# I. TOTAL SYNTHESIS OF AEGYPTINONES A AND B
# II. SYNTHETIC APPROACHES TO GLYCINOECLEPIN A

by

ALEXANDRE HENRI HUBOUX

B.Sc. University of Toronto (1990)

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

DOCTOR OF PHILOSOPHY

at the

MASSACHUSETTS INSTITUTE OF TECHNOLOGY

June, 1995



Signature of Author.....
Department of Chemistry
May 23, 1995

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

Accepted by.....
Dietmar Seyferth
Departmental Committee on Graduate Studies

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

Professor Julius Rebek, Jr. ....
Chairman

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

Professor Gregory C. Fu . .....

ACKNOWLEDGEMENTS

It will be impossible to do justice, in this section, to all the people that have made these past five years at MIT an experience that has been both stimulating and enjoyable but I want to thank all the friends (from MIT or other universities) that I have made here for everything they have given me.

My stay here has been made possible by MIT and the Department of Chemistry thanks to financial support in the form of a Teaching Assistantship and, especially as a foreigner, I am very thankful for this support. I would like to thank my research advisor Prof. Rick Danheiser for support in the form of a Research Assistantship and especially for the opportunity to work in his laboratories and for the great projects. The Rasmussen foundation has been kind enough to support my research here for the past year and a half and I would particularly like to thank Prof. Dave Marks for the generous funding that allowed me to go to Washington, DC to attend the ACS meeting.

My interest in chemistry all started in high school thanks to two dedicated teachers: Mrs Loutfy and Mrs Barton and I am eternally grateful for the solid background that they provided me with. The late Prof. John Dove, by the simple gift of a few books, introduced me to the joys of chemistry and organic chemistry and I regret the fact that I have never been able to thank him enough for his kindness. Prof. Mark Lautens, my undergraduate research advisor, provided the ideal environment for pursuing my interest in synthetic organic chemistry and I thank him for all the attention he gave me.

I have enjoyed taking part in a number of extracurricular activities at MIT and I will dearly miss the sports facilities. I will also miss the truly international feel of this institution. Taking part in and planning events for the European Club has been great. The soccer activities with the European Club or the French Connection led to some great games and even better parties (the 22 Magazine St address will not be forgotten)! Other sports activities also played a key part in staying physically and emotionally fit. I will miss the Cold Fusion and the Toxic Waste hockey teams, the Spam summer volleyball team and of course the opportunity to go windsurfing 200 m from the lab.

I have enjoyed the many interactions I had with the people from my year. The coffee / tea crowd (Blake, Roland, Ken, England (Anthony) and Linda) have been great friends and I will miss our daily ritual. Thanks also to Ken and Blake for the help with their groups' MacroModel program. Thanks to my baymates for putting up with my mess and my music and for making 18-265 a great bay to be in. Mike (MDL) Lawlor has been a most excellent baymate for the past two and a half years. He is a great coach (ya right!), a better player (hockey or volleyball) and a great friend. It's been a real pleasure

sharing the bay with you Mike! I hope we can go see some more Rush concerts together some day. The other members of the satellite lab have also been invaluable, both for their friendship and for their advice. My big sister, Jill (Netka) provided much comic relief with John Kane. John's sincerity and friendship have been missed since he left the group. Sandy Gould's helpfulness has been greatly appreciated and I wish her all the best. Our former japanese postdoc Kazu Takahashi and our former visiting professor Roberto Fernandez de la Pradilla are thanked for their help and friendship. I thank Melanie Bartow for showing me computer tricks and all those random acts of kindness. I have enjoyed working with my fellow glycinoeclepin A co-workers :Tosja, Jose and Matt. Last but not least, Kathy (or is it Cathy?) Lee who has been on the other side of the wall for the past four years. Kathy is a true friend and it doesn't get much better than that. She's always been there to provide support and I thank her for all the big and small things that she did for me and the group. I will miss the "evil eye"!

My fellow 5th years have had a lot to do with the good times at MIT. Fariborz Firooznia (what kind of name is Brice Bosnich anyway?) has amazed me with his music and soccer knowledge and has been a great friend over the years. Brian Bronk and his baymate Toshi Takahashi have made me laugh just about as much as Rob Niger and that's saying a lot. Brian Bronk is a great chemist and I have enjoyed the time we spent together. Jen Loebach has been a great introduction to the Midwest and I am thankful for having spent a few weeks with her in the computer room. Jen, it's been a pleasure knowing you and I wish you all the best. Rob Niger (Fullblown!!, Next Slide Please...), the original cigar-smoking cuz, has been a great addition to this group. This guy is incredible and I will miss his constant teasing remarks. Annie Helgasson and Susy Allemann, a fellow francophone and great squash partner, have also been very good friends. Best of luck to Adam Renslow, Dawn Bennett and Brenda Gacek. I have enjoyed my discussions with Drs Kanaya and Menichincheri as well as Carmen Garcia. Steve Tardivo has done a great job in the stockroom and I know he will be missed. Thanks again to all the proofreaders for the great job they have done. Finally, this thesis has been brought to you in no small way (my labmates can vouch for that) thanks to the inspiring, uplifting and just plain great music of RUSH, SNAP, Rachmaninoff and the likes. Thanks for the memories!

*To my Mother and Father*
*for their Support and Love.*

I. TOTAL SYNTHESIS OF AEGYPTINONES A AND B
II. SYNTHETIC APPROACHES TO GLYCINOECLEPIN A

by

Alexandre Henri Huboux

Submitted to the Department of Chemistry
on May 23, 1995 in partial fulfillment of the
requirements for the Degree of Doctor of Philosophy

## ABSTRACT

Part I:

The first total syntheses of the naturally occurring diterpene quinones aegyptinones A and B have been achieved using a Wolff rearrangement based photochemical aromatic annulation strategy developed in our laboratories. Aegyptinones A and B were synthesized in optically active form via the reaction of a chiral silyloxyacetylene and an aromatic diazo ketone. This strategy provides efficient routes (6 and 7 steps respectively) to aegyptinones A and B and should facilitate the systematic investigation of the biological properties of these interesting diterpenes.

Part II:

A vinylallene intramolecular cycloaddition strategy has been developed with the goal of providing rapid access to the C,D-ring system of glycinoeclepin A. This naturally occurring pentanortriterpene is an outstanding stimulating factor (active at $10^{-12}$ g/mL) for the hatching of the soybean cyst nematode, a serious agricultural pest.

A number of different model studies have been explored and it was found that the C,D-ring model systems can be formed, from acyclic precursors, via a tandem [2,3] Büchi rearrangement / intramolecular Diels-Alder reaction, a tandem palladium-catalyzed allenyl nitrile formation / intramolecular Diels-Alder reaction and a tandem palladium-catalyzed allenyl ester formation / intramolecular Diels-Alder reaction.

Having established the feasibility of our strategy for the total synthesis of glycinoeclepin A, we have begun our synthetic studies towards a key chiral propargylic alcohol intermediate.

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

## TABLE OF CONTENTS

# PART I

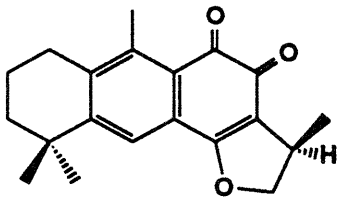
## TOTAL SYNTHESIS OF AEGYPTINONES A AND B

# CHAPTER 1

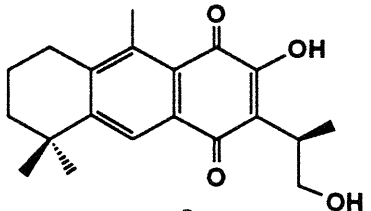
# INTRODUCTION AND BACKGROUND

## Introduction: Diterpene Quinones from *Salvia aegypiaca L*

A number of diterpene quinones with antimicrobial and anticancer properties have been isolated from the *Salvia* plants.[1] The interest generated by these findings has prompted Sabri and coworkers to investigate the indigenous species of Egypt.[2] These investigators found, in 1989, that the crude petrol extract of the roots of *Salvia aegypiaca L.*, a common herb which grows in the coastal areas, exhibits inhibitory activity against *Pseudomonas aeruginosa, Bacillus subtilis, Staphylococcus aureus*, and *Candida albicans*.[3] Sabri also reported the isolation and characterization of two new rearranged abietane diterpenes from these root extracts: aegyptinone A and aegyptinone B (**1** and **2** respectively).




**1**



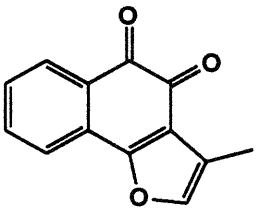

**2**

While no biological activity has yet been reported for these two compounds, the potential for activity is good in view of the activity reported for the root extracts. In

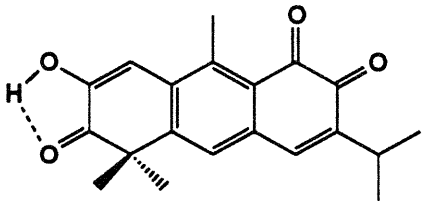
1 (a) Fang, C.; Chang, P.; Hsu, T. *Hua Hsueh Hsueh Pao* **1978**, *34*, 197; *Chem. Abstr.* **1978**, *88*, 177078z. (b) Kupchan, S. M.; Karim, A.; Marcks, C. *J. Am. Chem. Soc.* **1968**, *90*, 5923. (c) Ontisuka, M.; F-Ujiu, M.; Shinma, N.; Maruyama, H. B. *Chem. Pharm. Bull.* **1983**, *31*, 1670.

2 (a) Haddad, D. Y.; Saleh, M. R. I.; Sabri, N. N. *J. Pharm. Sci. U.A.R.* **1962**, *7*, 215. (b) Saleh, M. R. I.; Sabri, N. N.; Haddad, D. Y. *J. Pharm. Sci. U.A.R.* **1964**, *5*, 65. (c) Saleh, M. R. I.; Sabri, N. N.; El-Masry, S. *J. Pharm. Sci. U.A.R.* **1978**, *19*, 313. (d) Saleh, M. R. I.; Sabri, N. N. *Egypt. J. Pharm. Sci.* **1979**, *20*, 411. (e) Sabri, N. N.; Abou-Donia, A. A.; Assad, A. M.; Ghazy, N. M.; El-Lakany, A. M.; Tempesta, M. S.; Sanson, D. R. *Planta Medica* **1989**, *55*, 582.

3 Sabri, N. N.; Abou-Donia, A. A.; Ghazy, N. M.; Assad, A. M.; El-Lakany, A. M.; Sanson, D. R.; Gracz, H.; Barnes, C. L.; Schlemper, E. O.; Tempesta, M. S. *J. Org. Chem.* **1989**, *54*, 4097.



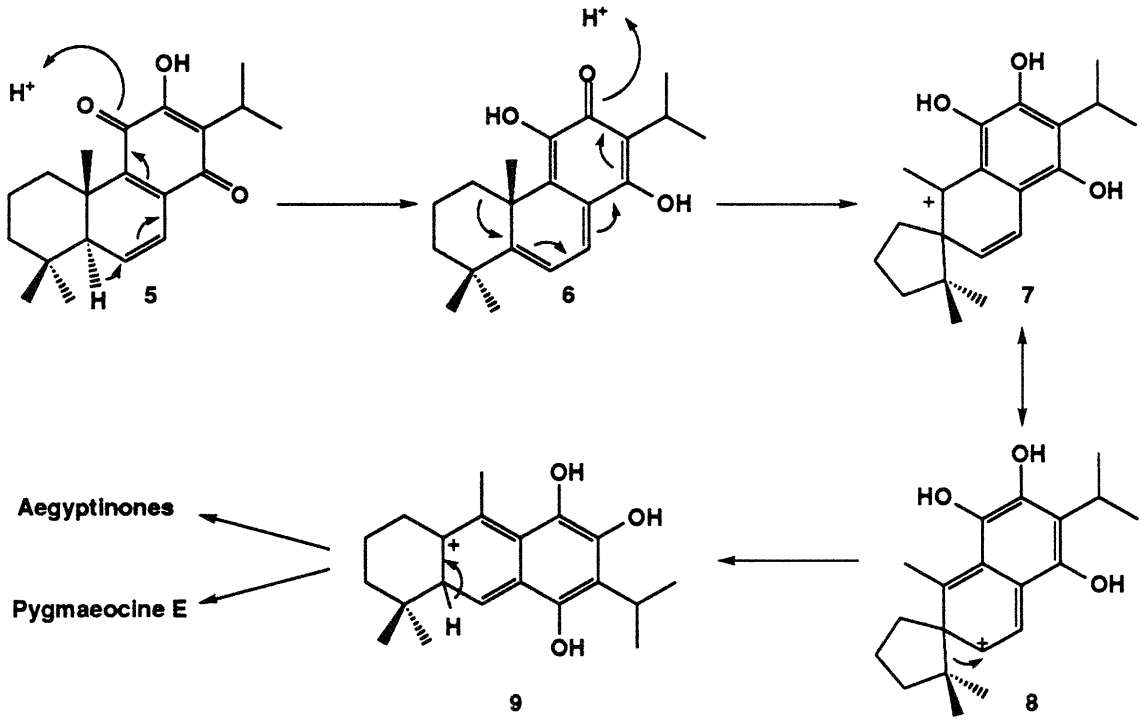
3



4

addition, the structurally related compound **3** was found to be highly active as measured by the Kenacid Blue (KB) assay method[4] and the cryptanshinones possess antineoplastic activity.[5] The rearranged abietane skeleton of the aegytinones has been reported previously in the orthoquinone pygmaeocine E (**4**) isolated from *Pygmeopremna herbacea* (Verbenaceae).[6]

6,7-Didehydroroyleanone (**5**), a compound that is commonly found in *Salvia*, is thought to be the biosynthetic precursor to **1**, **2** and **4**.[3] Tautomerization of the quinone




4 Hayashi, T.; Smith, F. T.; Lee, K.-H. *J. Med. Chem.* **1987**, *30*, 2005.
5 Wu, W. L.; Chang, W. L.; Lee, A. R.; Lin, H. C.; King, M. L. *J. Med. Sci.* **1985**, *6*, 159.
6 Meng, Q.; Zhu, N.; Chen, W. *Phytochemistry* **1988**, *27*, 1151.

(via protonation, followed by elimination of the ring juncture proton) and a series of alkylmigrations afford the linear anthracene carbon skeleton (**9**). Further oxidation of this intermediate provides either the aegyptinones or pygmaeocine E.

The potential for biological activity coupled with their novel structure makes the aegyptinones interesting targets for total synthesis. The first and, thus far, only total syntheses of aegyptinones A and B are described below. The aim of this study was to develop a route which would easily accomodate the production of gram quantities of each compound, thus facilitating the systematic investigation of their pharmacological activity. In addition, the total synthesis of the aegyptinones was undertaken to test the application of a "second generation" aromatic annulation, developed in our laboratory, towards the synthesis of linear tricyclic systems such as that found in these compounds.

## Aromatic Annulation Strategies Based on Vinylketenes

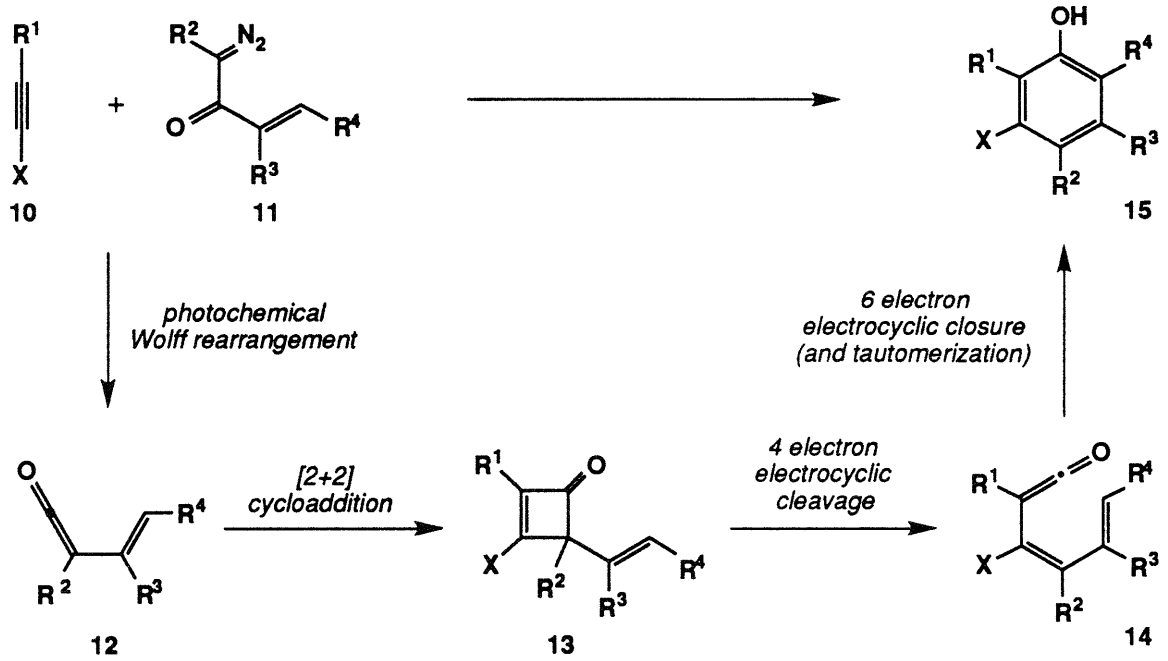
The classical approach towards highly substituted aromatic compounds has involved the use of both nucleophilic and electrophilic substitution reactions starting from commercially available aromatic precursors. These substitution reactions often result in poor regiochemical control during the stepwise build up of substituents and may require protection of sensitive functional groups. In addition, this approach, because it is linear in nature, usually suffers from a lack of efficiency as compared to a more convergent annulation strategy. An aromatic annulation involves the reaction of two acyclic units to generate a substituted aromatic nucleus in a single step.

Our group has developed an aromatic annulation strategy based on the reaction of vinylketenes with either activated (heterosubstituted)[7] or unactivated acetylenes.[8] The reaction involves the generation of a vinylketene via the $4\pi$ electrocyclic ring opening of a

7 (a) Danheiser, R. L.; Gee, S. K. *J. Org. Chem.* **1984**, *49*, 1672 and references cited therein. (b) Danheiser, R. L.; Gee, S. K.; Perez, J. J. *J. Am. Chem. Soc.* **1986**, *106*, 806. (c) Pal, K. Ph. D. Thesis, Massachusetts Institute of Technology, 1987. (d) Danheiser, R. L.; Nishida, A.; Savariar, S.; Trova, M. P. *Tetrahedron Lett.* **1988**, *29*, 4917.

8 Kowalczyk, J. J. Ph.D. Thesis, Massachusetts Institute of Technology, 1988.

cyclobutenone. Liebeskind[9] and Moore[10] independently, and simultaneously, discovered a related quinone annulation in which an aryl- or alkyllithium species and a cyclobutenedione are the two species reacting to give the aromatic product. More recently, a "second generation" aromatic annulation, in which the vinylketene is obtained by the photochemical Wolff rearrangement of an α-diazo ketone, has been developed in our group.[11] This variant has expanded the scope of the method to include the synthesis of polycyclic compounds which were not readily available using the original cyclobutenone-based version. The aromatic annulation appears to be limited to very ketenophilic, UV transparent acetylenes.[8]



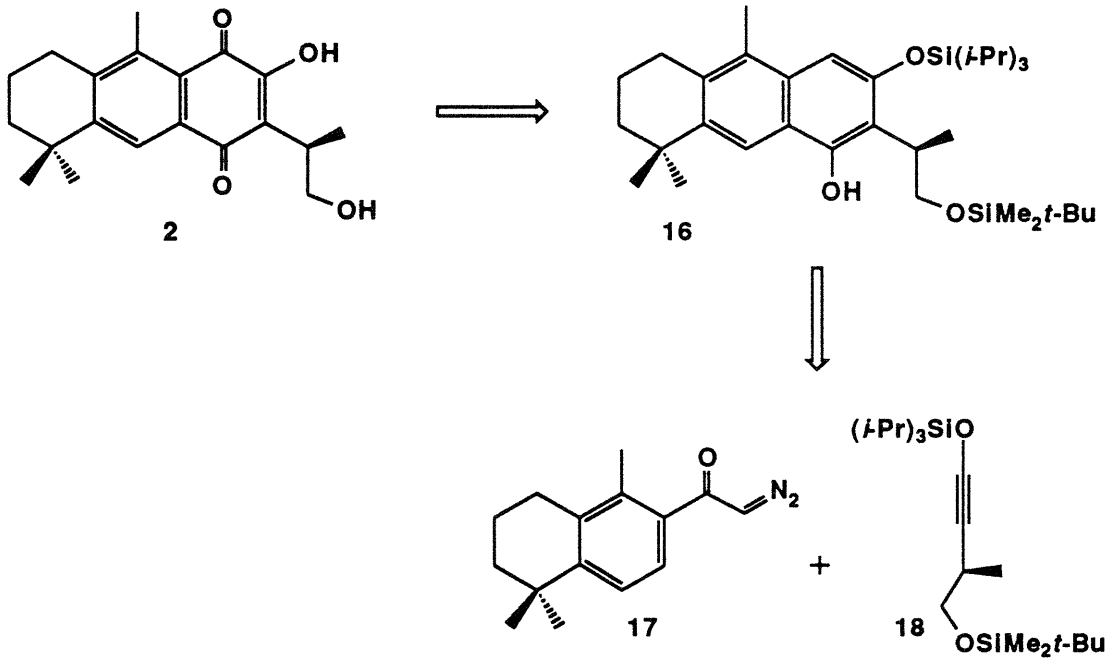

Irradiation of the α-diazo ketone **11** triggers a photochemical Wolff rearrangement[12] producing an aryl- or vinylketene (**12**) which can then undergo a [2 + 2]

9 Liebeskind, L. S.; Iyer, S.; Jewell, C. F. *J. Org. Chem.* **1986**, *51*, 3065.
10 Perri, S. T.; Foland, L. D.; Decker, O. H. W.; Moore, H. W. *J. Org. Chem.* **1986**, *51*, 3067.
11 Danheiser, R. L.; Brisbois, R. G.; Kowalczyk, J. J.; Miller, R. F. *J. Am. Chem. Soc.* **1990**, *112*, 3093. Danheiser, R. L.; Cha, D. D. *Tetrahedron Lett.* **1990**, *31*, 1527.
12 For reviews, see: (a) Gill, G. B. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, 1991, Vol 10, p. 887. (b) Meirer, M.; Zeller, K. -P. *Angew. Chem. Int. Ed. Engl.* **1975**, *14*, 32. (c) Ando, W. In *The Chemistry of the Diazonium and Diazo Groups*; Patai, S., Ed.; J. Wiley and Sons: New York, 1978, Part 1, p. 458. (d) Regitz, M.; Maas, G. *Diazo Compounds: Properties and Synthesis*; Academic Press: Orlando, 1986, p. 185.

cycloaddition with the acetylene **10**. Further irradiation (or in some cases thermolysis) of the resulting vinylcyclobutenone induces a 4π electrocyclic ring opening of the cyclobutenone ring to generate dienylketene **14**. This intermediate spontaneously undergoes a 6π electrocyclization[13] to afford, after tautomerization, the desired aromatic product.

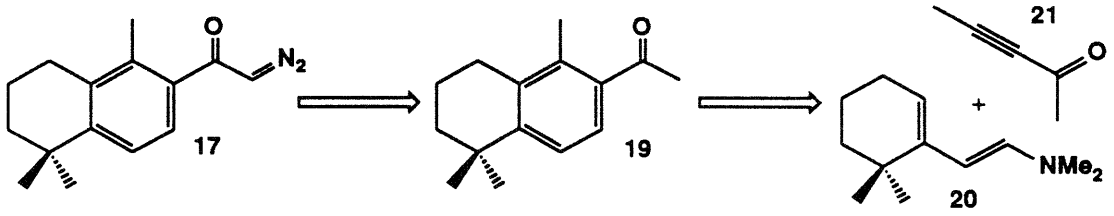
## Retrosynthetic Analysis

Previous work on the total synthesis of Dan Shen diterpene quinones[14] suggested that the phenol **16** derived from an aromatic annulation between α-diazo ketone **17** and siloxyacetylene **18** might serve as a common precursor to both aegyptinones A and B.



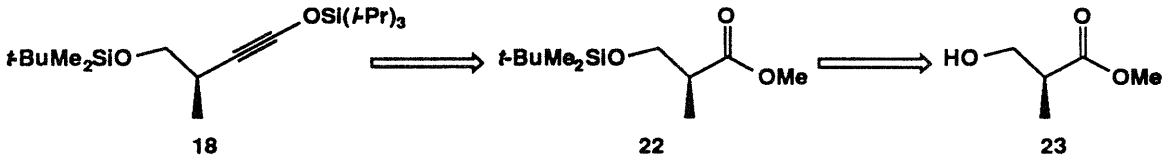

Our original plan for the synthesis of **17** involved the application of our diazo transfer methodology[15] to methyl ketone **19**. This ketone would, in turn, come from a Diels-Alder based benzannulation strategy employing dienamine **20** and 3-pentyn-2-one **21**

13 For a review, see: Okamura, W. K.; DeLera, A. R. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, 1991, Vol 5, p. 730.
14 Danheiser, R. L.; Casebier, D. S.; Loebach, J. L. *Tetrahedron Lett.* **1992**, *33*, 1149.
15 Danheiser, R. L.; Miller, R. F.; Brisbois, R. G.; Park, S. Z. *J. Org. Chem.* **1990**, *55*, 1959.




in which the initially formed cycloadduct would eliminate dimethylamine to give **19**.

The chiral siloxyacetylene **18** was expected to be readily synthesized in two steps, starting with the commercially available optically active ester, by protection of the hydroxyl function and elaboration of the ester in a Kowalski reaction.[16]




16 Kowalski, C. J.; Lal, G. S.; Hague, M. S. *J. Am. Chem. Soc.* **1986**, *108*, 7127.

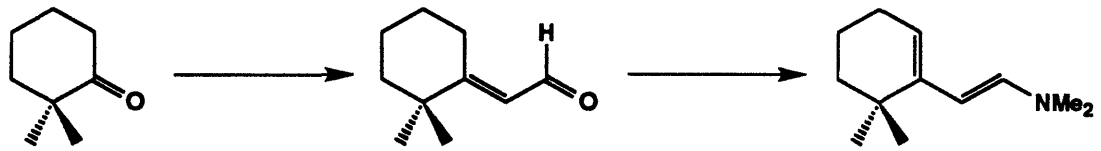
# CHAPTER 2

## RESULTS AND DISCUSSION:

### Total Synthesis of Aegyptinones A and B

The initial synthesis of aegyptinones A and B was carried out by David S. Casebier, a former Ph.D. student in our group. The aim of the studies described below was to optimize and scale up each reaction in the initial synthesis and to investigate alternative methods for accomplishing several inefficient transformations.

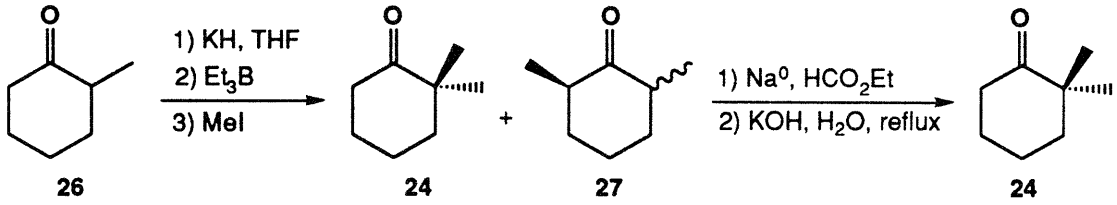
Our synthesis of the dienamine **20** required for the benzannulation step involves the assembly of the α,β-unsaturated aldehyde **25** by a two carbon homologation of 2,2-dimethylcyclohexanone **24** and subsequent amination of this aldehyde.




**24** **25** **20**

Casebier found that the synthesis of 2,2-dimethylcyclohexanone was not as trivial as some of the reports in the literature seemed to indicate. Tidwell[17a] has reported that the use of the general alkylation procedure of Negishi[17b] provides the desired 2,2-dimethylcyclohexanone free of its 2,6-regioisomer **27**. However, in our hands, the 2,6-dimethylcyclohexanone accounted for 15-20% of the crude product according to gas chromatographic analysis. The discrepancy in these results might be explained by the fact that Tidwell and coworkers do not report any gas chromatographic analysis of their product and simply state that they were unable to detect isomeric products by 60-MHz $^1$H-NMR analysis.

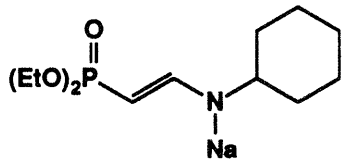
17 a) Baigrie, L. M.; Seiklay, H. R.; Tidwell, T. T. *J. Am. Chem. Soc.* **1985**, *107*, 5391. b) Negishi, E. -I.; Chatterjee, S. *Tetrahedron Lett.* **1983**, *24*, 1341.



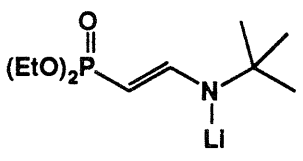

**26** **24** **27** **24**

Crude 2,2-dimethylcyclohexanone was obtained, as described by Tidwell, by treatment of 2-methylcyclohexanone **26** with potassium hydride, in tetrahydrofuran, to form the thermodynamic enolate. The enolate was converted to the enol borate upon addition of triethylborane and alkylated with methyl iodide. The procedure followed by Casebier to obtain pure 2,2-dimethylcyclohexanone involves stirring the mixture of regioisomeric alkylation products, overnight, with ethyl formate and sodium metal in ether. The formyl salt of the desired major ketone is insoluble in ether, but the formyl derivative of 2,6-dimethylcyclohexanone is not enolizable and thus remains in solution. The two compounds were separated by filtration and the filter cake washed with ether to remove any byproduct. The remaining solid was dissolved in 1.0 M aqueous sodium hydroxide and heated to reflux for several hours to regenerate **24** by cleavage of the formyl derivative. Pure 2,2-dimethylcyclohexanone (**24**) was obtained, after steam distillation, in 55-60% overall yield from 2-methylcyclohexanone.

Casebier then went on to synthesize the α,β-unsaturated aldehyde **25** and found that the two carbon homologating reagent **30** developed by Corey[18] was superior, both in terms of yield and ease of use, to Nagata's[19] phosphonate reagent **28**. A third method published by Meyers,[20] involving the *in situ* generation of the *tert*-butyl imine analog of the




**28**

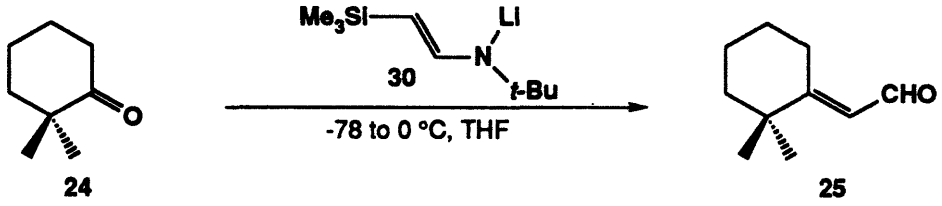



**29**

18 Corey, E. J.; Enders, D.; Bock, M. G. *Tetrahedron Lett.* **1976**, *17*, 7.
19 Nagata, W.; Wakabayashi, T.; Hayase, Y. *Org. Syn.* **1973**, *53*, 44 and ibid. **1973**, *53*, 104.
20 Meyers, A. I.; Tomioka, K.; Fleming, M. P. *J. Org. Chem.* **1978**, *43*, 3788.

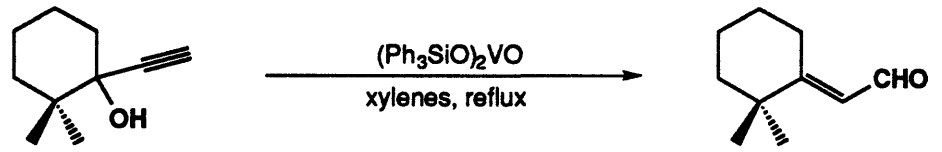
Nagata reagent **29**, was also examined, but none of the desired aldehyde was obtained from this reaction.

Thus, addition of Corey's silyl imine reagent to **24** yielded an α,β-unsaturated imine which was hydrolyzed, *in situ*, under mild conditions using aqueous oxalic acid to provide **25** in 79-92% yield.




**24** **25**

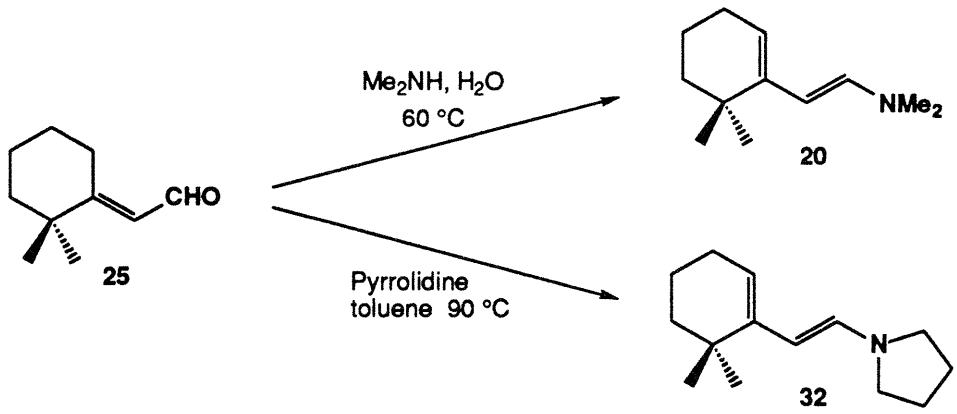
α,β-Unsaturated aldehyde **25** was first reported by Snowden and Wüst[21] as part of their work on a novel cyclohexannulation approach involving dienamine **20**. These investigators obtained **25** by the polymeric silylvanadate-catalyzed rearrangement[22] of propargyl alcohol **31**.



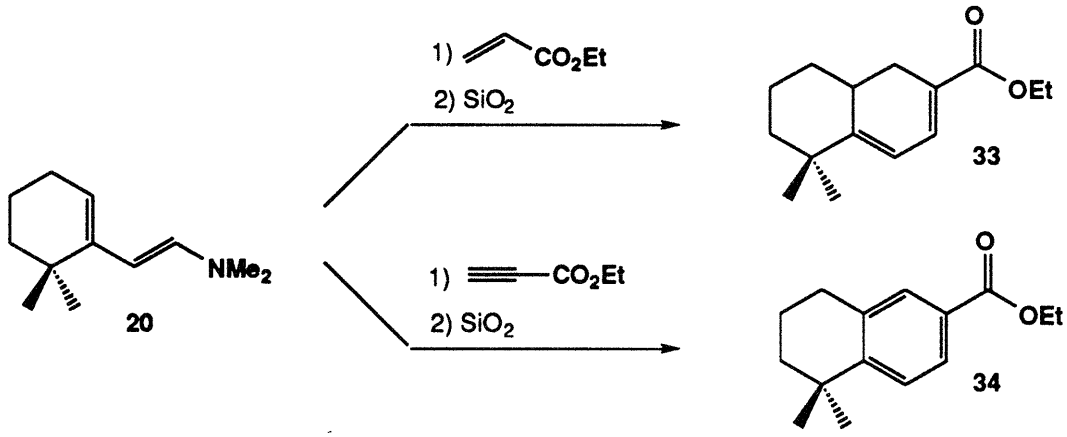

**31** **25**

Treatment of α,β-unsaturated aldehyde **25** with aqueous dimethylamine at 80 °C for 5 h, according to the previously described procedure of Snowden, afforded the dienamine **20** as a bright yellow oil in 78-88% yield after Kugelrohr distillation. Upon repeating Casebier's work, it was found that the related dienamine **32** could be synthesized in better yield (92%) by treating α,β-unsaturated aldehyde **25** with 1.2 equivalent of pyrrolidine in toluene at 90 °C for 1.5 h.

21 Snowden, R. L.; Wüst, M. *Tetrahedron Lett.* **1986**, *27*, 699.
22 Erman, M. B.; Aul'chenko, I. S.; Kiefits, L. A.; Dulova, V. G.; Novikov, J. N.; Vol'pin, M. E. *Tetrahedron Lett.* **1976**, *17*, 2981.



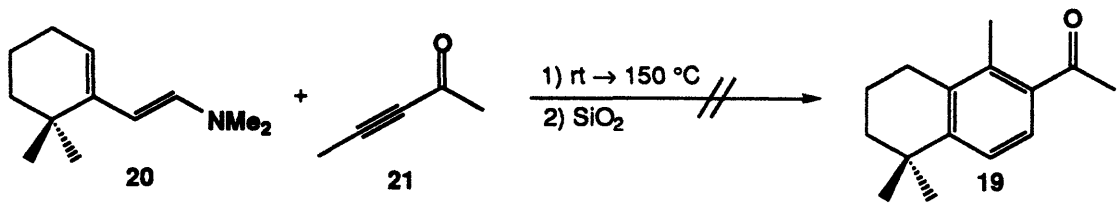

The Diels-Alder reaction of dienamine **20** with a variety of dienophiles was investigated by Snowden and coworkers and it was found that, depending on the degree of unsaturation in this dienophile, a cyclohexadiene[23] or an aromatic system[24] could be obtained upon elimination of dimethylamine from the intermediate cycloadduct.




It was hoped that, for the present synthesis, the reaction of the same dienamine with 3-pentyn-2-one (**21**) would afford, after warming with silica gel, the methyl ketone **19**. Casebier found, however, that while the dienamine **20** was consumed when heated in presence of the propargyl ketone **21**, none of the desired cycloaddition took place.

23 a) Snowden, R. L. *Tetrahedron Lett.* **1984**, *25*, 3835. b) Snowden, R. L.; Wüst, M. *Tetrahedron Lett.* **1986**, *27*, 699. c) Snowden, R. L.; Linder, S. M.; Wüst, M. *Helv. Chim. Acta.* **1989**, *72*, 892. d) Snowden, R. L.; Brauchli, R.; Wüst, M. *Helv. Chim. Acta.* **1990**, *73*, 640.

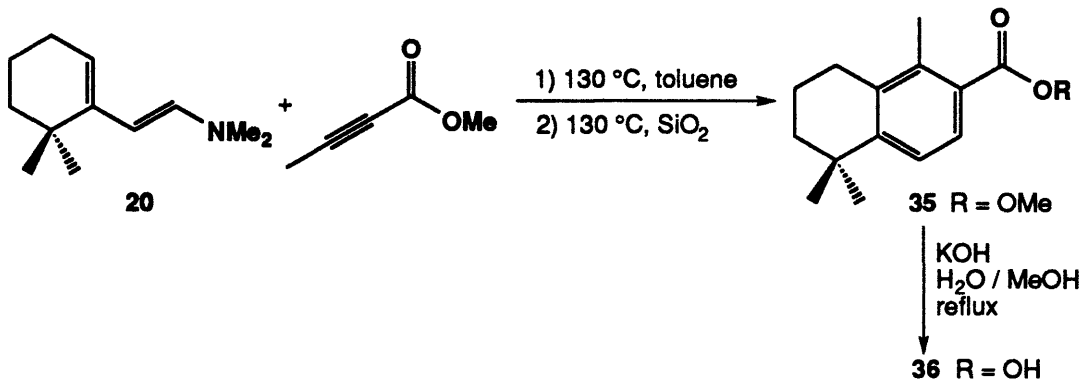
24 Snowden, R. L.; Wüst, M. *Tetrahedron Lett.* **1986**, *27*, 703.



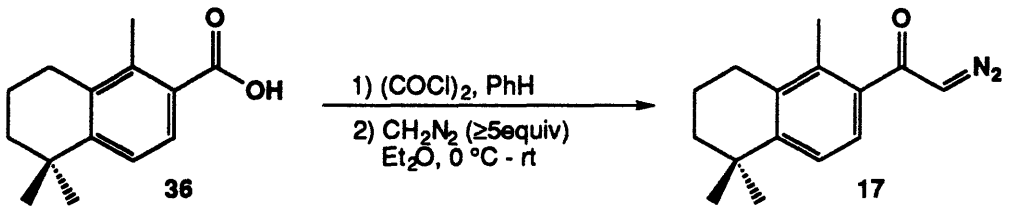

This result required a revision in the route planned for the synthesis of α-diazo ketone **17**. One method of choice for the synthesis of diazo ketones is the Arndt-Eistert reaction[25] which involves the addition of excess diazomethane to an acid chloride. Carboxylic acid **36**, the substrate required for this approach to **17**, thus became our new target compound.

Casebier found that the Diels-Alder reaction between dienamine **20** and methyl tetrolate required more severe conditions than that used by Snowden for the related reaction of the same dienamine with methyl propiolate. Both reagents had to be heated in toluene at 130 °C for 48 h, after which time, silica gel was added and the resulting mixture was heated further to provide the methyl naphthoate **35** in low yield.

Hydrolysis of ester **35** with potassium hydroxide in refluxing aqueous methanol gave the acid **36** in 85% yield. This acid was then converted to the desired α-diazo ketone **17** (84% overall yield from the acid **36**) by treatment with oxalyl chloride and addition of excess diazomethane to the crude acid chloride intermediate.




25 For a review, see Bachman, W. E.; Struve, W. S. *Org. Reactions* **1942**, *1*, 38.




36 17

While this route was shown to provide access to the α-diazo ketone **17** necessary for the key aromatic annulation step, concern over the fact that the benzannulation reaction was not reproducible made it necessary to investigate alternatives. I was assigned this task when I took over the project and it was decided that the reaction between dienamine **20** and 3-pentyn-2-one **21** should be reinvestigated.

While this cycloaddition had failed to take place under thermal conditions, it was reasoned that high pressure conditions might be able to force the two molecules to react. Indeed, it is well known that since the volume of activation in forming the transition state decreases during intermolecular Diels-Alder reactions, the application of high pressure significantly increases the rate of cycloaddition.[26] This technique has been used by Dauben[27] to achieve the cycloaddition of enamines and dienamines that were unreactive under "normal conditions". Compression of a mixture of dienamine **20** and propargylic ketone **21** at pressure of up to 7 Kbar did not, however, result in any Diels-Alder reaction. The only reaction observed was the partial hydrolysis of the dienamine to form the aldehyde **17**. This can be explained by the fact that water is the compression fluid that surrounds the plastic tube containing the reaction mixture during the high pressure experiment. While none of the desired product was obtained, this does not mean that the high pressure approach is not viable. It is very likely that the pressure we used is too low to have the desired effect. Equipment capable of delivering higher pressures was not readily available in the Boston area at the time this research was carried out.

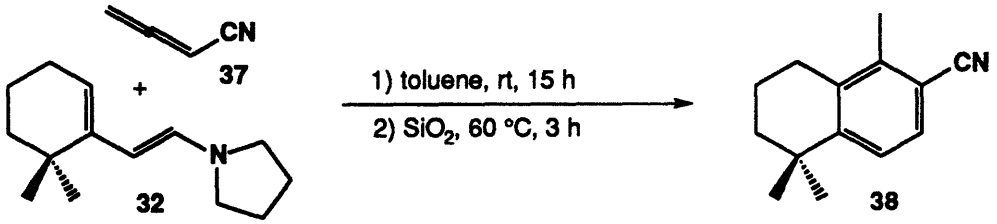
---

26 For a review, see: *Organic Synthesis at High Pressures*; Matsumoto, K.; Acheson, R. M., Ed.; Wiley Interscience: New York, 1990.

27 Dauben, W. G.; Kozikowski, A. P. *J. Am. Chem. Soc.* **1974**, *96*, 3664.

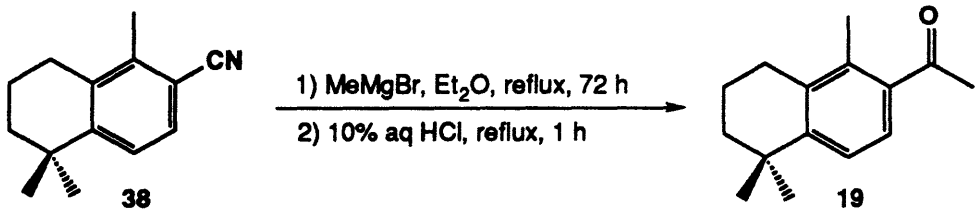
It was thus necessary to return to a less technology-intensive approach. The effect of lithium perchlorate promotion was investigated briefly by attempting the Diels-Alder reaction of **20** and **21** in 5.0 M $LiClO_4/Et_2O$, a solvent system that has been used by Grieco[28] to effect transformations that could hitherto only take place under very high pressure conditions. Once again, however, the desired cycloaddition would not take place under a variety of conditions.

The synthesis of the key tetrahydronaphthalene intermediate was ultimately achieved by employing cyanoallene **37** as the dienophile for the crucial Diels-Alder step. Dienophiles with allenic π bonds are often more reactive than similarly activated alkynes[29] and, as expected, it was found that dienamine **32** reacts smoothly with 2.5 equiv of cyanoallene at room temperature to give, after warming with silica gel, the desired bicyclic nitrile **38** in 49-55% yield. It should be noted that while small scale reactions were complete after 15 h at room temperature (for the cycloaddition) and 3 h at 60 °C (for the silica gel promoted elimination step), large scale runs (> 5 mmole) required at least 24 h for the Diels-Alder reaction and 10 h for the elimination step. Methyl buta-2,3-dienoate was also investigated as a dienophile, but difficulties encountered in its preparation,[30] coupled with the fact that it did not react cleanly, made it an unattractive alternative to the readily synthesized cyanoallene.[31]



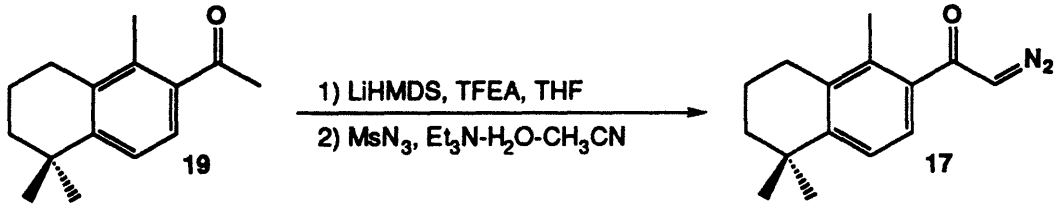

28 Grieco, P. A.; Nunes, J. J.; Gaul, M. D. *J. Am. Chem. Soc.* **1990**, *112*, 4595.
29 For example, see: (a) Samer, J.; Wiest, H.; Mielert, A. *Chem. Ber.* **1964**, 97, 3183. (b) Kurtz, P.; Gold, H.; Disselnkötter, H. *Liebigs Ann. Chem.* **1959**, *624*, 1: (c) Boger, D. L.; Zhang, M. *J. Am. Chem. Soc.* **1991**, *113*, 4230.
30 Lang, R. W.; Hansen, H. -J. *Org. Syn.* **1984**, *62*, 202.
31 The preparation of cyanoallene in >90% yield by the reaction of propargyl bromide with KCN-CuCN has been described: Brandsma, L.; Verkruijisse, H. D. *Synthesis of Acetylenes, Allenes and Cumulenes*; Elsevier Scientific Pub. Co.: New York, 1981; p 173.

Nitrile **38** was easily converted into methyl ketone **19** by reaction with excess methylmagnesium bromide in refluxing ether. The imine intermediate was hydrolyzed by heating the crude reaction product with aqueous hydrochloric acid to give, after isolation and recrystallization, the pure methyl ketone in 90% yield.




**38** **19**

With the methyl ketone in hand, we could now apply our improved "detrifluoroacetylative" diazo transfer method[15] to acquire the α-diazo ketone **17**. Thus, formation of the α-trifluoroacetyl derivative[32] of the methyl ketone and reaction with methanesulfonyl azide as the diazo transfer reagent gave **17** in 94% yield. It should be noted that this compound was isolated as a low melting yellow solid (mp 42.5-43 °C) whereas Casebier reported it to be an oil.

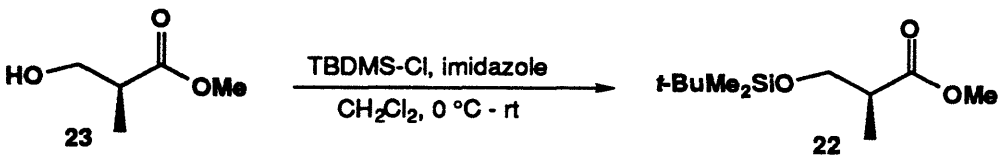



**19** **17**

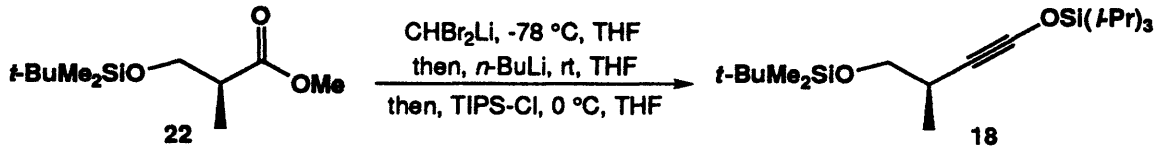
Casebier showed that the other component required for the aromatic annulation, the chiral siloxyacetylene **18**, could be readily obtained beginning with the commercially available, enantiomerically pure (S)-methyl-3-hydroxy-2-methylpropionate (**23**). Treatment of **23** with *t*-butyldimethylsilyl chloride in the presence of imidazole provided the silyl ether **22**.

The protected ester **22** was then converted to siloxyacetylene **18**, in approximately

32 Doyle, M. P.; Dorow, R. L.; Terpstra, J. W.; Rodenhouse, R. A. *J. Org. Chem.* **1985**, *50*, 1663.

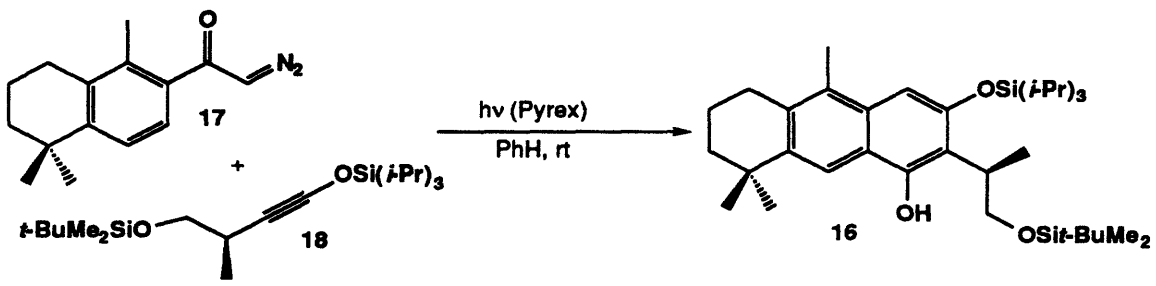



50% yield (from **23**), according to the general procedure of Kowalski,[33] by sequential treatment with lithiodibromomethane, *n*-butyllithium, and triisopropylsilyl chloride. This acetylene $[\alpha]_D^{25}$=-2.64° (c=0.65) was shown not to have undergone any racemization when Casebier was able to synthesize optically pure tanshinones from it.[14]

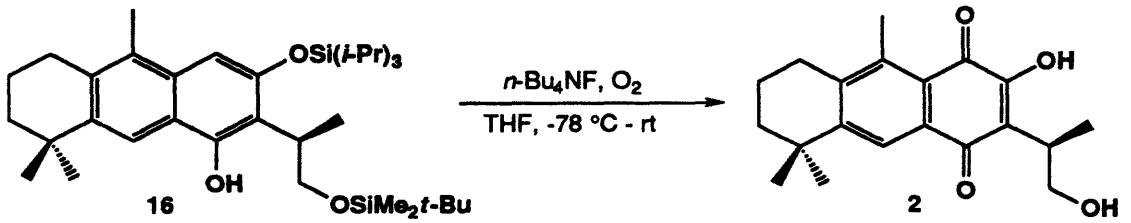



Having synthesized the two components necessary for the aromatic annulation, Casebier found that exposure of a solution of α-diazo ketone **17** and 2 equivalents of siloxyacetylene **18** in 1,2-dichloroethane to 254 nm light, at room temperature, gave the desired annulation product **16** (ca. 90% purity) in 51-60% yield. Casebier reported a 38% overall yield for the conversion of **17** to aegyptinone B via aromatic annulation followed by the deprotection/oxidation of **16**. Attempts to repeat his procedure were on the whole unsuccessful since the final product could only be obtained in approximately 15% yield and in an impure state. A major side product in the aromatic annulation reaction was a high molecular weight aromatic compound (54 carbons by $^{13}C$ NMR and M W ≥ 750 by mass spectrometry) whose structure has not been established. The amount of this side product present in the crude reaction mixture was found to depend on the solvent used and also on the concentration of the diazo ketone. Indeed, while previously it had been found that most aromatic annulations were best carried out in 1,2-dichloroethane at concentrations of 0.3 - 0.7 M, benzene was found to be the solvent of choice for this specific case.

33 (a) Kowalski, C. J.; Haque, M. S.; Fields, K. W. *J. Am. Chem. Soc.* **1985**, *107*, 1429. (b) Kowalski, C. J.; Haque, M. S. *J. Org. Chem.* **1985**, *50*, 5140.




Low concentrations of the α-diazo ketone **17** were also found to be beneficial, resulting in a marked reduction in the amount of high molecular weight byproduct produced. This is best explained by assuming that this byproduct results from some type of oligomerization of the α-diazo ketone **17**. Alternative sources of UV radiation were also tested since benzene absorbs strongly around the 254 nm region and it was found that radiation of 300 nm, or that produced by a medium pressure Hanovia lamp, also led to good yields of the polysubstituted aromatic compound **16**. This suggests that Pyrex™ reaction vessels can be used instead of Vycor™ vessels. The optimized conditions for the aromatic annulation reaction involve the irradiation of a benzene solution (0.04 M final concentration) of α-diazo ketone **17** , in the presence of 3.5 eq of siloxyacetylene **18**, at room temperature using a Hanovia lamp. The α-diazo ketone is added in two equal portions, with the second portion being added after the disappearance of the starting material. Chromatographic purification of the crude product on silica gel, with 5% chloroform-hexanes as the eluent resulted in the isolation of the desired product (**16**) as a white solid[34] in 58-70% yield. Subsequent treatment of this phenol in oxygen saturated THF with tetrabutylammonium fluoride, followed by an acid workup, led to the formation

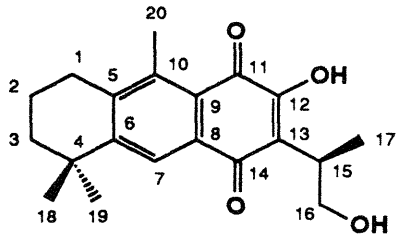



34 In contrast, Casebier was never able to isolate this compound which, he claimed, decomposes on silica gel.

of aegyptinone B in 87% yield.

It was found that the purity of the aegyptinone B obtained following this procedure depended on the purity of the phenol **16**. Indeed, Casebier obtained a low melting yellow-orange solid, mp 76-80 °C (lit.[3] red crystals from MeOH, mp 101-102 °C) upon deprotection and oxidation of material which was said to be roughly 90% pure phenol **16**. The improved procedure provides a yellow-orange solid with a melting point that is considerably higher and sharper: 118-119 °C (corrected). While we were unable to obtain a satisfactory authentic sample of aegyptinone B (the material that was obtained from Dr. Tempesta for comparison was an oil), it was found that our synthetic aegyptinone B has spectroscopic properties ($^1$H NMR, $^{13}$C NMR, IR) in excellent agreement to those reported for the natural compound.

While Sabri and coworkers did not report any optical rotation data for aegyptinone B, we found that the synthetic aegyptinone B had $[\alpha]^{25}_D = +8.7°$ ($CHCl_3$, c=2.09).

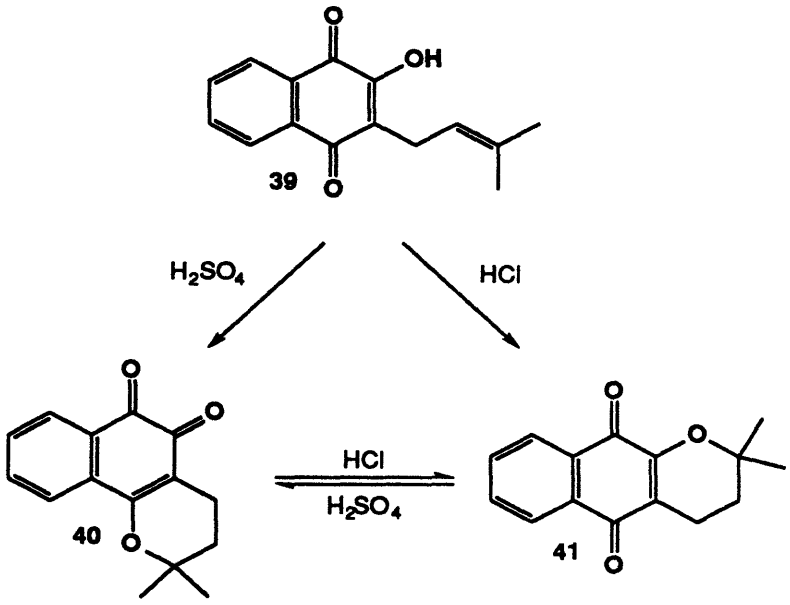



## Table 1: Spectral Data for Aegyptinone B

| | $^1$H NMR (300 MHz) | | $^{13}$C NMR (75 MHz) | |
|---|---|---|---|---|
| Atom # | Natural (ref 3) | Synthetic | Natural (ref 3) | Synthetic |
| 1 | 2.75 (bt, 6.3 Hz) | 2.75 (t, 6.2 Hz) | 19.6 | 19.1 |
| 2 | 1.87 (m) | 1.87 (m) | 29.0 | 28.6 |
| 3 | 1.68 (m) | 1.66 (m) | 38.2 | 37.8 |
| 4 | - | - | n.r.[a] | 35.2 |
| 5 | - | - | n.r. | 141.4 |
| 6 | - | - | n.r. | 141.9 |
| 7 | 8.12 (s) | 8.09 (s) | 125.7 | 124.5 |
| 8 | - | - | n.r. | 132.0 |
| 9 | - | - | n.r. | 124.0 |
| 10 | - | - | n.r. | 153.6 |
| 11 | - | - | n.r. | 185.6 |
| 12 | - | - | n.r. | 154.2 |
| 13 | - | - | n.r. | 123.1 |
| 14 | - | - | n.r. | 182.7 |
| 15 | 3.50 (m) | 3.45 (m) | 33.5 | 32.7 |
| 16α | 3.89 (m) | 3.85 (dd, ABX, 5, 11 Hz) | 66.0 | 65.6 |
| 16β | 3.95 (m) | 3.95 (dd, ABX, 7, 11 Hz) | | |
| 17 | 1.33 (d, 6.7 Hz) | 1.29 (d, 7.2Hz) | 15.0 | 14.6 |
| 18 and 19 | 1.35 (s) | 1.34 (s) | 31.4 | 31.3 |
| 20 | 2.60 (s) | 2.67 (s) | 17.2 | 16.7 |

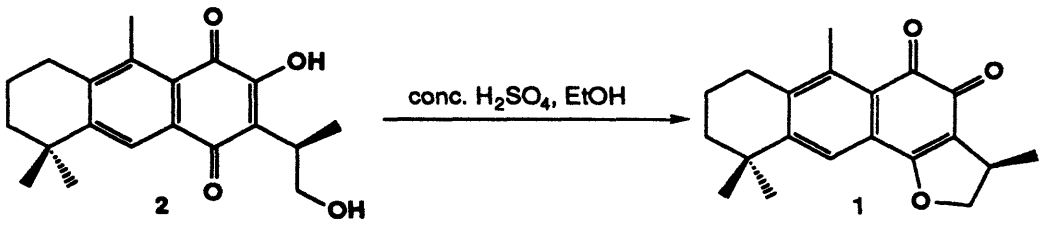
a) n.r. = not reported

The synthesis of aegyptinone A was achieved by an acid-catalyzed cyclization of aegyptinone B. Paternò[35] and Hooker[36] showed that in a related case, lapachol **39** could be converted into two possible naphthaquinones depending on the conditions used. The more stable *p*-quinone isomer **41** is formed upon treatment of lapachol with concentrated hydrochloric acid, while the *o*-quinone isomer **40** is obtained when lapachol is dissolved in concentrated sulfuric acid and quenched by pouring the mixture into water. Ettlinger[37] showed that this is due to the fact that the *o*-quinone isomer is the more basic of the two isomers and that as a result, this isomer is favored in sulfuric acid, the stronger acid. Hydrochloric acid is not a strong enough acid to shift the equilibrium in favor of the *o*-quinone isomer, so that only the more stable isomer **41** is formed.




This chemistry has also been used previously in connection with the synthesis of tanshinones.[38] In the present case, it was found that cyclization of aegyptinone B to generate the tetracyclic *o*-quinone system of aegyptinone A was accomplished in high yield upon brief exposure to an ethanolic solution of concentrated sulfuric acid.

35 Paternò, E. *Gazz. Chim. Ital.* **1882**, *12*, 622.
36 Hooker, S. C. *J. Chem. Soc.* **1892**, *61*, 611 and ibid. **1896**, *69*, 1355.
37 Ettlinger, M. G. *J. Am. Chem. Soc.* **1950**, *72*, 3472.
38 See Danheiser, R. L.; Casebier, D. S.; Loebach, J. L. *Tetrahedron Lett.* **1992**, *33*, 1149 and references therein.




Synthetic aegyptinone A [mp 137-138.5 °C (corrected)] was indistinguishable from an authentic sample of the natural product, provided by Professor Sabri, by comparison of NMR, IR, TLC, optical rotation, and melting point characteristics.

## Table 2: Physical Data for Aegyptinone A

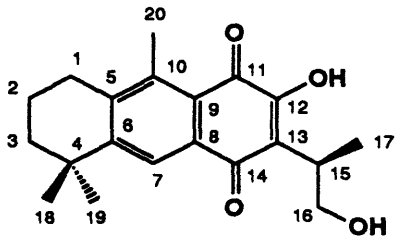
**Melting Point** (uncorrected)

| Natural | Synthetic | Mixed(a) |
|---|---|---|
| 140.5 - 142.5 °C | 140.5-143 °C | 140.5-143 °C |

(a) Material obtained by concentration of a solution of both natural and synthetic compounds.

**Optical Rotation Data**

| Natural | Synthetic |
|---|---|
| $[\alpha]^{25}_D$=-101° ($CHCl_3$, c=0.13) | $[\alpha]^{25}_D$=-102° ($CHCl_3$, c=0.13) |




## Table 3: Spectral Data for Aegyptinone A

| | $^1$H NMR (300 MHz) | | $^{13}$C NMR (75 MHz) | |
|---|---|---|---|---|
| Atom # | Natural | Synthetic | Natural (ref 3) | Synthetic |
| 1 | 2.70 (bt, 6.4 Hz) | 2.70 (t, 6.4 Hz) | 19.1 | 19.0 |
| 2 | 1.83 (m) | 1.83 (m) | 28.5 | 28.4 |
| 3 | 1.63 (m) | 1.63 (m) | 37.7 | 37.6 |
| 4 | - | - | 34.9 | 34.8 |
| 5 | - | - | 141.2 | 141.1 |
| 6 | - | - | 152.6 | 152.1 |
| 7 | 7.51 (s) | 7.51 (s) | 121.6 | 121.6 |
| 8 | - | - | 125.5 | 125.5 |
| 9 | - | - | 126.2 | 126.1 |
| 10 | - | - | 144.0 | 143.8 |
| 11 | - | - | 184.5 | 184.4 |
| 12 | - | - | 176.2 | 176.1 |
| 13 | - | - | 118.2 | 118.1 |
| 14 | - | - | 171.0 | 170.8 |
| 15 | 3.58 (m) | 3.58 (m) | 34.6 | 34.5 |
| 16α | 4.35 (dd, 6, 9 Hz) | 4.35 (dd, 6, 9 Hz) | 81.3 | 81.2 |
| 16β | 4.87 (t, 9.5 Hz) | 4.87 (t, 9.5 Hz) | | |
| 17 | 1.34 (d, 6.8 Hz) | 1.34 (d, 6.8 Hz) | 18.8 | 18.7 |
| 18,19 | 1.30 (s) | 1.30 (s) | 31.9 | 31.1, 31.2 |
| 20 | 2.57 (s) | 2.57 (s) | 16.6 | 16.4 |

The overall yield for the six step synthesis of aegyptinone B, starting with the known aldehyde **25**, is around 23%, while aegyptinone A was synthesized in seven steps

from **25** to afford the natural product in about 20% overall yield. This rapid and efficient access into potentially interesting linear multicyclic aromatic compounds constitutes the first total syntheses of aegyptinones A and B and is a powerful demonstration of the "second generation" aromatic annulation chemistry developed in our laboratory.

# PART II

## SYNTHETIC APPROACHES TO GLYCINOECLEPIN A

# CHAPTER 1

# INTRODUCTION AND BACKGROUND

## Introduction: Isolation of Glycinoeclepin A

Nematodes are elongated cylindrical worms of the class Nematoda parasitic to animals and plants and found free-living in soil and water.[39] These worms are probably the most abundant animals on the face of the earth. At least 32 species of nematodes have been found to parasitize humans,[39a] and since nematodes infect many of the plants and animals that we depend on for food, they are directly or indirectly responsible for a significant loss of human lives.

Nematodes of the genus *Heterodera* have been particularly serious pests because their larvae are protected by a cyst which makes them very resistant to adverse conditions.[40] Cysts nematodes frequently have a limited number of host plants, a specificity which is thought to be due to their dependence on key stimulants from the host plants during at least part of their lifecycle. This was first realized in 1922 when Baunacke[41] found that extracts from the host plant could stimulate the emergence of larvae from the cyst of the potato cyst nematode, a nematode that parasitizes potatoes. The soybean cyst nematode (*Heterodera glycines* Ichinohe) has attracted quite a lot of attention because it parasitizes a number of economically important plants such as soybeans (*Glycine max*), kidney beans (*Phaseolus vulgaris*), and adzuki beans (*Phaseolus angularis*).[42] In 1966, researchers in Japan showed[43] that as with the potato cyst

39 (a) Chitwood, B. G.; Chitwood, M. B. *Introduction to Nematology*; University Park Press: Baltimore, 1974. (b) Decker, H. *Plant Nematodes and their control (phytonematology)* (translated from Russian); Amerind: New Delhi, 1980; p128.

40 Whitehead, A. G. In *Cyst Nematodes*; NATO ASI, Series A, Vol 121; Lamberti, F. and Taylor, C. E., Eds.; Plenum: New York, 1985; p 413.

41 Baunacke, W. E. *Arb. Biol. Bund Anst. Land-u. Forstw.* **1922**, *11*, 185.

42 Noel, G. R. In *Cyst Nematodes*; NATO ASI, Series A, Vol 121; Lamberti, F. and Taylor, C. E., Eds.; Plenum: New York, 1985; p 257.

43 Tsutsumi, M.; Sakurai, K. *Japn. J. Appl. Ent. Zool.* **1966**, *10*, 129.

nematode, host plant extracts are potent stimulants for the hatching of the larvae of the soybean cyst nematode.

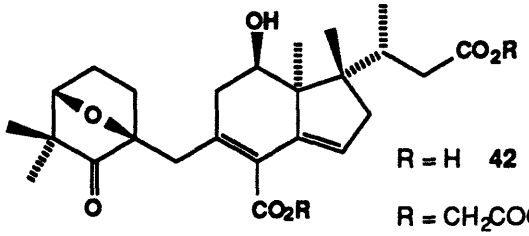
The potential ability to control the hatching of this economically important parasite has prompted the search for the exact nature of these stimulants, and starting in 1967, T. Masamune[44] embarked on an adventure that rivals the work on the isolation of the reproductive steroids of the first half of this century. Indeed, it was not until 15 years later that Masamune was able to savor a partial victory, and it required nearly 20 years before the quest for the identity of the mystery compounds reached a spectacular end.

The first success was the result of a heroic effort and led to the isolation of 50 μg of the *p*-bromophenacyl ester (*p*-BPE) of a substance that had a level of activity rarely found in nature.[45] The source of this compound was a ca. 100 kg sample of dried and powdered kidney bean roots which was extracted and refined numerous times to give fractions which were tested for activity by bioassay. The potency of the fractions to stimulate the hatching of the larvae of the soybean cyst nematode was determined as follows: a comparison was made between the effect of the test solution and that of a distilled water sample on the hatching of a known number of free eggs. These eggs were obtained by dissection of the cysts in which they were enclosed. The percentage of eggs that had hatched following incubation in the test solution minus the percentage of eggs that had hatched in the control gives the per cent hatching rate. A test solution was said to be active if the per cent hatching rate exceeded 50%. At the end of this first step in the isolation work, Masamune and coworkers had in their possession a pure sample that was found to stimulate hatching of the cyst nematode eggs, *in vitro*, at a level of $10^{-11}$ to $10^{-12}$ g/mL! However, the small amount of compound isolated was only adequate for preliminary analyses which revealed (by mass spectrometry) the molecular formula and (by $^1$H NMR analysis) the type of oxygen functions present in the sample. A more

44 Masamune, T. In *Natural Products and Biological Activities; a Naito Foundation Symposium*; University of Tokyo Press; Elsevier: New York, 1986; p 25.
45 Masamune, T.; Anetai, M.; Takasugi, M.; Katsui, N. *Nature* **1982**, *297*, 495.

detailed investigation into the structure of the stimulating agent, which was named glycinoeclepin A, required a greater amount of sample so that Masamune had to repeat his isolation procedure on a larger scale.

A "large amount" of glycinoeclepin A was finally obtained in the mid-1980s following the purification of a ton of dried and powdered kidney bean roots that had been harvested from a 10 hectare field.[46] The 1.25 mg of glycinoeclepin A *p*-BPE (**43**) that were isolated were subjected to numerous spectroscopic investigations which resulted in the proposal of the structure shown below.[47] This assignment was confirmed by X-ray analysis of a single crystal of glycinoeclepin A *p*-BPE.[47]




R = H **42**

R = $CH_2COC_6H_4Br$-*p* **43**

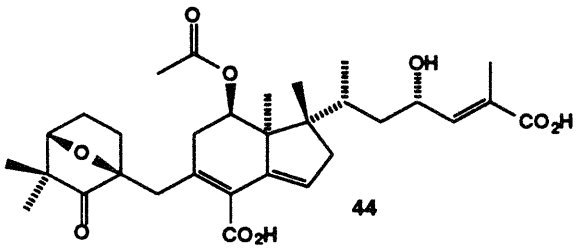
The hydrolysis of the glycinoeclepin A *p*-BPE derivative afforded the natural product (**42**) which was also found to be active, *in vitro*, at the $10^{-12}$ g/mL level. Two other compounds related to the pentanortriterpene glycinoeclepin A were isolated in this study, and while deacetylglycinoeclepin B stimulates the hatching of the soybean cyst nematode at ca. $10^{-8}$ to $10^{-9}$ g/mL, glycinoeclepin B (**44**) and C (**45**) showed no activity at $10^{-7}$ g/mL.[48] All three compounds possess a novel skeleton which bears little resemblance to other natural products isolated thus far.

---

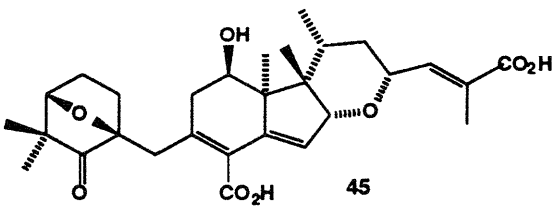
46 (a) Fukuzawa, A.; Furusaki, A.; Ikura, M.; Masamune, T. *Chem. Comun.* 1985, 222. (b) Masamune, T.; Anetai, M.; Fukuzawa, A.; Takasugi, M.; Matsue, H.; Kobayashi, K.; Ueno, S.; Katsui, N. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 981.

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

48 For activity data, see: Fukuzawa, A.; Matsue, H.; Ikura, M.; Masamune, T. *Tetrahedron Lett.* **1985**, *26*, 5539. For revised structure of glycinoeclepin C side chain (C-23) configuration, see: Masamune, T.; Fukuzawa, A.; Furuzaki, A.; Ikura, M.; Matsue, H.; Kaneko, T.; Abiko, A.; Sakamoto, N.; Tanimoto, N.; Murai, A. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 1001.

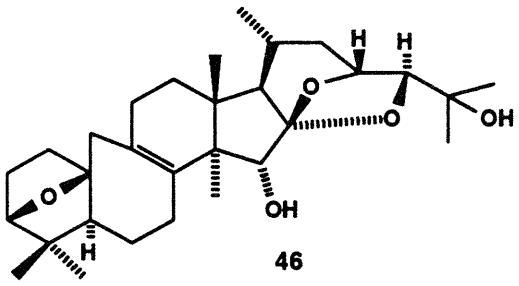



44

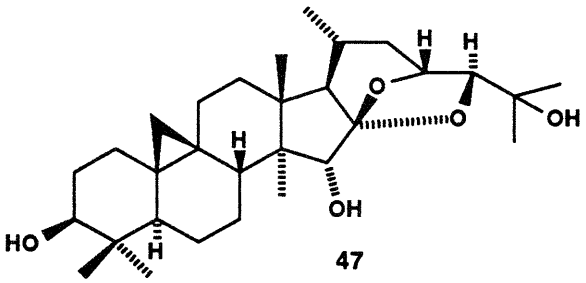



45

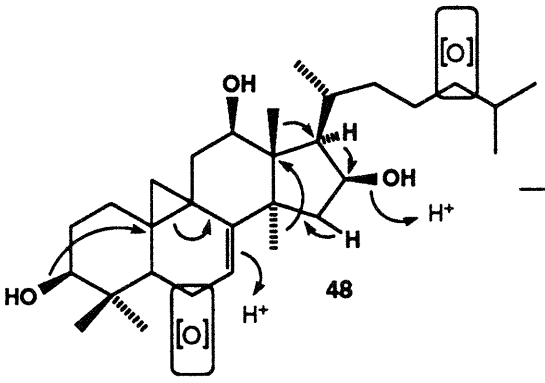
It has been proposed that the common biosynthetic precursor for the glycinoeclepins is a cycloartane, a number of which are known (**46** and **47** for example). This precursor (for example **48**) would undergo several methyl group migrations, oxidation, cleavage of the B ring with loss of one carbon atom, as well as oxabicyclic ring formation in the A ring fragment.[47] Oxidative manipulation of the D ring side chain could then give rise to the three different glycinoeclepins.



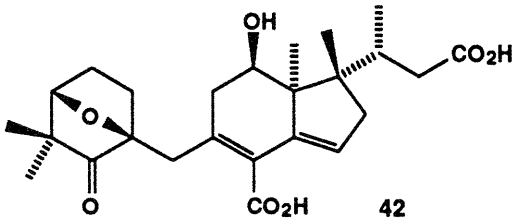

46




47




48




42

## Biological Activity

The lifecycle of the *Heterodera* cyst nematodes begins when the eggs hatch into

larvae which proceed to invade the host plant.[49] These larvae migrate to the vascular cylinder tissue and release glandular secretions which cause the enlargement and transformation of the surrounding plant cells. The cells provide nourishment for the developing nematode throughout its 4 week lifecycle. Following fertilization, the female fills with eggs and subsequently dies to become a cyst which protects the eggs until conditions (temperature, humidity, presence of host plant, etc.) are favorable to hatching. These cysts are resistant to adverse conditions and the eggs can remain viable for about four years.

It was found that treatment of cysts with a solution containing glycinoeclepin A not only stimulates the hatching of the larvae from the eggs, but also the emergence of these larvae from the cysts. It was observed from bioassays that the larvae which emerge upon treatment with glycinoeclepin A are active, whereas those which emerge in the absence of a stimulating substance (in much lower numbers) do not move actively. This, it has been suggested, may mean that hatching is only a result of the active motion of larvae and that glycinoeclepin A stimulates the motor nervous system of the larvae.[44]

The interest in the biological activity of glycinoeclepin A stems from the fact that pests are largely responsible for humanity's woes. Insects vastly outnumber humans and as the result of the competition for food, a large percentage of crops (~37% in the USA) is lost to insects and other pests.[50] The traditional approach to control the loss of crops to insects and other pests has involved the use of toxic agents (pesticides) that kill the pest by poisoning. Many of the substances that have been used are broad spectrum pesticides and since it is estimated that only 0.1% of the pesticide applied to crops usually gets to the target pest,[50] these compounds are normally deployed in relatively high dosages. Traditional agricultural pesticides are toxic, chemically stable, and usually lipophilic since these are desirable properties for field use. As a result, it has been found

49 Opperman, C. H.; Dong, K.; Chang, S. In *Advances in Molecular Plant Nematology*; NATO ASI, Series A, Vol 268; Lamberti, F.; De Giorgi, C. and McK. Bird, D., Eds.; Plenum: New York, 1985; p 65.
50 Pimentel, D. *Chem. Brit.* **1991**, 646.

that a number of the pesticides that have been used commercially have bioaccumulated in the environment. The effect of these pesticides on the ecosystem has been a cause for concern recently. In addition, their effectiveness in controlling pests has sometimes been questioned as evidence of pest resistance has increased. These factors, as well as the escalating costs in the research and development studies necessary for the introduction of new pesticides in the market, have created the need for new strategies for pest control.

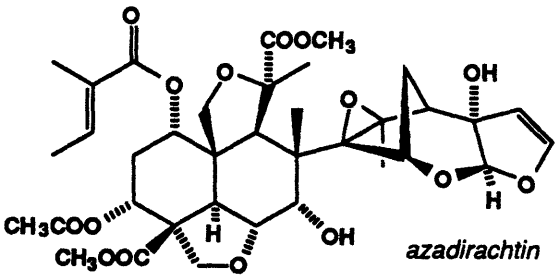
"Integrated pest management" (IPM) - the application of a number of different approaches to the problem of pest control - has been proposed as a desirable alternative to the traditional large scale use of pesticides.[51] IPM includes using the tools of genetic engineering, agricultural know-how, biological control by employing pest predators such as parasites, bacteria and viruses, as well as chemical control. This latter category includes rational design of synthetic pest control agents and the use of behavior-modifying chemicals (semiochemicals).

Semiochemicals[52] are usually highly selective in their action and often show high activity. They can be subdivided into two classes: the pheromones and the allelochemics. Pheromones are chemicals used by members of a species to communicate with each other. Sex pheromones are the means by which a number of insects detect potential mates and are presently used to monitor pests population and to time the application of pesticides. They are also capable of disrupting the mating habits of the pests, with a resulting decrease in pest population, and have been used in conjunction with insecticides ("attracticides") to kill the insects in traps.

Allelochemics are substances produced by one organism but that are significant to organisms of a different species. Two important groups of allelochemics are the allomones and the kairomones. An allomone is a substance produced or acquired by an organism that, when it contacts an individual of another species, evokes in the receiver a

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

behavioral or physiological reaction that is adaptively favorable to the emitter but not to the receiver. Examples of these natural defense agents include venoms and the antifeedant azadirachtin which is a natural compound found in the seeds of the neem-tree, a tree that has been used extensively in India to control insects. This compound is thought to be produced by the plant as a deterrent to insect attacks.



*azadirachtin*

A kairomone is a substance that evokes in the receiver a behavioral or physiological reaction that is adaptively favorable to the receiver but not to the emitter. Kairomones, as well as the pheromones, are very different from the allomones in that they themselves are generally not toxic to pests, and therefore potentially non-toxic towards the ecosystem in general. This advantage could make the highly active glycinoeclepin A, a kairomone, a potentially very useful antinematodic agent.

The target of interest, *H. glycines*, causes the so-called "yellow dwarf disease" or "daizu-iwo-byo" of soybean which leads to severe inhibition in plant growth. The leaves of the infected soybeans lack pigments and drop early. In addition, very few flowers and seeds are formed. The nematode not only damages the plant by attacking its cells and blocking vital transport channels, but also renders the plants susceptible to attacks by viruses, bacteria, and fungi. *H. glycines* is widespread in Japan and many other areas of the world and accounts for most of the approximately 2.5 billion dollars in crop loss due to nematodes.[53] In the USA, it was responsible for a 5.8% yield loss during 1985 which

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

translates into a loss of over 200 million dollars to farmers. The yield from an infected field is approximately 20% that of a non-infected field and the use of resistant varieties of soybeans, while somewhat successful, does not lead to a complete eradication of the symptoms. Furthermore, the four varieties of soybeans that have proved to be tolerant can only be cultivated in areas with warm climates.[54]

The soybean cyst nematode was first reported in the USA in 1954 and it had spread to at least 24 states by 1985.[55] Soybean is one of the most important crops in the USA and it ranks third in total area planted. There is also concern that other crops such as kidney beans, which have been found to be parasitized by the soybean cyst nematode, will also be affected in an economically significant way.

Presently, the soybean cyst nematode is controlled by crop rotation and by the use of pesticides such as halogenated aliphatic hydrocarbons (for example methyl bromide) and carbamates (for example aldicarb).[40] While an exact protocol for field use would have to be worked out and studies would have to be conducted to determine its effect on the ecosystem, it is possible that glycinoeclepin A could be used as an "environmentally benign" antinematodic agent. A major obstacle that needs to be addressed is the lack of a suitable source of glycinoeclepin A. While there does not appear to be much promise in obtaining a significant amount of the compound from nature, it is possible that chemical synthesis will eventually provide the supply necessary for testing and eventual application of glycinoeclepin A. The extremely high potential utility of this molecule as a nematode control agent and its extremely challenging novel structure make the total synthesis of glycinoeclepin A an unusually worthy target for the synthetic organic chemist. Not surprisingly, therefore, much attention has been directed towards this

54 Kir'yanova, E. S.; Krall', E'. L. *Plant-Parasitic Nematodes and their Control* (translated from Russian); Amerind: New Delhi, 1980, Vol II.

55 For a review on the economic importance of cyst nematodes in North America, see: Miller, L. I. In *Cyst Nematodes*; NATO ASI, Series A, Vol 121; Lamberti, F. and Taylor, C. E., Eds.; Plenum: New York, 1985; p 373.

endeavor and three total syntheses,[56] a biomimetic synthesis of a close derivative,[57] as well as a number of papers on synthetic approaches and structure-activity relationships of analogs[58] have been reported thus far.

**Previous Syntheses of Glycinoeclepin A**

The synthetic challenges posed by glycinoeclepin A are numerous. The molecule consists of two bicyclic systems linked by a one carbon atom chain. The oxabicyclic system (A ring based on the steroidal ring nomenclature), while it appears by no means trivial to synthesize, does not possess an intricate array of substituents. The presence of four contiguous stereogenic centers in the carbocyclic C,D-ring system is by far the most complicated stereochemical issue to be faced in this molecule. Besides the need to control the stereochemistry of the molecule, one should expect great difficulty in the rapid assembly of the C,D-ring system by conventional chemistry. The sterically crowded environment caused by the many substituents as well as the A-strain along the lower part of the C,D-ring system would be expected to hinder easy manipulation of the functionality in much of the molecule.

The first total synthesis of glycinoeclepin A was reported by Masamune, Murai, and their coworkers at Hokkaido University.[56a] While it has the merit of being the first approach to successfully solve the many synthetic problems presented by the structure, this route is rather lengthy (>40 total steps) and thus does not provide a means of increasing the supply of this important compound.

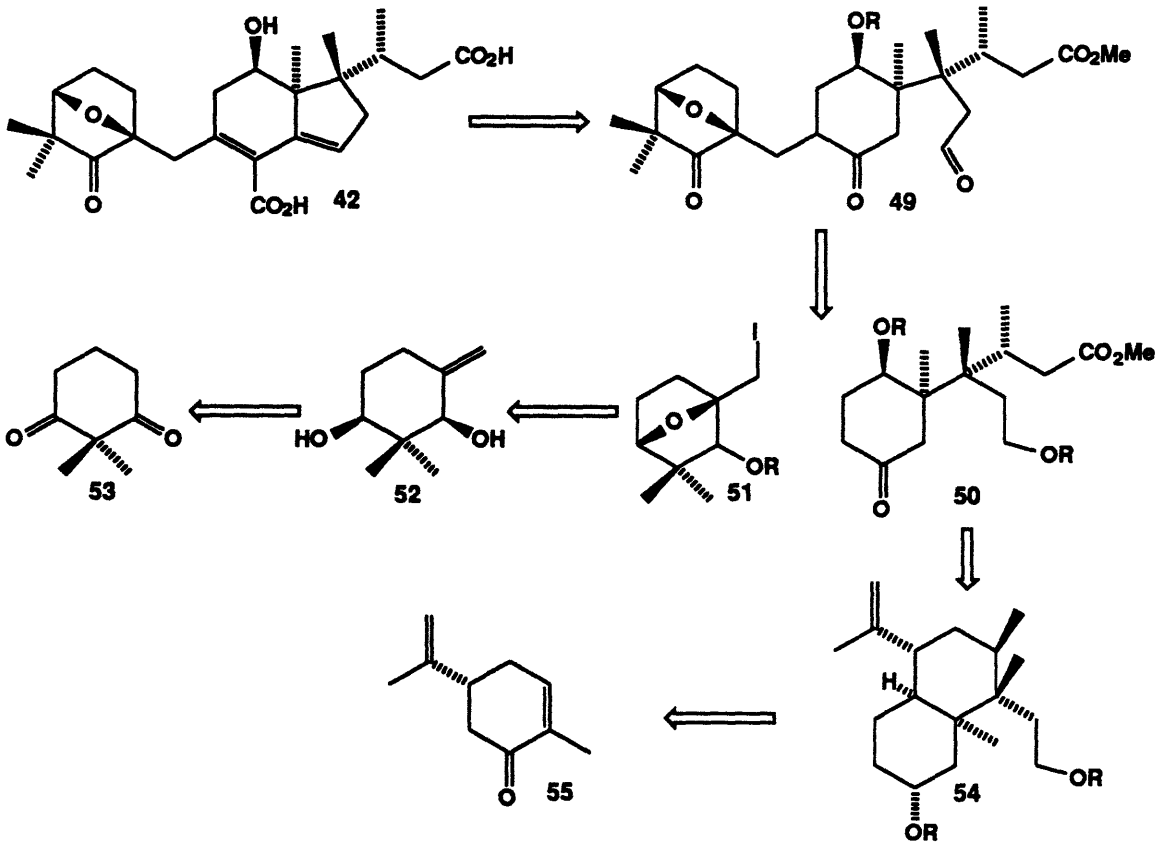
Murai's retrosynthetic analysis led him, as with others later on, to conclude that

---

56 (a) Murai, A.; Tanimoto, N.; Sakamoto, N.; Masamune, T. *J. Am. Chem. Soc.* **1988**, *110*, 1985. (b) Mori, K.; Watanabe, H. *Pure Appl. Chem.* **1989**, *61*, 543. (c) Corey, E. J.; Houpis, I. N. *J. Am. Chem. Soc.* **1990**, *112*, 8997.

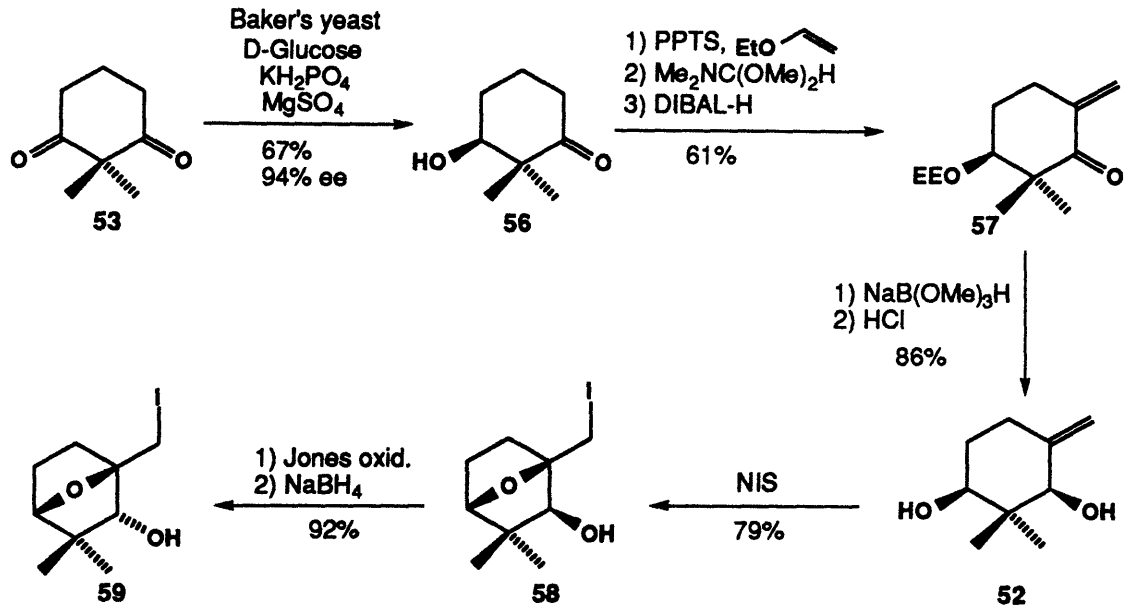
57 Corey, E. J.; Hong, B.- C. *J. Am. Chem. Soc.* **1994**, *116*, 3149.

58 For synthetic approaches to the D ring side chain, see: Okawara, H.; Nii, Y.; Miwa, A.; Sakakibara, M. *Tetrahedron Lett.* **1987**, *28*, 2597. For structure-activity work, see: (a) Miwa, A.; Nii, Y.; Okawara, H.; Sakakibara, M. *Agric. Biol. Chem.* **1987**, *51*, 3459. (b) Murai, A.; Ohkita, M.; Honma, T.; Hoshi, K.; Tanimoto, N.; Araki, S.; Fukuzawa, A. *Chem. Lett.* **1992**, 2103. (c) Kraus, G. A.; Johnston, B.; Kongsjahju, A.; Tylka, G. L. *J. Agric. Food. Chem.* **1994**, *42*, 1839.



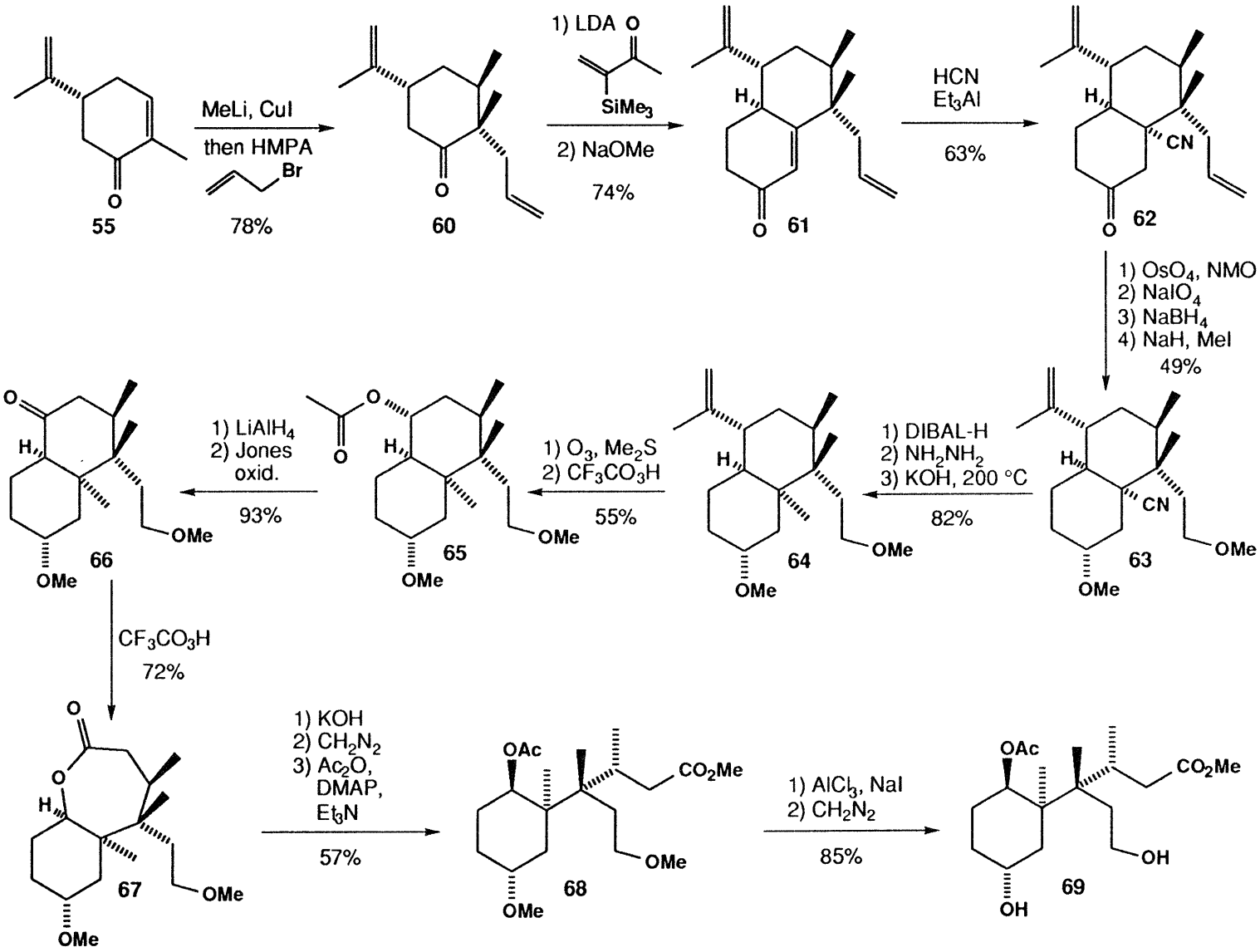

the problem was best approached by breaking the molecule in two halves. In this case, Murai chose to generate the A ring bicyclic system and to connect it to a C,D-ring system precursor by an alkylation of ketone **50** with iodide **51**. The final steps in his synthesis would involve the completion of the carbobicyclic skeleton by an internal aldol reaction and functional group manipulation. Cyclization of the iodonium ion derived from **52** was expected to provide access to the oxabicyclic system. Diol **52** would in turn come from an enantioselective yeast reduction of cyclohexanedione **53**. The carbocyclic ring system with the D ring side chain was ultimately derived from R-(-)-carvone (**55**) via the bicyclic intermediate **54**. This compound was obtained from **55** via a sequence involving conjugate addition of methyl cuprate, alkylation, Robinson annulation and Nagata hydrocyanation.

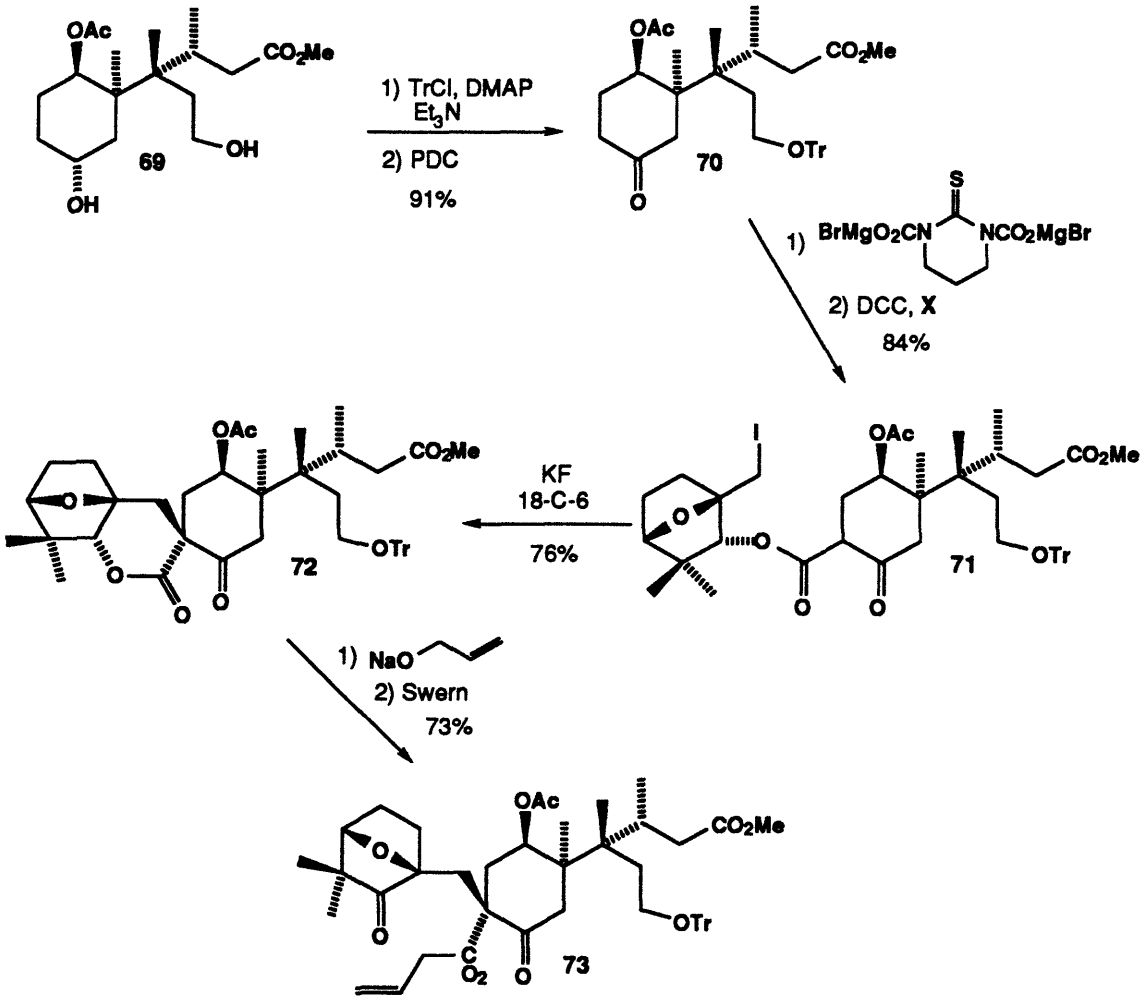
Murai's synthesis thus began with the yeast-promoted enantioselective reduction



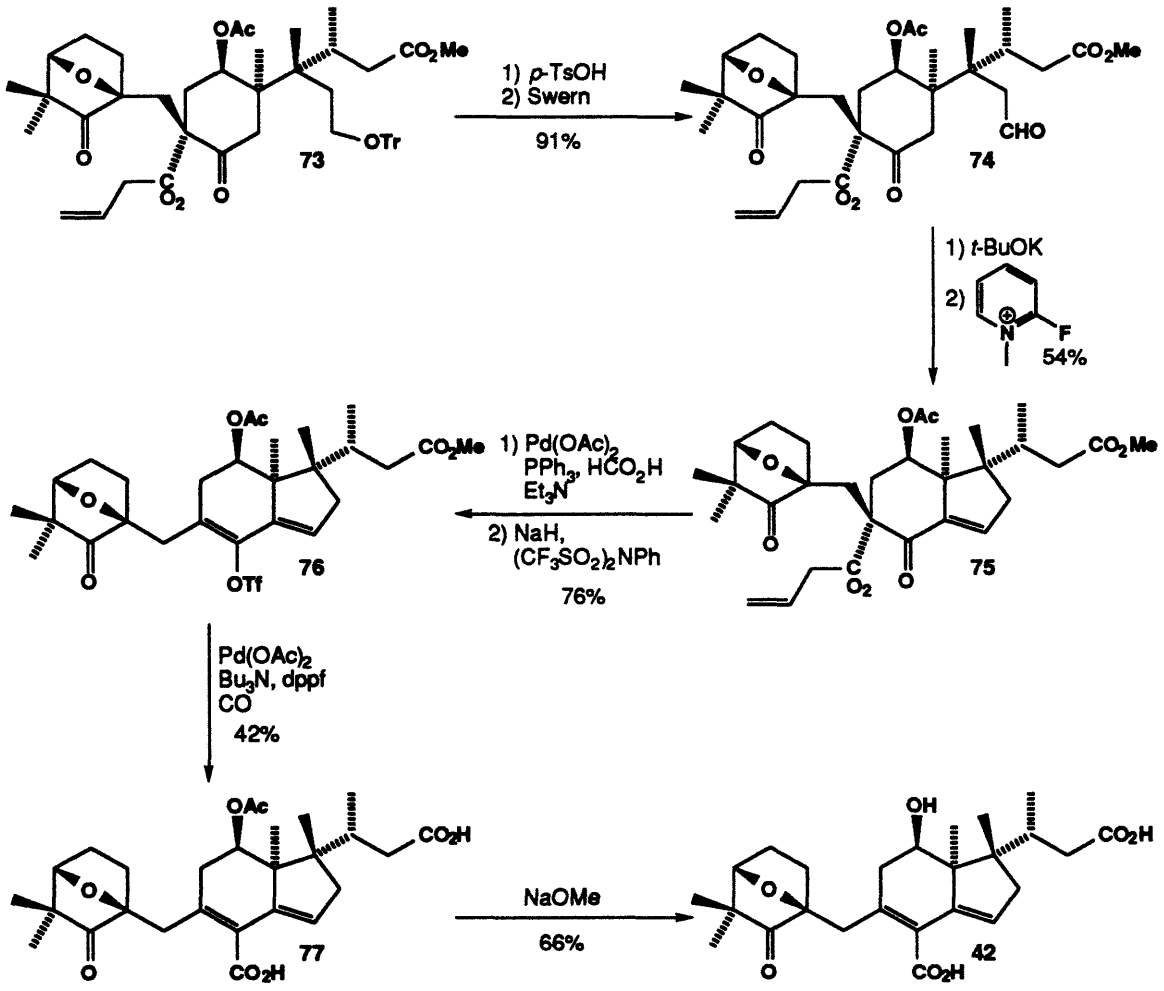

of diketone **53** which afforded (S)-2,2-dimethyl-3-hydroxycyclohexan-1-one (**56**) in 67% yield with 94% ee. Temporary protection of the hydroxyl function, and α-methylenation and then reduction of the ketone afforded diol **52** after deprotection of the intermediate alcohol. Conversion of this compound to the oxabicyclic system was accomplished via the iodonium ion to give **58**, the alkylating agent necessary for the coupling of the two bicyclic ring systems. Synthesis of its coupling partner **70** involved stereoselective cuprate addition to carvone followed by trapping of the resulting enolate with allyl bromide. Robinson annulation and conjugate addition of cyanide, according to the method of Nagata, afforded the desired cis-fused ß-cyano ketone **62** (63%) together with the undesired trans-fused isomer (30%). The major isomer was converted into ε-caprolactone **67** by oxidative cleavage of the monosubstituted olefin, reduction of the nitrile function to a methyl group, oxidative degradation of the isopropenyl side chain, and Baeyer-Villiger oxidation of the cyclohexanone **66**. Lactone hydrolysis followed by several functional group manipulation steps gave **70**.

The coupling of **70** to **58** via alkylation procedures was unsuccessful and it was thus necessary for Murai to seek other alternatives. He found that *intramolecular*

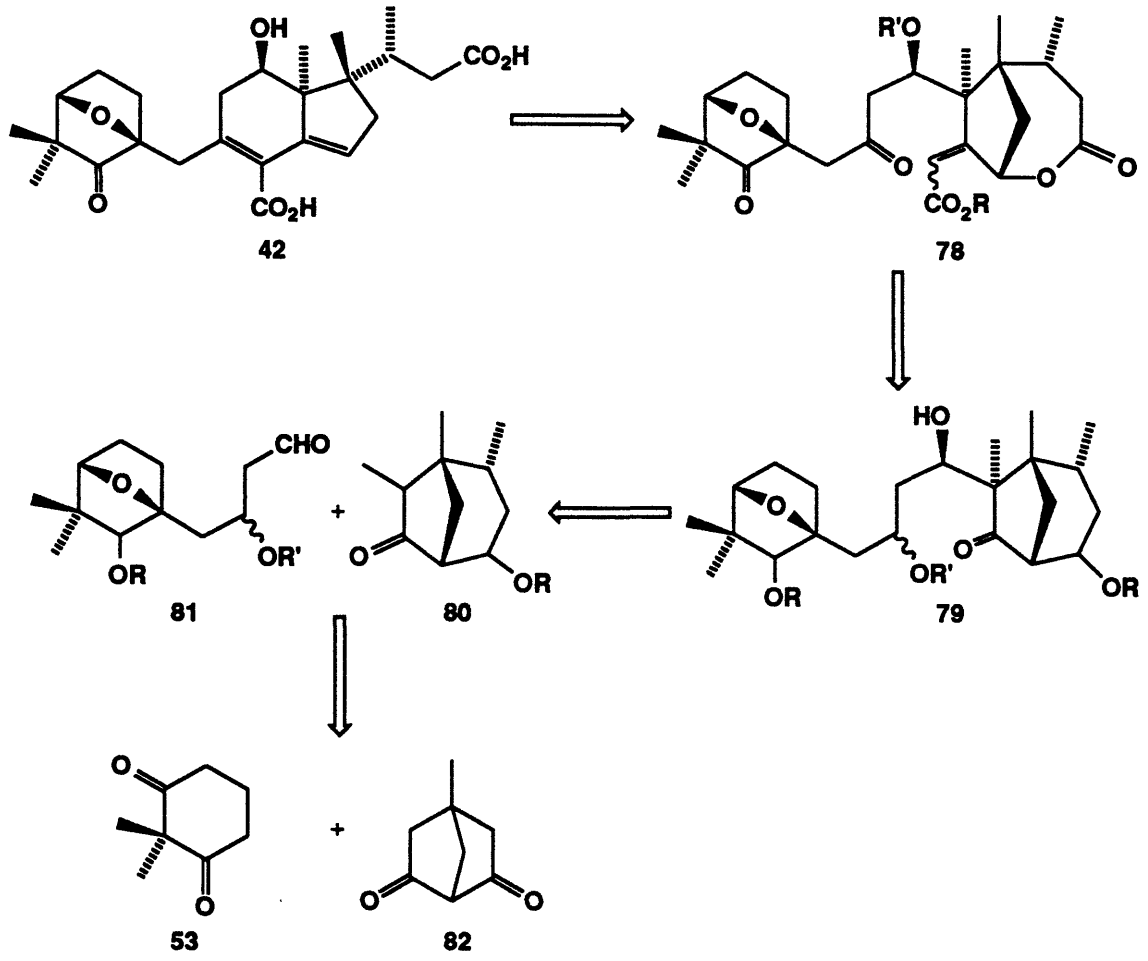

MeLi, CuI
then HMPA
Br
78%
55
60
1) LDA
SiMe3
2) NaOMe
74%
61
HCN
Et3Al
63%
62
1) OsO4, NMO
2) NaIO4
3) NaBH4
4) NaH, MeI
49%
1) DIBAL-H
2) NH2NH2
3) KOH, 200 °C
82%
63
1) O3, Me2S
2) CF3CO3H
55%
64
1) LiAlH4
2) Jones
oxid.
93%
65
CF3CO3H
72%
66
1) KOH
2) CH2N2
3) Ac2O,
DMAP,
Et3N
57%
67
1) AlCl3, NaI
2) CH2N2
85%
68
69




alkylation to connect the desired carbon atoms could be achieved after first linking the two partners as an ester. However, this intramolecular alkylation step could only be achieved if the original bicyclic alcohol **58** was inverted to the epimeric alcohol **59**. The final closure of the D ring was accomplished by an aldol reaction of the C ring ketone with the side chain aldehyde in **74**. The completion of the synthesis involved palladium promoted carboxylation of enol triflate **76** and deprotection of the resulting product to give glycinoeclepin A after a total of about 35 steps in the longest linear sequence.

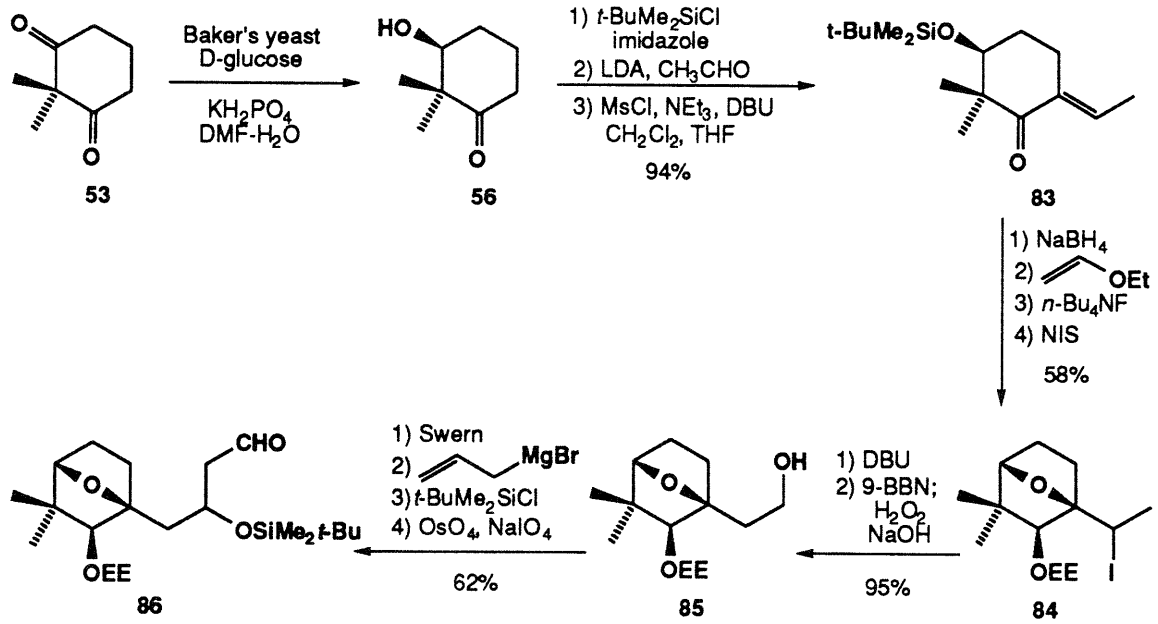


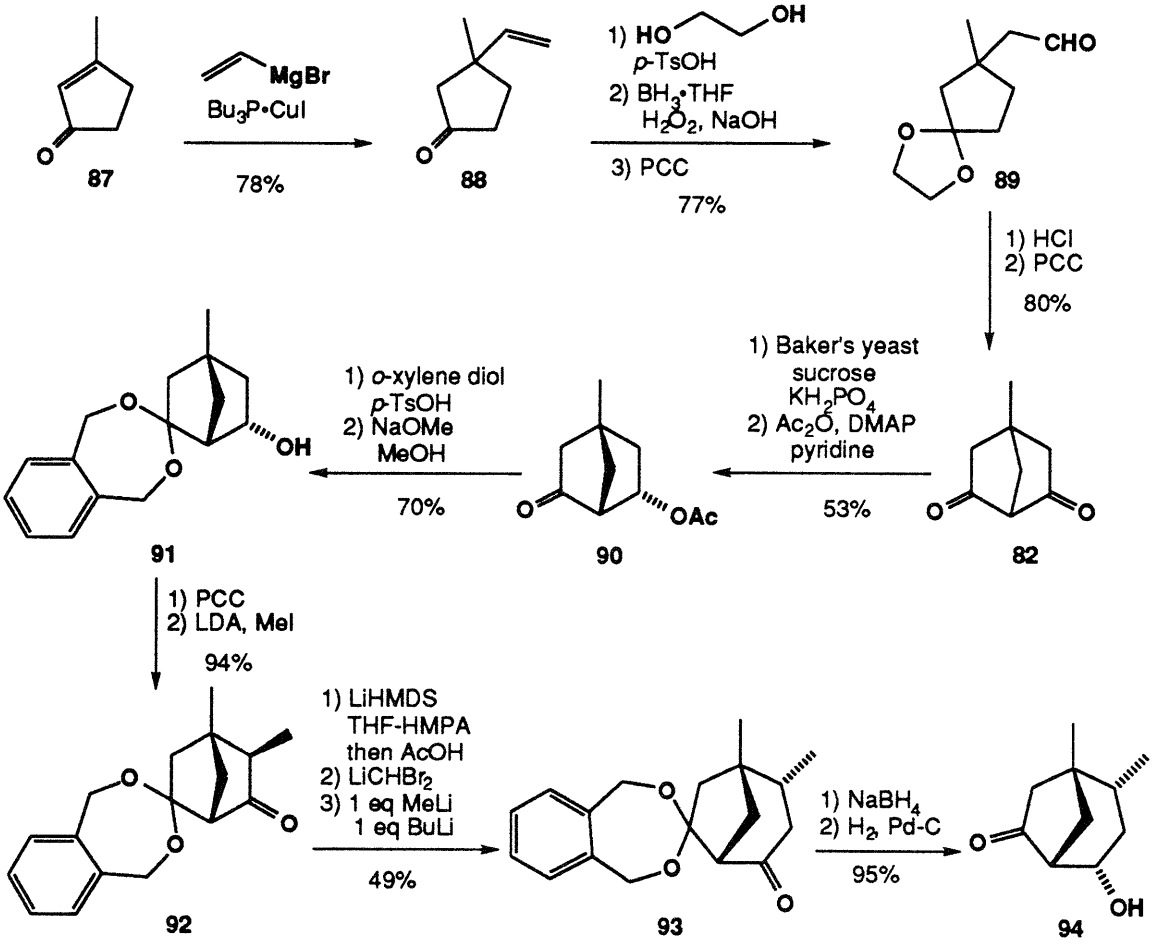

The second synthesis to be published was the result of work done by Mori and Watanabe.[56b] Their approach was similar to that of Masamune and Murai in that the oxabicyclic system was constructed using related chemistry, but the two coupling partners involved in the key step of the synthesis are rather different. Mori decided to employ an aldol reaction to link the A-ring system **81** to the proto C,D-ring system **80** generating the requisite alcohol stereoisomer **79** in the process. Subsequent intramolecular reductive coupling of **78**, it was hoped, would generate the C ring of glycinoeclepin A.



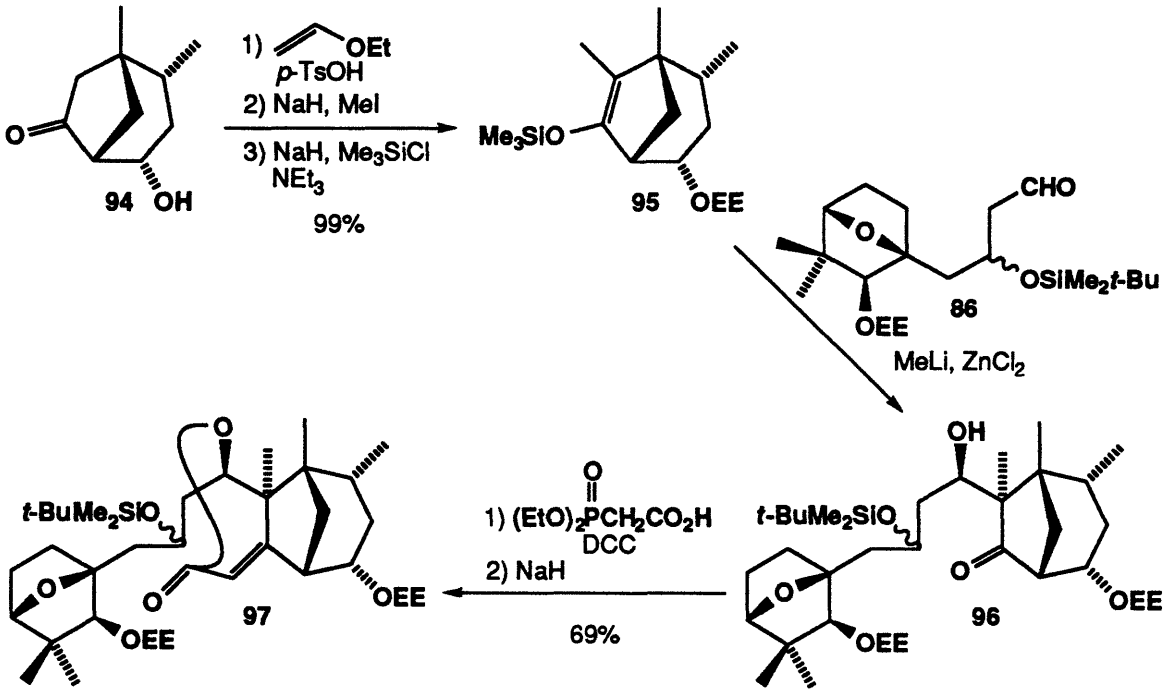

The early steps of the synthesis of the oxabicyclic compound rely, as with Murai's synthesis, on Baker's yeast reduction of diketone **53** followed by protection, α-olefination, and finally NIS-promoted cyclization to generate **84**, a homolog of Murai's intermediate. Mori completed the synthesis of this fragment by the addition of a three-carbon unit to the aldehyde resulting from the oxidation of **85**, and the subsequent oxidative cleavage of the terminal olefin.

The partner for the intermolecular coupling reaction was obtained in a number of steps from 3-methylcyclopentenone via vinyl cuprate addition followed by oxidative cleavage of the double bond to give aldehyde **89**, which upon intramolecular aldol cyclization and oxidation generated diketone **82**.

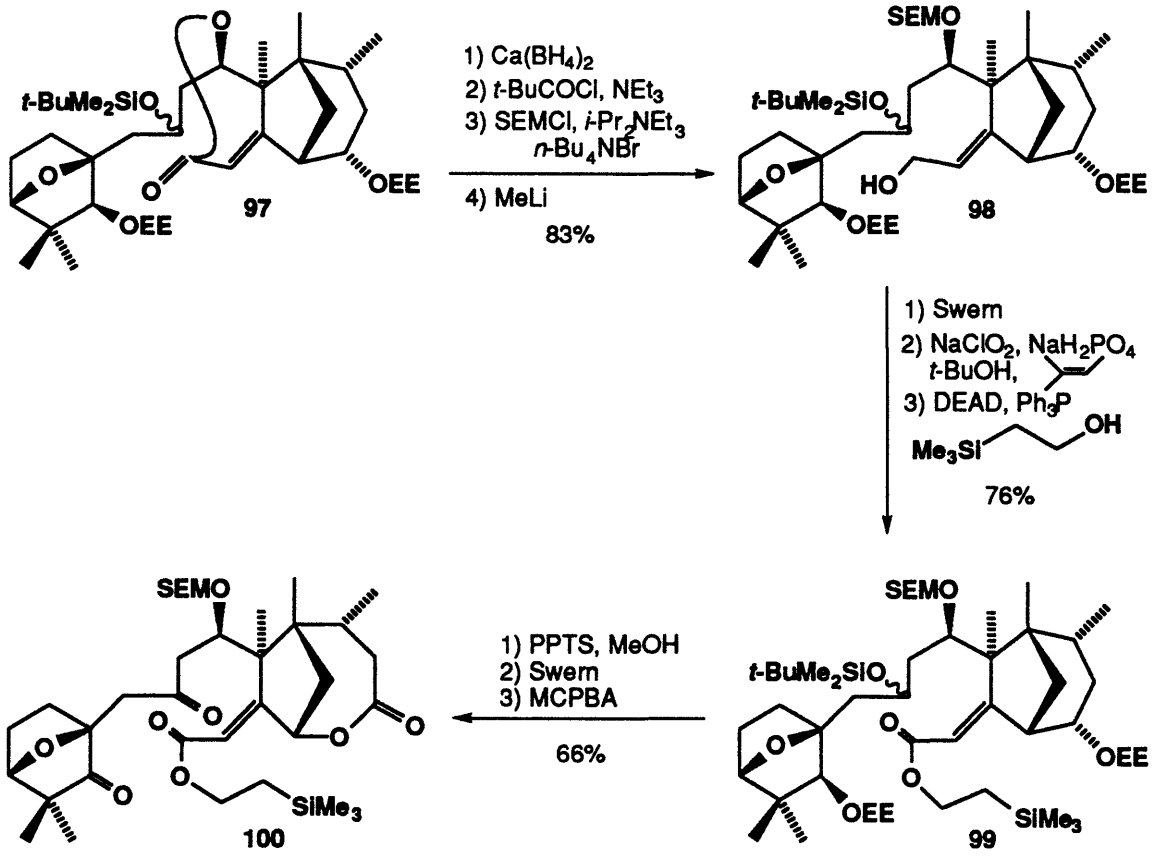

Baker's yeast
D-glucose
KH2PO4
DMF-H2O
1) t-BuMe2SiCl
imidazole
2) LDA, CH3CHO
3) MsCl, NEt3, DBU
CH2Cl2, THF
94%
1) NaBH4
2) OEt
3) n-Bu4NF
4) NIS
58%
1) DBU
2) 9-BBN;
H2O2
NaOH
95%
1) Swern
2) MgBr
3) t-BuMe2SiCl
4) OsO4, NaIO4
62%
53
56
83
84
85
86


MgBr
Bu3P•CuI
78%
1) HO OH
p-TsOH
2) BH3•THF
H2O2, NaOH
3) PCC
77%
1) HCl
2) PCC
80%
1) Baker's yeast
sucrose
KH2PO4
2) Ac2O, DMAP
pyridine
53%
1) o-xylene diol
p-TsOH
2) NaOMe
MeOH
70%
1) PCC
2) LDA, MeI
94%
1) LiHMDS
THF-HMPA
then AcOH
2) LiCHBr2
3) 1 eq MeLi
1 eq BuLi
49%
1) NaBH4
2) H2, Pd-C
95%
87
88
89
82
90
91
92
93
94

This diketone was the substrate for yet another Baker's yeast reduction to give after protection, acetate **90** (83% ee). Purification of an intermediate at a later stage of the synthesis by recrystallization afforded enantiomerically pure material. A series of protection/deprotection steps, oxidation, and a ketone alkylation step provided ketone **92**. This compound was treated with base and protonated under conditions of kinetic control to generate the methyl group epimer which upon treatment with lithiodibromomethane followed by 1 equiv of MeLi and 1 equiv *n*-BuLi led to ring expansion to give the [3.2.1]-bicyclic ketone **93**. Reduction of the ketone and deprotection of the ketal function generated compound **94**. The alcohol was next protected, and the ketone was alkylated with methyl iodide.

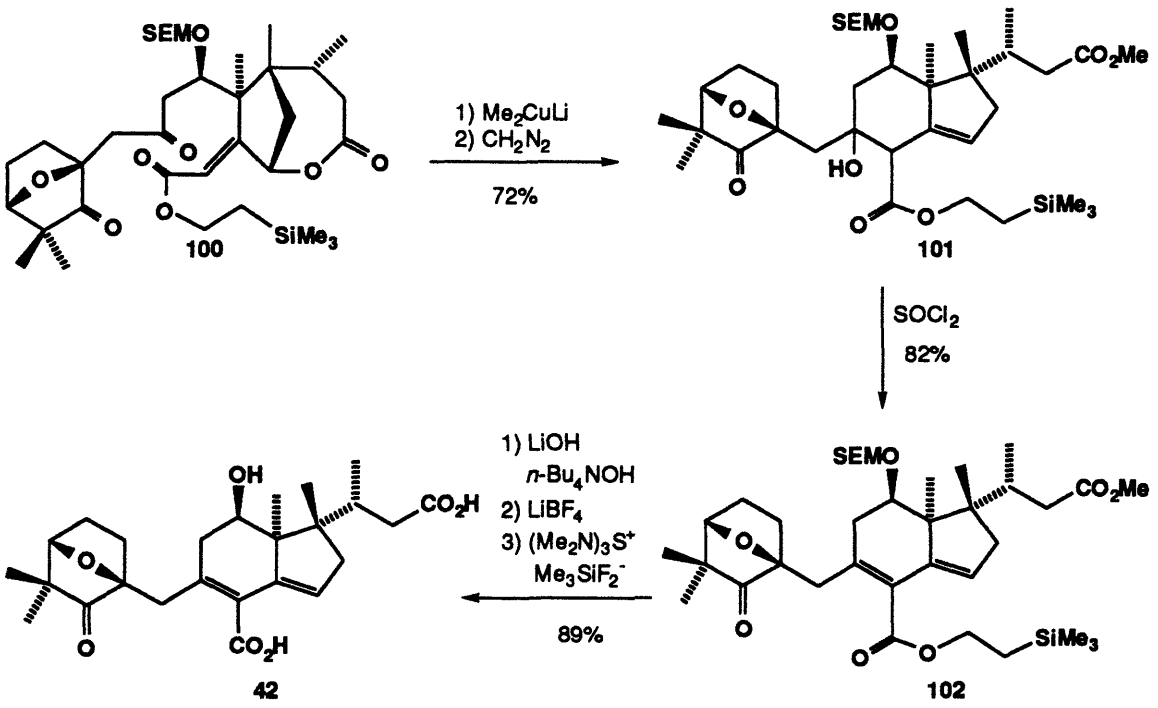



While model studies had suggested that formation of the ketone enolate followed by addition of aldehyde **86** would proceed to give the desired alcohol, the reaction on the real case did not proceed and it was thus necessary to study different reaction conditions. The coupling was accomplished by converting ketone **94** to the corresponding silyl enol ether **95**, generating the zinc enolate by addition of methyllithium and zinc chloride, and



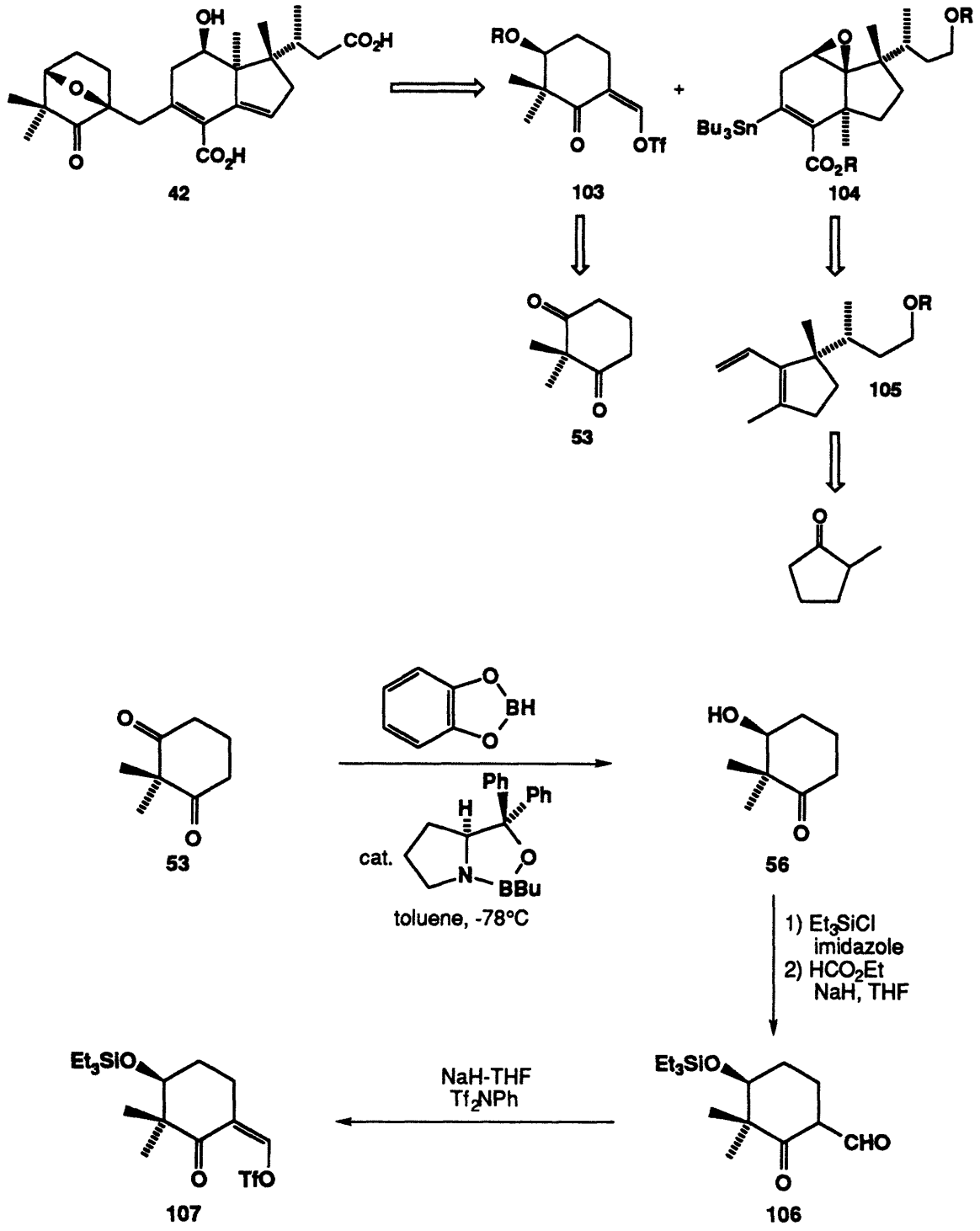

then adding aldehyde **86**. An intramolecular olefination reaction afforded lactone **97** which was converted into the fully protected ester **99** by a series of protection/deprotection steps and two oxidation steps.

Removal of the ethoxyethyl protecting group was followed by oxidation, first to the ketone then via Baeyer-Villiger rearrangement to the lactone **100**. It is from this lactone that the D ring side chain would arise. The intramolecular reductive cyclization step was accomplished by treatment of **100** with lithium dimethylcuprate to complete the glycinoeclepin A skeleton. Dehydration and deprotection of **101** afforded a product which was identical to natural glycinoeclepin A. This synthesis was longer than Murai's both in term of the total number of steps (ca. 52) and the number of steps in the longest linear sequence (ca. 38).

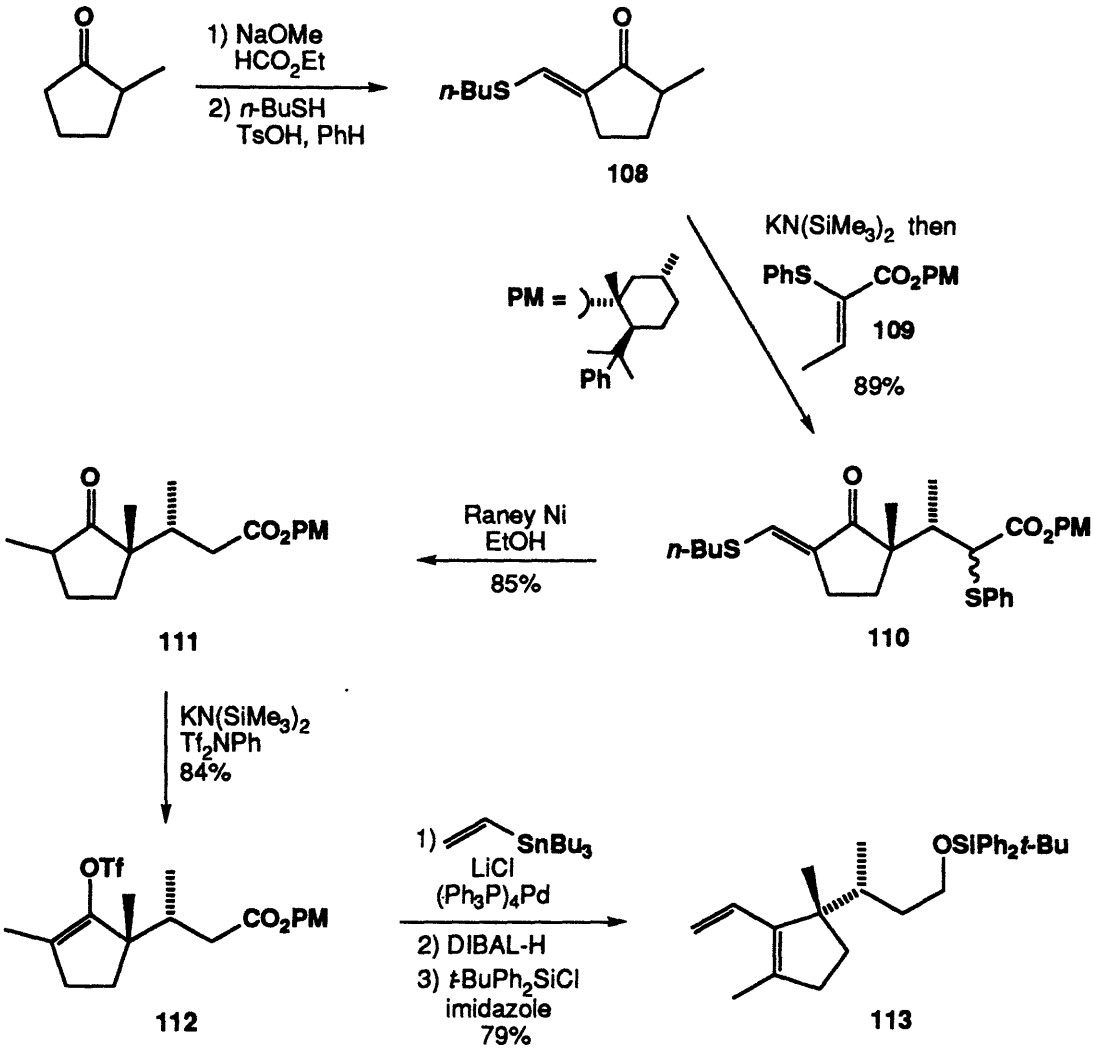



The third total synthesis of glycinoeclepin A to be reported was completed by Corey and Houpis in 1990.[56c] This synthesis is by far the most efficient to date. A key step in the Corey strategy involves the palladium-catalyzed coupling of an oxabicyclic ring precursor **103** to a nearly complete C,D-ring intermediate **104**. The enol triflate **103** is derived from the same starting material as in the previous syntheses, while the bicyclic ring system in **104** is made by a Diels-Alder reaction of a chiral diene **105**. This diene is ultimately synthesized from 2-methylcyclopentanone. The synthesis also features a methyl group migration with concomitant epoxide ring opening to generate the complete C,D-ring system skeleton.

The Corey-Houpis synthesis begins with the enantioselective reduction of diketone **53** either with Baker's yeast or with catecholborane in the presence of a catalytic amount of the oxazaborolidine derived from (R)-2-(diphenylhydroxymethyl)pyrrolidine and *n*-butylboronic acid. Protection of the resulting alcohol, formylation, and enol triflate formation afforded the first coupling partner (**107**).



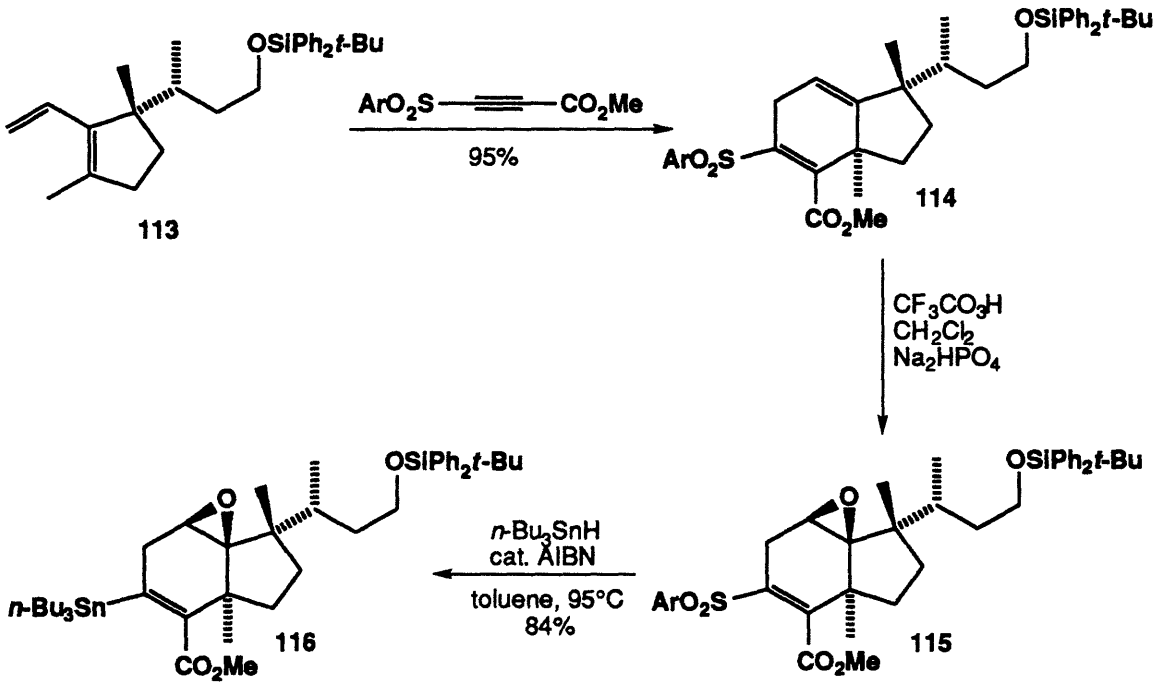

The synthesis of the C,D-ring system intermediate began with the conversion of 2-methylcyclopentanone to compound **108**. An enantioselective Michael addition to the




(-)-8-phenylmenthol ester of (Z)-2-(phenylthio)crotonic acid resulted in the formation of adduct **110** with 90% ee and 5 to 1 diastereoselectivity. Removal of the thiomethylene blocking group and enol triflate formation afforded compound **112**. Palladium catalyzed Stille coupling with vinyltributyltin followed by reduction of the side chain ester and protection of the resulting alcohol gave diene **113**.

A Diels-Alder reaction of the diene with 3-(*p*-toluenesulfonyl)propiolic acid methyl ester [*sic*][59] completed the C,D-ring skeleton and gave **114** together with the

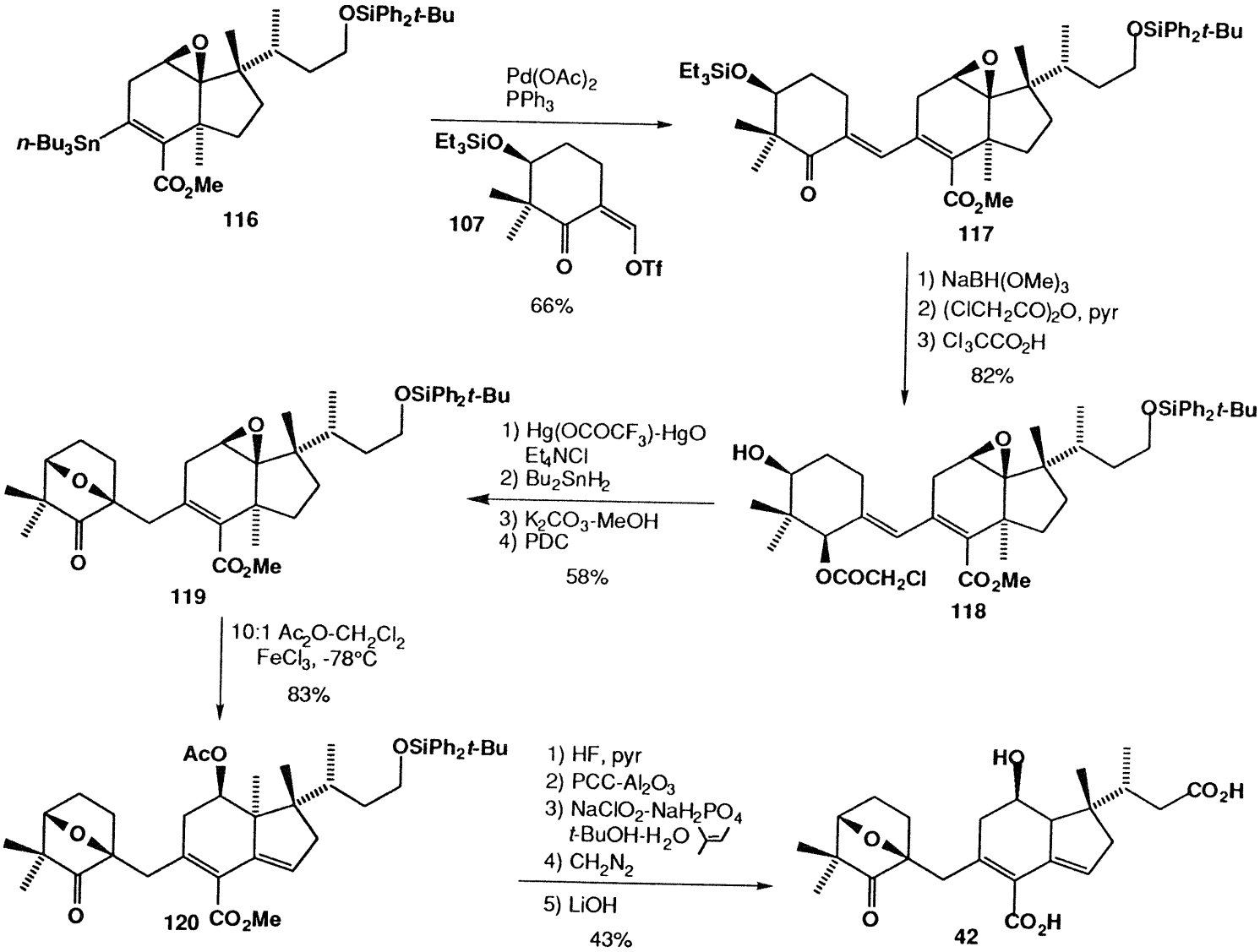
59 The methyl ester is indicated as the product of the reaction in Corey's reaction scheme while the propiolic acid is mentioned as the reagent in the text.



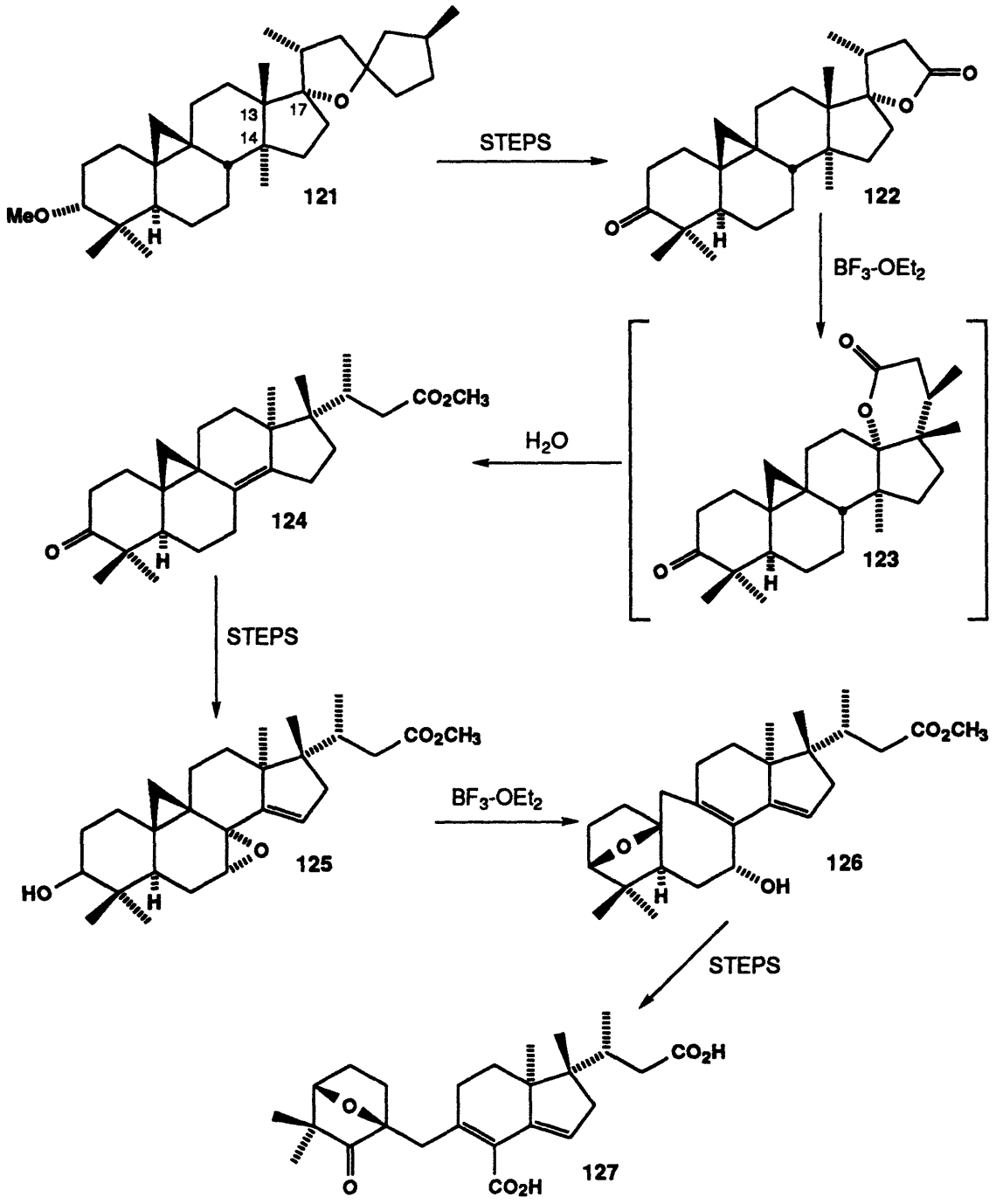

diastereomeric cycloadduct (3 : 1 ratio). Epoxidation of the isolated double bond in the major isomer and introduction of the tributylstannyl function led to the formation of **116.**

The palladium catalyzed coupling of **116** with the enol triflate fragment (**107**) gave the tricyclic epoxide **117.** Carbonyl reduction and a protection/deprotection sequence afforded **118** which gave the oxabicyclic ring upon internal oxymercuration. Demercuration, deprotection, and oxidation of the oxabicyclic ring alcohol provided keto ether **119.** Ferric chloride-promoted rearrangement followed by several deprotection and oxidation steps completed the synthesis of glycinoeclepin A, after a total of about 29 steps in the longest linear sequence.

Corey has also carried out a synthesis of a close derivative of glycinoeclepin A starting with the naturally occurring cycloartenol abietospiran (**121**). This chemical emulation of the natural biosynthesis of glycinoeclepin A was completed in just over twenty steps and affords 12-desoxyglycinoeclepin (**127**) as the final product. A number of interesting steps are worth noting. Cation formation at C-17 led to an overall double methyl migration. This was achieved by treatment of lactone **122** with 6 equiv of


OSiPh2t-Bu
n-Bu3Sn
CO2Me
116
Pd(OAc)2
PPh3
Et3SiO
107
O
OTf
66%
Et3SiO
OSiPh2t-Bu
O
CO2Me
117
1) NaBH(OMe)3
2) (ClCH2CO)2O, pyr
3) Cl3CCO2H
82%
HO
OSiPh2t-Bu
OCOCH2Cl
CO2Me
118
1) Hg(OCOCF3)-HgO
Et4NCl
2) Bu2SnH2
3) K2CO3-MeOH
4) PDC
58%
OSiPh2t-Bu
CO2Me
119
10:1 Ac2O-CH2Cl2
FeCl3, -78°C
83%
AcO
OSiPh2t-Bu
120 CO2Me
1) HF, pyr
2) PCC-Al2O3
3) NaClO2-NaH2PO4
t-BuOH-H2O
4) CH2N2
5) LiOH
43%
HO
CO2H
CO2H
42

$BF_3$-$OEt_2$ at 0 °C to force the rearrangement of the C-13 methyl to the C-17 position with formation of lactone **123**. Subsequent slow treatment with water at the same temperature resulted in the migration of the C-14 methyl group to C-17 to give a D ring that is identical to that found in glycinoeclepin A. Later in the synthesis, Corey achieved the closure of the oxabicyclic ring with concomitant cyclopropane ring opening by exposing

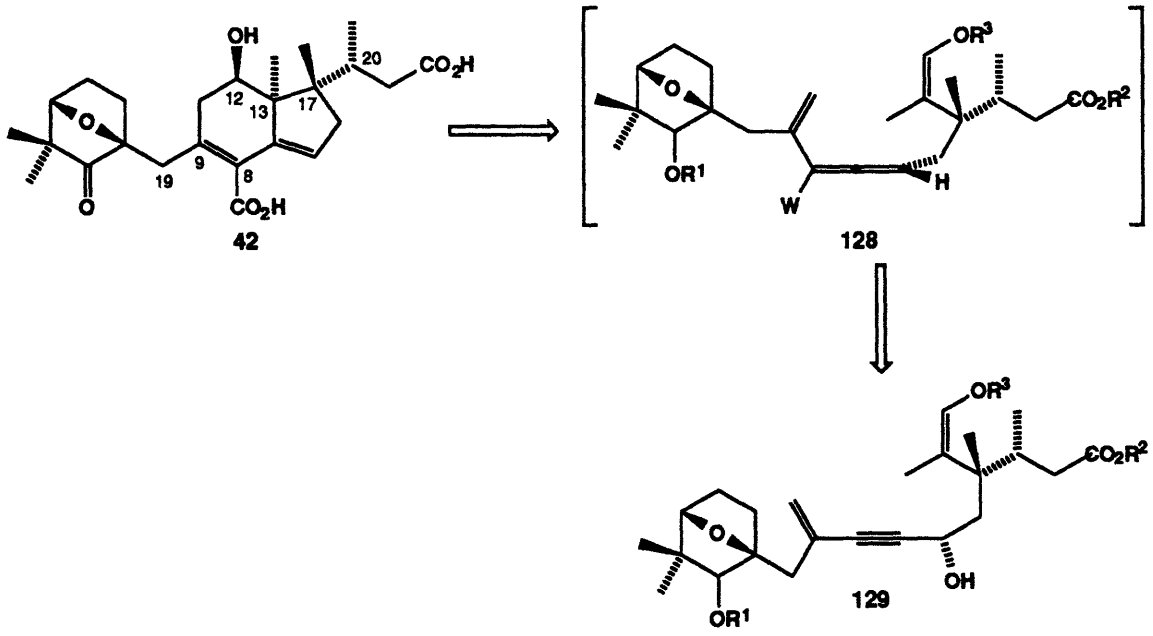


**125** to 2 equiv of $BF_3.OEt_2$ at -20 °C.

The length of the total syntheses of glycinoeclepin A that have already been published, a result of the complexity of the target, limits their suitability for the preparative scale synthesis of this important compound. Our goal at the beginning of this project was to develop a shorter and more practical synthesis of glycinoeclepin A that would be applicable to the preparation of sufficient material for extensive studies of biological activity and for the use of the compound as a nematode control agent.

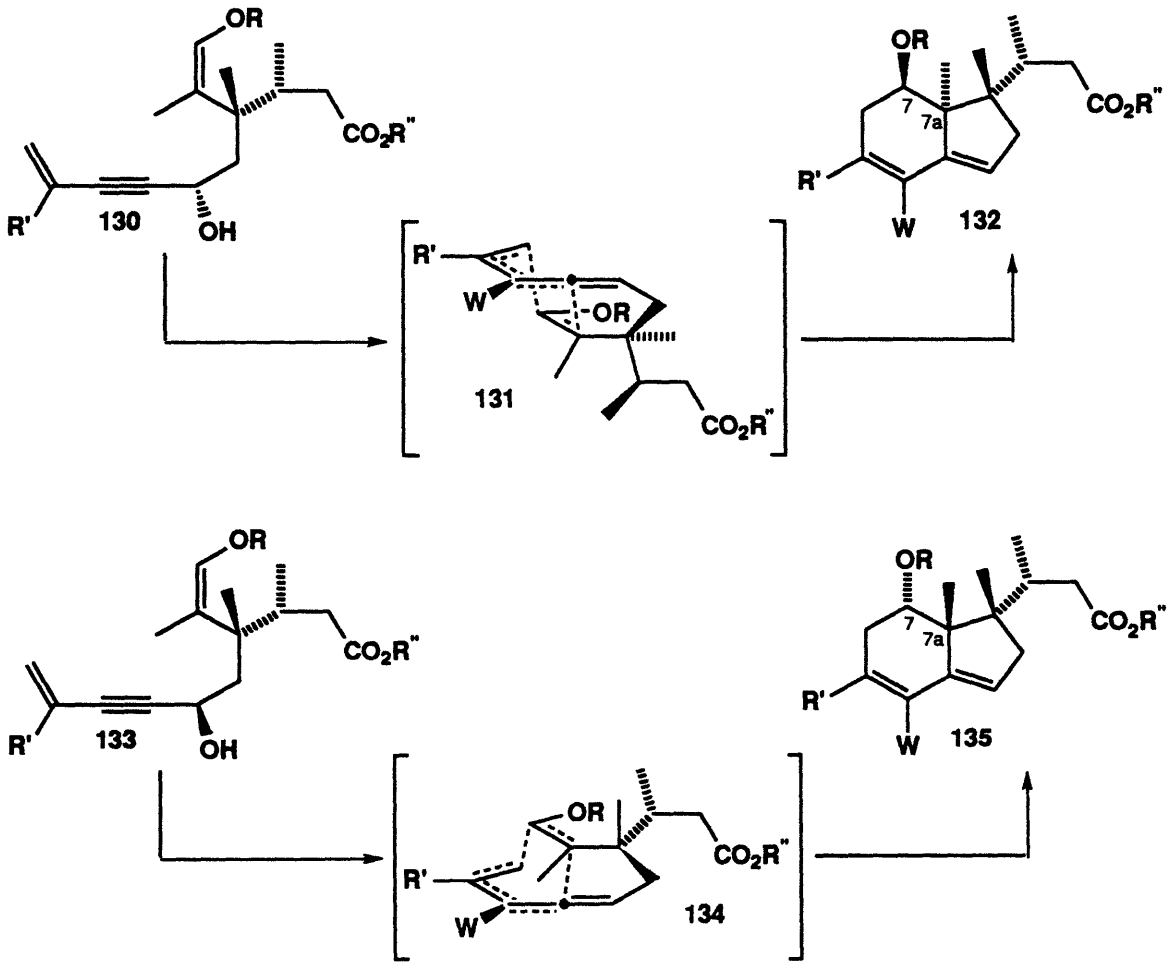
**An Intramolecular Cycloaddition Approach to Glycinoeclepin A**

While the formation of the oxabicyclic ring system seems to have been efficiently addressed by the previous groups, we felt there was a need for a more direct synthesis of the C,D-ring system. This is where our group targeted our efforts. Our key retrosynthetic transformation was arrived at by recognizing that the hydrindane skeleton with the requisite diene acid and alcohol functionalities could be formed by an intramolecular Diels-Alder reaction of a vinylallene with an enol ether dienophile. Diels-Alder reactions are in general the most powerful and direct reactions for the formation of six-membered



rings, and this intramolecular cycloaddition strategy would generate the bicyclic system in one step from an acyclic precursor. Note that this cycloaddition would be an inverse electron demand Diels-Alder reaction, and would need to be performed on an enantiomerically pure allene in order to generate the correct diastereomeric cycloadduct. The chiral allene portion of the substrate **128** was expected to be available via an appropriate chiral propargylic alcohol **129**.

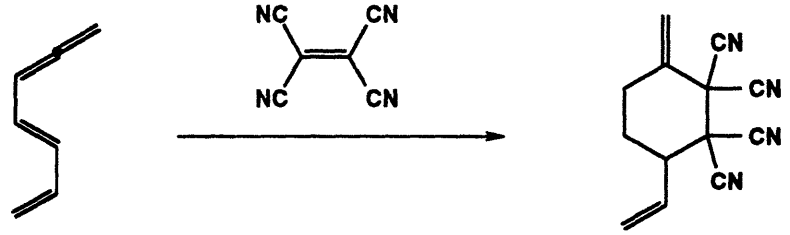
Each isomer of the propargylic alcohol is expected to generate a different optically active allene, and since the approach of the dienophile is controlled by orbital overlap, each allene must cyclize to give a different bicyclic diastereomer as shown below: Thus, in this unusual example of chirality transfer, the configuration of the propargylic alcohol determines the stereochemistry at C-7 and C-7a of the final bicyclic



product.

## [4+2] Cycloadditions of Vinylallenes

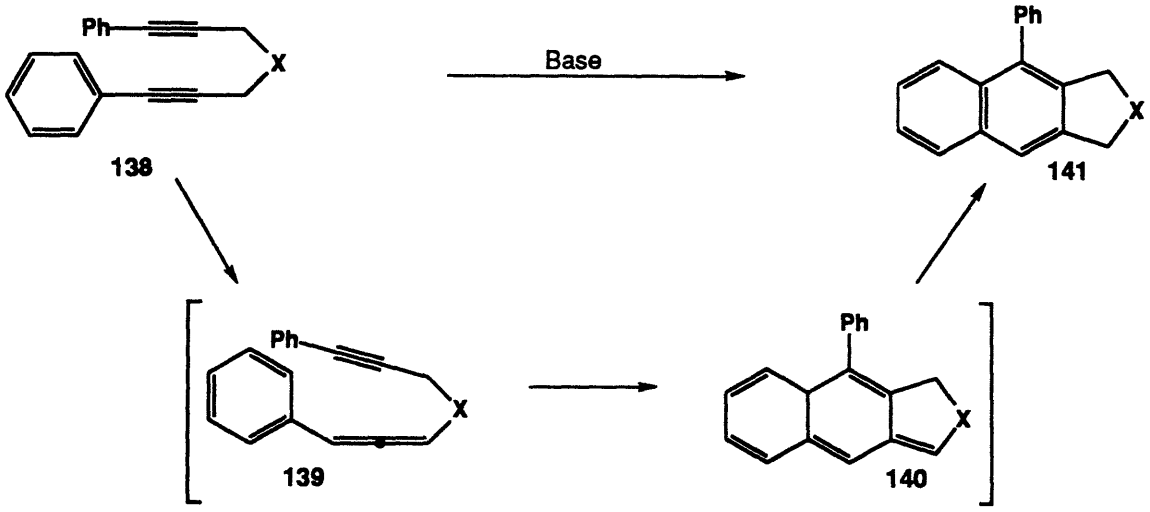
The intramolecular Diels-Alder reaction of vinylallenes has been used previously by a number of researchers to synthesize decalin and hydrindane systems and the application of this strategy to natural product synthesis has also been reported. Early studies of the intermolecular version of the reaction showed that vinylallenes are particularly reactive dienes.[60] For instance, it was reported[61] that substrate **136** which possesses both a vinylallene and a diene function reacts selectively with tetracyanoethylene to afford the adduct **137** resulting from a Diels-Alder reaction between the dienophile and the vinylallene portion of the molecule. This increased reactivity is due to the fact that the linear allene does not have any substituents at the central carbon atom, unlike the olefin of a butadiene derivative. This results in the requisite s-cis conformation of the vinylallene being more favorable than in the butadiene, and in less steric interaction between the diene and the dienophile in the case of the vinylallene.




**136** **137**

The first examples of intramolecular Diels-Alder reaction of a vinylallene were reported by Iwai,[62] and later on Ollis,[63] who showed that when the diene and dienophile were linked together by a variety of linkages, an intramolecular cycloaddition took place

60 For a review, see: Egenburg, I. Z. *Russ. Chem. Rev.* **1978**, *47*, 470.
61 Bross, H.; Schneider, R.; Hopf, H. *Tetrahedron Lett.* **1979**, *20*, 2121.
62 Iwai, I.; Ide, J. *Chem. and Pharm. Bull. (Japan)* **1964**, *12*, 1094.
63 Bartlett, A. J.; Laird, T.; Ollis, W. D. *Chem. Commun.* **1974**, 496.



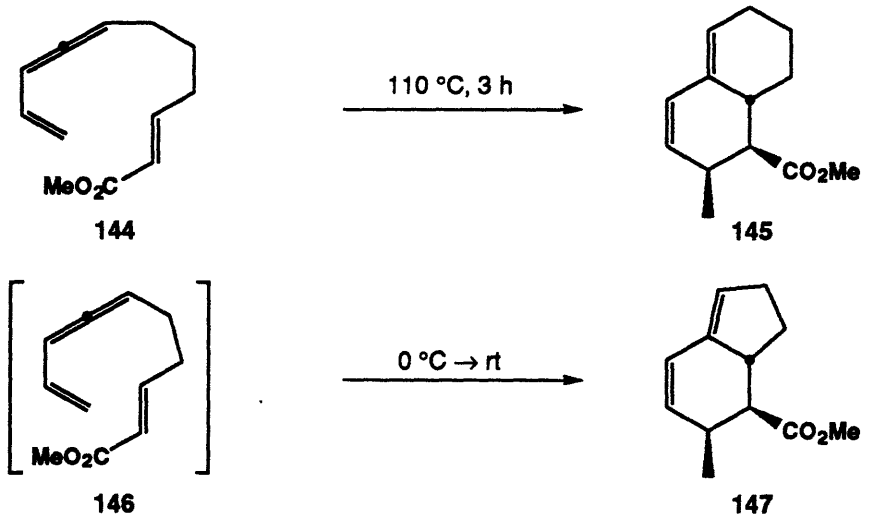

X = $CH_2$, O, S, N, NMe or $NMe_2^+$

to generate the corresponding cyclic compounds.

Snider found that substrate **142** underwent relatively facile cyclization to give, after reduction of the carbonyl group, the hexahydronaphthalene moiety of racemic compactin (**143**).[64]


Snider used similar reactions for the synthesis of the hexahydronaphtalene moiety of (+)-mevinolin[65] and in a model study directed at the synthesis of the bottom half of chlorothricolide.[66] In this model study, Snider found that while the Diels-Alder reaction giving rise to a decalin system (**145**) occurred at about 110 °C, the corresponding reaction to generate the hydrindane system (**147**) took place rapidly at room temperature.

64 Deutsch, E. A.; Snider, B. B. *J. Org. Chem.* **1982**, *47*, 2682.
65 Deutsch, E. A.; Snider, B. B. *Tetrahedron Lett.* **1983**, *24*, 3701.
66 Snider, B. B.; Burbaum, B. W. *J. Org. Chem.* **1983**, *48*, 4370.



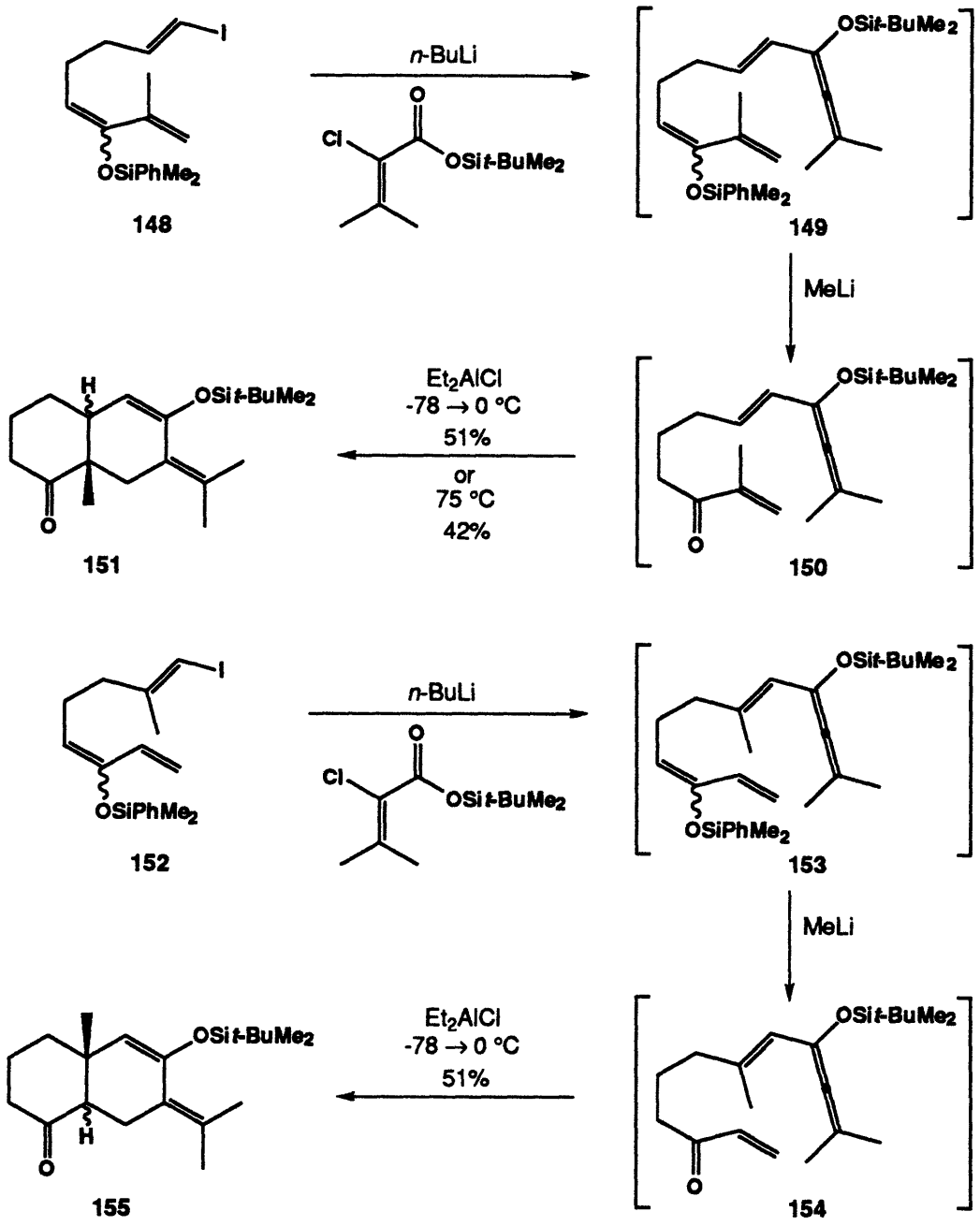

144 145 146 147

Examination of models showed that this latter system was ideally suited to adopt the conformation required for the Diels-Alder reaction. It was also noted that the reaction of a related substrate in which the diene is a terminal 1,3-diene requires 150 °C. This is in agreement with the faster rate of intermolecular vinylallene cycloadditions discussed above and in addition illustrates the ability of the allene to decrease the number of degrees of freedom as compared to a butadiene system, making the entropy of activation less negative.

Keck[67] used a cyclization very similar to Snider's for his beautiful total synthesis of (+)-compactin. This cyclization step was carried out on a racemic vinylallene intermediate and thus led to the formation of two diastereomers as discussed previously. Keck was able to obtain the desired stereomer of the target molecule by chromatographic separation of these two diastereomers.

Reich has also been one of the pioneers in the use of vinylallene intramolecular Diels-Alder reactions.[68] He has applied his synthesis of siloxy vinylallenes to the formation of eremophilane and eudesmane sesquiterpenes and has found that his cycloadditions could, under Lewis acid catalysis, take place at temperatures below 0 °C

67 Keck, G. E.; Kachensky, D. F. *J. Org. Chem.* **1986**, *51*, 2487.
68 Reich, H. J.; Eisenhart, E. K.; Olson, R. E.; Kelly, M. J. *J. Am. Chem. Soc.* **1986**, *108*, 7791.




in spite of the presence of substituents on the diene or dienophile. This is in marked contrast to the corresponding dienes in which cis substitution prevents cycloaddition.

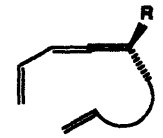
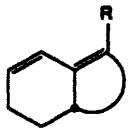
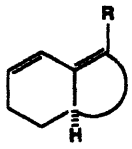
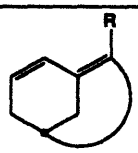
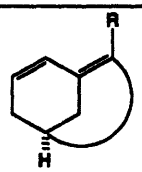
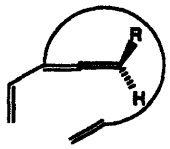
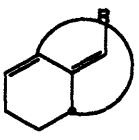
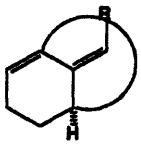
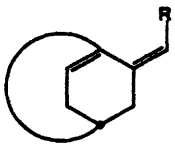
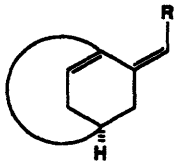
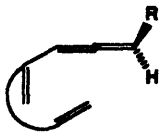
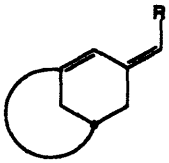
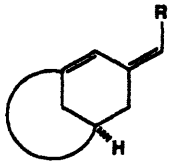
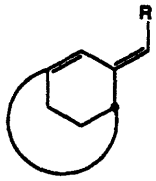
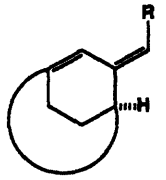
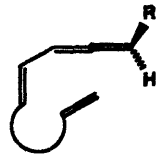
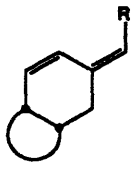
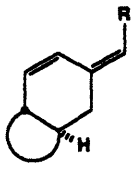
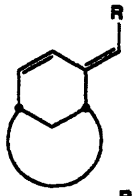
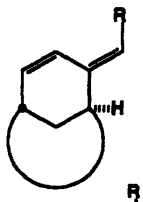
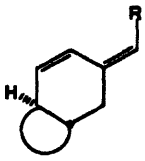
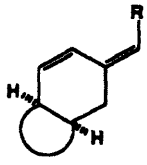
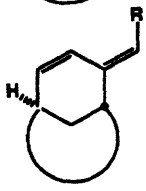
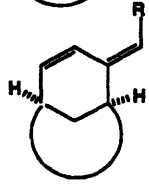
Okamura has introduced a classification system for the vinylallene intramolecular Diels-Alder reaction (see Table 4)[69] and studied type I cycloalkenylallene systems with

69 For a review, see: Okamura, W. H.; Curtin, M. L. *Synlett*, **1990**, 1.

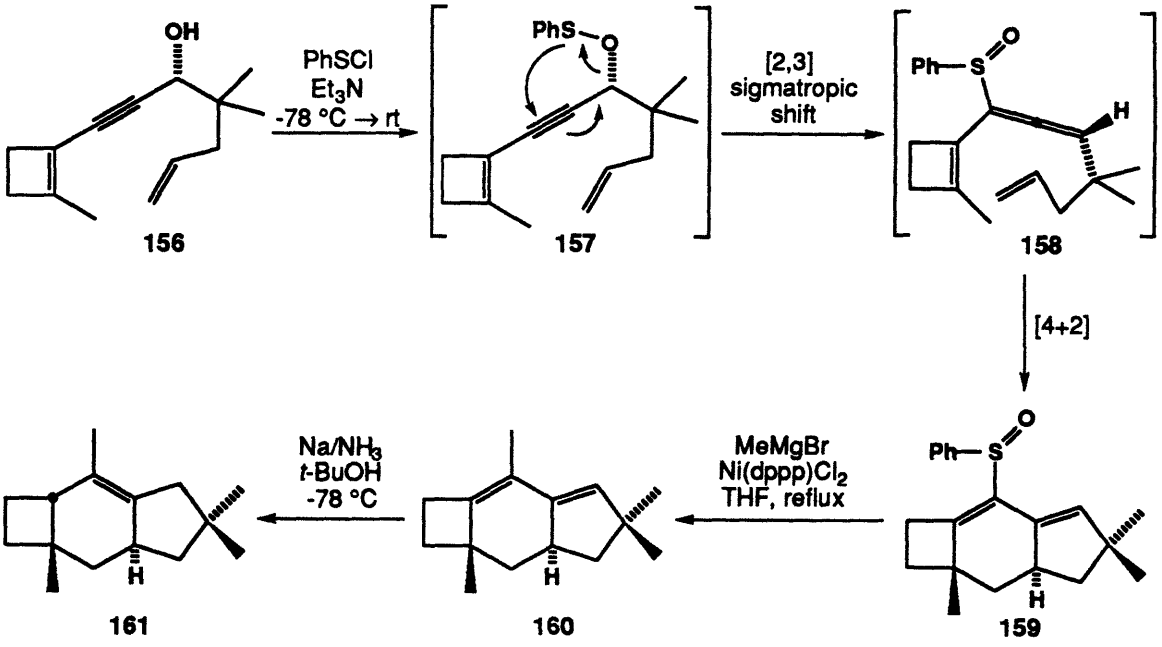
respect to the effect of substituents on the allene function (alkyl, PhSO- and $Ph_2PO$-), tether length, substitution on the tether, as well as cycloalkenyl ring size.

Okamura has found that the systems with sulfoxide and phosphine oxide substituted allenes are highly reactive and that a great variety of multicyclic compounds can be obtained via the vinylallene intramolecular Diels-Alder reaction. Okamura illustrated this fact by completing the asymmetric total synthesis of (+)-sterpurene via a completely enantioselective allene formation, through the use of the [2,3]-rearrangement of enantiomerically pure sulfenate ester **157**.[70] The desired cycloaddition took place with complete diastereoselectivity, at -78 °C to room temperature, to afford the tricyclic vinyl

**Table 4**

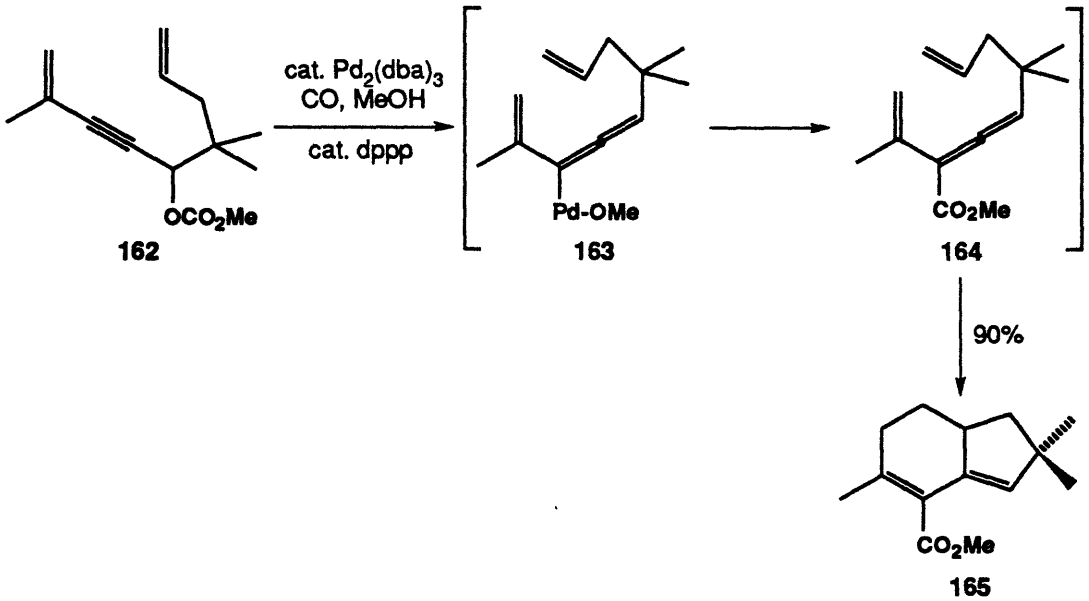
| Type | ENDO | EXO | ENDO | EXO |
|---|---|---|---|---|
| I |  |  |  |  |  |
| III |  |  |  |  |  |
| IV |  |  |  |  |  |
| $V_E$ |  |  |  |  |  |
| $V_Z$ |  |  |  |  |  |

70 Gibbs, R. A.; Bartels, K.; Lee, R. W. K.; Okamura, W. H. *J. Am. Chem. Soc.* **1989**, *111*, 3717.




sulfoxide **159** which was taken on to the target molecule.

Just as we were starting our work on the total synthesis of glycinoeclepin A, Mandai and Tsuji reported the intramolecular Diels-Alder reaction of vinylallenic esters to generate a number of decalin and hydrindane systems including one similar to our target molecule.[71] Mandai's and Tsuji's palladium catalyzed tandem carbonylation and

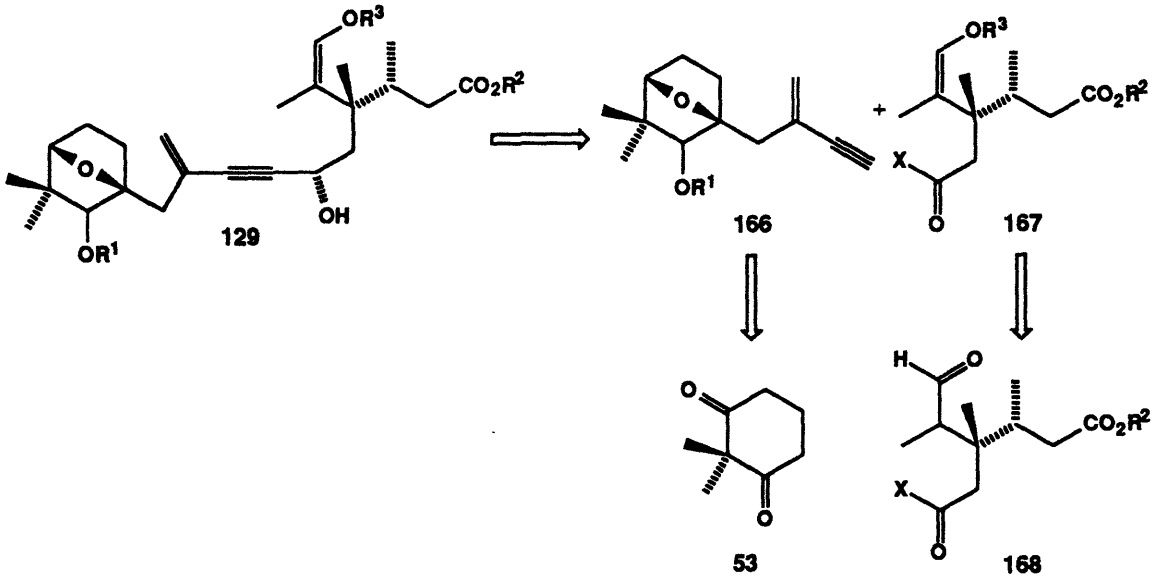



71 Mandai, T.; Suzuki, S.; Ikawa, A.; Murakami, T.; Kawada, M.; Tsuji, J. *Tetrahedron Lett.* **1991**, *52*, 7687.

intramolecular Diels-Alder involves the conversion of propargylic carbonate **162** to allenylpalladium species **163** which then incorporates the elements of carbon monoxide and methanol to give vinylallenic ester **164**. This intermediate is not isolated under the reaction conditions (50-60 °C) and undergoes the desired cycloaddition to afford **165**.

**Retrosynthetic Approach to Alcohol 129**

The precedent discussed above seemed to indicate that the key cycloaddition reaction in our synthesis of glycinoeclepin A should proceed with relative ease to generate the desired hydrindane system. The chiral propargylic alcohol or alcohol derivative involved in this key step would be prepared by the coupling of two fragments **166** and **167** to increase the convergency and hence the efficiency of this synthesis. The propargyl ketone intermediate would then be reduced enantioselectively to give optically active propargylic alcohol **129**. The acetylide fragment would ultimately be derived from the same diketone **53** which has been used by previous groups involved in the synthesis of the oxabicyclic system. The more complex side chain fragment can be simplified to the aldehyde **168** which is the logical precursor to enol ether **167**. The question of stereoselectivity in this transformation is very important as it would determine the spatial



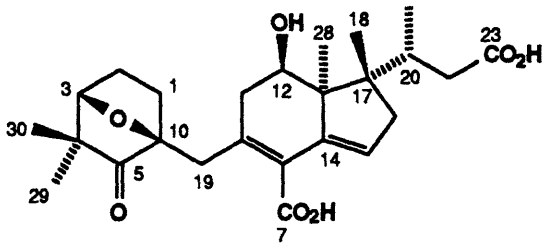
arrangement of the C-12 hydroxyl group. If the Z enol ether isomer was not readily available, the hydroxyl group at the C-12 position of glycinoeclepin would have to be inverted after the cycloaddition to give the correct epimer. Model studies, it was hoped, would help resolve this issue and at the same time establish the reactivity of the two enol ether isomers, since inspection of molecular models indicated that the cycloaddition of the Z enol ether would be subject to greater steric interactions during the cycloaddition step.

# CHAPTER 2

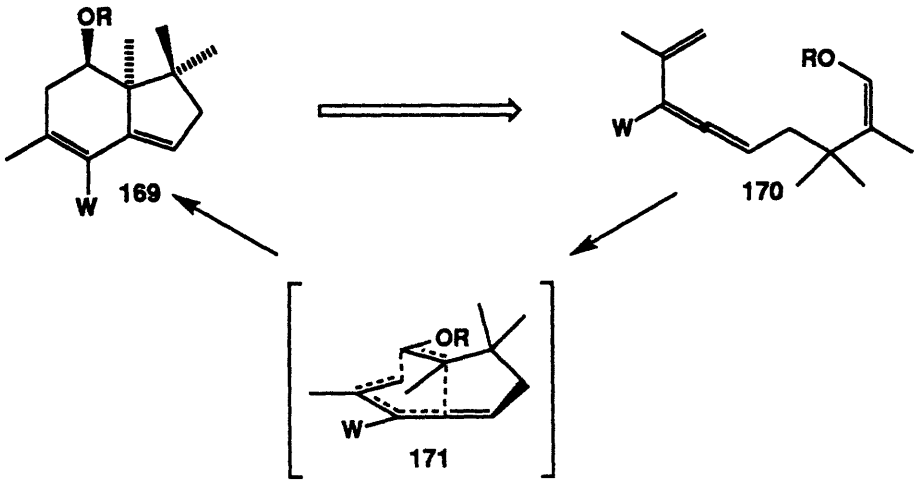
# MODEL STUDIES ON THE SYNTHESIS OF THE C,D-RING SYSTEM OF GLYCINOECLEPIN A

## Introduction

The key step in our proposed total synthesis of glycinoeclepin A involves an intramolecular asymmetric inverse electron demand vinylallene Diels-Alder reaction to generate the C,D-ring system of this important molecule. It was decided that model studies should be undertaken to determine (a) the feasibility of the intramolecular Diels-Alder reaction, (b) the relative viability of different routes to the vinylallene moiety, and (c) the relative effectiveness of different substituted alkenes as dienophile components in this key transformation. The synthesis of a simplified version of the glycinoeclepin A C,D-ring system (**169**) in which methyl groups replace the C-9 and C-17 substituents thus became




**42**



our first objective.

## The Cyanide $S_N2'$ Strategy

As discussed in the previous chapter, a critical requirement of our strategy was that the chiral vinylallene moiety would have to be generated in enantiomerically pure form. We decided to focus our attention on routes involving the stereospecific rearrangement of propargylic enynyl alcohols as a means of generating the requisite vinylallenes. Asymmetric reduction of α,ß-acetylenic ketones is well known to provide propargylic alcohols with high enantiomeric purity, and several stereospecific rearrangements of propargylic alcohols to allenes have been reported previously. In addition, it was our hope that the conversion of the propargylic alcohol to a vinylallene and subsequent Diels-Alder reaction might ultimately be achieved in a single synthetic operation as a "tandem rearrangement-cycloaddition" process.

If the total synthesis of glycinoeclepin A is to be efficient, the W group in the cycloaddition product **169** should be readily converted to the carboxylic acid function. Our success with cyanoallene as a dienophile in the total synthesis of the aegyptinones inspired us to investigate the use of vinylallenyl nitriles as the diene component in the proposed glycinoeclepin synthesis. Nitriles are readily converted to carboxylic acids, and it was felt that the nitrile function could be used advantageously as a protecting group for the C ring carboxylic acid in the synthesis of glycinoeclepin A. Several methods have been reported for the synthesis of cyanoallenes beginning with propargylic alcohol derivatives.

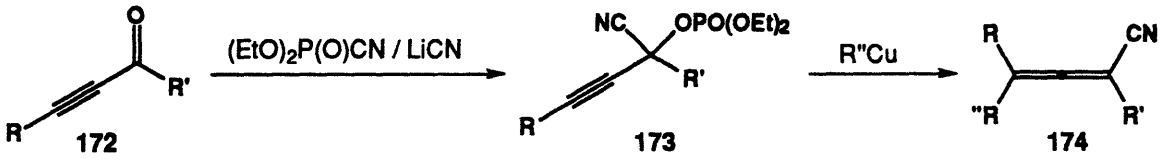
Previous work on the synthesis of allenyl nitriles[72] includes their synthesis by the treatment of bromoallenes with copper cyanide in dimethylformamide.[73] The bromoallenes themselves are made by the action of concentrated hydrobromic acid on propargylic

72 For reviews, see: (a) Landor, P. D. In *The Chemistry of Allenes*; Landor, S. R., Ed.; Academic Press; London, 1982, Vol 1, p 151. (b) Schuster, H. F.; Coppola, G. M. *Allenes in Organic Synthesis*; John Wiley & Sons; New York, 1984, p 204.

73 Greaves, P. M.; Landor, S. R. *J. Chem. Soc. C* **1965**, 321.

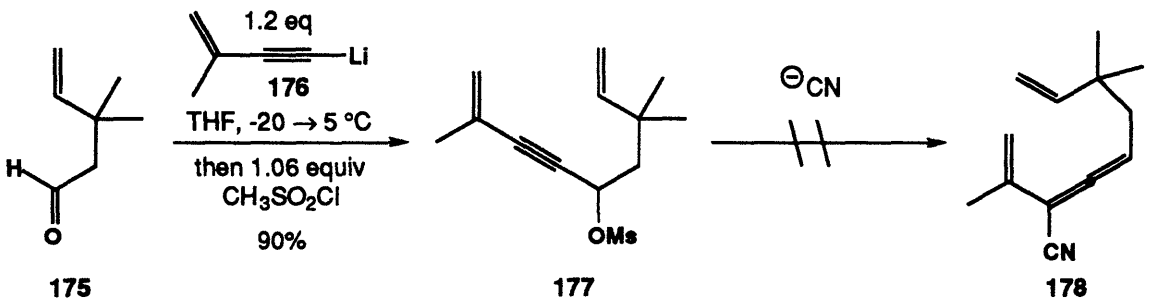
alcohols.[74] Another method, which combines these two steps in one, involves the treatment of propargylic alcohols with copper cyanide, a trace of copper, potassium cyanide, and concentrated hydrobromic acid.[75] Both of these methods require long reaction times and high temperatures. Furthermore, the use of concentrated acid would be unwise if this method were to be used on a highly functionalized substrate capable of generating glycinoeclepin A. The latter method also generates highly toxic hydrogen cyanide as a byproduct.

Recently, Kurihara[76] has reported a new synthesis of allenyl nitriles by the reaction of ynones with diethyl phosphorocyanidate / lithium cyanide and subsequent treatment of the product **173** with an organocopper reagent. This method, however, can only provide fully substituted allenyl nitriles (**174**) and thus would not be applicable to our target system.




The first approach we examined involved the generation of cyanoallenes via the $S_N2'$ displacement of a suitable leaving group by cyanide anion. Our initial studies began with the synthesis of mesylate **177** by the addition of the lithium derivative of commercially available 2-methyl-1-buten-3-yne (**176**) to the known aldehyde **175**[77] followed by trapping with methanesulfonyl chloride. Mesylate **177** was found to be very unstable when neat and was therefore rapidly treated with a cyanide anion source after isolation. A variety of conditions, including the copper-catalysed protocol[31] used in the synthesis of cyanoallene itself and the treatment of **177** with anhydrous lithium cyanide in

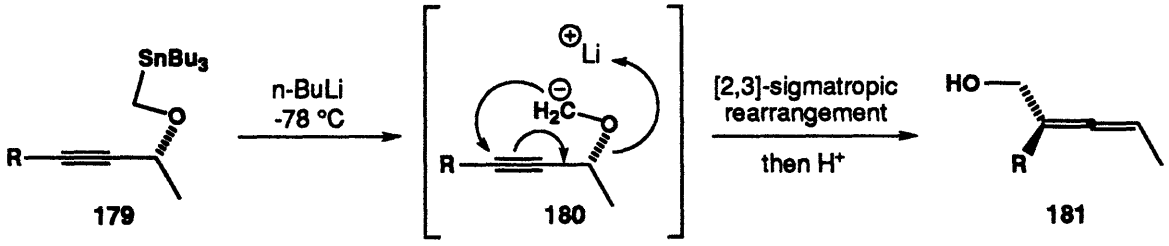
74 Black, D. K.; Landor, S. R.; Patel, A. N.; Whiter, P. F. *Tetrahedron Lett.* **1963**, 483.
75 Greaves, P. M.; Landor, S. R.; Laws, D. R. J. *Chem. Commun.* **1965**, 321.
76 Yoneda, R.; Inagaki, N.; Harusawa, S.; Kurihara, T. *Chem. Pharm. Bull.* **1992**, *40*, 21.
77 Prepared via Claisen rearrangement of 3-methyl-2-butenyl vinyl ether according to the procedure of: Boeckman, R. K.; Ko, S.S. *J. Am. Chem. Soc.* **1982**, *104*, 1033.




THF,[78] were examined, but none of the desired vinyl cyanoallene **178** or products derived from its formation could be isolated.

## The [2,3] Wittig Rearrangement Strategy

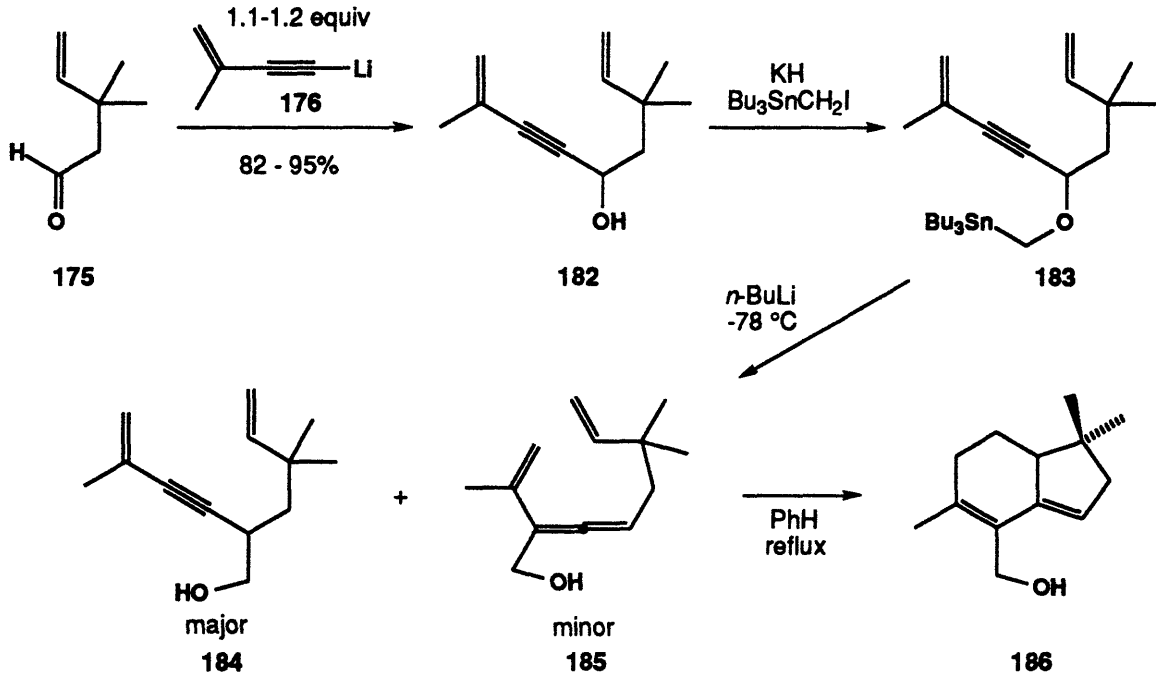
The next method investigated for the formation of a suitable vinylallene involved the version of the [2,3]-sigmatropic Wittig rearrangement[79] first reported by Still[80] for the formation of homoallylic alcohol systems and later applied to the synthesis of allenic systems by Marshall.[81] This method would generate a bicyclic allylic alcohol which could be later oxidized to the carboxylic acid of glycinoeclepin A. Marshall has found that treatment of the potassium salt of propargylic alcohols with iodomethyltributyltin, according to Still's general procedure, affords (tributylstannyl)methyl propargylic ethers **179**. Addition of *n*-BuLi at -78 °C results in tin / lithium exchange followed by a [2,3]-sigmatropic rearrangement with complete chirality transfer in the case of optically active




78 Harusawa, S.; Yoneda, R.; Omori, Y.; Kurihara, T. *Tetrahedron Lett.* **1987**, *28*, 4189.
79 For reviews, see: (a) Marshall, J. A. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, 1991, Vol. 3, p 975, and (b) Nakai, T.; Mikami, K. *Org Reactions* **1994**, *46*, 105.
80 Still, W. C.; Mitra, A. *J. Am. Chem. Soc.* **1978**, *100*, 1927.
81 Marshall, J. A.; Robinson, E. D.; Zapata, A. *J. Org. Chem.* **1989**, *54*, 5854.

substrates. The stereochemistry of this rearrangement is consistent with a five-membered ring cyclic transition state.

When this methodology was applied to our substrate of interest **183**, only a very small amount of allene **185** was formed, and the major product was **184** resulting from the alternate [1,2]-sigmatropic Wittig rearrangement pathway. The vinylallene formed was found to be stable at room temperature, but heating a benzene solution of the crude allene at reflux for several hours resulted in intramolecular Diels-Alder to give **186**. However, the difficulty in obtaining significant quantities of the desired allene prohibited the use of this route in further model studies, and we turned our attention to the investigation of alternative approaches.

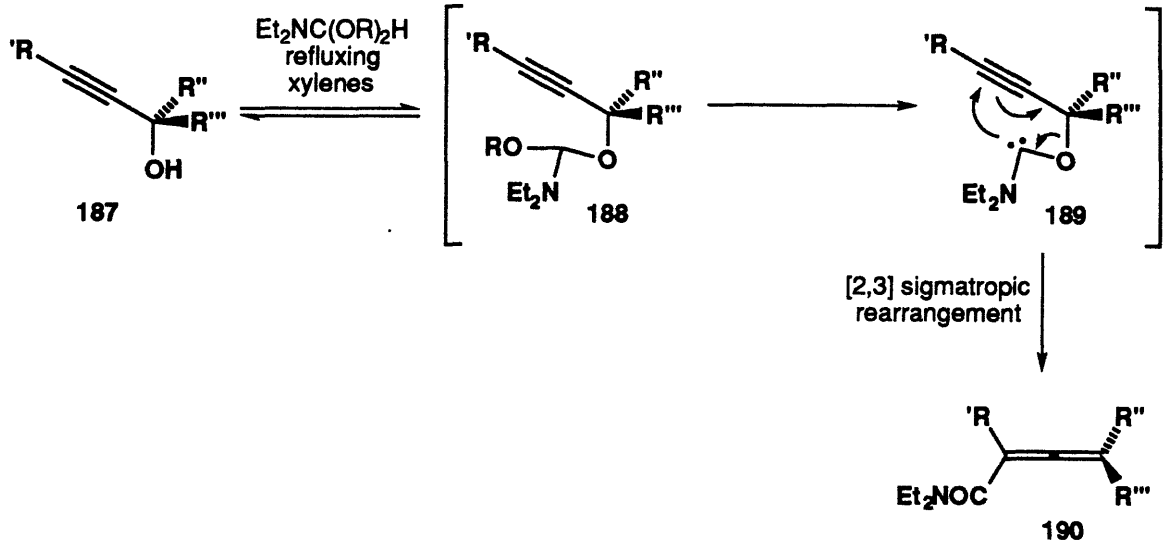



## The [2,3] Büchi Rearrangement Strategy

Büchi and coworkers[82] have reported that allylic alcohols are converted to homologous amides when treated with N,N-dimethylformamide acetals, and Parker[83] has

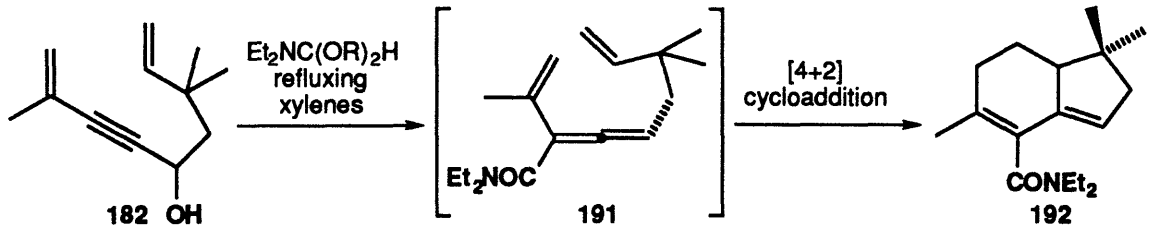
82 Büchi, G.; Gushman, M.; Wüest, H. *J. Am. Chem. Soc.* **1974**, *96*, 5563.
83 Parker, K. A.; Petraitis, J. J.; Kosley, R. W.; Buchwald, S. L. *J. Org. Chem.* **1982**, *47*, 389.

extended the scope of the Büchi rearrangement by showing that propargyl alcohols react in a similar fashion with N,N-diethylformamide acetals to generate allenyl amides. The mechanism of the Büchi rearrangement as applied to propargylic alcohols is outlined below. Propargylic alcohol **187** reacts reversibly with the formamide acetal to give mixed amide acetal **188** which undergoes α-elimination of ROH upon heating to generate a carbene **189**. This carbene undergoes a [2,3]-sigmatropic rearrangement to form allenyl amide **190**.

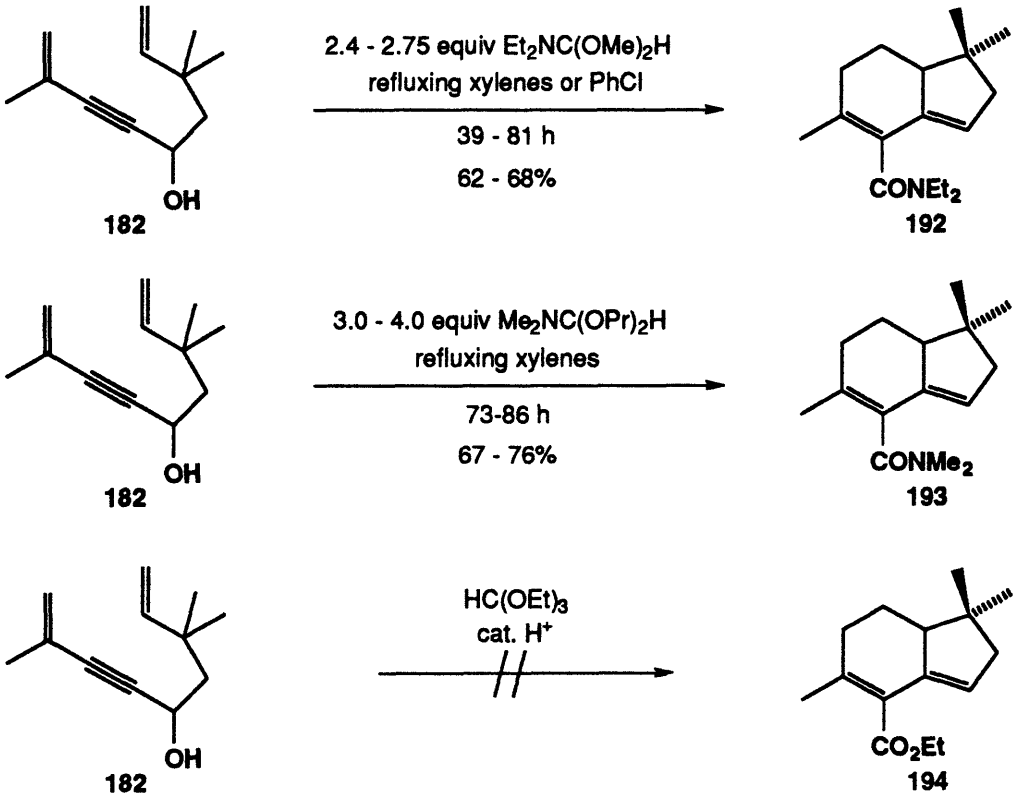



It was hoped that in the case of our model systems, the allenyl amide **191** would undergo the desired cycloaddition *in situ* as it was generated to give bicyclic amide **192**. Indeed, the elevated temperatures used in this reaction were expected to allow a tandem [2,3] sigmatropic rearrangement and intramolecular Diels-Alder reaction. The carboxylic acid systems ultimately required for the synthesis of glycinoeclepin A could be obtained from these tertiary amide systems by hydrolysis.[84] Finally, Chan[85] has reported that allylic alcohols undergo the Büchi rearrangement with nearly complete chirality transfer.

84 For a list of methods converting amides to carboxylic acids, see: Larock, R. C. "Comprehensive Organic Transformations"; VCH Publishers; New York, 1989, p 988.
85 Chan, K.-K.; Saucy, G. *J. Org. Chem.* **1977**, *42*, 3828.




We initially tested the feasibility of this strategy using the propargylic alcohol **182** prepared as discussed above. Treatment of **182** with excess N,N-diethylformamide dimethyl acetal in refluxing xylenes (ca. 140 °C) provided the desired bicyclic amide **192** in 62-68% yield. A Dean-Stark trap was used to drive the reversible mixed acetal formation step by azeotropic removal of the liberated alcohol (methanol in this case). It was found that the commercially available N,N-dimethylformamide acetals could also be used to effect a similar transformation. Thus, propargylic alcohol **182** reacted with N,N-dimethylformamide di-*n*-propyl acetal (bp>140 °C) to give the dimethylamide **193** in 67-76% yield. It should be noted that orthoesters, in the presence of a catalytic amount of a



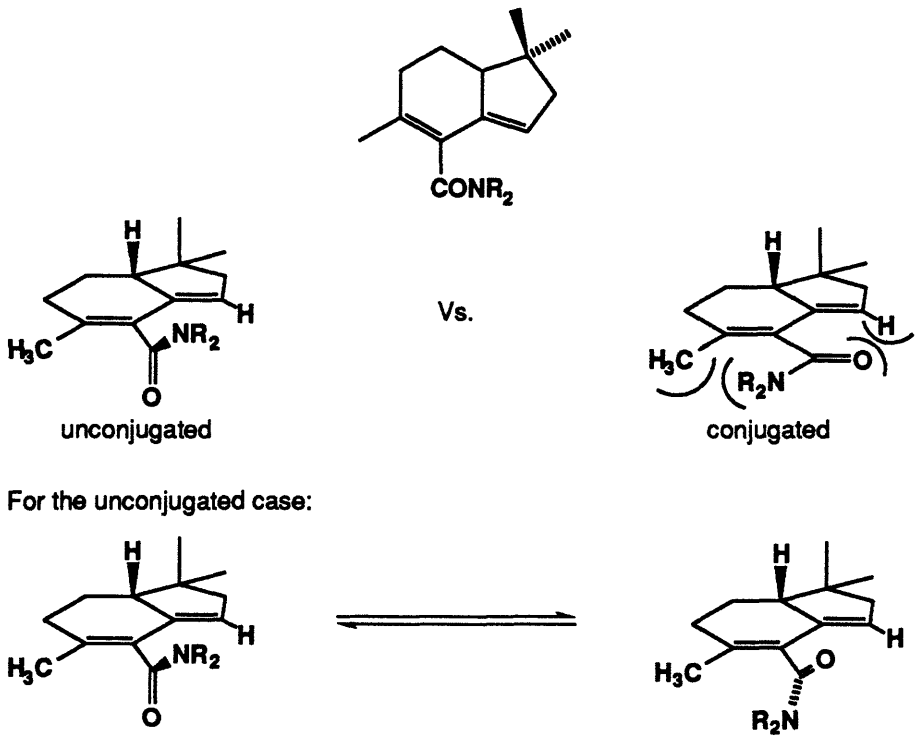
carboxylic acid, are unable to effect the corresponding reaction to give bicyclic ester systems. This is probably due to the fact that oxygen, a poorer donor atom than nitrogen, is not sufficiently able to stabilize the carbocationic carbene precursor or the carbenoid species itself.

The identity of the products obtained was arrived at by various spectroscopic analyses. For example, the molecular ion of **193** was found to have a mass corresponding to that of a molecule with the expected molecular formula $C_{15}H_{23}NO$ and the amide functionality is apparent both from the characteristic strong IR band for tertiary amides at 1630 $cm^{-1}$ and the presence of peaks at 170.7 and 170.4 ppm in the $^{13}C$ NMR spectrum. While most signals are doubled, for reasons indicated below, the $^{13}C$ NMR spectrum provides further evidence that the desired amide has been formed by the presence of four olefinic carbons and two amide methyl carbons at the expected positions of 34 and 38 ppm. The proton NMR spectrum shows the presence of one olefinic proton, the singlets expected for the different methyl groups, and the complicated pattern due to the three sets of methylene protons and the ring junction proton.

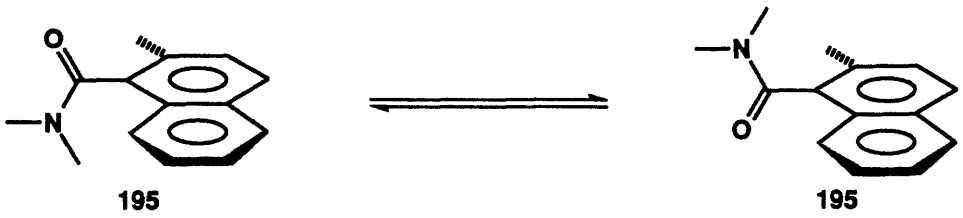
The interpretation of the bicyclic products' proton NMR spectra was complicated by the fact that two possible diastereomers exist due to the presence of substantial A strain.[86] As illustrated on the following page, this A strain is responsible for placing the amide function out of conjugation with the α,ß-double bond so that the plane occupied by this amide is perpendicular to the plane of the α,ß-π bond. This means that in addition to the usual existence of two rotational isomers due to the restricted rotation along the carbonyl carbon-nitrogen bond of the amide, two additional conformational isomers (diastereoisomers) are found in this system. Consequently, for example, four N-methyl singlets appear in the $^1H$ NMR spectrum of the desired cycloaddition product **193**.

These two diastereomers do not interconvert at room temperature on the NMR timescale and variable temperature $^1H$ NMR studies did not detect rotation of the dimethyl-

86 For a review on allylic strain, see: Johnson, F. *Chem. Rev.* **1968**, *68*, 375.



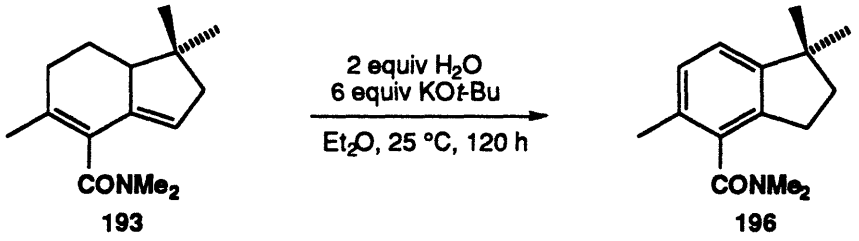

amide side chain of **193** even at 70 °C. It should be noted that Mannschreck has found that the related chiral aromatic amides **195** racemize upon rotation about the C(carbonyl)-C(aryl) bond at only 50 °C.[87]




The presence of A strain in the bicyclic amides synthesized was also found to have a profound impact on the reactivity of these compounds. Indeed, since the amide function would ultimately need to be converted to a carboxylic acid in order for these substrates to serve as intermediates for the synthesis of glycinoeclepin A, the hydrolysis of the amide side chain was investigated. Treatment of **192** or **193** with hydroxide ion under various

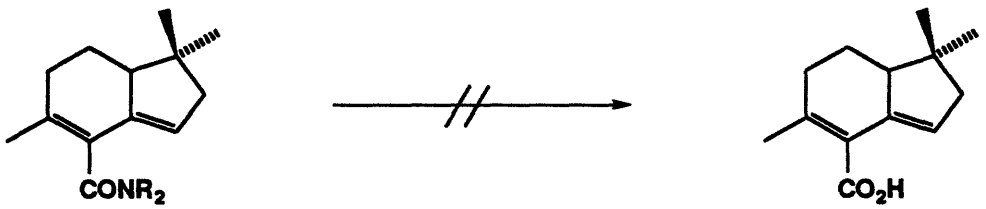
87 Cuyegkeng, M. A.; Mannschreck, A. *Chem. Ber.* **1987**, *120*, 803.

conditions did not result in any cleavage of the amide. Starting material was recovered upon treatment with lithium hydroxide in various solvents, tetrabutylammonium hydroxide, potassium hydroxide in refluxing ethanol, and sodium peroxide in water.[88] Treatment of the bicyclic amides with "anhydrous" hydroxide (KO*t*-Bu/$H_2O$),[89] a reagent which is reported to hydrolyze tertiary amides efficiently, led to the formation of the corresponding aromatic product without hydrolysis of the amide function. This transformation, which presumably involves initial base-catalyzed isomerization of **193** to a dihydroaromatic intermediate, would not be possible in the real system with its angular methyl group.




**193** **196**

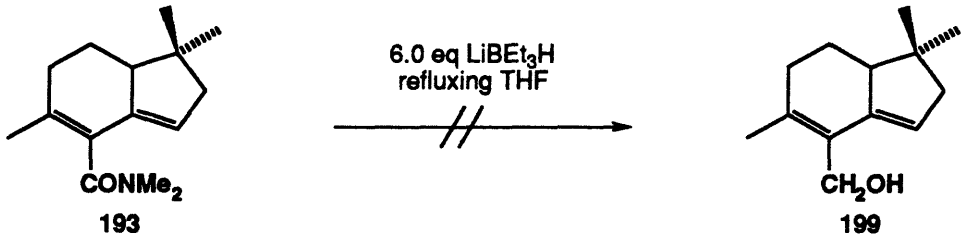
Hanessian's protocol for the hydrolysis of amides[90] was also examined. However, treatment of substrate **193** with triethyloxonium fluoroborate in the presence of sodium carbonate did not effect the desired transformation. While acidic conditions have also been used for the hydrolysis of amides, we felt that these procedures were not compatible with the intermediates we envisioned in our synthesis of glycinoeclepin A. This meant that the vigorous basic conditions that led to aromatization of substrates **192** and **193** would need to be repeated on more substituted model compounds which could not undergo this rearrangement



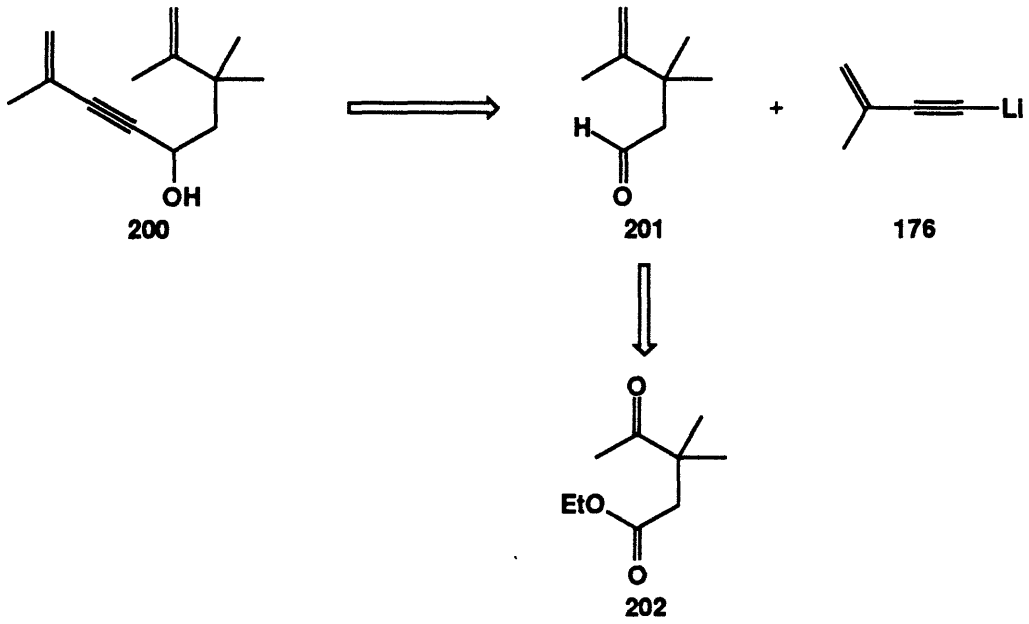

**197** **198**

88 Vaughn, H. L.; Robbins, M. D. *J. Org. Chem.* **1975**, *40*, 1187.
89 Gassman, P. G.; Hodgson, P. K. G.; Balchunis, R. J. *J. Am. Chem. Soc.* **1976**, *98*, 1275.
90 Hanessian, S. *Tetrahedron Lett.* **1967**, 1549.

Finally, we found that the amide in these bicyclic substrates is so shielded from attack that it is not even reduced by lithium triethylborohydride[91] (sold by Aldrich under the name Super-Hydride®) as starting material was recovered, mostly untouched, even in refluxing THF!



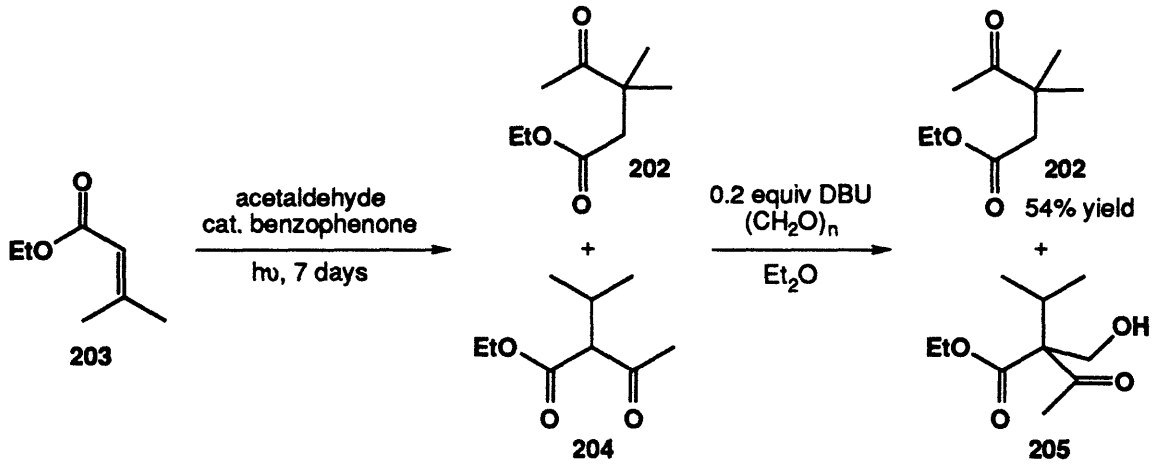

Although the amide in these systems could not be cleaved, this work did establish the feasibility of the tandem Büchi rearrangement / Diels-Alder cycloaddition strategy. The synthesis of a model compound with the ring junction methyl group found in glycinoeclepin A was examined next. This, it was hoped would allow further investigation into the hydrolysis of the amide function since the presence of the ring junction methyl group would prevent any aromatization from taking place, even under strongly basic




91 This reagent converts amides to the corresponding alcohols, see: Brown, H. C.; Kim, S.C. *Synthesis* **1977**, 635.

conditions. Our plans for the synthesis of the precursor to the desired bicyclic amide (**200**) involved the addition of acetylide **176** to aldehyde **201**. This aldehyde would be obtained from keto ester **202** by methylenation of the more reactive ketone carbonyl and subsequent reduction of the ester.

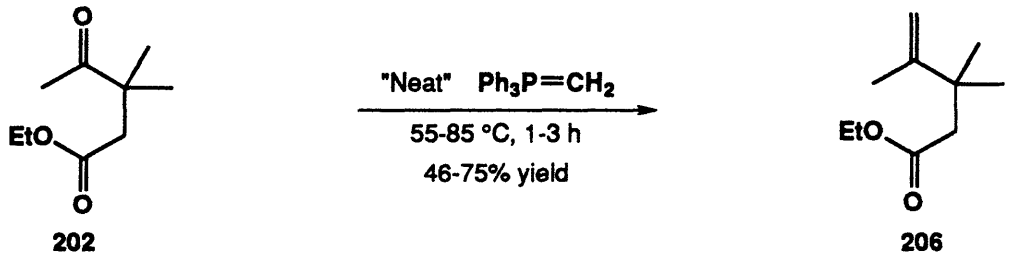
The starting material for this synthesis, keto ester **202**, is a known compound[92] which has been prepared by the photochemical reaction of acetaldehyde with the ethyl ester of 3,3-dimethylacrylic acid. As shown below, we found that this reaction proceeds to give a 4 : 1 mixture of the two possible isomeric addition products, a fact that was not noted by the original investigators. However, it was found that treatment of the more acidic ß-keto ester **204** with the base DBU and paraformaldehyde afforded a mixture of **202** and alcohol **205** which could be easily separated by flash chromatography. It should be noted that separation of **202** and **205** could not be achieved by distillation, as a retro-aldol reaction regenerates the original mixture of **202** and **204** at elevated temperatures.




The methylenation[93] of **202** proved to be somewhat difficult, probably as a result of the steric hindrance about the ketone carbonyl group of this substrate. The keto ester only partially reacted with the ylide formed from methyltriphenyphosphonium bromide and *n*-butyllithium in THF, under standard conditions, probably due to proton transfer. While

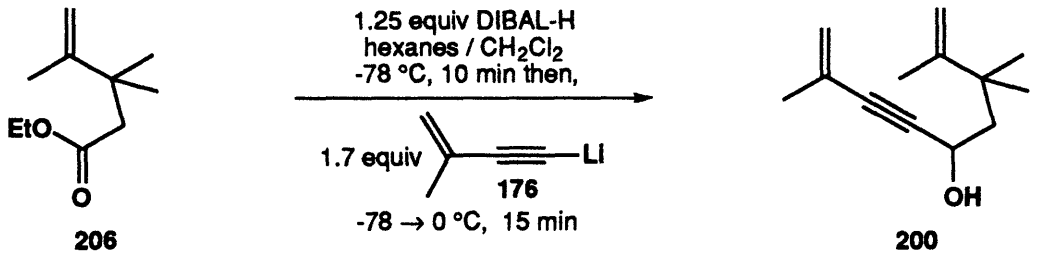
92 Cerfontain, H.; van Noort, P. C. M. *Synthesis* **1980**, 490.
93 For a review on olefin synthesis, see: Kelly, S. E. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, 1991, Vol 1, p. 729.

the Oshima reagent[94] (Zn - $CH_2Br_2$ - $TiCl_4$) was found to perform the desired transformation, the neat Wittig approach[95] was found to be more straightforward and to give better yields. This procedure involves the formation of the ylide by treatment of the phosphonium salt with potassium *t*-butoxide in ether, and the subsequent removal of the solvent by distillation. The neat ylide is then heated to the required temperature and the keto ester added to give the desired olefin in an exothermic reaction. This procedure has been found to work well with substrates that are very sterically hindered.




202 206

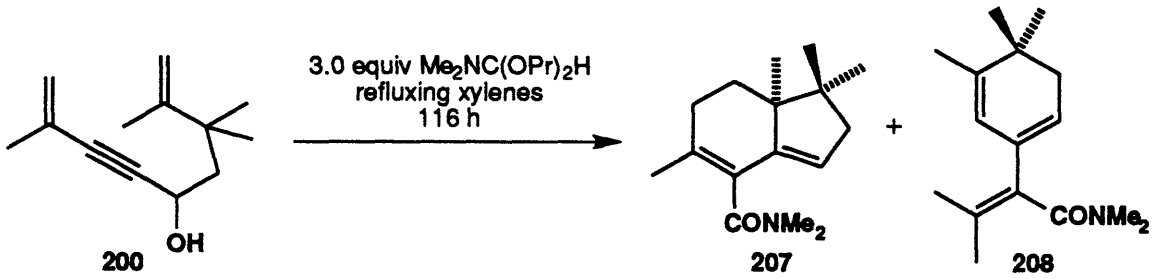
As expected, treatment of ester **206** with DIBAL-H at -78 °C followed by the *in situ* trapping of the aldehyde intermediate with the lithium acetylide **176** resulted in the formation of propargylic alcohol **20** in 73-78% yield.



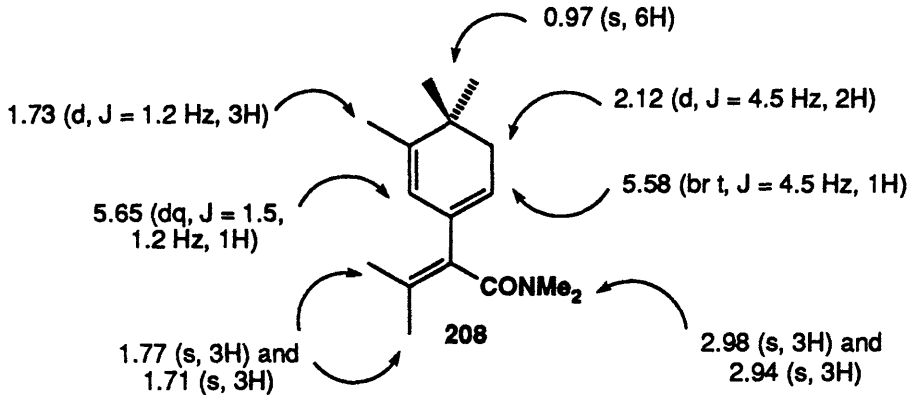

206 200

The reaction of this compound with N,N-dimethylformamide di-*n*-propyl acetal in refluxing xylenes led to the isolation of the desired bicyclic amide **207** (14-27% yield) as well as a side product (20-27% yield) which was identified as **208** on the basis of its $^1H$ and $^{13}C$ NMR spectra and proton / proton decoupling experiments as discussed below.

94 Takai, K.; Hotta, Y.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* **1978**, 2417.
95 Fitjer, L.; Quabexk, U. *Syn. Comun.* **1985**, *15*, 855.

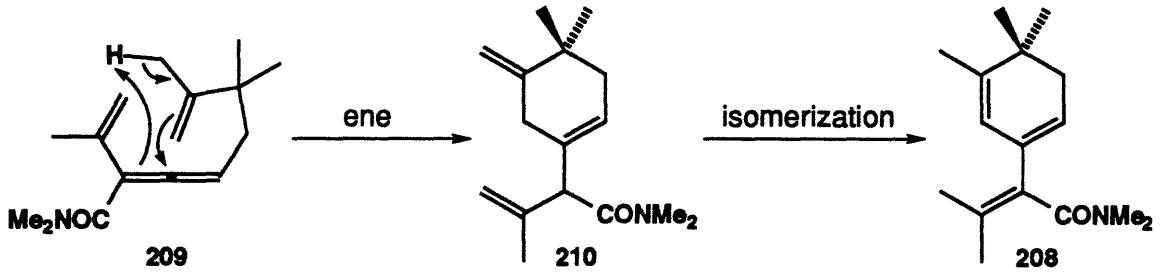



The molecular ion of **218** was found to have a mass corresponding to a molecular formula of $C_{16}H_{25}NO$ and a conjugated tertiary amide by IR (strong 1625 $cm^{-1}$ band). The $^{13}C$ NMR spectrum confirmed the presence of the dimethyl amide unit and showed the presence of 6 olefinic carbons (two of which have an odd number of protons attached to them by APT). The $^{1}H$ NMR spectrum indicated that the molecule possesses two olefinic protons which are found to be weakly coupled (J = 1.5 Hz) to each other. Further proton / proton decoupling studies show that one of these olefinic protons is strongly coupled (J = 4.5 Hz) to two methylene protons while the other olefinic proton only shows additional weak coupling to a methyl group. Two singlets (each signal integrating to three protons) and a broad singlet (weakly coupled to one of the olefinic protons and integrating to three protons) are found to lie in a region (1.7 - 1.8 ppm) which corresponds to that expected for methyl groups attached to a double bond.

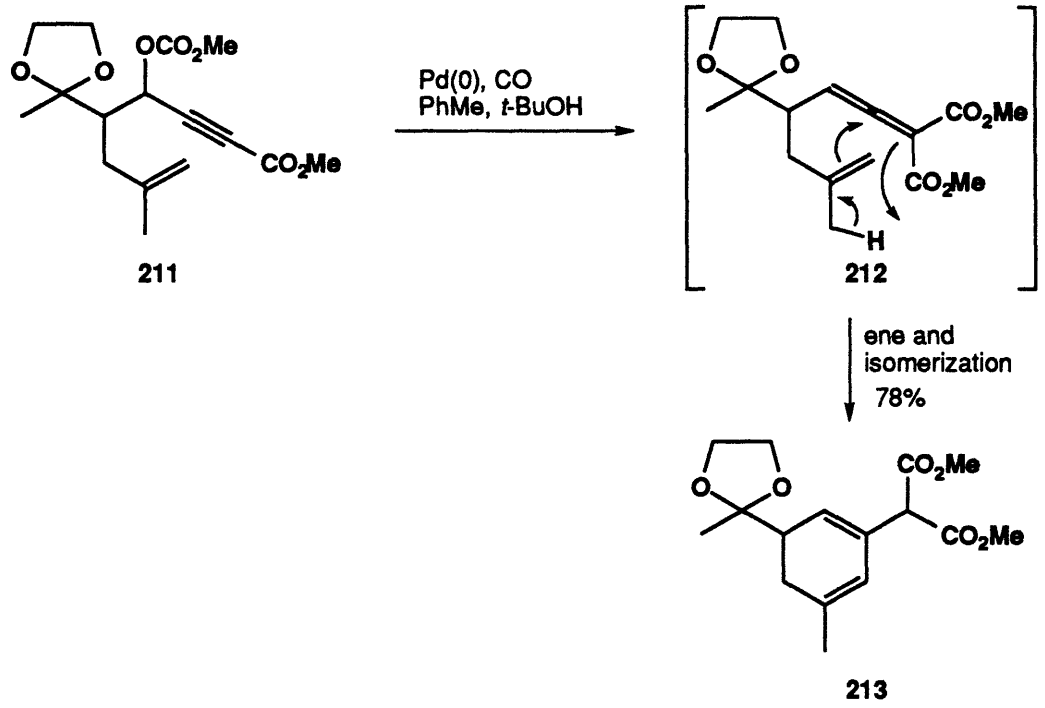



The amide side product **218** is most likely formed via the intramolecular Type II

ene reaction[96] of the lone isopropene unit with the allenyl amide function followed by isomerization of the double bonds to the thermodynamically more stable product.




After our observation of this intramolecular ene reaction, a very similar transformation was reported by Mandai[97] who found that 1-(2-methoxycarbonylethynyl)-4-alkenyl methyl carbonates undergo a tandem palladium catalyzed carbonylation and intramolecular ene reaction to give 6- and 5-membered ring products. For instance, propargyl carbonate **211** reacted to give cyclohexadiene **213** in 78% yield.



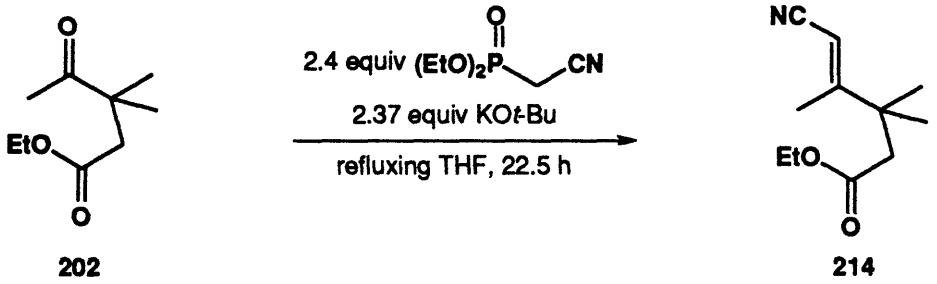

96 For reviews on the ene reaction, see: (a) Taber, D. F. *Intramolecular Diels-Alder and Alder Ene Reactions*; Springer: Berlin, 1984. (b) Snider, B. B. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, 1991, Vol. 5, p 1. (c) Mikami, K.; Shimizu, M. *Chem. Rev.* **1992**, *92*, 1021.

97 Mandai, T.; Tsujiguchi, Y.; Tsuji, J.; Saito, S. *Tetrahedron Lett.* **1994**, *35*, 5701.

A sample of the bicyclic amide **207** was subjected to the "anhydrous" hydroxide hydrolysis procedure reported by Gassman, but even in refluxing THF, the amide function emerged unscathed. As expected, no aromatic product was formed in this reaction.

While the ene reaction was found to compete with the intramolecular [4+2] cycloaddition in the case of substrate **200**, the effect of substituents on the isopropene dienophile needed to be investigated since the key step in our proposed total synthesis of glycinoeclepin A would involve a substituted double bond such as an enol ether. It was also our expectation that by using an alkene as dienophile that was activated by either an electron-donating or electron-withdrawing group, the desired [4+2] cycloaddition would be favored at the expense of the undesired ene reaction. It was decided that the next substrate to be investigated would be one with a cyano-substituted dienophile since the resulting nitrile could potentially be converted to the hydroxy function found at C-12 of glycinoeclepin A. Indeed, nitriles can be hydroxylated at the α-position by oxidizing agents[98] and the resulting cyanohydrins are precursors to ketones. Reduction of the ketone function would furnish the desired alcohol.

The synthesis of the substrate **214** was found to be straightforward. Either diethyl- or diisopropylcyanomethyl phosphonate when deprotonated with potassium *tert*-butoxide was found to react with keto ester **202** in refluxing THF to afford the desired unsaturated nitrile **214** in 61-86% yield.

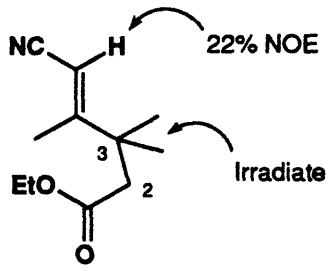



**202** **214**

The stereochemistry of the double bond was determined to be E on the basis of

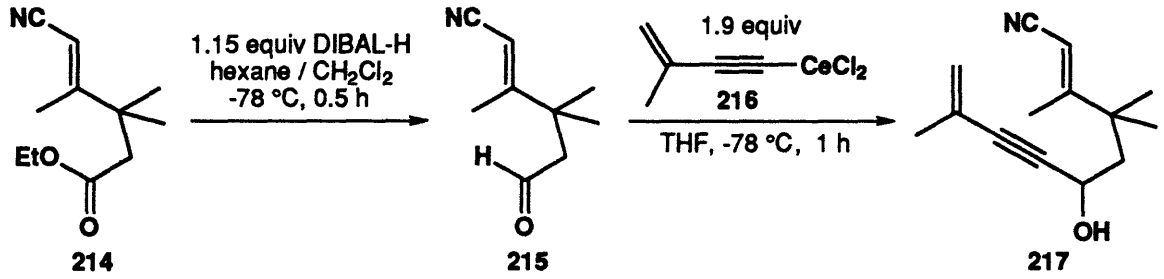
98 Vedejs, E.; Telschow, J. E. *J. Org. Chem.* **1976**, *41*, 740.

NOE studies: irradiation of the two allylic methyl groups resulted in a 22% enhancement of the olefinic proton. Furthermore, irradiation of the olefinic proton resulted in weak enhancements of the C-2 methylene group and the protons of the two C-3 methyl groups.




**214**

As the reduction of the ester function in **214** to the corresponding aldehyde followed by *in situ* trapping with acetylide **176** did not proceed smoothly, the ester was first reduced with DIBAL-H to give aldehyde **215** in quantitative yield. No evidence was found for attack of the reducing agent on the nitrile function. However, addition of the lithium derivative of isopropenylacetylene to **215** led to some 1,4-addition to the α,ß-unsaturated nitrile. Fortunately, treatment of the aldehyde with the cerium acetylide **216** gave the desired propargylic alcohol **217** in 88% yield. Cerium acetylides are known to add readily to enolizable substrates and to favor 1,2-addition over 1,4-addition.[99]

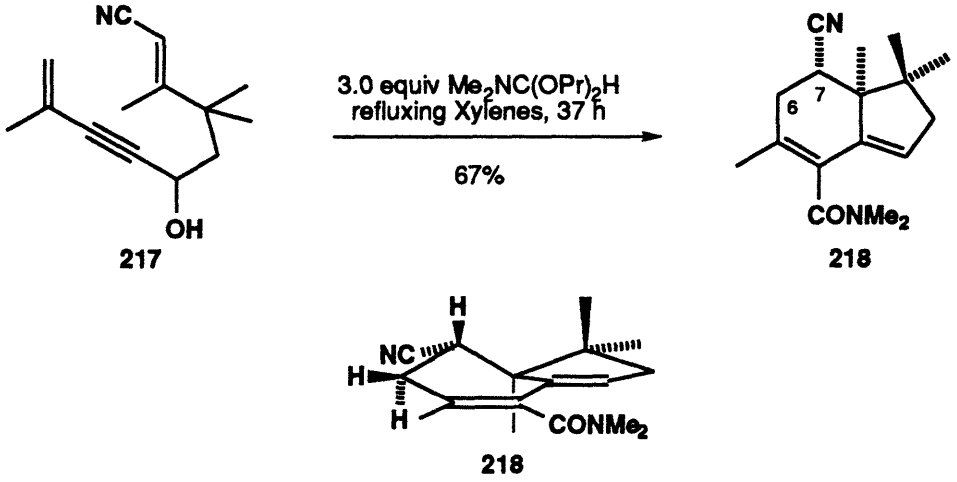



**214** **215** **217**

The reaction of alcohol **217** with N,N-dimethylformamide di-*n*-propyl acetal in refluxing xylenes led to the isolation of the desired bicyclic amide **218** in 67% yield. As hoped, no product resulting from an ene reaction analogous to that described above was

99 For a review on organocerium reagents, see: Imamoto, T. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, 1991, Vol 1, p. 231.

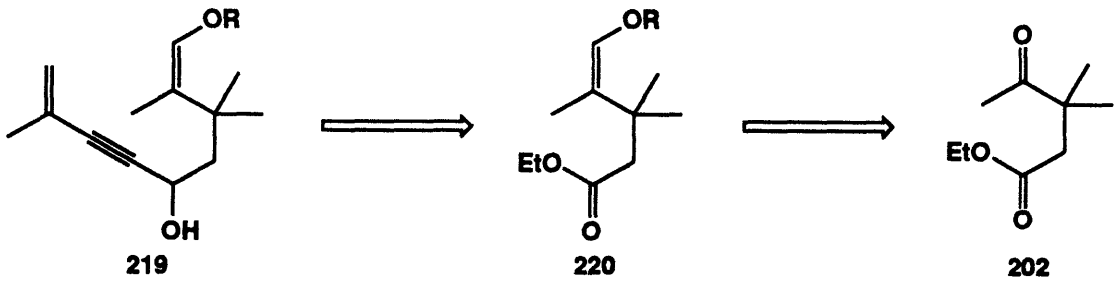
observed. In this case, we believe that the cyano group activates the dienophilic π bond and lowers the activation barrier for the desired Diels-Alder cycloaddition without accelerating the competing ene reaction. In addition, the steric effect of the cyano substituent may also retard the rate of the ene process. The bicyclic compound **218** was assigned the indicated stereochemistry given below on the basis of the large values[100] for the coupling constants (11 and 6.4 Hz for the major amide diastereomeric rotamer, 11 and 5.8 Hz for the minor amide diastereomeric rotamer) between the C-7 proton α to the nitrile and the adjacent C-6 methylene protons. This indicates that the C-7 proton and the methyl group on the adjacent carbon must both be axial and trans to each other. Inspection of molecular models and (as discussed later), MM2 calculations suggest that this and related bicyclic systems must adopt the conformation depicted below in order for the π bonds to remain in conjugation. Indeed, the coupling constants that would be expected for the opposite stereochemistry at C-7 are smaller on the basis of examination of molecular models and the known coupling constants in glycinoeclepin A (see later).



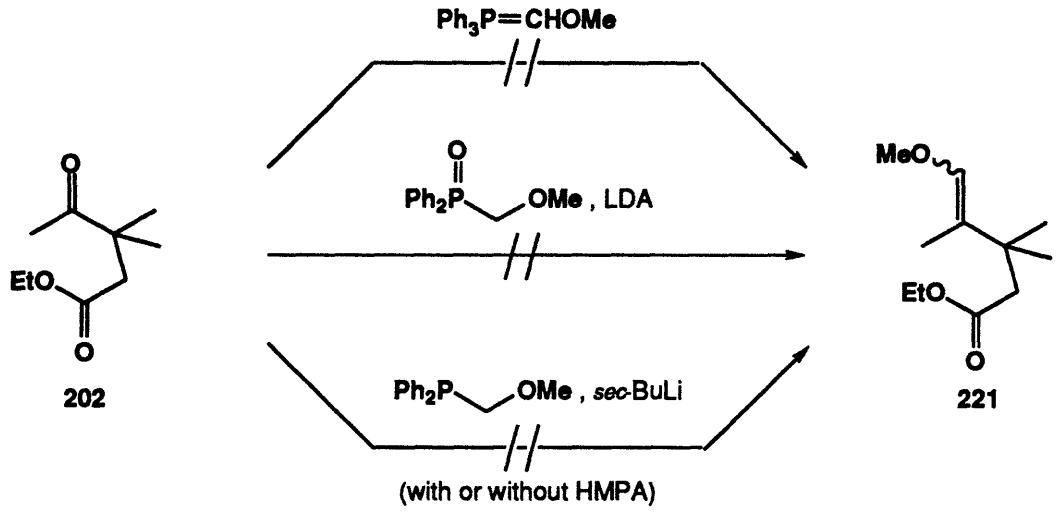

The next substrate of interest was the enol ether **219**, whose tandem rearrangement / cycloaddition would give a product having a ß-hydroxyl group at C-7, the arrangement found in the C,D-ring system of glycinoeclepin A. The propargylic alcohol **219** required

100 Since the system of interest is actually an ABX pattern, these J values are approximate.

for this reaction would be formed from ester **220** according to the procedures employed for the previous substrates. The enol ether portion of the molecule was expected to be available via application of one of several possible olefination strategies to keto ester **202.**



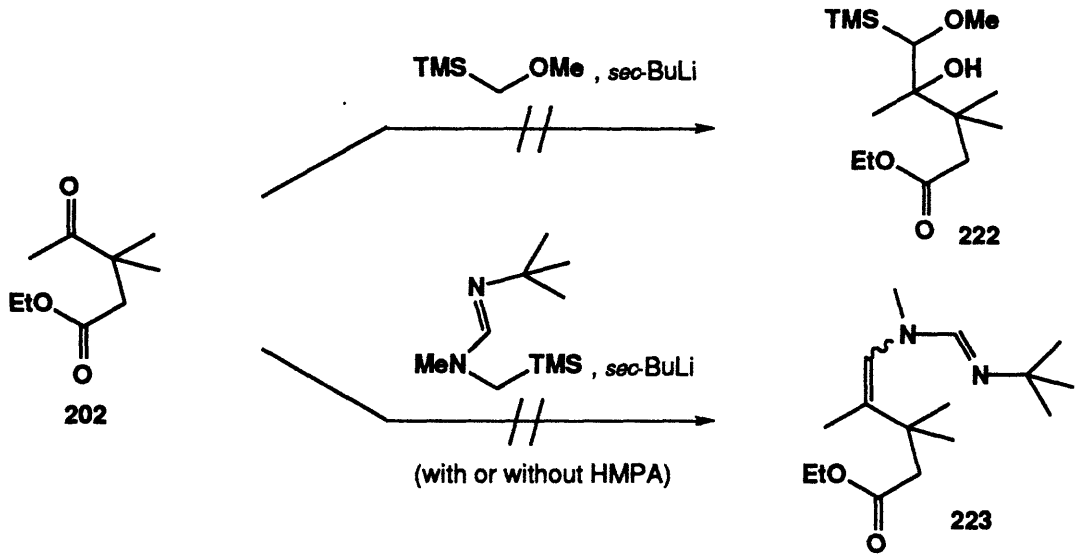

The generation of this enol ether[101] proved to be quite challenging, again because of the steric hindrance about the ketone carbonyl and its tendency to enolize. Treatment of **202** with the non-stabilized ylide derived from methoxymethyltriphenylphosphonium chloride either in solution, or neat, resulted in the recovery of starting material with the formation of only trace amounts of the desired product. The use of various bases with potassium, sodium, or lithium (with or without HMPA) as the counterions did not improve the outcome of the reaction. The Horner-Wittig reaction of diphenyl(methoxymethyl)-phosphine oxide[102] was examined, and although most of the starting material was




101 For a review on enol ether synthesis, see: Chan, T.-H. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, 1991, Vol 2, p. 595.
102 Earnshaw, C.; Wallis, C. J.; Warren, S. *J. C. S. Perkin I* **1979**, 3099.

consumed, the desired product was not observed. The reagent obtained upon deprotonating diphenyl(methoxymethyl)phosphine with *sec*-butyllithium, although reported to add to highly hindered ketones,[103] failed to combine with keto ester **202**.

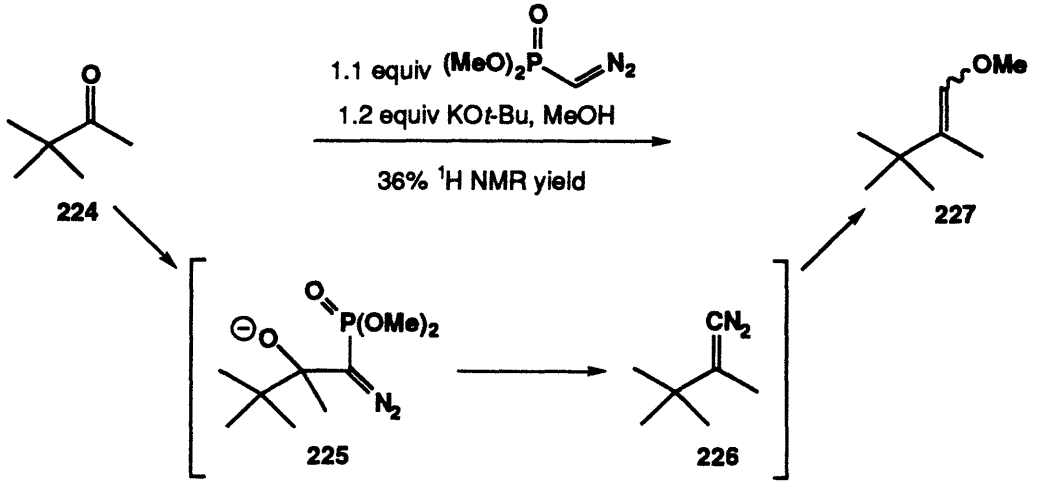
Another approach towards the synthesis of the enol ether substrate involved the use of the Peterson reagent shown below, a method employed previously by Magnus.[104] However, once again addition of this reagent to **202** did not proceed to any significant extent and alternatives had to be considered. Starting material was also recovered when Meyers' formamidine anion,[105] a reagent that effects the one carbon homologation of ketones, was added to the unreactive keto ester.




This series of failures was interrupted when the olefination procedure developed by Gilbert[106] was investigated. Gilbert has reported that pinacolone, which is as sterically hindered as keto ester **202**, reacts with the reagent formed by the deprotonation of dimethyl (diazomethyl)phosphonate (DAMP) with potassium *tert*-butoxide, in the presence of methanol, to generate enol ether **227**. The reported yield was low (36% yield by $^1$H NMR), but the alkylidenecarbene intermediate can be trapped by a variety of nucleophiles

103 Corey, E. J.; Tius, M. A. *Tetrahedron Lett.* **1980**, *21*, 3535.
104 Magnus, P. D.; Roy, G. *Organometallics* **1982**, *1*, 553.
105 Santiago, B.; Meyers, A. I. *Tetrahedron Lett.* **1993**, *34*, 5839.
106 Gilbert, J. C.; Weerasooriya, U. *J. Org. Chem.* **1983**, *48*, 448.

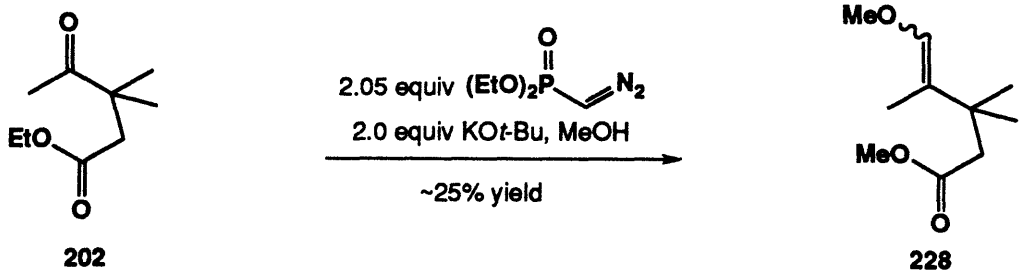
(amines generate enamines and alcohols give enol ethers), thus potentially providing us with access to a variety of dienophilic $\pi$ bonds.




Keto ester **202** was thus treated with diethyl (diazomethyl)phosphonate according to the Gilbert procedure and the desired enol ether **228** (the methyl ester was formed by transesterification under the reaction conditions) was isolated in approximately 25% yield as a 3 to 1 mixture of Z and E isomers respectively. The stereochemical assignment was made on the basis of NOE experiments on the major isomer **229**: irradiation of allylic methyl group led to a 5.8% enhancement of the olefinic proton. The low yield of the desired product could not be improved by varying reaction conditions, using different alcohols as traps for the alkylidenecarbene, or by employing trimethylsilyldiazomethane,[107] a safer alternative to DAMP that has been reported to effect the transformation of ketones to the homologous aldehydes when deprotonated with LDA.[108] The latter reagent failed to work presumably because it is not deprotonated by potassium *tert*-butoxide.

Unfortunately, the elaboration of the Z enol ether to the desired propargylic alcohol substrate proved to be impossible as the methyl ester function refused to be reduced under a variety of conditions! In some cases, as when DIBAL-H was the reducing agent, the stable

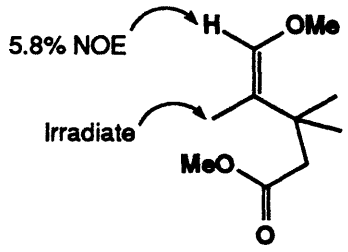
107 Ohira, S.; Okai, K.; Moritani, T. *Chem. Commun.* **1992**, 721.
108 Miwa, K.; Aoyama, T. Shioiri T. *Synlett*, **1994**, 109.




202 228

3 : 1

**NOE for major isomer :**

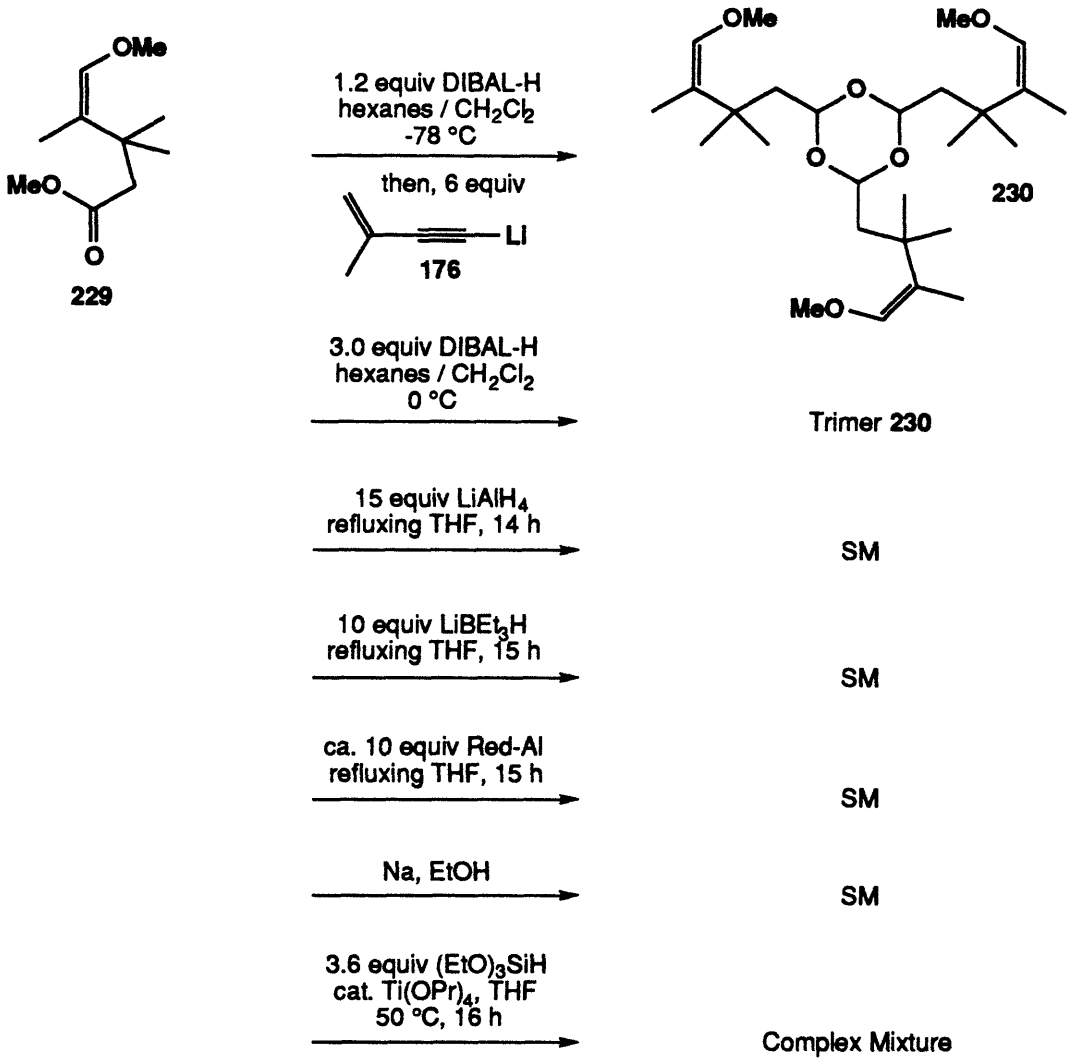



229

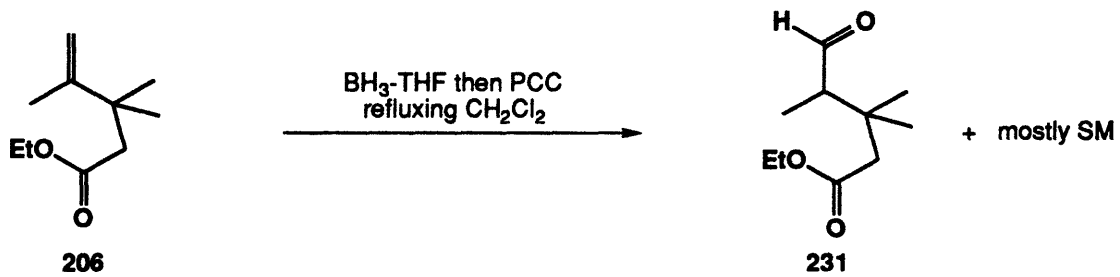
aldehyde trimer **230** formed preventing further reaction. It is remarkable that lithium aluminium hydride, Red-Al,® and Super-hydride® in refluxing THF were unable to attack this ester. This is presumably due to an interaction between the ether oxygen and the carbonyl of the ester group. It may be that the Lewis acidic aluminium in DIBAL-H is able to coordinate in a way that removes this interaction thus leading to a partial reduction to the aldehyde precursor at -78 °C. The aldehyde trimer does not react with the lithium acetylide used in the synthesis of the previous substrates and **230** is the sole compound isolated in this reaction. Reaction of **229** with Buchwald's air-stable catalyst system for the conversion of esters to alcohols[109] also led to a complex mixture of products.

As the direct appproach towards the synthesis of enol ethers was unsuccessful, an indirect approach via aldehyde **231** was investigated. This aldehyde can be converted potentially to any enol ether by trapping its enolate with the appropriate electrophile. The first route to **231** investigated involved hydroboration of olefin **206** followed by an oxidative workup with pyridinium chlorochromate (PCC).[110] While some of the desired

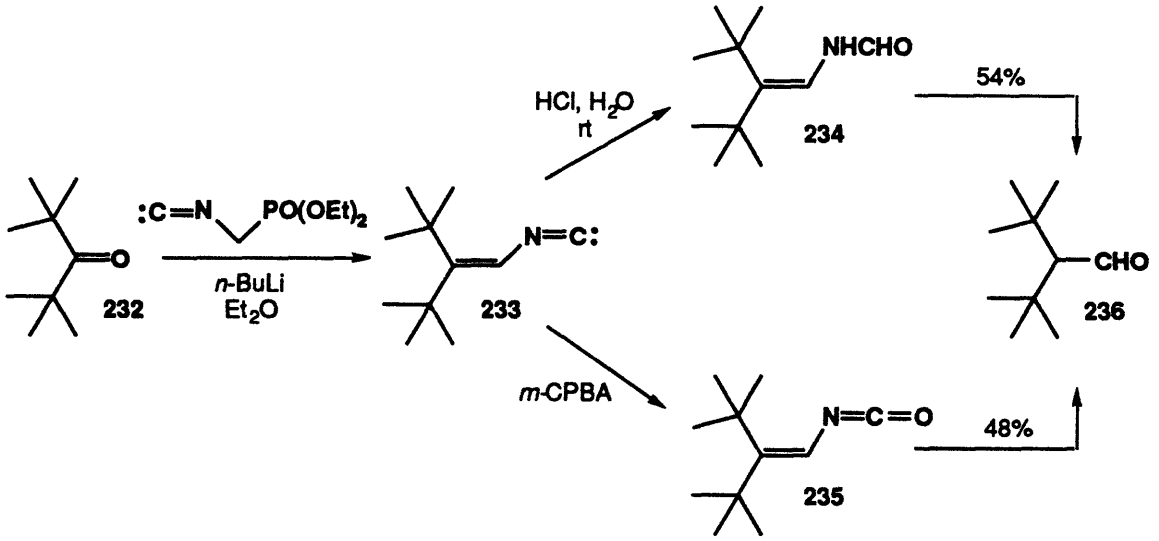
109 Berk, S. C.; Buchwald, S. L. *J. Org. Chem.* **1992**, *57*, 3751.
110 Brown, H. C.; Kulkarni, S. U.; Rao, C. G.; Patil, V. D. *Tetrahedron* **1986**, *42*, 5515.



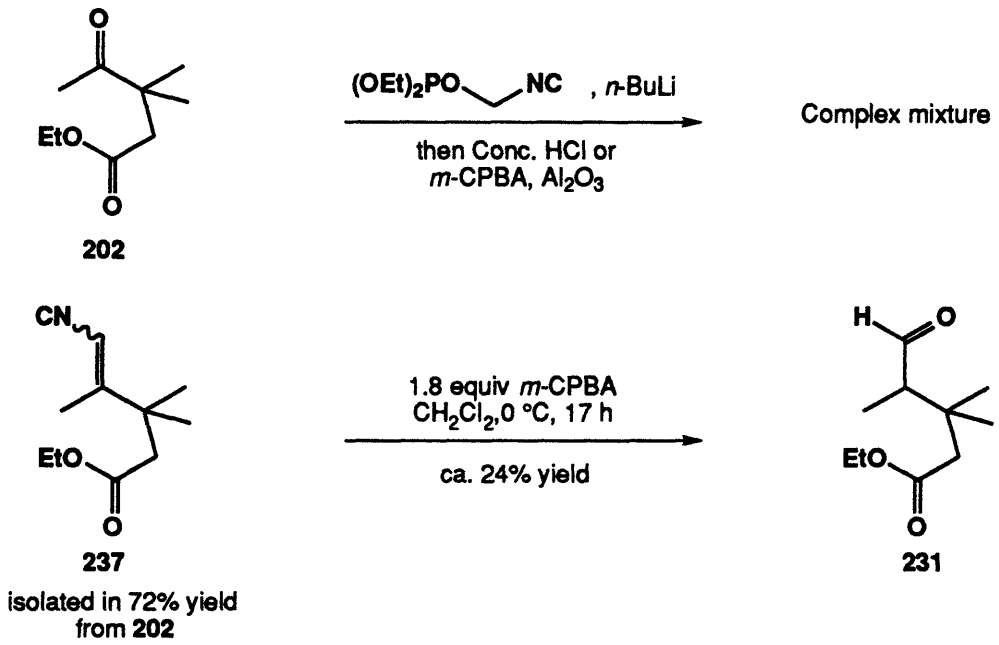

aldehyde was isolated, the low yields and poor conversion (starting material was recovered) made this method unappealing.



Van Leusen's synthesis of aldehydes[111] by a one-carbon homologation of ketones and aldehydes was examined next. This method has been reported to be applicable to the homologation of extremely hindered ketones such as di-*t*-butyl ketone as illustrated below.



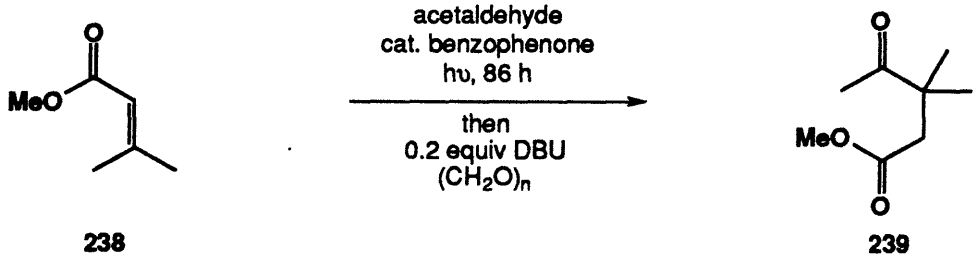

While the intermediate α,ß-unsaturated isocyanide **237** could be synthesized in moderately good yield neither the concentrated hydrochloric acid nor the *m*-CPBA protocol




111 Moskal, J.; Van Leusen, A. M. *Recl. Trav. Chim. Pays-Bas* **1987**, *106*, 137.

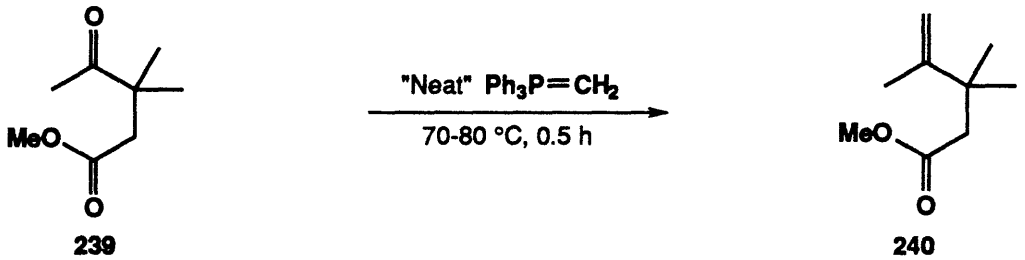
used by van Leusen converted **237** into the desired aldehyde efficiently. Moreover, we were unable to obtain the results reported by van Leusen when we applied his procedure to pinacolone.

The synthesis of aldehyde **242** was eventually achieved by a Lewis acid catalyzed rearrangement of epoxide **241**.[112] The sequence of reactions leading to **242** involves the formation of keto ester **239** in 27% yield from the methyl ester of 3,3-dimethylacrylic acid (**238**) in a manner analogous to that used for keto ester **202**. The low yield was at least partially due to the high volatility of the product.




**238** **239**

Keto ester **239** was then converted to olefin **240** in 39-49% yield using the neat Wittig procedure. The high volatility of the olefin is probably responsible for the low yield of this reaction.

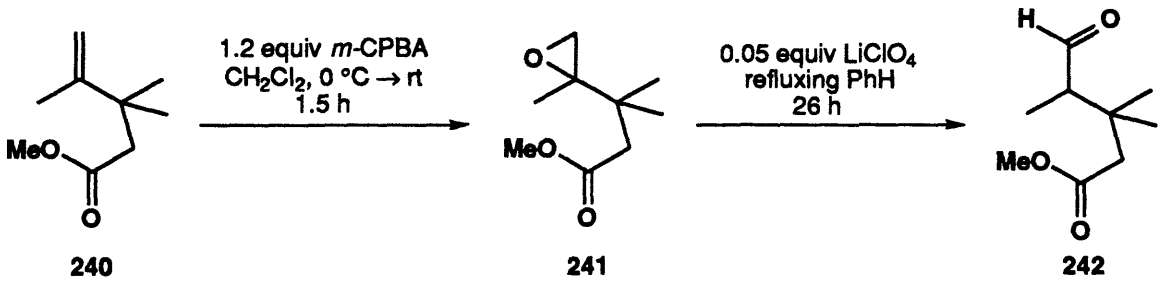



**239** **240**

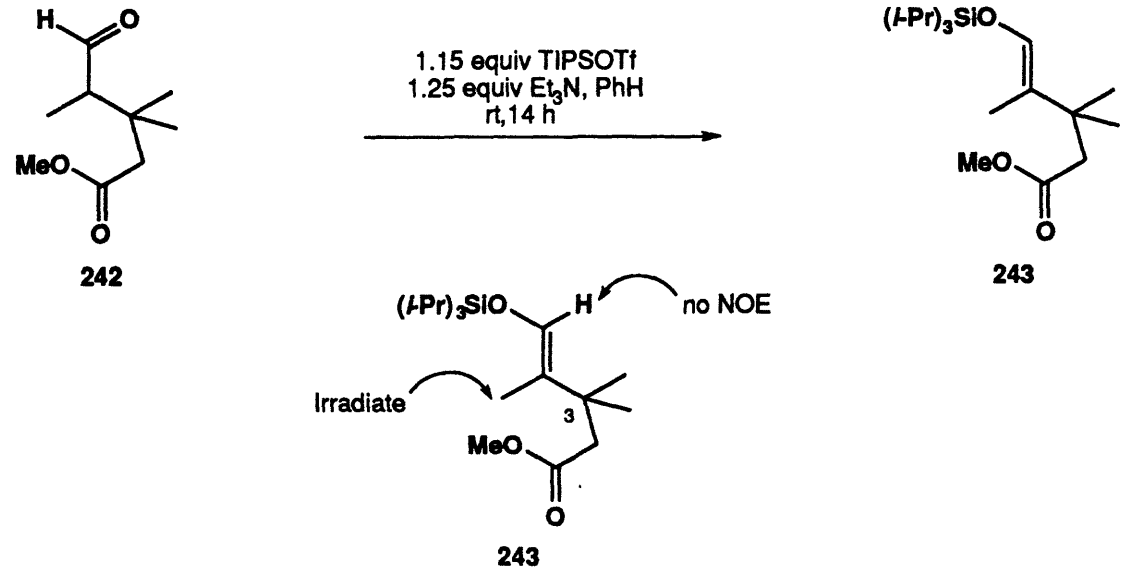
The action of *m*-CPBA on olefin **240** generated epoxide **241** in 75-81% yield. This epoxide was found to be quite sensitive and hence difficult to purify. Indeed, flash chromatography on silica gel frequently led to a *decrease* in the purity of material, due to

112 For a review on acid-catalyzed rearrangements of epoxides, see: Rickborn, B. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, 1991, Vol 3, p. 733.

the fact that silica gel appears to catalyze the rearrangement of epoxide **241** to aldehyde **242**. This rearrangement was best effected using $LiClO_4$.[113] The reaction proved to be somewhat capricious as the epoxide derived from ethyl ester **202** afforded the desired aldehyde in only ca. 10% yield, while the methyl ester rearranged in considerably higher yield. Use of a *catalytic* amount of $LiClO_4$ was best suited for this reaction, as the use of stoichiometric amounts led to extensive decomposition. Thus, exposure of **241** to 0.05 to 0.5 equiv of $LiClO_4$ in benzene at reflux afforded a 48-70% yield of aldehyde **242**. It should be noted that $BF_3$-$OEt_2$ was found to lead to immediate decomposition of the epoxide even at low temperature.



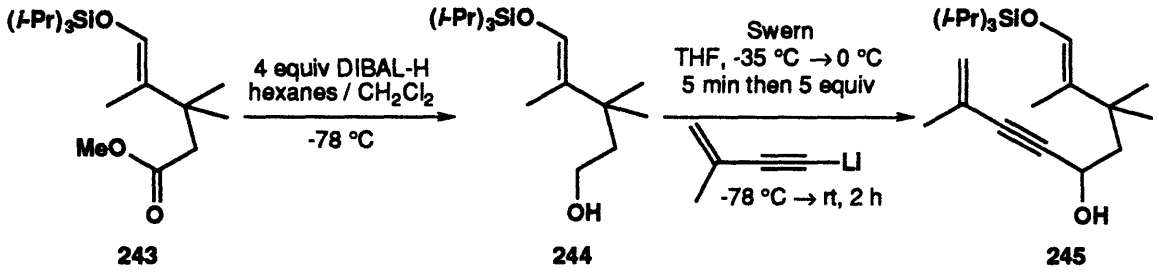

Aldehyde **242** was converted to the triisopropylsilyl (TIPS) enol ether **243** by treatment with triethylamine and triisopropylsilyl trifluoromethanesulfonate (TIPSOTf) in




113 Rickborn, B.; Gerkin, R. M. *J. Am. Chem. Soc.* **1971**, *93*, 1693.

73-79% yield.[114] The product was found to consist of an approximately 98 to 2 mixture of E to Z stereoisomers. The identity of the major isomer was determined by NOE studies: irradiation of the allylic methyl group did not result in any enhancement of the olefinic proton, while irradiation of this olefinic proton resulted in a small (ca. 1%) enhancement of the two C-3 methyl groups.

The ester **243** was converted in two steps to the required propargylic alcohol **245** as shown below. The first step involves DIBAL-H reduction at -78 °C to produce the alcohol **244** in 97-99% yield. Next, Swern oxidation of this alcohol and *in situ* reaction of the aldehyde intermediate with the lithium acetylide **176** used previously gave **245** in 78-82% yield. This sequence[115] gave better yields than the method we employed for other substrates involving partial reduction of the ester to the aldehyde followed by *in situ* reaction with the acetylide. In contrast to the reaction of DIBAL-H with the other esters used in this investigation, overreduction of ester **243** to alcohol **244** was a problem even at -78 °C.



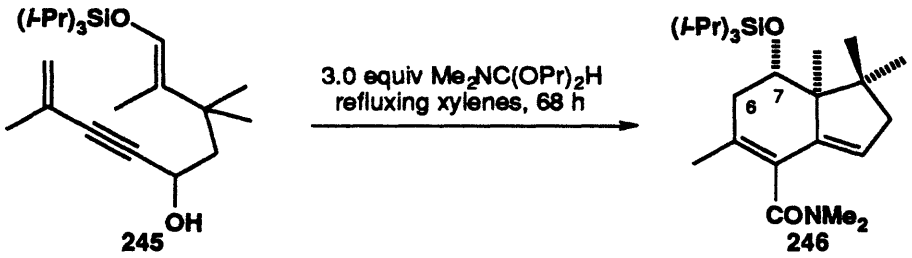

**243** **244** **245**

The rearrangement of **245** to a vinylallenyl amide and its tandem [4+2] cycloaddition took place as with the previous substrates to give the bicyclic amide **246** in 48-59% yield. Once again, no ene product was observed in this reaction. The alkoxy group is expected to significantly accelerate the desired inverse electron demand Diels-Alder reaction, and at the same time should retard the alternative ene reaction due to steric effects.

114 For a review on trialkylsilyl perfluoroalkanesulfonates and their use in the synthesis of silyl enol ethers, see: Emde, H.; Domsch, D.; Feger, H.; Frick, U.; Gotz, A; Hergott, H. H.; Hofmann, K.; Kober, W.; Krageloh, K.; Oesterle, T.; Steppan, W.; West, W.; Simchen, G. *Synthesis* **1982**, 1.

115 For previous work on the *in situ* addition of nucleophilic reagents to crude Swern oxidation mixtures, see: Ireland, R. E.; Norbeck, D. W. *J. Org. Chem.* **1985**, *50*, 2198.

A full stereochemical analysis of the structure of **246** was complicated by the presence of two amide rotamers, but it appears from the large coupling constants (an average of 7.8 Hz for the major rotamer, 10 and 5.9 Hz for the minor rotamer)[116] between the C-7 proton and the adjacent C-6 protons that the product has the expected configuration shown below.




Since the corresponding hydroxyl group in glycinoeclepin A has the ß (axial) configuration, in the actual synthesis we would either have to employ the Z enol ether corresponding to **245**, or devise a procedure for inversion of the alcohol.

Having shown that the basic skeleton of the glycinoeclepin A could be assembled using our tandem Büchi rearrangement / Diels-Alder cycloaddition strategy, there remained the problem of the lack of reactivity of the amide function. Though no exhaustive study of the hydrolysis of the bicyclic amide has yet been carried out, it seems clear that the conversion of the tertiary amide function to the desired carboxylic acid is not trivial. While it is possible that an internal nucleophile, for example a hydroxyl group in the A ring of the glycineclepin A precursor, could be employed to facilitate this process, a more attractive solution would be to form a bicyclic system with a more reactive carbocyclic acid precursor via the same general vinylallene formation / intramolecular Diels-Alder reaction. To this end, a paper published by Y. Tsuji in 1993 seemed to offer some hope.[117]

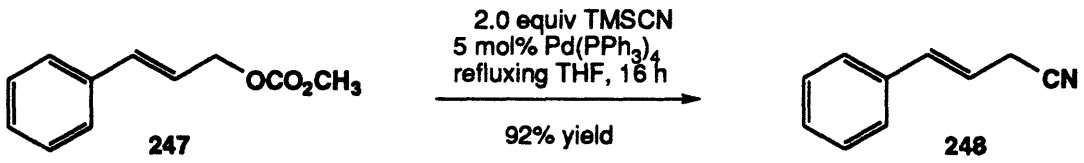
## Palladium-Catalyzed Cyanation Strategy

Tsuji has reported a palladium-catalyzed procedure for the conversion of allylic

116 This system is actually an ABX pattern, so that the J values are only approximate.
117 Tsuji, Y.; Yamada, N.; Tanaka, S. *J. Org. Chem.* **1993**, *58*, 16.

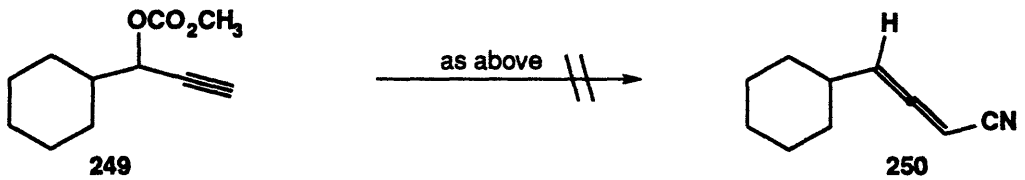
carbonates to the corresponding allylic nitriles. Extension of this procedure to propargylic carbonates should give rise to allenyl nitriles, the same intermediate that we had previously tried to generate by $S_N2'$ displacement of propargyl mesylates with cyanide anion. This theory was first tested on the model compound **248**. However, treatment of **249** with a catalytic amount of $Pd(PPh_3)_4$ and 2 equivalents of trimethylsilyl cyanide (TMSCN) in refluxing THF according to the Tsuji procedure led to the formation of two unidentified products, neither of which was the desired cyanoallene. Further experimentation with various cyanide sources including metal cyanides such as copper and zinc cyanide did not result in any reaction of interest. The use of cyanoformates as an "internal source" of cyanide was briefly investigated, but this approach was plagued by the incomplete formation of the cyanoformates from the corresponding chloroformates. Use of $Pd_2(dba)_3$ as the source of palladium (0) also failed to achieve the desired transformation. While the Tsuji chemistry was successfully repeated to give allylic nitrile **248** from **247** in nearly quantitative yield, it was clear that the desired extension to propargylic carbonates was not feasible, at least for the model compound **249**. The Tsuji conditions were nonetheless examined on an enynyl alcohol substrate that would yield as the final product a bicyclic nitrile analogous to those we had made previously.

Tsuji's literature precedent:



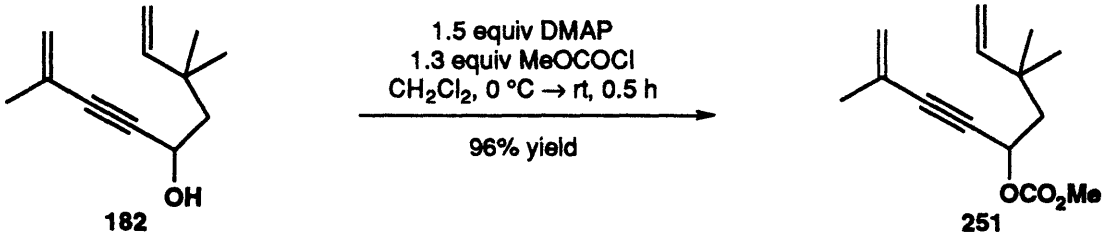

247 248

Extension to propargyl system:

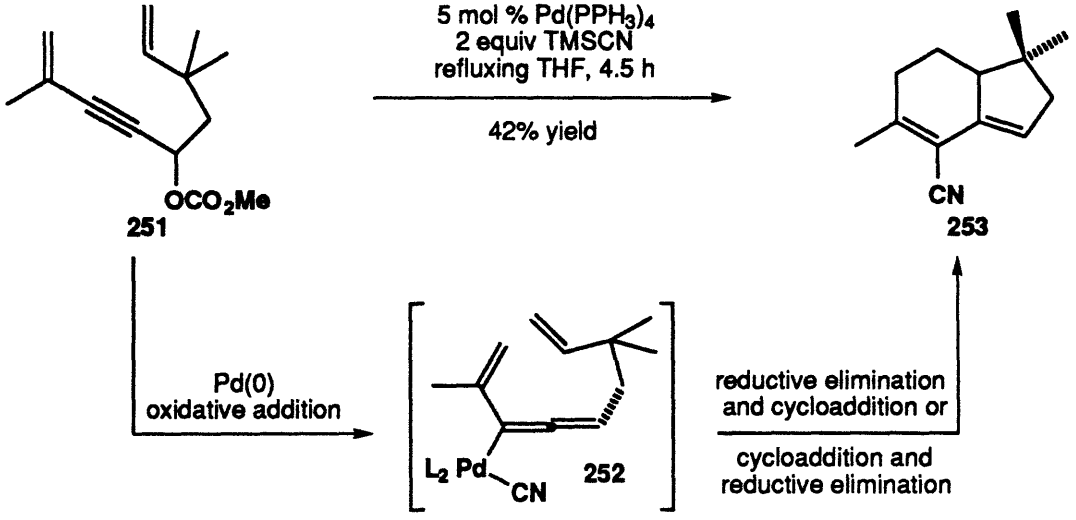



249 250

We decided to begin by examining a substrate from the readily available model series with a terminal vinyl group as the dienophile. The required propargyl carbonate **251** was made in 96% yield from the corresponding propargylic alcohol **182** using standard conditions.

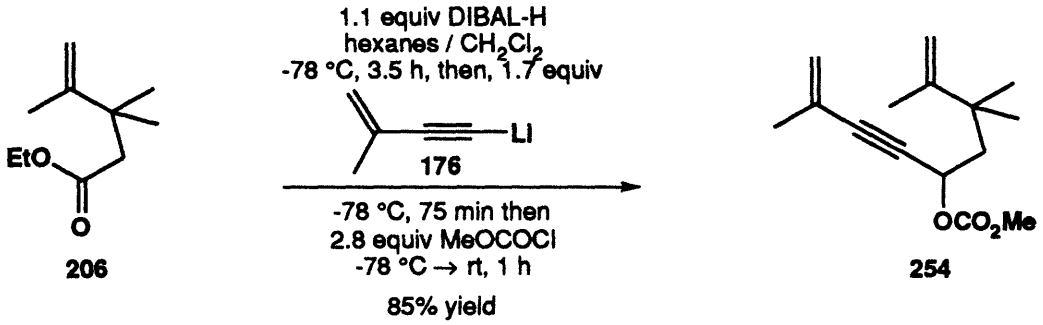



Treatment of this carbonate with 5 mol % of $Pd(PPh_3)_4$ and 2 equiv of TMSCN afforded, after 4.5 hours in refluxing THF, the bicyclic nitrile **253** in 42% yield. It appears therefore that, unlike the model compound, the substrate **251** reacts with the palladium catalyst to form an allenyl palladium species **252** (which is probably in equilibrium with the propargyl palladium species). Reductive elimination forms an allenyl nitrile intermediate which then takes part in a tandem [4+2] cycloaddition under the reaction conditions. It is also possible that the allenyl palladium species undergoes the cycloaddition and that subsequent reductive elimination furnishes **253**. Note that in this reaction, the intramolecular Diels-Alder reaction proceeds at a significantly lower

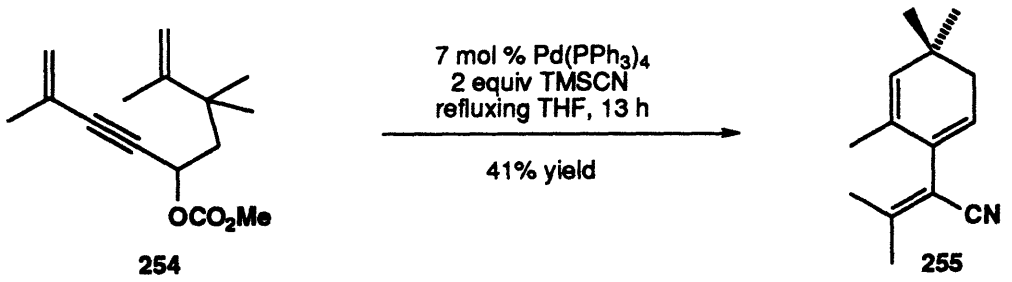


temperature (65 °C) as compared to in the Büchi rearrangement strategy (ca. 140 °C).

The model system with an isopropenyl group as dienophile was investigated next. Propargyl carbonate **254** was synthesized in one pot from ester **206** by partial reduction to the aldehyde, using DIBAL-H at -78 °C, followed by trapping with the lithium acetylide **176** and treatment of the propargyl alkoxide intermediate with methyl chloroformate. This series of reactions afforded **254** in 85% yield.

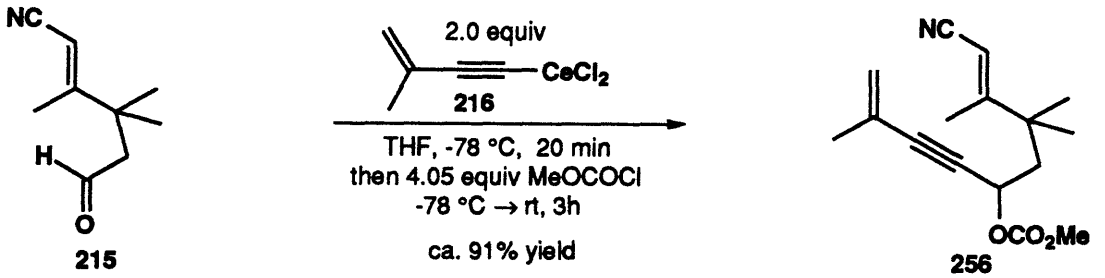


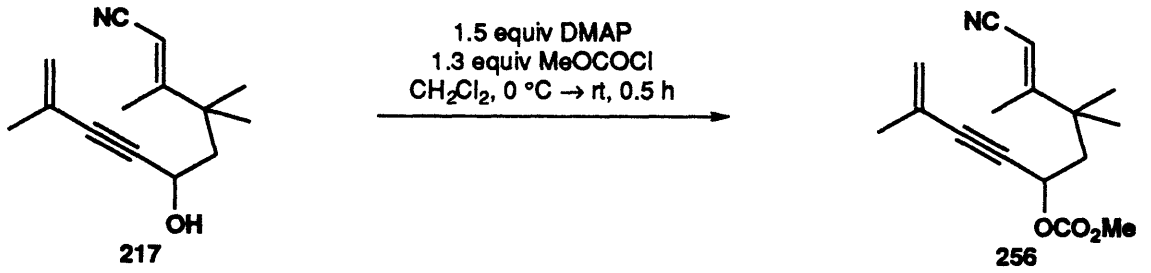

Treatment of this carbonate with 7 mol % of $Pd(PPh_3)_4$ and 2 equiv of TMSCN afforded, after 13 h in refluxing THF, nitrile **255** in 41% yield. As in the case of the reaction involving allenyl amides, this product is consistent with the involvement of an ene reaction between the electron-deficient allene function and the isopropenyl fragment of the molecule. It should be noted, however, that unlike the amide case, none of the bicyclic nitrile arising from a [4+2] intramolecular cycloaddition was isolated.



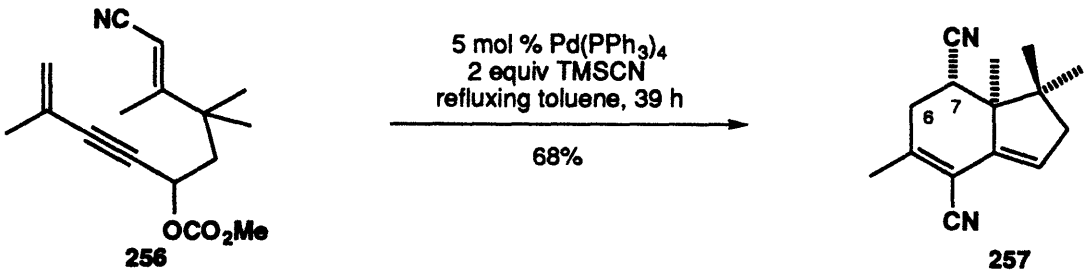

We next examined the application of this new allenyl nitrile synthesis to the synthesis of bicyclic dinitrile **257**. The propargylic carbonate precursor was synthesized in

91% yield from aldehyde **215** or in 89-95% yield from propargylic alcohol **217** using the chemistry previously discussed.



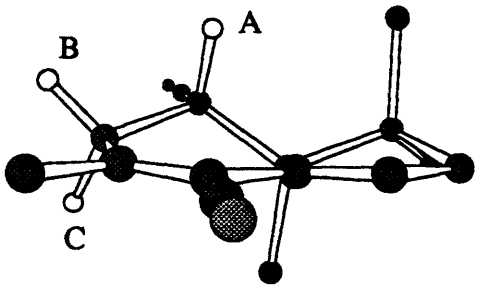

The propargylic carbonate **256** reacted very slowly with 5 mol % of $Pd(PPh_3)_4$ and 2 eq of TMSCN in refluxing THF so the solvent was switched to toluene in order to decrease the reaction time. The effect of the remote functional group on the rate of conversion of the propargylic carbonate to allenyl nitrile was quite surprising.




The resulting dinitrile **257** was shown to have the relative stereochemistry indicated below from the large coupling constants (an average of 8.3 Hz)[118] between the proton α to the cyano group and the adjacent methylene group protons. MM2 calculations implemented by the program MacroModel® gave rise to the model of this molecule shown below. This

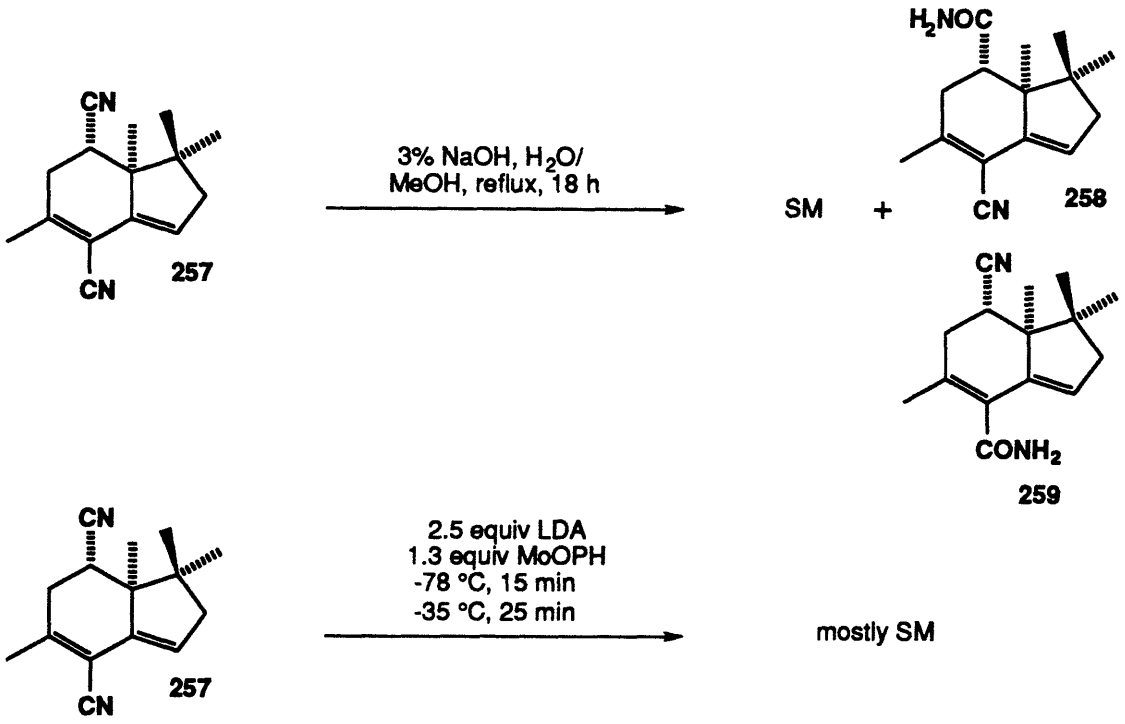
118 This is an ABC system which has not been rigorously analyzed and the J values are thus approximate.

energy minimized structure predicts coupling constants of 11.7 and 5.1 Hz for $J_{AC}$ and $J_{AB}$ respectively. The indicated structure is lowest in energy as it maintains the planar conjugated $\pi$ system and minimizes non-bonded interactions between substituents. This assignment is also consistent with the coupling constants measured for a system discussed later with an alkoxy group at C-7 in which both epimers were obtained and examined by NMR.




With the dinitrile compound in hand, two small scale exploratory reactions were carried out to determine the reactivity of this system. One involved the treatment of X with a 3% aqueous methanolic NaOH solution at reflux for 18 h. In addition to some recovered starting material, the two possible mononitrile compounds **258** and **259** were obtained in approximately 1 : 1 ratio. While no further hydrolysis seems to have taken place, it is possible that more vigorous conditions would achieve this feat. In addition, treatment of **257** with 2.5 equiv of LDA and addition to the resulting pink / purple solution of 1.3 equiv of MoOPh only resulted in the recovery of some crude starting material. While more experiments are needed, it may be that the failure of this experiment is due to the presence of the enolizable unsaturated nitrile system and by steric crowding in the molecule.

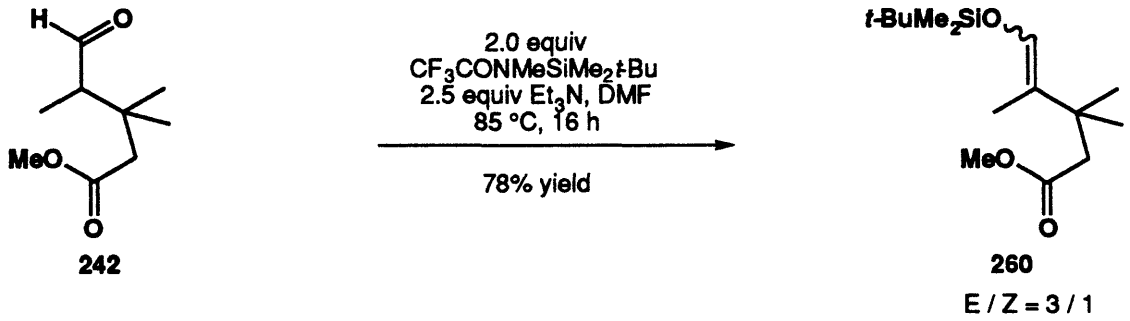
At this point, no substrate had been cyclized to provide the required carbon skeleton of the bicyclic CD-ring system of glycinoeclepin A, with a hydroxyl group of the proper configuration. While the formation of the TIPS silyl enol ether described previously did



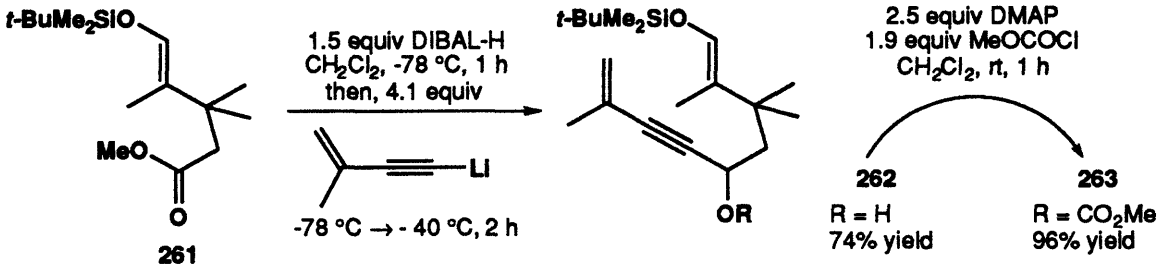

not afford any significant quantities of the Z stereoisomer required for the direct generation of the desired ß alcohol, it was found that the *tert*-butyldimethyl silyl (TBDMS) analog could be synthesized to give some of the Z stereoisomer.

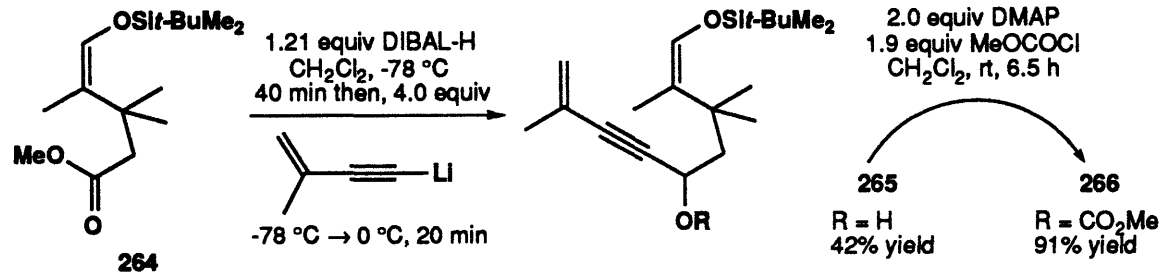
This sequence involved the treatment of aldehyde **242** with N-*tert*-butyldimethylsilyl-N-methyltrifluoroacetamide (MTBSTFA)[119] to provide silyl enol ether **260** in 66-78% yield. It should be noted that the ratio of stereoisomers was found to vary possibly depending on the age of the reagent. Indeed, the first bottle of the reagent afforded **260** as an 8 to 1 mixture of the E and Z stereoisomers respectively, as well as a small amount of an unidentified side-product. Subsequent bottles were found to give a 3 to 1 ratio of stereoisomers with no side-product formation. Recently, a bottle that had not been used for 1 year and which originally gave a 2.7 to 1 ratio was found to give a 4.2 to 1 ratio of E to Z. *tert*-Butyldimethylsilyl trifluoromethanesulfonate (TBDMSOTf)[120] gave a greater than 10 to 1 ratio of the E and Z stereoisomers, although in lower yield.

119 Mawhinney, T. P.; Madson, M. A. *J. Org. Chem.* **1982**, *47*, 3336.
120 Mander, L. N.; Sethi, S. P. *Tetrahedron Lett.* **1984**, *25*, 5953.



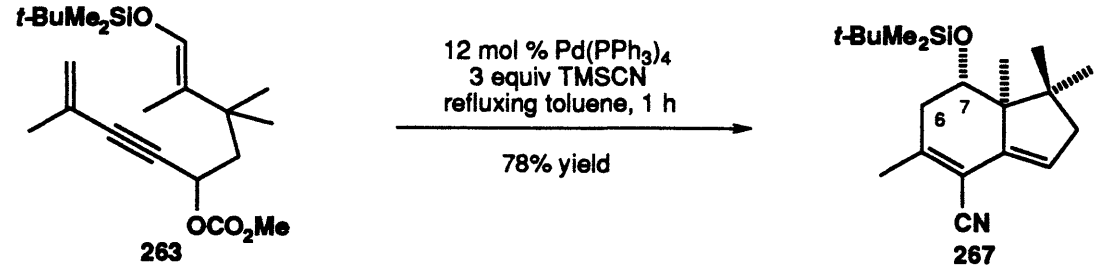

Separation of the two stereoisomers by silica gel chromatography, treatment of each compound with DIBAL-H, and *in situ* trapping of the resulting aldehyde intermediate with lithium acetylide **176** afforded the E propargylic alcohol **262** in 74% overall yield from **261**. The Z isomer (**265**) was formed in 42% overall yield (as a result of the poor quality of the DIBAL-H used in this run). The propargylic alcohols were converted to the corresponding propargylic carbonates **263** and **266** in 96% and 91% yield, respectively.

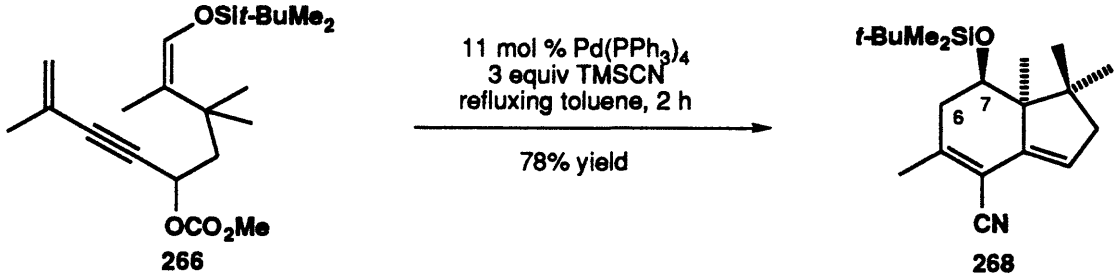



Treatment of each compound with 12 mol % of $Pd(PPh_3)_4$ and 3 equiv of TMSCN in refluxing toluene for 1 and 2 h (respectively for the E and Z stereoisomers) afforded bicyclic nitriles **267** and **268** in 78% yield for both substrates. The apparent ease of

cyclization for both stereoisomers is surprising, since examination of molecular models suggests that, for the Z stereoisomer, there might be significant steric interactions in the transition state of the intramolecular cycloaddition between the bulky siloxy group and the methyl group which bears a 1,3-diaxial relationship to it in the product.



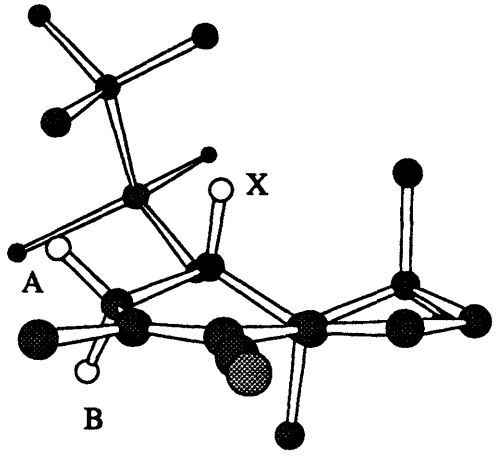




The E propargylic carbonate provided a product with NMR characteristics analogous to the bicyclic compounds previously synthesized. In particular, the coupling constants between the C-6 proton and the C-7 protons are large (an average value of 7.8 Hz).[121] The Z stereoisomer gave a product with much smaller coupling constants between the same sets of protons (an average of 2.9 Hz)[123]. These values are very similar to those between the C12 proton and the adjacent methylene protons ($J_{12\alpha,11\beta}$ = 1.5 Hz and $J_{12\alpha,11\alpha}$ = 3 Hz) of glycinoeclepin A.[122] The assignment of the two products given below is further supported by energy minimization calculations (MM2) which predict that **267** should have a large coupling constant ($J_{AX}$ = 3.6 Hz and $J_{BX}$ = 9.9 Hz) while its epimer at

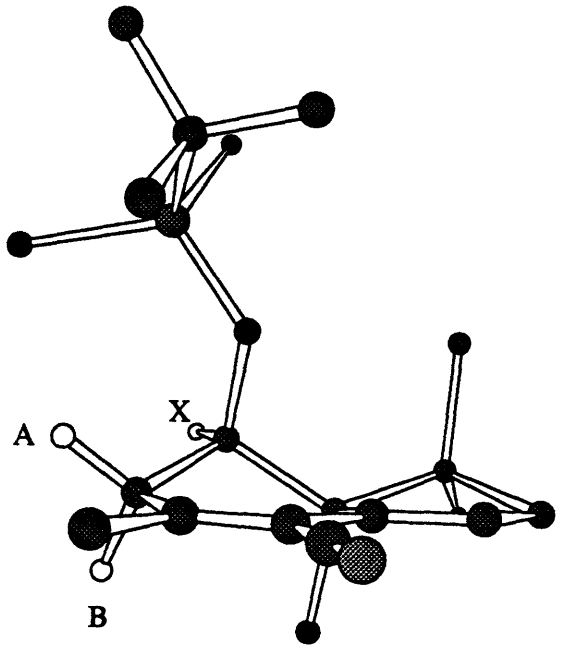
121 Since the system of interest is actually an ABX pattern, these J values are approximate.

122 Masamune, T.; Fukuzawa, A.; Furuzaki, A.; Ikura, M.; Matsue, H.; Kaneko, T.; Abiko, A.; Sakamoto, N.; Tanimoto, N.; Murai, A. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 1001.

the carbon bearing the siloxy function (**268**) should have smaller values ($J_{AX}$ = 3.0 Hz and $J_{BX}$ = 3.3 Hz).




**267**

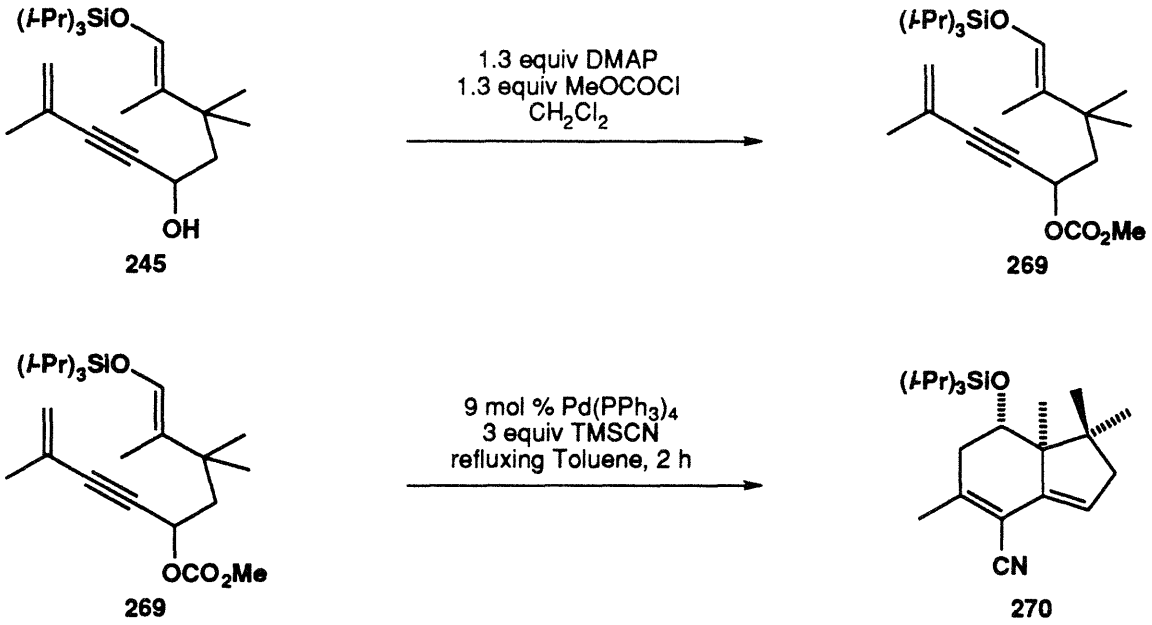



**268**

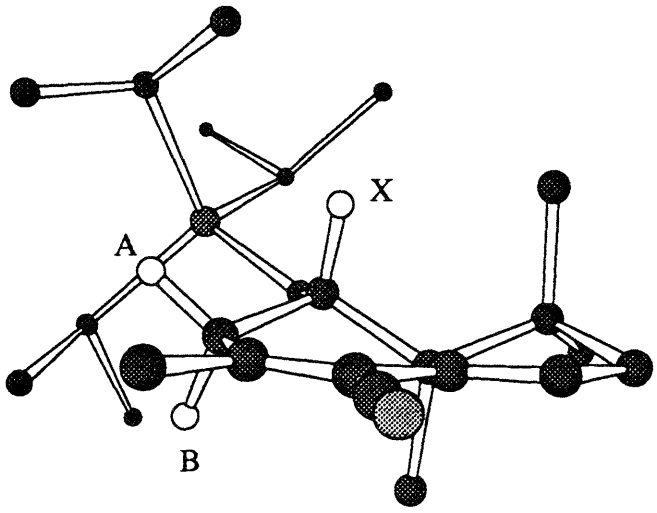
NOE studies also confirm the assignment given above. Irradiation of proton X in nitrile **267** gives rise to a weak (1%) NOE to only one of the methyl groups; presumably the axial methyl group ß to the siloxy group. Irradiation of proton X in nitrile **268** results in weak (<1%) NOEs to all three methyl groups at the carbons α and ß to the siloxy group.

Subjecting the TIPS substrate **269** (obtained in 94-96% yield from propargylic alcohol **245**) to the conditions used above furnished bicyclic nitrile **270** in 84-87% yield. The bulkier TIPS group does not have much of an effect on the rate of the intramolecular cyclization as compared to the TBDMS group.

It was observed once again that the E enol ether substrate **269** generated the product stereospecifically with the configuration shown. This conclusion is based on the coupling constants between the proton α to the siloxy group and the adjacent methylene




group protons which are large (an average value of 7.5 Hz).[123] MM2 calculations predict values of 5.7 Hz for $J_{AX}$ and 10.6 Hz for $J_{BX}$ in this quite rigid structure.



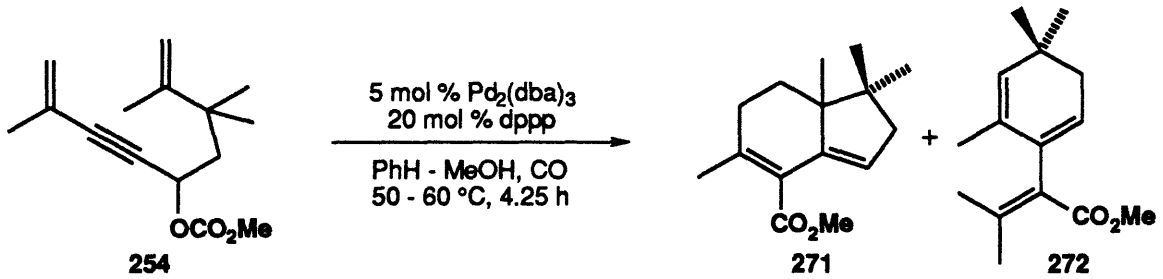

## Palladium-Catalyzed Carbonylation Strategy

As described earlier, Mandai and Tsuji reported a palladium catalyzed procedure for the conversion of propargylic carbonates to the corresponding bicyclic methyl esters via a

123 Once again, this system is actually an ABX pattern so that these J values are approximate.

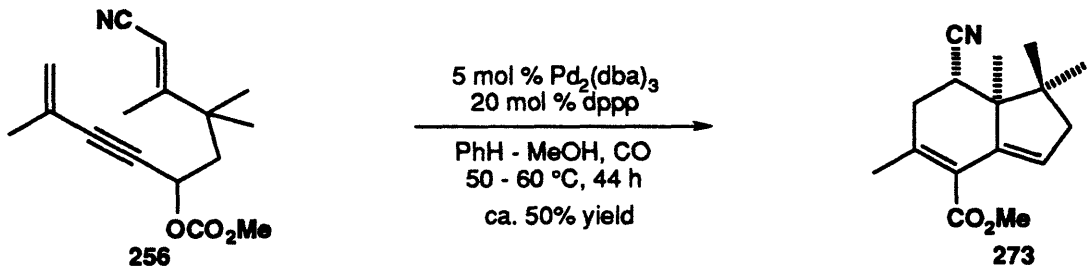
tandem carbonylation and intramolecular Diels-Alder approach[71] of the type we have studied in our studies towards the total synthesis of glycinoeclepin A. Since esters of glycinoeclepin A can be hydrolyzed to the parent molecule,[47] this procedure could give access to a system which would be well suited for further elaboration to the natural product.

The reaction of the isopropenyl substrate **254** with a 5 mol % of a preformed palladium (0) catalyst in benzene / methanol at 50-60 °C, under an atmosphere of carbon monoxide, gave in 50% yield a mixture of the desired bicyclic ester **271** and the ene reaction product **272** in a 1 to 4 ratio. This reaction did not proceed cleanly; at least one unidentified side compound was formed along with the expected products.




**254** **271** **272**

Substrate **256**, with the unsaturated nitrile dienophile, reacted under the Mandai / Tsuji conditions to give bicyclic ester **273** in approximately 50% yield. Isolation of pure product was very difficult as the reaction did not proceed cleanly. Altering the reaction conditions in any way resulted in decreased yields. The coupling constants relevant to the relative stereochemical assignment are large (11 and 6.2 Hz),[124] supporting the stereo-

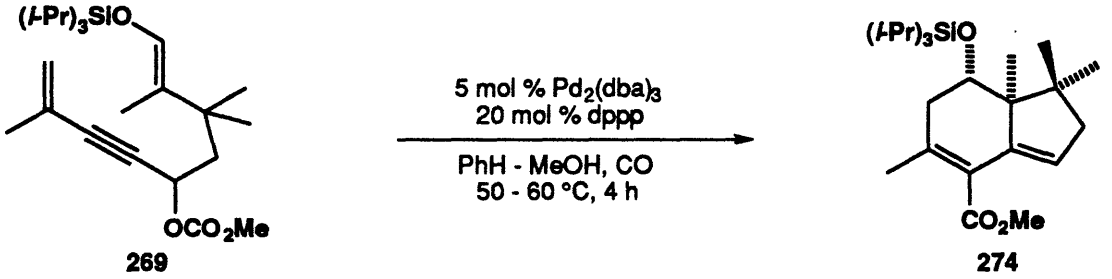



**256** **273**

124 This system is an ABX pattern and the J values are thus approximate.

chemistry assigned below.

Subjecting the TIPS substrate **269** to the conditions used above furnished bicyclic ester **274** in 47-61% yield. As with the previous reactions, at least one side product was present in the crude reaction mixture although the product was considerably easier to purify.




The configuration shown for **274** is based once again on the large (9.4 and 6.4 Hz)[125] coupling constants between the C-6 proton α to the siloxy group and the adjacent methylene group protons.

In conclusion, the tandem carbonylation and intramolecular Diels-Alder reaction can be used to stereoselectively construct a variety of bicyclic systems which are very similar in structure to the bicyclic core of glycineclepin A. Formation of the bicyclic ester systems is not as clean as the related reactions forming bicyclic amide or nitrile systems, and this leads to difficulty in the isolation of some of the ester products.

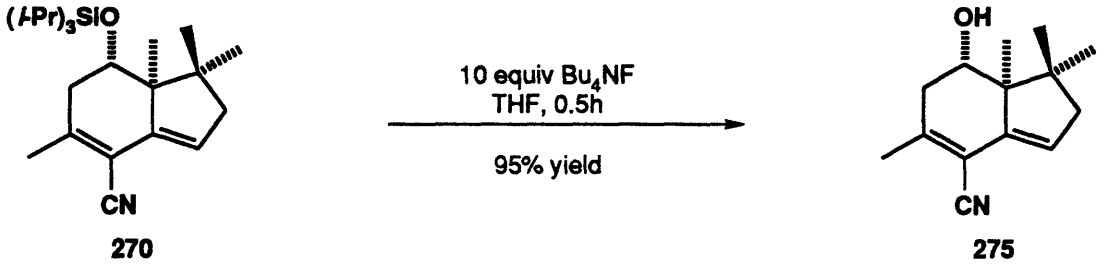
## Further Manipulation of Some CD-Ring Model Compounds.

While the problem of converting the amide, nitrile, or ester functions of the bicyclic products obtained above has been discussed, another issue that remains to be solved in the total synthesis involves the configuration of the hydroxy function. While both sets of epimers have been prepared by the conversion of substrates **263** and **266** to their respective bicyclic nitrile products, the ratio of stereoisomers obtained in the formation of

125 This system is an ABX pattern and the J values are thus approximate.

the TBDMS enol ether is poor and the separation procedure needed to isolate the desired isomer in the actual synthesis of glycinoeclepin A is not practical for a large-scale synthesis. While several solutions can be envisioned, it was decided to investigate the inversion of the wrong epimer by an oxidation / reduction protocol.

The TIPS protecting group was readily removed from the bicyclic products. Treatment of **270** with tetra-*n*-butylammonium fluoride gave alcohol **275** in 95% yield.




**270** **275**

This and other related alcohols were subjected to a variety of oxidation conditions on a small scale. Preliminary experiments using the Swern oxidation[126] indicate that if the desired ketone was formed, it appears unstable above -50 °C under these conditions. PCC oxidation[127] was not satisfactory as the initially formed product seems to decompose as the reaction proceeds. No reaction was observed upon reaction with either the Dess-Martin reagent[128] or barium manganate[129], and oxidation with TPAP[130] led to a complex mixture of products.

Thus, while a more extensive investigation is needed, it appears that the oxidation of the bicyclic alcohol systems is not trivial. As a result of this, no sample of the desired ketone was available to test whether reducing agents could effect the conversion to the epimer found in the glycinoeclepin A system.

126 For a review of oxidations by activated DMSO methods, see: Lee, T. V. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, 1991, Vol 7, p. 291.
127 For a review, see: Piancatelli, G.; Scettri, A.; D'Auria, M. *Synthesis*, **1982**, 245.
128 Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277.
129 For a review, see: Fatiadi, A. J. *Synthesis*, **1987**, 85.
130 For a review, see: Griffith, W. P.; Ley, S. V. *Aldrichimica Acta*, **1990**, *23*, 13.

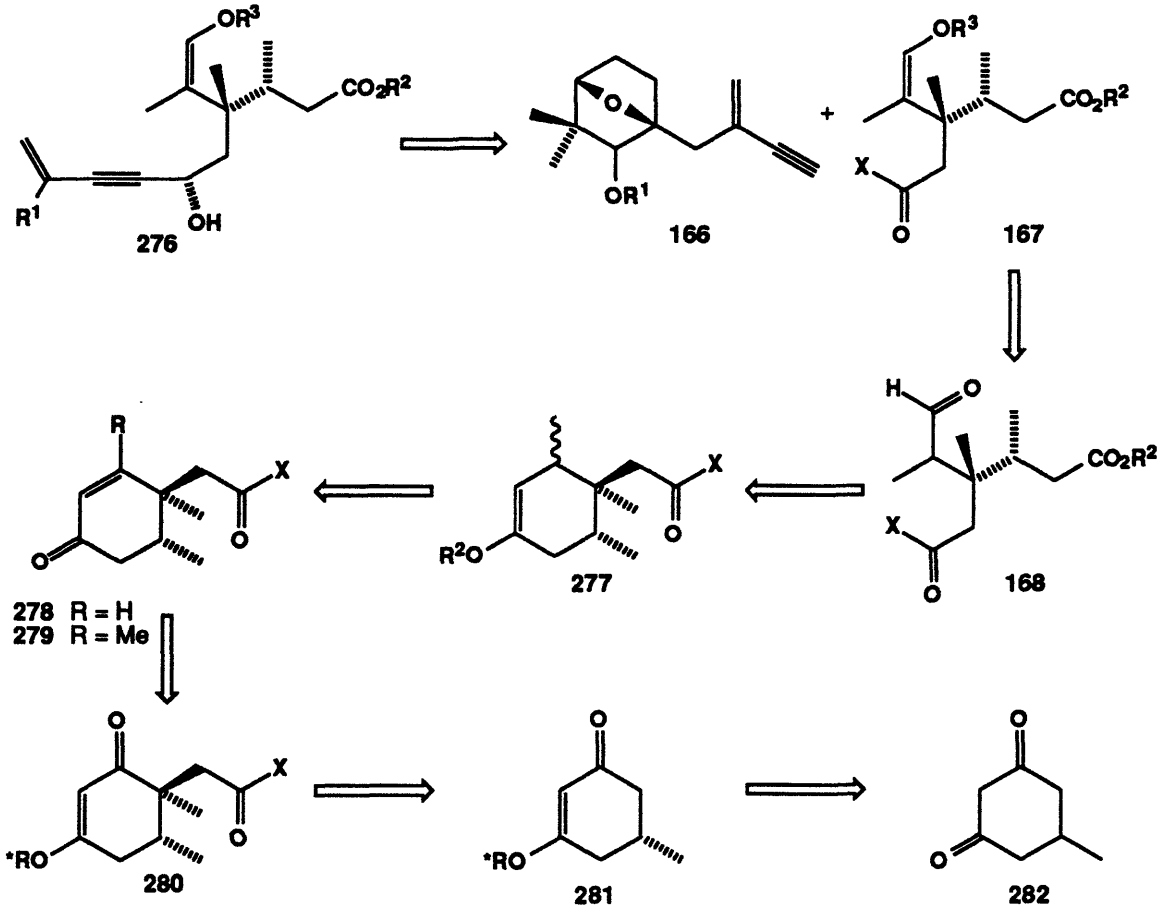
# CHAPTER 3

# STUDIES DIRECTED TOWARDS THE SYNTHESIS OF GLYCINOECLEPIN A

## Introduction

Having established the feasibility of the key step in our proposed total synthesis of glycinoeclepin A in C,D-ring system model studies, it was decided to set out on the long road towards glycinoeclepin A.

As discussed in Chapter 1 of this section, the key step would require propargylic alcohol **276** or a suitable derivative. Retrosynthetic analysis led us to conclude that the chiral vinologous ester **281** (R* = a chiral auxilliary group) was a suitable framework from



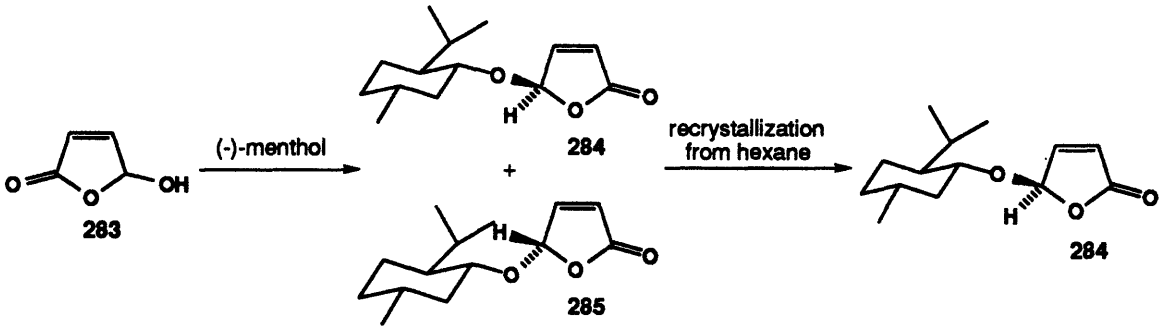
which to build the complete skeleton, including key stereogenic centers, of the D ring and its side chain.

Sequential Stork-Danheiser alkylation of enantiomerically pure **281** with methyl iodide and then an α-halo ester was expected to provide **280** with the required stereochemistry. Hydride reduction or addition of methyllithium would then furnish **278** and **279** after acidic workup, both of which could serve as precursors to the enol ether **277**. Oxidative cleavage and functional group manipulation would then lead to an intermediate **167** suitable for coupling to the enyne fragment **166**. Intermediate **276** was thus expected to be available in fewer than 10 steps, and it was hoped that the entire total synthesis could be accomplished in under 20 steps (in the longest linear sequence) according to this strategy. This would obviously be a significant improvement over the syntheses reported previously.

A number of routes can be imagined for the synthesis of key intermediate **168**, including several beginning with readily available optically active starting materials such as pulegone and 3-methylcyclohexanone. We decided, however, to focus our attention on approaches involving a novel resolution of the chiral vinylogous ester **281**. This approach has the merit that it does not add any steps to the synthetic plan since the vinylogous ester is required in any case for the Stork-Danheiser alkylation reaction, and the chiral auxilliary reagent R*OH would be released in the hydrolysis step **281** to **282**. In addition, the undesired diastereomeric form of **281** could in principle be completely recycled, since the hydrolysis should yield R*OH and the achiral diketone starting material.

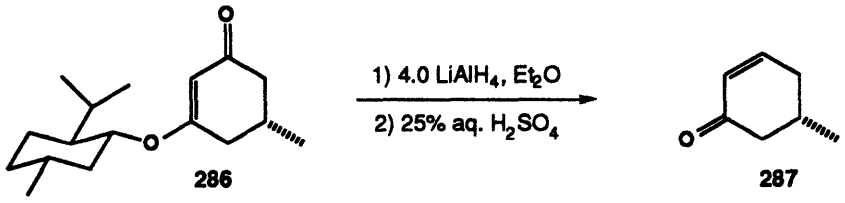
While this type of ß-alkoxycyclohexenone is well known, there are no previous reports of such compounds in which R* is acyclic or is a secondary alkyl group. Our first goal was to synthesize the compound **281** in which the chiral auxiliary is menthol. Indeed, menthol is readily available in both enantiomeric forms and its derivatives are often crystalline, making purification by recrystallization a viable option. For instance, Martel

has demonstrated that treatment of furanone **283** with either (+) or (-)-menthol provides the diastereomeric furanones **284** and **285** which can be separated by crystallization from *n*-hexane.[131]




## Results and Discussion

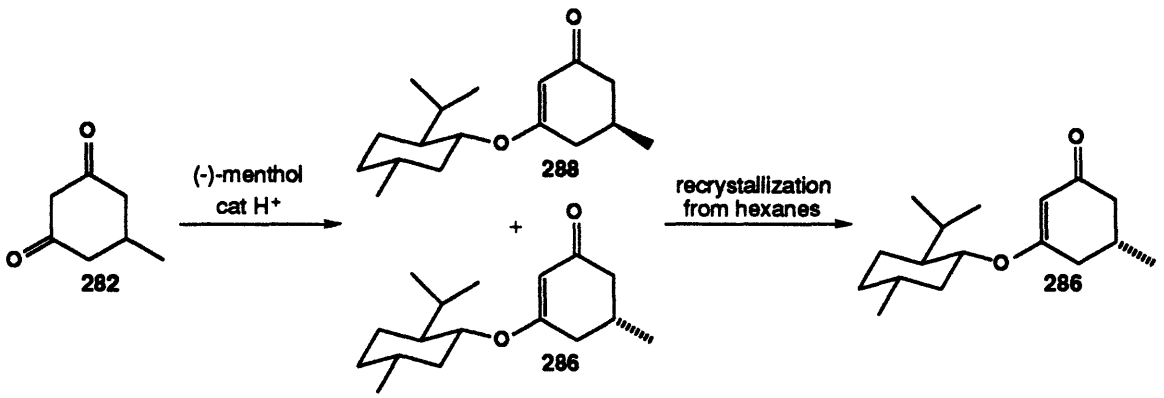
Preliminary studies by the author and J. Rivera showed that vinylogous esters **288** and **286** could be made by acid-catalyzed treatment of diketone **282** with (-)-menthol in refluxing benzene, with azeotropic removal of water. This mixture of two diastereomers was obtained as a solid and T. Zywietz was able to isolate **286**, after a total of 4 recrystallizations from hexanes, in highly enriched (ca. 96% ee) form. The absolute stereochemistry of this compound was determined by chemical degradation to **287** of known absolute stereochemistry and for which the optical rotation data is known.[132]



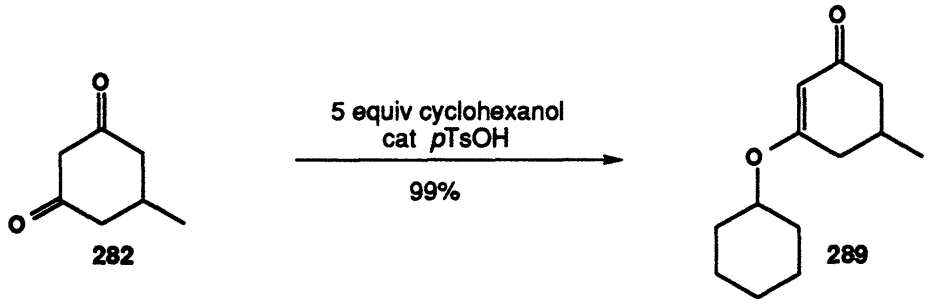

The undesired diastereoisomer is recovered enriched in the mother liquor. While there remains the need for optimization, this procedure should allow easy access to the

131 J. Martel, J. Tessier, J. P. Demoute (Roussel Ucalf), EP-B 23454, **1981**.
132 Oppolzer, W.; Petrzilka, M. *Helvet. Chim. Acta* **1978**, *61*, 2755.

required vinylogous ester. Noteworthy aspects of this resolution are that it would be carried out at a very early stage in the synthesis of glycinoeclepin A, a desirable feature since it is always more efficient to have low-yielding transformations early in a synthesis. Furthermore, the undesired diastereomer may be recycled readily by hydrolysis to regenerate the menthol chiral auxilliary and the achiral diketone **282**.




The next steps in the synthesis were first studied with racemic material since the achiral character of these early compounds would not affect the chemical outcome of the reactions. The model compound **289**, readily made in 94-99% from dione **282** and cyclohexanol, was the starting material for this first sequence.

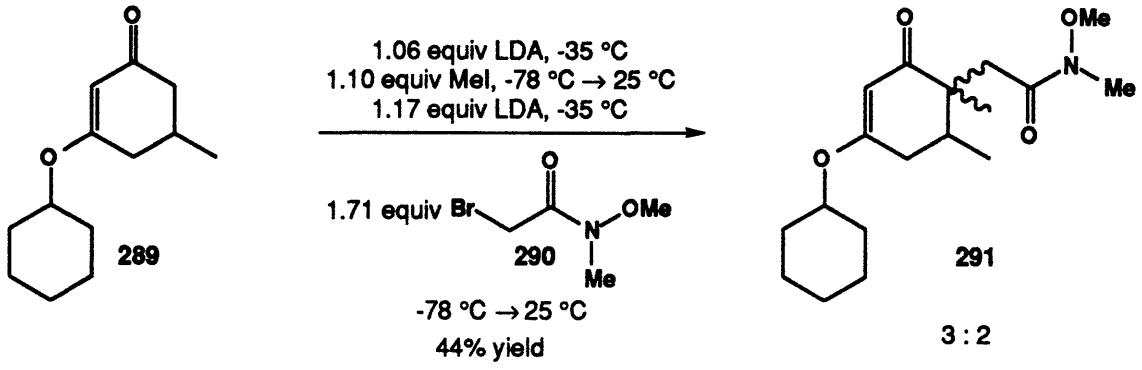



The first transformation to be carried out on **289** was a double alkylation by the procedure of Stork and Danheiser.[133] The order of addition of the reagents is critical to the relative stereochemistry of the substituents in the final product. It has been shown by

133 Stork, G.; Danheiser, R. L. *J. Org. Chem.* **1973**, *38*, 1775.

numerous investigators that for 3-alkoxycyclohexenones, the first electrophile to be added in the alkylation step ends up cis to the C-5 substituent in the final product.[134] The choice of alkylating partners is crucial in that the two carbon unit that is introduced will ultimately have to be reactive towards an acetylide. It was felt that bromide **290** would be an ideal alkylating agent since treatment of Weinreb amides with acetylides results in ynones.[135] If this transformation were successfully applied to the glycinoeclepin A synthesis, the resulting ketone function could then be reduced asymmetrically to provide the requisite chiral propargylic alcohol **276**.

Treatment of **289** with LDA and trapping of the resulting enolate with methyl iodide at -78 °C followed by warming to room temperature gave a dimethyl alkoxycyclohexenone intermediate. The reaction mixture was treated with more LDA to give the corresponding enolate which was then trapped with bromide **290**.[136] Two dialkylated products were produced in this reaction. Unfortunately, the yield[137] and stereoselectivity of this reaction was low, with one product formed in 14-17% yield and the other in 21-27% yield. The exact stereochemical identity of these two compounds was not determined.

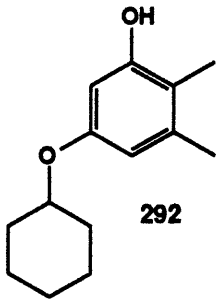



134 For example see: (a) Stork, G.; Danheiser, R. L.; Ganem, B. *J. Am. Chem. Soc.* **1973**, *95*, 3414. (b) Kozar, L.G.; Clark, R. D.; Heathcock, C. H. *J. Org. Chem.* **1977**, *42*, 1386.

135 For a review on nucleophilic addition to carboxylic acid derivatives, see: O'Neill. B. T. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, 1991, Vol 1, p 397.

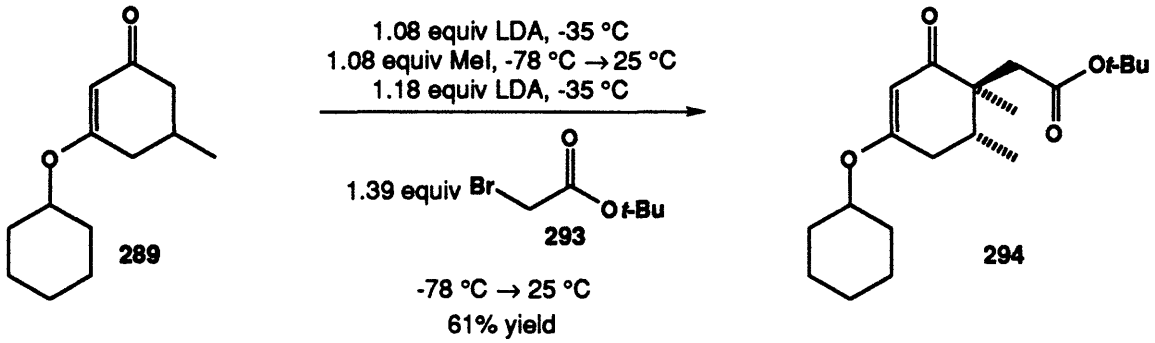
136 Jacobi, P. A.; Zheng, W. Z. *Tetrahedron Lett.* **1991**, *32*, 1279.

137 Weinreb amides have been shown to undergo side reactions in the presence of strong bases, see: Graham, S. L.; Scholz, T.H. *Tetrahedron Lett.* **1990**, *31*, 6269.




292

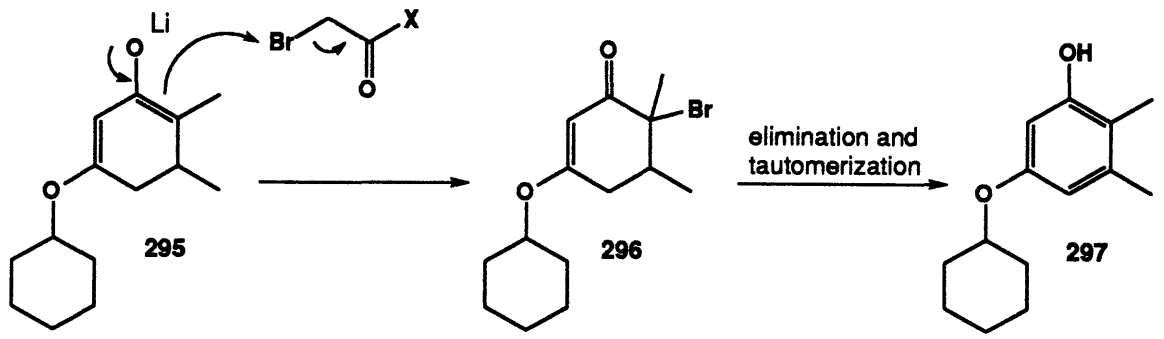
A side product of the reaction is phenol **292**. This side product was also produced (ca. 15%) when *t*-butyl bromoacetate was used as the second alkylating agent. In this case, however, only one doubly alkylated product, assumed to be the desired cis isomer **294** on the basis of literature precedent, was isolated in 56-61% yield. It was expected that the *t*-butyl ester function of **294** could be converted chemoselectively to the desired ynone at a later stage of the synthesis.



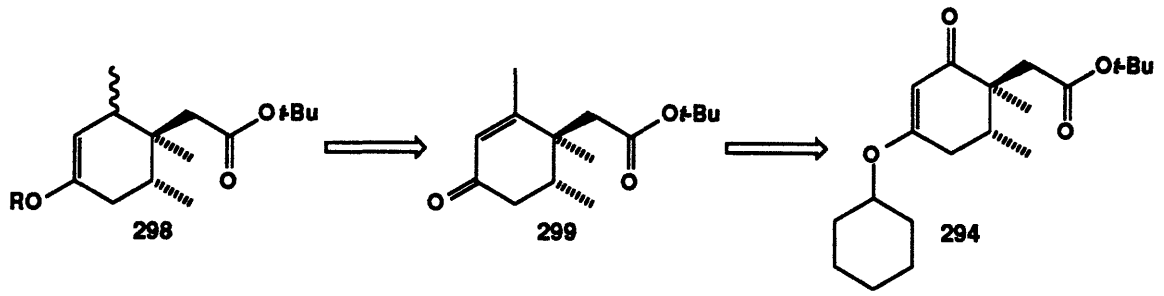

289 293 294

Changing the electrophile to the more reactive *t*-butyl iodoacetate resulted in the same outcome: 58% yield of the desired enone and a similar amount of phenol **292** was produced as determined by proton NMR analysis of the crude mixture. This side-product is most likely formed by halogenation of the enolate derived from **295**, followed by elimination of the bromide, and subsequent tautomerization.

With ester **294** in hand, we turned our attention to the addition of methyllithium followed by aqueous acid treatment which was expected to give the unsaturated ketone



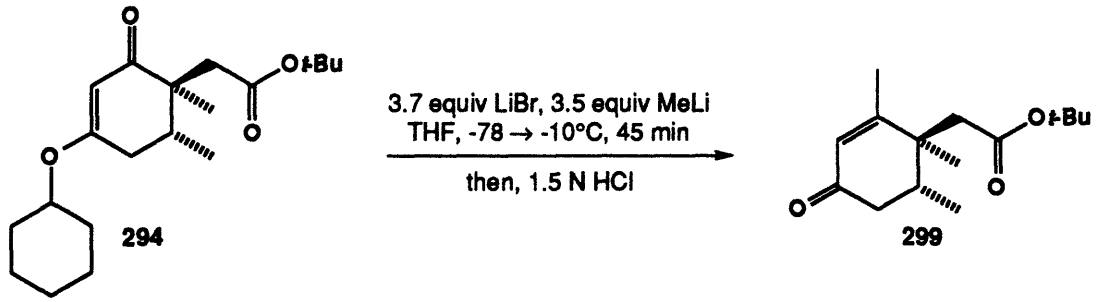

**299**. This enone was then expected to yield silyl enol ether **298**, upon 1,4-reduction with trapping of the resulting enolate.




Preliminary experiments quickly showed that ester **294** does not readily react with methyllithium or methylmagnesium halides. Several equivalents of methyllithium were required, and even then, significant amounts of starting material were recovered. The use of methyllithium with cerium chloride did not improve this reaction even though cerium nucleophiles are noted for their ability to add to enolizable substrates. Similarly, the reagent formed by adding methyllithium to titanium tetrachloride, a non-basic and highly selective Grignard analog[138] failed to add efficiently to the substrate. The problem seemed to be due to the presence of the enolizable ester side chain, but deprotonation of **294** with one equivalent of LDA followed by the addition of methyllithium did not offer improved results. After much experimentation, it was found that addition of approximately 4 equivalents of methyllithium, in the presence of approximately 4 equivalents of lithium

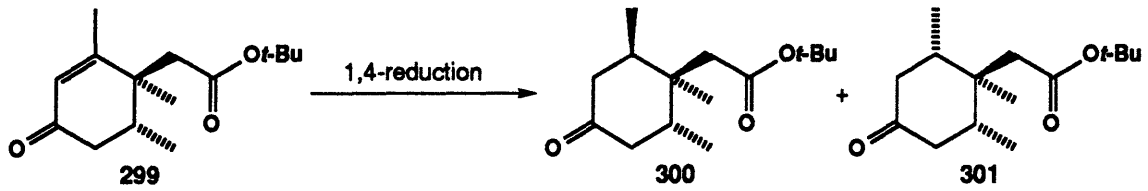
138 Reetz, M. T.; Kyung, S. H.; Hüllmann, M. *Tetrahedron* **1986**, *42*, 2931.

bromide gave the desired alcohol cleanly. Subsequent treatment of this alcohol with aqueous hydrochloric acid afforded enone **299** in 67-77% yield.




**294** **299**

The next step proved even more challenging. It requires the 1,4-reduction of hindered enone **299** and *in situ* trapping of the resulting enolate. Isolation of the saturated ketone is not an option since one isomer of this species is achiral. While this did not matter at this stage of the project, the reduction would need to be performed on a chiral substrate in the sequence leading to glycinoeclepin A and formation of ketone **301** would eradicate the asymmetric character that had been built up in the molecule.




**299** **300** **301**

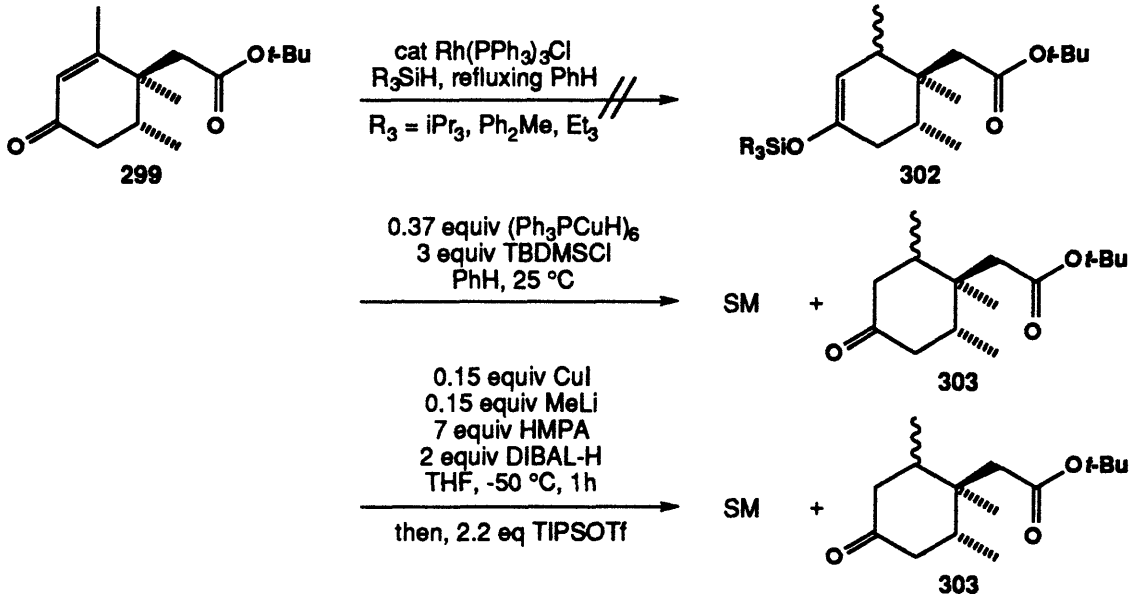
chiral achiral

A variety of methods were investigated to obtain silyl enol ether **298**.[139] Ojima's hydrosilylation procedure[140] using tris(triphenylphosphine)rhodium chloride (Wilkinson's catalyst) and silanes was not successful. Indeed, no reaction was observed with triisopropylsilane, diphenylmethylsilane, or triethylsilane in refluxing benzene. This appears to be due to the hindrance by bulky substituents at the position ß to the ketone

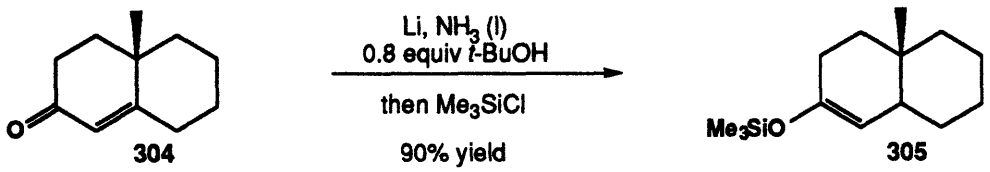
139 For a review on the partial reduction of enones and some applications towards the synthesis of silyl enol ethers, see: Keinan, E. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, 1991, Vol 8, p 523.

140 Ojima, I.; Kogure, T. *Organometallics* **1982**, *1*, 1390.

function. Use of the Stryker reagent,[141] (triphenylphosphine) copper hydride hexamer, with *t*-butyldimethylsilyl chloride had a similar outcome as only a trace of the saturated ketone was formed after several days at room temperature. Methylcopper in the presence of DIBAL-H and HMPA was found to lead to a partial 1,4-reduction of enone **299**, but the enolate intermediate could not be trapped by TIPSOTf.[142]



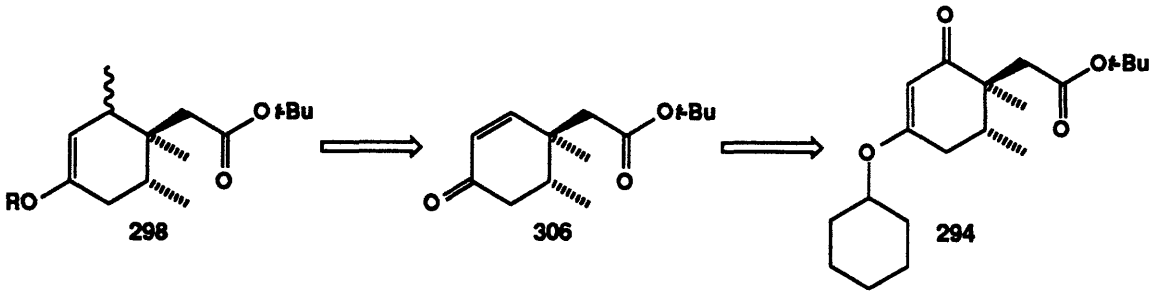

As steric hindrance seemed to prevent the desired transformation from taking place, an approach which has been shown to work on highly hindered enones was investigated next. Stork has showed that treatment of enone **304** with lithium in liquid ammonia in the presence of a proton donor affords the enolate resulting from 1,4-reduction. These enolates can be trapped to give the corresponding silyl enol ether **305**.[143]



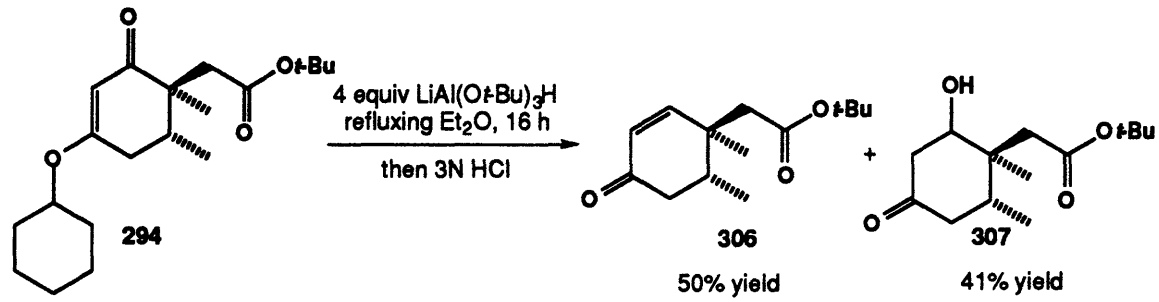

141 (a) Mahoney, W.S.; Brestensky, D. M.; Stryker, J. M. *J. Am. Chem. Soc.* **1988**, *110*, 291. and, (b) Brestensky, D. M.; Stryker, J. M. *Tetrahedron Lett.* **1989**, *30*, 5677.
142 Tsuda, T.; Hayashi, T.; Satomi, H.; Kawamoto, T.; Saegusa, T. *J. Org. Chem.* **1986**, *51*, 537.
143 Stork, G.; Singh, J. *J. Am. Chem. Soc.* **1974**, *96*, 6181.

Unfortunately, addition of approximately 2.5 equivalents of lithium to a solution of enone **299** in liquid ammonia and addition of TIPSOTf as described by Stork gave a complicated mixture of products, and consequently a new approach to the synthesis of silyl enol ether **298** had to be examined.

As outlined below, 1,4-addition of a methyl cuprate to enone **306**[144] and *in situ* trapping of the resulting enolate should provide silyl enol ether **298**. Enone **306** would be obtained by the chemoselective reduction of the vinologous ester function present in **294** and subsequent hydrolysis.



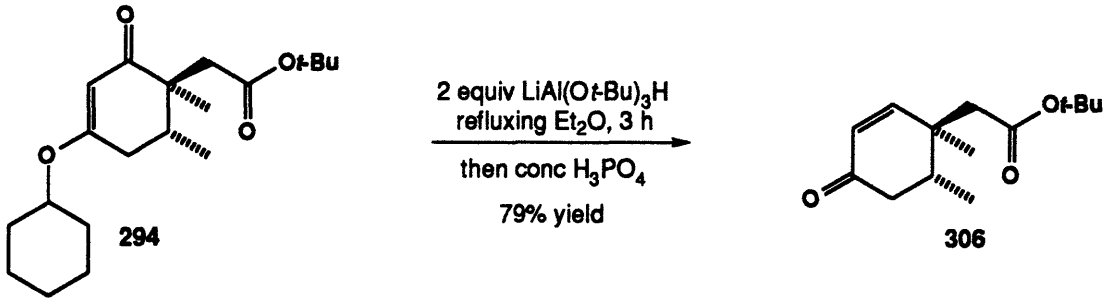

This first step was achieved by using either excess lithium borohydride or excess lithium tri-*t*-butoxyaluminohydride. The latter reagent led to clean reduction to give the intermediate vinylogous hemiacetal in nearly quantitative yield. The hydrolysis step, however, was unexpectedly stubborn as both the desired enone **306** and **307** were isolated upon treatment of the vinylogous hemiacetal intermediate with aqueous hydrochloric acid. It was found that the ratio of the two products depended on the amount of water present in



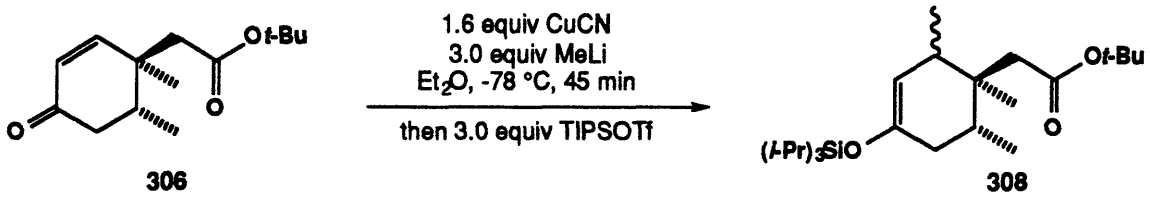

144 For a review on organocopper reagents, see: Lipshutz, B. H.; Sengupta, S. In *Organic Reactions*; Paquette, L. A. *et al*, Ed.; John Wiley & Sons; New York, 1992, Vol 41, p 135.

the system so that the more concentrated the acid, the more enone was formed.

The alcohol side product **307** was unusually stable to base. Eventually, it was found that quenching the reaction mixture, following reduction of vinologous ester **294**, with concentrated phosphoric acid afforded enone **306** in 79% yield. Repeating this experiment on a large scale (25 instead of 2.75 mmol) led to a decrease in yield (56%) as alcohol **307** was once again a major side product (23% yield). The *t*-butyl ester side chain was found to be stable to these conditions, but appeared to be cleaved if gaseous anhydrous hydrogen chloride was used.




Enone **306** reacted smoothly with the higher order methyl cuprate reagent and addition of TIPSOTf to the reaction mixture gave silyl enol ether **308** in 73-88% yield.




Further investigations are pending and while one preliminary cleavage of the silyl enol ether with ozone, followed by treatment with dimethylsulfide, has been attempted, none of the desired aldehyde has yet been isolated. Once this transformation is achieved, this aldehyde will be converted to a suitable silyl enol ether and chemoselective addition of acetylides to the *t*-butyl ester fuction will be investigated.

In summary, our model studies have established the feasibility of several alternative tandem / intramolecular cycloaddition strategies for the construction of the glycinoeclepin A C,D-ring system. As described in this chapter, we have also made significant progress towards the synthesis of the chiral key intermediate required for the application of this strategy to the total synthesis of glycinoeclepin A itself.

# PART III

## EXPERIMENTAL SECTION

**General Procedures.**

All reactions were performed in flame-dried glassware under a positive pressure of argon unless otherwise noted. Air and/or moisture sensitive reagents and solutions were transferred via syringe or cannula and were introduced into reaction vessels through rubber septa. Reaction mixtures were stirred magnetically unless otherwise noted. Reaction product solutions and chromatography fractions were concentrated using a Büchi rotary evaporator at approximately 20 mmHg unless otherwise indicated. Residual solvents were removed via a single stage vacuum pump at approximately 0.1 mmHg.

**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, dibromomethane, dichloromethane, diisopropylamine, 1,1,1,3,3,3-hexamethyldisilazane, methyl chloroformate, oxalyl chloride, 2,2,6,6-tetramethylpiperidine, triethylamine, triisopropyl chloride.

Distilled under nitrogen, argon, or vacuum from sodium benzophenone ketyl or dianion: benzene, diethyl ether, dimethyl sulfoxide, tetrahydrofuran, toluene, xylenes.

Distilled under argon, or vacuum: 2-methyl-1-buten-3-yne, triisopropylsilyl triflate, trimethylsilyl cyanide.

Other reagents were purified by the following methods: methyl iodide was passed through a short column of neutral alumina or distilled under argon from copper sulfate immediately prior to use. Methyltriphenylphosphonium bromide was dried at 100 °C (0.1 mmHg) for 12 h.

Alkyllithium and Grignard reagents were titrated in tetrahydrofuran with menthol using 1,10-phenanthroline as indicator.[145]

**Chromatography.**

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

Column chromatography (in a column or a separatory funnel) was performed using 230-400 mesh Merck or Baker silica gel.

**Instrumentation.**

Photolyses were performed with a 450 W medium pressure, quartz, mercury-vapor lamp manufactured by Canrad-Hanovia. A uranium absorption sleeve, immersion wells and reaction vessels manufactured by Ace Glass were used.

Melting points were determined with a Fisher-Johns melting point apparatus and are corrected, unless otherwise noted (calibrated using Fisher TherMetric standards) for the melting points reported in Part I and are uncorrected for the melting points reported in Part II. Boiling points are uncorrected.

Infrared spectra (IR) were recorded using a Perkin-Elmer 1320 grating or a Perkin-Elmer 1600 series FTIR spectrophotometer.

---

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

$^{1}H$ NMR spectra were recorded with a Varian XL-300 (300 MHz) spectrophotometer. Chemical shifts are expressed in parts per million (δ) downfield of tetramethylsilane.

$^{13}C$ NMR spectra were recorded on a Varian XL-300 (75 MHz) spectrophotometer. Chemical shifts are expressed in parts per million (δ) downfield of 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 spectrometer.

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

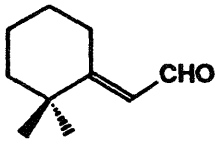

24 25

**2',2'-Dimethylcyclohexylidenacetaldehyde (25).**

A 500-mL, three-necked, round-bottomed flask equipped with an argon inlet adapter, a rubber septum, and a mechanical stirrer was charged with a solution of diisopropylamine (17 mL, 121 mmol) in 180 mL of THF and cooled at 0 °C while *n*-butyllithium solution (2.62 M in hexanes, 44 mL, 115 mmol) was added dropwise by syringe over 10 min. After 10 min, 2-trimethylsilylacetaldehyde *tert*-butylimine[18] (19.8 g, 115 mmol) was added dropwise at 0 °C over 10 min to the straw-colored solution. The reaction mixture was stirred at 0 °C for 30 min, then cooled at -78 °C while a solution of 2,2-dimethylcyclohexanone (**24**, 11.81 g, 93.6 mmol) in 20 mL of THF was added dropwise via cannula over 10 min (with a 5 mL THF rinse). The resulting mixture was allowed to warm to 25 °C, stirred for 12 h at that temperature, then diluted with 20 mL of water and acidified to pH 4.5 by the addition of oxalic acid (ca. 8 g). After 1 h, 300 mL of water was added, and the aqueous phase was separated and extracted with two 150-mL portions of diethyl ether. The combined organic phases were washed with 250 mL of saturated aqueous $NaHCO_3$ solution and 150 mL of saturated aqueous NaCl solution, dried over $Na_2SO_4$, filtered, and concentrated to afford a brown oil. Purification by distillation (86-94 °C, 10 mmHg) afforded 11.28 g (79%) of aldehyde **25** (a ca.4:1 mixture of the α,β and the β,γ isomers) as a colorless oil, with spectral data consistent with that previously reported for this compound.[21] The product could also be purified by column chromatography on silica gel (elution with 1% ethyl acetate / petroleum ether) in which case no isomerization to the β,γ isomer was observed.

IR (thin film): 2980, 2950, 2880, 2760, 1720, 1680, 1620, 1460, 1395, 1375, 1200, 1160, 1060, 990, and 745 $cm^{-1}$

| | |
|---|---|
| $^{1}H$ NMR (300 MHz, $CDCl_3$): | 9.97 (d, J = 8 Hz, 1H), 5.80 (d, J = 8 Hz, 1H), 2.69 (m, 2H), 1.57 (m, 4H), 1.43 (m, 2H), and 1.04 (s, 6H) |
| $^{13}C$ NMR (75 MHz, $CDCl_3$): | 191.6, 174.3, 123.2, 41.4, 38.0, 28.0, 27.2, 25.4, and 21.5 |



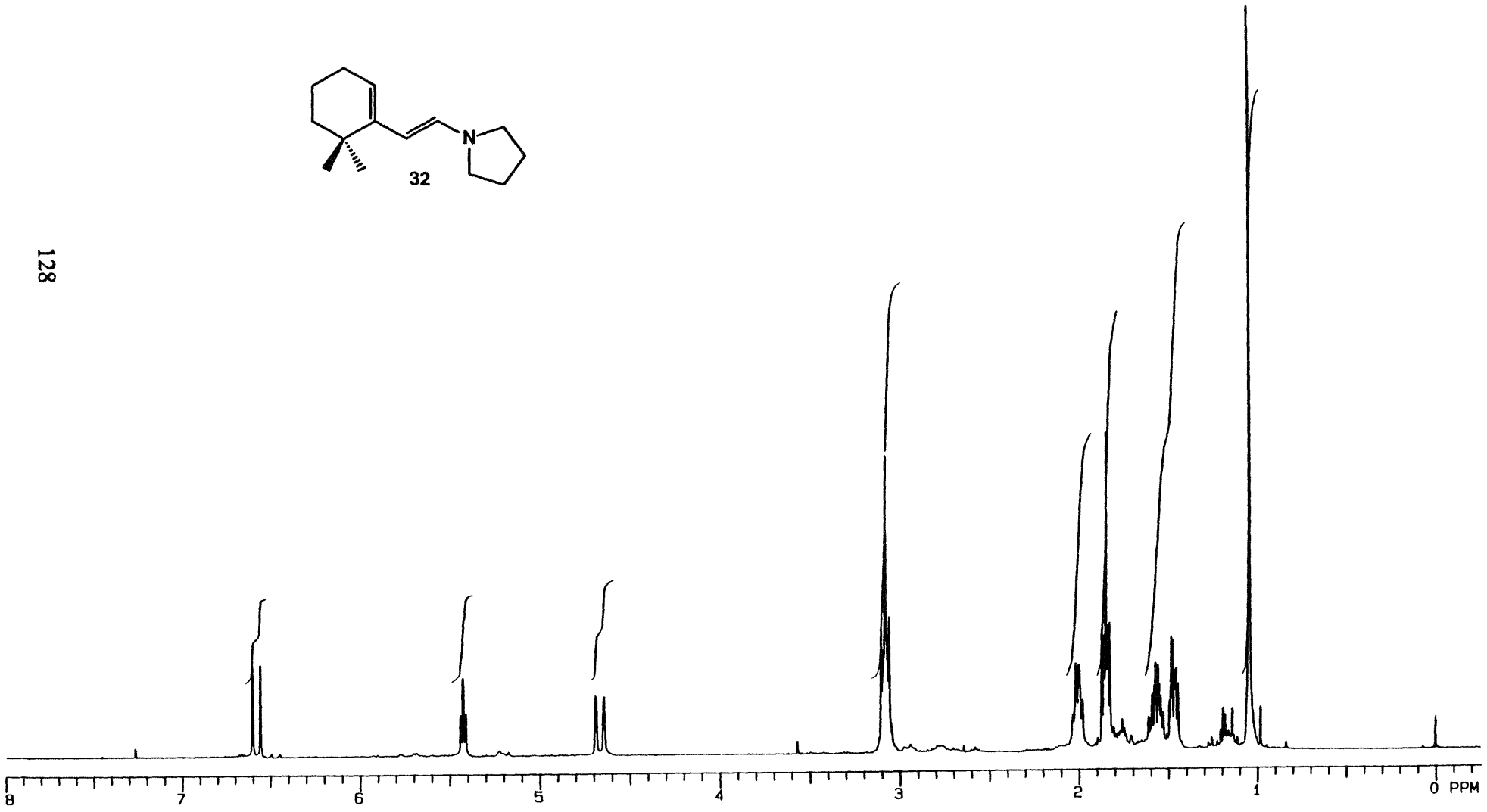

25

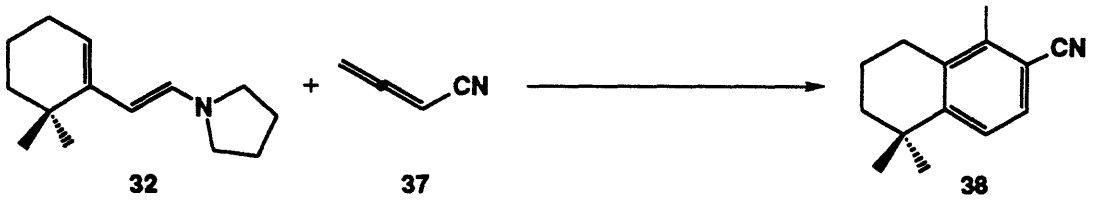

25 32

**(*E*)-2-(6',6'-Dimethylcyclohex-1'-enyl)ethenylpyrrolidine (32).**

A 100-mL, round-bottomed flask equipped with a reflux condenser fitted with an argon inlet adapter was charged with aldehyde **25** (a ca. 4:1 mixture of the α,β and the β,γ isomers) (4.444 g, 29.19 mmol), pyrrolidine (3.0 mL, 36 mmol), and 40 mL of toluene. The resulting solution was heated at 90 °C for 1.5 h and then concentrated under reduced pressure. The remaining solvent and starting material were removed by Kugelrohr distillation (bath temperature 65 °C, 0.25 mmHg), and Kugelrohr distillation of the residual brown oil (bath temperature 110 °C, 0.25 mmHg) afforded 5.466 g (92%) of dienamine **32** as a yellow oil.

| | | |
|---|---|---|
| IR ($CHCl_3$): | 2952, 2929, 2867, 1760, 1670, 1629, 1459, 1367, 1307, 1157, 1124, 1005, 931, and 880 $cm^{-1}$ | |
| $^1H$ NMR (300 MHz, $CDCl_3$): | 6.58 (d, J = 14 Hz, 1H), 5.43 (t, J = 4 Hz, 1H), 4.67 (d, J = 14 Hz, 1H), 3.06-3.11 (m, 4H), 2.01 (dt, J = 4, 6 Hz, 2H), 1.83-1.87 (m, 4H), 1.45-1.61 (m, 4H), and 1.05 (s, 6H) | |
| $^{13}C$ NMR (75 MHz, $CDCl_3$): | 144.1, 134.7, 114.4, 97.3, 48.9, 39.5, 33.7, 28.8, 26.3, 25.0, and 19.5 | |
| HRMS: | Calcd for $C_{14}H_{23}N$: | 205.1831 |
| | Found: | 205.1829 |


N
32
8
7
6
5
4
3
2
1
0 PPM

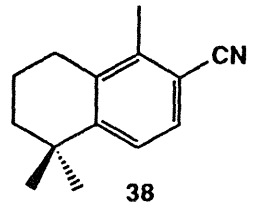



32 37 38

**2-Cyano-1,5,5-trimethyl-5,6,7,8-tetrahydronaphthalene (38).**

A 50-mL, round-bottomed flask fitted with a septum was charged with dienamine **32** (0.500 g, 2.43 mmol), 10 mL of toluene, and cyanoallene[31] (**37**, 0.400 g, 6.15 mmol). The septum was replaced with an argon inlet adapter and the reaction mixture was stirred at 25 °C for 15 h after which 1.5 g of silica gel (TLC grade, E. Merck PF-254) was added. The resulting slurry was heated at 60 °C for 3 h, allowed to cool to room temperature, and then filtered using ca. 50 mL of hexane (to wash the silica gel until a colorless filtrate was obtained). Concentration and purification by column chromatography on silica gel (gradient elution with 0-1% ethyl acetate / hexanes) afforded 0.238 g (49%) of nitrile **38** as an off-white solid (mp 78.5-79.5 °C).

| | |
|---|---|
| IR ($CHCl_3$): | 2930, 2860, 2215, 1585, 1475, 1450, 1410, 1380, 1360, 1280, 1260, 1210, and 820 $cm^{-1}$ |
| $^1H$ NMR (300 MHz, $CDCl_3$): | 7.39 (d, J = 8 Hz, 1H), 7.28 (d, J = 8 Hz, 1H), 2.63 (t, J = 6 Hz, 2H), 2.42 (s, 3H), 1.82-1.91 (m, 2H), 1.62-1.66 (m, 2H), and 1.29 (s, 6H) |
| $^{13}C$ NMR (75 MHz, $CDCl_3$): | 151.2, 140.2, 136.1, 129.3, 124.9, 119.1, 109.9, 38.0, 34.4, 31.5, 27.8, 18.9, and 18.0 |
| Elemental Analysis: | Calcd for $C_{14}H_{17}N$: C, 84.37; H, 8.60; N, 7.03<br>Found: C, 84.47; H, 8.66; N, 7.06 |




38

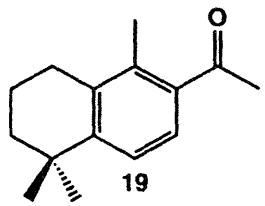

38 19

**1-(1,5,5-Trimethyl-5,6,7,8-tetrahydro-2-naphthoyl)ethanone (19).**

A 10-mL, round-bottomed flask equipped with a reflux condenser fitted with an argon inlet adapter was charged with a solution of nitrile **38** (0.523 g, 2.62 mmol) in 3.5 mL of diethyl ether. Methylmagnesium bromide (3.0 M in diethyl ether, 1.4 mL, 4.2 mmol) was added rapidly by syringe and the resulting solution was heated at reflux for 72 h. The reaction mixture was then cooled to room temperature and poured into a mixture of 60 mL of diethyl ether, 50 mL of ice-water, and 50 mL of 10% aqueous HCl. The aqueous layer (together with the insoluble material suspended at the interface of the two phases) was separated and transferred to a 250-mL, round-bottomed flask equipped with a reflux condenser. This mixture was heated at reflux for 1 h, allowed to cool to room temperature, and then extracted with four 25-mL portions of diethyl ether. The combined organic phases were washed with 25 mL of saturated aqueous $NaHCO_3$ and 25 mL of saturated aqueous NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford 0.609 g of a light brown solid. Column chromatography on silica gel (gradient elution with 0-50% benzene / hexanes) furnished 0.549 g of a cream-colored solid. Recrystallization from hot aqueous methanol (15:1 MeOH-$H_2O$) yielded (in two crops) 0.510 g (90%) of ketone **19** as colorless plates (mp 79.5-80.5 °C).

| | |
|---|---|
| IR (thin film): | 2930, 2870, 1675, 1585, 1440, 1400, 1380, 1350, 1270, 1245, 1130, 1060, 985, and 950 $cm^{-1}$ |
| $^1H$ NMR (300 MHz, $CDCl_3$): | 7.37 (d, J = 8 Hz, 1H), 7.25 (d, J = 8 Hz, 1H), 2.65 (t, J = 6 Hz, 2H), 2.54 (s, 3H), 2.31 (s, 3H), 1.80-1.88 (m, 2H), 1.60-1.66 (m, 2H), and 1.29 (s, 6H) |

| | | |
|---|---|---|
| $^{13}C$ NMR (75 MHz, $CDCl_3$): | 203.6, 149.2, 137.1, 136.3, 135.3, 125.3, 123.8, 38.2, 34.3, 31.7, 30.3, 28.0, 19.4, and 16.4 | |
| Elemental Analysis: | Calcd for $C_{15}H_{20}O$: | C, 83.29; H, 9.32 |
| | Found: | C, 83.43; H, 9.12 |




19

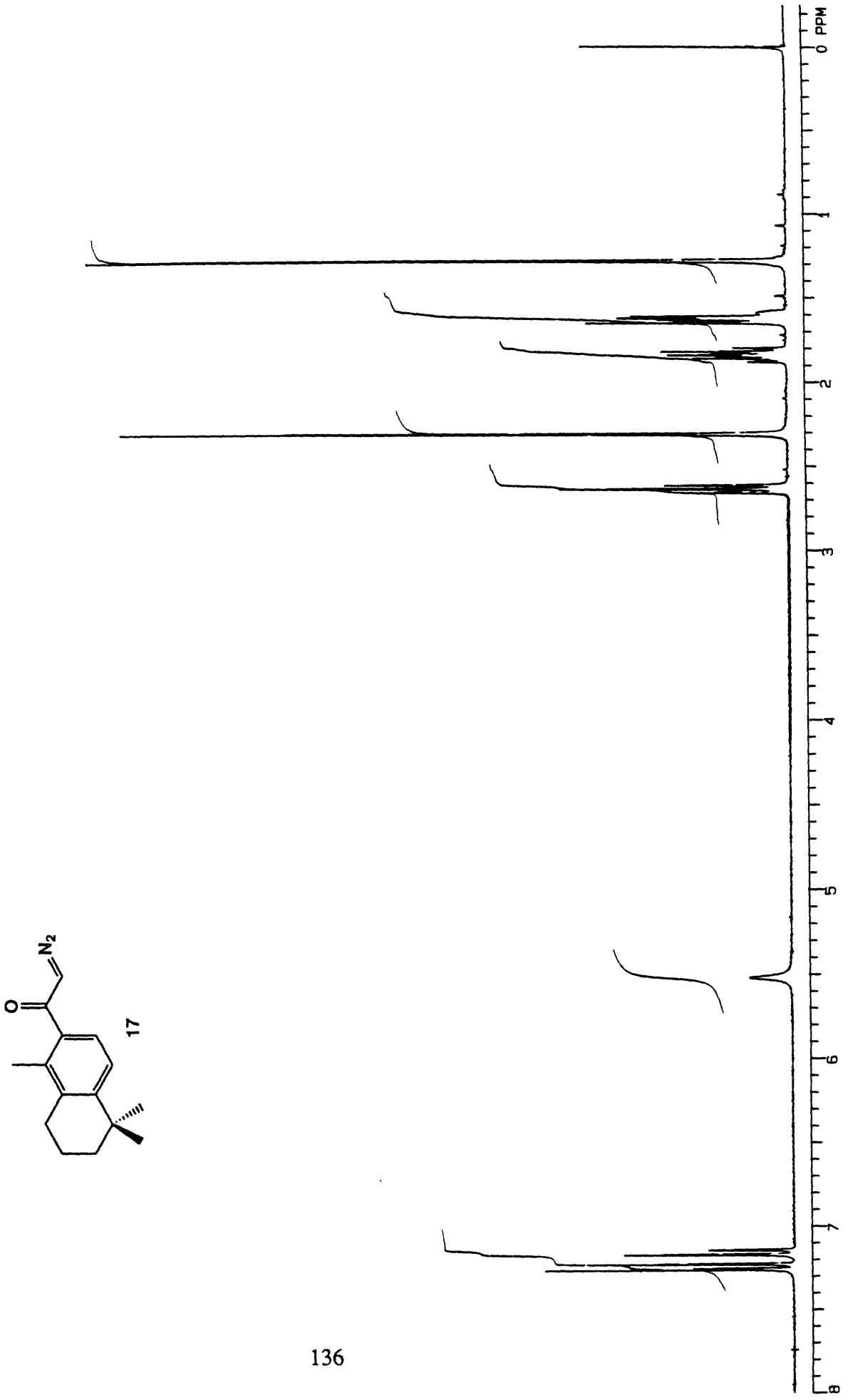

19 17

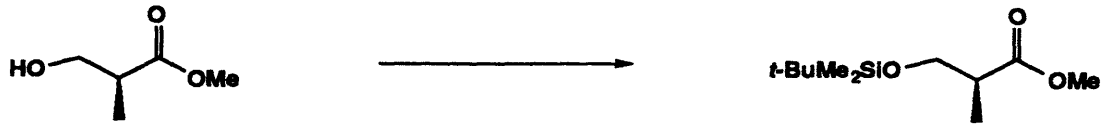
**2-Diazo-1-(1,5,5-trimethyl-5,6,7,8-tetrahydro-2-naphthoyl)-1-ethanone (17).**

A 25-mL, two-necked, round-bottomed flask equipped with an argon inlet adapter and a rubber septum was charged with a solution of 1,1,1,3,3,3-hexamethyldisilazane (1.43 mL, 6.78 mmol) in 6 mL of THF and then cooled at 0 °C while *n*-butyllithium solution (2.62 M in hexanes, 2.52 mL, 6.60 mmol) was added rapidly dropwise by syringe. After 10 min, the resulting solution was cooled at -78 °C, and a solution of methyl ketone **19** (1.298 g, 6.000 mmol) in 6 mL of THF was added dropwise via cannula (with a 2 mL THF rinse). The reaction mixture was stirred at -78 °C for 30 min, and then 2,2,2-trifluoroethyl trifluoroacetate (0.96 mL, 7.2 mmol) was added rapidly by syringe in one portion. After 10 min, the reaction mixture was poured into a separatory funnel containing 40 mL of 5% HCl solution and 40 mL of diethyl ether. The aqueous phase was extracted with 40 mL of diethyl ether and the combined organic phases were washed with 25 mL of saturated aqueous NaCl solution, dried over $Na_2SO_4$, filtered and concentrated to provide a light brown oil which was immediately dissolved in 6 mL of $CH_3CN$ and transferred to a 25-mL round-bottomed flask fitted with a rubber septum. Water (0.105 mL, 0.105 g, 5.83 mmol) and triethylamine (1.25 mL, 8.97 mmol) were added, and a solution of methanesulfonyl azide (1.095 g, 9.042 mmol) in 2 mL of $CH_3CN$ was added dropwise via cannula over 1 min. The resulting yellow solution was stirred at 25 °C for 3.25 h and then poured into a separatory funnel containing 25 mL of 5% NaOH solution and 70 mL of diethyl ether. The organic phase was separated, washed with two 25-mL portions of 5% NaOH solution, three 25-mL portions of water, and 25 mL of saturated aqueous NaCl solution, dried over $Na_2SO_4$, filtered, and concentrated.

Column chromatography on silica gel (elution with 5% ethyl acetate / hexanes) furnished 1.363 g (94%) of diazo ketone **17** as a yellow solid (mp 42.5-43 °C).

| | |
|---|---|
| IR (thin film): | 3100, 2920, 2880, 2110, 1620, 1460, 1410, 1350, 1290, 1270, 1235, 1200, 1145, 1120, 1060, 1015, 835, 800, and 725 $cm^{-1}$ |
| $^1H$ NMR (300 MHz, $CDCl_3$): | 7.24 (d, J = 8 Hz, 1H), 7.16 (d, J = 8 Hz, 1H), 5.42 (br s, 1H), 2.63 (t, J = 7 Hz, 2H), 2.31 (s, 3H), 1.80-1.86 (m, 2H), 1.61-1.65 (m, 2H), and 1.28 (s, 6H) |
| $^{13}C$ NMR (75 MHz, $CDCl_3$): | 191.5, 148.8, 136.3, 136.0, 134.3, 124.1, 124.0, 56.2, 37.9, 33.9, 31.3, 27.6, 18.9, and 15.7 |
| UV $\lambda_{max}$ ($CCl_4$): | 262 ($\varepsilon$= 12,300) and 285 (sh) |
| Elemental Analysis: | Calcd for $C_{15}H_{18}N_2O$: C, 74.60; H, 7.41; N, 11.42<br>Found: C, 74.35; H, 7.49; N, 11.56 |


O
N2
17
0 PPM
1
2
3
4
5
6
7
8

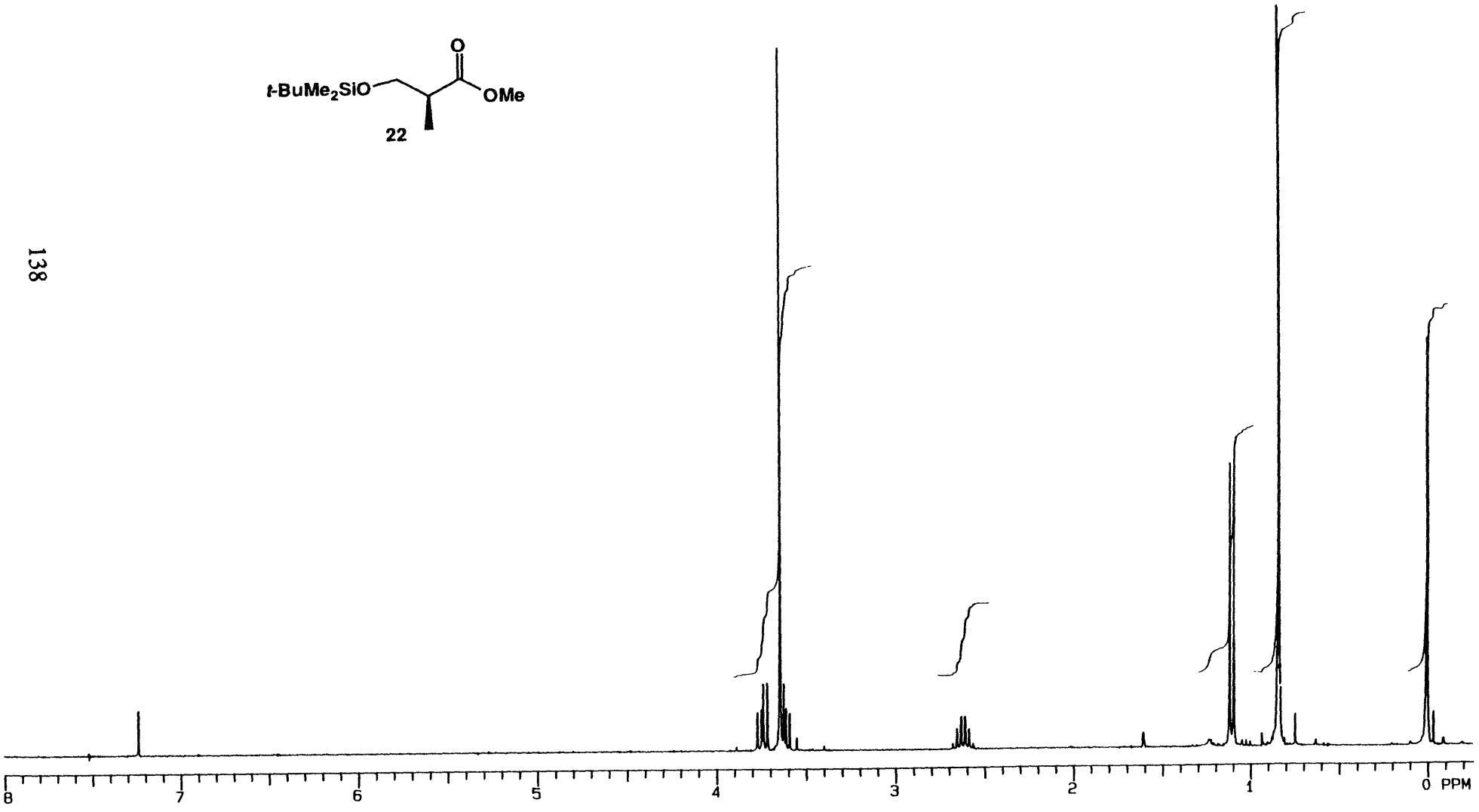



23 22

**(S)-(+)-Methyl-3-*tert*-butyldimethylsilyloxy-2-methylpropionate (22).**

A 250-mL, three-necked, round-bottomed flask equipped with an argon inlet adapter, a rubber septum, and a glass stopper was charged with (S)-(+)-methyl-3-hydroxy-2-methylpropionate (**23**, 11.81 g, 100.0 mmol) and 60 mL of dichloromethane. This solution was cooled at 0 °C while imidazole (total: 16.34 g, 240.0 mmol) and *tert*-butyldimethylsilyl chloride (total: 18.09 g, 120.0 mmol) were added alternately in portions over the course of 30 min. The ice bath was removed, and the mixture was stirred at room temperature for 24 h and then poured into 100 mL of diethyl ether and 150 mL of saturated aqueous NaCl solution. The two phases were separated and the aqueous layer extracted with three 100-mL portions of diethyl ether. The combined organic phases were washed with four 200-mL portions of water and with 200 mL of saturated aqueous NaCl solution, dried over $Na_2SO_4$, filtered and concentrated to give a colorless oil. Filtration through 150 g of silica gel (elution with 5% ethyl acetate / hexanes) afforded 22.68 g (97%) of **22** as a colorless oil. $[\alpha]_D$=+15.5 ° (c=1.25, $CHCl_3$)

| | | |
|---|---|---|
| IR (thin film): | 3970, 3950, 3880, 1750, 1480, 1470, 1440, 1400, 1370, 1265, 1205, 1185, 1100, 1065, 1030, 1010, 995, 845, and 785 $cm^{-1}$ | |
| $^1H$ NMR (300 MHz, $CDCl_3$): | 3.59-3.77 (m, 2H), 3.62 (s, 3H), 2.63 (m, 1H), 1.11 (d, J = 7 Hz, 3H), 0.82 (s, 9H), and 0.00 (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 | |
| HRMS: | Calcd for $C_{10}H_{21}O_2Si$ ($M^+$-OMe): | 201.1311 |
| | Found: | 201.1310 |


t-BuMe2SiO
O
OMe
22
8
7
6
5
4
3
2
1
0 PPM

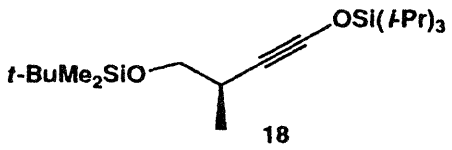

**2-((S)-(+)-1-*tert*-Butyldimethylsilyloxy-2-propyl)-1-triisopropylsilyloxy-acetylene (18).**

A 1-L, 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 (3.24 mL, 46.2 mmol) in 90 mL of THF and cooled to -78 °C in a dry ice-acetone bath.

A 250-mL, round-bottomed flask was charged with a solution of 2,2,6,6-tetramethylpiperidine (9.0 mL, 53 mmol) in 90 mL of THF and cooled at 0 °C while a *n*-butyllithium solution (2.63 M in hexanes, 19.5 mL, 51.3 mmol) was added dropwise over 15 min. The lithium tetramethylpiperidide solution was stirred at 0 °C for 15 min, then cooled to -78 °C and transferred via cannula into the dibromomethane solution over 10 min. The resulting bright yellow solution was stirred at -78 °C for 15 min. A precooled (-78 °C) solution of silyl ester **22** (5.01 g, 21.6 mmol) in 90 mL of THF was added via cannula dropwise over 10 min (with a 20 mL THF rinse), and the orange solution was stirred for 20 min at -78 °C. *n*-Butyllithium solution (2.62 M in hexanes, 40 mL, 105 mmol) was added via syringe over 15 min, the bath was removed, and the reaction mixture was stirred at 25 °C for 1 h. The orange / brown solution was cooled at -78 °C while a precooled (-78 °C) solution of triisopropylsilyl chloride (39.0 mL, 183 mmol) in 90 mL of THF was added via cannula over 15 min (with a 10 mL THF rinse). The dry ice-acetone bath was replaced with an ice bath and the reaction mixture was stirred at 0 °C for 6.5 h. The reaction mixture was poured into 150 mL of hexanes and 150 mL of saturated aqueous $NaHCO_3$ solution. The two phases were separated and the aqueous layer was extracted with two 150-mL portions of hexanes. The combined organic phases were washed with 250 mL of saturated aqueous $NaHCO_3$ solution, 250-mL of water, and

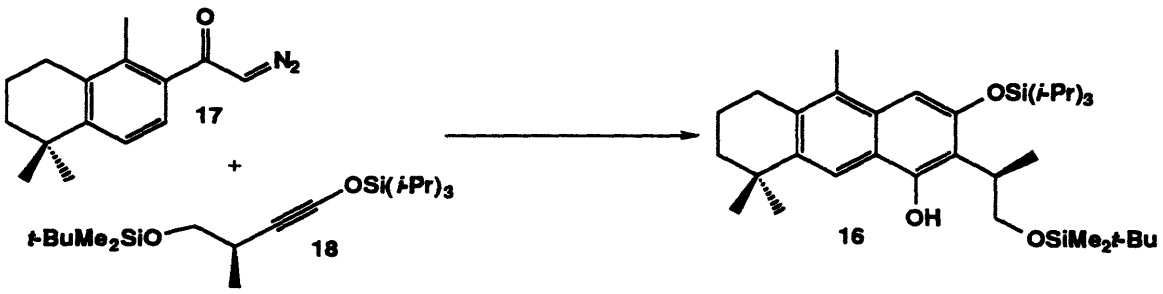
250 mL of saturated aqueous NaCl solution, dried over $Na_2SO_4$, filtered, and concentrated initially at 20 mmHg, then at 0.1 mmHg overnight. Approximately 10 mL of material was distilled off (bath temperature 50 °C, 0.1 mmHg) and the resulting brown oil was further concentrated at 0.007 mmHg to give 12.7 g of material. This material was purified in 0.4-0.5 g batches by rapid filtration through 4 g plugs of silica gel to give 4.95 g (ca. 95% purity) of **18** (59% yield) as a colorless oil.

| | |
|---|---|
| IR (thin film): | 2960, 2880, 2290, 1570, 1490, 1465, 1435, 1410, 1360, 1240, 1220, 1190, 1140, 1115, 890, 860, 840, 780, and 680 $cm^{-1}$ |
| $^1H$ NMR (300 MHz, $CDCl_3$): | 3.60 (dd, J = 10, 5 Hz, 1H), 3.31 (appar t, J = 10 Hz, 1H), 2.44 (m, 1H), 1.25 (m, 3H), 1.11 ( d, J = 6 Hz, 18H), 1.10 (d, 3H), 0.89 (s, 9H), 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<br>Found: 313.2019 |


t-BuMe2SiO
OSi(i-Pr)3

18


8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0 PPM
6.2
5.7
4.2
30.4
178.0
69.3
32.1

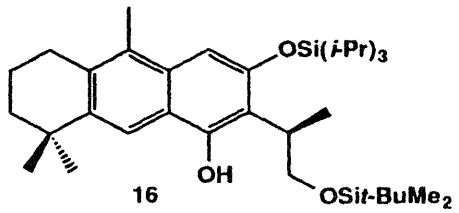



**2-((R)-1-*tert*-Butyldimethylsilyloxy-2-propyl)-3-triisopropylsilyloxy-8,8,10-trimethyl-5,6,7,8-tetrahydroanthr-1-ol (16).**

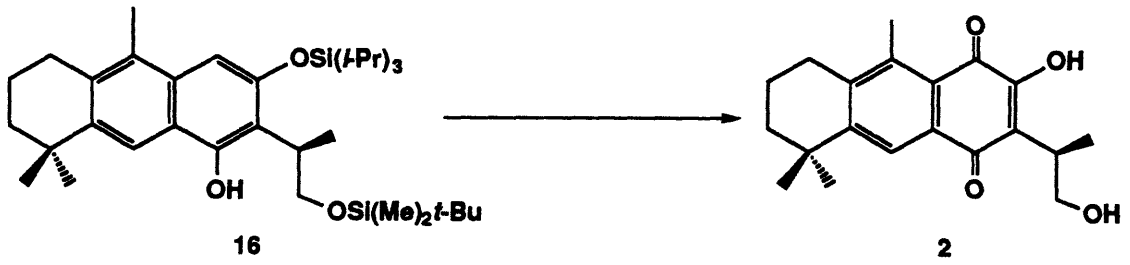
A solution of α-diazo ketone **17** (0.200 g, 0.825 mmol) and silyloxyacetylene **18** (1.84 g, 4.95 mmol) in 40 mL of benzene was divided into four portions of equal volume and transferred into four Pyrex® tubes (15 mm ID x 25 cm) fitted with rubber septa. Each solution was degassed by three freeze-pump-thaw cycles at -196 °C (≤0.5 mmHg), and the reaction tubes were then placed around a 450 W Hanovia® lamp in a water bath. The reaction tubes were irradiated for 2 h while keeping the temperature at ~20 °C. A second portion of α–diazo ketone (0.050 g, 0.21 mmol per tube, for a total of 0.400 g, 1.65 mmol) was then added (effervescence!) and the reaction flasks were again degassed (one freeze-pump-thaw cycle at -196 °C, ≤0.5 mmHg) and irradiated for another 15 h. The contents of the tubes were combined and concentrated to afford a brown oil. Column chromatography on silica gel (gradient elution with 0-5% $CHCl_3$ / hexanes) gave 0.540 g of unreacted silyloxyacetylene **18** and 0.617 g (64%) of the aromatic annulation product **16** as a white solid (mp 55-57 °C); $[\alpha]_D^{25}$ = -8.9° ($CHCl_3$, c=0.67).

| | |
|---|---|
| IR ($CHCl_3$): | 3190, 2940, 2860, 1625, 1590, 1460, 1405, 1380, 1360, 1255, 1135, 1085, 1000, and 880 $cm^{-1}$ |
| $^1H$ NMR (300 MHz, $CDCl_3$): | 9.66 (s, 1H), 8.15 (s, 1H), 6.81 (s, 1H), 4.01 (d, J = 2.5 Hz, 2H), 3.91 (m, 1H), 2.86 (t, 6 Hz, 2H), 2.40 (s, 3H), 1.84-1.93 (m, 2H), 1.65-1.70 (m, 2H), 1.40 (s, 6H), 1.39 (d, J = 7 Hz, 3H) 1.37 (m, 3H), 1.13 (d, J = 7 Hz, 18H), 0.98 (s, 9H), 0.19 (s, 3H), and 0.14 (s, 3H) |

| | | |
|---|---|---|
| $^{13}C$ NMR (75 MHz, $CDCl_3$): | 152.5, 151.7, 141.1, 132.9, 130.8, 128.1, 120.7, 117.9, 116.6, 100.8, 69.4, 39.1, 34.5, 32.8, 32.7, 31.6, 29.0, 25.9, 19.8, 18.5, 18.3, 15.1, 14.6, 13.1, and two peaks at -5.6 | |
| Elemental Analysis: | Calcd for $C_{35}H_{60}O_3Si_2$: | C, 71.86; H, 10.34 |
| | Found: | C, 71.81; H, 10.21 |




16

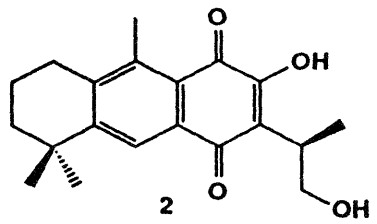



**2-((R)-1-Hydroxy-2-propyl)-3-hydroxy-8,8,10-trimethyl-5,6,7,8-tetrahydro-1,4-anthrandione, (2, (-)-aegyptinone B).**

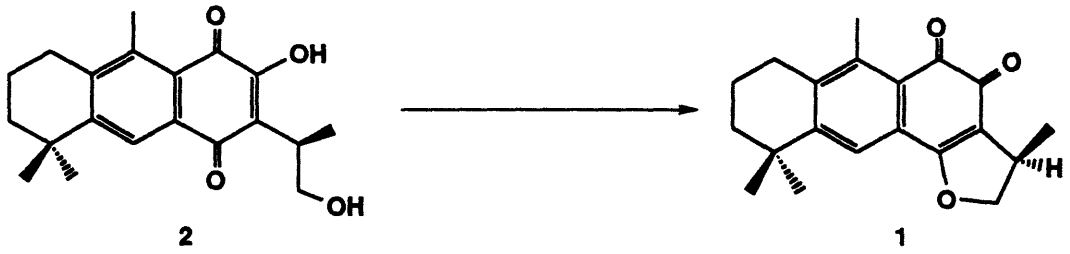
A 25-mL, pear-shaped flask fitted with a rubber septum was charged with a solution of the aromatic anulation product **16** (0.700 g, 1.20 mmol) in 12 mL of THF and cooled to -78°C. Oxygen was bubbled through the reaction mixture via a needle inlet while a tetra-*n*-butylammonium fluoride solution (1.0 M in THF, 3.0 mL, 3.0 mmol) was added dropwise by syringe over 1 min. The cold bath was then removed (the orange solution turned red), and oxygen was bubbled through the reaction mixture for 14 h at 25 °C. The resulting blood-red solution was poured into a mixture of 25 mL of saturated aqueous $NH_4Cl$ solution, 50 mL of diethyl ether, and 20 mL of THF. The aqueous layer was separated and extracted with three 50-mL portions of diethyl ether and the combined organic phases were washed with two 25-mL portions of 10% aqueous HCl solution and 50 mL of saturated aqueous NaCl solution, dried over $MgSO_4$, filtered, and concentrated to yield an orange-brown oil. Purification by column chromatography on silica gel (gradient elution with 10-20% ethyl acetate / hexanes) provided 0.340 g of a yellow-orange solid which was taken up in pentane and concentrated under reduced pressure to afford 0.340 g (87%) of aegyptinone B (**2**) as a yellow solid (mp 118-119 °C; lit:[3] red crystals from MeOH; mp 101-102 °C); $[\alpha]_D^{25} = +8.7°$ ($CHCl_3$, c=2.09).

IR (KBr): 3460, 3330, 2970, 2940, 2880, 1650, 1580, 1460, 1420, 1380, 1350, 1335, 1270, 1230, 1120, 1070, 1030, 1010, 990, 960, 920, 900, and 760 $cm^{-1}$

| | | |
|---|---|---|
| $^1$H NMR (300 MHz, $CDCl_3$): | 8.09 (s, 1H), 3.95 (dd, ABX pattern, J = 11, 7 Hz, 1H), 3.84 (dd, ABX pattern, J = 11, 5 Hz, 1H), 3.46 (m, 1H), 2.75 (t, J = 6.2 Hz, 2H), 2.67 (s, 3H), 1.83-1.91 (m, 2H), 1.68-1.64 (m, 2H), 1.34 (s, 6H), and 1.29 (d. J = 7.2 Hz, 3H) | |
| $^{13}$C NMR (75 MHz, $CDCl_3$): | 186.0, 183.0, 154.7, 153.6, 142.1, 141.5, 132.0, 124.5, 124.1, 123.2, 65.4, 37.6, 34.9, 32.7, 31.0, 28.3, 18.8, 16.4, and 14.3 | |
| UV $\lambda_{max}$ (MeOH): | 203 ($\varepsilon$ = 53,700), 268 (25,100), 280 (24,500), and 352 (3,630) | |
| Elemental Analysis: | Calcd for $C_{20}H_{24}O_4$: | C, 73.15; H, 7.37 |
| | Found: | C, 73.17; H, 7.27 |
| HRMS: | Calcd for $C_{20}H_{24}O_4$: | 328.1675 |
| | Found: | 328.1672 |




2



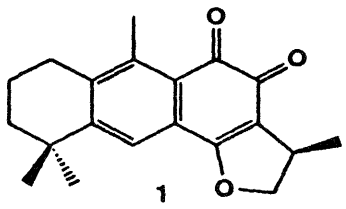

2 1

**1-Oxo-2,3-dihydro-(3R)-methylcyclopenta-7,11,11-trimethyl-8,9,10,11-tetrahydroanthran-5,6-dione, (1, (-)-aegyptinone A).**

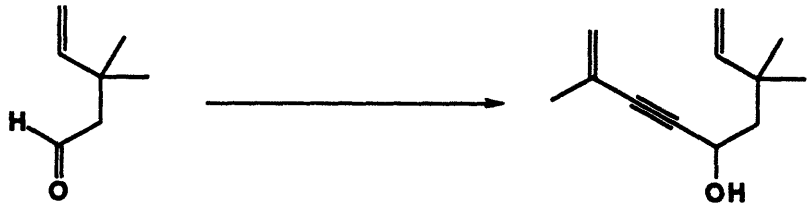
A 25-mL, pear-shaped flask fitted with a rubber septum was charged with a solution of aegyptinone B (**2**, 0.125 g, 0.381 mmol) in 3 mL of ethanol. Concentrated sulfuric acid (1.5 mL, CAUTION! EXOTHERMIC REACTION) was added dropwise over 2 min. The resultant dark red solution was stirred at 25 °C for 15 min, and then poured into 50 mL of water and extracted with two 50-mL portions of diethyl ether. The combined organic phases were washed with two 50-mL portions of 5% HCl solution and once with 50 ml of saturated aqueous $NaHCO_3$ solution, dried over $MgSO_4$, filtered, and concentrated to afford an orange / red solid. Column chromatography on silica gel (elution with dichloromethane) provided 0.108 g (91%) of aegyptinone A (**1**) as red-orange crystals (mp 137-138.5 °C; lit:[3] mp 136 °C); $[\alpha]_D^{25} = -102°$ ($CHCl_3$, c=0.13).

| | |
|---|---|
| IR (KBr): | 2970, 2950, 2940, 2880, 1690, 1655, 1645, 1620, 1580, 1555, 1470, 1410, 1395, 1375, 1350, 1290, 1260, 1215, 1195, 1185, 1160, 1135, 1110, 1055, 1000, 970, 945, 920, 905, 810, and 795 $cm^{-1}$ |
| $^1H$ NMR (300 MHz, $CDCl_3$): | 7.51 (s, 1H), 4.87 (t, J = 9.5 Hz, 1H), 4.35 (dd, J = 9.3, 6.0 Hz, 1H), 3.58 (m, 1H), 2.70 (t, J = 6.4 Hz, 2H), 2.57 (s, 3H), 1.79-1.88 (m, 2H), 1.61-1.66 (m, 2H), 1.34 (d. J = 6.8 Hz, 3H), and 1.30 (s, 6H) |
| $^{13}C$ NMR (75 MHz, $CDCl_3$): | 184.4, 176.1, 170.8, 152.1, 143.8, 141.1, 126.1, 125.5, 121.6, 118.1, 81.2, 37.6, 34.8, 34.5, 31.2, 28.4, 19.0, 18.7, and 16.4 |
| UV $\lambda_{max}$ (MeOH): | 268 ($\varepsilon$ = 31,600), 276 (30,900), 305 (30,900), and 370 (3,300) |

| | | |
|---|---|---|
| Analysis: | Calcd for $C_{20}H_{22}O_3$: | C, 77.39; H, 7.14 |
| | Found: | C, 77.28; H, 7.11 |


O
O
O
1


7.0
5.0
4.0
3.0
2.0
1.0
0.0 PPM



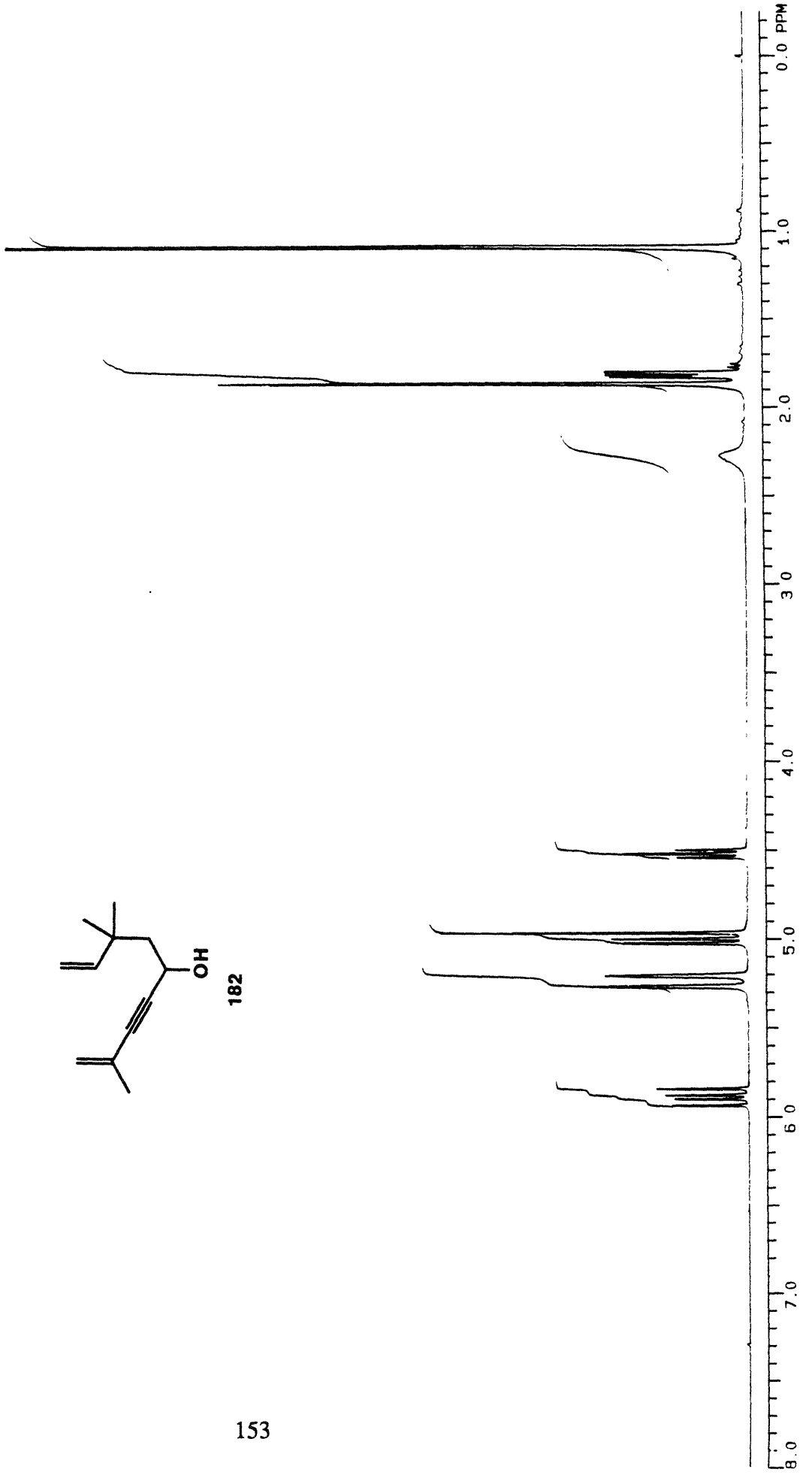

175 182

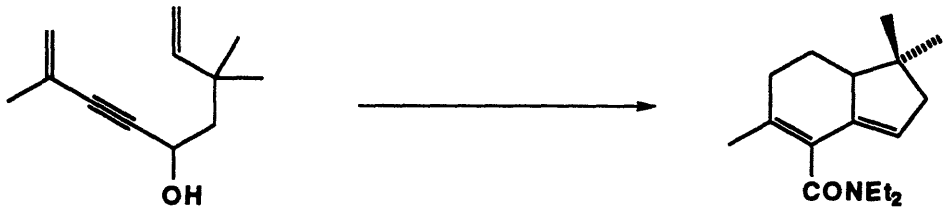
**2,7,7-Trimethylnona-1,8-dien-3-yn-5-ol (182).**

A 200-mL, three-necked, round-bottomed flask equipped with a rubber septum, a glass stopper, and an argon inlet adapter was charged with 80 mL of THF and 2-methyl-but-1-en-3-yne (2.85 mL, 30.0 mmol). The reaction mixture was cooled to -20 °C while *n*-butyllithium solution (2.46 M in hexanes, 12.0 mL, 29.1 mmol) was added dropwise via syringe over 5 min. The resulting light yellow solution was stirred at -20 °C for 30 min. A solution of 3,3-dimethylpent-4-enal[77] (**175**, 2.805 g, 25.01 mmol) in 20 mL of THF was added dropwise via cannula to the cooled acetylide solution over 10 min (with a 5 mL THF rinse). The reaction mixture was allowed to warm to 0 °C over 1 h and was then poured into 200 mL of saturated aqueous $NH_4Cl$ solution and 100 mL of diethyl ether. The phases were separated and the aqueous phase was extracted with four 100-mL portions of diethyl ether. The combined organic phases were washed with 100 mL of saturated aqueous NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford 4.173g (94%) of **182** as a colorless oil.

| | |
|---|---|
| IR (thin film): | 3340, 3080, 2955, 2920, 2870, 2210, 1630, 1610 1450, 1410, 1370, 1290, 1055, 1030, 1000, and 900 $cm^{-1}$ |
| $^1H$ NMR (300 MHz, $CDCl_3$): | 5.88 (dd, J = 17, 11 Hz, 1H), 5.26 (br s, 1H), 5.20 (appar quintet, J = 1.7 Hz, 1H), 4.99 (dd, J = 17, 1.2 Hz, 1H), 4.98 (dd, J = 11, 1.5 Hz, 1H), 4.52 (appar t, J = 6.5 Hz, 1H), 2.3 (br s, 1H), 1.87 (br s, 3H), 1.85 (dd, J = 14, 6.6 Hz, 1H), 1.79 (dd, J = 14, 5.8 Hz, 1H), 1.10 (s, 3H), and 1.09 (s, 3H) |
| $^{13}C$ NMR (75 MHz, $CDCl_3$): | 147.8, 126.3, 121.7, 111.1, 90.1, 85.8, 60.4, 50.4, 36.0, 27.6, 26.6, and 23.2 |

| | | |
|---|---|---|
| Elemental Analysis: | Calcd for $C_{12}H_{18}O$: | C, 80.85; H, 10.18 |
| | Found: | C, 80.90; H, 10.41 |


OH
182
0.0 PPM
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0

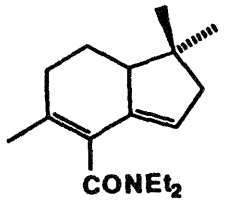



182 192

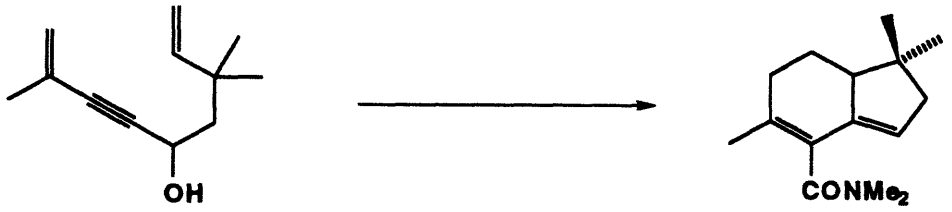
**Diethyl 1,1,5-trimethyl-2,6,7,7a-tetrahydro-1H-indene-4-carboxamide (192).**

A 25-mL, one-necked, round-bottomed flask was charged with propargyl alcohol **182** (0.535 g, 3.00 mmol), N,N-diethylformamide dimethyl acetal (1.10 g, 7.5 mmol) and 15 mL of xylenes. A Dean-Stark trap equipped with a reflux condenser and an argon inlet adapter was fitted to the flask and the reaction mixture was heated at reflux for 59 h. The cooled brown solution was loaded on to 50 g of silica gel and column chromatography (gradient elution with 25-50% diethyl ether / hexane) afforded 0.483 g (62%) of **192** as a viscous, yellow / brown oil.

| | |
|---|---|
| IR (thin film): | 3040, 2960, 2920, 2860, 2830, 1620, 1455, 1420, 1380, 1360, 1345, 1280, 1220, 1160, 1100, 1065, 980 and 815 $cm^{-1}$ |
| $^1H$ NMR (300 MHz, $CDCl_3$): * = minor rotamer | 5.23 (br s, 1H), 3.65-3.07 (m, 4H), 2.4-2.0 (m, 5H), 1.74 (s, 3H), 1.68 (m, 1H), 1.55-1.25 (m, 1H), 1.20 + 1.19* (2t, J = 7.1 Hz, 3H), 1.09 + 1.06* (2t, J = 7.1 Hz, 3H), 1.14 + 1.13* (2s, 3H), and 0.86* + 0.84 (2s, 3H) |
| $^{13}C$ NMR (75 MHz, $CDCl_3$): | Major rotamer: 169.8, 138.7, 134.4, 128.9, 119.8, 52.0, 48.1, 42.5, 41.1, 38.1, 32.0, 27.3, 23.4, 21.8, 20.5, 14.2, and 12.8<br>Minor rotamer: 169.5, 138.3, 134.2, 129.4, 119.7, 51.9, 48.3, 42.3, 40.9, 38.1, 31.9, 27.9, 23.7, 21.9, 20.4, 14.1, and 12.7 |
| HRMS: | Calcd for $C_{17}H_{27}NO$: 261.2093<br>Found: 261.2093 |




192

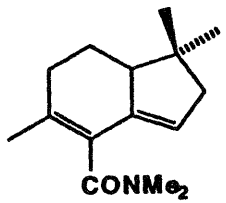



182 193

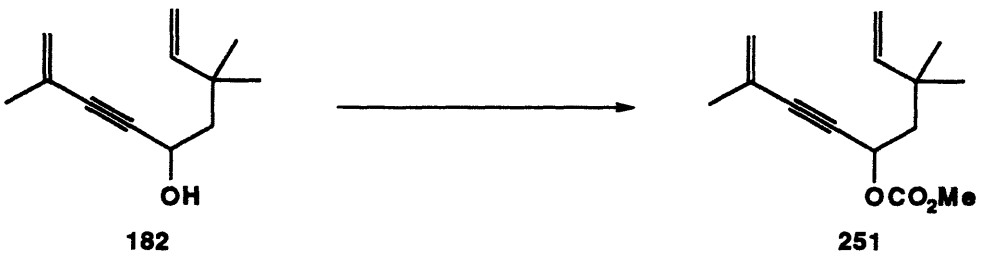
**Dimethyl 1,1,5-trimethyl-2,6,7,7a-tetrahydro-1H-indene-4-carboxamide (193).**

A 25-mL, one-necked, round-bottomed flask was charged with propargyl alcohol **182** (267 mg, 1.50 mmol), N,N-dimethylformamide di-*n*-propyl acetal (790 mg, 3.0 mmol) and 15 mL of xylenes. A Dean-Stark trap equipped with a reflux condenser and an argon inlet adapter was fitted to the flask and the reaction mixture was heated at reflux for 73 h. The cooled light brown solution was concentrated to give 398 mg of a light brown oil which was purified by chromatography on 15 g of silica gel (gradient elution with 20-70% diethyl ether / petroleum ether) to afford 266 mg (76%) of **193** as a viscous, pale yellow oil.

| | | |
|---|---|---|
| IR (thin film): | 3040, 2960, 2920, 2860, 2830, 1630, 1490, 1460, 1445, 1390, 1360, 1270, 1180, 1160, 1055, 980 and 810 $cm^{-1}$ | |
| $^1H$ NMR (300 MHz, $CDCl_3$): * = minor rotamer | 5.21 (br s, 1H), 3.05 + 3.04* (2s, 3H), 2.94 + 2.86* (2s, 3H), 2.4-2.0 (m, 5H), 1.74 (s, 3H), 1.68 (m, 1H), 1.54-1.25 (m, 1H), 1.14* + 1.13 (2s, 3H), and 0.86* + 0.84 (2s, 3H) | |
| $^{13}C$ NMR (75 MHz, $CDCl_3$): | Major rotamer: 170.7, 138.1, 134.8, 128.6, 119.9, 52.0, 48.2, 41.1, 37.7, 33.9, 32.0, 27.4, 23.5, 21.9, and 20.2<br>Minor rotamer: 170.4, 137.8, 134.7, 129.0, 119.9, 51.9, 48.3, 40.9, 37.5, 34.0, 31.9, 27.9, 23.6, 21.7, and 20.2 | |
| HRMS: | Calcd for $C_{15}H_{23}NO$:<br>Found: | 233.1780<br>233.1779 |




193



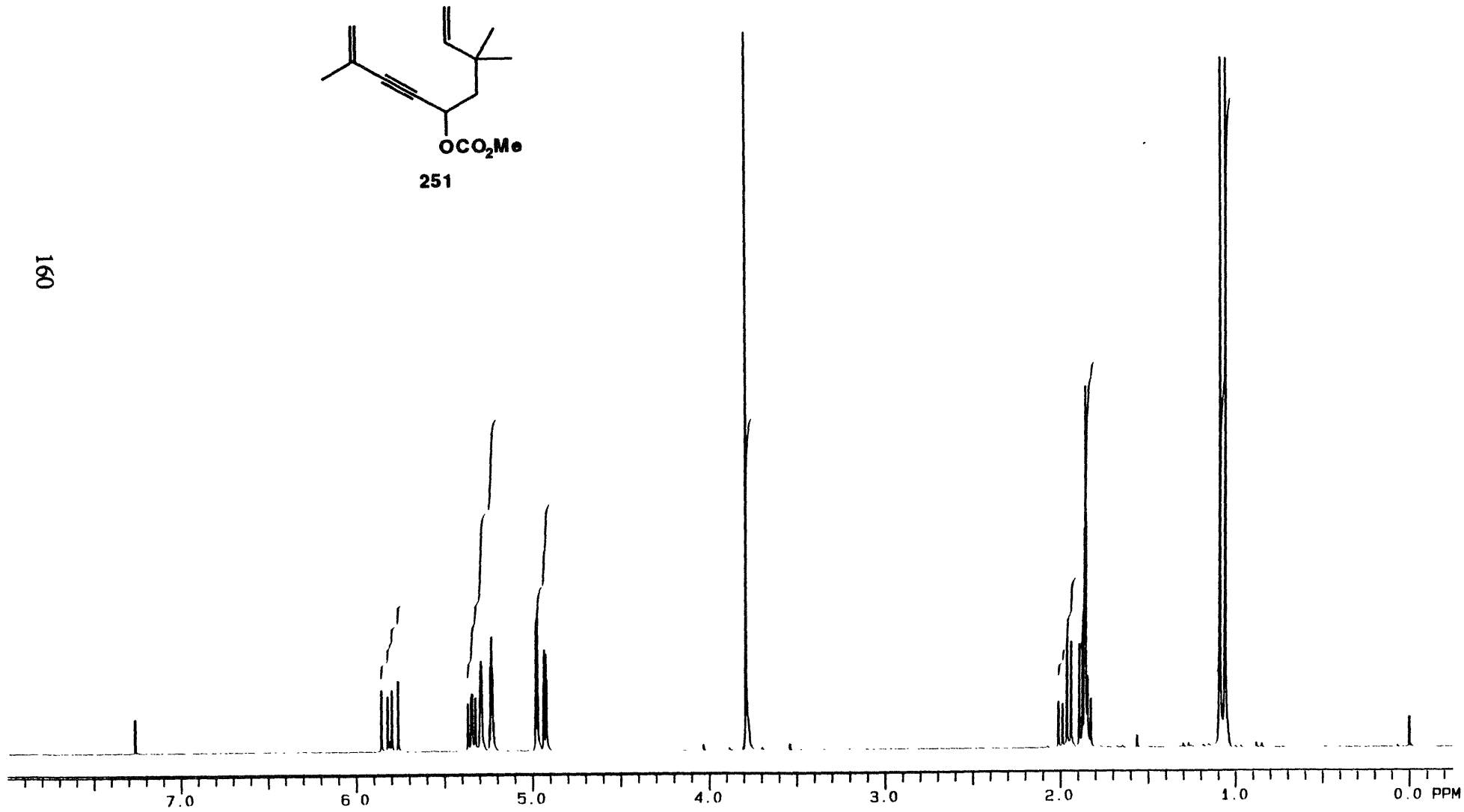

182 251

**Methyl 2,7,7-trimethylnona-1,8-dien-3-yn-5-yl carbonate (251).**

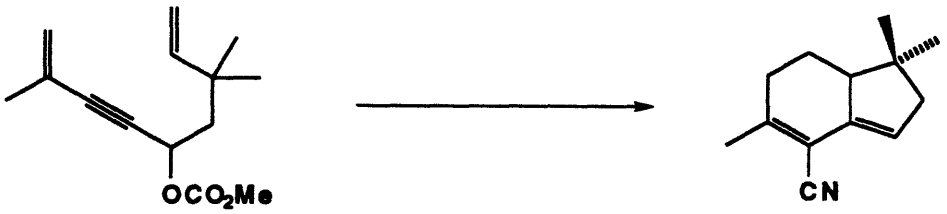
A 10-mL, one-necked, round-bottomed flask was charged with propargylic alcohol **182** (356 mg, 2.00 mmol), 4-dimethylaminopyridine (366 mg, 3.00 mmol), and 5 mL of dichloromethane. The reaction mixture was cooled at 0 °C while methylchloroformate (0.20 mL, 2.6 mmol) was added dropwise via syringe over 2 min. The ice bath was removed and the reaction mixture was stirred at room temperature for 30 min. After this time, the contents of the flask were poured into 5 mL of 1 N aqueous HCl solution and 40 mL of dichloromethane. The phases were separated and the organic phase was washed with 5 mL of 1 N aqueous HCl solution. The organic phase was washed with 10 mL of saturated aqueous NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford 462 mg of a nearly colorless oil contaminated by small solid particles. This crude product was purified by filtration through 9 g of silica gel (elution with 5% ethyl acetate / petroleum ether) and then by distillation in a Kugelrohr oven (60 °C, 0.1 mmHg) to give 456 mg (96%) of **251** as a colorless oil.

| | |
|---|---|
| IR (thin film): | 3080, 2960, 2225, 1750, 1635, 1610, 1440, 1265, 1005, 935, 910, and 790 $cm^{-1}$ |
| $^1H$ NMR (300 MHz, $CDCl_3$): | 5.81 (ABX pattern, appar dd, J = 17, 11 Hz, 1H), 5.35 (dd, J = 7.4, 5.9 Hz, 1H), 5.29 (br s, 1H), 5.24 (appar quintet, J = 1.7 Hz, 1H), 4.98 (ABX pattern, appar dd, J = 11, 1.2 Hz, 1H), 4.93 (ABX pattern, appar dd, J = 17, 1.2 Hz, 1H), 3.79 (s, 3H), 1.98 (dd, J = 15, 7.1 Hz, 1H), 1.86 (dd, J = 14, 5.4 Hz, 1H), 1.86 (appar t, J = 1.5 Hz, 3H), 1.09 (s, 3H), and 1.06 (s, 3H) |

| | | |
|---|---|---|
| $^{13}C$ NMR (75 MHz, $CDCl_3$): | 154.6, 146.6, 125.9, 122.5, 111.2, 87.2, 85.9, 66.4, 54.9, 47.5, 36.0, 27.5, 26.7, and 23.2 | |
| Elemental Analysis: | Calcd for $C_{14}H_{20}O_3$: | C, 71.16; H, 8.53 |
| | Found: | C, 71.55; H, 8.70 |




251

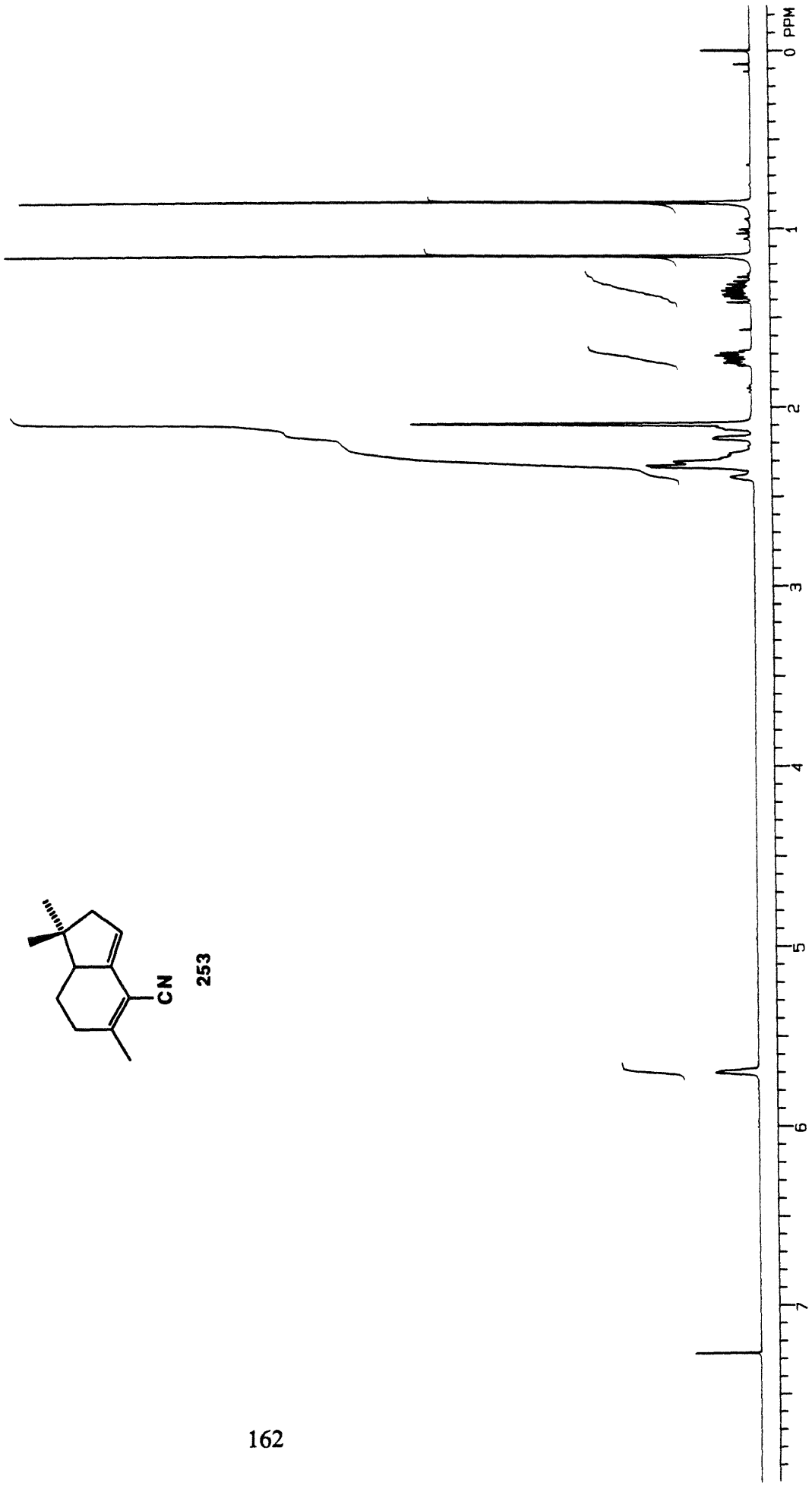


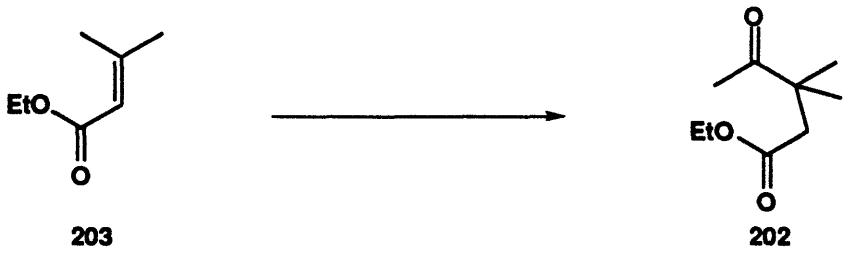

251 253

**1,1,5-Trimethyl-2,6,7,7a-tetrahydro-1H-indene-4-carbonitrile (253).**

A 25-mL, one-necked, round-bottomed flask was charged with propargylic carbonate **251** (354 mg, 1.50 mmol), $Pd(PPh_3)_4$ (87 mg, 0.075 mmol), 15 mL of THF, and TMSCN (0.40 mL, 3.0 mmol). A reflux condenser, equipped with an argon inlet adapter, was fitted to the flask and the reaction mixture was heated at reflux for 4.5 h. The cooled dark red / purple solution was filtered through 5 g of florisil® with 50 mL of diethyl ether and concentrated to give 360 mg of a viscous, dark red / purple oil. Column chromatography on 11 g of silica gel (gradient elution with 2-8% dichloromethane / petroleum ether) resulted in the isolation of 122 mg of material which afforded 117 mg (42%) of **253** as a colorless solid (mp 43-44.5 °C) after distillation in a Kugelrohr oven (60 °C, 0.1 mmHg).

| | |
|---|---|
| IR (KBr): | 3050, 2960, 2870, 2830, 2220, 1595, 1465, 1435, 1420, 1380, 1365, 1265, 1215, 1190, and 810 $cm^{-1}$ |
| $^1H$ NMR (300 MHz, $CDCl_3$): | 5.69 (br s, 1H), 2.41-2.24 (m, 4H), 2.15 (br d, J = 17 Hz, 1H), 2.09 (br s, 3H), 1.76-1.68 (m, 1H), 1.42-1.26 (m, 1H), 1.14 (s, 3H), and 0.84 (s, 3H) |
| $^{13}C$ NMR (75 MHz, $CDCl_3$): | 153.8, 136.8, 123.0, 116.3, 107.3, 51.6, 48.1, 41.7, 32.9, 27.6, 23.6, 22.8, and 21.1 |
| Elemental Analysis: | Calcd for $C_{13}H_{17}N$: C, 83.37; H, 9.15; N, 7.48<br>Found: C, 83.35; H, 9.15; N, 7.35 |


CN
253
0 PPM
1
2
3
4
5
6
7

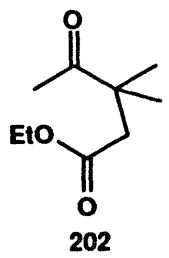



203 202

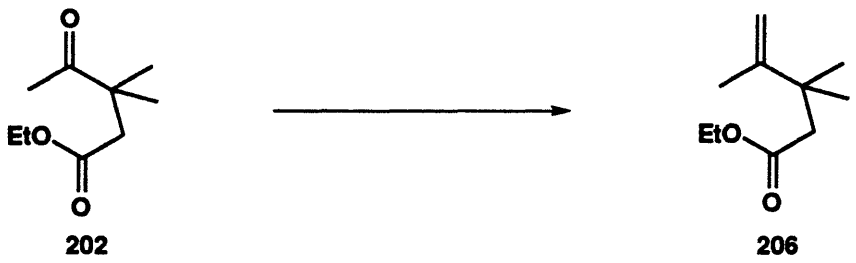
**Ethyl 3,3-dimethyl-4-oxopentanoate (202).**

A 2-L photochemical well was charged with ethyl 3,3-dimethylacrylate (**203**, 30.8 g, 240 mmol), 1.25 L of benzene, 200 mL of acetaldehyde (excess) and benzophenone (4.38 g, 24.0 mmol). The system was purged with argon gas and irradiated, at room temperature, with a 450 W medium pressure Hanovia lamp equipped with a uranium filter. After 7 days, the reaction mixture was transferred to a 2 L round-bottomed flask and the solvent was removed by distillation at atmospheric pressure through a short path distillation head. Continued fractional vacuum distillation provided a fraction at 75 - 125 °C (35 mmHg) consisting of a 4 : 1 mixture of desired product and ß-dicarbonyl isomer. This mixture (31.66 g) was dissolved in 300 mL of diethyl ether in a 500 mL round-bottomed flask and DBU (5.5 mL, 37 mmol) was added in one portion by syringe. The reaction mixture was stirred for 15 min and 10 g of paraformaldehyde (excess) was added. The orange-pink colored suspension was stirred for 3 h at 25 °C and then filtered. The filtrate was transferred to a separatory funnel, with 50 mL of diethyl ether, and washed with two 200-mL portions of 5% aqueous HCl. The combined aqueous phases were extracted with 100 mL of diethyl ether, and the combined organic fractions were washed with 100 mL of saturated aqueous $NaHCO_3$, dried over $MgSO_4$, filtered, and concentrated to give 33.3 g of a light brown oil. Column chromatography on a total of 350 g of silica gel, in two approximately equal-sized runs, (elution with 20% diethyl ether / pentane) afforded, after concentration of the appropriate fractions by distillation, 22.3 g (54%) of ketoester **202** as a colorless oil with spectral characteristics identical to those previously reported for this compound.[92]

| | |
|---|---|
| IR (thin film): | 2910, 1700, 1445, 1345, 1210, 1165, 1135, and 1025 $cm^{-1}$ |
| $^{1}H$ NMR (300 MHz, $CDCl_3$): | 4.09 (q, J = 7 Hz, 3H), 2.58 (s, 2H), 2.21 (s, 3H), 1.23 (t, J = 7 Hz, 3H), and 1.21 (s, 6H) |
| $^{13}C$ NMR (75 MHz, $CDCl_3$): | 212.2, 171.3, 60.2, 45.7, 44.0, 25.1, 24.7, and 14.0 |




202



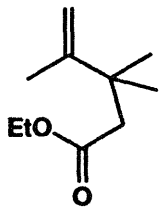

202 206

**Methyl 3,3,4-trimethylpent-4-enoate (206).**

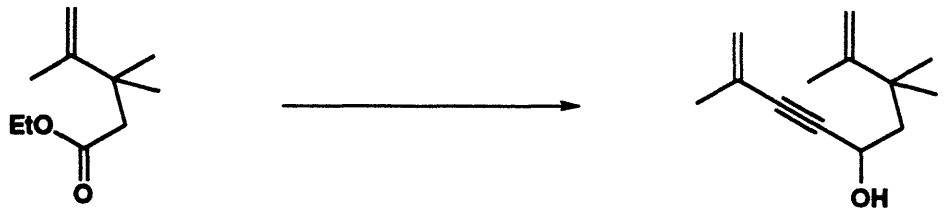
A 50-mL, one-necked, round-bottomed flask was charged with methyltriphenylphosphonium bromide (5.90 g, 16.5 mmol), 20 mL of diethyl ether, and KO*t*-Bu (1.85 g, 16.5 mmol) to give a yellow suspension which was stirred vigorously under argon for 30 min. A short path distillation apparatus was then fitted to the flask and the solvent was distilled off. The resulting yellow-brown slurry was heated to 60 °C and the distillation apparatus was replaced by a reflux condenser fitted with a septum and an argon inlet. The keto ester (**202**, 2.04 g, 11.8 mmol) was added dropwise, by syringe through the reflux condenser, over 20 min (EXOTHERMIC REACTION). The slurry was stirred at 60 °C for 1.5 h, after which it was cooled to room temperature. Water (20 mL) and 25 mL of pentane were added with vigorous stirring. The organic layer was decanted and the slurry was extracted with two 25-mL portions of pentane. The combined organic phases were dried over anhydrous $K_2CO_3$, filtered, and the solvent was removed by distillation at atmospheric pressure to give 2.08 g of almost colorless oil. Chromatography on 15 g of silica gel (gradient elution with 0-2% diethyl ether / pentane) afforded, after concentration of the desired fractions by distillation, 1.97 g (53%) of **206** as a colorless oil.

| | |
|---|---|
| IR (thin film): | 3090, 2970, 2870, 1730, 1630, 1460, 1440, 1365, 1315, 1185, 1100, 1030, and 890 $cm^{-1}$ |
| $^1H$ NMR (300 MHz, $CDCl_3$): | 4.76 (t, J = 1.1 Hz, 2H), 4.09 (q, J = 7.3 Hz, 2H), 2.37 (s, 2H), 1.79 (t, J = 1.1 Hz, 3H), 1.23 (t, J = 7.3 Hz, 3H), and 1.18 (s, 6H) |

| | |
|---|---|
| $^{13}C$ NMR (75 MHz, $CDCl_3$): | 171.7, 151.1, 109.5, 59.8, 45.4, 38.4, 27.1, 19.4, and 14.2 |




206




206 200

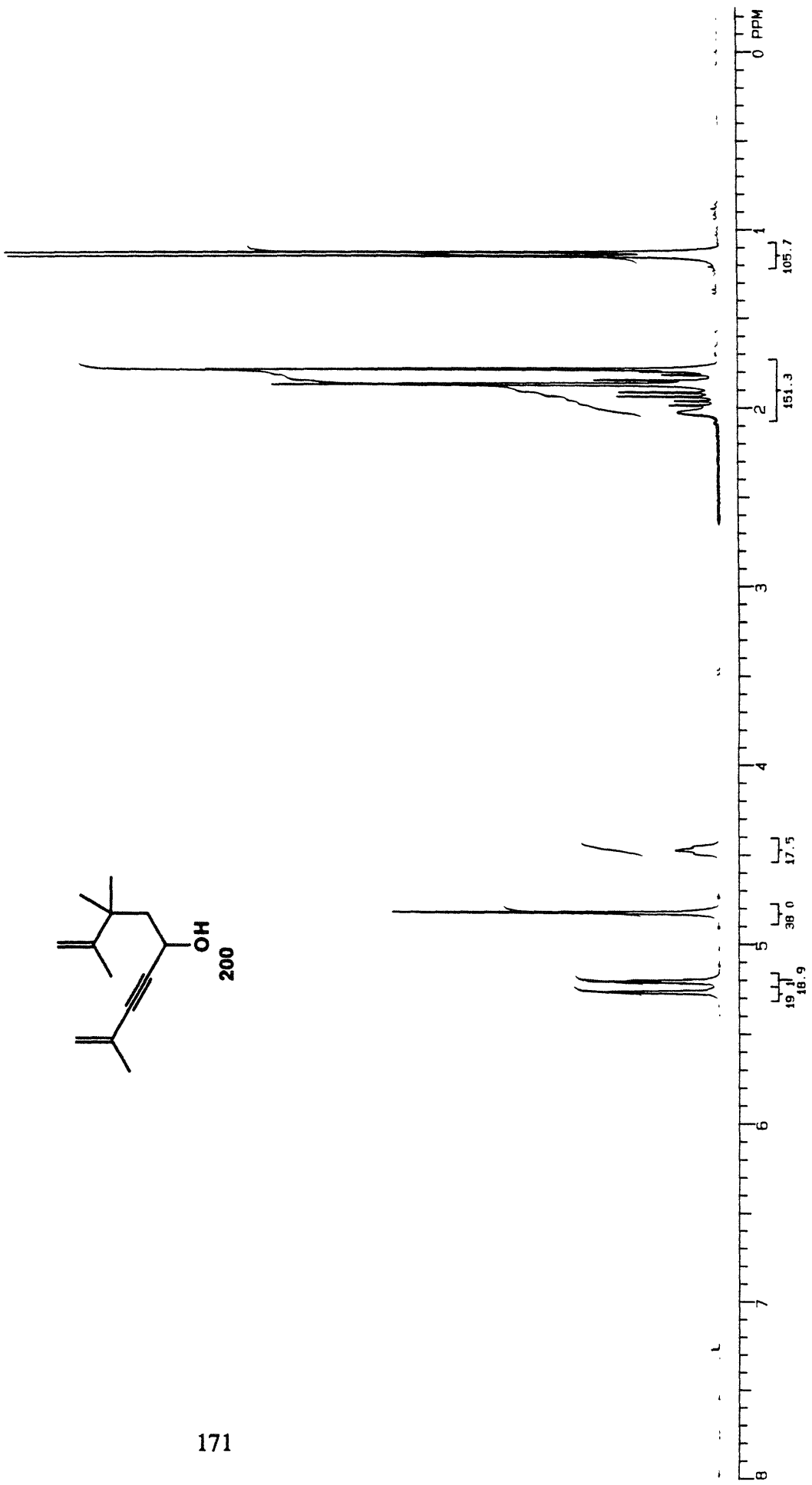
**2,7,7,8-Tetramethylnona-1,8-dien-3-yn-5-ol (200).**

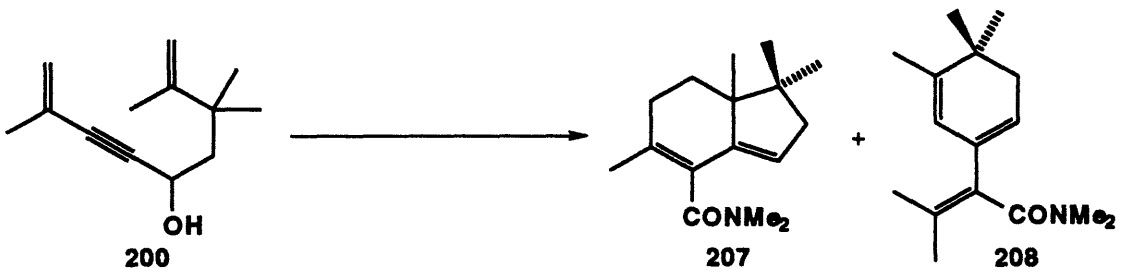
A 25-mL, one-necked, round-bottomed flask was charged with 15 mL of diethyl ether and 2-methyl-but-1-en-3-yne (1.00 mL, 10.5 mmol). The acetylene solution was cooled to -30 °C while a *n*-butyllithium solution (2.61 M in hexanes, 3.9 mL, 10 mmol) was added dropwise by syringe over 2 min. The resulting light yellow solution was stirred at -30 °C for 10 min and then cooled to -78 °C.

A 100-mL, one-necked, round-bottomed flask was charged with ester **206** (1.021 g, 5.997 mmol) and 30 mL of dichloromethane. This solution was cooled to -78 °C and a DIBAL-H solution (1.0 M in hexanes, 7.5 mL, 7.5 mmol) was added dropwise by syringe over 15 min. The reaction mixture was stirred at -78 °C for 10 min. The solution of the lithium acetylide was added via cannula over 5 min to the reaction mixture. The reaction mixture was stirred for 10 min at -78 °C and then warmed to 0 °C over 15 min. Rochelle's solution (25 mL) were then added and the resulting mixture was diluted with 25 mL of petroleum ether. The two phases were separated and the aqueous phase was extracted with three 25-mL portions of petroleum ether. The combined organic layers were dried over $K_2CO_3$, filtered, and concentrated to afford 1.056 g of a pale yellow oil. Chromatography on 15 g of silica gel (gradient elution with 2-6% diethyl ether / petroleum ether) afforded 895 mg (78 %) of **200** as a colorless oil.

| | |
|---|---|
| IR (thin film): | 3350, 3080, 2950, 2920, 2860, 1610, 1440, 1375, 1285, 1140, 1045, 1010, and 890 $cm^{-1}$ |
| $^1H$ NMR (300 MHz, $CDCl_3$): | 5.27 (br s, 1H), 5.21 (appar quintet, J = 1.7 Hz, 1H), 4.82 (s, 2H), 4.47 (br t, J = 5.5 Hz, 1H), 2.03 (br s, 1H), 1.95 (dd, J = 14, 7.2 Hz, 1H), 1.87 (appar |

| | | |
|---|---|---|
| | t, J = 1.4 Hz, 3H), 1.83 (dd, J = 14, 9.1 Hz, 1H), 1.79 (s, 3H), 1.15 (s, 3H), 1.13 (s, 3H) | |
| $^{13}C$ NMR (75 MHz, $CDCl_3$): | 152.0, 126.3, 121.6, 110.4, 90.1, 85.5, 60.4, 48.4, 38.1, 27.9, 27.1, 23.2, and 19.5 | |
| HRMS: | Calcd for $C_{13}H_{20}O$: | 192.1514 |
| | Found: | 192.1516 |


OH
200
0 PPM
105.7
151.3
17.5
38.0
19.1
18.9




200 207 208

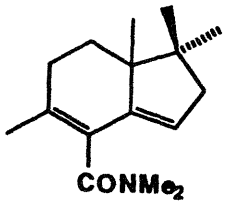
**Dimethyl 1,1,2,5-tetramethyl-2,6,7,7a-tetrahydro-1H-indene-4-carboxamide (207) and dimethyl 3-methyl-2-(4',4',5'-trimethylcyclohexa-1',5'-dienyl)-but-2-enamide (208).**

A 25-mL, one-necked, round-bottomed flask was charged with propargylic alcohol **200** (478 mg, 2.50 mmol), N,N-dimethylformamide di-*n*-propyl acetal (1.32 g, 7.50 mmol) and 20 mL of xylenes. A Dean-Stark trap, equipped with a reflux condenser and an argon inlet adapter, was fitted to the flask and the reaction mixture was heated at reflux for 116 h. The brown solution was cooled to room temperature and concentrated to give 833 mg of a brown oil which was purified by chromatography on 30 g of silica gel (gradient elution with 10-25% ethyl acetate / petroleum ether) to afford 134 mg (~90% purity) of **X** (20%) as a yellow oil and 115 mg of **X** as a yellow low-melting (mp<40°C) solid which upon vacuum sublimation (100 °C, 0.1 mmHg) afforded 88 mg (~95% purity) of **X** (14%) as a yellow solid (mp 53-58 °C).

For bicyclic amide **207**:

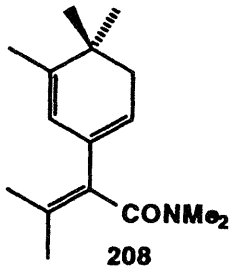
| | |
|---|---|
| IR (KBr): | 2920, 2860, 2830, 1620, 1440, 1390, 1360, 1265, 1175, 1080, and 1035 $cm^{-1}$ |
| $^1H$ NMR (300 MHz, $CDCl_3$): * = minor rotamer | 5.21 + 5.17* (2br s, 1H), 3.04* + 3.03 (2s, 3H), 2.93* + 2.84 (2s, 3H), 2.43* +2.38 (2br d, J = 16 Hz, 1H), 2.34-2.20 (m, 1H), 2.16-2.05 (m, 1H), 1.97 + 1.93* (2dd, J = 17 + 16*, 3.4 Hz, 1H), 1.76-1.54 (m, 1H), 1.72 + 1.71* (2s, 3H), 1.38-1.24 (m, 1H), 1.00 (s, 3H), 0.87 (s, 3H), and 0.85 (s, 3H) |
| $^{13}C$ NMR (75 MHz, $CDCl_3$): | Major rotamer: 170.5, 142.5, 133.2, 128.7, 119.8, 46.5, 46.2, 43.7, 37.4, 34.2, 29.3, 26.2, 25.8, 22.4, 20.1, and 18.8 |

| | | |
|---|---|---|
| | Minor rotamer: 170.8, 143.2, 132.9, 128.4, 119.5, 46.7, 46.1, 43.7, 37.8, 34.0, 29.2, 26.6, 25.9, 22.1, 20.1, and 18.7 | |
| HRMS: | Calcd for $C_{16}H_{25}NO$: | 247.1936 |
| | Found: | 247.1942 |
| For **208**: | | |
| IR (thin film): | 2960, 2920, 2860, 1625, 1490, 1445, 1390, 1275, 1260, 1170, 1070, and 1050 $cm^{-1}$ | |
| $^1H$ NMR (300 MHz, $CDCl_3$): | 5.65 (m, 1H), 5.58 (br t, J = 4.5 Hz, 1H), 2.98 (s, 3H), 2.94 (s, 3H), 2.12 (d, J = 4.5 Hz), 1.77 (s, 3H), 1.73 (d, J = 1.2 Hz, 3H), 1.71 (s, 3H), and 0.97 (s, 6H) | |
| $^{13}C$ NMR (75 MHz, $CDCl_3$): | 171.6, 143.7, 132.7, 132.0, 131.5, 123.1, 121.3, 39.4, 37.6, 34.3, 33.1, 25.3, 21.9, 20.8, and 18.8 | |
| HRMS: | Calcd for $C_{16}H_{25}NO$: | 247.1936 |
| | Found: | 247.1942 |


CONMe2

207


7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0 PPM
15.9
9.0
87.5
55.7
35.9
73.3
72.6
137.5
52.5
94.3
175.5


CONMe2

208


7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0 PPM
24.6
24.8
83.0
87.6
63.7
93.7
82.4
164.4


206 254

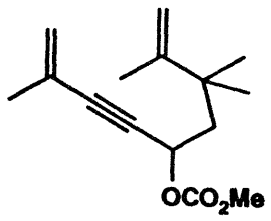
**Methyl 2,7,7,8-tetramethylnona-1,8-dien-3-yn-5-yl carbonate (254).**

A 25-mL, one-necked, round-bottomed flask was charged with 2-methyl-but-1-en-3-yne (1.00 mL, 10.5 mmol) and 15 mL of diethyl ether. The acetylene solution was cooled to -30 °C while *n*-butyllithium solution (2.49 M, 4.1 mL, 10 mmol) was added dropwise by syringe over 2 min. The resulting light yellow solution was stirred at -30 °C for 10 min and then cooled to -78 °C.

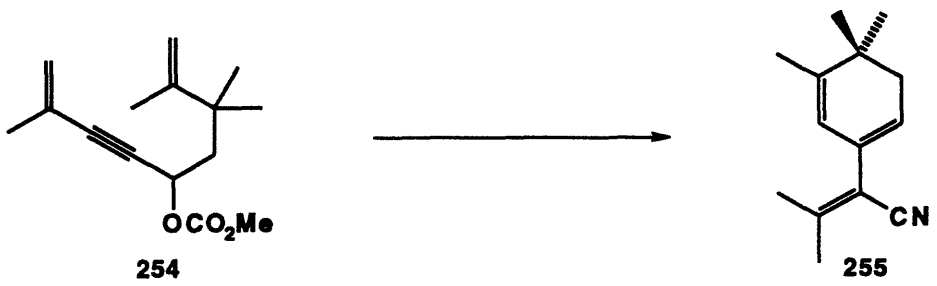
A 100-mL, one-necked, round-bottomed flask was charged with ester **206** (1.021 g, 5.997 mmol) and 30 mL of dichloromethane. This solution was cooled to -78 °C and DIBAL-H solution (1.0 M in hexanes, 6.6 mL, 6.6 mmol) was added dropwise by syringe over 15 min. The reaction mixture was stirred at -78 °C for 75 min. The solution of the lithium acetylide was added via cannula over 5 min to the reaction mixture. The reaction mixture was stirred for 30 min at -78 °C and methyl chloroformate (1.30 mL, 16.8 mmol) was added by syringe over 1 min. The resulting mixture was stirred for 30 min at -78 °C and then warmed to room temperature over 15 min. Rochelle's solution (30 mL) were then added and the reaction mixture was stirred rapidly for 30 min. The two phases were separated and the aqueous phase was extracted with three 25-mL portions of diethyl ether. The combined organic layers were dried over $K_2CO_3$, filtered, and concentrated to afford 1.632 g of a light brown oil. Chromatography on 14 g of silica gel (gradient elution with 0-2% ethyl acetate / petroleum ether) afforded 1.273 g (85%) of **254** as a colorless oil.

IR (thin film): 3080, 2950, 1745, 1605, 1440, 1370, 1335, 1260, 1150, 1045, 1000, 935, 895, and 785 $cm^{-1}$

| | | |
|---|---|---|
| $^1$H NMR (300 MHz, $CDCl_3$): | 5.29 (br s, 1H), 5.23 (appar quintet, J = 1.7 Hz, 1H), 4.78 (s, 1H), 4.75 (s, 1H), 3.78 (s, 3H), 1.99 (dd, J = 15, 7.3 Hz, 1H), 1.86 (s, 3H), 1.84 (dd, J = 15, 5.2 Hz, 1H), 1.75 (s, 3H), 1.14 (s, 3H), 1.10 (s, 3H) | |
| $^{13}$C NMR (75 MHz, $CDCl_3$): | 154.8, 150.6, 126.0, 122.6, 110.5, 86.9, 85.8, 66.4, 54.8, 45.5, 38.0, 27.6, 27.2, 23.0, and 19.4 | |
| HRMS: | Calcd for $C_{15}H_{22}O_3$: | 250.1569 |
| | Found: | 250.1568 |




254

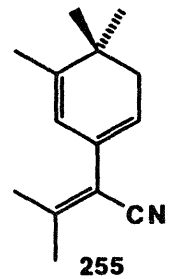



254 255

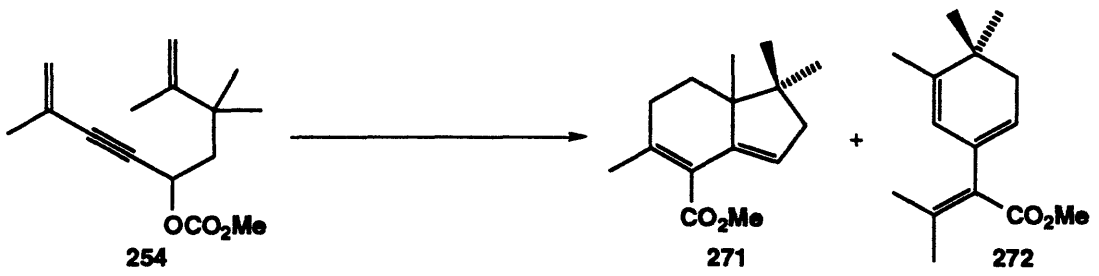
**3-Methyl-2-(4',4',5'-trimethylcyclohexa-1',5'-dienyl)-but-2-enenitrile (255).**

A 25-mL, one-necked, round-bottomed flask was charged with the propargylic carbonate (**254**, 250 mg, 1.00 mmol), $Pd(PPh_3)_4$ (80 mg, 0.069 mmol), 10 mL of THF, and TMSCN (0.27 mL, 2.0 mmol). A reflux condenser, equipped with an argon inlet adapter, was fitted to the flask and the reaction mixture was heated at reflux for 13 h. The cooled dark red / purple solution was filtered through 2.5 g of Florisil® with 30 mL of diethyl ether and concentrated to give 237 mg of a viscous, dark red / purple oil. Column chromatography on 20 g of silica gel (gradient elution with 0-1% diethyl ether / petroleum ether) afforded 82 mg (41%) of **255** as a colorless oil.

| | |
|---|---|
| IR (thin film): | 2955, 2910, 2860, 2200, 1585, 1435, 1370, 1255, 1135, and 785 $cm^{-1}$ |
| $^1H$ NMR (300 MHz, $CDCl_3$): | 5.64 (br t, J = 4.3 Hz, 1H), 5.57 (appar quintet, J = 1.8 Hz, 1H), 2.15 (d, J = 5.0 Hz, 2H), 2.12 (s, 3H), 1.89 (s, 3H), 1.76 (d, J = 1.8 Hz, 3H), and 0.99 (s, 6H) |
| $^{13}C$ NMR (75 MHz, $CDCl_3$): | 153.1, 145.2, 130.0, 125.2, 120.1, 118.6, 110.9, 39.3, 33.2, 25.4, 24.5, 21.6, and 18.8 |
| HRMS: | Calcd for $C_{14}H_{19}N$: 201.1518<br>Found: 201.1517 |




255




**Methyl 1,1,5,7a-tetramethyl-2,6,7,7a-tetrahydro-1H-indene-4-carboxylate (271) and methyl 3-methyl-2-(4',4',5'-trimethylcyclohexa-1',5'-dienyl)-but-2-enoate (272).**

A 25-mL, one-necked, round-bottomed flask was charged with $Pd_2(dba)_3$ (46 mg, 0.050 mmol), dppp (83 mg, 0.020 mmol), and 8 mL of benzene. The catalyst was stirred for 5 min to give an olive green solution and a solution of the propargylic carbonate (250 mg, 1.00 mmol) in 8 mL of benzene and 3 mL of methanol was added by cannula over 1 min (with a 1 mL benzene rinse). The system was flushed with CO, and a reflux condenser, equipped with a CO balloon, was fitted to the flask. The reaction mixture was heated at 50 °C for 4 h. The cooled reaction mixture was filtered through 5 g of florisil® with 50 mL of diethyl ether and concentrated to give 258 mg of a brown oil. Chromatography on 7.5 g of silica gel (gradient elution with 10-100% benzene / petroleum ether followed by 25% diethyl ether / benzene) resulted in the isolation of 118 mg of a 4 to 1 mixture of **271** (40 %) and **272** (10%) respectively as a colorless oil. A purified sample of each compound (as a colorless oil) was obtained by repeated preparative thin layer chromatography (elution with 10% diethyl ether / petroleum ether).

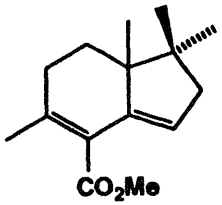
For **271**:

| | |
|---|---|
| IR (thin film): | 2930, 2840, 1720, 1625, 1430, 1365, 1270, 1240, 1220, 1195, 1130, 1105, 1085, 1045, 985, 850, 800, and 760 $cm^{-1}$ |
| $^1H$ NMR (300 MHz, $CDCl_3$): | 5.40 (br s, 1H), 3.80 (s, 3H), 2.43 (br t, J = 16 Hz, 1H), 2.31 (ddd, J = 18, 12, 6.0 Hz, 1H), 2.14 (dd, J = 19, 5.6 Hz, 1H), 1.98 (dd, J = 16, 3.3 Hz, 1H), 1.85 (s, 3H), 1.62 (dt, J = 12, 5.8 Hz, 1H), 1.31 (ddd, J = 13, 5.1, 1.3 Hz, 1H), 1.01 (s, 3H), 0.87 (s, 3H), and 0.84 (s, 3H) |

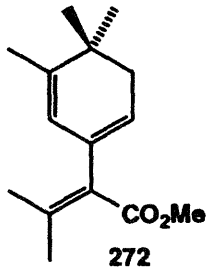
| | | |
|---|---|---|
| $^{13}C$ NMR (75 MHz, $CDCl_3$): | 169.5, 142.4, 139.0, 125.8, 120.7, 51.5, 46.9, 46.2, 43.5, 30.4, 26.3, 25.9, 22.4, 21.1, and 18.8 | |
| HRMS: | Calcd for $C_{15}H_{22}O_2$: | 234.1620 |
| | Found: | 234.1616 |

For **272**:

| | | |
|---|---|---|
| IR (thin film): | 2960, 2900, 2840, 1705, 1430, 1370, 1280, 1215, 1085, and 1060 $cm^{-1}$ | |
| $^1H$ NMR (300 MHz, $CDCl_3$): | 5.45 (br s, 1H), 5.44 (br t, J = 4.9 Hz, 1H), 3.69 (s, 3H), 2.13 (d, J = 4.5 Hz, 2H), 2.00 (s, 3H), 1.80 (s, 3H), 1.74 (br s, 3H), and 0.99 (s, 6H) | |
| $^{13}C$ NMR (75 MHz, $CDCl_3$): | 169.3, 144.1, 133.7, 133.2, 129.6, 51.4, 39.3, 33.3, 25.4, 23.1, 22.4, and 18.9 | |
| HRMS: | Calcd for $C_{15}H_{22}O_2$: | 234.1620 |
| | Found: | 234.1616 |




271



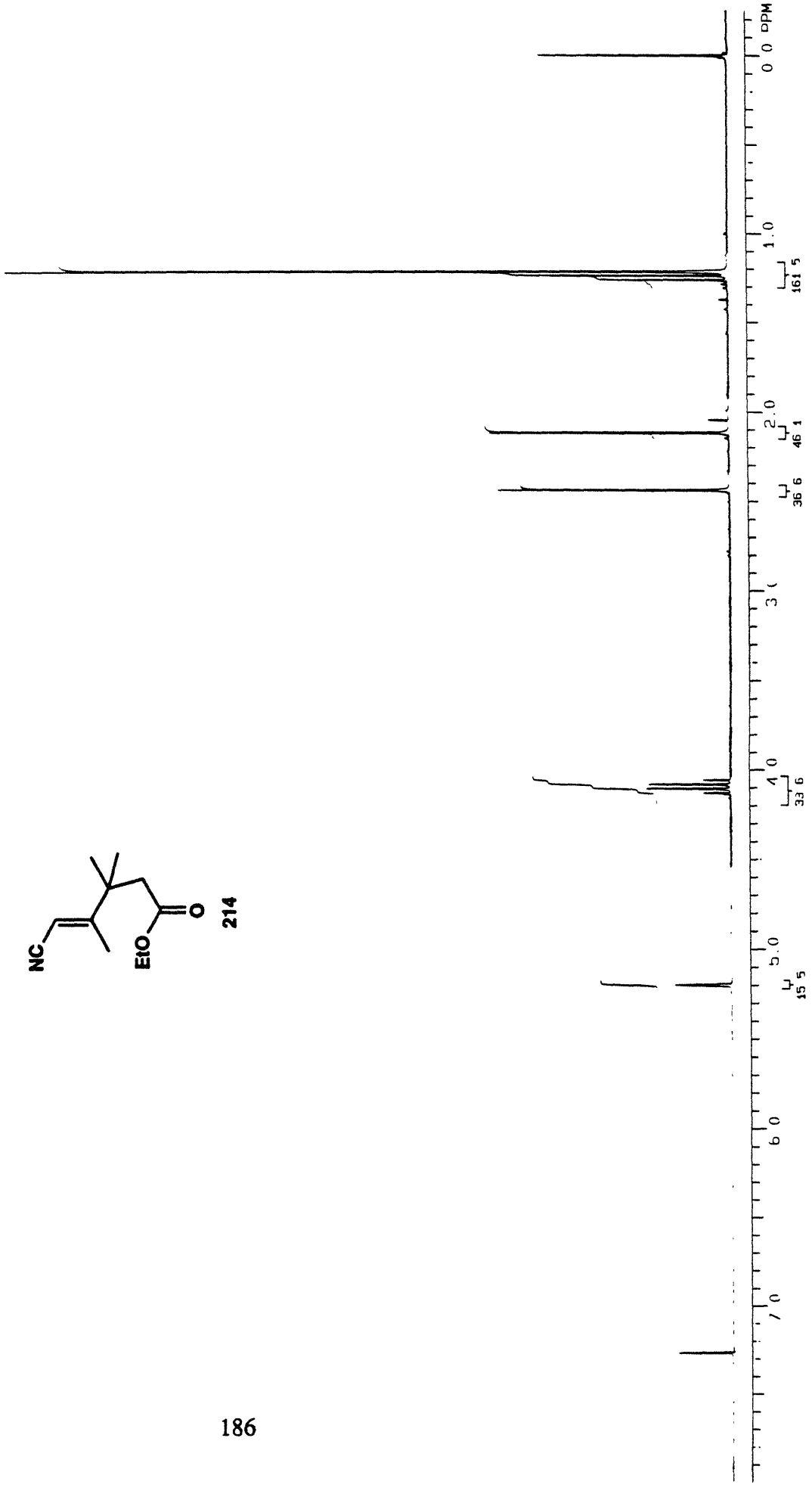

272

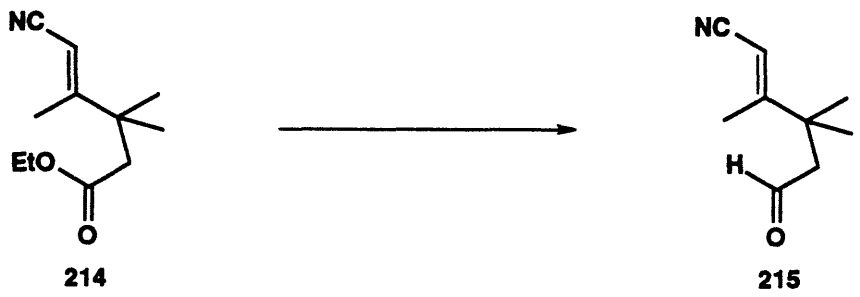

202 214

**(E)-Ethyl 5-cyano-3,3,4-trimethylpent-4-enoate (214).**

A 100-mL, one-necked, round-bottomed flask was charged with diethylcyanomethyl phosphonate (2.98 g, 16.8 mmol) and 60 mL of THF. Potassium *tert*-butoxide (1.85 g, 16.5 mmol) was added all at once. The reaction mixture was stirred for 15 min and a solution of the keto ester (**202**, 1.205 g, 7.00 mmol) in 7 mL of THF was added dropwise via cannula over 3 min (with a 3 mL THF rinse). A reflux condenser equipped with an argon inlet adapter was fitted to the reaction flask and the reaction mixture was heated at reflux for 22 h. The solution was cooled to room temperature and poured into 50 mL of saturated aqueous $NH_4Cl$ and 50 mL of diethyl ether. Water (20 mL) was added and the two phases were separated. The aqueous phase was extracted with three 50-mL portions of petroleum ether. The combined organic phases were dried over $MgSO_4$, filtered, and concentrated to give 2.94 g of a light brown oil. Chromatography on 29 g of silica gel (elution with 5 % ethyl acetate / 5 % dichloromethane / petroleum ether) afforded 1.181 g of **214** (86%) as a colorless oil.

| | |
|---|---|
| IR (thin film): | 3070, 2970, 2930, 2210, 1725, 1615, 1460, 1445, 1370, 1340, 1315, 1230, 1200, 1165, 1110, 1030, and 815 $cm^{-1}$ |
| $^1H$ NMR (300 MHz, $CDCl_3$): | 5.21 (br s, 1H), 4.09 (q, J = 7 Hz, 3H), 2.44 (s, 2H), 2.12 (s, 3H), 1.24 (t, J = 7 Hz, 3H), and 1.22 (s, 6H) |
| $^{13}C$ NMR (75 MHz, $CDCl_3$): | 170.4, 169.8, 117.4, 95.0, 60.3, 45.0, 39.7, 26.7, 17.9, and 14.1 |
| Elemental Analysis: | Calcd for $C_{11}H_{17}NO_2$: C, 67.66; H, 8.77; N, 7.17<br>Found: C, 67.62; H, 8.75; N, 7.29 |


NC
EtO
O
214
0.0 PPM
1.0
2.0
3.0
4.0
5.0
6.0
7.0
161.5
46.1
36.6
33.6
15.5

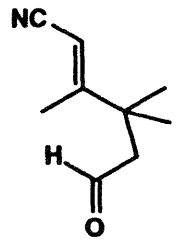



214 215

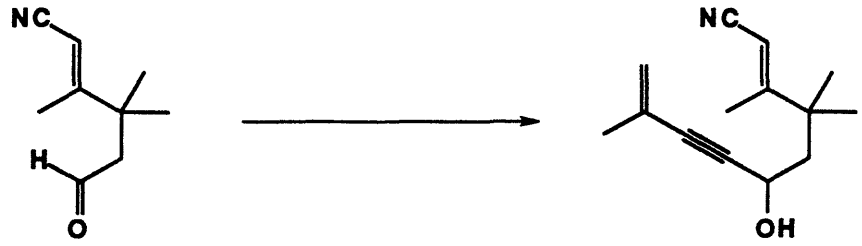
**(E)-5-Cyano-3,3,4-trimethylpent-4-enal (215).**

A 100-mL, one-necked, round-bottomed flask was charged with ester **214** (1.171 g, 5.997 mmol) and 60 mL of dichloromethane. The reaction mixture was cooled to -78 °C while DIBAL-H solution (1.0M in hexanes, 6.9 mL, 6.9 mmol) was added dropwise via syringe over 20 min. The resulting solution was stirred at -78 °C for 30 min and 6 mL of Rochelle's solution was added. The two phases were stirred vigorously for 1 h and then separated. The aqueous phase was extracted with two 25-mL portions of petroleum ether. The combined organic phases were dried over $MgSO_4$, filtered, and concentrated to give 919 mg of yellow oil. Distillation in a Kugelrohr oven (100 °C, 0.8 mmHg) afforded 905 mg (100%) of **215** as a colorless oil.

| | | |
|---|---|---|
| IR (thin film): | 3070, 2970, 2870, 2730, 2210, 1720, 1620, 1465, 1440, 1380, 1270, 1125, 1045, and 820 $cm^{-1}$ | |
| $^1H$ NMR (300 MHz, $CDCl_3$): | 9.66 (t, J = 2.4 Hz, 1H), 5.24 (appar d, J = 0.9 Hz, 1H), 2.54 (d, J = 2.4 Hz, 2H), 2.11 (d, J = 0.9 Hz, 3H), and 1.25 (s, 6H) | |
| $^{13}C$ NMR (75 MHz, $CDCl_3$): | 200.2, 169.1, 117.1, 95.6, 53.0, 39.3, 26.8, and 17.8 | |
| HRMS: | Calcd for $C_9H_{13}NO$: | 151.0997 |
| | Found: | 151.0996 |




215



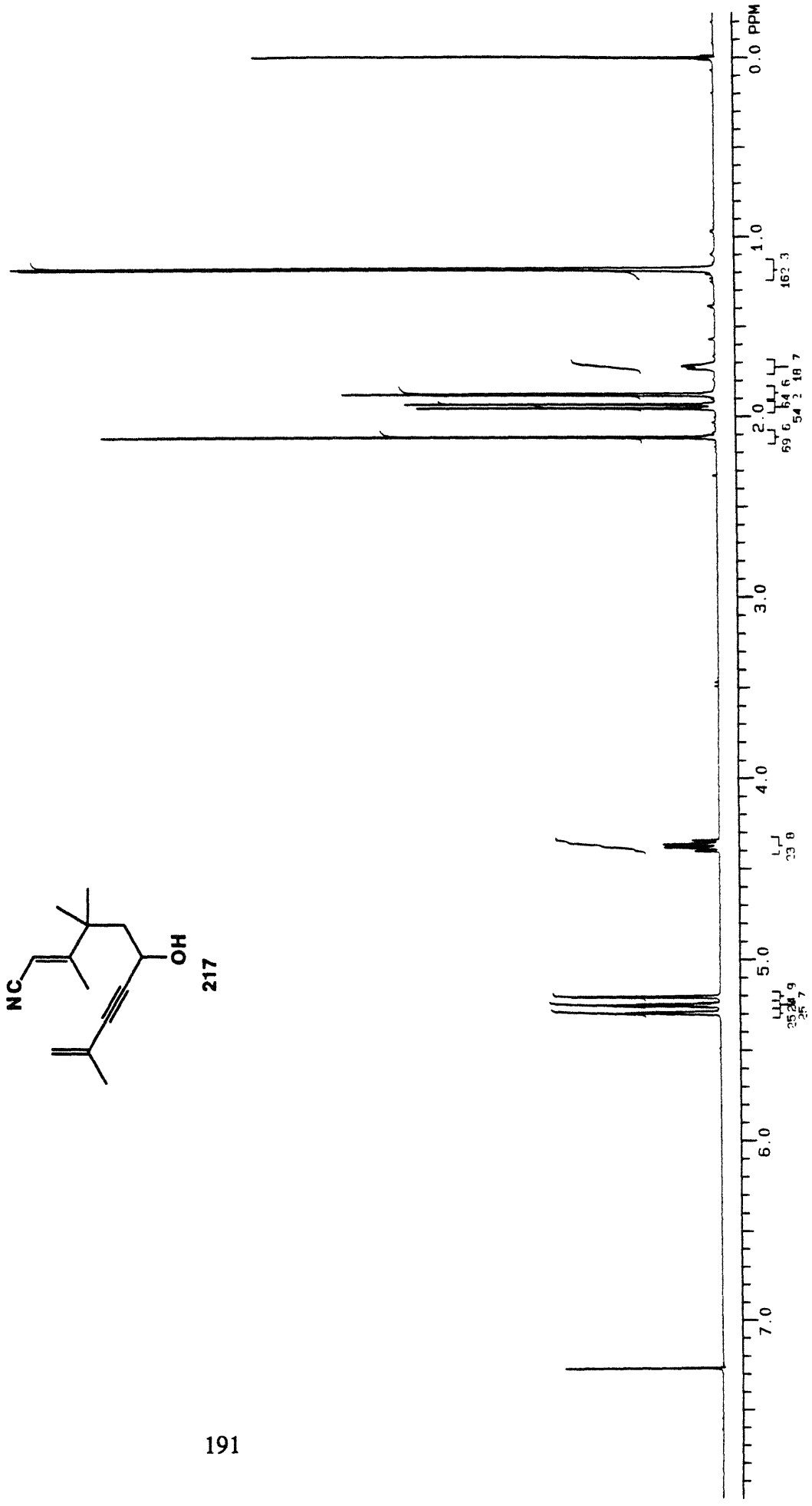

215 217

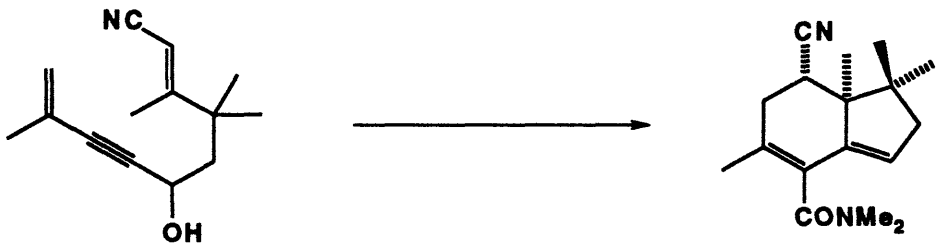
**(E)-9-Cyano-2,7,7,8-tetramethylnona-1,8-dien-3-yn-5-ol (217).**

A 100-mL, one-necked, round-bottomed flask was charged with cerium chloride (2.58 g, 10.5 mmol) and 20 mL of THF. The resulting suspension was stirred for 75 min. In the meantime, a 50-mL, round-bottomed flask was charged with 20 mL of THF and 2-methylbut-1-en-3-yne (1.05 mL, 11.0 mmol). The enyne solution was cooled to -20 °C while *n*-butyllithium solution (2.53 M in hexanes, 4.3 mL, 11 mmol) was added dropwise via syringe over 2 min. The resulting light yellow solution was stirred at -20 °C for 15 min. The cerium chloride suspension was cooled to -78 °C while the acetylide solution was added dropwise via cannula over 15 min (with a 10 mL THF rinse). The resulting suspension was stirred at -78 °C for 1 h and aldehyde **215** (834 mg, 5.52 mmol) was added dropwise via syringe over 5 min. The reaction mixture was stirred for 45 min at -78 °C and then 40 mL of half saturated aqueous $NH_4Cl$ solution was added slowly. The reaction mixture was brought to room temperature and then filtered, washing the solids with 50 mL of diethyl ether and 10 mL of water. The phases were separated, and the aqueous phase extracted with two 20-mL portions of diethyl ether. The combined organic phases were dried over $MgSO_4$, filtered, and concentrated to give 1.28 g of a brown oil. Chromatography on 13 g of silica gel (elution with 10 % ethyl acetate / petroleum ether) resulted in the isolation of 1.18 g of material which afforded 1.056 g of **217** (88%) as a colorless oil after distillation in a Kugelrohr oven (150 °C, 0.5 mmHg).

IR (thin film): 3400, 3070, 2940, 2840, 2190, 1600, 1425, 1365, 1275, 1110, 1010, 885, and 800 $cm^{-1}$

| | |
|---|---|
| $^1$H NMR (300 MHz, $CDCl_3$): | 5.29 (br s, 1H), 5.25 (appar quintet, J = 1.7 Hz, 1H), 5.20 (appar d, J = 1.5 Hz, 1H), 4.37 (dt, J = 6.3, 4.9 Hz, 1H), 2.12 (d, J = 0.9 Hz, 3H), 1.95 (d, J = 6.9 Hz, 2H), 1.88 (appar t, J = 1.4 Hz, 3H), 1.72 (br d, J = 4.9 Hz, 1H), 1.19 (s, 3H), and 1.18 (s, 3H) |
| $^{13}$C NMR (75 MHz, $CDCl_3$): | 170.9, 125.9, 122.5, 117.6, 95.1, 88.9, 86.6, 59.8, 47.9, 39.8, 27.2, 26.8, 23.2, and 18.1 |
| Elemental Analysis: | Calcd for $C_{14}H_{19}NO$: C, 77.38; H, 8.81; N, 6.45<br>Found: C, 77.10; H, 8.83; N, 6.41 |


NC
OH
217
0.0 PPM
1.0
2.0
3.0
4.0
5.0
6.0
7.0



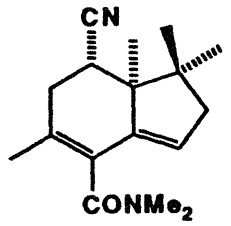

217 218

**(7R*,7aR*)Dimethyl 7-cyano-1,1,5,7a-tetramethyl-2,6,7,7a-tetrahydro-1H -indene-4-carboxamide (218).**

A 25-mL, round-bottomed flask was charged with propargyl alcohol **217** (270 mg, 1.24 mmol), N,N-dimethylformamide di-*n*-propyl acetal (657 mg, 3.75 mmol), and 12.5 mL of xylenes. A Dean-Stark trap equipped with a reflux condenser and an argon inlet adapter was fitted to the flask and the reaction mixture was heated at reflux for 37 h. The light brown solution was cooled to room temperature and then concentrated to give 398 mg of an orange / brown oil which was purified by chromatography on 15 g of silica gel (elution with 10-60% ethyl acetate / petroleum ether) to afford 304 mg (76%) of **218** as a light brown solid. Recrystallization from 8 mL of (~50 to 1) diethyl ether / petroleum ether by gradual cooling to -78 °C yielded (in two crops) 227 mg (67%) of **67** as a colorless solid (mp 141-143 °C).

| | |
|---|---|
| IR (KBr): | 3040, 2960, 2910, 2860, 2830, 2220, 1625, 1490, 1465, 1445, 1395, 1370, 1260, 1175, 1055, and 985 $cm^{-1}$ |
| $^1H$ NMR (300 MHz, $CDCl_3$): | major rotamer: 5.38 (br s, 1H), 3.04 (s, 3H), 2.92 (ABX pattern, appar dd, J = 11, 6.4 Hz, 1H), 2.84 (s, 3H), 2.65-2.37 (m, 3H), 2.10 (dd, J = 11, 3.5 Hz, 1 H), 1.74 (s, 3H), 1.76 (br s, 1H), 1.24 (s, 3H), 1.07 (s, 3H), and 1.04 (s, 3H)<br>minor rotamer: 5.33 (br s, 1H), 3.05 (s, 3H), 2.91 (s, 3H), 2.82 (ABX pattern, appar dd, J = 11, 5.8 Hz, 1H), 2.65-2.37 (m, 3H), 2.05 (dd, J = 12, 3.5 Hz, 1 H), 1.76 (br s, 1H), 1.24 (s, 3H), 1.08 (s, 3H), 1.03 (s, 3H) |

| | |
|---|---|
| $^{13}C$ NMR (75 MHz, $CDCl_3$): | Major rotamer: 169.0, 140.5, 129.8, 129.1, 122.8, 120.4, 47.8, 46.7, 44.3, 37.3, 34.2, 32.6, 29.1, 25.0, 22.7, 19.6, and 15.7<br>Minor rotamer: 169.3, 140.1, 129.7, 128.7, 122.4, 120.3, 48.1, 46.6, 44.3, 37.7, 34.0, 32.5, 29.5, 25.2, 22.4, 19.6, and 15.5 |
| Elemental Analysis: | Calcd for $C_{17}H_{24}N_2O$: C, 74.96; H, 8.88; N, 10.28<br>Found: C, 74.98; H, 9.03; N, 10.34 |



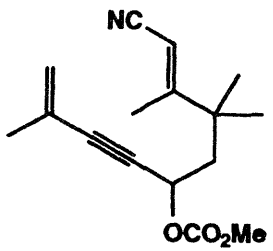

218


217 256

**(E)Methyl 9-cyano-2,7,7,8-tetramethylnona-1,8-dien-3-yn-5-yl carbonate (256).**

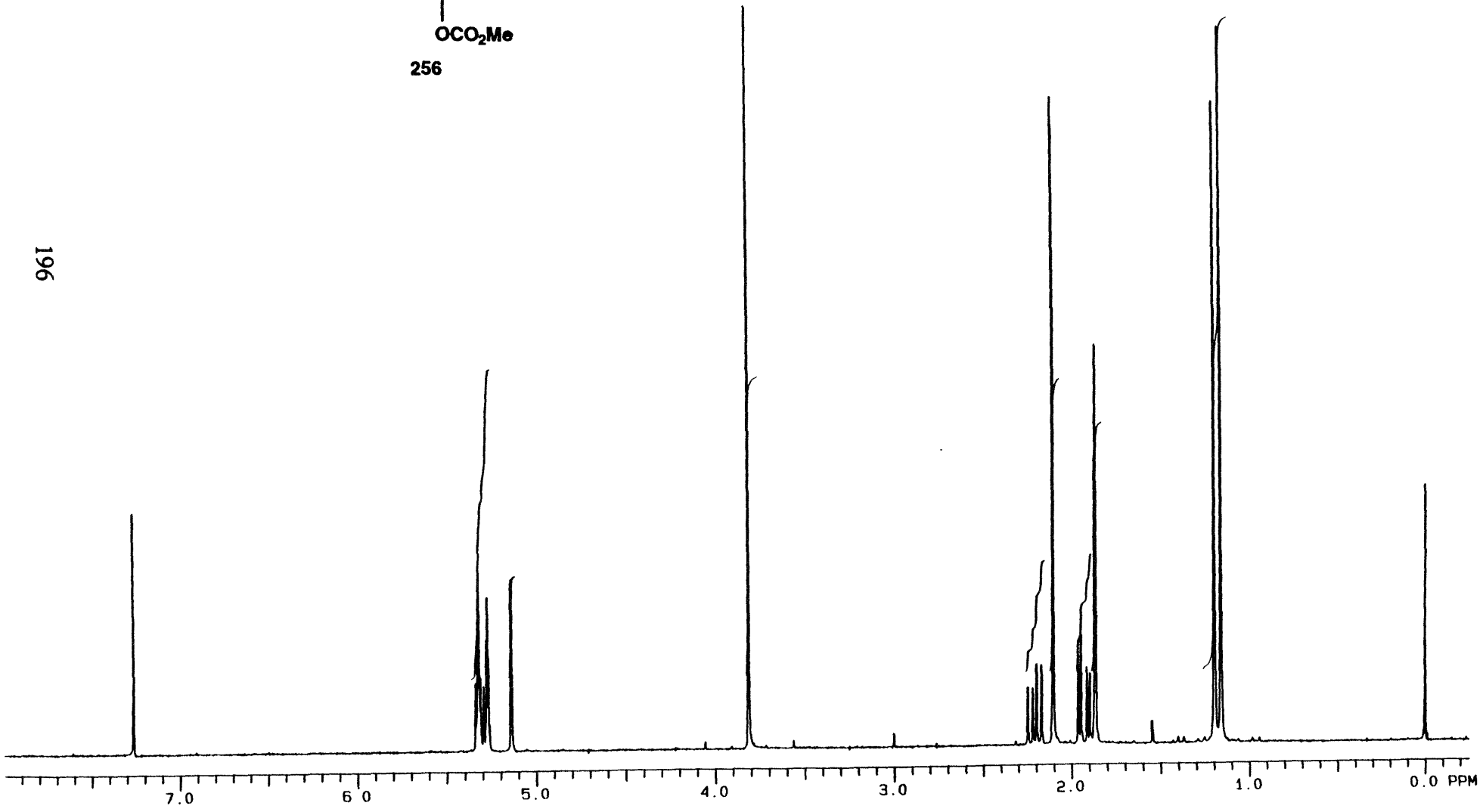
A 10-mL, round-bottomed flask was charged with propargyl alcohol **217** (216 mg, 0.994 mmol), 4-dimethylaminopyridine (183 mg, 1.50 mmol), and 4 mL of dichloromethane. The reaction mixture was cooled at 0 °C while methyl chloroformate (0.10 mL, 1.3 mmol) was added dropwise via syringe over 30 sec. The ice bath was removed and the reaction mixture was stirred at room temperature for 30 min. After this time, the stirbar was removed and the reaction mixture was concentrated to half of its original volume. Pentane (8 mL) was added to the flask and the resulting suspension was filtered, washing the solids with 10 mL of pentane. Concentration of the filtrate gave 302 mg of a greyish oil. The residue was further concentrated by Kugelrohr distillation (bath temperature 60 °C, 0.1 mmHg), and Kugelrohr distillation of the residual brown oil (bath temperature 130 °C, 0.1 mmHg) afforded 261 mg (95%) of **256** as a very pale brown oil.

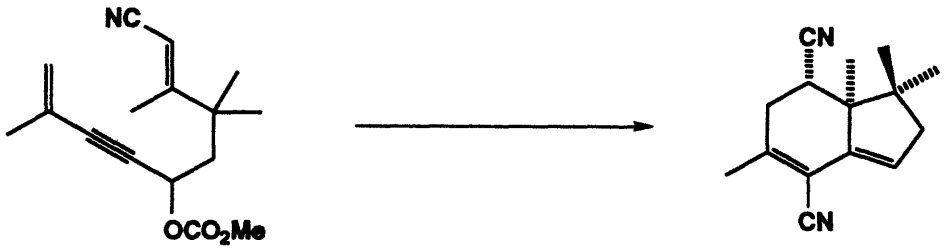
| | |
|---|---|
| IR (thin film): | 3080, 2960, 2870, 2215, 1750, 1610, 1440, 1375, 1340, 1265, 1125, 1050, 1000, 940, 920, and 785 $cm^{-1}$ |
| $^1H$ NMR (300 MHz, $CDCl_3$): | 5.32 (br s, 1H), 5.32 (dd, J = 8.3, 4.7 Hz, 1H), 5.27 (appar quintet, J = 1.3 Hz, 1H), 5.14 (appar d, J = 1.6 Hz, 1H), 3.81 (s, 3H), 2.21 (dd, J = 15, 8.5 Hz, 1H), 2.11 (d, J = 1.0 Hz, 3H), 1.93 (dd, J = 15, 4.6 Hz, 1H), 1.87 (appar t, J = 1.5 Hz, 3H), 1.20 (s, 3H), and 1.16 (s, 3H) |
| $^{13}C$ NMR (75 MHz, $CDCl_3$): | 169.9, 154.5, 125.5, 123.2, 117.2, 95.0, 87.7, 84.3, 65.4, 55.1, 45.5, 39.6, 27.4, 26.2, 23.2, and 18.0 |
| Elemental Analysis: | Calcd for $C_{16}H_{21}NO_3$: C, 69.79; H, 7.69; N, 5.09<br>Found: C, 70.06; H, 7.62; N, 5.11 |




256





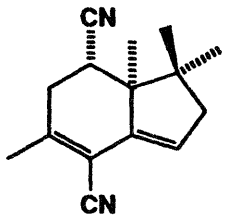



256 257

**(7R*,7aR*)-7-Cyano-1,1,5,7a-tetramethyl-2,6,7,7a-tetrahydro-1H-indene-4-carbonitrile (257).**

A 10-mL, one-necked, round-bottomed flask was charged with propargylic carbonate **256** (165 mg, 0.600 mmol), $Pd(PPh_3)_4$ (35 mg, 0.030 mmol), 6 mL of toluene, and TMSCN (0.160 mL, 1.20 mmol). A reflux condenser, equipped with an argon inlet adapter, was fitted to the flask and the reaction mixture was heated at reflux for 39 h. The reaction mixture was cooled to room temperature and the dark red / purple solution was filtered through 2 g of florisil® with 40 mL of diethyl ether and concentrated to give 151 mg of a dark red solid. Column chromatography on 4.5 g of silica gel (gradient elution with 0-8% ethyl acetate / petroleum ether) gave 99 mg of pale yellow solid. Recrystallization from ca. 10 mL of hexanes yielded (in two crops) 92 mg (68%) of **257** as an off-white solid (mp 155-155.5 °C).

| | |
|---|---|
| IR (KBr): | 3050, 2970, 2875, 2835, 2230, 2220, 1600, 1470, 1435, 1420, 1370, 1265, 1195, 980, and 845 $cm^{-1}$ |
| $^1H$ NMR (300 MHz, $CDCl_3$): | 5.86 (br s, 1H), 2.82 (ABC pattern, appar t, J = 8.3 Hz, 1H), 2.62 (ABC pattern, appar d, J = 8.0 Hz, 2H), 2.51 (br d, J = 17 Hz, 1H), 2.15 (dd, J = 17, 3.0 Hz, 1H), 2.13 (br s, 3H), 1.25 (s, 3H), 1.03 (s, 3H), and 1.02 (s, 3H) |
| $^{13}C$ NMR (75 MHz, $CDCl_3$): | 147.9, 139.1, 125.8, 119.6, 115.3, 107.6, 48.1, 46.6, 44.8, 33.4, 28.9, 25.1, 22.5, 22.1, and 15.7 |
| Elemental Analysis: | Calcd for $C_{15}H_{18}N_2$: C, 79.61; H, 8.02; N, 12.38<br>Found: C, 79.64; H, 7.95; N, 12.37 |




257

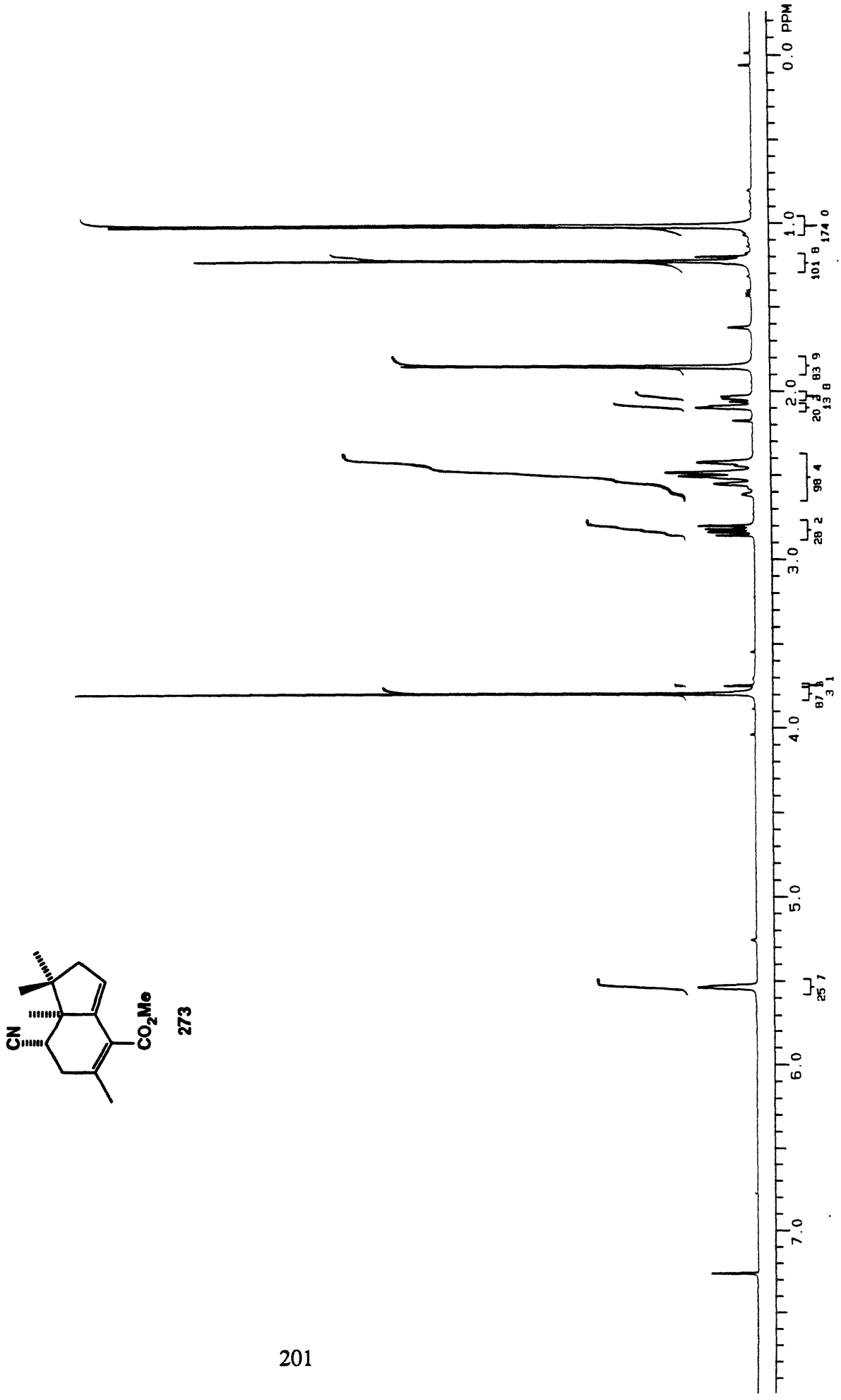

256 273

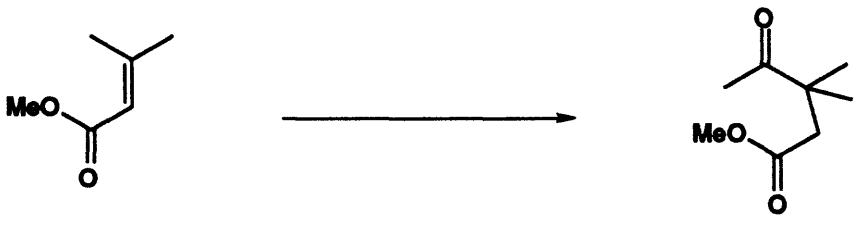
**(7R*,7aR*)Methyl 7-cyano-1,1,5,7a-tetramethyl-2,6,7,7a-tetrahydro-1H-indene-4-carboxylate (273).**

A 100-mL, one-necked, round-bottomed flask was charged with $Pd_2(dba)_3$ (114 mg, 0.125 mmol), dppp (206 mg, 0.500 mmol), and 20 mL of benzene. The catalyst was stirred for 5 min to give an olive green solution and a solution of propargyl carbonate **256** (131 mg, 0.310 mmol) in 15 mL of benzene and 10 mL of methanol was added by cannula over 1 min (with a 5 mL benzene rinse). The system was flushed with CO and a reflux condenser, equipped with a CO balloon, was fitted to the flask. The reaction mixture was heated at 50-60 °C for 44 h. The cooled orange/brown solution was filtered through 5 g of florisil® with 40 mL of diethyl ether and concentrated to give 960 mg of a brown oil. Column chromatography on 48 g of silica gel (gradient elution with 20-70% dichloromethane / petroleum ether) resulted in the isolation of 442 mg of impure product. Repeated flash chromatography on silica gel (elution with dichloromethane / benzene / petroleum ether) afforded 264 mg of ~90% pure **273** as a colorless oil and 80 mg of ~95 % pure **273** (combined yield ca. 50%) as a colorless solid (mp 65-70 °C).

| | |
|---|---|
| IR (KBr): | 2960, 2840, 2230, 1720, 1635, 1430, 1365, 1290, 1265, 1225, 1200, 1105, 1060, 980, and 785 $cm^{-1}$ |
| $^1H$ NMR (300 MHz, $CDCl_3$): | 5.26 (br s, 1H), 3.80 (s, 3H), 2.84 (ABX pattern, appar dd, J = 11, 6.2 Hz, 1H), 2.56 (ABX pattern, appar dd, J = 19, 11 Hz, 1H), 2.48 (ABX pattern, appar dd, J = 18, 5.7 Hz, 1H), 2.46 (d, J = 17 Hz, 1H), 2.08 (dd, J = 17, 3.0 Hz, 1H), 1.86 (s, 3H), 1.24 (s, 3H), and 1.03 (s, 6H), |

| | | |
|---|---|---|
| $^{13}C$ NMR (75 MHz, $CDCl_3$): | 168.2, 139.6, 135.0, 126.0, 123.6, 120.3, 51.6, 48.1, 46.7, 44.0, 33.3, 29.2, 25.1, 22.6, 20.5, and 15.6 | |
| HRMS: | Calcd for $C_{16}H_{21}O_2N$: | 259.1572 |
| | Found: | 259.1571 |


CN
CO2Me
273
0.0 PPM
1.0
2.0
3.0
4.0
5.0
6.0
7.0

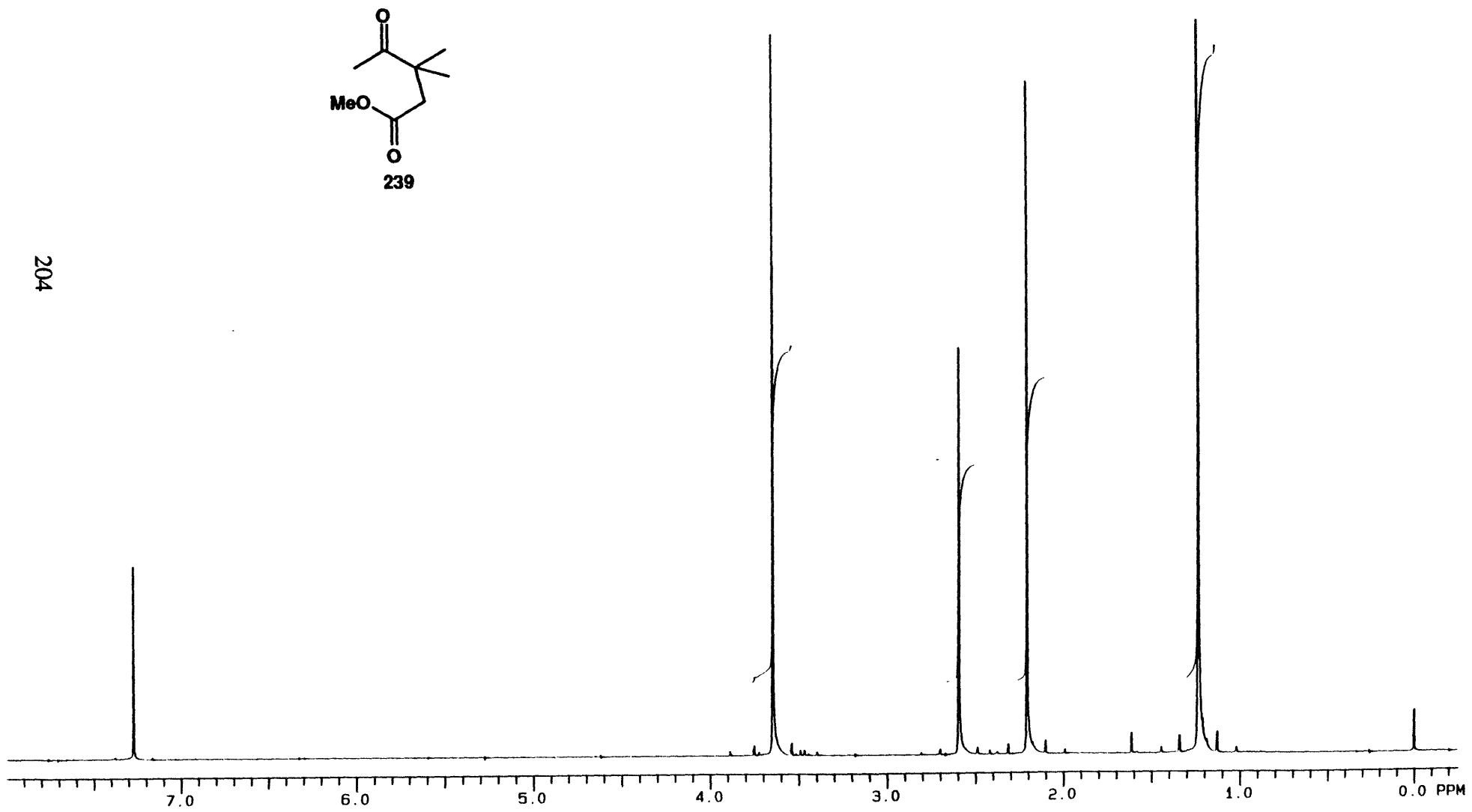


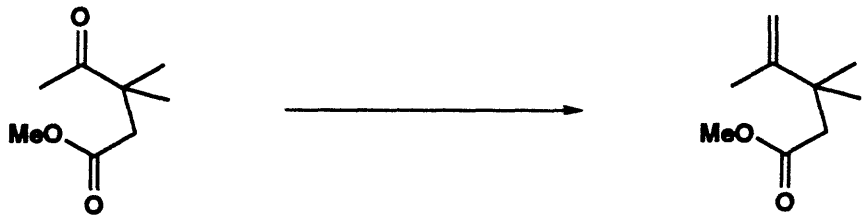

238 239

**Methyl 3,3-dimethyl-4-oxopentanoate (239).**

A 600-mL photochemical well was charged with methyl 3,3-dimethylacrylate (**238**, 24.31 g, 213 mmol), 350 mL of benzene, 200 mL of acetaldehyde (excess) and benzophenone (3.88 g, 21.3 mmol). The system was purged with argon gas and irradiated, at room temperature, with a 450 W medium pressure Hanovia lamp equipped with a uranium filter. After 86 h, the pale green solution was transferred to a 1 L round-bottomed flask and the solvent was removed by distillation at atmospheric pressure through a short path distillation head. Continued distillation provided a fraction at 160-205 °C consisting of a 3 : 1 mixture of desired product and ß-dicarbonyl isomer. This mixture was dissolved in 200 mL of diethyl ether in a 500 mL, one-necked, round-bottomed flask and DBU (6.4 g, 42 mmol) was added in one portion by syringe. The reaction mixture was stirred for 5 min and 5 g of paraformaldehyde (excess) was added. The orange-pink colored suspension was stirred for 2.5 h at 25 °C and then filtered. The filtrate was transferred to a separatory funnel with 50 mL of ether and washed with two 100-mL portions of 5% aqueous HCl. The combined aqueous phases were extracted with two 50-mL portions of diethyl ether, and the combined organic fractions were washed with 50 mL of saturated aqueous $NaHCO_3$, dried over $MgSO_4$, filtered, and concentrated to give 25.3 g of light brown oil. Column chromatography on a total of 370 g of silica gel, in two approximately equal sized runs, (gradient elution with 4-24% diethyl ether / pentane) afforded after concentration of the appropriate fractions by distillation, 9.07 g (27%) of ketoester **239** as a colorless oil.

| | | |
|---|---|---|
| IR (thin film): | 2960, 1735, 1705, 1460, 1435, 1385, 1355, 1215, 1165, 1135 and 1010 $cm^{-1}$ | |
| $^1H$ NMR (300 MHz, $CDCl_3$): | 3.65 (s, 3H), 2.59 (s, 2H), 2.21 (s, 3H), and 1.23 (s, 6 H) | |
| $^{13}C$ NMR (75 MHz, $CDCl_3$): | 211.9, 171.1, 51.4, 45.8, 43.7, 25.2, and 24.9 | |
| HRMS: | Calcd for $C_8H_{14}O_3$: | 158.0943 |
| | Found: | 158.0943 |


O
MeO
O
239
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0 PPM

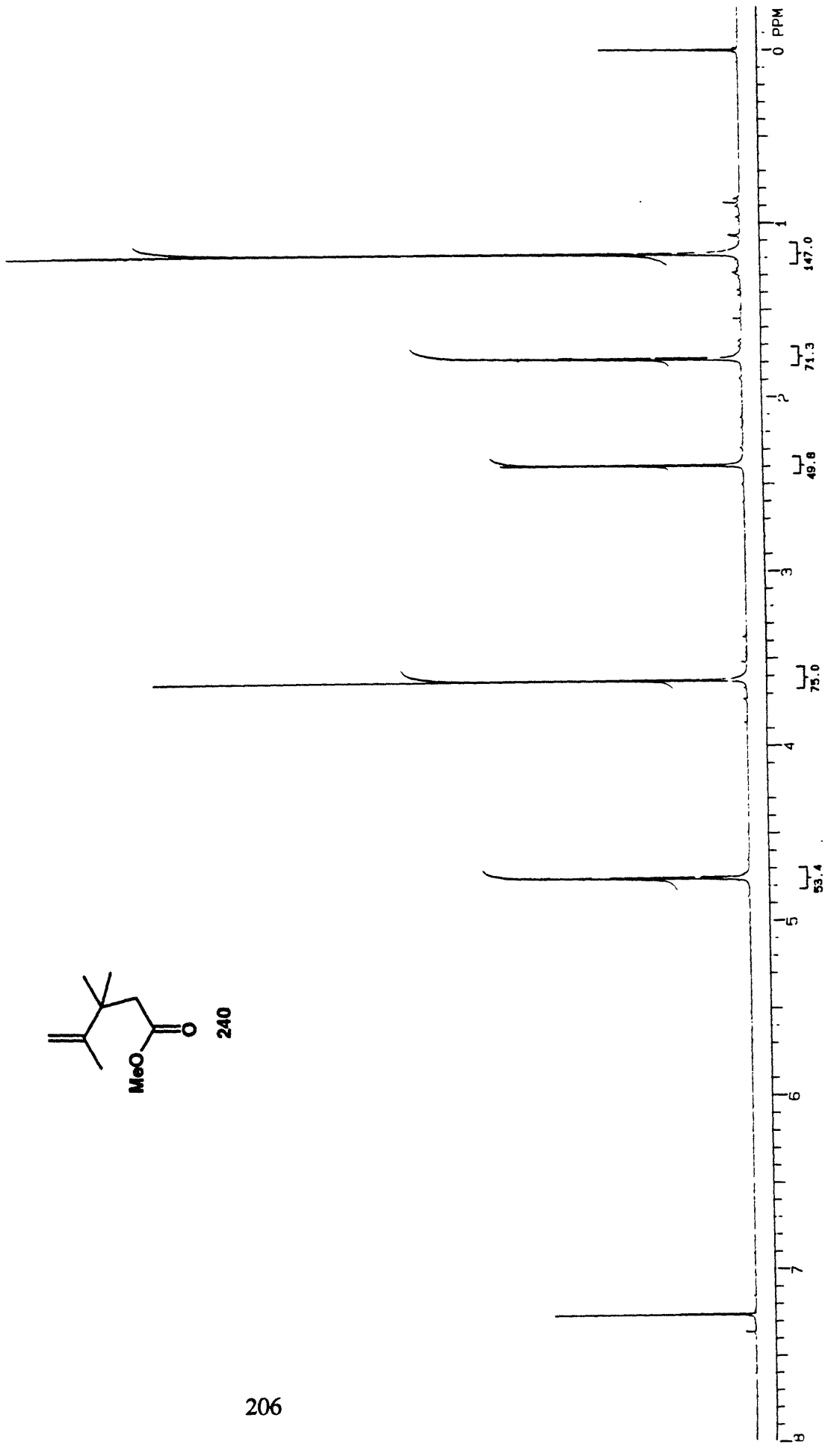


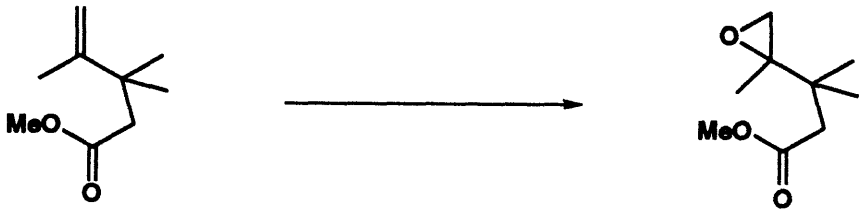

239 240

**Methyl 3,3,4-trimethylpent-4-enoate (240).**

A 250-mL, three-necked round-bottomed flask equipped with a mechanical stirrer, a septum and an argon inlet adapter was charged with methyltriphenylphosphonium bromide (32.1 g, 89.9 mmol), 200 mL of diethyl ether, and KO*t*-Bu (10.1 g, 90.0 mmol) to give a yellow suspension which was stirred vigorously under argon for 30 min. The septum was then replaced by a glass stopper and the argon inlet by a short path distillation apparatus. The solvent was distilled off at atmospheric pressure and the resulting yellow-brown slurry was heated to 60-70 °C. The distillation apparatus was replaced by a reflux condenser and the keto ester (9.49 g, 60.0 mmol) was added dropwise via cannula over 5 min (EXOTHERMIC REACTION). The slurry was stirred at 60-70 °C for 3.5 h after which it was cooled to room temperature. Water (20 mL) followed by 50 mL pentane were added with vigorous stirring. The organic layer was decanted and the slurry was extracted with three 50-mL portions of pentane. The combined organic phases were dried over $MgSO_4$, filtered, and the solvent removed by distillation. The residual oil was distilled (160-173 °C) to give 3.64 g (39%) of **240** as a colorless oil.

| | |
|---|---|
| IR (thin film): | 2960, 1735, 1635, 1435, 1320, 1190, 1110, 1015 and 890 $cm^{-1}$ |
| $^1H$ NMR (300 MHz, $CDCl_3$): | 4.74 (s, 2H), 3.61 (s, 3H), 2.38 (s, 2H), 1.77 (s, 3H), and 1.16 (s, 6H) |
| $^{13}C$ NMR (75 MHz, $CDCl_3$): | 172.3, 151.1, 109.6, 51.1, 45.3, 38.4, 27.1, and 19.5 |


MeO
O
240
PPM
147.0
71.3
49.8
75.0
53.4



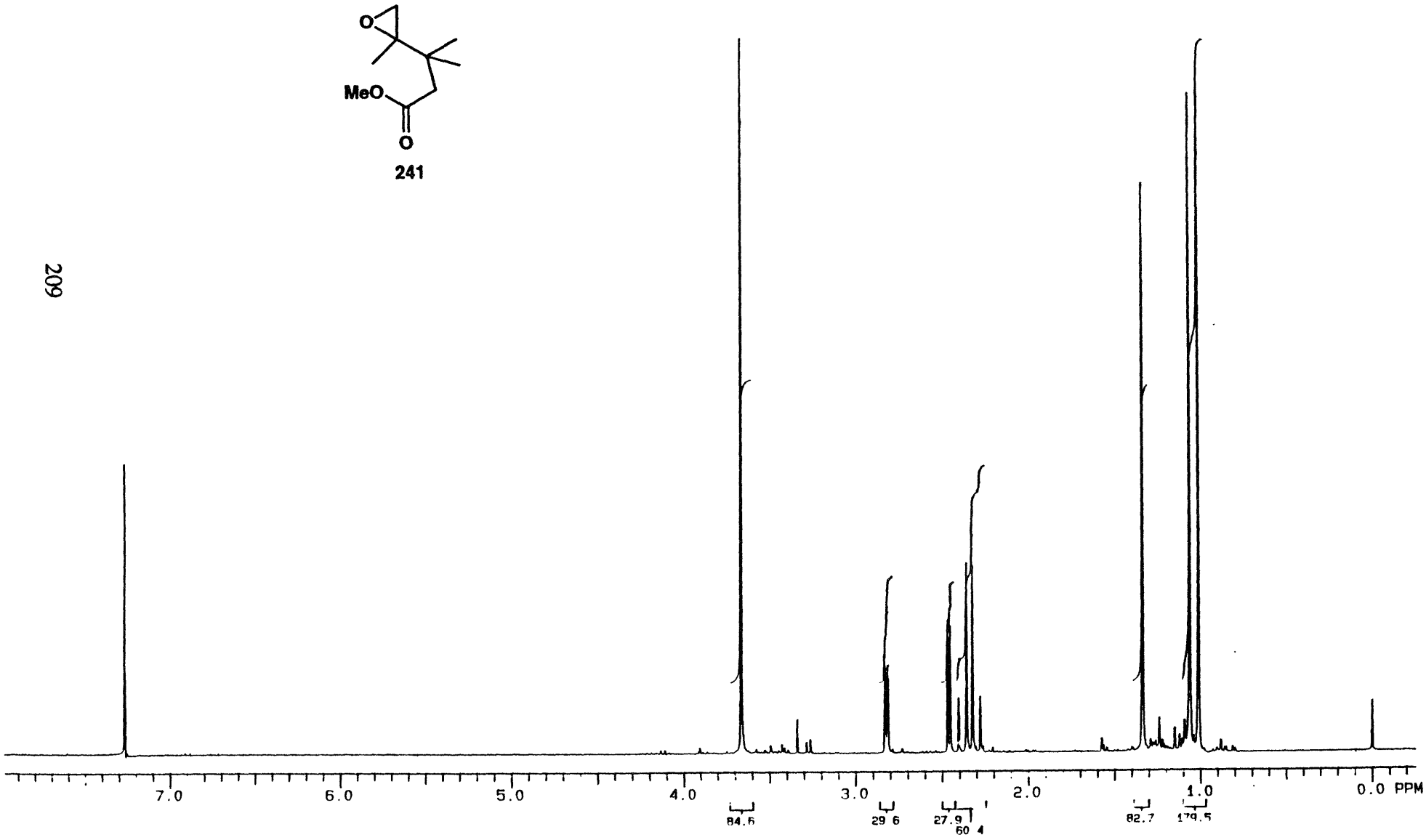

240 241

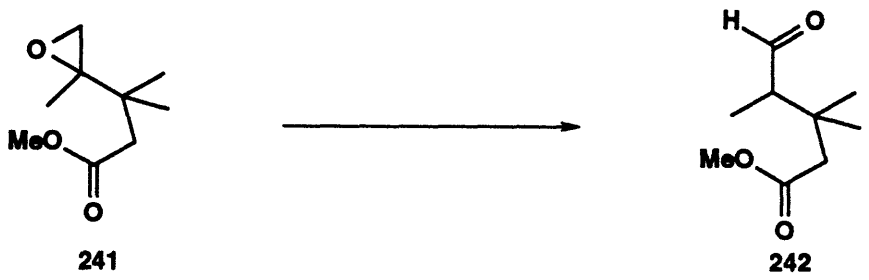
**Methyl 4,5-epoxy-3,3,4-trimethylpentanoate (241).**

A 250-mL, three-necked round-bottomed flask equipped with a glass stopper, a rubber septum, and an argon inlet adapter was charged with olefin **240** (3.515 g, 22.5 mmol) and 100 mL of dichloromethane. The solution was cooled to 0 °C and *m*-CPBA (4.66 g, 23.0 mmol) was added all at once. The ice bath was removed and the resulting white suspension was stirred at 25 °C for 1.5 h. The contents of the flask were poured into a 500-mL separatory funnel containing 100 mL of pentane and 50 mL of saturated aqueous $NaHCO_3$ solution (EFFERVESCENCE!!). The organic phase was separated and washed with three 50-mL portions of saturated aqueous $NaHCO_3$. The combined aqueous phases were back-extracted with two 50-mL portions of pentane. The combined organic phases were washed with one 50-mL portion of saturated aqueous $NaHCO_3$ solution and dried over anhydrous $Na_2CO_3$. Removal of the solvent by distillation through a short path head afforded 4.759 g of a very light yellow oil which was further purified by distillation in a Kugelrohr oven (60 °C, 3-5 mmHg) to give 3.150 g (81%) of **241** as a colorless oil.

| | |
|---|---|
| IR (thin film): | 2960, 1730, 1430, 1375, 1340, 1320, 1185, 1110, 1065 and 1015 $cm^{-1}$ |
| $^1H$ NMR (300 MHz, $CDCl_3$): | 3.66 (s, 3 H), 2.82 (appar dd, J = 4.5 and 0.8 Hz, 1H), 2.46 (d, J = 4.4 Hz, 1H), 2.38 (d, AB pattern, $J_{AB}$ = 14 Hz, 1H), 2.30 (d, AB pattern, $J_{AB}$ = 14 Hz, 1H), 1.34 (s, 3H), 1.06 (s, 3H) and 1.01 (s, 3H) |
| $^{13}C$ NMR (75 MHz, $CDCl_3$): | 172.1, 60.7, 51.8, 51.3, 43.2, 36.2, 24.0, 22.9, and 18.4 |

| | | |
|---|---|---|
| HRMS: | Calcd for $C_9H_{16}O_3$: | 172.1099 |
| | Found: | 172.1096 |


O
MeO
O
241
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0 PPM
84.6
29.6
27.9
60.4
82.7
179.5

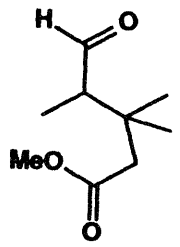



241 242

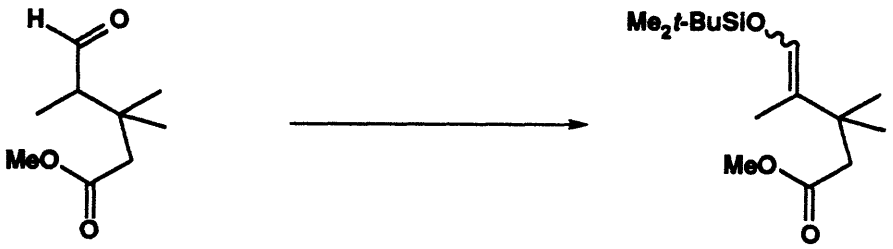
**Methyl 3,3,4-trimethyl-5-oxopentanoate (242).**

A 100-mL, one-necked, round-bottomed flask was charged with epoxide **241** (1.550 g, 9.00 mmol), 50 mL of benzene, and $LiClO_4$ (48 mg, 0.45 mmol), and equipped with a reflux condenser fitted with an argon inlet adapter. The colorless suspension was heated at reflux for 26 h after which time it was cooled to 25 °C. The resulting solution was transferred to a 250-mL separatory funnel, containing 50 mL of pentane, and washed with 10 ml of water. The aqueous layer was extracted with two 15-mL portions of pentane and the combined organic layers were dried over anhydrous $K_2CO_3$. Filtration and concentration by distillation at atmospheric pressure gave 1.514 g of the crude aldehyde as an almost colorless oil. Chromatography on 35 g of silica gel (gradient elution with 5-10% diethyl ether / pentane), concentration of the appropriate fractions by distillation through a short path head, and final concentration at 0 °C, on a rotary evaporator, afforded 0.832 g of aldehyde **242** as a colorless oil.

| | | |
|---|---|---|
| IR (thin film): | 2960, 2715, 1725, 1435, 1370, 1350, 1330, 1220, 1150, and 1010 $cm^{-1}$ | |
| $^1H$ NMR (300 MHz, $CDCl_3$): | 9.83 (d, J = 2.7 Hz, 1H), 3.67 (s, 3H), 2.52 (dq, J = 6.8 and 2.5 Hz, 1H), 2.36 (s, 2H), 1.16 (s, 3H), 1.10 (s, 3H), and 1.08 (d, J = 7.2 Hz, 3H) | |
| $^{13}C$ NMR (75 MHz, $CDCl_3$): | 205.0, 171.9, 53.3, 51.2, 44.3, 35.2, 25.3, 25.0 and 8.9 | |
| HRMS: | Calcd for $C_9H_{16}O_3$: | 172.1099 |
| | Found: | 172.1096 |




242




242 260

**Methyl 3,3,4-trimethyl-5-(*t*-butyldimethylsilyloxy)pent-4-enoate (260).**

A 25-mL, two-necked, round-bottomed flask equipped with an argon inlet adapter and a rubber septum was charged with aldehyde **242** (516 mg, 3.00 mmol), 18 mL of DMF, $Et_3N$ (1.05 mL, 7.53 mmol), and MTBSTFA (1.05 mL, 4.45 mmol). The argon inlet adapter was replaced by a glass stopper and the septum was replaced by a reflux condenser fitted with an argon inlet adapter. The reaction mixture was heated at 85 °C for 3 h at which time more MTBSTFA (0.35 mL, 1.5 mmol) was added via syringe. The solution was heated at the same temperature for an additional 13 h and then cooled to 25 °C. The solvent and reagents were then removed *in vacuo* to give 1.77 g of a light brown oil which is a 3/1 mixture of the E and Z products respectively. Purification was achieved on 35.5 g of silica gel eluting with 0.5% $Et_3N$-pentane to afford a total of 0.669 g (78%) of **260** (63 mg of an 82/18 mixture of Z/E isomers, 72 mg of a ca. 1/1 mixture of both isomers, and 534 mg of an 86/14 mixture of E/Z isomers).

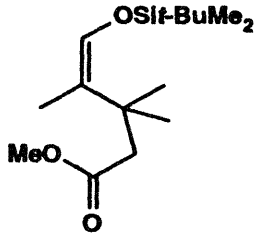
For the Z isomer:

| | |
|---|---|
| IR (thin film): | 2950, 2860, 1735, 1645, 1455, 1430, 1340, 1250, 1155, 1110, 835, and 775 $cm^{-1}$ |
| $^1H$ NMR (300 MHz, $CDCl_3$): | 5.98 (q, J = 1.5 Hz, 1H), 3.60 (s, 3H), 2.69 (s, 2H), 1.52 (d, J = 1.5 Hz, 3H), 1.19 (s, 6H), 0.92 (s, 9H), and 0.10 (s, 6H) |
| $^{13}C$ NMR (75 MHz, $CDCl_3$): | 173.0, 134.0, 119.9, 50.8, 44.8, 35.5, 27.3, 27.1, 25.6, 18.0, 17.0, and -5.5 |

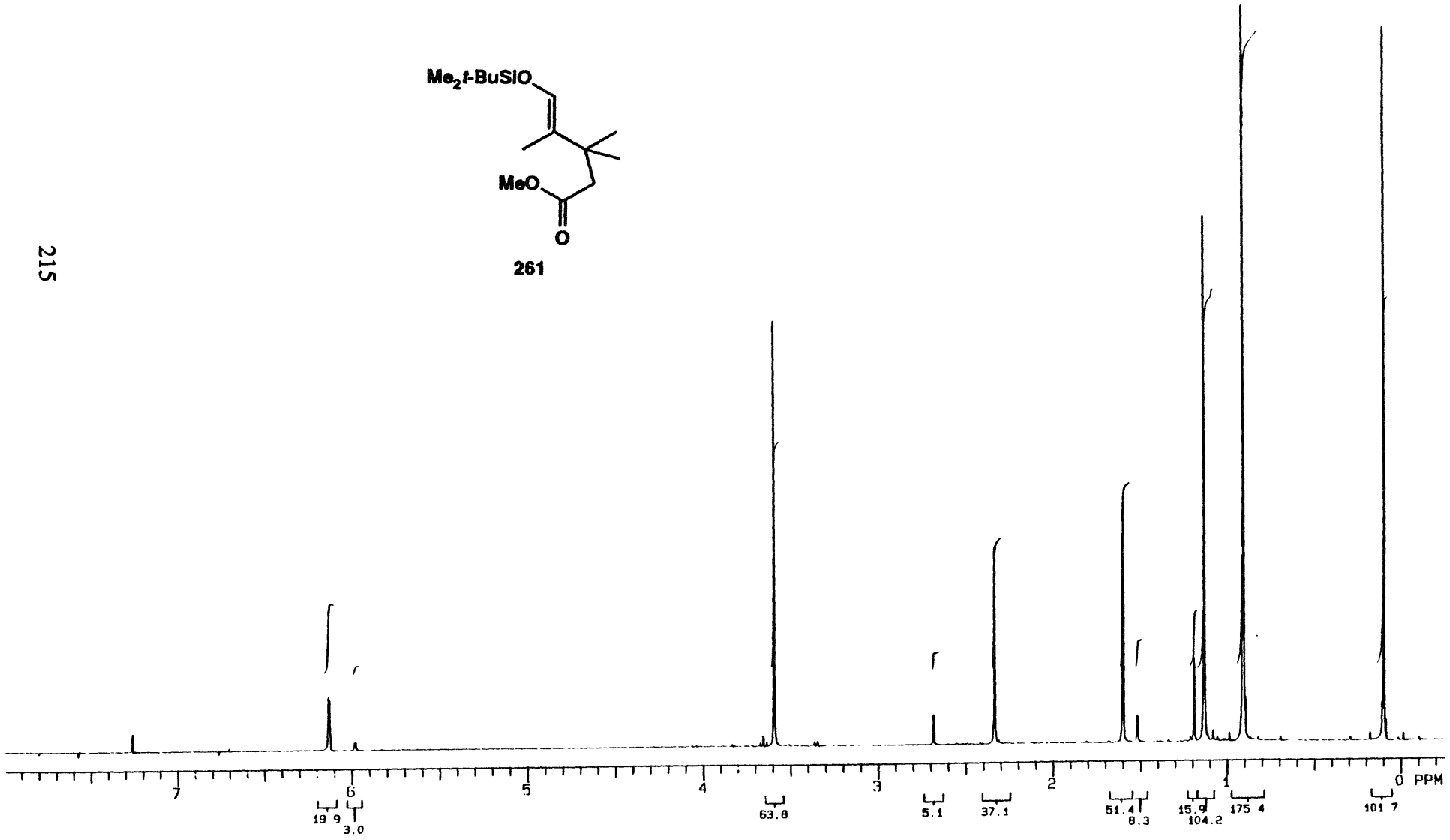
For the E isomer

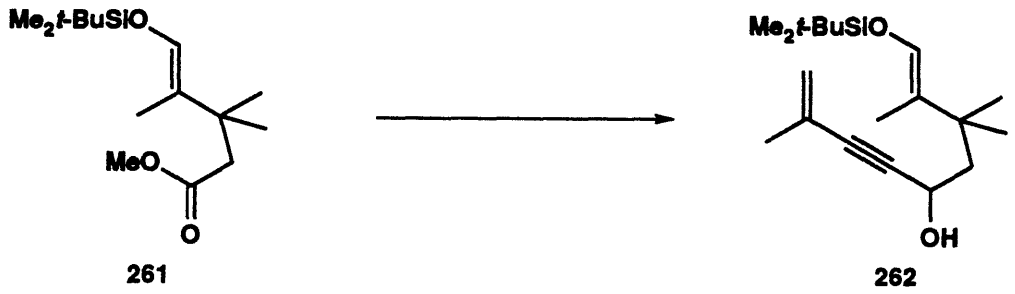
| | |
|---|---|
| IR (thin film): | 2940, 2840, 1730, 1650, 1460, 1250, 1200, 1160, 1110, and 835 $cm^{-1}$ |

| | |
|---|---|
| $^{1}H$ NMR (300 MHz, $CDCl_3$): | 6.14 (q, J = 1.3 Hz, 1H), 3.59 (s, 3H), 2.34 (s, 2H), 1.60 (d, J = 1.5 Hz, 3H), 1.13 (s, 6H), 0.91 (s, 9H), and 0.10 (s, 6H) |
| $^{13}C$ NMR (75 MHz, $CDCl_3$): | 172.3, 134.3, 123.4, 51.0, 45.5, 36.4, 27.1, 25.7, 18.3, 9.7, and -5.3 |




264


Me2t-BuSiO
MeO
O
261
7
6
5
4
3
2
1
0 PPM
19 9
3.0
63.8
5.1
37.1
51.4
8.3
15.9
104.2
175 4
101 7




261 262

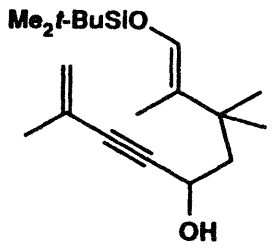
**(E)-2,7,7,8-tetramethyl-9-(*tert*-butyldimethylsilyloxy)nona-1,8-dien-3-yn-5-ol (262).**

A 10-mL, one-necked, round-bottomed flask was charged with 2 mL of diethyl ether and 2-methyl-but-1-en-3-yne (0.095 mL, 1.0 mmol). The acetylene solution was cooled to -30 °C while *n*-butyllithium solution (2.63 M in hexanes, 0.31 mL, 0.82 mmol) was added dropwise, by syringe, over 1 min. The resulting light yellow solution was stirred at -30 °C for 15 min and then cooled to -78 °C.

A 5-mL, one-necked, round-bottomed flask was charged with ester **261** (57.6 mg, 0.201 mmol) and 2 mL of dichloromethane. This solution was cooled to -78 °C and a DIBAL-H solution (1.0 M in hexanes, 0.30 mL, 0.30mmol) was added dropwise by syringe, along the side of the flask, over 3 min. The reaction mixture was stirred at -78 °C for 1 h and the acetylide solution was added via cannula over 1 min. The reaction mixture was stirred for 20 min, while allowing the temperature to go from -78 °C to -40 °C, and finally quenched with 1.5 mL of Rochelle's solution. The resulting mixture was brought to room temperature, with rapid stirring, and the two phases were separated. The aqueous phase was extracted with three 3-mL portions of pentane and the combined organic layers were dried over anhydrous $K_2CO_3$. Filtration and concentration afforded 64.1 mg of a colorless oil. Flash chromatography on 1.2 g of silica gel (elution with 1% ethyl acetate / pentane) followed by chromatography on 3 g of silica gel (gradient elution with 0-1% ethyl acetate / pentane) afforded 48.1 mg (74 %) of **262** as a colorless oil.

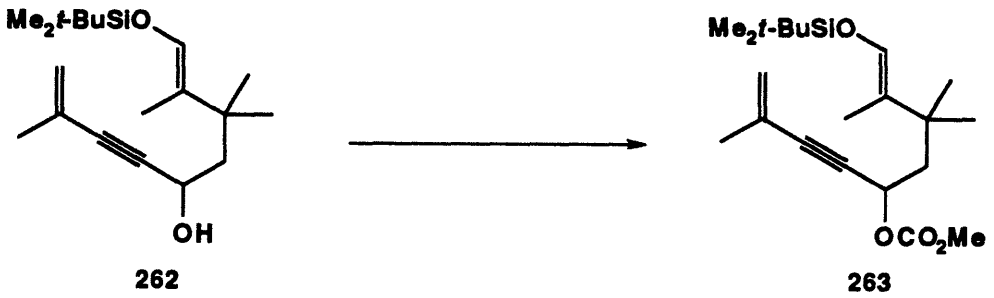
IR (thin film): 3360, 2940, 2860, 1645, 1610, 1460, 1370, 1250, 1170, 1110, 835, and 775 $cm^{-1}$

| | |
|---|---|
| $^1$H NMR (300 MHz, $CDCl_3$): | 6.16 (q, J = 1.4 Hz, 1H), 5.25 (br s, 1H), 5.19 (appar quintet, J = 1.7 Hz, 1H), 4.41 (dd, J = 6.9, 5.4 Hz, 1H), 1.98 (br s, 1H), 1.89 (dd, J = 14, 7.2 Hz, 1H), 1.86 (appar t, J = 1.4 Hz, 3H), 1.78 (dd, J = 14, 5.3 Hz, 1H), 1.60 (d, J = 1.5 Hz, 3H), 1.10 (s, 3H), 1.08 (s, 3H), 0.92 (s, 9H), and 0.12 (s, 6H) |
| $^{13}$C NMR (75 MHz, $CDCl_3$): | 134.7, 126.3, 123.4, 121.7, 90.1, 85.5, 60.8, 48.3, 36.0, 28.2, 27.1, 25.8, 23.4, 9.8 and -5.3 |


Me2t-BuSIO
OH

262


8
7
6
5
4
3
2
1
0 PPM
15 3
0 7
15 0
14 0
13 3
10 3
63 6
36 8
77 1
116.2
63 9

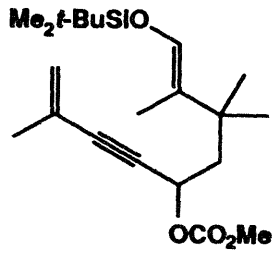



262 263

**(E) Methyl 2,7,7,8-tetramethyl-9-(*tert*-butyldimethylsilyloxy)nona-1,8-dien-3-yn-5-yl carbonate (263).**

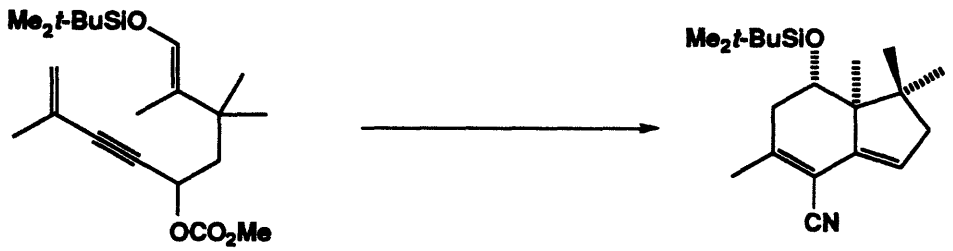
A 10-mL, one-necked, round-bottomed flask was charged with propargylic alcohol **262** (17.1 mg, 0.0530 mmol), 4-dimethylaminopyridine (16 mg, 0.13 mmol) and 1 mL of dichloromethane. The reaction mixture was cooled to 0 °C while methyl chloroformate (8 μL, 0.10 mmol) was added via syringe. The ice bath was removed and the reaction mixture was stirred at room temperature for 45 min. Pentane (2 mL) was added to the flask and the resulting suspension was filtered, washing the solids with 3 mL of pentane. The organic solution was concentrated and the crude product was taken up in 4 mL of pentane. Filtration and concentration gave 25.7 mg of material. Chromatography on 0.45 g of silica gel (elution with 2 % ethyl acetate / petroleum ether) afforded 19.3 mg (96%) of **263** as a colorless oil.

| | |
|---|---|
| IR (thin film): | 2950, 2920, 2850, 2220, 1745, 1640, 1440, 1260, 1170, 1115, 935, 835, and 780 $cm^{-1}$ |
| $^1H$ NMR (300 MHz, $CDCl_3$): | 6.11 (q, J = 1.1 Hz, 1H), 5.29 (br s, 1H), 5.23 (appar quintet, J = 1.5 Hz, 1H), 5.20 (t, J = 6.6 Hz, 1H), 3.78 (s, 3H), 1.99 (dd, J = 15, 6.8 Hz, 1H), 1.90 (dd, J = 15, 5.9 Hz, 1H), 1.86 (appar t, J = 1.5 Hz, 1H), 1.58 (d, J = 0.9 Hz, 3H), 1.09 (s, 3H), 1.06 (s, 3H), 0.92 (s, 9H), and 0.12 (s, 6H) |
| $^{13}C$ NMR (75 MHz, $CDCl_3$): | 154.7, 134.8, 126.1, 2 peaks at 122.5, 86.9, 86.1, 66.6, 54.7, 45.5, 35.9, 27.4, 25.7, 23.1, 18.2, 9.6, and -5.4 |
| HRMS: | Calcd for $C_{21}H_{36}O_4Si$: 380.2383<br>Found: 380.2382 |


Me2t-BuSiO
OCO2Me

263


7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0 PPM
17.8
17.4
34.4
50.9
77.1
47.5
94.4
149.6
80.2

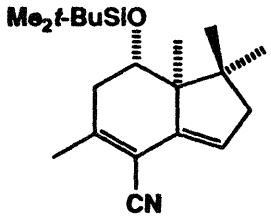



263 267

**(7R*,7aR*)-7-(*tert*-Butyldimethylsilyloxy)-1,1,5,7a-tetramethyl-2,6,7,7a-tetrahydro-1H-indene-4-carbonitrile (267).**

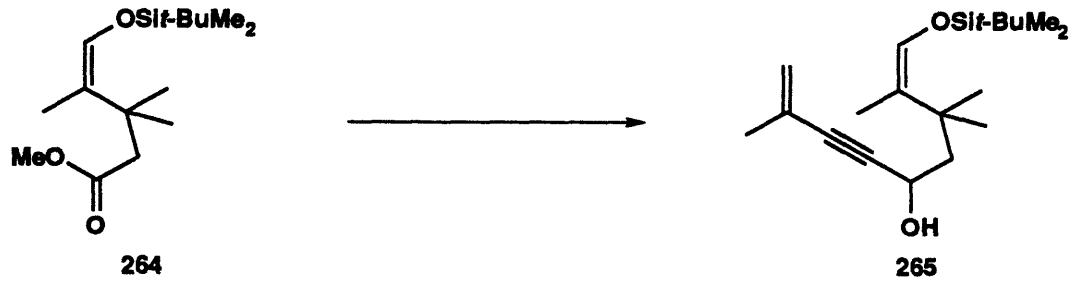
A 10-mL, round-bottomed flask was charged with propargyl carbonate **263** (16.4 mg, 0.0431 mmol), $Pd(PPh_3)_4$ (5.8 mg, 0.0050 mmol), 2 mL of toluene, and TMSCN (0.017 mL, 0.13 mmol). A reflux condenser, equipped with an argon inlet adapter, was fitted to the flask and the reaction mixture was heated at reflux for 1 h. The cooled dark red / purple solution was filtered through 0.4 g of florisil® with 5 mL of dichloromethane and concentrated to give 17.2 mg of a red solid. Chromatography on 0.84 g of silica gel (elution with 2% ethyl acetate / petroleum ether) resulted in the isolation of 16.0 mg of material. Chromatography on 0.40 g of silica gel (elution with 20% benzene / pentane) afforded 11.2 mg (78%) of **267** as a colorless solid (mp 124-126 °C). An analytical sample was obtained by recrystallization from aqueous methanol.

| | |
|---|---|
| IR (KBr): | 3038, 2956, 2217, 1633, 1602, 1470, 1434, 1374, 1264, 1095, 858, 834 and 774 $cm^{-1}$ |
| $^1H$ NMR (300 MHz, $CDCl_3$): | 5.73 (br s, 1H), 4.01 (ABX pattern, appar t, J = 7.8 Hz, 1H), 2.41 (br d, J = 17 Hz, 1H), 2.31 (ABX pattern, appar d, J = 7.3 Hz, 2H), 2.08 (s, 3H), 2.00 (dd, J = 17, 3.2 Hz, 1H), 1.14 (s, 3H), 0.97 (s, 3H), 0.90 (s, 9H), 0.83 (s, 3H), 0.10 (s, 3H), and 0.09 (s, 3H) |
| $^{13}C$ NMR (75 MHz, $CDCl_3$): | 150.1, 142.8, 124.5, 116.1, 107.1, 68.7, 51.5, 46.8, 44.5, 40.1, 25.9, 24.8, 23.9, 22.4, 18.0, 12.8, -3.2, and -4.3 |
| Elemental Analysis: | Calcd for $C_{20}H_{33}NOSi$:C, 72.45; H, 10.03; N, 4.22<br>Found: C, 72.70; H, 10.27; N, 4.12 |


Me2t-BuSiO
CN

267


7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0 PPM
1.0
18.7
21.0
20.3
41.2
58.6
22.8
59.1
58.0
52.2
96.6



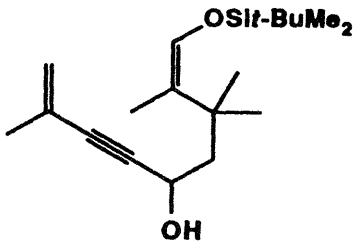

264 265

**(Z)-2,7,7,8-tetramethyl-9-(*tert*-butyldimethylsilyloxy)nona-1,8-dien-3-yn-5-ol (265).**

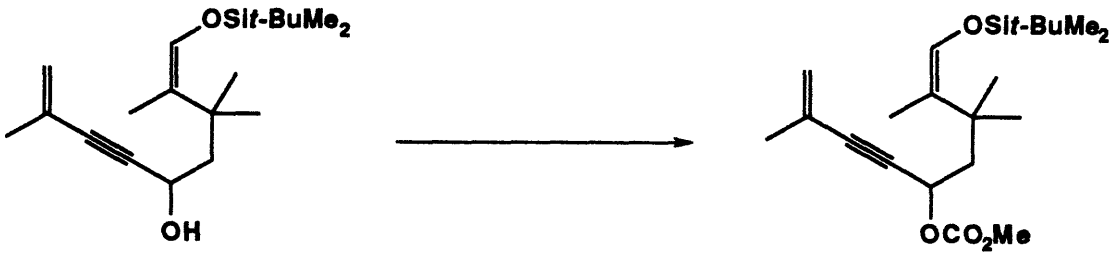
A 10-mL, one-necked, round-bottomed flask was charged with 2 mL of diethyl ether and 2-methyl-but-1-en-3-yne (0.095 mL, 1.0 mmol). The acetylene solution was cooled to -30 °C while *n*-butyllithium solution (2.44 M in hexanes, 0.34 mL, 0.83 mmol) was added dropwise, by syringe, over 1 min. The resulting light yellow solution was stirred at -30 °C for 15 min and then cooled to -78 °C.

A 25-mL, round-bottomed flask was charged with ester **264** (59.0 mg, 0.206 mmol; 9/1 ratio of Z to E isomers) and 4 mL of dichloromethane. This solution was cooled to -78 °C and a DIBAL-H solution (1.0 M in hexanes, 0.25 mL, 0.25mmol) was added dropwise, along the side of the flask, by syringe over 3 min. The reaction mixture was stirred at -78 °C for 40 min, and the acetylide solution was added, via cannula, over 1 min. The reaction mixture was stirred for 20 min, while allowing the temperature to go from -78 °C to 0 °C, and finally quenched with 2 mL of Rochelle's solution. The resulting mixture was brought to room temperature, stirred rapidly for 2 h, 10 mL of petroleum ether was added and the two phases were separated. The aqueous phase was extracted with two 10-mL portions of petroleum ether and the combined organic layers were dried over anhydrous $K_2CO_3$. Filtration and concentration afforded 71 mg of a colorless oil. Flash chromatography on 3 g of silica gel (elution with 0.5% $Et_3N$-petroleum ether) followed by chromatography on 1.5 g of deactivated silica gel (elution with 0-1% ethyl acetate / petroleum ether) afforded 28.1 mg (42 %) of alcohol **265** as a colorless oil.

| | |
|---|---|
| IR (thin film): | 3370, 2960, 2860, 1640, 1615, 1460, 1375, 1260, 1165, 1140, 1000, 835, and 770 $cm^{-1}$ |
| $^1H$ NMR (300 MHz, $CDCl_3$): | 6.05 (q, J = 1.3 Hz, 1 H), 5.24 (br s, 1H), 5.18 (appar quintet, J = 1.6 Hz, 1H), 4.58 (dt, J = 8.5 and 4.5 Hz, 1H), 2.25 (d, J = 5.0 Hz, 1H), 2.17 (dd, J = 14 and 8.5 Hz, 1 H), 1.96 (dd, J = 14 and 4.5 Hz, 1H), 1.86 (s, 3H), 1.52 (d, J = 1.2 Hz, 3H), 1.18 (s, 6 H), 0.93 (s, 9H), and 0.13 (s, 6H) |
| $^{13}C$ NMR (75 MHz, $CDCl_3$): | 134.7, 126.6, 121.4, 120.0, 90.7, 85.1, 61.5, 48.7, 36.2, 29.0, 28.0, 25.7, 23.4, 18.0, 17.2, and -5.4. |
| HRMS: | Calcd for $C_{19}H_{34}O_2Si$ 322.2328<br>Found: 322.2327 |




265

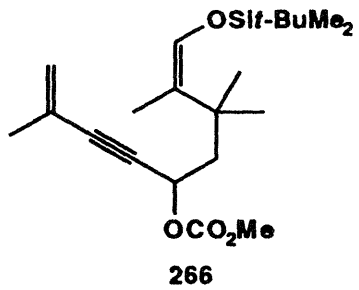



265 266

**(Z) Methyl 2,7,7,8-tetramethyl-9-(*tert*-butyldimethylsilyloxy)nona-1,8-dien -3-yn-5-yl carbonate (266).**

A 5-mL, one-necked, round-bottomed flask was charged with propargylic alcohol **265** (19.7 mg, 0.0611 mmol), 4-dimethylaminopyridine (14.8 mg, 0.121 mmol) and 1 mL of dichloromethane. The reaction mixture was cooled to 0 °C while methyl chloroformate (9 μL, 0.12 mmol) was added via syringe. The ice bath was removed and the reaction mixture was stirred at room temperature for 21 h. The reaction mixture was concentrated to give 50 mg of a light beige wet solid. Chromatography on 0.50 g of silica gel (gradient elution with 0-1 % ethyl acetate / petroleum ether) afforded 21.2 mg (91%) of **266** as a colorless oil.

| | |
|---|---|
| IR (thin film): | 2930, 2850, 1745, 1640, 1440, 1355, 1265, 1150, 1005, 940, 845, and 780 $cm^{-1}$ |
| $^1H$ NMR (300 MHz, $CDCl_3$): | 6.04 (appar d, J = 1.8 Hz, 1H), 5.36 (dd, J = 7.6, 5.6 Hz, 1H), 5.25 (br s, 1H), 5.20 (appar quintet, J = 1.8 Hz, 1H), 3.78 (s, 3H), 2.30 (dd, J = 14, 5.3 Hz, 1H), 2.10 (dd, J = 14, 7.8 Hz, 1H), 1.84 (appar t, J = 1.3 Hz, 1H), 1.48 (d, J = 1.2 Hz, 3H), 1.17 (s, 3H), 1.12 (s, 3H), 0.92 (s, 9H), and 0.13 (s, 6H) |
| $^{13}C$ NMR (75 MHz, $CDCl_3$): | 160.5, 155.0, 134.6, 126.2, 122.2, 118.7, two peaks at 86.6, 67.7, 54.7, 45.7, 36.1, 28.4, 28.2, 25.8, and -5.4. |



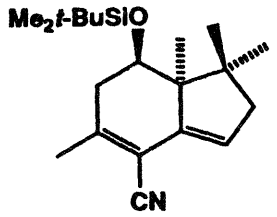

266


266 268

**(7R*,7aS*)-7-(*tert*-Butyldimethylsilyloxy)-1,1,5,7a-tetramethyl-2,6,7,7a-tetrahydro-1H-indene-4-carbonitrile (268).**

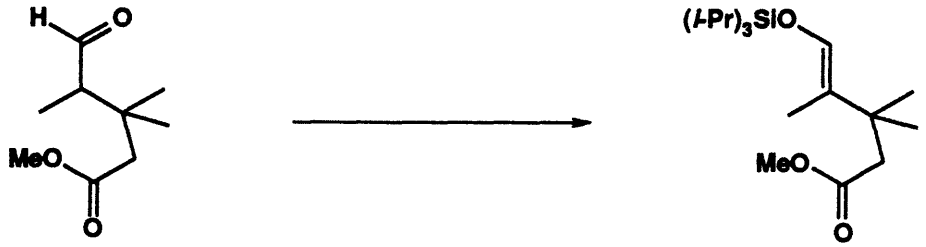
A 5-mL, one-necked, round-bottomed flask was charged with propargyl carbonate **266** (16.4 mg, 0.0431 mmol), $Pd(PPh_3)_4$ (5.7 mg, 0.0049 mmol), 2 mL of toluene, and TMSCN (0.017 mL, 0.13 mmol). A reflux condenser, equipped with an argon inlet adapter, was fitted to the flask and the reaction mixture was heated at reflux for 2 h. The cooled dark red / purple solution was passed through 0.4 g of florisil® with 5 mL of dichloromethane and concentrated to give 16.8 mg of an almost colorless oil. Column chromatography on 0.40 g of silica gel (elution with 5% benzene / petroleum ether) resulted in the isolation of 12.3 mg of material. Preparative thin layer chromatography on silica gel (elution with 50% dichloromethane / petroleum ether) afforded 11.2 mg (78%) of **268** as a colorless solid (mp 43.0-44.0 °C).

| | | |
|---|---|---|
| IR (KBr): | 2956, 2858, 2222, 1637, 1473, 1389, 1259, 1090, 838, and 775 $cm^{-1}$ | |
| $^1H$ NMR (300 MHz, $CDCl_3$): | 5.79 (br s, 1H), 3.96 (ABX pattern, appar t, J = 2.9 Hz, 1H), 2.59 (ABX pattern, appar br d, J = 19 Hz, 1H), 2.41 (br d, J = 16 Hz, 1H), 2.23 (ABX pattern, appar dd, J = 19, 1.9 Hz, 1H), 2.06 (s, 3H), 2.03 (dd, J = 17, 3.0 Hz, 1H), 1.11 (s, 3H), 1.07 (s, 3H), 0.81 (s, 9H), 0.75 (s, 3H), 0.06 (s, 3H), and 0.03 (s, 3H) | |
| $^{13}C$ NMR (75 MHz, $CDCl_3$): | 147.8, 140.3, 124.2, 116.4, 106.7, 69.8, 52.1, 47.6, 45.4, 40.7, 29.0, 26.0, 24.4, 22.8, 20.1, 18.2, -3.5 and -3.7 | |
| HRMS: | Calcd for $C_{20}H_{33}NOSi$: | 331.2331 |
| | Found: | 331.2327 |


Me2t-BuSiO
CN

268


7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0 PPM
17 8
2.2
23 7
21.9
4 2
74 3
23 7 22.7 14.1
127.1 19 66 8
7.2 77 4
11
94.0

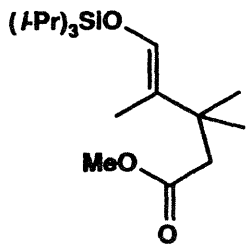



242 243

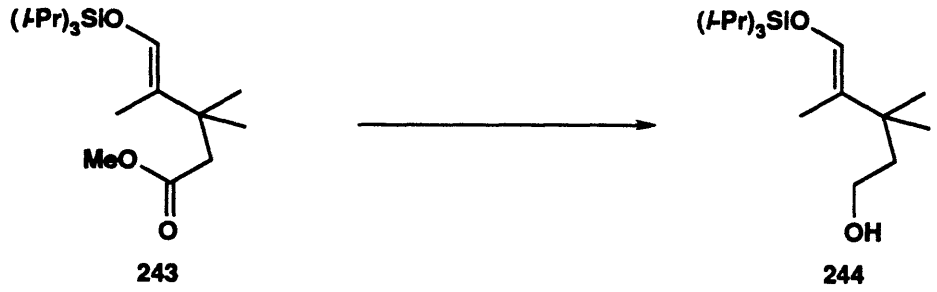
**(E)-Methyl 5-(triisopropylsilyloxy)-3,3,4-trimethylpent-4-enoate (243).**

A 50-mL, round-bottomed flask was charged with aldehyde **242** (458 mg, 2.66 mmol), 25 mL of benzene, and $Et_3N$ (0.46 mL, 3.3 mmol). TIPSOTf (0.82 mL, 3.1 mmol) was added by syringe over 1 min and the reaction mixture was stirred at room temperature for 14 h. The reaction mixture was quenched with 5 mL of saturated aqueous $NaHCO_3$ solution and diluted with 10 mL of petroleum ether. The phases were separated and the aqueous phase extracted with two 25-mL portions of petroleum ether. The combined organic phases were dried over anhydrous $K_2CO_3$, filtered and concentrated to give 883 mg of an oil. Chromatography on 22 g of silica gel (elution with 0.5 % ethyl acetate / petroleum ether) provided 655 mg of **243** (75%) as a colorless oil.

| | |
|---|---|
| IR (thin film): | 2940, 2870, 1735, 1650, 1455, 1380, 1315, 1240, 1205, 1165, 1115, 1010, 880, and 825 $cm^{-1}$ |
| $^1H$ NMR (300 MHz, $CDCl_3$): | 6.23 (q, J = 1.4 Hz, 1H), 3.60 (s, 3H), 2.35 (s, 2H), 1.63 (d, J = 1.6 Hz, 3H), 1.22-1.04 (m, 3H), 1.14 (s, 6H), 1.07 (d, J = 5.6 Hz, 18H) |
| $^{13}C$ NMR (75 MHz, $CDCl_3$): | 172.4, 134.7, 122.3, 51.1, 45.5, 36.3, 27.1, 17.7, 11.9, and 9.5 |



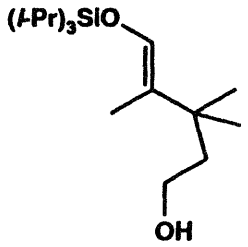

243



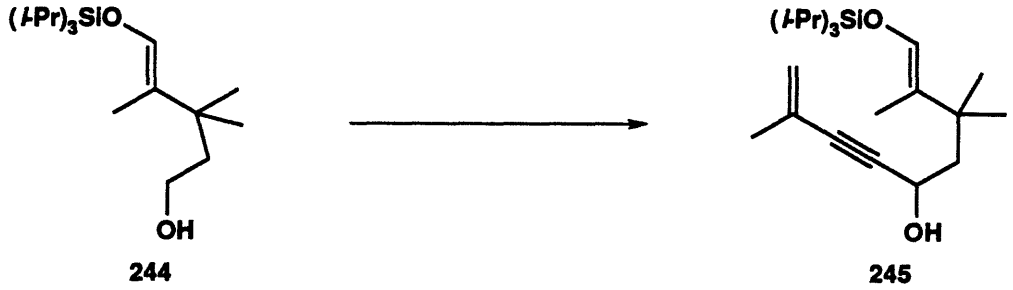

**(E)-5-(triisopropylsilyloxy)-3,3,4-Trimethylpent-4-en-1-ol (244).**

A 5-mL, one-necked, round-bottomed flask was charged with ester **243** (569 mg, 1.73 mmol), and 15 mL of dichloromethane. The reaction mixture was cooled to -78 °C while DIBAL-H solution (1.0M, 7.0 mL, 7 mmol) was added dropwise via syringe over 4 min. The dry ice-acetone bath was replaced by an ice bath and the resulting solution was stirred at 0 °C for 10 min and 6 mL of Rochelle's solution was added. The reaction mixture was diluted with 5 mL of water and 25 mL of diethyl ether and the two phases were stirred vigorously for 20 min. The two phases were separated and the aqueous phase was extracted with two 25-mL portions of diethyl ether. The combined organic phases were dried over anhydrous $K_2CO_3$, filtered, and concentrated to afford 514 mg (99%) of **244** as a colorless viscous oil.

| | | |
|---|---|---|
| IR (thin film): | 3290, 3060, 2930, 2860, 2730, 1645, 1445, 1375, 1365, 1210, 1170, 1115, 1055, 1015, 990, 880, 830 and 720 $cm^{-1}$ | |
| $^1H$ NMR (300 MHz, $CDCl_3$): | 6.19 (q, J = 1.6 Hz, 1H), 3.55 (dt, J = 7.2, 5.4 Hz, 2H), 1.65 (t, J = 6.9 Hz, 2H), 1.61 (d, J = 1.8 Hz, 3H), 1.33 (br s, 1H), 1.20-1.01 (m, 3H), 1.07 (d, J = 5.4 Hz, 18H), and 1.03 (s, 6H) | |
| $^{13}C$ NMR (75 MHz, $CDCl_3$): | 134.6, 122.9, 60.4, 43.1, 35.3, 27.5, 17.8, 12.0, and 9.5 | |
| Elemental Analysis: | Calcd for $C_{17}H_{36}O_2Si$: | C, 67.94; H, 12.07 |
| | Found: | C, 67.76; H, 12.20 |



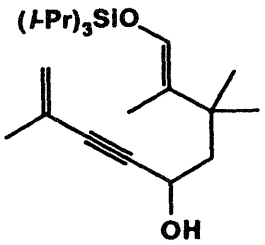

244




**(E)-2,7,7,8-tetramethyl-9-(triisopropylsilyloxy)nona-1,8-dien-3-yn-5-ol (245).**

A 50-mL, round-bottomed flask was charged with oxalyl chloride (0.300 mL, 3.42 mmol) and 15 mL of THF. The reaction mixture was cooled to -78 °C while DMSO (0.255 mL, 3.59 mmol) was added dropwise via syringe over 1 min. The temperature was brought to -35 °C for 3 min and then back to -78 °C. A solution of alcohol **244** (514 mg, 1.71 mmol) in 10 mL of THF was then added, via cannula, over 2 min (with a 5 mL THF rinse). The reaction mixture was stirred at -78 °C for 10 min, at -35 °C for 10 min, and then once again at -78 °C, before adding $Et_3N$ (2.3 mL, 17 mmol), via syringe, over 2 min. The resulting white suspension was stirred for 10 min at 0°C and then cooled to -78 °C. A solution of the acetylide (made by adding *n*-butyllithium solution (2.56 M, 3.3 mL, 8.4 mmol) to a solution of 2-methyl-but-1en-3-yne (0.90 mL, 9.46 mmol) in 10 mL of THF at -30 °C and warming up to 0°C for 10 min) cooled at -78°C was added, via cannula, over 5 min to the reaction mixture. The light brown solution was warmed to 10 °C over 2 h and 5 mL of saturated aqueous $NH_4Cl$ was added. The pH of the reaction mixture was adjusted to pH 8 with $NH_4OH$ and the resulting yellow suspension was poured into 5 mL of water and 5 mL of petroleum ether. The two phases were separated and the aqueous phase was extracted with three 25-mL portions of petroleum ether. The combined organic phases were dried over anhydrous $K_2CO_3$, filtered and concentrated to afford 678 mg of brown oil. Chromatography on 27 g of silica gel (gradient elution with 1-4 % ethyl acetate / petroleum ether) afforded 488 mg of **245** (78%) as a pale yellow oil.

| | |
|---|---|
| IR (thin film): | 3310, 2930, 2860, 1645, 1610, 1455, 1370, 1280, 1210, 1165, 1130, 1110, 1065, 990, 880, and 825 $cm^{-1}$ |
| $^1H$ NMR (300 MHz, $CDCl_3$): | 6.26 (q, J = 1.5 Hz, 1H), 5.27 (br s, 1H), 5.20 (appar quintet, J = 1.7 Hz, 1H), 4.44 (dt, J = 7.2, 4.8 Hz, 1H), 1.94 (d, J = 4.8 Hz, 1H), 1.91 (dd, J = 14, 7.5 Hz, 1H), 1.87 (dd, J = 1.8, 1.2 Hz, 3H), 1.79 (dd, J = 15, 5.3 Hz, 1H), 1.63 (d, J = 1.5 Hz, 3H), 1.21-1.05 (m, 3H), 1.10 (s, 3H), 1.08 (s, 3H), and 1.07 (d, J = 6 Hz, 18H) |
| $^{13}C$ NMR (75 MHz, $CDCl_3$): | 135.4, 126.4, 122.4, 121.7, 90.1, 85.6, 60.8, 48.4, 35.9, 28.2, 27.0, 17.8, 12.0, and 9.6 |
| HRMS: | Calc for $C_{22}H_{41}O_2Si$ $[M+H]^+$: 365.2876<br>Found: 365.2875 |




245

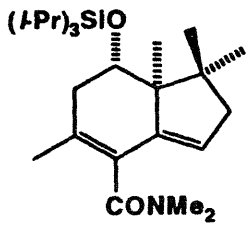

245 246

**(7R*,7aR*)-Dimethyl 7-(triisopropylsilyloxy)-1,1,5,7a-tetramethyl-2,6,7, 7a -tetrahydro-1H-indene-4-carboxamide (246).**

A 10-mL, one-necked, round-bottomed flask was charged with propargyl alcohol **245** (182 mg, 0.500 mmol), dimethylformamide di-*n*-propyl acetal (0.310 mL, 1.51 mmol), and 6 mL of xylenes. A Dean-Stark trap equipped with a reflux condenser and an argon inlet adapter was fitted to the flask and the reaction mixture was heated at reflux for 66 h. The cooled brown solution was concentrated to give 269 mg of a brown oil which was purified by chromatography on 8 g of silica gel (gradient elution with 5-20% ethyl acetate / petroleum ether) to afford 123 mg (59%) of **246** as a pale brown viscous oil. An analytical sample was obtained by distillation in a Kugelrohr oven (150 °C, 0.002 mmHg).

| | |
|---|---|
| IR (KBr): | 3020, 2920, 1615, 1450, 1390, 1360, 1260, 1170, 1095, 1060, 880, 800, and 725 $cm^{-1}$ |
| $^1H$ NMR (300 MHz, $CDCl_3$): | Major rotamer: 5.26 (br s, 1H), 4.27 (ABX pattern, appar t, J = 7.8 Hz, 1H), 3.03 (s, 3H), 2.85 (s, 3H), 2.36 (br d, J = 15 Hz, 1H), 2.32 (ABX pattern, appar d, J = 7.6 Hz, 2H), 1.97 (dd, J = 16, 3.0 Hz, 1H), 1.72 (s, 3H), 1.2-1.0 (m, 3H), 1.16 (s, 3H), 1.10 (s, 18H), 1.06 (s, 3H), and 0.92 (s, 3H)<br>Minor rotamer: 5.21 (br s, 1H), 4.18 (ABX pattern, appar dd, J = 10, 5.9 Hz, 1H), 3.04 (s, 3H), 2.91 (s, 3H), 2.46-2.20 (m, 3H), 1.91 (dd, J = 16, 3.0 Hz, 1H), 1.70 (s, 3H), 1.1 (s, 3H), 1.04 (s, 3H), 0.94 (s, 3H) |
| $^{13}C$ NMR (75 MHz, $CDCl_3$): | Major rotamer: 170.2, 144.0, 131.6, 129.0, 121.6, 70.3, 52.0, 47.1, 44.2, 39.1, 37.5, 34.3, 25.2, 24.3, 20.0, 18.4, 13.6, and 13.0 |

| | |
|---|---|
| | Minor rotamer: 170.4, 144.4, 131.0, 128.7, 121.2, 70.7, 52.2, 46.9, 44.2, 39.0, 37.8, 34.0, 25.2, 24.0, 20.0, 18.4, 13.6, and 12.7 |
| Elemental Analysis: | Calcd for $C_{25}H_{45}NO_2Si$: C, 71.54; H, 10.81; N, 3.34 |
| | Found: C, 71.35; H, 10.68; N, 3.19 |



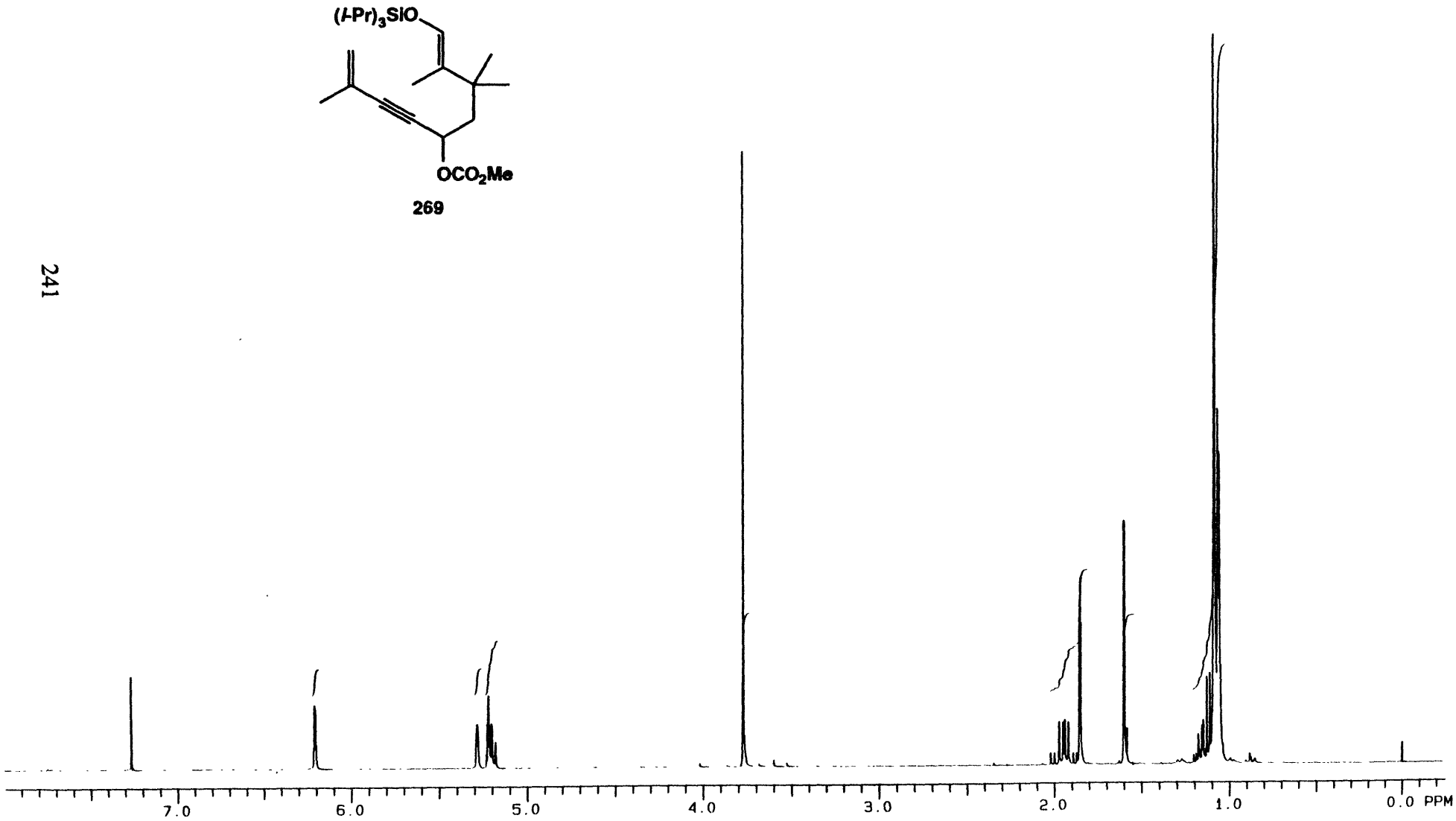

246


245 269

**(E)Methyl 2,7,7,8-tetramethyl-9-(triisopropylsilyloxy)nona-1,8-dien-3-yn-5-yl carbonate (269).**

A 25-mL, one-necked, round-bottomed flask was charged with propargyl alcohol **245** (305 mg, 0.836 mmol), 4-dimethylaminopyridine (133 mg, 1.09 mmol) and 8 mL of dichloromethane. Methyl chloroformate (0.084 mL, 1.09 mmol) was added dropwise via syringe over 30 sec and the reaction mixture was stirred at room temperature for 6.5 h. At this time, the stirbar was removed and the reaction mixture was concentrated *in vacuo*. Pentane (5 mL) was added to the flask and the resulting suspension was filtered, washing the solids with two 5-mL portions of pentane. Concentration of the organic solution gave 392 mg of oil. Chromatography on 8 g of silica gel (gradient elution with 0-1 % ethyl acetate / petroleum ether) afforded 332 mg of **269** (78%) as a colorless oil.

| | |
|---|---|
| IR (thin film): | 2930, 2860, 1745, 1645, 1435, 1365, 1250, 1165, 1115, 935, 880, and 825 $cm^{-1}$ |
| $^1H$ NMR (300 MHz, $CDCl_3$): | 6.21 (q, J = 1.6 Hz, 1H), 5.28 (br s, 1H), 5.22 (appar quintet, J = 1.9 Hz, 1H), 5.20 (t, J = 6.2 Hz, 1H), 3.77 (s, 3H), 1.99 (dd, J = 15, 6.8 Hz, 1H), 1.91 (dd, J = 15, 5.8 Hz, 1H), 1.86 (appar t, J = 1.5 Hz, 3H), 1.60 (d, J = 1.1 Hz, 3H), 1.21-1.05 (m, 3H), and 1.09-1.05 (m, 24H) |
| $^{13}C$ NMR (75 MHz, $CDCl_3$): | 154.7, 135.3, 126.1, 122.5, 121.5, 86.9, 86.1, 66.7, 54.7, 45.6, 35.8, 27.5, 27.4, 23.1, 17.8, 12.0, and 9.5 |
| Elemental Analysis: | Calcd for $C_{24}H_{42}O_2Si$: C, 68.20; H, 10.02<br>Found: C, 68.24; H, 10.22 |




269


269 270

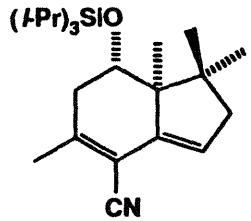
**(7R*,7aR*)-7-(Triisopropylsilyloxy)-1,1,5,7a-tetramethyl-2,6,7,7a-tetrahydro-1H-indene-4-carbonitrile (270).**

A 25-mL, round-bottomed flask was charged with propargyl carbonate **269** (159 mg, 0.375 mmol), $Pd(PPh_3)_4$ (39 mg, 0.034 mmol), 7.5 mL of toluene and TMSCN (0.150 mL, 1.12 mmol). A reflux condenser, equipped with an argon inlet adapter, was fitted to the flask and the reaction mixture was heated at reflux for 2 h. The cooled dark red / purple solution was passed through 3.7 g of florisil® with 25 mL of dichloromethane and concentrated to give 160 mg of a red oil. Column chromatography on 5 g of silica gel (gradient elution with 0-1% ethyl acetate / petroleum ether) resulted in the isolation of 127.1 mg of colorless solid (mp 50-55 °C). Recrystallization from 2 mL of hot methanol yielded upon slow cooling to -20 °C (in two crops) 121 mg (87%) of **270** as a colorless solid (mp 62.5-63.5 °C).

| | |
|---|---|
| IR (KBr): | 3045, 2950, 2870, 2215, 1595, 1460, 1380, 1365, 1305, 1255, 1205, 1105, 1070, 1010, 885, 825, and 760 $cm^{-1}$ |
| $^1H$ NMR (300 MHz, $CDCl_3$): | 5.74 (br s, 1H), 4.16 (ABX pattern, appar t, J = 7.5 Hz, 1H), 2.42 (ABX pattern, appar d, J = 8.1 Hz, 2H), 2.41 (br d, J = 16 Hz, 1H), 2.09 (s, 3H), 2.01 (dd, J = 18, 2.8 Hz, 1H), 1.20-0.99 (m, 3H), 1.16 (s, 3H), 1.09 (s, 18H), 1.03 (s, 3H), and 0.86 (s, 3H) |
| $^{13}C$ NMR (75 MHz, $CDCl_3$): | 149.9, 142.8, 124.5, 116.1, 107.2, 69.6, 52.0, 46.7, 44.6, 39.7, 25.1, 24.0, 22.5, 18.4, 13.6, and 12.8 |
| Analysis: For $C_{23}H_{39}NOSi$ | Calcd.: C, 73.93; H, 10.52; N, 3.75<br>Found: C, 73.95; H, 10.43; N, 3.79 |

HRMS:

| | |
|---|---|
| Calcd for $C_{23}H_{40}NOSi$ (M+H): | 374.2879 |
| Found: | 374.2876 |



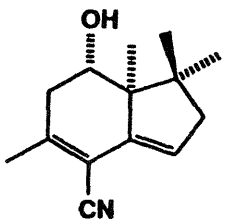

270


270 275

**(7R*,7aR*)-4-cyano-1,1,5,7a-tetramethyl-2,6,7,7a-tetrahydro-1H-inden-7-ol (275).**

A 5-mL, one-necked, round-bottomed flask was charged with nitrile **270** (26.0 mg, 0.0696 mmol), 1 mL of THF and a tetra-*n*-butylammonium fluoride solution (1.0 M in THF, 0.70 mL, 0.70 mmol). The reaction mixture was stirred at room temperature for 30 min. Half saturated aqueous $NH_4Cl$ solution (2 mL) was added and the two phases were separated. The aqueous phase was extracted with four 4-mL portions of diethyl ether and the combined organic phases were washed with 1 mL of saturated aqueous NaCl solution, dried over $MgSO_4$, filtered, and concentrated to yield 25.2 mg of a yellow oil. Column chromatography on 350 mg of silica gel (elution with 10% ethyl acetate / petroleum ether) afforded 14.4 mg of **275** as a colorless solid (mp 89.0-91.0 °C).

| | |
|---|---|
| IR (KBr): | 3510, 3420, 2970, 2210, 1590, 1420, 1370, 1355, 1060,and 760 $cm^{-1}$ |
| $^1H$ NMR (300 MHz, $CDCl_3$): | 5.76 (br s, 1H), 4.04 (ABX pattern, appar dd, J = 9.6, 6.2 Hz, 1H), 2.45 (d, J = 18 Hz, 1H), 2.44 (ABX pattern, appar dd, J = 19, 6.0 Hz, 1H), 2.33 (ABX pattern, appar dd, J = 19, 9.7 Hz, 1H), 2.10 (s, 3H), 2.04 (dd, J = 17 and 3.0 Hz, 1H), 1.43 (br s, 1H), 1.17 (s, 3H), 1.03 (s, 3H), and 0.85 (s, 3H) |
| $^{13}C$ NMR (75 MHz, $CDCl_3$): | 150.4, 142.6, 124.6, 116.1, 107.0, 68.1, 51.1, 46.4, 44.4, 39.2, 25.2, 24.4, 22.3, and 12.2 |




275

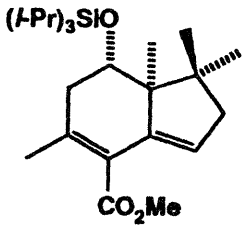

269 274

**(7R*,7aR*)Methyl 7-(triisopropylsilyloxy)-1,1,5,7a-tetramethyl-2,6,7,7a-tetrahydro-1H-indene-4-carboxylate (274).**

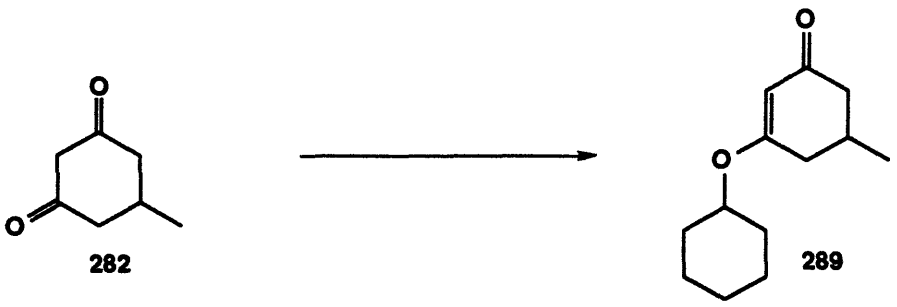
A 25-mL, one-necked, round-bottomed flask was charged with $Pd_2(dba)_3$ (14 mg, 0.016 mmol), dppp (26 mg, 0.062 mmol), and 3 mL of benzene. The catalyst was stirred for 5 min to give an olive green solution and a solution of propargyl carbonate **269** (131 mg, 0.310 mmol) in 3 mL of benzene and 1 mL of methanol was added, by cannula, over 1 min. The system was flushed with CO and a reflux condenser, equipped with a CO balloon, was fitted to the flask. The reaction mixture was heated at 50 - 60 °C for 4 h. The cooled brown solution was filtered through 2 g of florisil® with 25 mL of diethyl ether and concentrated to give 122 mg of an orange / brown oil. Column chromatography on 5.2 g of silica gel (gradient elution with 0-4% ethyl acetate / petroleum ether) resulted in the isolation of 77 mg (61%) of **274** as a colorless solid (mp 60-61 °C). An analytical sample was obtained by recrystallization from aqueous methanol.

| | |
|---|---|
| IR (KBr): | 2920, 2855, 1720, 1625, 1435, 1365, 1225, 1100, 1070, 980, 875, and 770 $cm^{-1}$ |
| $^1H$ NMR (300 MHz, $CDCl_3$): | 5.43 (br s, 1H), 4.19 (ABX pattern, appar dd, J = 9.4, 6.4 Hz, 1H), 3.80 (s, 3H), 2.39 (br d, J = 17 Hz, 1H), 2.38 (ABX pattern, appar dd, J = 18, 8 Hz, 1H), 2.32 (ABX pattern, appar dd, J = 18, 7 Hz, 1H), 1.95 (dd, J = 17, 3.0 Hz, 1H), 1.83 (s, 3H), 1.22-1.02 (m, 3H), 1.16 (s, 3H), 1.10 (s, 18H), 1.04 (s, 3H), and 0.90 (s, 3H) |
| $^{13}C$ NMR (75 MHz, $CDCl_3$): | 169.2, 143.6, 136.8, 126.0, 122.4, 70.2, 52.3, 51.5, 47.0, 43.9, 39.9, 25.2, 24.2, 20.9, 18.4, 13.6, and 12.8 |

| | | |
|---|---|---|
| Elemental Analysis: | Calcd for $C_{24}H_{42}O_3Si$: | C, 70.88; H, 10.41 |
| | Found: | C, 70.94; H, 10.72 |




274

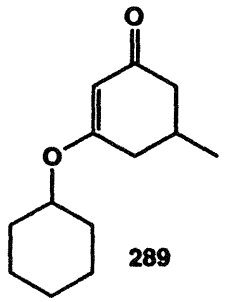


282 289

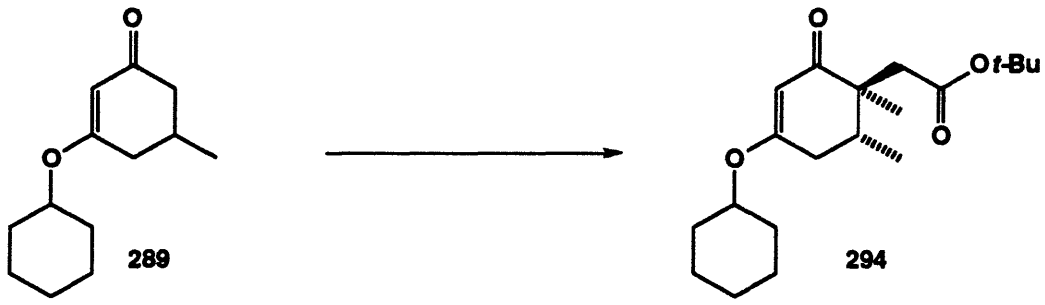
**3-cyclohexoxy-5-methylcyclohex-2-enone (289).**

A 25-mL, one-necked, round-bottomed flask was charged with dione **282** (1.26 g, 10.0 mmol), cyclohexanol (5.2 mL, 50 mmol), *p*-toluenesulfonic acid monohydrate (40 mg, 0.21 mmol), and 20 mL of benzene. A Dean-Stark trap equipped with a reflux condenser and an argon inlet adapter, was fitted to the flask and the reaction mixture was heated at reflux for 8 h. The cooled reaction mixture was concentrated and the excess cyclohexanol distilled off (40 °C at 0.2 mmHg) to give 2.16 g of a red solid. Chromatography on 20 g of silica gel (gradient elution with 5-20% ethyl acetate / petroleum ether) afforded 2.07 g (99%) of **289** as colorless solid (mp 47-48 °C).

| | | |
|---|---|---|
| IR (KBr): | 3060, 2940, 2860, 1640, 1590, 1450, 1375, 1210, 1130, and 1010 $cm^{-1}$ | |
| $^1H$ NMR (300 MHz, $CDCl_3$): | 5.35 (s, 1H), 4.14 (m, 1H), 2.44-2.06 (m, 3H), 2.41 (d, J = 16 Hz, 1H), 2.03 (dd, J = 16, 12 Hz, 1H), 1.97-1.85 (m, 2H), 1.80-1.65 (m, 2H), 1.61-1.20 (m , 6H), and 1.06 (d, J = 6.2 Hz, 3H) | |
| $^{13}C$ NMR (75 MHz, $CDCl_3$): | 199.8, 176.2, 102.5, 45.0, 37.6, 31.1, 30.9, 28.7, 25.2, 23.5, and 20.8 | |
| HRMS: | Calcd for $C_{13}H_{20}O_2$: | 208.1463 |
| | Found: | 208.1468 |



289

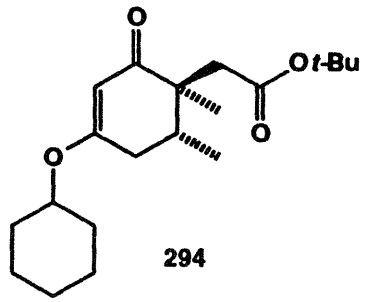



**(5R*,6S*)-3-Cyclohexoxy-5,6-dimethyl-6-(*tert*-butyl ethanoate)cyclohex-2-enone (294).**

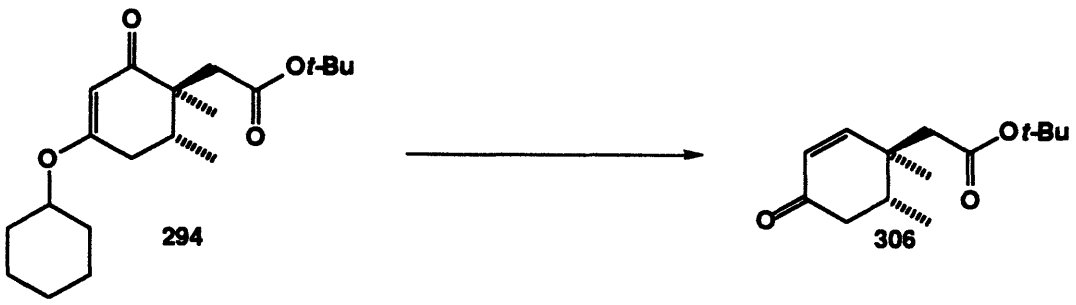
A 50-mL, one-necked, round-bottomed flask was charged with 15 mL of THF and diisopropylamine (1.52 mL, 10.8 mmol). The colorless solution was cooled to -35 °C while *n*-butyllithium solution (2.56M in hexanes, 4.2 mL, 10.8 mmol) was added dropwise via syringe over 1 min. The LDA solution was stirred at -25 °C for 10 min and then cooled to -78 °C. A solution of the vinylogous ester **289** (2.083 g, 10.00 mmol) in 15 mL of THF was added, via cannula, over 5 min to the reaction mixture (with a 5 mL THF rinse). The resulting solution was stirred 5 min at -35 °C and cooled to -78 °C while methyl iodide (0.670 mL, 10.8 mmol) was added, by syringe, over 1 min. The cooling bath was then removed and the reaction mixture was stirred at room temperature for 1.5 h. An LDA solution was made from diisopropylamine (1.68 mL, 12.0 mmol) and *n*-butyllithium solution (2.56 M in hexanes, 4.6 mL, 11.8 mmol) as described above in a 100-mL, round-bottomed flask. This LDA solution was cooled to -78 °C and the reaction mixture was added, via cannula, over 10 min (with a 5 mL THF rinse). The resulting yellow solution was stirred for 5 min at -35 °C and cooled to -78 °C while *t*-butyl bromoacetate (2.25 mL, 13.9 mmol) was added, by syringe, over 2 min. The reaction mixture was warmed to room temperature over 75 min and 20 mL of half saturated aqueous $NH_4Cl$ was added. The reaction mixture was transferred to a separatory funnel with 10 mL of petroleum ether and the two phases were separated. The aqueous phase was extracted with three 25-mL portions of diethyl ether and the combined organic

phases were dried over anhydrous $K_2CO_3$, filtered, and concentrated to give 4.23 g of wet orange / brown solid. This solid was crystallized from 30 mL of hot hexanes to give, after gradual cooling to -20 °C, 1.92 g of brown solid and 1.80 g of filtrate. The solid was recrystallized from 15 mL of hexanes to afford 1.707 g of **294** as a brown solid (mp 95-96 °C) and 0.20 g of filtrate. The combined filtrates were purified by chromatography on 30 g of silica gel (gradient elution with 10-20% diethyl ether / petroleum ether) to give 428 mg of a pale yellow solid. This solid was recrystallized from 3 mL of hexanes to give 359 mg of an off-white solid (mp 95-96 °C). Total yield of **294**: 2.066g (61%).

| | | |
|---|---|---|
| IR (KBr): | 2960, 2940, 2860, 1735, 1640, 1610, 1450, 1355, 1220, 1140, 1035, 1015, 970, and 840 $cm^{-1}$ | |
| $^1H$ NMR (300 MHz, $CDCl_3$): | 5.35 (s, 1H), 4.16 (m, 1H), 3.00 (d, J = 16 Hz, 1H), 2.65 (m, 1H), 2.35-2.19 (m, 3H), 2.00-1.87 (m, 2H), 1.81-1.68 (m, 2H), 1.63-1.16 (m , 6H), 1.42 (s, 9H), 0.98 (d, J = 7.7 Hz, 3H), and 0.96 (s, 3H) | |
| $^{13}C$ NMR (75 MHz, $CDCl_3$): | 202.8, 173.6, 170.7, 101.2, 80.1, 75.9, 46.1, 40.3, 34.6, 32.1, 31.2, 31.0, 28.0, 25.2, 23.5, 17.7, and 15.0 | |
| HRMS: | Calcd for $C_{20}H_{32}O_4$: | 336.2301 |
| | Found: | 336.2303 |




294

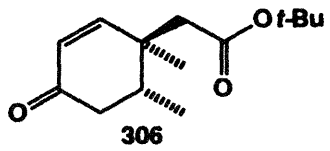



**(4R*,5S*)-4,5-Dimethyl-4-(*tert*-butyl ethanoate)cyclohex-2-enone (306).**

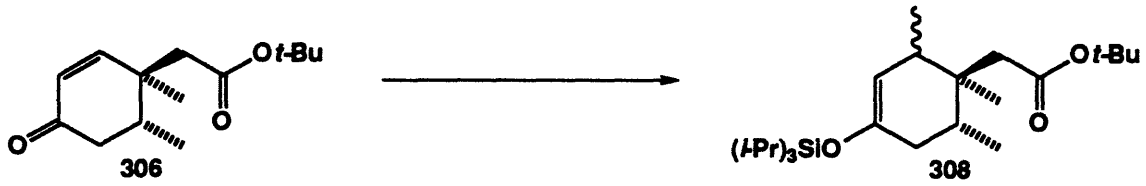
A 100-mL, one-necked, round-bottomed flask was charged with vinologous ester **294** (0.925 g, 2.75 mmol), $LiAl(Ot\text{-}Bu)_3H$ (1.40 g, 5.5 mmol) and 60 mL of diethyl ether. A reflux condenser equipped with an argon inlet adapter was then fitted to the flask and the reaction mixture was heated at reflux for 3 h. The reaction mixture was cooled to room temperature and 1 mL of concentrated phosphoric acid was added cautiously over 1 min. The resulting off-white suspension was stirred for 30 min and 2 g of anhydrous $K_2CO_3$ was added. The reaction mixture was stirred 2 min and filtered using four 10-mL portions of diethyl ether to wash the solids. The resulting solution was washed with 20 mL of saturated aqueous $NaHCO_3$ solution. The aqueous phase was back-extracted with two 10-mL portions of diethyl ether and the combined organic phases were washed with 20 mL of brine, dried over anhydrous $K_2CO_3$, filtered, and concentrated to give 647 mg of a light brown oil. Chromatography on 20 g of silica gel (gradient elution with 4-12% ethyl acetate / petroleum ether) afforded 520 mg (79%) of **306** as a colorless oil.

| | | |
|---|---|---|
| IR (thin film): | 2970, 1715, 1670, 1450, 1365, 1250, 1140, and 960 $cm^{-1}$ | |
| $^1H$ NMR (300 MHz, $CDCl_3$): | 6.97 (d, J = 10 Hz, 1H), 5.92 (d, J = 10 Hz, 1H), 2.42 (d, AB pattern, $J_{AB}$ = 14 Hz, 1H), 2.37 (d, AB pattern, $J_{AB}$ = 14 Hz, 1H), 2.37-2.22 (m, 3H), 1.43 (s, 9H), 1.07 (s, 3H) and 1.01 (d, J = 5.0 Hz, 3H) | |
| $^{13}C$ NMR (75 MHz, $CDCl_3$): | 199.4, 170.1, 158.8, 126.9, 81.0, 45.2, 42.0, 38.8, 35.1, 28.0, 18.9, and 15.5 | |
| HRMS: | Calcd for $C_{14}H_{22}O_3$: | 238.1569 |

Found: 238.1572



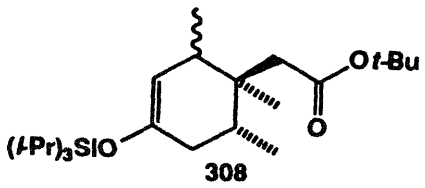

306




**(4R*,5S*)-4-(*tert*-butyl ethanoate)-1-triisopropylsiloxy-3,4,5-trimethylcy-clohex-1-ene (308).**

A 25-mL, round-bottomed flask was charged with copper(I) cyanide and the system was heated under vacuum (0.1 mmHg) with a heat gun (ca. 150 °C) for 5 min. The system was cooled to room temperature under argon and 5 mL of diethyl ether was added. The resulting off-white suspension was cooled to -78 °C and a methyl lithium solution (1.4M in diethyl ether, 1.1 mL, 1.5 mmol) was added dropwise, by syringe, over 2 min. The yellow suspension was stirred for 5 min at -78 °C and 10 min at -30 °C to give a slightly opaque solution. The methyl cuprate solution was cooled to -78 °C and a solution of the enone **306** (119 mg, 0.500 mmol) in 5 ml of diethyl ether was added, by cannula, over 3 min (with a 1 mL diethyl ether rinse). The resulting yellow / green suspension was stirred 45 min at -78 °C to give a thick yellow suspension which was treated with TIPSOTf (0.40 mL, 1.5 mmol) via syringe over 1 min to give at first a yellow / brown solution and then a yellow suspension. The cooling bath was removed after 5 min at -78 °C, and the reaction mixture was warmed to room temperature over 30 min. After stirring the reaction mixture for 15 min at room temperature, 1 mL of saturated aqueous $NaHCO_3$ solution was added, and the resulting light brown slurry was stirred an additional 10 min. The reaction mixture was passed through a plug of 3 g of Celite over 2 g of silica gel with 50 mL of diethyl ether. The resulting colorless solution was dried with anhydrous $K_2CO_3$ and concentrated to give 210 mg of a pale yellow oil. Chromatography on 5 g of silica gel (elution with petroleum ether) afforded 151 mg (73%) of **308** as a colorless viscous oil.

| | |
|---|---|
| IR (KBr): | 2950, 2865, 1720, 1665, 1455, 1365, 1200, 1165, 1140, 1070, 955, 880, and 850 $cm^{-1}$ |
| $^1H$ NMR (300 MHz, $CDCl_3$): | 4.59 (d, J = 3.3 Hz, 1H), 2.34 (ddd, J = 18, 6, 2 Hz, 1H), 2.27 (d, AB pattern, $J_{AB}$ = 14 Hz, 1H), 2.23 (ddq, J = 7, 3, 1 Hz, 1H), 2.04 (d, AB pattern, $J_{AB}$ = 14 Hz, 1H), 1.87 (ddq, J = 7, 6, 6 Hz, 1H), 1.72 (dddd, J = 17, 6, 1, 1 Hz, 1H), 1.43 (s, 9H), 1.22-1.04 (m, 3H), 1.07 (d, J = 6Hz, 18H), 1.04 (s, 3H), 0.88 (d, J = 7 Hz, 3H), and 0.88 (d, J = 7 Hz, 3H) |
| $^{13}C$ NMR (75 MHz, $CDCl_3$): | 172.5, 148.1, 107.7, 79.8, 41.0, 37.0, 36.5, 35.5, 33.4, 28.1, 20.8, 18.0, 16.4, 15.5, and 12.6 |
| HRMS: | Calcd for $C_{24}H_{46}O_3Si$: 410.3216<br>Found: 410.3222 |


Ot-Bu
O
(i-Pr)3SiO

308


7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0 PPM
8.2
24.9
8.4
8.3
9.1
71.7
180.7
45.8