuable method for the convenient and efficient preparation of α,β-unsaturated α'-diazo ketones. An example of this transformation is shown below (eq 48).



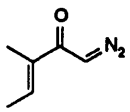
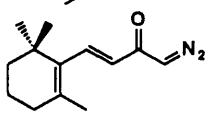
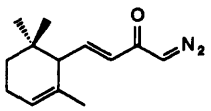
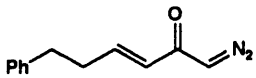
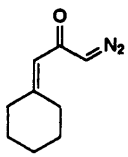
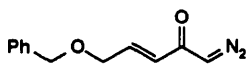
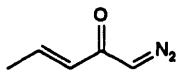
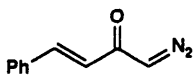
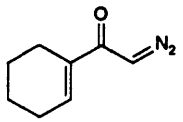
131 132 133 (48)

Thus, reaction of the ketone substrate **131** with 1.1 equivalents of lithium hexamethyldisilazide in THF at -78 °C for 30 min produces the corresponding lithium enolate, which is then acylated by exposure to 1.2 equivalents of trifluoroethyl trifluoroacetate (TFEA) at -78 °C for 5 to 10 min. This trifluoroacetylating agent is commercially available and inexpensive, and generally leads to trifluoroacetylation at carbon as desired. The resulting α-trifluoroacetyl ketone **132** is then treated at room temperature for 4 h with 1.5 equivalents of methanesulfonyl azide in acetonitrile containing 1.0 equivalent of water and 1.5 equivalents of triethylamine. Column chromatography on

silica gel furnishes the desired α-diazo ketone in 80% yield. The preparation of **141** on a 10 g scale using this procedure has recently been described in Organic Syntheses.[102]

The α-diazo ketones listed in Table 7 were prepared in very good yields using this "detrifluoroacetylative" diazo transfer procedure. Reactions were generally done on a scale that afforded between 500 mg and 2 g of product. The α-diazo ketones are stable, yellow solids or oils that can be stored neat for long periods of time at 0 °C in the dark.

Table 7. α-Diazo Ketones Synthesized via "Detrifluoroacetylative" Diazo Transfer

Entry	α-Diazo Ketone		% Yield
1		(134)[a]	75-79
2		(135)	80-97
3		(136)	85-94
4		(137)	74-86
5		(138)	62-66
6		(139)	74
7		(140)	41*
8		(141)[b]	86
9		(133)[c]	80

* Yield not optimized

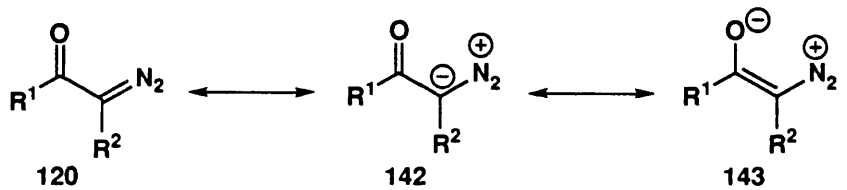
[a] Previously obtained in 84% yield by this method (ref. 29a)

[b] Previously obtained in 87% yield by this method (ref. 29a)

[c] Previously obtained in 87% yield by this method (ref. 29a)

102. Danheiser, R. L.; Miller, R. F.; Brisbois, R. G. *Organic Synthesis*, in press. See also, Table 7, entry 8.

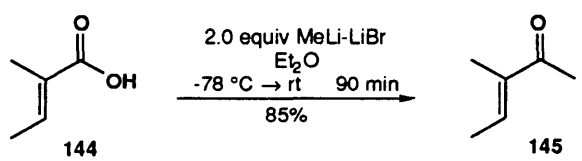
The spectra of α-diazo ketones include several characteristic features.[103] All of the diazo compounds exhibit a strong IR absorption in the region from 1950-2300 cm^{-1} which is assigned to either an N-N stretching mode or an asymmetric stretching of the C=N=N cumulene system. The carbonyl group of a diazo ketone has decreased double bond character due to the contributions of the resonance structures illustrated in equation 49. This results in a relative shift of the carbonyl stretch (ca. 20-60 cm^{-1}) toward lower frequency, resulting in an absorption in the range of 1650-1700 cm^{-1}.



(49)

The ^1H NMR spectrum of α-unsubstituted diazo ketones exhibits a singlet corresponding to the α-proton appearing in the 5.0-6.0 ppm range. This proton is exchangeable in the presence of D_2O and a catalytic amount of base. The ^{13}C NMR spectrum is very important for characterizing α-diazo ketones. The resonance for the diazo carbon appears at 50-70 ppm and the typical α,β-unsaturated diazo ketone carbonyl resonance falls in the range of 180-190 ppm. The typical maxima for the ultraviolet spectrum of α-diazo ketones is at 245-260 nm (ε = 10,000-20,000), corresponding to the π to π* transition of the diazo group.

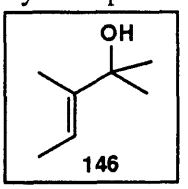
All of the requisite methyl ketone starting materials are commercially available with the exception of the precursors to **134**, **137**, **138**, and **139**. The preparation of 3-methyl-3-penten-2-one (**145**) starting from commercially available tiglic acid is shown below (eq 50).



(50)

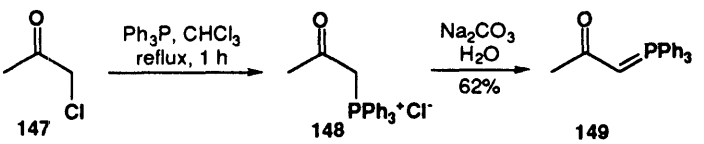
103. For detailed discussions, see: (a) Ref. 48b pp 113-117. (b) Ref. 48c pp 3-64.

Conversion of the carboxylic acid **144** to the methyl ketone **145**[27] was initially effected following a procedure by Frater[104] which involves the addition of 2 equivalents of methyllithium to the acid at low temperature. The reaction mixture is then gradually warmed to 0 °C, and then heated at reflux for 90 min. However, when we attempted to repeat this procedure for the conversion of **144** to **145**, the desired methyl ketone was obtained contaminated with a significant amount (~10-15%) of the tertiary alcohol **146**. In this case, it was found that optimal conditions for the production of **145** did not involve heating the reaction mixture to reflux. After warming to room temperature, the pure desired methyl ketone could be isolated in 85% yield upon workup and purification by distillation.

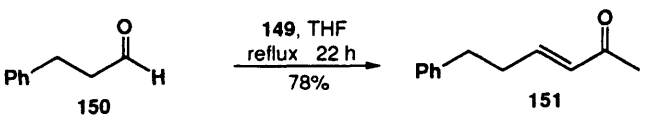


146

The preparation of enone **151** is presented below (eq 51 and 52). The acetyl ylide **149** is prepared using the standard procedure.[105a] Wittig reaction of ylide **149** with hydrocinnamaldehyde (**150**) provided 6-phenyl-3-hexen-2-one (**151**) in good yield.[110b]



147 **148** **149** (51)

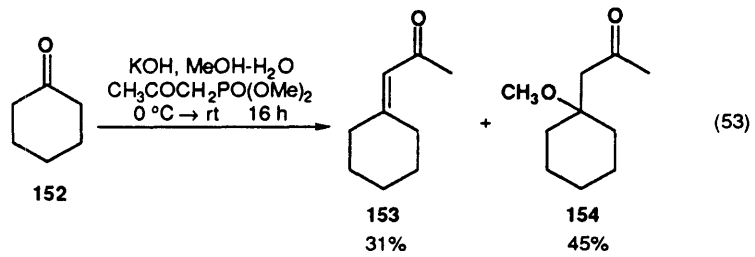


150 **151** (52)

The β,β-disubstituted methyl ketone **153** was prepared via a Horner-Wadsworth-Emmons reaction using commercially available dimethyl (2-oxopropyl) phosphonate as described by Smith (eq 53).[106] Methanol was used in this reaction (instead of ethanol as recommended by Smith) and was found to readily add to the desired enone to produce **154**

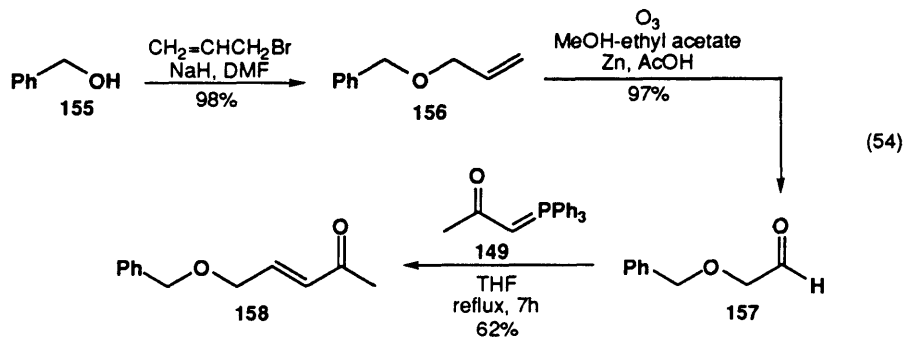
104. Nussbaumer, C.; Frater, G. *J. Org. Chem.* **1987**, *52*, 2096.
105. (a) Ramires, F.; Dershowitz, S. *J. Org. Chem.* **1957**, *22*, 41. (b) House, H. O.; Respess, W. L.; Whitesides, G. M. *J. Org. Chem.* **1966**, *31*, 35.
106. Smith, J. G. Ph. D. Dissertation, Harvard University, 1978, p. 130.

as the major product. However, the desired unsaturated ketone **153** was separated from **154** using column chromatography. No attempts were made to optimize this reaction.



(53)

The three step synthesis of 5-benzyloxy-3-penten-2-one (**158**) is described below (eq 54). Allylation of benzyl alcohol (**155**) was accomplished in excellent yield followed by ozonolysis of the terminal double bond to afford aldehyde **157**. The aldehyde was then olefinated with acetyl ylide **149** to produce the methyl ketone **158** in 59% overall yield from benzyl alcohol (**155**).

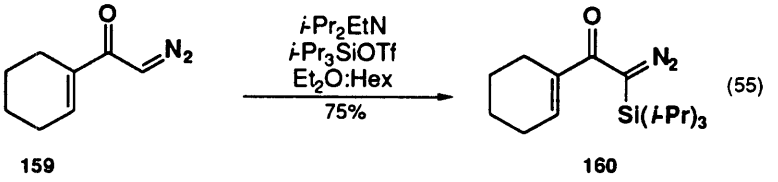


(54)

Synthesis of TAS-Diazo Ketones

Silylation of the α-diazo ketones was accomplished using a modification of the method of Maas[73] (eq 55). Maas has reported that the silylated α-diazo compounds undergo protodesilylation very easily due to the trialkylammonium triflate ($R_3NH^+OTf^-$) present in the reaction mixture (eq 56). We discovered that the yield of this silylation could be improved by ~25% by changing the solvent from Et_2O to Et_2O-hexane (1:1) in order to

make the trialkylammonium triflate less soluble and thus shift the equilibrium toward the desired product. For example, the silylation of diazo ketone **159** afforded the desired silyldiazo ketone **160** in 75% yield (eq 55), whereas using the Maas procedure the silyldiazo ketone **160** was obtained in only 48-64% yield.



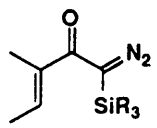
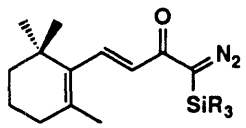
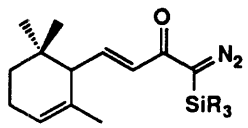
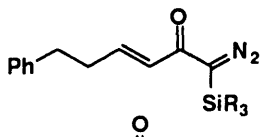
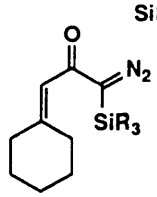
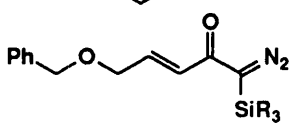
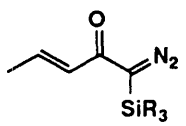
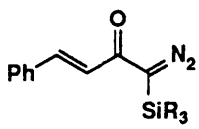
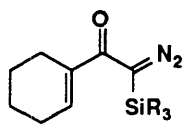
159 160 (55)

(56)

As illustrated in Table 8, a number of TAS-diazo ketones were synthesized including triisopropyl-, *tert*-butyldimethyl-, and triethylsilyl derivatives. All of the α-silyldiazo ketones prepared are new compounds that were previously unknown. Reactions were typically conducted on a scale to produce between 100 mg to 1 g of product. α-Silyldiazo ketones are unstable, yellow-brown oils that can be stored in solution for 2-3 days at 0 °C without significant decomposition.

In the ^{1}H NMR spectrum of α-silyldiazo ketones, the singlet corresponding to the α-proton of the diazo ketone precursor is absent and new resonances due to the trialkylsilyl group are observed. The ^{13}C NMR spectrum exhibits a carbonyl resonance in the range of 185-196 ppm which is shifted downfield by ~10 ppm when compared to the carbonyl resonance of the α-diazo ketone precursors. The IR spectrum of α-silyldiazo ketones show strong CN_2 and C=O stretching absorptions in the 2040-2070 cm^{-1} and the 1600-1650 cm^{-1} regions, respectively. These absorptions are shifted to slightly lower frequency as compared to the absorptions of the α-diazo ketones.

Table 8. Synthesis of TAS-Diazo Ketones

Entry	TAS-Diazo Ketone		R_3Si	Method of Preparation	% Yield
1		(161) (162)	*i*-Pr_3Si Et_3Si	A A	86-89 70-84
2		(163)	*i*-Pr_3Si	B	87
3		(164)	*i*-Pr_3Si	A	72
4		(165) (166)	*i*-Pr_3Si Et_3Si	B A	34-38 52
5		(167)	*i*-Pr_3Si	A	93-100
6		(168)	*i*-Pr_3Si	A	0
7		(169)	*i*-Pr_3Si	A	16
8		(170)	*i*-Pr_3Si	B	39
9		(171) (160)	*t*-$BuMe_2Si$ *i*-Pr_3Si	A A	53 75

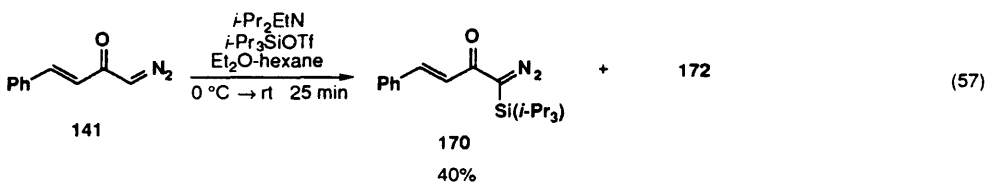
Method A: Addition of base and the appropriate trialkylsilyltriflate to the diazo ketone in Et_2O-hexane (total concn = 0.1 M) at 0 °C)
Method B: addition of base and the diazo ketone in Et_2O-hexane to the appropriate trialkylsilyl triflate in Et_2O-hexane (total concn = 0.02 M) at 0 °C)

The order of addition of reactants and the reaction concentration was found to be crucial to the success of the silylation particularly for substrates with disubstituted double

bonds (entries 2, 3, 4, 6, 7, and 8). In these cases, initial experiments led to the formation of the desired silyldiazo ketones contaminated with comparable amounts of a byproduct.

Upon further study, it was found that the side reaction leading to this byproduct could be suppressed if (a) the silylation is conducted under more dilute reaction conditions and (b) inverse addition of reactants is employed as described in Method B (addition of base and the diazo ketone in Et_2O-hexane to the appropriate trialkylsilyl triflate in Et_2O-hexane (total concn = 0.02 M) at 0 °C). As indicated in Table 8, silyldiazo ketones with disubstituted double bonds can be prepared in moderate yields using this Method B procedure. It should be noted that for entries 6 and 7, only Method A was examined for the synthesis of α-silyl diazos **168** and **169**. It is believed that these silyldiazo ketones would be obtained in higher yield if Method B was employed for their synthesis.

In most cases, the byproduct generated in reactions of disubstituted substrates (e.g. entries 4,6, and 7) could not be separated by column chromatography. However in the case of 1-diazo-4-phenyl-3-buten-2-one (**141**),[107] the products of the reaction were separable and the desired silyldiazo ketone **170** was isolated in 40% yield (370 mg) along with 240 mg of the byproduct **172** (eq 57). However, thus far we have been unable to assign a definite structure to this compound. It is noteworthy that heating a purified sample of silyldiazo ketone **165** at 40 °C for 22 h in C_6D_6 led to the formation of a mixture of **165** and a comparable amount of the byproduct.



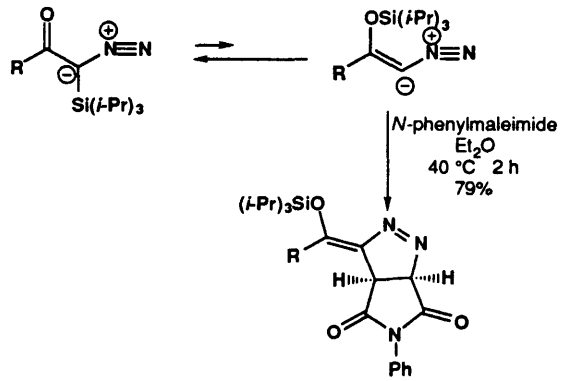
(57)

It is possible that this byproduct arises from a dipolar cycloaddition pathway. Maas reports that α-silyldiazo ketones can undergo a 1,3-(C→O) silyl shift to produce

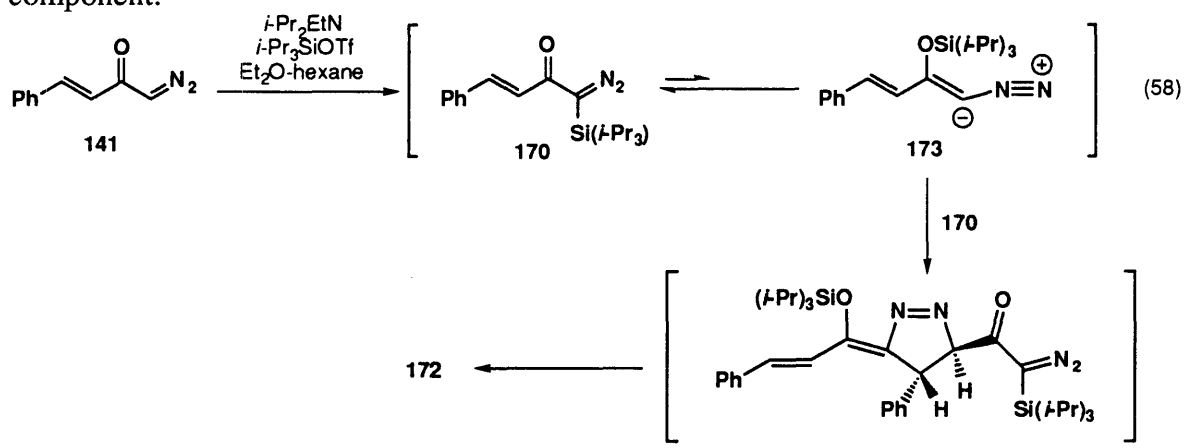
107. The author gratefully acknowledges Raymond F. Miller for the preparation and characterization of the diazo ketone **141**.

diazoalkenes as reactive intermediates which have been trapped in the presence of dipolarophilic alkenes such as *N*-phenylmaleimide (Scheme 17)[108]

Scheme 17



The cycloaddition of diazo compounds to alkenes is a well known method for the synthesis of pyrazoline rings.[109] It is possible that the diazoalkene **173** is generated and undergoes cycloaddition with the double bond of an additional molecule of silyldiazo ketone **170** to afford the indicated intermediate 1-pyrazoline. (eq 58). For this type of cycloaddition, the indicated product is the expected regiochemical isomer where the diazoalkane carbon is bonded to the β-position of the α,β-unsaturated carbonyl component.[110]



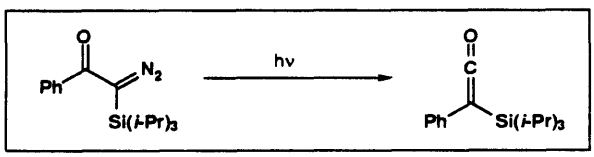
(58)

108. Munschauer, R. Maas, G. *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 306.
109. Regitz, M. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; John Wiley & Sons: New York, 1984, pp. 391-558.
110. Eberhard, P.; Huisgen, R. *Tetrahedron Lett.* **1971**, *45*, 4337.

The IR spectrum of the byproduct **172** (derived from silyldiazo ketone **170**) shows an N-H stretch at 3344 cm^{-1} and also a CN_2 stretch at 2064 cm^{-1} due to the silyldiazo functionality in the molecule. Two carbonyl stretching frequencies are observed at 1605 and 1630 cm^{-1}. In the ^1H NMR spectrum, an amino hydrogen appears at 7.1 ppm as a singlet and was found to be exchangeable with D_2O. The ^{13}C NMR spectrum shows resonances at 195.0 and 49.5 ppm corresponding to an α-silyldiazo ketone functionality. A second carbonyl resonance at 183.1, 11 sp^2-carbons between 121.9 and 156.3 ppm, additional resonances at 74.6, 54.7, 31.6, and 22.6, and triisopropylsilyl carbons at 18.4 and 17.7 ppm were also observed in the ^{13}C NMR spectrum. The ^1H NMR spectrum of **172** exhibits a pair of doublets at 4.62 and 4.77 ppm with J = 3.6 Hz. The spectrum also shows a doublet at 7.57 ppm with J = 15.8 Hz and a doublet at 6.60 ppm with J = 15.8 ppm. Each of the doublets described above integrates to one proton. One triisopropylsilyl group is observed in the proton NMR spectrum, and additional multiplets appear between 7.2 and 7.7 ppm, integrating to ca. 15 protons. To date, we have been unsuccessful in assigning a structure to this compound.

Photochemical Wolff Rearrangement to TAS-Vinylketenes

Research directed toward determining the optimal conditions for the photo-Wolff based generation of silylketenes was developed collaboratively with Dr. Kazu Takahashi. As illustrated below, the rearrangment of α-triisopropylsilyldiazoacetophenone was initially examined and optimal conditions for the transformation were established by Dr. Takahashi.

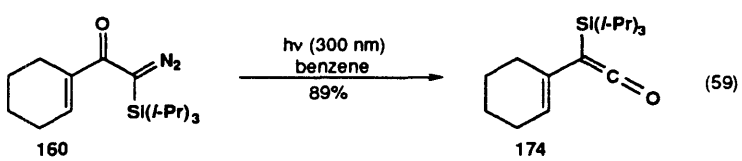


In general, the best results for the conversion of α-silyldiazo ketones to silylketenes were obtained by irradiating a 0.1 M solution of the α-silyldiazo ketone under a positive pressure of nitrogen at 300 nm in a Rayonet RPR-100 photochemical reactor. The internal temperature of the reactor chamber was maintained at 30-35 °C by use of a cooling fan.

Without the use of the fan, the chamber temperature rises to 65-75 °C, resulting in diminished yields of the desired products. The photochemical reactor was equipped with sixteen low-pressure mercury vapor bulbs, which have a highly monochromatic output. It was found that the highest yields and shortest reaction times were achieved when all sixteen lamps were working. The rearrangement can also be induced at 0 °C when the reaction mixture is irradiated in a Hanovia photochemical reactor, although yields were noted to be slightly decreased using this method. Benzene, dichloroethane, hexane, and toluene all proved to be suitable solvents for the reaction, whereas, acetonitrile was found to be unacceptable.

The reaction also proceeds under the influence of 254 nm light, albeit in not as good a yield. It is important to note that although all of the reactions subsequently described in this thesis were conducted with 300 nm light in vycor tubes, these do not necessarily represent the optimal conditions for every substrate. The UV spectrum of the α-silyldiazo ketone of interest should be carefully evaluated prior to the choice of reaction conditions. A strong absorbance at a wavelength significantly different than 300 nm should weigh heavily in the determination of the exact experimental protocol.

The first α,β-unsaturated silyldiazo ketone studied was the cyclohexenyl derivative **160**. Optimal conditions for the generation of the TAS-vinylketene **174** involved irradiating a degassed 0.1 M solution of the silyldiazo ketone in benzene in a vycor tube using a low-pressure mercury lamp (300 nm) (eq 59). Concentration and chromatographic purification furnished the desired ketene **174** as a stable, light yellow oil in 89% yield.



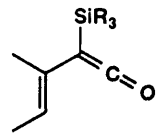
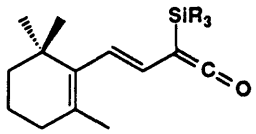
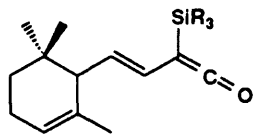
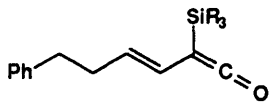
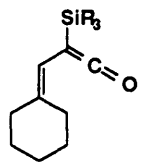
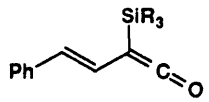
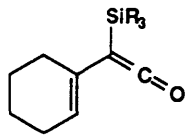
160 174 (59)

In general, the photochemical Wolff rearrangement produced the desired TAS-vinylketenes (100 mg to 1 g scale) in very good yield. In all cases, the reaction solution

was divided equally between two or three vycor tubes, which were simultaneously irradiated in the photochemical reactor. Two sizes of reaction tubes were employed. The standard vycor tube used in this investigation was 20-25 cm in length (9 mm O.D., 7 mm I.D.). Larger tubes were generally 30-35 cm in length (12 mm O.D., 10 mm I.D.) and were excellent for the preparation of larger amounts of material, but the greater volume of the reaction solution often required longer periods of irradiation. Optimal results are obtained when oxygen is scrupulously removed from the reaction tube. This can best be accomplished by degassing the mixture with three freeze-pump-thaw cycles (-196 °C, <0.5 mm Hg). Alternatively, when using larger tubes, we have found that it is acceptable to degas the reaction tube by passing dry nitrogen gas through the solution for at least 10 minutes.

We have established that the photo-Wolff methodolology can be applied for the efficient synthesis of TAS-vinylketenes with a wide range of vinyl and trialkylsilyl groups. A variety of substituted TAS-vinylketenes have been prepared using this method as shown in Table 9. α-Silyldiazo ketones with a disubstituted double bond rearrange to produce TAS-vinylketenes (**177**, **179**, **180**, and **182**) in only moderate yields. These are the same substrates mentioned above that require Method B for silylation. It is possible that the yields for these photolysis reactions are low due to the instability of the silyldiazo ketone starting material. These reaction mixtures also become dark red upon photolysis. The dark color can prevent the transmittance of light to the silyldiazo ketones which could then explain the poor conversion of silyldiazo ketone to ketene. The generation of the β,β-disubstituted silylketene **181** from α-silyldiazo ketone **167** was unsuccessful. By tlc analysis the reaction appeared to give one product, however, the yield of this product upon isolation was very low (20-25%). The IR spectrum for this compound did show a strong ketene stretch (~2100 cm^{-1}), but the ^1H NMR spectrum was not consistent with the desired β,β-disubstituted ketene. To date, the product of this reaction has not been identified.

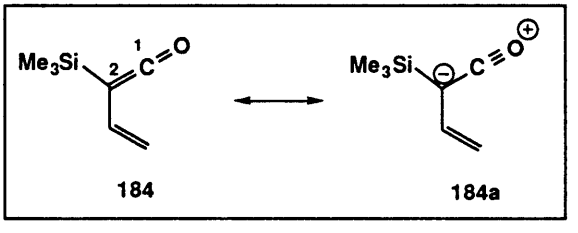
Table 9. TAS-Vinylketenes via Photochemical Wolff Rearrangement

Entry	TAS-Vinylketene		R_3Si	Irradiation Time (h)	% Yield
1		(175) (176)	*i*-Pr_3Si Et_3Si	4 3.5-7	79-80 65-73
2		(177)	*i*-Pr_3Si	2-3	54-61
3		(178)	*i*-Pr_3Si	2.5	81
4		(179) (180)	*i*-Pr_3Si Et_3Si	3 2.5	41 19-20
5		(181)	*i*-Pr_3Si	2-3	0
6		(182)	*i*-Pr_3Si	3	35
7		(174) (183)	*i*-Pr_3Si *t*-$BuMe_2Si$	4 4.5	89 58

As hoped, these TAS-vinylketenes have been found to be remarkably robust substances and are even stable to silica gel purification. The ketenes can be recovered in ~95% yield when the pure ketene is subjected to column chromatography. For example, when silylketene **174** (0.055 g) was subjected to column chromatography on 10 g of silica gel (elution with hexane) 95% of ketene **174** (0.052 g) was recovered unchanged.

^{1}H NMR was used as a tool to monitor the stability of TAS-vinylketenes under thermal conditions. The protocol developed for testing the ketene stability involved heating a solution of the silylketene and 1,4-dimethoxybenzene (as internal standard) in deuterated benzene under nitrogen in an NMR tube and monitoring by NMR the decomposition of the ketene versus the internal standard. Decomposition of the (triethylsilyl)vinylketene **176** was observed after heating in C_6D_6 at 80 °C for 6-10 hours; however, (triisopropylsilyl)vinylketenes **174, 175,** and **177** were found to be considerably more stable: no decomposition was seen after heating in C_6D_6 at 80 °C for 3-4 days.

TAS-vinylketenes exhibit a number of interesting spectral characteristics (Table 10) which make structure assignment a relatively straightforward task.[111] The IR spectra of TAS-vinylsilylketenes show a strong diagnostic stretch near 2100 cm^{-1} due to the symmetric stretching modes of the ketene backbone (C=C=O) and exhibit a principle absorption band for the C=O stretch found near 2080 cm^{-1}. TAS-vinylketenes absorb in the ultraviolet region with an absorption maxima near 220-240 nm. The ^{1}H NMR spectrum provides relatively little information since the TAS-vinylketenes do not contain a diagnostic proton on the ketene double bond. However, the ^{13}C NMR spectrum does contain some interesting features.[112] The C-1 carbon of the TAS-vinylketene is extensively deshielded and produces a signal at low field near 180 ppm. On the other hand, the C-2 carbon gives a very high field signal near 20 ppm, due in part to the contribution of the resonance structure **184a** illustrated below.



184 **184a**

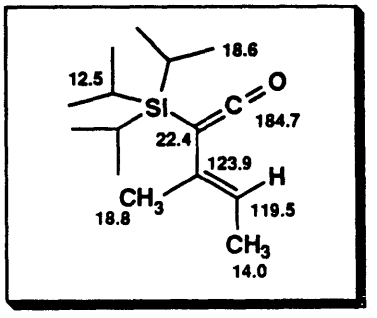
111. For spectral characteristics of ketenes see Ref. 33a pp 169-188.
112. Grishin, Y. K.; Ponomarev, S. V.; Lebedev, S. A. *Zh. Org. Khim.* **1974**, *10*, 402.

Table 10. Spectral Characteristics of 3-Methyl-3-penten-triisopropylsilylketene (175)

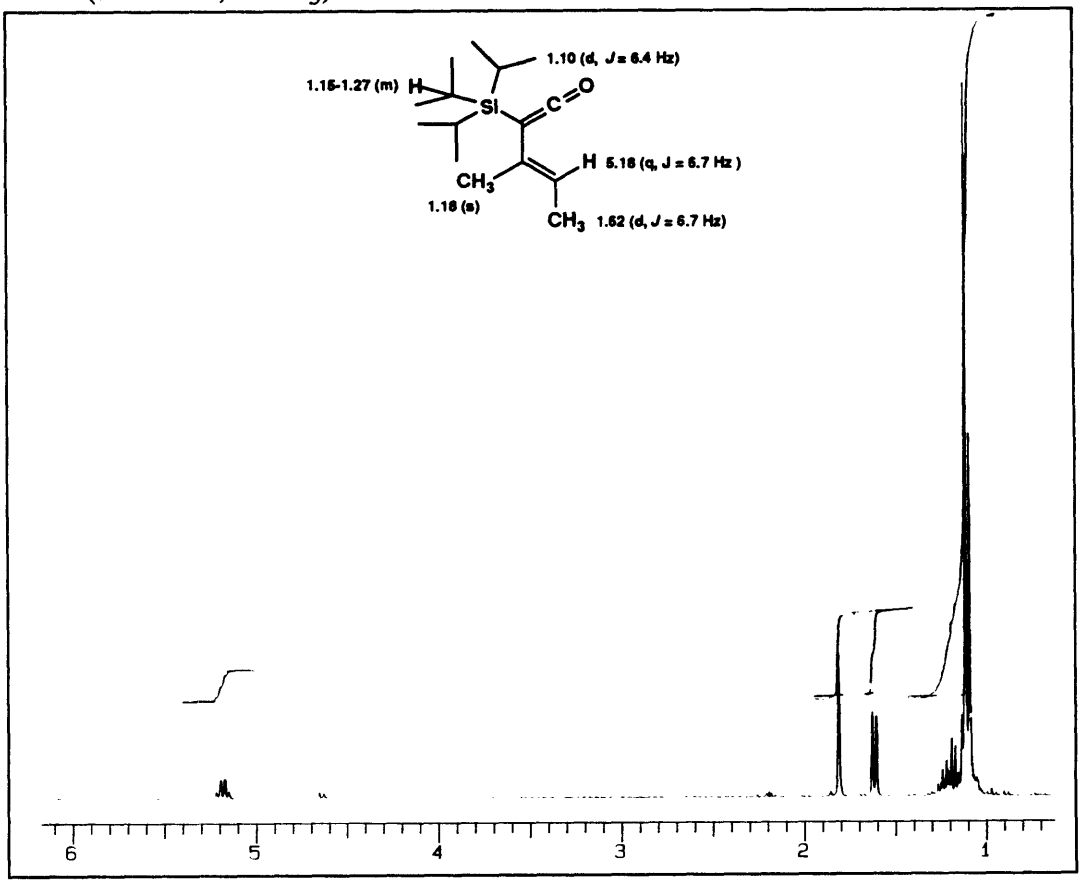
IR (film): 2941, 2881, 2081, 1461, 1381, 1291, 1181, 1071, and 1021 cm^{-1}

UV max (hexane): 229 nm (ε = 9000)

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



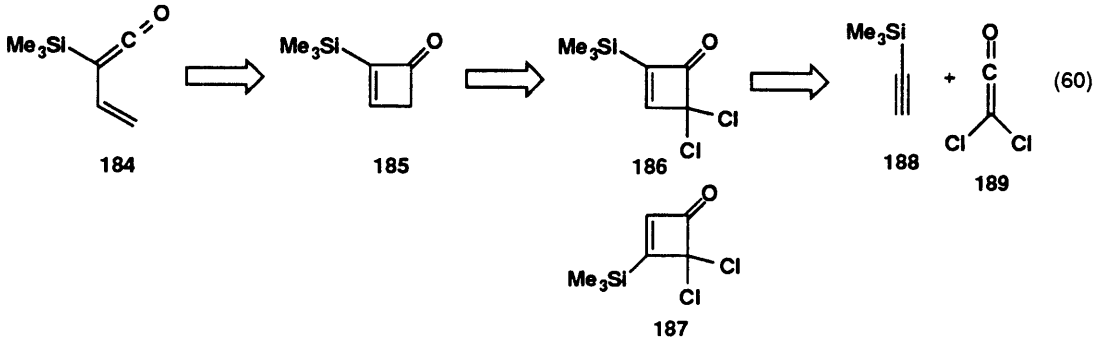
^{1}H NMR (300 MHz, $CDCl_3$):



Alternative Routes to TAS-Vinylketenes: Preliminary Studies

(1) TAS-Vinylketenes via Electrocyclic Ring Opening of Trialkylsilylcyclobutenones

One route to the parent (trimethylsilyl)vinylketene **112** (see eq 40, p. 67) examined in the original studies on this compound involved the electrocyclic ring opening of silylcyclobutenone **185** which was hoped to be available via a [2 + 2] cycloaddition of dichloroketene (**189**) and trimethylsilylacetylene (eq 60). Dichloroketene was chosen for this cycloaddition because ketene itself is unreactive toward most alkenes and alkynes in [2 + 2] cycloadditions.[113] Unfortunately, the cycloaddition of **188** and **189** afforded a mixture of the desired (trialkysilyl)cyclobutenone **186** and (predominately) the undesired β-silyl derivative **187**.[119]

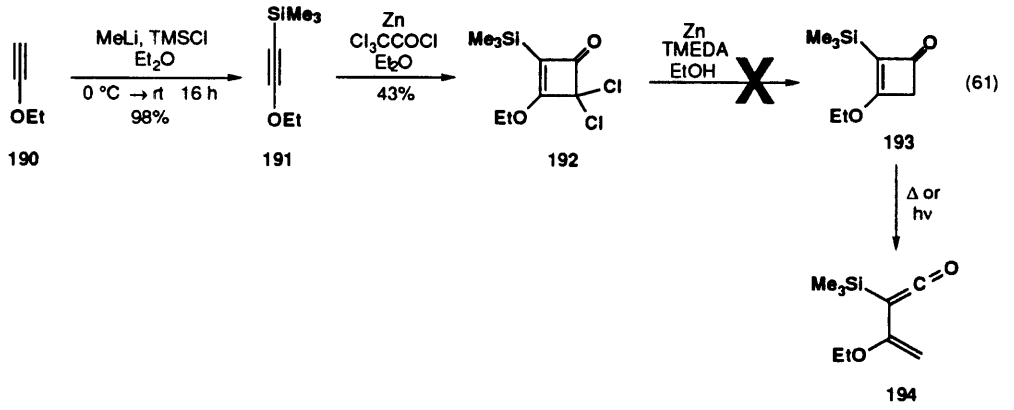


[2 + 2] Cycloadditions of dichloroketene with alkynylsilanes has been shown to proceed with high selectivity to produce the α-silyl cyclobutenones when the alkynylsilanes are substituted with directing groups such as phenyl and ethoxy.[114] In principle, we believed it would be possible to access substituted TAS-vinylketenes using the electrocyclic ring opening strategy by employing suitably substituted acetylenes such as **191** (eq 61). Silylation of ethoxyacetylene **190** proceeded in excellent yield to afford trimethylsilylethoxyacetylene[77a] which was then added to dichloroketene (generated via

113. (a) Dehmlow, E. V.; *Chem. Ber.* **1967**, *100*, 3829. (b) Knoche, H. *Justus Liebigs Ann. Chem.* **1969**, *722*, 232. (c) Krebs, A.; Kimling, *Justus Liebigs Ann. Chem.* **1974**, 2074. (d) Morita, N.; Asao, T.; Kithara, Y. *Chem. Lett.* **1972**, 927. (e) Wong, H. N. C.; Sondheimer, F.; Goodin, R.; Breslow, R. *Tetrahedron Lett.* **1976**, 2715. This method has also been successfully applied to cycloadditions involving simple alkynes: Hassner, A.; Dillon, J. *Synthesis*, **1979**, 689.

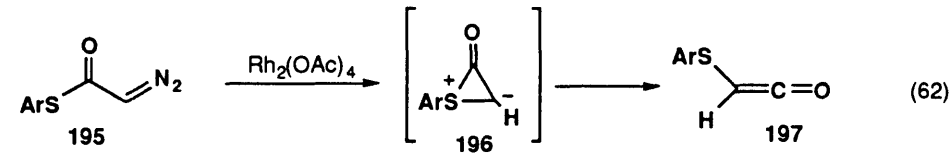
114. Danheiser, R. L.; Sard, H. *Tetrahedron Lett.* **1983** *24*, 23.

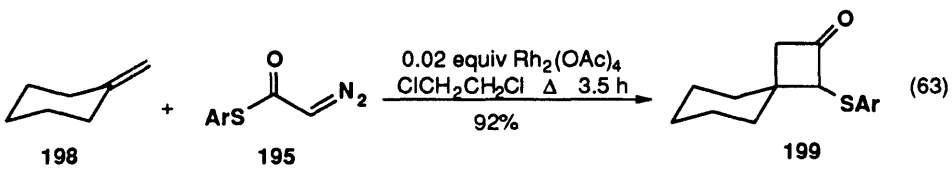
dehydrohalogenation of dichloroacetyl chloride) to produce the cycloadduct **192** in 43% yield (lit. 86%).[114] The next step in our scheme required the reductive dechlorination of a 4,4-dichlorocyclobutenone, which is considerably more difficult than in the case of the corresponding saturated derivatives, though it can be accomplished using procedures developed independently in our laboratory[115] and that of Dreiding.[116] Unfortunately, we were not able to achieve clean dechlorination of the 2-silyl-dichlorocyclobutenone **192** using these conditions and were forced to abandon this approach.



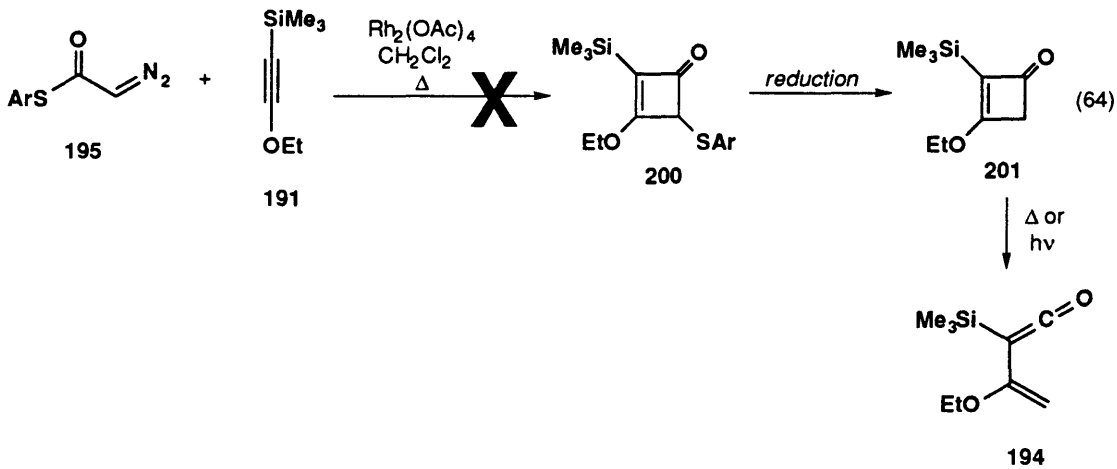
Thomas Lee of our laboratory has recently found that α-diazo thiol esters rearrange in the presence of catalytic rhodium acetate at 25-80 °C to generate (arylthio)ketenes in high yield (eq 62). The facility and efficiency of this Wolff-type rearrangement is attributable to the formation of a 3-membered sulfonium ylide intermediate **196** from an initial carbenoid species.[117] Remarkably, when this reaction is conducted in the presence of unactivated olefins such **198**, cyclobutanones are obtained in outstanding yields (no cyclopropane products are detected) (eq 63).

115. (a) Danheiser, R. L.; Savariar, S. *Tetrahedron Lett.* **1987**, *28*, 3299. (b) Danheiser, R. L.; Selvaraj, S.; Cha, D. D. *Organic Synthesis* **1989**, *68*, 32.
116. Ammann, A. A.; Rey, M.; Dreiding, A. S. *Helv. Chim. Acta* **1987**, *70*, 321.
117. (a) Hixson, S. S.; Hixson, S. H. *J. Org. Chem.* **1972**, *37*, 1279. (b) Boyer, S. K.; Edwards, B. *J. Org. Chem.* **1980**, *45*, 1686.



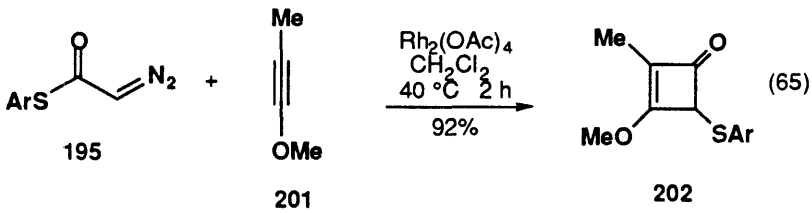


We believed that this chemistry could provide an important new route to the 2-trialkylsilylcyclobutenones needed for the generation of TAS-vinylketenes via electrocyclic ring opening. Our strategy is illustrated below (eq 64).



To date, the [2 + 2] cycloaddition of the (arylthio)ketenes with trialkysilyl-substituted acetylenes has produced only a mixture of complex products under the standard conditions we have successfully employed for cycloadditions with unactivated alkenes. When no catalyst is present, no reaction occurs between **195** and **191.** Exposure of the (trialkysilyl)acetylene **191** to the rhodium catalyst in the absence of **195** does *not* lead to alkyne decomposition.

In contrast to the silyl-substituted alkoxyacetylene **191**, methoxypropyne **201**[118] reacted with the (arylthio)ketene generated from **195** to afford the desired cyclobutenone in 92% yield (eq 65). A competition experiment was then conducted to determine the relative efficiency of this alkyne (**201**) and cyclopentadiene as traps for the (arylthio)ketene. The alkyne in fact proved to be a very effective trap producing cyclobutenone **202** in 79% yield. It thus appears that the complications arising in the [2 + 2] cycloaddition of the (arylthio)ketene and the silylalkyne **191** are due to the trialkylsilyl group attached to the alkyne.

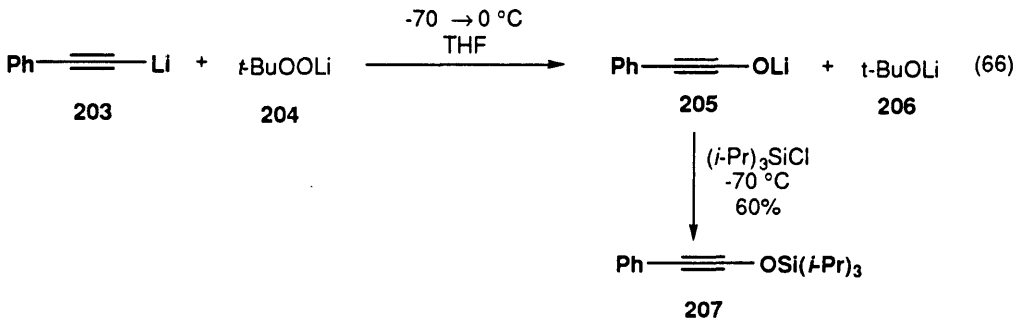


(65)

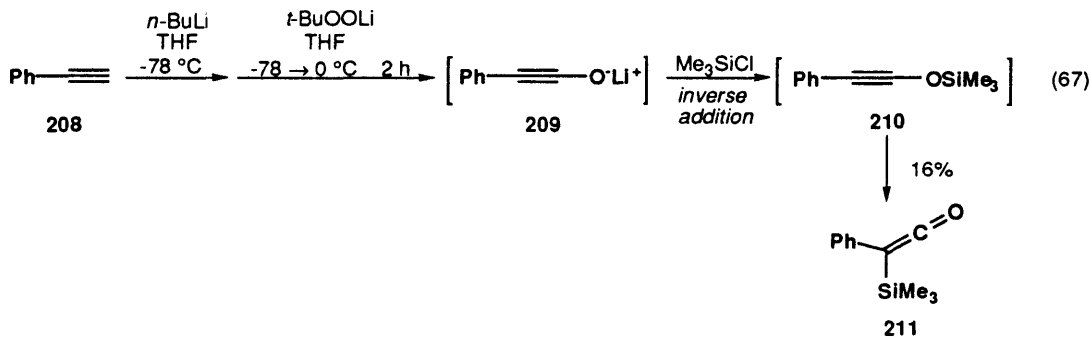
2) TAS-Vinylketenes via Isomerization of Trialkylsiloxyalkynes

As discussed earlier (p. 55), siloxyalkynes with small to medium-sized silyl groups (Me_3Si, Et_3Si, *t*-$BuMe_2Si$) undergo a facile salt-promoted isomerization to form silylketenes. Recently, Julia has reported that lithium acetylides react with lithium *tert*-butyl peroxide to produce lithium ynolates in good yield (eq 66).[119] We expected that the application of the Julia protocol to enynes might provide a very expeditious route to conjugated siloxyalkynes that upon warming to 25 °C might isomerize to produce TAS-vinylketenes.

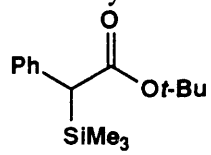
118. The author would like to thank Michael D. Lawlor for the preparation of methoxypropyne (**210**).
119. Julia, M.; Saint-Jalmes, V. P.; Vereaux, J.-N. *Synlett.* **1993**, 233.



Initially, model studies were conducted using commercially available phenylacetylene (**208**; eq 67). (Trimethylsilyl)phenylketene **211** was produced using this method in 16% yield.



Inverse addition of the lithium ynolate to a solution of excess trialkysilyl chloride was found to be necessary in order to isolate the silylketene. If the addition was reversed and the trialkysilyl chloride was added to the ynolate solution, the *t*-butoxide generated as a byproduct during the reaction added to the silylketene producing the ester **212**.



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When bulkier silyl chlorides such as *t*-BuMe$_2$SiCl and Et$_3$SiCl were used to quench the ynolate, formation of the desired acetylene was initially observed by IR. Upon stirring at room temperature (5-10 h), however, IR analysis revealed that isomerization to the

ketene did not occur and the acetylene decomposed. Further work will be necessary to determine whether this strategy can provide a useful route to silylvinylketenes.

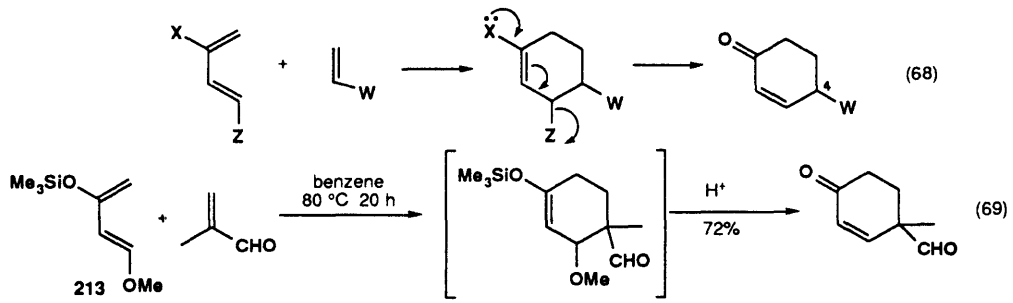
Summary

The photochemical Wolff rearrangement of α-silyldiazo ketones is an excellent method for the preparation of a variety of substituted TAS-vinylketenes. We believe that in principle some of the other strategies presented above will also provide access to substituted TAS-vinylketene derivatives; however, further investigation is necessary.

CHAPTER 4

APPLICATIONS OF TAS-VINYLKETENES AS DIENES IN THE DIELS-ALDER REACTION

The Diels-Alder reaction is a very powerful and versatile method for the construction of six-membered rings.[120] The use of highly substituted dienes has greatly expanded the utility of this reaction as applied to the synthesis of more richly functionalized rings.[121] The desired oxidation level at each carbon of the newly formed ring can often be obtained by choice of the appropriately functionalized diene. Cyclohexenones are valuable synthetic intermediates as well as attractive targets for assembly via the Diels-Alder strategy. For example, Danishefsky has developed a particularly elegant approach to achieve the synthesis 4-substituted cyclohexenones.[122] In general, this transformation employs an oxygenated diene where X and Z are alkoxy substituents which confer high reactivity and regiospecificity on the diene, and W is an electron withdrawing group such as a carbonyl (eq 68). An example of the cycloaddition of "Danishefsky's diene" (*trans*-1-methoxy-3-trimethylsilyloxy-1,3-butadiene) with methacrolein is shown below (eq 69).

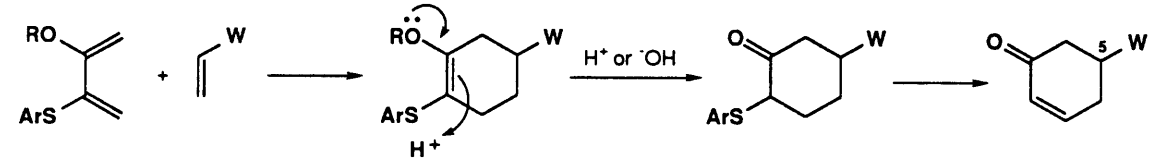


120. For reviews, see: (a) Oppolzer, W. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: New York, 1990, Vol. 5, pp 315-399. (b) Carruthers, W. In *Cycloaddition Reactions in Organic Synthesis*; Pergamon Press: New York, 1990, pp 1-208. (c) Wollweber, H. In *Methoden der organischen Chemie (Houben Weyl);* Mueller, E. Ed.; Georg Thieme; Stuttgart, 1970; Vol. 5/1c, pp. 977-1210. (d) Fringuelli, F.; Taticchi, A. *Dienes in the Diels-Alder Reaction*; John Wiley & Sons; New York, 1990.

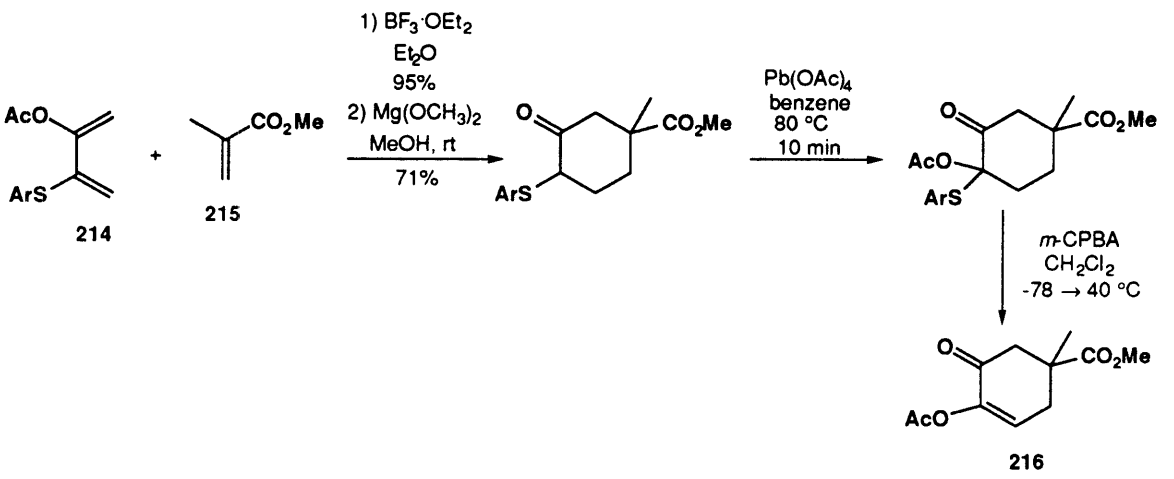
121. For some examples of cycloadditions of heterosubstituted dienes, see: (a) Petrzilka, M.; Grayson, J. I. *Synthesis*, **1981**, 753. (b) Danishefsky, S. *Acc. Chem. Res.* **1981**, 14, 400.

122. Danishefsky, S.; Kitahara, T. *J. Am. Chem. Soc.* **1974**, *96*, 7807. (b) Danishefsky, S.; Kitahara, T. *J. Org. Chem.* **1975**, *40*, 538.

Trost has also applied the Diels-Alder strategy for the synthesis of cyclohexenone ring systems.[123] In contrast to cycloadditions based on Danishefsky's diene, Trost's reaction leads to the formation of substituted cyclohexenones in which the electron-withdrawing group is located at the C-5 position of the new ring (eq 70). A typical example of Trost's cyclohexenone synthesis is shown in equation 71.



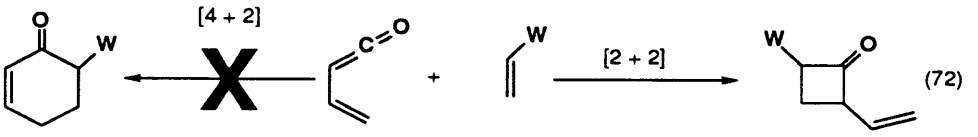
(70)



(71)

In principle, cyclohexenones bearing the electron-withdrawing substituent at C-6 of the new ring should also be accessible via a Diels-Alder strategy. This approach requires the cycloaddition of an electron-deficient olefin with a vinylketene. Unfortunately, vinylketenes are not effective dienes in [4 + 2] cycloadditions because they readily undergo [2 + 2] cycloadditions with olefins as predicted by frontier molecular orbital theory (eq 72). An objective of current interest is the development of a vinylketene equivalent which is capable of participating in [4 +2] Diels-Alder reactions.

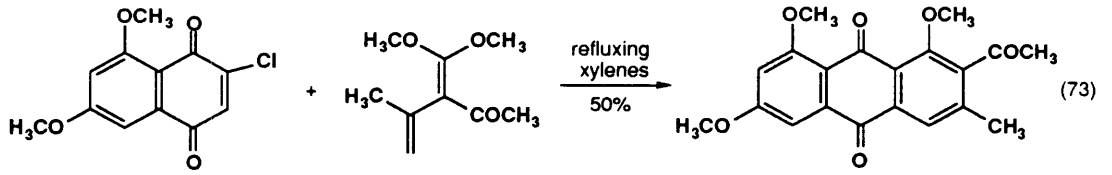
123. Trost, B. M.; Vladuchick, W. C.; Bridges, A. J. *J. Am. Chem. Soc.* **1980**, *102*, 3554.



(72)

Previous Vinylketene Equivalents

Considerable effort has been directed toward the development of stable vinylketene equivalents in which the critical ketene functionality is masked so that the desired [4 + 2] Diels-Alder reaction can occur. Both vinylketene acetals[124] and thioacetals[125] have been reported to undergo [4 + 2] cycloadditions in good yield. However, due to the limited reactivity of these hindered *Z*-dienes, only highly electrophilic dienophiles react. Brassard has condensed vinylketene acetals with 2-halogeno-1,4-napthoquinones in order to synthesize a number of naturally occuring anthraquinones.[124b-g] For example, 2-acetyl-1,1-dimethoxy-3-methylbuta-1,3-diene (**218**) has been added to the napthoquinone **217** to produce 2-acetyl-1,6,8-trimethoxy-3-methylanthraquinone (**219**) in 50% yield as a key step in the synthesis of a coccid pigment (eq 73).



(73)

217 **218** **219**

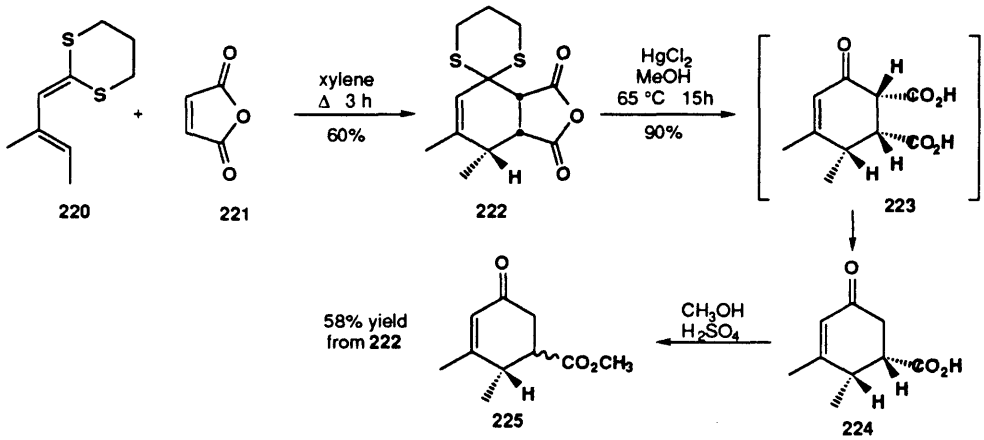
Carey has employed vinylketene thioacetals in [4 + 2] cycloadditions with highly reactive dienophiles (Scheme 18). The expected cycloadducts can be converted to cyclohexenones via a variety of hydrolytic methods. It is noteworthy that less reactive

124. For example of vinylketene acetals, see: (a) McElvain, S. M.; Morris, L. R. *J. Am. Chem. Soc.* **1952**, *74*, 2657. (b) Banville, J.; Grandmaison, J. L.; Lang, G.; Brassard, P. *Can. J. Chem.* **1974**, *52*, 80. (c) Banville, J.; Brassard, P. *J. Chem. Soc., Perkin Trans. 1* **1976**, 1852. (d) Banville, J.; Brassard, P. *J. Org. Chem.* **1976**, *41*, 3018. (e) Grandmaison, J. L.; Brassard, P. *Tetrahedron* **1977**, *33*, 2047. (f) Grandmaison, J. L.; Brassard, P. *J. Org. Chem.* **1978**, *43*, 1435. (g) Roberge, G.; Brassard, P. *J. Chem. Soc., Perkin Trans. 1* **1978**, 1041. (h) Gompper, R.; Sobotta, R. *Tetrahedron Lett.* **1979**, 921.

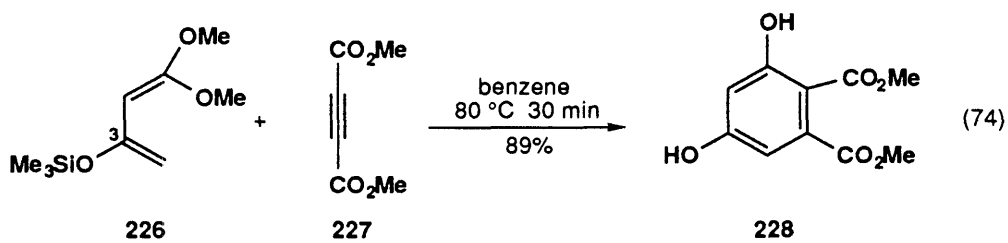
125. For some examples of vinylketene thioacetals, see (a) Carey, F. A.; Court, A. S. *J. Org. Chem.* **1972**, *37*, 4474. (b) Kelly, T. R.; Goerner, R. N.; Gillard, J. W.; Prazak, B. K. *Tetrahedron Lett.* **1976**, *43*, 3869.

dienophiles such as diethyl maleate, diphenylacetylene, and *p*-benzoquinone did not react with the unsaturated thioacetals.

Scheme 18



Activated vinylketene acetals and thioacetals have been prepared with electron donating groups at the C-3 position of the diene to help promote reaction with weaker dienophiles. Brassard and coworkers first prepared dienes activated by alkoxy and silyloxy groups positioned at C-3 and studied their reaction with naphthoquinones.[124c,f,g] Similarily, Danishefsky has reported the Diels-Alder reaction of the highly nucleophilic diene **226** with several dienophiles (eq 74).

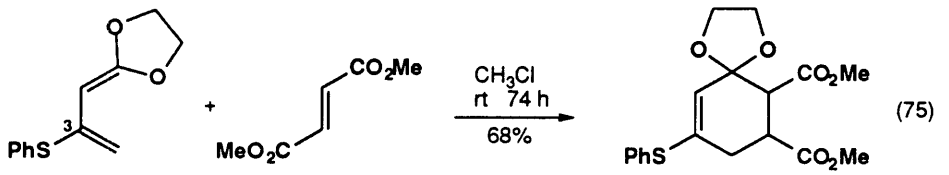


(74)

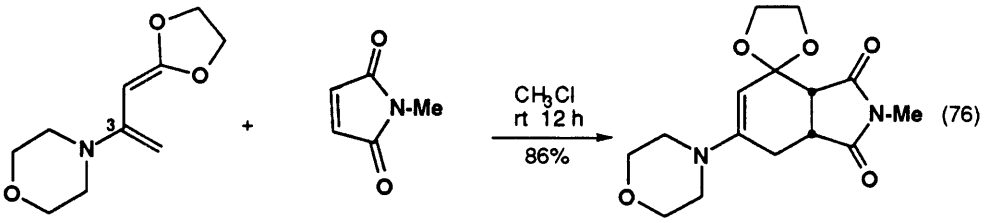
Recently, other heteroatoms such as sulfur and nitrogen have been positioned at C-3 to help activate dienes toward cycloaddition (eq 75 and 76).[126] These reactions proceed at much lower temperatures than the corresponding reactions with the C-3 methyl

126. Konopelski, J. P.; Kasar, R. A. *Tetrahedron Lett.* **1993**, *34*, 4587.

substituted diene which requires 110 °C in order for the cycloaddition to occur. No reactions with other less reactive dienophiles have been reported.

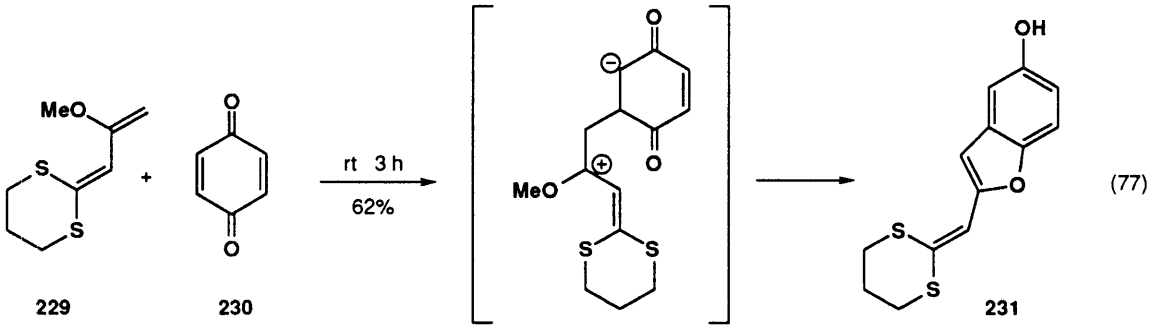


(75)



(76)

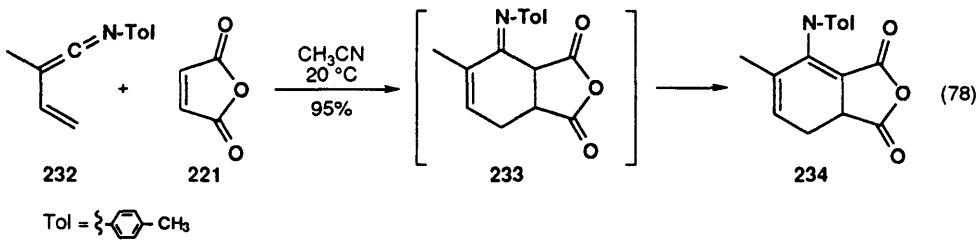
Due to the strong nucleophilic character of vinylketene thioacetals, these dienes were found to participate in a Michael-type stepwise process (eq 77).[127] As illustrated below, diene **229** adds to quinone **230** via a 1,4-Michael addition, followed by the elimination of methanol and tautomerization to produce **231**. It is believed that the nucleophilic diene reacts via its "s-trans" conformer, and therefore the Diels-Alder type cyclization is not competitive with ring closure to the furan ring.



(77)

127. Danishefsky, S.; McKee, R.; Singh, R. K. *J. Org. Chem.* **1976**, *41*, 2934.

Vinylketenimines such as **232** have been demonstrated to serve as useful vinylketene equivalents.[93,128] These dienes are isolable by distillation, stable at room temperature, and undergo [4 + 2] reactions to produce cycloadducts in moderate to good yields (eq 78). Diels-Alder reactions of (silyl)vinylketenimines are even reported to proceed in good yield with moderately reactive dienophiles such as methyl acrylate and crotonate.[93]



(78)

[4 + 2] Cycloadditions with TAS-Vinylketenes

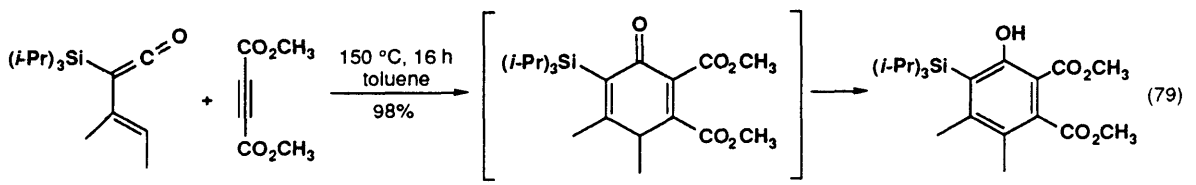
Previous work carried out in our laboratory had established that TMS-vinylketene can function as a diene component in Diels-Alder [4 + 2] cycloadditions. The scope of these reactions, however, is restricted by the limited thermal stability of this vinylketene which must be handled and stored in solution. As discussed in Chapter 3, the photochemical Wolff rearrangement provided us with access to a variety of substituted TAS-vinylketenes. These substituted derivatives were found to be more robust than the parent TMS-vinylketene, and are even stable to silica gel purification and heating in C_6D_6 at 80 °C for several days. We therefore undertook a systematic investigation of the utility of substituted TAS-vinylketenes as four-carbon diene components in [4 + 2] cycloadditions. Our objectives in this study included examining: (1) the scope of the reaction with respect to various types of TAS-vinylketene substitution; (2) the scope of the cycloaddition with regard to the degree of activation required on the dienophile; (3) the regiochemical course of the [4 + 2] cycloaddition; and (4) the stereochemical course of the reaction.

128. Sonveaux, E.; Ghosez, L. *J. Am. Chem. Soc.* **1973**, *95*, 5417.

(1) Reactions with Dimethyl Acetylenedicarboxylate

Cycloadditions with the highly reactive dienophile dimethyl acetylenedicarboxylate (DMAD) were examined first. The optimal procedure for the Diels-Alder reaction of TAS-vinylketenes and DMAD involves heating a 0.9 M degassed toluene solution of silylketene and 1.0-1.5 equiv of DMAD in a sealed tube at 150 °C until tlc analysis indicates that consumption of the silylketene is complete. At this point, the reaction is transferred to a round-bottomed flask and concentrated. The final product is isolated by column chromatography.

The reaction of silylketene **175** with 1.0 equiv of DMAD in toluene at 150 °C for 24 h produced the expected phenol **236** in 98% yield after purification by column chromatography (eq 79). Other conditions investigated for this transformation included: conducting the reaction at higher temperatures (180-200 °C), elevating the reaction temperature for lengths of time, and using a larger excess (2.0-2.5 equiv) of the dienophile. However, none of these variations afforded the desired product in as high a yield as the optimal conditions described above. It is believed that the Diels-Alder cycloadduct **235** forms initially and then undergoes a facile tautomerization to afford the more stable phenol.

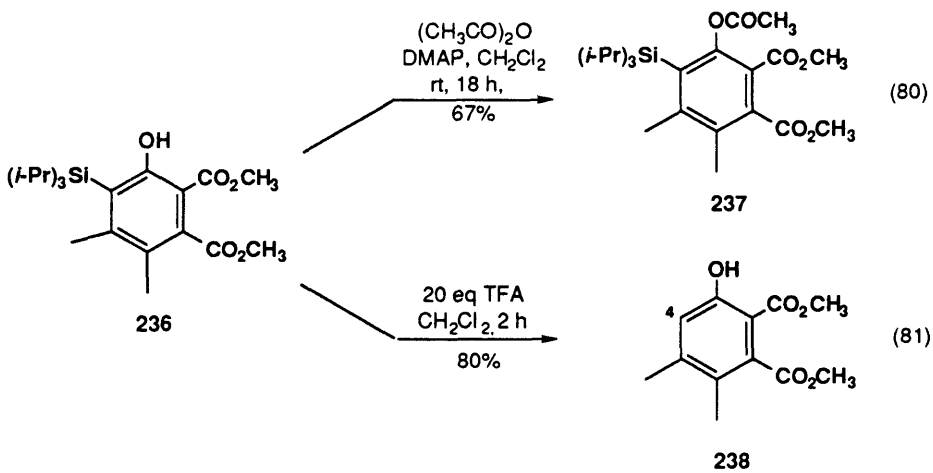


175 227 235 236 (79)

Although ^1H NMR spectral data supports the structural assignment of this compound and includes a resonance at 11.57 ppm due to the proton of the hydroxyl group, this proton was not exchangeable with D_2O. Also, no O-H stretching frequency of the hydroxyl group was observed in the IR spectrum. Therefore, in order to confirm the identity of phenol **236**, the compound was acetylated according to the procedure of Höfle

and Steglich (eq 80).[129] The ^{1}H NMR resonance at 11.57 ppm was not observed in the acetylated product **237**, and a new singlet appeared at 2.40 ppm corresponding to the three protons of the new acetate methyl group. Apparently, in phenol **236** a strong hydrogen bond exists between the hydrogen of the hydroxyl group and the carbonyl oxygen of the ester which affects both the IR stretching frequency of the O-H bond and the ability of the proton to undergo exchange with D_2O.

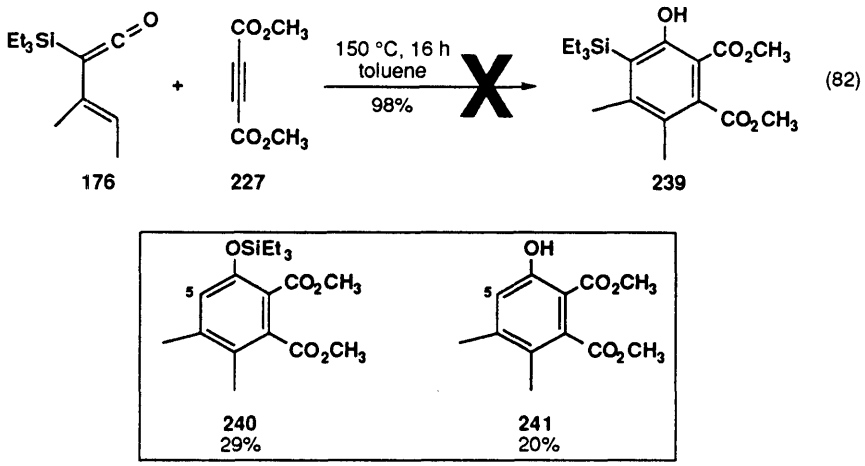
The presence of the trialkylsilyl group in the Diels-Alder adducts should facilitate further synthetic elaboration of these compounds. We have confirmed that protodesilylation of this type of phenol is a smooth process as evidenced by the production of **238** in good yield (eq 81). In the ^{1}H NMR spectrum of desilylated **238**, the resonances in the 1.0-1.6 ppm region corresponding to the triisopropylsilyl group were not observed, and a new singlet appeared at 6.84 ppm due to the aromatic proton at C-4.



Cycloadditions were also attempted with the less stable (triethylsilyl)-substituted vinylketene **176** and acetylene dimethyl dicarboxylate (eq 82). Interestingly, this reaction did not afford the expected phenol **239**, but instead produced a mixture of two compounds **240** and **241** as characterized by NMR and IR analysis (for a further discussion of this reaction, see p. 116). The ^{1}H NMR spectra of **240** and **241** contain singlets at 6.72 and

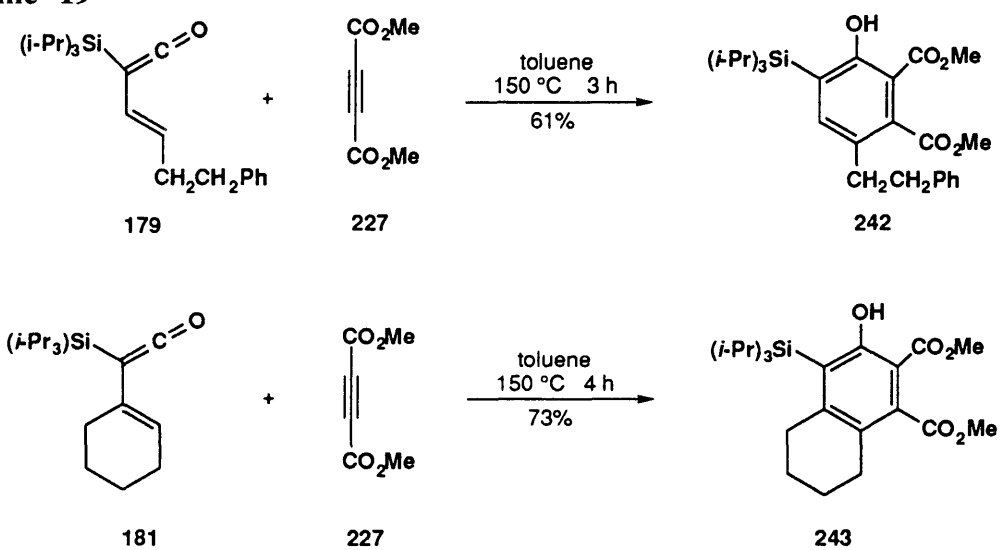
129. Höfle, G.; Steglich, W. *Synthesis* **1972**, 619.

6.80 ppm respectively corresponding to the C-5 aromatic protons. A phenolic proton was observed at 10.8 ppm for **241** but was not found in the spectrum of **240**.



The Diels-Alder reaction of DMAD and two other (triisopropylsilyl)vinylketenes was explored (Scheme 19). Optimal conditions for these reactions included heating the ketene with 1.0-1.5 equiv of DMAD at 150 °C in a solution of toluene contained in a sealed tube. *Tert*-butyldimethylsilyl-substituted ketene **183** (p. 87) also undergoes cycloaddition with DMAD in 61% yield (not optimized).

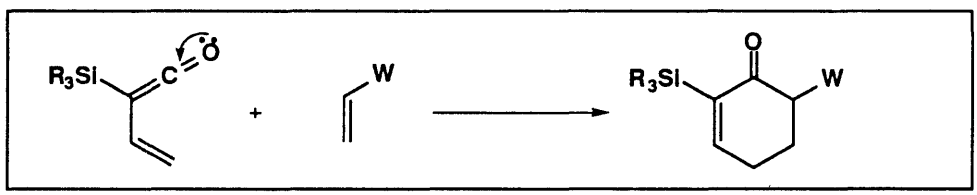
Scheme 19



(2) Reactions with Ethyl Cyanoacrylate

The reaction of TAS-vinylketenes with ethyl cyanoacrylate was next examined in order to investigate the regiochemical course of the cycloaddition.

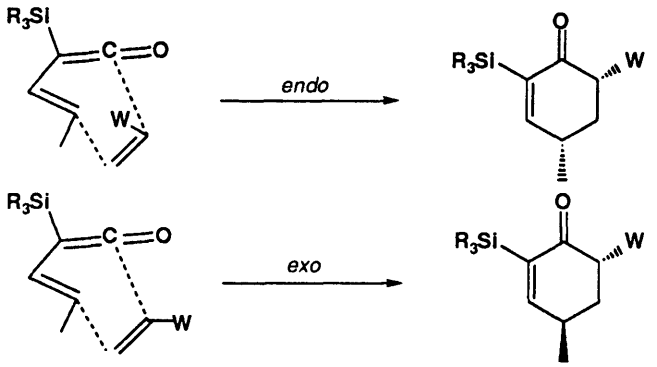
The regiochemical course of the cycloaddition of TAS-vinylketenes with dienophiles where W is an electron-withdrawing group is controlled by the directing effect of the carbonyl group as shown below. The carbonyl group of the ketene is also expected to donate enough electron density to the diene system via resonance to allow Diels-Alder reaction to occur with electron poor dienophiles. The trimethylsilyl substituent is known to exert only a weak directing effect on the Diels-Alder reactions of 1- and 2-(trimethylsilyl) 1,3-dienes.[130]



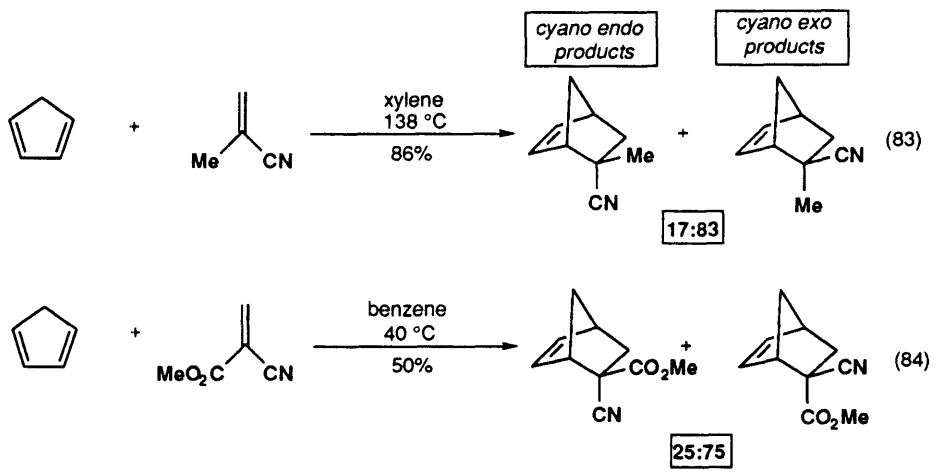
The cycloaddition of substituted TAS-vinylketenes with dienophiles where W is an electron-withdrawing group can produce two diastereomers as a result of the *endo* and *exo* orientations of the dienophile substituents in the transition state (Scheme 20). The Alder endo rule states that the *endo* mode of addition is usually preferred when an unsaturated substituent is present on the dienophile. The preference for the *endo* transition state is the result of secondary orbital interactions between the dienophile substituent and the π electrons of the diene.

130. (a) Fleming, I.; Percival, A. *J. Chem. Soc., Chem. Comm.* **1976**, 681. (b) Fleming, I.; Percival, A. *J. Chem. Soc., Chem. Comm.* **1978**, 178. (c) Jung, M. E.; Gaede, B. *Tetrahedron* **1979**, *35*, 621. (d) Batt, D. G.; Ganem, B. *Tetrahedron Lett.* **1978**, 3323.

Scheme 20

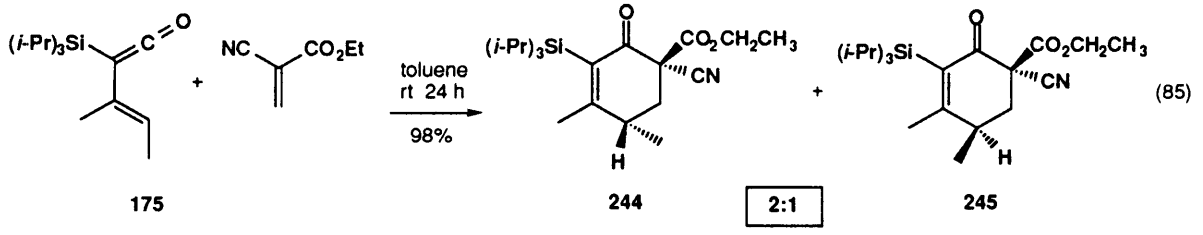


In the case of the dienophile ethyl cyanoacrylate both substituents contain unsaturation. Only one example in the literature has been cited concerning the *endo*-selectivity of ethyl cyanoacrylate.[131] Thus, Mellor and coworkers have investigated the Diels-Alder reaction of cyclopentadiene with a variety of α,β-unsaturated nitriles and found that the nitrile group affords low selectivity for the *endo* product (eq 83 and 84). This is believed to be partly a result of the centrosymmetric nature of the nitrile group which presumably leads to an unfavorable geometry for secondary overlap. It is also thought that substitution at the position alpha to the nitrile group in the dienophile can introduce repulsive interactions in the transition states of both the *exo*- and *endo*-addition, but that the interaction is greater in the *exo*-transition state.



131. Mellor, J. M.; Webb, C. F. I. *J. Chem. Soc. Perkin I* **1974**, 17.

The reaction of silylvinylketene **175** with 1.2 equivalents of ethyl cyanoacrylate[132] in toluene at room temperature produced a 2:1 mixture of two cycloadducts **244** and **245**, both which exhibited the expected regiochemistry (eq 85). The two diastereomers were separated by column chromatography and the structures of the major and minor products were established based on ^{1}H NMR spectral analysis as discussed below. The rate of reaction of silylvinylketene **175** with ethyl cyanoacrylate was much faster than with DMAD. Cycloaddition occurs with ethyl cyanoacrylate at room temperature, whereas reaction with DMAD requires heating at 150 °C.

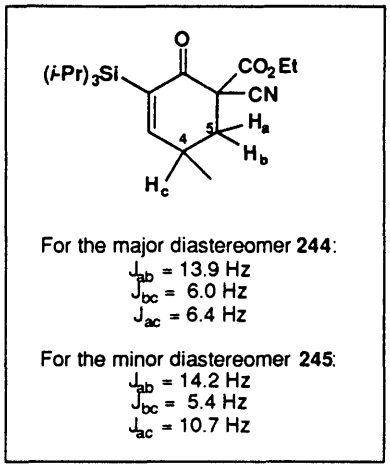


175 **244** **245** (85)

The ^{1}H NMR coupling constant data for the major and minor isomers is shown below (Figure 4). The spectrum for the major diastereomer **244** exhibits a large geminal coupling constant (J_{ab} = 13.9 Hz) between the protons H_a and H_b at C-5. Protons H_a and H_b also couple to the C-4 proton H_c, and have coupling constant values of similar magnitudes J_{ac} = 6.4 Hz and J_{bc} = 6.0 Hz. These values are consistent with typical equatorial-equatorial and equatorial-axial values. The proton H_c appears as a multiplet and is expected to be coupled to the protons of the methyl group attached at C-4 and H_a and H_b.

132. The author would like to thank the Loctite Corporation for a generous supply of ethyl cyanoacrylate.

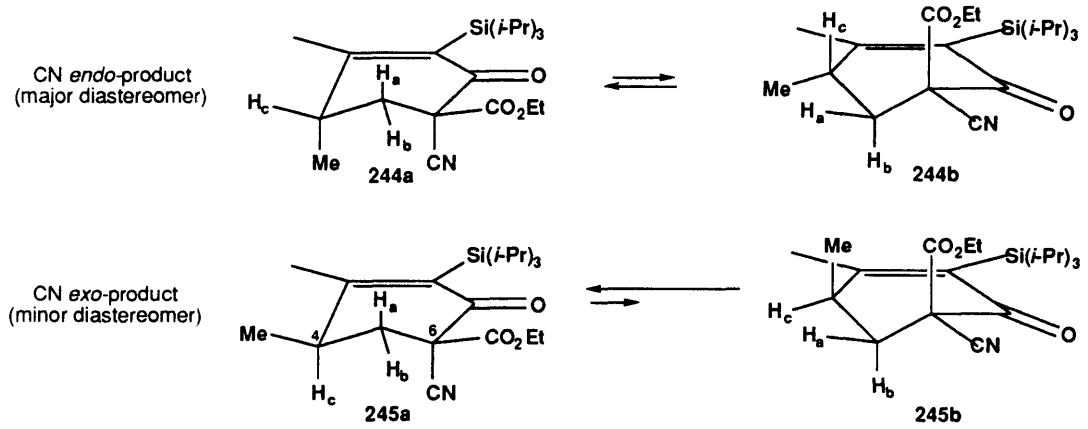
Figure 4



The spectrum of the minor diastereomer shows a large geminal coupling constant (J_{ab} = 14.2 Hz) between H_a and H_b, and the proton H_b is coupled to the proton H_c with J_{bc} = 5.4 Hz. A large axial-axial coupling constant (J_{ac} = 10.7 Hz) is observed between protons H_a and H_c. In this case, H_c is observed as a doublet of doublet of quartets at 2.81 ppm with coupling to both H_a and H_b as well as to the protons of the methyl group attached at C-4.

For each diasteromer two half-chair conformations are possible (Scheme 21). For the CN *endo*-product, it is difficult to predict which conformer is favored. However, for the CN *exo*-product, **245a** is predicted to be the more stable conformer with the C-4 methyl group and C-6 ethyl ester both positioned equatorially, since the alternative conformer **245b** has a very unfavorable 1,3 diaxial interaction between the methyl group and ethyl ester. The large axial-axial coupling constant (J_{ac} = 10.7 Hz) between H_a and H_c observed in the ^1H NMR of the minor isomer indicates that the C-4 methyl group must have an equatorial orientation. This is consistent with the conformation predicted for the CN *exo*-product **245a**. The conformer **244a** with the C-4 methyl group axial must correspond to the major diastereomer, and the ^1H NMR data is consistent with this assignment. Therefore, 2:1 selectivity for the CN *endo*-product is observed in the reaction between ethyl cyanoacrylate and silylketene **175**.

Scheme 21

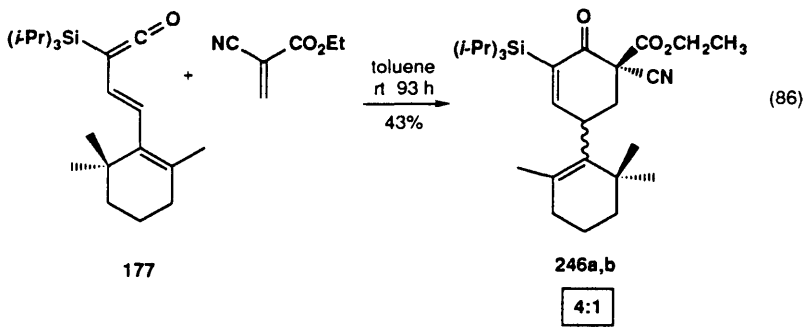


Interestingly, in the ^1H NMR spectrum the two products **244** and **245** the methylene protons of the ethyl ester are diastereotopic and each proton appears as a doublet of quartets in the 4.10-4.40 ppm region. The IR spectrum for **244** shows a stretching frequency at 2240 cm^{-1} due to the nitrile group as well as two carbonyl stretching frequencies at 1690 and 1750 cm^{-1} corresponding to the α,β-unsaturated ketone and ester carbonyl groups respectively. The IR spectrum of **243** likewise shows two carbonyl stretching frequencies at 1695 and 1755 cm^{-1}. The nitrile stretching frequency is not observed for this diastereomer, however, this is not surprising since nitriles are typically characterized by weak to medium absorptions in the triple-bond stretching region of the IR spectrum and their intensity is known to decrease when electron-attracting atoms are attached.[133] The structural formula for each of these diastereomers was determined separately by elemental analysis to be $C_{21}H_{35}O_3SiN$.

Ethyl cyanoacrylate also undergoes [4 + 2] cycloaddition with other substituted TAS-vinylketenes such as the β-ionone derived ketene **177** (eq 86). The overall yield of this reaction is 43% (86% yield based on recovered starting material). A 4:1 mixture of diastereomers **246a,b** was obtained and could not be separated by column chromatography. Polymerization of the dienophile ethyl cyanoacrylate appears to be a

133. Silverstein, R. M.; Bassler, G. C.; Morrill, T. C. *Spectrometric Identification of Organic Compounds; Fourth Edition*, John Wiley & Sons: New York, 1981, pp 129-130.

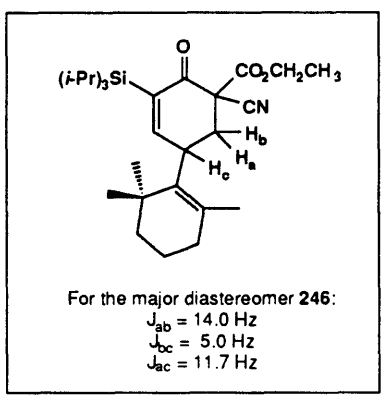
significant problem in this reaction. The cycloaddition of silylketene **177** with the dienophile may be slow as a result of the bulky cyclohexenyl group, and consequently in this case polymerization of the dienophile may be a more significant problem. The consistency of the reaction mixture often becomes "jelly-like", and typically 30-40% of the vinylketene starting material is recovered. Optimal conditions were achieved when 3.0 equivalents of the dienophile were added in small portions (0.5 equivalents) over the course of 93 h.



(86)

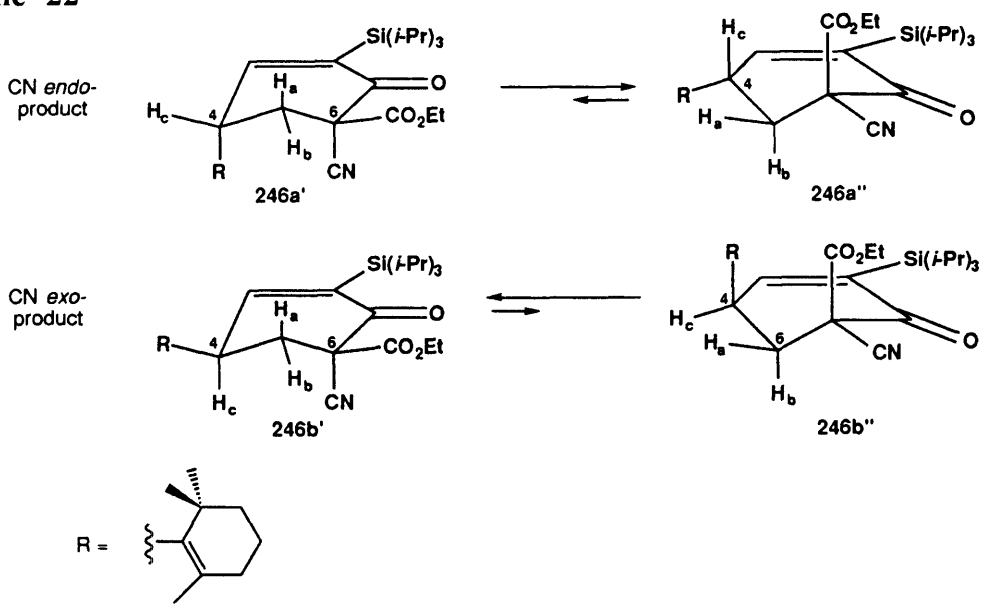
^{1}H NMR data was obtained for the major diastereomer of this reaction from examination of the spectrum of a mixture of the two diastereomers. The ^{1}H NMR coupling constant data for the major isomer is shown below (Figure 5). A large axial-axial coupling constant (J_{ac} = 11.7 Hz) was observed between H_a and H_c, and an equatorial-axial coupling constant (J_{bc} = 5.0 Hz) was noted between H_b and H_c. A large geminal coupling (J_{ab} = 14.0 Hz) is also seen between H_a and H_b.

Figure 5



Two half-chair conformations exist for each of the diastereomeric products formed in this cycloaddition (Scheme 22). For the CN *exo*-product the conformer **246b'** is predicted to be favored since the bulky C-4 substituent and C-6 ethyl ester are both equatorial. In the alternative conformer **246b"**, an unfavorable 1,3 diaxial interaction exists between these C-4 and C-6 substituents. For the CN *endo*-product, conformer **246a"** is expected to be favored in which the bulky C-4 group is equatorial. Conformer **246a'** has an unfavorable 1,3 diaxial interaction between the bulky group at C-4 and the C-6 nitrile. Consequently, for this reaction it was not possible to determine which diastereomer is the major product formed (CN *exo* or CN *endo*), since for both diastereomers the most stable conformation should have the bulky C-4 group positioned equatorial.

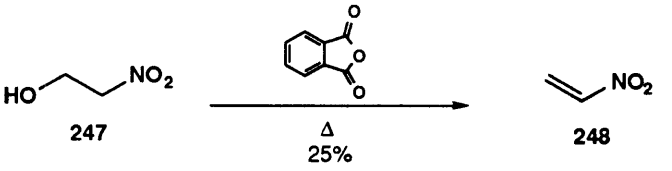
Scheme 22



(3) Reactions with Nitroethylene and Nitropropene

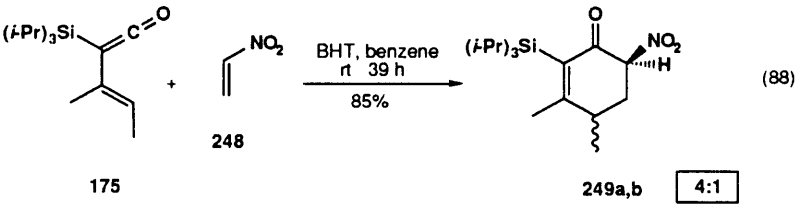
TAS-vinylketenes also undergo cycloaddition with nitro olefins, a class of compounds known to be excellent dienophiles that react under mild conditions. The electron-withdrawing nitro group controls the regiochemistry of the cycloaddition.

Nitroethylene (**248**) was prepared using the procedure of Ranganathan[134] (eq 87). Thus, commercially available 2-nitroethanol (**247**) was dehydrated using phthalic anhydride, and nitroethylene (**248**) was collected in 25% yield (lit. 80%)[134] via distillation at reduced pressure. Nitroethylene can be stored at 0 °C as an 1.0 M solution in benzene.



(87)

The reaction of silylketene **175** and 3.0 equivalents of nitroethylene (**248**) in benzene at room temperature provided a 2:1 mixture of diastereomers **249a,b** (eq 88). The dienophile was added in three portions (one equivalent each) over 39 h to help reduce polymerization that might occur when a high concentration of nitroethylene is present in the reaction mixture. Two crystals of BHT were also added as a radical inhibitor to help reduce polymerization.



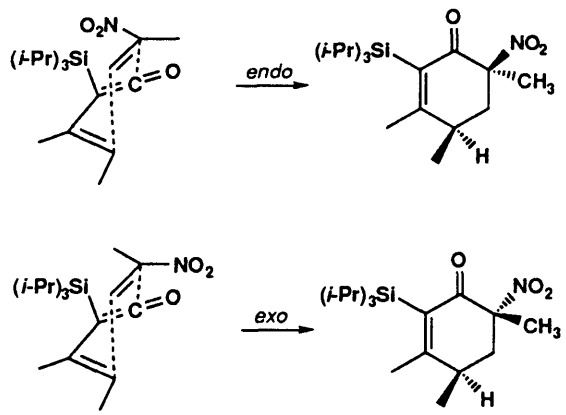
(88)

By analysis of the spectrum of the diastereomeric mixture of **249a,b**, ^{1}H NMR data was obtained for each individual diastereomer. The proton alpha to the nitro group appears at 5.30-5.40 ppm. ^{13}C NMR and IR spectral data were also obtained for the mixture of **249a,b**. At this point, it was difficult to determine the stererochemical assignment of the major and minor diastereomers. This was due to the physical inseparability of the two diastereomers and the poor resolution in the ^{1}H NMR spectrum

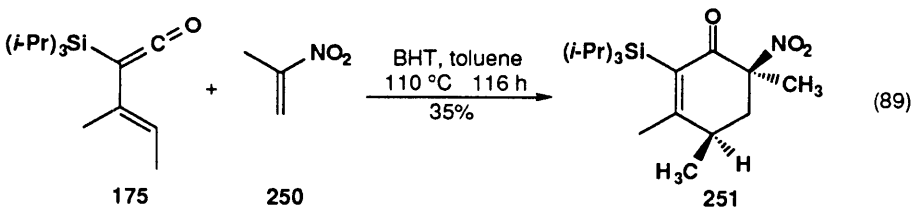
134. Ranganathan, D.; Rao, C. B.; Ranganathan, S.; Mehrotra, A.; Ivengar, R. *J. Org. Chem.* **1980**, *45*, 1185.

from which it was impossible to extract necessary coupling constant data. In any case, due to the high acidity of the doubly-activated α'-proton, the initial product of this cycloaddition probably readily undergoes equilibration, and so the identity of the major isomer would not necessarily provide insight into the stereochemical course of the Diels-Alder step.

In order to specifically investigate the stereochemical course of these cycloadditions, we next investigated the cycloaddition of silylketene **175** and nitropropene (**250**). As shown below, there are again two possible approaches (*endo* versus *exo*) for the dienophile in the transition state of the cycloaddition. We believed that the *endo* product would be the only adduct formed in this reaction, thus demonstating the *endo* selectivity of this cycloaddition.



Indeed, the reaction of silylketene **175** and 2.0 equivalents of nitropropene in toluene at 110 °C for 116 h produced only the *endo* cycloadduct **251** as a white solid in 35% yield (eq 89). A single crystal of BHT was added to the reaction mixture to help prevent polymerization. Elevated temperature was found to be necessary for this reaction: when the reaction was conducted at room temperature for 23 h, the desired cyclohexenone **251** was produced in only 2% yield with 75% of the vinylketene **175** recovered.



(89)

Proof of the structure of **251** was established from ^{1}H NMR coupling constant data and an NOE study (Figures 6,7, and 8). The protons at C-5, H_a and H_b exhibit a strong geminal coupling (J_{ab} = 13.5 Hz). Proton H_a is assigned to be on the same side of the ring as the nitro group (this assignment is confirmed in an NOE study discussed below) and it is shifted downfield in the ^{1}H NMR spectrum. H_a appears at 2.71 ppm as a doublet of doublets, and a large axial-axial coupling constant (J_{ac} = 9.8 Hz) is observed between H_a and the C-4 proton H_c. Protons H_b and H_c, in contrast, show equatorial-axial coupling (J_{bc} = 5.8 Hz). Conformer **251** is predicted to be favored since **251a** has an unfavorable 1,3 diaxial interaction between the C-4 methyl and C-6 nitro groups. The ^{1}H NMR data presented matches that predicted for the major conformer of the *endo* cycloadduct (Figure 7).

Figure 6

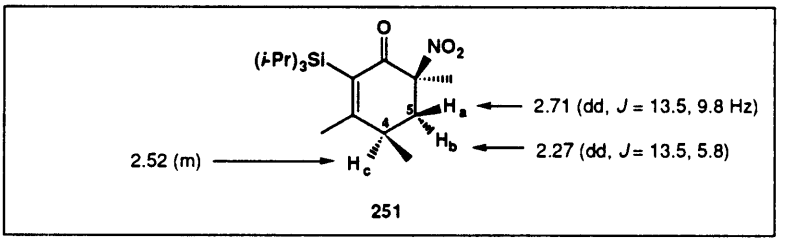
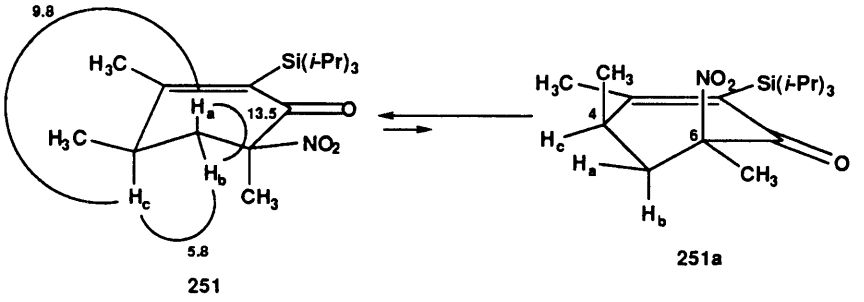
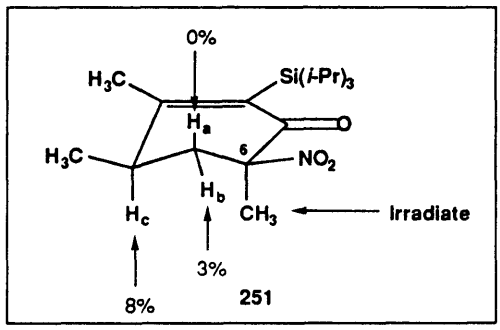


Figure 7



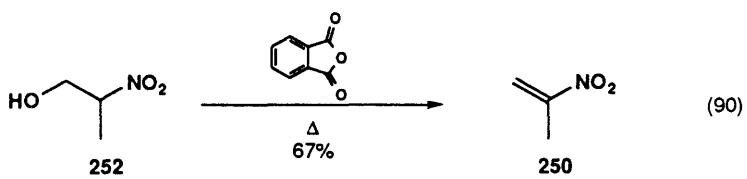
An NOE experiment was conducted to confirm the assignment of H_a and H_b (Figure 8). Irradiation of the methyl group at C-6 led to enhancement at H_b and H_c. No enhancement was observed for the resonance assigned as H_a, thus confirming the fact that H_a is on the opposite side of the ring as the methyl group and on the same side of the ring as the electron-withdrawing nitro group.

Figure 8



The IR spectrum for cyclohexenone **251** has a carbonyl stretching frequency at 1670 cm^{-1} and characteristic C-NO_2 stretching frequencies at 1540, 1380, and 1350 cm^{-1}.

The nitropropene used in the Diels Alder reaction described above was prepared on a small scale (1.5 g of product) according to the procedure of Noland (eq 90).[135] Commercially available 2-nitropropanol (**252**) was dehydrated using phthalic anhydride and 2-nitropropene (**250**) was collected via distillation at reduced pressure as a faint green liquid in 67% (lit. 57-72%)[135] yield. Nitropropene can be stored neat at 20 °C as a low melting solid for several days without decomposition.

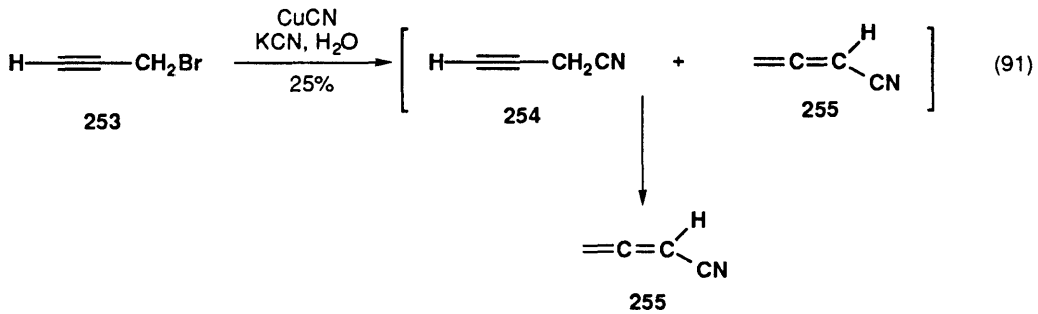


(90)

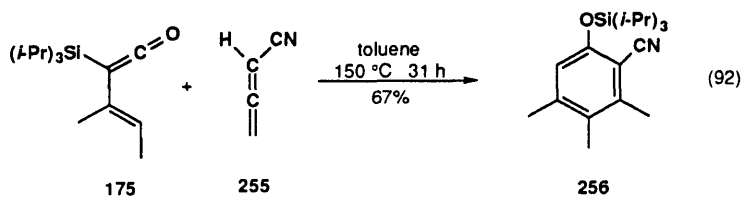
135. Miyashita, M.; Yanami, T.; Yoshikoshi, A. *Organic Syntheses*, **1990**, *Coll. Vol. 7*, p 396.

(4) Reactions with Cyanoallene

Cyanoallene (**255**) was prepared via a known method[136] from propargyl bromide (eq 91). This reaction involves a complex of CuCN and KCN and initially affords propargyl cyanide (**254**) and cyanoallene. The isomerization of acetylene **254** to cyanoallene is caused by the slightly basic KCN present in the reaction mixture. Cyanoallene was produced in 25% yield (lit. 90%)[136] and can be stored neat under nitrogen at -20 °C for several months.

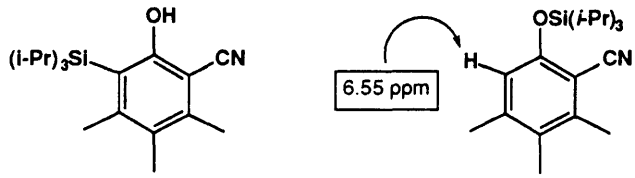


The reaction of silylketene **175** and 3.4 equivalents of cyanoallene (**255**) occurred in toluene at 150 °C in a sealed tube to produce a white solid in 67% yield (eq 92). Examination of the ^{1}H NMR spectrum revealed that the product was not the expected phenol **257**, but rather the isomeric silyl ether **256** (Figure 9). Thus, the ^{1}H NMR spectrum of **256** contained a resonance at 6.55 ppm and no phenolic proton in the 10-11 ppm region.



136. Brandsma, L.; Verkruijsse, H. D. *Studies in Organic Chemistry 8: Synthesis of Acetylenes, Allenes, and Cumulenes;* Elsevier Scienfific: New York, 1981, pp 173-175.

Figure 9

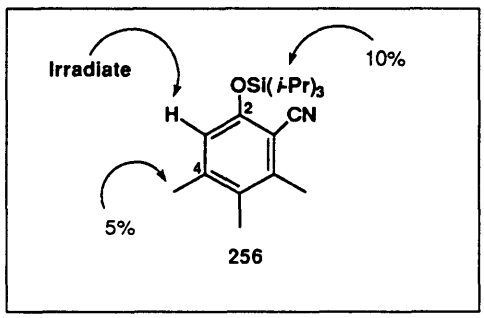


257
expected product

256
product obtained

The structure of the compound resulting from the cycloaddition of silylketene **175** and cyanoallene was established using an NOE study. Irradiation of the resonance at 6.55 ppm resulted in enhancement of resonances corresponding to both the C-4 methyl group and the triisopropylsilyloxy group at C-2 (Figure 10).

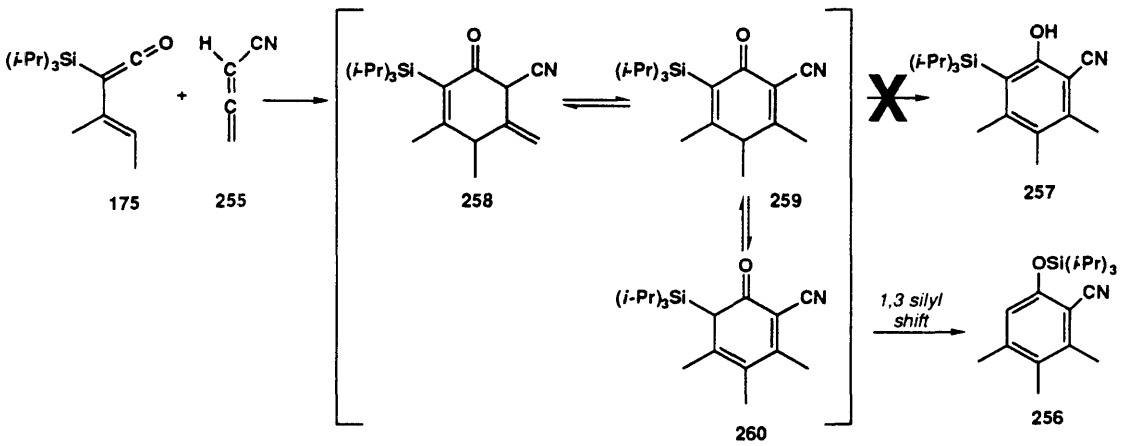
Figure 10



The cycloaddition of silylketene **175** and cyanoallene (**255**) is presumed to occur through the intermediate tautomers **258, 259**, and **260** (Scheme 23). α-Silyl carbonyl compounds are known to rearrange to afford silyl enol ethers in good yield and this reactions requires only moderate temperatures.[137] Therefore, it is believed that the α-silyl carbonyl tautomer **260** readily undergoes a 1,3-silyl shift to produce **256** (for an earlier example of a Diels-Alder reaction that gives an aryl silyl ether see p. 104).

137. Colvin, E. *Silicon in Organic Synthesis*; Buttersworths: London, 1981, pp 33-36.

Scheme 23



(5) Cycloadditions with Other Dienophiles

Unfortunately, we found that less reactive dienophiles such as *N*-phenyl maleimide and chloroacrylonitrile did not undergo the desired [4 + 2] cycloaddition with TAS-vinylketenes. Reaction with each of these dienophiles led in low yields to complicated mixtures of several products.

Overall, we have demonstrated that a variety of substituted TAS-vinylketenes undergo [4 + 2] Diels Alder reactions with reactive olefinic and acetylenic dienophiles in good to excellent yields. Consistent with the reactivity of the parent (trimethylsilyl)vinylketene (**112**, p. 69), the reactivity of these substituted TAS-vinylketenes compares favorably to previously reported vinylketene equivalents. The ketene carbonyl group dominates in controlling the regiochemical course of these reaction. Cycloadditions of TAS-vinylketenes with monosubstituted dienophiles result in the formation of a 6-substitued cyclohexenones. Particularly noteworthy is the stereochemical course of these cycloadditions: the reaction with nitropropene produced the *endo* cycloadduct as the only isomer. Overall, we have demonstrated the use of TAS-vinylketenes as interesting four-carbon dienes in [4 + 2] cycloadditions to afford cyclohexenone and phenolic products.

At present, the main limitation of this methodology is the modest reactivity of the TAS-vinylketenes. In this connection it would be extremely interesting to investigate the reactions of TAS-vinylketenes bearing electron-donating substituents (e.g. -OR, -$OSiR_3$) at the C-3 carbon. As in the case of Danishefsky's diene, these vinylketenes should exhibit greatly enhanced reactivity and should combine in good yield with less activated dienophiles such as acrylate. Studies are planned to examine the synthesis and chemistry of this new class of TAS-vinylketenes.

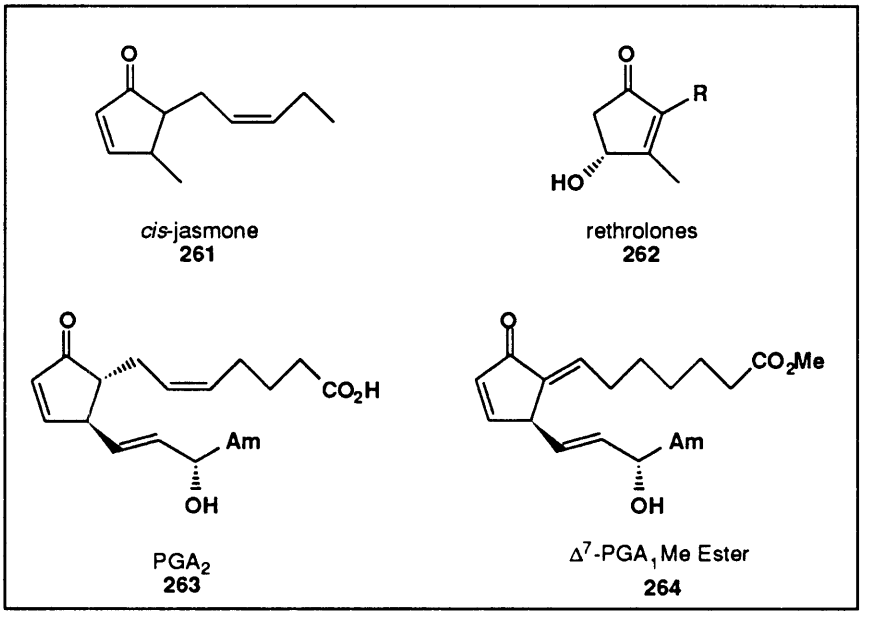
CHAPTER 5

TAS-VINYLKETENES AS FOUR-CARBON COMPONENTS IN NEW [4 + 1] ANNULATION REACTIONS

Introduction

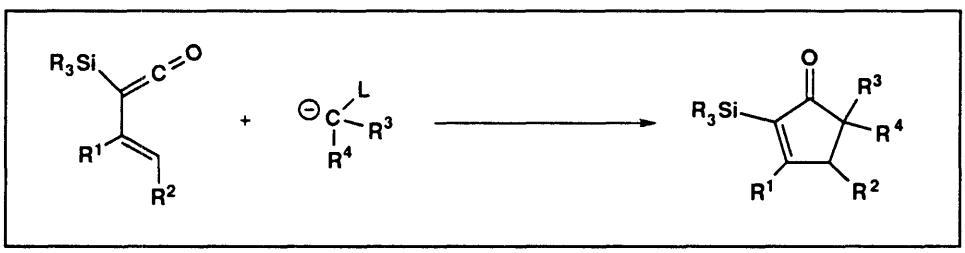
Currently there exists a great deal of interest in the development of new methods for the construction of the cyclopentenone ring system. This is due to the fact that many biologically active natural products have this 5-membered ring moiety as a major structural feature. For example, molecules which incorporate the cyclopentenone ring system include (Figure 11) *cis*-jasmone (**261**), an important constituent of many perfumes; the rethrolones (**262**), the alcohol components of the insecticidal pyrethrin esters; and prostaglandins such as PGA_2 (**263**) and Δ^7-PGA_1 methyl ester (**264**), both which are promising anticancer agents.[138]

Figure 11



138. Noyori, R.; Suzuki, M. *Science* **1993**, *259*, 44.

Cyclopentenones can be synthesized[139] by a variety of different methods such as the Nazarov[140] and related cationic cyclizations, the Pauson-Khand colbalt-mediated cyclization of alkynes with olefins,[141] intramolecular aldol condensations, the insertion of vinyl carbenes into C-H bonds,[142] and [3 + 2] coupling reactions.[143] There is also a limited number of [4 + 1] cycloaddition strategies for the construction of the cyclopentenone ring system.[144] As described in Part II Chapter 3, we have recently developed methodology that provides efficient access to a variety of stable TAS-vinylketenes. We believed that these unusual molecules could function as four-carbon components in a versatile and conceptually novel [4 + 1] annulation strategy to synthesize cyclopentenones. As illustrated below, we anticipated that it would be possible to add "carbenoid reagents" (nucleophilic species bearing appropriate leaving groups) to TAS-vinylketenes so as to generate a dienolate intermediate which could then cyclize to form a new five-membered ring.



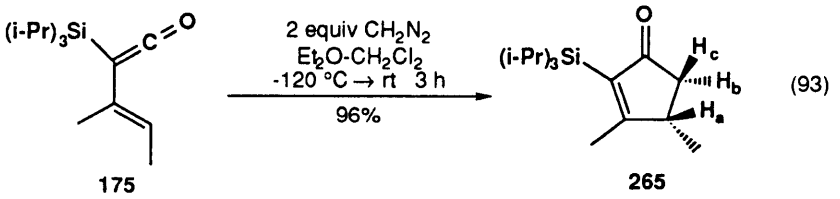
139. For reviews of methods to synthesize cyclopentenones, see: (a) Ellison, R. A. Synthesis, **1973**, 397. (b) Piancatelli, G.; D'Auria, M.; D'Onofrio, F. *Synthesis*, **1994**, 867.
140. (a) Denmark, S. E. In *Comprehensive Organic Synthesis;* Trost, B. M., Fleming, I., Eds.; Pergamon Press: New York, 1990, Vol. 5, p 751. (b) Habermas, K. L.; Denmark, S. E. In *Organic Reactions*; Paquette, L. A. Ed.; John Wiley & Sons: New York, 1994; Vol 45, pp 1-158.
141. (a) Schore, N. E. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: New York, 1990; Vol. 5, p 1037. (b) Schore, N. E. In *Organic Reactions*; Paquette, L. A. Ed., John Wiley & Sons: New York, 1991, Vol. 40, pp 1-90.
142. (a) Karpf, M.; Huguet, J.; Dreiding, A. S. *Helv. Chim. Acta* **1982**, *65*, 13. (b) Williamson, B. L.; Tykwinski, R. R.; Stang, P. *J. Am. Chem.* **1994**, *116*, 93.
143. (a) Noyori, R.; Shimizu, F.; Fukuta, K.; Takaya, H.; Hayakawa, Y. *J. Am. Chem. Soc.* **1977**, *99*, 5196. (b) Noyori, R.; Yokoyama, K.; Hayakawa, Y. *J. Am. Chem. Soc.* **1973**, *95*, 2722.
144. For some examples of [4 + 1] annulations to form cyclopentenones, see: Ogura, K.; Yamashita, M.; Furukawa, S.; Suzuki, M.; Tsuchihashi, G. *Tetrahedron Lett.* **1975**, 2767. (b) Ogura, K.; Yamashita, M.; Tsuchihashi, G. *Tetrahedron Lett.* **1976**, 759. (c) Johnson, B. F. G.; Lewis, J.; Thompson, D. J. *Tetrahedron Lett.* **1974**, 3789.

[4 + 1] Annulation with Diazo Compounds

The first goal of our study was to establish the feasibility of the [4 + 1] annulation strategy and to identify "methylene transfer" reagents that can participate in the reaction. As discussed in Part II Chapter 2 of this thesis, TMS-ketene (and other silylketenes) are known to react with a variety of carbanionic species including organolithium and organocerium compounds, alkoxystannanes, and stabilized phosphorous ylides. Based on this precedent, we anticipated that both unstabilized and moderately stabilized carbanion derivatives would add to TAS-vinylketenes in the desired fashion. Highly stabilized carbanion derivatives, however, were expected to be unsuitable partners for our annulation due to the possible intervention of internal proton transfer at an intermediate stage of the reaction.

The TAS-vinylketene **175** was selected as a representative ketene to test the feasibility of the proposed annulation. Initial studies focused on diazomethane as the "carbenoid" annulation component. We found that the desired transformation proceeds smoothly to afford the expected (triisopropylsilyl)cyclopentenone system **265** in 96% yield (eq 93). This reaction is remarkably facile, with tlc analysis indicating that the formation of the 5-membered ring product is complete upon warming to -20 °C.

It was neccessary to cool the solution of ketene **175** at -120 °C while diazomethane was added. When the reaction was conducted at a higher temperature such as -78 °C, the desired product was isolated in only 70% yield with a ~30% recovery of silylketene **175**. The annulation was also conducted using an excess of diazomethane (5 equiv), and the desired cyclopentenone was produced in 93% yield. Interestingly, no cyclobutanone formation due to the ring expansion of a possible cyclopropanone intermediate (see discussion of the mechanism, p.123) was observed.



(93)

The structural assignment for cyclopentenone **265** is based on analogy with data reported for similar α-silylcyclopentenones. The carbonyl stretching frequency for cyclopentenone **265** is observed in the IR spectrum at 1685 cm^{-1} and is consistent with the stretching frequency reported for similar cyclopentenones (Figure 12).[145,146] The ^{13}C NMR spectrum for cyclopentenone **265** exhibits a carbonyl resonance at 213.3 ppm which is very similar to the ^{13}C NMR resonances reported for the carbonyl carbons in other α-silylcyclopentenones such as **268** and **269** (Figure 13).[146]

Figure 12

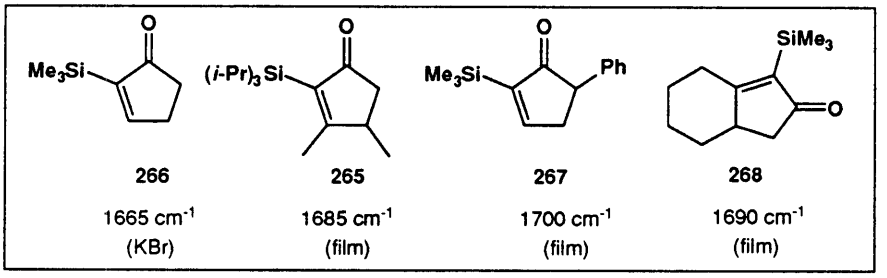
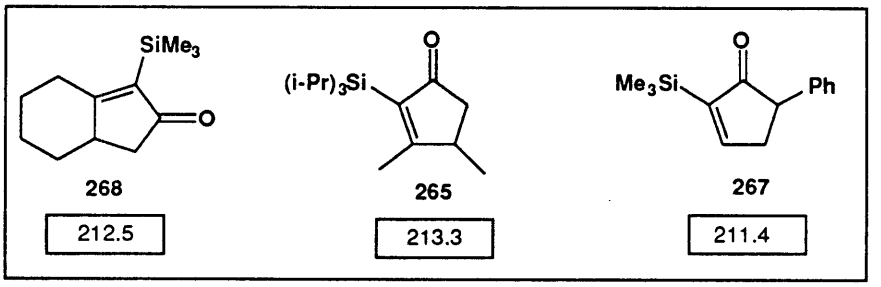


Figure 13

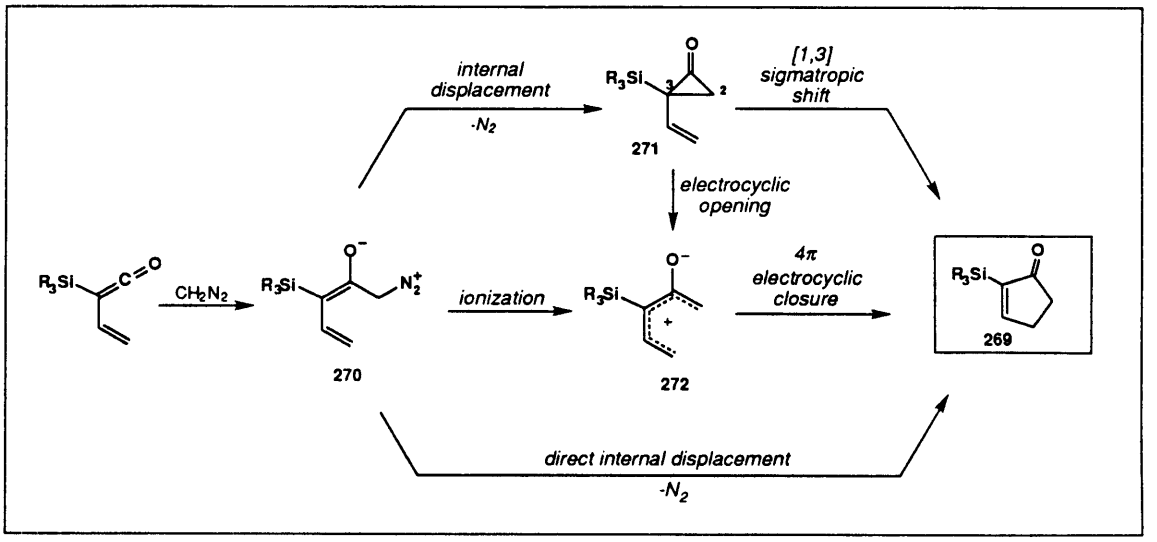


Scheme 24 outlines several alternative pathways which could account for the mechanistic course of this [4 + 1] annulation. The initial addition of diazomethane to the

145. Shih, C.; Fritzen, E. L.; Swenton, J. S. *J. Org. Chem.* **1980**, *45*, 4462.
146. (a) Sawada, H.; Webb, M.; Stoll, T.; Negishi, E. *Tetrahedron Lett.* **1986**, *27*, 775. (b) Negishi, E.; Holmes, S. J.; Tour, J. M.; Miller, J. A.; Cederbaum, F. E.; Swanson, D. R.; Takahashi, T. *J. Am. Chem. Soc.* **1989**, *111*, 3336.

vinylketene should be highly stereoselective due to the shielding effect of the bulky silyl group[74] and should result in the formation of the Z enolate **270**.

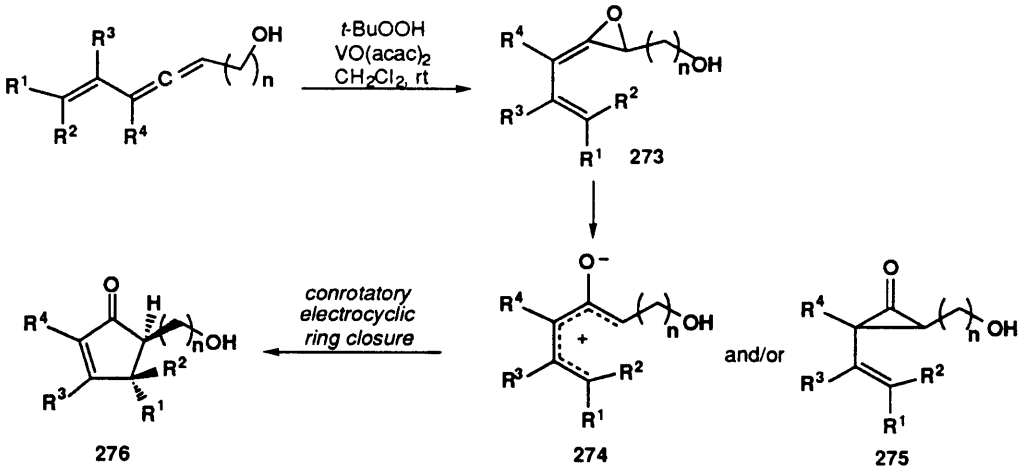
Scheme 24



Enolate **270** may undergo internal displacement of nitrogen and produce the five-membered ring system directly. However, the planar structure of the dienolate system probably makes it difficult for **270** to achieve an arrangement in which the π electrons are suitably situated for a direct backside displacement of nitrogen. A second possible pathway involves ionization of the enolate **270** to give the pentadienyl cation **272** which can undergo 4π electrocyclic ring closure to the cyclopentenone ring. This type of 4π electrocyclic closure of a pentadienyl cation is well known in synthetic methods such as the Nazarov cyclization[140] and the cyclization of a species generated via the *in situ* epoxidation of vinylallenes (Scheme 25).[147] Mechanistically, this stereoselective process is rationalized by the initial hydroxyl-directed formation of allene oxide **273**, which subsequently isomerizes to the oxidopentadienyl cation **274** or vinylcyclopropanone **275**. Conrotatory electrocyclic ring closure then affords the cyclopentenone ring **276**.

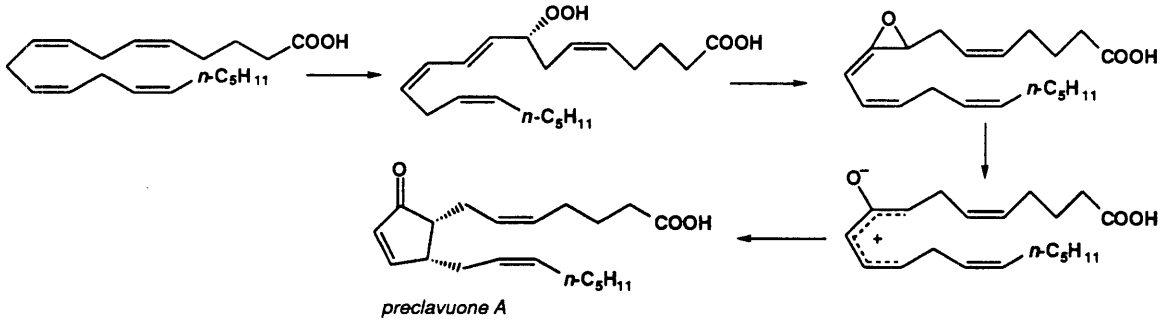
147. Kim, S. J.; Cha, J. K. *Tetrahedron Lett.* **1988**, *29*, 5613.

Scheme 25



This type of 4π electrocyclic closure of a pentadienyl cation is also proposed in the biosynthetic pathway for prostanoid synthesis by marine organisms.[148] For example, the biosynthesis of prostanoid preclavuone A from arachidonic acid involves the conversion of an allene oxide intermediate to a cyclopentenone product (Scheme 26).

Scheme 26

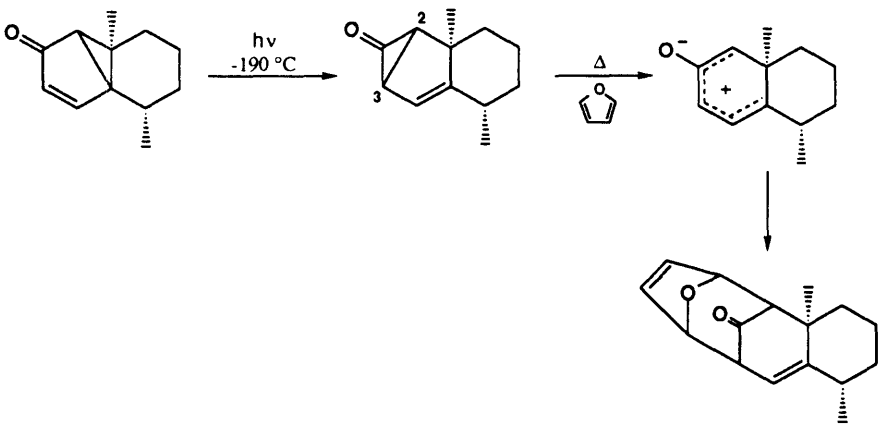


A third alternative mechanism to account for our [4+1] annulation (Scheme 24) involves the internal displacement of nitrogen to form the vinylcyclopropanone **271** followed by electrocyclic ring opening to generate pentadienyl cation **272**. Electrocyclic

148. For evidence for such a biosynthetic pathway, see: (a) Brash, A. R.; Bairtschi, S. W.; Ingram, C. D.; Harris, T. M.; *J. Biol. Chem.* **1987**, *262*, 15829. (b) Baertschi, S. W.; Ingram, C. D.; Harris, T. M.; Brash, A. R. *Biochemistry*, **1988**, *27*, 18. (c) Brash, A. R.; Baertschi, S. W.; Ingram, C. D.; Harris, T. M. *Proc. Natl. Acad. Sci. USA* **1988**, *85*, 3382. (d) Corey, E. J.; d'Alarcao, M.; Matsuda, S. P. T.; Lansbury, P. T.; Yamada, Y. *J. Am. Chem. Soc.* **1987**, *109*, 289. (e) Corey, E. J.; Matsuda, S. P. T.; Nagata, R.; Cleaver, M. B. *Tetrahedron Lett.* **1988**, *29*, 2555. (f) Hamberg, M.; Miersch, O.; Sembdner, G. *Lipids*, **1988**, *23*, 521. For a demonstration of the feasibility of this proposal, see: Corey, E. J.; Ritter, K.; Yus, M.; Najera, C. *Tetrahedron Lett.* **1987**, *28*, 3547.

closure would then produce the cyclopentenone product. Recall, that Baukov has found that diazomethane adds to TMS-ketene to produce the three-membered ring TMS-cyclopropanone in 50% yield.[88] Cyclopropanones, because of their instability, are generally only observed as transient intermediates and trapped with nucleophiles.[149] The proposed vinylcyclopropanone **271** is predicted to be very unstable and the C_2-C_3 bond is expected to readily undergo cleavage to the oxallyl species. An example of a vinylcyclopropane which presumably undergoes C_2-C_3 bond cleavage to produce a pentadienyl cation system which is then trapped by furan is illustrated in Scheme 27.[150]

Scheme 27

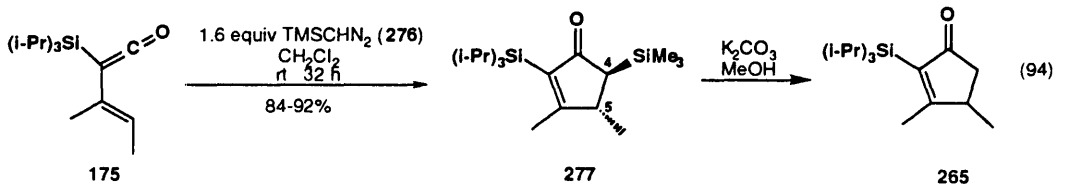


Currently, for our [4 + 1] annulation we favor the mechanistic pathway proceeding via ionization of the initial adduct **270** to form the oxidopentadienyl cation **272** followed by electrocyclization. Obviously, further study is needed to elucidate the details of the mechanism of the annulation and this problem will be the subject of future investigations in our laboratory.

We next examined the [4 + 1] annulation using commercially available TMS-diazomethane (**276**),[151] a thermally stable diazoalkane often used in place of hazardous

149. For a review of cyclopropanone chemistry, see: (a) Wasserman, H. H.; Clark, G. M.; Turley, P. C. *Top. Curr. Chem.* **1974**, *74*, 73. (b) Wasserman, H. H.; Berdahl, D. R.; Lu, T.-J. In *The Chemistry of the Cyclopropyl Group*, Rappoport, Z., Ed., John Wiley & Sons: New York, 1987, pp 1455-1532.
150. Barber, L. L.; Chapman, O. L.; Lassila, J. D. *J. Am. Chem. Soc.* **1969**, *91*, 3664.
151. (a) Seyferth, D.; Dow, A. W.; Menzel, H.; Flood, T. C. *J. Am. Chem. Soc.* **1968**, *90*, 1080. (b) Shioiri, T.; Aoyama, T.; Mori, S. *Organic Synthesis* **1990**, *68*, 1. (c) Mori, S.; Sakai, I. Aoyama, T.; Shioiri, T. *Chem. Pharm. Bull.* **1982**, *30*, 3380.

diazomethane. TMS-diazomethane reacts with silylketene **175** at room temperature to afford cyclopentenone **277** in 84-92% yield. Desilylation of **277** with potassium carbonate and methanol affords **265** (eq 94).



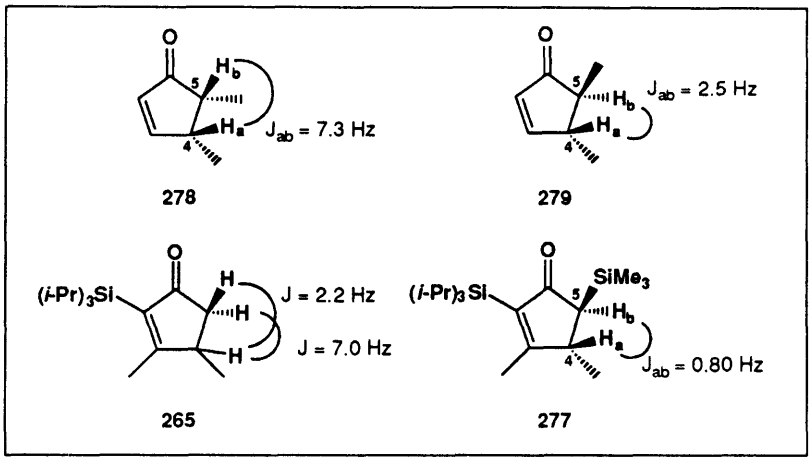
175 277 265

The bis-silylcyclopentenone **277** exhibits a characteristic carbonyl stretching frequency at 1665 cm^{-1} in the IR spectum. The substituents at C-4 and C-5 on the cyclopentenone ring were assigned to be trans based on ^1H NMR coupling constant data reported for *cis* and *trans-4,5*-dimethyl-cyclopent-2-en-1-one (**278** and **279**; Figure 15).[152] For the cis stereoisomer **278**, the C-5 proton (H_b) is reported to appear at 2.44 ppm as a doublet of quartets in the ^1H NMR spectrum. The coupling constant between H_a and H_b is 7.3 Hz, and the dihedral angle between the two protons is estimated to be 0°. On the other hand, in the ^1H NMR spectrum for the trans stereoisomer **279**, the C-5 proton (H_b) appears at 1.86 ppm as a multiplet with a small coupling constant between H_a and H_b of 2.5 Hz with an estimated dihedral angle of 120° between these two protons. It should be noted that the coupling constants observed for silylcyclopentenone **265** (eq 80, p. 123) are also consistent with these values (Figure 14). In the ^1H NMR spectrum for our bis-silyl annulation product **277**, a very small coupling constant (J_{ab} = 0.80 Hz) is observed between H_a and H_b which is consistent with the small coupling constant reported for *trans*-4,5-dimethyl-cyclopent-2-en-1-one (**279**), and therefore, the stereochemistry of the C-4 and C-5 substituents on the ring is assigned to be trans. This trans stereochemistry agrees with the mechanistic pathway we predict for this [4 + 1] annulation where ring closure

152. Strike, D.; Smith, H. *Ann. N. Y. Acad. Sci.* **1971**, *180*, 91.

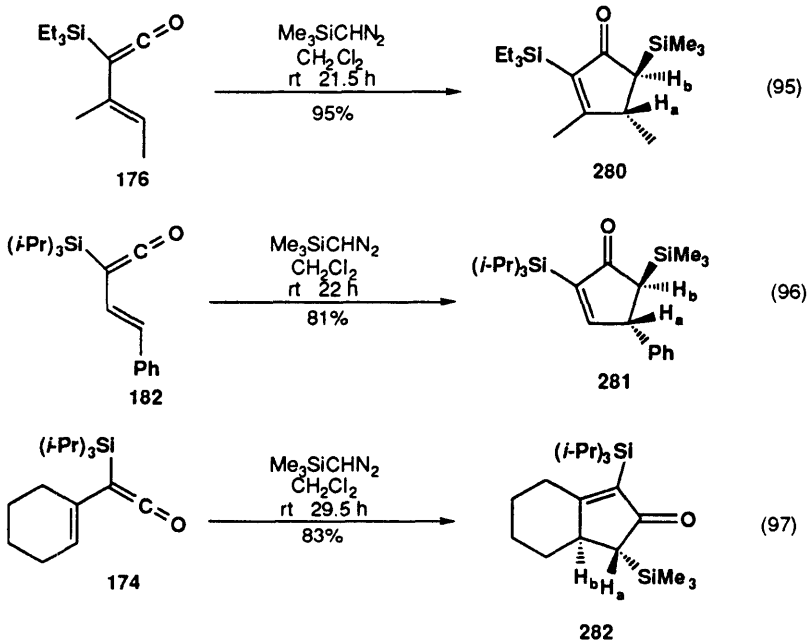
occurs via a 4π electrocyclic conrotatory process (for a more detailed discussion see p. 143).

Figure 14



Solvents have a significant effect on the rate of this [4 +1] annulation. When the reaction is conducted in a non-polar solvent such as hexane, the desired cyclopentenone **277** is produced in 45% yield after 48 h at room temperature. In contrast, when a very polar solvent such as acetonitrile is employed, the cyclopentenone is generated in 68% yield after only 22 h at room temperature. This result suggests that charge separation is involved in the transition state of the reaction. Stabilization of this charge occurs through interactions with polar solvent molecules and results in an increase in the rate of the reaction when it is conducted in a polar solvent.

A variety of other TAS-vinylketenes react with TMS-diazomethane to afford silyl cyclopentenones in good yield (eq 95, 96, and 97). These reactions were conducted using 1.5 equiv of TMS-diazomethane on a scale to give 130-140 mg of products which were purified using column chromatography. Note, that the annulation is not limited to (triisopropylsilyl)ketenes; the somewhat less stable triethylsilyl derivative **176** also was found to react in excellent yield (eq 95).



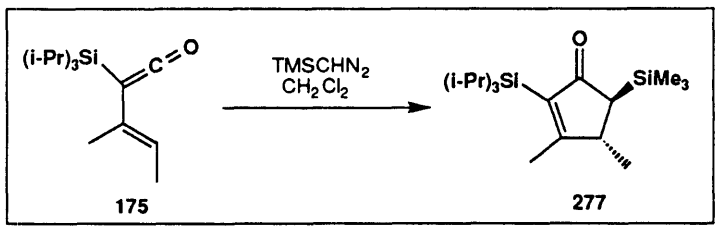
The structural assignment for the trans stereoisomers **280** and **281** was based upon ^{1}H NMR coupling constant data. For both compounds the coupling constant observed between H_a and H_b is relatively small (**280**, J_{ab} = 1.9 Hz and **281**, J_{ab} = 2.1 Hz) which is consistent with the data for *trans*-4,5-dimethyl-cyclopent-2-en-1-one **279**[152] discussed earlier. The ^{1}H NMR spectral data for the bicyclic enone **282** is in excellent agreement with data reported by Negishi[146b] for the related compound 9-(trimethylsilyl)bicyclo[4.3.0]non-1(9)-en-8-one (**268**; p. 123). The very small coupling constant (J_{ab} = 1.0 Hz) suggests that the trimethylsilyl group has the indicated exo orientation.

Ketones generally do not react with TMS-diazomethane. However, it has been found that in the presence of boron trifluoride etherate, ketones can be homologated.[153] It is presumed that the $BF_3{\cdot}OEt_2$ coordinates to the oxygen atom of the ketone and helps activate the carbonyl toward the nucleophilic addition of TMS-diazomethane.

153. (a) Hashimoto, N.; Aoyama, T.; Shioiri, T. *Chem. Pharm. Bull.* **1982**, *30*, 119. (b) Hashimoto, N.; Aoyama, T.; Shioiri, T. *Tetrahedron Lett.* **1980**, *21*, 4619.

Consequently, we believed that Lewis acids such as $BF_3 \cdot OEt_2$ might be effective at accelerating our [4 + 1] annulation and studies were conducted accordingly (Table 11).

Table 11



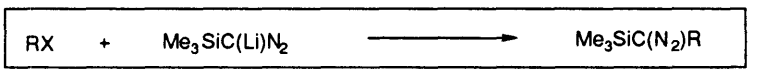
175 277

Entry	Conditions	Results
1	1.5 equiv $BF_3 \cdot OEt_2$ -10 °C, 2 h	complex mixture of products
2	1.0 equiv $BF_3 \cdot OEt_2$ -78 °C to rt, 24 h	37% yield
3	0.05 equiv $BF_3 \cdot OEt_2$ 0 °C to rt, 4 h	43% yield; ketene recovered in 43% yield
4	1.0 equiv TMSCl 0 °C to rt, 26 h	48% yield
5	0.05 equiv Me_2AlCl -78 °C	ketene decomposed upon exposure to Lewis acid
6	1.5 equiv $AlCl_3$ rt	ketene decomposed upon exposure to Lewis acid
7	0.5 equiv $AlCl_3$ -78 °C to rt, 5 h	ketene recovered in 100% yield
8	1.5 equiv $ZnCl_2$ rt to 50 °C, 4 h	complex mixture of products; ketene recovered in 39% yield
9	0.5 equiv $ZnCl_2$ -78 °C to rt, 24 h	no reaction observed by tlc
10	0.5 equiv $TiCl_4$ -78 °C	ketene decomposed upon exposure to Lewis acid

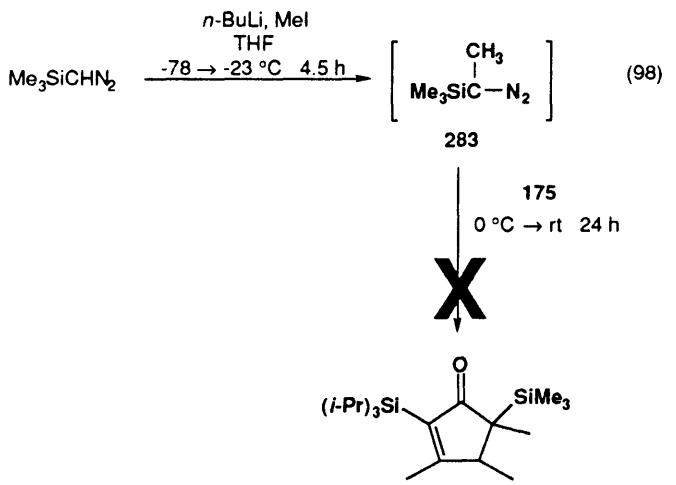
Overall, Lewis acid catalysis of the addition of TMS-diazomethane to silylketene **175** was unsuccessful. In a few cases (entries 2-4), the desired cyclopentenone **277** was produced, however, no increase in the rate of formation of product was observed. Unfortunately, in most cases decomposition of the silylketene was observed immediately

upon exposure to the Lewis acid (entries 5, 6, and 10) or a complex mixture of products resulted upon the addition of TMS-diazomethane (entries 1 and 8).

Shioiri has reported the preparation of a number of α-trimethylsilyldiazoalkanes via the alkylation of the lithium salt of TMS-diazomethane and an alkyl halide as illustrated below.[154] In principle, these reagents should be useful in our [4 + 1] annulation as "alkylidene transfer" reagents to synthesize cyclopentenones bearing two substituents at the C-5 position of the new 5-membered ring.



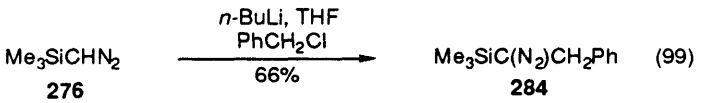
Initially, we attempted to generate α-trimethylsilyldiazoethane (**283**) from the alkylation of the lithium salt of TMS-diazomethane with methyl iodide and then add it without isolation to a TAS-vinylketene. Thus, methylation was conducted at -23 °C, the silylketene **175** was then added at 0 °C, and the reaction mixture was allowed to warm to room temperature (eq 98). Unfortunately, upon work-up the silylketene **175** was recovered in 100% yield, and it is believed that α-silyldiazoalkane **283** was not generated. Note that Shioiri has not reported the synthesis of this specific α-silyldiazoalkane.



(98)

154. Aoyama, T.; Shioiri, T. *Tetrahedron Lett.* **1980**, *27*, 2005.

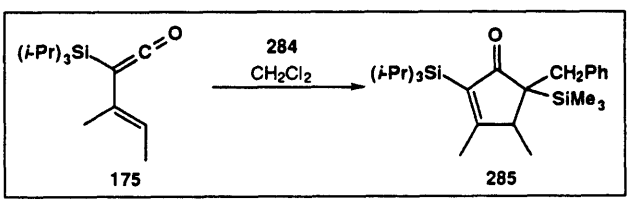
Shiori has reported the preparation of **284** in 77% yield.[154] Employing his procedure, we alkylated lithium TMS-diazomethane (prepared from TMS-diazomethane and *n*-butyllithium) with benzyl chloride and obtained **284** after vacuum distillation (140 °C, 0.25 mmHg) in 66% yield (eq 99).



(99)

Unfortunately, no significant reaction was observed between silylketene **175** and α-silyldiazoalkane **284** in dichloromethane at temperatures ranging from 0 to 50 °C (entries 1-2; Table 12). Attempted catalysis of the reaction using $BF_3{\cdot}OEt_2$ only afforded unreacted TAS-vinylketene and a complex mixture of products (entries 3-4).

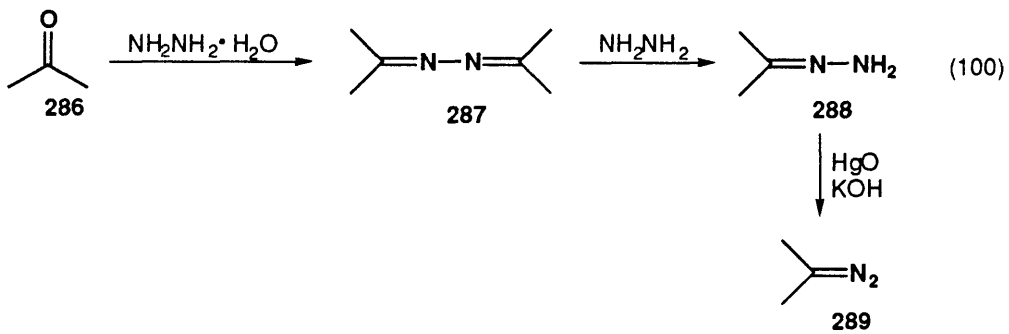
Table 12



Entry	Conditions	Results
1	1.5 equiv $TMSC(N_2)CH_2Ph$ 0 °C to rt, 3 d	no reaction observed by tlc
2	1.3 equiv $TMSC(N_2)CH_2Ph$ rt, 24 h then 50 °C, 2 h	no reaction observed by tlc
3	0.05 equiv $TMSC(N_2)CH_2Ph$ 0.05 equiv $BF_3{\cdot}OEt_2$ rt to 50 °C, 4 h	complex mixture of products; ketene recovered in 50% yield
4	1.5 equiv $TMSC(N_2)CH_2Ph$ 1.0 $BF_3{\cdot}OEt_2$ -78 °C to rt, 24 h	complex mixture of products

The preceeding results led us to conclude that TMS-diazoalkanes are considerably less reactive than diazoalkanes, and that substitution of bulky groups such as benzyl further

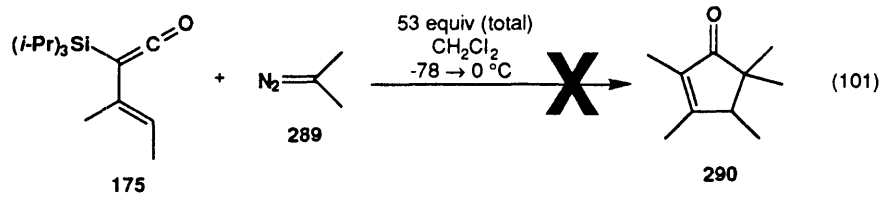
retard the rate of addition to vinylketenes. We therefore next turned our attention back to simple diazoalkanes lacking the silyl substituent. 2-Diazopropane (**289**) was selected for our initial studies and was prepared according to the literature procedure (eq 100).[155] Thus, the acetone azine **287** was first prepared via the reaction of acetone and hydrazine monohydrate. Azine **287** was then treated with anhydrous hydrazine (distilled from refluxing hydrazine hydrate and sodium hydroxide pellets) to produce essentially pure acetone hydrazone **288**. Next, a solution of **288** in diethyl ether was treated with mercuric oxide and potassium hydroxide in ethanol. 2-Diazopropane (**289**) was codistilled with diethyl ether at reduced pressure into a cooled receiver to yield a bright orange ~2.0 M ethereal solution.



286 287 288 289 (100)

The silylketene **175** was treated with several portions (5, 10, and 38 equiv) of 2-diazopropane (eq 101). No significant reaction was observed by tlc analysis, and 73% of the silylketene was eventually recovered. Two minor products were isolated, and ketene carbonyl stretching frequencies were observed in the IR spectrum for both compounds indicating that no addition of 2-diazopropane had occurred. Again, the steric bulk of this reagent is thought to be an important factor preventing the addition of the diazo compound to the ketene.

155. (a) Day, A. C.; Whiting, M. C. *Organic Syntheses*, **1988**, *Coll. Vol. 6* 10. (b) Andrews, S. D.; Day, A. C.; Raymond, P.; Whiting, M. C. *Organic Syntheses*, **1988**, *Coll. Vol. 6*, 392.



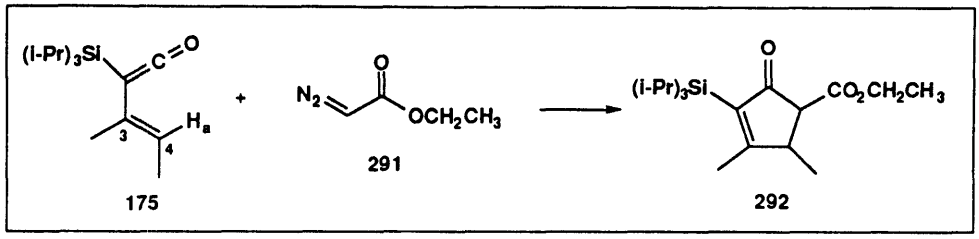
(101)

Several attempts were made to add commercially available ethyl diazoacetate (**291**) to TAS-vinylketene **175** (Table 13). When silylketene **175** and ethyl diazoacetate were stirred together at room temperature followed by elevated temperatures, no reaction occurred (entry 1). Reaction in the presence of catalytic amounts of rhodium acetate also gave none of the desired product, and in this case it appeared that cyclopropanation had occurred at the C-3/C-4 double bond of the silylketene to afford a cyclopropyl silylketene in ~20% yield (entry 2). $BF_3{\cdot}OEt_2$ catalysis also did not promote formation of the desired cyclopentenone and the TAS-vinylketene was recovered in 45% yield (entry 4). The ^1H NMR spectrum of the minor product isolated in this reaction showed a quartet at 5.40 ppm presumably corresponding to H_a, thus suggesting that no cyclization had occurred.

It is well known that ketones undergo smooth homologation using the lithium anion of ethyl diazoacetate.[156] We therefore generated, the anion of ethyl diazoacetate using lithium diisopropylamide and added it to a solution of the silylketene **175** in THF (entry 3). Tlc analysis indicated that although several products had formed, there appeared to be no cyclized product as evidenced by the quartet present in the ^1H NMR spectrum presumably corresponding to H_a.

156. Nagao, K.; Chiba, M.; Kim, S.-W. *Synthesis*, **1983**, 197.

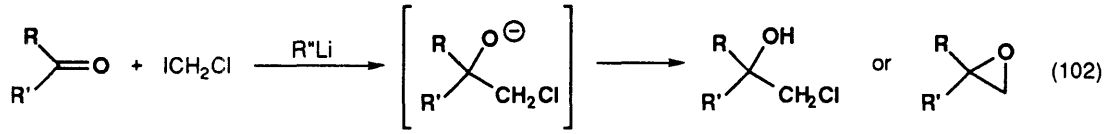
Table 13



Entry	conditions	Results
1	CH_2Cl_2 rt to 40 °C, 29 h	ketene recovered in 83% yield
2	0.02 equiv $Rh_2(OAc)_4$, CH_2Cl_2, rt, 30 min	~20% C-3/C-4 double bond addition ketene recovered in 42% yield
3	1.0 equiv *n*-BuLi, THF -78 °C to rt, 5 h	mixture of uncyclized products
4	0.01 equiv $BF_3{\cdot}OEt_2$ CH_2Cl_2 -78 °C to rt, 20 h	mixture of uncyclized products ketene recovered in 45% yield

[4 + 1] Annulation with α-Halocarbanions

(Chloromethyl)lithium, $ClCH_2Li$, has limited synthetic utility due to its extreme thermal instability. However, this reagent has been generated and captured in nearly quantitative yield by the addition of *n*-butyllithium or methyllithium to mixtures of chloroiodomethane with aldehydes and ketones in THF at -78 °C to produce epoxides and chlorohydrins (eq 102).[157]



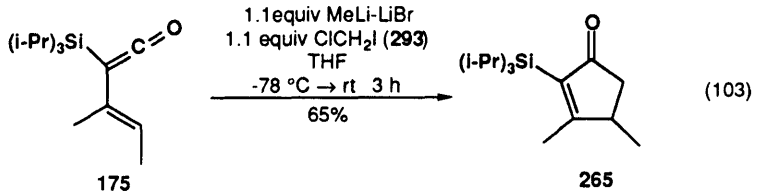
(102)

The success of this method depends on rate relationships between several fast reactions. Halogen-metal exchange between chloroiodomethane and the organolithium reagent must be faster than the addition of the organolithium reagent to the carbonyl

157. Sadhu, K. M.; Matteson, D. S. *Tetrahedron Lett.* **1986**, *27*, 795 and references cited therein.

compound. Also, the reaction of (chloromethyl)lithium with the carbonyl compound must be faster than its decomposition.

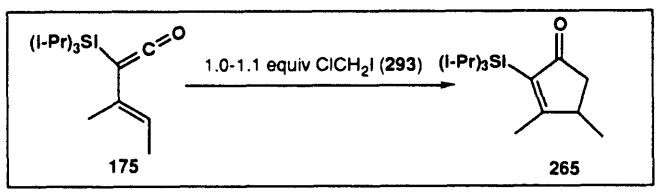
We believed that α-halocarbanions such as (chloromethyl)lithium would react with TAS-vinylketenes in the desired fashion to afford cyclopentenones. In fact, in the very first reaction tried, (chloromethyl)lithium added to vinylketene **175** to furnish α-silylcyclopentenone **265** in 65% yield (eq 103).



175 265 (103)

Unfortunately, although several attempts have been made to repeat this reaction, all efforts have been unsuccessful and resulted in the formation of a complex mixture of products. Unless otherwise indicated, for all the reactions below (Table 14), 1.0-1.1 equiv of chloroiodomethane (**293**) were used after filtration through alumina, and the concentration of the reaction mixture was 0.1 M.

Table 14



175 265

Entry	Conditions		Results
1	1.1 equiv MeLi-LiBr, THF THF, -78 °C to rt, 2 h	(**293** not filtered)	complex mixture
2	1.0 equiv *n*-BuLi, THF -78 °C to rt, 2 h	(**293** not filtered)	complex mixture
3	1.2 equiv *n*-BuLi, THF -78 °C, 2 h		complex mixture
4	1.0 equiv MeLi-LiBr, THF -78 °C	(distilled **293** and filtered)	complex mixture

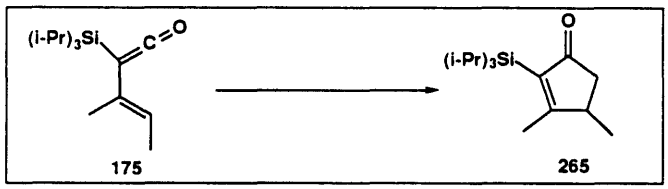
5	1.1 equiv MeLi-LiBr, THF -78 °C	(new bottle RLi)	complex mixture
6	1.1 equiv MeLi-LiBr, CH_2Cl_2 -78 °C	(different solvent)	complex mixture
7	1.1 equiv MeLi-LiBr, Et_2O -78 °C	(different solvent)	complex mixture
8	1.0 equiv MeLi-LiBr, THF -78 °C, 2 h	(concn. = 0.5 M)	complex mixture
9	1.0 equiv *n*-BuLi, THF -93 °C	(lower temperature)	complex mixture
10	1.0 equiv MeLi-LiBr, THF -50 °C	(higher temperature)	complex mixture
11	1.2 equiv MeLi-LiBr, THF THF, -78 °C		complex mixture
12	1.2 equiv MeLi-LiBr, THF -78 °C, 15 min	(concn. = 0.15 M)	**265**<16% yield complex mixture
13	1.0 equiv MeLi-LiBr, THF 0.5 equiv $LiBF_4$, -78 °C	(added salt)	complex mixture
14	1.0 equiv MeLi-LiBr, THF 0.5 equiv LiBr, -78 °C to rt, 3 h	(added salt)	complex mixture
15	1.0 *t*-BuLi, THF, -78 °C		complex mixture

Attempts to reproduce the result achieved in the initial reaction included the following measures: (1) The reaction was conducted at higher concentrations (entry 8) in anticipation of trapping the highly unstable α-halocarbanion before it decomposes. (2) Other bases such as *n*-BuLi and *t*-BuLi were used to generate the α-halocarbanion (entries 2,3,9, and 15). (3) Other solvents were employed (entries 6 and 7). (4) Lithium salts were added to the reaction mixture to promote the addition to the carbonyl group (entries 13 and 14). (5) Several related α-halocarbanions were also examined for the [4 + 1] annulation. However, neither bromomethyllithium (from CH_2Br_2/*n*-BuLi)[158] or

158. Michnick, T. J.; Matteson, D. S. *Synlett* **1991**, 631.

chloromethylmagnesium chloride (from $ClCH_2I/i$-PrMgCl)[159] produced the desired cyclopentenone upon reaction with TAS-vinylketene **175** (Table 15).

Table 15



Entry	Conditions		Results
1	1.2 equiv *n*-BuLi, THF 1.2 CH_2Br_2 -78 °C,		complex mixture
2	1.0 equiv *n*-BuLi, THF 1.0 CH_2Br_2 -78 °C	concn = 0.5 M	complex mixture
3	1.2 equiv *n*-BuLi, THF -78 °C, 1 h rt, 1.5 h	concn = 0.2 M	complex mixture
4	1.0 equiv *i*-PrMgCl, THF -78 °C		no reaction observed by tlc

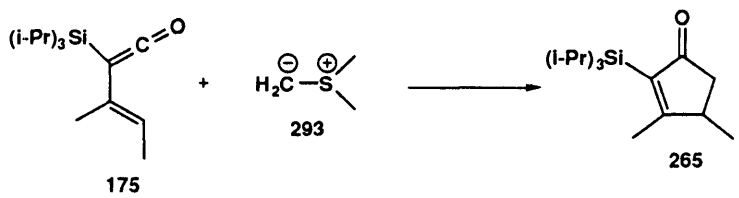
At this point, the initial result of the [4 + 1] annulation (eq 91) with chloromethyllithium has not been reproduced and no explanation as to why this is the case has been determined.

[4 + 1] Annulation with Sulfur Ylide Reagents

Sulfur ylide reagents such as dimethyloxosulfonium methylide and dimethylsulfonium methylide are widely used to transfer methylene groups to unsaturated linkages such as C=O, C=N, C=S, and in some cases C=C.[160] We have found that

159. De Lima, C.; Julia, M.; Verpeaux, J.-N. *Synlett* **1992**, 133.
160. For reviews on sulfur ylide chemistry, see: (a) Johnson, A. W. In *Ylid Chemistry*; Academic Press: New York, 1966. (b) Trost, B. M.; Melvin, L. S. In *Sulfur Ylides*; Academic Press: New York, 1975. (c) Johnson, C. R. In *Comprehensive Organic Chemistry*; Jones, D. N., Ed.; Pergamon Press: New York, 1979; pp 247-260. (d) Knipe, A. C. In *The Chemistry of the Sulfonium Group*; Stirling, C. J. M., Ed.; John Wiley & Sons: New York, 1981, 313-387. (e) Aube, J. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: New York, 1991, pp 819-825. (f) Metzner, P.; Thuillier, A. *Sulfur Reagents in Organic Synthesis*; Academic Press: London, 1994.

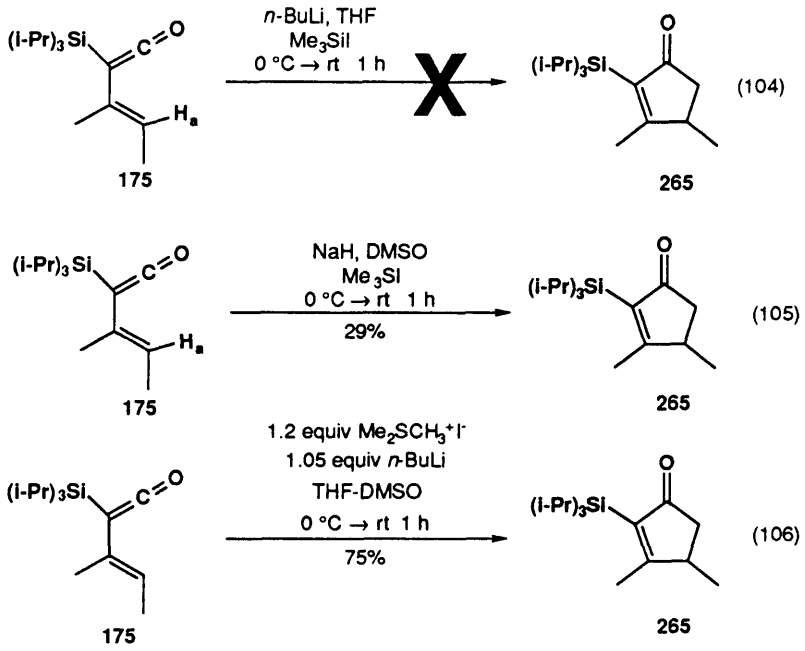
dimethylsulfonium methylide **293**[161] is a methylene transfer reagent that reacts smoothly with TAS-vinylketenes to produce cyclopentenones as shown below.



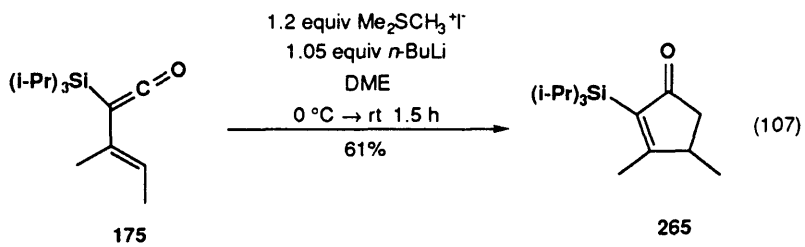
In this reaction it is necessary to add the ylide to a solution of the ketene. When the ylide is present in excess, the desired cyclopentenone product can react further. It is also noteworthy that when the ylide is present in excess, or when the reaction is conducted at higher concentrations (> 0.2 M in silylketene), there is evidence of byproduct formation by tlc, and the isolated yield of the desired product is significantly decreased.

Two bases were investigated for the generation of the dimethylsulfonium methylide from commercially available trimethylsulfonium iodide. Initially, we generated the ylide from trimethylsulfonium iodide using *n*-butyllithium in a solution of THF at 0 °C (eq 104). None of the desired cyclopentenone **265** was formed, and ^{1}H NMR spectral analysis suggested that no cyclized product had formed as indicated by the quartet observed at 5.40 ppm for the proton H_a. In contrast, when dimsyl anion (generated from NaH and DMSO) was used to form the ylide in DMSO at 0 °C (eq 105), the desired cyclopentenone was produced in 29% yield. In fact, it was found that *n*-butyllithium could be used to generate the ylide, if DMSO was used as a polar co-solvent with THF to promote the cyclization. Under these conditions the [4 + 1] annulation proceeded in 75% yield (eq 106). Lower yields were obtained when the reaction was conducted in mixtures of THF with other polar co-solvents such as DMF and DMPU.

161. (a) Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1965**, *87*, 1353. (b) Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1962**, *84*, 3782.



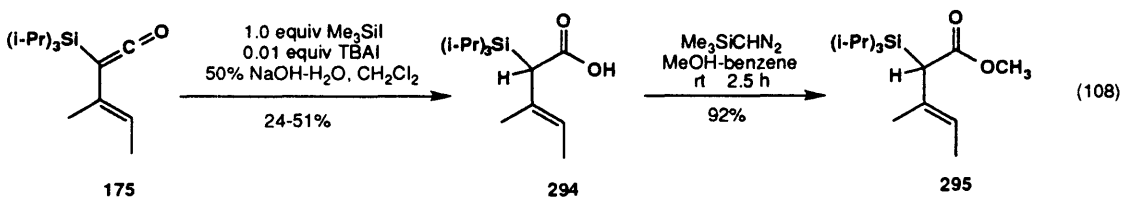
One limitation of using DMSO as a co-solvent is that its relatively high melting point (18.4 °C) prevents the reaction from being conducted at temperatures below 0 °C. In general, sulfonium ylides have a limited thermal stability, and it is therefore important that it be possible to conduct the reaction at low temperatures. It was discovered that DME can also be used as a solvent, and the annulation can be accomplished in 61% yield (eq 107). The melting point (-50 °C) of DME is low enough that if necessary this reaction can be conducted at much lower temperatures than the corresponding THF-DMSO reaction.



Dimethylsulfonium methylide can also be generated from trimethylsulfonium iodide using phase transfer catalysis under aqueous conditions.[162] This method of ylide

162. Merz, A.; Märkl, G. *Angew. Chem., Int. Ed. Engl.* **1973**, *12*, 846.

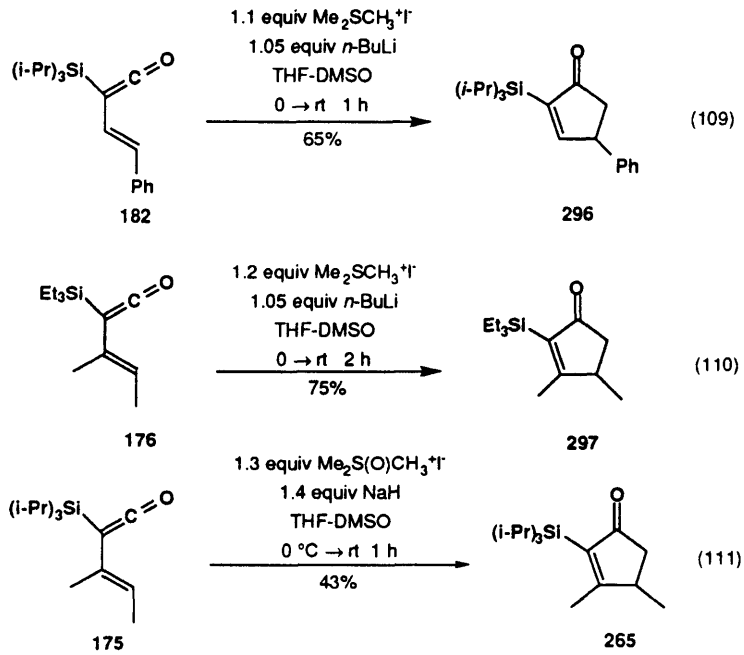
formation was investigated for reaction with TAS-vinylketene **175**. However, as expected, hydrolysis of the silylketene was a facile process, and this reaction afforded the carboxylic acid **294** in 24-51% yield depending on the temperature of the reaction mixture. The acid **294** is characterized by the broad O-H stretching frequency at 3100-2500 cm^{-1} and the carbonyl stretching frequency at 1680 cm^{-1} in the IR spectrum. The structure of acid **294** was further confirmed by conversion to the methyl ester **295** using TMS-diazomethane (eq 108).[163]



175 **294** **295** (108)

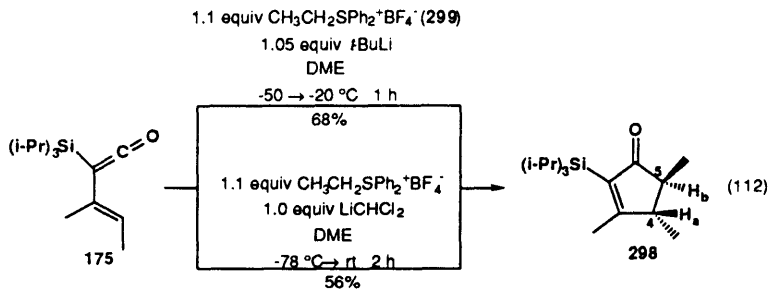
Dimethylsulfonium ylide (generated from trimethylsulfonium iodide and *n*-BuLi) also reacted efficiently with other TAS-vinylketenes (eq 109 and 110). Reactions were conducted by generating 1.05 equiv of the sulfur ylide in THF and then adding it to a solution of ketene (0.1 M) in 1:1 THF-DMSO on a scale to afford 60-120 mg of product. The more stable, less reactive dimethyloxosulfonium methylide[161] also added to the TAS-vinylketene **175** to produce the silylcyclopentenone **265** in 41% yield (not optimized) (eq 111).

163. Hashimoto, N.; Aoyama, T.; Shiori, T. *Chem. Pharm. Bull.* **1981**, *29*, 1475.



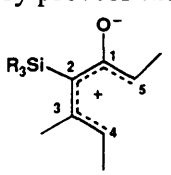
We have also recently found that sulfur ylide reagents can serve as effective "alkylidene transfer" reagents. Specifically, diphenylsulfonium ethylide[164] was generated from the commercially available salt, diphenylethylsulfonium fluoroborate (**299**). This sulfur ylide added to silylketene **175** in a solution of DME cooled at -50 °C to produce the desired cyclopentenone **298** in 68% yield (eq 112). The reaction was conducted at low temperature due to the ylide instability. Diphenylsulfonium ethylide is known to decompose in THF with a half life of ca. 5 h at -20 °C and very rapidly at 0 °C. *t*-BuLi was found to be the most convenient base for ylide generation. However, it is also possible to produce the ylide using dichloromethyllithium (formed via the deprotonation of dichloromethane with lithium diisopropylamide) at -78 °C. Using this method, the reaction of the silylketene and diphenylsulfonium ethylide afforded the desired cyclopentenone in 56% yield (eq 112).

164. Corey, E. J.; Jautelat, M.; Oppolzer, W. *Tetrahedron Lett.* **1967**, 2325.



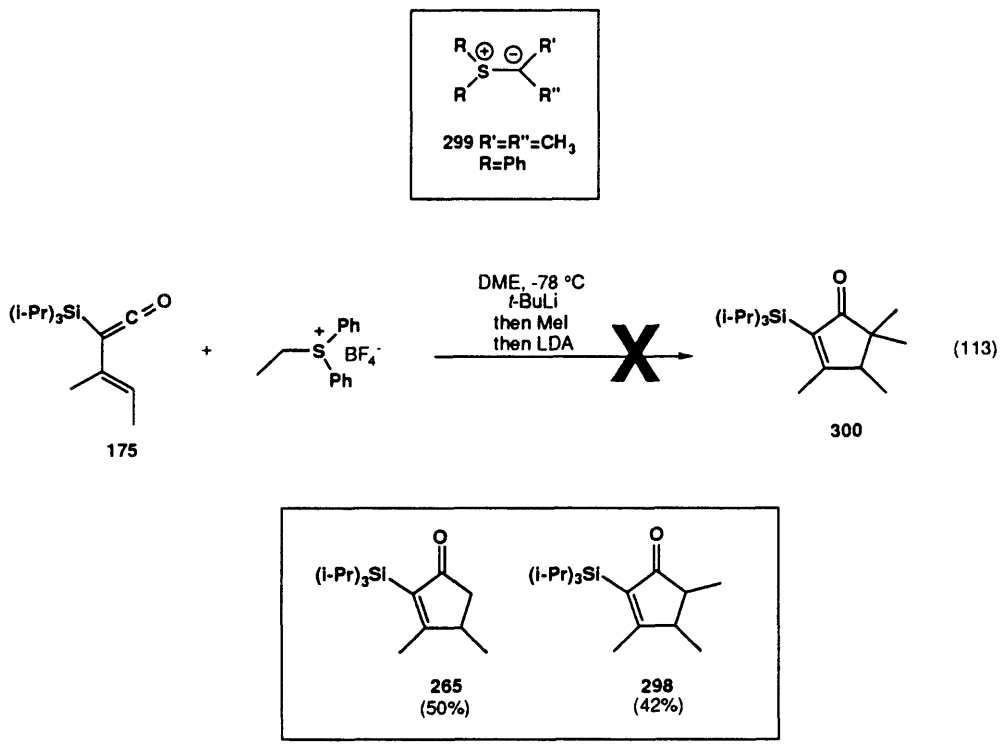
The structural assignment for α-silylcyclopentenone **298** was again based on the coupling constant observed between the protons at C-4 and C-5 of the cyclopentenone ring. As mentioned earlier, the coupling constant for the protons attached at C-4 and C-5 of *trans*-4,5-dimethyl-cyclopent-2-en-1-one (H_a and H_b) is relatively small (J_{ab} = 2.5 Hz).[150] This is similar to the coupling constant observed between H_a and H_b (J_{ab} = 3.2 Hz) for silylcyclopentenone **298**. Dreiding models of both the cis and trans α-silyl cyclopentenones have been constructed. For the cis isomer, it appears that the dihedral angle between H_a and H_b cannot be much greater than ~30°, thus a large (J_{ab} = 8-9 Hz) coupling constant is predicted. In contrast, the dihedral angle between H_a and H_b in the trans isomer appears to be much larger (~110°) and therefore should result in a much smaller coupling constant (J_{ab} = 2-3 Hz) which is consistent for the J_{ab} value observed for cyclopentenone **298**.

As mentioned earlier for the reaction of silylvinylketene **175** and TMS-diazomethane (see p. 127), the stereochemical assignment of the C-4 and C-5 substituents as trans offers insight into the mechanistic pathway of the annulation. It is believed that initially the sulfur ylide adds to the vinylketene in a stereoselective fashion to form the Z enolate which can then ionize to produce the pentadienyl cation with the substituents at C-4 and C-5 positioned outward to avoid unfavorable steric interactions as shown below. Ring closure via a 4π electrocyclic conrotatory process then affords the trans substituted product.



Ylides in which both R' and R" are alkyl have been noted to be the least stable of all sulfonium ylides and the most difficult to prepare. There are two possible methods for the formation of isopropyl ylide **299** (Figure 16).[164] The first procedure involves the alkylation of diphenylsulfonium ethylide (generated from diphenylethylsulfonium fluoroborate (**299**) and *t*-BuLi) with methyl iodide followed by deprotonation using lithium diisopropylamide. However, attempts to generate the ylide using this method and then add it to the silylketene did not lead to the desired cyclopentenone (eq 113).

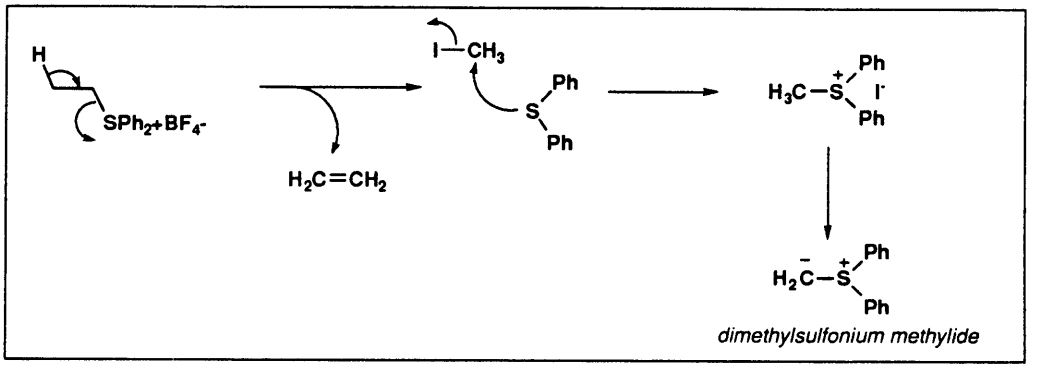
Figure 16



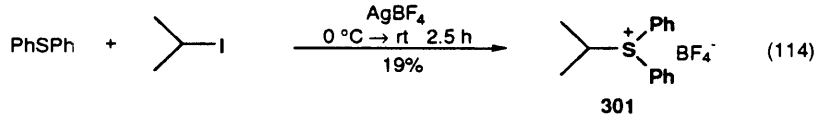
Instead, the two products isolated were the methylide addition product **265** (50%) and the ethylide addition product **298** (42%). Cyclopentenone **298** is presumably produced via the addition of the unalkylated initial ethylide to the TAS-vinylketene. Alternatively, decomposition of diphenylethylsulfonium fluoroborate to the methylide can

occur via β–elimination as illustrated below (Scheme 28). We believe that the resulting methylide then adds to ketene **175** to give **265**. In this reaction, it is very likely that none of the desired isopropylide was generated under the reaction conditions.

Scheme 28



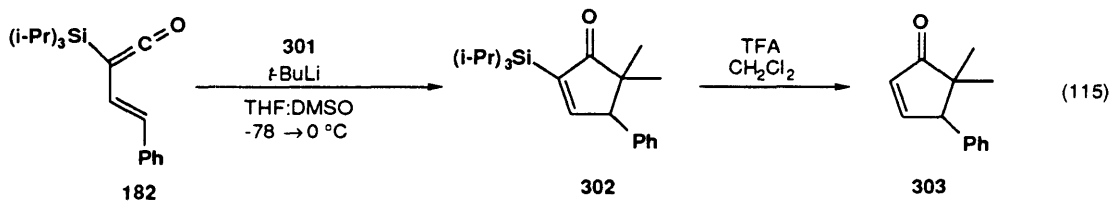
An alternative method for the preparation of the isopropylide **299** involves the use of the crystalline salt, diphenylisopropylsulfonium fluoroborate (**301**) which can be formed from diphenyl sulfide, isopropyl iodide, and silver fluoroborate (eq 114).[165] The crude salt was recrystallized from dichloromethane-ether two times to give a white crystalline product in 19% yield (lit. 55%).[165]



301 (114)

Preliminary studies have shown that the reaction of silylvinylketene **182** with diphenylsulfonium isopropylide (generated via the deprotonation of **301** using *t*-butyllithium) affords as a viscous oil α-silylcyclopentenone **302** in ~60-70% yield (eq 115). Unfortunately, the cyclopentenone is inseparable by column chromatography from other byproducts produced in the reaction and has not yet been isolated in >95% purity. Studies are presently being conducted in which the annulation product is protodesilylated (for a discussion of this type of desilylation, see p. 168) prior to purification in attempts to isolate uncontaminated **303**.

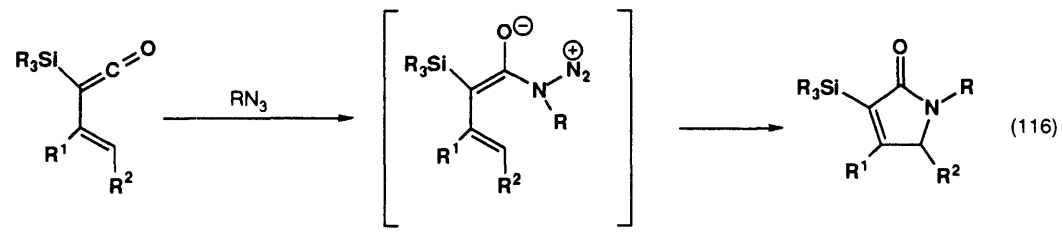
165. Nadeau, R. G.; Hanzlik, R. P. *Methods in Enzymology*, **1969**, *15*, 347.



(115)

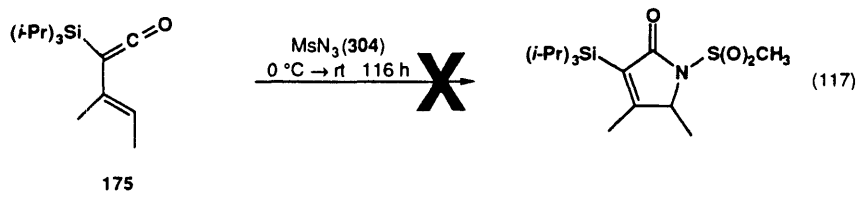
Attempted Synthesis of Heterocycles

In principle, our [4 + 1] annulation could provide efficient access to five-membered heterocycles in addition to the carbocycles described in the preceding sections. We have investigated a number of reagents that could potentially function as "nitrenoid" equivalents to make nitrogen heterocycles. We have focused our attention on a number of organic azides, which we had hoped would combine with TAS-vinylketenes and afford unsaturated lactams (eq 116).



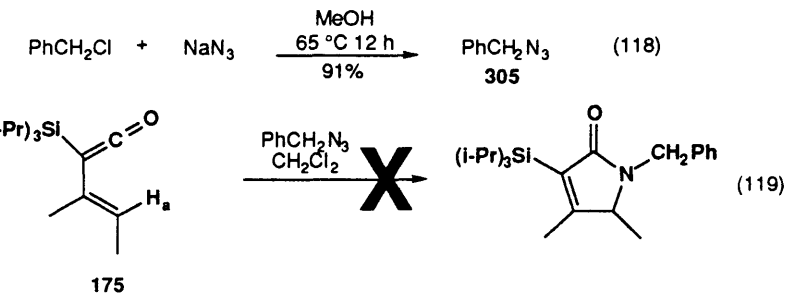
(116)

We first explored the reaction of silylvinylketene **175** with methanesulfonyl azide (**304**), an azide reagent that was readily available from our earlier diazo transfer studies. The ketene and azide **304** were combined in dichloromethane and stirred at room temperature for 116 h (eq 117). No reaction was observed by tlc analysis, and ~80% of the silylketene was recovered. It is believed that the electron withdrawing sulfonyl group stabilizes azide **304** to such an extent that it does not readily undergo nucleophilic addition to the silylketene.



175

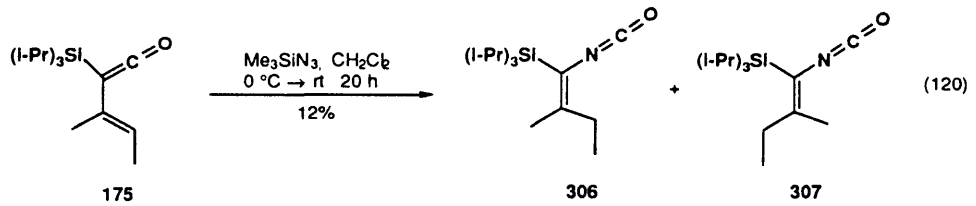
We next turned our attention to an azide in which the nitrogen atom was expected to be more nucleophilic than MsN_3. Benzyl azide (**305**) was prepared in 91% yield as shown below (eq 118).[166] When silylketene **175** was combined with benzyl azide in dichloromethane and stirred for several days at room temperature, no reaction was observed (eq 119). Catalysis of the reaction using $BF_3{\cdot}OEt_2$ was also attempted. At -78 °C, no reaction was observed by tlc analysis, but as the reaction warmed to room temperature, a complex mixture of products formed at -16 °C.



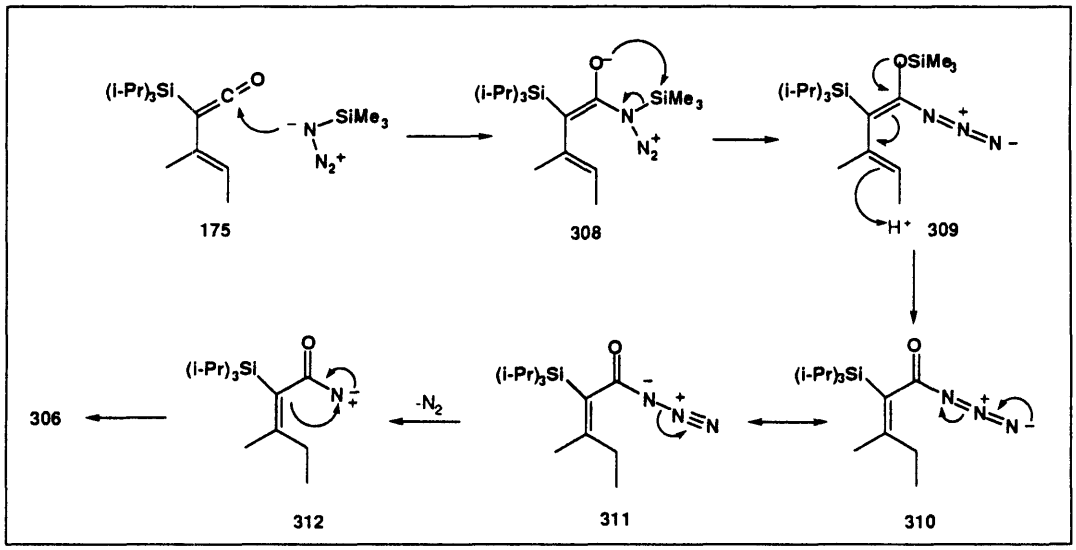
175

Commercially available TMS-azide was found to react with silylketene **175** to produce regioisomeric isocyanates **306** and **307** in 12% overall yield (eq 120). In this reaction, 33% of the ketene starting material was also recovered, and minor amounts of two other unidentified products were formed as well. We believe the isocyanates **306** and **307** arise from the pathway depicted in Scheme 29.

166. Wiley, R. H.; Hussung, K. F. *J. Chem. Soc.* **1955**, *21*, 190.



Scheme 29

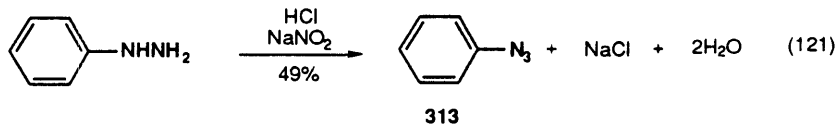


Initially, TMS-azide adds to the ketene carbonyl to form enolate **308** which can undergo protonation with cleavage of the trimethylsilyl group to produce acyl azide **310.** Acyl azides are well known to rearrange to isocyanates, and this process is a key step in a number of important synthetic methods such as the Curtius and Schmidt rearrangements.

Phenyl azide (**313**) was prepared from commercially available phenylhydrazine by the action of nitrous acid upon phenylhydrazine hydrochloride (eq 121).[167] Thus, phenyl hydrazine was added to an aqueous HCl acid solution at -20 °C, and the precipitation of phenylhydrazine hydrochloride was observed. A small amount of diethyl ether was added to the reaction mixture, then an aqueous solution of sodium nitrite was added slowly over time, and the reaction mixture was subjected to steam distillation. Phenyl azide was extracted from the aqueous phase of the distillate and then distilled under reduced pressure

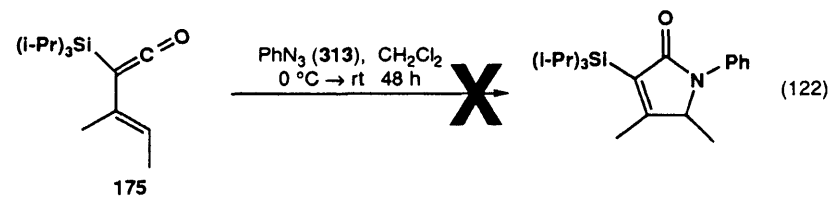
167. Lindsay, R. O.; Allen, C. F. H. *Organic Syntheses Coll Vol 3*, **1955**, 710.

to yield phenyl azide (**313**) as a pungent, pale yellow, oily azide in 49% yield (lit. 65-68%).[167]



313

Silylketene **175** and phenyl azide (**313**) were combined at 0 °C in dichloromethane, and the reaction mixture was allowed to warm to room temperature and stirred for 48 h (eq 122). No significant reaction was observed between the ketene and phenyl azide by tlc analysis.

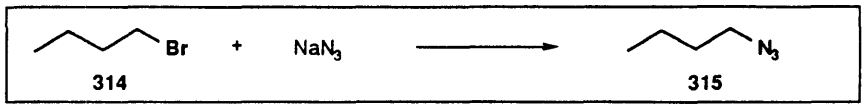


175

Initial attempts to prepare butyl azide (**315**) from butyl bromide (**314**) and sodium azide were unsuccessful (entries 1 and 2; Table 16). In one experiment, 1.0 equiv of butyl bromide was combined with 2.0 equiv of NaN_3 in DMSO at room temperature for 6 h,[168] and in methanol at 70 °C for 15 h.[169] After filtration of the crude reaction mixture, in both cases the IR spectrum lacked typical azide stretches (2250-2080 cm^{-1}). Using phase transfer catalysis, we were finally able to prepare butyl azide (**315**) beginning with butyl bromide and sodium azide using Aliquat 336 (tricaprylylmethylammonium chloride) as the catalyst (entry 3).[170] Butyl azide was isolated after distillation under reduced pressure as a clear liquid in 39% yield with a characteristic azide IR stretching frequency at 2090 cm^{-1}.

Table 16

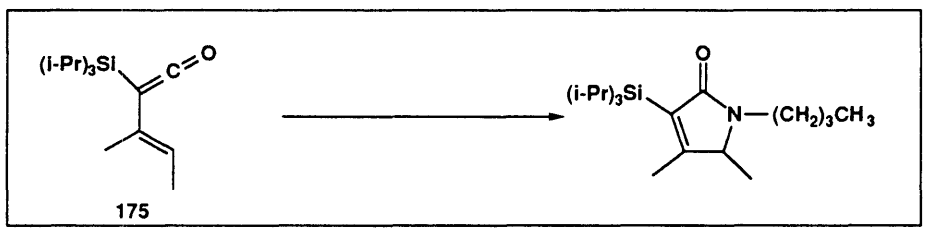
168. (a) Brown, H. C.; Salunkhe, A. M.; Singaram, B. *J. Org. Chem.* **1991**, *56*, 1170. (b) Evans, D. A.; Weber, A. E. *J. Am. Chem. Soc.* **1987**, *109*, 7151.
169. Lieber, E.; Chao, T. S.; Rao, C. N. R. *J. Org. Chem.* **1957**, *22*, 238.
170. Reeves, W. P.; Bahr, M. L. *Synthesis* **1976**, 823.



Entry	Conditions	Results
1	DMSO, rt, 6 h	no reaction
2	MeOH, 70 °C, 15 h	no reaction
3	Aliquat 336, H_2O rt to 100 °C, 5 h	39% yield

The addition of butyl azide (**315**) to silylketene **175** was attempted under a range of conditions as illustrated below (Table 17). In general, no significant reaction was observed between the ketene and azide, and ~65% of the silylketene was recovered. One exception included when the temperature was elevated to 174 °C and in this case a complex mixture of products formed (entry 4).

Table 17

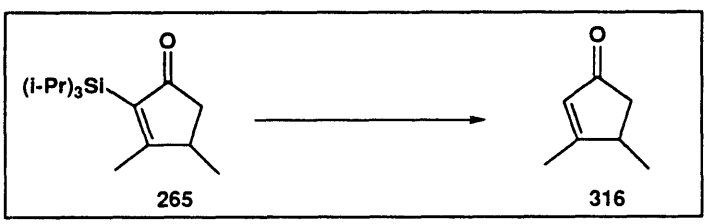


Entry	Conditions	Results
1	1.5 equiv BuN_3 $ClCH_2CH_2Cl$, 60 °C, 5 h	No reaction observed by tlc ketene recovered in 69% yield
2	1.1 equiv BuN_3 benzene, 80 °C, 5 h	No reaction observed by tlc
3	1.3 equiv BuN_3 xylene, 140 °C, 2 h	No reaction observed by tlc ketene recovered in 64% yield
4	1.0 equiv BuN_3 decane, 174 °C, 2 h	complex mixture observed by tlc

Protodesilylation

α-Silylcyclopentenones serve as important intermediates in organic synthesis. We have investigated the protodesilylation of our [4 + 1] annulation products to establish that our method can provide access to cyclopentenones lacking a 2-silyl substituent. Protodesilyation of (trimethylsilyl)vinylsilanes is known to be a relatively facile process.[171] However, difficulty can arise in the removal of more bulky silyl substituents such as the triisopropylsilyl group. In fact, optimization of the desilylation of our triisopropylsilyl-substituted cyclopentenones required considerable experimentation. A number of acidic and fluoride-based reagents were examined (Table 18).

Table 18

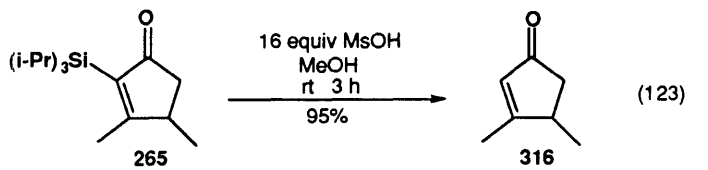


Entry	Conditions	Results
1	20 equiv TFA, CH_2Cl_2, rt, 2 h then MeOH, rt, 3 h	no reaction observed by tlc
2	20 equiv TFA, CH_3CN, rt, 2 h then MeOH, rt, 3 h	no reaction observed by tlc
3	20 equiv TFA, $CDCl_3$, rt, 2 h MeOH, rt, 3 h	no reaction observed by tlc
4	HF·py, THF, rt	no reaction observed by tlc
5	48% HF, CH_3CN, rt, 22 h	no reaction observed by tlc

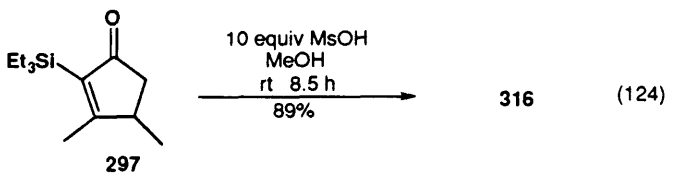
171. For a review on protodesilylation of vinylsilanes, see: Fleming, I.; Dunogues, J.; Smithers, R. *Organic Reactions*, **1989**, *37*, 93.

6	HBF_4, CH_3CN, rt, 22 h	no reaction observed by tlc
7	HCl-$CHCl_3$, rt, 19 h	no reaction observed by tlc
8	BF_3·2AcOH, CH_2Cl_2 0 °C to rt, 9 h	no reaction observed by tlc
9	20 equiv MsOH, MeOH rt, 6 h	complete conversion by tlc to more polar product

In contrast to the other procedures listed, protodesilylation using methanesulfonic acid was found to be an efficient process even in the case of the bulky triisopropylsilyl group. For example, desilylation of **265** proceeds in 95% yield on exposure to 16 equiv of methanesulfonic acid in methanol at room temperature to afford cyclopentenone **316**[172] (eq 123). Efforts to reduce the number of equivalents of acid to <10 equiv were unsuccessful, and the complete conversion of starting material to product was not observed by tlc. Likewise, the triethylsilyl substituted cyclopentenone undergoes desilylation with 10 equiv of methanesulfonic acid in 89% yield (eq 124).



265 **316** (123)



297 **316** (124)

Summary

In summary, we have presented a new strategy which provides an efficient and convenient route to a variety of *substituted* TAS-vinylketenes based on the photochemical Wolff rearrangement. We have found these substituted vinylketenes to be remarkably robust substances and have investigated their reactivity as four-carbon building blocks in

172. Conia, J.-M.; Leriverend, M.-L. *Bull. Soc. Chim. Fr.* **1970**, 2981.

synthesis. TAS-vinylketenes serve as reactive dienes in the Diels-Alder reaction with a number of reactive dienophiles. We have found that TAS-vinylketenes also participate in novel [4 + 1] cycloadditions with a number of "carbenoid" reagents which provide an interesting new route to 5-membered carbocyclic products. Overall, we anticipate that improved accesss to substituted TAS-vinylketenes via the photo Wolff strategy will enhance the synthetic utility of silylvinylketenes, and we will continue to explore their promising new applications in synthesis.

Part III

Experimental Section

General Procedures

All reactions were performed in flame-dried glassware under a positive pressure of argon or nitrogen. Reaction mixtures were stirred magnetically unless otherwise indicated, except for photochemical reactions which were *not stirred* unless otherwise indicated. Air and/or moisture sensitive reagents and solutions were transferred via syringe or cannula and were introduced into reaction vessels through rubber septa. Reaction product solutions were concentrated with the use of a Büchi rotary evaporator at approximately 20 mm Hg unless otherwise indicated.

Materials

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

Distilled under nitrogen, argon, or vacuum from calcium hydride: acetonitrile, dichloromethane, diisopropylamine, diisopropylethylamine, dimethyl acetylenedicarboxylate, 1,1,1,3,3,3-hexamethyldisilazane, 2,2,6,6-tetramethylpiperidine, dibromomethane, dichloroethane, triethylamine, triisopropylsilyl chloride, trisopropyl-, *tert*-butyldimethyl-, and triethylsilyl trifluoromethanesulfonate.

Distilled under nitrogen, argon, or vacuum from sodium benzophenone ketyl or dianion: benzene, diethyl ether, dimethyl sulfoxide, ethylene glycol dimethyl ether (DME), tetrahydrofuran, and toluene

Distilled under argon or nitrogen: 1-acetyl-1-cyclohexene, 4-(2,6,6-trimethyl-1-cyclohexen-1-yl)-3-buten-2-one, 4-(2,6,6-trimethyl-1-cyclohexen-2-yl)-3-buten-2-one, and *trans*-3-penten-2-one.

Purification of other reagents was accomplished in the following manner; methyl iodide was distilled under argon and filtered through alumina.

Alkyllithium reagents were titrated in tetrahydrofuran or hexane at 0 °C with *sec*-butanol using 1,10-phenanthroline as an indidcator.[173]

Chromatography

Analytical thin-layer chromatography (TLC) was performed on Merck pre-coated glass-backed silica gel 60 F-254 0.25 mm plates. Visualization of spots was effected by one or more of the following techniques: (a) ultraviolet irradiation, (b) exposure to iodine vapor, (c) immersion of the plate in a 10% solution of phosphomolybdic acid in ethanol followed by heating to ca. 200 °C, (d) immersion of the plate in an ethanolic solution of 3% *p*-anisaldehyde containing 0.5% concentrated sulfuric acid followed by heating to ca. 200 °C, and (e) 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.

Column chromatography was performed by using 230-400 mesh Merck or Baker silica gel.

173. Watson, S. C.; Eastham, J. F. *J. Organomet. Chem.* **1967**, *9*, 165.

Instrumentation

Photolyses were performed in a Rayonet Photochemical Reactor Model RPR-100 or RPR-200, both produced by the Southern New England Ultraviolet Company. The reactors each contained sixteen low pressure mercury bulbs of 253.7 or 300 nm ultraviolet light. The photolyses were conducted with an internal fan in operation, and the internal temperature of the chamber was never higher than 35 °C.

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

Infrared spectra (IR) were recorded using a Perkin-Elmer 1320 grating spectrophotometer.

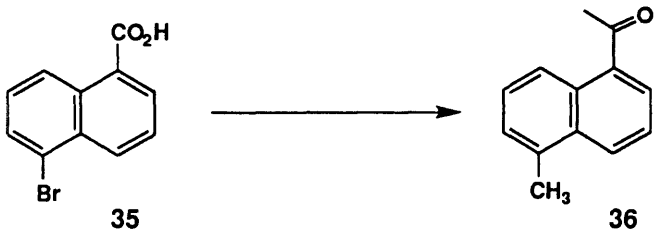
^{1}H NMR specta were recorded with a Varian XL-300 (300 MHz) and a Varian Unity 300 (300 MHz) spectophotometer. Chemical shifts are expressed in parts per million (δ) downfield from tetramethylsilane.

^{13}C NMR spectra were determined on a Varian XL-300 (75 MHz) spectrophotometer. Chemical shifts are reported in parts per million (δ), relative to tetramethylsilane (with the central peak of $CDCl_3$ at 77.0 ppm used as a standard).

Ultraviolet-visible spectra were recorded with a Perkin-Elmer 552 UV-vis spectrophotometer, and absorbances are reported in nanometers (nm).

High resolution mass spectra (HRMS) were measured on a Finnegan MATT-8200 spectometer.

Elemental analyses were performed by Robertson Microlit Laboratories, Inc., of Madison, New Jersey.



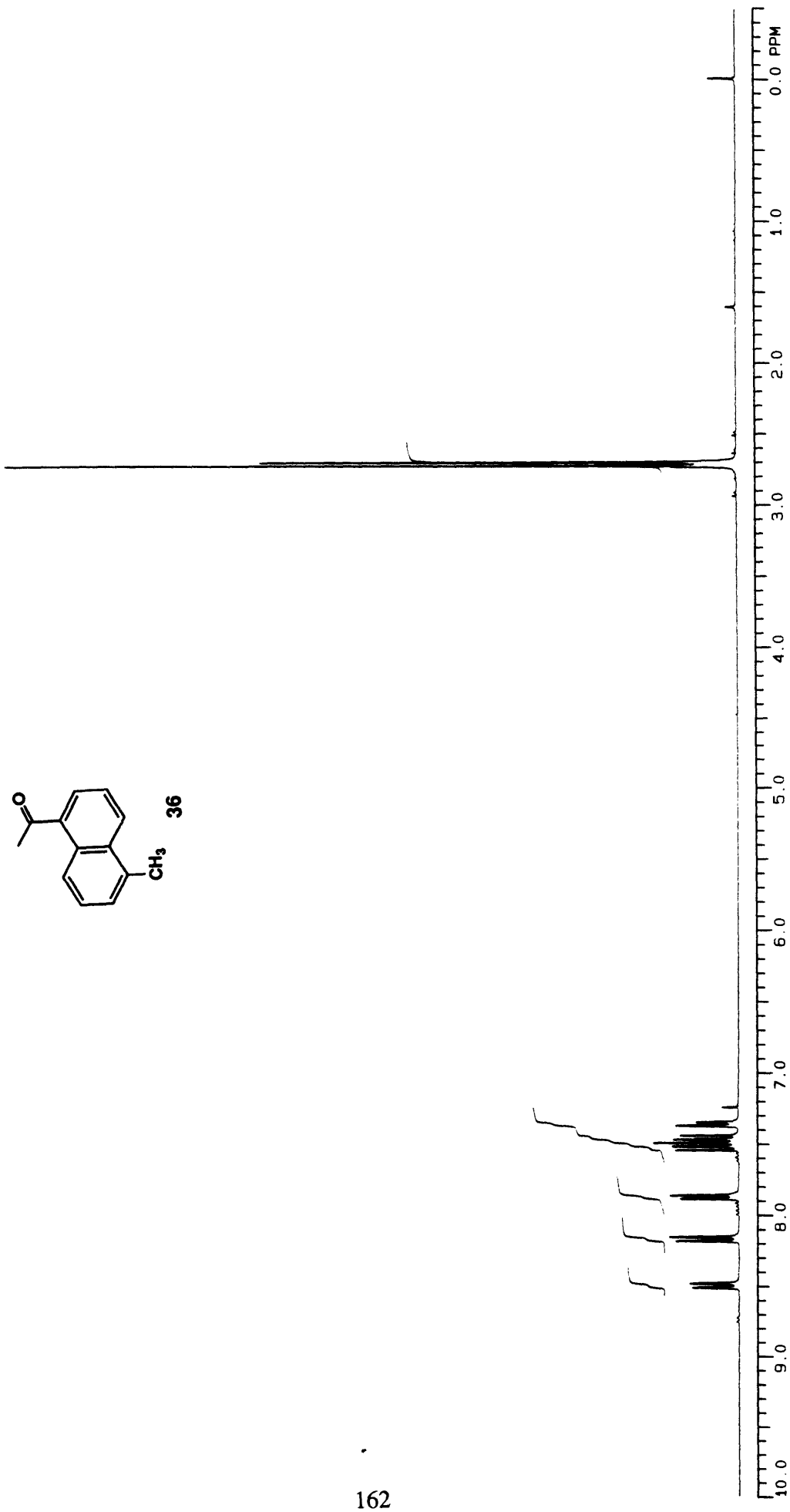
35 36

1-(5-Methyl-1-naphthoyl)-ethanone (36).

A 500-mL, three-necked, round-bottomed flask equipped with an argon inlet adapter, rubber septum, and a mechanical stirrer was charged with a solution of 5-bromo-1-napthoic acid **35** (6.09 g, 24.2 mmol) in 200 mL of tetrahydrofuran and cooled at 0 °C while methyllithium solution (1.53 M in diethyl ether, 16.0 mL, 24.5 mmol) was added dropwise over 5 min. The resultant carboxylate salt solution was stirred at 0 °C for 5 min and then cooled at -78 °C while *tert*-butyllithium solution (1.70 M in pentane, 29.5 mL, 50.2 mmol) was added dropwise via syringe over 5 min. The green suspension was stirred at -78 °C for 2.5 h, methyl iodide (4.07 g, 1.80 mL, 28.7 mmol) was added in one portion, and the orange reaction mixture was allowed to warm to 25 °C over a 2 h period. The solution was next cooled at -78 °C while methyllithium solution (1.53 M in diethyl ether, 31.2 mL, 47.8 mmol) was added over 5 min, and the reaction mixture was stirred for 20 h at 25 °C. The brown reaction mixture was cooled to 0 °C and freshly distilled chlorotrimethylsilane (51.9 g, 60.7 mL, 478 mmol) was rapidly added over ca. 1 min. The ice bath was then removed and the reaction mixture was allowed to come to room temperature and then transferred via cannula into 300 mL of a rapidly stirring 10% HCl solution. The organic layer was separated and the aqueous phase was extracted with three 150 mL portions of diethyl ether. The combined organic phases were washed with 200 mL of 10% HCl solution, 200 mL of water, and 200 mL of saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford 4.96 g of a brown oil. Column

chromatography on 100 g of silica gel (gradient elution with 0-5% EtOAc-hexane) provided 3.73 g (83%) of the methyl ketone **36** as a yellow oil.

IR (CCl_4):	3060, 2990, 2960, 2880, 1950, 1690, 1605, 1590, 1520, 1475, 1410, 1390, 1360, 1270, 1240, 1210, 1180, 1170, 1090, 1040, 1020, 1000, 970, and 800 cm^{-1}	
^1H NMR (300 MHz, $CDCl_3$):	8.51 (d, *J*=8.5 Hz, 1H), 8.13 (d, *J*=8.4 Hz, 1H), 7.83 (d, *J*=8.3 Hz, 1H), 7.48 (t, J=8.4 Hz, 1H), 7.45 (t, *J*=8.4 Hz, 1H), 7.33 (d, *J*=7.1 Hz, 1H), 2.70 (s, 3H), and 2.66 s, 3H)	
^{13}C NMR (75 MHz, $CDCl_3$):	202.7, 136.6, 134.6, 133.2, 130.2, 128.7, 127.7, 127.6, 127.3, 124.2, 30.0, and 19.5 (one carbon overlapping with another peak)	
UV max (CCl_4)	287 (ε = 2 300) nm	
Elemental Analysis:	Calcd for $C_{13}H_{12}O$:	C, 84.75; H, 6.57
	Found:	C, 84.48; H, 6.59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4.0
5.0
6.0
7.0
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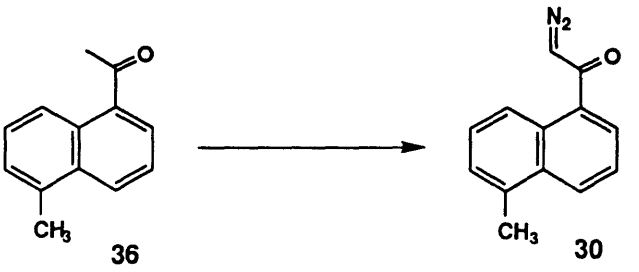
9.0
10.0

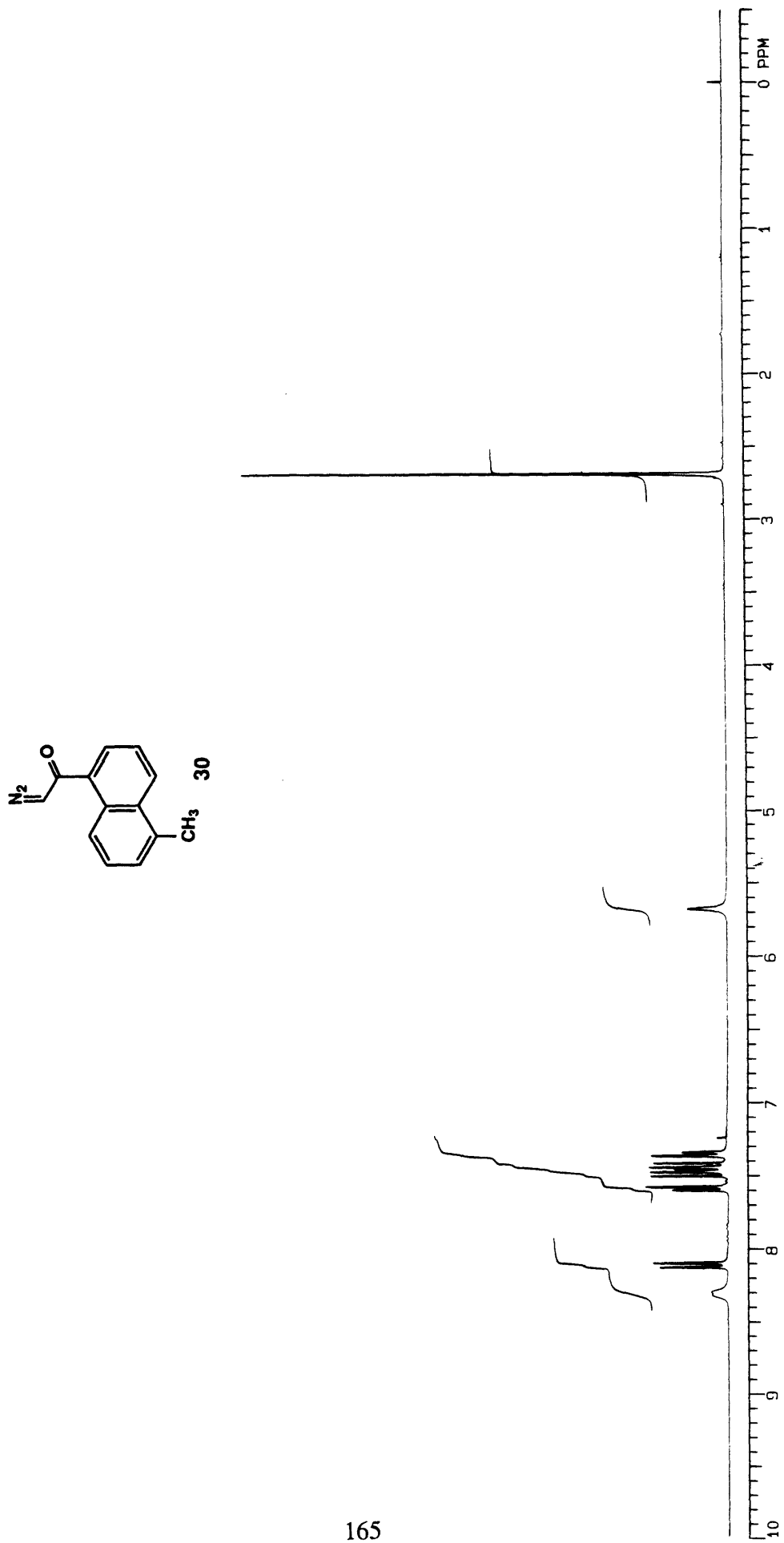


2-Diazo-1-(5-methyl-1-naphthoyl)-ethanone (30).

A 500-mL, three-necked, round-bottomed flask equipped with an argon inlet adapter, a glass stopper, and a magnetic stir bar was charged with a solution of 1,1,1,3,3,3-hexamethyldisilazane (2.60 g, 3.40 mL, 16.1 mmol) in 75 mL of tetrahydrofuran and cooled at 0 °C while *n*-butyllithium solution (2.70 M in hexane, 5.40 mL, 14.7 mmol) was added dropwise over 3 min. The resultant solution of LiHMDS was stirred at 0 °C for 10 min, then cooled at -78 °C while a solution of 1-(5-methyl-1-naphthoyl)-ethanone **36** (2.47 g, 13.4 mmol) in 25 mL of tetrahydrofuran was transferred dropwise via cannula over ca. 5 min. The enolate solution was stirred at -78 °C for 30 min and then 2,2,2-trifluoroethyl trifluoroacetate (3.22 g, 2.20 mL, 16.1 mmol) was added rapidly in one portion. The reaction mixture was stirred at -78 °C for 10 min and then partitioned between 100 mL of 5% HCl solution and 100 mL of diethyl ether. The organic phase was separated and washed with 100 mL of saturated NaCl, dried over Na_2SO_4, filtered, and concentrated to afford a yellow oil. The oil was dissolved immediately in 45 mL of acetonitrile and a rubber septum was fitted to the flask. Water (0.240 g, 0.240 mL, 13.4 mmol), triethylamine (2.03 g, 2.80 mL, 20.1 mmol), and methanesulfonyl azide (2.43 g, 2.30 mL, 20.1 mmol) were added and the resultant yellow solution was stirred at 25 °C for 7.5 h. The solution was poured into a separatory funnel containing 100 mL of diethyl ether. The organic layer was separated and washed with three 75 mL portions of 10% NaOH solution, 75 mL of water, 75 mL of saturated NaCl solution, dried over

Na_2SO_4, filtered, and concentrated to afford 2.60 g of a yellow solid. Column chromatography on 20 g of silica gel (gradient elution with 0-10% EtOAc-hexane) provided 2.36 g (84%) of the α-diazo ketone **30** as a bright yellow solid: mp 84-85 °C.

IR (CCl_4):	3040, 2950, 2100, 1615, 1600, 1540, 1510, 1460, 1330, 1230, 1155, and 1185 cm^{-1}
^1H NMR (300 MHz, $CDCl_3$):	8.30 (br m, 1H), 8.11 (d, *J*=8.4 Hz, 1H), 7.58 (d, *J*=7.1, 1H), 7.47 (t, *J*=7.8 Hz, 1H), 7.44 (t, *J*=7.8 Hz, 1H), 7.35 (d, *J*=6.9 Hz, 1H), 5.68 (s, 1H), and 2.69 (s, 3H)
^{13}C NMR (75 MHz, $CDCl_3$):	190.0, 136.3, 134.5, 133.0, 129.9, 127.7, 127.3, 127.1, 125.3, 124.3, 123.6, 57.2, and 19.7
UV max (CCl_4):	260 (ε = 10 500), and 303 (8 100) nm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1
2
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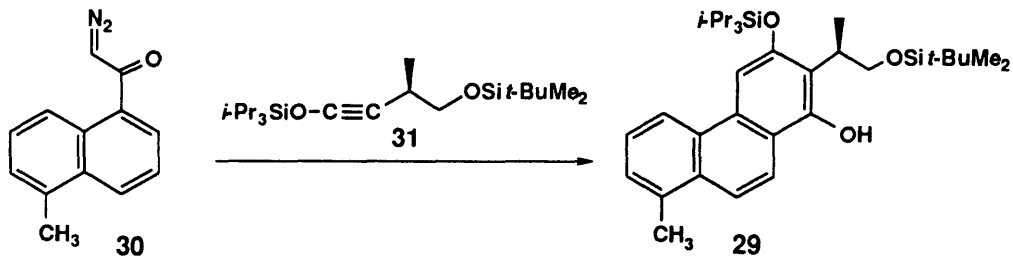
4
5
6
7
8
9
10

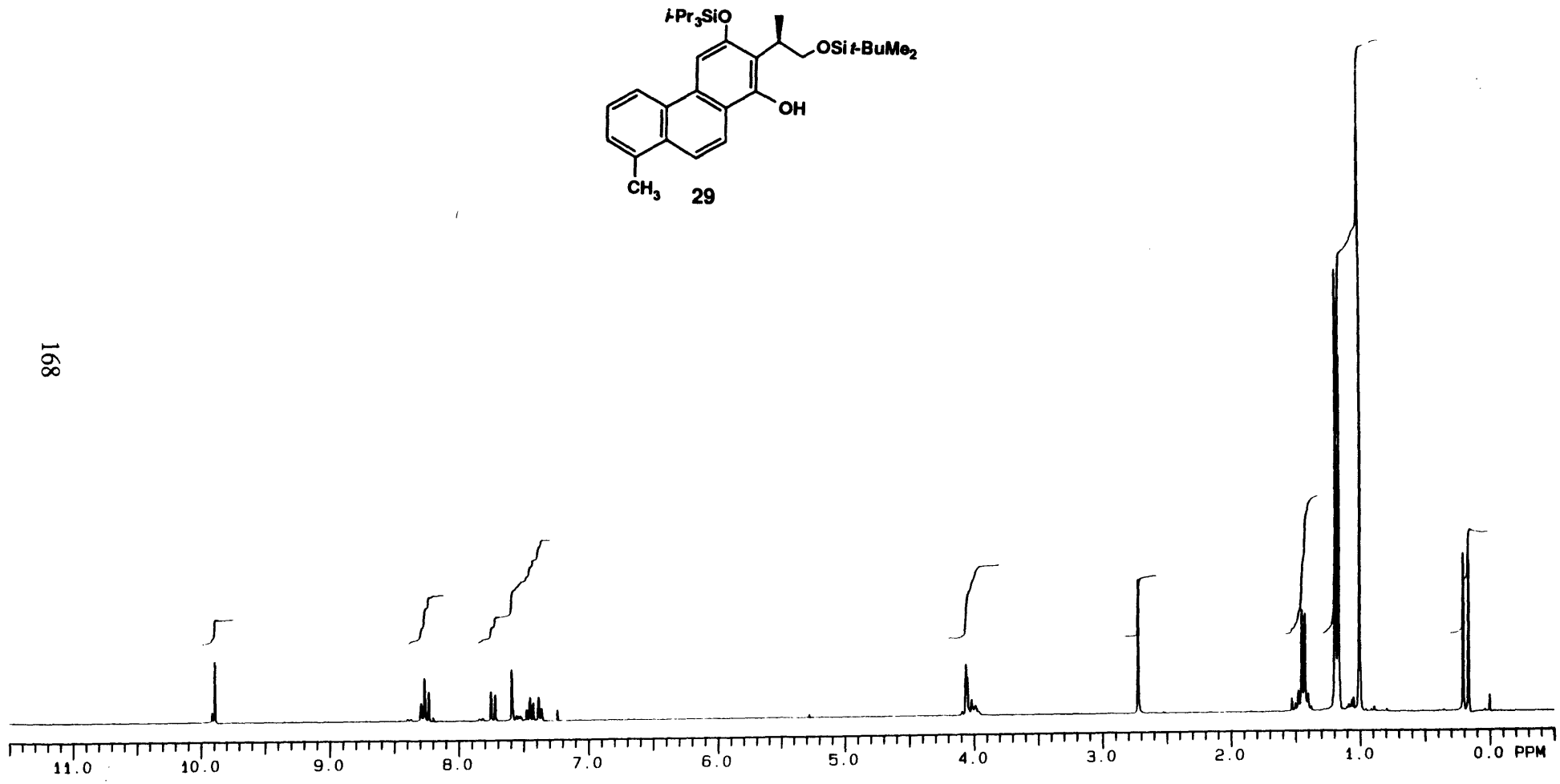


4-Hydroxy-3-((S)-1-*tert*-butyldimethylsilyloxy-2-propyl)-7-methyl-2-triisopropylsilyloxy-phenanthrene (29).

A 30 cm vycor tube (9 mm O.D., 7 mm I.D.) was charged with a solution of the α-diazo ketone **30** (0.147 g, 0.699 mmol) and silyloxyacetylene **31** (0.365 g, 0.985 mmol) in 2 mL of 1,2-dichloroethane. The tube was fitted with a rubber septum and a second rubber septum (inverted) was secured with wire to the tube to insure a good seal. The reaction mixture was degassed (three freeze-thaw cycles at -196 °C, ≤ 0.5 mm Hg) and then irradiated with 253.7 nm light for 8 h in a Rayonet reactor. The resulting solution was diluted with 1 mL of additional 1,2-dichloroethane and then heated for 8-12 h in a 90 °C oil bath. Concentration afforded 0.58 g of an orange-brown oil. Column chromatography on 15 g of silica gel (gradient elution with 0-1% EtOAc-hexane) provided 0.27 g (70%) of **29** as a yellow oil $[\alpha]_D$ 28.3° (*c* = 0.12, $CHCl_3$).

IR (thin film):	3200, 2960, 2890, 1930, 1825, 1725, 1635, 1610, 1590, 1530, 1505, 1475, 1380, 1335, 1300, and 1285 cm^{-1}
^1H NMR (300 MHz, $CDCl_3$):	9.89, (s, 1H), 8.28 (d, *J*=8.5 Hz, 1H), 8.24 (d, *J*=9.4 Hz, 1H), 7.74 (d, *J*=9.4 Hz, 1H), 7.59 (s, 1H), 7.43 (t, *J*=7.8 Hz, 1H), 7.38 (d, *J*=7.0 Hz, 1H), 3.92-4.06 (m, 3H), 2.73 (s, 3H), 1.40-1.48 (m, 3H), 1.17 (d, *J*=7.3 Hz, 18 H), 1.00 (s, 9H), 0.21 (s, 3H), and 0.17 (s, 3H)
^{13}C NMR (75 Mz, $CDCl_3$):	153.6, 153.2, 134.8, 131.6, 131.0, 129.5, 127.4, 125.4, 121.5, 121.0, 119.0, 118.9, 118.8, 101.8,

	69.0, 31.6, 25.6, 19.7, 18.2, 18.0, 14.9, 12.9, -5.9, and 6.0	
UV max (CCl_4):	266 (ε = 15 800) and 311 (5 000) nm	
HRMS:	For $C_{33}H_{52}O_3Si_2$:	Calcd: 552.3455 Found: 552.3432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3.0
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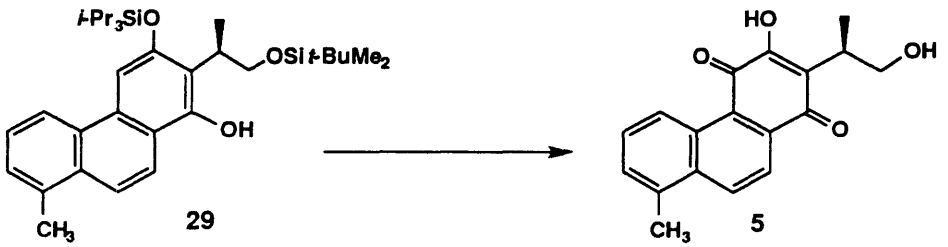
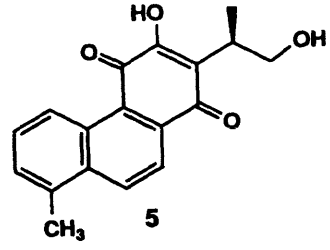


3-Hydroxy-2-((R)-1-hydroxy-2-propyl)-8-methyl-1,4-phenanthren-quinone (5, (+) danshexinkin A).

A 250-mL, round-bottomed flask fitted with a rubber septum was charged with a solution of the phenol **29** (0.890 g, 1.61 mmol) in 50 mL of dichloromethane and cooled at 0 °C while a stream of oxygen was bubbled through the mixture via a syringe needle and tetra-*n*-butylammonium fluoride solution (1.0 M in tetrahydrofuran, 3.20 mL, 3.20 mmol) was added dropwise over 2 min. The cooling bath was removed and the reaction mixture was allowed to warm to 25 °C and stir under a stream of oxygen for 18 h. The reaction mixture was partitioned between 150 mL of 5% HCl solution and 150 mL of dichloromethane and the aqueous phase was separated and extracted with two 100 mL portions of dichloromethane. The combined organic phases were washed with 100 mL of 5% HCl solution, 100 mL of water, 100 mL of saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford 1.43 g of an orange solid. Low temperature (-78 °C) recrystallization from diethyl ether afforded 0.22 g (47%) of (+)-danshexinkun A (**5**) as orange crystals: mp 200-201 °C (lit 200 °C),[9a] $[\alpha]_D$ =30.0 ° (*c* =0.01, $CHCl_3$)

IR (CCl_4):	3340, 3040, 2980, 1660, 1630, 1595, 1580, 1470, 1400, 1375, 1320, and 1220 cm^{-1}
^1H NMR (300 MHz, $CDCl_3$):	9.43 (d, *J*=8.8 Hz, 1H), 8.43 (d, *J*=8.8 Hz, 1H), 8.27 (d, *J*=8.8 Hz, 1H), 8.05 (br s, 1H), 7.64 (dd, *J*=7.0, 8.7 Hz, 1H), 7.48 (d, *J*=7.0 Hz, 1H), 4.01 (dd, *J*=7.8, 10.9 Hz, 1H), 3.87 (dd, *J*=5.3, 10.9 Hz, 1H), 3.50-3.52 (m, 1H), 2.74 (s, 3H), and 1.34 (d, *J*=2.4 Hz, 3H)

^{13}C NMR (75 MHz, DMSO-d_6):	185.2, 184.3, 156.8, 135.5, 134.7, 133.0, 131.9, 130.2, 129.7, 129.4, 125.1, 124.8, 122.2, 122.0, 63.7, 32.7, 19.3 and 14.6
UV max (MeOH):	288 (ε = 24 000), 330 (6 900), and 375 (4 000) nm
Elemental Analysis:	Calcd for $C_{18}H_{16}O_4$: C, 72.96; H, 5.44 Found: C, 73.25; H, 5.37



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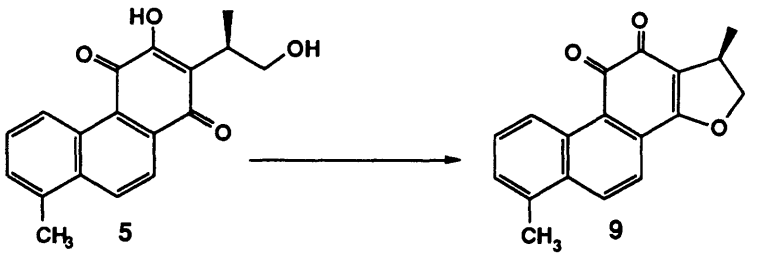
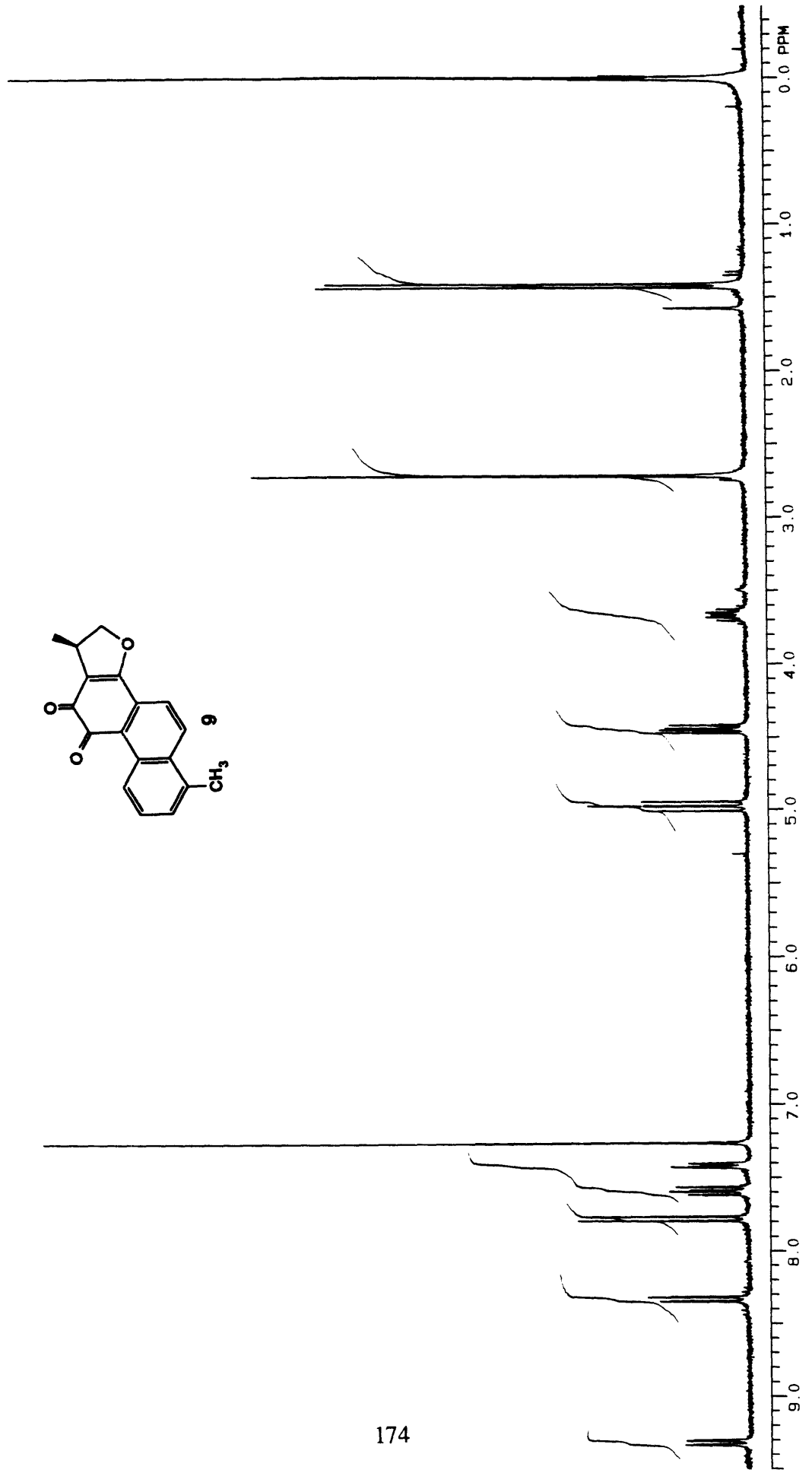


3,4-Dihydro-3-(R)-methyl-[3,2-c]-furo-8-methylphenanthra-1,2-dione (9, dihydrotanshinone-I).

A 100-mL, round-bottomed flask was charged with a heterogeneous solution of danshexinkun A (0.921 g, 3.11 mmol) in 40 mL of ethanol. To this solution was added 12 ml of concentrated H_2SO_4 over 5 min (CAUTION! EXOTHERMIC REACTION!) and the resultant deep red mixture was stirred at 25 °C for 30 min. The reaction mixture was poured into 200 mL of water and extracted with three 200 mL portions of diethyl ether. The combined organic phases were washed with two 200 mL portions of 10% HCl solution, 100 mL of saturated $NaHCO_3$ solution, dried over $MgSO_4$, filtered, and concentrated to afford 0.79 g of a red solid. Column chromatography on 30 g of silica gel (elution with $CHCl_3$) afforded 0.55 g (65%) of (-)-dihydrotanshinone I (**9**) as a red solid: mp 221-222 °C (lit 224-225 °C);[11] $[\alpha]_D$ -300° (*c* = 0.01, $CHCl_3$,) (lit. $[\alpha]_D$ -328° (*c* = 0.11, $CHCl_3$))[11]

IR (CCl_4):	3050, 2990, 1655, 1630, 1590, 1540, 1510, 1470, 1420, 1400, 1370, 1350, 1330, 1300, 1260, 1190, 1170, 1150, 1020, 995, 955, 930, and 895 cm^{-1}
^1H NMR (300 MHz, $CDCl_3$):	9.32 (d, *J*=8.8 Hz, 1H), 8.33 (d, *J*=8.9 Hz, 1H), 7.79 (d, *J*=8.4 Hz, 1H), 7.59 (dd, *J*=7.0, 8.8 Hz, 1H), 7.42 (d, *J*=7.1 Hz, 1H), 4.98 (app t, *J*=9.6 Hz, 1H), 4.44 (dd, *J*=5.9, 9.4 Hz, 1H), 3.61 (ddq, *J*=6.6, 9.9, 7.0 Hz, 1H), 2.72 (s, 3H), and 1.42 (d, *J*=7.1 Hz, 3H)

^{13}C NMR (75 MHz, $CDCl_3$):	184.3, 175.7, 170.6, 134.9, 134.8, 132.0, 130.4, 128.8, 128.2, 126.1, 125.0, 120.3, 118.4, 81.6, 53.4, 34.7, 19.9, and 18.8
UV max (MeOH):	218 (ε = 19 500), 262 (28 800), 270 (22 900), 290 (7 100), and 353 (2 800) nm
Elemental Analysis:	Calcd for $C_{18}H_{14}O_3$: C, 77.00; H, 6.80 Found: C, 77.21; H, 6.78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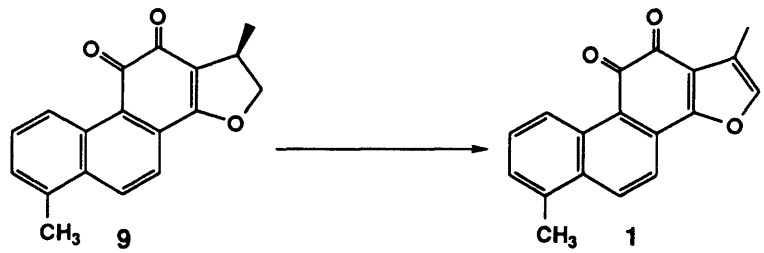
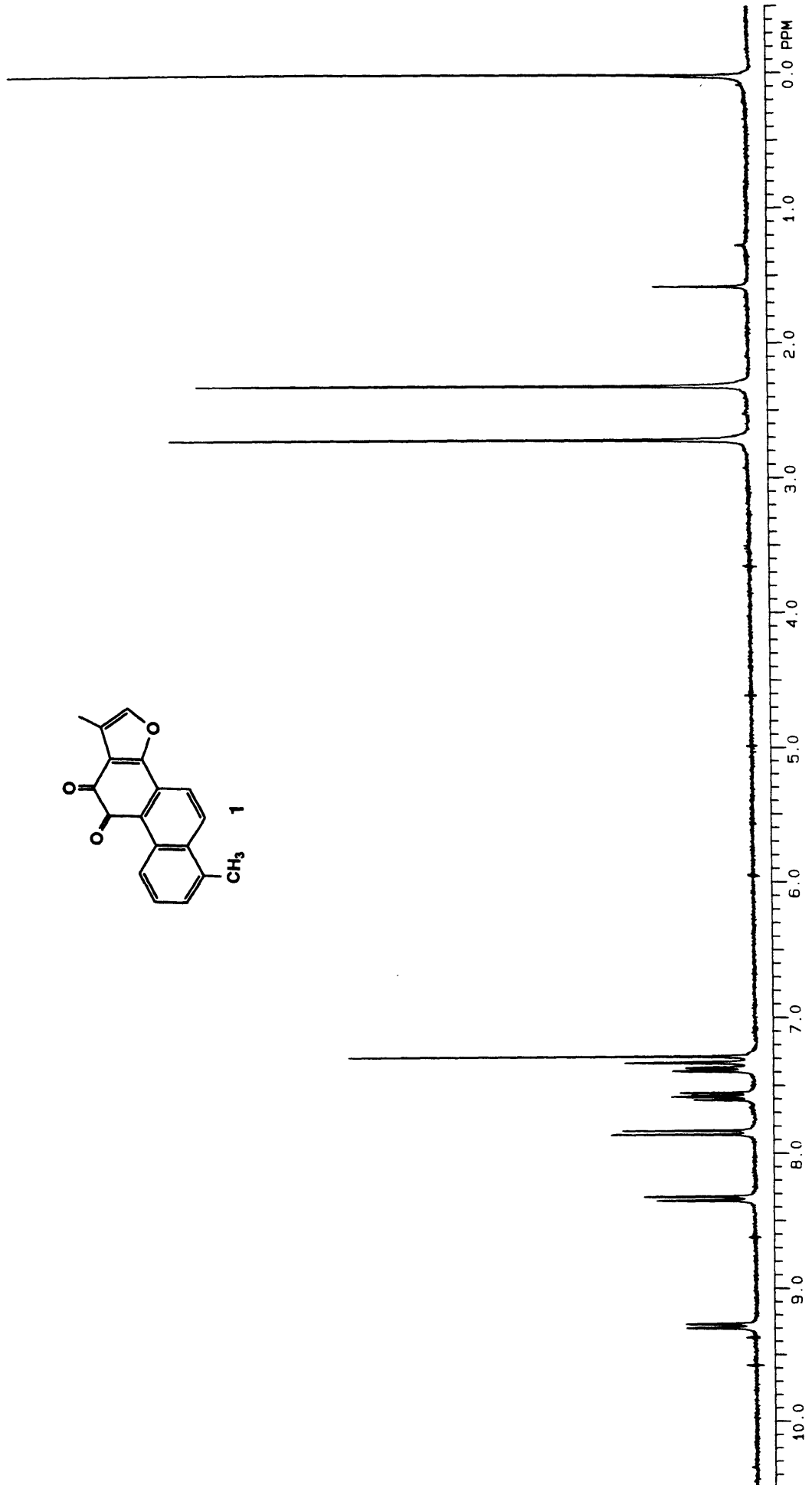
8.0
9.0

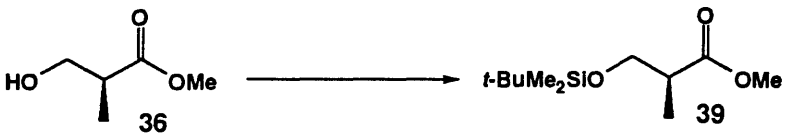


3,8-Dimethyl-[3,2-c]-furophenanthra-1,2-dione (1, tanshinone-I).

A 100-mL, three-necked, round-bottomed flask equipped with an argon inlet, glass stopper and rubber septum was charged with a solution of dihydrotanshinone-I (**9**, 0.426 g, 1.53 mmol) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ, 0.700 g, 3.08 mmol) in 40 mL of benzene. The reaction mixture was stirred at 25 °C for 75 h. An additional portion of DDQ (0.073 g, 0.319 mmol) was added and the reaction mixture was stirred for 20 h, filtered, and concentrated. Column chromatography on 12 g of silica gel (elution with 30% $CHCl_3$-benzene) afforded 0.21 g (48%) of tanshinone-I (**1**) as dark red needles: mp 226-227 °C (lit 233-234 °C).[11]

IR (KBr):	3100, 2950, 2900, 1650, 1580, 1535, 1490, 1420, 1390, 1370, 1320, 1260, 1170, and 1150 cm^{-1}
^1H NMR (300 MHz, $CDCl_3$):	9.22 (d, *J*=8.5 Hz, 1H), 8.27 (d, *J*=8.8 Hz, 1H), 7.78 (d, *J*=8.9 Hz, 1H), 7.52 (dd, *J*=6.9, 8.8 Hz, 1H), 7.32 (d, *J*=7.0 Hz, 1H), 7.22 (s, 1H), 2.66 (s, 3H), and 2.25 (s, 3H)
^{13}C NMR (75 MHz, $CDCl_3$):	183.4, 175.5, 161.1, 142.0, 135.2, 133.6, 132.8, 130.6, 129.5, 128.3, 124.7, 123.0, 122.0, 121.7, 120.4, 118.7, 19.8, and 8.8
UV max (CCl4):	266 (ε = 15 800) and 311 (5 000) nm
HRMS:	For $C_{33}H_{52}O_3Si_2$: Calcd: 552.3455 Found: 552.3452

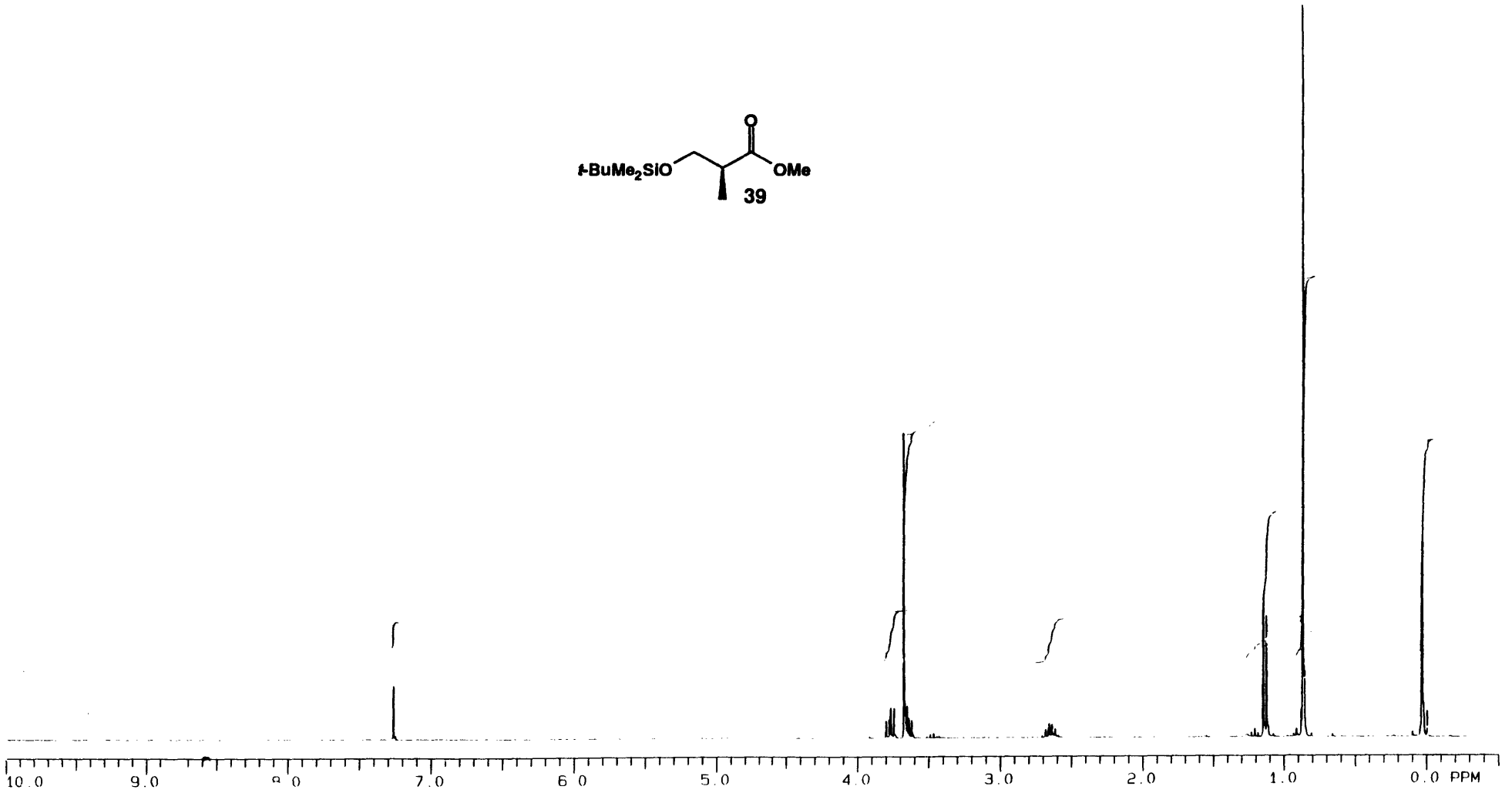

O
O
O
CH3
1
0.0 PPM
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
9.0
10.0

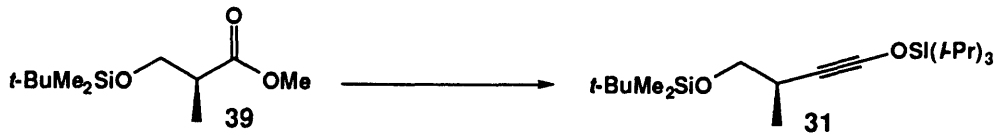


(S)-(+)-Methyl-3-*tert*-butyldimethylsilyloxy-2-methylpropionate (39).

A 100-mL, three-necked, round-bottomed flask equipped with an argon inlet adapter, a glass stopper and a rubber septum was charged with a solution of (S)-(+)-methyl-3-hydroxy-2-methylpropionate **36** (2.57 g, 2.40 mL, 21.5 mmol) in 50 mL of dichloroethane and cooled at 0 °C in an ice bath while imidazole (total: 3.50 g, 51.6 mmol) and *tert*-butyldimethylsilyl chloride (total: 3.90 g, 25.8 mmol) were added alternately in small portions over ca. 15 min. The reaction mixture was stirred for 12 h allowing the ice bath to warm to room temperature, and poured into 60 mL of saturated NaCl solution and extracted with two 100 mL portions of diethyl ether. The combined organic phases were washed with three 100 mL portions of water and one time with 100 mL of saturated NaCl solution, dried over Na_2SO_4, filtered, and concentrated to afford a clear liquid. Filtration through silica gel (elution with 5% EtOAc-hexane) and concentration afforded 5.03 g (100%) of the silyloxyester **39** as a colorless liquid.[30c] $[\alpha]_D$=+15.5 ° (*c*=1.25, $CHCl_3$)

IR (thin film):	2975, 2945, 2880, 1750, 1470, 1440, 1400, 1370, 1265, 1200, 1180, 1100, 1030, 1010, 995, 950, 840, and 790 cm^{-1}
^1H NMR (300 MHz, $CDCl_3$):	3.73 (dd, *J*=6.4, 10.1 Hz, 1H), 3.62 (s, 3H), 3.57-3.62 (m, 1H), 2.60 (app q, *J*=7.0 Hz, 1H), 1.08 (d, *J*=6.1 Hz, 3H), 0.82 (s, 9H), and 0.01 (s, 6H)
^{13}C NMR (75 MHz, $CDCl_3$):	175.7, 65.2, 51.3, 42.4, 25.5, 17.9, 13.2, and -5.9


t-BuMe2SiO
OMe
39
10.0
9.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0 PPM



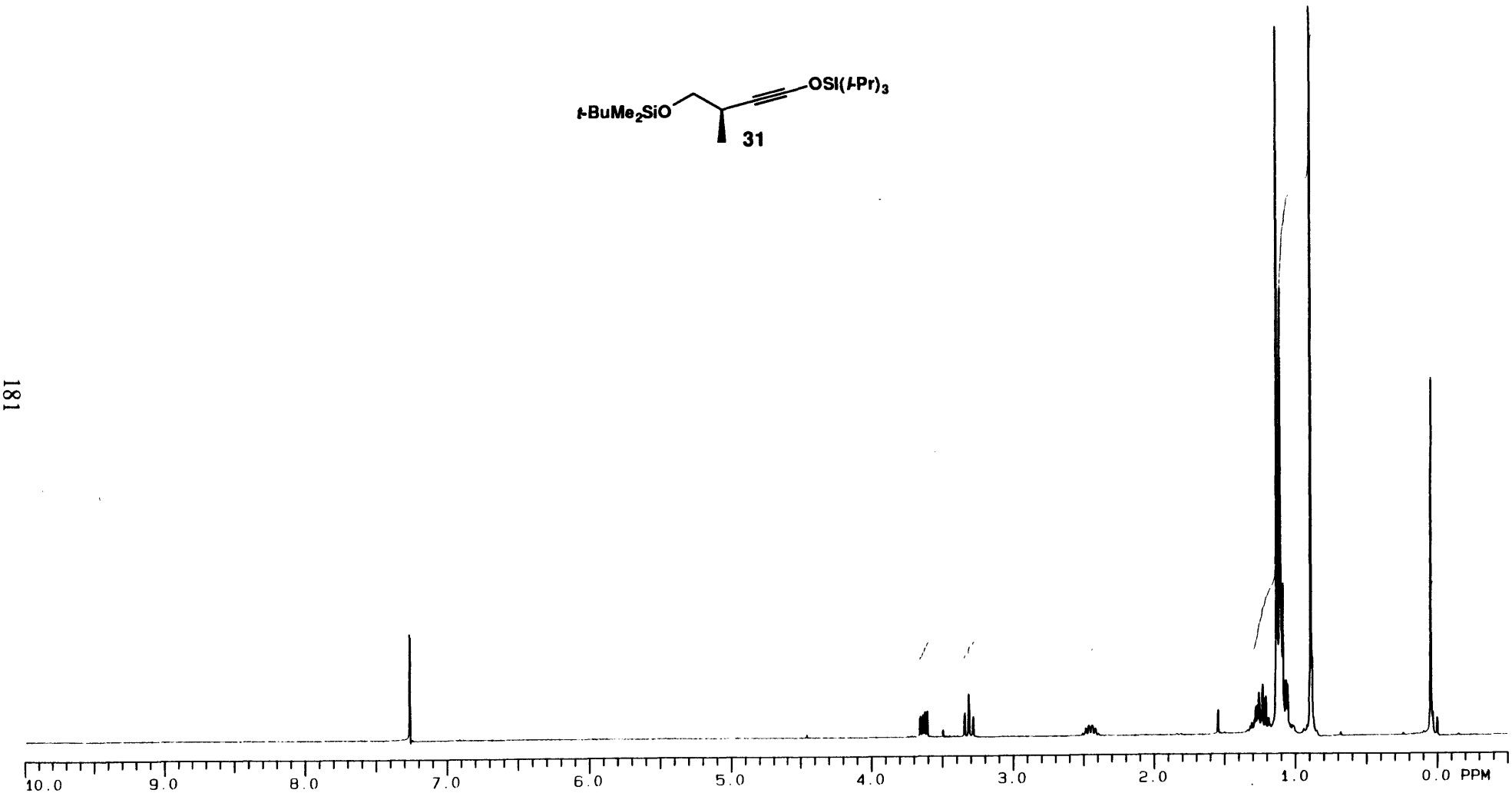
2-((R)-1-*tert*-Butyldimethylsilyloxy-2-propyl)-1-triisopropylsilyloxy-acetylene (31).

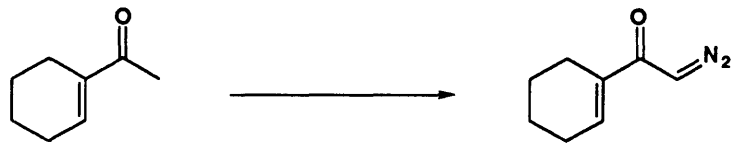
A 500-mL, three-necked, round-bottomed flask equipped with an argon inlet adapter, a rubber septum, and a glass stopper was charged with a solution of dibromomethane (5.70 g, 2.30 mL, 33.1 mmol) in 40 mL of tetrahydrofuran and cooled at -78 °C in a dry ice-acetone bath.

A 100-mL, three-necked round-bottomed flask equipped with an argon inlet adapter, a rubber septum and a glass stopper was charged with a solution of 2,2,6,6-tetramethylpiperidine (5.36 g, 6.40 mL, 37.7 mmol) in 40 mL of tetrahydrofuran and cooled at 0 °C, while *n*-butyllithium solution (2.70 M in hexane, 13.2 mL, 35.6 mmol) was added dropwise over ca. 5 min. The LiTMP solution was stirred at 0 °C for 15 min, then cooled at -78 °C and transferred dropwise via cannula into the bromide solution over ca. 10 min and the resulting yellow solution was stirred at -78 °C for 15 min. A precooled (-78 °C) solution of the silylester **39** (3.52 g, 15.1 mmol) in 40 mL of tetrahydrofuran was added dropwise via cannula over 15 min, and the solution was then stirred for 15 min at -78 °C. *n*-Butyllithium solution (2.70 M in hexane, 27.3 mL, 73.8 mmol) was added over 5 min, the cooling bath was removed, and the reaction mixture was allowed to stir at 25 °C for 45 min. The solution was cooled at -78 °C while a solution of triisopropylsilyl chloride (14.8 g, 16.4 mL, 76.8 mmol) in 40 mL of tetrahydrofuran was added via cannula over ca. 10 min. The dry ice-acetone bath was replaced with an ice bath and the reaction mixture was stirred at 0 °C for 5 h. The reaction mixture was partitioned between 100 mL of pentane and 100 mL of saturated $NaHCO_3$ solution, and the aqueous layer was separated and extracted with 100 mL of pentane. The combined organic phases were washed with

200 mL of water, 200 mL of saturated NaCl solution, dried over Na_2SO_4, filtered, and concentrated initially at 20 mm Hg, then at ≤0.005 mm Hg for 48 h to afford an orange oil. The crude product was divided into three equal portions and column chromatography on silica gel (elution with hexane) afforded 1.09 g (20%) of the silyloxyacetylene **31** as a colorless oil.

IR (thin film):	2960, 2880, 2990, 1460, 1385, 1365, 1305, and 1250 cm^{-1}
^1H NMR (300 MHz, $CDCl_3$):	3.62 (dd, *J*=5.2, 10.0 Hz, 1H), 3.31 (app t, *J*=9.0 Hz, 1H), 2.40-2.52 (m, 1H), 1.18-1.28 (m, 3H), 1.11 (d, *J*=6.7 Hz, 18 H), 1.05 (d, *J*=10.3 Hz, 3H), 0.89 (s, 9H), and 0.04 (s, 6H)
^{13}C NMR (75 MHz, $CDCl_3$):	88.0, 68.4, 32.5, 27.7, 25.7, 18.5, 18.1, 17.1, 11.6, and -5.7
HRMS:	Calcd for $C_{16}H_{33}O_2Si_2$ (M^+-C_4H_9): 313.2017 Found: 313.2019


t-BuMe2SiO
OSi(i-Pr)3
31
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0 PPM

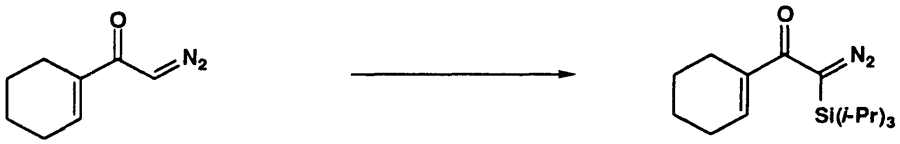


131 133

General Procedure for Diazo Transfer. 1-Diazo-2-(1-cyclohexenyl)-2-ethanone (133).

A 50-mL, three-necked, round-bottomed flask equipped with a rubber septum, argon inlet adapter, and a glass stopper was charged with a solution of 1,1,1,3,3,3,-hexamethyldisilazane (1.0 mL, 0.781 g, 4.84 mmol) in 10 ml of THF and then cooled at 0 °C in an ice-water bath while *n*-butyllithium solution (2.70 M in hexane, 1.6 mL, 4.43 mmol) was added rapidly dropwise over 2 min. After 10 min, the resulting solution was cooled at -78 °C in a dry ice-acetone bath while a solution of 1-acetyl-1-cyclohexene (0.52 mL, 0.500 g, 4.03 mmol) in 8 mL of THF was added dropwise over 5 min (the flask was rinsed with 1 mL of additional THF). The reaction mixture was stirred at -78 °C for 30 min, and then 2,2,2-trifluoroethyl trifluoroacetate (0.65 mL, 0.949 g, 4.84 mmol) was added rapidly (1 s) by syringe in one portion. After 10 min, the reaction was poured into a separatory funnel containing 20 mL of 5% aqueous HCl solution and 25 mL of Et_2O. The aqueous phase was extracted with two 15 ml portions of Et_2O, and the combined organic phases were then washed with 20 mL of saturated NaCl solution, dried over Na_2SO_4, and concentrated at reduced pressure to give 1.90 g of a yellow oil which was immediately dissolved in 15 mL of CH_3CN and transferred to a 50-mL, three-necked, round-bottomed flask equipped with a rubber septum, argon inlet adapter and a glass stopper. Water, (0.073 mL, 0.073 g, 4.03 mmol), Et_3N (0.84 mL, 0.612 g, 6.05 mmol), and methanesulfonyl azide (0.70 mL, 0.733 g, 6.05 mmol) were added rapidly dropwise in that order. The resulting solution was stirred at room temperature for 3 h and then diluted with 50 mL of Et_2O and washed with three 15-mL portions of 10% aqueous NaOH solution,

three 15-mL portions of H_2O, and 20 mL of saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford 0.51 g of a yellow oil. Column chromatography on 10 g of silica gel (elution with 10% EtOAc-hexane) provided 0.48 g (80 %) of the diazo ketone **133** as a yellow solid, mp 28-28.5 °C, with spectral characteristics identical with those reported previously.[29]

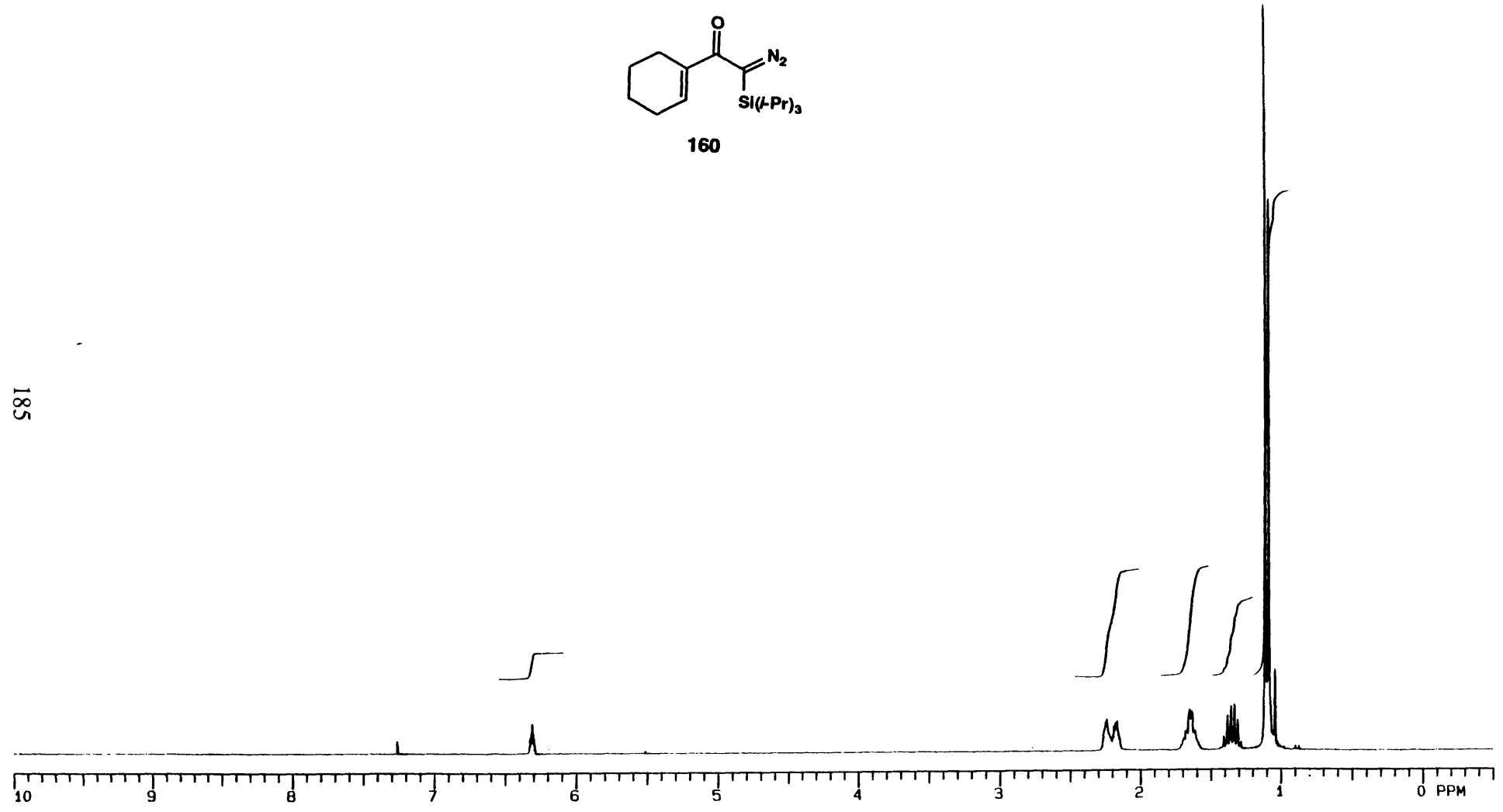


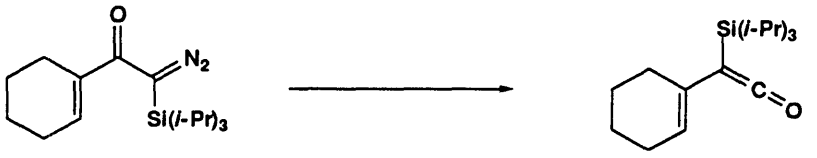
133 160

1-Diazo-2-(1-cyclohexenyl)-1-triisopropylsilyl-2-ethenone (160).

A 50-mL, three-necked, round-bottomed flask equipped with a rubber septum, magnetic stir bar, and argon inlet adapter was charged with diazo ketone **133** (0.403 g, 2.69 mmol) in 20 mL of a 50:50 solution of Et_2O-hexane and then cooled at 0 °C in an ice-water bath while *i*-Pr_2EtN (0.47 mL, 0.349 g, 2.70 mmol) was added dropwise over 1 min. Triisopropylsilyl trifluoromethanesulfonate (0.72 mL, 0.820 g, 2.69 mmol) was then added dropwise over 1 min and the resulting solution was stirred for 4 h while the ice-water bath warmed to room temperature. The reaction mixture was filtered through Celite with the aid of 5 mL of Et_2O and the filtrate was concentrated to afford a yellow oil. Column chromatography on 10 g of silica gel (gradient elution with 0-2% EtOAc-hexane) provided 0.62 g (75%) of the silyldiazo ketone **160** as a yellow oil.

IR (film):	2930, 2870, 2240, 2060, 1595, 1460, and 1365 cm^{-1}
^1H NMR (300 MHz, $CDCl_3$):	6.32 (m, 1H), 2.25-2.26 (m, 2H), 2.18-2.20 (m, 2H), 1.64-1.67 (m, 4H), 1.35 (sept, *J* = 7.1 Hz, 3H), and 1.11 (d, J = 7.3 Hz, 18H)
^{13}C NMR (75 MHz, $CDCl_3$):	196.0, 138.0, 132.5, 49.7, 25.1, 24.7, 22.0, 21.7, 18.5, and 11.5
UV max (hexane):	292 (ε = 2700) and 220 (8400) nm
HRMS:	Calcd for $C_{17}H_{30}ON_2Si$: 306.2127 Found: 306.2129


O
N2
Si(i-Pr)3
160
10
9
8
7
6
5
4
3
2
1
0 PPM

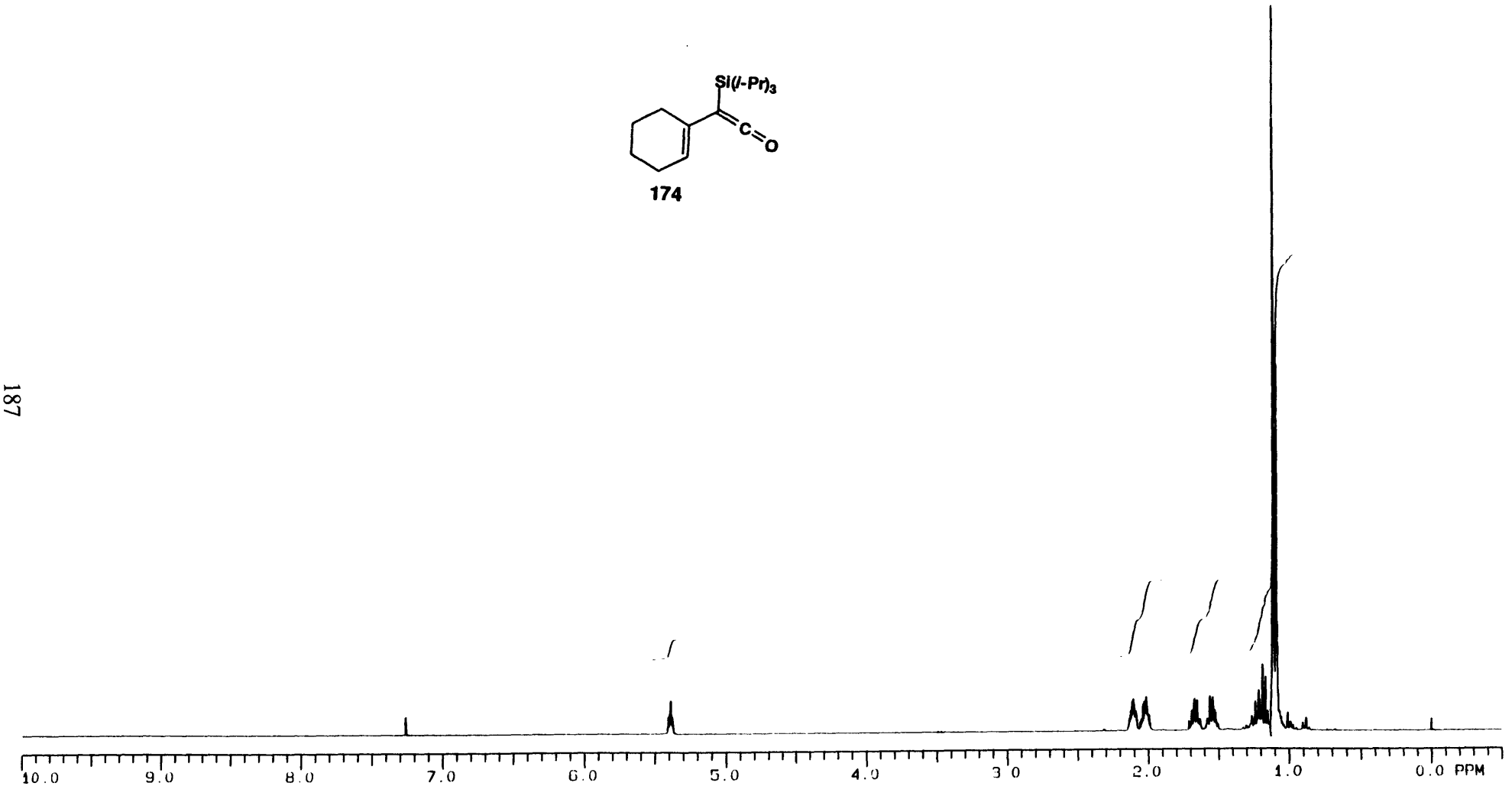


160 174

2-(1-Cyclohexenyl)-2-triisopropylsilylketene (174).

A solution of silyldiazo ketone **160** (1.16 g, 3.78 mmol) in 38 mL of benzene was distributed evenly between two 25-cm vycor tubes (15 mm O.D., 13 mm I.D.) fitted with rubber septa. A second rubber septum (inverted) was secured with wire to each tube to insure a good seal, and each solution was degassed (three freeze-pump-thaw cycles at -196 °C, < 0.5 mm Hg) and then irradiated with 300 nm light for 4 h in a Rayonet reactor. The resulting solutions were combined and concentrated to afford 2.20 g of an orange-brown oil. Column chromatography on 15 g of silica gel (elution with hexane) provided 0.94 g (89%) of ketene **174** as a viscous yellow oil.

IR (thin film):	2936, 2866, 2076, 1676, 1641, and 1461 cm^{-1}	
^1H NMR (300 MHz, $CDCl_3$):	5.40 (t, J = 3.0 Hz, 1H), 2.09-2.12 (m, 2H), 2.01-2.03 (m, 2H), 1.66-1.69 (m, 2H), 1.53-1.56 (m, 2H), 1.15-1.23 (m, 3H), and 1.11 (d, J = 6.5 Hz, 18 H)	
^{13}C NMR (75 MHz, $CDCl_3$):	184.5, 125.9, 122.2, 31.6, 26.1, 23.4, 22.1, 21.2, 18.6, and 12.6	
UV max (hexane):	231 nm (ε = 9200)	
HRMS:	Calcd for $C_{17}H_{30}OSi$:	278.2066
	Found:	278.2067



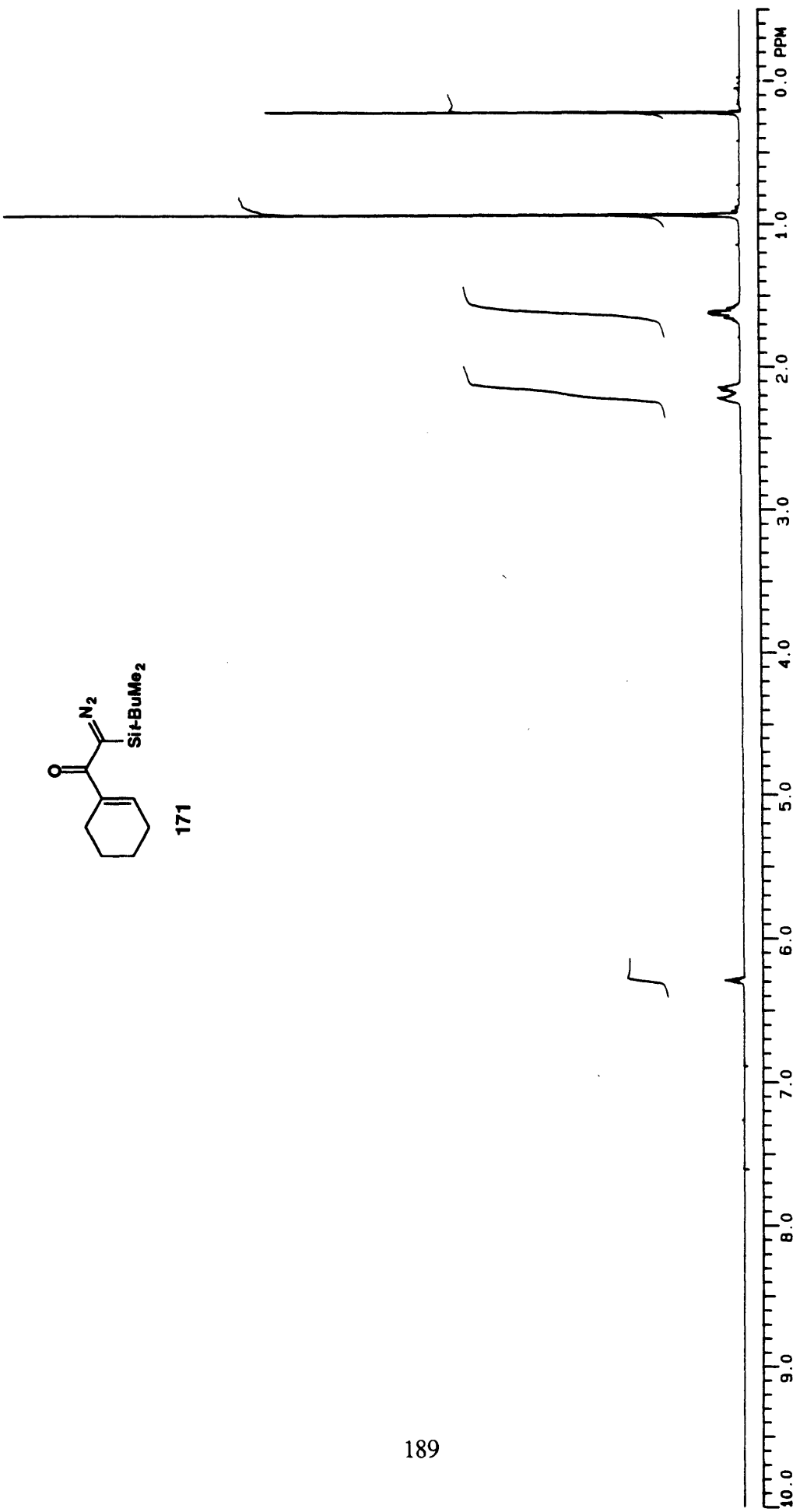
174

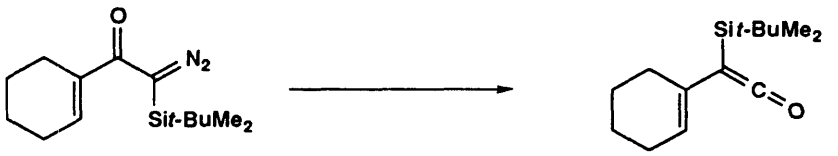
133 171

1-Diazo-2-(1-cyclohexenyl)-1-(*tert*-butylsilyl)-2-ethenone (171).

A 25-mL, two-necked, round-bottomed flask equipped with a rubber septum, magnetic stir bar, and argon inlet adapter was charged with diazo ketone **133** (0.139 g, 0.930 mmol) in 4 mL of a 50:50 solution of Et_2O-hexane and then cooled at 0 °C in an ice-water bath while *i*-Pr_2EtN (0.16 mL, 0.120 g, 0.930 mmol) was added dropwise over 1 min. *Tert*-butyldimethylsilyl trifluoromethanesulfonate (0.21 mL, 0.242 g, 0.914 mmol) was added dropwise over 1 min and the resulting solution was stirred for 2 h while the ice-water bath was allowed to warm to room temperature. The reaction mixture was filtered through Celite with the aid of 5 mL of Et_2O and the filtrate was concentrated to afford 0.25 g of an orange oil. Column chromatography on 10 g of silica gel (gradient elution with 5-10% EtOAc-hexane) provided 0.13 g (53%) of the silyldiazo ketone **171** as a yellow oil.

IR (thin film):	2935, 2867, 1704, 1675, 1578, 1550, 1249, 1221, 1119 and 1005 cm^{-1}
^1H NMR (300 MHz, $CDCl_3$):	6.25-6.32 (m, 1H), 2.20-2.26 (m, 2H), 2.10-2.18 (m, 2H), 1.58-1.65 (m, 4H), 0.94 (s, 9H), and 0.22 (s, 6H)


N2
Si-t-BuMe2
O
171
0.0 PPM
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
9.0
10.0

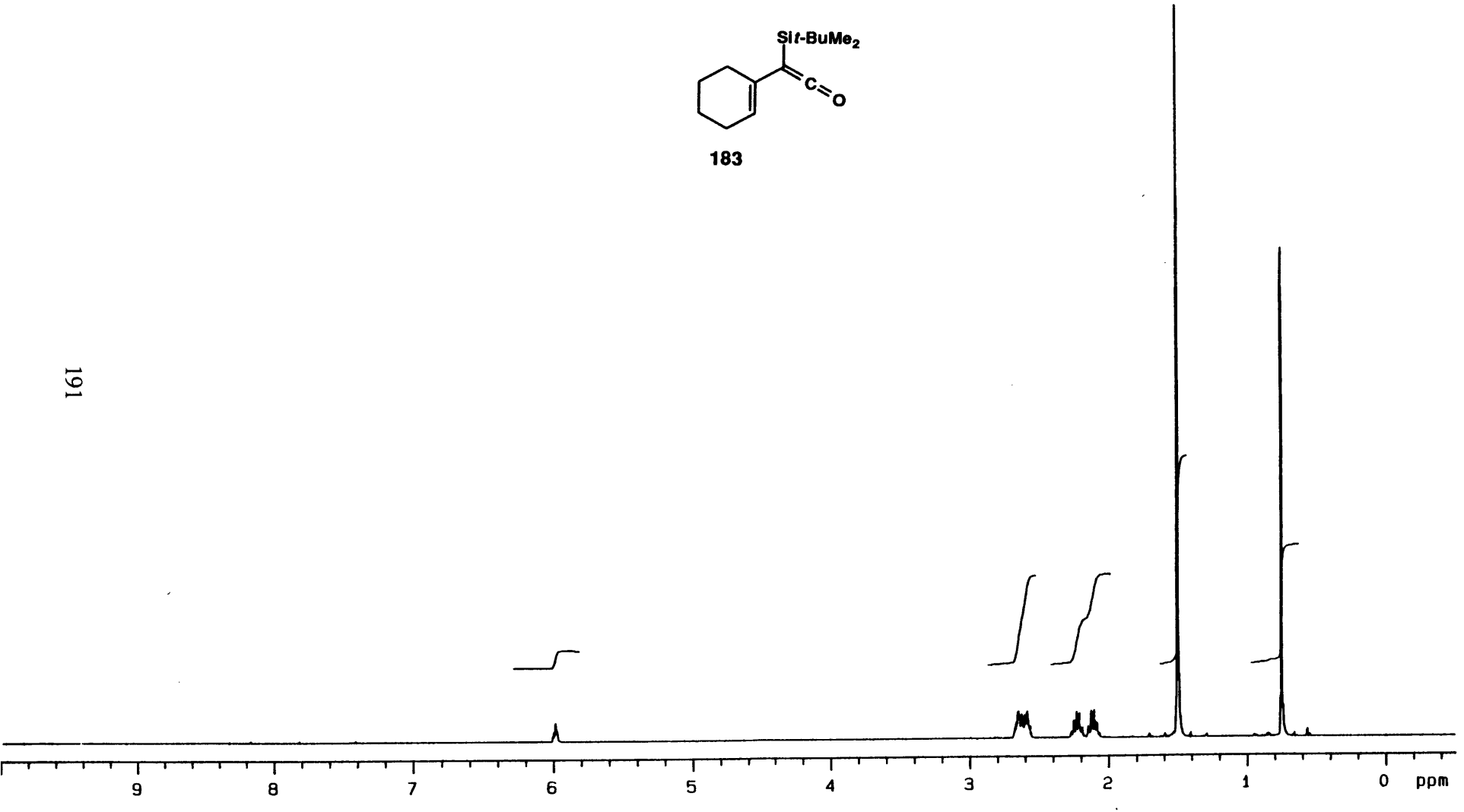


171 183

(1-Cyclohexenyl)-2-(*tert*-butyldimethylsilyl)-ketene (181).

A 25-cm vycor tube (15 mm O.D., 13 mm I.D.) fitted with a rubber septum was charged with a solution of silyldiazo ketone **171** (0.130 g, 0.490 mmol) in 5 mL of benzene. A second rubber septum (inverted) was secured with wire to the tube to insure a good seal, and the reaction mixture was degassed (three freeze-pump-thaw cycles at -196 °C, < 0.5 mm Hg) and then irradiated with 300 nm light for 4.5 h in a Rayonet reactor. The resulting solution was concentrated to afford 0.11 g of an orange-brown oil. Column chromatography on 10 g of silica gel (elution with hexane) provided 0.067 g (58%) of ketene **183** as a viscous yellow oil.

IR (film):	2930, 2860, 2080, 1540, 1460, and 1250 cm^{-1}
^1H NMR (300 MHz, $CDCl_3$):	5.97-6.00 (m, 1H), 2.25-2.68 (m, 4H), 2.19-2.24 (m, 2H), 2.09-2.15 (m, 2H), 1.50 (s, 9H), and 0.75 (s, 6 H)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C=O
O
183
9
8
7
6
5
4
3
2
1
0
ppm

145 134

1-Diazo-3-methyl-3-penten-2-one (134).

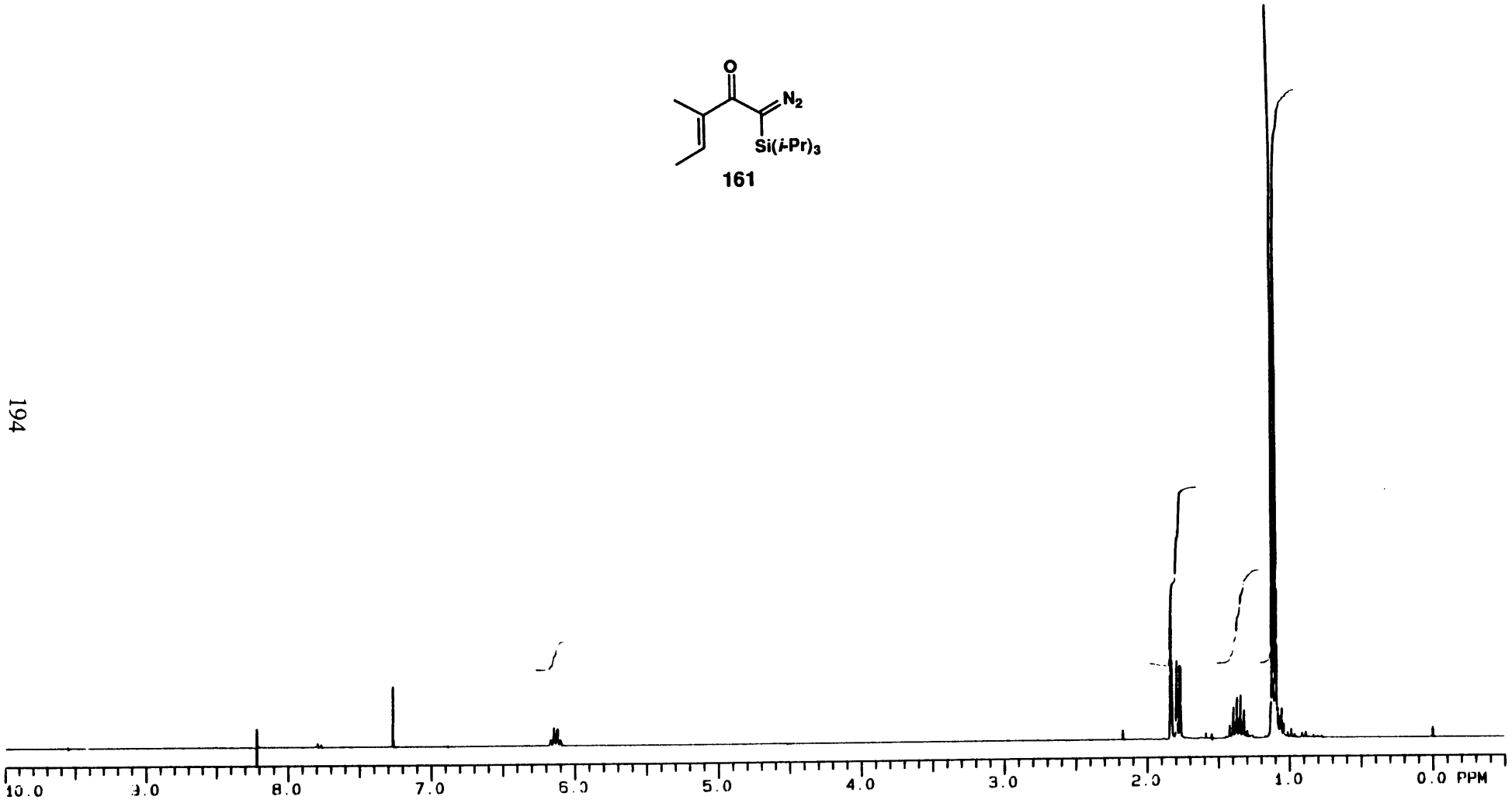
Reaction of methyl ketone **145** (3.04 g, 31.0 mmol) with LiHMDS (32.5 mmol) and 2,2,2-trifluoroethyl trifluoroacetate (4.6 mL, 6.73 g, 34.4 mmol) in 60 ml of THF according to the general procedure provided an orange oil which was then treated with H_2O (0.56 mL, 0.56 g, 31.0 mmol), Et_3N (6.5 mL, 4.70 g, 46.5 mmol), and methanesulfonyl azide (5.4 mL, 5.63 g, 46.5 mmol) in 35 mL of CH_3CN at room temperature for 4 h to yield 4.67 g of an orange oil. Column chromatography on 50 g of silica gel (elution with 20% EtOAc-hexane) provided 3.03 g (79%) of diazo ketone (**134**) as a yellow solid, mp 25.0-26.5 °C with spectral characteristics identical with those reported previously.[29]

134 161

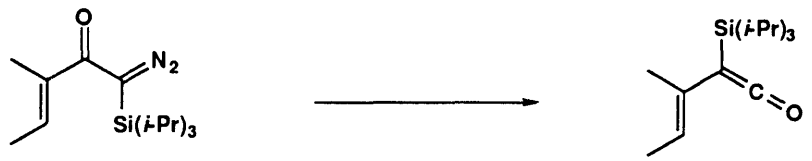
1-Diazo-3-methyl-1-(triisopropylsilyl)-3-penten-2-one (161).

A 100-mL, three-necked, round-bottomed flask equipped with a rubber septum, magnetic stir bar, and argon inlet adapter was charged with diazo ketone **134** (0.854 g, 6.87 mmol) in 40 mL of a 1:1 solution of Et_2O-hexane and then cooled at 0 °C in an ice-water bath while *i*-Pr_2EtN (1.2 mL, 0.89 g, 6.87 mmol) was added dropwise over 1 min. After 5 min, triisopropylsilyl trifluoromethanesulfonate (1.8 mL, 2.05 g, 6.70 mmol) was added dropwise over 1 min and the resulting solution was stirred for 2.5 h while the ice-water bath warmed to room temperature. The reaction mixture was filtered through Celite with the aid of 10 mL of Et_2O and the filtrate was concentrated to afford 2.09 g of an orange oil. Column chromatography on 25 g of silica gel (elution with 5% EtOAc-hexane) provided 1.71g (89%) of the silyldiazo ketone **161** as a yellow oil.

IR (CCl_4):	2940, 2860, 2065, 1610, 1460, 1383, 1340, 1279, 1209, and 1140 cm^{-1}
^1H NMR (300 MHz, $CDCl_3$):	6.13 (q, J = 6.6 Hz, 1H), 1.83 (s, 3H), 1.78 (d, J = 6.8 Hz, 3H), 1.37 (sept, J = 6.7 Hz, 3H), and 1.10 (d, J = 7.9 Hz, 18H)
^{13}C NMR (75 MHz, $CDCl_3$):	196.9, 136.3, 129.9, 49.8, 18.4, 13.6, 13.1, and 11.5
UV max (CH_3CN):	292 (ε = 3000), 238 (6200) and 221 (6300) nm
HRMS:	Calcd for $C_{15}H_{28}ON_2Si$: 280.1971 Found: 280.1963



161

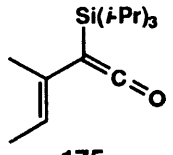


161 175

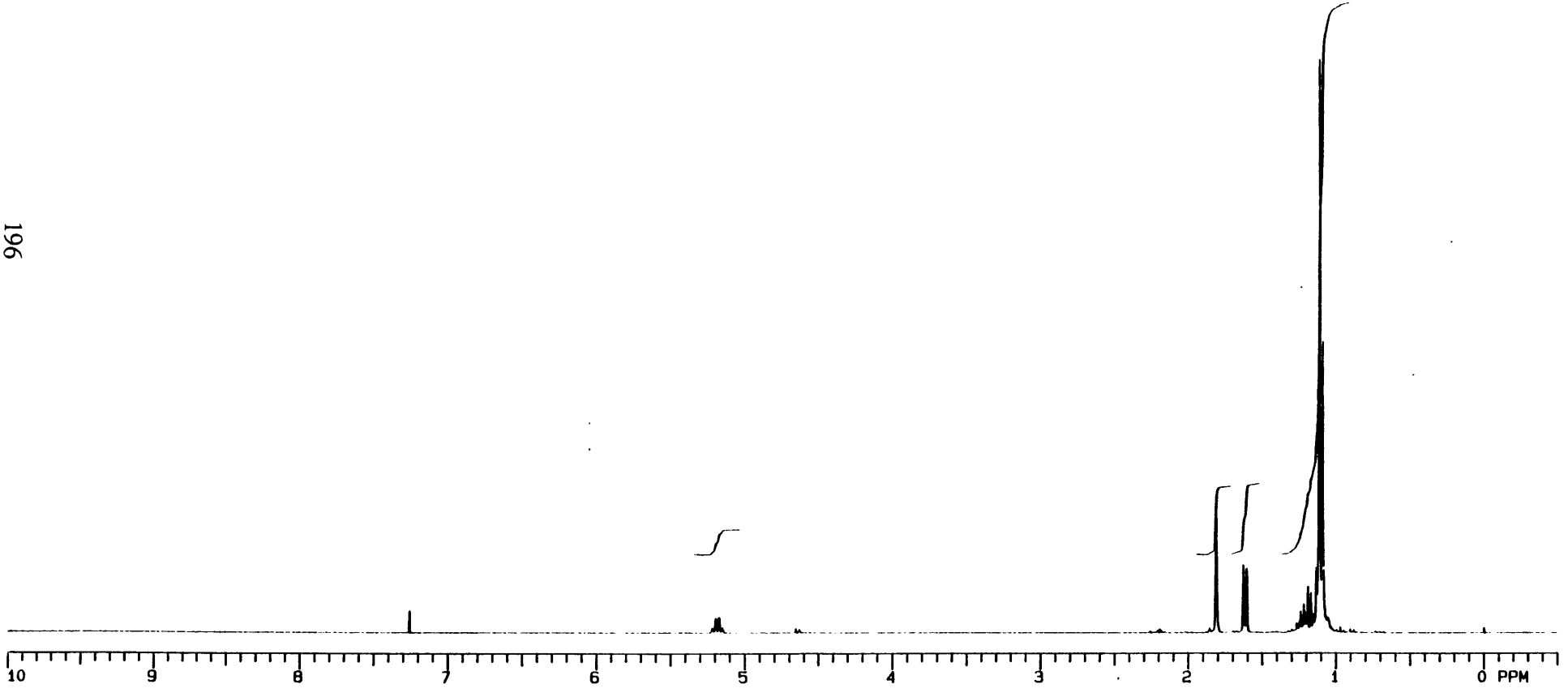
3-Methyl-3-penten-2-triisopropylsilylketene (175)

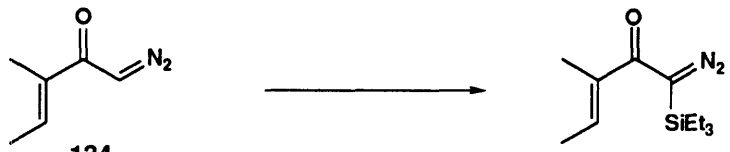
A solution of silyldiazo ketone **161** (0.76 g, 2.71 mmol) in 27 mL of benzene was distributed evenly between two 25-cm vycor tubes (15 mm O.D., 13 mm I.D.) fitted with rubber septa. A second rubber septum (inverted) was secured with wire to each tube to insure a good seal, and the reaction mixtures were degassed (three freeze-pump-thaw cycles at -196 °C, < 0.5 mm Hg) and then irradiated with 300 nm light for 4 h in a Rayonet reactor. The resulting solutions were combined and concentrated to afford 0.71 g of a yellow oil. Column chromatography on 30 g of silica gel (elution with hexane) provided 0.55 g (80%) of ketene **175** as a viscous yellow oil.

IR (film):	2941, 2881, 2081, 1461, 1381, 1291, 1181, 1071, and 1021 cm^{-1}	
^1H NMR (300 MHz, $CDCl_3$):	5.18 (q, J = 6.7 Hz, 1H), 1.81 (s, 3H), 1.62 (d, J= 6.7 Hz, 3H), 1.15-1.27 (m, 3H), 1.10 (d, J = 6.4 Hz, 18H)	
^{13}C NMR (75 MHz, $CDCl_3$):	184.7, 123.9, 119.5, 22.4, 18.8, 18.6, 14.0, and 12.5	
UV max (hexane):	229 nm (ε = 9000)	
HRMS	Calcd For $C_{15}H_{28}OSi$:	252.1909
	Found:	252.1907



175



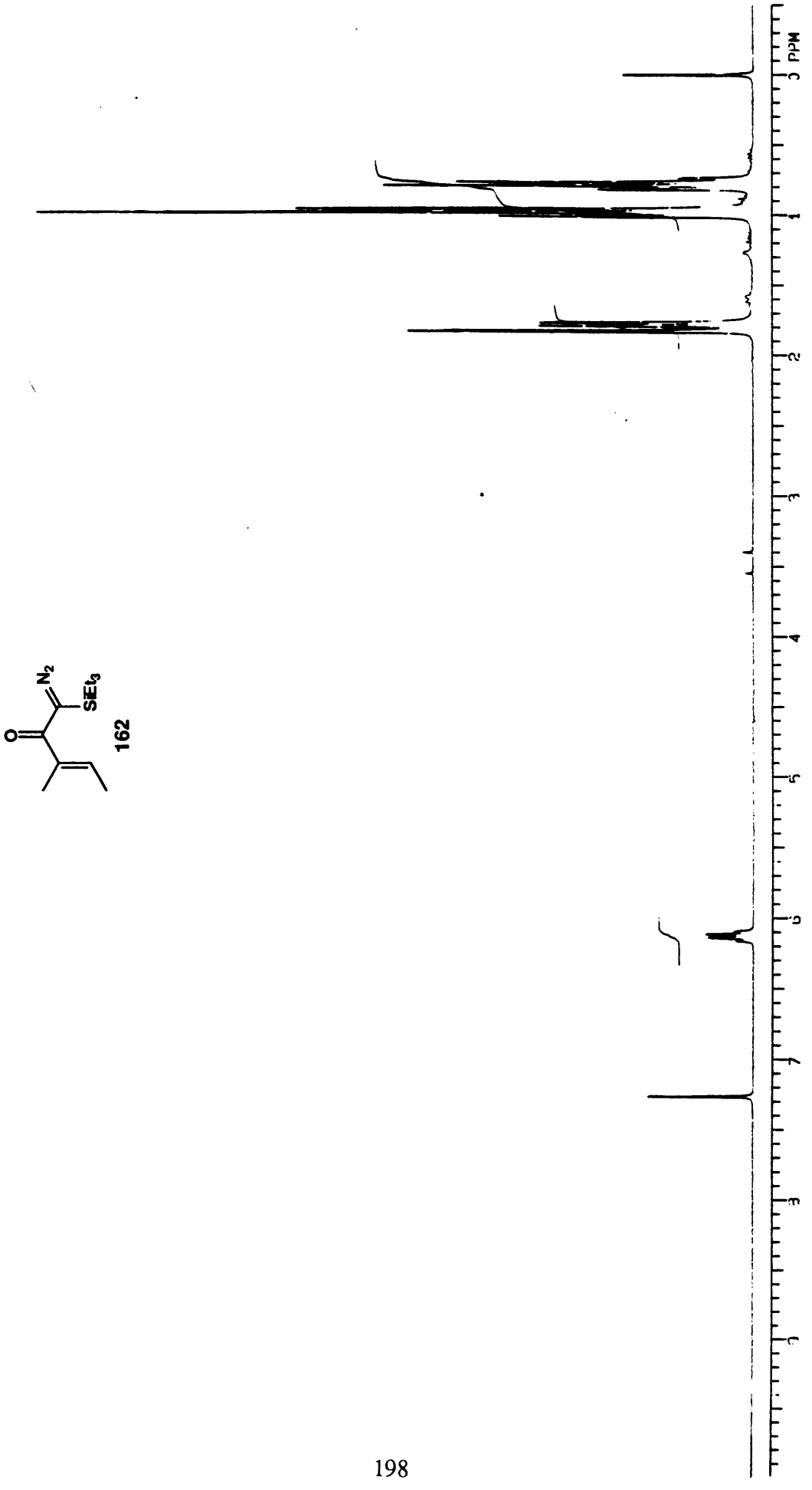


134 162

1-Diazo-3-methyl-1-triethylsilyl-3-penten-2-one (162).

A 25-mL, two-necked, round-bottomed flask equipped with a rubber septum, magnetic stir bar, and argon inlet adapter was charged with diazo ketone **134** (0.201 g, 1.62 mmol) in 8 mL of a 50:50 solution of Et_2O-hexane and then cooled at 0 °C in an ice-water bath while *i*-Pr_2EtN (0.28 mL, 0.208 g, 1.61 mmol) was added dropwise over 1 min. After 5 min, triethylsilyl trifluoromethanesulfonate (0.36 mL, 0.43 g, 1.61 mmol) was added slowly dropwise over 1 min and the resulting solution was stirred for 3 h while the ice-water bath warmed to room temperature. The reaction mixture was filtered through Celite with the aid of 5 mL of Et_2O and the filtrate was concentrated to afford an orange oil. Column chromatography on 10 g of silica gel (gradient elution with 0-5% EtOAc-hexane) provided 0.326 g (84%) of the silyldiazo ketone **162** as a yellow oil.

IR (CCl_4):	2940, 2860, 2060, 1600, 1450, 1410, 1375, 1350, 1280, 1210, 1140, and 1000 cm^{-1}
^1H NMR (300 MHz, $CDCl_3$):	6.13 (q, J = 6.8 Hz, 1H), 1.82 (s, 3H), 1.78 (d, J = 6.8 Hz, 3H), 0.98 (t, J = 7.8 Hz, 9H), and 0.77 (q, J = 7.4 Hz, 6H)
^{13}C NMR (75 MHz, $CDCl_3$):	196.4, 136.5, 130.3, 50.2, 13.6, 12.9, 7.1, and 2.9
UV max (CH_3CN):	219 (ε = 6000), 240 (6100) and 292 (3100) nm
HRMS:	Calcd for $C_{12}H_{22}N_2OSi$ (-N_2): 210.1440 Found: 210.1433

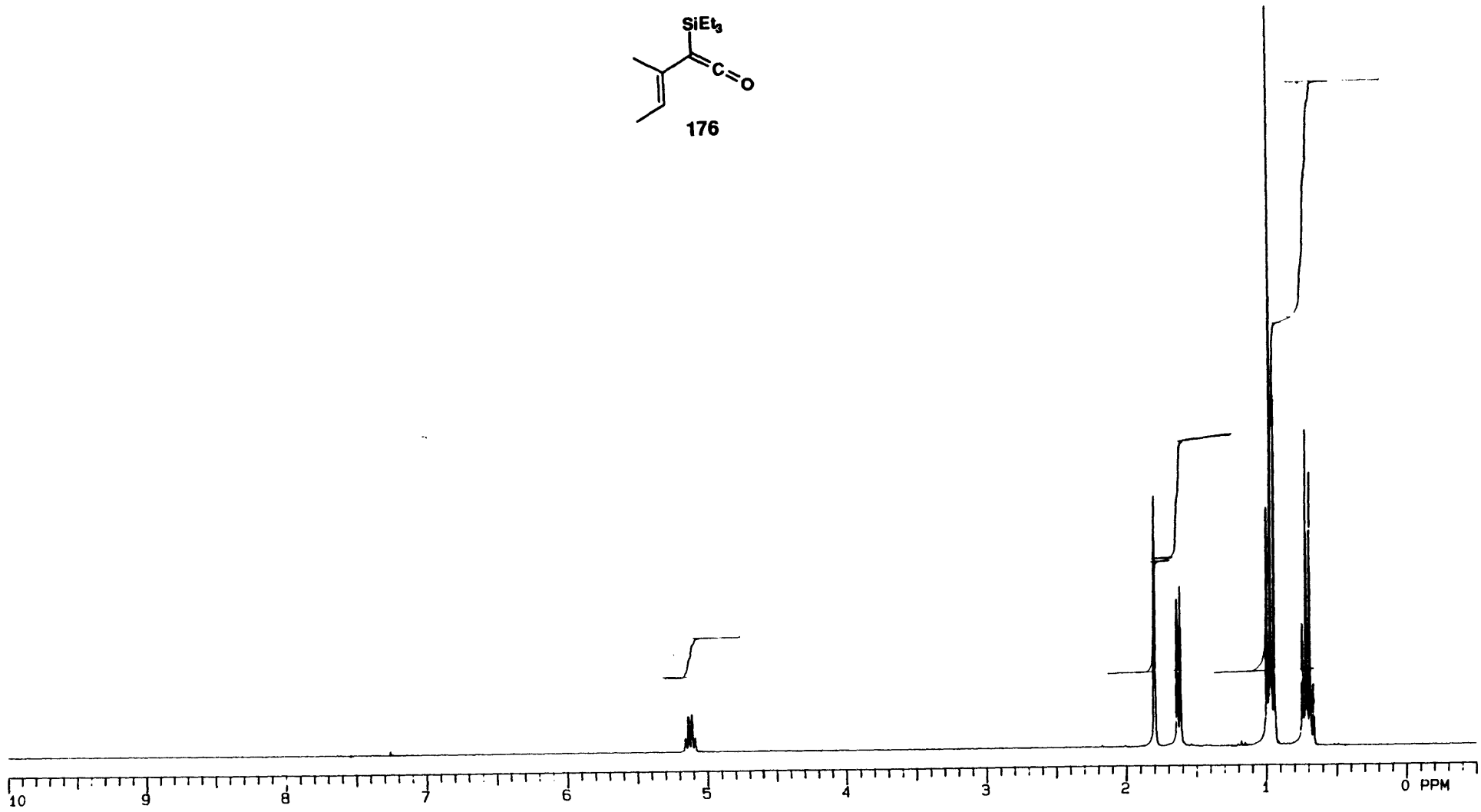

O
N2
SEt3
162
3 PPM

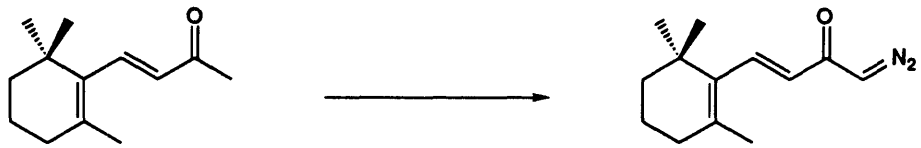
162 176

3-Methyl-3-penten-2-triethylsilylketene (176)

A solution of silyldiazo ketone **162** (0.419 g, 1.76 mmol) in 18 mL of benzene was distributed evenly between two 25-cm vycor tubes (15 mm O.D., 13 mm I.D.) fitted with rubber septa. A second rubber septum (inverted) was secured with wire to each tube to insure a good seal, and the reaction mixtures were degassed (three freeze-pump-thaw cycles at -196 °C, < 0.5 mm Hg) and then irradiated with 300 nm light for 4 h in a Rayonet reactor. The resulting solutions were combined and concentrated to afford a yellow-orange oil. Column chromatography on 10 g of silica gel (elution with hexane) provided 0.27 g (73%) of ketene **176** as a viscous yellow oil.

IR (film):	2940, 2860, 2065, 1445, 1380, 1300, 1235, 1280, and 1010 cm^{-1}	
^1H NMR (300 MHz, $CDCl_3$):	5.12 (q, *J* = 5.5 Hz, 1H), 1.80 (s, 3H), 1.62 (d, *J*= 5.9 Hz, 3H), 0.97 (t, *J*=7.9 Hz, 9H), and 0.70 (q, *J* = 7.5 Hz, 6H)	
^{13}C NMR (75 MHz, $CDCl_3$):	184.0, 124.0, 117.7, 23.7, 18.6, 13.9, 7.2 and 3.9	
UV max (CH_3CN):	226 (ε = 7500) and 352 (90) nm	
HRMS:	Calcd for $C_{12}H_{22}OSi$:	210.1440
	Found:	210.1437


SiEt3
C=O
176
200
10
9
8
7
6
5
4
3
2
1
0 PPM

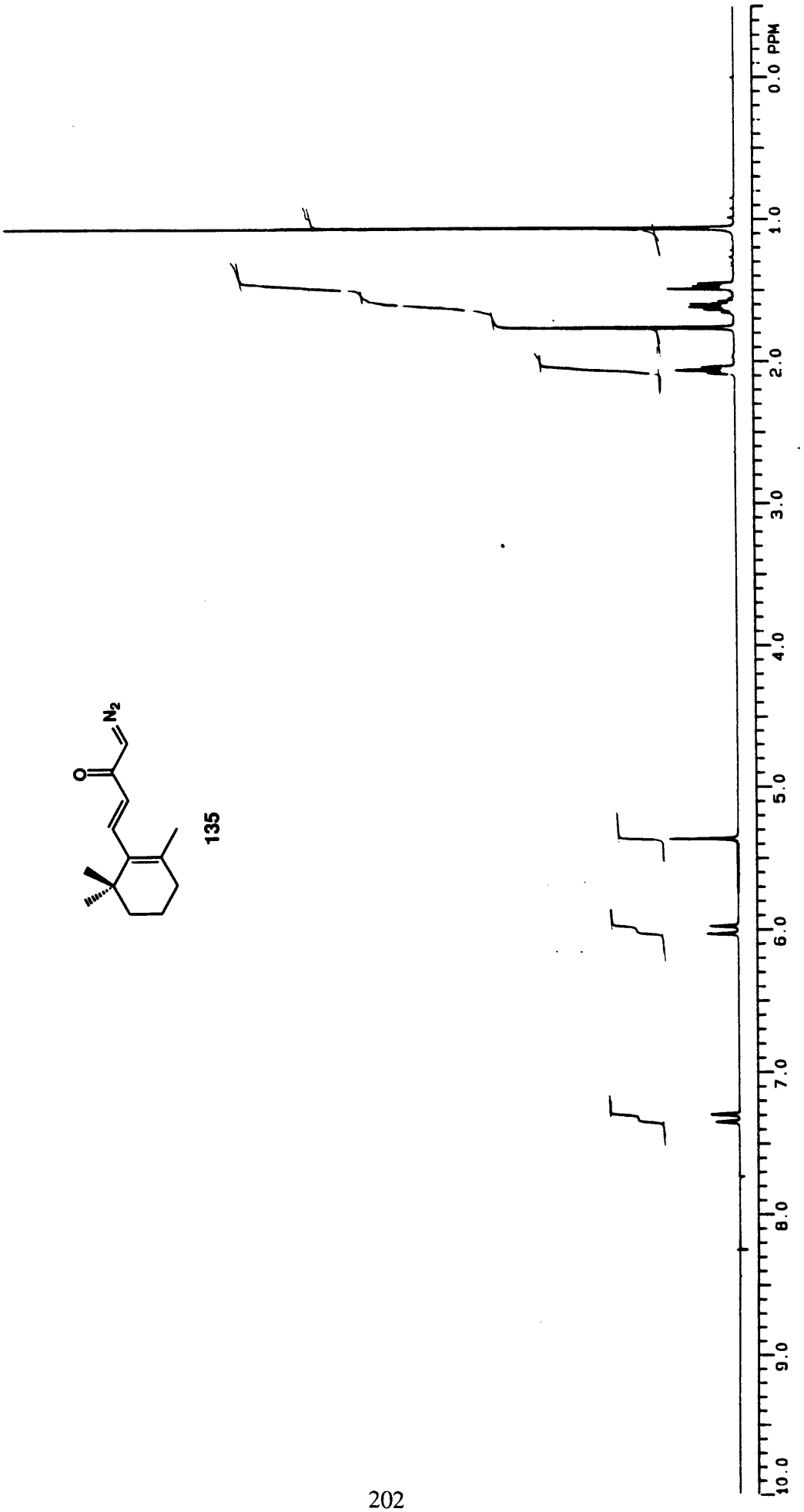


135

1-Diazo-4-(2,6,6-trimethyl-1-cyclohexen-1-yl)-3-buten-2-one (135).

Reaction of 4-(2,6,6-trimethyl-1-cyclohexen-1-yl)-3-buten-2-one (2.1 mL, 2.00 g, 10.4 mmol) with LiHMDS (11.4 mmol) and 2,2,2-trifluoroethyl trifluoroacetate (1.7 mL, 2.45 g, 12.5 mmol) in 50 ml of THF according to the general procedure provided a yellow-orange oil which was then treated with H_2O (0.19 mL, 0.187 g, 10.4 mmol), Et_3N (2.2 mL, 1.58 g, 15.6 mmol), and methanesulfonyl azide (1.8 mL, 1.89 g, 15.6 mmol) in 36 mL of CH_3CN at room temperature for 3 h to yield 3.96 g of an orange oil. Column chromatography on 50 g of silica gel (gradient elution with 0-10% EtOAc-hexane) provided 2.18 g (97%) of diazo ketone **135** as a yellow-orange oil.

IR (CCl_4):	3076, 2916, 2856, 2196, 2076, 1636, 1596, 1456, 1356 and 1296 cm^{-1}	
^1H NMR (300 MHz, $CDCl_3$):	7.32 (d, J = 15.8 Hz, 1H), 6.00 (d, J = 15.8 Hz, 1H), 5.36 (s, 1H), 2.06 (t, J = 6.0 Hz, 2H), 1.76 (s, 3H), 1.60-1.64 (m, 2H), 1.45-1.49 (m, 2H), and 1.06 (s, 6H)	
^{13}C NMR (75 MHz, $CDCl_3$):	184.7, 140.1, 135.9, 135.8, 127.6, 55.3, 39.7, 34.0, 33.5, 28.7, 21.6, and 18.8	
UV max (hexane):	300 nm (ε = 18 000)	
Elemental Analysis:	Calcd for $C_{13}H_{18}ON_2$:	C, 71.52; H, 8.31; N, 12.84
	Found:	C, 71.81; H, 8.40; N, 12.69


N2
O
135
0.0 PPM
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
9.0
10.0

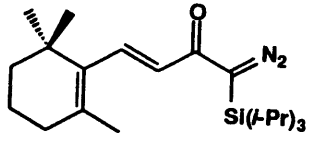
135 163

1-Diazo-1-triisopropylsilyl-4-(2,6,6-trimethyl-1-cyclohexen-1-yl)-3-buten-2-one (163).

A 50-mL, two-necked, round-bottomed flask equipped with a rubber septum, magnetic stir bar and argon inlet adapter was charged with triisopropylsilyl trifluoromethanesulfonate (0.19 mL, 0.217 g, 0.707 mmol) in 17 mL of hexane and 10 mL of Et_2O and then cooled at 0 °C in an ice-water bath. A 10-mL, two-necked, round-bottomed flask equipped with a rubber septum and argon inlet adapter was charged with diazo ketone **135** (0.150 g, 0.687 mmol) in 7 mL of Et_2O and cooled at 0 °C in an ice-water bath while *i*-Pr_2EtN (0.12 mL, 0.088 g, 0.689 mmol) was added dropwise over 30 seconds. The diazo ketone solution was then transferred dropwise via cannula over 3 min to the triflate solution. The reaction mixture was stirred for 1.5 h allowing the bath to warm to room temperature and then filtered through Celite with the aid of 10 mL of Et_2O and the filtrate was concentrated to afford 0.27 g of an orange oil. Column chromatography on 10 g of silica gel (gradient elution with 0-3% EtOAc-hexane) provided 0.23 g (87%) of the silyldiazo ketone **163** as an orange oil.

IR (film):	2942, 2967, 2057, 1632, 1601, 1461, and 1362 cm^{-1}
^1H NMR (300 MHz, $CDCl_3$):	7.35 (d, *J* = 15.5 Hz, 1H), 6.41 (d, *J* = 15.5 Hz, 1H) , 2.07 (t, *J* = 6.2 Hz, 2H), 1.79 (s, 3H), 1.60-1.64 (m, 2H), 1.46-1.50 (m, 2H), 1.37 (sept, *J* = 7.1 Hz, 3H), 1.13 (d, *J* = 7.3 Hz, 18H), and 1.08 (s, 6H)

^{13}C NMR (75 MHz, $CDCl_3$):	188.5, 140.4, 136.3, 135.9, 124.6, 52.9, 39.8, 34.1, 33.7, 28.8, 21.8, 18.9, 18.4, and 11.7
UV max (hexane):	291 (ε = 5200) and 272 (4500) nm
HRMS:	Calcd for $C_{22}H_{38}ON_2Si$: 374.2753 Found: 374.2755



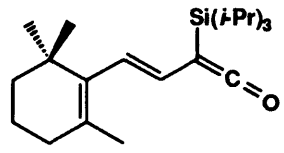
163

163 178

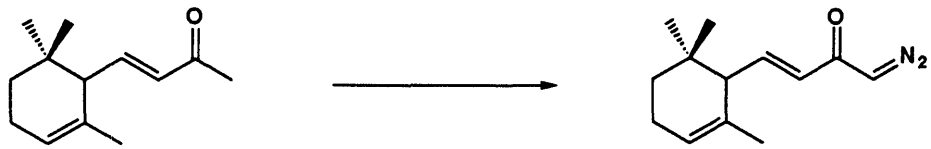
4-(2,6,6-Trimethyl-1-cyclohexen-1-yl)-3-buten-2-triisopropylsilylketene (178).

A 20-cm vycor tube (8 mm O.D., 7 mm I.D.) fitted with a rubber septum was charged with a solution of silyldiazo ketone **163** (0.23 g, 0.63 mmol) in 6 mL of benzene. A second rubber septum (inverted) was secured with wire to insure a good seal, and the reaction mixture was degassed (three freeze-pump-thaw cycles at -196 °C, < 0.5 mm Hg) and then irradiated with 300 nm light for 2 h in a Rayonet reactor. The resulting solution was concentrated to afford 0.21 g of a yellow-brown oil. Column chromatography on 10 g of silica gel (elution with hexane) provided 0.13 g (61%) of ketene **178** as a viscous yellow oil.

IR (CCl_4):	2946, 2876, 2066, 1746, 1606, 1456 and 1346 cm^{-1}
^1H NMR (300 MHz, $CDCl_3$):	5.90 (d, J = 15.8 Hz, 1H), 5.19 (d, J = 15.8 Hz, 1H), 1.97 (t, J = 6.1 Hz, 2H), 1.68 (s, 3H), 1.57-1.61 (m, 2H), 1.42-1.46 (m, 2H), 1.16-1.23 (m, 3H), 1.11 (d, J = 6.2 Hz, 18H) and 0.98 (s, 6H)
^{13}C NMR (75 MHz, $CDCl_3$):	185.3, 138.2, 128.3, 127.5, 120.4, 38.5, 34.3, 32.9, 28.8, 21.6, 19.4, 18.5, 15.6, and 12.0
UV max (hexane):	261 (ε = 11 000), 206 (7100) nm
HRMS:	Calcd for $C_{22}H_{38}OSi$: 346.2692 Found: 346.2695



178

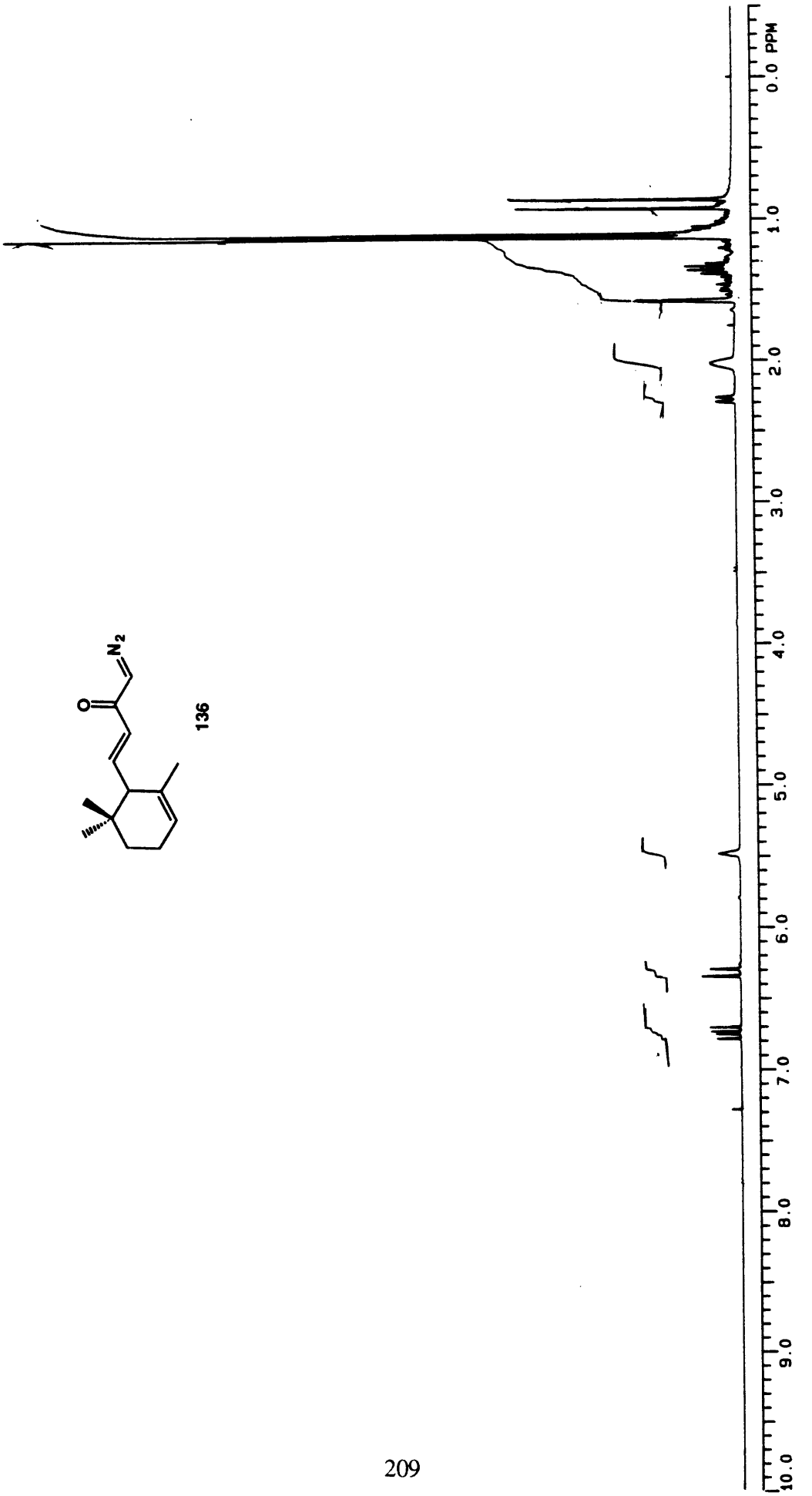


136

1-Diazo-4-(2,6,6-trimethyl-2-cyclohexen-1-yl)-3-buten-2-one (136).

Reaction of 4-(2,6,6-trimethyl-1-cyclohexen-2-yl)-3-buten-2-one (2.2 mL, 2.00 g, 10.4 mmol) with LiHMDS (11.4 mmol) and 2,2,2-trifluoroethyl trifluoroacetate (1.7 mL, 2.45 g, 12.5 mmol) in 30 ml of THF according to the general procedure provided a yellow-orange oil which was then treated with H_2O (0.19 mL, 0.19 g, 10.4 mmol), Et_3N (2.2 mL, 1.57 g, 15.6 mmol), and methanesulfonyl azide (1.8 mL, 1.89 g, 15.6 mmol) in 36 mL of CH_3CN at room temperature for 4.5 h to yield 3.32 g of a yellow-orange oil. Column chromatography on 80 g of silica gel (gradient elution with 0-10% EtOAc-hexane) provided 2.17 g (94%) of diazo ketone **136** as a yellow-orange oil.

IR (thin film):	3080, 2960, 2920, 2880, 2100, 1640, 1600, 1440 and 1360 cm^{-1}	
^1H NMR (300 MHz, $CDCl_3$):	6.64 (dd, J = 15.1, 9.7 Hz, 1H), 5.96 (d, J = 15.5 Hz, 1H), 5.49 (br s, 1H), 5.33 (s, 1H), 2.25 (d, J = 9.4 Hz, 1H), 2.04 (s, 3H), 1.56 (s, 3H), 1.46 (dt, J = 13.4, 8.2 Hz, 1H), 1.21 (dt, J = 13.4, 4.8 Hz, 1H), 0.92 (s, 3H), and 0.85 (s, 3H)	
^{13}C NMR (75 MHz, $CDCl_3$):	184.5, 145.8, 131.9, 128.5, 122.6, 55.0, 54.1, 32.6, 31.2, 27.8, 26.9, 23.0, and 22.8	
UV max (hexane):	293 (ε = 8200) and 255 (15 800) nm	
Elemental Analysis:	Calcd for $C_{13}H_{18}ON_2$:	C, 71.52; H, 8.31; N, 12.84
	Found:	C, 71.59; H, 8.40; N, 12.63


O
N2
136
0.0 PPM
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
9.0
10.0

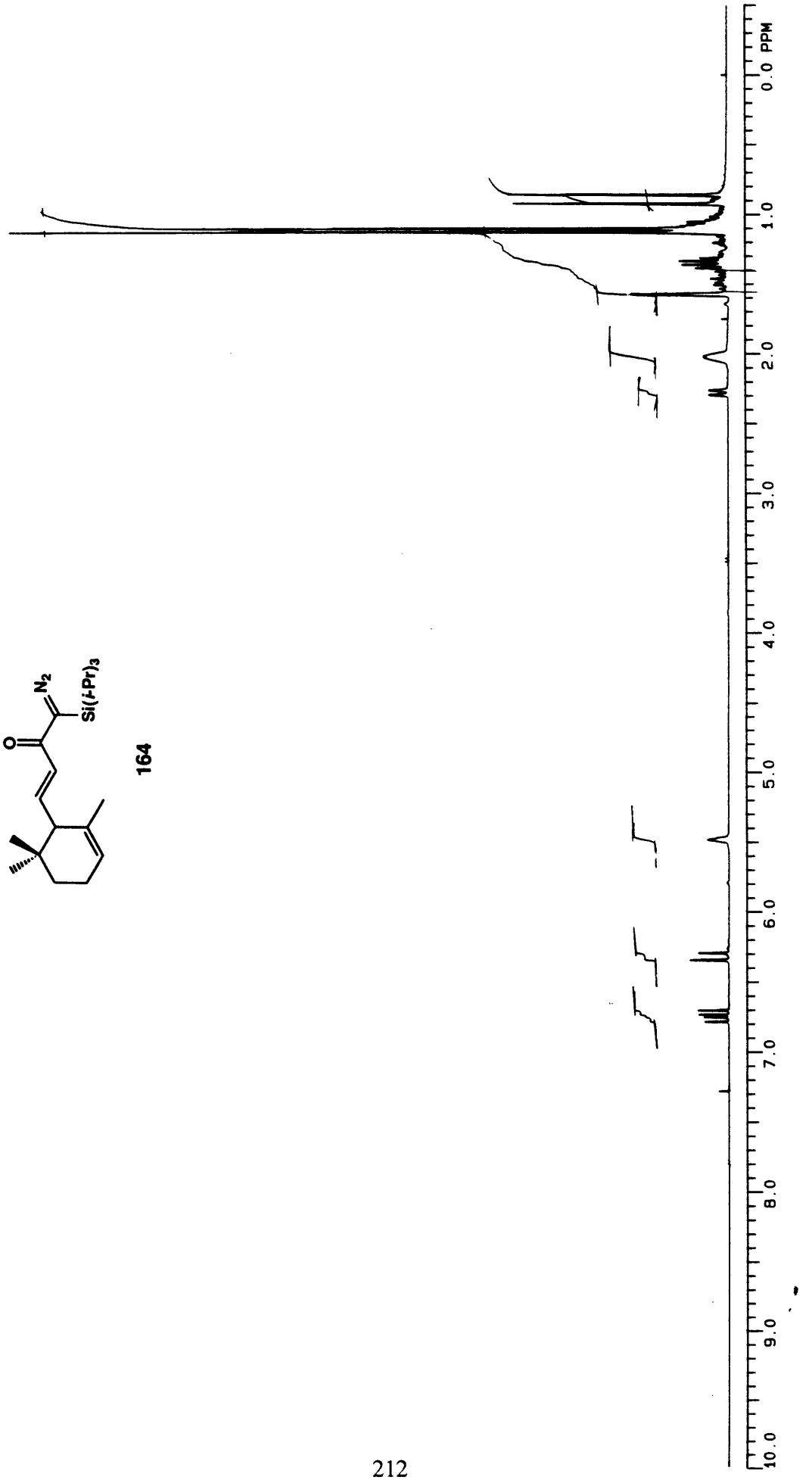
136 164

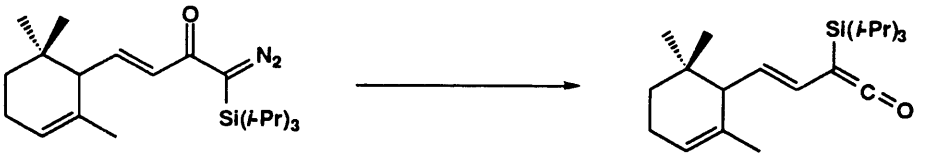
1-Diazo-1-triisopropylsilyl-4-(2,6,6-trimethyl-2-cyclohexen-1-yl)-3-buten-2-one (164).

A 10-mL, two-necked, round-bottomed flask equipped with a rubber septum, magnetic stir bar, and argon inlet adapter was charged with diazo ketone **136** (0.152 g, 0.690 mmol) in 3 mL of Et_2O and then cooled at 0 °C in an ice-water bath while *i*-Pr_2EtN (0.12 mL, 0.089 g, 0.69 mmol) was added dropwise over 1 min. Triisopropylsilyl trifluoromethanesulfonate (0.19 mL, 0.217 g, 0.707 mmol) was added dropwise over 1 min and the resulting solution was stirred for 1 h while the ice-water bath warmed to room temperature. The reaction mixture was filtered through Celite using 3 mL of Et_2O and the filtrate was concentrated to afford 0.28 g of an orange oil. Column chromatography on 10 g of silica gel (gradient elution with 0-2% EtOAc-hexane) provided 0.19 g (72%) of the silyldiazo ketone **164** as a yellow oil.

IR (CCl_4):	2930, 2860, 2050, 1635, 1600, 1540, 1240, and 1200 cm^{-1}
^1H NMR (300 MHz, $CDCl_3$):	6.74 (dd, *J* = 14.9, 9.8 Hz, 1H), 6.32 (d, *J* = 14.9 Hz, 1H), 5.48 (s, 1H), 2.27 (d, *J* = 9.7 Hz, 1H), 2.01-2.04 (m, 2H), 1.57 (s, 3H), 1.40-1.56 (m, 2H), 1.35 (sept, *J* = 5.7 Hz, 3H), 1.12 (d, *J* = 7.3 Hz, 18H), 0.93 (s, 3H) and 0.86 (s, 3H)
^{13}C NMR (75 MHz, $CDCl_3$):	188.3, 146.1, 132.1, 125.4, 122.5, 54.1, 53.2, 32.6, 31.0, 27.9, 26.9, 23.1. 22.9, 18.5, and 11.7
UV max (hexane):	297 (ε = 6100), 241 (10 000) and 225 (8800) nm

HRMS:	Calcd for $C_{22}H_{38}ON_2Si$:	374.2753
	Found:	374.2752


N2
Si(i-Pr)3
O
164
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0 PPM

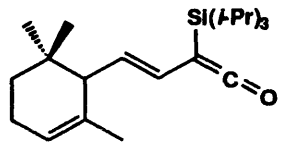


164 178

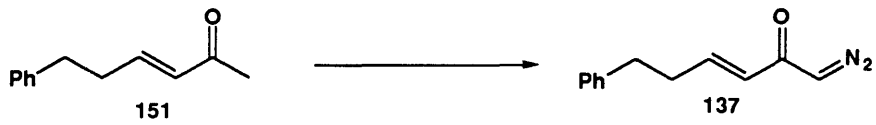
4-(2,6,6-Trimethylcyclo-2-hexen-1-yl)-3-buten-2-triisopropylsilylketene (178).

A 20-cm vycor tube (8 mm O.D., 7 mm I.D.) fitted with a rubber septum was charged with a solution of silyldiazo ketone **164** (0.16 g, 0.43 mmol) in 4 mL benzene. A second rubber septum (inverted) was secured with wire to each tube to insure a good seal, and the reaction mixture was degassed (three freeze-pump-thaw cycles at -196 °C, < 0.5 mm Hg) and then irradiated with 300 nm light for 2.5 h in a Rayonet reactor. The resulting solution was concentrated to afford 0.16 g of a red oil. Column chromatography on 10 g of silica gel (elution with hexane) provided 0.12 g (81%) of ketene **178** as a viscous yellow oil.

IR (CCl_4):	2916, 2856, 2066, 1536, and 1251 cm^{-1}	
^1H NMR (300 MHz, $CDCl_3$):	5.37 (br s, 1H), 5.19-5.32 (m, 2H), 2.10 (d, J = 7.6 Hz, 1H), 1.98 (br s, 2H), 1.57 (s, 3H), 1.39 (dt, J = 13.5, 7.8 Hz, 2H), 1.05-1.22 (m, 3H), 1.10 (d, J = 5.5 Hz, 18H), 0.87 (s, 3H), and 0.81 (s, 3H)	
^{13}C NMR (75 MHz, $CDCl_3$):	185.3, 134.4, 131.4, 120.8, 117.9, 55.2, 32.5, 31.8, 27.6, 27.0, 23.1, 22.9, 18.4, 14.7, and 11.9	
UV max (hexane):	243 nm (ε = 10 000)	
HRMS:	Calcd for $C_{22}H_{38}OSi$:	346.2692
	Found:	346.2690



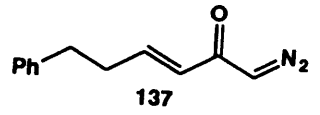
178



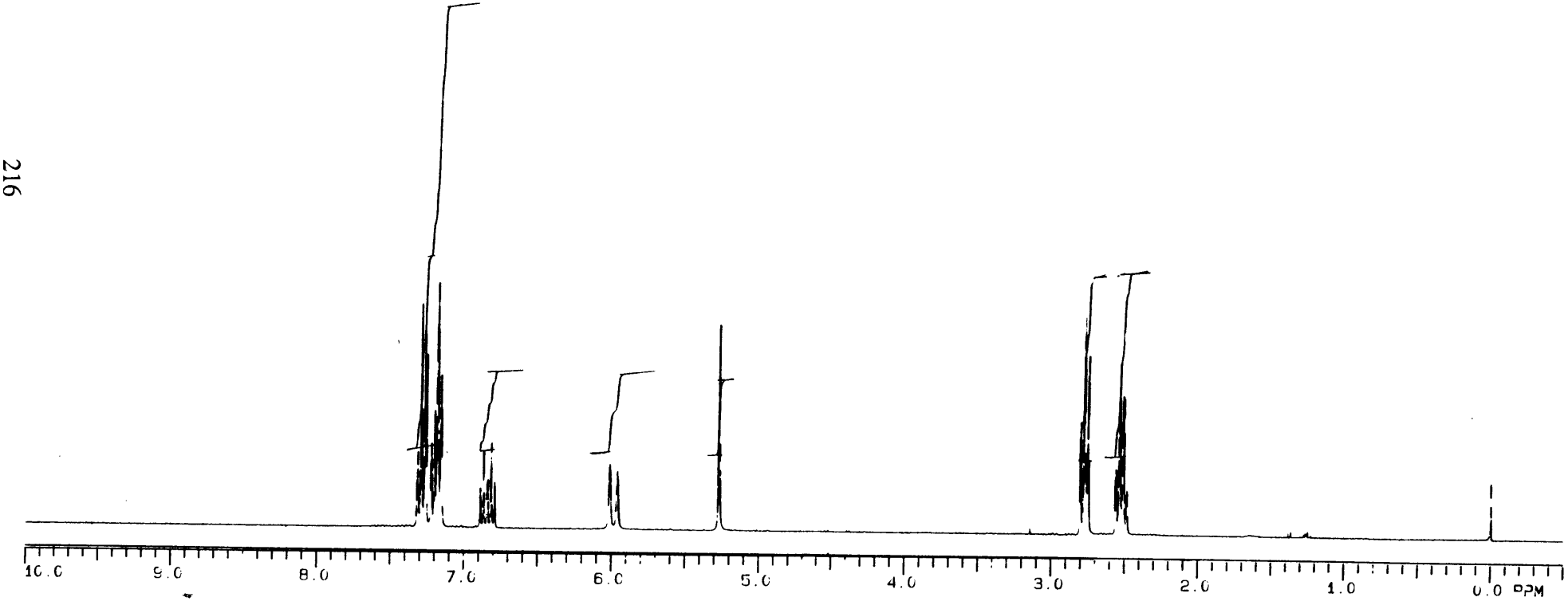
(E)-1-Diazo-6-phenyl-3-hexen-2-one (137).

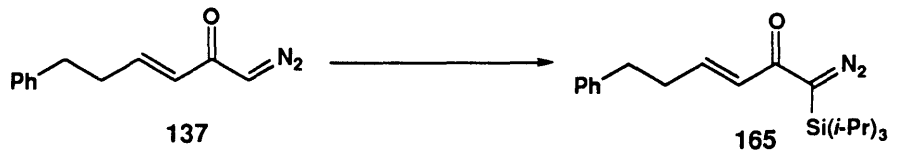
Reaction of methyl ketone **151** (0.687 g, 3.94 mmol) with LiHMDS (4.33 mmol) and 2,2,2-trifluoroethyl trifluoroacetate (0.63 mL, 0.922 g, 4.70 mmol) in 28 ml of THF according to the general procedure provided a yellow-orange oil which was then treated with H_2O (0.071 mL, 0.071 g, 3.94 mmol), Et_3N (0.82 mL, 0.600 g, 5.91 mmol), and methanesulfonyl azide (0.75 mL, 0.782 g, 6.45 mmol) in 14 mL of CH_3CN at room temperature for 2.5 h to yield 1.43 g of an orange oil. Column chromatography on 50 g of silica gel (gradient elution with 0-20% EtOAc-hexane) provided 0.68 g (86%) of diazo ketone **137** as a yellow oil.

IR (CCl_4):	3024, 2924, 2099, 1655, 1614, and 1364 cm^{-1}	
^1H NMR (300 MHz, $CDCl_3$):	7.26-7.32 (m, 2H), 7.16-7.23 (m, 3H), 6.84 (dt, *J* = 15.4 Hz, 6.8 Hz, 1H), 5.99 (d, *J* = 15.5 Hz, 1H), 5.27 (s, 1H), 2.77 (t, *J* = 7.6 Hz, 2H), 2.52 (dt, *J* = 7.1 Hz, 7.3 Hz, 2H)	
^{13}C NMR (75 MHz, $CDCl_3$):	184.6, 143.9, 140.8, 128.5, 128.4, 127.7, 126.2, 55.2, 34.5 and 34.0	
UV max (hexane):	202 (ε = 6400) and 247 (5700) nm	
Elemental Analysis:	Calcd for $C_{12}H_{12}ON_2$:	C, 71.97; H, 6.04; N, 13.99
	Found:	C, 71.72; H, 5.85; N, 13.85



137



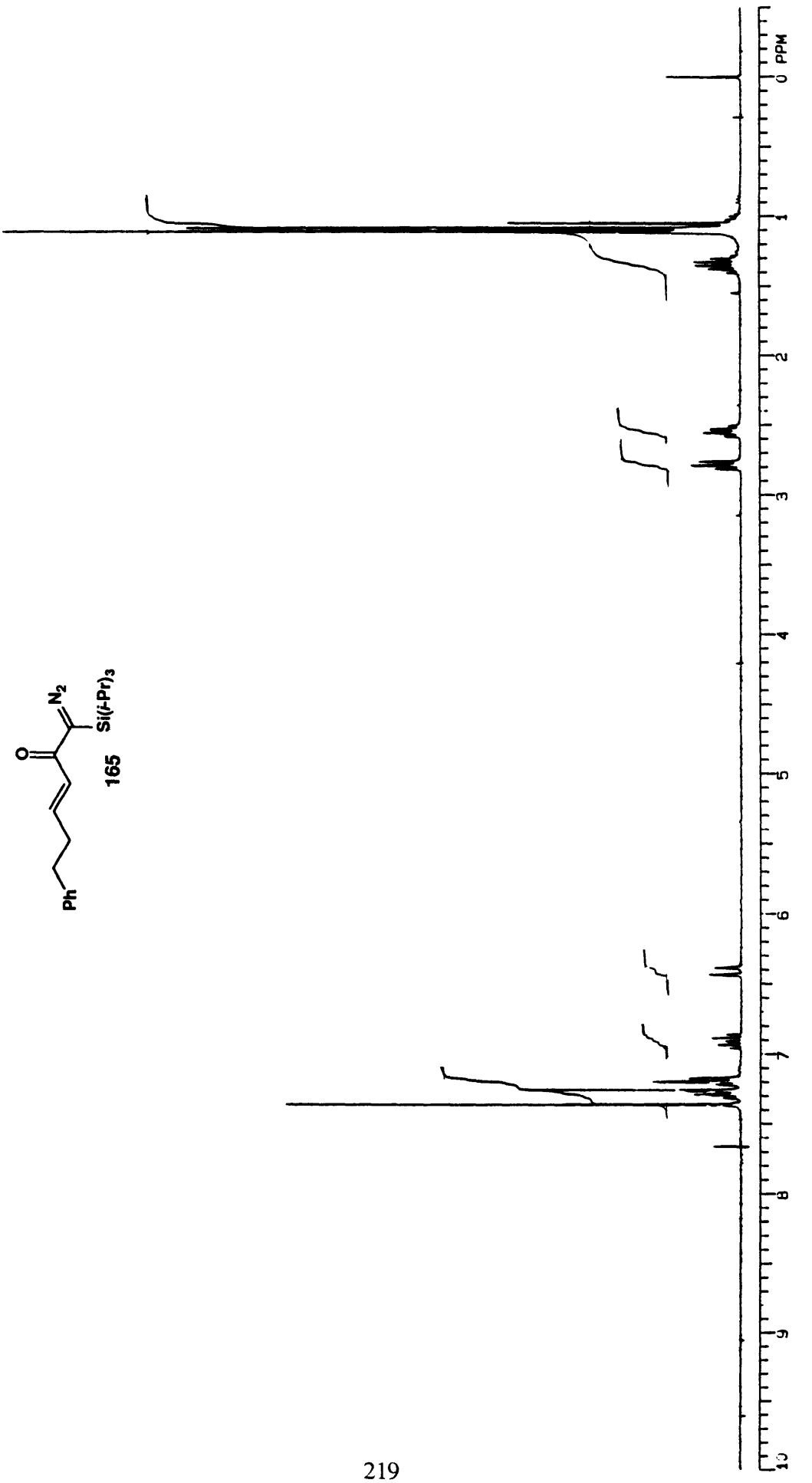


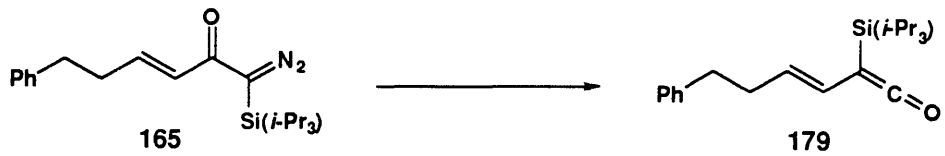
(E)-1-Diazo-6-phenyl-triisopropyl-3-hexen-2-one (165).

A 250-mL, three-necked, round-bottomed flask equipped with a rubber septum, magnetic stir bar, glass stopper, and argon inlet adapter was charged with triisopropyl trifluoromethanesulfonate (0.67 mL, 0.760 g, 2.48 mmol) in 90 mL of a 50:40 solution of hexane-Et_2O then cooled at 0 °C in an ice-water bath. A 50-mL, two-necked, round-bottomed flask equipped with a rubber septum, magnetic stir bar, and argon inlet adapter was charged with diazo ketone **137** (0.496 g, 2.48 mmol) in 20 mL of ether and cooled at 0 °C in an ice-water bath while *i*-Pr_2EtN (0.43 mL, 0.320 g, 2.48 mmol) was added dropwise over 10 seconds. The diazo ketone solution was then transferred dropwise via cannula over 5 min to the triflate solution. The reaction mixture was stirred for 1.5 h allowing the ice-water bath to warm to room temperature and then filtered though Celite using 5 mL of Et_2O and the filtrate was concentrated to afford 2.80 g of an orange oil. Column chromatography on silica gel (gradient elution with 0-50% benzene-hexane) provided 0.34 g (38%) of the silyldiazo ketone **165** as an orange oil.

IR (thin film):	3015, 2935, 2855, 2040, 1650, 1605, 1460, and 1345 cm^{-1}
^1H NMR (300 MHz, $CDCl_3$):	7.17-7.32 (m, 5H), 6.91 (dt, *J* = 15.1, 7.5 Hz, 1H), 6.42 (d, *J* = 15.1 Hz, 1H), 2.79 (t, *J* = 7.7 Hz, 2H), 2.55 (dt, *J* = 7.0, 7.1 Hz, 2H), 1.35 (sept, *J* = 7.1 Hz, 3H) and 1.10 (d, *J* = 7.3 Hz, 18H)
^{13}C NMR (75 MHz, $CDCl_3$):	188.2, 144.2, 140.9, 128.5, 128.3, 126.1, 124.4, 50.0, 34.5, 34.0, 18.4, and 11.6

UV max (hexane):	352 (ε = 2500), 302 (6000) and 212 (16 000) nm	
HRMS:	Calcd for $C_{21}H_{32}ON_2Si$:	356.2284
	Found:	356.2282


N2
Si(i-Pr)3
O
165
Ph
PPM

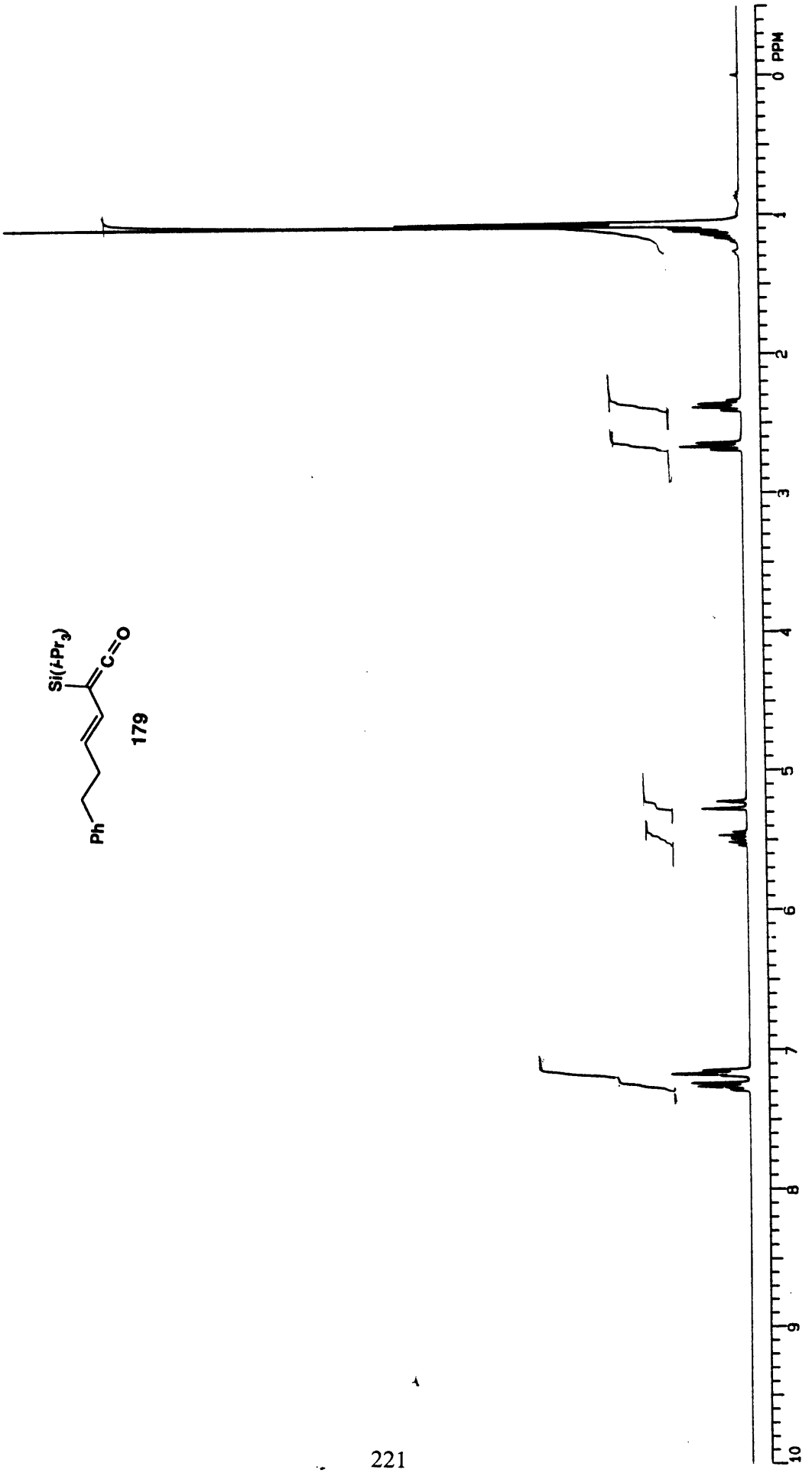


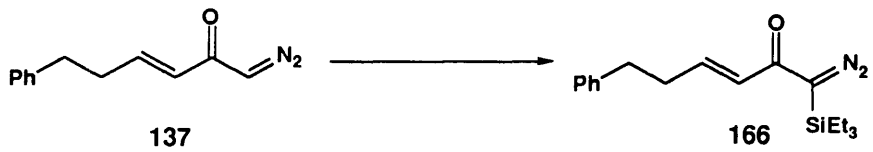
165 179

(E)-6-Phenyl-3-hexen-2-triisopropylsilylketene (179).

A solution of silyldiazo ketone **179** (0.29 g, 0.81 mmol) in 8 mL of benzene was placed in a 20-cm vycor tube (8 mm O.D., 7 mm I.D.) fitted with a rubber septum. A second rubber septum (inverted) was secured with wire to the tube to insure a good seal, and the reaction mixture was degassed (three freeze-pump-thaw cycles at -196 °C, < 0.5 mmHg) and then irradiated with 300 nm light for 2 h in a Rayonet reactor. The resulting solution was concentrated to afford 0.30 g of a red oil. Column chromatography on 10 g of silica gel (elution with hexane) provided 0.11 g (41%) of ketene **179** as a viscous yellow oil.

IR (film):	3006, 2916, 2836, 2056, 1486, 1456 and 1386 cm^{-1}
^1H NMR (300 MHz, $CDCl_3$):	7.15-7.29 (m, 5H), 5.49 (dt, *J* = 15.0, 6.9 Hz, 1H), 5.25 (d, *J* = 15.2 Hz, 1H), 2.67 (t, *J* = 7.6 Hz, 2H), 2.37 (dt, *J* = 7.0,7.6 Hz, 2H), 1.06-1.18 (m, 3H) and 1.06 (d, *J* = 5.1 Hz, 18H)
^{13}C NMR (75 MHz, $CDCl_3$):	184.9, 141.8, 129.7, 128.5, 128.3, 125.8, 117.5, 36.2, 35.0, 18.4, 14.6, and 11.9
UV max (hexane):	242 (ε = 8600) and 204 nm (16 000)
HRMS:	Calcd for $C_{21}H_{32}OSi$: 328.2222 Found: 328.2221

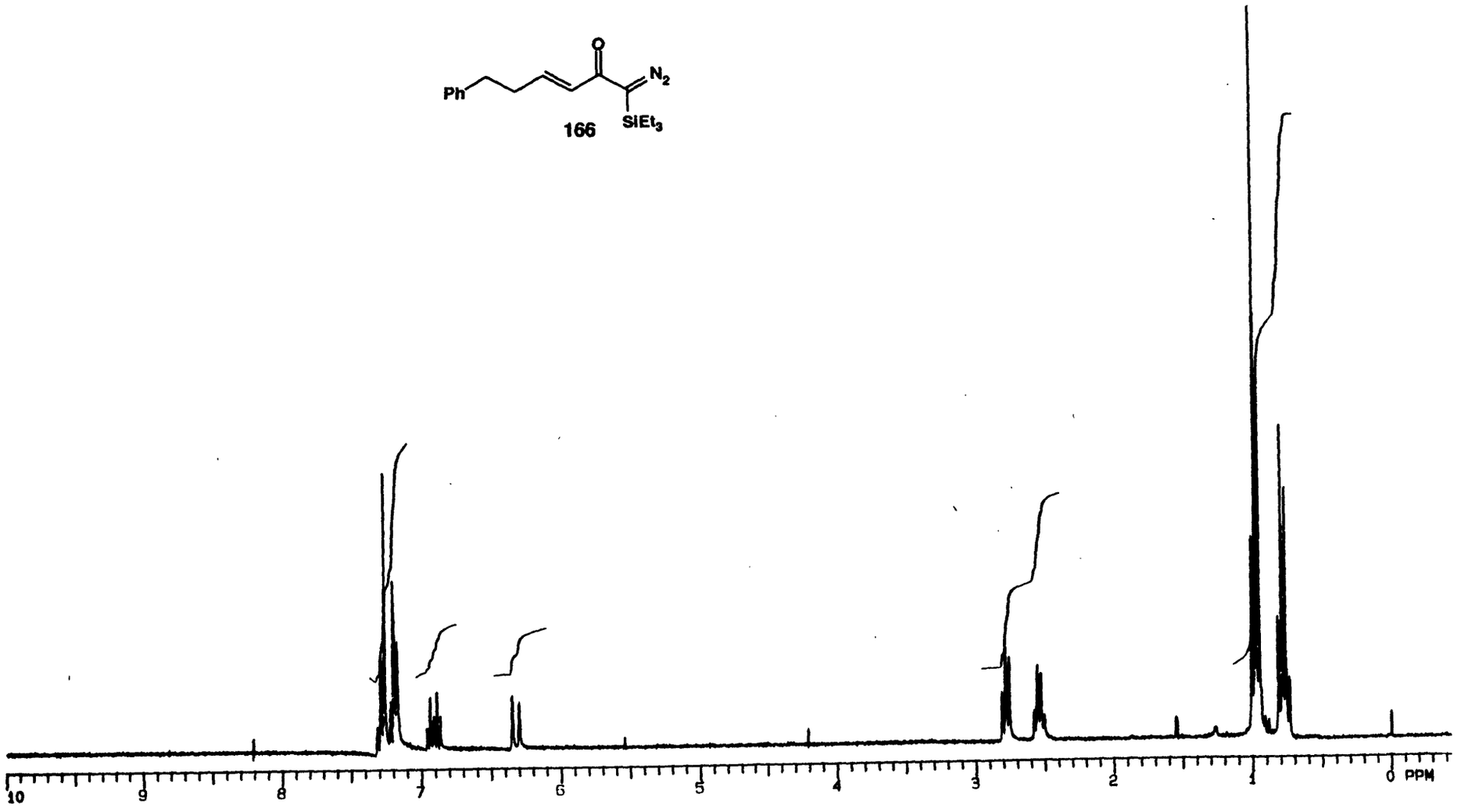

Si(i-Pr)3
C=O
Ph
179
PPM
0
1
2
3
4
5
6
7
8
9
10

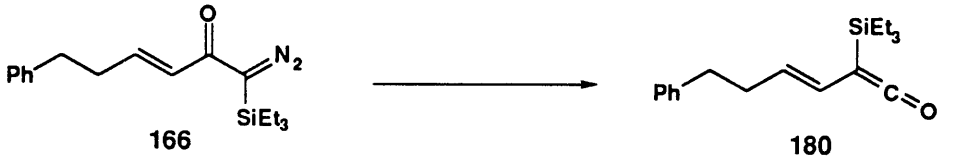


(E)-1-Diazo-6-phenyl-1-triethylsilyl-3-buten-2-one (166).

A 25-mL, two-necked, round-bottomed flask equipped with a rubber septum, magnetic stir bar, and argon inlet adapter was charged with diazo ketone **137** (0.173 g, 0.860 mmol) in 6 mL of a 50:50 solution of Et_2O-hexane and then cooled at 0 °C in an ice-water bath while *i*-Pr_2EtN (0.15 mL, 0.110 g, 0.860 mmol) was added dropwise over 1 min. Triethylsilyl trifluoromethanesulfonate (0.19 mL, 0.222 g, 0.840 mmol) was added dropwise over 1 min, and the resulting solution was stirred for 2 h while the ice-water bath warmed to room temperature. The reaction mixture was filtered through Celite using 5 mL of Et_2O and the filtrate was concentrated to afford 0.29 g of an orange oil. Column chromatography on 10 g of silica gel (gradient elution with 0-5% EtOAc-hexane) provided 0.14 g (52%) of the silyldiazo ketone **166** as a yellow oil.

IR (film):	2940, 2860, 2055, 1645, 1600, 1455, and 1380 cm^{-1}
^1H NMR (300 MHz, $CDCl_3$):	7.22-7.30 (m, 2H), 7.17-7.20 (m, 3H), 6.82 (dt, *J* = 6.9, 15.0 Hz, 1H), 6.33 (d, *J* = 15.0 Hz, 1H), 2.78 (t, *J* = 7.3 Hz, 2H), 2.53 (dt, *J* = 7.0, 6.9 Hz, 2H), 0.96 (t, *J* = 7.8 Hz, 9H), and 0.79 (q, *J* = 7.8 Hz, 6 H)
^{13}C NMR (75 MHz, $CDCl_3$):	188.0, 144.1, 140.9, 128.4, 128.3, 126.1, 124.8, 53.5, 34.5, 33.9, 7.1, and 3.1

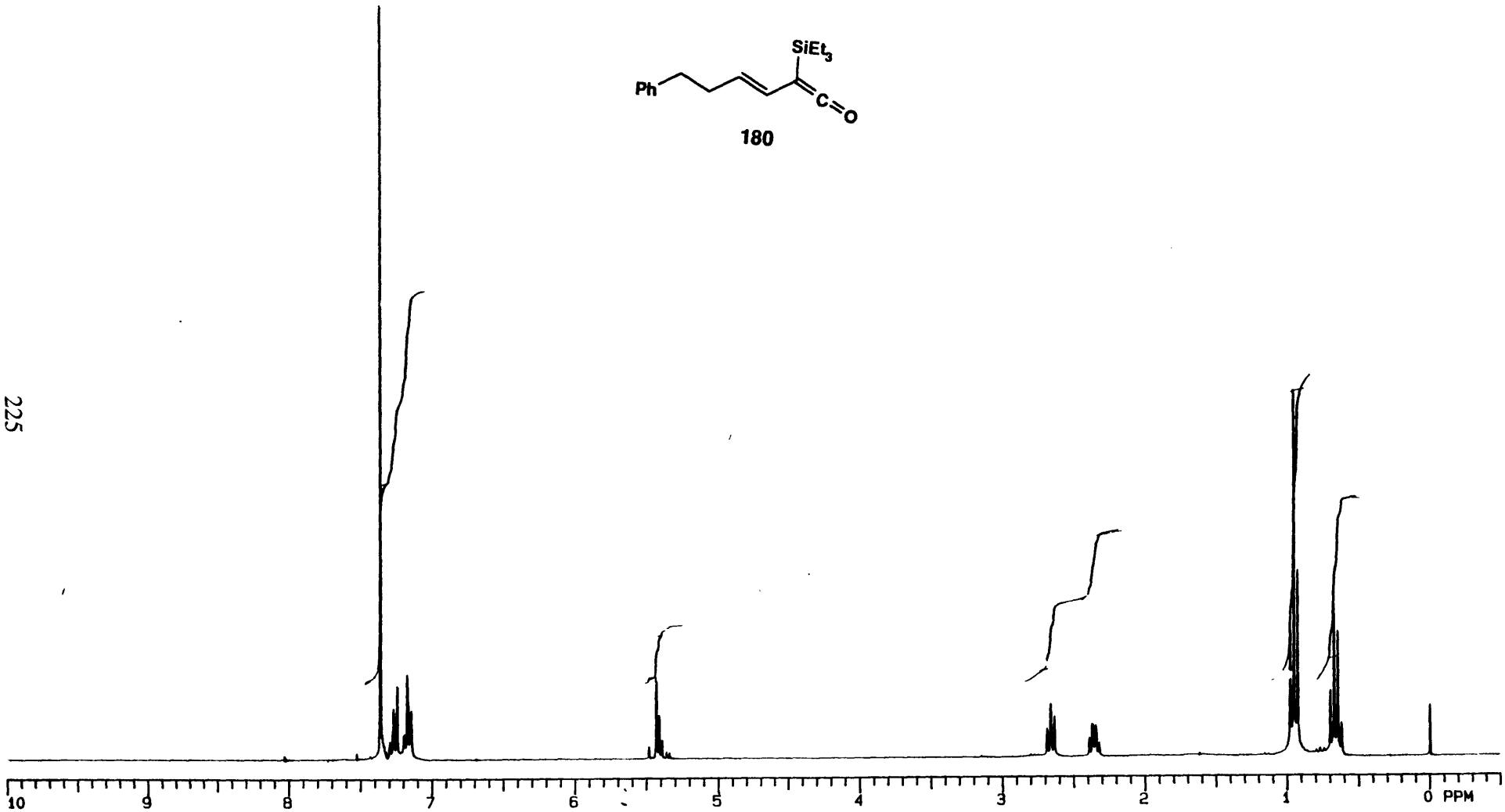

Ph
O
N2
SiEt3
166
10
9
8
7
6
5
4
3
2
1
0 PPM

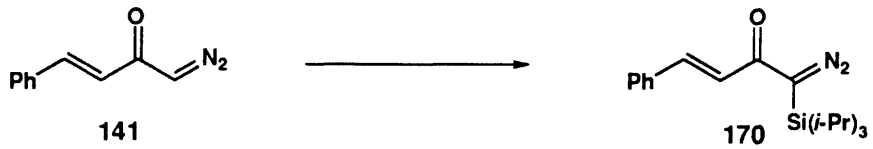


(E)-6-Phenyl-3-buten-2-triethylsilylketene (180).

A 20-cm vycor tube (8 mm O.D., 7 mm I.D.) fitted with a rubber septum was charged with a solution of silyldiazo ketone **166** (0.140 g, 0.450 mmol) in 4 mL of benzene. A second rubber septum (inverted) was secured with wire to the tube to insure a good seal, and the reaction mixture was degassed (three freeze-pump-thaw cycles at -196 °C, < 0.5 mm Hg) and then irradiated with 300 nm light for 2.5 h in a Rayonet reactor. The resulting solution was concentrated to afford 0.15 g of a dark red oil. Column chromatography on 10 g of silica gel (elution with hexane) provided 0.028 g (20%) of ketene **180** as a viscous yellow oil.

IR (thin film):	3023, 2995, 2867, 2083, 1730, 1633, and 1450 cm^{-1}
^1H NMR (300 MHz, $CDCl_3$):	7.24-7.36 (m, 2H), 7.15-7.17 (m, 3H), 5.32-5.50 (m, 2H), 2.65 (t, J = 7.6 Hz, 2H), 2.37 (dt, J = 7.3, 7.6 Hz, 2H), 0.95 (t, J = 7.5 Hz, 9 H), and 0.65 (q, J = 7.5 Hz, 6H)


SiEt3
Ph
C=O
180
10
9
8
7
6
5
4
3
2
1
0 PPM

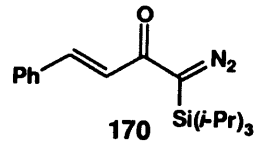


(E)-1-Diazo-4-phenyl-1-triisopropylsilyl-3-buten-2-one (170).

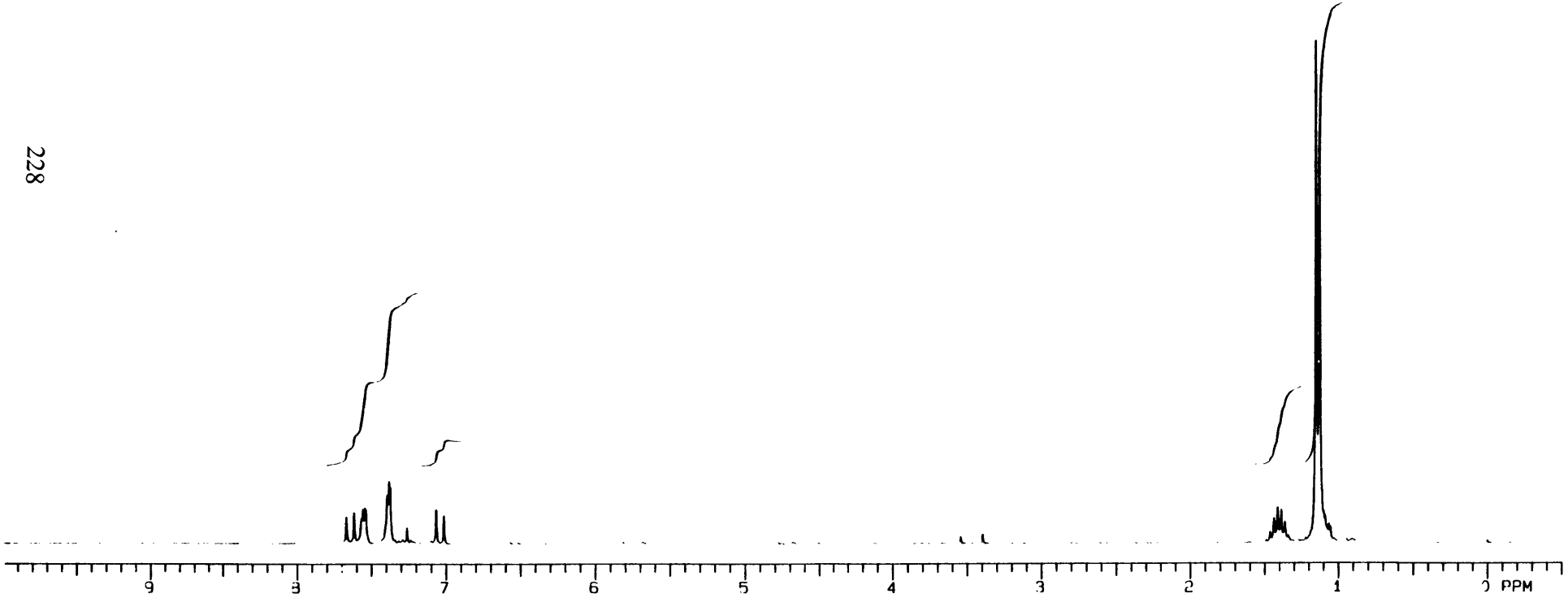
A 250-mL, three-necked, round-bottomed flask equipped with a rubber septum, magnetic stir bar, glass stopper, and argon inlet adapter was charged with a solution of triisopropyl trifluoromethanesulfonate (0.78 mL, 0.889 g, 2.90 mmol) in 115 mL of Et_2O then cooled at 0 °C in an ice-water bath. A 50-mL, two-necked, round-bottomed flask equipped with a rubber septum, magnetic stir bar, and argon inlet adapter was charged with diazo ketone **141** (0.509 g, 2.90 mmol) in 23 mL of Et_2O and cooled at 0 °C in an ice-water bath while *i*-Pr_2EtN (0.51 mL, 0.380 g, 2.90 mmol) was added dropwise over 10 seconds. The solution of diazo ketone was then transferred dropwise via cannula over 4 min to the solution of triflate. The reaction mixture was stirred for 15 min while the ice-water bath warmed to room temperature and then filtered through Celite using 10 mL of Et_2O and the filtrate was concentrated to afford 1.08 g of a red-orange oil. Column chromatography on 40 g silica gel (gradient elution with 0-5 % EtOAc-hexane) provided 0.37 g (39%) of the silyldiazo ketone **170** as an orange oil.

IR (CCl_4):	2940, 2860, 2058, 1640, 1600, 1460, 1330, 1280, 1210, and 1180 cm^{-1}
^1H NMR (300 MHz, $CDCl_3$):	7.64 (d, *J* = 15.3 Hz, 1H), 7.54-7.57 (m, 2H), 7.37-7.40 (m, 3H), 7.04 (d, *J* = 15.4 Hz, 1H), 1.40 (sept, *J* = 7.2 Hz, 3H), and 1.14 (d, *J* = 7.4 Hz, 18H)
^{13}C NMR (75 MHz, $CDCl_3$):	187.9, 141.1, 134.7, 130.2, 128.9, 128.2, 120.4, 54.0, 18.4, and 11.6
UV max (CH_3CN):	351 (ε = 3100) and 223 (6900) nm

HRMS:	Calcd For $C_{19}H_{28}ON_2Si$ (-N_2):	300.1909
	Found:	300.1901



170

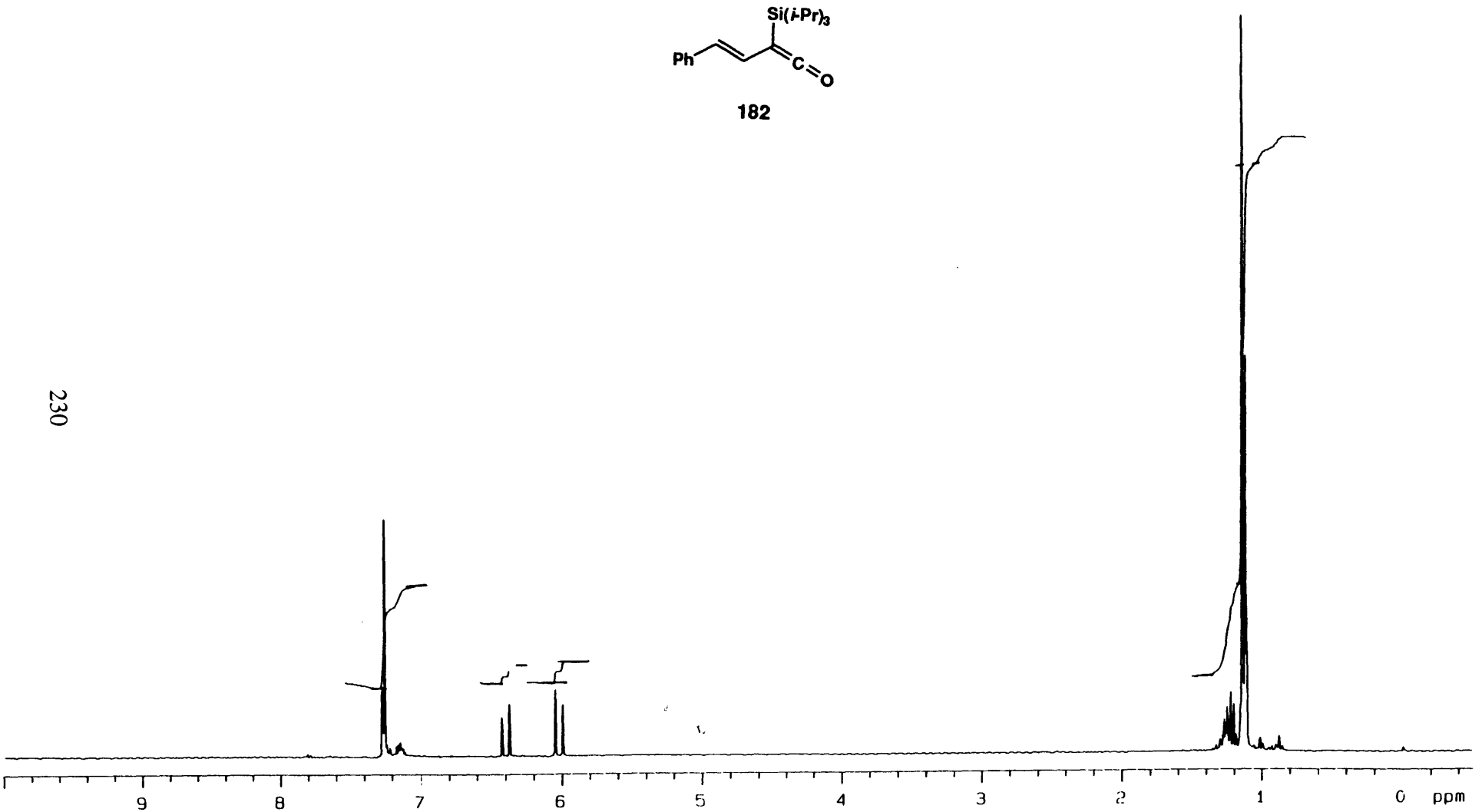


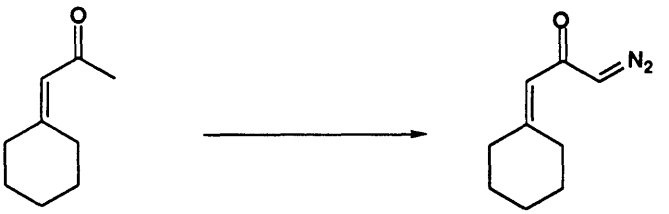
170 182

(E)-4-Phenyl-3-buten-2-triisopropylsilylketene (182).

A solution of silyldiazo ketone **170** (0.37 g, 1.13 mmol) in 12 mL of benzene was placed in a 25-cm vycor tube (15 mm O.D., 13 mm I.D.) fitted with a rubber septum. A second rubber septum (inverted) was secured with wire to the tube to insure a good seal, and the reaction mixture was degassed (three freeze-pump-thaw cycles at -196 °C, < 0.5 mm Hg) and then irradiated with 300 nm light for 3 h in a Rayonet reactor. The resulting solution was concentrated to afford 0.25 g of a red oil. Column chromatography on 10 g of silica gel (elution with hexane) provided 0.12 g (35%) of ketene **182** as a viscous yellow oil.

IR (thin film):	2934, 2869, 2083, 1604, 1460, 1375, 1320, and 1010 cm^{-1}
^1H NMR (300 MHz, $CDCl_3$):	7.15-7.27 (m, 5H), 6.40 (d, J = 15.8 Hz, 1H), 6.01 (d, J = 15.8 Hz, 1H), 1.24 (sept, J = 6.3 Hz, 3H), and 1.13 (d, J = 6.6 Hz, 18H)
^{13}C NMR (75 MHz, $(CD_3)_2SO$):	184.5, 137.4, 128.6, 128.4, 126.6, 125.2, 117.4, 18.2, 16.5, and 11.1
HRMS:	Calcd For $C_{19}H_{28}OSi$: 300.1909 Found: 300.1904


Si(i-Pr)3
Ph
C=O
182
9
8
7
6
5
4
3
2
1
0
ppm

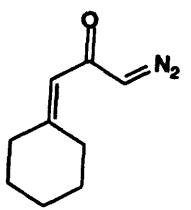


153 138

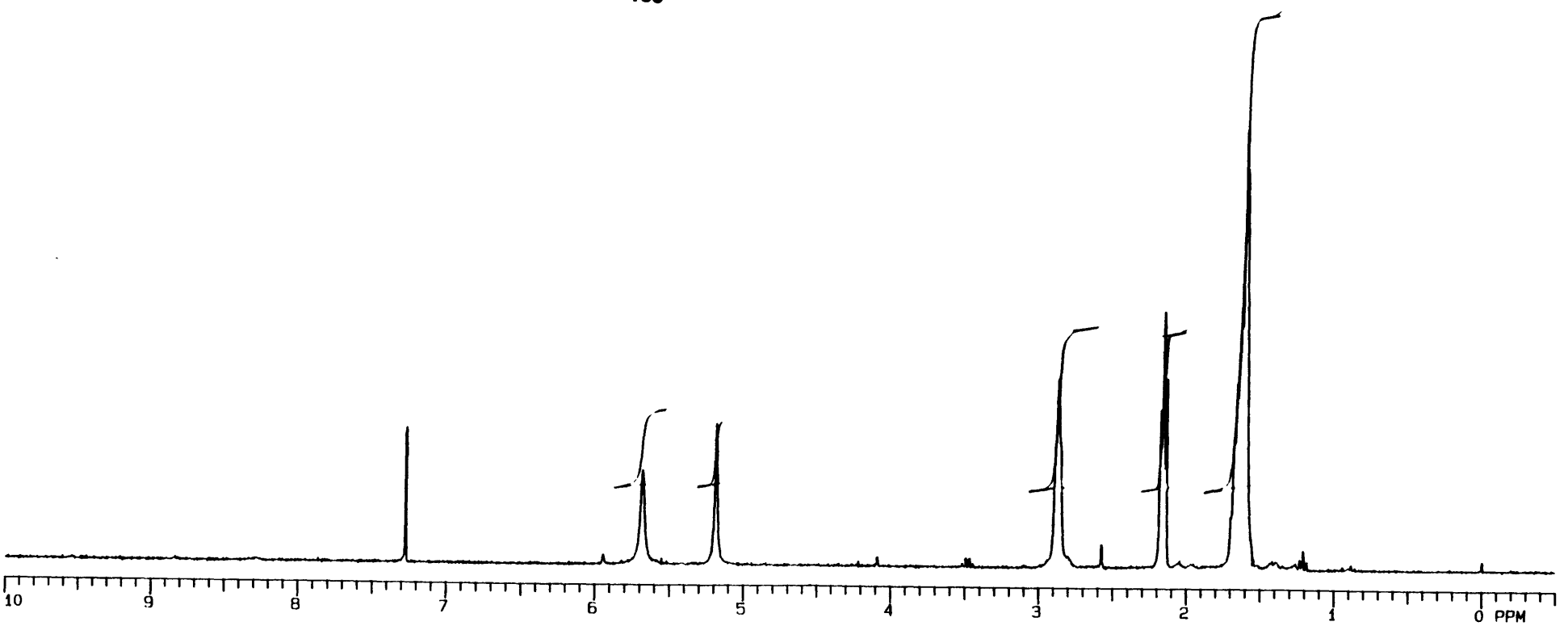
1-Diazo-3-cyclohexyl-3-buten-2-one (138).

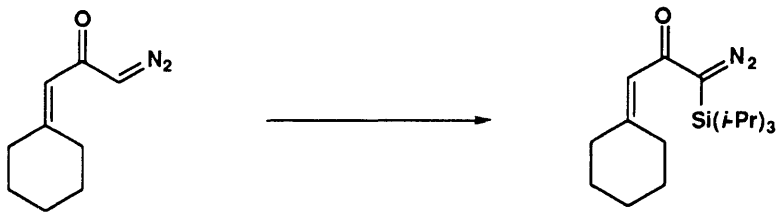
Reaction of methyl ketone **153** (0.216 g, 1.56 mmol) with LiHMDS (1.75 mmol) and 2,2,2-trifluoroethyl trifluoroacetate (0.26 mL, 0.381 g, 1.91 mmol) in 5 ml of THF according to the general procedure provided a yellow oil which was then treated with H_2O (0.029 mL, 0.029 g, 1.59 mmol), Et_3N (0.33 mL, 0.240 g, 2.39 mmol), and methanesulfonyl azide (0.28 mL, 0.292 g, 2.39 mmol) in 6.5 mL of CH_3CN at room temperature for 2 h to yield 0.28 g of a yellow oil. Column chromatography on 10 g of silica gel (gradient elution with 0-10 % EtOAc-hexane) provided 0.170 g (66%) of diazo ketone (**138**) as a yellow oil.

IR (CCl_4):	2926, 2831, 2096, 1646, 1619, 1601, 1551, 1492, and 1446 cm^{-1}
^1H NMR (300 MHz, $CDCl_3$):	5.68 (s, 1H), 5.19 (s, 1H), 2.87 (br s, 2H), 2.16 (t, J = 5.9 Hz, 2H), and 1.61-1.68 (m, 6H)
^{13}C NMR (75 MHz, $CDCl_3$):	186.0, 161.0, 118.7, 56.4, 37.9, 30.1, 28.7, 27.8, and 26.2



138



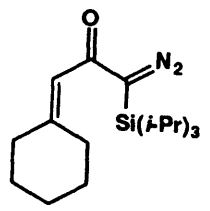


138 167

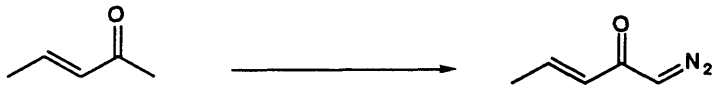
1-Diazo-4-cyclohexyl-1-triisopropylsilyl-3-buten-2-one (167).

A 25-mL, two-necked, round-bottomed flask equipped with a rubber septum, magnetic stir bar, and argon inlet adapter was charged with diazo ketone **138** (0.110 g, 0.670 mmol) in 6 mL of a 50:50 solution of Et_2O-hexane and then cooled at 0 °C in an ice-water bath while *i*-Pr_2EtN (0.11 mL, 0.0816 g, 0.632 mmol) was added dropwise over 1 min. After 5 min, triisopropylsilyl trifluoromethanesulfonate (0.18 mL, 0.200 g, 0.660 mmol) was added dropwise over 1 min and the resulting solution was stirred for 2 h while the ice-water bath warmed to room temperature. The reaction mixture was filtered through Celite with the aid of 5 mL of Et_2O and the filtrated was concentrated to afford 0.33 g of a yellow oil. Column chromatography on 10 g of silica gel (gradient elution with 0-5% EtOAc-hexane) provided 0.200 g (93%) of the silyldiazo ketone **167** as a yellow oil.

IR (thin film):	2954, 2884, 2074, 1654, 1624, 1474, 1404, 1284, 1254, and 1184 cm^{-1}
^1H NMR (300 MHz, $CDCl_3$):	6.06 (s, 1H), 2.68 (t, J = 5.9 Hz, 2H), 2.18 (t, J = 5.8 Hz, 2H), 1.59-1.67 (m, 6H), 1.36 (sept, J = 7.1 Hz, 3H), and 1.11 (d, J = 7.3 Hz, 18H)
^{13}C NMR (75 MHz, $CDCl_3$):	190.9, 158.0, 117.9, 53.1, 37.6, 30.1, 28.6, 27.8, 26.3, 18.4, and 11.7



167

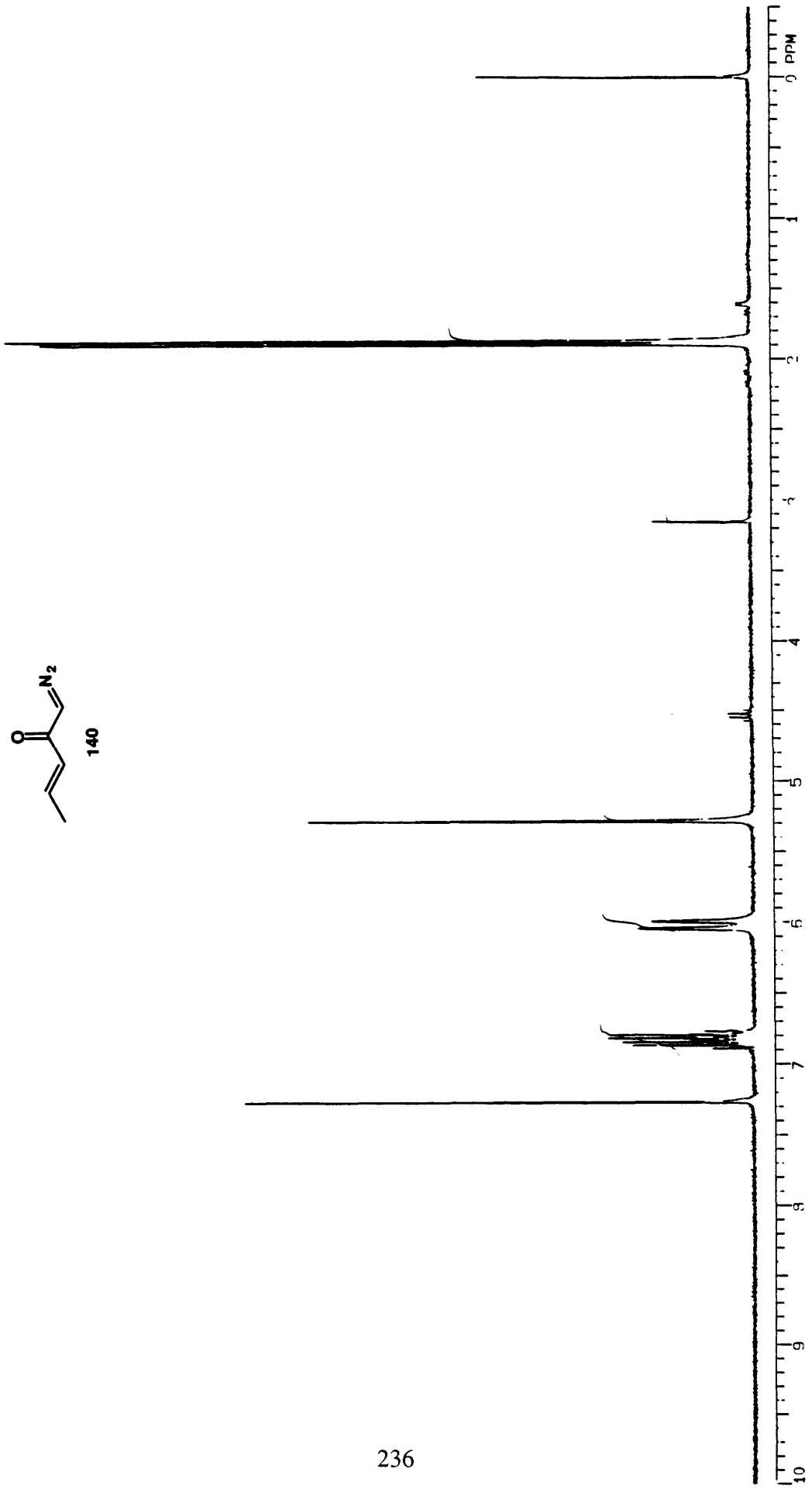


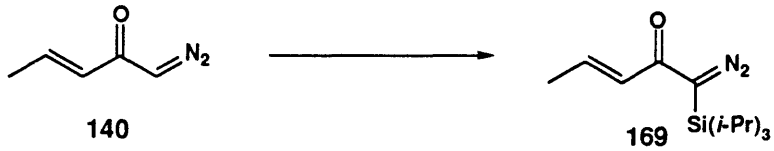
140

(E)-1-Diazo-3-penten-2-one (140).

Reaction of *trans*-3-penten-2-one (0.58 mL, 0.500 g, 5.94 mmol) with LiHMDS (6.54 mmol) and 2,2,2-trifluoroethyl trifluoroacetate (0.95 mL, 1.39 g, 7.09 mmol) in 15 ml of THF according to the general procedure provided an orange-brown oil which was then treated with H_2O (0.11 mL, 0.110 g, 6.10 mmol), Et_3N (1.2 mL, 0.871 g, 8.61 mmol), and methanesulfonyl azide (1.0 mL, 1.04 g, 8.60 mmol) in 20 mL of CH_3CN at room temperature for 4 h to yield 0.47 g of an orange oil. Column chromatography on 10 g of silica gel (gradient elution with 0-20% EtOAc-hexane) provided 0.27 g (41%) of diazo ketone (**140**) as a yellow oil.

IR (CCl_4):	3120, 2950, 2090, 1650, 1615, 1540, 1440, 1360, 1300, and 1150 cm^{-1}
^1H NMR (300 MHz, $CDCl_3$):	6.83 (dq, *J* = 15.0, 7.0 Hz, 1H), 6.00 (d, *J* = 15.2 Hz, 1H), 5.29 (s, 1H), and 1.89 (d, J = 7.0 Hz, 3H)

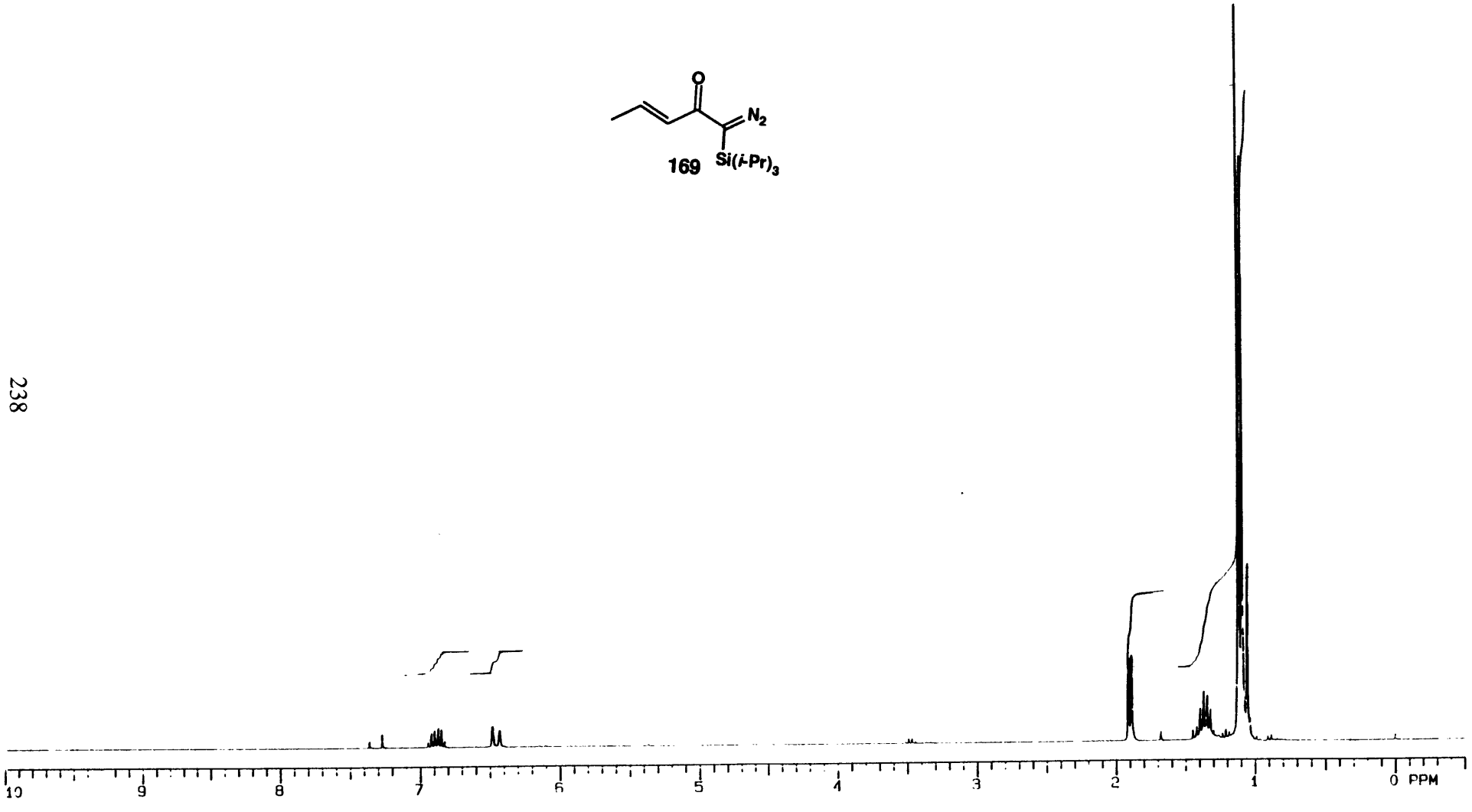

N2
O
140
PPM
0
1
2
3
4
5
6
7
8
9
10

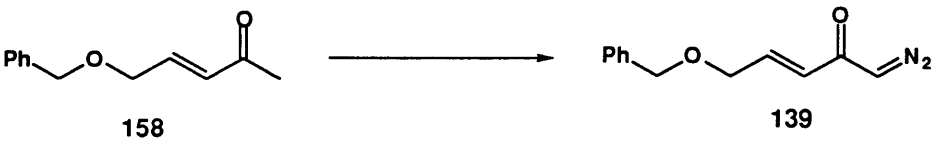


(E)-1-Diazo-1-triisopropylsilyl-3-penten-2-one (169).

A 25-mL, two-necked, round-bottomed flask equipped with a rubber septum, magnetic stir bar, and argon inlet adapter was charged with diazo ketone **140** (0.159 g, 1.44 mmol) in 14 mL of a 50:50 solution of Et_2O-hexane and then cooled at 0 °C in an ice-water bath while *i*-Pr_2EtN (0.26 mL, 0.193 g, 1.49 mmol) was added dropwise over 1 min. After 5 min, triisopropylsilyl trifluoromethanesulfonate (0.39 mL, 0.445 g, 1.45 mmol) was added dropwise over 1 min and the resulting solution was stirred for 3 h while the ice-water bath warmed to room temperature. The reaction mixture was filtered through Celite with the aid of 5 mL of Et_2O and the filtrate was concentrated to afford 0.42 g of an orange oil. Column chromatography on 10 g of silica gel (gradient elution with 0-5% EtOAc-hexane) provided 0.060 g (16%) of the silyldiazo ketone **169** as a yellow oil:

IR (CCl_4):	2950, 2880, 2080, 1660, 1610, 1550, 1470, 1389, 1300, 1220, and 1125 cm^{-1}
^1H NMR (300 MHz, $CDCl_3$):	6.89 (dq, J = 15.3, 7.2 Hz, 1H), 6.46 (d, J = 15.0 Hz, 1H), 1.90 (d, J = 7.0 Hz, 3H), 1.37 (sept, J = 7.6 Hz, 3H), and 1.11 (d, J = 7.3, 18 H)
^{13}C NMR (75 MHz, $CDCl_3$):	188.3, 140.6, 125.5, 50.0, 18.4, 17.9, and 11.6


O
N2
Si(i-Pr)3
169
10
9
8
7
6
5
4
3
2
1
0 PPM

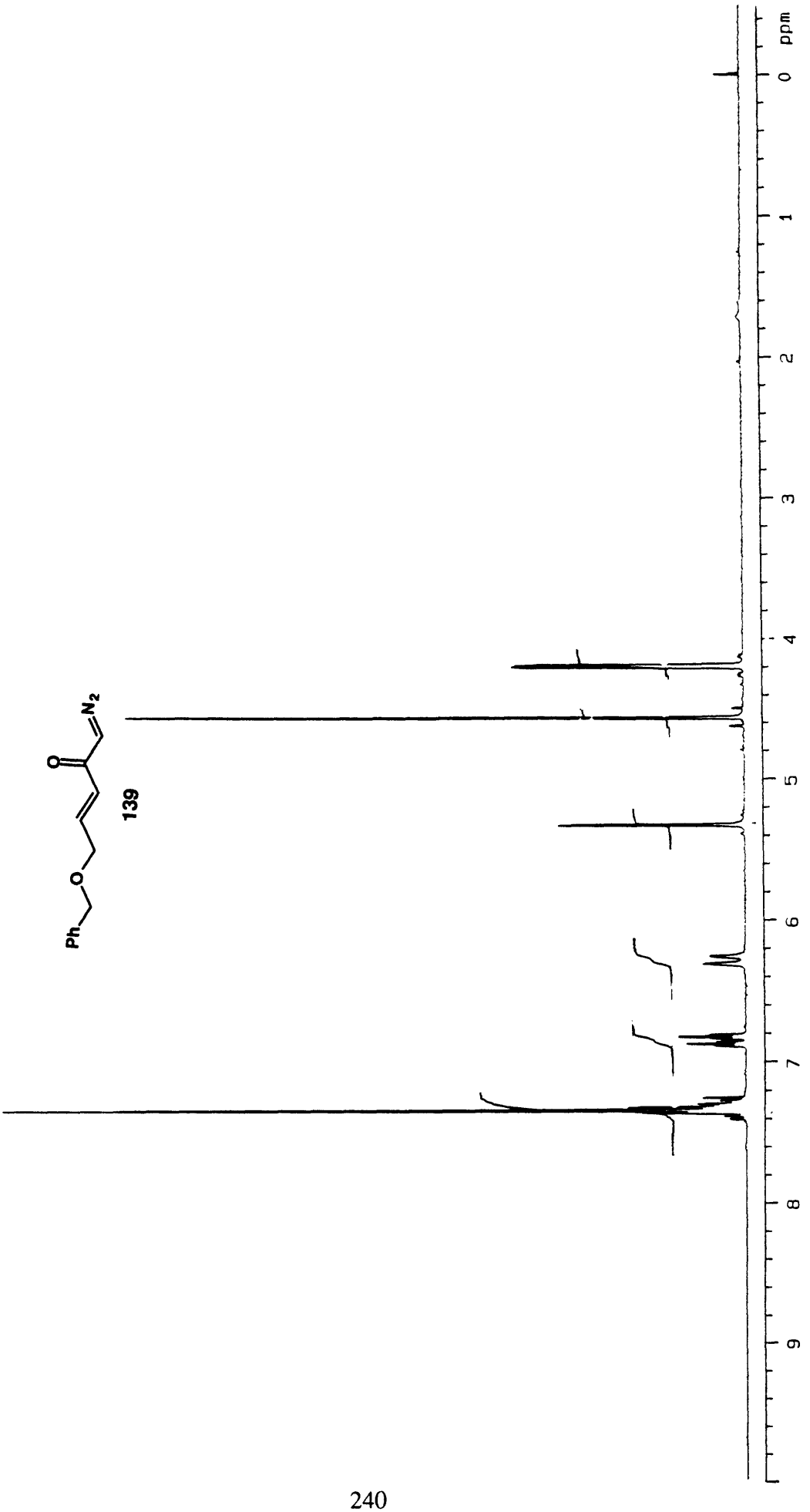


158 139

(E)-1-Diazo-5-benzyloxy-3-penten-2-one (139).

Reaction of methyl ketone **158** (0.274 g, 1.44 mmol) with LiHMDS (1.58 mmol) and 2,2,2-trifluoroethyl trifluoroacetate (0.23 mL, 0.339 g, 1.73 mmol) in 6 ml of THF according to the general procedure provided a yellow-orange oil which was then treated with H_2O (0.025 mL, 0.025 g, 1.39 mmol), Et_3N (0.30 mL, 0.219 g, 2.16 mmol), and methanesulfonyl azide (0.25 mL, 0.262 g, 2.16 mmol) in 10 mL of CH_3CN at room temperature for 3 h to yield 0.30 g of an orange oil. Column chromatography on 30 g of silica gel (gradient elution with 0-20% EtOAc-hexane) provided 0.23 g (74%) of diazo ketone **139** as a yellow oil.

IR (thin film):	3090, 2860, 2110, 1660, 1600, 1590, 1455, and 1360 cm^{-1}
^1H NMR (300 MHz, $CDCl_3$):	7.22-7.41 (m, 5H), 6.83 (dt, J = 15.5, 4.1 Hz, 1H), 6.24 (d, J = 16.1 Hz, 1H), 5.32 (s, 1H), 4.58 (s, 2H), and 4.10 (dd, J = 2.0, 4.0 Hz, 2H)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139
ppm
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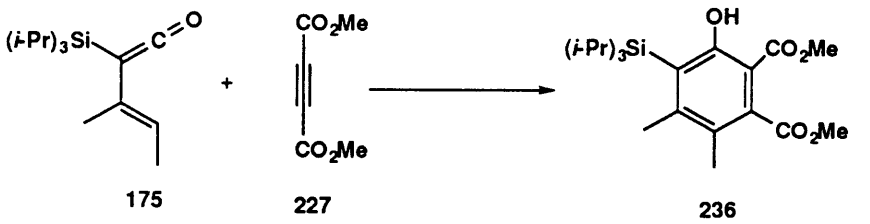
7
8
9

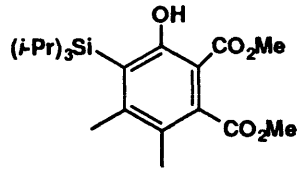


175 227 236

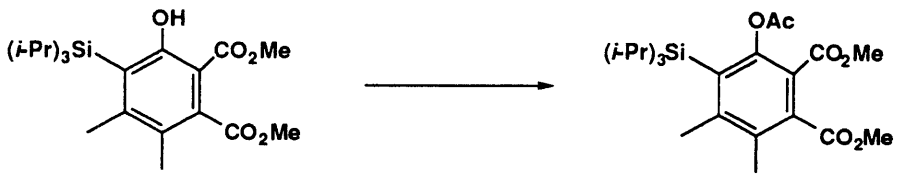
Dimethyl-5,6-dimethyl-3-hydroxy-4-triisopropylsilyl phthalate (236).

A flame-dried, threaded Pyrex tube (20 mm O.D., 16 mm I.D.) was charged with a solution of silylketene **175** (0.092 g, 0.370 mmol) and dimethyl acetylenedicarboxylate (0.045 mL, 0.052 g, 0.370 mmol) in 0.4 mL of toluene and sealed with a rubber septum. The reaction mixture was degassed (three freeze-pump-thaw cycles at -196 °C, < 0.5 mm Hg) and then tightly sealed with a teflon cap. The reaction mixture was heated at 150 °C for 24 h and then transferred to a round-bottomed flask using 1 mL of benzene and concentrated to afford 0.20 g of an orange oil. Column chromatography on 10 g of silica gel (gradient elution with 0-70% benzene-hexane) provided 0.14 g (95%) of **236** as white crystals: mp 73-75 °C.

IR (CCl_4):	2950, 2870, 1740, 1670, 1445, 1350, 1330, 1225, and 1050 cm^{-1}
^1H NMR (300 MHz, $CDCl_3$):	11.57 (s, 1H), 3.90 (s, 3H), 3.88 (s, 3H), 2.37 (s, 3H), 2.10 (s, 3H), 1.58 (sept, J = 7.5 Hz, 3H), and 1.08 (d, J = 7.2 Hz, 18H)
^{13}C NMR (75 MHz, $CDCl_3$):	170.4, 170.2, 165.7, 135.2, 128.3, 126.5, 124.5, 104.9, 52.6, 52.2, 22.1, 19.3, 16.9, and 13.6
UV max (CH_3CN):	322 (ε = 9700), 257 (9900), and 220 (32 000) nm
Elemental Analysis:	Calcd for $C_{21}H_{34}O_5Si$: C, 63.92; H, 8.69 Found: C, 63.88; H, 8.67



236

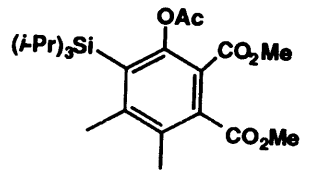


236 237

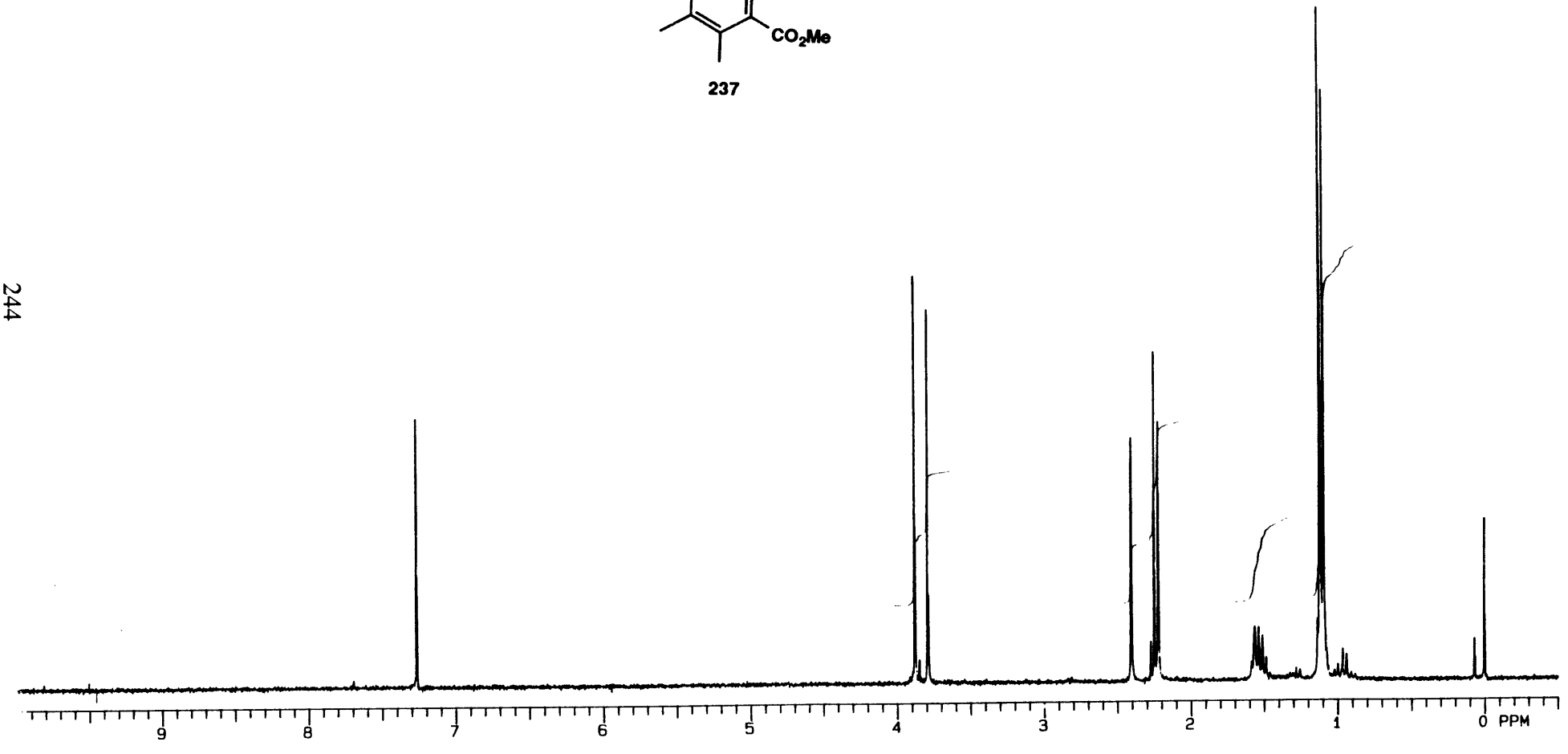
Dimethyl 3-acetoxy-5,6-dimethyl-4-triisopropylsilyl phthalate (237).

A 5-mL, two-necked, round-bottomed flask equipped with a rubber septum and argon inlet adapter was charged with a solution of phenol **236** (0.0629 g, 0.160 mmol). DMAP (0.023 g, 0.19 mmol) and acetic anhydride (0.021 mL, 0.023 g, 0.21 mmol) in 2 mL of dichloromethane were then added at room temperature. The reaction mixture was stirred for 18 h at room temperature and 1 mL of methanol was then added. The reaction mixture was then transferred to a round-bottomed flask using 1 mL of dichloromethane and concentrated to afford a brown-green oil. The oil was then dissolved in 2 mL of Et_2O and washed with 5 mL of 5% HCl, 5 mL of $NaHCO_3$, dried over $MgSO_4$, filtered, and concentrated to afford 0.056 g of a brown oil. Column chromatography on 5 g of silica gel (gradient elution with 0-20% EtOAc-hexane) provided 0.047 g (67%) of **237** as a yellow oil.

IR (CCl_4):	2950, 2880, 1770, 1735, 1550, 1435, 1390, 1365, 1290, 1270, 1210, 1190, 1050, and 1010 cm^{-1}
^1H NMR (300 MHz, $CDCl_3$):	3.89 (s, 3H), 3.78 (s, 3H), 2.40 (s, 3H), 2.25 (s,3H), 2.22 (s, 3H), 1.55 (sept, J = 7.2 Hz, 3H), and 1.10 (d, J = 7.5 Hz, 18H)
^{13}C NMR (75 MHz, $CDCl_3$):	170.0, 169.3, 169.2, 166.0, 132.3, 127.5, 125.1, 123.8, 107.6, 52.5, 52.4, 23.0, 21.6, 19.4, 17.3, and 14.0



237

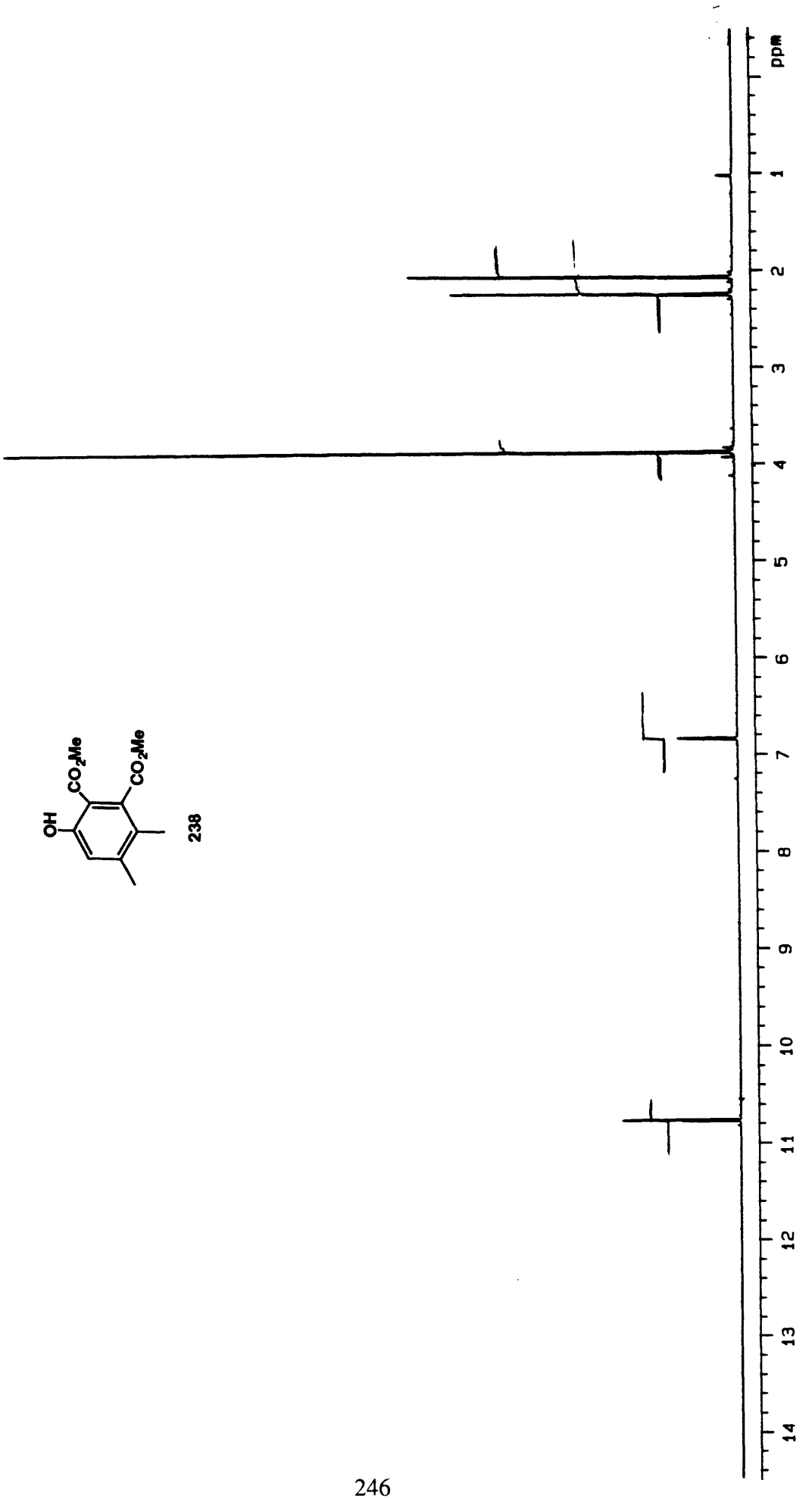


236 238

Dimethyl 5,6-dimethyl-3-hydroxy phthalate (238).

A 10-mL, two-necked, round-bottomed flask equipped with a rubber septum and argon inlet adapter was charged with a solution of phthalate **236** (0.200 g, 0.507 mmol) and 0.6 mL of dichloromethane. Trifluoroacetic acid (0.78 mL, 1.16 g, 10.1 mmol) was added dropwise to the reaction mixture over 1 min and the resulting solution was stirred at room temperature for 2 h. The reaction mixture was then transferred using 0.5 mL of dichloromethane to a round-bottomed flask and concentrated to afford 0.29 g of a brown oil. Column chromatography on 15 g of silica gel (gradient elution with 0-10% EtOAc-hexane) provided 0.092 g (76%) of phthalate **238** as a colorless oil.

IR ($CHCl_3$):	3700, 3640, 3040, 2990, 1730, 1660, 1525, 1480, 1450, 1430, and 1340 cm^{-1}
^1H NMR (300 MHz, $CDCl_3$):	10.76 (s, 1H), 6.84 (s, 1H), 3.88 (s, 6H), 2.25 (s, 3H), and 2.07 (s, 3H)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CO2Me
CO2Me
238
ppm
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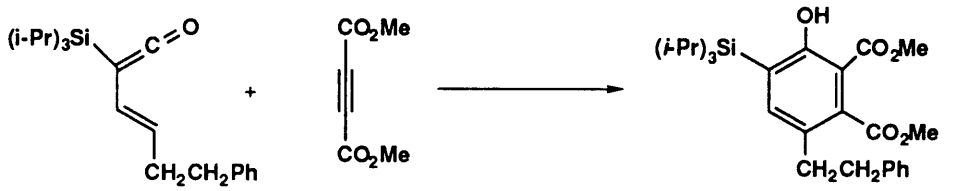
9
10
11
12
13
14

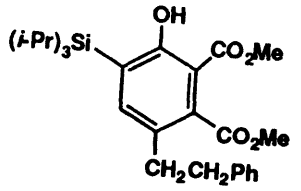


179 227 242

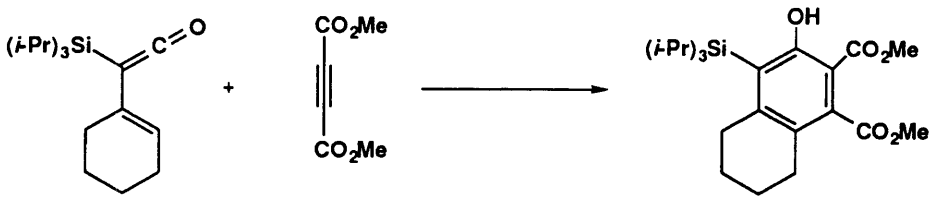
Dimethyl 6-(2-phenylethyl)-3-hydroxy-4-triisopropylsilyl phthalate (242).

A flame-dried, threaded Pyrex tube (20 mm O.D., 16 mm I.D.) was charged with a solution of silylketene **179** (0.090 g, 0.27 mmol) and dimethyl acetylenedicarboxylate (0.050 mL, 0.058 g, 0.41 mmol) in 0.3 mL of toluene and sealed with a rubber septum. The reaction mixure was degassed (three freeze-pump-thaw cycles at -196 °C, < 0.5 mm Hg) and then tightly sealed with a teflon cap. The reaction mixture was heated at 150 °C for 3 h and then transferred to a round-bottomed flask using 1 mL of benzene and concentrated to afford 0.12 g of a brown oil. Column chromatography on 10 g of silica gel (gradient elution with 0-50% CH_2Cl_2-petroleum ether) provided 0.079 g (61%) of **242** as a white solid: mp 77.5-79.0 °C.

IR (CCl_4):	2943, 2860, 1740, 1670, 1585, 1440, 1400, 1340, 1210, 1135, and 1030 cm^{-1}
^1H NMR (300 MHz, $CDCl_3$):	11.19 (s, 1H), 7.12-7.29 (m, 6H), 3.91 (s, 3H), 3.90 (s, 3H), 2.79-2.85 (m, 4H), 1.43 (sept, J = 7.6 Hz, 3H), and 1.04 (d, J = 7.6 Hz, 18 H)
^{13}C NMR (75 MHz, $CDCl_3$):	170.0, 169.6, 165.0, 144.6, 141.1, 134.9, 128.5, 128.5, 128.4, 126.3, 126.0, 107.7, 52.8, 52.3, 37.7, 35.0, 18.8, and 11.5
UV max (CH_3CN):	310 (ε = 5900), 317 (7500), and 219 (32 000) nm
Elemental Analysis:	Calcd for $C_{27}H_{38}O_5Si$: C, 68.90; H, 8.14 Found: C, 68.80; H, 8.17



242

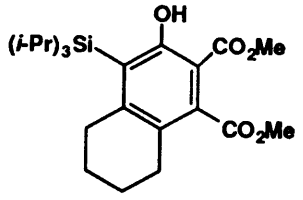


181 227 243

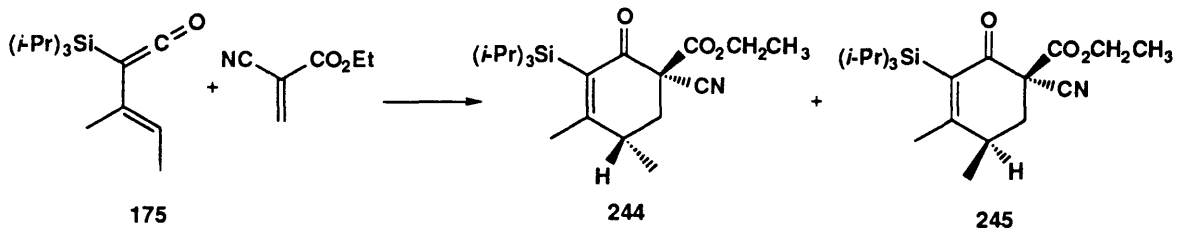
1,2-Dimethyl 5,6,7,8-Tetrahydro-4-triisopropylsilyl-3-napthol dicarboxylate (243).

A flame-dried, threaded Pyrex tube (20 mm O.D., 16 mm I.D.) was charged with a solution of silylketene **181** (0.154 g, 0.55 mmol) and dimethyl acetylenedicarboxylate (0.066 mL, 0.076 g, 0.54 mmol) in 0.4 mL of toluene and sealed with a rubber septum. The reaction mixure was degassed (three freeze-pump-thaw cycles at -196 °C, < 0.5 mm Hg) and then tightly sealed with a teflon cap. The reaction mixture was heated at 150 °C for 22 h and then transferred to a round-bottomed flask using 1 mL of benzene and concentrated to afford 0.29 g of a brown oil. Column chromatography on 10 g of silica gel (gradient elution with 0-80% benzene-hexane) provided 0.17 g (73%) of **243** as a light yellow oil.

IR (CCl_4):	2950, 2870, 1740, 1670, 1575, 1440, 1380, 1325, and 1212 cm^{-1}
^1H NMR (300 MHz, $CDCl_3$):	11.45 (s, 1H), 3.90 (s, 3H), 3.89 (s, 3H), 2.86 (t, J = 5.9 Hz, 3H), 2.59 (t, J = 6.4 Hz, 3H), 1.60-1.71 (m, 4H), 1.54 (sept, J = 7.3 Hz, 3H), and 1.06 (d, J = 7.3 Hz, 18H)
^{13}C NMR (75 MHz, $CDCl_3$):	170.0, 169.9, 165.0, 155.1, 135.7, 125.6, 125.3, 105.1, 52.8, 52.3, 31.8, 26.3, 22.1, 21.7, 19.5, and 13.8



243



175 244 245

6-Cyano-6-ethylcarboxylate-3,4-dimethyl-2-triisopropylsilyl-2-cyclohexen-1-one (244,245).

A 10-mL, two-necked round-bottomed flask equipped with a rubber septum and argon inlet adapter was charged with a solution of silylketene **175** (0.201 g, 0.800 mmol) in toluene while ethyl cyanoacrylate (0.11 mL, 0.12 g, 0.96 mmol) was added dropwise at room temperature over 0.5 min. The reaction mixture was stirred at room temperature for 24 h and then transferred to a round-bottomed flask using 1 mL of benzene and concentrated to afford 0.39 g of a light yellow oil. Column chromatography on 10 g of silica gel (gradient elution with 0-20% EtOAc-hexane) provided 0.113 g (38%) of **244**, mp 81.5-82 °C and 0.625 g (20%) of **245**, mp 65-66.5 °C, and 0.120 g (40%) of a mixture of **244** and **245** as white solids (total yield, 98%).

IR (CCl_4): For the major diastereomer **244**: 2940, 2870, 2240, 1750, 1690, 1570, 1450, 1370, 1240, 1215, 1160, 1110, 1070, and 1020 cm^{-1}
For the minor diastereomer **245**: 2950, 2870, 1755, 1695, 1550, 1460, 1370, 1250, 1160, and 1075 cm^{-1}

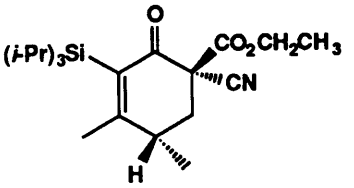
^1H NMR (300 MHz, $CDCl_3$): For the major diastereomer **244**: 4.29 (dq, J = 10.8, 7.1 Hz, 1H), 4.18 (dq, J = 10.7, 7.1 Hz, 1H), 2.89 (dd, *J* = 13.9, 6.0 Hz, 1H), 2.72 (app q, *J* = 6.7 Hz, 1H), 2.15 (dd, *J* = 13.9, 6.4 Hz, 1H), 2.08 (s, 3H), 1.44 (sept, *J* = 7.5 Hz, 3H), 1.35 (d, *J* = 7.1 Hz, 3H), 1.31 (t, *J* = 7.1 Hz, 3H), 1.06 (d, *J* = 7.5 Hz, 12H), and 1.04 (d, *J* = 7.4 Hz, 6H)

For the minor diastereomer **245**:
4.39 (dq, J = 10.8, 7.2 Hz, 1H), 4.30 (dq, J = 12.0, 7.2 Hz, 1H), 2.81 (ddq, J = 5.4, 10.7, 7.0 Hz, 1H), 2.52 (dd, J = 14.2, 5.4 Hz, 1H), 2.25 (dd, J = 14.2, 10.7 Hz, 1H), 2.10 (s, 3H), 1.43 (sept, J = 7.5 Hz, 3H), 1.34 (t, J = 7.1 Hz, 3H), 1.27 (d, J = 7.0 Hz, 3H), and 1.08 (app t, J = 7.5 Hz, 18H)

^{13}C NMR (75 MHz, $CDCl_3$): For the major diastereomer **244**:
189.7, 174.6, 165.0, 132.1, 117.4, 63.9, 55.1, 37.3, 35.9, 24.6, 21.0, 19.4, 19.3, 14.2, 13.1, and 13.0
For the minor diastereomer **245**:
191.0, 172.5, 164.9, 132.3, 115.9, 63.1, 55.0, 37.1, 36.0, 23.4, 20.2, 19.1, 18.9, 14.0, and 12.7

Elemental Analysis:

Calcd for $C_{21}H_{35}O_3SiN$: C, 66.79; H, 9.34; N, 3.71
Found for the major diastereomer **244**: C, 66.57; H, 9.42; N, 3.62
Found for the minor diastereomer **245**: C, 66.86; H, 9.41; N, 3.62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CN
H

244

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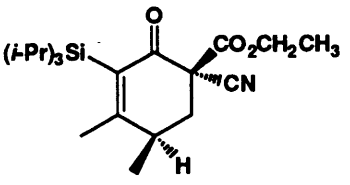
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245

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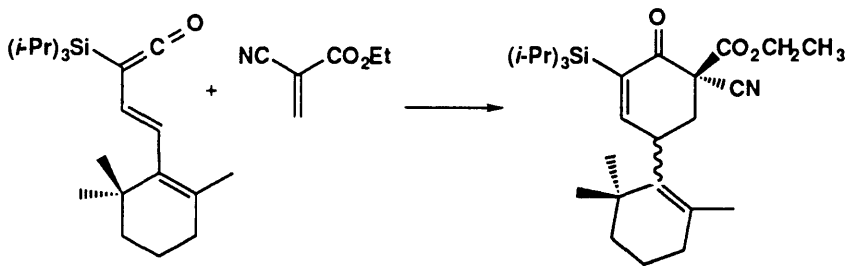


177 246a,b

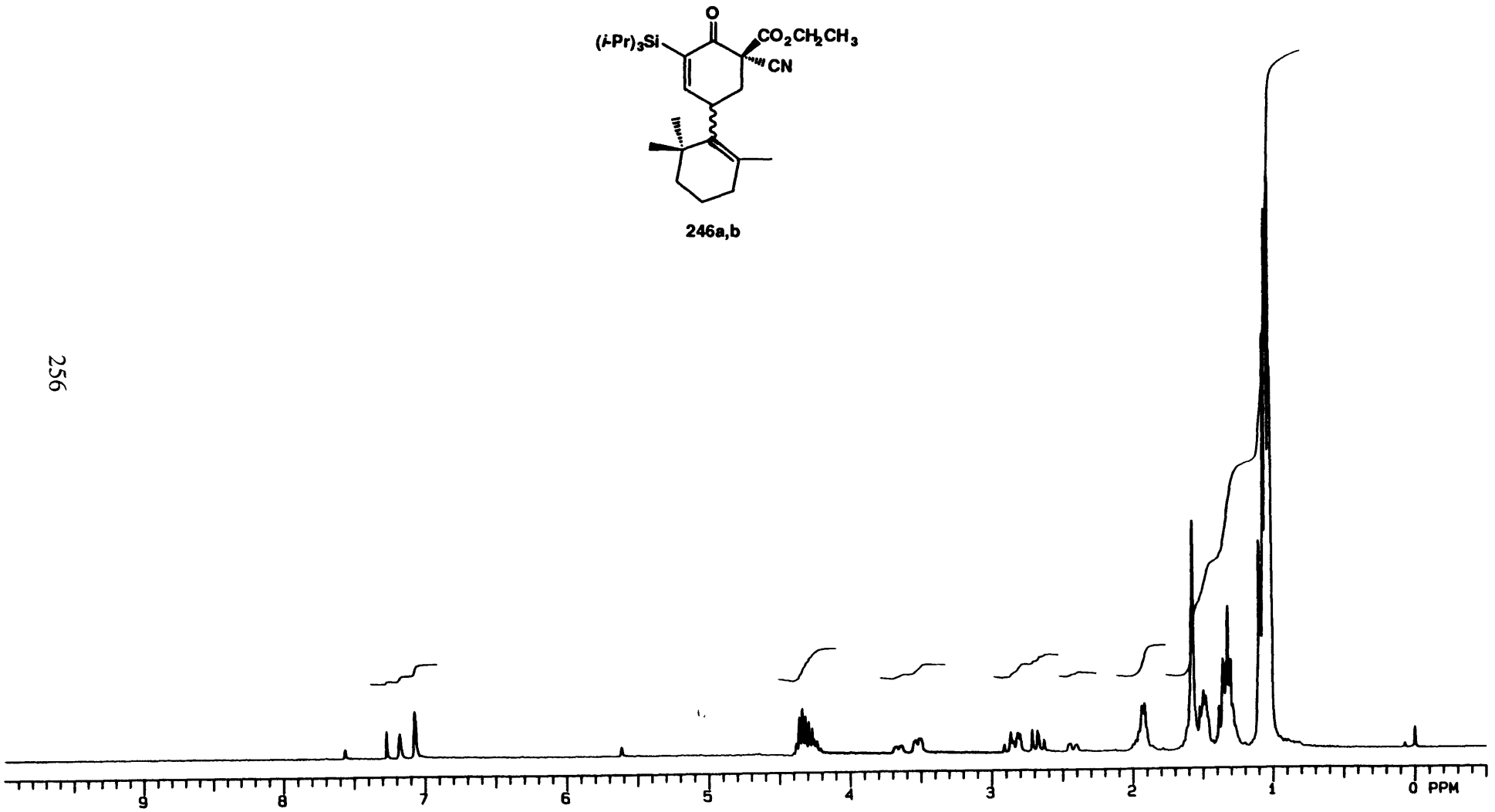
6-Cyano-6-ethylcarboxylate-2-triisopropylsilyl-4-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2-cyclohexen-1-one (246a,b).

A 10-mL, two-necked round-bottomed flask equipped with a rubber septum and argon inlet adapter was charged with a solution of silylketene **177** (0.209 g, 0.600 mmol) in toluene while ethyl cyanoacrylate (0.11 mL, 0.118 g, 0.940 mmol) was added dropwise at room temperature over 0.25 min. Five additional (0.05 mL, 0.054 g, 0.43 mmol) portions of ethyl cyanoacrylate were added at intervals of ~15 h. After 93 h, the reaction mixture was transferred to a round-bottomed flask using 2 mL of benzene-acetone and concentrated to afford 0.75 g of a light yellow oil. Column chromatography on 10 g of silica gel (gradient elution with 0-3% EtOAc-hexane) provided 0.12 g (43%; 86% yield based on recovered starting material) of a 4:1 mixture of diastereomers **246a** and **246b** as a yellow oil.

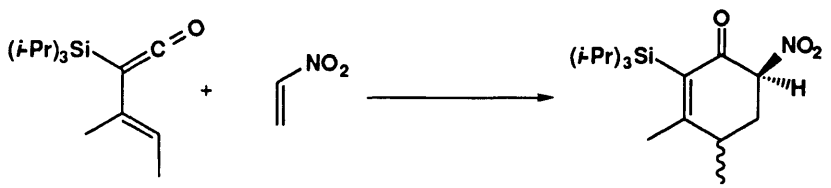
IR (CCl_4): For the mixture of diastereomers: 2940, 2860, 1740, 1680, 1540, 1460, 1430, 1360, 1230, 1100, 1060, and 1001

^1H NMR (300 MHz, $CDCl_3$): For the major diastereomer **246a**: 7.07 (s, 1H), 4.29 (dq, J = 9.0, 7.1 Hz, 1H), 4.26 (dq, J = 10.8, 7.2 Hz, 1H), 3.53 (dd, J = 11.2, 3.1 Hz, 1H), 2.84 (dd, J = 14.0, 5.0 Hz, 1H), 2.66 (dd, J = 14.0, 11.7 Hz, 1H), 1.89-1.96 (m, 2H), 1.57 (s, 3H), 1.43-1.65 (m, 4H), 1.26-1.41 (m, 3H), 1.33 (t, J = 7.1 Hz, 3H), 1.05 (s, 6H), and 1.04 (d, J = 7.5 Hz, 18 H)

HRMS:	Calcd for $C_{28}H_{45}O_3NSi$:	471.3169
	Found:	471.3164



246a,b



175 248 249a,b

cis-6-Nitro-3,4-trimethyl-2-triisopropylsilyl-2-cyclohexen-1-one and _trans_-6-Nitro-3,4-trimethyl-2-triisopropylsilyl-2-cyclohexen-1-one (249a,b).

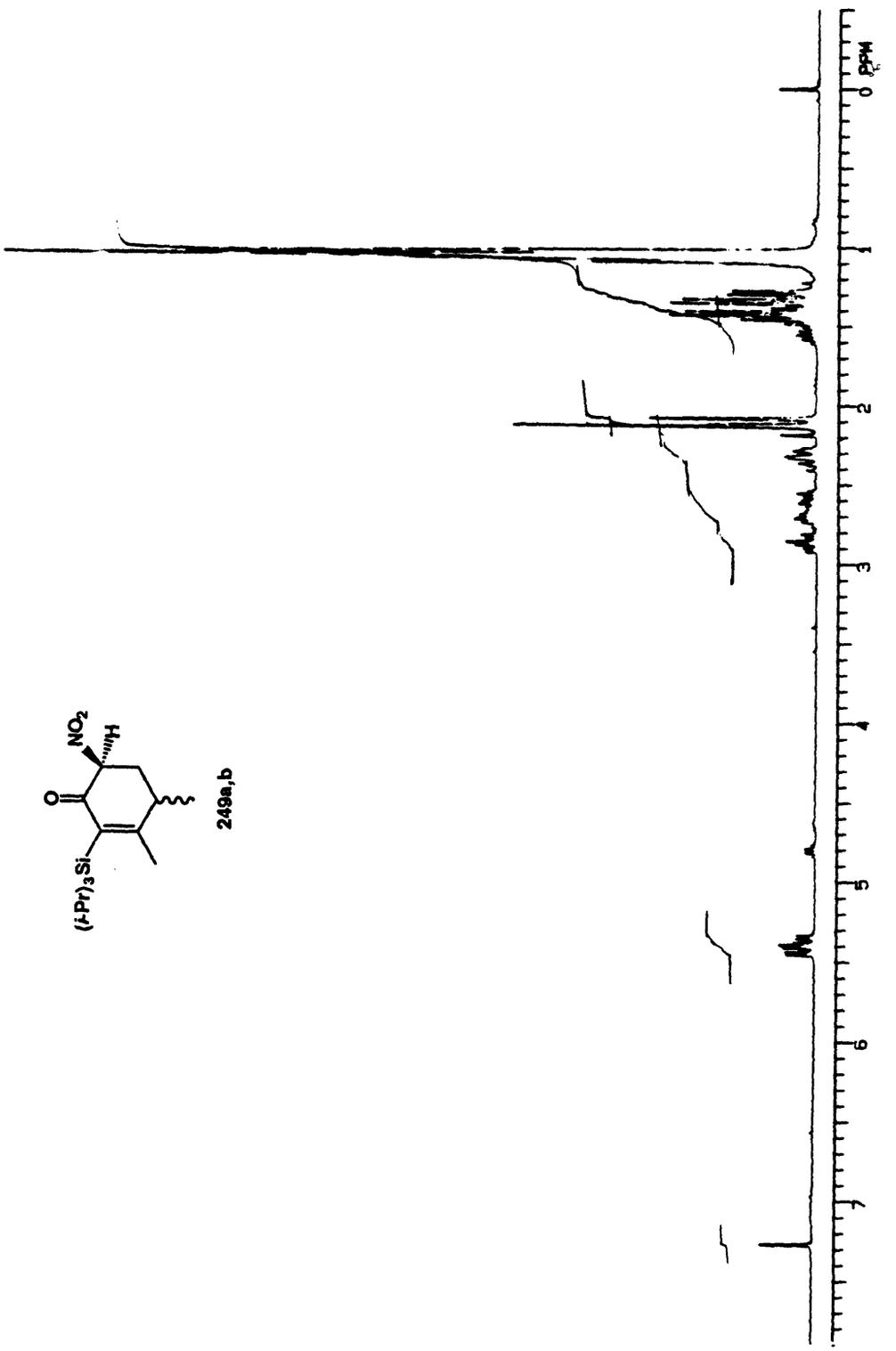
A 10-mL, two-necked, round-bottomed flask equipped with a rubber septum and argon inlet adapter was charged with a solution of silylketene **175** (0.208 g, 0.822 mmol), two crystals of BHT, and 0.8 mL of benzene. A solution of nitroethylene[133] (0.99 M in benzene, 0.83 mL, 0.82 mmol) was added, and the resulting mixture was stirred at room temperature. Two additional portions of nitroethylene solution were added (0.99 M in benzene, 0.83 mL, 0.82 mmol) after 12 h and 20 h. The reaction mixture was stirred for a total of 39 h and then transferred to a round-bottomed flask using 1 mL of benzene and concentrated to afford 0.29 g of a light yellow oil. Column chromatography on 30 g of silica gel (gradient elution with 0-10% EtOAc-hexane) provided 0.23 g (85%) of a 2:1 mixture of diastereomers **249a** and **249b** as a yellow oil.

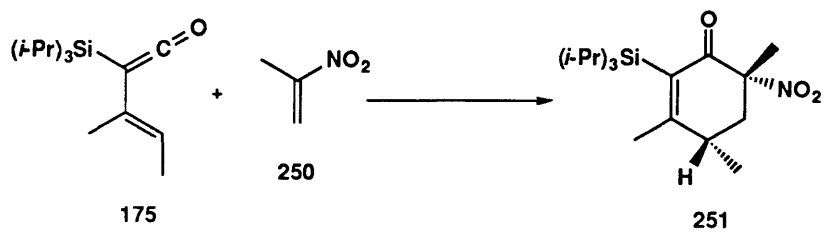
IR (CCl_4): For the mixture of diastereomers **249a,b**: 2930, 2850, 1735, 1670, 1550, 1450, 1360, 1280, 1240, and 1200 cm^{-1}

^1H NMR (300 MHz, $CDCl_3$): For the major diastereomer **249a**: 5.42 (dd, J =4.2, 12.5 Hz, 1H), 2.88 (dd, J = 5.7, 13.1 Hz, 1H), 2.53-2.75 (m, 1H), 2.27-2.41 (m, 1H), 2.13 (s, 3H), 1.43 (sept, J = 7.6 Hz, 3H), 1.34 (d, J = 7.2 Hz, 3H), and 1.05 (d, J = 7.4 Hz, 18 H)

For the minor diastereomer **249b**: 5.37 (dd, J = 4.7, 12.4 Hz, 1H), 2.80 (dd, J = 6.0, 13.7 Hz, 1H), 2.53-2.73 (m, 1H), 2.27-2.41 (m, 1H), 2.08 (s, 3H), 1.54 (sept, J = 7.5 Hz, 3H), 1.29 (d, J = 6.9 Hz, 3H), and 1.08 (d, J = 7.4 Hz, 18H)

^{13}C NMR (75 MHz, $CDCl_3$): For the mixture of diastereomers **249a** and **249b**: 191.9, 191.6, 174.6, 172.7, 132.6, 132.1, 88.9, 86.5, 37.6, 37.5, 34.3, 33.6, 24.5, 23.3, 20.9, 19.0, 19.1, 18.9, 18.5, 12.5, 12.6, and 11.4.


NO2
H
O
(i-Pr)3Si
249a,b
PPM
0
1
2
3
4
5
6
7

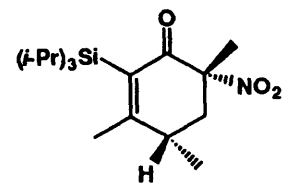


175 250 251

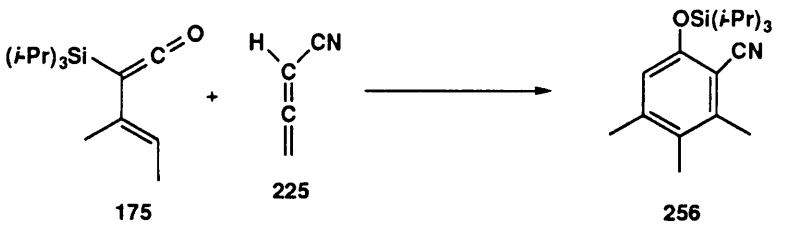
6-Nitro-3,4,6-trimethyl-2-triisopropylsilyl-2-cyclohexen-1-one (251).

A flame-dried, threaded Pyrex (20 mm O.D., 16 mm I.D.) was charged with a solution of silylketene **175** (0.154 g, 0.610 mmol), nitropropene (0.10 mL, 0.104 g, 1.20 mmol), and one crystal of BHT in 0.6 mL of toluene and then sealed with a rubber septum. The reaction mixure was degassed (three freeze-pump-thaw cycles at -196 °C, < 0.5 mm Hg) and tightly sealed with a teflon cap. The reaction mixture was heated at 110 °C for 16 h and then transferred to a round-bottomed flask using 1 mL of benzene and concentrated to afford 0.23 g of a brown oil. Column chromatography on 15 g of silica gel (gradient elution with 0-10% EtOAc-hexane) provided 0.073 g (35%) of **251** as a white solid: mp 82-84 °C.

IR (CCl_4):	2930, 2860, 1670, 1540, 1455, 1380, 1350, 1280, and 1220 cm^{-1}
^1H NMR (300 MHz, $CDCl_3$):	2.71 (dd, J = 13.5, 9.8 Hz, 1H), 2.52 (m, 1H), 2.27 (dd, J = 13.5, 5.8 Hz, 1H), 2.08 (s, 3H), 1.78 (s, 3H), 1.43 (sept, J = 7.4 Hz, 3H), 1.28 (d, J = 7.1 Hz, 3H), and 1.04 (app t, J = 7.6 Hz, 18H)
^{13}C NMR (75 MHz, $CDCl_3$):	194.9, 171.8, 132.2, 93.1, 40.4, 37.0, 23.4, 20.9, 20.4, 19.1, 19.0, 12.7, and 12.5



251

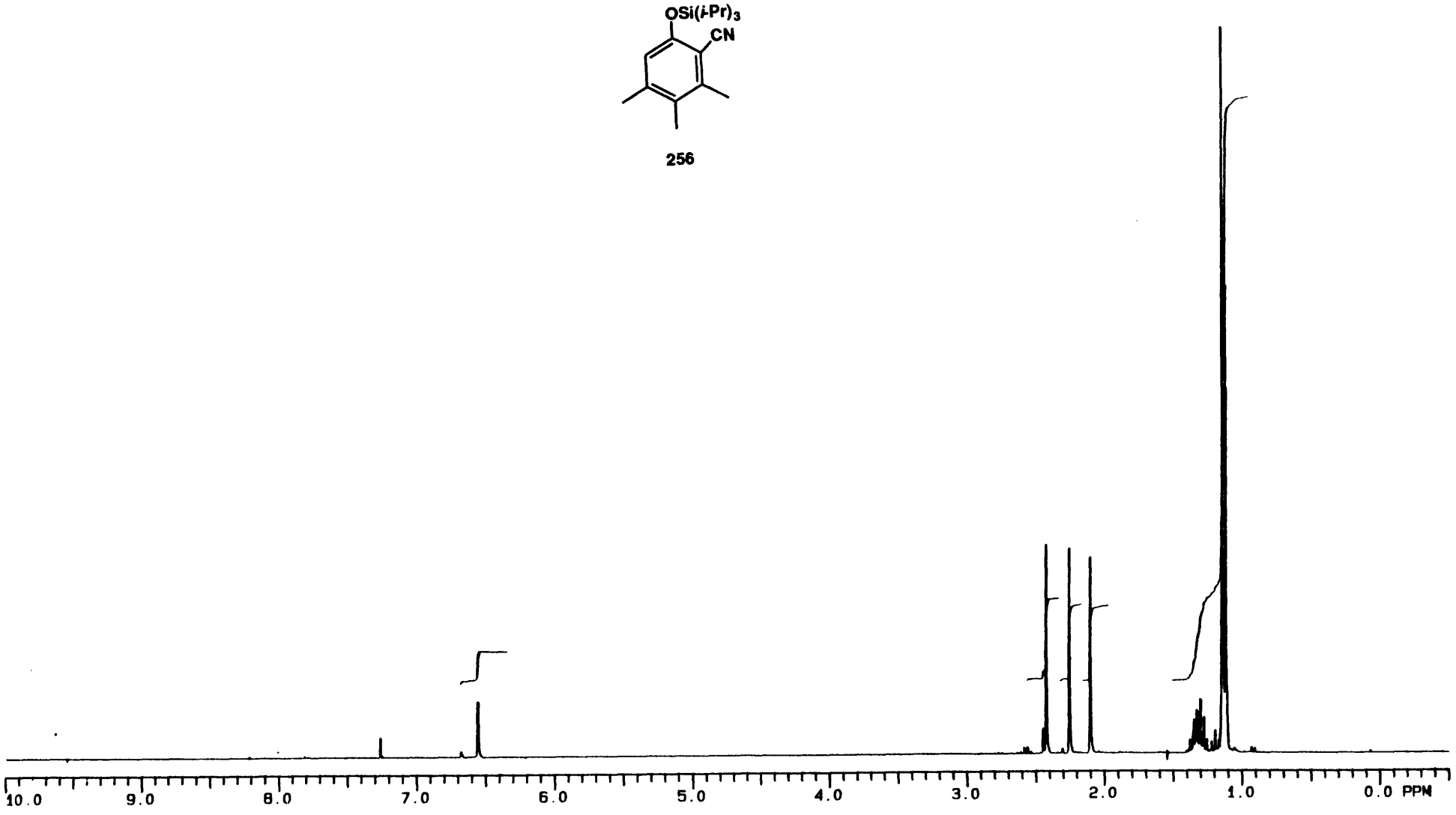


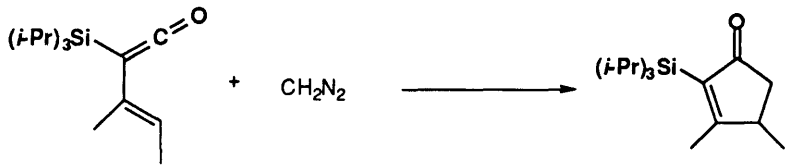
175 225 256

4,5,6-Trimethyl-2-[(triisopropylsilyl)oxy]-benzonitrile (256).

A flame-dried, threaded Pyrex tube (20 mm O.D., 16 mm I.D.) was charged with a solution of silylketene **175** (0.153 g, 0.605 mmol) and cyanoallene (0.132 g, 2.03 mmol) in 0.6 mL of toluene and sealed with a rubber septum. The reaction mixure was degassed (three freeze-pump-thaw cycles at -196 °C, < 0.5 mm Hg) and tightly sealed with a teflon cap. The reaction mixture was heated at 150 °C for 31 h and then transferred to a round-bottomed flask using 1 mL of benzene and concentrated to afford a brown oil. Column chromatography on 10 g of silica gel (gradient elution with 0-45% CH_2Cl_2-petroleum ether) provided 0.13 g (67%) of **256** as white crystals: mp 58-59 °C.

IR (CCl_4):	2950, 2870, 2225, 1730, 1550, 1470, 1330, and 1240 cm^{-1}
^1H NMR (300 MHz, $CDCl_3$):	6.55 (s, 1H), 2.43 (s, 3H), 2.26 (s, 3H), 2.11 (s, 3H), 1.32 (sept, J = 6.9 Hz, 3H), and 1.13 (d, J = 7.0 Hz, 18H)
^{13}C NMR (75 MHz, $CDCl_3$):	155.9, 142.5, 140.7, 127.9, 117.7, 117.0, 103.5, 21.6, 18.9, 18.0, 15.1, and 13.0
UV max (CH_3CN):	222 nm (ε = 470)
HRMS:	Calcd for $C_{19}H_{31}ONSi$: 317.2175 Found: 317.2165


OSi(i-Pr)3
CN
256
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0 PPM



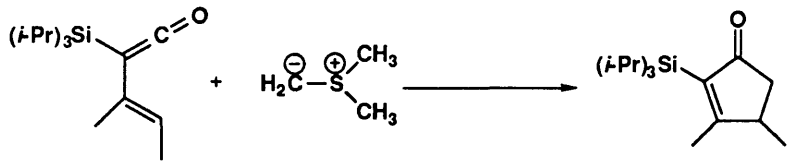
175 265

3,4-Dimethyl-2-triisopropylsilyl cyclopent-2-en-1-one (265).

A 10-mL, one-necked, round-bottomed flask (note: *clearseal joint*) was charged with a solution of silylketene **175** (0.208 g, 0.82 mmol) in 4 mL of dichloromethane and cooled at -120 °C in a pentane-liquid nitrogen bath. A solution of CH_2N_2 (ca. 1.6 mmol) generated from diazald (0.47 g, 2.2 mmol) was added rapidly to the silylketene solution over 0.5 min via a fire-polished pipette. The reaction mixture was allowed to warm to room temperature over 3 h and then concentrated to provide 0.24 g of a yellow oil. Column chromatography on 10 g of silica gel (gradient elution with 0-10% ethyl acetate-hexane) afforded 0.21 g (96%) of cyclopentenone **265** as a yellow oil..

IR (thin film):	2940, 2860, 1685, 1570, 1460, 1370, 1250, 1140, 1015, and 990 cm^{-1}
^1H NMR (300 MHz, $CDCl_3$):	2.74 (app quintet, J = 7.0 Hz, 1H), 2.58 (dd, J = 18.3, 7.0 Hz, 1H), 2.15 (s, 3H), 1.96 (dd, J = 18.1, 2.2 Hz, 1H), 1.50 (sept, J = 7.1 Hz, 3H), 1.17 (d, J = 6.9 Hz, 3H), and 1.02 (d, J = 7.7 Hz, 18H)
^{13}C NMR (75 MHz, $CDCl_3$):	213.3, 191.1, 135.5, 44.7, 41.4, 20.0, 18.8, 17.7, and 11.7

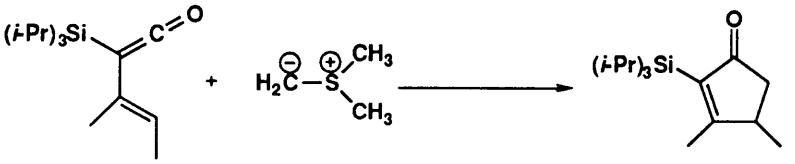
265



175 265

3,4-Dimethyl-2-triisopropylsilyl cyclopent-2-en-1-one (265).

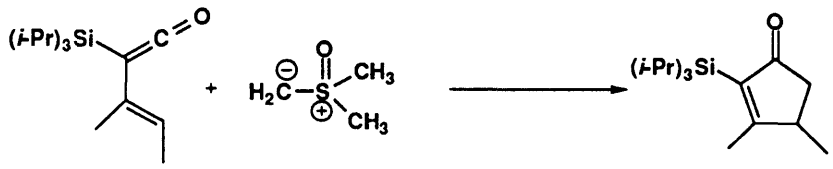
A 10-mL, two-necked, round-bottomed flask equipped with an argon inlet adapter and a rubber septum was charged with a solution of trimethylsulfonium iodide (0.155 g, 0.762 mmol) in 1.7 mL of DME and cooled at 0 °C in an ice bath while *n*-butyllithium solution (2.61 M in hexane, 0.25 mL, 0.65 mmol) was added over 0.5 min and the resulting solution of ylide was stirred for 3 min at 0 °C. A 25-mL, two-necked, round-bottomed flask equipped with an argon inlet adapter and a rubber septum was charged with a solution of silylketene **175** (0.156 g, 0.619 mmol) in 3.3 mL of DME and cooled at 0 °C. The ylide solution was then transferred dropwise via cannula over 2 min to the ketene solution, and the resulting mixture was stirred for 5 min at 0 °C. The cooling bath was then removed, and the reaction mixture was allowed to warm to room temperature over 1.5 h. The reaction mixture was diluted with 5 mL of water and extracted with three 3-mL portions of diethyl ether. The combined organic phases were washed with 5 mL of saturated NaCl solution, dried over Na_2SO_4, filtered, and concentrated to give 0.17 g of a yellow oil. Column chromatography (twice) on 10 g of silica gel (gradient elution with 0-30% dichloromethane-petroleum ether) afforded 0.10 g (61%) of cyclopentenone **265** as a colorless oil with spectral characteristics identical with those listed above.



175 265

3,4-Dimethyl-2-triisopropylsilyl cyclopent-2-en-1-one (265).

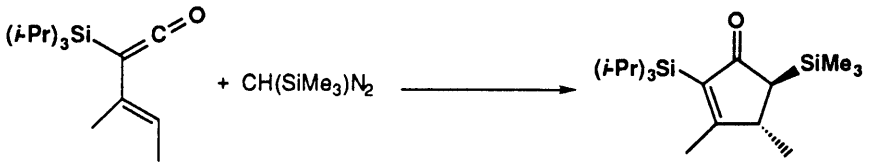
A 10-mL, two-necked, round-bottomed flask equipped with an argon inlet adapter and a rubber septum was charged with a solution of trimethylsulfonium iodide (0.118 g, 0.581 mmol) in 1.4 mL of THF and cooled at 0 °C in an ice bath while *n*-butyllithium solution (2.50 M in hexane, 0.20 mL, 0.51 mmol) was added over 0.5 min and the resulting solution of ylide was stirred for 3 min at 0 °C. A 25-mL, two-necked, round-bottomed flask equipped with an argon inlet adapter and a rubber septum was charged with a solution of silylketene **175** (0.122 g, 0.482 mmol) in 2.4 mL of 50:50 THF-DMSO and cooled at 0 °C. The ylide solution was then transferred dropwise via cannula over 2 min to the ketene solution, and the resulting mixture was stirred for 30 min at 0 °C. The cooling bath was then removed, and the reaction mixture was allowed to warm to room temperature over 1 h. The reaction mixture was diluted with 5 mL of water and extracted with three 2-mL portions of diethyl ether. The combined organic phases were washed with 5 mL of saturated NaCl solution, dried over Na_2SO_4, filtered, and concentrated to give 0.13 g of a yellow oil. Column chromatography (twice) on 10 g of silica gel (gradient elution with 0-5% ethyl acetate-hexane) afforded 0.097 g (75%) of cyclopentenone **265** as a colorless oil with spectral characteristics identical with those listed above.



175 265

3,4-Dimethyl-2-triisopropylsilyl cyclopent-2-en-1-one (265).

A 10-mL, two-necked, round-bottomed flask equipped with an argon inlet adapter and a rubber septum was charged with sodium hydride (0.023 g, 0.585 mmol) as a 60% mineral oil dispersion which was washed with three 1-mL portions of hexane by swirling, allowing the hydride to settle, and decanting in order to remove the mineral oil. The rubber septum was replaced and the flask was fitted with a reflux condenser. A solution of trimethylsulfoxonium iodide (0.113 g, 0.515 mmol) in 0.5 mL of DMSO was added to the dispersion and the resulting mixture was stirred for 15 min. A 25-mL, two-necked, round-bottomed flask equipped with an argon inlet adapter and a rubber septum was charged with a solution of silylketene **175** (0.100 g, 0.395 mmol) in 2 mL of a 1:1 DMSO-THF solution and cooled at 0 °C in an ice bath. The ylide solution described above was then transferred dropwise via cannula over 2 min to the ketene solution (the flask was rinsed with an additional 0.5 mL of THF). The reaction mixture was stirred for 1.25 h and then diluted with 5 mL of water and extracted with three 2-mL portions of diethyl ether. The combined organic phases were washed with 5 mL of saturated NaCl solution, dried over Na_2SO_4, and concentrated to give 0.12 g of a yellow oil. Column chromatography on 10 g of silica gel (gradient elution with 0-5% ethyl acetate-hexane) afforded 0.045 g (43%) of cyclopentenone **265** as a colorless oil with spectral characteristics identical to those listed above.



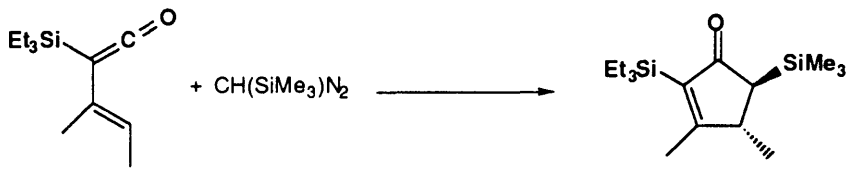
175 277

***trans*-3,4-Dimethyl-2-triisopropylsilyl-5-trimethylsilyl cyclopent-2-en-1-one (277).**

A 5-mL, two-necked, round-bottomed flask equipped with an argon inlet adapter and a rubber septum was charged with a solution of silylketene **175** (0.105 g, 0.41 mmol) in 0.4 mL of dichloromethane. A solution of (trimethylsilyl)diazomethane (1.7 M in hexane, 0.40 mL, 0.077 g, 0.68 mmol) was added dropwise over 30 sec, and the reaction mixture was stirred at room temperature for 32 h. The resulting yellow solution was then concentrated to afford 0.16 g of a yellow oil. Column chromatography on 10 g of silica gel (gradient elution with 0-5% ethyl acetate-hexane) afforded 0.12 g (86%) of cyclopentenone **277** as a colorless oil.

IR (CCl_4):	2945, 2955, 1665, 1575, 1455, 1365, and 1245 cm^{-1}	
^1H NMR (300 MHz, $CDCl_3$): (s,	2.56 (dq, J = 0.8, 7.4 Hz, 1H), 2.15 (s, 3H), 1.82 1H), 1.52 (sept, J = 7.4 Hz, 3H), 1.18 (d, J = 7.0 Hz, 3H), 1.04 (d, J = 7.5 Hz, 18H), and 0.05 (s, 9H)	
^{13}C NMR (75 MHz, $CDCl_3$):	213.9, 188.9, 135.8, 50.9, 45.6, 21.3, 18.9, 18.7, 11.8, and -2.8	
HRMS:	Calcd for $C_{19}H_{38}OSi_2$:	338.2461
	Found:	338.2459

SiMe3
(iPr)3Si
O
277
0 PPM
1
2
3
4
5
6
7
8
9
10

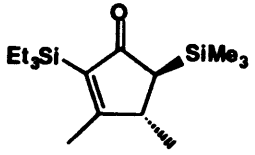


176 280

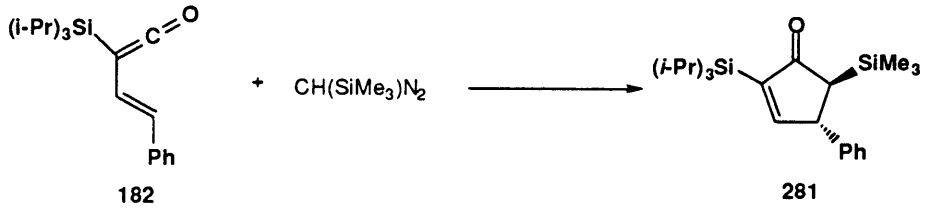
***trans*-3,4-Dimethyl-2-triethylsilyl-5-trimethylsilyl cyclopent-2-en-1-one (176).**

A 10-mL, two-necked, round-bottomed flask equipped with an argon inlet adapter and a rubber septum was charged with a solution of silylketene **176** (0.105 g, 0.500 mmol) in 0.5 mL of dichloromethane. A solution of (trimethylsilyl)diazomethane (1.5 M in hexane, 0.50 mL, 0.75 mmol) was added dropwise over 30 sec, and the reaction mixture was stirred at room temperature for 21.5 h. The reaction mixture was then concentrated to afford 0.16 g of a yellow oil. Column chromatography on 10 g of silica gel (gradient elution with 0-5% ethyl acetate-hexane) afforded 0.14 g (95%) of cyclopentenone **280** as a yellow oil.

IR (CCl_4):	2941, 2861, 1663, 1587, 1451, 1412, 1370, 1251, 1146, 1105, and 1001 cm^{-1}	
^1H NMR (300 MHz, $CDCl_3$):	2.52 (qd, J = 6.2, 1.9 Hz, 1H), 2.05 (s, 3H), 1.73 (d, J = 1.8 Hz, 1H), 1.11 (d, J = 6.7 Hz, 3H), 0.86 (t, J = 6.9 Hz, 9H), 0.71 (q, J = 6.9 Hz, 6H), and -0.01 (s, 9H)	
^{13}C NMR (75 MHz, $CDCl_3$):	188.2, 184.9, 137.1, 50.6, 45.3, 20.7, 17.6, 7.4, 3.5, and -3.0	
HRMS:	Calcd for $C_{16}H_{32}OSi_2$:	296.1992
	Found:	296.1988



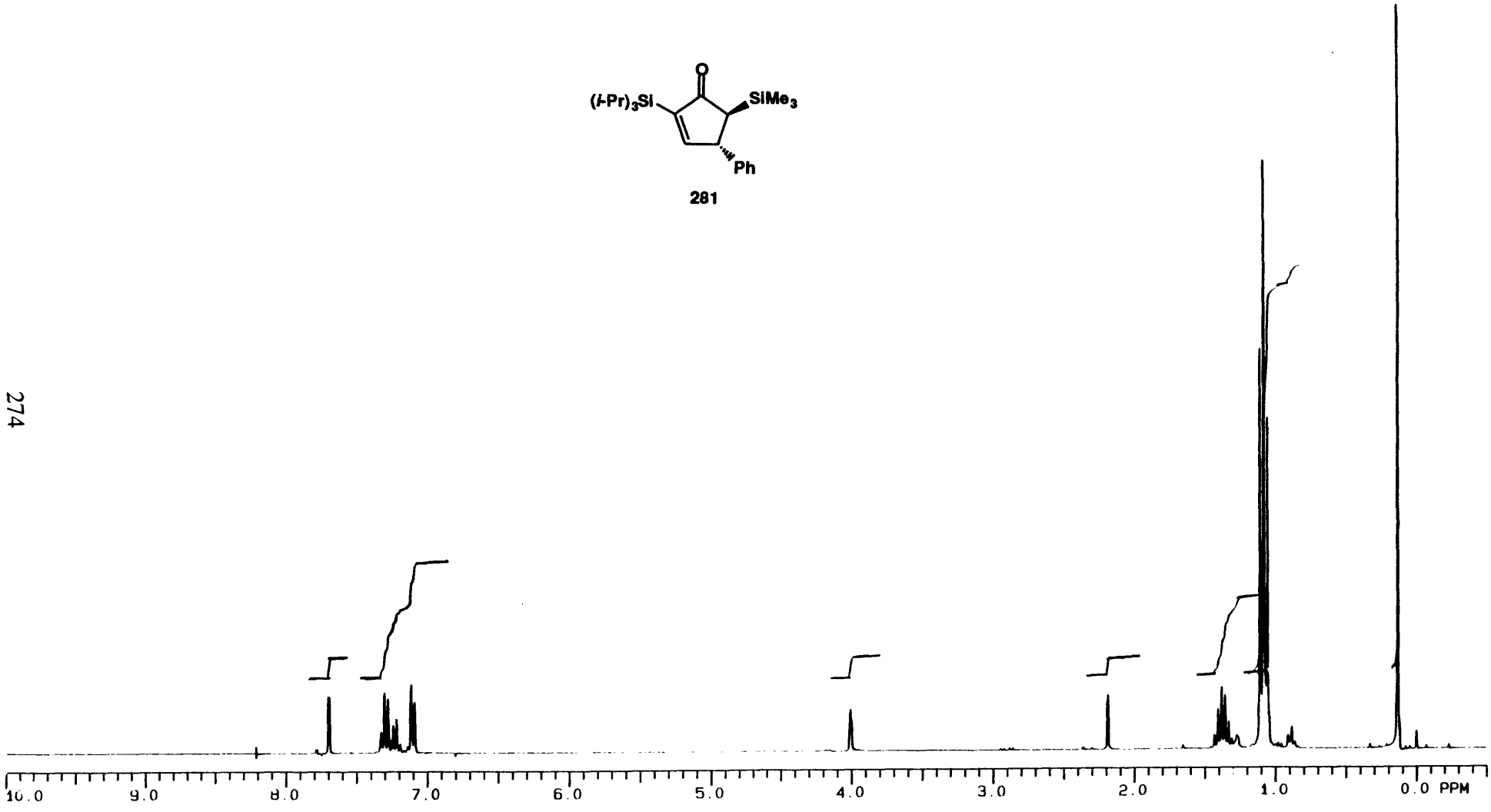
280



***trans*-4-phenyl-2-triisopropylsilyl-5-trimethylsilylcyclopent-2-en-1-one (281).**

A 10-mL, two-necked, round-bottomed flask equipped with an argon inlet adapter and a rubber septum was charged with a solution of silylketene **182** (0.130 g, 0.433 mmol) in 0.4 mL of dichloromethane. A solution of (trimethylsilyl)diazomethane (1.2 M in hexane, 0.55 mL, 0.65 mmol) was added dropwise over 30 sec and the resulting mixture was stirred at room temperature for 22 h. The reaction mixture was concentrated to afford 0.15 g of a yellow oil. Column chromatography on 10 g of silica gel (gradient elution with 0-2% ethyl acetate-hexane) afforded 0.14 g (81%) of cyclopentenone **281** as a yellow oil.

IR (CCl_4):	3030, 2959, 2869, 1770, 1678, 1570, 1490, 1460, 1383, 1280, 1250, 1160, 1070, 1040, and 1020 cm^{-1}
^1H NMR (300 MHz, $CDCl_3$):	7.69 (d, J = 2.8 Hz, 1H), 7.12-7.30 (m, 3H), 7.10 (d, J = 7.6 Hz, 2H), 4.00 (s, 1H), 2.19 (d, J = 2.1 Hz, 1H), 1.36 (sept, J = 7.7 Hz, 3H), 1.09 (d, J = 8.2 Hz, 6H), 1.06 (d, J = 7.9 Hz, 12 H), and 0.13 (s, 9H)
^{13}C NMR (75 MHz, $CDCl_3$):	214.8, 174.6, 143.0, 142.3, 129.0, 127.3, 127.2, 126.9, 52.7, 51.7, 18.7, 11.0, and -2.6
HRMS:	Calcd for $C_{23}H_{38}OSi_2$: 386.2461 Found: 386.2457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Ph
281
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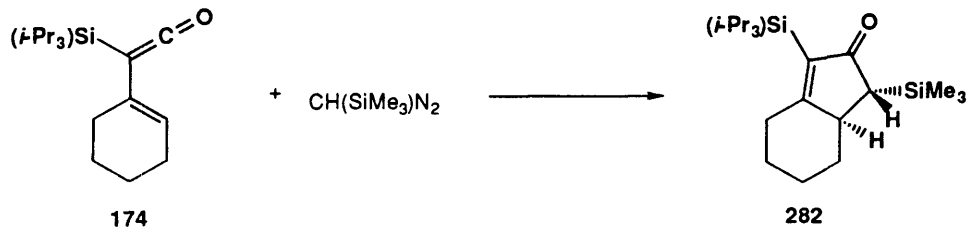
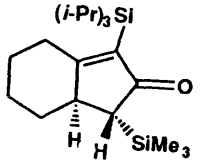


174 282

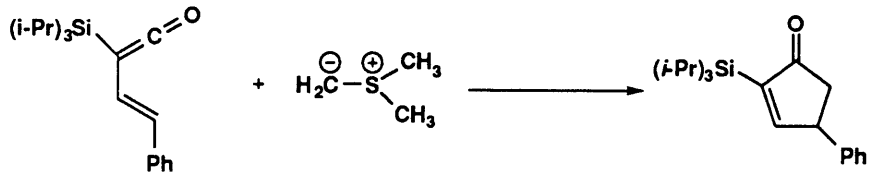
7-Trimethylsilyl-9-(triisopropylsilyl)bicyclo[4.3.0]non-1(9)-en-8-one (282).

A 10-mL, two-necked, round-bottomed flask equipped with an argon inlet adapter and a rubber septum was charged with a solution of silylketene **174** (0.119 g, 0.430 mmol) in 0.4 mL of dichloromethane. A solution of (trimethylsilyl)diazomethane (1.7 M in hexane, 0.38 mL, 0.64 mmol) was added dropwise over 30 sec and the reaction mixture was stirred at room temperature for 29.5 h. The reaction mixture was concentrated to afford 0.200 g of a yellow oil. Column chromatography on 10 g of silica gel (gradient elution with 0-5% ethyl acetate-hexane) afforded 0.130 g (83%) of cyclopentenone **282** as a colorless oil.

IR (CCl_4):	2940, 2870, 1685, 1575, 1460, 1440, 1350, and 1290 cm^{-1}
^1H NMR (300 MHz, $CDCl_3$):	2.96 (m, 1H), 2.40 (ddd, J = 12.0, 5.0, 2.0 Hz, 1H), 2.23 (dd, *J* = 13.3, 5.3 Hz, 1H), 1.76-2.17 (m, 2H), 1.73 (d, *J* = 1.0 Hz,1H), 1.52 (sept, *J* = 7.7 Hz, 3H), 1.02 (d, *J* = 7.4 Hz, 18H), 0.80-1.60 (m, 4H), and 0.05 (s, 9H)
^{13}C NMR (75 MHz, $CDCl_3$):	212.0, 190.9, 132.8, 48.3, 48.0, 37.1, 32.4, 28.1, 25.6, 18.9, 11.7, and -2.7
HRMS:	Calcd for $C_{21}H_{40}OSi_2$: 364.2617 Found: 364.2616



282



182 296

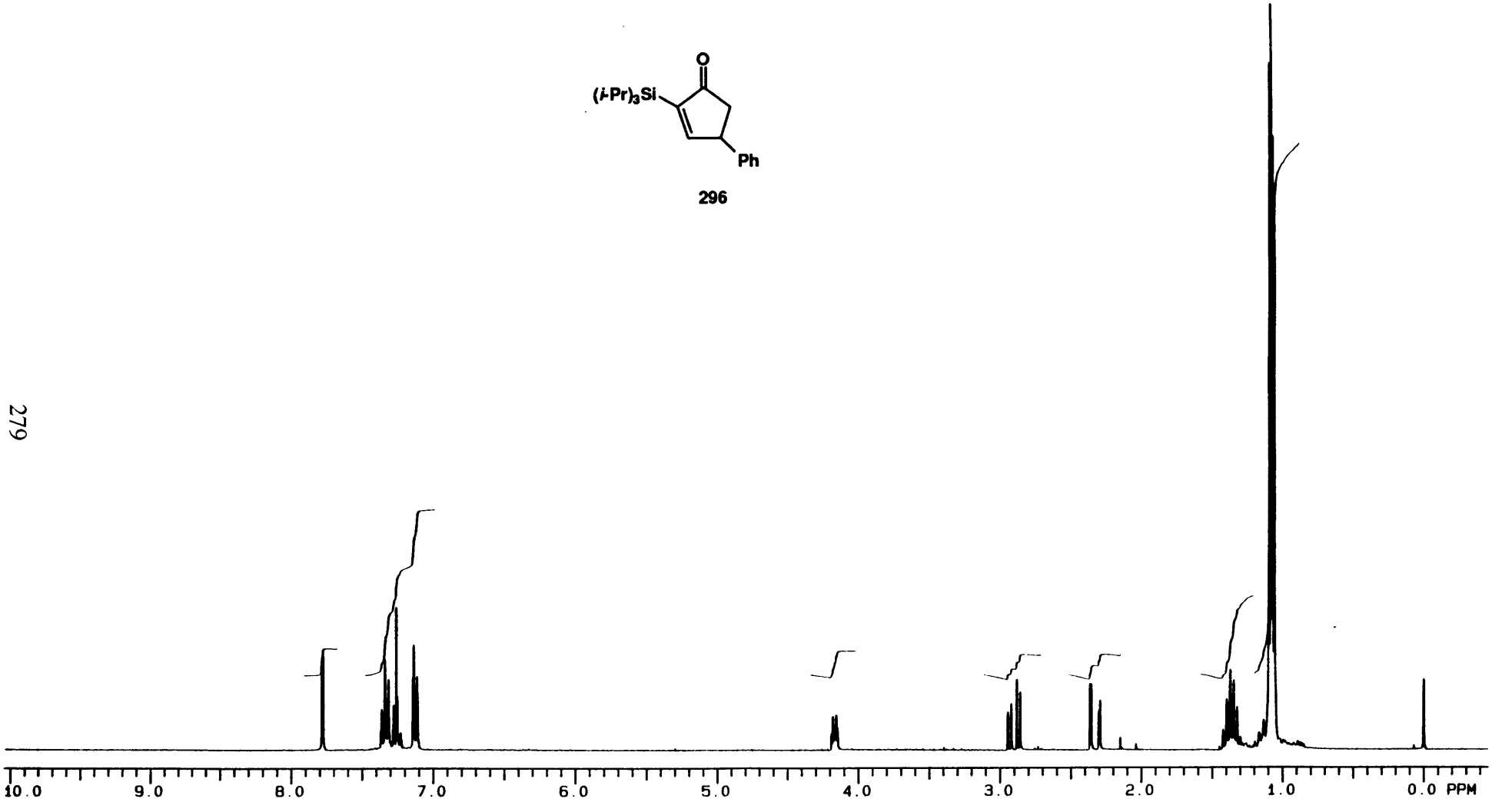
4-Phenyl-2-triisopropylsilylcyclopenten-1-one (296).

A 10-mL, two-necked, round-bottomed flask equipped with an argon inlet adapter and a rubber septum was charged with a solution of trimethylsulfonium iodide (0.0891 g, 0.437 mmol) in 1.1 mL of DME and cooled at 0 °C in an ice bath while *n*-butyllithium solution (2.65 M in hexane, 0.16 mL, 0.421 mmol) was added over 0.5 min and the resulting ylide was stirred for 5 min at 0 °C. A 25-mL, two-necked, round-bottomed flask equipped with an argon inlet adapter and a rubber septum was charged with a solution of silylketene **182** (0.121 g, 0.401 mmol) in 1.8 mL of DME and cooled at 0 °C. The ylide solution was then transferred dropwise via cannula over 2 min to the ketene solution (the flask was rinsed with 0.5 mL of additional DME). The cooling bath was then removed and the reaction mixture was allowed to warm to room temperature for 1 h and then diluted with 5 mL of water. The aqueous layer was separated extracted with three 3-mL portions of diethyl ether, and the combined organic phases were washed with 5 mL of saturated NaCl solution, dried over Na_2SO_4, filtered, and concentrated to give 0.17 g of a yellow oil. Column chromatography on 10 g of silica gel (gradient elution with 0-5% ethyl acetate-hexane) afforded 0.082 g (65%) of cyclopentenone **296** as a colorless oil.

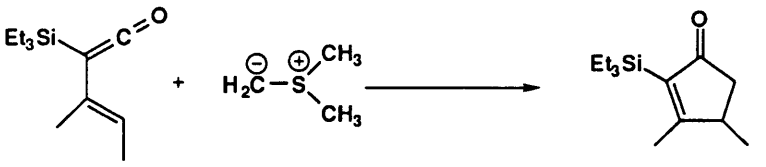
IR (CCl_4): 2940, 2860, 1695, 1565, 1490, 1460, 1410, 1380, 1280, 1260, and 1060 cm^{-1}

^1H NMR (300 MHz, $CDCl_3$): 7.78 (d, J = 2.4 Hz, 1H), 7.23-7.37 (m, 3H), 7.13 (d, J = 6.9 Hz, 2H), 4.17 (dt, J = 7.5, 2.3 Hz, 1H), 2.90 (dd, J = 18.8, 7.0 Hz, 1H), 2.33 (dd, J = 18.4, 3.0 Hz, 1H), 1.37 (sept, J = 7.3 Hz, 3H),

	1.08 (d, J = 7.2 Hz, 12H), and 1.07 (d, J = 7.2 Hz, 6H)
^{13} C NMR (75 MHz, $CDCl_3$):	213.6, 176.2, 142.6, 142.2, 129.0, 127.2, 127.0, 48.4, 45.1, 18.6, and 10.9



296



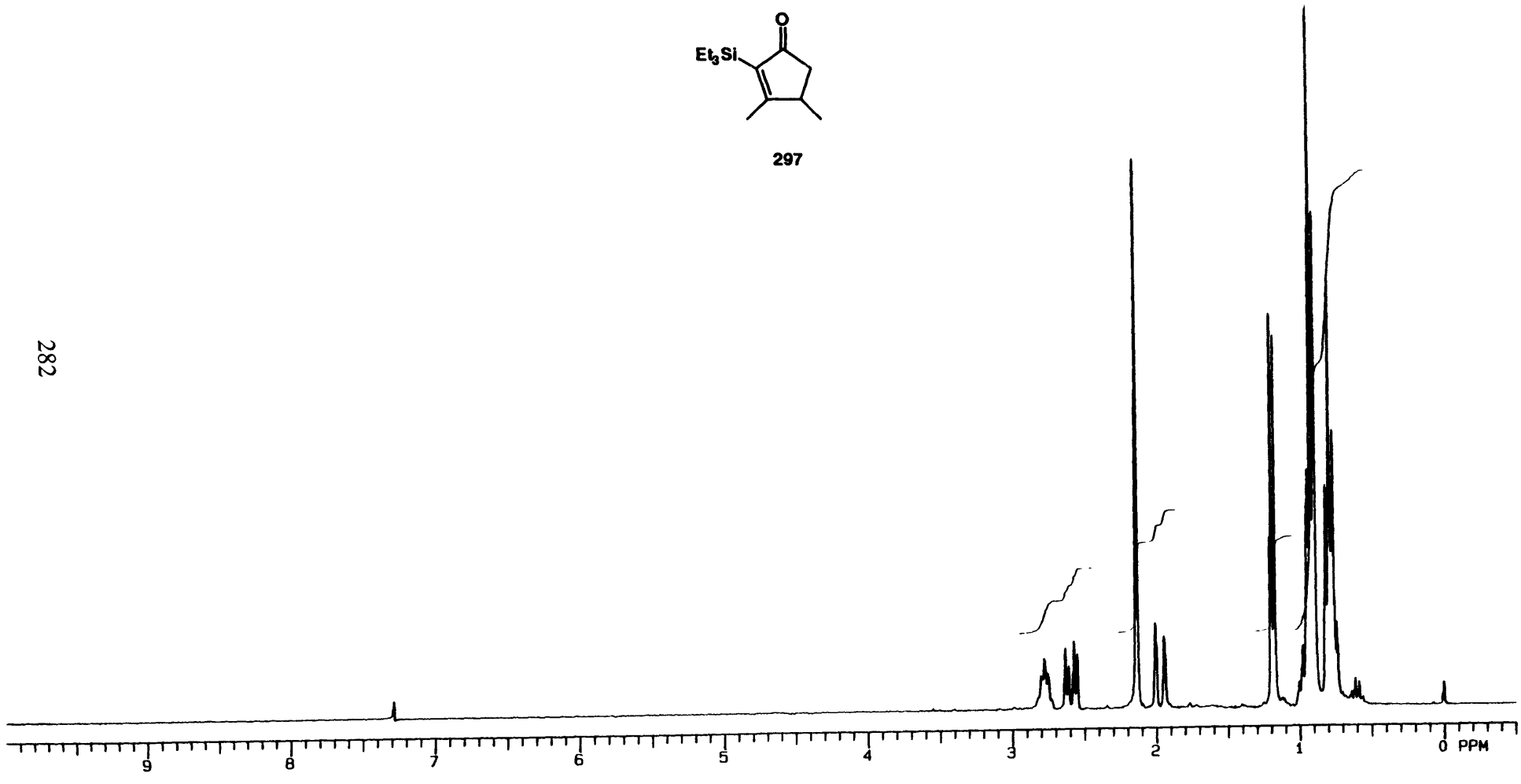
176 297

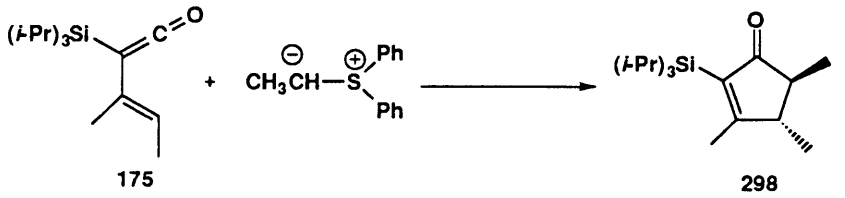
3,4-Dimethyl-2-triethylsilyl cyclopent-2-en-1-one (297).

A 10-mL, two-necked, round-bottomed flask equipped with an argon inlet adapter and a rubber septum was charged with a solution of trimethylsulfonium iodide (0.091 g, 0.448 mmol) in 1.1 mL of tetrahydrofuran and cooled at 0 °C in an ice bath while *n*-butyllithium (2.48 M in hexane, 0.15 mL, 0.372 mmol) was added over 0.5 min and the resulting ylide was stirred for 2 min at 0 °C. A 25-mL, two-necked, round-bottomed flask equipped with an argon inlet adapter and a rubber septum was charged with a solution of silylketene **176** (0.0764 g, 0.365 mmol) in 1.8 mL of 50:50 THF-DMSO and cooled at 0 °C. The ylide solution was then transferred dropwise via cannula over 2 min to the ketene solution (the flask was rinsed with 0.5 mL of additional THF), and the reaction mixture was stirred for 15 min at 0 °C. The cooling bath was removed and the reaction mixture was allowed to warm to room temperature over 2 h and then diluted with 5 mL of water. The aqueous layer was separated and extracted with five 3-mL portions of diethyl ether, and the combined organic phases were washed with 5 mL of saturated NaCl solution, dried over Na_2SO_4, and concentrated to give 0.083 g of a yellow oil. Column chromatography on 10 g of silica gel (gradient elution with 0-5% ethyl acetate-hexane) afforded 0.062 g (75%) of cyclopentenone **297** as a colorless oil.

IR (CCl_4):	2940, 2885, 1685, 1580, 1410, 1250, 1200, and 1065 cm^{-1}
^1H NMR (300 MHz, $CDCl_3$):	2.78 (app quintet, J = 7.1 Hz, 1H), 2.59 (dd, J = 18.6, 7.0 Hz, 1H), 2.13 (s, 3H), 1.97 (dd, J = 18.3, 2.4 Hz, 1H), 1.18 (d, J = 7.1 Hz, 3H), 0.97

	(t, J = 7.6 Hz, 3H), 0.91 (t, J = 6.9 Hz, 6H), 0.78 (q, J = 7.5 Hz, 2H), and 0.77 (t, J = 6.7 Hz, 4H)
^{13} C NMR (75 MHz, $CDCl_3$):	213.2, 190.6, 136.6, 44.6, 41.1, 19.5, 18.0, 7.4, and 3.4
HRMS:	Calcd for $C_{13}H_{24}OSi$: 224.1596 Found: 224.1594


O
Et3Si
297
9
8
7
6
5
4
3
2
1
0 PPM



175 298

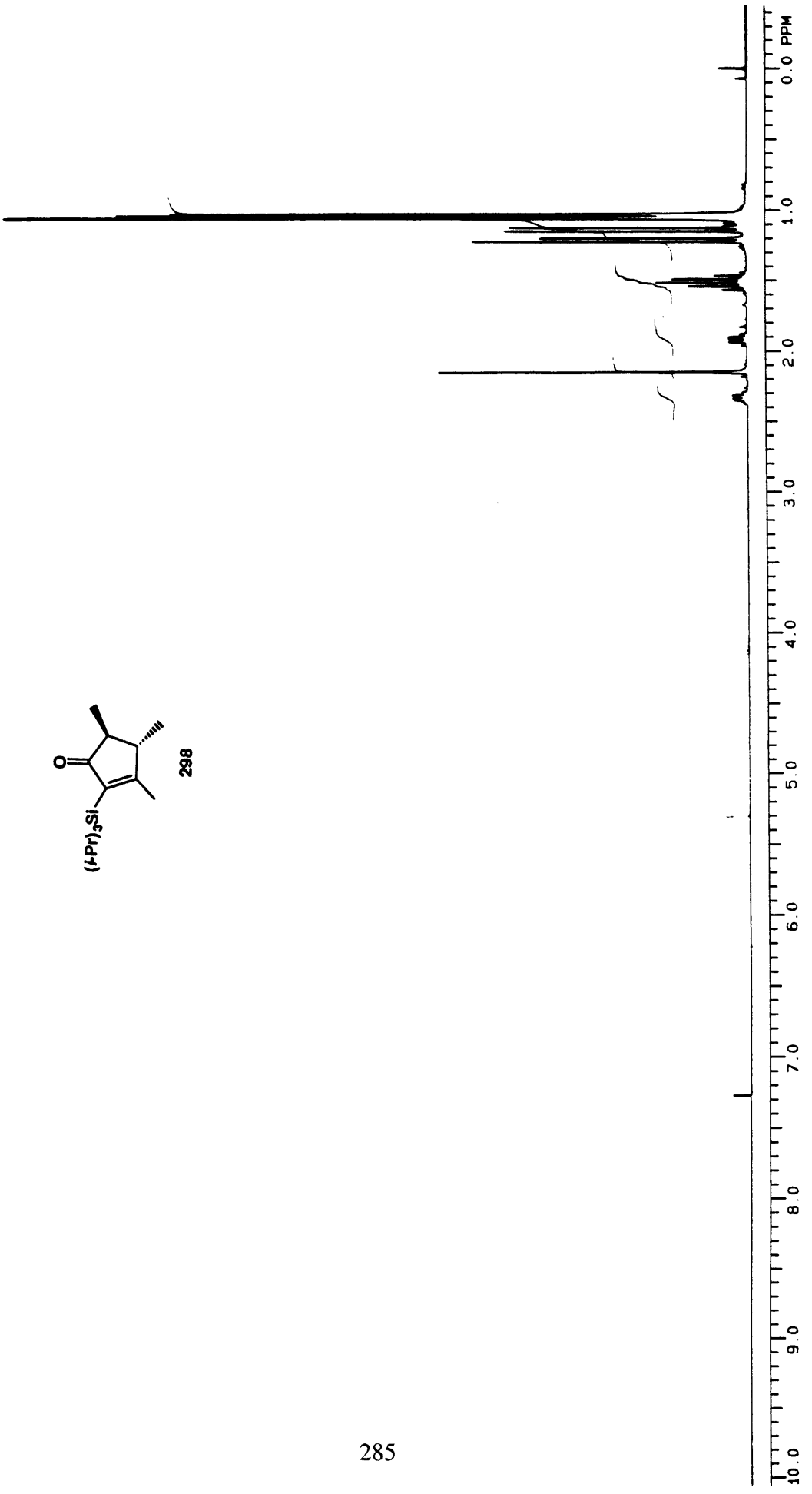
***trans*-3,4,5-Trimethyl-2-triisopropylsilyl cyclopent-2-en-1-one (298).**

A 10-mL, two-necked, round-bottomed flask equipped with an argon inlet adapter and a rubber septum was charged with a solution of diphenylethylsulphonium fluoroborate (0.087 g, 0.287 mmol) in 1.1 mL of DME and cooled at -50 °C in an dry ice-acetone bath while*t*-butyllithium (1.84 M in pentane, 0.15 mL, 0.281 mmol) was added over 0.5 min. The resulting bright yellow ylide solution was stirred for 30 min at -50 °C. A 25-mL, two-necked, round-bottomed flask equipped with an argon inlet adapter and a rubber septum was charged with a solution of silylketene **175** (0.0676 g, 0.268 mmol) in 1.1 mL of DME and cooled at -50 °C. The ylide solution was then transferred dropwise via cannula over 2 min to the ketene solution (the flask was rinsed with an additional 0.5 mL of DME). The cooling bath was removed, and the reaction mixture was allowed to warm from -50 °C to -20 °C over 1 h, and then diluted with 5 mL of water. The aqueous layer was separated and extracted with three 2-mL portions of diethyl ether, and the combined organic phases were washed with 5 mL of saturated NaCl solution, dried over Na_2SO_4, and concentrated to give 0.092 g of a yellow oil. Column chromatography (twice) on 10 g of silica gel (gradient elution with 0-5% ethyl acetate-hexane) afforded 0.051 g (68%) of cyclopentenone **298** as a colorless oil.

IR (CCl_4): 2940, 2882, 1685, 1570, 1455, 1370, 1255, 1225, 1142, 1020, 990, and 890 cm^{-1}

^1H NMR (300 MHz, $CDCl_3$): 2.34 (qd, J = 6.9, 3.5 Hz, 1H), 2.15 (s, 3H), 1.92 (qd, J = 7.3, 3.2 Hz, 1H), 1.52 (sept, J = 7.2 Hz, 3H), 1.21 (d, J = 6.6 Hz, 3H), 1.13 (d, J = 7.3 Hz,

	3H), 1.05 (d, J = 7.2 Hz, 12H), and 1.04 (d, J = 8.0 Hz, 6H)
^{13}C NMR (75 MHz, $CDCl_3$):	215.2, 188.7, 134.1, 50.1, 49.9, 18.9, 18.8, 18.7, 15.5, and 11.8

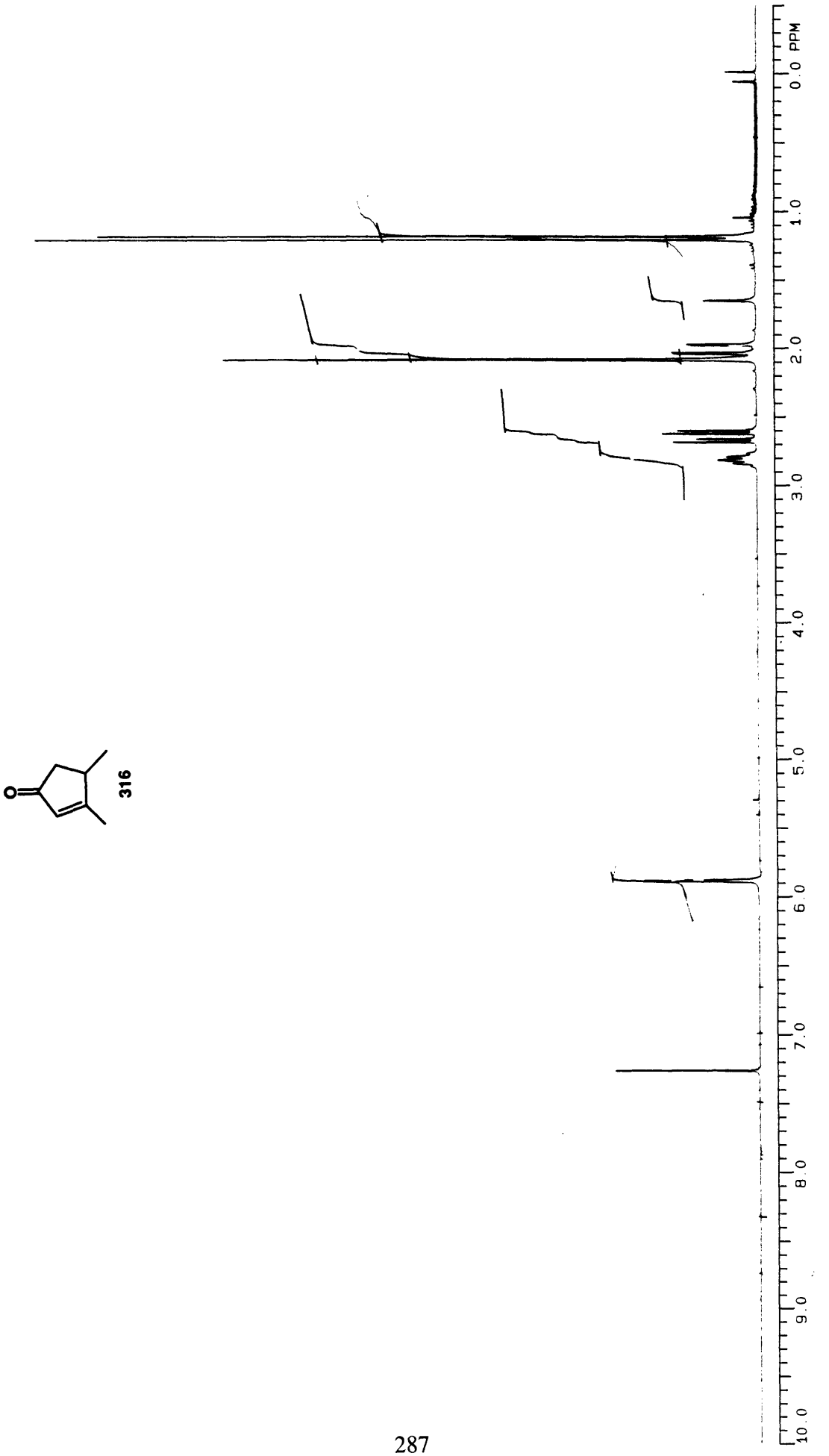

O
(i-Pr)3Si
298
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0 PPM

265 316

3,4-Dimethyl cyclopenten-1-one (316).

A 10-mL, two-necked, round-bottomed flask equipped with an argon inlet adapter and a rubber septum was charged with a solution of silylcyclopentenone **265** (0.114 g, 0.426 mmol) in 3.5 mL of methanol. Methanesulfonic acid (0.45 mL, 0.66 g, 6.90 mmol) was added rapidly dropwise, and the resulting mixture was stirred at room temperature for 3 h. The reaction mixture was diluted with 5 mL of dichloromethane and transferred to a separatory funnel. The aqueous phase was extracted with two 2-mL portions of CH_2Cl_2, and the combined organic layers were washed with 5 mL of saturated NaCl solution, dried over Na_2SO_4, filtered, and concentrated to afford 0.094 g of a colorless oil. Column chromatography on 10 g of silica gel (gradient elution with 0-30% ethyl acetate-hexane) afforded 0.045 g (95%) of cyclopentenone **316**[172] as a colorless oil.

IR (CCl_4):	2920, 2860, 1710, 1620, 1540, 1430, 1370, 1260, and 1000 cm^{-1}
^1H NMR (300 MHz, $CDCl_3$):	5.89 (s, 1H), 2.79 (app quintet, J = 7.0 Hz, 1H), 2.64 (dd, J = 18.6, 6.7 Hz, 1H), 2.08 (s, 3H), 1.98 (dd, J = 18.0, 1.9 Hz, 1H), and 1.18 (d, J = 7.4, 3H)
^{13}C NMR (75 MHz, $CDCl_3$):	208.9, 182.8, 130.3, 53.4, 44.2, 18.8, and 17.1


316
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0 PPM

297 316

3,4-Dimethyl cyclopent-2-en-1-one (316).

A 25-mL, two-necked, pear-shaped flask equipped with an argon inlet adapter and a rubber septum was charged with a solution of silylcyclopentenone **297** (0.131 g, 0.584 mmol) in 5.8 mL of methanol. Methanesulfonic acid (0.19 mL, 0.28 g, 2.92 mmol) was added rapidly dropwise, and the reaction mixture was stirred at room temperature. After 4 h, a second portion of methanesulfonic acid (0.19 mL, 0.28 g, 2.92 mmol) was added, and the reaction mixture was stirred for an additional 4.5 h and then diluted with 5 mL of water. The aqueous phase was separated and extracted with three 5-mL portions of CH_2Cl_2, and the combined organic layers were washed with 15 mL of saturated NaCl solution, dried over Na_2SO_4, filtered, and concentrated to afford 0.12 g of a yellow-brown oil. Column chromatography on 10 g of silica gel (gradient elution with 0-30% ethyl acetate-hexane) afforded 0.057 g (89%) of cyclopentenone **316** as a colorless oil with spectral characteristics identical to those listed above.